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(71) Applicant: Furanix Technologies B.V
 1014 BV Amsterdam (NL)

(72) Inventor: Gruter, Gerardus Johannes Maria
 2106 BA Heemstede (NL)

(74) Representative: Kortekaas, Marcel C.J.A.
 Exter Polak & Charlouis B.V.
 Postbus 3241
 2280 GE Rijswijk (NL)

(54) Hydroxymethylfurfural ethers from sugars and di- and triols

(57) The current invention provides a method for the manufacture of an ether of 5-hydroxymethylfurfural by reacting a hexose-containing starting material or HMF with a C2 to C6 di- or triol other than 2-methyl-1,3-propanediol, in the presence of an acid catalyst.

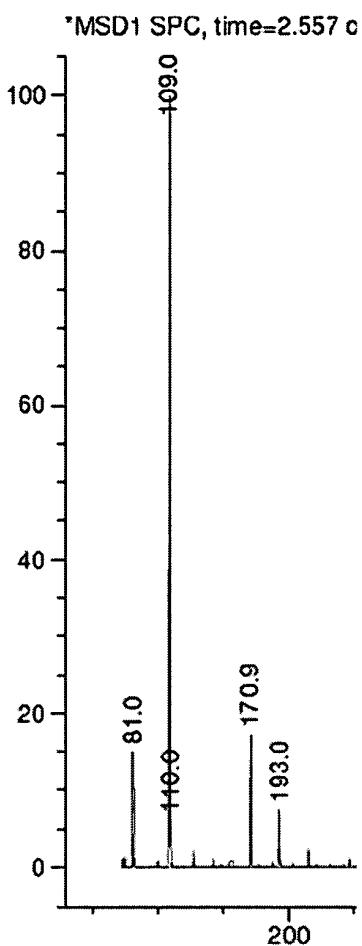


Fig. 1

Description**Technical Field**

[0001] The present invention concerns a method for the manufacture of an ether of 5-hydroxymethylfurfural (5-(hydroxymethyl)-2-furaldehyde, or HMF) from biomass.

Background Art

[0002] Fuel, fuel additives and various chemicals used in the petrochemical industry are derived from oil, gas and coal, all finite sources. Biomass, on the other hand, is considered a renewable source. Biomass is biological material (including biodegradable wastes) which can be used for the production of fuels or for industrial production of e.g. fibres, chemicals or heat. It excludes organic material which has been transformed by geological processes into substances such as coal or petroleum.

[0003] Production of biomass derived products for non-food applications is a growing industry. Biobased fuels are an example of an application with strong growing interest..

[0004] Biomass contains sugars (hexoses and pentoses) that may be converted into value added products. Current biofuel activities from sugars are mainly directed towards the fermentation of sucrose or glucose into ethanol or via complete breakdown via Syngas to synthetic liquid fuels. EP 0641 854 describes the use of fuel compositions comprising of hydrocarbons and/or vegetable oil derivatives containing at least one glycerol ether to reduce particulate matter emissions.

[0005] More recently, the acid catalysed reaction of fructose has been re-visited, creating HMF as an intermediate of great interest. Most processes investigated have the disadvantage that HMF is not very stable at the reaction conditions required for its formation. Fast removal from the water-phase containing the sugar starting material and the acid catalyst has been viewed as a solution for this problem. Researchers at the University of Wisconsin-Madison have developed a process to make HMF from fructose. HMF can be converted into monomers for plastics, petroleum or fuel extenders, or even into fuel itself. The process by prof. James Dumesic and co-workers first dehydrates the fructose in an aqueous phase with the use of an acid catalyst (hydrochloric acid or an acidic ion-exchange resin). Salt is added to salt-out the HMF into the extracting phase. The extracting phase uses an inert organic solvent that favors extraction of HMF from the aqueous phase. The two-phase process operates at high fructose concentrations (10 to 50 wt %), achieves high yields (80% HMF selectivity at 90% fructose conversion), and delivers HMF in a separation-friendly solvent (DUMESIC, James A, et al. "Phase modifiers promote efficient production of Hydroxymethylfurfural from fructose". Science. 30 juni 2006, vol.312, no. 5782, p.1933-1937). Although the HMF yields from this

process are interesting, the multi-solvent process has cost-disadvantages due to the relatively complex plant design and because of the less than ideal yields when cheaper and less reactive hexoses than fructose, such as glucose or sucrose, are used as a starting material. HMF is a solid at room temperature which has to be converted in subsequent steps to useful products. Dumesic has reported an integrated hydrogenolysis process step to convert HMF into dimethylfuran (DMF), which is assumed to be an interesting gasoline additive.

[0006] In WO 2006/063220 a method is provided for converting fructose into 5- ethoxymethylfurfural (EMF) at 60 °C, using an acid catalyst either in batch during 24 hours or continuously via column elution during 17 hours.

15 [0007] Applications of EMF were not discussed.

[0007] Also in copending patent application PCT/EP2007/002145 the manufacture of HMF ethers are described, including the use of such ethers as fuel or fuel additive. Indeed, both the methyl ether and the 20 ethyl ether (methoxymethylfurfural, or MMF; ethoxyethylfurfural or EMF) were prepared and tested. The invention of the copending patent application, however, was limited to the use of primary aliphatic alcohols, and preferably primary C1-C5 alcohols. Use of secondary and tertiary

25 alcohols was not considered, whereas the only example of a branched primary alcohol was considered, was a diol ("2-hydroxymethyl-propanol", which is 2-methyl-1,3-propanediol). Although MMF and EMF are useful as fuel or fuel additive, the inventors found that the ethers leave room for improvement, in particular when used in higher concentration blends with fuels such as gasoline, kerosene, diesel, biodiesel or green diesel. The inventors have therefore set out to overcome this shortfall.

[0008] Surprisingly, the inventors have found that 35 ethers of HMF obtained from di- or triols have superior blending properties compared to ethers obtained from methanol or ethanol analogs.

[0009] The ethers of HMF with these alcohols may be produced in a reasonable yield from hexose containing 40 feedstock or from HMF, with reduced levels of by-product formation and in a manner that does not require cumbersome process measures (such as 2-phase systems) or lengthy process times.

Disclosure of Invention

[0010] Accordingly, the current invention provides a method for the manufacture of an ether of 5-hydroxymethylfurfural by reacting a hexose-containing 50 starting material or HMF with a C2 to C6 di- or triol other than 2-methyl-1,3-propanediol, in the presence of an acid catalyst.

[0011] When the reaction product of the above method is used as such or when it is used as an intermediate for a subsequent conversion, the selectivity of the reaction is preferably high as the product is preferably pure. However, when the reaction product of the above method is used as a fuel, a fuel additive or as a fuel or a fuel additive 55

intermediate, the reaction product does not necessarily need to be pure. Indeed, in the preparation of fuel and fuel additives from biomass, which in itself is a mixture of various monosaccharides, disaccharides and polysaccharides, the reaction product may contain non-interfering components such as levulinic acid derivatives and/or derivatives of pentoses and the like. For ease of reference, however, the method and the reaction product are described in terms of the reaction of a hexose-containing starting material, resulting in an ether of HMF. Also within the scope of the invention is the reaction of HMF with the branched alcohol, since HMF is believed to be produced as intermediate from the hexose-containing starting material.

[0012] The current invention also provides for the use of the reaction product made according to the present invention as fuel or as fuel additive. Fuels for blending with the product of the present invention include but are not limited to gasoline and gasoline-ethanol blends, kerosene, diesel, biodiesel (all renewable fuels combustible in a diesel engine), Fischer-Tropsch liquids (for example obtained from GTL, CTL or BTL gas-to-liquids/coal-to-liquids/biomass to liquids processes), diesel-biodiesel blends and green diesel and blends of diesel and/or biodiesel with green diesel (green diesel is a hydrocarbon obtained by hydrotreating biomass derived oils, fats, greases or pyrolysis oil; see for example the UOP report OPPORTUNITIES FOR BIORENEWABLES IN OIL REFINERIES FINAL TECHNICAL REPORT, SUBMITTED TO: U.S. DEPARTMENT OF ENERGY (DOE Award Number: DE-FG36-05GO15085)). Fuels for blending with the product of the present invention may also include one or more other furanics, wherein the expression furanics is used to include all derivatives of furan and tetrahydrofuran. The invention also provides a fuel composition comprising a fuel element as described above and the reaction product made according to the present invention.

Mode(s) for Carrying Out the Invention

[0013] Biomass resources are well known. The components of interest in biomass are the mono-, di- or polysaccharides (hereinafter referred to as hexose containing starting material). Suitable 6-carbon monosaccharides include but are not limited to fructose, glucose, galactose, mannose and their oxidized, reduced, etherified, esterified and amidated derivatives, e.g. aldonic acid or alditol, with glucose being the most abundant, the most economic and therefore the most preferred monosaccharide, albeit less reactive than fructose. On the other hand, the current inventors have also succeeded to convert sucrose, which is also available in great abundance. Other disaccharides that may be used include maltose, cellobiose and lactose. The polysaccharides that may be used include cellulose, inulin (a polyfructan), starch (a polyglucan), and hemi-cellulose. The polysaccharides and disaccharides are converted into their mon-

osaccharide component(s) and dehydrated during the manufacture of the 5-HMF ether.

[0014] The di- or triol used in the method of the current invention preferably bears two or three hydroxyl groups, which may be in a primary, secondary or even tertiary position. 2-Methyl-1,3-propanediol is preferably excluded from the scope of the present application. The alcohol may comprise from 2 to 6 carbon atoms, preferably from 2 or 3 carbon atoms. Examples include 1,2-ethanediol (ethylene glycol); 1,2-propanediol, 1,3-propanediol; 1,2,3-propanetriol (glycerol); and 1,6-hexanediol. Also cycloaliphatic diols and triols may be used, including such compounds containing oxygen in the aliphatic ring. Examples include dihydroxymethylfuran and dihydroxymethyl tetrahydrofuran, which both may be derived from biomass.

[0015] Also blends of alcohols may be used, e.g., of glycol and glycerol. The current method thus provides an excellent high value outlet for glycerol that is "contaminated" with ethylene glycol and/or propylene glycol.

[0016] The amount of di- or triol used during the manufacture of the HMF ether is preferably at least equimolar on the hexose content of the feedstock, but typically is used in much greater excess. Indeed, the alcohol (such as ethylene glycol) may be used as solvent or co-solvent. In such a case, a sufficient amount of alcohol is present to form the HMF ether.

[0017] The acid catalyst in the method of the present invention can be selected from amongst (halogenated) organic acids, inorganic acids, Lewis acids, ion exchange resins and zeolites or combinations and/or mixtures thereof. It may be a homogeneous catalyst, but heterogeneous catalysts are preferred for purification reasons. The HMF ethers can be produced with a protonic, Brønsted or, alternatively, a Lewis acid or with catalysts that have more than one of these acidic functionalities.

[0018] The protonic acid may be organic or inorganic. For instance, the organic acid can be selected from amongst oxalic acid, levulinic acid, maleic acid, trifluoro acetic acid (triflic acid), methansulphonic acid or para-toluenesulphonic acid. Alternatively, the inorganic acid can be selected from amongst (poly)phosphoric acid, sulphuric acid, hydrochloric acid, hydrobromic acid, nitric acid, hydroiodic acid, optionally generated in situ.

[0019] Certain salts may be used as catalyst, wherein the salt can be any one or more of $(\text{NH}_4)_2\text{SO}_4/\text{SO}_3$, ammonium phosphate, pyridinium chloride, triethylamine phosphate, pyridinium salts, pyridinium phosphate, pyridinium hydrochloride/hydrobromide/perbromate, DMAP, aluminium salts, Th and Zr ions, zirconium phosphate, Sc and lanthanide ions such as Sm and Y as their acetate or trifluoroacetate (triflate) salt, Cr-, Al-, Ti-, Ca-, In-ions, ZrOCl_2 , $\text{VO}(\text{SO}_4)_2$, TiO_2 , V-porphyrine, Zr-, Cr-, Ti-porphyrine.

[0020] Lewis acids selected as dehydration catalyst can be any one of ZnCl_2 , AlCl_3 , BF_3 .

[0021] Ion exchange resins can be suitable dehydration catalysts. Examples include Amberlite™ and Am-

berlyst™, Diaion™ and Levatit™. Other solid catalyst that may be used include natural clay minerals, zeolites, supported acids such as silica impregnated with mineral acids, heat treated charcoal, metal oxides, metal sulfides, metal salts and mixed oxides and mixtures thereof.

[0022] An overview of catalysts that may be used in the method of the current invention may be found in Table 1 of the review article prepared by Mr. Lewkowski: "Synthesis, chemistry and applications of 5-hydroxymethylfurfural and its derivatives" Arkivoc. 2001, p.17-54.

[0023] The amount of catalyst may vary, depending on the selection of catalyst or catalyst mixture. For instance, the catalyst can be added to the reaction mixture in an amount varying from 0.01 to 40 mole % drawn on the hexose content of the biomass resource, preferably from 0.1 to 30 mole %, more preferably from 1 to 20 mole %.

[0024] In the preferred embodiment, the catalyst is a heterogeneous catalyst.

[0025] The temperature at which the reaction is performed may vary, but in general it is preferred that the reaction is carried out at a temperature from 50 to 300 degrees Celsius, preferably from 125 to 250 degrees Celsius, more preferably from 150 to 225 degrees Celsius. In general, temperatures higher than 300 are less preferred as the selectivity of the reaction reduces and as many by-products occur, inter alia caramelisation of the sugar. Performing the reaction below the lowest temperature is also less preferable because of the low reaction rate.

[0026] The HMF or hexose-containing starting material is typically dissolved or suspended in a solvent which can also be the branched alcohol reactant, in order to facilitate the reaction. The solvent system may be selected from one or more of the group consisting of water, sulfoxides, preferably DMSO, ketones, preferably methyl ethylketone, methylisobutylketone and acetone, ethylene glycol ethers, preferably diethyleneglycol dimethyl ether (diglyme). Also so-called ionic liquids may be used. The latter refers to a class of inert ionic compounds with a low melting point, which may therefore be used as solvent. Examples thereof include e.g., 1-H-3-methyl imidazolium chloride, discussed in "Dehydration of fructose and sucrose into 5-hydroxymethylfurfural in the presence of 1-H-3-methyl imidazolium chloride acting both as solvent and catalyst", by Claude Moreau et al, Journal of Molecular Catalysis A: Chemical 253 (2006) 165-169.

[0027] Basically a sufficient amount of solvent is preferable present to dissolve or suspend the starting material and to limit undesired side-reactions.

[0028] The method of the current invention may be carried out in a batch process or in a continuous process, with or without recycle of (part of) the product stream to control the reaction temperature (recycle via a heat exchanger). For instance, the method of the invention can be performed in a continuous flow process. In such method, homogenous catalysts may be used and the residence time of the reactants in the flow process is between 0.1 second and 10 hours, preferably from 1 second to 1

hours, more preferably from 5 seconds to 20 minutes.

[0029] Alternatively, the continuous flow process may be a fixed bed continuous flow process or a reactive (catalytic) distillation process with a heterogeneous acid catalyst. To initiate or regenerate the heterogeneous acid catalyst or to improve performance, an inorganic or organic acid may be added to the feed of the fixed bed or reactive distillation continuous flow process. In a fixed bed process, the liquid hourly space velocity (LHSV) can be from 1 to 1000, preferably from 5 to 500, more preferably from 10 to 250 and most preferably from 25 to 100 min⁻¹.

[0030] The above process results in a stable HMF ether, which can then be used as such or be converted into a further derivative before being used as fuel and/or as fuel additive. The inventors are of the opinion that some of the products prepared by the method of the current invention are actually new. Thus, the monoethers and diethers made with ethylene glycol, 1,2-propylene

glycol, 1,3-propylene glycol, glycerol, dihydroxymethylfuran or dihydroxymethyl THF as alcohol, are new and are excellent fuel components or fuel additives. Since these alcohols may be made from biomass, this might open a class of products that are fully biomass-derived.

25 Accordingly, these new ethers are claimed as well.

[0031] The HMF ethers of the invention can also be used as or can be converted to compounds that can be used as solvent, as monomer in a polymerization (such as 2,5-furan dicarboxylic acid or FDCA), as fine chemical or pharmaceutical intermediate, or in other applications.

Oxidation of the HMF ethers using an appropriate catalyst under appropriate conditions such as for example described for p-xylene with a NHPI/Co(OAc)₂/MnOAc₂ catalyst system in Adv. Synth. Catal. 2001, 343, 220-225 or such as described for HMF with a Pt/C catalyst system at pH < 8 in EP 0 356 703 or or such as described for HMF with a Pt/C catalyst system at pH > 7 in FR 2 669 634, all with air as an oxidant, resulted in the formation of 2,5-furan dicarboxylic acid (FDCA).

[0032] The invention further concerns the use of the HMF ethers prepared by the method of the current invention as fuel and/or as fuel additive. Of particular interest is the use of the ethers in diesel, biodiesel or "green diesel", given its (much) greater solubility therein than ethanol. Conventional additives and blending agents for diesel fuel may be present in the fuel compositions of this invention in addition to the above mentioned fuel components. For example, the fuels of this invention may contain conventional quantities of conventional additives

50 such as cetane improvers, friction modifiers, detergents, antioxidants and heat stabilizers, for example. Especially preferred diesel fuel formulations of the invention comprise diesel fuel hydrocarbons and HMF ether as above described together with peroxidic or nitrate cetane improvers such as tertiary butyl peroxide, amyl nitrate and ethyl hexyl nitrate for example.

[0033] Examples are enclosed to illustrate the method of the current invention and the suitability of the products

prepared therefrom as fuel. The examples are not meant to limit the scope of the invention.

Example 1. 5-(hydroxymethyl)furfural ethylene glycol ether (5-(2-hydroxyethoxymethyl)furfural) formation

[0034] In a 7.5 mL batch reactor, equipped with on-line transmission turbidity measurement, 0.82 mmol fructose was added to 0.8 mL ethylene glycol containing 0.5 wt% sulphuric acid. The reaction mixture was heated at 85 °C until all fructose was dissolved (approx. 10 minutes). Two main furanics peaks were detected using HPLC with UV detection and their identity was shown to be HMF and 2-(hydroxyethyl)oxymethyl)furfural by LC-MS (Cl). See fig. 1.

References

[0035]

- DUMESIC, James A, et al. "Phase modifiers promote efficient production of Hydroxymethylfurfural from fructose". Science. 30 June 2006, vol.312, no. 5782, p.1933-1937.
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- EP 0 356 703
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Claims

1. Method for the manufacture of an ether of 5-hydroxymethylfurfural by reacting a hexose-containing starting material with a C2-C6 di- or triol, other than 2-methyl-1,3-propanediol, in the presence of an acid catalyst.
2. Method according to claim 1, wherein the C2-C6 di- or triol is selected from the group comprising 1,2-

ethanediol, 1,2-propanediol, 1,3-propanediol; 1,2,3-propanetriol, 1,6-hexanediol, di(hydroxymethyl)furan and di(hydroxymethyl)tetrahydrofuran

- 5 3. Method according to claim 1 or 2, wherein the acid catalyst is selected from the group consisting of homogeneous or heterogeneous acids selected from solid organic acids, inorganic acids, salts, Lewis acids, ion exchange resins, zeolites or mixtures and/or combinations thereof.
- 10 4. Method according to claim 1, wherein the acid is a solid Brønsted acid.
- 15 5. Method according to claim 1, wherein the acid is a solid Lewis acid.
6. Method according to any one of the claims 1 to 5, 20 wherein the reaction is performed at a temperature from 50 to 300 degrees Celsius, preferably from 125 to 250, more preferably from 150 to 225 degrees Celsius.
- 25 7. Method according to any one of the claims 1 to 6, wherein a hexose-containing starting material is used and wherein the hexose starting material is selected from the group of
 - 30 • starch, amylose, galactose, cellulose, hemicellulose,
 - glucose-containing disaccharides such as sucrose, maltose, cellobiose, lactose, preferably glucose-containing disaccharides, more preferably sucrose,
 - 35 • glucose or fructose.
8. Method according to any one of the claims 1 to 6, 40 wherein the starting material is 5-(hydroxymethyl)furfural.
- 45 9. Method according to any one of the claims 1 to 6, wherein the starting material comprises glucose, fructose, galactose and mannose and their oxidized (aldonic acid) or reduced (alditol) derivatives or mixtures thereof.
- 50 10. Method according to any one of the claims 1 to 6 wherein the starting material is an esterified, etherified monosaccharide or an amido sugar.
- 55 11. Method according to any one of the claims 1 to 10, wherein the solvent or solvents are selected from the group consisting of water, sulfoxides, preferably DMSO, ketones, preferably methyl ethylketone, ionic liquids, methylisobutylketone and/or acetone, esters, ethers, preferably ethylene glycol ethers, more preferably diethyleneglycol dimethyl ether (diglyme) or the reactant olefin and mixtures thereof.

12. Method according to any one of the claims 1 to 11, wherein the method is performed in a continuous flow process.
13. Method according to claim 12, wherein the residence time in the flow process is between 0.1 second and 10 hours, preferably from 1 second to 1 hours, more preferably from 5 seconds to 20 minutes.
14. Method according to claim 13, wherein the continuous flow process is a fixed bed continuous flow process.
15. Method according to claim 14, wherein the fixed bed comprises a heterogeneous acid catalyst.
16. Method according to claim 15, wherein the continuous flow process is a reactive distillation or a catalytic distillation process.
17. Method according to claim 16, wherein in addition to a heterogeneous acid catalyst, an inorganic or organic acid catalyst is added to the feed of the fixed bed or catalytic distillation continuous flow process.
18. Method according to claim 14-17, wherein the LHSV is from 1 to 1000, preferably from 5 to 500, more preferably from 10 to 250 and most preferably from 25 to 100.
19. Use of the ether produced by the method of any one of claims 1-18 as a solvent, as a pharmaceutical intermediate or as an olefinically unsaturated monomer from an olefinically unsaturated di- or triol or as an intermediate for the production of a polyester monomer.
20. Use of the ether produced by the method of any one of claims 1-18 as fuel or fuel additive.
21. A fuel or fuel composition comprising the ether produced by the method of any one of claims 1-18 as fuel component, optionally blended with one or more of gasoline and gasoline-ethanol blends, kerosene, diesel, biodiesel, Fischer-Tropsch liquids, diesel-biodiesel blends and green diesel and blends of diesel and/or biodiesel with green diesel and other furanics.
22. 5-(hydroxymethyl)furfural 2-hydroxyethyl ether (ether of 1,2-ethanediol and HMF)
23. bis 5-(hydroxymethyl)furfural 1,2-ethane-diyl diether (di-ether of 1,2-ethanediol and 2 equivalents of HMF)
24. 5-(hydroxymethyl)furfural 2-hydroxy-2-methylethyl ether (ether of 1,2-propanediol and HMF)
25. bis 5-(hydroxymethyl)furfural 2-methyl-1,2-propane-diyl di-ether (di-ether of 1,2-propanediol and 2 equivalents of HMF)
26. 5-(hydroxymethyl)furfural 3-hydroxypropyl ether (ether of 1,3-propanediol and HMF)
27. bis 5-(hydroxymethyl)furfural 1,3-propane-diyl diether (di-ether of 1,3-propanediol and 2 equivalents of HMF)
28. 5-(hydroxymethyl)furfural 2,3-dihydroxypropyl ether (ether of 1,2,3-propanetriol and HMF)
29. bis 5-(hydroxymethyl)furfural 2-hydroxypropaandiy diether (di-ether of 1,2,3-propanetriol with 2 equivalents of HMF)
30. 5-(hydroxymethyl)furfural 6-hydroxyhexyl ether (ether of 1,6-hexanediol and HMF)
31. bis 5-(hydroxymethyl)furfural 1,6-hexane-diyl diether (di-ether of 1,6-hexanediol and 2 equivalents of HMF)
32. ether of 2,5-di(hydroxymethyl)furan en HMF
33. di-ether of 2,5-di(hydroxymethyl)furan and 2 equivalents of HMF
34. ether of 2,5-di(hydroxymethyl)tetrahydrofuran en HMF
35. di-ether of 2,5-di(hydroxymethyl)tetrahydrofuran and 2 equivalents of HMF

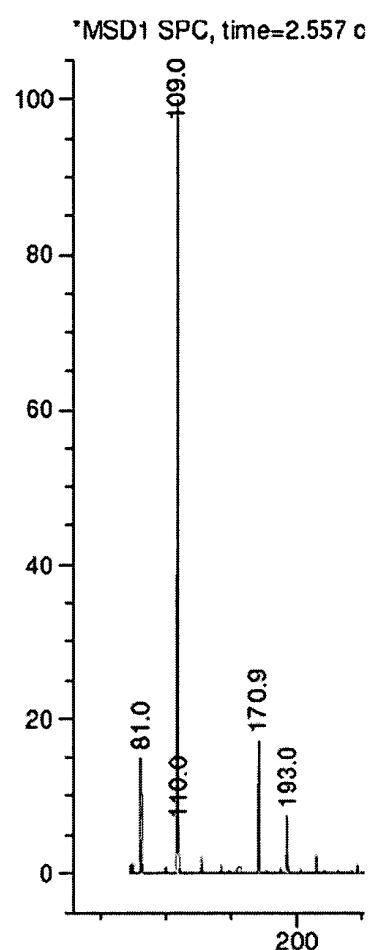


Fig. 1



DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	MOORE J A ET AL: "Polyesters derived from Furan and Tetrahydrofuran Nuclei" MACROMOLECULES, ACS, WASHINGTON, DC, US, vol. 11, no. 3, 1978, pages 568-573, XP002413093 ISSN: 0024-9297 1st full paragraph * page 568 *	19	INV. C07D307/46
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			C07D
2	The present search report has been drawn up for all claims		
Place of search		Date of completion of the search	Examiner
The Hague		12 December 2007	Fritz, Martin
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 07 07 5774

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
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12-12-2007

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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Cram

[11] **3,965,116**
[45] **June 22, 1976**

[54] **MULTIOXYMACROCYCLES**

[75] Inventor: **Donald J. Cram**, Los Angeles, Calif.
[73] Assignee: **The Regents of the University of California**, Berkeley, Calif.
[22] Filed: **Sept. 12, 1974**
[21] Appl. No.: **505,576**

[52] U.S. Cl. **260/338; 260/296 H;**
 260/297 B; 260/340.3; 260/347.8
[51] Int. Cl.² **C07D 307/00**
[58] Field of Search **260/338**

[56] **References Cited**

OTHER PUBLICATIONS

Winberg et al., J.A.C.S. vol. 82 (1960), pp. 1428-1434.

Primary Examiner—Henry R. Jiles

Assistant Examiner—Bernard Dentz

Attorney, Agent, or Firm—John T. Reynolds; Willard L. Cheesman

[57] **ABSTRACT**

Multiheteromacrocycles are disclosed that contain as part of the macrocycle, assemblies of 2,6-dimethylpyridine (and their corresponding amine oxides), 2,5-dimethylfuran, 2,5-dimethyltetrahydrofuran, Diels-Alder adducts of 2,5-dimethylfuran (and their reduction products), 2- and 4-substituted 1,3-dimethylbenzenes, pentamethylene, or p-phenylene coupled through oxygen to one another or to ethylene, o-phenylene, or 1,1-binaphthyl-2,2-units (always coupled through oxygens) to form multidentate ligands for complexing selectively alkylammonium or metal cations.

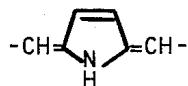
9 Claims, No Drawings

MULTIOXYMACROCYCLES

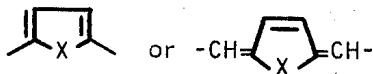
This work was supported in part by the U.S. Public Health Service Research Grant No. GM12640-10 from the Department of Health, Education and Welfare, and in part by a grant from the National Science Foundation, GP33533X.

BACKGROUND OF THE INVENTION

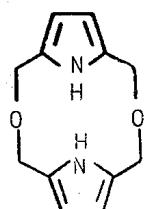
Many heteromacrocycles are known that incorporate as part of the large ring structure, the simpler known heterocyclic or benzene units. For example, hemoglobin, chlorophyll, vitamin B₁₂, many of the macrocyclic antibiotics (e.g. nonactin) contain such structural units. Multiheteromacrocycles that contain as part of the major ring 2,6-substituted pyridine units have been synthesized combined with just —CH₂CH₂— units [J. Chem. Soc. 3594 (1958) and Chimia, 22, 306 (1968)], just —CH₂SCH₂— units [Tet. Letters, 3623 (1968), Chem. Ber., 102, 2677 (1969) and J. Chem. Soc., B, 2307 (1971)], just —CH₂SCH₂— combined with CH₂OCH₂ units [Nachr. Chem. Techn., 22, 2 (1974)], and just —CH₂OCH₂— combined with —O—C₆H₄— (ortho phenylene) units. Multiheteromacrocycles that contain as part of the major ring 2,5-disubstituted furane units have been synthesized combined with just —CH₂CH₂— units [J. Amer. Chem. Soc., 82, 1428 (1960)], just —CH=CH— units, just —CH=CH— units combined with 2,5-disubstituted thiophene units [Chem. Commun., 269 (1965)], just —(CH₃)₂C— units [J. Org. Chem., 20, 1147 (1956) and Chem. Commun., 534 (1973)], just —CH=CH— units combined with ortho-C₆H₄ units [J. Amer. Chem. Soc., 90, 1631 (1968)], just



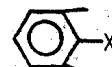
units [Chem. Commun., 23 (1969)], just —CH=CH— combined with



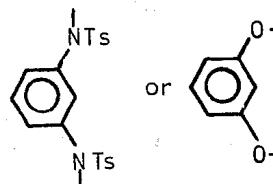
units (X = S or NH) [J. Austral. Chem., 20, 2669 (1967) and Chem. Commun., 807 (1972)], and with just a p-CH₂CH₂C₆H₄-CH₂CH₂- unit [J. Amer. Chem. Soc., 88, 515 (1966)]. Many multiheteromacrocycles that contain as part of the major ring system, 1,1-binaphthyl-2,2'-disubstituted units have been reported (U.S. patent application Ser. No. 346,089, filed Mar. 29, 1973), but none which contain the -m-C₆H₄- (meta-phenylene), 2,6-disubstituted pyridyl or pentamethylene units have been reported. Many multiheteromacrocycles that contain as part of the major ring system the disubstituted 2,5-dipyrrole unit have been synthesized, but only one report has appeared which involves combining it with just —CH₂OCH₂— units [Gazz. Chim. Ital., 62, 844 (1932)] to give:



Multiheteromacrocycles that contain as part of the major ring



units have been synthesized combined with just —CH₂CH₂— units [Angew. Chem. Internat. Ed., 8, 274 (1969)], just —CH₂SCH₂— units [Chem. Ber., 102, 2677 (1969) and J. Chem. Soc., B, 2307 (1971)], just



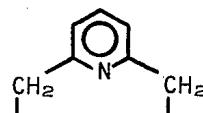
units [Chem. Ber., 102, 3071 (1969)], and with just



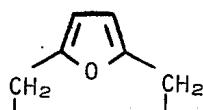
or —CH₂CO₂(CH₂)_nO₂CCH₂— units [Tet. Letters, 115 (1970)].

BRIEF DESCRIPTION OF THE INVENTION

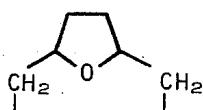
Unique to this invention are compounds that contain only units A through L, all of which contain unit L that serves to connect all other units to one another in a ring system, and all of which contain at least one unit taken from the group, A through G.



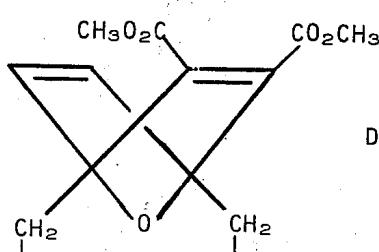
A



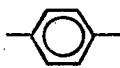
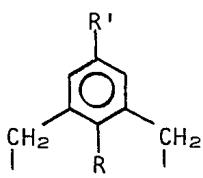
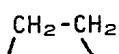
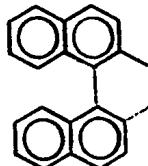
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C



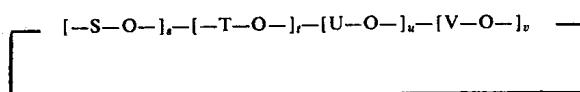
D

3-(CH₂)_s-

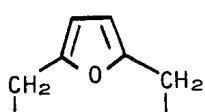
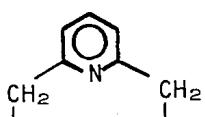
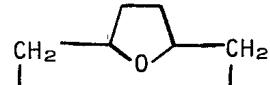
-O-

SUMMARY OF THE INVENTION**Character of the Compounds**

This invention relates to multiheteromacrocycles of 50 where $\text{---S---} = \text{U} =$
the following formula:

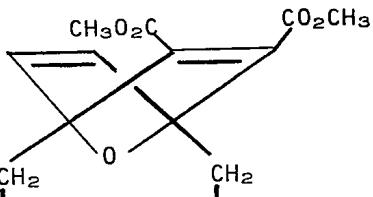


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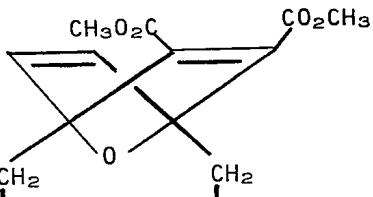
where $\text{---S---} =$ **4**

s = 2 through 4, and t=u=v = 0;
where $\text{---S---} =$ the same ---S--- units as above as well as

10

**F**

15

**G**T = -CH₂-CH₂-,

s = 1, and

20 t = 2 through 7, and u=v = 0; where $\text{---S---} = \text{U} =$ the same initially mentioned above units,T=V= -CH₂-CH₂-,

s=u = 1,

t = 1 through 6,

25 v = 0, and 1 through 6;

where $\text{---S---} =$ 

30

T = -CH₂-CH₂-,

s = 1,

t = 3 through 9,

35 u=v = 0;

where $\text{---S---} = \text{U} =$ 

40

T=V= -CH₂-CH₂-,

s=u = 2,

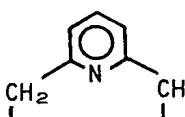
t=v = 3 through 9;

45 where $\text{---S---} = -(CH_2)_5-$,T = -CH₂-CH₂-,

s = 1,

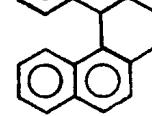
t = 4,

u=v = 0;

50 where $\text{---S---} = \text{U} =$ 

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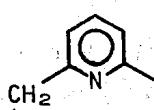
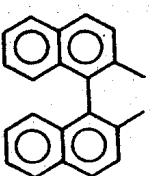
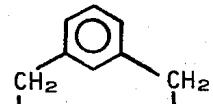
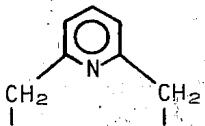
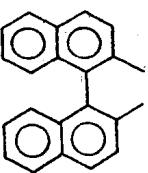
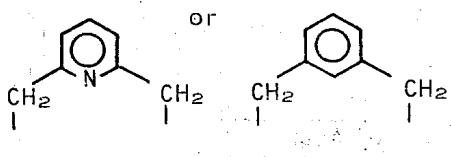
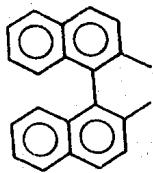
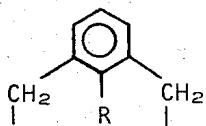
T=V=



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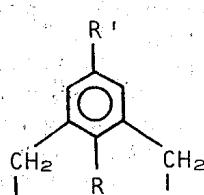
s=u = 1,
t=v = 1;

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where $-S-$ = $T=V=$  $U =$  $s=t=u=v=1;$
where $-S-$ = $T=V=$  $U = -(CH_2)_5-,$
 $s=t=u=v=1;$
where $-S-$ = $T=V=$  $U = -CH_2-CH_2-, s=t=v=1,$
 $u=2;$
where $-S-$ =

$R = H, Cl, Br, CO_2CH_3, CO_2H, CN, CONH_2, NH_2,$
 OH or $OCH_3,$
 $T = -CH_2-CH_2-,$
 $s = 1,$
 $t = 3$ through $8, u=v=0;$

6

where $-S-$ =

10 $R = CO_2CH_3$ or CO_2H (except when $R' = CO_2CH_3$),
 $R' = CO_2CH_3, CO_2H, CH_2OH, CH_2OCH_2CO_2CH_3$, or
 $CH_2OCH_2CO_2H,$
 $T = -CH_2-CH_2-,$
 $s = 1,$
 $t = 3$ through $8, u=v=0;$
 where $-S-$ =

20 or $-CH_2-$ $-CH_2-$ CO_2 lower alkyl

25 $T=V=$,
 30 ,

 $U = -CH_2CH_2-, s=t=v=1,$
 $u=2.$

35 Compounds 1 are unique in their structures, and in their cooperating molecular parts, which make them useful for the variety of purposes described below.

The systematic names of most of the compounds are too complicated for ready translation into structural formulas. Therefore structural formulas will be assigned unique numbers and specific compounds as entities will be coupled to their structures by these numbers.

40 45 Each cycle's oxygen or nitrogen provide ligands for metal, alkyl or arylammonium, hydronium or hydrogen cations. When complexed, the oxygens or nitrogens of the multiheterocycle turn toward the cation and serve as binding points to provide highly structured molecular complexes. These multiheterocycles act as "host" compounds that complex "guest" compounds.

The basicity and ligand properties of the heteroatoms of the above units are all different from one another, and show different tendencies to bind different cations.

55 60 55 The sizes of the holes in the cyclic hosts have been varied to accommodate guest cations of various sizes. By loss of a proton in the units that contain acidic groups, anions have been generated in the host compounds that serve as counterions for the cations of the guest compounds. Thus complementary host-guest relationships have been arranged that involve ligand specificity, hole size and charge type.

Some of the host compounds contain chiral elements, and when optically active, the hosts complex preferentially one enantiomer of a racemate and change its solubility properties as compared to the non-complexed enantiomer. Thus optical resolutions of racemic primary amines, amino acids and their derivatives

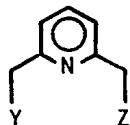
can be caused by differential distribution of diastereomeric complexes between two phases (these properties are important in applications involving countercurrent extraction and chromatographic separations).

Some of the host compounds contain both pyridine and chiral units. These compounds serve as optically active catalysts for asymmetric induction in synthesis of new chiral centers, in selective destruction of chiral

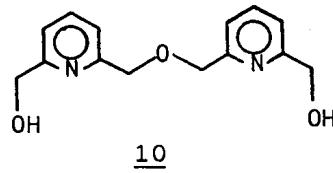
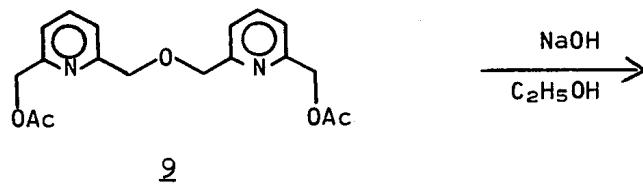
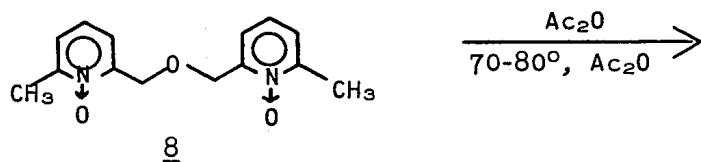
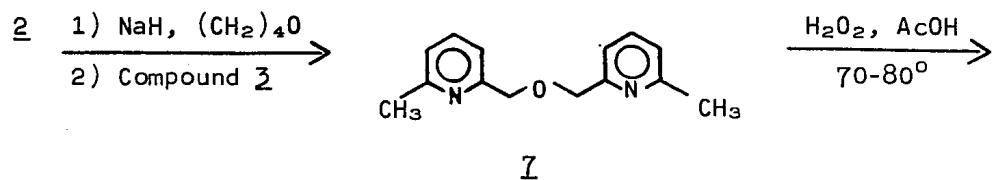
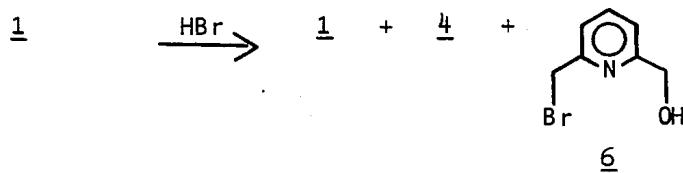
centers, or in interconversion of ligands attached at chiral centers.

Synthesis of Multiheteramacrocycles

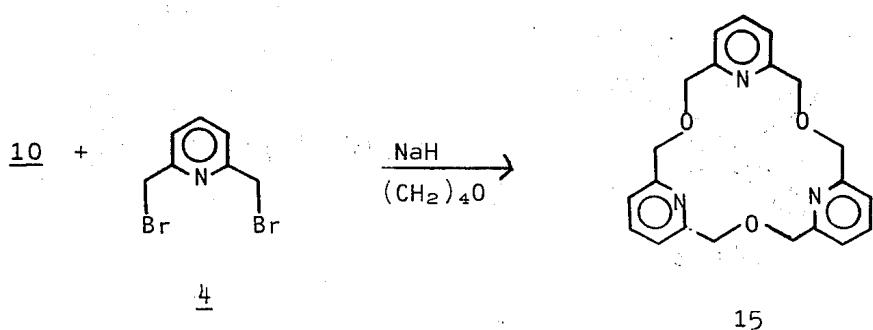
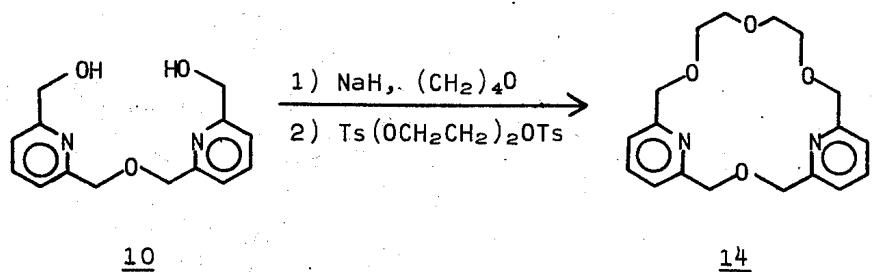
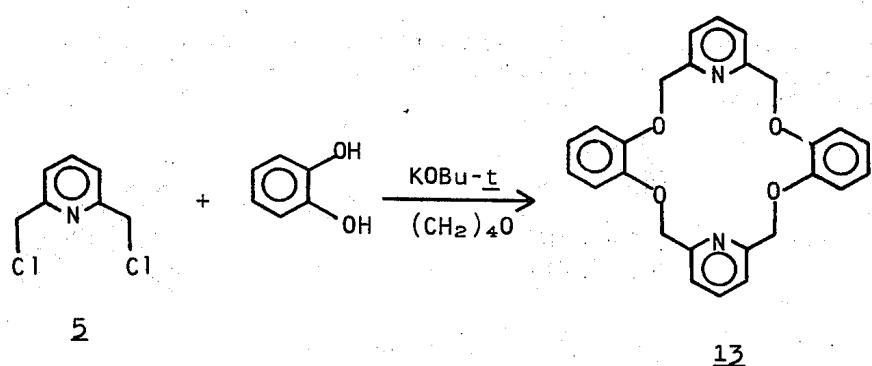
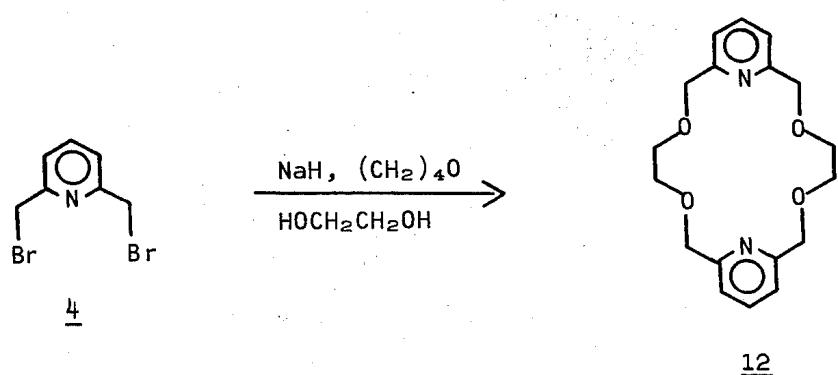
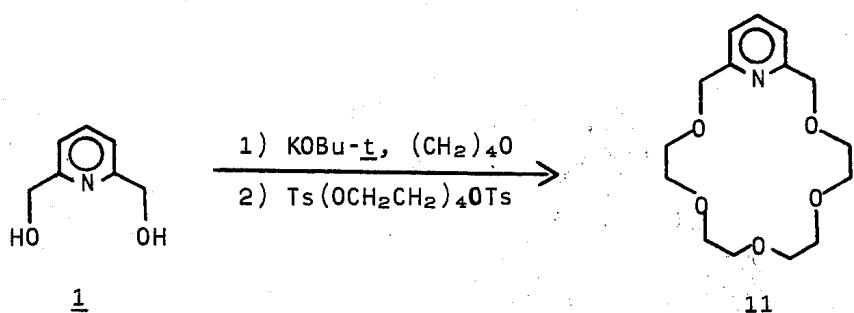
Known compounds 1 to 5 served as starting materials for syntheses of the pyridine-containing host compounds. New open-chain compounds, 6 to 10 were prepared by the sequences formulated.



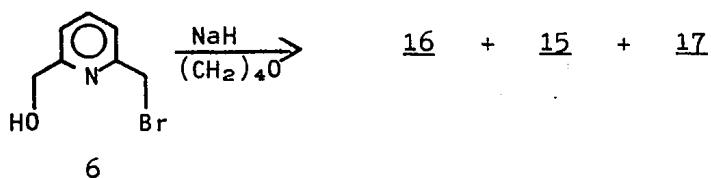
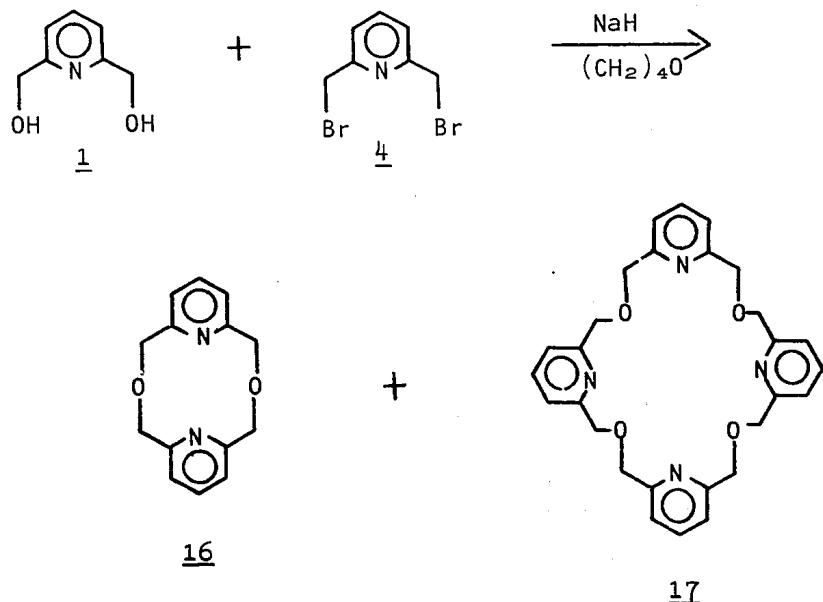
- 1, Y=Z=OH
- 2, Y=OH, Z=H
- 3, Y=Cl, Z=H
- 4, Y=Z=Br
- 5, Y=Z=Cl



Pyridine-containing multiheteromacrocycles were prepared from open-chain compounds by the sequences formulated.

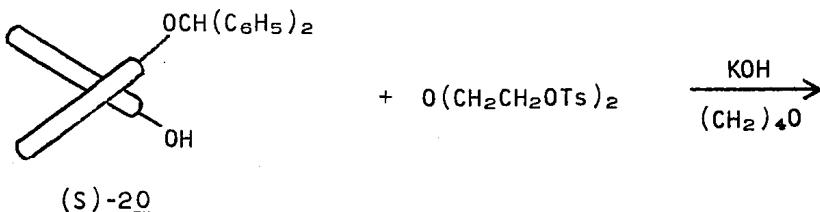
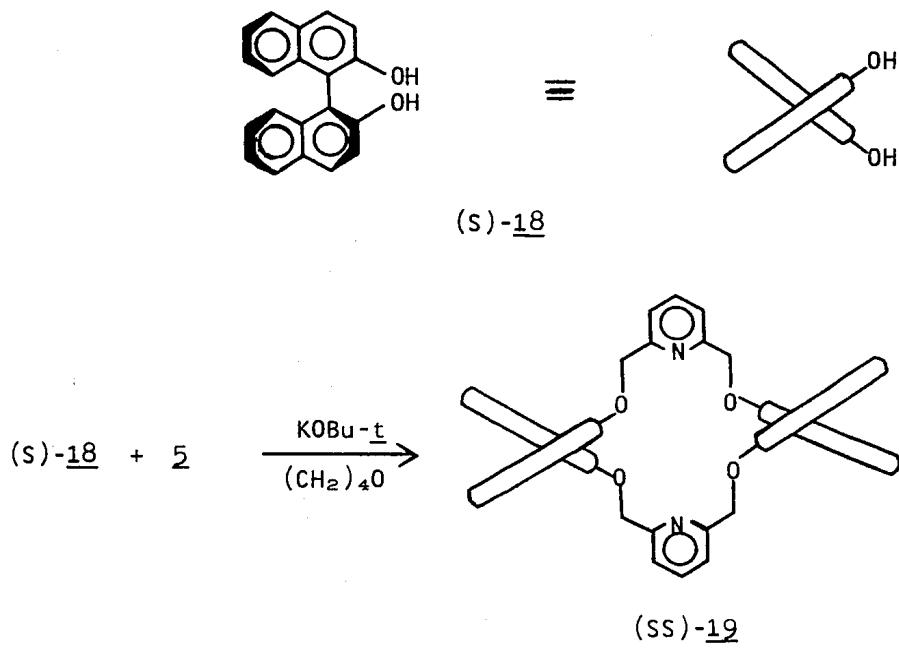


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11**12**

From reaction of (S)-2,2-dihydroxy-1,1-binaphthyl (S)-18 and 5 was obtained 19. Compound (S)-20 with diethyleneglycol ditosylate gave (S,S)-21, whose benz-

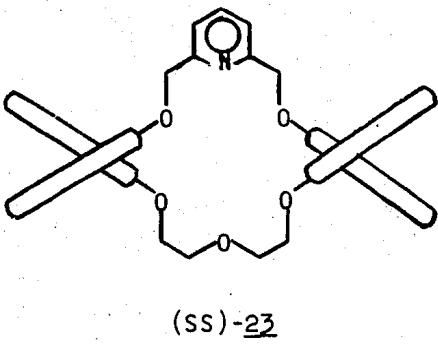
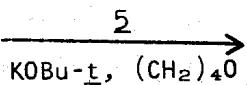
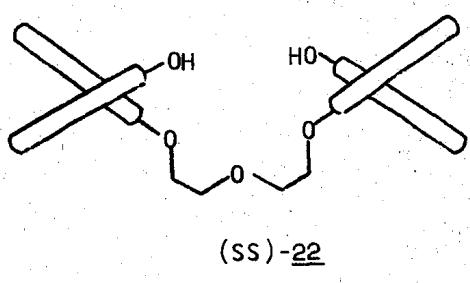
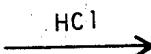
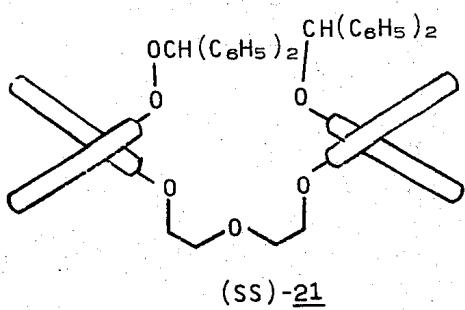
hydryl groups were removed to give (S,S)-22. Compound (S,S)-22 with 5 and base gave (S,S)-23.



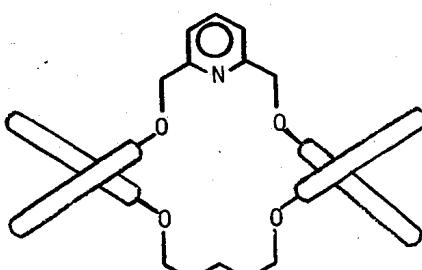
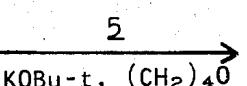
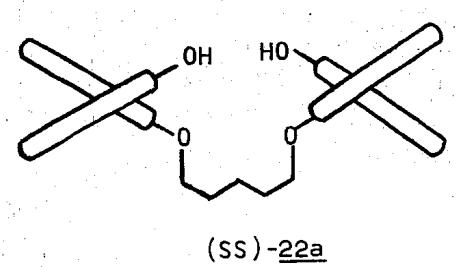
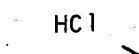
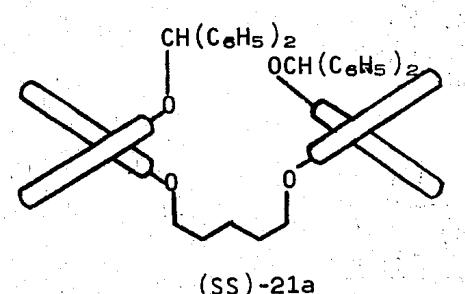
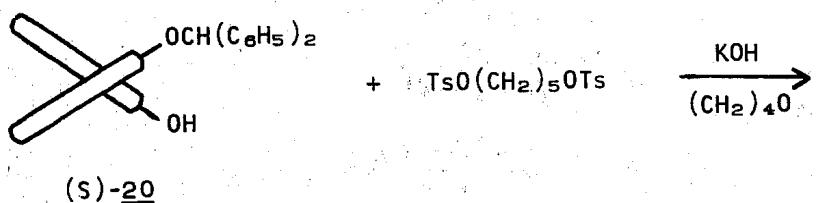
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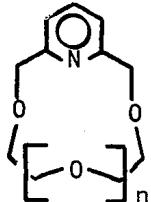


In a similar series of reactions, (ss)-23a was prepared.



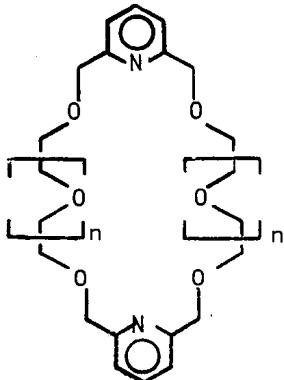
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In reactions similar to 1 → 11, 1 is treated with base and diethyleneglycol, triethyleneglycol, pentaethyleneglycol and heptaethyleneglycol ditosylates to give respectively, cycles 24–28.



- 24, $n = 1$
25, $n = 2$
26, $n = 4$
27, $n = 5$
28, $n = 6$

In reactions similar to 4 → 12, 4 is treated with diethyleneglycol, triethyleneglycol and tetraethyleneglycol to give respectively, multiheteromacrocycles, 29–31.



- 29, $n = 1$
30, $n = 2$
31, $n = 3$

In reactions similar to 10 → 14, 10 is treated with ethyleneglycol, triethyleneglycol, tetraethyleneglycol, pentaethyleneglycol and hexaethyleneglycol ditosylates to give respectively, multiheteromacrocycles 32–36.

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- 32, $n = 0$
33, $n = 2$
34, $n = 3$
35, $n = 4$
36, $n = 5$

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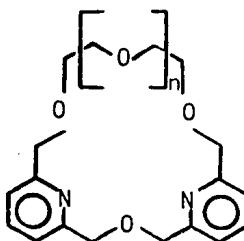
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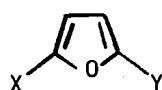
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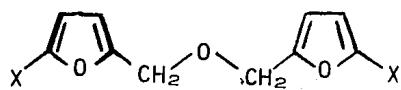
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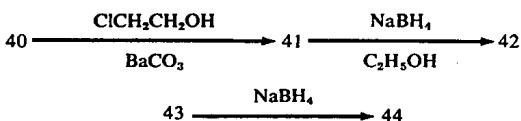
The furane-containing multiheteromacrocycles involved as starting materials, 37–40 and 43, which are known compounds. Compounds 41, 42 and 44 were prepared by the indicated sequences.



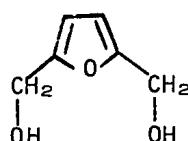
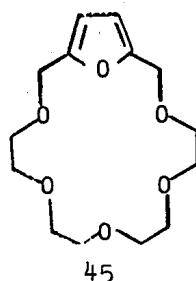
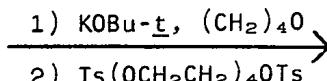
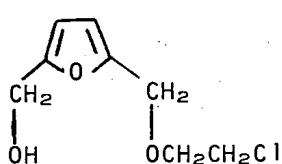
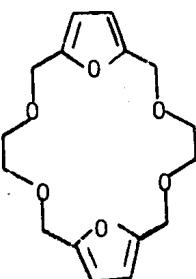
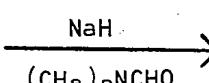
- 37, $X = \text{CH}_2\text{OH}$, $Y = \text{CHO}$
38, $X = Y = \text{CH}_2\text{OH}$
39, $X = Y = \text{CH}_2\text{Cl}$
40, $X = \text{CH}_2\text{Cl}$, $Y = \text{CHO}$
41, $X = \text{CH}_2\text{OCH}_2\text{CH}_2\text{Cl}$, $Y = \text{CHO}$
42, $X = \text{CH}_2\text{OH}$, $Y = \text{CH}_2\text{OCH}_2\text{CH}_2\text{Cl}$

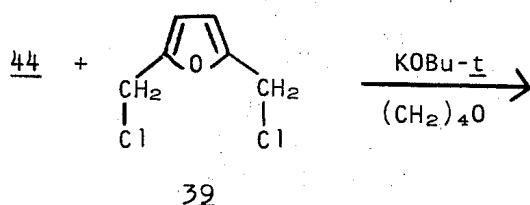
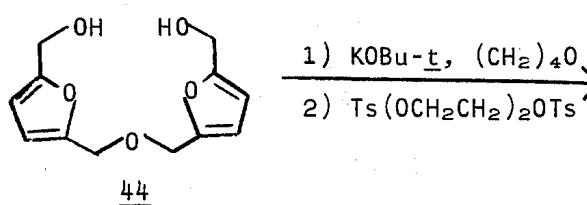


- 43, $X = \text{CHO}$
44, $X = \text{CH}_2\text{OH}$

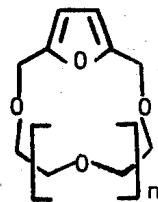


Furan-containing multiheteromacrocycles were prepared from open-chain compounds by the sequences formulated.

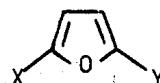
**38****45****42****46**



In reactions similar to $38 \rightarrow 45$, 38 is treated with base and diethyleneglycol, triethyleneglycol, pentaethyleneglycol, hexaethyleneglycol and heptaethyleneglycol ditosylates to give respectively, multiheteromacrocycles 50–54.

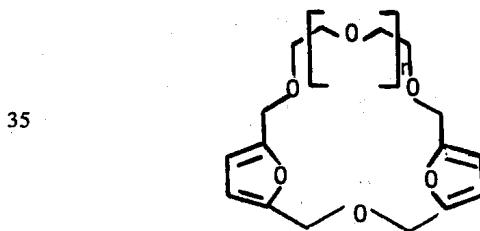


In reactions similar to $40 \rightarrow 41$, 40 is treated with monochlorodiethyleneglycol, monochlorotriethyleneglycol and monochlorotetraethyleneglycol to give respectively 55, 56 and 57. In reactions similar to $41 \rightarrow 42$, 55, 56 and 57 are reduced with sodium borohydride in ethanol to give respectively 58, 59 and 60. In reactions similar to $42 \rightarrow 46$, 58, 59 and 60 are treated with sodium hydride in dimethylformamide give the respective multiheteromacrocycles 61, 62 and 63.



25 In reactions similar to $44 \rightarrow 47$, 44 is treated with base and ethyleneglycol, triethyleneglycol, tetraethyleneglycol, pentaethyleneglycol and hexaethyleneglycol ditosylates to give respectively, multiheteromacrocycles 64–68.

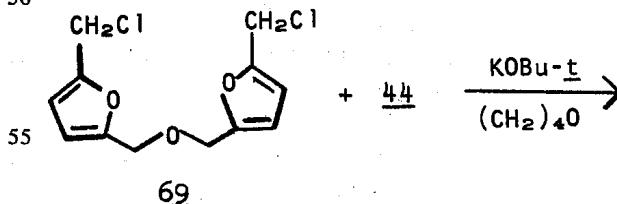
30



40 64, $n = 0$
65, $n = 2$
66, $n = 3$
67, $n = 4$
68, $n = 5$

45 In reaction similar to the conversion $38 \rightarrow 39$, 44 is treated with thionyl chloride to give 69. In a reaction similar to $44 + 39 \rightarrow 48$, treatment of 44 with base and 69 gives 70.

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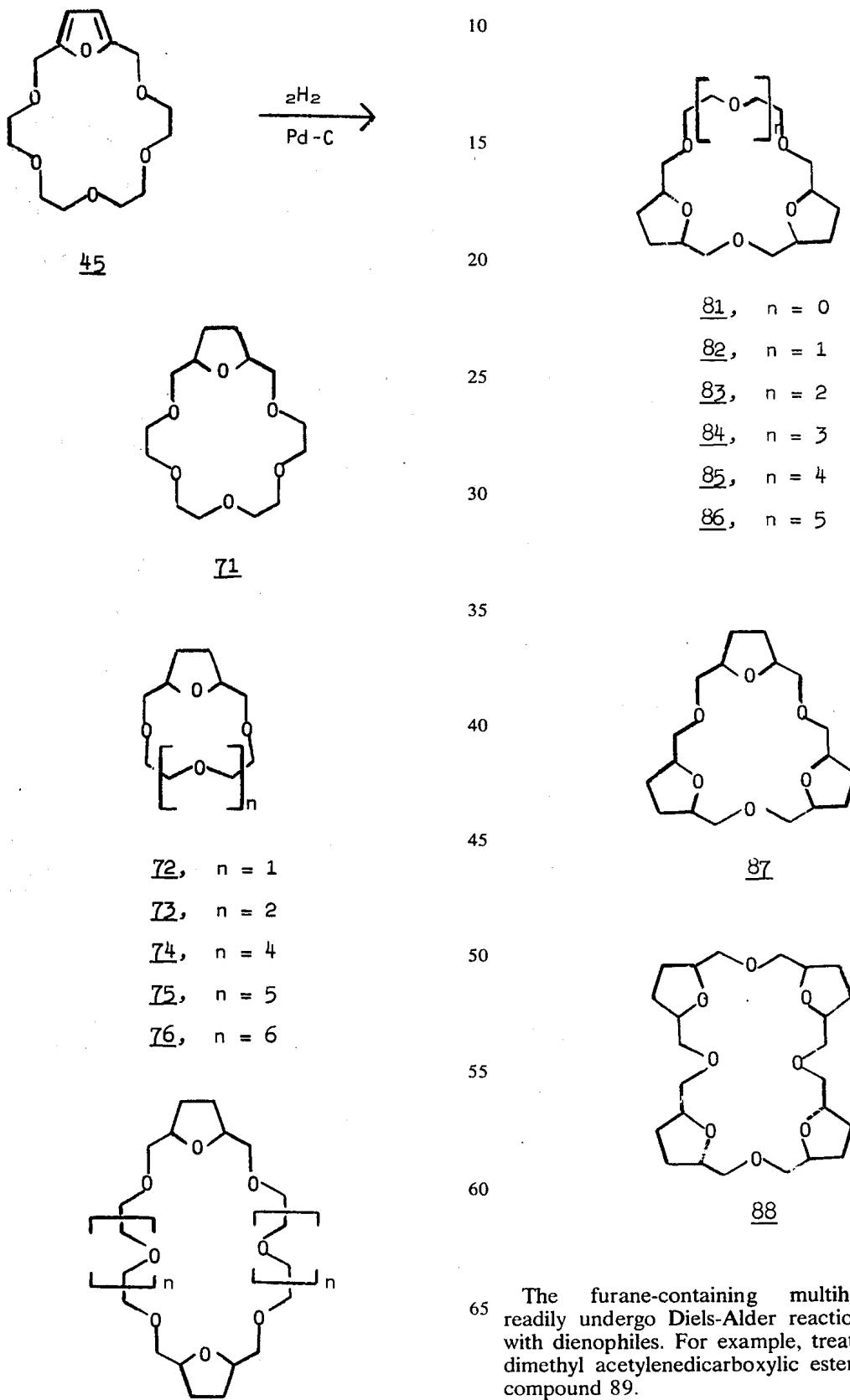


19

Catalytic reduction of furane-containing multiheteromacrocycles 45 with hydrogen and palladium-on-carbon gave the tetrahydrofurane-containing multiheteromacrocycles, 71. Similarly, furane-containing cycles 50–54, 46, 61–63, 47, 64–68, 48 and 70 are catalytically reduced to give respectively tetrahydrofurane-containing cycles, 72–88.

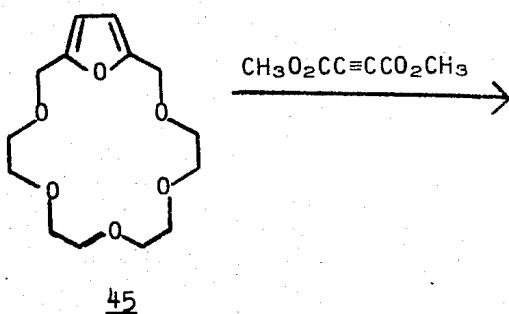
20

- 77, n = 0
- 78, n = 1
- 79, n = 2
- 80, n = 3



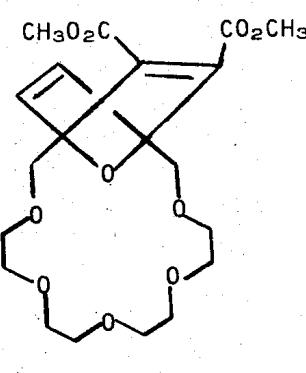
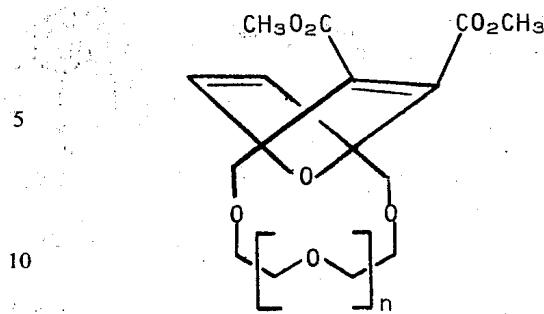
65 The furane-containing multiheteromacrocycles readily undergo Diels-Alder reactions when treated with dienophiles. For example, treatment of 45 with dimethyl acetylenedicarboxylic ester gave polycyclic compound 89.

21



45

22

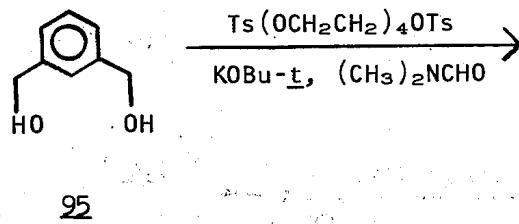


89

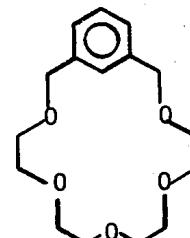
Similarly the furane-containing multiheteromacrocycles 50–54 when treated with dimethyl acetylenedicarboxylate give the respective polycyclic compounds 90–94.

90, $n = 1$ 91, $n = 2$ 92, $n = 4$ 93, $n = 5$ 94, $n = 6$

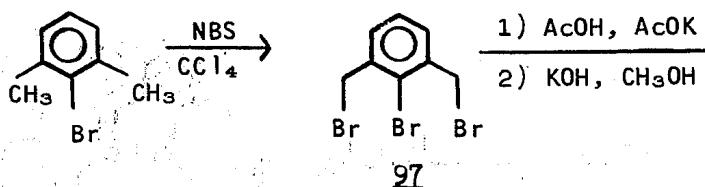
Multiheteromacrocycles containing m-xylyl units were prepared as follows. Xylyl alcohol, 95, when treated with tetraethyleneglycol ditosylate in dimethylformamide and potassium tert-butoxide gave multiheteromacrocycle, 96. Treatment of 2-bromo-1,3-dimethylbenzene with N-bromosuccinimide (NBS) gave tribromide 97, which was converted to cycle 102 with base and tetraethyleneglycol. Cycle 102 was also prepared by converting 97 to diol 98, which when treated with tetraethyleneglycol ditosylate gave 102. The chlorocompound 99 was prepared from 2-chloro-1,3-dimethylbenzene by treatment with NBS. Cyclization of 99 with tetraethyleneglycol and base gave 103. Ester 100 was prepared by treating methyl 2,6-dimethylbenzoate with NBS. Diester 101 was prepared from dimethyl 2,6-dimethylterephthalate and NBS. Cyclization of 100 with tetraethyleneglycol and base gave 104, and of 101 with the same reagents, gave 106. Hydrolysis of ester 104 gave acid 105. Similar hydrolysis of 106 gives 107. In like manner, 101' was prepared and converted to 106'.



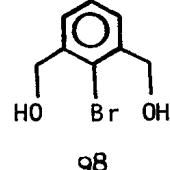
95



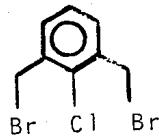
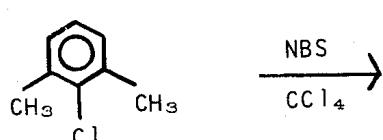
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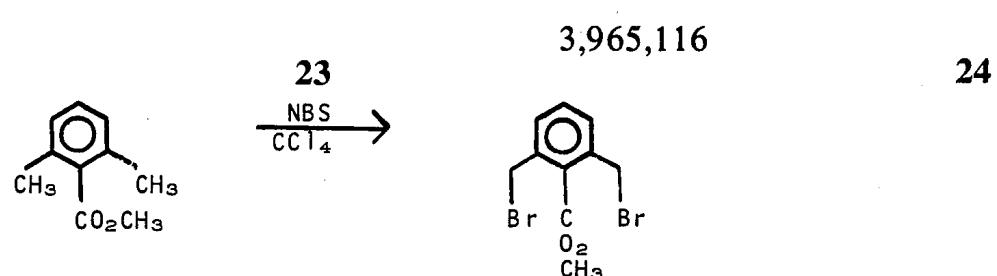
97



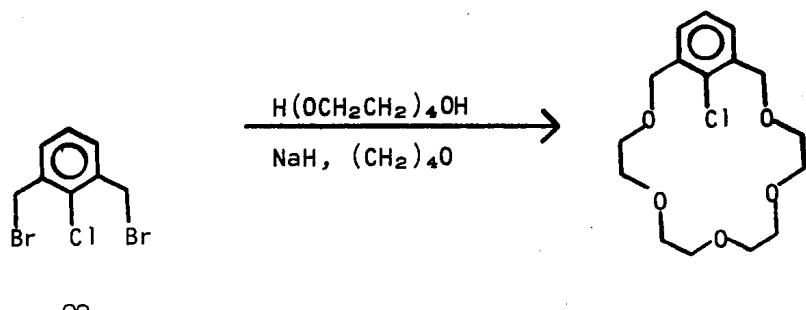
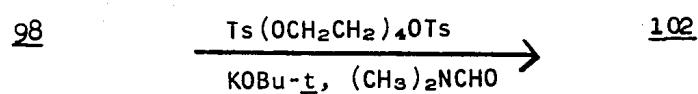
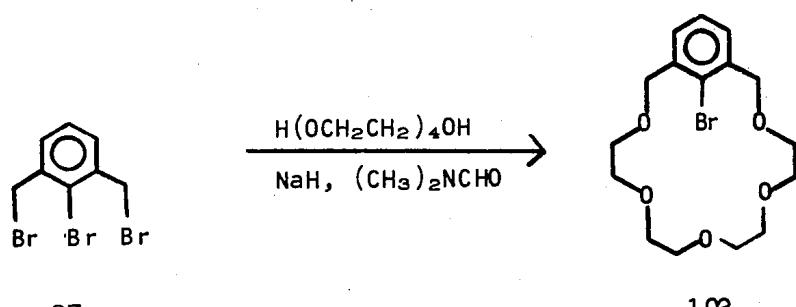
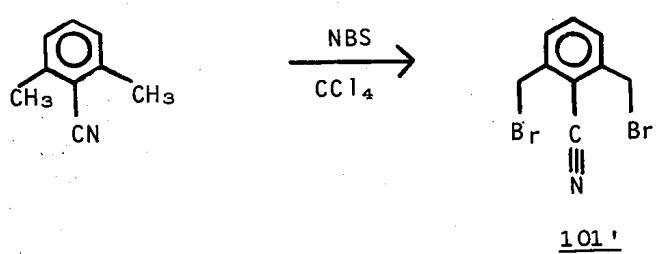
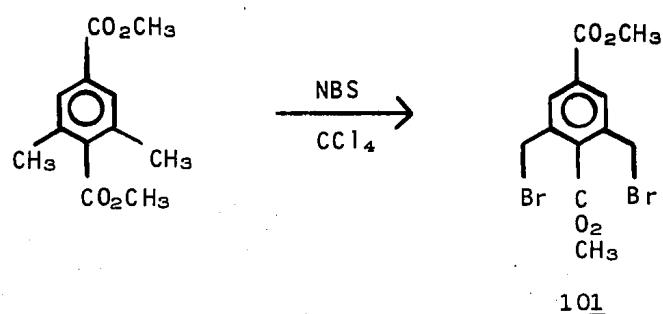
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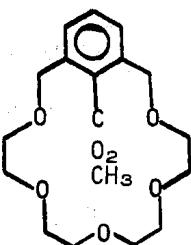
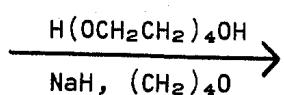
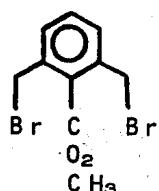
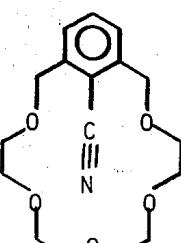
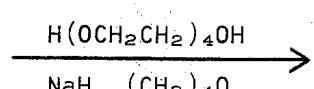
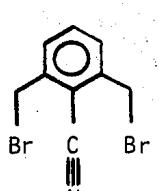
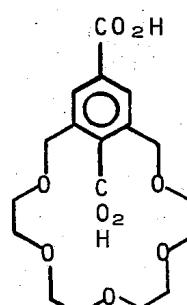
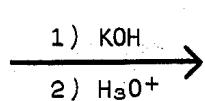
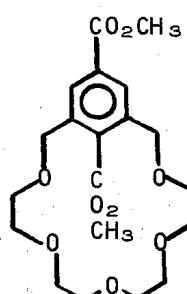
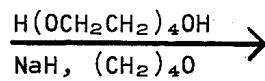
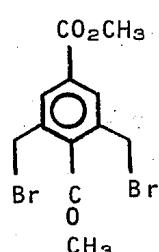
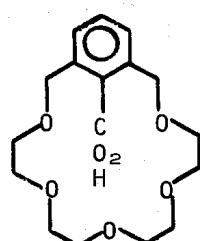
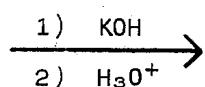
99



100

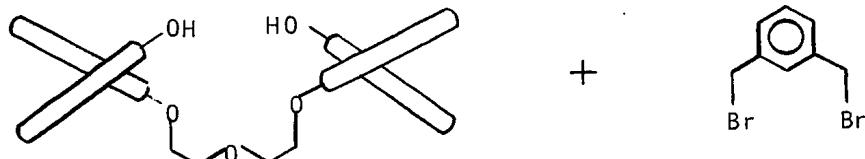


3,965,116

25**26****104**

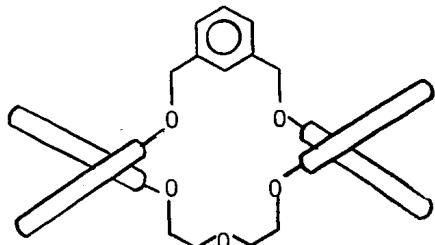
Binaphthyl and m-xylyl units were combined in the following syntheses. Treatment of (SS)-22 with base and 1,3-bis-bromomethylbenzene gave (SS)-108. From (S)-20 and 1,3-bis-bromomethylbenzene was obtained (SS)-109, which was freed of its benzhydryl groups

with acid to give (SS)-110. With base and 2,6-bis-chloromethylpyridine (5), (SS)-110 produced (SS)-111. Throughout these syntheses, the (R)-binaphthyl unit can be substituted for the (S)-enantiomer.

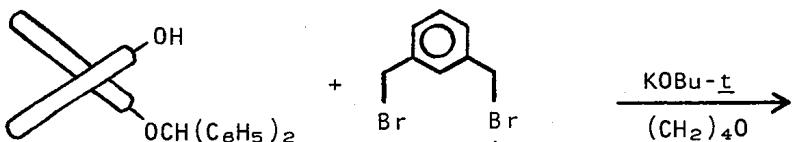


(SS)-22

$\xrightarrow[\text{KOBu-t}]{(\text{CH}_2)_4\text{O}}$

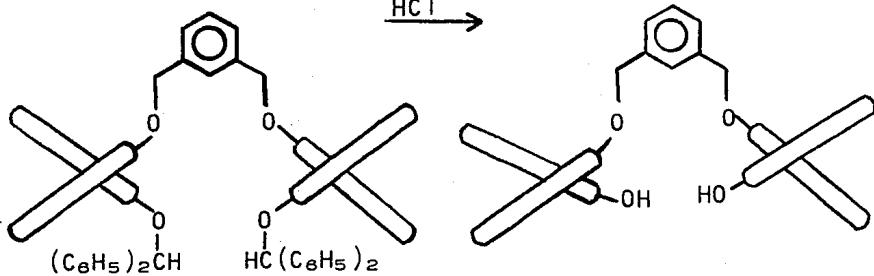


(SS)-108



(S)-20

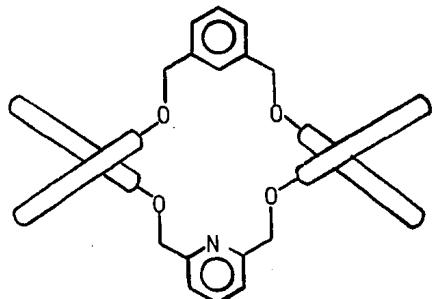
$\xrightarrow{\text{HCl}}$



(SS)-109

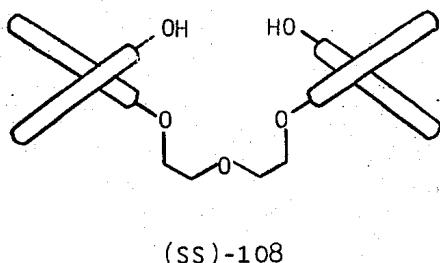
(SS)-110

$\xrightarrow[\text{KOBu-t}, (\text{CH}_2)_4\text{O}]{\text{Cl}-\text{C}_6\text{H}_4-\text{Cl}}$



(SS)-111

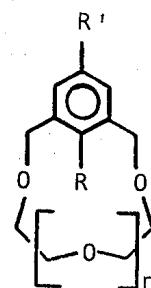
By procedures similar to the syntheses of (SS)-108 and of 104 and 105, cycles (SS)-112 and (SS)-113 are prepared as formulated.



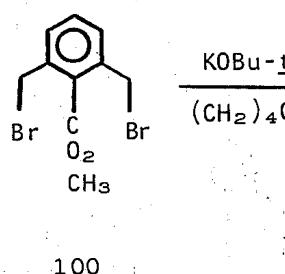
+ 10

5

By procedures similar to the syntheses of 96, 102, 103, 104-107, and by use of the appropriate ethylglycol or polyethyleneglycol or their corresponding tosylates, cycles 114-148 are prepared.



15



KOBu-t
 $(\text{CH}_2)_4\text{O}$

20

25

30

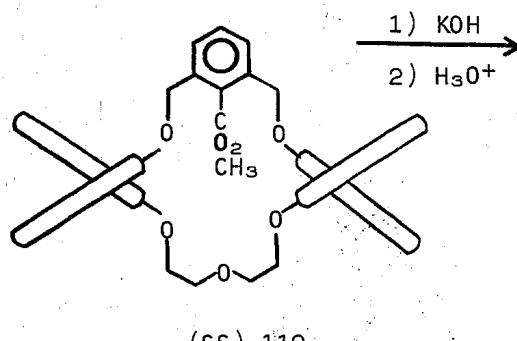
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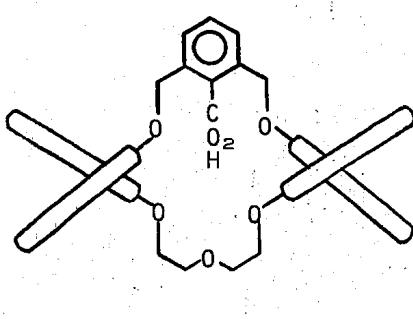
45

50

No.	n	R	R'
114	1	H	H
115	2	H	H
116	4	H	H
117	5	H	H
118	6	H	H
118a	7	H	H
119	1	Cl	H
120	2	Cl	H
121	4	Cl	H
122	5	Cl	H
123	6	Cl	H
123a	7	Cl	H
124	1	Br	H
125	2	Br	H
126	4	Br	H
127	5	Br	H
128	6	Br	H
128a	7	Br	H
129	1	CO_2CH_3	H
130	2	CO_2CH_3	H
131	4	CO_2CH_3	H
132	5	CO_2CH_3	H
133	6	CO_2CH_3	H
133a	7	CO_2CH_3	H
134	1	CO_2H	H
135	2	CO_2H	H
136	4	CO_2H	H
137	5	CO_2H	H
138	6	CO_2H	H
138a	7	CO_2H	H
139	1	CO_2CH_3	CO_2CH_3
140	2	CO_2CH_3	CO_2CH_3
141	4	CO_2CH_3	CO_2CH_3
142	5	CO_2CH_3	CO_2CH_3
143	6	CO_2CH_3	CO_2CH_3
143a	7	CO_2CH_3	CO_2CH_3
144	1	CO_2H	CO_2H
145	2	CO_2H	CO_2H
146	4	CO_2H	CO_2H
147	5	CO_2H	CO_2H
148	6	CO_2H	CO_2H
148a	7	CO_2H	CO_2H



1) KOH
2) H_3O^+



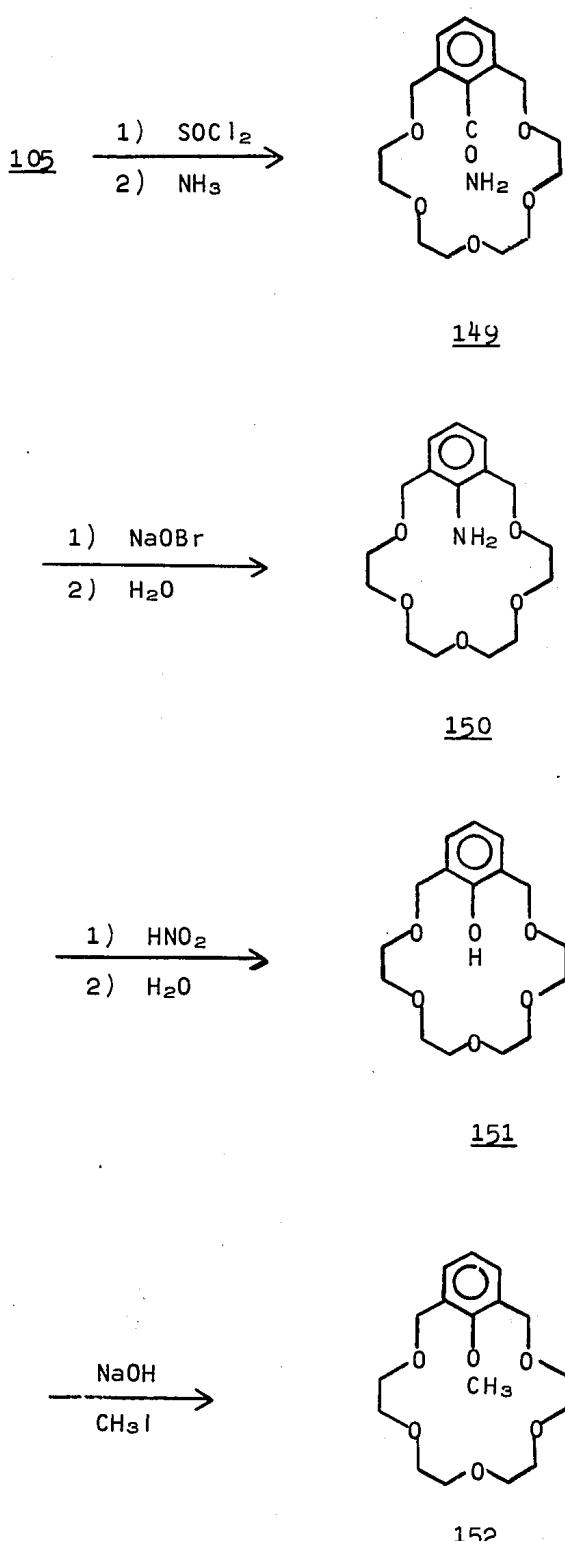
55 Cycles 96, 102-107 and their analogues, cycles 114-148a serve as starting materials for preparing compounds containing other functional groups either pointed inward toward (R groups), or outward away (R' groups) from the hole. The reaction sequences are exemplified with the cycles containing 18 atoms in their major ring, but are equally applicable to those with smaller or larger rings. The sequence, 105 → 149 → 150 → 151 → 152 provides the compounds with R' = H and R = CONH_2 , NH_2 , OH and OCH_3 . Analogues of 149 through 152 of general formula 153 with n = 1, 2, 4, 5, 6, and 7,

60

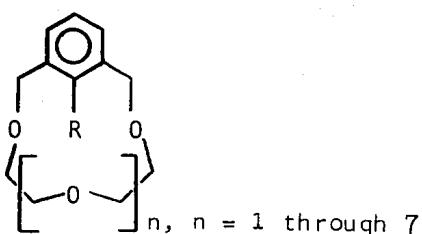
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3,965,116

31

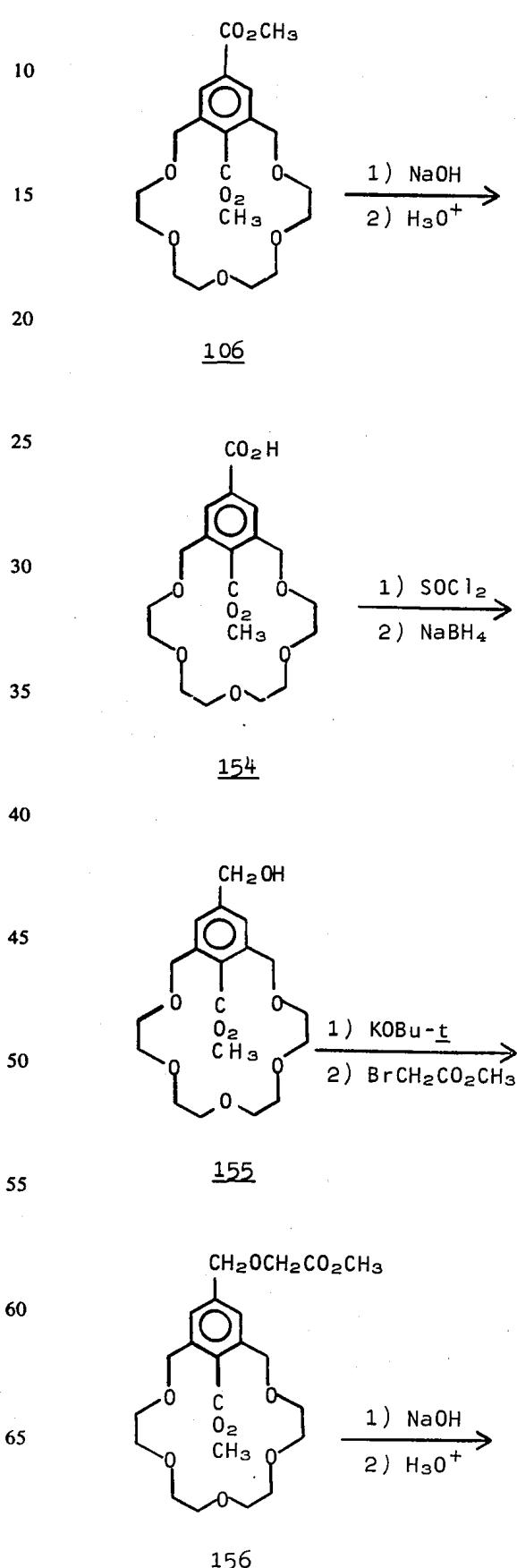


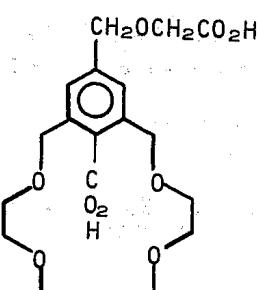
and R = CONH₂, NH₂, OH and OCH₃ are similarly prepared.



32

The sequence 106 → 154 → 155 → 156 → 157 provides a compound containing two carboxyl groups, one pointing into the hole, the other in the proper conformation reaches the edge of the hole. The first step involves hydrolysis of only the less hindered ester.



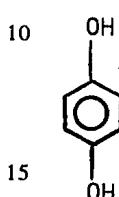
33**157**

Multiheteromacrocycles 158-163 were prepared from hydroquinone, base, and the appropriate polyethyleneglycol ditosylates. Although 158 and 160 were detected in the reaction mixtures, they were not characterized.

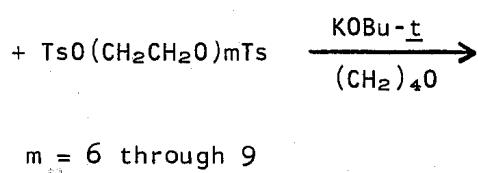
34

Similarly, multiheteromacrocycles 164-171 are prepared by the sequences shown.

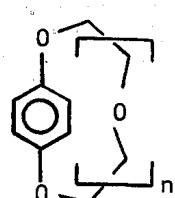
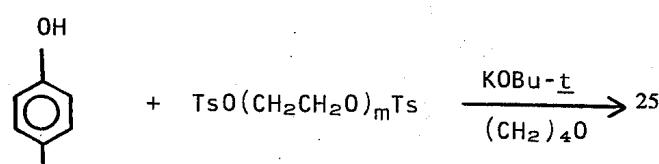
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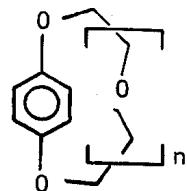
15



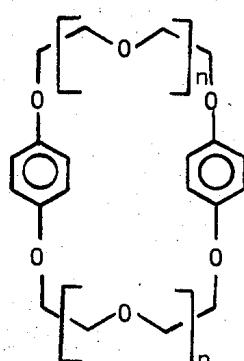
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158, *n* = 2160, *n* = 3162, *n* = 4

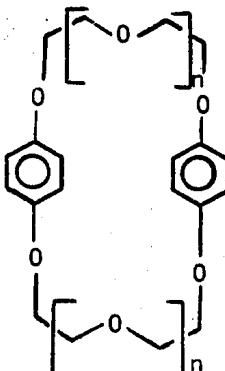
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164, *n* = 5166, *n* = 6168, *n* = 7170, *n* = 8

40

159, *n* = 2161, *n* = 3163, *n* = 4

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165, *n* = 5167, *n* = 6169, *n* = 7171, *n* = 8

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55

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65

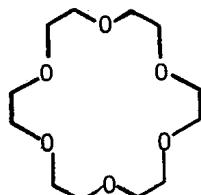
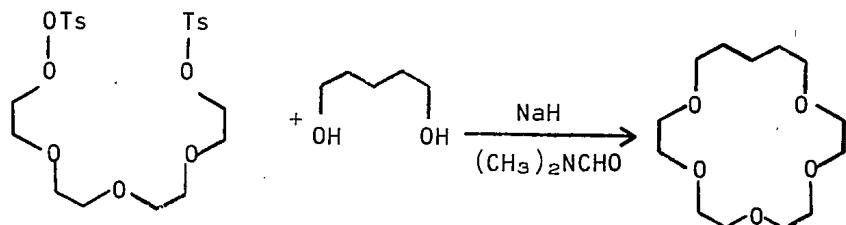
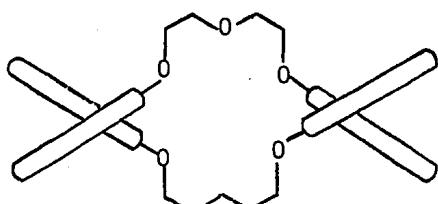
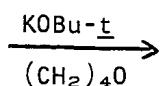
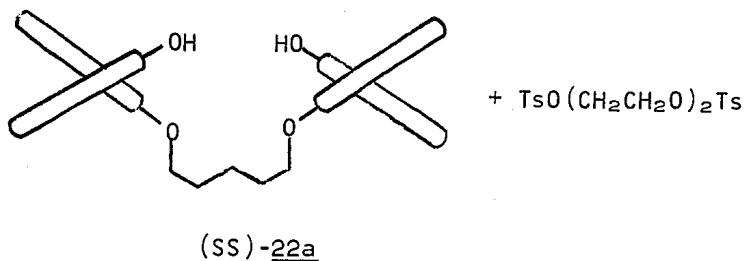
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Open-chain polyether compound 172, a model for cycle 173, was prepared as formulated. Mul-

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tiheteromacrocycles, 174 and 174a, that contain the pentamethylene unit, were prepared as formulated.

172173174(ss)-174a

DETAILED DESCRIPTION OF THE INVENTION

General

Racemic 2,2'-dihydroxy-1,1'-binaphthyl (18) was resolved as before [Tetrahedron Lett., 3617 (1971)] to give optically pure (+)-(R)-18, m.p. 207.5°–208.5°, $[\alpha]_D^{25} +34.1^\circ$ (C 1.0, $(\text{CH}_2)_4\text{O}$), and (–)-(S)-18, m.p. 207°–208°, $[\alpha]_D^{25} -34.3^\circ$ (C 1.0, $(\text{CH}_2)_4\text{O}$). The absolute configurations of these isomers are established (Tetrahedron, 27, 5999 (1971)) and are formulated both in a conventional and a more illustrative form, which will be used here and elsewhere. Although optically stable at 100° for 24 hours as a solution in dioxane-water, (–)-18 racemized 72% with HCl (~1.2 N) present in the same solution at 100° for 24 hours, and 69% in butanol-0.67 M in potassium hydroxide at 118° for 23 hours.

Preparation

To a solution of 28.6 g. of optically pure (–)-(S)-18, 11.76 g. of potassium tert-butoxide and 750 ml. of pure tetrahydrofuran stirred under nitrogen was added 26 g. of benzhydryl bromide dissolved in 250 ml. of tetrahydrofuran. The resulting solution was stirred and refluxed for 12 hours. The solvent was evaporated under vacuum, and the residue was shaken with 500 ml. of ice water and 500 ml. of dichloromethane. The organic layer was washed with 10% aqueous sodium hydroxide solution to remove any unused 18. The organic layer was washed with water, dried, evaporated and chromatographed on 700 g. of alumina. The column was washed with 2.3 liters of 15% dichloromethane in pentane, and the product eluted with dichloromethane-pentane, and the product eluted with dichloromethane-pentane (4 liter, 1:1), dichloromethane (1 liter) and 5% ethanol in dichloromethane (2 liters) to give 33 g. (73%) of (+)-20 as a foam, $[\alpha]_{589}^{25} +18.7^\circ$, $[\alpha]_{578}^{25} +19.6^\circ$, $[\alpha]_{546}^{25} +21.3^\circ$ (C 0.55 CHCl_3).

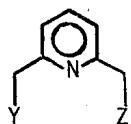
Anal. Calcd for $\text{C}_{33}\text{H}_{24}\text{O}_2$: C, 87.58; H, 5.35. Found: C, 87.49; H, 5.57.

In the first of the following Examples, the syntheses of the new compounds are described. In the last Examples, their properties and uses are indicated. The temperatures are given in degrees centigrade.

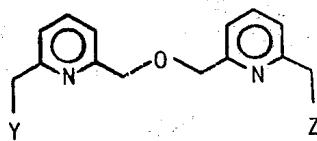
EXAMPLE 1

Preparation of Pyridine Unit-Containing Host

Compounds



- 1, Y=Z=OH
- 2, Y=OH, Z=H
- 3, Y=Cl, Z=H
- 4, Y=Z=Br
- 5, Y=Z=Cl
- 6, Y=Br, Z=OH



- 7, Y=Z=H
- 9, Y=Z=OAc
- 10, Y=Z=OH

PROCEDURE 1

Procedure 1 reports the syntheses of the new open-chain starting materials for the preparation of the multiheterocyclics containing the pyridyl unit. Compound 6 was prepared as follows. Diol 1 [J. Amer. Chem. Soc., 76, 1286 (1954)], 10.0 g., was heated at reflux in 100 ml. of 48% aqueous hydrobromic acid for 1.0 hour. The solution was cooled to 0°, neutralized slowly with 40% aqueous sodium hydroxide, diluted to 300 ml., and extracted with 500 ml. of dichloromethane in five portions. The extract was dried, evaporated (vacuum) and the residue was chromatographed on silica gel (200 g.). Column elution with 2 liters of dichloromethane gave 3.0 g. (16%) of 4, m.p. 85°–89° (dec.) [J. Chem. Soc., 3594 (1955)]. Elution with 2 liters of wet ether gave 6.0 g. (41%) of 6, m.p. 74°–78° (dec.), whose pmr spectrum was consistent with the assigned structure, and whose 70 eV mass spectrum gave a parent ion peak at 201.

Anal. Calcd for $\text{C}_7\text{H}_8\text{BrNO}$: C, 41.61; H, 3.99. Found: C, 41.78; H, 4.04.

Compounds 7, 9 and 10 were prepared as follows. To alcohol 2 [J. Amer. Chem. Soc., 76, 1286 (1954)], 10 g., dissolved in 200 ml. of tetrahydrofuran at 25° was added 4.3 g. of 50% sodium hydride in mineral oil. The mixture was stirred 15 minutes, and 11.3 g. of 3 [J. Chem. Soc., 3594 (1958)] dissolved in 50 ml. of dry tetrahydrofuran was added. After stirring for 13 hours, the mixture was quenched by addition of a small amount of water, and the solvent was evaporated under vacuum. The residue was mixed with 100 ml. of dichloromethane and 50 ml. of water. The organic phase was dried, evaporated under vacuum and chromatographed on 200 g. of silica gel with dichloromethane elution. Fractions 5–22 (500 ml. each) contained 13.4 g. (74%) of 7, m.p. 77°–78° (after recrystallization), pmr spectrum was as expected (i.e. it was consistent with the assigned structure) mass spectrum (70 eV, m/e 228 as molecular ion).

Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}$: C, 73.66; H, 7.06. Found: C, 73.83; H, 6.90.

A solution of 9.0 g. of 7, 100 ml. of glacial acetic acid and 10 ml. of 30% aqueous hydrogen peroxide was heated at 70°–80° and stirred for 2 hours. An additional 10 ml. of 30% aqueous hydrogen peroxide was added, and the resulting mixture was heated at 70°–80° for 12 hours. The mixture was cooled and evaporated under vacuums. Water (50 ml.) was added to the residue, and the solution was again evaporated under vacuum. The residue was dissolved in chloroform, the solution was washed with 10% aqueous potassium carbonate solution, dried, and the solvent was evaporated under vacuum to give 8.80 g. (85%) of crude di-N-oxide 8, m.p. 161°–173°.

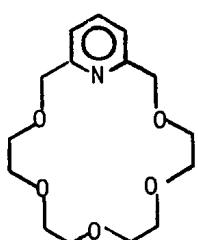
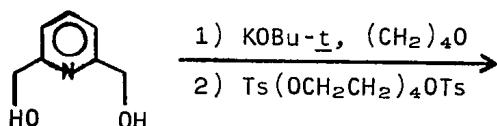
A solution of 2.7 g. of crude 8 in 50 ml. of acetic anhydride was heated on a steam bath for 9 hours. The solvent was evaporated under vacuum, and the residue was chromatographed on 200 g. of silica gel with ethyl acetate as eluting agent. The middle fractions crystallized to give 0.63 g. of crude diacetate 9, m.p. 85°–95° (95% pure by pmr). The material was recrystallized from ethanol to give 9 as white plates, m.p. 97°–98.5°, osmometric molecular weight 352 (calculated = 344).

Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_5$: C, 62.78; H, 5.85. Found: C, 62.97; H, 5.97.

Hydrolysis of diacetate 9 in the usual way, i.e., with sodium hydroxide in refluxing 95% ethanol (8 hours)

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gave 90% of crude diol 10, which was used directly without further purification.



PROCEDURE 2

Procedure 2 involves the synthesis of 11, and illustrates a means of incorporating one pyridyl unit into a cycle. A solution of 6.95 g. of 1, 12 g. of potassium tert-butoxide and 27 g. of tetraethylene glycol ditosylate dissolved in 200 ml. of tetrahydrofuran was heated at reflux with stirring for 1 hour. Water (5 ml.) was added. After 20 hours of refluxing, the solution was cooled, and the potassium tosylate that precipitated was collected (16.2 g., 77%). The solvent was evaporated from the filtrate, and the residue was chromatographed on 400 g. of alumina. Elution of the column with 1% ethanol in dichloromethane gave 5.1 g. (29%) of 11, which was crystallized from dichloromethane-pentane, m.p. (sealed capillary) 40°–41°, mass spectrum (70 eV), m/e 297 (molecular ion), pmr spectrum (60 MHz, CDCl₃), δ: 3.55 and 3.65 (s, s, CH₂CH₂O, 18H); 4.70 (s, ArCH₂, 4H); 6.0–7.66 (6 lines, A₂B, ArH, 3H).

Anal. Calcd for C₁₅H₂₃NO₅: C, 60.59; H, 7.80.
Found: C, 60.69; H, 7.80.

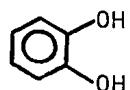
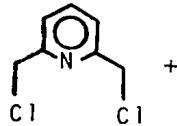
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PROCEDURE 3

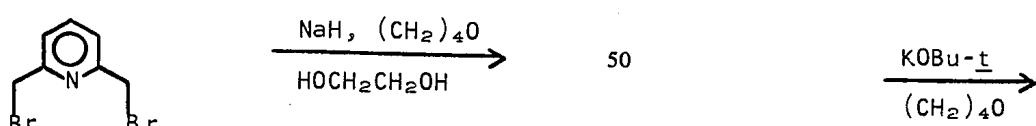
Procedure 3 involves the synthesis of 12, and illustrates a means of incorporating two pyridyl units into a cycle. To a solution of 0.45 g. of ethyleneglycol in 100 ml. of tetrahydrofuran was added 0.80 g. of 50% sodium hydride in oil. The mixture was stirred for 30 minutes at 25°, and a solution of 1.9 g. of dibromide 4 in 100 ml. of dry tetrahydrofuran was added dropwise. The mixture was stirred at 25° for 70 hours, 30 ml. of water was added, and the solvent was evaporated under vacuum. The residue was dissolved in water, and the aqueous solution was washed with 150 ml. of dichloromethane in three portions. The combined extracts were evaporated under vacuum, and the residue was sublimed at 0.1 Torr, 130°–140°. The sublimate was recrystallized from dichloromethane-pentane to give 243 mg. (21%) of 12, m.p. 147°–148°, pmr spectrum (60 MHz, CDCl₃) δ: 7.1–7.7 (m, ArH, 6H); 4.53 (s, ArCH₂, 8H); 3.73 (s, OCH₂, 8H), 70 eV mass spectrum, m/e 330 (molecular ion).

Anal. Calcd for C₁₈H₂₂N₂O₄: C, 65.44; H, 6.71.
Found: C, 65.58; H, 6.83.

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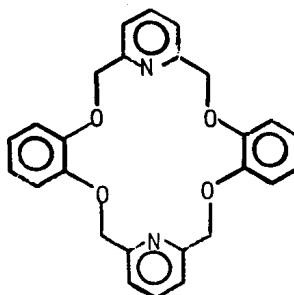
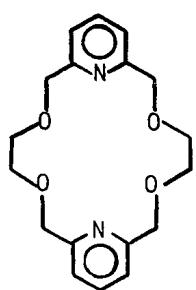


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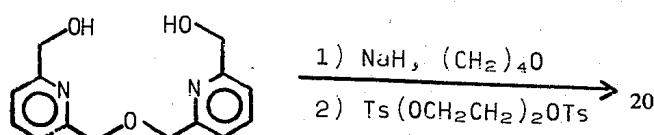
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PROCEDURE 4

Procedure 4 records the synthesis of 13 which illustrates the incorporation of pyridyl and o-phenylene units into the same cycles. To a solution of catechol (2.75 g.) and potassium hydroxide (6.16 g.) in tetrahydrofuran (450 ml.) was added 5 (4.40 g.) dissolved in 50 ml. of tetrahydrofuran. The resulting solution was stirred and heated at reflux for 24 hours, evaporated under vacuum, and chromatographed on alumina. Elution of the column with dichloromethane gave 13, 0.94 g. (9%), m.p. 184°-186° (from dichloromethane), mass spectrum (70 eV), molecular ion at m/e = 426.

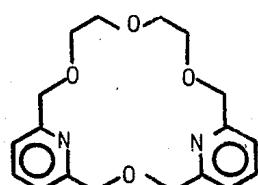
Anal. Calcd for $C_{26}H_{22}N_2O_4$: C, 73.22; H, 5.20.
Found: C, 73.13; H, 5.32.



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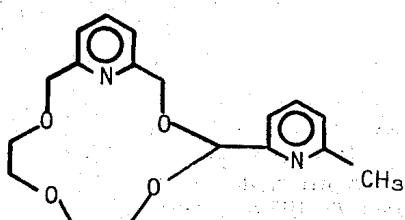
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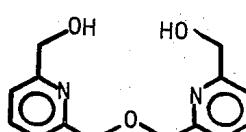
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Procedure 5

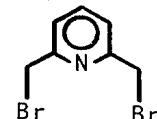
Procedure 5 records the synthesis of 14 which illustrates the incorporation of two pyridyl units separated by one CH_2OCH_2 unit into cycles. To a stirred mixture of 0.77 g. of diol 10 (80% pure by pmr) and 0.75 g. of potassium tert-butoxide in 200 ml. of dry tetrahydrofuran under nitrogen was added 1.5 g. of diethyleneglycol ditosylate. The mixture was stirred at 25° for 3 days. An additional 0.10 g. of potassium tert-butoxide was added, and the mixture was heated to reflux for 4 hours. The solvent was evaporated under vacuum, and the residue was dissolved in chloroform. The chloroform solution was washed with water, dried and evaporated. The residue was chromatographed on 300 g. of alumina with benzene-ethanol as eluting solvent. Cycle 14 was obtained as an oil which was subjected to gel permeation chromatography (Bio Beads SX-8) to give 0.15 of a mixture of 80% 14 and an impurity identified by its pmr spectrum as probably



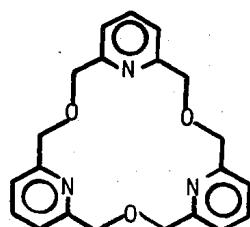
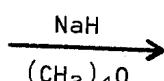
The identity of 14 as established by its gel permeation chromatography retention volume in relation to that of cycles 11, 12 and 15, and particularly by its 60 MHz pmr spectrum in CDCl_3 , δ : 6.9-7.7 (m, ArH, 6H); 4.7 (s, ArCH_2 , 4H); 4.5 (s, ArCH_2 , 4H); 3.6 (s, $\text{CH}_2\text{CH}_2\text{O}$, 8H).



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PROCEDURE 6

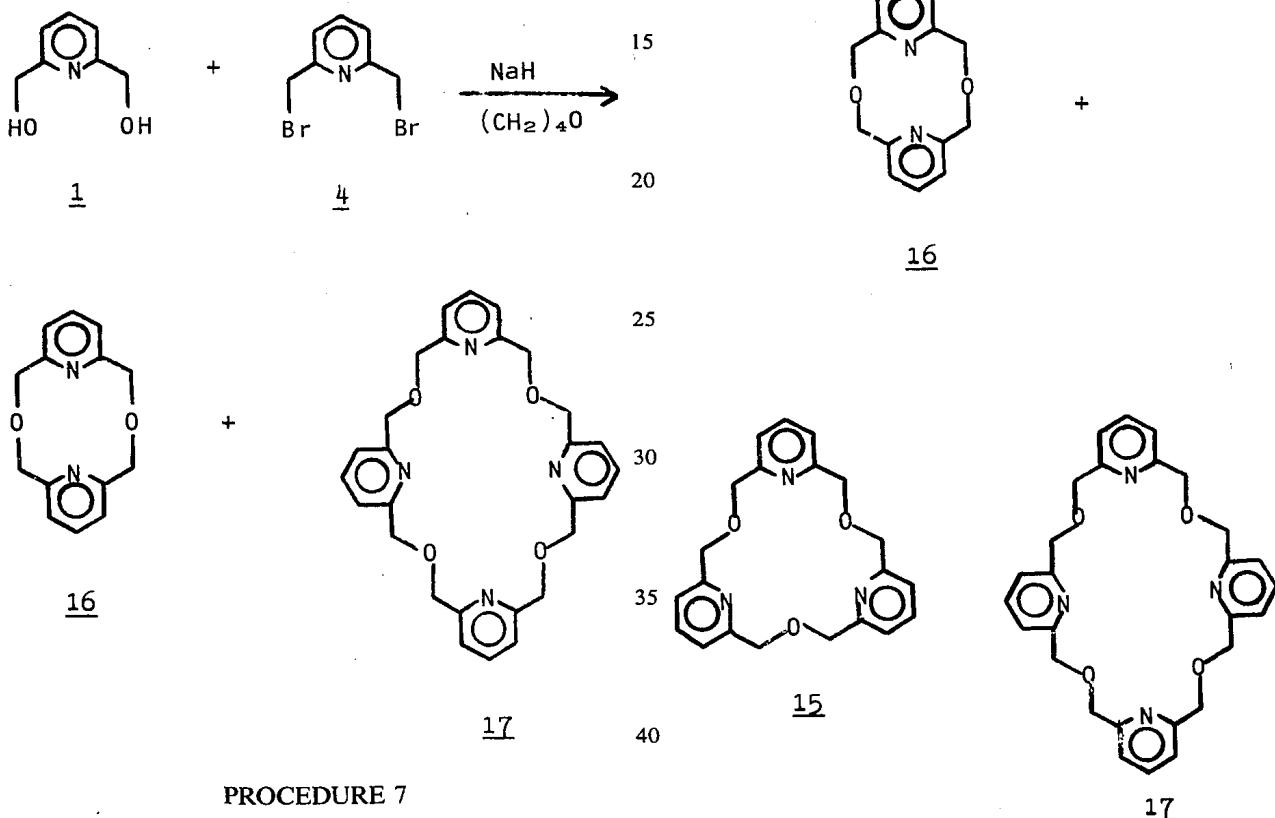
Procedure 6 records the synthesis of 15 from 10 and 4. To a solution of 1.07 g. of diol 10 in 200 ml. of tetrahydrofuran was added 0.50 g. of 50% sodium hydride suspended in oil, and the mixture was stirred at 25° for 30 min. A solution of 1.2 g. of dibromide 4 in 100 ml. of dry tetrahydrofuran was added over one hour, and the mixture was stirred for 13 hours at 25°, and mixed with water. The solvent was evaporated under vacuum, and the residue was chromatographed on 250 g. of alumina. Products were eluted with 5 liters

of dichloromethane and 2 liters of 1% ethanol in dichloromethane. The latter fractions contained 15, which was submitted to gel permeation chromatography on Bio Beads SX-8 (149 ml. retention volume) to give 0.480 g. (32%) of 15, which was recrystallized from dichloromethanepentane, m.p. 125°–128° (dec), osmometric molecular weight, 359 (calculated 363), 60 MHz pmr spectrum in CDCl_3 , δ : 7.1–7.8 (m, ArH, 9H); 4.6 (s, ArCH_2 , 12H).

Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_3$: C, 69.40; H, 5.82;
Found: C, 69.18; H, 6.03.



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PROCEDURE 7

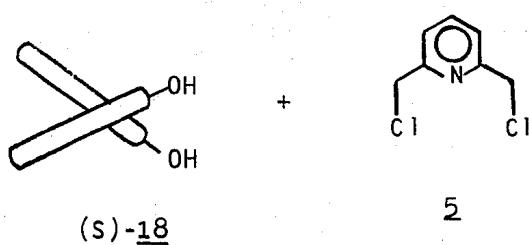
Procedure 7 records the synthesis of 16 and 17 from 1 and 4. To a solution of 1.4 g. of diol 1 in 100 ml. of dry tetrahydrofuran was added 1.10 g. of 50% sodium hydride in oil. After the mixture had stirred for 45 minutes at 25°, a solution of 2.6 g. of 4 in 100 ml. of dry tetrahydrofuran was added, and the mixture was stirred for 100 hours at 25°. Water (2 ml.) was added, the mixture was filtered, the residue was washed with dichloromethane, and the combined filtrates were evaporated under vacuum. The residue was chromatographed on 100 g. of alumina with 1% ethanol in dichloromethane. Cycles 16 and 17 eluted in early fractions. The combined fractions were chromatographed on 500 g. of silica gel with dichloromethane-ethanol as eluting agent. The first eluting fraction was 17, 320 mg. m.p. 170°–173°. The second eluting fraction contained a mixture of 16 and 17, which were separated by gel permeation chromatography (Bio Beads SX-8) to give 160 mg. of 17, and 20 mg. (1%) of 16. Cycle 16 was identified by comparison (m.p., pmr, retention volume) with authentic material prepared in Procedure 8. Cycle 17, 20%, gave m.p. 173°–176° (dec.), 60 MHz pmr spectrum in CDCl_3 , δ : 7.1–7.7 (m, ArH, 12H); 4.6 (s, ArCH_2 , 16H), and osmometric molecular weight 466, calculated 484.

Anal. Calcd for $\text{C}_{28}\text{H}_{28}\text{N}_4\text{O}_4$: C, 69.40; H, 5.82.
Found: C, 69.34; H, 6.00.

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Procedure 8 records the synthesis of 16, 15 and 17 from 6. A mixture of 5.3 g. of 6, 1.5 g. of 50% sodium hydride in oil, and 500 ml. of dry tetrahydrofuran was stirred at 25° for 100 hours. Water, 3 ml., was added, the mixture was filtered, the cake was washed with dichloromethane, and the filtrate was evaporated under vacuum. The residue was chromatographed on 60 g. of alumina with dichloromethane as eluting agent. The early eluting material was rechromatographed on 200 g. of silica gel with dichloromethane-ethanol as eluting agent. The cycles eluted in the order, 17 (172 mg. or 6%), 15 (30 mg. or 1%) and 16 (202 mg. or 6.5%), m.p. 170°–175° (dec.). The samples of 17 and 15 were found identical in all respects (m.p., pmr and gel permeation retention volumes) with authentic material. The sample of 16 was recrystallized from dichloromethanepentane to give material, m.p. 172°–175° (dec.), pmr spectrum (60 MHz) in CDCl_3 , δ : 6.7–7.4 (m, ArH, 6H); 4.6 (s, ArCH_2 , 8H), osmometric molecular weight 239 (calculated 242).

Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$: C, 69.40; H, 5.82
Found: C, 69.45; H, 5.83.



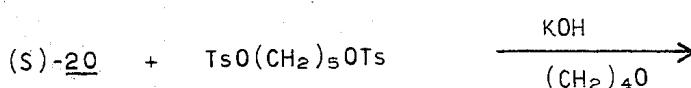
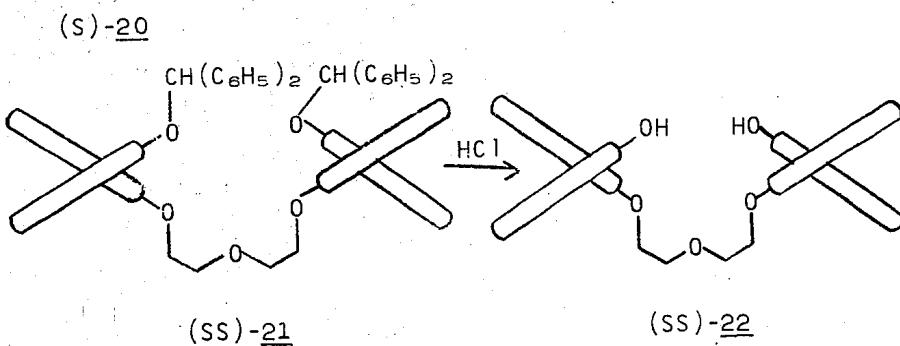
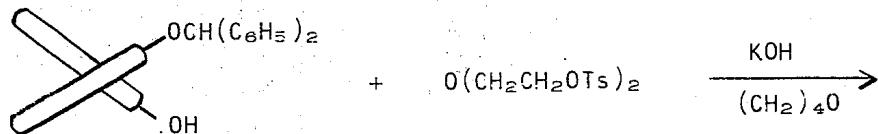
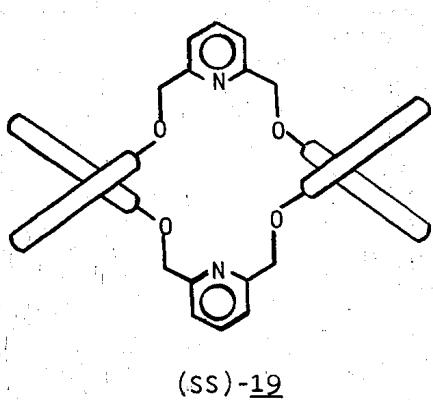
PROCEDURE 9

Procedure 9 records the preparation of (SS)-19. To a solution of 14.3 g. of optically pure (S)-1,1-binaphthyl [J. Amer. Chem. Soc., 95, 2692 (1973)] in tetrahydrofuran (500 ml.) was added 12.3 g. of potassium tert-butoxide in one portion, which was washed in with 350 ml. of tetrahydrofuran. The solution became a slurry during 15 minutes of stirring at 25°. A solution of 8.8 g. of 5 was added in one portion, and the reaction mixture was stirred and heated under reflux in a nitrogen atmosphere for 96 hours, and cooled. The brown solution was decanted from the precipitated semi solid mass and evaporated to 150 ml. The solution deposited (crystalline) 3.7 g. of (SS)-19.2(CH₂)₄O (pmr integration). The filtrate from the crystals was mixed with the original residue, the solvent was evaporated, and the residue was partitioned between water and dichloromethane. The organic layer was evaporated, and the residue was dissolved in 150 ml. of tetrahydrofuran. The crystals of solvate of (SS)-19 that separated were collected to give 3.6 g. of material, which was combined with the original material to give 7.2 g. (31%), m.p. (dried at 25° for 48 hours) 295°–298° (dec.), mass spectrum (70 eV) gave molecular ion for (SS)-19 at m/e = 778, $[\alpha]_{589}^{25} -250^\circ$, $[\alpha]_{578}^{25} -264^\circ$, $[\alpha]_{546}^{25} -319^\circ$, $[\alpha]_{436}^{25} -772^\circ$ (c 1.1, CHCl₃, corrected for solvate), pmr (100 MHz, CDCl₃), δ: 6.8–7.9 (m, naphthalene ArH and pyridine-γ-H, 26H); 6.32 and 6.40 (s,s, pyridine-β-H, 4H); 4.82 (s, ArCH₂, 8H); 3.66 and 1.76 (m, m, tetrahydrofuran, 16H).

Anal. Calcd for C₅₄H₃₈N₂O₄C₈H₁₆O₂: C, 80.69; H, 5.86. Found: C, 80.50; H, 6.06.

The solvate was dissolved in dichloromethane, the solution was evaporated, and the oil was dried to a foam at 120° and 0.1 mm, pmr spectrum (100 MHz in CDCl₃), δ: 4.82 (s, ArCH₂, 8H); 6.32–7.9 (m, ArH, 30).

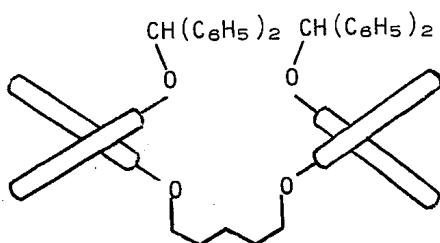
Anal. Calcd for C₅₄H₃₈N₂O₄: C, 83.27; H, 4.92. Found: C, 83.20; H, 5.03.



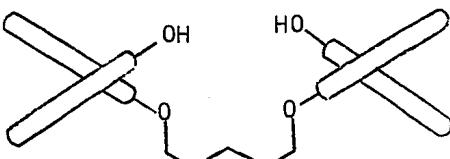
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(SS)-21a



(SS)-22a

PROCEDURE 10

Procedure 10 records the preparation of (SS)-21, (SS)-21a, (SS)-22 and (SS)-22a. Optically pure (S)-20, 9.05 g., 4.14 g. of diethyleneglycol ditosylate and 1.45 g. of potassium hydroxide in 5 ml. of water was mixed with 200 ml. of tetrahydrofuran, and the solution was refluxed for 36 hours. The solution was cooled slightly, and 2 ml. of 50% aqueous potassium hydroxide and 2 g. of diethyleneglycol ditosylate were added, and refluxing was resumed for 12 hours. The mixture was cooled, filtered, and the filtrate was evaporated under vacuum. the residue was chromatographed on alumina, with dichloromethane in pentane as eluting agent. The product, (SS)-21, was eluted in two successive one liter fractions (40% dichloromethane by volume), 7.15 g. (73%), as a white foam. The compound's mass spectrum (70 eV) gave a molecular ion at m/e = 974, [math>\alpha]_{578}^{25} -3.04^\circ, [math>\alpha]_{546}^{25} -5.18^\circ, [math>\alpha]_{436}^{25} -30.25^\circ (c 1, CHCl₃), and a pmr spectrum consistent with the assigned structure.

Anal. Calcd for C₇₀H₅₄O₅: C, 86.21; H, 5.58. Found: C, 86.08; H, 5.69.

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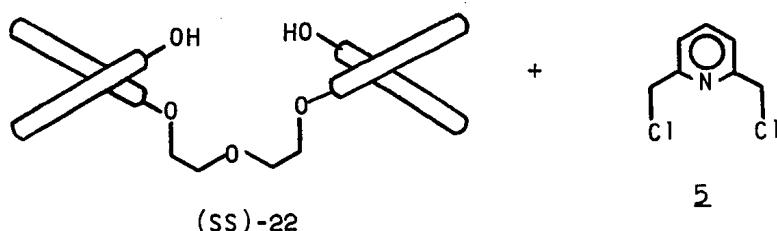
A solution of 4.35 g. of (SS)-21a in 50 ml. dichloromethane, 50 ml. of methanol and 5 ml. of concentrated hydrochloric acid was stirred 24 hours at 25°. The solution was shaken with 200 ml. of dichloromethane and 200 ml. of ice water, and the organic phase was washed with water, dried and evaporated. The mixture of (SS)-22 and benzhydryl methyl ether produced was used directly in the next step (preparation of (SS)-23, see Procedure 11).

Compound (SS)-21a was prepared by the same procedure used to obtain (SS)-21 except that pentamethyleneglycol ditosylate was substituted for diethyleneglycol ditosylate. Compound (SS)-21a, a white foam, was obtained in 55% yield, gave a mass spectrum (70 eV) molecular ion at m/e = 972, [math>\alpha]_{578}^{25} -20.8^\circ, [math>\alpha]_{546}^{25} -25.5^\circ, [math>\alpha]_{436}^{25} -69.3^\circ (c 0.8 CHCl₃), and a pmr spectrum consistent with its assigned structure.

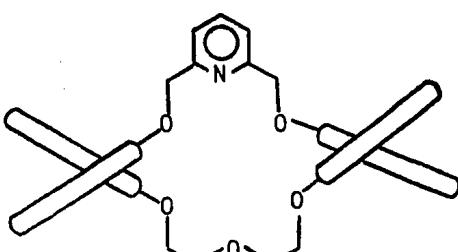
Anal. Calcd for C₇₁H₅₆O₄: C, 87.62; H, 5.80.

Found: C, 87.32; H, 5.58.

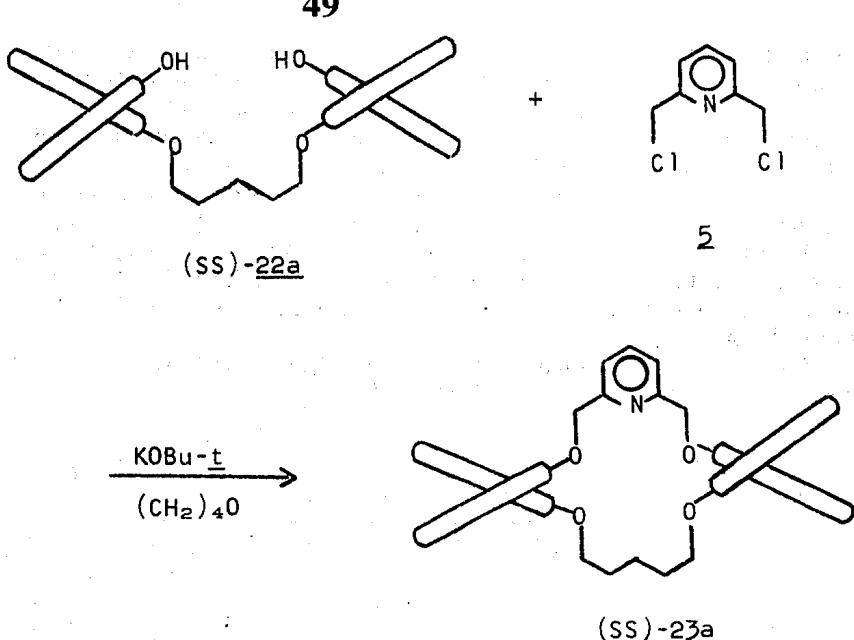
Acid hydrolysis of (SS)-21a to give (SS)-22a mixed with benzhydryl methyl ether was carried out by the same procedure used to produce (SS)-22 from (SS)-21. The mixture was used directly in the preparation of (SS)-23a.



$\xrightarrow[\text{KOBu-}\text{t}]{(\text{CH}_2)_4\text{O}}$



(SS)-23



25

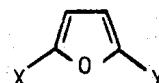
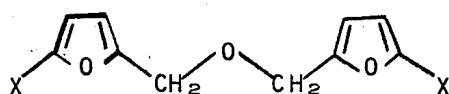
PROCEDURE 11

Procedure 11 reports the preparation of (SS)-23 and (SS)-23a. The mixture of benzhydryl methyl ether and (SS)-22 produced from 7.65 g. of (SS)-21 was dissolved in 100 ml. of tetrahydrofuran, and mixed with 1.93 g. of potassium tert-butoxide, 1.4 g. of 5 and an additional 100 ml. of tetrahydrofuran. The solution was refluxed for 24 hours, the mixture was cooled, filtered, and the filtrate was evaporated. The residue was chromatographed on 250 g. of alumina. Elution of the column with one liter of 1:9 dichloromethane-pentane removed the benzhydryl methyl ether. The product, (SS)-23, was eluted with 2:3 dichloromethane-pentane, weight 2.54 g. (44%), after drying at 110° for 20 hours (foam), $[\alpha]_{578}^{25} -242^\circ$, $[\alpha]_{546}^{25} -288^\circ$, $[\alpha]_{436}^{25} -665^\circ$ (c 0.7, CHCl₃), pmr spectrum (100 MHz in CDCl₃), δ: 7.0–7.9 (m, naphthalene ArH and pyridine-γ-H, 25H); 6.68, 6.76 (s, s, pyridine-β-H, 2H); 4.89 (s, ArCH₂, 4H); 3.62 (pseudo-t, ArOCH₂, 4H); 2.9 (m, CH₂OCH₂, 4H).

Anal. Calcd for C₅₁H₃₉N₅: C, 82.12; H, 5.27. Found: C, 82.33; H, 5.43.

Cycle (SS)-23a was similarly prepared. A solution of a mixture of (SS)-22a and benzhydryl methyl ether prepared by methanolysis of 4.5 g. of optically pure (SS)-21a in 200 ml. of tetrahydrofuran was mixed with 2.02 g. of 5 and 1.14 g. of potassium tert-butoxide. The resulting mixture was refluxed for 48 hours, and the product isolated by extraction and chromatography, weight 1.5 g. (29%), white foam after drying at 145° and 0.01 mm, mass spectrum (70 eV) molecular ion at m/e = 743, $[\alpha]_{589}^{25} -240^\circ$, $[\alpha]_{578}^{25} -250^\circ$, $[\alpha]_{546}^{25} -301^\circ$, $[\alpha]_{436}^{25} -702^\circ$ (c 0.5, CHCl₃), pmr spectrum (60 MHz) in CDCl₃, δ: 7.0–7.9 (m, naphthalene ArH, and pyridine ArH-γ, 25H); 6.62, 6.73 (s, s, pyridine ArH-β, 2H); 4.88 (s, ArCH₂, 4H); 3.52 (broad s, ArOCH₂, 4H); 0.8 (broad s, CH₂(CH₂)₃CH₂, 6H).

Anal. Calcd for C₅₂H₄₁NO₄: C, 83.96; H, 5.56. Found: C, 83.98; H, 5.69.

EXAMPLE 2
Preparation of Furan Unit-Containing Host Compounds37, X = CH₂OH, Y = CHO38, X = Y = CH₂OH39, X = Y = CH₂Cl40, X = CH₂Cl, Y = CHO41, X = CH₂OCH₂CH₂Cl, Y = CHO42, X = CH₂OH, Y = CH₂OCH₂CH₂Cl

43, X = CHO

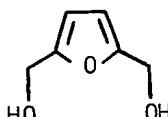
44, X = CH₂OH

PROCEDURE 1

Procedure 1 deals with the starting materials for preparation of the furan-containing cycles. Compound 37 was prepared from sucrose [J. Chem. Soc., 667 (1944)]. Reduction of 37 with sodium borohydride gave 38 [J. Chem. Soc., 3917 (1963)]. Dropwise addition with stirring of a solution of 38 in 2,6-lutidine to a stirred solution of thionyl chloride in ethyl acetate at -20° gave a frozen solid that was warmed to 75° and stirred for 1 hour. Water and pentane were added, and the unstable 39 [British Pat. No. 911,221; Chem. Abstr., 58, 9027f (1963)] was isolated at low temperature without distillation, and was used immediately. Compound 40 was also prepared from sucrose [J.

Chem. Soc., 667 (1944); *Can. J. Chem.*, 37, 1056 (1959)]. Water was azeotropically distilled (4 hours) from 37 in toluene-containing 0.2% p-toluenesulfonic acid to give after chromatographic purification, 43 [British Pat. No. 887,360; *Chem. Abstr.*, 57, 2196b (1962)].

New compound 41 was prepared as follows. Chloroaldehyde 40, 13.9 g., was added to 210 ml. of 2-chloroethanol containing 28 g. of barium carbonate. The mixture was stirred at 70° for 16 hours. The solution was cooled, filtered, and 200 ml. of dichloromethane was added. The mixture was washed with water three times. The organic layer was dried, the solvent



38

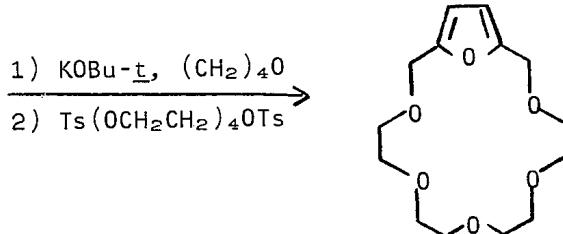
was evaporated followed by the excess 2-chloroethanol (under vacuum), and the residue was distilled at 0.4 mm, b.p. 117°, weight 15.1 g. (87%), mass spectrum (70 eV) molecular ion at m/e = 188, pmr (100 MHz in CDCl₃), δ: 3.72 (m, OCH₂CH₂Cl, 4H); 4.62 (s, ArCH₂, 2H); 6.57 (d, J = 3.5 Hz, 3-ArH, 1H); 7.22 (d, J = 3.5 Hz, 4-ArH, 1H); 9.62 (s, CHO, 1H).

Anal. Calcd for C₈H₉ClO₃: C, 50.95; H, 4.81. Found: C, 50.90; H, 4.81.

New compound 42 was prepared as follows. Chloroaldehyde 41, (8.7 g.) was dissolved in 300 ml. of absolute ethanol, 1.75 g. of sodium borohydride was added, and the resulting solution was stirred at 25° for 2 days. The solution was acidified with concentrated hydrochloric acid, solid sodium bicarbonate was added immediately; the mixture was filtered, the solvent was evaporated from the filtrate, and the residue was dis-

refluxed for 4 hours. The solution was cooled, the mixture was acidified with concentrated hydrochloric acid, solid sodium bicarbonate was immediately added, the mixture was filtered, and the solvent was evaporated from the filtrate. The residue was crystallized from chloroform to give 7.5 g. (98%) of diol 44, m.p. 92°–93°, mass spectrum (70 eV) molecular ion at m/e = 236, pmr (100 MHz, (CD₃)₂CO), δ: 3.0 (s, OH, 2H); 4.42 (s, CH₂OCH₂, 4H); 4.49 (s, CH₂OH, 4H); 6.20 (d, J = 2.9 Hz, 3-Ar-H, 2H); 6.30 (d, J = 2.9 Hz, 4-Ar-H, 2H).

Anal. Calcd for C₁₂H₁₄O₅: C, 60.50; H, 5.92. Found: C, 60.55; H, 6.07.

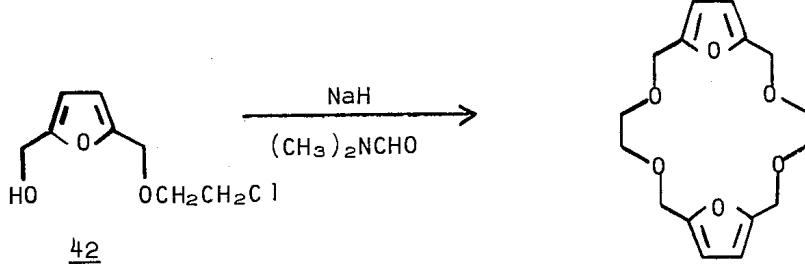


45

PROCEDURE 2

Procedure 2 records the preparation cycle 45, and exemplified the synthesis of other analogues that contain one furan unit. In a nitrogen atmosphere, 54 g. of tetraethyleneglycol ditosylate in 200 ml. of tetrahydrofuran was added dropwise to 1 liter of tetrahydrofuran containing 12.5 g. of diol 38 and 24 g. of potassium tert-butoxide. The solution was stirred at 25° for 12 hours, refluxed for 12 hours, cooled, dried and the solvent was evaporated. The residue was chromatographed on 1 Kg of alumina with dichloromethane-ether (1:1) as eluting agent to give 10 g. (36%) of 45, m.p. ~0°, mass spectrum (70 eV), molecular ion at m/e 286, pmr (100 MHz, CDCl₃), δ: 3.60 (s, OCH₂CH₂O, 16H); 4.46 (s, ArCH₂O, 4H); 6.11 (s, ArH, 2H).

Anal. Calcd for C₁₄H₂₂O₆: C, 58.73; H, 7.74. Found: C, 58.43; H, 7.88.



46

PROCEDURE 3

Procedure 3 records the synthesis of cycle 46, and exemplifies the synthesis of the other analogues that contain two furan units located 180° from one another. In a nitrogen atmosphere, sodium hydride, 0.75 g., was slowly added to 500 ml. of dimethylformamide containing 4 g. of 42. The solution was stirred at room temperature for 2 days, 500 ml. of dichloromethane was added, and the solution was extracted with water to remove the dimethylformamide. The dichloromethane

tilled to give 8.5 g. (97%) of chloroalcohol 42, b.p. 104°–105° at 0.2 mm, mass spectrum (70 eV) gave a molecular ion at m/e = 190.

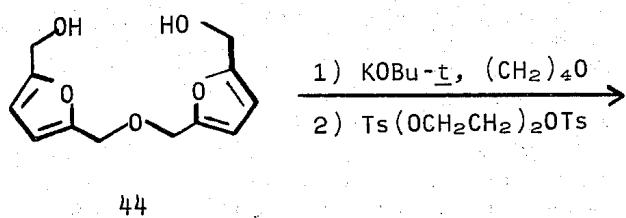
Anal. Calcd for C₈H₁₁ClO₃: C, 50.40; H, 5.80; Cl, 18.59.

Found: C, 50.32; H, 5.86; Cl, 18.32.

New compound 44 was prepared as follows. Dialdehyde ether 43, 7.8 g., was dissolved in -Ar-H, 230 ml. of absolute ethanol, 2.5 g. of sodium borohydride was added, the mixture was stirred at 25° for 4 hours, and

solution was dried, evaporated, and the 4.4 g. of residue was chromatographed on 120 g. of alumina with dichloromethane as eluent to give 1 g. (28%) of vinyl ether derived from 42, followed by 0.40 g. (11%) of cycle 46, m.p. 109°–111°. The compound gave a molecular ion at m/e = 308 in its mass spectrum, and a 100 MHz spectrum in CDCl_3 , δ : 3.57 (s, $\text{OCH}_2\text{CH}_2\text{O}$, 8H); 4.44 (s, ArCH_2O , 8H); 6.20 (s, ArH, 4H).

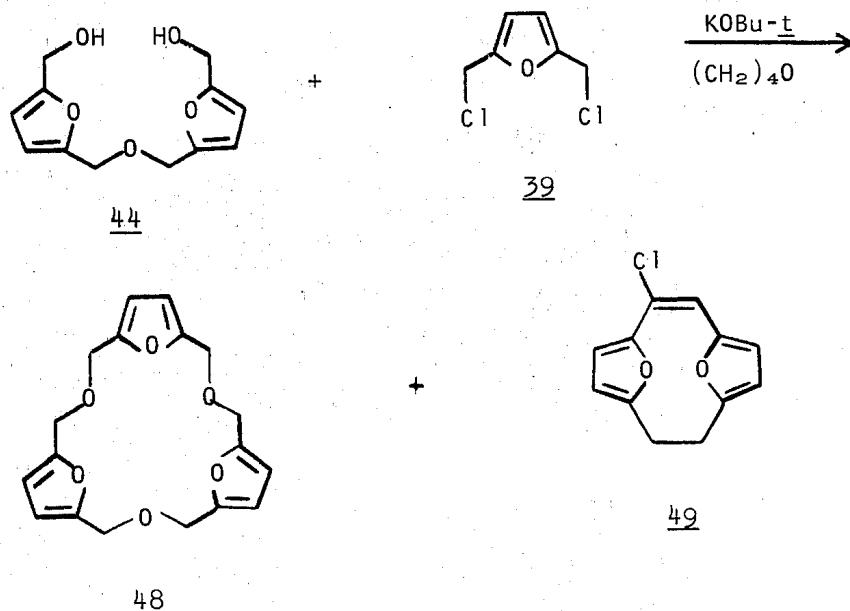
Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_6$: C, 62.32; H, 6.54. Found: C, 62.15; H, 6.69.



PROCEDURE 4

Procedure 4 reports the synthesis of cycle 47, and exemplifies the synthesis of macrocycles containing two furanyl units separated by a CH_2OCH_2 unit. In a nitrogen atmosphere, 6.6 g. of diethyleneglycol ditosylate in 100 ml. of tetrahydrofuran was added dropwise to 200 ml. of tetrahydrofuran containing 3.7 g. of diol 44 and 4.05 g. of potassium tert-butoxide. The mixture was stirred at 25° for 24 hours, more ditosylate (0.66 g.) was added, and the solution was refluxed for 6 hours. The solution was cooled, filtered, and the solvent was evaporated from the filtrate to give 7 g. of residue, which was chromatographed on 300 g. of alumina with dichloromethane as eluting agent. Product, 1.7 g. (35%) of 97 was eluted which was recrystallized from dichloromethane-pentane to give m.p. 69°–70°, mass spectrum (70 eV) molecular ion at m/e = 308, pmr spectrum (100 MHz in CDCl_3), δ : 3.64 (s, $\text{OCH}_2\text{CH}_2\text{O}$, 8H); 4.48 (s, ArCH_2 , 8H); 6.22 (AB quartet, $J_{AB} \sim 3.4$ Hz, ArH, 4H).

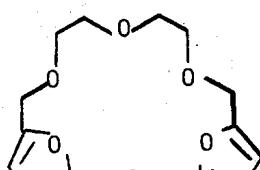
Anal. Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_6$: C, 62.32; H, 6.54. Found: C, 62.25; H, 6.36.



PROCEDURE 5

Procedure 5 reports the synthesis of cycle 48, and byproduct 49. In a nitrogen atmosphere, 5.2 g. of dichloride 39 in 100 ml. of tetrahydrofuran was added dropwise with stirring to 400 ml. of tetrahydrofuran containing 7.5 g. of diol 44 and 7.8 g. of potassium tert-butoxide. The solution gradually turned dark red. The mixture was stirred at 25° for 2 days, filtered, and the solvent was evaporated from the filtrate to give

10



47

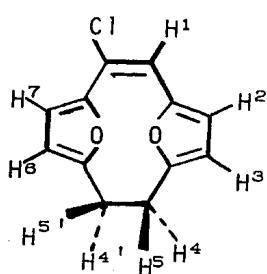
10.7 g. of dark red residue. This material was chromatographed on 230 g. of silica gel with dichloromethane to give 1.2 g. of a dark red oil, 5.2 g. (70%) of diol 44, and 1 g. of solid which was recrystallized from dichloromethane-pentane to give 48 (10% based on starting diol, or 32% based on consumed diol), m.p. 124°–126°, mass spectrum (70 eV) molecular ion at m/e = 330, pmr spectrum (100 MHz in CDCl_3), δ : 4.47 (s, CH_2 , 12H); 6.27 (s, ArH, 6H).

Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{O}_6$: C, 65.45; H, 5.49. Found: C, 65.56; H, 5.65.

The red fraction was purified by gel permeation chromatography (Bio-Rad SX-8 packing, 3/8 inch by 18 foot column, tetrahydrofuran as solvent, 3 ml. per min. flow rate, pressure 350 psi, 2 ml. injection with 0.1 to 0.5 g. per injection). Compound 49 was isolated as a slightly yellow liquid, weight 1.0 g. (29%), mass spectrum (70 eV) molecular ion m/e = 220, pmr spectrum at 30° (100 MHz, CDCl_3), 2.0–3.5 (very broad s, CH_2 , 4H); 6.14 and 6.17 (two overlapping d, $J_{3,2} = J_{6,7} = 3.4$ Hz, H^3 and H^6 , 2H); 6.55 (d of d, $J_{2,3} = 3.4$ Hz, $J_{2,1} = 0.7$ Hz, H^2 , 1H); 6.77 (d, $J_{1,2} = 0.7$ Hz, $J_{1,2} = 0.7$ Hz, H^1 ,

45

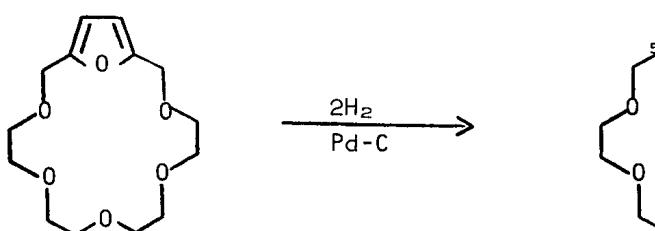
1H); 6.88 (d, $J_{7,6} = 3.4$ Hz, H⁷, 1H). The broad singlet became a sharp singlet at δ 2.60 (coalescence temperature about 30°), and separated into an AB quartet below 0°, $v_A = 2.03$, $v_B = 3.23$, $J_{AB} = 10$ Hz. Apparently the members of each pair of vicinal protons have the same chemical shifts, but the geminal protons do not for conformational reasons. The ring-system conformations inhibit equilibration of the geminal protons below 30°. Compound 49 undoubtedly arises from ring closure of a diradical formed by head-to-head dimerization of a triene (formed from 39 by base-catalyzed elimination) followed by elimination of one mole of hydrochloric acid from the product [J. Amer. Chem. Soc., 82, 1428 (1960); ibid., 88, 515 (1966)].

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EXAMPLE 3

Preparation of Tetrahydrofuran Unit-Containing Host Compounds.

Many naturally occurring antibiotics, generally isolated from various Streptomyces strains, uncouple oxidative phosphorylation in rat liver mitochondria, and have been shown to affect ion permeability through both natural and synthetic membranes [Science, 178, 24 (1972); Helv. Chim. Acta, 54, 286 (1971); "Antibiotics I", D. Gottlieb and P. D. Shaw, ed., Springer-Verlag, New York, 1967, p. 649; J. Membrane Biol., 1, 294 (1969)]. Many of these antibiotics contain one or several tetrahydrofuran units (e.g. the actins, grisorixin and nigericin), and are either multiheteromacrocycles, or form cycles through hydrogen bonding. This example indicates how the furan-containing units of the multiheteromacrocycles of Example 2 can be converted to the tetrahydrofuran-containing multiheteromacrocycles, which Example 8 indicates are excellent complexing agents.

4571

PROCEDURE 1

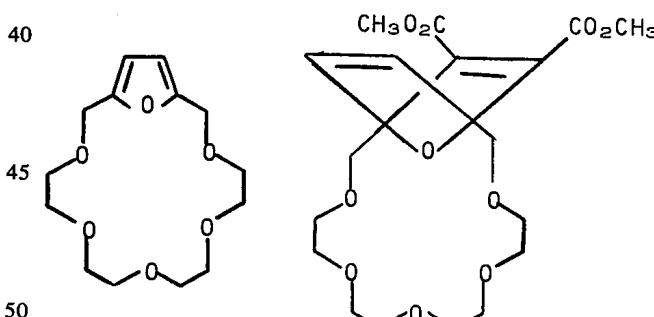
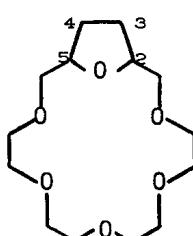
Procedure 1 reports the reduction of 45 to 71, and exemplifies a general procedure by which all furan units of multiheteromacrocycles can be reduced to their corresponding tetrahydrofuran-containing multiheteromacrocycles. A mixture of 200 mg. of 45, 100 ml. of absolute ethanol and 30 mg. of 10% palladium on charcoal was stirred for 1 hour at 25° in an atmosphere of hydrogen. The hydrogen uptake had stopped. The mixture was filtered, the solvent evaporated, and the 200 mg. of residue was submitted to preparative glc chromatography [5% SE-30 on Fluoropak (>20 mesh), 6 g. per foot, 6 foot column at 260°, retention time 12 minutes]. The product, 71, emerged as a single band, mass spectrum (70 eV) molecular ion m/e = 290, pmr (100 MHz, CDCl₃, δ: 1.90 (m, H³ and H⁴, 4H, collapses to a slightly broadened singlet upon irradiating at 4.1); 3.60 (m, CH—CH₂—O, 4H), 3.68 (s, OCH₂CH₂O, 16H); 4.1 (m, H² and H⁵, 2H, collapses to a triplet, $J = 4.5$ Hz, upon irradiation at 1.90). Anal. Calcd for C₁₄H₂₆O₆: C, 57.91; H, 9.03. Found: C, 58.00; H, 9.16.

When complexed with Eu (PPM)₃, the methine region of the pmr spectrum of 71 splits into two broad, overlapping peaks, which fact indicates the compound to be a mixture of cis-trans isomers.

EXAMPLE 4

Preparation of Diels-Alder Adducts of Furan-Containing Host Compounds

The Diels-Alder adducts of the furan-containing host compounds are themselves strong complexing agents, and also serve as highly versatile starting materials for preparation of a large number of arm containing host compounds. This example indicates how the furan-containing units of the multiheteromacrocycles of Example 3 can be converted to their Diels-Alder adducts.

4589

PROCEDURE 1

Procedure 1 reports the addition of dimethyl acetylene dicarboxylic ester to 45 to give 89, and exemplifies a general procedure by which furan units of multiheteromacrocycles can be converted to the product of their Diels-Alder addition reactions. A solution of 1.0 g. of 45, 3.0 g. of dimethyl acetylenedicarboxylic ester in 20 ml. of toluene was heated to 110° for 15 hours. The solvent was evaporated, and the residue was subjected to gel permeation chromatography with tetrahydrofuran as solvent to give 89 as an oil, 1.1 g. (75%), mass spectrum (70 eV) molecular ion at m/e = 428, pmr (100 MHz in CDCl_3), δ : 3.58 (s, $\text{OCH}_2\text{CH}_2\text{O}$, 16H); 3.72 (s, CH_3 , 6H); 4.17 (AB quartet, $J_{AB} \sim 11\text{Hz}$, $\Delta\delta \sim 7\text{Hz}$, C— CH_2 —O, 4H), 6.94 (s, $\text{CH}=\text{CH}$, 2H).

Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{O}_{10}$: C, 56.07; H, 6.59. Found: C, 56.00; H, 6.42.

The temperature dependent pmr spectrum of 89 was demonstrated by these data.

PROCEDURE 1

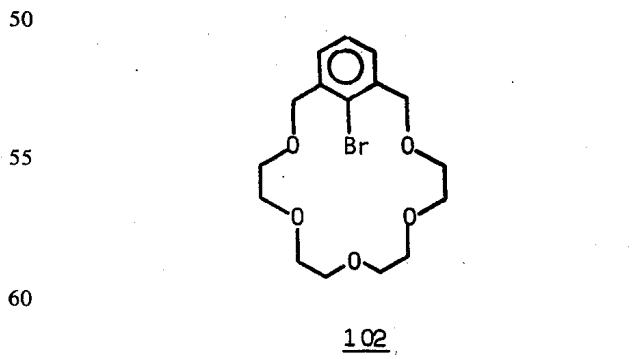
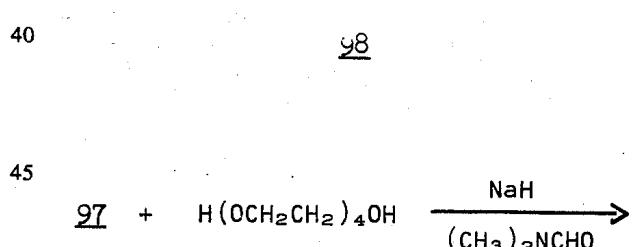
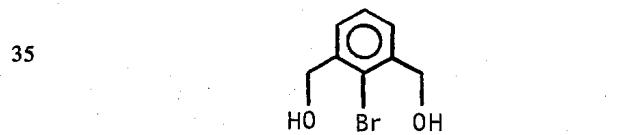
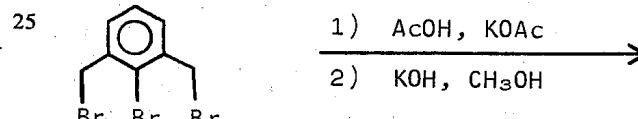
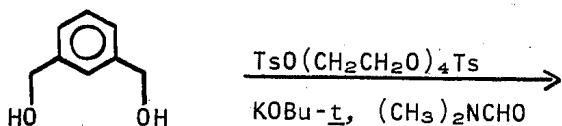
Procedure 1 reports the preparation of cycle 96. To a solution of 5.52 g. of diol 95 [Can. J. Research, 23B, 106 (1945)] in 400 ml. of dry dimethylformamide was added 9.43 g. of potassium tert-butoxide, and the solution was stirred at 25° for 1 hour. A solution of 20.1 g. of tetraethyleneglycol ditosylate in 100 ml. of dry dimethylformamide was added, and the solution was stirred at 25° for 3 days. The solvent was evaporated under vacuum, and the residue was shaken with a mixture of 3% hydrochloric acid and dichloromethane. The organic layer was washed with water, dried, and the solvent was evaporated. The residual oil was chromatographed on silica gel. Elution of the column with ether gave 96, 3.6 g. (30%) as an oil that crystallized, and was recrystallized from pentane, m.p. 44°–46°, mass spectrum (70 eV) molecular ion at m/e = 296, pmr spectrum (60 MHz, CDCl_3), δ : ~3.73 (d, $\text{OCH}_2\text{CH}_2\text{O}$, 16H); 4.65 (s, ArCH_2O , 4H); 7.1–7.3 (m, ArH , 3H); 7.7 (broad s, ArH , 1H).

Anal. Calcd for $\text{C}_{18}\text{H}_{24}\text{O}_5$: C, 64.84; H, 8.16. Found: C, 65.00; H, 8.06.

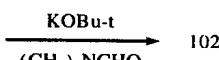
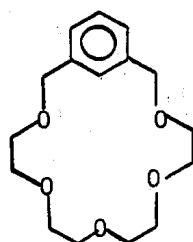
Solvent	Temp °C	$\Delta\delta$ (separation of inner two lines of AB quartet)
$\text{C}_6\text{H}_5\text{Cl}$	25	14 Hz
$\text{C}_6\text{H}_5\text{Cl}$	60	10 Hz
$\text{C}_6\text{H}_5\text{Cl}$	80	8 Hz
$\text{C}_6\text{H}_5\text{Cl}$	127	5 Hz
$\text{o-C}_6\text{H}_4\text{Cl}_2$	25	13 Hz
$\text{o-C}_6\text{H}_4\text{Cl}_2$	116	5 Hz
$\text{o-C}_6\text{H}_4\text{Cl}_2$	136	4 Hz
$\text{o-C}_6\text{H}_4\text{Cl}_2$	163	3 Hz

EXAMPLE 5

Preparation of m-Xylyl Unit-Containing Host Compounds



95



59

PROCEDURE 2

Procedure 2 records two preparations of cycle 102. In the first, sodium hydride, 1.62 g., was added to a solution of 2.91 g. of tetraethyleneglycol in 150 ml. of dry dimethylformamide at 25°. After 45 minutes of stirring, tribromide 97 [Chem. Ber., 102, 1734 (1969)], 5.14 g. in 15 ml. of dry dimethylformamide was added, and the resulting mixture was stirred at 25° for 4 days. The reaction mixture was evaporated under vacuum to dryness, and the residue was shaken with a mixture of 3% aqueous hydrochloric acid and dichloromethane. The organic layer was washed with water, dried, evaporated and chromatographed on silica gel. Elution of the column with benzene gave 350 mg. (7%) of 102 as a colorless liquid, mass spectrum (70 eV) molecular ions at m/e = 374 and 376, pmr spectrum (60 MHz in CDCl_3), δ : 3.6 and 3.5 (two peaks, $\text{OCH}_2\text{CH}_2\text{O}$, 16H); 4.67 (s, ArCH_2O , 4H); 7.25 (m, ArH, 3H).

Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{O}_5\text{Br}$: C, 51.21; H, 6.18. Found: C, 51.22; H, 6.30.

Tribromide 97 was converted to its diacetate by refluxing 97 in a potassium acetate solution (0.5 M) in glacial acetic acid for 24 hours. The solvent was distilled through a short column, and the residue was dissolved in dichloromethane. The solution was washed with water, dried, and the solvent was evaporated. The residual oil was refluxed in 90% methanol-potassium hydroxide (1M) for 24 hours, the solvent was evaporated, and the residual oil was dissolved in dichloromethane to give a solution that was washed with water, dried and evaporated. The residual oil, 98 (94 %) was used in the next step without further purification or characterization.

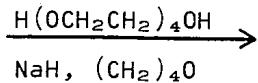
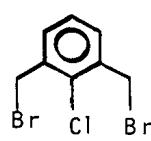
Cycle 102 was prepared from 98 as follows. To a solution of 6.08 g. of diol 98 and 14.1 g. of tetraethyleneglycol ditosylate in 250 ml. of dry dimethylformamide was added 6.0 g. of potassium tert-butoxide, and the solution was stirred for 4 days at 25°. Cycle 102 was isolated as in the above preparation, weight 750 mg. (7%). Its properties were identical to those of the sample prepared directly from 97.

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PROCEDURE 3

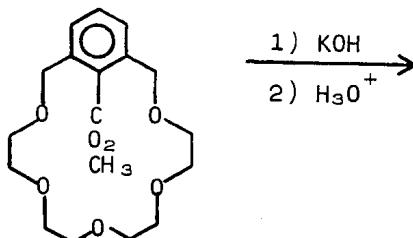
Procedure 3 records the synthesis of 103 from 99. Tetraethyleneglycol, 5.82 g., was dissolved in 500 ml. of dry tetrahydrofuran, and 1.8 g. of sodium hydride was added. The mixture was stirred for 1 hour, and to the stirred reaction mixture at 25° was added dropwise over a 3 hour period, 8.94 g. of 99 [Chem. Ber., 102, 1784 (1969)] dissolved in 500 ml. of dry tetrahydrofuran. The mixture was stirred an additional 12 hours at 25°, the solvent was evaporated, and the residue was shaken with dichloromethane and dilute hydrochloric acid. The organic layer was washed with water, dried, evaporated, and chromatographed on 500 g. of alumina. Dichloromethane eluted 103 which was obtained as an oil, 5.3 g. (53%). An analytical sample (oil) was purified by preparative glpc on a 0.25 inch by 6 foot, 5% SE-30 on Fleuropak column at 285°, 60 ml./min. flow rate, mass spectrum (70 eV) molecular ion at m/e = 330, pmr spectrum (60 MHz, CDCl_3), δ : 3.4-3.6 (m, $\text{OCH}_2\text{CH}_2\text{O}$, 16H); 4.6 (s, ArCH_2 , 4H), 7.0-7.3 (m, ArH, 3H).

Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{ClO}_5$: C, 58.09; H, 7.01.

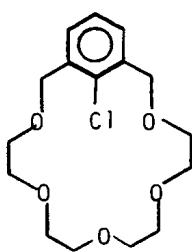
Found: C, 57.89; H, 7.06.

**99**

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100

45

**103**

60

105

PROCEDURE 4

Procedure 4 records the syntheses of 100, 104 and 105. To a stirred and refluxing mixture of 1.5 g. of sodium hydride in 500 ml. of dry tetrahydrofuran was added dropwise over a period of 3 hours at 25° a solution of 4.85 g. of tetraethyleneglycol and 8.05 g. of 100

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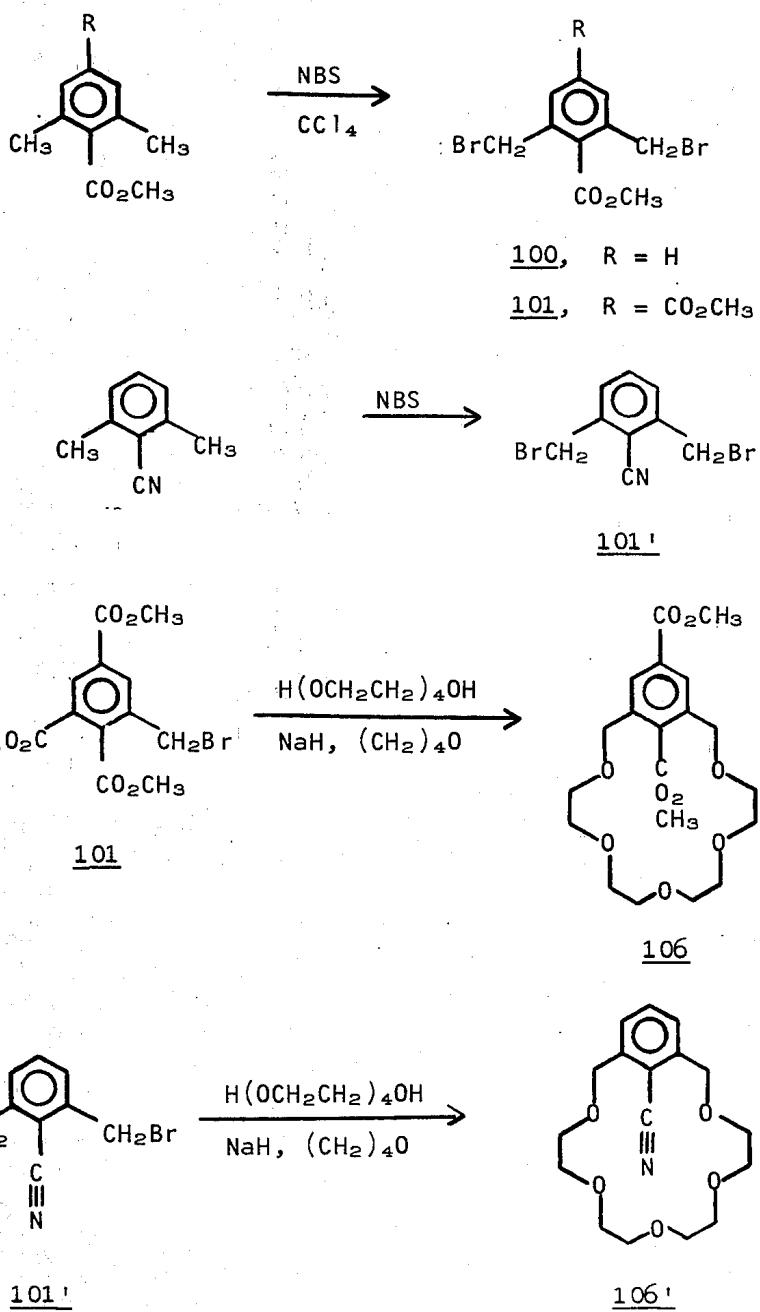
(see Procedure 5 of this section) in 500 ml. of dry tetrahydrofuran. The resulting mixture was stirred at 25° for 12 hours, the solvent was evaporated, and the residue was shaken with a mixture of dichloromethane and dilute hydrochloric acid. The organic layer was washed with water, dried and evaporated, and the residue was chromatographed on 500 g. of silica gel. Product 104 was eluted with dichloromethane-acetone mixtures, and was chromatographed on a gel permeation chromatograph column Bio-Beads SX-8 packing, 3/16 inch by 18 foot column) with tetrahydrofuran as eluting agents (132 ml. retention volume) to give 4.43 g. (50%) of 104 as a hygroscopic oil, mass spectrum (70 eV) molecular ion at m/e = 354, pmr spectrum (60 MHz, CDCl_3), δ : 3.47 and 3.54 (two peaks, $\text{OCH}_2\text{C}_6\text{H}_4\text{O}$, 16H); 3.9 (s, CH_3O , 3H); 4.6 (s, ArCH_2O , 4H); 7.3 (s, ArH , 3H). A sample of 104 was submitted to preparative glpc (column 0.25 inch by 6 foot, 15% SE-30 on 60/80 firebrick, 285°, 50 ml./min., 15 minutes retention time).

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Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{O}_7$: C, 61.00; H, 7.39. Found: C, 60.81; H, 7.47.

Ester 104 was hydrolyzed to 105 as follows. A mixture of 0.200 g. of 104 and 2 g. of sodium hydroxide in 50 ml. of 95% ethanol was refluxed for 20 hours. The solvent was evaporated, and the residue was shaken with a mixture of water and chloroform. The aqueous phase was washed with chloroform, acidified with hydrochloric acid, extracted with chloroform, and the chloroform solution was dried and evaporated to give 0.190 g. (~ 100%) of 105, m.p. 88°–96°, which was molecularly distilled at 180° and 20 μ to give 104, m.p. 97°–100°. Recrystallization of this material from dichloromethane-pentane gave 104, m.p. 100°–101°, mass spectrum (70 eV) molecular ion at m/e = 340, pmr spectrum (60 MHz, CDCl_3), δ : 3.9–4.0 (two peaks, $\text{OCH}_2\text{CH}_2\text{O}$ and CO_2H , 17H); 4.5 (s, ArCH_2O , 4H); 7.0 (s, ArH , 3H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{24}\text{O}_7$: C, 59.99; H, 7.11. Found: C, 60.03; H, 7.08.



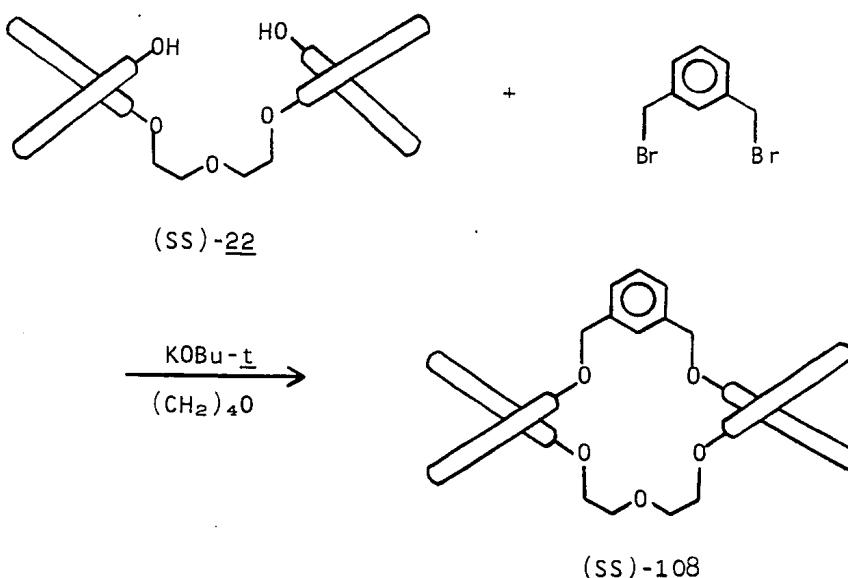
PROCEDURE 5

Procedure 5 reports the preparations of 100, 101 and 101', and the conversion of 101 to 106, and of 101' to 106'. The preparations of 100, 101 and 101' were similar, and are described together. The appropriate substituted m-xylene [J. Amer. Chem. Soc., 76, 787 (1954); Chem. Ber., 27, 3741 (1894); J. Amer. Chem. Soc., 62, 2091 (1940)] was dissolved in carbon tetrachloride dried over calcium hydride, and 2.2 equivalent of N-bromosuccinimide (NBS) and a trace of dibenzoyl peroxide were added. The mixture was warmed at reflux with stirring for 12 hours in an apparatus fitted with a drying tower. The mixture was filtered. The solvent was evaporated from the organic phase, and the product crystallized. In the preparation of 100, the product was recrystallized from cyclohexane to give 100, m.p. 77°-79°, (46% yield) mass spectrum (70 eV) molecular ion at m/e = 320, pmr spectrum as expected.

Anal. Calcd for $C_{10}H_{10}Br_2O_2$: C, 37.30; H, 3.13.
Found: C, 37.16; H, 3.23.

In the preparation of 101, the product was recrystallized from cyclohexane and gave a 35% yield, m.p. 123°-125°, mass spectrum (70 eV) gave a molecular ion at m/e = 378, pmr spectrum as expected.

Anal. Calcd for $C_{12}H_{12}Br_2O_4$: C, 37.92; H, 3.18.
Found: C, 37.97; H, 3.20.



In the preparation of 101', the product was obtained as a mixture with its mono and tribromo analogues and was used in the conversion to 106' without purification. Compound 101' has been prepared previously [Chem. Ber., 105, 2955 (1972)].

Cycle 106 was prepared as follows. To a stirred and refluxing mixture of 0.51 g. of sodium hydride in 500 ml. dry tetrahydrofuran was added dropwise over a period of 3 hours at 25° a solution of 1.36 g. of tetraethyleneglycol and 2.65 g. of dibromide 101 dissolved in 500 ml. of dry tetrahydrofuran. The mixture was stirred at 25° for 12 hours, the solvent was evaporated, and the residue was shaken with a mixture of dilute hydrochloric acid and dichloromethane. The organic layer was washed with water, dried, evaporated, and the residue was chromatographed on 200 g. of silica gel. Dichloromethane-acetone eluted crude 106, which was chromatographed on a gel permeation chromatograph column (Bio-Beads SX-8 packing, 3/8 inch by 18 foot

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column) with tetrahydrofuran as solvent, retention volume, 126 ml. The product crystallized to give 0.95 g. (33%) of 106, which was recrystallized from dichloromethane pentane to give m.p. 78°-80°, mass spectrum (70 eV) molecular ion at m/e = 412, pmr spectrum (60 MHz, $CDCl_3$), δ: 3.5, 3.6 (two peaks, $OCH_2C_6H_5$, 16H); 3.9 (s, CH_3O , 6H); 4.6 (s, $ArCH_2$, 4H); 7.9 (s, ArH , 2H).

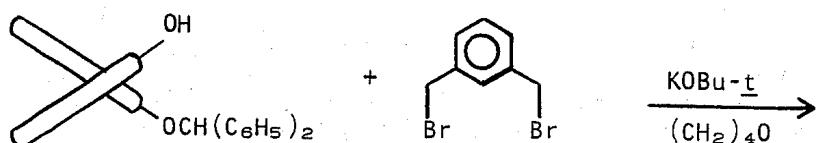
Anal. Calcd for $C_{20}H_{28}O_9$: C, 58.24; H, 6.84. Found: C, 58.26; H, 6.85.

Cycle 106' was prepared from 101' by the same procedure used in the preparation of 103 from 99. The product from the reaction was chromatographed on alumina (dichloromethane-benzene-ethanol elution), then on silica gel (dichloromethane-acetone elution), and on Bio Beads SX-8 (gel permeation) with tetrahydrofuran (132 ml. retention volume, column 3/8 inch by 18 feet). The product was an oil (10%), mass spectrum (70 eV) molecular ion at m/e = 321, ir spectrum (neat) 2220 cm^{-1} , pmr spectrum (60 MHz, $CDCl_3$), δ: 3.5-3.6 (two peaks, OCH_2CH_2O , 16H); 4.7 (s, $ArCH_2$, 4H); 7.4 (s, ArH , 3H). The compound was subjected to glpc (0.25 inch by 6 foot, 15% SE-30 on 60/80 firebrick, 280°, 50 ml./min., 13 minute retention time).

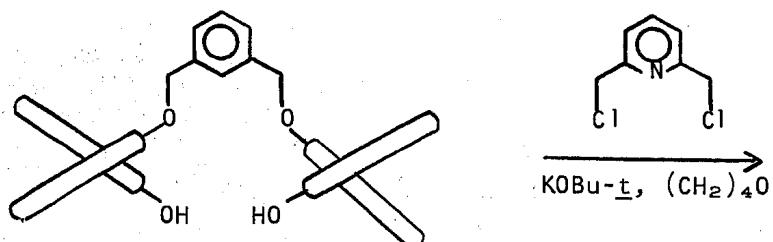
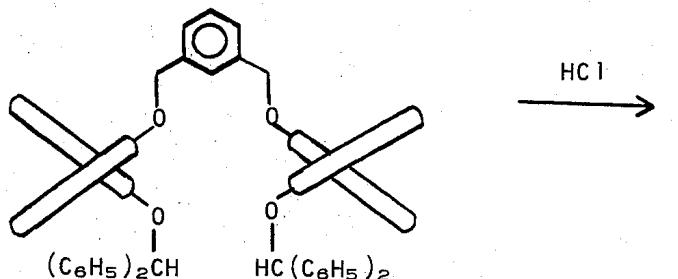
Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21.
Found: C, 63.43; H, 7.40.

PROCEDURE 6

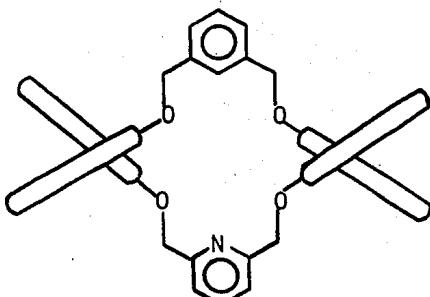
Procedure 6 reports the preparation of (SS)-108 from (SS)-22 [Example 1, Procedure 10] from m-xylyl dibromide. To a solution of optically pure (SS)-22, 6.0 g., and 2.30 g. of potassium tert-butoxide in tetrahydrofuran (200 ml.) was added 2.47 g. of m-xylyl dibromide. The solution was refluxed for 69 hours, filtered to remove salts, and the filtrate was evaporated under vacuum. The residue was dissolved in dichloromethane, and that solution was washed with water, dried, evaporated, and the residue was chromatographed on 400 g. of alumina. Dichloromethane-pentane (2:3) eluted 0.9 g. (13%) of (SS)-108, white foam, mass spectrum (70 eV) molecular ion m/e = 744, pmr spectrum (100 MHz, $CDCl_3$), δ: 2.78 (m, $ArOCH_2CH_2$, 4H); 3.52 (t, $ArOCH_2CH_2$, 4H); 4.80 (s, $ArCH_2O$, 4H); 6.7-7.9 -(complex m, ArH , 28H). The compound gave the rotations, $[\alpha]_{589}^{25} -215^\circ$, $[\alpha]_{578}^{25} -231^\circ$, $[\alpha]_{546}^{25} -275^\circ$ and $[\alpha]_{436}^{25} -630^\circ$ (c 0.5, $CHCl_3$).



(S)-20



(S,S)-110

**PROCEDURE 7**

This procedure reports the preparations of (SS)-109, 55 (SS)-110 and (SS)-111. To a solution of 19.9 g. of optically pure (S)-20 in 400 ml. of tetrahydrofuran was added 4.93 g. of potassium tert-butoxide. The solution was stirred for 10 minutes, and a solution of 5.80 g. of m-xylyl dibromide in 100 ml. of tetrahydrofuran was added. The resulting solution was heated at reflux for 36 hours, the solvent was evaporated, and the dichloromethane-soluble residue was chromatographed on 700 g. of alumina. Product, 14.9 g. (67%), was washed from the column with dichloromethane-pentane (1:3). The substance, (SS)-109 was a foam, mass spectrum (70 eV) molecular ion at m/e = 1006, $[\alpha]_{578}^{25} -8.9^\circ$, $[\alpha]_{546}^{25} -11.7^\circ$, $[\alpha]_{436}^{25} -34.7^\circ$ (c 0.6, CHCl_3), pmr (100 MHz, CDCl_3), δ : 4.64 (s, Ar_2CH , 2H). CHCl

Anal. Calcd for $\text{C}_{74}\text{H}_{54}\text{O}_4$: C, 88.24; H, 5.40. Found: C, 88.02; H, 5.40.

To a solution of 15.8 g. of (SS)-109 in 160 ml. of dichloromethane was added 16 ml. of concentrated hydrochloric acid and 160 ml. of methanol. The resulting cloudy mixture was stirred for 11 hours, poured into ice water, the layers were separated, and the aqueous layer was extracted with dichloromethane.

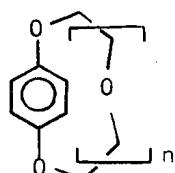
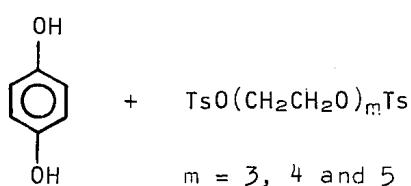
The combined organic extract was washed with water, dried and evaporated under vacuum to give 17 g. of (SS)-110, which was used in the next step without purification. It was dissolved in 300 ml. of tetrahydrofuran and mixed with 3.87 g. of potassium tert-butoxide. The solution was stirred for 10 minutes, and mixed with a solution of 2.76 g. of 2,6-bis-chloromethylpyridine in 100 ml. of tetrahydrofuran. The resulting solu-

tion was refluxed for 42 hours. An additional 1 g. portion of 2,6-bis-chloromethylpyridine and 1 g. of potassium tert-butoxide were added, and the reflux was continued for 24 hours. The solvent was evaporated, and the residue was chromatographed on 500 g. of alumina. After the column was washed with one liter of dichloromethane-pentane (1:9), product was eluted with 6 liters of dichloromethane-pentane (1:1) and 3 liters of dichloromethane-pentane (3:1) to give 5.3 g. (43%) of (SS)-111 as a foam, mass spectrum (70 eV) molecular ion m/e = 777, $[\alpha]_{589}^{25} -269^\circ$, $[\alpha]_{578}^{25} -283^\circ$, $[\alpha]_{546}^{25} -339^\circ$, $[\alpha]_{436}^{25} -798^\circ$ (c 0.54, CHCl_3). pmr spectrum (100 MHz, CDCl_3), δ : 4.57, 4.82 (s,s, $J_{AB} = 4\text{Hz}$, ArOCH_2 , 8H); 6.4–7.9 (complex m, ArH, 31H).

Anal. Calcd for $\text{C}_{55}\text{H}_{39}\text{O}_4\text{N}$: C, 84.92; H, 5.05. Found: C, 84.83; H, 5.18.

EXAMPLE 6

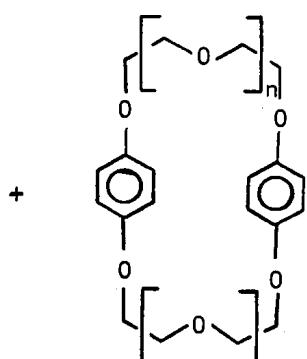
Preparation of p-Phenylene Unit-Containing Host Compounds



158, $n = 2$

160, $n = 3$

162, $n = 4$



159, $n = 2$

161, $n = 3$

163, $n = 4$

Procedure 1 is illustrated by the preparation of cycles 162 and 163. To a solution of 11.0 g. of hydroquinone and 24 g. of potassium tert-butoxide in 600 ml. of tetrahydrofuran under nitrogen was added 98.4 g. of pentaethyleneglycol ditosylate in 400 ml. of tetrahydrofuran. The solution was refluxed for 24 hours, the potassium tosylate was collected, the solvent was evaporated from the filtrate, and the residue was dissolved in dichloromethane. The solution was washed with water, dried, evaporated, and the residue was chromatographed on 1 Kg of alumina. First ether and then chloroform was used as eluting agent, and 62 moved slightly faster than 163. The fractions rich in 163 were evaporated, and 163 was crystallized to give 2.1 g. (7%) of product, m.p. 67°–69°, mass spectrum (70 eV) molecular ion at m/e = 624, pmr spectrum (100 MHz, CDCl_3), δ : 3.6–4.1 (m, $\text{OCH}_2\text{CH}_2\text{O}$, 40); 6.7 (s, ArH, 8H). Anal. Calcd for $\text{C}_{32}\text{H}_{48}\text{O}_{12}$: C, 61.52; H, 7.74. Found: C, 61.54; H, 7.54.

The fractions rich in 162 were combined with the mother liquors from the crystallization of 163, and the solvent was evaporated. The residue was subjected to a molecular distillation at 125° and 0.1 mm. to give 1.0 g. (6%) as an oil, mass spectrum (70 eV) molecular ion at m/e = 312, pmr spectrum (100 MHz, CDCl_3), δ : 3.2–3.8, 4.2 (m, CH_2CH_2 , 20H), 6.9 (s, ArH, 4H). Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_6$: C, 64.27; H, 7.74. Found: C, 61.53; H, 8.02.

Cycle 159 was similarly prepared, 7%, (except that triethyleneglycol ditosylate was employed), m.p. 96°–97°, mass spectrum (70 eV) molecular ion at m/e = 448, pmr spectrum (100 MHz, CDCl_3), δ : 3.6–4.0 (m, CH_2CH_2 , 24H), 6.7 (s, ArH, 8H).

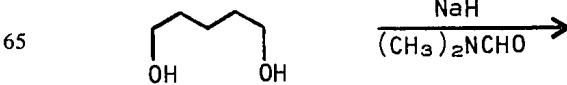
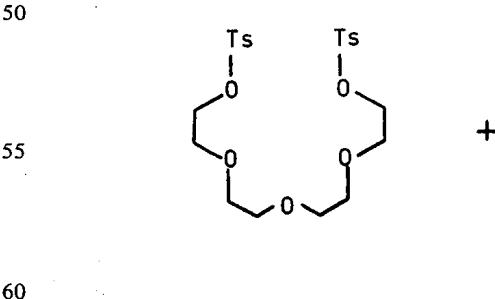
Anal. Calcd for $\text{C}_{24}\text{H}_{32}\text{O}_8$: C, 64.27; H, 7.19. Found: C, 64.29; H, 7.12.

Cycle 161 was similarly prepared, 8%, (except that tetraethyleneglycol ditosylate was employed), mass spectrum (70 eV) molecular ion at m/e = 536, pmr spectrum (100 MHz, CDCl_3), δ : 3.6–4.0 (m, CH_2CH_2 , 32H); 6.7 (s, ArH, 8H).

Anal. Calcd for $\text{C}_{28}\text{H}_{40}\text{O}_{10}$: C, 62.57; H, 7.51. Found: C, 62.93; H, 7.50.

EXAMPLE 7

Preparation of Pentamethylene Unit-Containing Host Compounds



PROCEDURE 2

This procedure records the synthesis of cycle (SS)-174a which contains the pentamethylene unit. To a solution of 3.0 g. of (SS)-22a (mixed with an equivalent amount of benzhydryl methyl ether) [see Method 1, Procedure 10] and 1.14 g. of potassium tert-butoxide in 200 ml. of tetrahydrofuran was added 2.02 g. of diethyleneglycol ditosylate. The clear solution was refluxed for 48 hours, evaporated in vacuum, and the residue was shaken with dichloromethane and water. The organic layer was dried, evaporated, and the residue was chromatographed on 200 g. of alumina. The benzhydryl methyl ether impurity (1.24 g.) was eluted with 1:9 dichloromethane-pentane. The cycle product was eluted in three one liter fractions of dichloromethane-pentane (3:7) to give 1.37 g. (71%) of 174a, obtained as a white foam, mass spectrum (70 eV) molecular ion at m/e = 710, $[\alpha]_{589}^{25} - 193^\circ$, $[\alpha]_{578}^{25} - 203^\circ$, $[\alpha]_{546}^{25} - 242^\circ$, $[\alpha]_{436}^{25} - 553^\circ$ (c 0.15, CDCl_3), pmr spectrum (100 MHz, CDCl_3), δ : 1.2 [m, $\text{CH}_2(\text{CH}_2)_3\text{CH}_2$, 6H]; 3.06 (m, CH_2OCH_2 , 4H); 3.7 (m, ArOCH_2 , 8H); 7.14 and 7.8 (m, m, ArH, Ar'H, 24H). Anal. Calcd for $\text{C}_{49}\text{H}_{42}\text{O}_5$: C, 82.79; H, 5.96. Found: C, 82.80; H, 5.88.

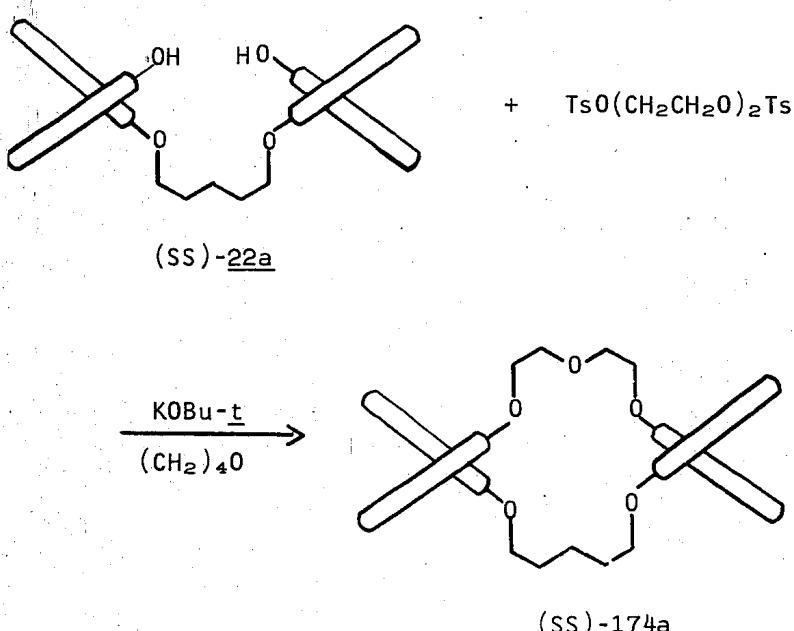
In the above examples, an (R)-binaphthyl unit may be substituted for an (S)-binaphthyl unit with analogous results.

EXAMPLE 8

General Complexing Power of Host Compounds as a Function of Structure, and Resulting Uses

The uses of the host compounds reported here depend on their abilities to complex and change the properties of guest compounds. The hosts are multiheteromacrocycles whose heteroatoms provide electron pairs turned inward toward their central hole. These electrons provide multiple binding sites for metal or alkylammonium cations (guest compounds) through

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pole-dipole interactions. By complexation, the polar cations are lipophilized by the "skin" of methylene and other hydrocarbon groups that form around the cations. Different structural units of the guest compounds play different roles. Incorporation of rigid heterocyclic or aromatic units reduces the number of conformations available to the host compounds. The shapes of such host compounds complexed and uncomplexed more resemble one another, and conformational ambiguity is reduced in both states. The rigid units further provide positions for attachment of arms terminating in functional groups that act as additional binding sites. Some of the heterocyclic units incorporated into the macrocycle serve as starting points for synthesis of a variety of other units that provide for complementary steric and electronic relationships between host and guest.

Selective association between organic host and guest compounds is a phenomenon central to nature's enzymatic, regulatory and transport systems. Knowledge of the variation in binding ability of the host compounds with variation in structure is important to predicting the uses to which the compounds of this invention are put. As a probe for binding ability, the association constants, K_a , were determined in chloroform for tert-butylammonium thiocyanate and representatives of the multiheteromacrocycles of this invention. Equation (1) defines the association constant. The procedure used is as follows.

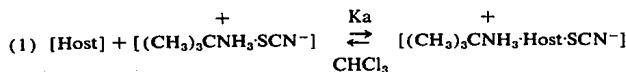


TABLE 1

Comp. No.	Host Structure	Association Constants in Chloroform Between Hosts and tert-Butylammonium Thiocyanate		
		No. atoms macro- ring	$K_a(M^{-1})$	
24°	0°			
172	$\text{CH}_3(\text{OCH}_2\text{CH}_2)_5\text{OCH}_3$	0	40	30
173	$\text{A}=\text{CH}_2\text{CH}_2, a=6, b=0$	18	7.5×10^{-5}	8.9×10^{-5}
174	$\text{A}=\text{CH}_2\text{CH}_2, a=4, \text{B}=(\text{CH}_2)_5, b=1$	18	5.0×10^2	6.5×10^2
96	$\text{A}=\text{CH}_2\text{CH}_2, a=4, \text{B}=\text{m-CH}_2\text{C}_6\text{H}_4\text{CH}_2, b=1$	18	1.5×10^3	2.0×10^3
175	$\text{A}=\text{CH}_2\text{CH}_2, a=5, \text{B}=\text{o-C}_6\text{H}_4, b=1$	18	1.4×10^5	2.8×10^5
176	$\text{A}=\text{B}=\text{o-C}_6\text{H}_4(\text{OCH}_2\text{CH}_2)_2, a=b=1$	18	1.3×10^4	1.5×10^4
177	$\text{A}=\text{B}=\text{Cyclohexane ring substituted with } (\text{OCH}_2\text{CH}_2)_2, a=b=1$	18	9.5×10^4	2.5×10^5
71	$\text{A}=\text{Cyclopentane ring substituted with } \text{O-CH}_2\text{CH}_2, a=1, \text{B}=\text{CH}_2\text{CH}_2, b=4$	18	1.1×10^6	6.6×10^5
45	$\text{A}=\text{Cyclohexene ring substituted with } \text{O-CH}_2\text{CH}_2, a=1, \text{B}=\text{CH}_2\text{CH}_2, b=4$	18	4.8×10^4	3.3×10^4
46	$\text{A}=\text{Cyclopentene ring substituted with } \text{O-CH}_2\text{CH}_2, a=2, \text{B}=\text{CH}_2\text{CH}_2, b=2$	18	4.1×10^3	4.0×10^3

A 0.14 M solution of host in CDCl_3 (0.6 ml.) was shaken at 24° or 0° with 1.6 ml. of 0.1M $(\text{CH}_3)_3\text{CN}^+\text{H}_3\text{SC}^- \text{N}$ in D_2O (scale A), with 0.6 ml. of 0.4M salt (scale B) or with 0.3 ml. of 1.0M salt (scale C). With 100 MHz pmr spectra, the relative concentrations of guest (CH_3 protons) to host (all protons) in CDCl_3 were measured ($\pm 2\%$). The amount of host that dissolved in D_2O was $\gtrsim 0.5\%$ of the total used except for 18-crown-6 (173)[J. Amer. Chem. Soc., 89, 2495 (1967)]. The value of K_a for compound 173 was corrected accordingly. The absolute amounts at equilibrium of salt extractable at 24° and 0° were determined by large scale experiments in the absence of host at initial guest concentrations of scales A, B and C. Values of K were calculated from equation (2) for each scale in which: $[\text{BX}]_{\text{D}_2\text{O}}$ and $[\text{BX}]_{\text{CDCl}_3}$ were equilibrium concentrations of salt in the absence of host; R is the ratio of concentrations of guest to host in CDCl_3 at equilibrium; $[\text{BX}]_i$ is the initial salt concentration in D_2O ; $[\text{H}]_i$ is the initial host concentration in CDCl_3 ; V_{CDCl_3} and $V_{\text{D}_2\text{O}}$ are the volumes of CDCl_3 and D_2O . Scales A and B were corrected to scale C by multiplying K values for scales A and B by 1.5 to give K_a values. This

$$(2) K = \frac{[\text{BX}]_{\text{D}_2\text{O}}^2 R}{[\text{BX}]_{\text{CDCl}_3}(1-R) \{ [\text{BX}]_i - [\text{H}]_i R(V_{\text{CDCl}_3}/V_{\text{D}_2\text{O}}) \}^2}$$

factor ($\pm 20\%$) represents an average of the factors by which the K's of several hosts common to scales A and C or B and C differed. The values of K_a for compounds 159, 161 and 163 were not corrected for the fact that they contain two sets of binding sites. Table 1 reports the results.

TABLE 1-continued

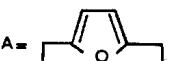
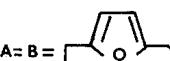
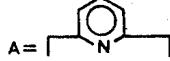
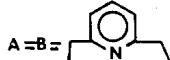
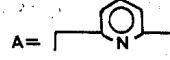
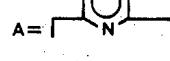
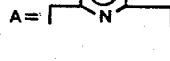
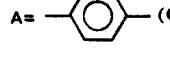
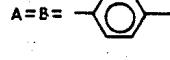
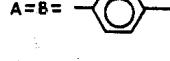
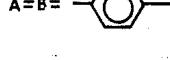
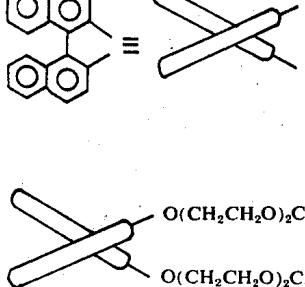
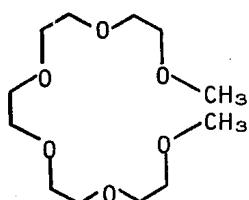
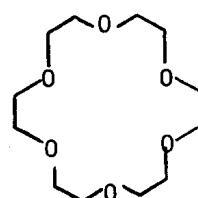
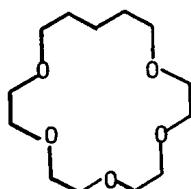
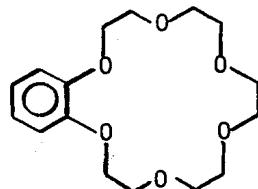
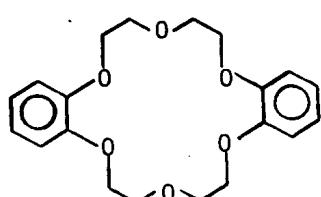
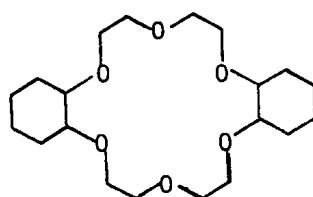
Comp. No.	Host Structure	Association Constants in Chloroform Between Hosts and tert-Butylammonium Thiocyanate		No. atoms macro- ring	$K_a(M^{-1})$ 24°	0°
48	 , a=3, b=0			18	3.1×10^2	4.0×10^2
47	 , a=b=1			18	8.0×10^1	7.0×10^1
11	 , a=1, B=CH ₂ CH ₂ , b=4			18	1.4×10^6	3.0×10^6
12	 , a=b=1			18	4.2×10^5	1.2×10^6
15	 , a=3, b=0			18	6.6×10^5	2.0×10^6
16	 , a=2, b=0			12	2.4×10^2	8.0×10^1
17	 , a=4, b=0			24	2.1×10^2	1.1×10^2
162	 , a=1, b=0			20	<40	<30
163	 , a=b=1			36	5.0×10^1	3.0×10^1
161	 , a=b=1			30	8.0×10^1	4.0×10^1
159	 , a=b=1			24	<40	<30
				0	5.0×10^1	4.0×10^1

TABLE 1-continued

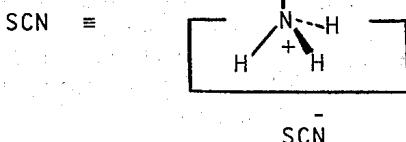
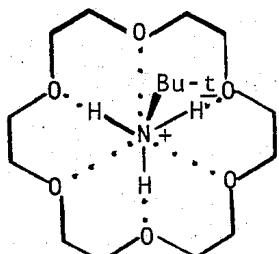
Comp. No.	Host Structure	Association Constants in Chloroform Between Hosts and tert-Butylammonium Thiocyanate		
		No. atoms macro- ring	Ka(M ⁻¹) 24°	Ka(M ⁻¹) 0°
179		20	4.2×10 ²	6.0×10 ²
180		22	<40	<30

Compounds 173 and 175-177 were included for 25 study (see Example 7, Procedure 1). Compounds 178-180 were previously prepared, (U.S. patent application Ser. No. 346,089, filed Mar. 29, 1973). Compounds 173 and 175-177 have been reported, [J. Amer. Chem. Soc., 89, 2495 (1967)], and 174 were prepared specifically for this

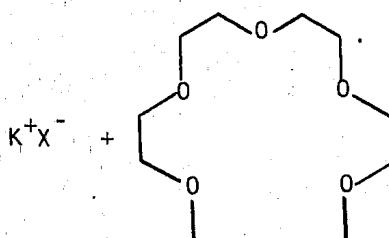
172173174175176177

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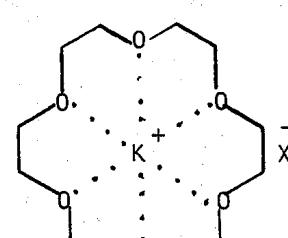
Of the cycles of Table I, 173 has the highest symmetry. The reasonable structure for its complex with tert-butylammonium thiocyanate is 181, in which three hydrogen bonds hold host to guest in a rigid arrangement. Complex 181 resembles 182, in which a potassium ion is complexed by 173 [J. Amer. Chem. Soc., 89, 2495 (1967)].



181



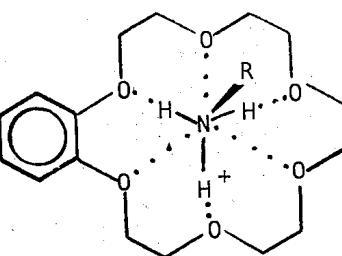
173



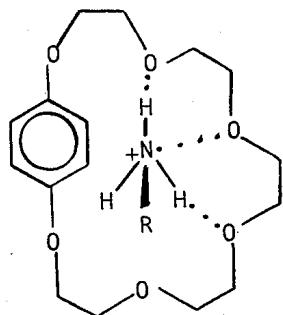
182

The data of Table I support the mode of complexation envisioned in 181, and provides indirect evidence for the structures of the other complexes as well. (1) In

whereas in 175, all six oxygens are available. Compound 175 is the better host by a factor of $>3.5 \times 10^3$ (compare the K_a values).



Complex of 175



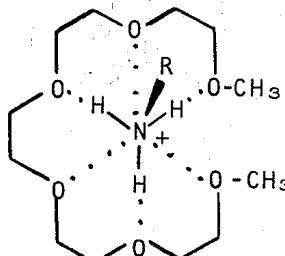
Complex of 162

compound 162, the aryl oxygens are remote from one another because of their attachment to a

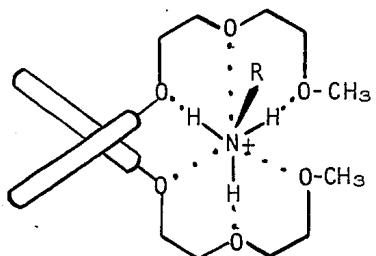


unit. In isomeric compound, 175, the aryl oxygens are held close to one another by the

(2) Cycle 173, whose six oxygens are well organized for binding, possesses a K_a value a factor of $>10^4$ higher than that of its open-chain counterpart, 172. Clearly, high molecular organization prior to complexation increases the tendency to complex. Furthermore, cyclic binaphthyl compound

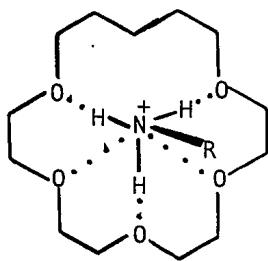
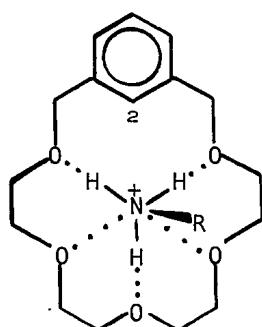


Complex of 172



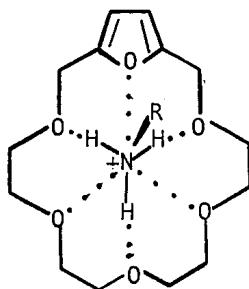
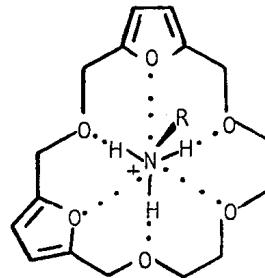
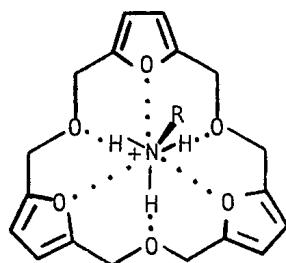
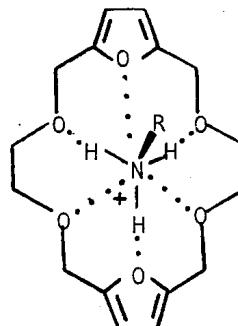
Complex of 178

179 has a K_a about 10 times higher than that of its non-cyclic counterpart, 178. Again the effect of organization of binding sites prior to complexation is visible. 3) Substitution by a methylene for one of the oxygens of 173 as in 174 reduced the constant by a factor of 1.5×10^3 . Molecular models of the complexes of 173 and 174 indicate them to be sterically comparable. The difference in their binding constants appears to be due to the difference between five and six binding sites. Thus the non-hydrogen bonded electron pairs of the alternate oxygens stabilize electrostatically the N^+ , which molecular models (CPK) indicate are very close in the complex of 181. (4) Substitution of a m-xylyl group as in cycle 96 for one of the $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$ groups of 173 reduced the constant by a factor of about 500.

Complex of 174Complex of 96

Again the absence of the sixth oxygen in 96 is reflected in its binding constant, but the effect is less pronounced than in that of 174. Molecular models of 35

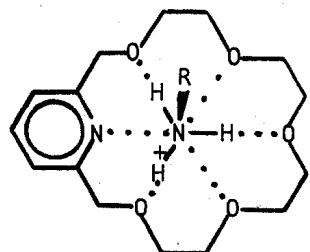
of the furan systems. When two furan units are 180° from one another as in the complex of 46, K_a is about 50 times lower than when they are 120° as in that of 47. In

Complex of 45Complex of 47Complex of 48Complex of 46

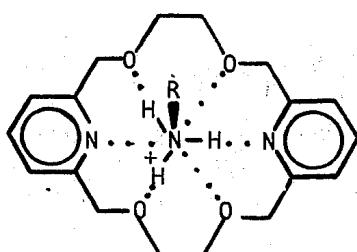
the complex of 96 indicate the plane of the aryl is tilted somewhat relative to that of the best plane of the oxygens. This geometry places substituents attached to the 2-position of the aryl in complexes such as 96 directly under the complexed cation. (5) Successive substitution of o-phenyl for ethylene units of 173 as in the complexes of 175 and 176 reduced the constant by a factor about 2×10^3 for the first and by an additional factor of >8 for the second. The aryl inductive and delocalization effects on the electron pairs of the oxygens are visible in these results. (6) Successive substitution of 2,5-furandimethyl for $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$ units of 173 as in the complexes of 45, 46 and 48 reduced the constant by factors of 12 to 16 per unit. These effects probably are due to electron-delocalization from oxygen into the furan systems, and to the inductive effect

the complex of 47, three hydrogen bonds can go to the more basic three non-furanyl oxygens. In the complex of 46, one hydrogen bond must involve a relatively non-basic furanyl oxygen. (7) Substitution of 2,6-pyridinedimethyl for the $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$ units of 173 as in the complexes of 11, 12 and 15 produces little change in K_a . In the complex of 12, one of the hydrogen bonds must go to the pyridyl nitrogen

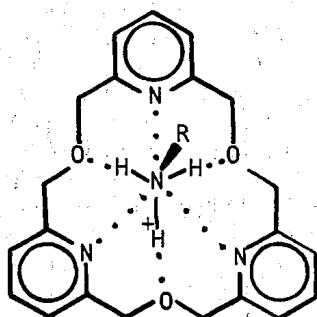
bind in these ways. Although the hydrogen bonds in the complexes of 11 and 15 are drawn to oxygen, molecular models indicate they could be drawn equally well to nitrogen. The pyridyl rings are slightly tilted out of the best plane of the heteroatoms in models of the complexes, and the complex is superbly well organized. When the macroring is reduced to 12 atoms as in 16 or expanded to 24 as in 17, the K_a values are reduced by



Complex of 11



Complex of 12

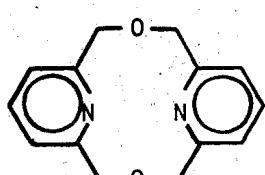


Complex of 15

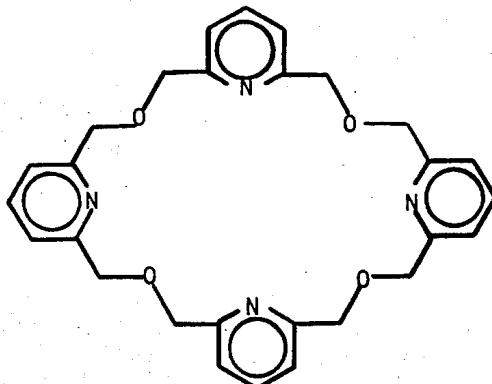
electron pair ($\text{N}^+ \cdots \text{H} \cdots \text{N}$), and one pyridyl nitrogen electron pair must electrostatically stabilize the ion by near contact ($\text{N}^+ \cdots \text{N}$). Apparently oxygen and pyridyl nitrogen are nearly equivalent in their abilities to

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factors of about 10^4 . The organization of three hydrogen bonds are three pole to dipole binding forces appears critical to strong binding. (8) Introduction of a

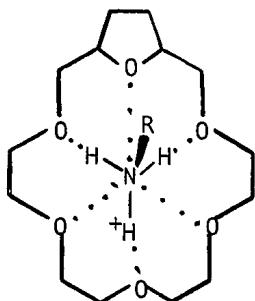


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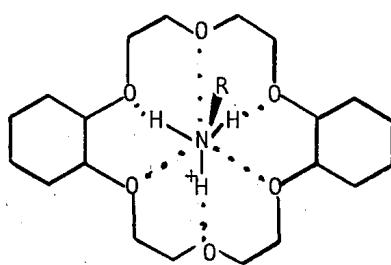


17

tetrahydro-2,5-furandimethyl in place of a $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$ unit of 173 as in the complex of 71 produced little change in K_a . However, substitution of two 1,2-cyclohexyl for two $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$ units of 173 as in the complex of 177 reduced K_a by about a factor of 10. (9) The binding constants of 163 and 161 are close to one another, and are higher by a



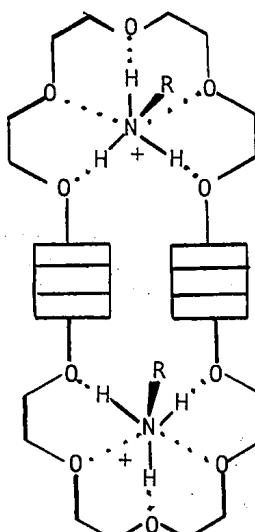
Complex of 71



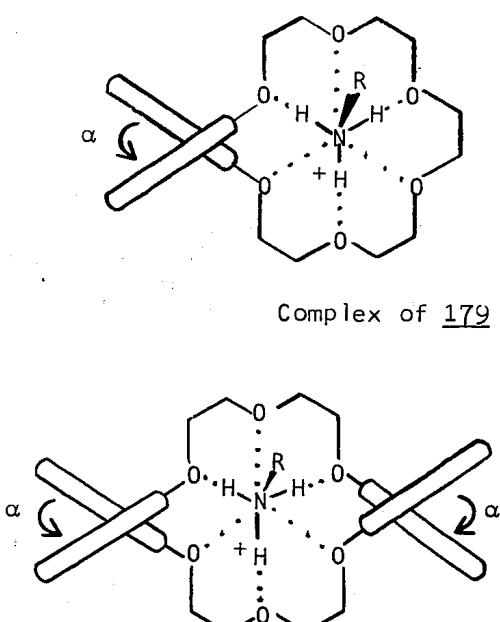
Complex of 177

factor of 1.5 to 2 than that of 172 or 159. Molecular models of the complex of 161 appears the best organized of the four in spite of only five oxygens being available at each of its two binding loci. The thickness of the benzene rings prevents all six oxygens of each end of the ethyleneoxy chains of 163 from completely surrounding the NH_3^+ group, and models suggest that only five are used. (10) Substitution of binaphthyl

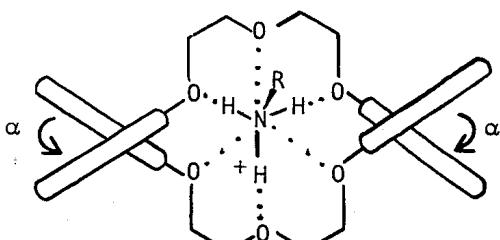
25 structural variety are available for designing host molecules for a variety of purposes. (11) A temperature lowering of 24° produced a maximum increase in binding constant by a factor of 3(pyridyl systems), and a maximum decrease by a factor of 3(pyridyl systems). Thus the large changes of K_a with changes in structure appear to be more associated with enthalpy than with entropy changes upon complexation.



Complex of 161



Complex of 179



Complex of 180

for ethylene units of 173 as in the complexes of 179 and 180 reduced the constant by a factor of 2×10^3 for the first, and by an additional factor of > 8 for the second. Unlike most of the other units, the binaphthyl can locate its attached oxygens either as close together as an ethylene unit, or considerably further apart, depending on the value of the dihedral angle, α , between the planes of the two naphthalene rings. This additional

60 Others have demonstrated that multiheteromacrocycles such as 175-177 complex Group I and II, and silver cations [J. Amer. Chem. Soc., 93, 600 (1971)] and lipophilize them [J. Amer. Chem. Soc., 89, 7017 (1967); ibid., 92, 386, 391 (1970); ibid., 95, 3023 (1973)]. As with 175-177, the compounds of this invention complex and lipophilize selectively ammonium, alkylammonium, and metal cations of lithium,

sodium, potassium, rubidium, cesium, silver, magnesium, calcium, strontium, zinc, lead, manganese, cobalt, iron, copper, chromium, mercury and molybdenum.

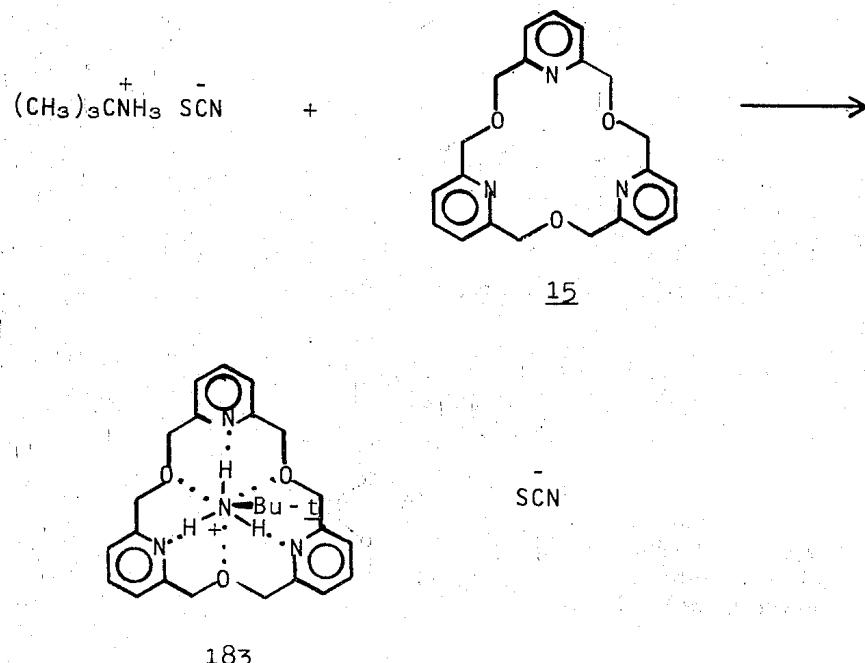
As with the compounds reported in the above references, the complexing ability of the compounds reported here varies with: (1) the match between hole diameter of host and diameter of ionic guest; (2) the match in stable arrangement of heteroatoms of the uncomplexed host, and the most stable ligand arrangement for the ionic guest; (3) the match in heteroatom type of the host, and the most stabilizing ligand type for the ionic guest; (4) in the appropriate cases, the match between negative charges located in the host and positive ions in the guest.

Selective complexation and lipophilization of alkylammonium and metal cations provides the compounds of this invention with a variety of uses that depend on complexed ions having different properties than non-complexed. The uses are: antibiotics, or antibiotic potentiators; drug delivery systems; fermentation aids; fungicides; herbicides; agents for delivery of ions in and out of cells; antielectrostatic agents; antiscaling agents; agents that catalyze more complete combustion; electrolytic agents; antifoaming agents; desalination agents; nuclear magnetic resonance shift reagents; gelling agents; dispersing agents; anticorrosion agents; asymmetric reagents and catalysts for causing asymmetric induction during reactions; resolving agents for amines, amino acids and their derivatives; agents for introduction of trace metals into living systems in biologically useful forms; agents for aiding in the separation of elements that are products of atomic piles; agents for isotope fractionation; sterically and electronically tailored compounds for transition metal catalysis in lipophilic media; agents for dispersing metal ions evenly in gels used in photographic processes.

EXAMPLE 9

Specific Examples of Complexing Power of Multiheteromacrocycles

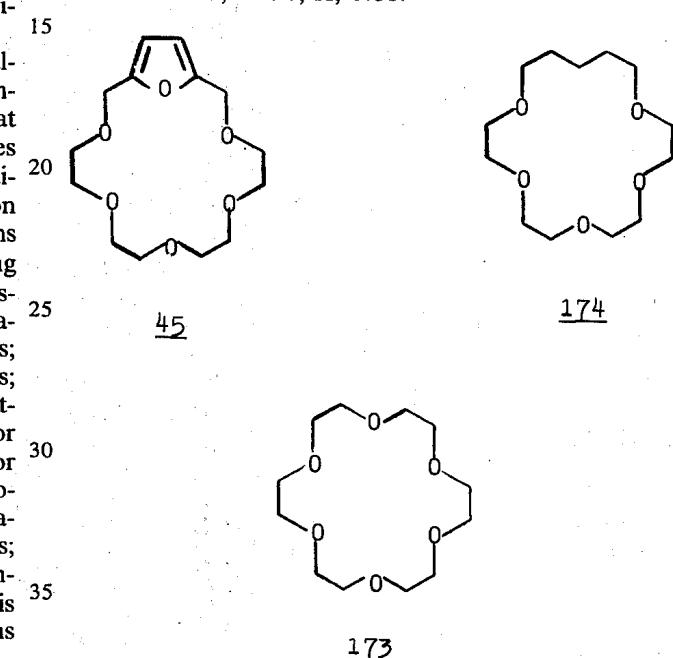
Examples are provided here of the formation of specific complexes between multiheteromacrocycles and several types of host compounds.



86 PROCEDURE 1

Procedure 1 illustrates how crystalline one-to-one complexes between primary amine salts and multiheteromacrocycles can be prepared. For example, to a solution of 45 mg. of 15 in 1 ml. of chloroform was added 15 mg. of tert-butylammonium thiocyanate. A few drops of tetramethylsilane were added, and the mixture was cooled to 0°. The crystals that separated (48 mg. of 83%) gave m.p. 198°-201° (dec.), mass spectrum (70 eV), parent ion m/e = 363 (molecular ion of 15).

Anal. Calcd for $\text{C}_{26}\text{H}_{33}\text{N}_5\text{O}_3\text{S}$: C, 63.01; H, 6.71. Found: C, 62.90; H, 6.88.



PROCEDURE 2

Procedure 2 illustrates how crystalline one-to-one complexes of multiheteromacrocycles such as 45, 174 and 173 and dimethyl acetylenedicarboxylic ester can be formed. A mixture of 1.0 g. of 45, 1.5 g. of dimethyl

acetylenedicarboxylic ester and 5 ml. of benzene was stirred at 25°. A white crystalline solid separated, 1.1 g. (74%), m.p. 72°–73°, mass spectrum (70 eV) molecular ion of 45 m/e = 286, pmr (100 MHz, CDCl_3), δ : 3.57 (s, $\text{OCH}_2\text{CH}_2\text{O}$, 16H); 3.78 (s, CH_3 , 6H); 4.44 (s, $\text{C}-\text{CH}_2\text{O}$, 4H); 6.18 (s, ArH, 2H).

Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{O}_{10}$: C, 56.07; H, 6.59. Found: C, 56.02; H, 6.67.

This complex undergoes molecular distillation from its melt, and solid complex accumulates on the condenser. When submitted to gel permeation chromatography in tetrahydrofuran as solvent, the complex separates into two overlapping components. When submitted to the extraction-complexation experiments with $(\text{CH}_3)_3\text{CN}^+\text{H}_3\text{SCN}^-$ (Example 8) at both 24° and 0°, the complex gave results identical to those given by 45 alone. The pmr spectrum in CDCl_3 of 45 alone and its complex are almost identical except for the presence in that of the latter of the CH_3 signal.

Similarly 174 formed a one-to-one complex with dimethyl acetylenedicarboxylic ester. A solution of 1.0 g. of 174 was mixed with 1.0 g. of dimethyl acetylenedicarboxylic ester (heat was evolved). The resulting solution deposited crystals, which were triturated with pentane to give complex, which after drying at high vacuum and 25° for 48 hours gave 1.2 g. of complex, m.p. 63°–64°, pmr spectrum (60 MHz, CDCl_3), δ : 1.53 (broad s, $\text{CH}_2(\text{CH}_2)_3\text{CH}_2$, 6H); 3.53, 3.60 (s, s, OCH_2 , 2OH); 3.78 (s, OCH_3 , 6H).

Anal. Calcd for $\text{C}_{19}\text{H}_{32}\text{O}_9$: C, 56.42; H, 7.98. Found: C, 56.44; H, 8.09.

Both 174 and dimethyl acetylenedicarboxylic ester are non-crystalline. The fact that heat is evolved when they are mixed indicates molecular complexation occurs in solution as well as in their crystalline state.

Similarly, 173 formed a one-to-one complex with dimethyl acetylenedicarboxylic ester. A solution of 0.40 g. of about 85% pure (pmr) 173 and 0.40 g. of dimethyl acetylenedicarboxylic ester in 5 ml. of benzene was allowed to stand for 2 days at 25°. The crystals that separated were collected, 0.32 g. (50%), m.p. 100°–101°. An osmometric molecular weight of an 0.02 M solution of the complex in chloroform gave an apparent molecular weight of 201, as compared to a molecular weight calculated for the complex of 406. Thus the complex is dissociated in chloroform at this concentration and temperature.

Anal. Calcd for $\text{C}_{18}\text{H}_{30}\text{O}_{10}$: C, 53.19; H, 7.44. Found: C, 53.27; H, 7.53.

The X-ray crystal structures of the complex of 173 has been determined. The acetylene is not threaded through the hole of 173, nor are the ester groups coordinated with the ether oxygens of 173. Rather, the methyl of the ester group is inserted into the hole of 173 to form two hydrogen bonds of the unusual sort, C-H . . . O, and one unusual



electrostatic interaction per methyl group. These two types of binding are indicated by the fact that the intermolecular distances between the indicated atoms are about 0.3 Å units shorter than the usual van der Waals distances.

PROCEDURE 3

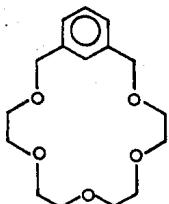
Dry macroreticular resin [Amberlyst-15, polystyrenesulfonic acid, Rohm and Hass, 40–60 mesh, average pore diameter, 200–600 Å] saturated with H_3O^+ , Na^+ , K^+ , NH_4^+ or Cs^+ (25–50 mg.) was mixed with 5 to 12×10^{-5} M solution of cycle in dry dichloromethane. The solution's optical density (λ 250–340 mm) was measured before mixing and monitored until constant while the mixture was shaken at 25°. For each cycle and cation, the resin became saturated with cycle to an extent ($\pm 5\%$) independent of cycle concentration in dichloromethane. Saturation constants are defined as $K_s = 100 \times (\text{moles absorbed cycle}) / (\text{moles cation present})$, and provide a measure of the complexing power of each cycle for each cation at the resin-solvent interface. Table II records the results. The syntheses of compounds 175, 176 and 184 have been reported [J. Amer. Chem. Soc., 89, 2495 7017 (1967)]. Tribenzylamine is included for comparative purposes with resin- H_3O^+ , $K_s = 18.6$. The constants for 175, 176 and 184 have been reported [J. Amer. Chem. Soc., 95, 2691 (1973)].

TABLE II

Host	Saturation Constants (K_s) For Host Molecules in Dichloromethane Against Resin- SO_3^-M^+ at 25°				
	H_3O^+	Na^+	K^+	NH_4^+	Cs^+
175	3.6	1.1	1.3	1.05	0.69
184	1.3	1.2	0.69	0.43	0.19
176	1.35	0.89	0.97	0.65	0.40
60	24.5	1.26	1.29	1.73	0.75

TABLE II-continued

Host	Saturation Constants (K_s) For Host Molecules in Dichloromethane Against Resin- $\text{SO}_3^- \text{M}^+$ at 25°				
	H_3O^+	Na^+	K^+	NH_4^+	Cs^+
	4.56	4.0	1.76	0.91	0.00



96

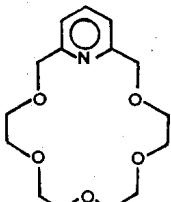
These data indicate that host compound 11 in this test is a better complexer of H_3O^+ , Na^+ , NH_4^+ and Cs^+ than reference compounds 175, 184 or 176, and a comparable or better complexer of K^+ . Host compound 96 is a better complexer of H_3O^+ , Na^+ , K^+ than reference compounds 175, 184 and 176. Toward NH_4^+ , 96 is between 175 and 184, and toward Cs^+ is the poorest complexer of the five cycles.

PROCEDURE 4

In procedure 4, the pKa values of the pyridine-containing cycles are reported, and are compared with those of pyridine and of 2,4,6-trimethylpyridine [Pure and Applied Chemistry, Suppl. (1965) report pKa values of 5.2 for pyridine and 7.4 for 2,4,6-trimethylpyridine]. Solutions of about 0.1 milliequivalent of host in 40 ml. of water at 20° were titrated with 0.10 ± 0.01 N LiOH and 0.10 ± 0.01 N HCl solutions. The pH of the solutions was monitored with a glass electrode and pH meter. The pKa values were determined by graphic analysis of a plot of pH vs ml. of added titrant, and are recorded in Table III.

TABLE III

Compound	Values of pKa of the Conjugate Acids of Pyridine-Containing Host and Reference Compounds		
	Acid (A) or Base (B) titration	pKa	average
	A	4.75	
	B	4.75	4.8
	A	4.85	
	B	4.70	



11

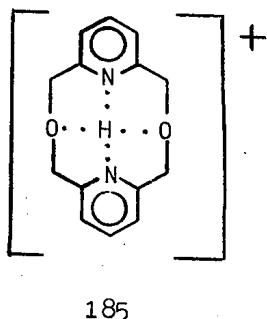
TABLE III-continued

Compound	Values of pKa of the Conjugate Acids of Pyridine-Containing Host and Reference Compounds		
	Acid (A) or Base (B) titration	pKa	average
10	B	5.2, 3.7	
	A	5.4, 3.6	5.3, 3.6
	B	5.4, 3.7	
	A	5.3, 3.6	
12			
20	B	4.9, 3.5	
	A	5.5, 3.6	5.3, 3.7
	B	5.5, 4.0	
	A	5.2, 3.8	
15			
16	B	7.8	
	A	7.9	
	B	7.8	
	A	7.85	7.9, <3
	B	8.0	
17			
55	B	4.5, >3	
	A	5.0, >3	4.8, >3
60			
	B	5.1	5.15
	A	5.0	
	B	7.4	7.4
	A	7.4	

The pKa values of 11, 12, 15 and 17 are remarkably close together (4.8–5.3), a fact that indicates that the microscopic environment of the monoprotonated compounds are rather similar. The other pyridine units or ether oxygens of the compound seem to play little role

in solvating the N⁺-H species, and in inhibiting water from solvating it. These pKa values are close to that of pyridine (5.2) itself. The diconjugate acids of 12, 15 and 17 have pKa values of between 3 and 4.

In contrast, the monoconjugate acid of 16 was 7.9, and that of the diconjugate acid of 16 was well below 3 (not measurable). Clearly the monoconjugate acid of 16 is unusually stabilized. CPK molecular models of the monoconjugate acid of 16 suggest that its structure is 185, in which the one proton is shared by two nitrogens and two oxygens of 16. Thus 16 is a stronger base than 2,4,6-trimethylpyridine.



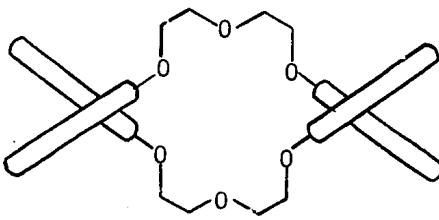
whose three methyl groups are electron releasing (considerably more than the OCH_2 groups of the cycles). Since the nitrogens of 16 are far too hindered to be nucleophilic, and the pK_a of 185 is close to physiological pH, 16 like imidazole is a good general basic catalyst for reactions carried out under physiological conditions.

EXAMPLE 10

Chiral Recognition in Selective Complexation by Host Compounds of Enantiomers of Amino Ester Salts

Procedures were developed previously (application Ser. No. 346,089, filed Mar. 29, 1973) to use compound (SS)-180 and its analogues to resolve amino esters through chiral recognition and selective complexation in solution [see also *J. Amer. Chem. Soc.*, 95, 2692 (1973)]. The technique involves distributing the two enantiomers of racemic amino ester hexafluoro-

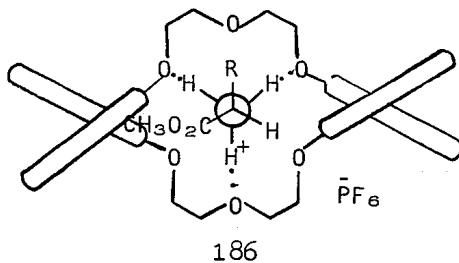
phosphate salts between a chloroform phase containing host compound, and an aqueous phase containing NaPF₆ or LiPF₆ as a salting out agent. The relative amounts of host and guest at equilibrium in each phase were



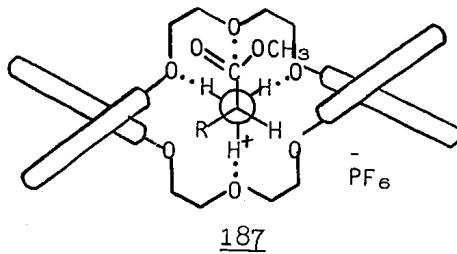
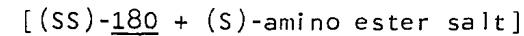
(SS)-180

determined by pmr spectral measurements. The absolute configurations and maximum rotations of all hosts and guests have been previously determined.

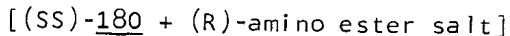
The procedure was as follows. Enough racemic amine hexafluorophosphate was dissolved in D₂O, 1.0 to 4.0 M in LiPF₆ (at pH ~ 4 to 5) to give a 1 M solution of amine salt. This solution was shaken at the desired temperature with solutions of optically active host compounds (about 0.2 M) in CDCl₃. The pmr spectra of each layer was taken, and no host compound was detected in the aqueous layer. The layers were separated, the amines were isolated from each layer, and their optical purities and configurations determined. The results provided enantiomer distribution constants, EDC = D_A/D_B, where D_A is the distribution coefficient of the enantiomer more complexed in CDCl₃, and D_B is that of the enantiomer less complexed. Both enantiomers of amino esters were found to complex (SS)-180, and the two diastereomeric structures formulated were referred to as the three-point binding model (186) and the four-point binding model (187). In the latter, besides the three hydrogen bonds, the complex is held together by a carbonyl-to-ether oxygen dipole-to-dipole interaction.



Three-Point Binding Model



Four-Point Binding Model



Optically pure compounds (SS)-19, (SS)-23, (SS)-23a, (SS)-108, (SS)-111, (SS)-174a and (SS)-108 were examined similarly, for their complexing power (how much amino ester salt do they draw into chloroform?), for their chiral recognition (how much greater than unity are their EDC values), and for the direction of their chiral recognition (which diastereomeric complex is the more stable, that represented by the three-point binding model, or that represented by the four-point binding model?). Table IV records the results. The values reported previously in [application Ser. No. 346,089 filed Mar. 29, 1973], for compound (SS)-180 are included for purposes of comparison.

The results clearly indicate that whereas (SS)-174a and (SS)-108 are too poor at complexing to be useful for

purpose. By multiplate processes (countercurrent or liquid-liquid chromatographic), or by attachment of the host compounds to solid supports [as with (SS)-180, see application Ser. No. 346,089 filed Mar. 29, 1973] employed in solid-liquid chromatography, the latter compounds can be used for total resolution of primary amine racemates, amino acids, amino esters, amino amides, and peptides. Analytical reagents for determination of absolute configuration or determining optical purity (e.g. optically active "shift reagents" for use in pmr spectra) are further uses to which the enantiomers of 23, 23a, 111 and 19 are put.

Compounds 23, 23a, 111 and 19 are chiral, and contain the basic pyridyl function in a highly shaped environment. Pyridine unit-containing compounds catalyze a variety of reactions, such as acyl transfers, elimination reactions, allylic rearrangements, oxidations and reductions. These compounds in an optically active

TABLE IV

Binding Power, Enantiomer Distribution Constants (EDC), and Direction of Chiral Recognition in Molecular Complexation

A	B	No.	R of R-CH-CO ₂ CH ₃ NH ₃ PF ₆	T °C	pH D ₂ O	[Guest]/ [Host]	Applicable Model	EDC
		(SS)-180	C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ (CH ₃) ₂ CH	-5 -10 -14 -10	4 4 4 4	0.9 0.9 0.9 0.9	three-point three-point three-point four-point	3.0 2.8 3.1 1.5
		(SS)-174a	C ₆ H ₅	-15	4	<0.1	—	—
		(SS)-108	C ₆ H ₅	-15	4	<0.1	—	—
		(SS)-23	C ₆ H ₅ (CH ₃) ₂ CH	-10 -10	4.3 4.4	1.0 0.8	three-point three-point	1.7 1.24
		(SS)-23a	C ₆ H ₅ (CH ₃) ₂ CH	-13 -16	5.2 5.2	0.38 <0.1	three-point —	1.35 —
		(SS)-19	C ₆ H ₅ (CH ₃) ₂ CH	-16 -16	5 5	0.7 0.3	three-point three-point	2.0 1.3

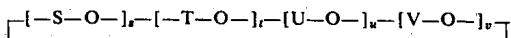
optical resolution of amino esters, compounds (SS)-23, (SS)-23a, (SS)-111 and (SS)-19 provide large enough EDC factors (1.24 to 2.0) to make them useful for this

state, catalyze reactions of one enantiomer of a racemate more than the other, and asymmetric induction results. Thus enantiomers of racemates can be caused

to react selectively to form optically active products. Conversely the reactions of reagents that react to form a new asymmetric center can be catalyzed by these optically active host compounds, and provide products in which one enantiomer predominates. Reductions of unsymmetrical ketones to secondary alcohols with aluminum or borohydride reagents complexed to 23, 23a, 111 or 19 provide examples. In those compounds that contain an (SS)-binaphthyl unit performs the same kinds of tasks.

I claim:

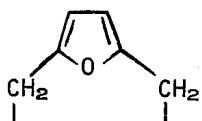
1. A compound of the formula



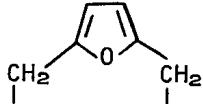
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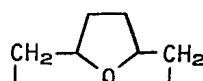
selected from the group consisting of a compound where $-S-$ is



or



or

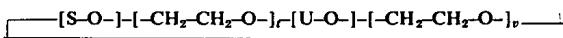


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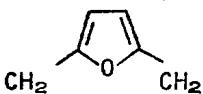
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t is 2 through 7.

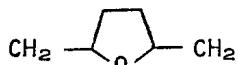
4. A compound according to claim 1 having the formula



30 where $-S-$ and $-U-$ are



or



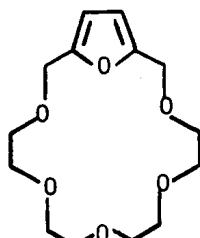
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t is 1 through 6, and
 v is 0 through 6.

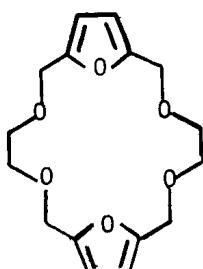
5. A compound according to claim 3 having the formula:



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6. A compound according to claim 4 having the formula:



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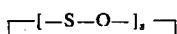
each of T and V is $-CH_2-CH_2-$,

s and u are 1,

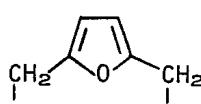
t is 1 through 6,

v is 0 through 6.

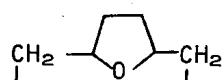
2. A compound according to claim 1 having the formula:



where $-S-$ is



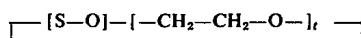
, or



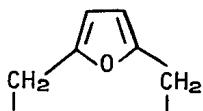
, and

s is 2 through 4.

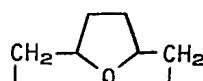
3. A compound of the formula:



where $-S-$ is



or

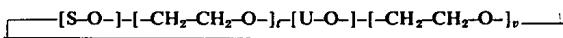


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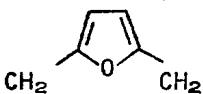
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t is 2 through 7.

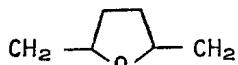
4. A compound according to claim 1 having the formula



30 where $-S-$ and $-U-$ are



or



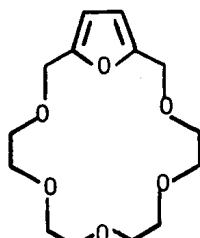
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t is 1 through 6, and
 v is 0 through 6.

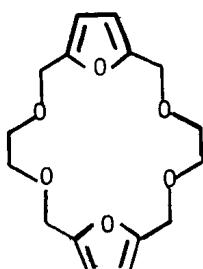
5. A compound according to claim 3 having the formula:



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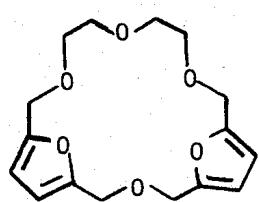
6. A compound according to claim 4 having the formula:



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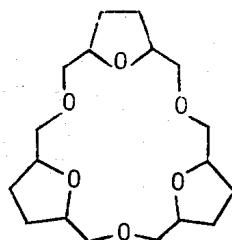
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7. A compound according to claim 4 having the formula:

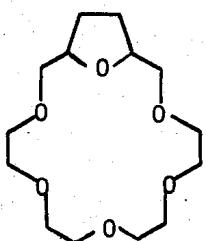


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9. A compound of the formula



8. A compound according to claim 3 having the formula:



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(71) Demandeur/Applicant:
FURANIX TECHNOLOGIES B.V., NL

(72) Inventeur/Inventor:
GRUTER, GERARDUS JOHANNES MARIA, NL

(74) Agent: GOWLING LAFLEUR HENDERSON LLP

(54) Titre : 2-(ALCOXYMETHYL) FURANES 5-SUBSTITUES
(54) Title: 5-SUBSTITUTED 2-(ALKOXYMETHYL)FURANS

(57) Abrégé/Abstract:

The present invention concerns a method for the manufacture of a 5-substituted 2- (alkoxymethyl)furan (or a mixture of such furans) by reacting a starting material comprising at least a 5-substituted furfural with hydrogen in the presence of an alcohol and a catalyst system.



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(71) Applicant (*for all designated States except US*): **FURANIX TECHNOLOGIES B.V.** [NL/NL]; Zekeringstraat 29, NL-1014 BV Amsterdam (NL).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): **GRUTER, Gerardus, Johannes, Maria** [NL/NL]; Asterkade 14, NL-2106 BA Heemstede (NL).



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(54) Title: 5-SUBSTITUTED 2-(ALKOXYMETHYL)FURANS

(57) Abstract: The present invention concerns a method for the manufacture of a 5-substituted 2-(alkoxymethyl)furan (or a mixture of such furans) by reacting a starting material comprising at least a 5-substituted furfural with hydrogen in the presence of an alcohol and a catalyst system

Title: 5-substituted 2-(alkoxymethyl)furans

5

Technical Field

The present invention concerns a method for the manufacture of a 5-substituted 2-(alkoxymethyl)furan (or a mixture of such furans) by reacting a starting material comprising at least a 5-substituted furfural with hydrogen in the presence of an alcohol and a catalyst system. The invention also concerns a method for the manufacture of mixtures of 5-substituted 2-(alkoxymethyl)furan(s) and 2-(alkoxymethyl)furan(s) by reacting a starting material further comprising furfural. The invention also concerns the use of the products or product mixtures obtained by the method according to the invention as a fuel or a fuel additive. The invention also relates to the use of 2-(alkoxymethyl)furan(s) as a fuel or fuel additive.

Background Art

Fuel, fuel additives and various chemicals used in the petrochemical industry are derived from oil, gas and coal, all finite sources. Biomass, on the other hand, is considered a renewable source. Biomass is biological material (including biodegradable wastes) which can be used for the production of fuels or for industrial production of e.g. fibres, chemicals or heat. It excludes organic material which has been transformed by geological processes into substances such as coal or petroleum.

Production of biomass derived products for non-food applications is a growing industry. Bio-based fuels are an example of an application with strong growing interest. Biomass contains sugars (hexoses and pentoses) that may be converted into value added products. Current biofuel activities from sugars are mainly directed towards the fermentation of sucrose or glucose into ethanol or via complete breakdown via Syngas to synthetic liquid fuels. EP 0641 854 describes the use of fuel compositions comprising of hydrocarbons and/or vegetable oil derivatives containing at least one glycerol ether to reduce particulate matter emissions.

More recently, the acid catalysed reaction of fructose has been re-visited, creating HMF as an intermediate of great interest. Most processes investigated have the disadvantage that HMF is not very stable at the reaction conditions required for its formation. Fast removal from the water-phase containing the sugar starting material and the acid catalyst has been viewed as a solution for this problem. Researchers at the University of Wisconsin-Madison have developed a process to make HMF from fructose. HMF can be

converted into monomers for plastics, petroleum or fuel extenders, or even into fuel itself.

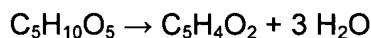
The process by prof. James Dumesic and co-workers first dehydrates the fructose in an aqueous phase with the use of an acid catalyst (hydrochloric acid or an acidic ion-exchange resin). Salt is added to salt-out the HMF into the extracting phase. The extracting phase uses

- 5 an inert organic solvent that favors extraction of HMF from the aqueous phase. The two-phase process operates at high fructose concentrations (10 to 50 wt %), achieves high yields (80% HMF selectivity at 90% fructose conversion), and delivers HMF in a separation-friendly solvent (DUMESIC, James A, et al. "Phase modifiers promote efficient production of Hydroxymethylfurfural from fructose" . Science. 30 juni 2006, vol.312, no.5782, p.1933-1937).
- 10 Although the HMF yields from this process are interesting, the multi-solvent process has cost-disadvantages due to the relatively complex plant design and because of the less than ideal yields when cheaper and less reactive hexoses than fructose, such as glucose or sucrose, are used as a starting material. HMF is a solid at room temperature which has to be converted in subsequent steps to useful products. Dumesic has reported an integrated
- 15 hydrogenolysis process step to convert HMF into dimethylfuran (DMF), which is assumed to be an interesting gasoline additive.

In WO 2006/063220 a method is provided for converting fructose into 5-ethoxymethylfurfural (EMF) at 60 °C, using an acid catalyst either in batch during 24 hours or continuously via column elution during 17 hours. Applications of EMF were not discussed.

- 20 Also in copending patent application PCT/EP2007/002145 the manufacture of HMF ethers are described, including the use of such ethers as fuel or fuel additive. Indeed, both the methyl ether and the ethyl ether (methoxymethylfurfural, or MMF; ethoxyethylfurfural or EMF) were prepared and tested. A similar case is co-pending patent application PCT/EP2007/002146, which describes the manufacture of HMF esters, such as
- 25 acetyl methylfurfural (AMF).

Moreover, it is known to make furfural from the polysaccharide hemicellulose, a polymer of sugars containing five carbon atoms each. When heated with sulphuric acid, hemicellulose undergoes hydrolysis to yield these sugars, principally xylose. Under the same conditions of heat and acid, xylose and other five carbon sugars undergo dehydration, losing three water molecules to become furfural:



- 30 Although MMF, EMF, AMF and other ethers and esters of HMF and furfural are useful as fuel or fuel additives, the inventors found that these ethers and esters leave room for improvement, in particular when used in higher concentration blends with fuels such as
- 35 gasoline, kerosene, diesel, biodiesel or green diesel. The inventors have therefore set out to overcome this shortfall. It is known that HMF may be converted into 2,5-dimethylfuran. For instance, in "Production of dimethylfuran for liquid fuels from biomass-derived

carbohydrates", Nature, vol. 447 (21 June 2007), pp. 982-985, James Dumesic et al. describes the conversion of fructose into HMF, which is subsequently converted into several hydrogenation steps via 2,5-dihydroxymethylfuran and 2-methyl-5-hydroxymethylfuran into DMF. Thus, a large amount of hydrogen is required to generate a liquid fuel suitable for the
5 transportation sector.

Surprisingly, the current inventors found that the conversion of HMF into DMF is not required in order to prepare a product with a high energy density, suitable boiling point and suitable solubility. Moreover, suitable fuel or fuel additives may even be made from furfural, HMF, HMF ethers and HMF esters such as EMF and AMF and/or mixtures containing these
10 components with much smaller amounts of hydrogen and without losing molecular mass but with adding molecular mass to the products. This would therefore provide a route to an alternative fuel or fuel additive from a renewable (and hence CO₂ neutral) source.

Disclosure of Invention

15 Accordingly, the current invention provides a method for the manufacture of ethers of 5- substituted furfural via the corresponding alcohol by reacting 5-substituted furfural with hydrogen in the presence of an alcohol and a catalyst system, comprising of one or more catalysts. Within the scope of the current invention is the use of 5-substituted furfural, and in particular 5-hydroxymethylfurfural and the ethers or esters thereof, which may be obtained
20 from C6 sugars. The synthesis of furfural (from C5 sugars) and/or of the 5-substituted furfural are not part of the current invention. It is noted, however, that the current process is ideally suitable for the manufacture of fuel components or additives from feed containing 5- substituted furfural and optionally unsubstituted furfural, which in turn was obtained from a pentose and hexose containing biomass source. The current invention relates also to the use
25 of 2-alkoxymethyl furan as a fuel or fuel additive, which may be obtained from furfural (pure or in a mixture as described herein elsewhere), hydrogen, alcohol in the presence of a catalyst.

When the reaction product of the above method is used as such or when it is used as an intermediate for a subsequent conversion, the selectivity of the reaction is preferably high
30 as the product is preferably pure. However, when the reaction product of the above method is used as a fuel, a fuel additive or as a fuel or a fuel additive intermediate, the reaction product does not necessarily need to be pure. Indeed, in the preparation of fuel and fuel additives from biomass, which in itself is a mixture of various pentoses and hexoses is an advantage. Next to the 5-substituted 2-(alkoxymethyl)furan and 2-(alkoxymethyl)furan, the reaction
35 product may contain additional non-interfering components such as levulinic acid derivatives and/or products of non-selective hydrogenation such as 5-substituted 2-methylfuran, 2- methylfuran, dimethylfuran, tetrahydrofuran derivatives and the like. For ease of reference,

however, the method and the reaction product of the current invention are described in terms of the reaction of a 5-substituted furfural starting material to the di-ether 5-substituted 2-(alkoxymethyl)furan. Also within the scope of the invention is the reaction of HMF and mixtures of HMF and HMF ethers or esters which may contain furfural with hydrogen in the presence of an alcohol and a catalyst system, since HMF is believed to be produced as intermediate from the fructose and/or glucose-containing starting material during the synthesis of HMF ethers and esters.

The current invention also provides for the use of the reaction product made according to the present invention as fuel or as fuel additive. Fuels for blending with the product of the present invention include but are not limited to gasoline and gasoline-ethanol blends, kerosene, diesel, biodiesel (refers to a non-petroleum-based diesel fuel consisting of short chain alkyl (methyl or ethyl) esters, made by transesterification of vegetable oil, which can be used (alone, or blended with conventional petrodiesel), Fischer-Tropsch liquids (for example obtained from GTL, CTL or BTL gas-to-liquids/coal-to-liquids/biomass to liquids processes), diesel-biodiesel blends and green diesel and blends of diesel and/or biodiesel with green diesel (green diesel is a hydrocarbon obtained by hydrotreating biomass derived oils, fats, greases or pyrolysis oil; see for example the UOP report OPPORTUNITIES FOR BIORENEWABLES IN OIL REFINERIES FINAL TECHNICAL REPORT, SUBMITTED TO: U.S. DEPARTMENT OF ENERGY (DOE Award Number: DE-FG36-05GO15085). The product is a premium diesel fuel containing no sulfur and having a cetane number of 90 to 100). Fuels for blending with the product of the present invention may also include one or more other furanics, wherein the expression furanics is used to include all derivatives of furan and tetrahydrofuran. The invention also provides a fuel composition comprising a fuel element as described above and the reaction product made according to the present invention.

Mode(s) for Carrying Out the Invention

The synthesis of HMF from fructose, glucose and sucrose as a biomass source is a hot topic. HMF has been obtained in processes using both homogeneous and heterogeneous catalysts, using different diluent systems such as water, 2 phase systems for extracting the HMF into an organic phase after its formation, or using diluent systems such as acetone, dmso or ionic liquids.

The current method provides for the conversion of 5-substituted furfural into 5-substituted 2-(alkoxymethyl)furan and as furfural may be present when pentoses were present in the sugar dehydration step or when furfural is formed during hexose dehydration, the current method also provides for the concurrent conversion of the furfural into furfuryl

alcohol and its etherification with the added alcohol. Surprisingly, little or no ethers are found derived by the etherification of the added alcohol with itself.

The alcohol used in the method of the current invention preferably bears a single hydroxyl group, which may be in a primary, secondary or even tertiary position. Diols and 5 polyhydric compounds may be used, but provide little benefit. The alcohol may comprise from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms. Examples include methanol, ethanol, 2-propanol, 2-butanol, 2-methyl-1-propanol (isobutanol), 2-methyl-2-propanol (*tert*-butanol), 2-pentanol (s-amyl alcohol); 2-methyl-1-butanol (p-amyl alcohol); 2-methyl-2-butanol (*t*-amyl alcohol); 3-methyl-1-butanol (isoamyl alcohol); 2,2-dimethyl-1-propanol 10 (neopentyl alcohol); 2-hexanol; 2-ethyl-1-hexanol (isoctyl alcohol). Preferred alcohols used in the method of the current invention include methanol, ethanol, propanol, *iso*-propanol, isobutanol, *tert*-butanol, isoamyl alcohol, isoctyl alcohol. Also blends of alcohols may be used, e.g., of methanol and ethanol.

The amount of alcohol used during the manufacture of the HMF ether is preferably at 15 least equimolar on the furfural, but typically is used in much greater access. Indeed, the alcohol may be used as solvent or co-solvent. In such a case, a sufficient amount of alcohol is present to form the furfuryl ether.

The catalyst system used in the method of the present invention may comprise one or more (co)catalysts, and preferably comprises a single catalyst having hydrogenation and 20 etherification functionality or a combination of (a) hydrogenation catalyst(s) and (an) etherification catalyst(s), for the hydrogenation and for the etherification steps. The single catalyst may for instance be used in the form of an acidic hydrogenation catalyst, or a combination of 2 or more catalysts can be used, for the hydrogenation and for the etherification steps.

25 The hydrogenation catalyst (or the single hydrogenation/etherification catalyst) is preferably a heterogeneous (meaning solid) catalyst. Suitably, it is a granular catalyst which may be formed into any suitable shape, e.g. pellets, rings or saddles.

Hydrogenation catalysts for aldehydes are known and believed suitable in the method 30 of the current invention. Typical aldehyde hydrogenation catalysts include copper-containing catalysts and Group VIII metal-containing catalysts. Examples of suitable copper-containing catalysts include copper-on-alumina catalysts, reduced copper oxide/zinc oxide catalysts, with or without a promoter, manganese promoted copper catalysts, and reduced copper chromite catalysts, with or without a promoter, while suitable Group VIII metal-containing catalysts include platinum, rhodium, ruthenium and palladium catalysts, preferably on a 35 refractory support such as carbon, silica, alumina, aluminasilica, a carbonate such as barium carbonate, diatomaceous earth and the like.

Suitable copper oxide/zinc oxide catalyst precursors include CuO/ZnO mixtures wherein the Cu:Zn weight ratio ranges from about 0.4:1 to about 2:1. Promoted copper oxide/zinc oxide precursors include CuO/ZnO mixtures wherein the Cu:Zn weight ratio ranges from about 0.4:1 to about 2:1 which are promoted with from about 0.1% by weight up to 5 about 15% by weight of barium, manganese or a mixture of barium and manganese. Suitable copper chromite catalyst precursors include those wherein the Cu:Cr weight ratio ranges from about 0.1:1 to about 4:1, preferably from about 0.5:1 to about 4:1. Promoted copper chromite precursors include copper chromite precursors wherein the Cu:Cr weight ratio ranges from about 0.1:1 to about 4:1, preferably from about 0.5:1 to about 4:1, which are 10 promoted with from about 0.1% by weight up to about 15% by weight of barium, manganese or a mixture of barium and manganese. Manganese promoted copper catalyst precursors typically have a Cu:Mn weight ratio of from about 2:1 to about 10:1 and can include an alumina support, in which case the Cu:Al weight ratio is typically from about 2:1 to about 4:1. Other catalysts which can be considered for use include Pd/ZnO catalysts of the type 15 mentioned by P. S. Wehner and B. L. Gustafson in Journal of Catalysis 136, 420-426 (1992), supported palladium/zinc catalysts of the type disclosed in U.S. Pat. No. 4,837,368 and U.S. Pat. No. 5,185,476, and chemically mixed copper-titanium oxides of the type disclosed in U.S. Pat. No. 4,929,777.

Further catalysts of interest for use in the process of the invention include the 20 rhodium/tin catalysts reported in A. El Mansour, J. P. Candy, J. P. Bourronville, O. A. Ferrehi, and J. M Basset, Angew. Chem. 101, 360 (1989).

Any recognised supporting medium may be used to provide physical support for the catalyst used in the process of the invention. This support can be provided by materials such as zinc oxide, alumina, silica, aluminasilica, silicon carbide, zirconia, titania, carbon, a zeolite, 25 or any suitable combination thereof. Particularly preferred are catalyst systems comprising a Group VIII metal ("noble metal") on a carbon support, since such catalysts systems may be used to perform the hydrogenation and etherification.

The acid etherification catalyst system in the method of the present invention can be selected from amongst (halogenated) organic acids, inorganic acids, Lewis acids, ion 30 exchange resins and zeolites or combinations and/or mixtures thereof. It may be a homogeneous catalyst, but heterogeneous catalysts are preferred for purification reasons. The HMF ethers can be produced with a protonic, Brønsted or, alternatively, a Lewis acid or with catalysts that have more than one of these acidic functionalities.

The protonic acid may be organic or inorganic. For instance, the organic acid can be 35 selected from amongst oxalic acid, levulinic acid, maleic acid, trifluoro acetic acid (triflic acid), methansulphonic acid or para-toluenesulphonic acid. Alternatively, the inorganic acid can be

selected from amongst (poly)phosphoric acid, sulphuric acid, hydrochloric acid, hydrobromic acid, nitric acid, hydroiodic acid, optionally generated in situ.

Certain salts may be used as catalyst, wherein the salt can be any one or more of $(\text{NH}_4)_2\text{SO}_4/\text{SO}_3$, ammonium phosphate, pyridinium chloride, triethylamine phosphate,

- 5 pyridinium salts, pyridinium phosphate, pyridinium hydrochloride/hydrobromide/perbromate, DMAP, aluminium salts, Th and Zr ions, zirconium phosphate, Sc and lanthanide ions such as Sm and Y as their acetate or trifluoroacetate (triflate) salt, Cr-, Al-, Ti-, Ca-, In-ions, ZrOCl_2 , $\text{VO}(\text{SO}_4)_2$, TiO_2 , V-porphyrine, Zr-, Cr-, Ti-porphyrine.

Lewis acids selected as dehydration catalyst can be any one of ZnCl_2 , AlCl_3 , BF_3 .

- 10 Ion exchange resins can be suitable dehydration catalysts. Examples include Amberlite™ and Amberlyst™, Diaion™ and Levatit™. Other solid catalyst that may be used include natural clay minerals, zeolites, supported acids such as silica impregnated with mineral acids, heat treated charcoal, metal oxides, metal sulfides, metal salts and mixed oxides and mixtures thereof. If elevated reactions temperatures are used, as defined hereafter, then the
15 catalyst should be stable at these temperatures.

An overview of catalysts that may be used in the method of the current invention may be found in Table 1 of the review article prepared by Mr. Lewkowski: "Synthesis, chemistry and applications of 5-hydroxymethylfurfural and its derivatives" Arkivoc. 2001, p.17-54.

The amount of catalyst may vary, depending on the selection of catalyst or catalyst mixture.

- 20 For instance, the catalyst can be added to the reaction mixture in an amount varying from 0.01 to 40 mole % drawn on the (substituted) furfural content of the feed, preferably from 0.1 to 30 mole %, more preferably from 1 to 20 mole %.

In the preferred embodiment, the catalyst is a heterogeneous catalyst.

The temperature at which the reaction is performed may vary, but in general it is

- 25 preferred that the reaction is carried out at a temperature from 0 to 200 degrees Celsius, preferably from 10 to 150 degrees Celsius, more preferably from 20 to 120 degrees Celsius. Also, the hydrogenation reaction is most selective at low temperatures such as e.g. between 20 and 80 degrees Celsius, depending on the selected catalyst. The reaction of the invention can also be carried out in a system with 2 reactors in series, whereby the hydrogenation step
30 and the etherification step are carried out in the first and second reactor at lower and higher temperature, respectively. The reaction may be performed in a single reactor, at a temperature from 20 to 140 degrees Celsius, or in two reactors, where in the first reactor the hydrogenation is performed at a temperature from 20 to 80 degrees Celsius, and where in the second reactor the hydrogen is removed for the etherification at a temperature from 40 to
35 160 degrees Celsius, preferably from 60 to 120 degrees Celsius. The operation in one batch reactor can start with a low temperature hydrogenation, followed by increasing the temperature and removing the hydrogen gas.

Hydrogen is supplied in sufficient abundance, and either bubbled through the reaction medium introduced concurrently or counter currently with one of the feed streams or dissolved using another form of mixing. Depending on the catalyst and the selected process temperature, the reaction is carried out at a hydrogen pressure from 1 to 100 bars, preferably 5 from 2 to 25 bars, more preferably from 2 to 10 bars. In general, pressures higher than 100 bars are less preferred as the selectivity of the reaction reduces and too much hydrogen is consumed for by-products formation.

The furfural, HMF and HMF ether and ester containing starting material is typically dissolved in a solvent or more preferably in the alcohol reactant, in order to facilitate the 10 reaction. The non-alcohol solvent may be selected from the group consisting of organic solvents such as, ketones, ethers, alkanes and the like.

The alcohol solvent is the alcohol selected for the etherification. The amount of solvent is preferably sufficient to dissolve or suspend the starting material and to prevent certain side-reactions.

15 The method of the current invention may be carried out in a batch process or in a continuous process, with or without recycle of (part of) the product stream to control the reaction temperature (recycle via a heat exchanger). For instance, the method of the invention can be performed in a continuous flow process. In such method, one or two homogenous catalysts may be used and the residence time of the reactants in the flow 20 process is between 0.1 second and 10 hours, preferably from 1 second to 1 hours, more preferably from 5 seconds to 20 minutes.

Alternatively, the continuous flow process may be a fixed bed continuous flow process or a reactive (catalytic) distillation process with a heterogeneous acid catalyst. To initiate or regenerate the heterogeneous acid catalyst or to improve performance, or when a 25 heterogeneous hydrogenation catalyst is used in combination with a homogeneous acidic etherification catalyst, an inorganic or organic acid may be added to the feed of the fixed bed or reactive distillation continuous flow process. In a fixed bed process, the liquid hourly space velocity (LHSV) can be from 1 to 1000, preferably from 5 to 500, more preferably from 10 to 250 and most preferably from 25 to 100 min⁻¹.

30 The above process results in stable furan ethers, which can then be used as such or be converted into a further derivative before being used as fuel and/or as fuel additive. The inventors are of the opinion that some of the products prepared by the method of the current invention are actually new. Thus, the ethers made from alkoxyethylfurfural with C1 to C20 alcohols, preferably C1 to C8 alcohols are new and are excellent fuel components or fuel 35 additives. Since these alcohols may be made from biomass, this might open a class of products that are fully biomass-derived. Accordingly, these new ethers are claimed as well.

The HMF ethers of the invention can also be used as or can be converted to compounds that can be used as solvent, as monomer in a polymerization (such as 2,5-furan dicarboxylic acid or FDCA), as fine chemical or pharmaceutical intermediate, or in other applications. Oxidation of the HMF ethers using an appropriate catalyst under appropriate conditions such as for example described for p-xylene with a NHPI/Co(OAc)₂/MnOAc)₂ catalyst system in Adv. Synth. Catal. 2001, 343, 220-225 or such as described for HMF with a Pt/C catalyst system at pH < 8 in EP 0 356 703 or such as described for HMF with a Pt/C catalyst system at pH > 7 in FR 2 669 634, all with air as an oxidant, resulted in the formation of 2,5- Furan dicarboxylic acid (FDCA).

10 The invention further concerns the use of the HMF ethers prepared by the method of the current invention as fuel and/or as fuel additive. Of particular interest is the use of the ethers in diesel, biodiesel or "green diesel", given its (much) greater solubility therein than ethanol. Conventional additives and blending agents for diesel fuel may be present in the fuel compositions of this invention in addition to the above mentioned fuel components. For 15 example, the fuels of this invention may contain conventional quantities of conventional additives such as cetane improvers, friction modifiers, detergents, antioxidants and heat stabilizers, for example. Especially preferred diesel fuel formulations of the invention comprise diesel fuel hydrocarbons and HMF ether as above described together with peroxidic or nitrate cetane improvers such as ditertiary butyl peroxide, amyl nitrate and ethyl hexyl nitrate for example.

20 Examples are enclosed to illustrate the method of the current invention and the suitability of the products prepared therefrom as fuel. The examples are not meant to limit the scope of the invention.

25 **Example 1. Formation of 2,5-di(ethoxymethyl)furan**

In a 7.5 ml batch reactor, 0.06 mmol 5-(ethoxymethyl)furfural (EMF) in ethanol/H₂O (90/10) and 3.3 mmol H₂ was reacted for 2 hours at a temperature of 150 or 80 degrees Celsius with 5 mg heterogeneous hydrogenation catalyst and in some cases with 5 mg acid catalyst. Four furan peaks were observed in the UV spectrum. Mass spectrometry (LC-MS CI) identified 30 these products as 5-(ethoxymethyl)furfural (EMF; starting material), 2,5-di(ethoxymethyl)furan (DEMF), 2-(ethoxymethyl)-5-(hydroxymethyl)furan (EMHMF) and 2-(ethoxymethyl)-5-methylfuran (EMMeF).

Conversion of substrate, selectivity and yield of furan derivatives were calculated according to the following formulae:

$$35 \quad X = 100 * m_r \text{ substrate} / m_0 \text{ substrate}$$

X conversion (%)

$m_r \text{ substrate}$ amount of reacted substrate (mg)

n_0 substrate amount of substrate in feed (mg)

$$S_{\text{compound}} = \frac{100 \cdot n_r}{n_0} \text{ substrate / } n_0 \text{ substrate}$$

S_{compound} selectivity to compound (%)

5 n_r substrate moles of substrate reacted

n_0 substrate moles of substrate in feed

$$\text{Yield} = \frac{100 \cdot n_{\text{product}}}{n_0} \text{ substrate / } n_0 \text{ substrate}$$

Yield yield (%)

10 n_{product} moles of product formed

Selectivities and conversions for catalysts used in this example can be found in table below.

Table 1. Conversion and selectivities for the hydrogenation of 5-(ethoxymethyl)furfural in the presence of ethanol at different temperatures and reaction times.

Catalyst 1	Catalyst 2	T [°C]	Conversion [%]	sEMHMF [%]	sDEM福 [%]	sEMMeF [%]	sEMHMF+DEM福 [%]	s Further hydrogenate products[%]
1.85%Ru on silica	None	80	29.0	92.5	0.1	0.0	92.6	7.4
1.85%Ru on silica	CrCl ₂	80	42.4	13.8	28.7	0.2	42.5	57.3
5% Ru on alumina	None	150	92.4	52.5	0.2	0.0	52.7	47.3
5% Ru on alumina	None	80	73.3	85.0	0.8	0.1	85.8	14.2
5% Ru on alumina	Amberlyst36Wet	80	91.1	33.1	27.7	0.4	60.8	38.9
5% Ru on alumina	CrCl ₂	80	70.8	15.9	28.5	0.3	44.3	55.4
5%Pt/0.5%V	None	80	99.5	65.5	5.2	3.6	70.7	25.8
5%Pt/0.5%V	CrCl ₂	80	70.7	13.0	21.8	3.4	34.8	61.9
5%Rh on active C	Bentonite	80	66.9	32.4	6.3	7.9	38.7	53.4
Ni on silica	None	150	93.2	33.0	0.1	0.8	33.2	66.1
Ni on silica	None	80	98.6	51.1	0.0	0.0	51.1	48.9
Ni on silica	Amberlyst36Wet	80	99.3	22.3	21.5	0.1	43.8	56.2
Ni on silica	CrCl ₂	80	31.0	98.5	0.7	0.5	99.2	0.3

Analytical Method

The reaction products were quantified with the aid of HPLC-analysis with an internal standard (saccharine, Sigma Aldrich). An Agilent 1100 series chromatograph, equipped with UV and

20 ELSD detectors, was used. Stationary phase was reverse phase C18 (Sunfire 3.5 µm, 4.6x100mm, Waters) column. A gradient elution at a constant flow 0.6 ml/min and temperature 40 °C was used according to the following scheme.

Time	H ₂ O(vol%)	MeOH (vol%)	MeCN (vol%)	Flow (ml/min)	T (C)
Initial	95	0	5	1	40
1	89	3	8	1	40
8	25	3	72	1	40

C.I. Mass spectrum of DEMF (MW=184.2 g/mol)**Example 2. Batch experiment with hydrogenation/etherification of 5-****5 (ethoxymethyl)furfural**

In a 7.5 ml batch reactor, 0.06 mmol 5-(ethoxymethyl)furfural (EMF) in 1 mL ethanol and 5 bars of hydrogen was reacted with 3 mol% of a Pt/C catalyst for 4 days at room temperature. The starting material was completely converted in 100% selectivity to 5-(ethoxymethyl)-2-hydroxymethyl)furan. Subsequently, the mixture was heated to 75 °C for 1 day without hydrogen. The 5-(ethoxymethyl)-2-hydroxymethyl)furan was fully converted and 2,5-bis(ethoxymethyl)furan was obtained in 80% yield. 20% Side products are ring opened levulinate derivatives. The experiment was successfully repeated on a 20 gram scale.

Example 3. Batch experiment with hydrogenation/etherification of 5-(tert-**15 butoxymethyl)furfural**

In a 7.5 ml batch reactor, 0.06 mmol 5-(tert-butoxymethyl)furfural (tBMF) in 1 mL ethanol and 2 bars of hydrogen was reacted with 3 mol% of a 5% Rh on alumina catalyst for 4 hours at room temperature. The starting material was completely converted in 100% selectivity to 5-(tertbutoxymethyl)-2-(ethoxymethyl)furan. The experiment was successfully repeated on a 20 gram scale.

No reduction of the furan ring could be detected.

Example 4. Batch experiment with hydrogenation/etherification of 5-**(hydroxymethyl)furfural**

25 In a 7.5 ml batch reactor, 0.06 mmol 5-(hydroxymethyl)furfural (HMF) in 1 mL ethanol and 5 bars of hydrogen was reacted with 3 mol% of a Pt/C catalyst for 2 days at room temperature. The starting material was completely converted in 100% selectivity to 2,5-di(hydroxymethyl)furan. Subsequently, the mixture was heated to 75 °C for 1 day without hydrogen. The 2,5-di(hydroxymethyl)furan was fully converted and 2,5-bis(ethoxymethyl)furan was obtained in 75% yield. 25% Side products are ring opened levulinate derivatives. The experiment was successfully repeated on a 20 gram scale.

Example 5. Diesel fuel applications**Fuel solubility**

35 Fuel solubility is a primary concern for diesel fuel applications. Not all highly polar oxygenates have good solubility in the current commercial diesel fuels. Results show that 2,5-di(ethoxymethyl)furan and 5-(tert-butoxymethyl)-2-(ethoxymethyl)furan are miscible in all blend ratio's with commercial diesel. In a comparative set of experiments it was shown that

ethoxymethylfurfural (EMF) is completely miscible in a 5 vol% blend with commercial diesel, but that phase separation occurs with the 25 vol% and with the 40 vol% blends of EMF and diesel.

5 Example 6. 5-substituted 2-(alkoxymethyl)furans

A teflon lined, 7.5 mL stainless steel batch reactor containing 350 mg (2.3 mmol) of 5-(ethoxymethyl)furfural in 0.5 mL methanol, a hydrogenation catalyst (Ni on Silica) and an etherification catalyst (zeolite β - SAR 75) was pressurized to 12.5 bar with hydrogen and subsequently heated, under stirring, to 100 °C for 3 hours. After the reaction, the reactor is

10 cooled quickly in an ice bath and depressurized. A sample is diluted with methanol and analysed of the products with GC and GC-MS. The results are shown in the below Table.

In this experiment, the selectivity was calculated slightly different, based on the formula:

$$\text{Selectivity} = 100 * n_t(\text{product}) / [n_0(\text{substrate}) - n_t(\text{substrate})]$$

Where:

15 n_0 - the initial number of moles

n_t - the number the moles of a compound at time "t".

Table 1. Hydrogenation/etherification of EMF in MeOH to EMF alcohol and ethers

Cat. 1	Cat. 1 [mg]	Cat. 2	Cat. 2 [mg]	Conversion [%]	S-EMHMF [%]	S-DMMF [%]	S- EMMeF [%]	S-DMMF + EMMeF [%]
Ni on silica	50	Zeolite Beta (SAR 75)	50	92	3.8	47.9	30.1	78.0
Ni on silica	10	Zeolite Beta (SAR 75)	10	37	7.9	46.7	36.0	82.7

20 Example 7. 5-substituted 2-(alkoxymethyl)furans using a mixture of EMF and Furfural

Example 6, was repeated with 180 mg (1.9 mmol) of furfural and 180 mg (1.2 mmol) 5-(ethoxymethyl)furfural in 0.48 mL methanol. The batch reactor was pressurized to 20 bar of hydrogen and subsequently heated, under stirring, to 100 °C for 2 hours. The results are shown in Table 2.

Table 2. Hydrogenation/etherification of Furfural and EMF in MeOH

<u>Cat.</u> <u>1</u>	<u>Cat. 1</u> <u>[mg]</u>	<u>Cat. 2</u> <u>[mg]</u>	<u>Cat. 2</u> <u>[mg]</u>	<u>Conversion</u> <u>[%]</u>	<u>S-EMHMF</u> <u>[%]</u>	<u>S-DMMF</u> <u>[%]</u>	<u>S-</u> <u>EMMeF</u> <u>[%]</u>	<u>F-OH</u>	<u>F-</u> <u>OMe</u>
Ni on silica	20	Zeolite Beta (SAR 75)	20	(EMF) 31.6	24	6.3	36.5		
				(F) 64.7				32.3	29.7

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¹⁴
Claims

1. Method for the manufacture of a 5-substituted 2-(alkoxymethyl)furan by reacting a starting material comprising at least one 5-substituted furfural and optionally comprising furfural with hydrogen in the presence of an alcohol and a catalyst system.
2. Method according to claim 1, wherein the alcohol may comprise from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms.
- 10 3. Method according to claim 1, wherein the alcohol is selected from methanol, ethanol, 2-propanol, 2-butanol, 2-methyl-1-propanol (isobutanol), 2-methyl-2-propanol (*tert*-butanol), 2-pentanol (s-amyl alcohol); 2-methyl-1-butanol (p-amyl alcohol); 2-methyl-2-butanol (t-amyl alcohol); 3-methyl-1-butanol (isoamyl alcohol); 2,2-dimethyl-1-propanol (neopentyl alcohol); 2-hexanol; 2-ethyl-1-hexanol (isooctyl alcohol) or a blends from two or more of the above alcohols.
- 15 4. Method according to claim 1 or 2, wherein the catalyst system is a heterogeneous acid hydrogenation catalyst
- 20 5. Method according to claim 4, wherein the heterogeneous acid hydrogenation catalyst comprises at least one noble metal on a carbon support.
- 25 6. Method according to claim 1 or 2, wherein the catalyst system comprises of two catalysts, one being a hydrogenation catalyst and the other being a etherification catalyst.
- 30 7. Method according to any one of the claims 1 to 5, wherein the reaction is performed in a single reactor, at a temperature from 20 to 140 degrees Celsius, or in two reactors, where in the first reactor the hydrogenation is performed at a temperature from 20 to 80 degrees Celsius, and where in the second reactor the hydrogen is removed for the etherification at a temperature from 40 to 160 degrees Celsius, preferably from 60 to 120 degrees Celsius, wherein the operation in one batch reactor can start with a low temperature hydrogenation, followed by increasing the temperature and removing the hydrogen gas.
- 35 8. Method according to any one of the claims 1 to 8, wherein the starting material is selected from one or more of the group comprising 5-(hydroxymethyl)furfural and ethers and esters of 5-(hydroxymethyl)furfural, optionally comprising furfural.

9. Method according to claim 8, wherein the starting material is 5-(hydroxymethyl)furfural.

5 10. Method according to any one of the claims 1 to 9, wherein a solvent or solvent mixture is used, and wherein the solvent or solvents are selected from the group consisting of ketones, ethers, alkanes and aromatic hydrocarbons and mixtures thereof.

10 11. Method according to any one of the claims 1 to 9, wherein a solvent or solvent mixture is used, and wherein the solvent is the alcohol.

12. Method according to any one of the claims 1 to 11, wherein the method is performed in a continuous flow process.

15 13. Method according to claim 12, wherein the residence time in the flow process is between 0.1 second and 10 hours, preferably from 1 second to 1 hours, more preferably from 5 seconds to 20 minutes.

20 14. Method according to claim 13, wherein the continuous flow process is a fixed bed continuous flow process.

15. Method according to claim 14, wherein the fixed bed comprises a heterogeneous acid catalyst.

25 16. Method according to claim 15, wherein the continuous flow process is a reactive distillation or a catalytic distillation process.

17. Method according to claim 16, wherein in addition to a heterogeneous acid catalyst, an inorganic or organic acid catalyst is added to the feed of the fixed bed or catalytic 30 distillation continuous flow process.

18. Method according to claim 14-17, wherein the liquid hourly space velocity ("LHSV") is from 1 to 1000, preferably from 5 to 500, more preferably from 10 to 250 and most preferably from 25 to 100.

35

19. 5-(tertbutoxymethyl)-2-(methoxymethyl)furan

20. 5-(tertbutoxymethyl)-2-(ethoxymethyl)furan¹⁶

21. 5-(2-butoxymethyl)-2-(methoxymethyl)furan

5 22. Use of the ether produced by the method of any one of claims 1-18 or the ether of
claim 19, 20 or 21 as fuel or fuel additive.

10 23. A fuel or fuel composition comprising the ether produced by the method of any
one of claims 1-18 or the ether of claim 19, 20 or 21 as fuel component, optionally
blended with one or more of gasoline and gasoline-ethanol blends, kerosene,
diesel, biodiesel, Fischer-Tropsch liquids, diesel-biodiesel blends and green diesel
and blends of diesel and/or biodiesel with green diesel and other furanics.

15 24. Use of 2-alkoxymethylfuran as a fuel or fuel additive.

25. Use of 2-alkoxymethylfuran obtainable by reacting furfural with hydrogen in the
presence of an alcohol and a catalyst system as a fuel or fuel additive.

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(71) Applicant(s)
Furanix Technologies B.V.

(72) Inventor(s)
Gruter, Gerardus Johannes Maria

(74) Agent/Attorney
Wallington-Dummer, Suite 1005 37 Bligh Street Sydney, NSW, 2000

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- (71) Applicant(s)
Furanix Technologies B.V.
- (72) Inventor(s)
Gruter, Gerardus Johannes Maria
- (74) Agent / Attorney
Wallington-Dummer, Suite 1005 Level 10 37 Bligh Street, Sydney, NSW, 2000
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(74) Agent: **KORTEKAAS, M.C.J.A.**; Exter Polak & Charles B.V., P.O. Box 3241, NL-2280 GE Rijswijk (NL).

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(71) Applicant (for all designated States except US): **FURANIX TECHNOLOGIES B.V.** [NL/NL]; Zekeringstraat 29, NL-1014 BV Amsterdam (NL).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **GRUTER, Gerardus, Johannes, Maria** [NL/NL]; 14 Asterkade, NL-2106 BA Heemstede (NL).

(54) Title: MIXTURE OF FURFURAL AND 5-(ALKOXYMETHYL)FURFURAL DERIVATIVES FROM SUGARS AND ALCOHOLS

(57) Abstract: Accordingly, the current invention provides a method for the manufacture of a mixture of a furfural and a 5-(alkoxymethyl)furfural derivative by reacting a C5 and C6 sugar- containing starting material with an alcohol in the presence of an acid catalyst, followed by the hydrogenation and/or etherification of the mixture of furfural and 5-(alkoxymethyl)furfural to convert the aldehyde function of both 5-(alkoxymethyl)furfural and furfural into an alkoxymethyl function or methyl function.

WO 2009/030511 A1

Title: Mixture of furfural and 5-(alkoxymethyl)furfural derivatives from sugars and
5 alcohols

Technical Field

The present invention concerns a method for the manufacture of a mixture of furfural and 5-
10 (alkoxymethyl)furfural (RMF) derivatives from a mixed feed containing both pentoses (C5
sugars) and hexoses (C6 sugars).

Background Art

From DE635783 the preparation of alkoxymethylfurfurals and levulinic acid alkyl esters is
15 known, using glucose or a glucose-containing starting material. For instance, saccharose, a
disaccharide of glucose and fructose (both C6 sugars) has been used. The reactions provide
primarily levulinic acid derivatives.

Fuel, fuel additives and various chemicals used in the petrochemical industry are derived
20 from oil, gas and coal, all finite sources. Biomass, on the other hand, is considered a
renewable source. Biomass is biological material (including biodegradable wastes) which can
be used for the production of fuels or for industrial production of e.g. fibres, chemicals or
heat. It excludes organic material which has been transformed by geological processes into
substances such as coal or petroleum.

25 Production of biomass derived products for non-food applications is a growing industry. Bio-
based fuels are an example of an application with strong growing interest.

Biomass contains sugars (hexoses and pentoses) that may be converted into value added
30 products. Current biofuel activities from sugars are mainly directed towards the fermentation
of sucrose or glucose into ethanol or via complete breakdown via Syngas to synthetic liquid
fuels. EP 0641 854 describes the use of fuel compositions comprising of hydrocarbons
and/or vegetable oil derivatives containing at least one glycerol ether to reduce particulate
matter emissions.

35 More recently, the acid catalysed reaction of fructose has been re-visited, creating HMF as
an intermediate of great interest. Most processes investigated have the disadvantage that

HMF is not very stable at the reaction conditions required for its formation. Fast removal from the water-phase containing the sugar starting material and the acid catalyst has been viewed as a solution for this problem. Researchers at the University of Wisconsin-Madison have developed a process to make HMF from fructose. HMF can be converted into monomers for

5 plastics, petroleum or fuel extenders, or even into fuel itself. The process by prof. James Dumesic and co-workers first dehydrates the fructose in an aqueous phase with the use of an acid catalyst (hydrochloric acid or an acidic ion-exchange resin). Salt is added to salt-out the HMF into the extracting phase. The extracting phase uses an inert organic solvent that favors extraction of HMF from the aqueous phase. The two-phase process operates at high

10 fructose concentrations (10 to 50 wt %), achieves high yields (80% HMF selectivity at 90% fructose conversion), and delivers HMF in a separation-friendly solvent (DUMESIC, James A, et al. "Phase modifiers promote efficient production of Hydroxymethylfurfural from fructose" . Science. 30 juni 2006, vol.312, no.5782, p.1933-1937). Although the HMF yields from this process are interesting, the multi-solvent process has cost-disadvantages due to

15 the relatively complex plant design and because of the less than ideal yields when cheaper and less reactive hexoses than fructose, such as glucose or sucrose, are used as a starting material. HMF is a solid at room temperature which has to be converted in subsequent steps to useful products. Dumesic has reported an integrated hydrogenolysis process step to convert HMF into dimethylfuran (DMF), which is assumed to be an interesting gasoline

20 additive.

In WO 2006/063220 a method is provided for converting fructose into 5-ethoxymethylfurfural (EMF) at 60 °C, using an acid catalyst either in batch during 24 hours or continuously via column elution during 17 hours. Applications of EMF were not discussed.

25 Also in copending patent application PCT/EP2007/002145 the manufacture of HMF ethers are described, including the use of such ethers as fuel or fuel additive. Indeed, both the methyl ether and the ethyl ether (methoxymethylfurfural, or MMF; ethoxyethylfurfural or EMF) were prepared and tested. The invention of the copending patent application, however, was

30 limited to the use of hexose feedstock with preferably primary C1-C5 alcohols. Use of hexose and pentose mixed feed with secondary and tertiary alcohols was not considered, whereas the only example of a branched primary alcohol was considered. Although 5-alkoxymethylfurfural derivatives are useful as fuel or fuel additive, the inventors found that the ethers leave room for improvement, in particular when used in higher concentration blends

35 with fuels such as gasoline, kerosene, diesel, biodiesel or green diesel. The inventors have developed further derivatization routes addressing the negative effect of the aldehyde functionality of furfural and its derivatives on the fuel blend properties, allowing now also to

start with a mixed pentose/hexose feed as the poorly fuel-soluble furfural that is obtained from pentoses will now concurrently be converted to better soluble furfuryl ethers or methylfuran during aldehyde to alcohol hydrogenation/etherification or aldehyde to CH₃ hydrogenation, respectively. Therefore the removal of the pentoses from the mixed

- 5 pentose/hexose biomass feed is no longer required.

Surprisingly, the inventors have found that a combination of a derivative from 5-alkoxymethylfurfural and a derivative of furfural, preferably the corresponding furfural derivative, have superior blending properties compared to the 5-alkoxymethylfurfural alone or

- 10 the blend of 5-alkoxymethylfurfural with furfural.

Disclosure of Invention

Accordingly, the current invention provides a method for the manufacture of a mixture of a furfural and a 5-(alkoxymethyl)furfural derivative by reacting a C5 and C6 sugar-containing

- 15 starting material with an alcohol in the presence of an acid catalyst, followed by the hydrogenation and/or etherification of the mixture of furfural and 5-(alkoxymethyl)furfural to convert the aldehyde function of both 5-(alkoxymethyl)furfural and furfural into an alkoxymethyl function or a methyl function.

- 20 When the reaction product of the above method is used as a starting material for a subsequent conversion to a fuel, a fuel additive or as a fuel or a fuel additive intermediate, the reaction product does not necessarily need to be pure. Indeed, in the preparation of fuel and fuel additives from biomass, the reaction product may contain non-interfering components such as levulinic acid derivatives and the like. For ease of reference, however,
- 25 the method and the reaction product are described in terms of the reaction of a mixed pentose/hexose-containing starting material, resulting in a mixture of furfural and 5-(alkoxymethyl)furfural. The current invention also provides for the use of the reaction product made according to the present invention as fuel or as fuel additive. Fuels for blending with the product of the present invention include but are not limited to gasoline and gasoline-
- 30 ethanol blends, kerosene, diesel, biodiesel (refers to a non-petroleum-based diesel fuel consisting of short chain alkyl (methyl or ethyl) esters, made by transesterification of vegetable oil, which can be used (alone, or blended with conventional petrodiesel), Fischer-Tropsch liquids (for example obtained from GTL, CTL or BTL gas-to-liquids/coal-to-liquids/biomass to liquids processes), diesel-biodiesel blends and green diesel and blends of
- 35 diesel and/or biodiesel with green diesel (green diesel is a hydrocarbon obtained by hydrotreating biomass derived oils, fats, greases or pyrolysis oil; see for example the UOP report OPPORTUNITIES FOR BIORENEWABLES IN OIL REFINERIES FINAL TECHNICAL

REPORT, SUBMITTED TO: U.S. DEPARTMENT OF ENERGY (DOE Award Number: DE-FG36-05GO15085). The product is a premium diesel fuel containing no sulfur and having a cetane number of 90 to 100). Fuels for blending with the product of the present invention may also include one or more other furanics, wherein the expression furanics is used to include all

- 5 derivatives of furan and tetrahydrofuran. The invention also provides a fuel composition comprising a fuel element as described above and the reaction product made according to the present invention.

Mode(s) for Carrying Out the Invention

- 10 Biomass resources are well known. The components of interest in biomass are those feeds that can release a mixture of hexoses and at least 5% of pentoses (hereinafter referred to as mixed pentose and hexose-containing starting material. In organic chemistry, a hexose is a monosaccharide with six carbon atoms having the chemical formula C₆H₁₂O₆. Hexoses are classified by functional group, with aldohexoses having an aldehyde at position 1, and
- 15 ketohexoses having a ketone at position 2. Suitable 6-carbon monosaccharides include but are not limited to fructose, glucose, galactose, mannose, and their oxidized, reduced, etherified, esterified and amidated derivatives, e.g. aldonic acid or alditol, with glucose being the most abundant, the most economic and therefore the most preferred monosaccharide albeit less reactive than fructose. A pentose is a monosaccharide with five carbon atoms, having the
- 20 chemical formula C₅H₁₀O₅. They either have an aldehyde functional group in position 1 (aldopentoses), or a ketone functional group in position 2 (ketopentoses). Suitable 5-carbon monosaccharides include but are not limited to Arabinose, Ribose, Ribulose, Xylose, Xylulose, Lyxose and their oxidized, reduced, etherified, esterified and amidated derivatives.
- 25 On the other hand, the current inventors have also succeeded to convert sucrose, which is also available in great abundance. Other disaccharides that may be used include maltose, cellobiose and lactose. The polysaccharides that may be used include cellulose, inulin (a polyfructan), starch (a polyglucan) and hemi-cellulose. The polysaccharides and disaccharides are converted into their monosaccharide component(s) and dehydrated during
- 30 the manufacture of the 5-HMF ether.

The alcohol used in the method of the current invention preferably bears a single hydroxyl group, which may be in a primary, secondary or even tertiary position. The alcohol may comprise from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms, whereby the

- 35 alcohols with 4 or more carbon atoms preferably have a branched carbon backbone.

Preferred alcohols used in the method of the current invention include methanol, ethanol, 1-propanol, 2-propanol, isobutanol, *tert*-butanol, isoamyl alcohol, isoctyl alcohol. Also blends of alcohols may be used, e.g., of isobutanol and *tert*-butanol.

- 5 The amount of alcohol used during the manufacture of the HMF ether of the present invention is preferably at least equimolar on the hexose content of the feedstock, but typically is used in much greater excess. Indeed, the alcohol (such as *tert*-butanol) may be used as solvent or co-solvent. In such a case, a sufficient amount of alcohol is present to form the HMF ether.

10

The acid catalyst in the method of the present invention can be selected from amongst (halogenated) organic acids, inorganic acids, Lewis acids, ion exchange resins and zeolites or combinations and/or mixtures thereof. It may be a homogeneous catalyst, but heterogeneous catalysts (meaning solid catalysts) are preferred for purification reasons. The 15 HMF ether can be produced with a protonic, Brønsted or, alternatively, a Lewis acid or with catalysts that have more than one of these acidic functionalities.

The protonic acid may be organic or inorganic. For instance, the organic acid can be selected from amongst oxalic acid, levulinic acid, maleic acid, trifluoro acetic acid (triflic acid),

- 20 methansulphonic acid or para-toluenesulphonic acid. Alternatively, the inorganic acid can be selected from amongst (poly)phosphoric acid, sulphuric acid, hydrochloric acid, hydrobromic acid, nitric acid, hydroiodic acid, optionally generated in situ.

Certain salts may be used as catalyst, wherein the salt can be any one or more of

- 25 $(\text{NH}_4)_2\text{SO}_4/\text{SO}_3$, ammonium phosphate, pyridinium chloride, triethylamine phosphate, pyridinium salts, pyridinium phosphate, pyridinium hydrochloride/hydrobromide/perbromate, DMAP, aluminium salts, Th and Zr ions, zirconium phosphate, Sc and lanthanide ions such as Sm and Y as their acetate or trifluoroacetate (triflate) salt, Cr-, Al-, Ti-, Ca-, In-ions, ZrOCl_2 , $\text{VO}(\text{SO}_4)_2$, TiO_2 , V-porphyrine, Zr-, Cr-, Ti-porphyrine.

30

Lewis acids selected as dehydration catalyst can be any one of ZnCl_2 , AlCl_3 , BF_3 .

Ion exchange resins can be suitable dehydration catalysts. Examples include Amberlite™ and Amberlyst™, Diaion™ and Levatit™. Other solid catalyst that may be used include

- 35 natural clay minerals, zeolites, supported acids such as silica impregnated with mineral acids, heat treated charcoal, metal oxides, metal sulfides, metal salts and mixed oxides and

mixtures thereof. If elevated reactions temperatures are used, as defined hereafter, then the catalyst should be stable at these temperatures.

An overview of catalysts that may be used in the method of the current invention may be

- 5 found in Table 1 of the review article prepared by Mr. Lewkowski: "Synthesis, chemistry and applications of 5-hydroxymethylfurfural and its derivatives" Arkivoc. 2001, p.17-54.

The amount of catalyst may vary, depending on the selection of catalyst or catalyst mixture.

For instance, the catalyst can be added to the reaction mixture in an amount varying from 0.01 to 40 mole % drawn on the hexose content of the feed, preferably from 0.1 to 30 mole

- 10 %, more preferably from 1 to 20 mole %.

In the preferred embodiment, the catalyst is a heterogeneous catalyst.

The temperature at which the reaction is performed may vary, but in general it is preferred

- 15 that the reaction is carried out at a temperature from 50 to 300 degrees Celsius, preferably from 125 to 250 degrees Celsius, more preferably from 150 to 225 degrees Celsius. In general, temperatures higher than 300 are less preferred as the selectivity of the reaction reduces and as many by-products occur, inter alia caramelisation of the sugar. Performing the reaction below the lowest temperature is also less preferable because of the low reaction
20 rate. If the reactions are carried out above the boiling temperature of water, then the reactions are preferably carried out under pressure, e.g., 10 bar nitrogen or higher.

The mixed pentose/hexose starting material is typically dissolved or suspended in a solvent, which can also be the alcohol reactant, in order to facilitate the reaction. The solvent system

- 25 may be one or more selected from the group consisting of water, sulfoxides, preferably DMSO, ketones, preferably methyl ethylketone, methylisobutylketone and acetone, ethylene glycol ethers, preferably diethyleneglycol dimethyl ether (diglyme) or the reactant alcohol. Also so-called ionic liquids may be used. The latter refers to a class of inert ionic compounds with a low melting point, which may therefore be used as solvent. Examples thereof include
30 e.g., 1-H-3-methyl imidazolium chloride, discussed in "Dehydration of fructose and sucrose into 5-hydroxymethylfurfural in the presence of 1-H-3-methyl imidazolium chloride acting both as solvent and catalyst", by Claude Moreau et al, Journal of Molecular Catalysis A: Chemical 253 (2006) 165-169.

- 35 The amount of solvent is preferably present in sufficient amounts to dissolve or suspend the starting material and enough to limit undesired side-reactions.

The method of the current invention may be carried out in a batch process or in a continuous process, with or without recycle of (part of) the product stream to control the reaction temperature (recycle via a heat exchanger). For instance, the method of the invention can be performed in a continuous flow process. In such method, homogenous catalysts may be used

- 5 and the residence time of the reactants in the flow process is between 0.1 second and 10 hours, preferably from 1 second to 1 hours, more preferably from 5 seconds to 20 minutes.

Alternatively, the continuous flow process may be a fixed bed continuous flow process or a reactive (catalytic) distillation process with a heterogeneous acid catalyst. To initiate or

- 10 regenerate the heterogeneous acid catalyst or to improve performance, an inorganic or organic acid may be added to the feed of the fixed bed or reactive distillation continuous flow process. In a fixed bed process, the liquid hourly space velocity (LHSV) can be from 1 to 1000, preferably from 5 to 500, more preferably from 10 to 250 and most preferably from 25 to 100 min⁻¹.

15

The above process results in a mixture of a stable HMF ether with furfural, which mixture can then be converted into a further derivative before being used as fuel and/or as fuel additive.

The invention further concerns the use of the mixture of 5-(alkoxymethyl)furfural and furfural

- 20 in a hydrogenation/etherification process to convert the aldehyde function of both 5-(alkoxymethyl)furfural and furfural into an alkoxymethyl function to use the resulting product as a fuel or fuel component. The invention further concerns the use of the mixture of 5-(alkoxymethyl)furfural and furfural in a hydrogenation process to convert the aldehyde function of, preferably, both 5-(alkoxymethyl)furfural and furfural into a CH₃ function to use as
25 a fuel and/or fuel component. Of particular interest is the use of the ethers in diesel, biodiesel or "green diesel", given its (much) greater solubility therein than ethanol. Conventional additives and blending agents for diesel fuel may be present in the fuel compositions of this invention in addition to the above mentioned fuel components. For example, the fuels of this invention may contain conventional quantities of conventional additives such as cetane
30 improvers, friction modifiers, detergents, antioxidants and heat stabilizers, for example. Especially preferred diesel fuel formulations of the invention comprise diesel fuel hydrocarbons and HMF ether as above described together with peroxidic or nitrate cetane improvers such as tertiary butyl peroxide, amyl nitrate and ethyl hexyl nitrate for example.

- 35 The addition of the ethers of the invention to diesel fuel results in similar NO_x numbers and a slight increase in CO emissions; however, the addition of sufficient amounts of cetane

improvers can be utilized to reduce the NO_x and CO emissions well below the base reference fuel.

- Examples are enclosed to illustrate the method of the current invention and the suitability of
- 5 the products prepared therefrom as fuel. The examples are not meant to limit the scope of the invention.

The following abbreviations are used:

F = Furfural

10 HMF = 5- (hydroxymethyl)furfural

MMF = 5-(methoxymethyl)furfural

EMF = 5-(ethoxymethyl)furfural

nBuMF = 5-n(butoxymethyl)furfural

FME = Furfuryl methyl ether

15 FEE = Furfuryl ethyl ether

DMMF = di(methoxymethyl)furan

DEMF = di(ethoxymethyl)furan

The substrate conversions and the selectivities and yields were calculated according to the

20 formulas:

Conversion = $100 * [n_0 \text{ (substrate)} - n_t \text{ (substrate)}] / n_0 \text{ substrate}$

Selectivity = $100 * n_t \text{ (product)} / [n_0 \text{ (substrate)} - n_t \text{ (substrate)}]$

Yield = $100 * n_t \text{ (product)} / n_0 \text{ substrate}$,

Where:

25 n_0 - the initial number of moles

n_t - the number the moles of a compound at time "t".

Example 1

- 30 In a typical experiment, 32.5 mg of xylose, 32.5 mg glucose or fructose and 0.8 ml of ethanol were added in a reactor coated inside with Teflon. The mixture reacted under nitrogen (12.5 bar) in the presence of a solid acid catalyst (6.5 mg) for 1 h at 150 °C. The three main peaks observed in the UV spectrum were identified as Furfural (F), 5-(hydroxymethyl)furfural (HMF) and 5-(ethoxymethyl)furfural EMF.

Table1.

Xylose and	Catalyst	Y F (%)	Y HMF (%)	Y EMF (%)
Glucose	CrCl ₂	23.2	4.8	11.5
Glucose	Zeolite HY 5	7.9	2.1	5.7
Glucose	Al(III) triflate	24.6	0.3	4.3
Fructose	CrCl ₂	20.7	5.7	14.8
Fructose	Zeolite HY 5	8.0	4.2	14.6
Fructose	Al(III) triflate	20.6	0.0	0.4

Example 2

- 5 In a typical experiment, 32.5 mg of xylose, 32.5 mg glucose or fructose and 0.8 ml of methanol were added in a reactor coated inside with Teflon. The mixture reacted under nitrogen (12.5 bar) in the presence of a solid acid catalyst (6.5 mg) for 1 h at 150 °C. The three main peaks observed in the UV spectrum were identified as furfural (F), 5-(hydroxymethyl)furfural (HMF) and 5-(methoxymethyl)furfural (MMF).

10

Table 2

Xylose and	Catalyst	Y F (%)	Y HMF (%)	Y MMF (%)
Glucose	CrCl ₂	11.0	0.9	11.3
Glucose	Al(III) triflate	17.8	0.1	2.1
Fructose	CrCl ₂	9.6	2.2	18.9
Fructose	Al(III) triflate	18.4	0.0	1.5
Fructose	Montmorillonite K 5	4.0	1.0	8.1

Example 3

- 15 In a typical experiment, 65 mg of a mixture of xylose, glucose and fructose (1:1:1, mass ratios) and 6.5 mg of a solid acid catalyst were mixed in a reactor coated inside with Teflon. 0.8 ml of an alcohol mixture (Methanol, Ethanol and n-Butanol with 1/2/1 volume ratio) was added and pressurized at 12.5 bar with nitrogen. The mixture reacted under for 1 h at 150 °C. The main peaks observed in the UV spectrum were identified as F, HMF, EMF, MMF and
- 20 nBuMF.

Table3

Catalyst	Y F (%)	Y HMF (%)	Y EMF (%)	Y MMF (%)	Y nBuMF (%)
CrCl ₂	11.8	6.9	7.5	7.6	2.6
Zeolite HY 5	5.1	5.4	4.2	5.1	0.8
Zeolite HY 15	5.6	1.6	5.3	5.2	1.5
Montmorillonite K 5	5.3	1.3	6.2	6.1	2.0
Montmorillonite K 10	4.4	1.9	5.1	5.0	1.6
Amberlyst36Wet	3.3	2.1	6.2	6.4	1.7
Zeolite β	9.8	0.3	5.5	5.3	1.9

Example 4.

Phase separation / crystallization temperature (°C) of different Furanics / diesel mixtures.

5

The synthesized furanic compounds and their mixtures have been blended with regular diesel fuel at 1:1 ratio by volume. The miscibility of the blends was assessed in a Crystal 16™, a multiple reactor system developed by Avantium Technologies, Amsterdam. Therefore, the samples were cooled at a rate of 0.375°C/min, under continuous stirring at 700 rpm with a magnetic stir bar. Phase separation and/or crystallization was recorded by turbidity measurements. Furfural (F) and ethoxymethylfurfural (EMF) were not miscible with diesel at 1/1 ratio. DMMF is completely miscible at room temperature below 40% addition. Compared to diethers alone the presence of C-5 related monoethers improves the miscibility, especially when methanol is used as etherification agent.

10

Table 4: The miscibility of different furanics with regular diesel

	Fuel composition	Component ratio v/v	Phase separation/ crystallization temperature (°C)
1	Diesel		-12
2	Diesel + DMMF	1:1	>25
3	Diesel + FME	1:1	-7
4	Diesel + DMMF + FME	2:1:1	14
5	Diesel + DEMF	1:1	-8
6	Diesel + FEE	1:1	-11
7	Diesel + DEMF + FEE	2:1:1	-11
8	Diesel + EMF	1:1	>25
9	Diesel + F	1:1	>25
10	Diesel + EMF + F	2:1:1	>25

Example 5.

20 Emission engine testing with diesel, FEE and DEMF

In a D9B diesel engine of a Citroen Berlingo test car, comparative testing was performed with normal commercial diesel fuel (experiment 1) and the same commercial diesel to which 25 vol. % FEE (experiment 2) or 25 vol % DEMF (experiment 3) was added, respectively. FEE

25 and DEMF were added as a liquid and do not yield any mixing or flocculation problems at the blend ratio's used. The engine was run stationary with regular diesel initially, after which the fuel supply is switched to the 25 vol% FEE-diesel blend and the 25 vol% DEMF-diesel blend, respectively.

During stationary operation with the commercial diesel fuel and with the 25 vol% FEE and 25% DEMF blend, the following measurements were made: total particulate matter, volume, O₂, CO, CO₂, NO_x (NO + NO₂) and total hydrocarbons.

- 5 Total particulate matter was sampled according to NEN-EN 13284-1
Particle size distribution was sampled according to VDI 2066-5
Volume was measured according to ISO 10780
Gases were sampled according to ISO 10396
O₂, CO and CO₂ were analysed according to NEN-ISO 12039
- 10 NO_x (NO + NO₂) was analysed according to NEN-ISO 10849
Total hydrocarbons were analysed according to NEN-EN 13526.

Table 5: Gas analysis results of 100% commercial diesel fuel.

Experiment	Component	Average Concentration	Emission
1	CO	240 mg/Nm ³	12 g/h
	CO ₂	2.2 % v/v	-
	O ₂	17.8 % v/v	-
	TOC (C ₃ H ₈)	22 mg/Nm ³	1 g/h
	NO _x	295 mg/Nm ³	14 g/h

- 15 Table 6: Particulate matter results of 100% commercial diesel fuel.

Experiment	Volume		Total particulate matter	
	Actual [m ³ /h]	Normal [Nm ³ /h]	Concentration [mg/Nm ³]	Emission [g/h]
1	63	49	8.0	<1

Table 7: Gas analysis results of blend of commercial diesel with 25 vol% FEE.

Experiment	Component	Average Concentration	Emission
2	CO	302 mg/Nm ³	15 g/h
	CO ₂	2.2 % v/v	-
	O ₂	17.7 % v/v	-
	TOC (C ₃ H ₈)	38 mg/Nm ³	2 g/h
	NO _x	290 mg/Nm ³	14 g/h

Table 8: Particulate matter results of blend of commercial diesel with 25 vol% FEE.

Experiment	Volume		Total particulate matter	
	Actual [m ³ /h]	Normal [Nm ³ /h]	Concentration [mg/Nm ³]	Emission [g/h]
2	63	49	12.6	<1

Table 9: Gas analysis results of blend of commercial diesel with 25 vol% DEMF.

Experiment	Component	Average Concentration	Emission
3	CO	520 mg/Nm ³	25 g/h
	CO ₂	2.2 % v/v	-
	O ₂	17.7 % v/v	-
	TOC (C ₃ H ₈)	96 mg/Nm ³	5 g/h
	NO _x	278 mg/Nm ³	14 g/h

Table 10: Particulate matter results of blend of commercial diesel with 25 vol% DEMF.

Experiment	Volume		Total particulate matter	
	Actual [m ³ /h]	Normal [Nm ³ /h]	Concentration [mg/Nm ³]	Emission [g/h]
3	63	49	23.4	11

5

Example 6.

Emission engine testing with diesel, FME and DMMF

- 10 In a manner similar to Example 5, a D9B diesel engine of a Citroen Berlingo test car, comparative testing was performed with normal commercial diesel fuel (experiment 4) and the same commercial diesel to which 25 vol. % FME (experiment 5) or 12.5 vol % DMMF (experiment 6) was added, respectively. FME and DMMF were added as a liquid and do not yield any mixing or flocculation problems at the blend ratio's used. The engine is run 15 stationary with regular diesel initially, after which the fuel supply is switched to the 25 vol% FME-diesel blend and the 12.5 vol% DMMF-diesel blend, respectively.

The results of the measurements are listed in the Tables 11 to 15

Table 11: Gas analysis results of 100% commercial diesel fuel.

Experiment	Component	Average Concentration	Emission
4	CO	205 mg/Nm ³	7 g/h
	CO ₂	2.2 % v/v	-
	O ₂	17.9 % v/v	-
	TOC (C ₃ H ₈)	24 mg/Nm ³	1 g/h
	NO _x	293 mg/Nm ³	9 g/h

Table 12: Particulate matter results of 100% commercial diesel fuel.

Experiment	Volume		Total particulate matter	
	Actual [m ³ /h]	Normal [Nm ³ /h]	Concentration [mg/Nm ³]	Emission [g/h]
4	39	32	6.3	<1

5 Table 13: Gas analysis results of blend of commercial diesel with 25 vol% FME.

Experiment	Component	Average Concentration	Emission
5	CO	288 mg/Nm ³	9 g/h
	CO ₂	2.2 % v/v	-
	O ₂	17.8 % v/v	-
	TOC (C ₃ H ₈)	33 mg/Nm ³	1 g/h
	NO _x	308 mg/Nm ³	9 g/h

Table 14: Particulate matter results of blend of commercial diesel with 25 vol% FME.

Experiment	Volume		Total particulate matter	
	Actual [m ³ /h]	Normal [Nm ³ /h]	Concentration [mg/Nm ³]	Emission [g/h]
5	36	30	8.5	<1

Table 15: Gas analysis results of blend of commercial diesel with 12.5 vol% DMMF.

Experiment	Component	Average Concentration	Emission
6	CO	260 mg/Nm ³	8.5 g/h
	CO ₂	2.2 % v/v	-
	O ₂	17.9 % v/v	-
	TOC (C ₃ H ₈)	31 mg/Nm ³	1 g/h
	NO _x	275 mg/Nm ³	8.5 g/h

Table 16: Particulate matter results of blend of commercial diesel with 12.5 vol% DMMF.

Experiment	Volume		Total particulate matter	
	Actual [m ³ /h]	Normal [Nm ³ /h]	Concentration [mg/Nm ³]	Emission [g/h]
6	39	32	10.6	<1

5 Example 7. diesel fuel applications

Fuel solubility

Fuel solubility is a primary concern for diesel fuel applications. Not all highly polar oxygenates have good solubility in the current commercial diesel fuels. Results show that mixtures of 2,5-10 di(ethoxymethyl)furan and 2-(ethoxymethyl)furan (etherification product, prepared from a mixed C6/C5 starting material) with commercial diesel and mixtures of 5-(ethoxymethyl)-2-methylfuran and 2-methylfuran (hydrogenation product, prepared from a mixed C6/C5 starting material) with commercial diesel are completely miscible in all ratio's. In a comparative set of experiments it was shown that ethoxymethylfurfural (EMF) (prepared from 15 a C6 starting material) is completely miscible in a 5 vol% blend with commercial diesel, but that phase separation occurs with the 25 vol% and with the 40 vol% blends of EMF and diesel. Results with an EMF/furfural blend were worse than that with EMF alone.

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EDITORIAL NOTE

APPLICATION NUMBER – 2008295006

**The correct number of claims is 19 as there is no claim
numbered 10**

Claims

1. Method for the manufacture of a mixture of a furfural and a 5-alkoxymethylfurfural derivative by reacting a hexose and pentose-containing starting material with an aliphatic C1 - C20 alcohol in the presence of an acid catalyst, resulting in a mixture of furfural and a 5- (alkoxymethyl)furfural, followed by the hydrogenation and/or etherification of the mixture of furfural and 5-alkoxymethylfurfural to convert the aldehyde function of both 5- (alkoxymethyl)furfural and furfural into an alkoxymethyl function or methyl function.
 2. Method according to claim 1, wherein the alcohol is a primary, secondary or tertiary, preferably a primary or secondary, more preferably a primary, monoalcohol and whereby the monoalcohols with 4 or more carbon atoms preferably have a branched carbon backbone.
 3. Method according to claim 2, wherein the monoalcohol is selected from one or more of the group consisting of C3 to C8 alcohols comprising 2-propanol, 2-butanol, 2-methyl-1-propanol (isobutanol), 2-methyl-2-propanol (*tert*-butanol), 2-pentanol (s-amyl alcohol); 2-methyl-1-butanol (p-amyl alcohol); 2-methyl-2-butanol (t-amyl alcohol); 3-methyl-1-butanol (isoamyl alcohol); 2,2-dimethyl-1-propanol (neopentyl alcohol); 2-hexanol; and 2-ethyl-1-hexanol (isooctyl alcohol), preferably from isobutanol, *tert*-butanol, isoamyl alcohol, isooctyl alcohol, preferably selected from the group consisting of methanol, ethanol, 1-propanol, 2-propanol, isobutanol, *tert*-butanol, isoamyl alcohol, isooctyl alcohol and mixtures thereof
 4. Method according to claims 1-3, wherein the acid catalyst is selected from the group consisting of homogeneous or heterogeneous acids selected from solid organic acids, inorganic acids, salts, Lewis acids, ion exchange resins, zeolites or mixtures and/or combinations thereof.
 5. Method according to claim 1, wherein the acid catalyst is a solid Brønsted acid.
 6. Method according to claim 1, wherein the acid catalyst is a solid Lewis acid.
- 30
7. Method according to any one of the claims 1 to 6, wherein the reaction is performed at a temperature from 50 to 300 degrees Celsius, preferably from 125 to 250 degrees Celsius, more preferably from 150 to 225 degrees Celsius.

8. Method according to any one of the claims 1 to 7, wherein the hexose is selected from the group consisting of

- starch, amylose, galactose, cellulose, hemi-cellulose,
- glucose-containing disaccharides such as sucrose, maltose, cellobiose, lactose,
5 preferably glucose-containing disaccharides, more preferably sucrose,
- glucose or fructose

and their oxidized, reduced, etherified, esterified and amidated derivatives.

9. Method according to any of the claims 1-7, wherein the pentose is selected from the
10 group consisting of Arabinose, Ribose, Ribulose, Xylose, Xylulose, Lyxose and their oxidized, reduced, etherified, esterified and amidated derivatives.

11. Method according to any one of the claims 1 to 9, performed in the presence of a solvent, wherein the solvent or solvents are selected form the group consisting of water, sulfoxides, preferably DMSO, ketones, preferably methyl ethylketone, ionic liquids, methylisobutylketone and/or acetone, esters, ethers, preferably ethylene glycol ethers, more 15 preferably diethyleneglycol dimethyl ether (diglyme) or the reactant alcohol as defined in claims 2 and 3, and mixtures thereof.

20 12. Method according to any one of the claims 1 to 11, wherein the method is performed in a continuous flow process.

13. Method according to claim 12, wherein the residence time in the flow process is between 0.1 second and 10 hours, preferably from 1 second to 1 hours, more preferably from 25 5 seconds to 20 minutes.

14. Method according to claim 13, wherein the continuous flow process is a fixed bed continuous flow process.

30 15. Method according to claim 14, wherein the fixed bed comprises a heterogeneous acid catalyst.

16. Method according to claim 15, wherein the continuous flow process is a reactive distillation or a catalytic distillation process.

EDITORIAL NOTE

APPLICATION NUMBER – 2008295006

There is no page 18

AMENDED CLAIMS**received by the International Bureau on 29 January 2009 (29.01.2009)**

17. Method according to claim 16, wherein in addition to a heterogeneous acid catalyst, an inorganic or organic acid catalyst is added to the feed of the fixed bed or catalytic distillation continuous flow process.

5

18. Method according to claim 14-17, wherein the liquid hourly space velocity ("LHSV") is from 1 to 1000, preferably from 5 to 500, more preferably from 10 to 250 and most preferably from 25 to 100.

10 19. Use of the ether produced by the method of any one of claims 1-18 as fuel or fuel additive for engines.

20. A fuel or fuel composition comprising the ether produced by the method of any one of claims 1-18 as fuel component for engines, optionally blended with one or more of gasoline
15 and gasoline-ethanol blends, kerosene, diesel, biodiesel, Fischer-Tropsch liquids, diesel-biodiesel blends and green diesel and blends of diesel and/or biodiesel with green diesel and other derivatives of furan and tetrahydrofuran.



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(54) **HYDROXYMETHYLFURFURAL ETHERS
FROM SUGARS OR HMF AND BRANCHED
ALCOHOLS**

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(75) Inventor: **Gerardus Johannes Maria
Gruter**, Heemstede (NL)

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Correspondence Address:

**HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791 (US)**

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(52) **U.S. Cl.** **ABSTRACT**

(73) Assignee: **FURANIX TECHNOLOGIES
B.V.**, Amsterdam (NL)

(21) Appl. No.: **12/676,529**

(22) PCT Filed: **Sep. 5, 2008**

The current invention provides a method for the manufacture of an ether of 5-hydroxymethylfurfural by reacting a hexose-containing starting material with a branched C3-C20 monoalcohol in the presence of a catalytic or sub-stoichiometric amount of an acid catalyst.

Fig 1

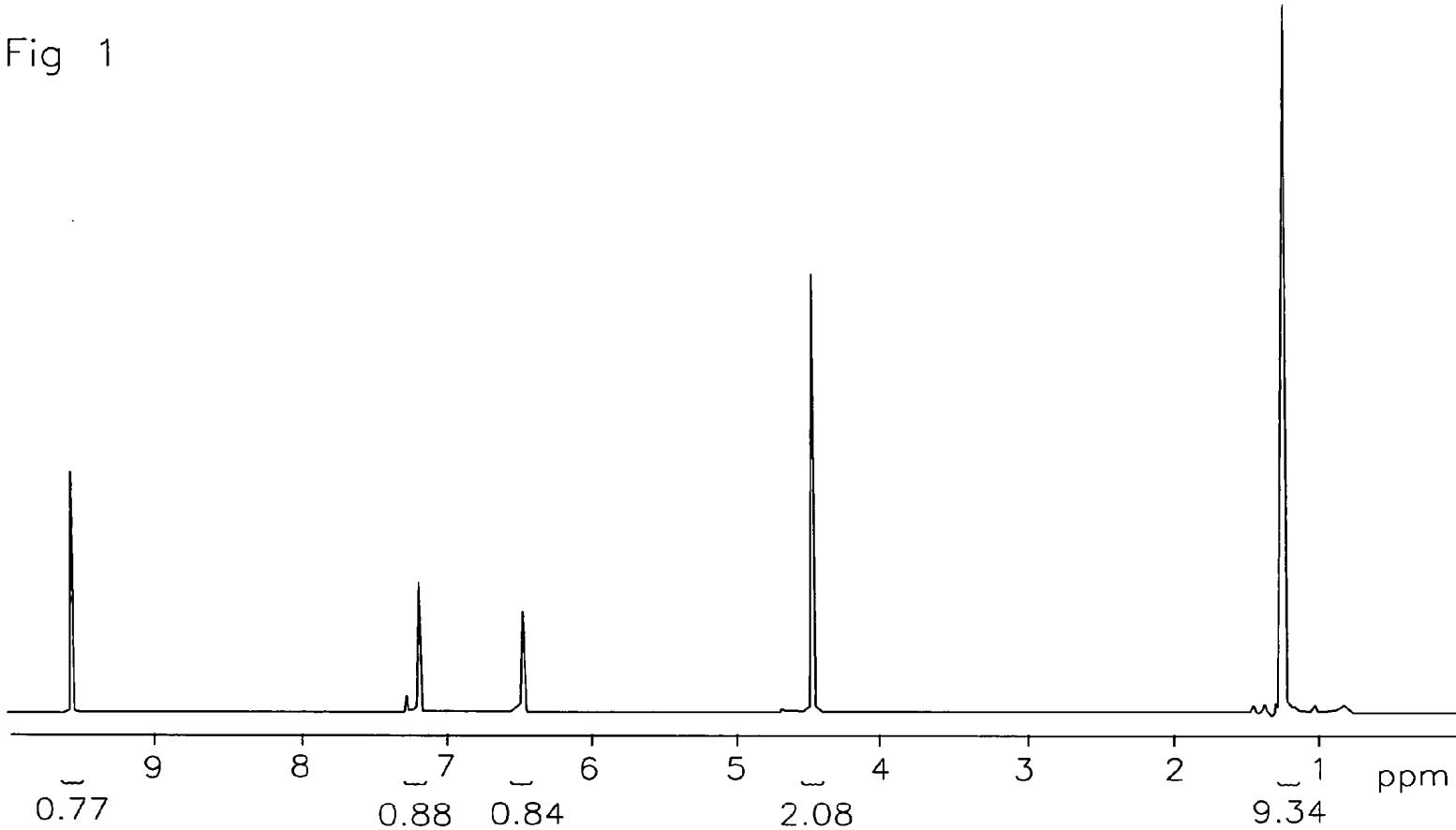
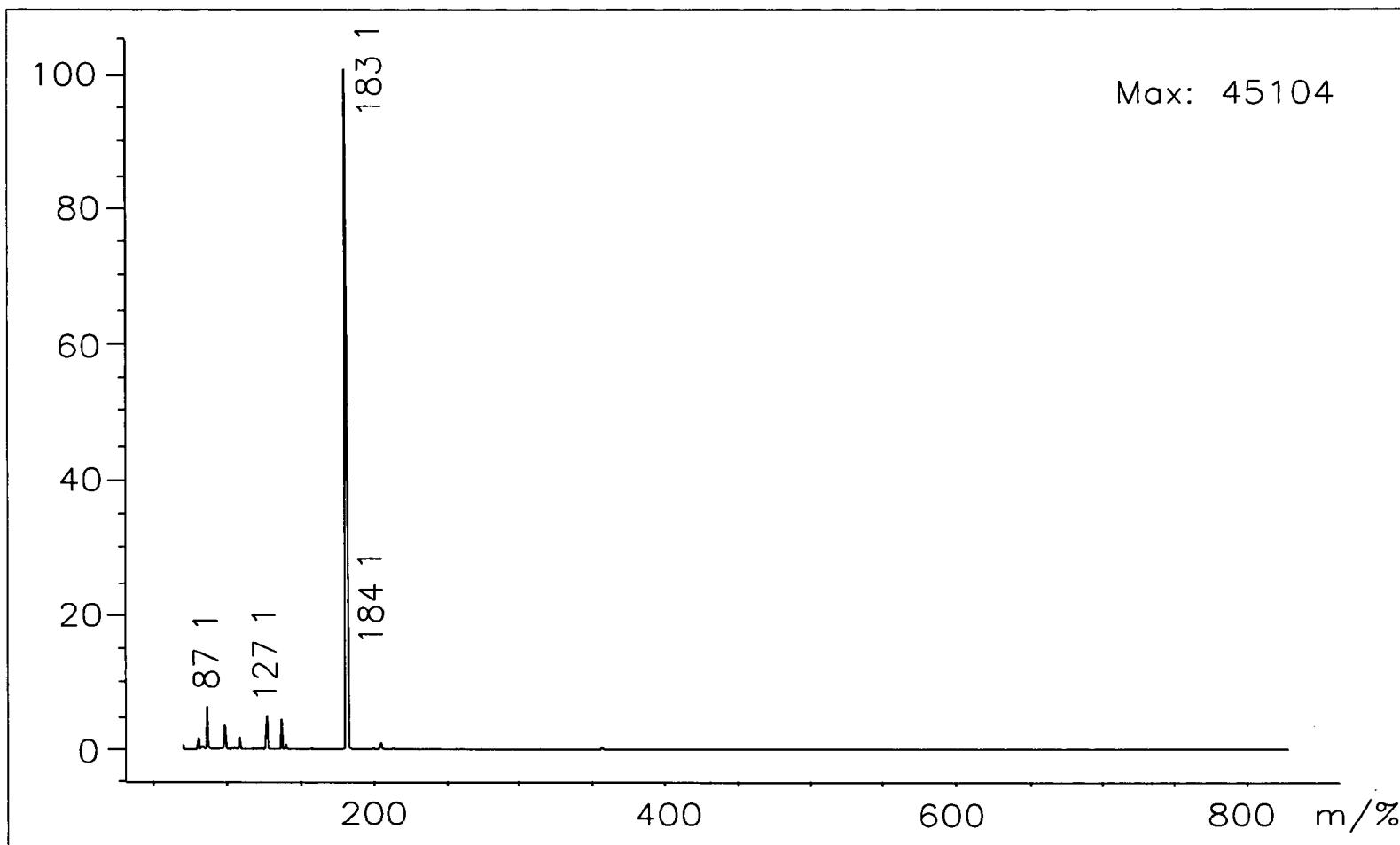


Fig 2



HYDROXYMETHYLFURFURAL ETHERS FROM SUGARS OR HMF AND BRANCHED ALCOHOLS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is the National Stage of International Application No. PCT/E2008/007412, filed Sep. 5, 2008, which claims priority to European Application No. 07075773.7, filed Sep. 7, 2007, the entire contents of each of which are incorporated by reference herein.

FIELD OF THE INVENTION

[0002] The present invention concerns a method for the manufacture of an ether of 5-hydroxymethylfurfural (5-(hydroxymethyl)-2-furaldehyde, or HMF) from biomass.

BACKGROUND OF THE INVENTION

[0003] Fuel, fuel additives and various chemicals used in the petrochemical industry are derived from oil, gas and coal, all finite sources. Biomass, on the other hand, is considered a renewable source. Biomass is biological material (including biodegradable wastes) which can be used for the production of fuels or for industrial production of e.g. fibres, chemicals or heat. It excludes organic material which has been transformed by geological processes into substances such as coal or petroleum.

[0004] Production of biomass derived products for non-food applications is a growing industry. Bio-based fuels are an example of an application with strong growing interest.

[0005] Biomass contains sugars (hexoses and pentoses) that may be converted into value added products. Current biofuel activities from sugars are mainly directed towards the fermentation of sucrose or glucose into ethanol or via complete breakdown via Syngas to synthetic liquid fuels. EP 0641 854 describes the use of fuel compositions comprising of hydrocarbons and/or vegetable oil derivatives containing at least one glycerol ether to reduce particulate matter emissions.

[0006] More recently, the acid catalysed reaction of fructose has been re-visited, creating HMF as an intermediate of great interest. Most processes investigated have the disadvantage that HMF is not very stable at the reaction conditions required for its formation. Fast removal from the water-phase containing the sugar starting material and the acid catalyst has been viewed as a solution for this problem. Researchers at the University of Wisconsin-Madison have developed a process to make HMF from fructose. HMF can be converted into monomers for plastics, petroleum or fuel extenders, or even into fuel itself. The process by prof. James Dumesic and co-workers first dehydrates the fructose in an aqueous phase with the use of an acid catalyst (hydrochloric acid or an acidic ion-exchange resin). Salt is added to salt-out the HMF into the extracting phase. The extracting phase uses an inert organic solvent that favors extraction of HMF from the aqueous phase. The two-phase process operates at high fructose concentrations (10 to 50 wt %), achieves high yields (80% HMF selectivity at 90% fructose conversion), and delivers HMF in a separation-friendly solvent (DUMESIC, James A, et al. "Phase modifiers promote efficient production of Hydroxymethylfurfural from fructose". Science. 30 Jun. 2006, vol. 312, no. 5782, p. 1933-1937). Although the HMF yields from this process are interesting, the multi-solvent process has cost-

disadvantages due to the relatively complex plant design and because of the less than ideal yields when cheaper and less reactive hexoses than fructose, such as glucose or sucrose, are used as a starting material. HMF is a solid at room temperature which has to be converted in subsequent steps to useful products. Dumesic has reported an integrated hydrogenolysis process step to convert HMF into dimethylfuran (DMF), which is assumed to be an interesting gasoline additive.

[0007] In WO 2006/063220 a method is provided for converting fructose into 5-ethoxymethylfurfural (EMF) at 60° C., using an acid catalyst either in batch during 24 hours or continuously via column elution during 17 hours. Applications of EMF were not discussed.

[0008] Also in copending patent application PCT/EP2007/002145 the manufacture of HMF ethers are described, including the use of such ethers as fuel or fuel additive. Indeed, both the methyl ether and the ethyl ether (methoxymethylfurfural, or MMF; ethoxyethylfurfural or EMF) were prepared and tested. The invention of the copending patent application, however, was limited to the use of primary aliphatic alcohols, and preferably primary C1-C5 alcohols. Use of secondary and tertiary alcohols was not considered, whereas the only example of a branched primary alcohol was considered, was a diol ("2-hydroxymethyl-propanol", which is 2-methyl-1,3-propanediol). Although MMF and EMF are useful as fuel or fuel additive, the inventors found that the ethers leave room for improvement, in particular when used in higher concentration blends with fuels such as gasoline, kerosene, diesel, biodiesel or green diesel. The inventors have therefore set out to overcome this shortfall.

[0009] Surprisingly, the inventors have found that ethers of HMF obtained from branched alcohols have superior blending properties compared to ethers obtained from unbranched alcohol analogs. In this context, branched alcohols are defined as

[0010] C4-C20 primary alcohols with branched carbon backbones

[0011] C3-C20 secondary alcohols with straight chain carbon backbones

[0012] C4-C20 secondary alcohols with branched carbon backbones

[0013] C4-C20 tertiary alcohols with branched carbon backbones

[0014] The ethers of HMF with these alcohols may be produced in a reasonable yield from hexose containing feedstock, with reduced levels of by-product formation and in a manner that does not require cumbersome process measures (such as 2-phase systems) or lengthy process times.

SUMMARY OF THE INVENTION

[0015] Accordingly, the current invention provides a method for the manufacture of an ether of 5-hydroxymethylfurfural by reacting a hexose-containing starting material with a branched C3-C20 monoalcohol in the presence of a catalytic or sub-stoichiometric amount of an acid catalyst.

[0016] When the reaction product of the above method is used as such or when it is used as an intermediate for a subsequent conversion, the selectivity of the reaction is preferably high as the product is preferably pure. However, when the reaction product of the above method is used as a fuel, a fuel additive or as a fuel or a fuel additive intermediate, the reaction product does not necessarily need to be pure. Indeed, in the preparation of fuel and fuel additives from biomass, which in itself is a mixture of various monosaccharides, dis-

accharides and polysaccharides, the reaction product may contain non-interfering components such as levulinic acid derivatives and/or derivatives of pentoses and the like. For ease of reference, however, the method and the reaction product are described in terms of the reaction of a hexose-containing starting material, resulting in an ether of HMF. Also within the scope of the invention is the reaction of HMF with the branched alcohol, since HMF is believed to be produced as intermediate from the hexose-containing starting material.

[0017] The current invention also provides for the use of the reaction product made according to the present invention as fuel or as fuel additive. Fuels for blending with the product of the present invention include but are not limited to gasoline and gasoline-ethanol blends, kerosene, diesel, biodiesel (refers to a non-petroleum-based diesel fuel consisting of short chain alkyl (methyl or ethyl) esters, made by transesterification of vegetable oil, which can be used (alone, or blended with conventional petrodiesel), Fischer-Tropsch liquids (for example obtained from GTL, CTL or BTL gas-to-liquids/coal-to-liquids/biomass to liquids processes), diesel-biodiesel blends and green diesel and blends of diesel and/or biodiesel with green diesel (green diesel is a hydrocarbon obtained by hydrotreating biomass derived oils, fats, greases or pyrolysis oil; see for example the UOP report OPPORTUNITIES FOR BIORENEWABLES IN OIL REFINERIES FINAL TECHNICAL REPORT, SUBMITTED TO: U.S. DEPARTMENT OF ENERGY (DOE Award Number: DE-FG36-05GO15085). The product is a premium diesel fuel containing no sulfur and having a cetane number of 90 to 100). Fuels for blending with the product of the present invention may also include one or more other furanics, wherein the expression furanics is used to include all derivatives of furan and tetrahydrofuran. The invention also provides a fuel composition comprising a fuel element as described above and the reaction product made according to the present invention.

FIGURES

[0018] FIG. 1 is the 1H-NMR of 5-(tert-butoxymethyl)furfural, tBMF, prepared by the process of the current invention.

[0019] FIG. 2 is the spectrum of tBMF using a mass spectrometer in Chemical Ionization (C.I.) Mode.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0020] Biomass resources are well known. The components of interest in biomass are the mono-, di- or polysaccharides (hereinafter referred to as hexose-containing starting material). Suitable 6-carbon monosaccharides include but are not limited to fructose, glucose, galactose, mannose, and their oxidized, reduced, etherified, esterified and amidated derivatives, e.g. aldonic acid or alditol, with glucose being the most abundant, the most economic and therefore the most preferred monosaccharide albeit less reactive than fructose. On the other hand, the current inventors have also succeeded to convert sucrose, which is also available in great abundance. Other disaccharides that may be used include maltose, cellobiose and lactose. The polysaccharides that may be used include cellulose, inulin (a polyfructan), starch (a polyglucan) and hemi-cellulose. The polysaccharides and disaccharides are converted into their monosaccharide component(s) and dehydrated during the manufacture of the 5-HMF ether.

[0021] The branched alcohol used in the method of the current invention preferably bears a singly hydroxyl group,

which may be in a primary, secondary or even tertiary position. The alcohol may comprise from 3 to 20 carbon atoms, preferably from 3 to 8 carbon atoms, whereby the alcohols with 4 or more carbon atoms have a branched carbon backbone.

[0022] In this context, branched alcohols are defined as

[0023] C4-C20 primary alcohols with branched carbon backbones ($R-\text{CH}_2\text{OH}$, with $R=\text{cyclic}$ or non cyclic alkyl, aralkyl, aryl, alkenyl, and where R can contain 0, 1 or 2 elements not being C or H) such as the following non-limiting examples: 2-methylpropanol, 2,2-dimethylpropanol, 2-methylbutanol, 3-methylbutanol, 2,2-dimethylbutanol, 3,3-dimethylbutanol, 2,3-dimethylbutanol, 2-ethylbutanol, hydroxymethylcyclopentane, 2-hydroxymethyltetrahydrofuran, 4-tert-butylbenzylalcohol, isoctanol (3-(hydroxymethyl)heptanol), etc.

[0024] C3-C20 secondary alcohols with straight chain carbon backbones ($R-\text{C}(\text{H})\text{OH}-R'$, with $R, R'=\text{n-alkyl}$, $n\text{-alkenyl}$ and where R and R' can be connected to form a ring, and where R can contain 0, 1 or 2 elements not being C or H) such as the following non-limiting examples: 2-propanol, 2-butanol, 2-pentanol, 3-pentanol, 4-hydroxy-1-pentene, 3-methoxy-2-propanol, etc

[0025] C4 secondary alcohols with branched backbones such as 2- and 3-hydroxytetrahydrofuran and C5-C20 secondary alcohols with branched carbon backbones ($R-\text{C}(\text{H})\text{OH}-R'$, with $R, R'=\text{alkyl}$, aralkyl, aryl, alkenyl, where R and R' can be connected to form a ring, and where R can contain 0, 1 or 2 elements not being C or H) such as the following non-limiting examples: cyclopentanol, 4-cyclopentenol, 3-methyl-2-butanol, 3-methyl-2-pentanol, etc.

[0026] C4-C20 tertiary alcohols with branched carbon backbones such as tert-Amyl alcohol (2-Methyl-2-Butanol).

[0027] Preferred alcohols used in the method of the current invention include isobutanol, tert-butanol, isoamyl alcohol, isoctyl alcohol. Also blends of alcohols may be used, e.g., of isobutanol and tert-butanol.

[0028] The amount of branched monoalcohol used during the manufacture of the HMF ether is preferably at least equimolar on the hexose content of the feedstock, but typically is used in much greater excess. Indeed, the alcohol (such as isobutanol) may be used as solvent or co-solvent. In such a case, a sufficient amount of alcohol is present to form the HMF ether.

[0029] The acid catalyst in the method of the present invention can be selected from amongst (halogenated) organic acids, inorganic acids, Lewis acids, ion exchange resins and zeolites or combinations and/or mixtures thereof. It may be a homogeneous catalyst, but heterogeneous catalysts (meaning solid) are preferred for purification reasons. The HMF ethers can be produced with a protonic, Brønsted or, alternatively, a Lewis acid or with catalysts that have more than one of these acidic functionalities.

[0030] The protonic acid may be organic or inorganic. For instance, the organic acid can be selected from amongst oxalic acid, levulinic acid, maleic acid, trifluoro acetic acid (triflic acid), methansulphonic acid or para-toluenesulphonic acid. Alternatively, the inorganic acid can be selected from amongst (poly)phosphoric acid, sulphuric acid, hydrochloric acid, hydrobromic acid, nitric acid, hydroiodic acid, optionally generated in situ.

[0031] Certain salts may be used as catalyst, wherein the salt can be any one or more of $(\text{NH}_4)_2\text{SO}_4/\text{SO}_3$, ammonium phosphate, pyridinium chloride, triethylamine phosphate, pyridinium salts, pyridinium phosphate, pyridinium hydrochloride/hydrobromide/perbromate, DMAP, aluminium salts, Th and Zr ions, zirconium phosphate, Sc and lanthanide ions such as Sm and Y as their acetate or trifluoroacetate (triflate) salt, Cr—, Al—, Ti—, Ca—, In—, ZrOCl_2 , $\text{VO}(\text{SO}_4)_2$, TiO_2 , V-porphyrine, Zr—, Cr—, Ti-porphyrine.

[0032] Lewis acids selected as dehydration catalyst can be any one of ZnCl_2 , AlCl_3 , BF_3 .

[0033] Ion exchange resins can be suitable dehydration catalysts. Examples include Amberlite™ and Amberlyst™, Diaion™ and Levatit™. Other solid catalyst that may be used include natural clay minerals, zeolites, supported acids such as silica impregnated with mineral acids, heat treated charcoal, metal oxides, metal sulfides, metal salts and mixed oxides and mixtures thereof. If elevated reaction temperatures are used, as defined hereafter, then the catalyst should be stable at these temperatures.

[0034] An overview of catalysts that may be used in the method of the current invention may be found in Table 1 of the review article prepared by Mr. Lewkowski: "Synthesis, chemistry and applications of 5-hydroxymethylfurfural and its derivatives" Arkivoc. 2001, p. 17-54.

[0035] A catalytic or sub-stoichiometric amount of catalyst is used. Within this range, the amount of catalyst may vary, depending on the selection of catalyst or catalyst mixture. For instance, the catalyst can be added to the reaction mixture in an amount varying from 0.01 to 40 mole % drawn on the hexose content of the biomass resource, preferably from 0.1 to 30 mole %, more preferably from 1 to 20 mole %.

[0036] In the preferred embodiment, the catalyst is a heterogeneous catalyst.

[0037] The temperature at which the reaction is performed may vary, but in general it is preferred that the reaction is carried out at a temperature from 50 to 300 degrees Celsius, preferably from 125 to 250 degrees Celsius, more preferably from 150 to 225 degrees Celsius. In general, temperatures higher than 300 are less preferred as the selectivity of the reaction reduces and as many by-products occur, *inter alia* caramelisation of the sugar. Performing the reaction below the lowest temperature is also less preferable because of the low reaction rate. If the reactions are carried out above the boiling temperature of water, then the reactions are preferably carried out under pressure, e.g., 10 bar nitrogen or higher.

[0038] The HMF or hexose-containing starting material is typically dissolved or suspended in a solvent, which can also be the alcohol reactant, in order to facilitate the reaction. The solvent system may be one or more selected from the group consisting of water, sulfoxides, preferably DMSO, ketones, preferably methyl ethylketone, methylisobutylketone and acetone, ethylene glycol ethers, preferably diethyleneglycol dimethyl ether (diglyme) or the reactant olefin. Also so-called ionic liquids may be used. The latter refers to a class of inert ionic compounds with a low melting point, which may therefore be used as solvent. Examples thereof include e.g., 1-H-3-methylimidazolium chloride, discussed in "Dehydration of fructose and sucrose into 5-hydroxymethylfurfural in the presence of 1-H-3-methyl imidazolium chloride acting both as solvent and catalyst", by Claude Moreau et al, Journal of Molecular Catalysis A: Chemical 253 (2006) 165-169.

[0039] The amount of solvent is preferably present in sufficient amounts to dissolve or suspend the starting material.

[0040] The method of the current invention may be carried out in a batch process or in a continuous process, with or without recycle of (part of) the product stream to control the reaction temperature (recycle via a heat exchanger). For instance, the method of the invention can be performed in a continuous flow process. In such method, homogenous catalysts may be used and the residence time of the reactants in the flow process is between 0.1 second and 10 hours, preferably from 1 second to 1 hours, more preferably from 5 seconds to 20 minutes.

[0041] Alternatively, the continuous flow process may be a fixed bed continuous flow process or a reactive (catalytic) distillation process with a heterogeneous acid catalyst. To initiate or regenerate the heterogeneous acid catalyst or to improve performance, an inorganic or organic acid may be added to the feed of the fixed bed or reactive distillation continuous flow process. In a fixed bed process, the liquid hourly space velocity (LHSV) can be from 1 to 1000, preferably from 5 to 500, more preferably from 10 to 250 and most preferably from 25 to 100 min^{-1} .

[0042] The above process results in a stable HMF ether, which can then be used as such or be converted into a further derivative before being used as fuel and/or as fuel additive. The inventors are of the opinion that some of the products prepared by the method of the current invention are actually new. Thus, the t-butoxy-, isobutyl-, isoamyl- or isooctyl-ether of HMF, prepared by using isobutanol, isopentanol or isooctanol as alcohol, are new and are excellent fuel components or fuel additives. Since these alcohols may be made from biomass, this might open a class of products that are fully biomass-derived. Accordingly, these new ethers are claimed as well.

[0043] The HMF ethers of the invention can also be used as or can be converted to compounds that can be used as solvent, as monomer in a polymerization (such as 2,5-furan dicarboxylic acid or FDCA), as fine chemical or pharmaceutical intermediate, or in other applications. Oxidation of the HMF ethers using an appropriate catalyst under appropriate conditions such as for example described for p-xylene with a NHPI/ $\text{Co}(\text{OAc})_2/\text{MnOAc}$)₂ catalyst system in Adv. Synth. Catal. 2001, 343, 220-225 or such as described for HMF with a Pt/C catalyst system at pH<8 in EP 0 356 703 or such as described for HMF with a Pt/C catalyst system at pH>7 in FR 2 669 634, all with air as an oxidant, resulted in the formation of 2,5-furan dicarboxylic acid (FDCA).

[0044] The invention further concerns the use of the HMF ethers prepared by the method of the current invention as fuel and/or as fuel additive. Of particular interest is the use of the ethers in diesel, biodiesel or "green diesel", given its (much) greater solubility therein than ethanol. Conventional additives and blending agents for diesel fuel may be present in the fuel compositions of this invention in addition to the above mentioned fuel components. For example, the fuels of this invention may contain conventional quantities of conventional additives such as cetane improvers, friction modifiers, detergents, antioxidants and heat stabilizers, for example. Especially preferred diesel fuel formulations of the invention comprise diesel fuel hydrocarbons and HMF ether as above described together with peroxidic or nitrate cetane improvers such as tertiary butyl peroxide, amyl nitrate and ethyl hexyl nitrate for example.

[0045] The addition of the HMF ether of the invention to diesel fuel results in similar NO_x numbers and a slight increase in CO emissions; however, the addition of sufficient

amounts of cetane improvers can be utilized to reduce the NO_x and CO emissions well below the base reference fuel. [0046] Examples are enclosed to illustrate the method of the current invention and the suitability of the products prepared therefrom as fuel. The examples are not meant to limit the scope of the invention.

[0047] The substrate conversion, the selectivity and yield were calculated according to the formulas:

$$\text{Conversion} = 100 * \frac{n_t(\text{substrate}) - n_i(\text{substrate})}{n_0(\text{substrate})}$$

$$\text{Selectivity} = 100 * \frac{n_t(\text{product})}{[n_0(\text{substrate}) - n_i(\text{substrate})]}$$

$$\text{Yield} = 100 * \frac{n_t(\text{product})}{n_0(\text{substrate})}$$

[0048] Where:

[0049] n₀—the initial number of moles

[0050] n_t—the number the moles of a compound at time "t".

Example 1

5-(tert-Butoxymethyl)furfural (tBMF) Formation from HMF and tert-butyl Alcohol

[0051] To 10 g (0.079 mol) of HMF was added 16.26g (0.22 mol) t-butyl alcohol and 0.5 g Amberlyst-15. The reactor was flushed with N₂(g) and heated to 75° C. for 2 days. The mixture was concentrated and the brown oil was purified by column chromatography over SiO₂ (EtOAc:heptane, 5:95) to give tBMF (6.1 gr, 42.2%) as a yellow oil.

[0052] The reaction products were characterized by ¹H NMR and LC-MS (CI). See FIG. 1.

Example 2

tBMF Formation from Fructose (or Glucose) and tert-butyl Alcohol

[0053] A 1.25 wt % solution of sugar (Frc or Glc) in water/tert-butanol mixture (89 or 84 wt % tert-butanol respectively) was flowed through a fixed bed (200 µl) of a Amberlyst-36 dry catalyst at 190° C. Flow rates were selected such to achieve a space velocity of 0.25 or 0.5 min⁻¹, i.e. a contact time of 2 or 4 min.

[0054] In all cases tBMF was detected by HPLC and identified by LC-MS (CI) in the effluent stream.

Example 3

tBMF Formation from Sugars and tert-butyl Alcohol

[0055] The reactions were performed in the batch parallel reactors system (Block 96). In a typical experiment, 65 mg of glucose or fructose was weighted in into a reactor lined with Teflon. 0.8 ml of tert-butyl alcohol was added and the mixture reacted under nitrogen (12.5 bar) in the presence of a solid acid catalyst (6.5 mg).

Substrate	Catalyst	T (° C.)	Time (h)	s Conv. (%)	s HMF (%)	s tBMF (%)
Fructose	CrCl ₂	150	1	96.6	37.7	9
	Zeolite HY 5	150	3	80.5	42.1	5.8
	Zeolite HY 15	150	3	44	53	5.9
	Amberlyst 36	150	3	70	30.5	9.4

-continued

Substrate	Catalyst	T (° C.)	Time (h)	s Conv. (%)	s HMF (%)	s tBMF (%)
Glucose	Wet					
	Amberlyst 36	150	3	81.1	34.6	14.6
	Dry	135	2	97.8	21.3	6.5
	CrCl ₂	135	16	98.9	14.7	4.4
	Zeolite HY 5					

Example 4

5-(Isopropoxymethyl)furfural (iPropMF) Formation from Sugars and isopropyl Alcohol

[0056] In these experiments, 65 mg of glucose or fructose was weighted in into a reactor lined with Teflon. 0.8 ml of isopropyl alcohol was added and the mixture reacted under nitrogen (12.5 bar) for 1 h at 150° C., in the presence of a solid acid catalyst (6.5 mg). The two main peaks observed in the UV spectrum were identified as HMF and 5-(isopropoxymethyl)furfural (iPropMF).

Substrate	Catalyst	Conversion [%]	HMF select. (%)	iPropMF select. (%)
Glucose	CrCl ₂	97.6	31.1	10.2
	Zeolite HY 5	68.2	57.7	1.7
	Zeolite HY 15	71.3	24.8	22.9
	Montmorillonite K 5	79.6	23.2	15.9
	Montmorillonite K 10	68.4	22.8	18.6
	Montmorillonite K 70	72.6	46.3	13.7
	Amberlyst 70	92.0	40.6	11.3
	Amberlyst36Wet	22.7	9.6	0.0
Fructose	SulphatedZirconia	98.7	33.5	14.5
	Amberlyst36Dry			

Example 5

5-(tert-butoxymethyl)furfural (tBuMF) Formation from HMF and tert-butyl Alcohol

[0057] In these experiments, a mixture of 0.36 mmol of HMF, and 0.8 ml of tert-butyl alcohol reacted under nitrogen (12.5 bar), in the presence of a solid acid catalyst (6.5 mg), 3 h at 100° C.

Catalyst	Conv. (%)	s (tBuMF) (%)
Montmorillonite K5	59.3	79.1
Zeolite HY 5	46.2	76.8
Al(III)triflate	51.2	78.6
Zeolite HY 15	49.3	76.9

Example 6

Diesel Fuel Applications

[0058] Fuel Solubility

[0059] Fuel solubility is a primary concern for diesel fuel applications. Not all highly polar oxygenates have good solubility in the current commercial diesel fuels. Results show that in the 5 vol %, in the 25 vol % and in the 40 vol % blends

of tBMF with commercial diesel, both liquid blend components are completely miscible. In a comparative set of experiments it was shown that ethoxymethylfurfural (EMF) is completely miscible in a 5 vol % blend with commercial diesel, but that phase separation occurs with the 25 vol % and with the 40 vol % blends of EMF and diesel.

[0060] Cetane Number

[0061] Oxygenated fuel additives may reduce the natural cetane number of the base diesel fuel. A 0.1 vol % blend of tBMF with additive free diesel fuel was prepared at an outside laboratory for cetane determination according to an ASTM D 6890 certified method. While the reference additive-free diesel showed an average cetane number of 52.5, surprisingly the 0.1 vol % tBMF blend showed an increase with 0.5 to an average cetane number of 53.0.

[0062] Oxidation Stability

[0063] Likewise, oxygenated fuel additives, certainly when containing an aldehyde functional group, often reduce the oxidation stability of the base diesel fuel. A 0.1 vol % blend of tBMF with additive free diesel fuel was prepared at an outside laboratory for oxidation stability determination according to NF en ISO 12205 certified methods. Surprisingly, both the reference additive-free diesel and the 0.1 vol % tBMF blend showed the same oxidation stability, indicating that the oxygenated tBMF added to an additive free diesel base fuel does not decrease the oxidation stability of the blend relative to the pure base diesel.

Example 7

Emission Engine Testing

[0064] In a D9B diesel engine of a citroen Berlingo test car, comparative testing is performed with normal commercial diesel as a fuel and the same commercial diesel to which 25 vol. % 5-(t-butoxymethyl)furfural (tBMF) was added, respectively. tBMF is added as a liquid and does not yield any mixing or flocculation problems up to a 40 vol % blend ratio. The engine is run stationary with regular diesel initially, after which the fuel supply is switched to the 40 vol % tBMF-diesel blend.

[0065] During stationary operation with the commercial diesel fuel and with the 25 vol % tBMF blend, the following measurements were made: total particulate matter, volume, O₂, CO, CO₂, NO (NO+NO₂) and total hydrocarbons.

[0066] Total particulate matter was sampled according to NEN-EN 13284-1

[0067] Particle size distribution was sampled according to VDI 2066-5

[0068] Volume was measured according to ISO 10780

[0069] Gases were sampled according to ISO 10396

[0070] O₂, CO and CO₂ were analysed according to NEN-ISO 12039

[0071] NO_x (NO+NO₂) was analysed according to NEN-ISO 10849

[0072] Total hydrocarbons were analysed according to NEN-EN 13526.

TABLE 1

gas analysis results of 100% commercial diesel fuel.				
Experiment	Component	Average Concentration	Emission	
1	CO	191 mg/Nm ³	13 g/h	
	CO ₂	2.4% v/v	—	

TABLE 1-continued

gas analysis results of 100% commercial diesel fuel.				
Experiment	Component	Average Concentration	Emission	
	O ₂	17.8% v/v	—	
	TOC (C ₃ H ₈)	29 mg/Nm ³	2 g/h	
	NO _x	323 mg/Nm ³	21 g/h	

TABLE 2

particulate matter results of 100% commercial diesel fuel.					
Experiment	Actual [m ³ /h]	Normal [Nm ³ /h]	Total particulate matter		Particle size PSD < 10 μm [%]
			Concentration [mg/Nm ³]	Emission [g/h]	
1	80	60	6.1	98.5	

TABLE 3

gas analysis results of blend of commercial diesel with 25 vol % tBMF.				
Experiment	Component	Average Concentration	Emission	
2	CO	243 mg/Nm ³	16 g/h	
	CO ₂	2.5% v/v	—	
	O ₂	17.7% v/v	—	
	TOC (C ₃ H ₈)	40 mg/Nm ³	3 g/h	
	NO _x	333 mg/Nm ³	22 g/h	

TABLE 4

particulate matter results of blend of commercial diesel with 25 vol % tBMF.					
Experiment	Actual [m ³ /h]	Normal [Nm ³ /h]	Total particulate matter		Particle size PSD < 10 μm [%]
			Concentration [mg/Nm ³]	Emission [g/h]	
3b (**)	80	60	5.1	100	

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- [0078] EP 0641 854
- [0079] UOP report OPPORTUNITIES FOR BIORENEWABLES IN OIL REFINERIES FINAL TECHNICAL REPORT, SUBMITTED TO: U.S. DEPARTMENT OF ENERGY (DOE Award Number: DE-FG36-05GO15085)
- [0080] Adv. Synth. Catal. 2001, 343, 220-225
- [0081] EP 0 356 703
- [0082] FR 2 669 634
1. Method for the manufacture of an ether of 5-hydroxymethylfurfural by reacting a hexose-containing starting material with a branched aliphatic C3-C20 monoalcohol in the presence of a catalytic or sub-stoichiometric amount of an acid catalyst.
 2. Method according to claim 1, wherein the monoalcohol is selected from the group consisting of:
primary alcohols with branched carbon backbones;
secondary alcohols with straight chain carbon backbones;
secondary alcohols with branched carbon backbones; and
tertiary alcohols with branched carbon backbones;
preferably comprising from 3-20 carbon atoms, more preferably from 3-8 carbon atoms
 3. Method according to claim 1, wherein the monoalcohol is selected from one or more of the group of C3 to C8 alcohols comprising 2-propanol, 2-butanol, 2-methyl-1-propanol (isobutanol), 2-methyl-2-propanol (tert-butanol), 2-pentanol (s-amyl alcohol); 2-methyl-1-butanol (p-amyl alcohol); 2-methyl-2-butanol (t-amyl alcohol); 3-methyl-1-butanol (isoamyl alcohol); 2,2-dimethyl-1-propanol (neopentyl alcohol); 2-hexanol; and 2-ethyl-1-hexanol (isooctyl alcohol), preferably from isobutanol, tert-butanol, isoamyl alcohol, isooctyl alcohol.
 4. Method according to claim 1, wherein the acid catalyst is selected from the group consisting of homogeneous or heterogeneous acids selected from solid organic acids, inorganic acids, salts, Lewis acids, ion exchange resins, zeolites or mixtures and/or combinations thereof.
 5. Method according to claim 1, wherein the acid is a solid Brønsted acid.
 6. Method according to claim 1, wherein the acid is a solid Lewis acid.
 7. Method according to claim 1, wherein the reaction is performed at a temperature from 50 to 300 degrees Celsius.
 8. Method according to claim 1, wherein a hexose-containing starting material is used and wherein the hexose starting material is selected from the group of:
starch, amylose, galactose, cellulose, hemi-cellulose;
glucose-containing disaccharides such as sucrose, maltose, cellobiose, lactose, preferably glucose-containing disaccharides, more preferably sucrose; and
glucose or fructose.
 9. Method according to claim 1, wherein the starting material comprises glucose, fructose, galactose and mannose and their oxidized (aldonic acid) or reduced (alditol) derivatives or esterified, etherified monosaccharide or an amido sugar or mixtures thereof.
10. Method according to claim 1, wherein the starting material further comprises 5-(hydroxymethyl)furfural.
11. Method according to claim 1, performed in the presence of a solvent, wherein the solvent or solvents are selected from the group consisting of water, sulfoxides, preferably DMSO, ketones, preferably methyl ethyl ketone, ionic liquids, methylisobutylketone and/or acetone, esters, ethers, preferably ethylene glycol ethers, more preferably diethylene glycol dimethyl ether (diglyme) or the reactant olefin and mixtures thereof.
12. Method according to claim 1, wherein the method is performed in a continuous flow process.
13. Method according to claim 12, wherein the residence time in the flow process is between 0.1 second and 10 hours.
14. Method according to claim 13, wherein the continuous flow process is a fixed bed continuous flow process.
15. Method according to claim 14, wherein the fixed bed comprises a heterogeneous acid catalyst.
16. Method according to claim 15, wherein the continuous flow process is a reactive distillation or a catalytic distillation process.
17. Method according to claim 16, wherein in addition to a heterogeneous acid catalyst, an inorganic or organic acid catalyst is added to the feed of the fixed bed or catalytic distillation continuous flow process.
18. Method according to claim 14, wherein the liquid hourly space velocity ("LHSV") is from 1 to 1000, preferably from 5 to 500, more preferably from 10 to 250 and most preferably from 25 to 100.
19. Use of a 5-hydroxymethyl)furfural ether of a branched aliphatic C3-C20 monoalcohol as fuel or fuel additive.
20. A fuel or fuel composition comprising the ether produced by the method of claim 1, optionally blended with one or more of gasoline and gasoline-ethanol blends, kerosene, diesel, biodiesel (a non-petroleum-based diesel fuel consisting of short chain alkyl (methyl or ethyl) esters, made by transesterification of vegetable oil), Fischer-Tropsch liquids, diesel-biodiesel blends and green diesel (a hydrocarbon obtained by hydrotreating biomass derived oils, fats, greases or pyrolysis oil; containing no sulfur and having a cetane number of 90 to 100) and blends of diesel and/or biodiesel with green diesel and other derivatives of furan or tetrahydrofuran.
21. A composition comprising 5-(hydroxymethyl)furfural iso-butyl ether.
22. A composition comprising 5-(hydroxymethyl)furfural iso-octyl ether.
23. A composition comprising 5-(hydroxymethyl)furfural tert-alkyl ether having 4 to 20 carbon atoms in the tert-alkyl group.
24. A composition comprising 5-hydroxymethylfurfural tert-butyl ether.

* * * * *

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Stanley J. Opella, Donald J. Nelson, Oleg Jarrettzky*

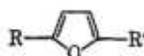
Department of Chemistry and
Stanford Magnetic Resonance Laboratory, Stanford University
Stanford, California 94305

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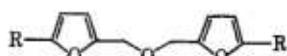
The Furanyl Unit in Host Compounds¹

Sir:

The 2,5-dimethyltetrahydrofuran unit is commonly encountered in antibiotics which complex cations and affect their permeability to natural and synthetic membranes.² Most of these antibiotics, generally isolated from various *Streptomyces* strains, uncouple oxidative phosphorylation in rat liver mitochondria. This paper reports the first synthesis of a series of 18-crown-6³ compounds containing furanyl units spaced in many possible ways as part of the multiheteromacrocycles. These compounds are themselves hosts for binding organic and inorganic cations. More importantly, they serve as starting materials for preparing host compounds whose periphery is lined with a variety of binding and shaping units (e.g., tetrahydrofuran).



1, R = CHO, R' = CH₂OH



2, R = R' = CH₂OH

3, R = R' = CH₂Cl

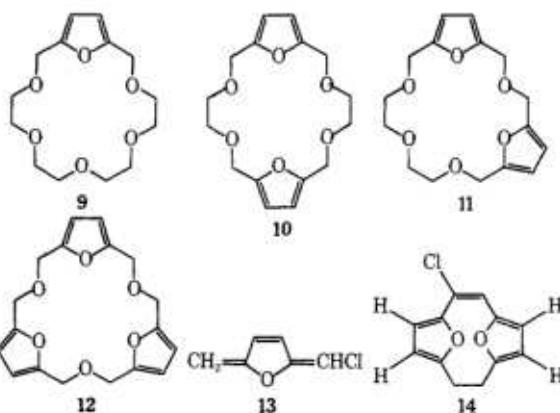
4, R = CHO; R' = CH₂Cl

5, R = CHO; R' = CH₂OCH₂CH₂Cl

6, R = CH₂OH; R' = CH₂OCH₂CH₂Cl

7, R = CHO

8, R = CH₂OH



Multiheteromacrocycle 9 was prepared by treatment of tetraethyleneglycol ditosylate with diol 2 in tetrahydrofuran-potassium *tert*-butoxide (12 hr at 25°, 12 hr at reflux under nitrogen). The crude product was chromatographed on alumina (dichloromethane-ether) to give 9⁶ (36%), mp ~0°. Treatment of a dimethylformamide solution of chloroalcohol 6 with sodium hydride in portions gave a mixture which was stirred for 48 hr at 25°. Cycle 10⁶ was isolated by extraction and chromatography (11%), mp 109–111°. Cycle 11⁶ was prepared from diol 8 and diethylene glycol ditosylate (see preparation of 9) to give product (35%), mp 69–70°. Dropwise addition of a solution of 3 in tetrahydrofuran to a stirred tetrahydrofuran solution of 8 and potassium *tert*-butoxide gave after 48 hr reaction time at 25° a mixture of materials. These were separated by chromatography (dichloromethane-pentane on alumina) to give 70% recovered 8,⁶ 10% cycle 12,⁶ mp 124–126°, and 14^{6b,e} (29%), which required gel permeation chromatography for purification (oil). Above 52°, in the pmr spectrum of 14 (CDCl₃, 100 MHz, δ), the methylenes are a sharp singlet (2.60), which at 0° become an AB quartet, V_A = 2.03, V_B = 3.23 (J_{AB} = 10 Hz), the coalescence temperature being ca. 30°. Apparently the members of each pair of vicinal protons have the same chemical shifts, but the geminal protons do not for conformational reasons. The ring-system constraints inhibit equilibration of the geminal protons at lower temperatures. Cycle 14 probably arose by ring closure of a diradical formed by head-to-head dimerization of 13 (formed from 3)¹¹ followed by elimination of 1 mol of hydrochloric acid from the product.

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Host-Guest Complexation. 2. Structural Units That Control Association Constants Between Polyethers and *tert*-Butylammonium Salts^{1a,2}

Joseph M. Timko,^{1b} Stephen S. Moore, David M. Walba, Philippe C. Hiberty, and Donald J. Cram*

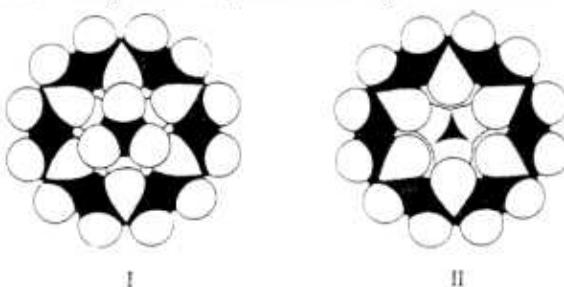
Contribution No. 3667 from the Department of Chemistry, University of California at Los Angeles, Los Angeles, California 90024. Received January 3, 1977

Abstract: The synthesis and characterization of 12 new macrocyclic polyethers are reported which contain pentamethylene, *m*-xylol, *p*-phenylene, furan-2,5-dimethylol and tetrahydrofuran-2,5-dimethylol units combined with oxygen and ethylene units. A technique is reported for determining the association constants of these polyether hosts with *tert*-butylammonium thiocyanate in chloroform at 24 and 0 °C. For 13 18-membered ring systems, the free energies of association with the salt were calculated at 24 and 0 °C, and found to range from -9.0 to <-2.9 kcal/mol at 24 °C, depending on the units incorporated in the cycle. The values for four cycles were dissected into six host-guest contact site parameters whose addition equaled their free energies of association. The parameters taken in appropriate combinations were then used to calculate the free energies of association for three other cycles that combined the same units in other ways. The calculated and measured values agreed within experimental error. Ab initio molecular orbital calculations of relative values of binding energies of the contact site parameters were in qualitative agreement with those observed. The dimethyl ether of hexaethylene glycol at 24 °C was found to bind the salt ~5.9 kcal/mol less well than did 18-crown-6. Benzo-18-crown-6 bound the salt >5.0 kcal/mol better than its isomer, *p*-phenylene-18-crown-6, whose binding sites are mislocated. Tetrahydrofuran-18-crown-6 bound the salt ~4.2 kcal/mol better than tetrahydrofuran-15-crown-5 and ~3.0 kcal/mol better than *sym*-bis(tetrahydrofuranyl)-30-crown-10. A fully complementary location of binding sites is present in the first, but not in latter cycles.

The systematic study of the structural features of organic molecular complexes in solution not involving proteins largely has been limited to the cyclodextrins as hosts dissolved in aqueous media. A variety of guest compounds has been studied.³ The main driving force for inclusion of an organic guest in the interior of a cyclodextrin appears to be the tendency of water to bind to itself better than to either the interior of a cyclodextrin or the exterior of the guest compounds. The molecular organization of the host-guest complex is dictated largely by the rigid torus shape of the host and the relative molecular dimensions of the guest. The hydroxyl and other attached groups on the rims of the cyclodextrins have been used as binding sites for transition states in transacylation reactions of ester hosts.³

The first paper of this series⁴ indicated how cyclic polyether hosts could be used to complex in chloroform, *tert*-butylammonium, guanidinium, and arenediazonium salts as guests. Three important qualitative conclusions emerged. (1) Space-filling scale molecular models of potential complexes can be used roughly to evaluate potentially complementary organic host-guest relationships. (2) Convergence in host compounds that organizes binding sites prior to complexation provides better binding than when guests must impose convergence during complexation. (3) Matching of sizes, shapes, and electronic properties of binding portions of hosts and guests is necessary for strong binding.

This paper reports the beginning of a systematic study of the effects of structural relationships on the binding properties of organic hosts and guests. The highly structured relationship suggested by the Corey-Pauling-Koltun (CPK) molecular models of hydrogen-bonded complexes of alkylammonium ions and cyclic polyethers provides a starting point that has the following advantages. The cyclic polyethers of the "crown" type⁵ are relatively easily made hosts that are subject to wide structural modification. A variety of alkyl and substituted alkyl groups can be attached to the ammonium ion, and the counterion is subject to manipulation. Drawings I and II are made



from photographs (taken from front and back) of CPK models of the complex between methylammonium ion and 18-crown-6.

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Conjugated Polymer Nanoparticles via Intramolecular Crosslinking of Dendrimeric Precursors**

By Prasad Taranekar, Jin-Young Park, Derek Patton, Timothy Fulghum, Glenn J. Ramon, and Rigoberto Advincula*

π -Conjugated electro-optically active dendrimers are of current interest for developing efficient electroluminescent display devices and other photonic applications.^[1] They have unusual electronic and photophysical properties, for example, intramolecular energy transfer in multichromophoric systems, exciton and charge localization phenomena, and photovoltaic effects have been observed.^[2,3] A number of these conjugated polymer dendrimer systems are based on poly(phenylene ethynelenes),^[4] polyphenylenes,^[5] polythiophenes,^[5,6] etc. Conjugated polymers based on the carbazole unit are of interest because of their role in electrochromic devices, electrochemical transistors, microcavity photoconduction, electroxerography, and as photovoltaic components that can provide a very efficient matrix for current carrier transport.^[7] Polycarbazole and carbazole containing dendrimers that show efficient hole-transport properties and nonlinear optical properties have also been reported.^[8]

Intramolecular crosslinking of nano-objects after assembly has emerged as a viable strategy for imparting robustness created by intramolecular crosslinking. This allows expansion of applications for these objects as synthetic antibodies,^[9] core crosslinked nanoparticles,^[10] shell crosslinked nanoparticles,^[11a,b] and shell crosslinked rods.^[11c] An advantage is their environmental stability, i.e., both chemical and physical, compared to their noncrosslinked precursors. Chemical or physical crosslinking of dendrimers has attracted a lot of attention recently with focus on both inter- and intramolecular crosslinking.^[12,13] For example, the placement of functional groups at the termini or in well-defined segments can ultimately dictate their properties and provide highly controlled macromolecular systems.^[14]

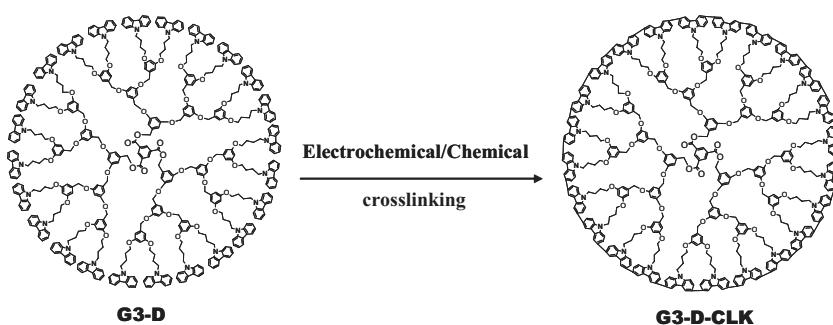
In the present work, we have used a third generation carbazole-terminated Fréchet-type polybenzylether dendrimers (G3-D), which have been synthesized in our group.^[14,15] The concentration of the dendrimer was controlled in such a way that individual dendrimers are allowed to intramolecularly crosslink either chemically in solution or electrochemically at an interface. The crosslinking affects the size and rigidity of the electroactive dendrimer, which can be altered by controlling the extent of crosslinking of the peripheral carbazole groups using various polymerization methods. To our knowledge, this is one of the first attempts to produce intramolecularly cross-linked, conjugated dendrimers and investigate their nanoparticle properties. The crosslinking of the peripheral carbazole at the 3,6-positions leads to the formation of polycarbazole units.^[16] In order to make the crosslinked dendrimer nanoparticles soluble and processable, precautions were made to avoid having any high degree of intermolecular crosslinking between the dendrimers. Thus, even after crosslinking, the dendrimer was found to be soluble in common organic solvents such as CHCl₃, CH₂Cl₂, tetrahydrofuran, and other polar solvents. The chemical crosslinking was performed using FeCl₃ as an oxidizing agent. The electrochemical crosslinking was also performed *in situ* using electrochemical nanolithography, in which the crosslinking occurs at the interface of an electrode substrate in a conducting atomic force microscopy (AFM) setup.

Firstly, the chemical crosslinking was performed using an ultradilute concentration (6.2×10^{-7} M) of the dendrimer G3-D in chloroform. The molar ratio of FeCl₃ to G3-D was set as 200:1.^[16] At this dilution level, mostly intramolecular crosslinking occurs, i.e., formation of polycarbazole units at the surface of the dendrimer molecule, resulting in a crosslinked dendrimer (G3-D-CLK) as shown in Scheme 1. The extent of crosslinking was monitored using UV-vis spectroscopy. The G3-D shows an absorption peak at 325 nm and 345 nm, which are typically assigned to the $\pi-\pi^*$ and n- π^* transitions of carbazole, respectively. After crosslinking, the $\pi-\pi^*$ transition is red-shifted and observed as an adsorption tail extending into the visible range centered at 375 nm. This indicated the formation of higher π -conjugated species. The polymerization or crosslinking was performed until no further change was observed.

In addition to the electronic properties, one can utilize the fluorescent properties of polycarbazole to further confirm the crosslinking reaction. It was found that the dendrimer shows entirely different fluorescence spectra before and after crosslinking. The fluorescence of the carbazole units present on G3-D is observed at 360 nm (Figure 1B); this peak is

* Dr. R. Advincula, P. Taranekar, J.-Y. Park, D. Patton, T. Fulghum, G. J. Ramon
Department of Chemistry, University of Houston
136 Fleming Building, Houston, TX 77204-5003 (USA)
E-mail: radvincula@uh.edu

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Scheme 1. Intramolecular crosslinking of peripheral carbazole to form polycarbazole. Note that the diagram is just a 2D representation of the crosslinking process.

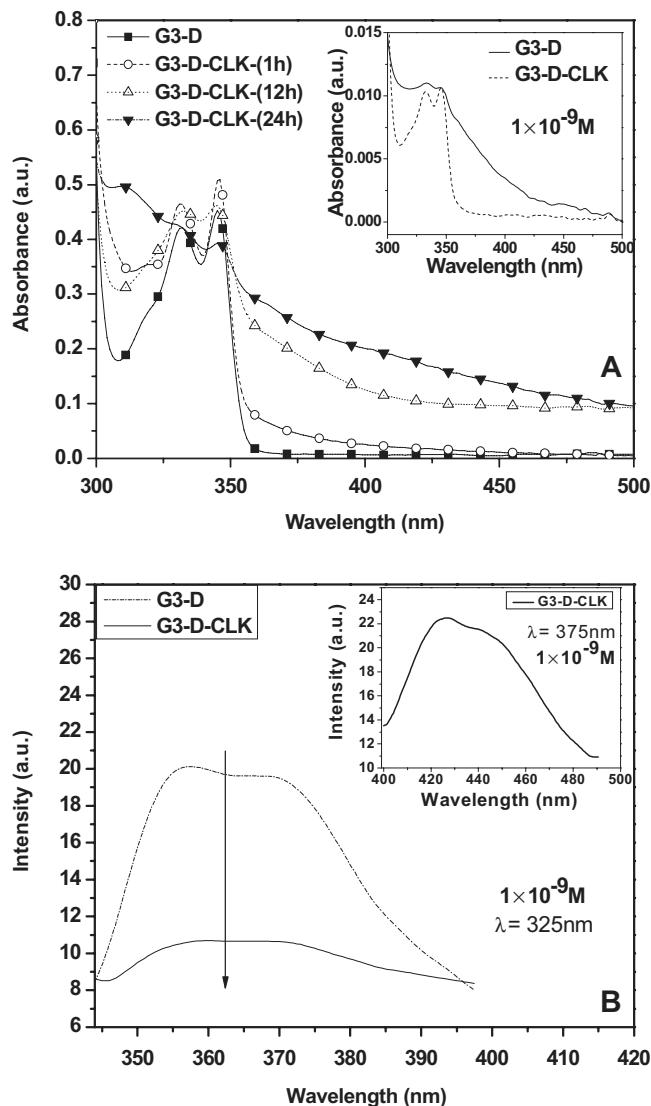


Figure 1. A) UV-vis spectra recorded at various intervals to monitor the extent of crosslinking, and inset showing a solution of 1×10^{-9} M G3-D dendrimer before and after crosslinking. Absorbance in absorbance units (a.u.). B) Fluorescence spectrum of G3-D at excitation of $\lambda = 325$ nm and inset showing the fluorescence spectrum G3-D-CLK (resulting from polycarbazole) after exciting at $\lambda = 375$ nm.

quenched in the case of G3-D-CLK, where a new peak arises at 420 nm resulting from the formation of polycarbazole (inset, Figure 1B).

In order to further confirm the intramolecular crosslinking of the individual dendrimers based on a change in size, size exclusion chromatography (SEC) analysis was performed as shown in Figure 2A. A higher retention time was observed in going from G3-D (24.6 min) to G3-D-CLK (25.0 min), reflecting the more compact size of the crosslinked dendrimer, i.e., reduced hydrodynamic volume. In addition, at lower retention times the SEC elution curve of the

G3-D-CLK also shows very small traces of dimer, trimer, or even higher analogs, which is evidence of some intermolecular crosslinking between dendrimer units. The extent of intramolecular crosslinking was also quantified using NMR spectroscopy. The integration of the peaks showed the extent of intramolecular crosslinking was more than 80 %. The protons at the 3- and 6-positions of the carbazole have a distinct signal at around $\delta = 8.01$ ppm that decreases upon crosslinking, indicating the formation of polycarbazole, as shown in Figure 2B. It

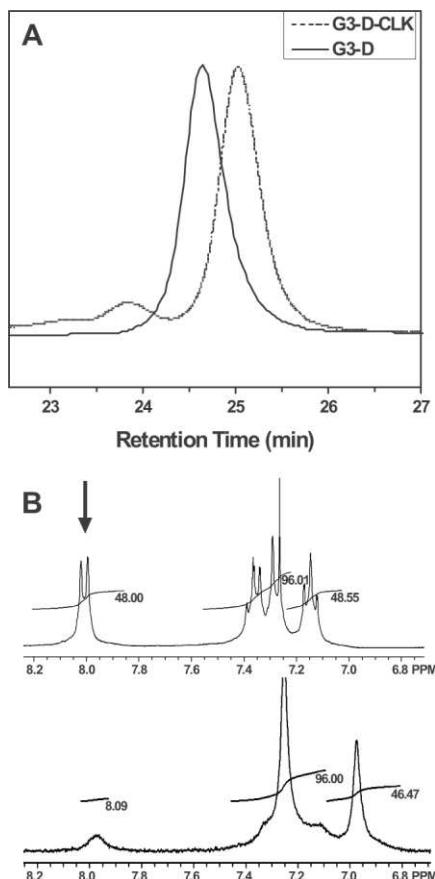


Figure 2. A) SEC analysis before and after crosslinking. B) NMR before and after crosslinking.

is highly unlikely to get complete intramolecular crosslinking within a dendrimer considering its 3D structure.

After crosslinking, both the crosslinked and uncrosslinked dendrimers were diluted to $1 \times 10^{-12} \text{ M}$ in chloroform and subsequently spin-coated (5000 rpm for 2 min) on atomically flat mica (freshly cleaved). AFM was performed using an acoustic mode (238.143 kHz, 1.49 lines s^{-1}) to visualize the distribution in size, shape, and rigidity of the dendrimer before and after crosslinking. However, the lateral size could not be determined due to convolution effects created by the AFM tip. Figure 3A shows a random distribution of the G3-D dendrimer nanoparticles and upon analysis of the statistical distribution, the height profile revealed the particle size to be $2.46 \pm 0.24 \text{ nm}$. Figure 3D shows a high-resolution AFM image and the line profile of an individual uncrosslinked nanoparticle which was found to be 2.4 nm in height.

The G3-D dendrimer was found to lie more flat on the surface of mica. It is quite rational to observe this behavior because the uncrosslinked G3-D is more flexible in its structure. On the other hand, G3-D-CLK was found to have a higher statistical distribution in height ($3.47 \pm 0.23 \text{ nm}$) and a more compact shape, as shown in Figure 3B. Figure 3E shows a high-resolution AFM image and the line profile of an individual crosslinked dendrimer nanoparticles which was found to be 3.48 nm in height. Thus, the results show seemingly contradictory data in terms of change in height, while crosslinking results in the formation of a more rigid structure and a lower radius of gyration R_g value, owing to the compact nature of the crosslinked dendrimer.^[12]

To delineate the effect of rigidity and dendrimer nanoparticle–substrate interaction, we also studied the uncrosslinked and intramolecularly crosslinked dendrimer on a low free-energy silanized silicon wafer as compared to the high free-energy surface of mica. The dendrimers were spin-coated following similar protocols and using exactly the same solution concentrations as before. The sizes of these nanoparticles were found to be 2.7 nm and 3.6 nm for G3-D and G3-D-CLK, respectively. (Supporting Information, Figure S1) Clearly, there is a height difference of the dendrimer nanoparticles in going from one substrate to the other. Thus, for the case of G3-D on mica, a pancakelike conformation is seen, while G3-D-CLK adopts a more egglike conformation and re-

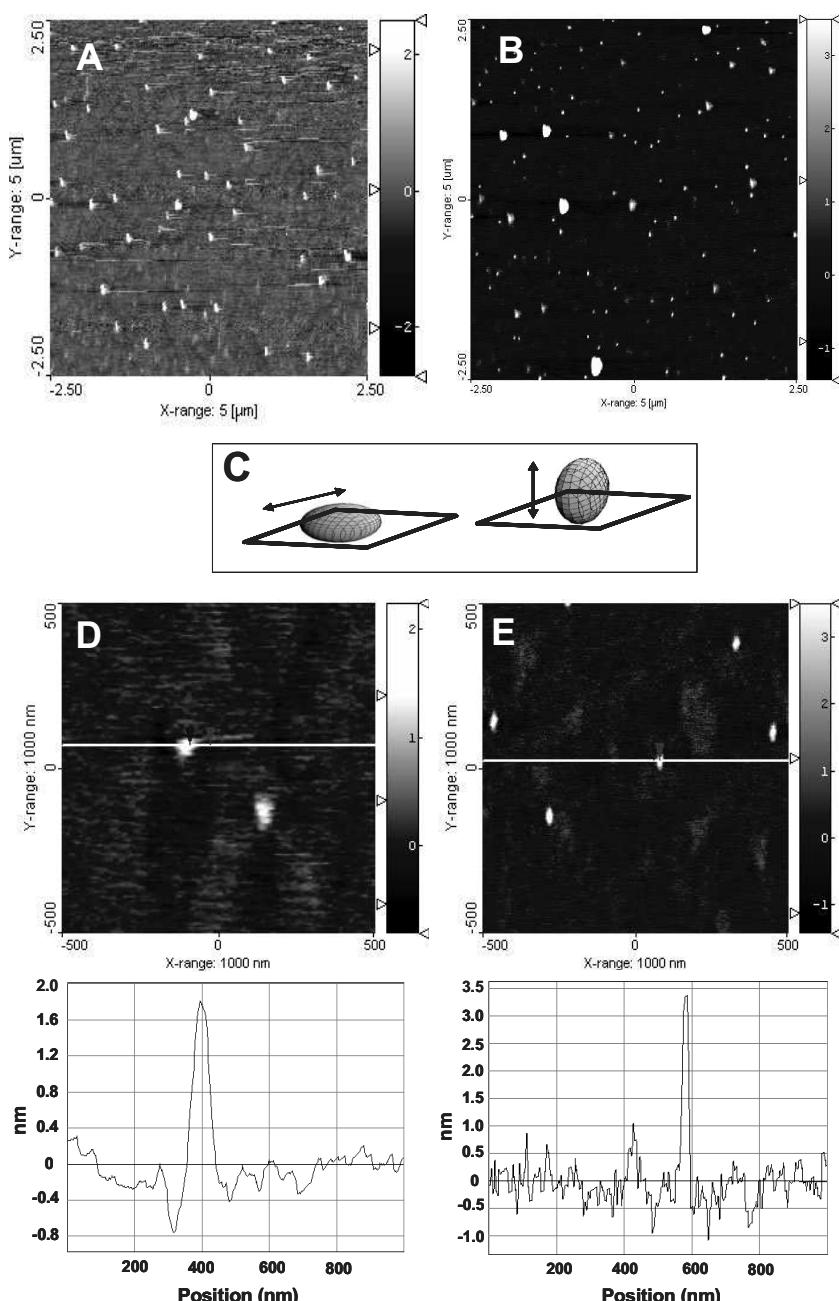


Figure 3. Tapping mode AFM pictures of A) G3-D ($5 \mu\text{m} \times 5 \mu\text{m}$) and B) G3-D-CLK ($5 \mu\text{m} \times 5 \mu\text{m}$). C) Model showing the effect of crosslinking (before (left) and after (right)). D) G3-D ($1 \mu\text{m} \times 1 \mu\text{m}$), E) G3-D-CLK ($1 \mu\text{m} \times 1 \mu\text{m}$).

mains unchanged in either case, as observed by AFM. In order to further probe the observed disparity in shape and size, we performed theoretical calculations aimed at understanding the structural changes of the dendrimers upon crosslinking. Figure 4 shows the optimized structures that were obtained using a molecular mechanics force-field implemented in Spartan'04 starting from an initial structure (Spartan'04, Wavefunction Inc. Irvine, CA, see Supporting Information).

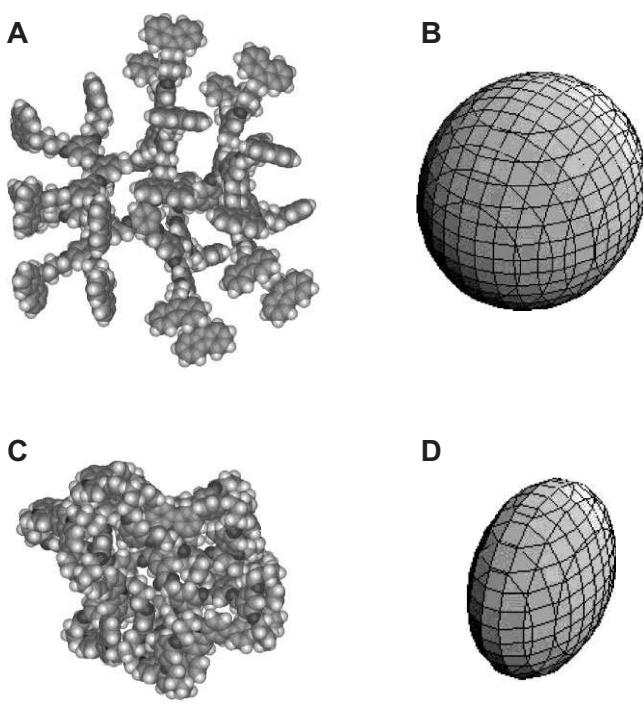


Figure 4. Energy optimized structures: A) Space filling representations of G3-D, B) expected shape of G3-D, C) space filling representations of G3-D-CLK, D) expected shape of G3-D-CLK. The decreased hydrodynamic volume is evident in the more compact structure after crosslinking.

The data, and the images in Figure 4B and D illustrate the shape of the dendrimer before and after crosslinking, and are generated from the final optimized structure. The shapes of the dendrimer were predicted by calculating the moment of inertia for the G3-D dendrimer before and after crosslinking. The moments of inertia were obtained by diagonalizing the moment of inertia tensor, I

$$I_{jk} = \sum_n m_n (r_n^2 \delta_{jk} - x_{nj} x_{nk})$$

where x is the center of mass, m_n is the mass of the n^{th} atom (not the total mass), x corresponds to the (x, y, z) cartesian coordinates of the n^{th} atom relative to center of mass of the molecule, and r is the distance between atom i and the center of mass. (δ) corresponds to Kronecker delta; i , j , and k correspond to the Cartesian coordinates, and n corresponds to the index of the atom. I_A , I_B , and I_C are the components of the moment of inertia in the principal axis frame. Because $I_A < I_B \approx I_C$ (conventionally $I_C \geq I_B \geq I_A$) in each case, the molecules are roughly prolate-shaped ellipsoids. The fact that the G3-D has less disparity between I_A and $I_B \approx I_C$ than the G3-D-CLK case, indicates that the uncrosslinked molecule is less elongated (i.e., more spherical) than the crosslinked molecule as shown from I values in Table 1.

In order to compare and verify the height disparity observed in chemical crosslinking, we also attempted to study the *in situ* electrochemical crosslinking using the conducting AFM method. In the past, we have demonstrated that the car-

Table 1. Moments of inertia for G3-D and G3-D-CLK dendrimers (amu: atomic mass unit).

Dendrimer	I_A [\AA^2 amu]	I_B [\AA^2 amu]	I_C [\AA^2 amu]
G3-D-CLK	2.14×10^5	6.31×10^5	7.39×10^5
G3-D	0.779×10^6	1.08×10^6	1.15×10^6

bazole moiety can be electrochemically crosslinked using electrochemical nanolithography to form polycarbazole units, by using conducting AFM on a linear precursor polymer system.^[17] Although the aim of this work is to investigate the effect of crosslinking on the size and rigidity of an individual dendrimer nanoparticles, the potential of local electrochemical manipulation at the nanometer scale can be extended to a range of applications such as the fabrication of conjugated molecular wires, optical microlenses, complex quantum devices, or tailored chemical surfaces for controlling biorecognition processes.^[18] We have also previously investigated the electrochemical crosslinking of linear polycarbazole precursors in thin films to form conjugated polymer networks.^[19]

An ultradilute solution of G3-D dendrimer (1×10^{-12} M) was again spin-coated on a gold (vacuum deposited on silicon wafer) substrate. Figure 5A shows a statistical distribution of the G3-D dendrimer particle size as 2.54 ± 0.19 nm along with some aggregates of dendrimers ranging from 15–21 nm. The average size of 2.54 nm of the G3-D dendrimer nanoparticles is very similar in size to the previous case on mica. The electrochemical crosslinking was performed by applying a voltage bias of -10 V in contact mode directly above the nanoparticles. The details of the conducting AFM setup and experimental conditions are described in the Supporting Information. The difference in the height is apparent as seen from Figure 5B, which shows a significant increase in height to about 3.82 ± 0.32 nm for most of the particles. We also found some particles in the size range of 4.2 nm. The variation in size was initially surprising, as one would expect to get a size range between 3 and 4 nm after crosslinking, as observed with the solution chemical crosslinking. It should be noted that these results are repeatable with variation of scan speed and that no crosslinking was observed below the -10 V bias.

Clearly, there is a difference in height and shape between the chemically crosslinked versus the electrochemically cross-linked dendrimer. One possibility is that in the process of applying a bias voltage, neighboring dendrimers can collectively crosslink intermolecularly, e.g., two closely located dendrimers can come together and crosslink to form a dimer. This is not unreasonable considering the size of the cantilever probe surface and the distribution of the electric field on the substrate (hundreds of nanometers). Another is the effect of humidity in the meniscus between the tip and the substrate and possible degradative oxidation with this method.^[20] Yet another possibility is the combined effect of localized Joule heating and crosslinking.^[21] However, more studies are needed using different experimental conditions in order to verify these possibilities.

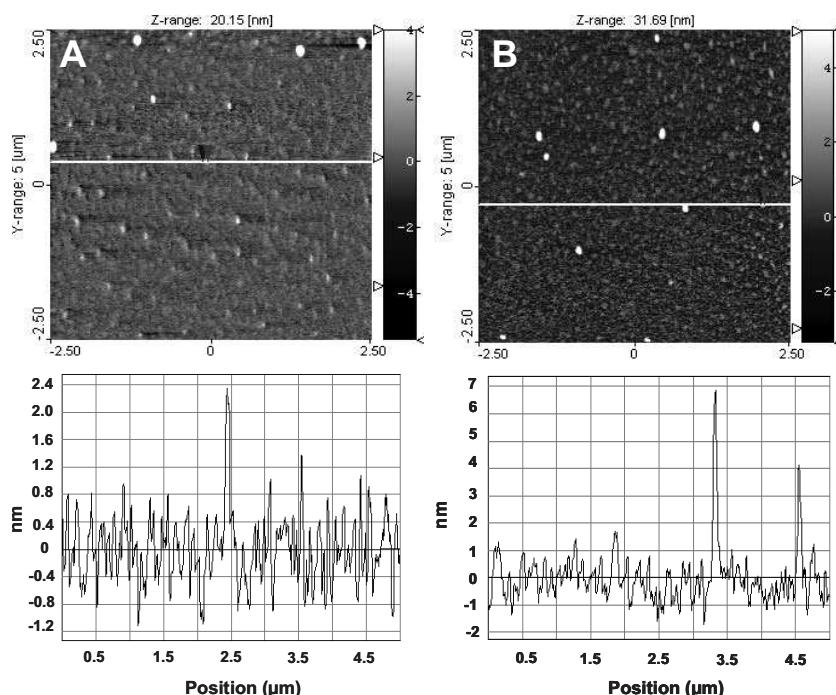


Figure 5. AFM images ($5 \mu\text{m} \times 5 \mu\text{m}$) of G3-D dendrimers A) before and B) after electrochemical crosslinking using tapping mode (topographical imaging) with a scan rate of $1.49 \text{ lines s}^{-1}$.

In conclusion, we have performed experimental and theoretical investigations of conjugated polymer nanoparticles brought upon by the intramolecular crosslinking of dendritic precursors using both chemical and in situ electrochemical methods. Both methods have shown variations in size and rigidity of the dendrimer nanoparticles, and regardless of crosslinking methods, the height of the crosslinked dendrimer was found to be higher than its uncrosslinked form. Finally, the models presented confirm both the size and rigidity of the organic nanoparticles, which can be fine-tuned by choosing the right conditions for either crosslinking method. Further studies are underway to investigate their current–voltage characteristics by current sensing AFM.

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[CA/CA]; 3650 Gilmore Way, Burnaby, British Columbia V5G 4W8 (CA). **SVIRIDOV, Serguei** [CA/CA]; 3650 Gilmore Way, Burnaby, British Columbia V5G 4W8 (CA). **ZHANG, Zaihui** [CA/CA]; 3650 Gilmore Way, Burnaby, British Columbia V5G 4W8 (CA).

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(74) **Agent:** **ROTH, Carol J.**; Seed Intellectual Property Law Group PLLC, Suite 5400, 701 Fifth Avenue, Seattle, Washington 98104, (US).

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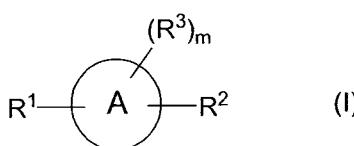
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(54) Title: AROMATIC AND HETEROAROMATIC COMPOUNDS USEFUL IN TREATING IRON DISORDERS



(57) **Abstract:** This invention is directed to compounds of formula (I), wherein m, formula (II), R¹, R² and R³ are as defined herein, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof, for the treatment of iron disorders. This invention is also directed to pharmaceutical compositions comprising the compounds and methods of using the compounds to treat iron disorders.

**AROMATIC AND HETEROAROMATIC COMPOUNDS USEFUL IN
TREATING IRON DISORDERS**

FIELD OF THE INVENTION

The present invention is directed to aromatic and heteroaromatic compounds
5 which are divalent metal transporter-1 inhibitors. The compounds of the invention, and
pharmaceutical compositions comprising the compounds, are therefore useful in
treating iron disorders.

BACKGROUND OF THE INVENTION

Iron is an essential metal for life because it is a key constituent of a family of
10 fundamental proteins, which includes hemoglobin, cytochromes, and NADH-coenzyme
Q reductase. Maintaining body iron homeostasis is paramount to health because iron
deficiency or excess results in morbidity and mortality.

Divalent metal transporter-1 (DMT1), also known as natural resistance-associated macrophage protein-2 (NRAMP2) and divalent cation transporter-1 (DCT1),
15 is a ubiquitously expressed transmembrane protein involved in the maintenance of
iron levels in the body. DMT1 is particularly important for iron absorption in the
duodenum of the small intestine, where it is localized in the cytoplasm and brush
border membrane of the villus enterocytes and mediates the influx of dietary non-heme
iron from the intestinal lumen into the enterocytes (Gunshin et al., *J. Clin. Invest.*,
20 2005, 115:1258-1266). Once dietary iron is absorbed across the intestinal wall, there
is no physiologic mechanism for excreting iron from the body. Thus, excess absorbed
iron is largely retained in the body and can accumulate throughout life. Excess
accumulation of iron leads to considerable tissue damage and increased subsequent
disease risk such as, for example, cirrhosis or hepatocellular carcinoma. Therefore,
25 DMT1 is the primary focal point of controlling intestinal iron absorption for the
maintenance of body iron homeostasis.

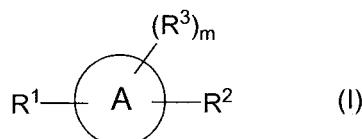
There is compelling evidence to support that DMT1 activity is tightly associated
with many common diseases, such as, but not limited to, primary iron overload
disorders, especially diseases related to hereditary hemochromatosis (Rolfs et al., *Am.
30 J. Physiol. Gastrointest. Liver Physiol.*, 2002, 282(4):G598-607). Further, DMT1 plays
a significant role in intestinal iron hyperabsorption in patients suffering from
hypochromic microcytic anemias and related disorders (Morgan et al., *Blood Cell,
Molecules, and Diseases*, 2002, 29(3):384-399).

To date, there are only three known small-molecule, drug-like compounds that specifically modulate or inhibit DMT1 (Welti et al., *Chem. Biol.*, 2006, 13:965-972). Accordingly, there is an unmet medical need to treat iron disorders, preferably primary iron overload and transfusional iron overload, including thalassemia, in mammals, 5 preferably in humans, effectively and without adverse side effects. The present invention provides compounds and methods to meet these critical needs.

SUMMARY OF THE INVENTION

The present invention is directed to aromatic and heteroaromatic compounds of the invention and pharmaceutical compositions comprising the compounds for the 10 treatment of iron disorders.

Accordingly, in one aspect this invention provides compounds of formula (I):



wherein:

m is 0, 1, 2, 3, or 4;



15 is aryl or heteroaryl;

R¹ and R² are each independently selected from the group consisting of

- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

each R³ is independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂, -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)R⁹, -S(O)OR⁹, -S(O)_pR⁸, -S(O)N(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

20 -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted

- cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;
- 5 each R⁸ is independently hydrogen or alkyl; and
each R⁹ is alkyl;
as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof;
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

In another aspect, the invention provides pharmaceutical compositions
10 comprising a pharmaceutically acceptable excipient and a compound of formula (I), as
a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or as a
pharmaceutically acceptable salt, solvate or prodrug thereof.

In another aspect, the invention provides methods for treating an iron disorder
in a mammal, wherein the methods comprise administering to the mammal in need
15 thereof a therapeutically effective amount of a compound of the invention, as set forth
above, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or a
pharmaceutically acceptable salt, solvate or prodrug thereof, or a therapeutically
effective amount of a pharmaceutical composition comprising a compound of the
invention, as set forth above, as a stereoisomer, enantiomer, tautomer thereof or
20 mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and
a pharmaceutically acceptable excipient.

In another aspect, the invention provides methods for treating a disease or
condition associated with an iron disorder in a mammal, wherein the methods comprise
administering to the mammal in need thereof a therapeutically effective amount of a
25 compound of the invention, as set forth above, as a stereoisomer, enantiomer,
tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or
prodrug thereof, or a therapeutically effective amount of a pharmaceutical composition
comprising a compound of the invention, as set forth above, as a stereoisomer,
enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically acceptable
30 salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

In another aspect, the invention provides methods for treating a disease or
condition associated with an iron disorder in a mammal due to accumulation of iron in
the body tissues of the mammal, wherein the methods comprise administering to the
mammal in need thereof a therapeutically effective amount of a compound of the
35 invention, as set forth above, as a stereoisomer, enantiomer, tautomer thereof or

mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of the invention, as set forth above, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

In another aspect, the invention provides methods for treating an iron disorder in a mammal or a disease or condition associated with an iron disorder in a mammal, wherein the iron disorder, disease or condition is associated with increased DMT1 activity and wherein the methods comprise administering to the mammal in need thereof a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of the invention, as set forth above, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

In another aspect, the invention provides methods of inhibiting the activity of DMT1 in a cell, preferably a mammalian cell, wherein the methods comprise contacting the mammalian cell with a DMT1-inhibitory amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof.

In another aspect, the invention provides methods of treating an iron disorder in a mammal, wherein the iron disorder is ameliorated by the inhibition of the activity of DMT1 in the mammal and wherein the methods comprise administering to the mammal a DMT1-inhibiting amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a DMT1-inhibiting amount of a pharmaceutical composition comprising a compound of the invention, as set forth above, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

In another aspect, the invention provides pharmaceutical therapy in combination with one or more other compounds of the invention or one or more other accepted therapies or as any combination thereof to increase the potency of an existing or future drug therapy or to decrease the adverse events associated with the

accepted therapy.

In one embodiment, the invention relates to a pharmaceutical composition combining compounds of the present invention with established or future therapies for the indications listed in the invention.

- 5 In another aspect, this invention is directed to the use of the compounds of the invention, as set forth above, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or the use of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of the invention, as set forth above, as a stereoisomer,
- 10 enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, in the preparation of a medicament for the treatment of iron disorders in a mammal.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

- 15 Certain chemical groups named herein may be preceded by a shorthand notation indicating the total number of carbon atoms that are to be found in the indicated chemical group. For example; C₇-C₁₂alkyl describes an alkyl group, as defined below, having a total of 7 to 12 carbon atoms, and C₄-C₁₂cycloalkylalkyl describes a cycloalkylalkyl group, as defined below, having a total of 4 to 12 carbon
- 20 atoms. The total number of carbons in the shorthand notation does not include carbons that may exist in substituents of the group described.

In addition to the foregoing, as used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

- "Amino" refers to the -NH₂ radical.
- 25 "Cyano" refers to the -CN radical.
- "Hydroxy" refers to the -OH radical.
- "Imino" refers to the =NH substituent.
- "Nitro" refers to the -NO₂ radical.
- "Oxo" refers to the =O substituent.
- 30 "Thioxo" refers to the =S substituent.
- "Trifluoromethyl" refers to the -CF₃ radical.
- "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to

twelve carbon atoms, preferably one to eight carbon atoms or one to six carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, and the like. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilanyl, -OR¹⁴, -OC(O)-R¹⁴, -N(R¹⁴)₂, -C(O)R¹⁴, -C(O)OR¹⁴, -C(O)N(R¹⁴)₂, -N(R¹⁴)C(O)OR¹⁶, -N(R¹⁴)C(O)R¹⁶, -N(R¹⁴)S(O)_tR¹⁶ (where t is 1 to 2), -S(O)_tOR¹⁶ (where t is 1 to 2), -S(O)_pR¹⁶ (where p is 0 to 2), and -S(O)_tN(R¹⁴)₂ (where t is 1 to 2) where each R¹⁴ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and each R¹⁶ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to twelve carbon atoms, preferably two to eight carbon atoms and which is attached to the rest of the molecule by a single bond, e.g., ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilanyl, -OR¹⁴, -OC(O)-R¹⁴, -N(R¹⁴)₂, -C(O)R¹⁴, -C(O)OR¹⁴, -C(O)N(R¹⁴)₂, -N(R¹⁴)C(O)OR¹⁶, -N(R¹⁴)C(O)R¹⁶, -N(R¹⁴)S(O)_tR¹⁶ (where t is 1 to 2), -S(O)_tOR¹⁶ (where t is 1 to 2), -S(O)_pR¹⁶ (where p is 0 to 2), and -S(O)_tN(R¹⁴)₂ (where t is 1 to 2) where each R¹⁴ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and each R¹⁶ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Alkynyl" refers to a straight or branched hydrocarbon chain radical group comprising solely of carbon and hydrogen atoms, containing at least one triple bond, optionally containing at least one double bond, having from two to twelve carbon atoms, preferably two to eight carbon atoms and which is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted by one or more of the following substituents: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo,

trimethylsilanyl, -OR¹⁴, -OC(O)-R¹⁴, -N(R¹⁴)₂, -C(O)R¹⁴, -C(O)OR¹⁴, -C(O)N(R¹⁴)₂, -N(R¹⁴)C(O)OR¹⁶, -N(R¹⁴)C(O)R¹⁶, -N(R¹⁴)S(O)R¹⁶ (where t is 1 to 2), -S(O)_tOR¹⁶ (where t is 1 to 2), -S(O)_pR¹⁶ (where p is 0 to 2), and -S(O)_tN(R¹⁴)₂ (where t is 1 to 2) where each R¹⁴ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, 5 aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and each R¹⁶ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely 10 of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, e.g., methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two 15 carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilanyl, -OR¹⁴, -OC(O)-R¹⁴, -N(R¹⁴)₂, -C(O)R¹⁴, -C(O)OR¹⁴, -C(O)N(R¹⁴)₂, -N(R¹⁴)C(O)OR¹⁶, -N(R¹⁴)C(O)R¹⁶, -N(R¹⁴)S(O)R¹⁶ (where t is 1 to 2), -S(O)_tOR¹⁶ 20 (where t is 1 to 2), -S(O)_pR¹⁶ (where p is 0 to 2), and -S(O)_tN(R¹⁴)₂ (where t is 1 to 2) where each R¹⁴ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and each R¹⁶ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

25 "Alkenylene" or "alkenylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one double bond and having from two to twelve carbon atoms, e.g., ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to 30 the radical group through a double bond or a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkenylene chain may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilanyl, -OR¹⁴, -OC(O)-R¹⁴, -N(R¹⁴)₂,

- C(O)R¹⁴, -C(O)OR¹⁴, -C(O)N(R¹⁴)₂, -N(R¹⁴)C(O)OR¹⁶, -N(R¹⁴)C(O)R¹⁶, -N(R¹⁴)S(O)_tR¹⁶ (where t is 1 to 2), -S(O)_tOR¹⁶ (where t is 1 to 2), -S(O)_pR¹⁶ (where p is 0 to 2), and -S(O)_tN(R¹⁴)₂ (where t is 1 to 2) where each R¹⁴ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, 5 heteroaryl or heteroarylalkyl; and each R¹⁶ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Alkynylene" or "alkynylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one triple bond and having from two to 10 twelve carbon atoms, e.g., propynylene, *n*-butynylene, and the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in 15 the specification, an alkynylene chain may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilanyl, -OR¹⁴, -OC(O)-R¹⁴, -N(R¹⁴)₂, -C(O)R¹⁴, -C(O)OR¹⁴, -C(O)N(R¹⁴)₂, -N(R¹⁴)C(O)OR¹⁶, -N(R¹⁴)C(O)R¹⁶, -N(R¹⁴)S(O)_tR¹⁶ (where t is 1 to 2), -S(O)_tOR¹⁶ (where t is 1 to 2), -S(O)_pR¹⁶ (where p is 0 to 2), and 20 -S(O)_tN(R¹⁴)₂ (where t is 1 to 2) where each R¹⁴ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and each R¹⁶ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Alkoxy" refers to a radical of the formula -OR_a where R_a is an alkyl radical as 25 defined above containing one to twelve carbon atoms. The alkyl part of the alkoxy radical may be optionally substituted as defined above for an alkyl radical.

"Alkoxyalkyl" refers to a radical of the formula -R_b-O-R_a where R_b is an alkylene chain as defined above and R_a is an alkyl radical as defined above. The oxygen atom may be bonded to any carbon in the alkylene chain and in the alkyl radical. The alkyl 30 part of the alkoxyalkyl radical may be optionally substituted as defined above for an alkyl group. The alkylene chain part of the alkoxyalkyl radical may be optionally substituted as defined above for an alkylene chain.

"Aryl" refers to a hydrocarbon ring system radical comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring. For purposes of this invention, the aryl 35 radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may

included fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, 5 pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents independently selected from the group consisting of alkyl, akenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, aralkyl, heteroaryl, heteroarylalkyl, $-R^{15}-OR^{14}$, $-R^{15}-OC(O)-R^{14}$, $-R^{15}-N(R^{14})_2$, $-R^{15}-C(O)R^{14}$, 10 $-R^{15}-C(O)OR^{14}$, $-R^{15}-C(O)N(R^{14})_2$, $-R^{15}-N(R^{14})C(O)OR^{16}$, $-R^{15}-N(R^{14})C(O)R^{16}$, $-R^{15}-N(R^{14})S(O)_tR^{16}$ (where t is 1 to 2), $-R^{15}-N=C(OR^{14})R^{14}$, $-R^{15}-S(O)_tOR^{16}$ (where t is 1 to 2), $-R^{15}-S(O)_pR^{16}$ (where p is 0 to 2), and $-R^{15}-S(O)_tN(R^{14})_2$ (where t is 1 to 2) where each R^{14} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, 15 aralkyl, heterocycl, heterocyclalkyl, heteroaryl or heteroarylalkyl; each R^{15} is independently a direct bond or a straight or branched alkylene or alkenylene chain; and each R^{16} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycl, heterocyclalkyl, heteroaryl or heteroarylalkyl.

"Aralkyl" refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene chain as defined above and R_c is one or more aryl radicals as defined above, for example, 20 benzyl, diphenylmethyl and the like. The alkylene chain part of the aralkyl radical may be optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical may be optionally substituted as described above for an aryl group.

"Aralkenyl" refers to a radical of the formula $-R_d-R_c$ where R_d is an alkenylene chain as defined above and R_c is one or more aryl radicals as defined above. The aryl 25 part of the aralkenyl radical may be optionally substituted as described above for an aryl group. The alkenylene chain part of the aralkenyl radical may be optionally substituted as defined above for an alkenylene group.

"Aralkynyl" refers to a radical of the formula $-R_eR_c$ where R_e is an alkynylene chain as defined above and R_c is one or more aryl radicals as defined above. The aryl 30 part of the aralkynyl radical may be optionally substituted as described above for an aryl group. The alkynylene chain part of the aralkynyl radical may be optionally substituted as defined above for an alkynylene chain.

"Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which may 35 include fused or bridged ring systems, having from three to fifteen carbon atoms,

preferably having from three to ten carbon atoms, and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic radicals include, for example, adamantyl, 5 norbornyl, decalinyl, bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, the term "cycloalkyl" is meant to include cycloalkyl radicals which are optionally substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, oxo, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, 10 heteroaryl, heteroarylalkyl, -R¹⁵-OR¹⁴, -R¹⁵-OC(O)-R¹⁴, -R¹⁵-N(R¹⁴)₂, -R¹⁵-C(O)R¹⁴, -R¹⁵-C(O)OR¹⁴, -R¹⁵-C(O)N(R¹⁴)₂, -R¹⁵-N(R¹⁴)C(O)OR¹⁶, -R¹⁵-N(R¹⁴)C(O)R¹⁶, -R¹⁵-N(R¹⁴)S(O)_tR¹⁶ (where t is 1 to 2), -R¹⁵-N=C(OR¹⁴)R¹⁴, -R¹⁵-S(O)_tOR¹⁶ (where t is 1 to 2), -R¹⁵-S(O)_pR¹⁶ (where p is 0 to 2), and -R¹⁵-S(O)_tN(R¹⁴)₂ (where t is 1 to 2) where each R¹⁴ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, 15 aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; each R¹⁵ is independently a direct bond or a straight or branched alkylene or alkenylene chain; and each R¹⁶ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Cycloalkylalkyl" refers to a radical of the formula -R_bR_g where R_b is an alkylene chain as defined above and R_g is a cycloalkyl radical as defined above. The alkylene chain and the cycloalkyl radical may be optionally substituted as defined above.

"Fused" refers to any ring structure described herein which is fused to an existing ring structure in the compounds of the invention. When the fused ring is a heterocyclyl ring or a heteroaryl ring, any carbon atom on the existing ring structure 25 which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring may be replaced with a nitrogen atom.

"Halo" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., trifluoromethyl, difluoromethyl, 30 trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like. The alkyl part of the haloalkyl radical may be optionally substituted as defined above for an alkyl group.

"Haloalkenyl" refers to an alkenyl radical, as defined above, that is substituted by one or more halo radicals, as defined above. The alkenyl part of the haloalkenyl 35 radical may be optionally substituted as defined above for an alkenyl group.

"Heterocycl" refers to a stable 3- to 18-membered non-aromatic ring radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocycl radical may be a monocyclic, 5 bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocycl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocycl radical may be partially or fully saturated. Examples of such heterocycl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, 10 decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. 15 Unless stated otherwise specifically in the specification, the term "heterocycl" is meant to include heterocycl radicals as defined above which are optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, oxo, thioxo, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, -R¹⁵-OR¹⁴, 20 -R¹⁵-OC(O)-R¹⁴, -R¹⁵-N(R¹⁴)₂, -R¹⁵-C(O)R¹⁴, -R¹⁵-C(O)OR¹⁴, -R¹⁵-C(O)N(R¹⁴)₂, -R¹⁵-N(R¹⁴)C(O)OR¹⁶, -R¹⁵-N(R¹⁴)C(O)R¹⁶, -R¹⁵-N(R¹⁴)S(O)R¹⁶ (where t is 1 to 2), -R¹⁵-N=C(OR¹⁴)R¹⁴, -R¹⁵-S(O)_tOR¹⁶ (where t is 1 to 2), -R¹⁵-S(O)_pR¹⁶ (where p is 0 to 2), and -R¹⁵-S(O)_tN(R¹⁴)₂ (where t is 1 to 2) where each R¹⁴ is independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycl, 25 heterocyclalkyl, heteroaryl or heteroarylalkyl; each R¹⁵ is independently a direct bond or a straight or branched alkylene or alkenylene chain; and each R¹⁶ is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycl, heterocyclalkyl, heteroaryl or heteroarylalkyl.

"Heterocyclalkyl" refers to a radical of the formula -R_bR_h where R_b is an 30 alkylene chain as defined above and R_h is a heterocycl radical as defined above, and if the heterocycl is a nitrogen-containing heterocycl, the heterocycl may be attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclalkyl radical may be optionally substituted as defined above for an alkyene chain. The heterocycl part of the heterocyclalkyl radical may be optionally 35 substituted as defined above for a heterocycl group.

"Heteroaryl" refers to a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. For purposes of this invention, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzthiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzoaxazolyl, benzothiazolyl, benzothiadiazolyl,

5 10 15 20 25 30 35

benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkoxy, halo, haloalkyl, haloalkenyl, cyano, oxo, thioxo, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R¹⁵-OR¹⁴, -R¹⁵-OC(O)-R¹⁴, -R¹⁵-N(R¹⁴)₂, -R¹⁵-C(O)R¹⁴, -R¹⁵-C(O)OR¹⁴, -R¹⁵-C(O)N(R¹⁴)₂, -R¹⁵-N(R¹⁴)C(O)OR¹⁶, -R¹⁵-N(R¹⁴)C(O)R¹⁶, -R¹⁵-N(R¹⁴)S(O)_tR¹⁶ (where t is 1 to 2), -R¹⁵-N=C(OR¹⁴)R¹⁴, -R¹⁵-S(O)_tOR¹⁶ (where t is 1 to 2), -R¹⁵-S(O)_pR¹⁶ (where p is 0 to 2), and -R¹⁵-S(O)_tN(R¹⁴)₂ (where t is 1 to 2) where each R¹⁴ is independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; each R¹⁵ is independently a direct bond or a straight or branched alkylene or alkenylene chain; and each R¹⁶ is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Heteroarylalkyl" refers to a radical of the formula -R_bR_i where R_b is an alkylene chain as defined above and R_i is a heteroaryl radical as defined above. The heteroaryl part of the heteroarylalkyl radical may be optionally substituted as defined above for a heteroaryl group. The alkylene chain part of the heteroarylalkyl radical may be
5 optionally substituted as defined above for an alkylene chain.

"Prodrugs" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound of the invention. Thus, the term "prodrug" refers to a metabolic precursor of a compound of the invention that is pharmaceutically acceptable. A prodrug may be inactive when
10 administered to a subject in need thereof, but is converted *in vivo* to an active compound of the invention. Prodrugs are typically rapidly transformed *in vivo* to yield the parent compound of the invention, for example, by hydrolysis in blood. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs (1985), pp.
15 7-9, 21-24 (Elsevier, Amsterdam)). A discussion of prodrugs is provided in Higuchi, T., *et al.*, "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, Ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

20 The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound of the invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of the invention may be prepared by modifying functional groups present in the compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or *in*
25 *vivo*, to the parent compound of the invention. Prodrugs include compounds of the invention wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the compound of the invention is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate
30 and benzoate derivatives of alcohol or amide derivatives of amine functional groups in the compounds of the invention and the like.

The invention disclosed herein is also meant to encompass all pharmaceutically acceptable compounds of the invention being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number.
35 Examples of isotopes that can be incorporated into the disclosed compounds include

isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I , respectively. These radiolabelled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for 5 example, the binding affinity to pharmacologically important site of action on DMT1. Certain isotopically-labelled compounds of the invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^3H , and carbon-14, *i.e.* ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready 10 means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

15 Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Preparations and Examples as set out below using 20 an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

The invention disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of 25 the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising administering a compound of this invention to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabelled compound of the invention in a detectable dose to an animal, such as rat, 30 mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction 35 mixture, and formulation into an efficacious therapeutic agent.

"Mammal" includes humans and both domestic animals such as laboratory animals and household pets, (e.g. cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

"Optional" or "optionally" means that the subsequently described event of 5 circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution. When a functional group is described as "optionally 10 substituted," and in turn, substitutents on the functional group are also "optionally substituted" and so on, for the purposes of this invention, such iterations are limited to five, preferably such iterations are limited to two.

"Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, 15 preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

"Pharmaceutically acceptable salt" includes both acid and base addition salts. 20 The term also includes quaternary ammonium salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, 25 phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic 30 acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic 35 acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid,

oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

- 5 "Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, 10 magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, 15 isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, 20 piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

Often crystallizations produce a solvate of the compound of the invention. As used herein, the term "solvate" refers to an aggregate that comprises one or more molecules of a compound of the invention with one or more molecules of solvent. The solvent may be water, in which case the solvate may be a hydrate. Alternatively, the solvent may be an organic solvent. Thus, the compounds of the present invention may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. The 25 compound of the invention may be true solvates, while in other cases, the compound of the invention may merely retain adventitious water or be a mixture of water plus some adventitious solvent.

A "pharmaceutical composition" refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically 30 active compound to mammals, e.g., humans. Such a medium includes all

pharmaceutically acceptable carriers, diluents or excipients therefor.

"Therapeutically effective amount" refers to that amount of a compound of the invention which, when administered to a mammal, preferably a human, is sufficient to effect treatment, as defined below, of an iron disorder or a disease or condition

5 associated with an iron disorder, in the mammal, preferably a human. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the iron disorder, disease or condition and its severity, the manner of administration, and the age of the mammal to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own
10 knowledge and to this disclosure. Preferably, for purposes of this invention, a "therapeutically effective amount" is that amount of a compound of invention which is sufficient to inhibit the activity of DMT1.

"Treating" or "treatment", as used herein, covers the treatment of an iron disorder in a mammal, preferably a human, or a disease or condition associated with
15 an iron disorder in a mammal, preferably a human, and includes:

- (i) preventing an iron disorder in a mammal, or a disease or condition associated with an iron disorder in the mammal, from occurring in the mammal;
- (ii) inhibiting an iron disorder in a mammal, or a disease or condition associated with an iron disorder in the mammal, *i.e.*, arresting its development;
- 20 (iii) relieving an iron disorder in a mammal, or a disease or condition associated with an iron disorder in the mammal, *i.e.*, causing regression of the iron disorder or the disease or condition;
- (iv) relieving the symptoms of an iron disorder in a mammal, or a disease or condition associated with an iron disorder in the mammal, *i.e.*, relieving the symptoms without addressing the underlying iron disorder, disease or condition; or
- (v) restoring and/or maintaining normal serum iron levels, transferrin saturation, serum ferritin, liver iron and/or bodily iron levels in a mammal having an iron disorder or having a disease or condition associated with an iron disorder.

As used herein, the terms "disease" and "condition" may be used
30 interchangeably or may be different in that the particular malady or condition may not have a known causative agent (so that etiology has not yet been worked out) and it is therefore not yet recognized as a disease but only as an undesirable condition or syndrome, wherein a more or less specific set of symptoms have been identified by clinicians.

35 The compounds of the invention, or their pharmaceutically acceptable salts

may contain one or more asymmetric centres and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their 5 racemic and optically pure forms. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallisation. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or 10 resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centres of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

15 A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

20 A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any compounds of the invention.

25 Also within the scope of the invention are intermediate compounds of the compounds of the invention (*i.e.*, compound which are used and/or formed in the preparation of the compounds of the invention) and all polymorphs of the aforementioned species and crystal habits thereof.

The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using the ChemDraw Versions 10.0 or 11.0 software naming program (CambridgeSoft), wherein the compounds of the 30 invention are named herein as derivatives of the central core structure, *e.g.*, the aryl or heteroaryl central structure. For complex chemical names employed herein, a substituent group is named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with cyclopropyl substituent. In chemical structure diagrams, all bonds are identified, except for some carbon atoms, 35 which are assumed to be bonded to sufficient hydrogen atoms to complete the

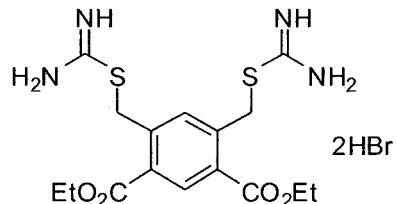
valency.

Thus, for example, a compound of formula (I) wherein m is 2, each R³ is

A

ethoxycarbonyl, is phenyl, and R¹ and R² are the same and are each -CH₂-S-C(=NH)NH₂; e.g., a compound of the following formula:

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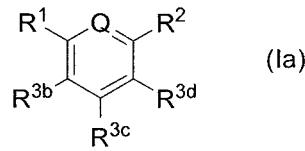


is named herein as diethyl 4,6-bis(carbamimidoylthiomethyl)isophthalate.

EMBODIMENTS OF THE INVENTION

Of the various aspects of the invention set forth above in the Summary of the Invention, certain embodiments are preferred.

- 10 Of the compounds of formula (I) described above in the Summary of the Invention, one embodiment is wherein the compound of formula (I) is a compound of formula (Ia):



wherein:

- 15 Q is -C(R^{3a})= or -N=;
- R¹ and R² are each independently selected from the group consisting of
 -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
 20 -R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;
- R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,
 -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,
 -S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 25 -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is

- independently 1 or 2 and each p is 0, 1 or 2;
- each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;
- each R⁶ is independently a direct bond or a straight or branched alkylene chain;
- each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;
- each R⁸ is independently hydrogen or alkyl; and
- each R⁹ is alkyl.

One embodiment of the compounds of formula (Ia) is a compound of formula (Ia) wherein:

Q is -C(R^{3a})=;

R¹ and R² are the same and are selected from the group consisting of

-R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,

-R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

-R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,

-R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of

hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,

-R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,

-S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

-R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and

each R⁹ is alkyl.

Another embodiment of the compounds of formula (Ia) is a compound of formula (Ia) wherein:

Q is $-C(R^{3a})=$;

R¹ and R² are each -R⁶-S-C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of

hydrogen, alkyl, halo, -R⁶-OR⁷, -R⁶-CN, -R⁶-C(O)OR⁸ and

5 -R⁶-S-C(=NR⁴)N(R⁴)R⁵;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,

optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally

10 substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and

each R⁸ is independently hydrogen or alkyl.

Another embodiment of the compounds of formula (Ia) is the compound of
15 formula (Ia) selected from the group consisting of:

1,3-phenylenebis(methylene) dicarbamimidothioate;

(2,4,6-trimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;

(2-fluoro-1,3-phenylene)bis(methylene) dicarbamimidothioate;

1,3-phenylene dicarbamimidothioate;

20 (5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;

(2,4,6-trimethylbenzene-1,3,5-triyl)tris(methylene) tricarbamimidothioate;

2-{1-[3-(1-carbamimidoylsulfanyl-1-methylethyl)phenyl]-1-methylethyl}isothiourea;

(2-cyano-1,3-phenylene)bis(methylene) dicarbamimidothioate;

(4,6-dimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;

25 diethyl 4,6-bis(carbamimidoylthiomethyl)isophthalate;

(5-bromo-4,6-dimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;

(2,4,5,6-tetramethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;

2-{1-[3-(1-carbamimidoylsulfanylethyl)-2,4,6-trimethylphenyl]ethyl}isothiourea;

(2-hydroxy-5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;

30 1,3-di[(methylamidino)thiomethyl]-2,4,6-trimethylbenzene;

(5-hydroxy-2,4,6-trimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;

(2,4,5,6-tetrachloro-1,3-phenylene)bis(methylene) dicarbamimidothioate;

(2-methoxy-5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;

(2-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;

35 (4-methoxy-1,3-phenylene)bis(methylene) dicarbamimidothioate;

(5-methoxy-1,3-phenylene)bis(methylene) dicarbamimidothioate;
(4,6-dibromo-1,3-phenylene)bis(methylene) dicarbamimidothioate; and
(4,6-diisopropyl-1,3-phenylene)bis(methylene) dicarbamimidothioate.

Another embodiment of the compounds of formula (Ia) is a compound of
5 formula (Ia) wherein:

Q is $-C(R^{3a})=$;

R¹ and R² are the same and selected from $-R^6-N(R^7)C(=NCN)N(R^4)R^5$ and
 $-R^6-C(=NR^4)N(R^4)R^5$;

10 R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of
hydrogen, alkyl, halo, -R⁶-OR⁷, -R⁶-CN, -R⁶-C(O)OR⁸ and
 $-R^6-S-C(=NR^4)N(R^4)R^5$;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,
15 optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally
substituted aralkyl, optionally substituted heterocycl, optionally substituted
heterocyclalkyl, optionally substituted heteroaryl or optionally substituted
heteroarylalkyl; and
each R⁸ is independently hydrogen or alkyl.

20 Another embodiment of the compounds of formula (Ia) is the compound of
formula (Ia) selected from the group consisting of:

1,3-di[(2-cyano-3-methylguanidino)methyl]-2,4,6-trimethylbenzene; and
2,2'-(1,3-phenylene)diacetimidamide.

Another embodiment of the compounds of formula (Ia) is a compound of
25 formula (Ia) wherein:

Q is $-C(R^{3a})=$;

R¹ and R² are each $-R^6-N(R^7)C(=NR^4)N(R^4)R^5$;

30 R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of
hydrogen, alkyl, halo, -R⁶-OR⁷, -R⁶-CN, -R⁶-C(O)OR⁸ and
 $-R^6-S-C(=NR^4)N(R^4)R^5$;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,
optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally
substituted aralkyl, optionally substituted heterocycl, optionally substituted

heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
each R⁸ is independently hydrogen or alkyl.

Another embodiment of the compounds of formula (Ia) is the compound of
5 formula (Ia) that is N-(3-guanidinomethyl-2,4,6-trimethylbenzyl)guanidine.

Another embodiment of the compounds of formula (Ia) is a compound of
formula (Ia) wherein:

Q is -N=;

R¹ and R² are the same and are selected from the group consisting of

- 10 -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
 -R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of

- 15 hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,
 -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,
 -S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is
 independently 1 or 2 and each p is 0, 1 or 2;

- 20 each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and

each R⁹ is alkyl.

Another embodiment of the compounds of formula (Ia) is a compound of
30 formula (Ia) wherein:

Q is -N=;

R¹ and R² are each -R⁶-S-C(=NR⁴)N(R⁴)R⁵;

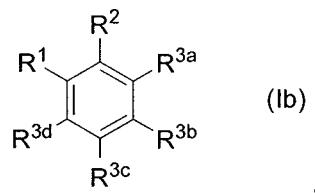
R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of
hydrogen, alkyl, and halo;

- 35 each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain; and each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, 5 optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl.

Another embodiment of the compounds of formula (Ia) is the compound of formula (Ia) selected from the group consisting of:
pyridine-2,6-diylbis(methylene) dicarbamimidothioate; and
10 (2,4,6-trimethylpyridine-3,5-diyl)bis(methylene) dicarbamimidothioate.

Of the compounds of formula (I) described above in the Summary of the Invention, one embodiment is wherein the compound of formula (I) is a compound of formula (Ib):



15 wherein:

R¹ and R² are each independently selected from the group consisting of
 -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
 20 -R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of
 hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,
 -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)R⁹, -S(O)OR⁹, -S(O)_pR⁸,
 -S(O)N(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 25 -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is
 independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;
 each R⁶ is independently a direct bond or a straight or branched alkylene chain;
 each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted 30 cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally

substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and

each R⁹ is alkyl.

5 One embodiment of the compounds of formula (Ib) is a compound of formula (Ib) wherein:

R¹ and R² are the same and selected from the group consisting of

-R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,

-R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

10 -R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,

-R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of

hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,

-R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,

15 -S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

-R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is

independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

20 each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

25 each R⁸ is independently hydrogen or alkyl; and

each R⁹ is alkyl.

Another embodiment of the compounds of formula (Ib) is a compound of formula (Ib) wherein:

R¹ and R² are the same and are -R⁶-S-C(=NR⁴)N(R⁴)R⁵;

30 R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of

hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN and -R⁶-C(O)OR⁸;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,

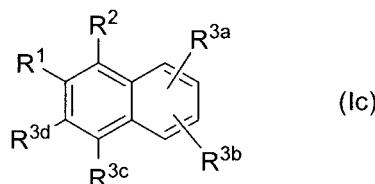
35 optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally

substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
 each R⁸ is independently hydrogen or alkyl.

5 Another embodiment of the compounds of formula (Ib) is the compound of formula (Ib) selected from the group consisting of:

(1,2-phenylene)bis(methylene) dicarbamimidothioate; and
 (3,4,5,6-tetramethyl-1,2-phenylene)bis(methylene) dicarbamimidothioate.

10 Of the compounds of formula (I) described above in the Summary of the Invention, one embodiment is wherein the compound of formula (I) is a compound of formula (Ic):



wherein:

R¹ and R² are each independently selected from the group consisting of

15 -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
 -R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of

20 hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,
 -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,
 -S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is
 independently 1 or 2 and each p is 0, 1 or 2;

25 each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally

30 substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and
 each R⁹ is alkyl.

One embodiment of the compounds of formula (Ic) is a compound of formula (Ic) wherein:

- 5 R¹ and R² are the same and selected from the group consisting of
 $-R^6-S-C(=NR^4)N(R^4)R^5$, $-R^6-C(O)-S-C(=NR^4)N(R^4)R^5$,
 $-R^6-S-C(=NR^4)N(R^4)N(R^4)R^5$, $-R^6-O-C(=NR^4)N(R^4)R^5$,
 $-R^6-C(O)-N=C[N(R^4)(R^5)]N(R^4)R^5$, $-R^6-C(=NR^4)N(R^4)R^5$, $-R^6-C(=NCN)N(R^4)R^5$,
 $-R^6-N(R^7)C(=NCN)N(R^4)R^5$ and $-R^6-N(R^7)C(=NR^4)N(R^4)R^5$;
- 10 R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of
 hydrogen, alkyl, halo, haloalkyl, $-R^6-OR^7$, $-R^6-CN$, $-R^6-NO_2$, $-R^6-N(R^8)_2$,
 $-R^6-C(O)OR^8$, $-R^6-C(O)N(R^8)_2$, $-N(R^8)S(O)_tR^9$, $-S(O)_tOR^9$, $-S(O)_pR^8$,
 $-S(O)_tN(R^8)_2$, $-R^6-S-C(=NR^4)N(R^4)R^5$, $-R^6-O-C(=NR^4)N(R^4)R^5$,
 $-R^6-C(=NR^4)N(R^4)R^5$, and $-R^6-N(R^7)-C(=NR^4)N(R^4)R^5$, wherein each t is
 15 independently 1 or 2 and each p is 0, 1 or 2;
 each R⁴ and R⁵ is independently hydrogen, alkyl, or $-OR^7$;
 each R⁶ is independently a direct bond or a straight or branched alkylene chain;
 each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted
 cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl,
 20 optionally substituted aralkyl, optionally substituted heterocycl, optionally
 substituted heterocyclalkyl, optionally substituted heteroaryl or optionally
 substituted heteroarylalkyl;
 each R⁸ is independently hydrogen or alkyl; and
 each R⁹ is alkyl.

25 Another embodiment of the compounds of formula (Ic) is a compound of
 formula (Ic) wherein:

R¹ and R² are both $-R^6-S-C(=NR^4)N(R^4)R^5$;

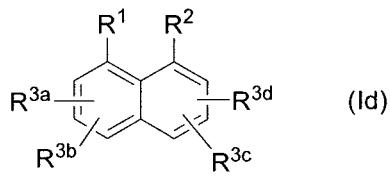
R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of
 hydrogen, alkyl, halo, haloalkyl, $-R^6-OR^7$, $-R^6-CN$ and $-R^6-C(O)OR^8$;

- 30 each R⁴ and R⁵ is independently hydrogen, alkyl, or $-OR^7$;
 each R⁶ is independently a direct bond or a straight or branched alkylene chain;
 each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,
 optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally
 substituted aralkyl, optionally substituted heterocycl, optionally substituted
 35 heterocyclalkyl, optionally substituted heteroaryl or optionally substituted

heteroarylalkyl; and
each R⁸ is independently hydrogen or alkyl.

Another embodiment of the compounds of formula (Ic) is the compound of formula (Ic) that is naphthalene-1,2-diylbis(methylene) dicarbamimidothioate.

- 5 Of the compounds of formula (I) described above in the Summary of the Invention, one embodiment is wherein the compound of formula (I) is a compound of formula (Id):



wherein:

- 10 R¹ and R² are each independently selected from the group consisting of
 -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
 -R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;
- 15 R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of
 hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,
 -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)R⁹, -S(O)OR⁹, -S(O)_pR⁸,
 -S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is
 20 independently 1 or 2 and each p is 0, 1 or 2;
 each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;
 each R⁶ is independently a direct bond or a straight or branched alkylene chain;
 each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted
 cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl,
 25 optionally substituted aralkyl, optionally substituted heterocyclyl, optionally
 substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally
 substituted heteroarylalkyl;
 each R⁸ is independently hydrogen or alkyl; and
 each R⁹ is alkyl.
- 30 One embodiment of the compounds of formula (Id) is a compound of formula (Id) wherein:

R^1 and R^2 are the same and selected from the group consisting of

- R^6 -S-C(=NR⁴)N(R⁴)R⁵, - R^6 -C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R^6 -S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, - R^6 -O-C(=NR⁴)N(R⁴)R⁵,
- R^6 -C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, - R^6 -C(=NR⁴)N(R⁴)R⁵, - R^6 -C(=NCN)N(R⁴)R⁵,
- R^6 -N(R⁷)C(=NCN)N(R⁴)R⁵ and - R^6 -N(R⁷)C(=NR⁴)N(R⁴)R⁵;

5 R^{3a} , R^{3b} , R^{3c} and R^{3d} are each independently selected from the group consisting of

- hydrogen, alkyl, halo, haloalkyl, - R^6 -OR⁷, - R^6 -CN, - R^6 -NO₂, - R^6 -N(R⁸)₂,
- R^6 -C(O)OR⁸, - R^6 -C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,
- S(O)_tN(R⁸)₂, - R^6 -S-C(=NR⁴)N(R⁴)R⁵, - R^6 -O-C(=NR⁴)N(R⁴)R⁵,
- R^6 -C(=NR⁴)N(R⁴)R⁵, and - R^6 -N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is

10 independently 1 or 2 and each p is 0, 1 or 2;

- each R^4 and R^5 is independently hydrogen, alkyl, or -OR⁷;
- each R^6 is independently a direct bond or a straight or branched alkylene chain;
- each R^7 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted

15 cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

- each R^8 is independently hydrogen or alkyl; and

20 each R^9 is alkyl.

Another embodiment of the compounds of formula (Id) is a compound of formula (Id) wherein:

R^1 and R^2 are both - R^6 -S-C(=NR⁴)N(R⁴)R⁵;

R^{3a} , R^{3b} , R^{3c} and R^{3d} are each independently selected from the group consisting of

25 hydrogen, alkyl, halo, haloalkyl, - R^6 -OR⁷, - R^6 -CN and - R^6 -C(O)OR⁸;

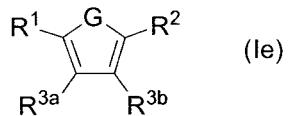
- each R^4 and R^5 is independently hydrogen, alkyl, or -OR⁷;
- each R^6 is independently a direct bond or a straight or branched alkylene chain;
- each R^7 is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally

30 substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and

- each R^8 is independently hydrogen or alkyl.

Another embodiment of the compounds of formula (Id) is the compound of formula (Id) that is naphthalene-1,8-diylbis(methylene) dicarbamimidothioate.

Of the compounds of formula (I) described above in the Summary of the Invention, one embodiment is wherein the compound of formula (I) is a compound of formula (Ie):



5 wherein:

G is -O- or -S-;

R¹ and R² are each independently selected from the group consisting of

-R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,

-R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

10 -R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
-R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R³a and R³b are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂,
-R⁶-N(R⁸)₂, -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)tR⁹, -S(O)tOR⁹, -S(O)pR⁸,
15 -S(O)tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
-R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is
independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

20 each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

25 each R⁸ is independently hydrogen or alkyl; and
each R⁹ is alkyl.

One embodiment of the compounds of formula (Ie) is a compound of formula (Ie) wherein:

G is -O- or -S-;

30 R¹ and R² are the same and selected from the group consisting of

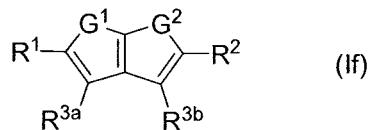
-R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,

-R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
 -R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;
- R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂,
 5 -R⁶-N(R⁸)₂, -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)R⁹, -S(O)OR⁹, -S(O)_pR⁸,
 -S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is independently 1 or 2 and each p is 0, 1 or 2;
- each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;
- 10 each R⁶ is independently a direct bond or a straight or branched alkylene chain; each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;
- 15 each R⁸ is independently hydrogen or alkyl; and each R⁹ is alkyl.
- Another embodiment of the compounds of formula (Ie) is a compound of formula (Ie) wherein:
- 20 G is -S-; R¹ and R² are the same and selected from -R⁶-S-C(=NR⁴)N(R⁴)R⁵ and -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵;
- R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, -R⁶-OR⁷, -R⁶-CN and
 25 -R⁶-C(O)OR⁸;
- each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;
- each R⁶ is independently a direct bond or a straight or branched alkylene chain;
- each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
- 30 each R⁸ is independently hydrogen or alkyl.
- Another embodiment of the compounds of formula (Ie) is the compound of formula (Ie) selected from the group consisting of:

- 2-(5-carbamimidoylsulfanecarbonyl-3,4-dichlorothiophene-2-carbonyl)isothiourea;
 thiophene-2,5-diylbis(methylene) dicarbamimidothioate;
 (3,4-diphenylthiophene-2,5-diyl)bis(methylene) dicarbamimidothioate;
 and
 5 (3,4-dimethylthiophene-2,5-diyl)bis(methylene) dicarbamimidothioate.

Of the compounds of formula (I) described above in the Summary of the Invention, one embodiment is wherein the compound of formula (I) is a compound of formula (If):



- 10 wherein:
- G¹ and G² are both -O-;
 or G¹ and G² are both -S-;
- R¹ and R² are each independently selected from the group consisting of
- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
 - R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 - R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
 - R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;
- 15 R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂,
- 20 -R⁶-N(R⁸)₂, -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tOR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,
- S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is
- 25 independently 1 or 2 and each p is 0, 1 or 2;
- each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;
- 30 each R⁶ is independently a direct bond or a straight or branched alkylene chain; each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;
- each R⁸ is independently hydrogen or alkyl; and
- each R⁹ is alkyl.

One embodiment of the compounds of formula (If) is a compound of formula (If) wherein:

G^1 and G^2 are both -O-;

or G^1 and G^2 are both -S-;

5 R^1 and R^2 are the same and selected from the group consisting of

- R^6 -S-C(=NR⁴)N(R⁴)R⁵, - R^6 -C(O)-S-C(=NR⁴)N(R⁴)R⁵,
 - R^6 -S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, - R^6 -O-C(=NR⁴)N(R⁴)R⁵,
 - R^6 -C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, - R^6 -C(=NR⁴)N(R⁴)R⁵, - R^6 -C(=NCN)N(R⁴)R⁵,
 - R^6 -N(R⁷)C(=NCN)N(R⁴)R⁵ and - R^6 -N(R⁷)C(=NR⁴)N(R⁴)R⁵;

10 R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, - R^6 -OR⁷, - R^6 -CN, - R^6 -NO₂,

- R^6 -N(R⁸)₂, - R^6 -C(O)OR⁸, - R^6 -C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,
 -S(O)_tN(R⁸)₂, - R^6 -S-C(=NR⁴)N(R⁴)R⁵, - R^6 -O-C(=NR⁴)N(R⁴)R⁵,
 - R^6 -C(=NR⁴)N(R⁴)R⁵, and - R^6 -N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is

15 independently 1 or 2 and each p is 0, 1 or 2;

each R^4 and R^5 is independently hydrogen, alkyl, or -OR⁷;

each R^6 is independently a direct bond or a straight or branched alkylene chain;

each R^7 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl,

20 optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R^8 is independently hydrogen or alkyl; and

each R^9 is alkyl.

25 Another embodiment of the compounds of formula (If) is a compound of formula (If) wherein:

G^1 and G^2 are both -S-;

R^1 and R^2 are the same and selected from - R^6 -S-C(=NR⁴)N(R⁴)R⁵ and

- R^6 -C(O)-S-C(=NR⁴)N(R⁴)R⁵;

30 R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, - R^6 -OR⁷, - R^6 -CN and
 - R^6 -C(O)OR⁸;

each R^4 and R^5 is independently hydrogen, alkyl, or -OR⁷;

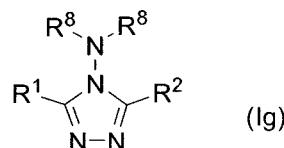
each R^6 is independently a direct bond or a straight or branched alkylene chain;

35 each R^7 is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,

- optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
- 5 each R⁸ is independently hydrogen or alkyl.

Another embodiment of the compounds of formula (If) is the compound of formula (If) that is (3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl)bis(methylene) dicarbamimidothioate.

- Of the compounds of formula (I) described above in the Summary of the
10 Invention, one embodiment is wherein the compound of formula (I) is a compound of formula (Ig):



wherein:

R¹ and R² are each independently selected from the group consisting of

- 15 -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
 -R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

- 20 each R⁶ is independently a direct bond or a straight or branched alkylene chain;
 each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and

25 each R⁸ is independently hydrogen or alkyl.

One embodiment of the compounds of formula (Ig) is a compound of formula (Ig) wherein:

R¹ and R² are the same and selected from the group consisting of

- 30 -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

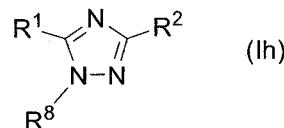
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;
- each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;
- each R⁶ is independently a direct bond or a straight or branched alkylene chain;
- 5 each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
- 10 each R⁸ is independently hydrogen or alkyl.

Another embodiment of the compounds of formula (Ig) is a compound of formula (Ig) wherein:

- R¹ and R² are both -R⁶-S-C(=NR⁴)N(R⁴)R⁵;
- each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;
- 15 R⁶ is a direct bond or a straight or branched alkylene chain;
- R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
- 20 each R⁸ is independently hydrogen or alkyl.

Another embodiment of the compounds of formula (Ig) is the compound of formula (Ig) that is (4-amino-4H-1,2,4-triazole-3,5-diyil)bis(methylene) dicarbamimidothioate.

- 25 Of the compounds of formula (I) described above in the Summary of the Invention, one embodiment is wherein the compound of formula (I) is a compound of formula (Ih):



wherein:

- 30 R¹ and R² are each independently selected from the group consisting of -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;
- each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;
- each R⁶ is independently a direct bond or a straight or branched alkylene chain;
- 5 each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
- 10 R⁸ is independently hydrogen or alkyl.

One embodiment of the compounds of formula (Ih) is a compound of formula (Ih) wherein:

- R¹ and R² are the same and selected from the group consisting of
- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- 15 -R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;
- each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;
- each R⁶ is independently a direct bond or a straight or branched alkylene chain;
- 20 each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
- 25 R⁸ is independently hydrogen or alkyl.

Another embodiment of the compounds of formula (Ih) is a compound of formula (Ih) wherein:

- R¹ and R² are both -R⁶-S-C(=NR⁴)N(R⁴)R⁵;
- each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;
- 30 R⁶ is a direct bond or a straight or branched alkylene chain;
- R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
- 35

R⁸ is independently hydrogen or alkyl.

Another embodiment of the compounds of formula (Ih) is the compound of formula (Ih) that is (1*H*-1,2,4-triazole-3,5-diyl)bis(methylene) dicarbamimidothiodate.

Another aspect of the invention are methods for treating an iron disorder in a mammal, preferably a human, or a disease or condition associated with an iron disorder in a mammal, preferably a human, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of the invention, as set forth above in the Summary of the Invention, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of the invention, as set forth above in the Summary of the Invention, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

One embodiment of this aspect is where the disease or condition associated with the iron disorder is due to an accumulation of iron in the body tissues of the mammal.

Another embodiment of this aspect is where the iron disorder is a primary iron overload disorder.

Of this embodiment, a preferred embodiment is where the primary iron overload disorder is independently selected from the group consisting of hereditary hemochromatosis, juvenile hemochromatosis, ferroportin disease, neonatal hemochromatosis, Bantu siderosis, African iron overload, gracile syndrome, ataxia, and Friedreich Ataxia. A more preferred embodiment is where the primary iron overload is hereditary hemochromatosis.

Another embodiment of this aspect is where the iron disorder is a secondary iron overload disorder.

Another embodiment of this aspect is where the iron disorder is transfusional iron overload disorder.

Another embodiment of this aspect is where the disease or condition is independently selected from the group consisting of thalassemia (beta and alpha, major, minor and intermedia), hypochromic microcytic anemia, sickle cell anemia, microcytic iron loading anemia, hereditary sideroblastic anemia, congenital dyserythropoietic anemia, porphyria cutanea tarda, pyruvate kinase deficiency, hereditary atransferrinemia, ceruloplasmin deficiency, myelodysplastic syndromes,

pulmonary hemosiderosis, aceruloplasminemia and x-linked sideroblastic anemia.

Another embodiment of this aspect is where the disease or condition associated with an iron overload is independently selected from the group consisting of neurodegenerative disease (including ALS, prion diseases, Parkinson's, and

5 Alzheimers), cardiovascular disease (including atherosclerosis, ischemic cerebrovascular disease and ischemic stroke), inflammation (including arthritis and disease progression in viral hepatitis), cancer, insulin resistance, non-alcoholic liver disease, alcoholic liver disease, and infectious disease (including HIV, malaria and Yersinia infections).

10 Another embodiment of the invention are methods for treating an iron disorder associated with DMT1 activity in a mammal, preferably a human, or for treating a disease or condition associated with DMT1 activity in a mammal, preferably a human, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of the invention, as set forth above in
15 the Summary of the Invention, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of the invention, as set forth above in the Summary of the Invention, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof, or a pharmaceutically
20 acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

Of this embodiment, one embodiment is where the DMT1 activity is upregulated (*i.e.*, increased levels of DMT1 activity as compared to normal levels of DMT1 activity).

25 Of this embodiment, another embodiment is where the therapeutically effective amount administered to the mammal is a DMT1-inhibitory amount.

Specific embodiments of the compounds of the invention are described in more detail below in the following sections.

UTILITY AND TESTING OF THE COMPOUNDS OF THE INVENTION

The present invention is directed to compounds and pharmaceutical
30 compositions comprising the compounds, as described herein and above in the Summary of the Invention, which are useful in the treatment of iron disorders in a mammal, preferably a human, by modulating, preferably inhibiting, DMT1 activity.

The term "iron disorder" refers to a condition in a mammal, preferably a human, wherein the level of iron in the body is outside the normal range for the particular

mammal (*i.e.* abnormal iron level), such as an elevated or a decreased iron serum level compared to the normal iron serum level for the mammal or an increased or decreased level of iron in the liver of the mammal as compared to the normal level of iron in the liver in the mammal. Abnormal iron serum levels can be determined by
5 direct measurement of serum iron using a colorimetric assay, or by the standard transferrin saturation assay (which reveals how much iron is bound to the protein that carries iron in the blood), or by the standard serum ferritin assay. For example, transferrin saturation levels of 45% or higher are usually indicative of abnormally high levels of iron in the serum. Abnormal iron levels in the liver can be determined
10 measuring the iron content of the liver from tissue obtained by a liver biopsy or by imaging technique such as MRI and/or SQUID. The degree of iron levels in other tissues (*e.g.*, brain, heart) may also be estimated using these and other imaging techniques. Preferably, for purposes of this invention, an abnormal iron level is an elevated iron level in serum or tissue.

15 The term "iron disorders" therefore includes both iron deficiency disorders and iron overload disorders. Preferably, the iron disorder is an iron overload disorder, such as primary iron overload disorder (including, but not limited to, hereditary hemochromatosis, juvenile hemochromatosis, ferroportin disease, neonatal hemochromatosis, Bantu siderosis, African iron overload, gracile syndrome, ataxia,
20 and Friedreich Ataxia, as well as all of the anemias listed below in which patients may not be transfused but may become iron overloaded due to increased erythroid drive and the resulting increased iron absorption in the gut) and secondary (or transfusional) iron overload disorder which can be caused by repeated transfusions used to treat a number of distinct anemias, including, but not limited to, thalassemia (beta and alpha,
25 major, minor and intermedia), hypochromic microcytic anemias, sickle cell anemia, microcytic iron loading anemias, hereditary sideroblastic anemias, congenital dyserythropoietic anemias, porphyria cutanea tarda, pyruvate kinase deficiency, hereditary atransferrinemia, ceruloplasmin deficiency, myelodysplastic syndromes, pulmonary hemosiderosis, aceruloplasminemia and x-linked sideroblastic anemia.

30 Iron disorders of particular interest in the practice of the invention are iron overload disorders where the level of iron in a mammal is higher than the normal level of iron in the mammal. Such iron overload disorders including, but are not limited to, primary iron overload disorders (including, but not limited to, hereditary hemochromatosis, juvenile hemochromatosis, ferroportin disease, neonatal hemochromatosis, Bantu siderosis, African iron overload, gracile syndrome, ataxia,
35

and Friedreich Ataxia, as well as all of the anemias listed below, in which patients may not be transfused but may become iron overloaded due to increased erythroid drive and the resulting increased iron absorption in the gut), and secondary (transfusional) iron overload disorders (including, but not limited to, thalassemia (beta and alpha, major, minor and intermedia)), hypochromic microcytic anemias, sickle cell anemia, microcytic iron loading anemias, hereditary sideroblastic anemias, congenital dyserythropoietic anemias, porphyria cutanea tarda, pyruvate kinase deficiency, hereditary atransferrinemia, ceruloplasmin deficiency, myelodysplastic syndromes, pulmonary hemosiderosis, aceruloplasminemia, and x-linked sideroblastic anemia.

5 Iron overload may also be responsible for a portion of the pathology observed in neurodegenerative diseases (including ALS, prion diseases, Parkinson's, Alzheimers), cardiovascular diseases (including atherosclerosis, ischemic cerebrovascular disease and ischemic stroke), inflammatory diseases and conditions (including arthritis and disease progression in viral hepatitis), cancer, insulin resistance, non-alcoholic liver

10 disease, alcoholic liver disease, and infectious disease (including HIV, malaria and Yersinia infections).

The compounds of the invention, and pharmaceutical compositions comprising the compounds of the invention, are useful in treating iron disorders by modulating, preferably inhibiting, DMT1 activity. There is evidence that the upregulation (i.e., increased activity) of DMT1 has a role in iron disorders caused by genetic abnormalities, such as hereditary hemochromatosis. Hereditary hemochromatosis is an iron overload disorder due to intestinal iron hyperabsorption. Hereditary hemochromatosis is characterized by a slow accumulation of iron from the diet to toxic levels resulting in tissue injury and multi-organ malfunction. Patients, typically men, develop symptoms of hemochromatosis in their fourth and fifth decade with variable combinations of cirrhosis, hepatoma, arthritis, hypogonadism, diabetes mellitus and cardiomyopathy. The biochemical profile shows elevated transferrin saturation above 45% and a high serum ferritin. The underlying genetic defect in hereditary hemochromatosis is a mutation in the hemochromatosis gene (HFE) on chromosome 6p21. 90% of Northern Europeans with hereditary hemochromatosis are homozygous for a single missense mutation, C282Y in exon 4 of the HFE gene.

DMT1 activity has also been implicated in the etiology and pathophysiology of hypochromic microcytic anemias, thalassemia, microcytic iron loading anemias, hereditary sideroblastic anemias, hereditary hypochromic anemias, congenital dyserythropoietic anemias, pyruvate kinase deficiency, hereditary atransferrinemia,

and certain myelodysplastic syndromes, as there is a direct correlation between the degree of iron limited anemia, increased DMT1 expression in the duodenum and, by extension, increased iron absorption via DMT1 (Morgan et al., *Blood Cells Molecules and Diseases*, 2002, 29:384-399).

5 There is also evidence that DMT1 has a role in iron disorders such as acquired iron overload. The risk factors for acquired iron overload might include for example excessive ingestion of red meat, iron supplements or foods that are iron fortified. Acquired iron overload can also occur from the use of iron cookware, drinking unpurified tap water, use of oral contraceptives, blood transfusions and cigarette
10 smoking. DMT1 pattern of expression and function supports it as a candidate target for the treatment of acquired iron overload and other related maladies.

In addition to the small intestine, DMT1 is also highly expressed in the kidney suggesting a role in renal iron handling and possibly reabsorption of filtered iron (Ferguson et al., *Am. J. Physiol. Renal. Physiol.*, 2001, 280: F803-F814) and is also
15 involved in the delivery of iron to peripheral tissues by transferrin (Fleming et al., *Proc. Natl. Acad. Sci.*, 1998, 85:1148-1153). DMT1 inhibitors, when dosed in a fashion that increases their systemic exposure, may be useful in an acute unloading of iron via the urine, by inhibiting DMT1 expressed in the kidney.

DMT1 may also play a role in regulating iron flux to the brain. As there is some
20 indication that iron overload in the brain may play a role in brain pathology, such as Alzheimer's, DMT1 inhibitors may act to reduce the amount of iron absorbed by the brain, when dosed in a fashion that increases their systemic exposure and allows them to play a role at the blood brain barrier or within the brain (Lehmann et al., 2006, *J. Med. Genet.*, 2006, 43(10):e52; Schenck et al., *Top. Magn Reson. Imaging.*,
25 2006, 17(1):41-50).

Studies show that mutant mice that are defective in DMT1 activity (*mk/mk*) develop hypochromic microcytic anemia, a severe form of iron deficiency anemia, due to a defect in intestinal iron absorption. In contrast, the *hfe*^{-/-} knockout mouse model of hereditary hemochromatosis is characterized by an enhanced intestinal iron uptake
30 and total body iron overload. The *hfe*^{-/-}:*mk/mk* double mutant mouse, which carries mutations in both the HFE and DMT1 genes, fails to load iron, indicating that hemochromatosis (*hfe*^{-/-}) can be prevented by blocking the flux of iron through the DMT1 protein (Levy et al., *J. Clin. Invest.*, 2000, 105:1209-16). In addition, studies of human patients with hereditary hemochromatosis show that DMT1 is inappropriately
35 upregulated at the intestinal brush border. This aberrant excessive expression of

DMT1 in hereditary hemochromatosis is fundamental to the primary pathophysiology of this condition (Zoller *et al.*, *Gastroenterology*, 2001, 120:1412-1419). These findings have made DMT1 a therapeutic target for the treatment of iron overload disorders in general, and, in particular, for the treatment of hereditary hemochromatosis. In further support of DMT1 as a therapeutic target in the treatment of iron overload, it has been shown in clinical studies that the majority of the excess iron burden is absorbed in the form of ferrous (non-heme) iron, as opposed to heme-iron (Lynch *et al.*, *Blood*, 1989, 74:2187-2193).

While not wishing to be bound to any particular mechanism of action, the compounds of the invention, and pharmaceutical compositions comprising the compounds of the invention, are useful in treating iron disorders by directly interacting with a region of the DMT1 protein that modulates or controls iron flux. A direct interaction is supported by the fact that the compounds are not potent inhibitors of cation flux in the closely related transporter Natural Resistance-Associated Macrophage Protein-1 (NRAMP1). In general, the compounds of the invention modulate the activity of DMT1 downwards, thereby inhibiting the ability of DMT1 to uptake non-heme iron across the cellular membrane. The compounds of the invention are therefore considered to be DMT1 inhibitors and are therefore useful in treating iron disorders which are ameliorated by the modulation, preferably the inhibition, of DMT1 activity. The compounds of the invention, as DMT1 inhibitors, are also useful in reducing normal or slightly abnormal iron serum levels in a mammal, preferably a human, wherein the reduction of iron serum levels provides a therapeutic benefit to the mammal, preferably a human, such as neuroprotective activity after a stroke.

The compounds of the invention, and pharmaceutical compositions comprising the compounds of the invention, are also useful in treating or preventing symptoms, diseases and/or conditions in a mammal associated with hereditary hemochromatosis due to accumulation of iron in body tissues such as arthritis, liver disease, heart disease, impotence, early menopause, abnormal skin pigmentation, thyroid deficiency, damage to pancreas, diabetes, and damage to adrenal gland (Sheth *et al.*, *Annu. Rev. Med.*, 2000, 51:443-464).

The compounds of the invention, and pharmaceutical compositions comprising the compounds of the invention, are also useful in treating or preventing other forms of hemochromatosis including, but are not limited to, juvenile hemochromatosis and neonatal hemochromatosis. Juvenile hemochromatosis has a much earlier onset and exhibits more severe symptoms such as endocrine dysfunction, joint disease, and

cardiac abnormalities due to excessive iron deposition from an early age. Neonatal hemochromatosis is a rare fetal gestational condition that results in iron accumulation in the liver of the fetus.

The compounds of the invention, and pharmaceutical compositions comprising
5 the compounds of the invention, are also useful in treating or preventing transfusional iron overload. Chronic blood transfusion is the established therapy for thalassaemia major, bone marrow failure and complications of sickle cell anaemia and other related disorders. With hypertransfusion, the systemic iron load accumulates. Because there
10 is no natural way for the body to eliminate the iron, the excess iron in the transfused blood builds up to cause iron overload and becomes toxic to tissues and organs, particularly the liver, heart, and pancreas. Transfusional iron overload typically results in the patient's premature death from organ failure. The transfusional iron overload is unfortunately augmented by increased iron absorption, which is the natural attempt of the body to increase iron levels in order to promote erythropoiesis, which is itself
15 compromised by the disease states above. Decreased absorption of iron by the inhibition of DMT1 activity may reduce the iron overload related to the transfusional iron overload and supports the use of DMT1 inhibitors for the treatment of this disease.

In addition, due to iron's ability to generate reactive oxygen species (free radicals), which can result in inflammation and tissue damage, the compounds of the
20 invention, and pharmaceutical compositions comprising the compounds of the invention, may also be useful as anti-inflammatory or neuroprotective agents due to their ability to reduce iron serum levels by the modulation, preferably inhibition, of DMT1 activity.

The general value of the compounds of the invention, and pharmaceutical
25 compositions comprising the compounds of the invention, in modulating, preferably inhibiting, DMT1 activity can be determined using the assays described herein or below in the Biological Assays section. Alternatively, the general value of the compounds of the invention, and pharmaceutical compositions comprising the compounds of the invention, in treating iron disorders in humans may be established in
30 industry standard animal models for demonstrating the efficacy of compounds in treating iron disorders.

In particular, identification of the compounds of the invention ability to modulate, preferably to inhibit, DMT1 activity, can be assessed using a variety of *in vitro* and *in vivo* assays, for measuring uptake of reduced iron (Fe^{2+}). One such protocol involves
35 the screening of chemical agents for ability to modulate the activity of DMT1 thereby

identifying it as a modulating agent. The *in vitro* activity of DMT1 can be measured in cell based assays by either directly measuring iron flux (using a radioactively labelled iron ^{55}Fe) or by measuring the fluorescence of a cell permeable iron fluorophore such as calcein. Stable cell lines overexpressing DMT1 are exposed to ^{55}Fe or loaded with 5 calcein and then compound is applied. Decreased flux of ^{55}Fe or lack of fluorescence quenching indicates that the given modulator has inhibited DMT1 function (Picard et al., *J. Biol. Chem.*, 2000, 275(46):35738-45 and Wetli et al., *Chem. Biol.* 2006 Sep;13(9):965-72). Alternatively, in another format electrophysiological techniques can be used to measure the current or iron or other metals traversing the cell membrane 10 with DMT1 in a Xenopus oocyte or other cell based system (Gunshin et al., *Nature*, 1997, 31;388(6641):482-8).

Other assays may involve intestinal cells or tissues which express endogenous DMT1, using the same detection techniques such as fluorescence, radiolabelled iron or electrophysiology. A human Caco2 cell line can be used for such assays (Alvarez- 15 Hernandez et al., *Biochimica et Biophysica Acta.*, 1991, 1070:205-208). These assays can be performed in the presence of desferroxamine to render the cells iron deficient and upregulate DMT1 expression. Alternatively, intestinal tissue may be used, either as gut rings which will take up iron (Raja et al., *Cell. Biochemistry and Function*, 1987, 5:69-76; Leppert et al., *J. of Pharm. Sci.*, 1994, 83:976-981), or as gut 20 slices ex vivo (Vaghefi et al., *Reprod. Nutr. Dev.*, 1998, 38:559-566) where iron flux across the epithelial layer can be assessed in an Ussing chamber. In these assays, tissue can be excised from iron replete or iron deficient animals. In addition, the heme versus non-heme iron absorptive capacity of the tissue can be measured.

These assays can be carried out in transfected cells, or cell or tissue 25 endogenously expressing the channel of interest in a natural endogenous setting or in a recombinant setting. Other methods of testing the compounds disclosed herein are also readily known and available to those skilled in the art.

Compounds of the invention can also be tested in a variety of *in vivo* models so as to determine if they alleviate a particular iron disorder in a mammal, particularly an 30 iron overload disorder, with minimal adverse events. The assays described herein and below in the Biological Assays Section are useful in assessing the *in vivo* activity of the compounds of the invention.

For example, a typical rat model of iron overload disorder can be created by establishing an iron deficient state in the rat, which will then cause the upregulation of 35 DMT1 expression and activity, resulting in increased iron absorption. These models

can be used to demonstrate that compounds of the invention have the ability to modulate, preferably inhibit, the activity of DMT1 as demonstrated by the increase in serum iron levels in the iron-deficient rat. Iron deficiency is induced in these rat models in order to mimic the DMT1 over-expression and iron hyperabsorption observed in
5 humans having iron overload disorders such as hereditary hemochromatosis as well as humans suffering from thalassemia.

Alternatively, an iron deficient, and therefore hyperabsorptive state, may be induced by dietary means, such as, for example, treatment with phenylhydrazine, or by phlebotomy (Refino *et al.*, *Am. J. Clin. Nutr.* 1983, 37:904-909; Redondo *et al.*, *Lab. 10 Animal Sci.* 1995, 45:578-583; Frazer *et al.*, *Gastroenterology*, 2002, 123:835-844). Alternatively, iron absorption can also be stimulated by creating an hypoxic state to stimulate erythropoiesis (Raja *et al.*, *Br. J. Haematol.*, 1988, 68:373-378). In these models, a compound's efficacy can be assessed by measuring reduced iron flux via the duodenum acutely or by monitoring whether chronic exposure to a compound
15 causes a decrease in the amount of iron loading as measured by serum iron, transferrin saturation, ferritin and liver iron. Alternatively, iron flux in these animals can be measured by tracing the absorption of radioactive iron administered orally. These experiments can also be performed in iron replete animals, although changes in these parameters will be less pronounced and therefore compound efficacy will be more
20 difficult to judge.

Genetic rat models of iron overload offers another format to show efficacy of DMT1 inhibitors in preventing further iron loading. These models are applicable to a variety of iron disorders such as hereditary hemochromatosis (Levy *et al.*, *Blood*, 1999, 94:9-11), juvenile hemochromatosis (Huang *et al.*, *J. Clin. Invest.*, 2005 115:2187-2191), beta-2-microglobulin (de Sousa *et al.*, *Immun. Lett.*, 1994, 39:105-111), thalassemia (Ciavatta *et al.*, *Proc. Nat. Acad. Sci.*, 1995, 92: 9259-9263), hypotransferrinemia (Craven *et al.*, *Proc. Nat. Acad. Sci.*, 1987, 84(10):3457-61) and other hypochromic microcytic anemias. A compound's efficacy can be assessed by measuring reduced iron flux via the duodenum acutely or by monitoring whether
25 chronic exposure to a compound causes a decrease in the amount of iron loading as judged by serum iron, transferrin saturation, ferritin and liver iron. Alternatively, iron flux in these animals can be measured by tracing the absorption of radioactive iron administered orally.

Typically, a successful therapeutic agent of the present invention will meet
35 some or all of the following criteria. Oral availability should be at less than 5%. Animal

- model efficacy is less than about 0.1 µg to about 100 mg/Kg body weight and the target human dose is between 0.1 µg to about 100 mg/Kg body weight, although doses outside of this range may be acceptable ("mg/Kg" means milligrams of compound per kilogram of body mass of the subject to whom it is being administered). The
- 5 therapeutic index (or ratio of toxic dose to therapeutic dose) should be greater than 100. The potency (as expressed by IC₅₀ value) should be less than 10 µM, preferably below 1 µM and most preferably below 50 nM. The IC₅₀ ("Inhibitory Concentration – 50%") is a measure of the amount of compound required to achieve 50% inhibition of DMT1, over a specific time period, in an assay of the invention.
- 10 In another use of the invention, the compounds of the invention can be used in *in vitro* or *in vivo* studies as exemplary agents for comparative purposes to find other compounds useful in the treatment of an iron disorder or diseases or conditions associated with an iron disorder.

In another use of the invention, the compounds of the invention can be used in
15 the preparation of a medicament for the treatment of an iron disorder in a mammal or for the treatment of a disease or condition associated with an iron disorder in a mammal.

PHARMACEUTICAL COMPOSITIONS OF THE INVENTION AND ADMINISTRATION

The present invention also relates to pharmaceutical composition containing
20 the compounds of the invention disclosed herein. In one embodiment, the present invention relates to a composition comprising compounds of the invention in a pharmaceutically acceptable carrier, excipient or diluent and in an amount effective to modulate, preferably inhibit, DMT1 in order to treat iron disorders when administered to an animal, preferably a mammal, most preferably a human patient.

25 Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration of agents for serving similar utilities. The pharmaceutical compositions of the invention can be prepared by combining a compound of the invention with an appropriate pharmaceutically
30 acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. Typical routes of administering such pharmaceutical compositions include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual,

rectal, vaginal, and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. Pharmaceutical compositions of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of
5 the composition to a patient. Compositions that will be administered to a subject or patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of a compound of the invention in aerosol form may hold a plurality of dosage units. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *The*
10 *Science and Practice of Pharmacy*, 20th Edition (Philadelphia College of Pharmacy and Science, 2000). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease or condition of interest in accordance with the teachings of this invention.

15 The pharmaceutical compositions useful herein also contain a pharmaceutically acceptable carrier, including any suitable diluent or excipient, which includes any pharmaceutical agent that does not itself induce the production of antibodies harmful to the individual receiving the composition, and which may be administered without undue toxicity. Pharmaceutically acceptable carriers include, but are not limited to, liquids,
20 such as water, saline, glycerol and ethanol, and the like. A thorough discussion of pharmaceutically acceptable carriers, diluents, and other excipients is presented in REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Pub. Co., N.J. current edition).

A pharmaceutical composition of the invention may be in the form of a solid or
25 liquid. In one aspect, the carrier(s) are particulate, so that the compositions are, for example, in tablet or powder form. The carrier(s) may be liquid, with the compositions being, for example, an oral syrup, injectable liquid or an aerosol, which is useful in, for example, inhalatory administration.

When intended for oral administration, the pharmaceutical composition is
30 preferably in either solid or liquid form, where semi-solid, semi-liquid, suspension and gel forms are included within the forms considered herein as either solid or liquid.

As a solid composition for oral administration, the pharmaceutical composition may be formulated into a powder, granule, compressed tablet, pill, capsule, chewing gum, wafer or the like form. Such a solid composition will typically contain one or more
35 inert diluents or edible carriers. In addition, one or more of the following may be

present: binders such as carboxymethylcellulose, ethyl cellulose, microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch, lactose or dextrans, disintegrating agents such as alginic acid, sodium alginate, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin; a flavoring agent such as peppermint, methyl salicylate or orange flavoring; and a coloring agent.

When the pharmaceutical composition is in the form of a capsule, for example, a gelatin capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or oil.

- 10 The pharmaceutical composition may be in the form of a liquid, for example, an elixir, syrup, solution, emulsion or suspension. The liquid may be for oral administration or for delivery by injection, as two examples. When intended for oral administration, preferred composition contain, in addition to the present compounds, one or more of a sweetening agent, preservatives, dye/colorant and flavor enhancer.
- 15 In a composition intended to be administered by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent may be included.

The liquid pharmaceutical compositions of the invention, whether they be solutions, suspensions or other like form, may include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Physiological saline is a preferred adjuvant. An injectable pharmaceutical composition is preferably sterile.

A liquid pharmaceutical composition of the invention intended for either parenteral or oral administration should contain an amount of a compound of the invention such that a suitable dosage will be obtained. Typically, this amount is at least 0.01% of a compound of the invention in the composition. When intended for oral administration, this amount may be varied to be between 0.1 and about 70% of the

weight of the composition. Preferred oral pharmaceutical compositions contain between about 4% and about 50% of the compound of the invention. Preferred pharmaceutical compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.01 to 10% by weight of
5 the compound prior to dilution of the invention.

The pharmaceutical composition of the invention may be intended for topical administration, in which case the carrier may suitably comprise a solution, emulsion, ointment or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bee wax, mineral oil, diluents such
10 as water and alcohol, and emulsifiers and stabilizers. Thickening agents may be present in a pharmaceutical composition for topical administration. If intended for transdermal administration, the composition may include a transdermal patch or iontophoresis device. Topical formulations may contain a concentration of the compound of the invention from about 0.1 to about 10% w/v (weight per unit volume).

15 The pharmaceutical composition of the invention may be intended for rectal administration, in the form, for example, of a suppository, which will melt in the rectum and release the drug. The composition for rectal administration may contain an oleaginous base as a suitable nonirritating excipient. Such bases include, without limitation, lanolin, cocoa butter and polyethylene glycol.

20 The pharmaceutical composition of the invention may include various materials, which modify the physical form of a solid or liquid dosage unit. For example, the composition may include materials that form a coating shell around the active ingredients. The materials that form the coating shell are typically inert, and may be selected from, for example, sugar, shellac, and other enteric coating agents.

25 Alternatively, the active ingredients may be encased in a gelatin capsule.

The pharmaceutical composition of the invention in solid or liquid form may include an agent that binds to the compound of the invention and thereby assists in the delivery of the compound. Suitable agents that may act in this capacity include a monoclonal or polyclonal antibody, a protein or a liposome.

30 The pharmaceutical composition of the invention may consist of dosage units that can be administered as an aerosol. The term aerosol is used to denote a variety of systems ranging from those of colloidal nature to systems consisting of pressurized packages. Delivery may be by a liquefied or compressed gas or by a suitable pump system that dispenses the active ingredients. Aerosols of compounds of the invention
35 may be delivered in single phase, bi-phasic, or tri-phasic systems in order to deliver the

active ingredient(s). Delivery of the aerosol includes the necessary container, activators, valves, subcontainers, and the like, which together may form a kit. One skilled in the art, without undue experimentation may determine preferred aerosols.

The pharmaceutical compositions of the invention may be prepared by
5 methodology well known in the pharmaceutical art. For example, a pharmaceutical composition intended to be administered by injection can be prepared by combining a compound of the invention with sterile, distilled water so as to form a solution. A surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the
10 compound of the invention so as to facilitate dissolution or homogeneous suspension of the compound in the aqueous delivery system.

The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount, which will vary depending upon a variety of factors including the activity of the specific compound employed; the
15 metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy. Generally, a therapeutically effective daily dose is (for a 70 Kg mammal) from about 0.001 mg/Kg (i.e., 0.07 mg) to about 100 mg/Kg (i.e., 7.0
20 g); preferably a therapeutically effective dose is (for a 70 Kg mammal) from about 0.01 mg/Kg (i.e., 0.7 mg) to about 50 mg/Kg (i.e., 3.5 g); more preferably a therapeutically effective dose is (for a 70 Kg mammal) from about 1 mg/Kg (i.e., 70 mg) to about 25 mg/Kg (i.e., 1.75 g).

The ranges of effective doses provided herein are not intended to be limiting
25 and represent preferred dose ranges. However, the most preferred dosage will be tailored to the individual subject, as is understood and determinable by one skilled in the relevant arts. (see, e.g., Berkow et al., eds., *The Merck Manual*, 16th edition, Merck and Co., Rahway, N.J., 1992; Goodman et al., eds., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th edition, Pergamon Press, Inc., Elmsford, N.Y., (2001); *Avery's Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics*, 3rd edition, ADIS Press, LTD., Williams and Wilkins, Baltimore, MD. (1987), Ebadi, *Pharmacology*, Little, Brown and Co., Boston, (1985); Osolci et al., eds., *Remington's Pharmaceutical Sciences*, 18th edition, Mack Publishing Co., Easton, PA (1990); Katzung, *Basic and Clinical Pharmacology*, Appleton and Lange, Norwalk, CT
30 (1992)).

The total dose required for each treatment can be administered by multiple doses or in a single dose over the course of the day, if desired. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under 5 the circumstances is reached. The diagnostic pharmaceutical compound or composition can be administered alone or in conjunction with other diagnostics and/or pharmaceuticals directed to the pathology, or directed to other symptoms of the pathology. The recipients of administration of compounds and/or compositions of the invention can be any vertebrate animal, such as mammals. Among mammals, the 10 preferred recipients are mammals of the Orders Primate (including humans, apes and monkeys), Arteriodactyla (including horses, goats, cows, sheep, pigs), Rodenta (including mice, rats, rabbits, and hamsters), and Carnivora (including cats, and dogs). Among birds, the preferred recipients are turkeys, chickens and other members of the same order. The most preferred recipients are humans.

15 For topical applications, it is preferred to administer an effective amount of a pharmaceutical composition according to the invention to target area, e.g., skin surfaces, mucous membranes, and the like, which are adjacent to peripheral neurons which are to be treated. This amount will generally range from about 0.0001 mg to about 1 g of a compound of the invention per application, depending upon the area to 20 be treated, whether the use is diagnostic, prophylactic or therapeutic, the severity of the symptoms, and the nature of the topical vehicle employed. A preferred topical preparation is an ointment, wherein about 0.001 to about 50 mg of active ingredient is used per cc of ointment base. The pharmaceutical composition can be formulated as transdermal compositions or transdermal delivery devices ("patches"). Such 25 compositions include, for example, a backing, active compound reservoir, a control membrane, liner and contact adhesive. Such transdermal patches may be used to provide continuous pulsatile, or on demand delivery of the compounds of the present invention as desired.

30 The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art. Controlled release drug delivery systems include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Pat. Nos. 3,845,770 and 4,326,525 and in P. J. Kuzma et al, 35 Regional Anesthesia 22 (6): 543-551 (1997), all of which are incorporated herein by

reference.

The compositions of the invention can also be delivered through intra-nasal drug delivery systems for local, systemic, and nose-to-brain medical therapies.

Controlled Particle Dispersion (CPD)TM technology, traditional nasal spray bottles,

- 5 inhalers or nebulizers are known by those skilled in the art to provide effective local and systemic delivery of drugs by targeting the olfactory region and paranasal sinuses.

The invention also relates to an intravaginal shell or core drug delivery device suitable for administration to the human or animal female. The device may be comprised of the active pharmaceutical ingredient in a polymer matrix, surrounded by a 10 sheath, and capable of releasing the compound in a substantially zero order pattern on a daily basis similar to devices used to apply testosterone as described in PCT Patent No. WO 98/50016.

Current methods for ocular delivery include topical administration (eye drops), subconjunctival injections, periocular injections, intravitreal injections, surgical implants 15 and iontophoresis (uses a small electrical current to transport ionized drugs into and through body tissues). Those skilled in the art would combine the best suited excipients with the compound for safe and effective intra-ocular administration.

The most suitable route will depend on the nature and severity of the condition being treated. Those skilled in the art are also familiar with determining administration 20 methods (oral, intravenous, inhalation, sub-cutaneous, rectal etc.), dosage forms, suitable pharmaceutical excipients and other matters relevant to the delivery of the compounds to a subject in need thereof.

COMBINATION THERAPY

The compounds of the invention may be usefully combined with one or more 25 other compounds of the invention or one or more other therapeutic agent or as any combination thereof, in the treatment of iron disorders. For example, a compound of the invention may be administered simultaneously, sequentially or separately in combination with other therapeutic agents, including, but not limited to iron chelators, e.g. deferasirox (ICL-670), deferiprone, and desferrioxamine, and erythropoietin (EPO), 30 e.g. rh-EPO. In addition, compounds of the invention, as inhibitors of DMT1 activity, could also be combined with phlebotomy therapy for the treatment of iron overload disorders.

As used herein "combination" refers to any mixture or permutation of one or more compounds of the invention and one or more other compounds of the invention

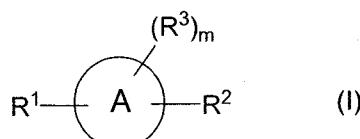
or one or more additional therapeutic agent. Unless the context makes clear otherwise, "combination" may include simultaneous or sequentially delivery of a compound of the invention with one or more therapeutic agents. Unless the context makes clear otherwise, "combination" may include dosage forms of a compound of the invention with another therapeutic agent. Unless the context makes clear otherwise, "combination" may include routes of administration of a compound of the invention with another therapeutic agent. Unless the context makes clear otherwise, "combination" may include formulations of a compound of the invention with another therapeutic agent. Dosage forms, routes of administration and pharmaceutical compositions include, but are not limited to, those described herein.

KITS-OF-PARTS

The present invention also provides kits that contain a pharmaceutical composition which includes one or more compounds of the invention. The kit also includes instructions for the use of the pharmaceutical composition for treating iron disorders as well as other utilities as disclosed herein. Preferably, a commercial package will contain one or more unit doses of the pharmaceutical composition. For example, such a unit dose may be an amount sufficient for the preparation of an intravenous injection. It will be evident to those of ordinary skill in the art that compounds which are light and/or air sensitive may require special packaging and/or formulation. For example, packaging may be used which is opaque to light, and/or sealed from contact with ambient air, and/or formulated with suitable coatings or excipients.

PREPARATION OF THE COMPOUNDS OF THE INVENTION

The following Reaction Schemes illustrate methods to make compounds of the invention, i.e., compounds of formula (I):



wherein m, , R¹, R² and R³ are as defined above in the Summary of the Invention for compounds of formula (I), as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof; or a pharmaceutically acceptable salt, solvate or prodrug

thereof.

In particular, the following Reaction Schemes illustrate methods to make compounds of formula (Ia), compounds of formula (Ib), compounds of formula (Ic), compounds of formula (Id), compounds of formula (Ie), compounds of formula (If), 5 compounds of formula (Ig) and compounds of formula (Ih) as described above in the Embodiments of the Invention. These compounds are compounds of formula (I), as set forth above in the Summary of the Invention. It is understood that one skilled in the art would be able to make these compounds by similar methods or by methods known to one skilled in the art. It is also understood that one skilled in the art would be able to 10 make in a similar manner as described below other compounds of the invention not specifically illustrated below by using the appropriate starting components and modifying the parameters of the synthesis as needed. In general, starting components may be obtained from sources such as Sigma Aldrich, Lancaster Synthesis, Inc., Maybridge, Matrix Scientific, TCI, and Fluorochem USA, etc. or synthesized according 15 to sources known to those skilled in the art (see, e.g., Smith, M.B. and J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition (Wiley, December 2000)) or prepared as described herein.

It is understood that in the following description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions 20 result in stable compounds.

It will also be appreciated by those skilled in the art that in the process described below the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include 25 trialkylsilyl or diarylalkylsilyl (e.g., *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R" (where R" is alkyl, aryl or 30 arylalkyl), *p*-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or arylalkyl esters.

Protecting groups may be added or removed in accordance with standard techniques, which are known to one skilled in the art and as described herein.

The use of protecting groups is described in detail in Greene, T.W. and P.G.M. Wuts, *Greene's Protective Groups in Organic Synthesis* (2006), 4th Ed., Wiley. The 35 protecting group may also be a polymer resin such as a Wang resin or a 2-chlorotriyl-

chloride resin.

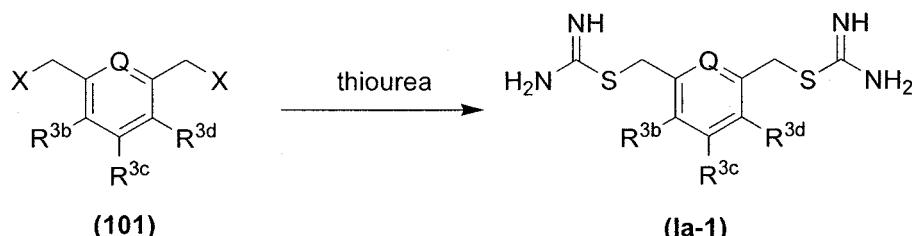
It will also be appreciated by those skilled in the art, although such protected derivatives of compounds of this invention may not possess pharmacological activity as such, they may be administered to a mammal and thereafter metabolized in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". All prodrugs of compounds of this invention are included within the scope of the invention.

The starting materials for the reaction schemes described below are commercially available or can be prepared according to methods known to one skilled in the art or by methods disclosed herein.

A. Preparation of Compounds of Formula (la-1)

Compounds of formula (la-1) are compounds of formula (la), as set forth above in the Embodiments of the Invention, where R¹ and R² are each -R⁶-S-C(=NR⁴)N(R⁴)R⁵, each R⁴ and each R⁵ are hydrogen and each R⁶ is -CH₂- and Q, R^{3b}, R^{3c} and R^{3d} are each as described above in the Embodiments of the Invention for compounds of formula (la), and X is halo, preferably bromo or chloro, and are prepared as set forth below in Reaction Scheme 1.

REACTION SCHEME 1

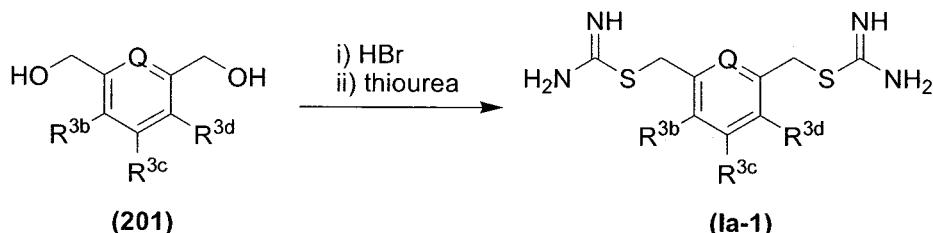


The starting materials for the above reaction scheme are commercially available or can be prepared according to methods known to one skilled in the art or by methods disclosed herein. In general, the compounds of formula (la-1) are prepared in the above reaction scheme as follows:

The displacement of halogen groups of the compound of formula (101) with thiourea under standard conditions known to one skilled in the art affords the compound of formula (la-1) of the invention.

Alternatively, the compounds of formula (la-1), as set forth above, can be prepared as set forth below in Reaction Scheme 2.

REACTION SCHEME 2



The starting materials for the above reaction scheme are commercially available or can be prepared according to methods known to one skilled in the art or by 5 methods disclosed herein. In general, the compounds of the invention are prepared in the above reaction scheme as follows:

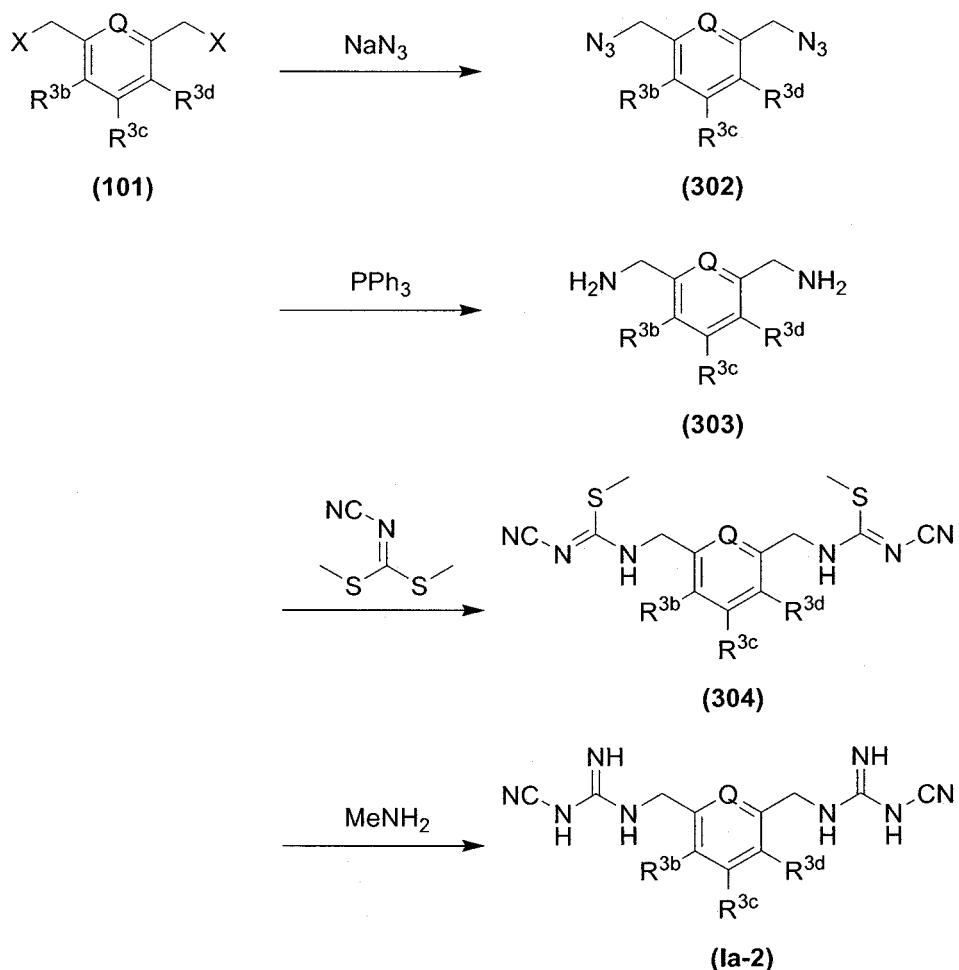
A compound of formula (201) is treated with HBr and subsequently with thiourea under standard conditions known to one skilled in the art to afford the compound of formula (Ia-1) of the invention.

10 **B. Preparation of Compounds of Formula (Ia-2)**

Compounds of formula (Ia-2) are compounds of formula (Ia), as set forth above in the Embodiments of the Invention, where R¹ and R² are each -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵, each R⁴ and each R⁷ are hydrogen, each R⁵ is -CN and each R⁶ is -CH₂-; and Q, R^{3b}, R^{3c} and R^{3d} are each as described above in the

15 Embodiments of the Invention for compounds of formula (Ia), and X is halo, preferably bromo or chloro, and are prepared as set forth below in Reaction Scheme 3.

REACTION SCHEME 3



The starting materials for the above reaction scheme are commercially available or can be prepared according to methods known to one skilled in the art or by methods disclosed herein. In general, the compounds of formula (Ia-2) are prepared in the above reaction scheme as follows:

- Displacement of the halogen groups of a compound of formula (101) with sodium azide affords an azide compound of formula (302), which, upon reduction with a suitable reducing agent such as, but not limited to, triphenylphosphine, yields a 10 diamino compound of formula (303). Sequential treatment of the diamino compound of formula (303) with dimethyl N-cyanodithioiminocarbonate followed by methylamine affords a compound of formula (Ia-2) of this invention.

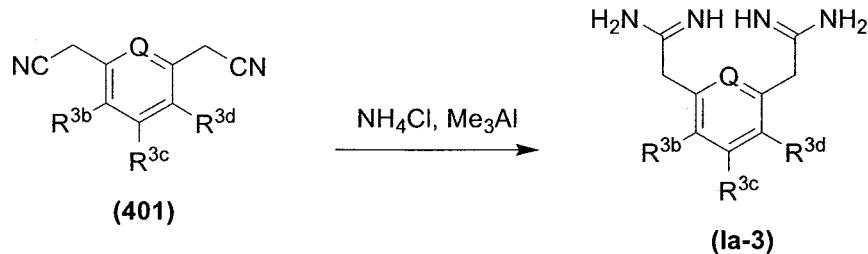
C. Preparation of Compounds of Formula (Ia-3)

Compounds of formula (Ia-3) are compounds of formula (Ia), as set forth above

in the Embodiments of the Invention, where R¹ and R² are -R⁶-C(=NR⁴)N(R⁴)R⁵, each R⁴ and each R⁵ are hydrogen and each R⁶ is -CH₂- and Q, R^{3b}, R^{3c} and R^{3d} are each as described above in the Embodiments of the Invention for compounds of formula (Ia), and are prepared as set forth below in Reaction Scheme 4.

5

REACTION SCHEME 4



The starting materials for the above reaction scheme are commercially available or can be prepared according to methods known to one skilled in the art or by methods disclosed herein. In general, the compounds of formula (Ia-3) are prepared in the above reaction scheme as follows:

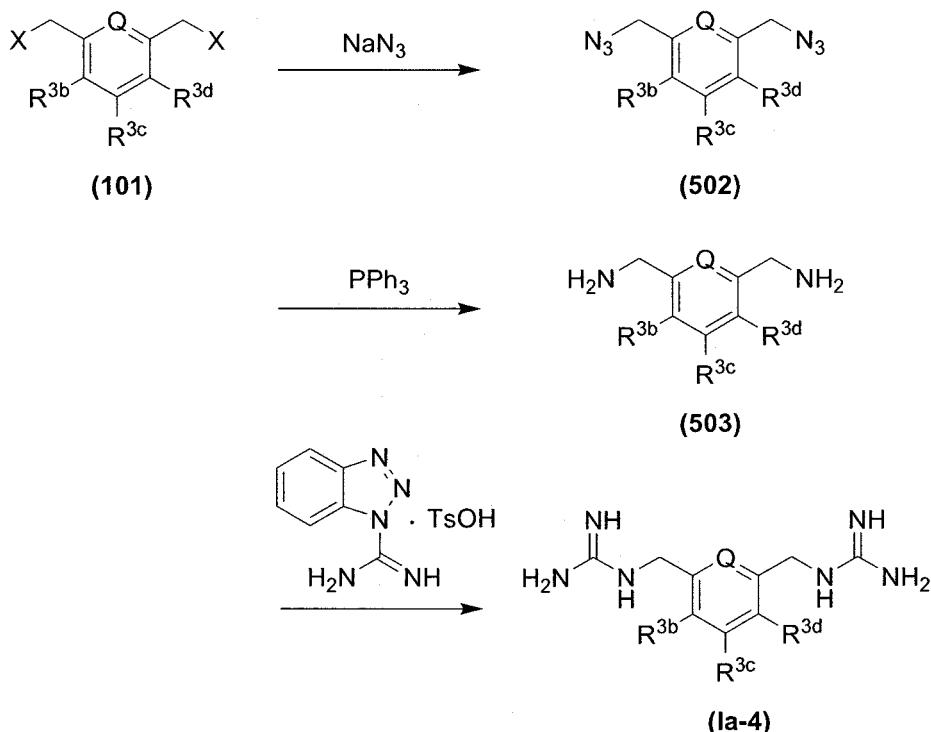
A cyano compound of formula (401) is treated with ammonium chloride and trimethylaluminum under conditions known to one skilled in the art to afford a compound of formula (Ia-3) of this invention.

D. Preparation of Compounds of Formula (Ia-4)

Compounds of formula (Ia-4) are compounds of formula (Ia), as set forth above in the Embodiments of the Invention, where R¹ and R² are -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵, R⁴, R⁵ and R⁷ are hydrogen and R⁶ is -CH₂- and Q, R^{3b}, R^{3c} and R^{3d} are each as described above in the Embodiments of the Invention for compounds of formula (Ia), and X is halo, preferably bromo or chloro, and are prepared as set forth below in Reaction Scheme 5.

20 Reaction Scheme 5.

REACTION SCHEME 5



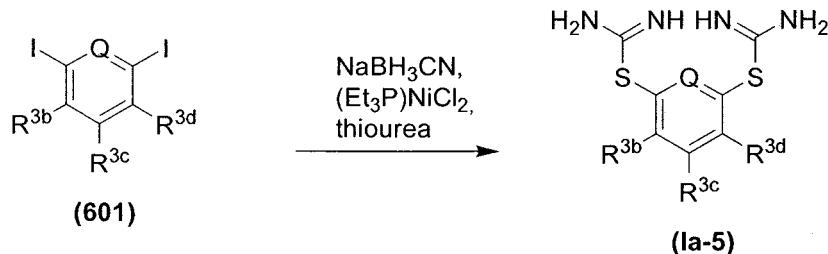
The starting materials for the above reaction scheme are commercially available or can be prepared according to methods known to one skilled in the art or by 5 methods disclosed herein. In general, the compounds of formula (Ia-4) are prepared in the above reaction scheme as follows:

Displacement of the halogen groups of a compound of formula (101) with sodium azide affords an azide compound of formula (502), which upon reduction with a suitable reducing agent such as, but not limited to, triphenylphosphine yields a diamino 10 compound of formula (503). Treatment of the diamino compound of formula (503) with 1-benzotriazole-carboxamidinium tosylate in a suitable solvent such as, but not limited to, N,N-dimethylformamide in the presence of a suitable base such as, but not limited to, N,N-diisopropylethylamine affords a compound of formula (Ia-4) of the invention.

E. Preparation of Compounds of Formula (Ia-5)

Compounds of formula (Ia-5) are compounds of formula (Ia), as set forth above 15 in the Embodiments of the Invention, where R¹ and R² are -R⁶-S-C(=NR⁴)N(R⁴)R⁵, R⁴ and R⁵ are hydrogen, R⁶ is a direct bond and Q, R^{3b}, R^{3c} and R^{3d} are each as described above in the Embodiments of the Invention for compounds of formula (Ia), and are prepared as set forth below in Reaction Scheme 6.

REACTION SCHEME 6



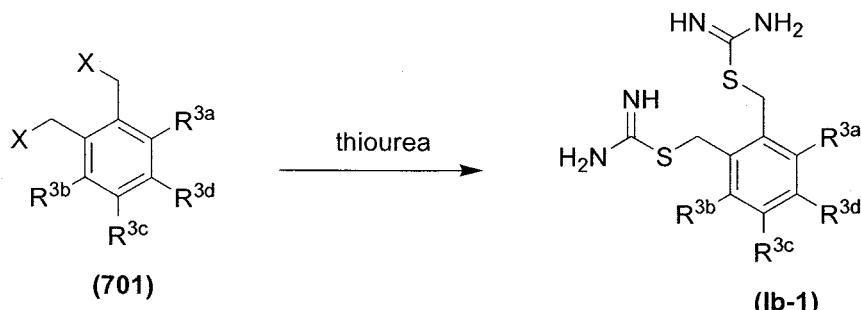
The starting materials for the above reaction scheme are commercially available or can be prepared according to methods known to one skilled in the art or by 5 methods disclosed herein. In general, the compounds of formula (Ia-5) are prepared in the above reaction scheme as follows:

An aryl diiodide of formula (601) is treated with thiourea, a low-valent nickel complex formed from bis(triethylphosphine)nickel(II) chloride and a suitable reductant, such as, but not limited to, sodium cyanoborohydride, to afford a compound of formula 10 (Ia-5) of the invention.

F. Preparation of Compounds of Formula (Ib-1)

Compounds of formula (Ib-1) are compounds of formula (Ib), as set forth above in the Embodiments of the Invention, where R¹ and R² are each -R⁶-S-C(=NR⁴)N(R⁴)R⁵, each R⁴ and each R⁵ are hydrogen and each R⁶ is -CH₂- and 15 R^{3a}, R^{3b}, R^{3c} and R^{3d} are each as described above in the Embodiments of the Invention for compounds of formula (Ib), and X is halo, preferably bromo or chloro, and are prepared as set forth below in Reaction Scheme 7.

REACTION SCHEME 7



20 The starting materials for the above reaction scheme are commercially available or can be prepared according to methods known to one skilled in the art or by

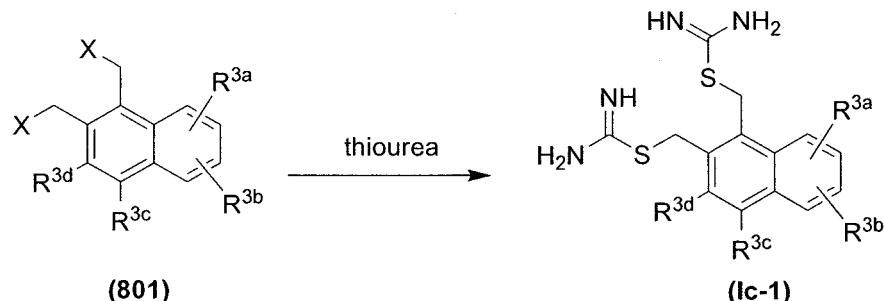
methods disclosed herein. In general, the compounds of formula (Ib-1) are prepared in the above reaction scheme as follows:

The displacement of halogen groups of the compound of formula (701) with thiourea under conditions known to one skilled in the art affords the compound of 5 formula (Ib-1) of the invention.

G. Preparation of Compounds of Formula (Ic-1)

Compounds of formula (Ic-1) are compounds of formula (Ic), as set forth above in the Embodiments of the Invention, where R¹ and R² are -R⁶-S-C(=NR⁴)N(R⁴)R⁵, each R⁴ and each R⁵ are hydrogen, each R⁶ is -CH₂- and R^{3a}, R^{3b}, R^{3c} and R^{3d} are 10 each as described above in the Embodiments of the Invention for compounds of formula (Ic), and are prepared as set forth below in Reaction Scheme 8.

REACTION SCHEME 8



The starting materials for the above reaction scheme are commercially 15 available or can be prepared according to methods known to one skilled in the art or by methods disclosed herein. In general, the compounds of formula (Ic-1) are prepared in the above reaction scheme as follows:

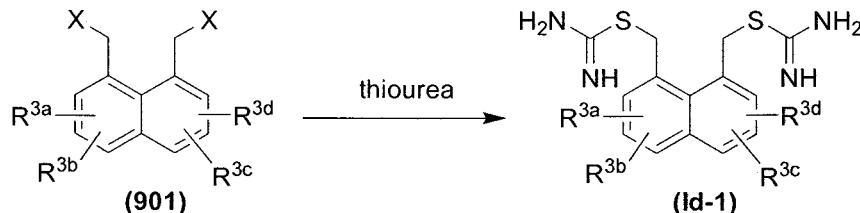
The displacement of halogen groups of the compound of formula (801) with thiourea under conditions known to one skilled in the art affords the compound of 20 formula (Ic-1) of the invention.

H. Preparation of Compounds of Formula (Id-1)

Compounds of formula (Id-1) are compounds of formula (Id), as set forth above in the Embodiments of the Invention, where R¹ and R² are each -R⁶-S-C(=NR⁴)N(R⁴)R⁵, each R⁴ and each R⁵ are hydrogen, each R⁶ is -CH₂- and R^{3a}, 25 R^{3b}, R^{3c} and R^{3d} are each as described above in the Embodiments of the Invention for compounds of formula (Id), and X is halo, preferably bromo or chloro, and are prepared

as set forth below in Reaction Scheme 9.

REACTION SCHEME 9



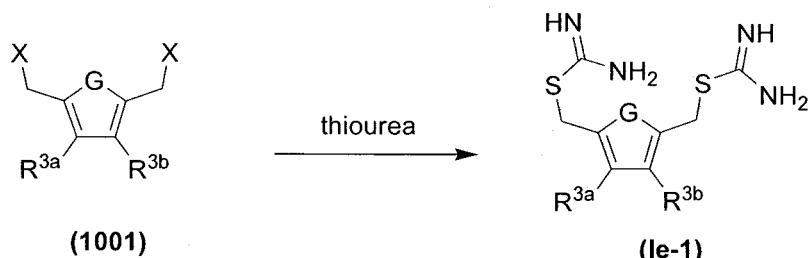
- The starting materials for the above reaction scheme are commercially available or can be prepared according to methods known to one skilled in the art or by methods disclosed herein. In general, the compounds of formula (Id-1) are prepared in the above reaction scheme as follows:

The displacement of halogen groups of the compound of formula (901) with thiourea affords the compound of formula (Id-1) of the invention.

10 I. Preparation of Compounds of Formula (Ie-1)

Compounds of formula (Ie-1) are compounds of formula (Ie), as set forth above in the Embodiments of the Invention, where R¹ and R² are -R⁶-S-C(=NR⁴)N(R⁴)R⁵, each R⁴ and each R⁵ are hydrogen and each R⁶ is -CH₂- and G, R^{3a} and R^{3b} are each as described above in the Embodiments of the Invention for compounds of formula (Ie), and X is halo, preferably bromo or chloro, and are prepared as set forth below in Reaction Scheme 10.

REACTION SCHEME 10



- The starting materials for the above reaction scheme are commercially available or can be prepared according to methods known to one skilled in the art or by methods disclosed herein. In general, the compounds of formula (Ie-1) are prepared in the above reaction scheme as follows:

The displacement of halogen groups of the compound of formula (1001) with

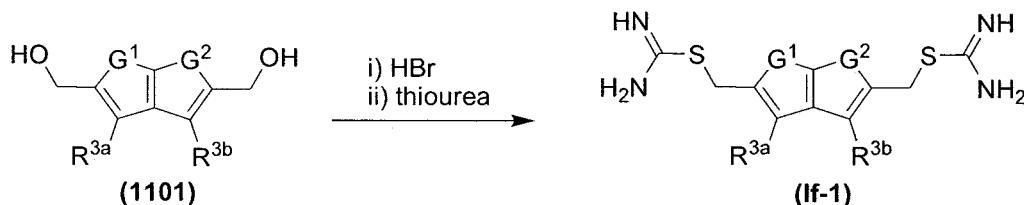
thiourea under conditions known to one skilled in the art affords the compound of formula (If-1) of the invention.

J. Preparation of Compounds of Formula (If-1)

Compounds of formula (If-1) are compounds of formula (If), as set forth above in the Embodiments of the Invention, where R¹ and R² are -R⁶-S-C(=NR⁴)N(R⁴)R⁵, each R⁴ and each R⁵ are hydrogen and each R⁶ is -CH₂- and G¹, G², R^{3a} and R^{3b} are each as described above in the Embodiments of the Invention, and X is halo, preferably bromo or chloro, and are prepared as set forth below in Reaction Scheme 11.

10

REACTION SCHEME 11



The starting materials for the above reaction scheme are commercially available or can be prepared according to methods known to one skilled in the art or by methods disclosed herein. In general, the compounds of formula (If-1) are prepared in the above reaction scheme as follows:

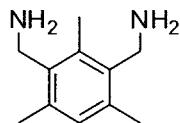
A compound of formula (1101) is treated with HBr and subsequently with thiourea under conditions known to one skilled in the art to afford the compound of formula (If-1) of the invention.

All compounds of the invention as prepared above and below which exist in free base or acid form may be converted to their pharmaceutically acceptable salt by treatment with the appropriate inorganic or organic base or acid by methods known to one skilled in the art. Salts of the compounds prepared herein may be converted to their free base or acid by standard techniques known to one skilled in the art.

The following Preparations, which are directed to the preparation of intermediates used in the preparation of the compounds of the invention, and the following Examples, which are directed to the preparation of the compounds of the invention, are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention.

PREPARATION 1

Preparation of (2,4,6-trimethyl-1,3-phenylene)dimethanamine

A. Synthesis of 2,2'-(2,4,6-trimethyl-1,3-phenylene)bis(methylene)diisoindoline-1,3-dione

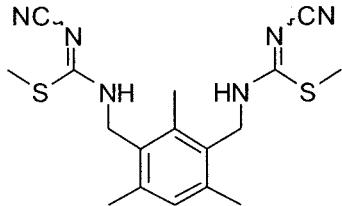
A mixture of 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene (2.39 g, 11.00 mmol), potassium phthalimide (8.15 g, 44.00 mmol), potassium iodide (3.65 g, 22.00 mmol) and *N,N*-dimethylformamide (80 mL) was heated at 100 °C for 16 h. The reaction mixture was poured into water (300 mL) and the precipitate was collected by filtration and washed with water (50 mL). The resultant solid was triturated with boiling methanol (25 mL), air-dried and dried under high vacuum to afford 2,2'-(2,4,6-trimethyl-1,3-phenylene)bis(methylene)diisoindoline-1,3-dione as a colorless solid in 63% yield (3.02 g): ^1H NMR (300 MHz, CDCl_3) δ 7.79-7.75 (m, 4H), 7.70-7.64 (m, 4H), 6.92 (s, 1H), 4.88 (s, 4H), 2.43 (s, 3H), 2.41 (s, 6H); MS (ES+) m/z 439.5 ($M + 1$).

B. Synthesis of (2,4,6-trimethyl-1,3-phenylene)dimethanamine

To a suspension of 2,2'-(2,4,6-trimethyl-1,3-phenylene)bis(methylene)diisoindoline-1,3-dione (3.02 g, 6.89 mmol) in anhydrous ethanol (20 mL) was added hydrazine monohydrate (3.6 mL, 74.0 mmol). The reaction mixture was heated at reflux for 5 h, cooled to ambient temperature and filtered. The filtrate was concentrated *in vacuo* to dryness to afford (2,4,6-trimethyl-1,3-phenylene)dimethanamine as a pale yellow solid in 96% yield (1.18 g): ^1H NMR (300 MHz, DMSO-d_6) δ 6.76 (s, 1H), 3.67 (s, 4H), 2.88 (br s, 4H), 2.35 (s, 3H), 2.26 (s, 6H); MS (ES+) m/z 179.4 ($M + 1$).

PREPARATION 2

Preparation of dimethyl *N,N'*-(2,4,6-trimethyl-1,3-phenylene)bis(methylene)bis(*N'*-cyanocarbamimidothioate)



5 A. Synthesis of 2,4-bis(azidomethyl)-1,3,5-trimethylbenzene

To a solution of 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene (2.00 g, 9.21 mmol) in acetone (40 mL) was added sodium azide (1.32 g, 20.20 mmol) and the reaction mixture was heated at reflux for 6 h. Most of the acetone was removed on a rotary evaporator without heating. The resultant oily residue was diluted with diethyl ether (20 mL) and transferred to a separatory funnel. The organic phase was washed with water (3 × 20 mL) and brine (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2,4-bis(azidomethyl)-1,3,5-trimethylbenzene as a colorless oil which was used in the next step without purification: MS (ES+) *m/z* 231.3 (M + 1).

15 B. Synthesis of (2,4,6-trimethyl-1,3-phenylene)dimethanamine

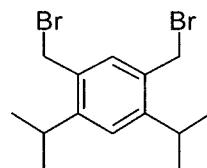
To a solution of the crude 2,4-bis(azidomethyl)-1,3,5-trimethylbenzene in tetrahydrofuran (40 mL) and water (4 mL) was added triphenylphosphine (7.24 g, 27.60 mmol). The reaction mixture was stirred vigorously for 16 h at ambient temperature. The tetrahydrofuran was removed *in vacuo* and the residue was partitioned between 0.1 M aqueous hydrochloric acid (100 mL) and diethyl ether (50 mL) and transferred to a separatory funnel. The aqueous phase was washed with diethyl ether (2 × 50 mL) and carefully basified to pH ~10 by the addition of a 10% aqueous solution of sodium carbonate. The aqueous phase was then extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to dryness to afford (2,4,6-trimethyl-1,3-phenylene)dimethanamine as a pale yellow solid in 38% yield over two steps (0.62 g): ¹H NMR (300 MHz, DMSO-*d*₆) δ 6.76 (s, 1H), 3.67 (s, 4H), 2.88 (br s, 4H), 2.35 (s, 3H), 2.26 (s, 6H); MS (ES+) *m/z* 179.4 (M + 1).

C. Synthesis of dimethyl N',N-(2,4,6-trimethyl-1,3-phenylene)bis(methylene)bis(N'-cyanocarbamimidothioate)

To a solution of (2,4,6-trimethyl-1,3-phenylene)dimethanamine (0.62 g, 3.41 mmol) in anhydrous ethanol (15 mL) was added dropwise a solution of dimethyl N-cyanodithioiminocarbonate (90% purity, 1.02 g, 6.80 mmol) in anhydrous ethanol (15 mL). The resultant heterogeneous mixture was stirred for 16 h at ambient temperature. The precipitate was collected by filtration and air-dried. A 100 mg sample of this material was recrystallized from acetonitrile/water (1:1) to afford dimethyl N',N-(2,4,6-trimethyl-1,3-phenylene)bis(methylene)bis(N'-cyanocarbamimidothioate) as a colorless solid (0.08 g): MS (ES+) *m/z* 375.6 (M + 1).

PREPARATION 3

Preparation of 1,5-bis(bromomethyl)-2,4-diisopropylbenzene

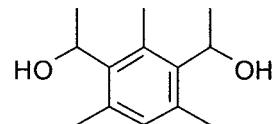


To a stirred solution of 1,3-diisopropylbenzene (2.50 mL, 13.20 mmol) and paraformaldehyde (1.40 g, 46.10 mmol) in acetic acid (8.0 mL) was added a solution of 33% hydrobromide in acetic acid (10 mL) at ambient temperature. The mixture was stirred at 130 °C for 15 h, poured into ice-water and filtered. The filtrate was neutralized with saturated sodium bicarbonate solution and extracted with dichloromethane (3 x 30 mL). The combined organic layers was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography eluted with hexane to afford 1,5-bis(bromomethyl)-2,4-diisopropylbenzene as a colorless solid in 43% yield (0.25 g). ¹H NMR (300 MHz, CDCl₃) δ 7.23 (s, 1H), 7.21 (s, 1H), 4.51 (s, 4H), 3.30-3.18 (m, 2H), 1.27 (d, *J* = 6.8 Hz, 12H).

25

PREPARATION 4

Preparation of 1,1'-(2,4,6-trimethyl-1,3-phenylene)diethanol



A. Synthesis of 1,1'-(2,4,6-trimethyl-1,3-phenylene)diethanone

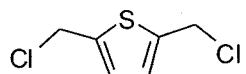
To a stirred suspension of aluminum trichloride (11.50 g, 86.24 mmol) in dichloromethane (15 mL) was added acetyl chloride (3.10 mL, 43.6 mmol) slowly under nitrogen atmosphere. The resulting reaction mixture was refluxed for 30 minutes, and 5 mesitylene (2.00 mL, 14.40 mmol) in dichloromethane (8 mL) was added dropwise. The resulting reaction mixture was refluxed for 3 h, cooled to ambient temperature and poured into crushed ice. Dichloromethane (60 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (60 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (100 10 mL), brine (100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 1,1'-(2,4,6-trimethyl-1,3-phenylene)diethanone in a quantitative yield: ^1H NMR (300 MHz, CDCl_3) δ 6.88 (s, 1H), 2.45 (s, 6H), 2.21 (s, 6H), 2.11 (s, 3H).

B. Synthesis of 1,1'-(2,4,6-trimethyl-1,3-phenylene)diethanol

To a stirred solution of 1,1'-(2,4,6-trimethyl-1,3-phenylene)diethanone (1.00 g, 4.90 mmol) in tetrahydrofuran (20 mL) at 0 °C under nitrogen atmosphere was added 15 lithium aluminum hydride (4.90 mL of 2.0 M solution in tetrahydrofuran, 9.80 mmol) dropwise. The resulting reaction mixture was stirred at ambient temperature for 1.5 h, followed by the addition of sodium sulfate decahydrate. The solid was separated by filtration and washed with dichloromethane. The filtrate was concentrated and the 20 crude material was recrystallized from ethyl acetate/hexanes to afford 1,1'-(2,4,6-trimethyl-1,3-phenylene)diethanol (0.694 g, 68%): ^1H NMR (300 MHz, CDCl_3) δ 6.82 (s, 1H), 5.44 (q, J = 6.6 Hz, 2H), 2.54 (d, J = 5.4 Hz, 3H), 2.40 (s, 6H), 1.55 (d, J = 6.6 Hz, 6H).

PREPARATION 5

25 Preparation of 2,5-bis(chloromethyl)thiophene



A. Synthesis of thiophene-2,5-diyldimethanol

A solution of thiophene-2,5-dicarboxylic acid (1.40 g, 10.00 mmol) and lithium aluminium hydride (0.76 g, 20.00 mmol) in tetrahydrofuran (150 mL) was warmed up to 30 50 °C for 3 h, cooled to ambient temperature, neutralized with saturated sodium sulfate and filtered through celite cake. The filtrate was concentrated *in vacuo* and thiophene-

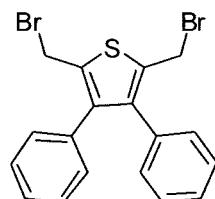
2,5-diylidemethanol was obtained as a colorless solid 70% yield (1.01 g): MS (ES+) *m/z* 145.2 (*M* + 1).

B. Synthesis of 2,5-bis(chloromethyl)thiophene

Thiophene-2,5-diylidemethanol (1.01 g, 7.00 mmol) was dissolved in chloroform (50 mL) and 2 drops of *N,N*-dimethylformamide and thionyl chloride (1.67 g, 14.00 mmol) was added. The reaction mixture was stirred under nitrogen at ambient temperature for 20 h. The solvents were evaporated *in vacuo* and the residue was purified by column chromatography eluted with hexanes/ethyl acetate (4/1 to 1/1) to afford 2,5-bis(chloromethyl)thiophene as a colorless solid 49% yield (0.63 g): MS (ES+) *m/z* 182.2 (*M* + 1).

PREPARATION 6

Preparation of 2,5-bis(bromomethyl)-3,4-diphenylthiophene



A. Synthesis of (3,4-diphenylthiophene-2,5-diyl)dimethanol

15 A mixture of 3,4-diphenylthiophene-2,5-dicarboxylic acid (5.00 g, 15.00 mmol) in tetrahydrofuran (150 mL) and borane-tetrahydrofuran complex solution (22.5 mL of 2 M solution, 45 mmol) was stirred at ambient temperature for 16 h. Methanol (100 mL) was added to the mixture and followed by the addition of 10 M HCl solution (20 mL). The reaction mixture was stirred at 60 °C for 3 h and concentrated *in vacuo* to dryness.

20 The residue was purified by column chromatography eluted with hexanes/ethyl acetate (2/1 to 1/1) to afford (3,4-diphenylthiophene-2,5-diyl)dimethanol as a colorless solid in 65% yield (2.90 g): MS (ES+) *m/z* 279.2 (*M* - 17).

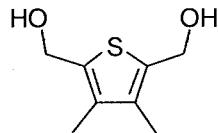
B. Synthesis of 2,5-bis(bromomethyl)-3,4-diphenylthiophene

A mixture of (3,4-diphenylthiophene-2,5-diyl)dimethanol (2.90 g, 9.80 mmol) in dichloromethane (10 mL) and 33% hydrogen bromide solution in acetic acid (5 mL) was stirred at ambient temperature for 2 h. The reaction mixture was poured in water (100 mL) and the solid obtained was collected by filtration and dried *in vacuo* to afford 2,5-bis(bromomethyl)-3,4-diphenylthiophene as a colorless solid in 51% yield (2.10 g):

MS (ES+) m/z 423.2 ($M + 1$).

PREPARATION 7

Preparation of (3,4-dimethylthiophene-2,5-diyl)dimethanol



5 A. Synthesis of 3,4-dimethylthiophene-2,5-dicarboxylic acid

A solution of 3,4-dimethylthiophene-2,5-dicarbonitrile (5.00 g, 31.00 mmol) and sodium hydroxide (4.00 g, 100.00 mmol) in water (50 mL) was refluxed for 24 h, cooled to ambient temperature and acidified. The solid residue was collected by filtration and dissolved in 30% sulfuric acid (100 mL). This mixture was refluxed for 20 h, cooled to 10 ambient temperature. The solid residue was collected by filtration, washed with water and dried *in vacuo* to afford 3,4-dimethylthiophene-2,5-dicarboxylic acid as a colorless solid in 63% yield (3.90 g): MS (ES+) m/z 180.09 ($M - 17$).

B. Synthesis of dimethyl 3,4-dimethylthiophene-2,5-dicarboxylate

A mixture of 3,4-dimethylthiophene-2,5-dicarboxylic acid (3.90 g, 19.40 mmol), 15 thionyl chloride (10.00 g, 85.00 mmol) and *N,N*-dimethylformamide (7.30 g, 100 mmol) in dichloromethane (50 mL) was stirred at ambient temperature for 48 h and concentrated *in vacuo*. The residue was refluxed in methanol (100 mL) for 16 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography eluted with hexanes/ethyl acetate (2/1 to 1/1) to afford dimethyl 3,4-dimethylthiophene-20 2,5-dicarboxylate as a colorless solid in 52% yield (2.31 g): MS (ES+) m/z 229.2 ($M + 1$).

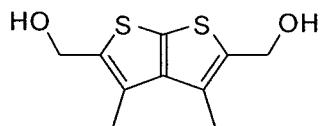
C. Synthesis of (3,4-dimethylthiophene-2,5-diyl)dimethanol

A mixture of dimethyl 3,4-dimethylthiophene-2,5-dicarboxylate (2.31 g, 10.00 mmol) and lithium aluminum hydride (20 mL of 2 M solution in tetrahydrofuran, 40 25 mmol) was stirred at ambient temperature for 24 h. The reaction mixture was neutralized with saturated sodium sulfate solution and filtered through celite. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography eluted with hexanes/ethyl acetate (3/1 to 1/1) to afford (3,4-dimethylthiophene-2,5-diyl)dimethanol as a colorless solid in 64% yield (1.10 g): MS

(ES+) m/z 155.1 (M - 17).

PREPARATION 8

Preparation of (3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)dimethanol



5 A. Synthesis of dipropyl 3,4-dimethylthieno[2,3-b]thiophene-2,5-dicarboxylate

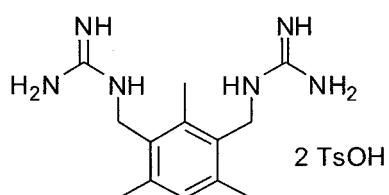
A solution of 3,4-dimethylthieno[2,3-b]thiophene-2,5-dicarboxylic acid (5.00 g, 19.50 mmol), thionyl chloride (10.00 g, 85.00 mmol) and *N,N*-dimethylformamide (7.30 g, 100.00 mmol) in dichloromethane (50 mL) was stirred at ambient temperature for 48 h. The solvents were removed *in vacuo*. The residue was dissolved in *n*-propanol (100 mL) and the resulting solution was heated under reflux for 16 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography eluted with dichloromethane/ethyl acetate (4/1 to 2/1) to afford dipropyl 3,4-dimethylthieno[2,3-b]thiophene-2,5-dicarboxylate (4.70 g, 71%) as a colorless solid: MS (ES+) m/z 341.3 (M + 1).

15 B. Synthesis of (3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)dimethanol

A solution of 3,4-dimethylthiophene-2,5-dicarboxylate (4.70 g, 13.8 mmol) and lithium aluminum hydride (27.5 mL of 2 M solution, 55 mmol) was stirred at ambient temperature for 48 h. After completion of the reaction, the reaction mixture was neutralized with saturated sodium sulfate solution and filtered through celite. The 20 filtrate was concentrated *in vacuo* and the residue was recrystallized from toluene/hexane to afford (3,4-dimethylthieno[2,3-b]thiophene-2,5-diyl)dimethanol (2.40 g, 76%) as a colorless solid: MS (ES+) m/z 211.2 (M - 17).

EXAMPLE 1

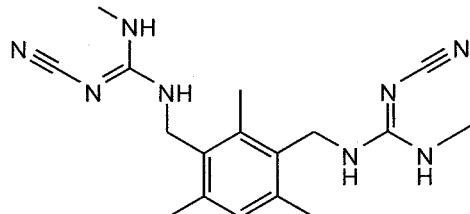
Synthesis of *N*-(3-guanidinomethyl-2,4,6-trimethylbenzyl)guanidine, bis(*p*-toluenesulfonate)



A mixture of (2,4,6-trimethyl-1,3-phenylene)dimethanamine (1.18 g, 6.62 mmol), 1-benzotriazolecarboxamidinium tosylate (prepared according to Katritzky et al. *Synth. Commun.* 1995; 25(8): 1173-1186) (4.41 g, 13.2 mmol), *N,N*-diisopropylethylamine (2.3 mL, 13.1 mmol) and anhydrous *N,N*-dimethylformamide (17.0 mL) was stirred at ambient temperature for 46 h. The reaction mixture was diluted with diethyl ether (70 mL) and stirred for 10 min. The precipitate was collected by filtration, washed with diethyl ether (50 mL) and air-dried. The crude product was triturated with boiling anhydrous ethanol (50 mL) and, after cooling to ambient temperature, the solid was collected by filtration, washed with anhydrous ethanol (25 mL), air-dried and dried under high vacuum to afford *N*-(3-guanidinomethyl-2,4,6-trimethylbenzyl)-guanidine, bis(*p*-toluenesulfonate) as a colorless solid in 44% yield (1.76 g): mp > 250 °C (ethanol); ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.47-7.40 (m, 14H), 7.12 (d, *J* = 7.2 Hz, 4H), 7.01 (s, 1H), 4.29 (d, *J* = 4.2 Hz, 4H), 2.31-2.26 (m, 15H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 156.6, 145.1, 138.0, 137.4, 137.2, 130.6, 130.2, 128.2, 125.4, 20.8, 19.3, 15.0); MS (ES+) *m/z* 263.3 (M + 1).

EXAMPLE 2

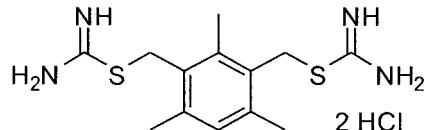
Synthesis of 1,3-di[(2-cyano-3-methylguanidino)methyl]-2,4,6-trimethylbenzene



To an 8 M solution of methylamine in anhydrous ethanol (10 mL) was added 1,3-di((2-cyanoguanidino)methyl)-2,4,6-trimethylbenzene bistosylate (0.15 g, 0.40 mmol). The reaction mixture was stirred for 16 h at ambient temperature and concentrated *in vacuo* to dryness. The residue was recrystallized three times from boiling methanol to afford 1,3-di[(2-cyano-3-methylguanidino)methyl]-2,4,6-trimethylbenzene as a colorless solid in 5% yield (0.007 g): mp 270-272 °C (methanol); ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.05 (m, 2H), 6.91 (s, 1H), 6.55 (br s, 2H), 4.31 (d, *J* = 4.2 Hz, 4H), 2.68 (d, *J* = 4.8 Hz, 6H), 2.29 (s, 6H), 2.24 (s, 3H); MS (ES+) *m/z* 341.6 (M + 1).

EXAMPLE 3

Synthesis of (2,4,6-trimethyl-1,3-phenylene)bis(methylene)dicarbamimidothioate dihydrochloride

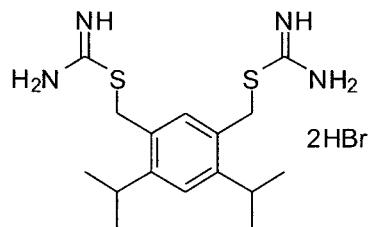


5 To a solution of 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene (35.00 g, 161.00 mmol) in anhydrous ethanol (1000 mL) was added thiourea (24.50 g, 322.10 mmol). The reaction mixture was heated for 15 h at to 80 °C and was allowed to cool to ambient temperature, during which time a thick precipitate was deposited. The precipitate was collected by filtration, washed with ethanol (200 mL), air-dried and
10 dried under high vacuum to afford (2,4,6-trimethyl-1,3-phenylene)bis(methylene)dicarbamimidothioate dihydrochloride as a colorless solid in 92% yield (54.0 g): mp > 250 °C (ethanol); ¹H NMR (300 MHz, DMSO-d₆) δ 9.40 (br s, 8H), 7.02 (s, 1H), 4.55 (s, 4H), 2.41 (s, 3H), 2.33 (s, 6H); ¹³C NMR (75 MHz, DMSO-d₆) δ 169.9, 138.0, 137.8, 130.6, 127.7, 30.7, 19.3, 15.2; MS (ES+) m/z 297.3 (M + 1).

15

EXAMPLE 3.1

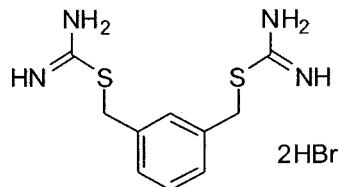
Synthesis of (4,6-diisopropyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide



Following the procedure as described in Example 3, making non-critical
variations using 1,5-bis(bromomethyl)-2,4-diisopropylbenzene to replace 2,4-
20 bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (4,6-diisopropyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide was obtained as a white solid in 93% yield: mp 208-210 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 9.34-8.87 (br s, 8H), 7.32 (s, 1H), 7.28 (s, 1H), 4.48 (s, 4H), 3.21-3.03 (m, 2H), 1.17 (d, J = 6.7 Hz, 12H); ¹³C NMR (75 MHz, DMSO-d₆) δ 169.6, 148.9, 133.0, 128.4, 124.3, 32.4, 28.9, 24.4; MS (ES+) m/z 339.3 (M + 1).

EXAMPLE 3.2

Synthesis of 1,3-phenylenebis(methylene) dicarbamimidothioate dihydrobromide

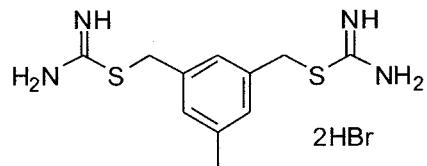


Following the procedure as described in Example 3, making non-critical
 5 variations using 1,3-bis(bromomethyl)benzene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, 1,3-phenylenebis(methylene) dicarbamimidothioate was obtained as a white solid in 97% yield: mp 216-218 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 9.24 (br s, 4H), 9.05 (br s, 4H), 7.46 (s, 1H), 7.39 (d, J = 1.1 Hz, 3H), 4.53 (s, 4H); MS (ES+) m/z 255.4 (M + 1).

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EXAMPLE 3.3

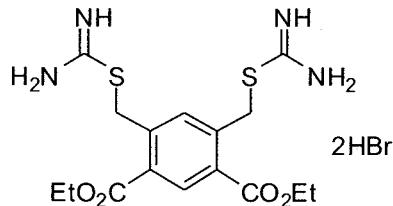
Synthesis of (5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide



Following the procedure as described in Example 3, making non-critical
 15 variations using 1,3-bis(bromomethyl)-5-methylbenzene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide was obtained as a white solid in 65% yield: mp 240-241 °C; ¹H NMR (300 MHz, CD₃OD) δ 7.33 (s, 1H), 7.26 (s, 2H), 4.44 (s, 4H), 2.36 (s, 3H); ¹³CNMR (75 MHz, CD₃OD) δ 172.1, 141.2, 136.2, 131.0, 128.1, 36.1, 21.3; MS (ES+) m/z 269.5 (M + 1).

EXAMPLE 3.4

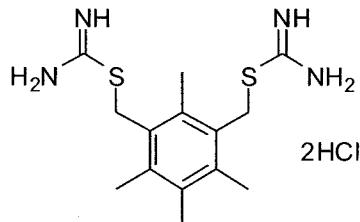
Synthesis of diethyl 4,6-bis(carbamimidoylthiomethyl)isophthalate dihydrobromide



Following the procedure as described in Example 3, making non-critical variations using diethyl 4,6-bis(bromomethyl)isophthalate to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, diethyl 4,6-bis(carbamimidoylthiomethyl)isophthalate dihydrobromide was obtained as a white solid in 54% yield: mp 237-238 °C; ¹H NMR (300 MHz, CD₃OD) δ 8.64 (s, 1H), 7.80 (s, 1H), 4.87 (s, 4H), 4.44 (q, J = 7.1 Hz, 4H), 1.43 (t, J = 7.1 Hz, 6H); ¹³CNMR (75 MHz, CD₃OD) δ 172.1, 166.8, 142.2, 135.7, 135.5, 130.9, 63.3, 34.6, 14.5; MS (ES+) *m/z* 399.5 (M + 1).

EXAMPLE 3.5

Synthesis of (2,4,5,6-tetramethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrochloride

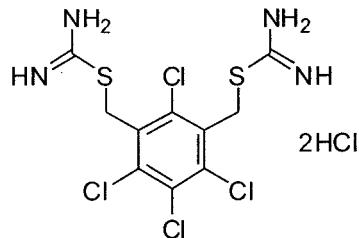


15

Following the procedure as described in Example 3, making non-critical variations using 1,3-bis(chloromethyl)-2,4,5,6-tetramethylbenzene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (2,4,5,6-tetramethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrochloride was obtained as a white solid in 87% yield: mp > 260 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 9.41 (s, 8H), 4.58 (s, 4H), 2.40 (s, 3H), 2.29 (s, 6H), 2.17 (s, 3H); ¹³CNMR (75 MHz, DMSO-d₆) δ 169.8, 136.7, 134.7, 134.1, 127.1, 31.4, 16.5; MS (ES+) *m/z* 311.5 (M + 1).

EXAMPLE 3.6

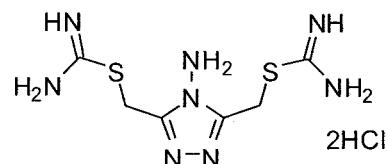
Synthesis of (2,4,5,6-tetrachloro-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrochloride



- 5 Following the procedure as described in Example 3, making non-critical variations using 1,2,3,5-tetrachloro-4,6-bis(chloromethyl)benzene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (2,4,5,6-tetrachloro-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrochloride was obtained as a white solid in 90% yield: mp 208-210 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 9.57 (s, 8H), 4.79 (s, 4H); ¹³C NMR (75 MHz, DMSO-d₆) δ 168.6, 134.9, 134.8, 131.9, 131.3, 33.4; MS (ES+) *m/z* 393.3 (M + 1).
- 10

EXAMPLE 3.7

Synthesis of (4-amino-4*H*-1,2,4-triazole-3,5-diyl)bis(methylene) dicarbamimidothioate dihydrochloride

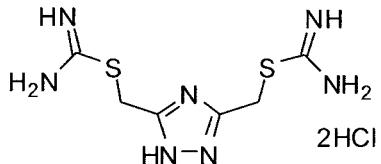


15

- Following the procedure as described in Example 3, making non-critical variations using 3,5-bis(chloromethyl)-4*H*-1,2,4-triazol-4-amine (prepared according to Alonso, *et al.*, *Heterocycles* 1987; 26(4): 989-1000) to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (4-amino-4*H*-1,2,4-triazole-3,5-diyl)bis(methylene) dicarbamimidothioate dihydrochloride was obtained as a white solid in 91% yield: mp 213 °C (dec.) (ethanol); ¹H NMR (300 MHz, DMSO-d₆) δ 9.44 (br s, 4H), 9.34 (br s, 4H), 6.30 (s, 2H), 4.69 (s, 4H); ¹³C NMR (75 MHz, DMSO-d₆) δ 169.3, 151.6, 23.7; MS (ES+) *m/z* 261.2 (M + 1).
- 20

EXAMPLE 3.8

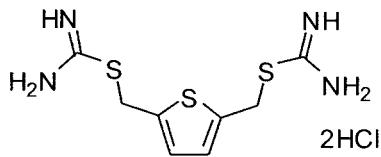
Synthesis of (*1H*-1,2,4-triazole-3,5-diyl)bis(methylene) dicarbamimidothiodate dihydrochloride



5 Following the procedure as described in Example 3, making non-critical variations using 3,5-bis(chloromethyl)-4*H*-1,2,4-triazole (Novikov, *et al.*, *Chem. Heterocycl. Compd.* 1969; 5(1):121-122) to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (*1H*-1,2,4-triazole-3,5-diyl)bis(methylene) dicarbamimidothiodate dihydrochloride was obtained as a white solid in 70% yield: mp
10 196-200 °C (ethanol/acetonitrile); ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.53 (br s, 4H), 9.40 (br s, 4H), 4.64 (s, 4H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 169.3, 155.9, 26.2; MS (ES+) *m/z* 246.2 (M + 1).

EXAMPLE 3.9

Synthesis of thiophene-2,5-diylbis(methylene) dicarbamimidothioate dihydrochloride

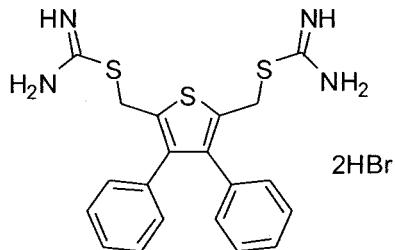


15

Following the procedure as described in Example 3, making non-critical variations using 2,5-bis(chloromethyl)thiophene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, thiophene-2,5-diylbis(methylene) dicarbamimidothioate dihydrochloride was obtained as a white solid in 30% yield: ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.42 (d, 8H), 6.97 (s, 2H), 4.79 (s, 4H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 169.2, 139.3, 128.2, 29.; MS (ES+) *m/z* 261.2 (M + 1).

EXAMPLE 3.10

Synthesis of (3,4-diphenylthiophene-2,5-diyl)bis(methylene) dicarbamimidothioate dihydrobromide

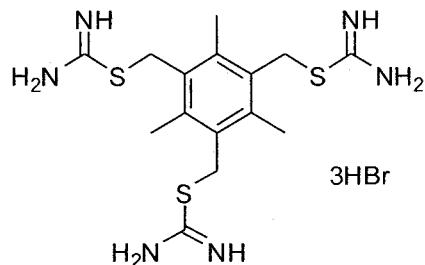


5 Following the procedure as described in Example 3, making non-critical variations using 2,5-bis(bromomethyl)-3,4-diphenylthiophene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (3,4-diphenylthiophene-2,5-diyl)bis(methylene) dicarbamimidothioate dihydrobromide was obtained as a white solid in 30% yield: ^1H NMR (300 MHz, DMSO- d_6) δ 9.17 (s, 4H), 9.01 (s, 4H), 7.31-6.97 (m, 10H), 4.59 (s, 4H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 168.9, 142.5, 134.6, 132.4, 130.2, 128.8, 128.1, 29.4; MS (ES+) m/z 413.2 (M + 1).

10

EXAMPLE 3.11

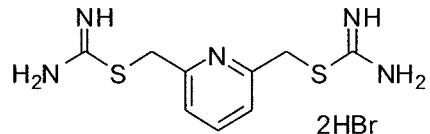
Synthesis of (2,4,6-trimethylbenzene-1,3,5-triyl)tris(methylene) tricarbamimidothioate trihydrobromide



15 Following the procedure as described in Example 3, making non-critical variations using 1,3,5-trisbromomethyl-2,4,6-trimethylbenzene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (2,4,6-trimethylbenzene-1,3,5-triyl)tris(methylene) tricarbamimidothioate trihydrobromide was obtained as a white solid in 66% yield: mp >290 0 °C (ethanol); ^1H NMR (300 MHz, CD3OD) δ 4.59 (s, 6H), 2.46 (s, 9H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 169.1, 138.3, 128.3, 31.1, 15.7; MS (ES+) m/z 385.5 (M + 1).

EXAMPLE 3.12

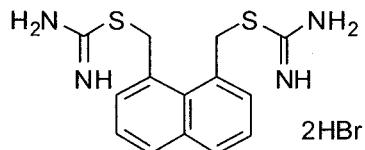
Synthesis of pyridine-2,6-diylbis(methylene) dicarbamimidothioate dihydrobromide



Following the procedure as described in Example 3, making non-critical variations using 2,6-bis(bromomethyl)pyridine to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, pyridine-2,6-diylbis(methylene) dicarbamimidothioate dihydrobromide was obtained as a white solid in 82% yield: mp 208-210 °C(ethanol); ^1H NMR (300 MHz, DMSO- d_6) δ 8.41 (s, 4H), 7.98 (s, 4H), 6.85 (t, J = 7.8 Hz, 1H), 6.45 (d, J = 7.8 Hz, 2H), 3.62 (s, 4H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 169.4, 154.8, 138.9, 122.6, 35.5; MS (ES+) m/z 256.5 ($M + 1$).

EXAMPLE 3.13

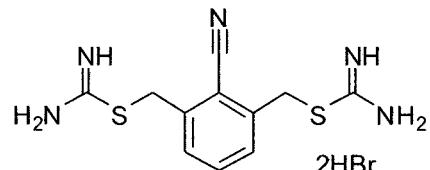
Synthesis of naphthalene-1,8-diylbis(methylene) dicarbamimidothioate dihydrobromide



Following the procedure as described in Example 3, making non-critical variations using 1,8-bis(bromomethyl)naphthalene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, naphthalene-1,8-diylbis(methylene) dicarbamimidothioate dihydrobromide was obtained as a white solid in 76% yield: mp 230-233 °C (ethanol); ^1H NMR (300 MHz, DMSO- d_6) δ 9.28 (s, 4H), 9.11 (s, 4H), 8.06 (d, J = 7.9 Hz, 2H), 7.81 (d, J = 7.1 Hz, 2H) 7.60-7.54 (m, 2H), 5.07 (s, 4H); MS (ES+) m/z 305.4 ($M + 1$).

EXAMPLE 3.14

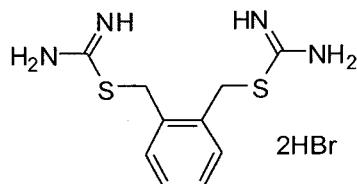
Synthesis of (2-cyano-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide



Following the procedure as described in Example 3, making non-critical variations using 2,6-bis(bromomethyl)benzonitrile to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (2-cyano-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide was obtained as a white solid in 90% yield: mp 270-272 °C (dec, ethanol); ¹H NMR (300 MHz, DMSO-d₆) δ 9.28 (s, 4H), 9.11 (s, 4H), 7.80-7.66 (m, 3H), 4.72 (s, 4H); ¹³C NMR (75 MHz, DMSO-d₆) δ 168.1, 139.6, 133.8, 129.9, 115.0, 112.5, 32.9; MS (ES+) *m/z* 280.5 (M + 1).

EXAMPLE 3.15

Synthesis of (1,2-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide

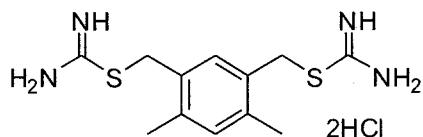


10

Following the procedure as described in Example 3, making non-critical variations using 1,2-bis(bromomethyl)benzene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (1,2-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide was obtained as a white solid in 52% yield: mp 235-238 °C (ethanol); ¹H NMR (300 MHz, DMSO-d₆) δ 9.36 (s, 4H), 9.17 (s, 4H), 7.48-7.38 (m, 4H), 4.61 (s, 4H); ¹³C NMR (75 MHz, DMSO-d₆) δ 168.7, 133.0, 130.9, 129.0, 31.9; MS (ES+) *m/z* 255.5 (M + 1).

EXAMPLE 3.16

Synthesis of (4,6-dimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrochloride

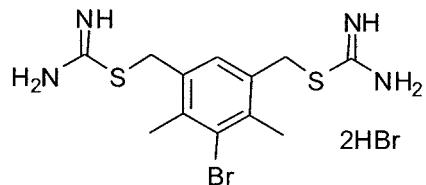


Following the procedure as described in Example 3, making non-critical variations using 1,5-bis(chloromethyl)-2,4-dimethylbenzene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (4,6-dimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrochloride was obtained as a white solid in 94% yield: mp 248-251 °C (ethanol); ¹H NMR (300 MHz, DMSO-d₆) δ

9.45 (s, 8H), 7.35 (s, 1H), 7.07 (s, 1H), 4.48 (s, 4H), 2.27 (s, 6H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 169.5, 137.4, 133.3, 131.6, 130.4, 32.8, 18.5; MS (ES+) m/z 283.5 (M + 1).

EXAMPLE 3.17

- 5 Synthesis of (5-bromo-4,6-dimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrochloride

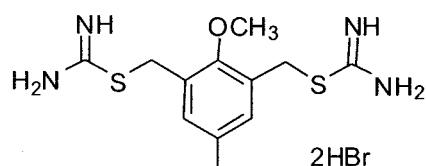


Following the procedure as described in Example 3, making non-critical variations using 3-bromo-1,5-bis(chloromethyl)-2,4-dimethylbenzene to replace 2,4-10 bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (5-bromo-4,6-dimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrochloride was obtained as a white solid in 51% yield: mp 270-273 °C (ethanol); ^1H NMR (300 MHz, DMSO- d_6) δ 9.33 (br s, 8H), 7.44 (s, 1H), 4.58 (s, 4H), 2.45 (s, 6H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 168.8, 137.2, 131.9, 130.8, 129.8, 33.8, 20.2; MS (ES+) m/z 361.4 (M + 1).

15

EXAMPLE 3.18

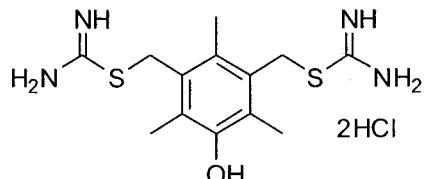
- Synthesis of (2-methoxy-5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydriobromide



Following the procedure as described in Example 3, making non-critical variations using 1,3-bis(bromomethyl)-2-methoxy-5-methylbenzene to replace 2,4-20 bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (2-methoxy-5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate was obtained as a white solid in 97% yield: mp 236-239 °C (ethanol); ^1H NMR (300 MHz, DMSO- d_6) δ 9.18 (s, 4H), 9.04 (s, 4H), 7.21 (s, 2H), 4.41 (s, 4H), 3.76 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 169.2, 154.6, 134.1, 131.7, 127.8, 62.7, 29.5, 20.2; MS (ES+) m/z 299.5 (M + 1).

EXAMPLE 3.19

Synthesis of (5-hydroxy-2,4,6-trimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrochloride

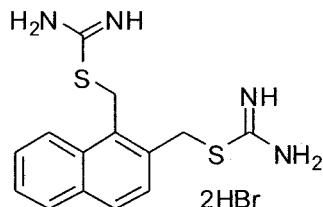


5

Following the procedure as described in Example 3, making non-critical variations using 3,5-bis(chloromethyl)-2,4,6-trimethylphenol to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (5-hydroxy-2,4,6-trimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrochloride was obtained as a white solid in 27% yield: mp 175-178 °C(ethanol); ¹H NMR (300 MHz, CD₃OD) δ 4.53 (s, 4H), 2.43 (s, 3H), 2.33 (s, 6H); ¹³C NMR (75 MHz, DMSO-d₆) δ 171.6, 151.8, 128.8, 127.3, 126.4, 31.3, 14.1, 11.5; MS (ES+) *m/z* 313.6 (M + 1).

EXAMPLE 3.20

Synthesis of naphthalene-1,2-diylbis(methylene) dicarbamimidothioate dihydrobromide

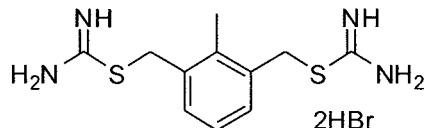


15

Following the procedure as described in Example 3, making non-critical variations using 1,2-bis(bromomethyl)naphthalene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, naphthalene-1,2-diylbis(methylene) dicarbamimidothioate dihydrobromide was obtained as a semi solid in 89% yield: ¹H NMR (300 MHz, CD₃OD) δ 8.24-8.21 (m, 1H), 7.98-7.93 (m, 2H), 7.71-7.58 (m, 3H), 5.15 (s, 2H), 4.87 (s, 2H); ¹³C NMR (75 MHz, CD₃OD) δ 170.9, 170.5, 133.8, 131.8, 130.9, 130.3, 128.7, 127.7, 127.6, 127.2, 126.8, 123.4, 33.7, 29.1; MS (ES+) *m/z* 305.5 (M + 1).

EXAMPLE 3.21

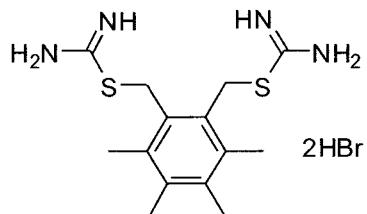
Synthesis of (2-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide



Following the procedure as described in Example 3, making non-critical variations using 1,3-bis(bromomethyl)-2-methylbenzene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (2-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide was obtained as a white solid in 80% yield: mp 258-261 °C(ethanol); ¹H NMR (300 MHz, DMSO-d₆) δ 9.18-9.04 (m, 8H), 7.37-7.35 (m, 2H), 7.22-7.17 (m, 1H), 4.52 (s, 4H), 2.27 (s, 3H); ¹³C NMR (75 MHz, DMSO-d₆) δ 169.5, 137.1, 133.8, 130.9, 126.9, 33.9, 15.1; MS (ES+) m/z 269.5 (M + 1).

EXAMPLE 3.22

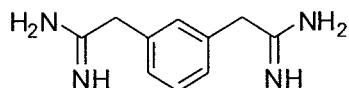
Synthesis of (3,4,5,6-tetramethyl-1,2-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide



Following the procedure as described in Example 3, making non-critical variations using 1,2-bis(bromomethyl)-3,4,5,6-tetramethylbenzene to replace 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene to react with thiourea, (3,4,5,6-tetramethyl-1,2-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide was obtained as a semi solid in 41% yield: mp >265 °C(ethanol); ¹H NMR (300 MHz, DMSO-d₆) δ 9.42 (s, 8H), 4.65 (s, 4H), 2.29 (s, 6H), 2.19 (s, 6H); MS (ES+) m/z 311.6 (M + 1).

EXAMPLE 4

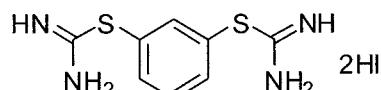
Synthesis of 2,2'-(1,3-phenylene)diacetimidamide



To a stirred suspension of ammonium chloride (0.69 g, 12.81 mmol) in dry toluene (3.8 mL) at 0 °C was added dropwise trimethylaluminum (2.0 M solution in toluene, 6.6 mL, 13.2 mmol). The resulting reaction mixture was stirred at ambient temperature for 1.5 h and 1,3-phenylenediacetonitrile (0.50 g, 3.20 mmol) in dry toluene (2.1 mL) was added at ambient temperature. The resulting reaction mixture was stirred at reflux for 5 h, cooled to ambient temperature and poured into slurry of silica gel (20 g) in dichloromethane (20 mL) and the mixture was stirred for 5 minutes. The silica gel was separated by filtration and washed with methanol (100 mL). The filtrate was concentrated *in vacuo* and the residue was purified by LC/MS and the fractions were collected and dried *in vacuo* to afford 2,2'-(1,3-phenylene)diacetimidamide as a white waxy solid (0.06 g): mp. 200-205 °C; ¹H NMR (300 MHz, CD₃OD) δ 7.52-7.35 (m, 4H), 3.86 (s, 4H); ¹³C NMR (75 MHz, CD₃OD) δ 171.3, 135.5, 131.0, 130.98, 129.83, 39.1; MS (ES+) *m/z* 191.3 (M + 1).

EXAMPLE 5

Synthesis of 1,3-phenylene dicarbamimidothioate dihydroiodide

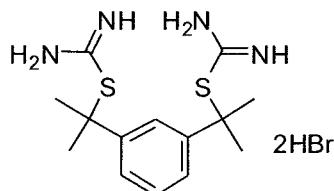


A flask containing 1,3-diiodobenzene (0.50 g, 1.52 mmol), bis(triethylphosphine)nickel(II) chloride (0.028 g, 0.050 mmol), sodium cyanoborohydride (0.007 g, 0.072 mmol) and thiourea (0.35 g, 4.60 mmol) was flushed with nitrogen. Anhydrous *N,N*-dimethylformamide (3 mL) was added and the flask was again flushed with nitrogen. The reaction mixture was stirred at 80 °C for 4 h, allowed to cool to ambient temperature, diluted with water (25 mL) and extracted with dichloromethane (3 × 25 mL). The aqueous layer was concentrated and the residue was heated at reflux in ethanol (10 mL) for 15 minutes. The solution was filtered while hot and the filtrate was allowed to cool to ambient temperature, and then concentrated. The residue was purified by column chromatography and dried *in vacuo* to afford 1,3-phenylene dicarbamimidothioate dihydroiodide as a brown oil: ¹H NMR (300 MHz,

CD_3OD) δ 8.17 (dd, J = 1.6, 1.6 Hz, 1H), 8.00 (dd, J = 1.6, 7.9 Hz, 2H), 7.84-7.76 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 170.1, 144.2, 133.2, 125.5; MS (ES+) m/z 227.3 (M + 1).

EXAMPLE 6

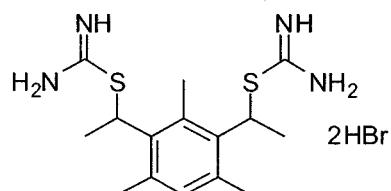
- 5 Synthesis of 2-{1-[3-(1-carbamimidoylsulfanyl-1-methylethyl)phenyl]-1-methylethyl}-isothiourea dihydrobromide



To a stirred suspension of thiourea (0.39 g, 5.15 mmol) in 48% aqueous hydrobromic acid (2 mL) was added 2,2'-(1,3-phenylene)dipropan-2-ol (0.50 g, 2.57 mmol) at 0 °C. The resulting thick paste was stirred at 0 °C for 2 h and ice-cold water (15 mL) was added. The white precipitate was collected by filtration and washed with ether. The solid was recrystallized from hot ethanol/ether to afford 2-{1-[3-(1-carbamimidoylsulfanyl-1-methylethyl)phenyl]-1-methylethyl}-isothiourea dihydrobromide as white crystals in 17% yield (0.21 g): mp 142-144 °C; ^1H NMR (300 MHz, CD_3OD) δ 7.91-7.88 (m, 1H), 7.71-7.66 (m, 2H), 7.58-7.52 (m, 1H), 1.99 (s, 12H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.3, 145.4, 131.1, 127.7, 125.8, 56.9, 31.2; MS (ES+) m/z 311.5 (M + 1).

EXAMPLE 6.1

- 20 Synthesis of 2-{1-[3-(1-carbamimidoylsulfanylethyl)-2,4,6-trimethylphenyl]ethyl}-isothiourea dihydrobromide

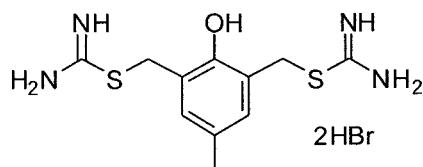


Following the procedure as described in Example 6, making non-critical variations using 1,1'-(2,4,6-trimethyl-1,3-phenylene)diethanol to replace 2,2'-(1,3-phenylene)dipropan-2-ol, 2-{1-[3-(1-carbamimidoylsulfanyl-ethyl)-2,4,6-trimethyl-phenyl]-ethyl}-isothiourea dihydrobromide was obtained as a white solid in 57% yield:

mp 204-206 °C; ^1H NMR (300 MHz, DMSO- d_6) δ 9.34 (s, 4H), 9.11 (s, 4H), 6.96 (s, 1H), 5.52-5.24 (m, 2H), 2.5 (s, 3H), 2.44 (s, 3H), 2.34 (s, 3H), 1.74 (d, J = 6.6 Hz, 6H); MS (ES+) m/z 325.6 ($M + 1$).

EXAMPLE 6.2

- 5 Synthesis of (2-hydroxy-5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydobromide

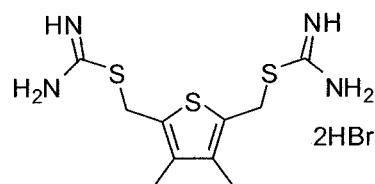


Following the procedure as described in Example 6, making non-critical variations using 2,6-bis(hydroxymethyl)-*p*-cresol to replace 2,2'-(1,3-phenylene)dipropan-2-ol, of (2-hydroxy-5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydobromide was obtained as a white solid in 20% yield: mp 223-225 °C; ^1H NMR (300 MHz, DMSO- d_6) δ 9.36 (s, 1H), 9.14 (s, 4H), 9.01 (s, 4H), 7.11 (s, 2H), 4.42 (s, 4H), 2.17 (s, 3 H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 169.6, 151.2, 131.5, 128.7, 121.8, 30.6, 19.9; MS (ES+) m/z 285.5 ($M + 1$).

15

EXAMPLE 6.3

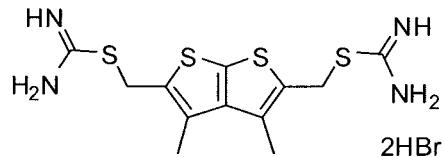
- Synthesis of (3,4-dimethylthiophene-2,5-diyl)bis(methylene) dicarbamimidothioate dihydribromide



Following the procedure as described in Example 6, making non-critical variations using (3,4-dimethylthiophene-2,5-diyl)dimethanol to replace 2,2'-(1,3-phenylene)dipropan-2-ol, the title compound was obtained as a white solid in 73% yield: ^1H NMR (300 MHz, DMSO- d_6) δ 9.23 (s, 4H), 9.06 (s, 4H), 4.70 (s, 4H), 2.03 (s, 6H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 169.1, 137.7, 129.3, 28.9, 13.1; MS (ES+) m/z 289.2 ($M + 1$).

EXAMPLE 6.4

Synthesis of (3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl)bis(methylene) dicarbamimidothioate dihydrobromide

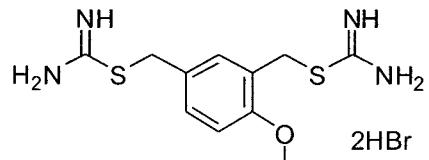


5 Following the procedure as described in Example 6, making non-critical variations using (3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl)dimethanol to replace 2,2'-(1,3-phenylene)dipropan-2-ol, (3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl)bis(methylene) dicarbamimidothioate dihydrobromide was obtained as a white solid in 99% yield: ^1H NMR (300 MHz, DMSO- d_6) δ 9.26 (s, 4H), 9.08 (s, 4H), 4.80 (s, 4H), 2.39 (s, 6H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 169.0, 146.3, 134.9, 132.6, 130.8, 29.6, 13.2; MS (ES+) m/z 345.4 ($M + 1$).

10

EXAMPLE 6.5

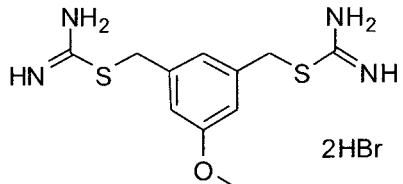
Synthesis of (4-methoxy-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide



15 Following the procedure as described in Example 6, making non-critical variations using (4-methoxy-1,3-phenylene)dimethanol to replace 2,2'-(1,3-phenylene)dipropan-2-ol, (4-methoxy-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide was obtained as a white solid in 94% yield: ^1H NMR (300 MHz, CDCl₃) δ 9.16 (s, 4H), 8.99 (m, 4H), 7.39 (s, 1H), 7.37 (dd, $J = 8.5, 2.1$ Hz, 1H), 7.03 (d, 1H, $J = 8.5$ Hz), 4.42 (s, 2H), 4.36 (s, 2H), 3.79 (s, 3H); MS (ES+) m/z 285.5 ($M + 1$).

EXAMPLE 6.6

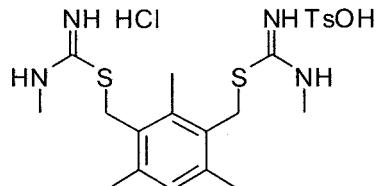
Synthesis of (5-methoxy-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide



5 Following the procedure as described in Example 6, making non-critical variations using (5-methoxy-1,3-phenylene)dimethanol to replace 2,2'-(1,3-phenylene)dipropan-2-ol, (5-methoxy-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydrobromide was obtained as a white solid in 95% yield: ^1H NMR (300 MHz, CDCl_3) δ 9.16 (s, 4H), 8.99 (s, 4H), 6.99-6.96 (m, 1H), 6.96-6.93 (m, 2H), 4.43 (s, 4H), 3.72 (s, 3H); MS (ES+) m/z 285.5 (M + 1).

EXAMPLE 7

Synthesis of 1,3-di[(methylamidino)thiomethyl]-2,4,6-trimethylbenzene 4-methylbenzenesulfonate hydrochloride

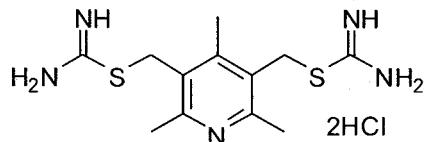


15 A mixture of 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene (0.50 g, 2.30 mmol) and 1-methyl-2-thiourea (0.42 g, 4.60 mmol) in absolute ethanol (10 mL) was refluxed for 16 h and cooled to ambient temperature. To the reaction mixture was added 2.0 M ammonia in methanol (2.5 mL, 5.00 mmol) dropwise at 0 °C, stirred for 30 min and filtered. p-Toluenesulfonic acid monohydrate (0.95 g, 5.01 mmol) was added to the 20 filtrate, and the resulting mixture was stirred for 30 minutes and concentrated to one half of the original volume and acetonitrile was added. The white solid obtained was collected by filtration, washed with acetonitrile and dried *in vacuo* to afford 1,3-di[(methylamidino)thiomethyl]-2,4,6-trimethylbenzene 4-methylbenzenesulfonate hydrochloride as a white solid in 68% yield (0.84 g): mp 223-225 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.88 (d, J = 4.7 Hz, 2H), 9.53 (s, 2H), 9.23 (s, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.00 (s, 1H), 4.57 (s, 4H), 2.94 (d, J = 4.7 Hz, 6H),

2.41 (s, 3H), 2.33 (s, 6H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 166.0, 145.4, 138.0, 137.8, 137.6, 130.5, 128.0, 127.8, 125.4, 31.1, 30.6, 20.7, 19.3, 15.1; MS (ES+) m/z 324.5 (M + 1).

EXAMPLE 8

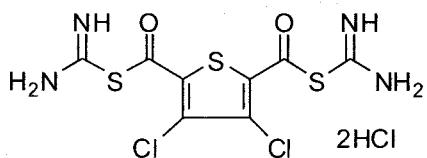
- 5 Synthesis of (2,4,6-trimethylpyridine-3,5-diyl)bis(methylene) dicarbamimidothioate dihydrochloride



A mixture of (5-hydroxymethyl-2,4,6-trimethylpyridin-3-yl)methanol (0.10 g, 0.55 mmol) and thionylchloride (5 mL) was refluxed for 10 min and then concentrated to dryness *in vacuo*. The residue and thiourea (0.08 g, 1.10 mmol) were dissolved in anhydrous ethanol (50 mL). The resulting mixture was refluxed for 4 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in minimum amount of methanol (2-3 mL) and triturated with acetonitrile. The white solid obtained was collected by filtration, washed with acetonitrile, and dried *in vacuo*. (2,4,6-trimethylpyridine-3,5-diyl)bis(methylene) dicarbamimidothioate dihydrochloride was obtained as a white crystals in 14% yield (0.02 g): mp 185-187 °C (ethanol); ^1H NMR (300 MHz, CD₃OD) δ 4.47 (s, 4H), 2.87 (s, 6H), 2.79 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 171.2, 160.5, 154.2, 130.1, 30.6, 18.4, 17.6; MS (ES+) m/z 298.5 (M + 1).

EXAMPLE 9

- 20 Synthesis of 2-(5-carbamimidoylsulfanecarbonyl-3,4-dichlorothiophene-2-carbonyl)isothiourea dihydrochloride



A mixture of 3,4-dichlorothiophene-2,5-dicarbonyl dichloride (0.07 g, 0.25 mmol) and thiourea (0.04 g, 0.49 mmol) was refluxed in benzene (5 mL) for 1 h and cooled to ambient temperature. The mixture was concentrated *in vacuo* and the residue was recrystallized from ethanol to afford 2-(5-carbamimidoylsulfanecarbonyl-3,4-dichlorothiophene-2-carbonyl)isothiourea dihydrochloride as a white solid in 95%

yield (0.08 g): mp 215-218 °C (ethanol); ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.01 (m, 8H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 184.3, 160.7, 131.1, 129.3.

EXAMPLE 10

In a similar manner as described above utilizing the appropriately substituted
5 starting materials, the following compounds of the invention were prepared:
(2-fluoro-1,3-phenylene)bis(methylene) dicarbamimidothioate; and
(4,6-dibromo-1,3-phenylene)bis(methylene) dicarbamimidothioate; mP 161-163 °C; ¹H
NMR (300 MHz, CD₃OD) δ 6.44(s, 1H), 6.18(s, 1H), 2.97(s, 4H); ¹³C NMR (75
MHz, CD₃OD) δ 168.7, 135.6, 132.3, 131.7, 123.5, 33.6; MS (ES+) *m/z* 411.0
10 (M + 1), 413.0 (M + 1), 415.0 (M + 1).

BIOLOGICAL ASSAYS

Various techniques are known in the art for testing the activity of compounds of
the invention. In order that the invention described herein may be more fully
understood, the following biological assays are set forth. It should be understood that
15 these examples are for illustrative purposes only and are not to be construed as
limiting this invention in any manner.

BIOLOGICAL EXAMPLE 1

DMT1 Activity Assay (*In vitro* assay)

This example discloses various *in vitro* assay for testing and profiling test
20 agents against DMT1 stably expressed in cells of either an endogenous or
recombinant origin. These assays can use stable cell lines overexpressing DMT1 or
intestinal cells and intestinal tissue expressing endogenous DMT1. DMT1 function
could also be assessed in other cell types that express DMT1. Of greatest relevance
would be the erythrocytes (e.g. K562 cells) or hepatocytes (e.g. HepG3).

25 DMT1 function can be assessed in a number of ways, including monitoring
fluorescence changes of an iron fluorophore (e.g. calcein), monitoring uptake of
radiolabelled iron (⁵⁵Fe or ⁵⁹Fe) (Picard et al., *J. Biol. Chem.*, 2000, 275(46):35738-45
and Wetli et al., *Chem. Biol.* 2006 Sep;13(9):965-72), or by assessing the current or
transport of iron and other metals into the cells or tissues using standard
30 electrophysiological techniques (Gunshin et al., *Nature*, 1997, 388(6641):482-8.).

Variations of these assays involve alterations of incubation times, the iron
status of the cells and tissues (which may be modulated by chemical chelators or by

harvesting from iron deficient animals), the metal cation detected and the pH of the reaction can generally be made by conventional techniques known to those skilled in the art.

BIOLOGICAL EXAMPLE 2

5

In Vivo Assay for Treatment of Iron Disorders

This test measures the efficacy of compounds of the invention in blocking ferrous iron uptake in the duodenum in rats. The animals were rendered iron deficient by feeding an iron deficient diet for 3 weeks, which causes a marked decrease in serum iron and transferrin saturation. As a result of the iron deficiency, DMT1 expression in the duodenum is upregulated. The test animals were then given an oral bolus (or an "iron challenge") of ferrous iron at 1 mg/Kg resulting in a 20-fold increase in serum iron 1 hour post challenge. It was observed that when test animals were dosed with compound 1 hour prior to the iron challenge, there was a substantial reduction in the increase in serum iron level 1 hour post iron challenge. Compounds of the present invention were shown to be efficacious within a range of 30 mg/Kg and 0.1 mg/Kg.

Representative compounds of the invention, when tested in the above assay, demonstrated an IC₅₀ (nM) activity level as set forth below in Table 1 wherein "A" refers to an IC₅₀ activity level of from 1 nM to 10 nM, "B" refers to an IC₅₀ activity level from 10 nM to 100 nM, "C" refers to an IC₅₀ activity level from 100 nM to 1.0 μM, and "D" refers to an IC₅₀ activity level equal to or greater than 1.0 μM. The Example numbers provided in Table 1 correspond to the Examples herein:

TABLE 1

Example No.	Compound Name	IC ₅₀ Activity Level
1	<i>N</i> -(3-guanidinomethyl-2,4,6-trimethylbenzyl)guanidine, bis(<i>p</i> -toluenesulfonate)	D
2	1,3-di[(2-cyano-3-methylguanidino)methyl]-2,4,6-trimethylbenzene	D
3	(2,4,6-trimethyl-1,3-phenylene)bis(methylene)dicarbamimidothioate dihydrochloride	C
3.1	(4,6-diisopropyl-1,3-phenylene)bis(methylene) dicarbamimidothioate dihydribromide	D
3.2	1,3-phenylenebis(methylene) dicarbamimidothioate	D

Example No.	Compound Name	IC ₅₀ Activity Level
3.3	(5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate	D
3.4	diethyl 4,6-bis(carbamimidoylthiomethyl)isophthalate	D
3.5	(2,4,5,6-tetramethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate	D
3.6	(2,4,5,6-tetrachloro-1,3-phenylene)bis(methylene) dicarbamimidothioate	D
3.7	(4-amino-4 <i>H</i> -1,2,4-triazole-3,5-diyl)bis(methylene) dicarbamimidothioate	D
3.8	(1 <i>H</i> -1,2,4-triazole-3,5-diyl)bis(methylene) dicarbamimidothiodate	D
3.9	thiophene-2,5-diylbis(methylene) dicarbamimidothioate	D
3.10	(3,4-diphenylthiophene-2,5-diyl)bis(methylene) dicarbamimidothioate	D
3.11	(2,4,6-trimethylbenzene-1,3,5-triyl)tris(methylene) tricarbamimidothioate	D
3.12	pyridine-2,6-diylbis(methylene) dicarbamimidothioate	D
3.13	naphthalene-1,8-diylbis(methylene) dicarbamimidothioate	D
3.14	(2-cyano-1,3-phenylene)bis(methylene) dicarbamimidothioate	D
3.15	(1,2-phenylene)bis(methylene) dicarbamimidothioate	D
3.16	(4,6-dimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate	C
3.17	(5-bromo-4,6-dimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate	D
3.18	(2-methoxy-5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate	D
3.19	(5-hydroxy-2,4,6-trimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate	C
3.20	naphthalene-1,2-diylbis(methylene) dicarbamimidothioate	D
3.21	(2-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate	C
3.22	(3,4,5,6-tetramethyl-1,2-phenylene)bis(methylene) dicarbamimidothioate	D
4	2,2'-(1,3-phenylene)diacetimidamide	D
5	1,3-phenylene dicarbamimidothioate	D

Example No.	Compound Name	IC ₅₀ Activity Level
6	2-{1-[3-(1-carbamimidoylsulfanyl-1-methylethyl)phenyl]-1-methylethyl}isothiourea	D
6.1	2-{1-[3-(1-carbamimidoylsulfanylethyl)-2,4,6-trimethyl-phenyl]ethyl}isothiourea	C
6.2	(2-hydroxy-5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate	D
6.3	(3,4-dimethylthiophene-2,5-diyl)bis(methylene) dicarbamimidothioate	D
6.4	(3,4-dimethylthieno[2,3- <i>b</i>]thiophene-2,5-diyl)bis(methylene) dicarbamimidothioate	D
6.5	(4-methoxy-1,3-phenylene)bis(methylene) dicarbamimidothioate	D
6.6	(5-methoxy-1,3-phenylene)bis(methylene) dicarbamimidothioate	D
7	1,3-di[(methylamidino)thiomethyl]-2,4,6-trimethylbenzene 4-methylbenzenesulfonate	D
8	(2,4,6-trimethylpyridine-3,5-diyl)bis(methylene) dicarbamimidothioate	D
9	2-(5-carbamimidoylsulfanecarbonyl-3,4-dichlorothiophene-2-carbonyl)isothiourea	D
10	(2-fluoro-1,3-phenylene)bis(methylene) dicarbamimidothioate	D
10	(4,6-dibromo-1,3-phenylene)bis(methylene) dicarbamimidothioate	C

- A variation of this assay can be used for longer term studies. In this variation, animals are again rendered iron deficient by feeding of an iron deficient diet for 3 weeks. Then animals are switched back to an iron replete diet, while receiving a daily dose of either vehicle or a compound described herein. The vehicle animals recover their iron status, as measured by serum iron and other iron indicies, after 13 days. The drug treated animals, however, do not recover in this timeframe, as the compound is blocking the uptake of dietary iron. Other parameters that can be measured in both models include transferrin saturation, haemoglobin, hematocrit, liver iron and ferritin.
- More detailed assays can involve the use of radioactive metals as opposed to a bolus of ferrous iron. Multiple metals transported by DMT1 can be used to judge specificity of compound on cation uptake by DMT1, if any.

Genetic rat models of iron overload offers another format to show efficacy of DMT1 inhibitors in preventing further iron loading as development proceeds. These

models are applicable to variety of human iron overload disorders such as hereditary hemochromatosis (Levy et al, *Blood*, 1999, 94:9-11, 1999), juvenile hemochromatosis (Huang et al, *J. Clin. Invest.*, 2005 115:2187-2191), beta-2-microglobulin (de Sousa et al., *Immun. Lett.*, 1994, 39:105-111, 1994), thalassemia (Ciavatta et al., *Proc. Nat. Acad. Sci.*, 1995, 92: 9259-9263), hypotransferrinemia (Craven et. al., *Proc. Nat. Acad. Sci.*, 1987, U S A. 84(10):3457-61) and other hypochromic microcytic anemias.

In these models, the knock-out animals above are bred and treated with compound as they develop. Compound efficacy can be assessed by measuring reduced iron flux via the duodenum in a radioactive flux study or by monitoring whether chronic exposure to compounds cause a decrease in the amount of iron loading, as judged by serum iron, transferrin saturation, ferritin and liver iron. These models can be used with an iron bolus, or challenge, as above or iron may be absorbed from the diet. Where appropriate, a model of transfusional iron overload can be created in the rodent by transfusion of iron from another animal in order to exacerbate the iron overload as seen clinically in the treatment of thalassemia.

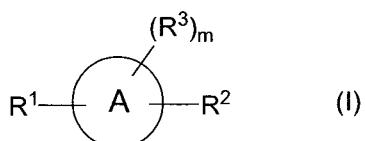
* * * * *

All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification are incorporated herein by reference in their entireties.

Although the foregoing invention has been described in some detail to facilitate understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims. Accordingly, the described embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

WHAT IS CLAIMED IS

1. A method of treating a disease or condition in a mammal wherein the disease or condition is selected from the group consisting of iron overload, transfusional iron overload and thalassemia and wherein the method comprises administering to the mammal a therapeutically effective amount of a compound of formula (I):



wherein:

m is 0, 1, 2, 3, or 4;



is aryl or heteroaryl;

R^1 and R^2 are each independently selected from the group consisting of

- $R^6-S-C(=NR^4)N(R^4)R^5$, - $R^6-C(O)-S-C(=NR^4)N(R^4)R^5$,
- $R^6-S-C(=NR^4)N(R^4)N(R^4)R^5$, - $R^6-O-C(=NR^4)N(R^4)R^5$,
- $R^6-C(O)-N=C[N(R^4)(R^5)]N(R^4)R^5$, - $R^6-C(=NR^4)N(R^4)R^5$, - $R^6-C(=NCN)N(R^4)R^5$,
- $R^6-N(R^7)C(=NCN)N(R^4)R^5$ and - $R^6-N(R^7)C(=NR^4)N(R^4)R^5$;

each R^3 is independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, - R^6-OR^7 , - R^6-CN , - R^6-NO_2 , - $R^6-N(R^8)_2$, - $R^6-C(O)OR^8$, - $R^6-C(O)N(R^8)_2$, - $N(R^8)S(O)_tR^9$, - $S(O)_tOR^9$, - $S(O)_pR^8$, - $S(O)_tN(R^8)_2$, - $R^6-S-C(=NR^4)N(R^4)R^5$, - $R^6-O-C(=NR^4)N(R^4)R^5$, - $R^6-C(=NR^4)N(R^4)R^5$, and - $R^6-N(R^7)-C(=NR^4)N(R^4)R^5$, wherein each t is independently 1 or 2 and each p is 0, 1 or 2;

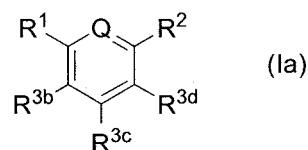
each R^4 and R^5 is independently hydrogen, alkyl, or - OR^7 ;

each R^6 is independently a direct bond or a straight or branched alkylene chain;

each R^7 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and
 each R⁹ is alkyl;
 as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof;
 or a pharmaceutically acceptable salt, solvate or prodrug thereof.

2. The method of Claim 1 wherein the compound of formula (I) is a compound of formula (Ia):



wherein:

Q is -C(R^{3a})= or -N=;

R¹ and R² are each independently selected from the group consisting of

- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of

- hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,

- R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,

- S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

- R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is

- independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and

each R⁹ is alkyl.

3. The method of Claim 2 wherein the compound of formula (I) is a compound of formula (Ia) wherein:

Q is $-C(R^{3a})=$;

R^1 and R^2 are the same and are selected from the group consisting of

- $-R^6-S-C(=NR^4)N(R^4)R^5$, $-R^6-C(O)-S-C(=NR^4)N(R^4)R^5$,
- $-R^6-S-C(=NR^4)N(R^4)N(R^4)R^5$, $-R^6-O-C(=NR^4)N(R^4)R^5$,
- $-R^6-C(O)-N=C[N(R^4)(R^5)]N(R^4)R^5$, $-R^6-C(=NR^4)N(R^4)R^5$, $-R^6-C(=NCN)N(R^4)R^5$,
- $-R^6-N(R^7)C(=NCN)N(R^4)R^5$ and $-R^6-N(R^7)C(=NR^4)N(R^4)R^5$;

R^{3a} , R^{3b} , R^{3c} and R^{3d} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, $-R^6-OR^7$, $-R^6-CN$, $-R^6-NO_2$, $-R^6-N(R^8)_2$, $-R^6-C(O)OR^8$, $-R^6-C(O)N(R^8)_2$, $-N(R^8)S(O)_tR^9$, $-S(O)_tOR^9$, $-S(O)_pR^8$, $-S(O)_tN(R^8)_2$, $-R^6-S-C(=NR^4)N(R^4)R^5$, $-R^6-O-C(=NR^4)N(R^4)R^5$, $-R^6-C(=NR^4)N(R^4)R^5$, and $-R^6-N(R^7)-C(=NR^4)N(R^4)R^5$, wherein each t is independently 1 or 2 and each p is 0, 1 or 2;

each R^4 and R^5 is independently hydrogen, alkyl, or $-OR^7$;

each R^6 is independently a direct bond or a straight or branched alkylene chain;

each R^7 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R^8 is independently hydrogen or alkyl; and

each R^9 is alkyl.

4. The method of Claim 3 wherein the compound of formula (I) is a compound of formula (Ia) wherein:

Q is $-C(R^{3a})=$;

R^1 and R^2 are each $-R^6-S-C(=NR^4)N(R^4)R^5$;

R^{3a} , R^{3b} , R^{3c} and R^{3d} are each independently selected from the group consisting of hydrogen, alkyl, halo, $-R^6-OR^7$, $-R^6-CN$, $-R^6-C(O)OR^8$ and $-R^6-S-C(=NR^4)N(R^4)R^5$;

each R^4 and R^5 is independently hydrogen, alkyl, or $-OR^7$;

each R^6 is independently a direct bond or a straight or branched alkylene chain;

each R^7 is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally

substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
each R⁸ is independently hydrogen or alkyl.

5. The method of Claim 4 wherein the compound of formula (I) is a compound of formula (Ia) selected from the group consisting of:

1,3-phenylenebis(methylene) dicarbamimidothioate;
(2,4,6-trimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;
(2-fluoro-1,3-phenylene)bis(methylene) dicarbamimidothioate;
1,3-phenylene dicarbamimidothioate;
(5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;
(2,4,6-trimethylbenzene-1,3,5-triyl)tris(methylene) tricarbamimidothioate;
2-{1-[3-(1-carbamimidoylsulfanyl-1-methylethyl)phenyl]-1-methylethyl}isothiourea;
(2-cyano-1,3-phenylene)bis(methylene) dicarbamimidothioate;
(4,6-dimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;
diethyl 4,6-bis(carbamimidoylthiomethyl)isophthalate;
(5-bromo-4,6-dimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;
(2,4,5,6-tetramethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;
2-{1-[3-(1-carbamimidoylsulfanylethyl)-2,4,6-trimethylphenyl]ethyl}isothiourea;
(2-hydroxy-5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;
1,3-di[(methylamidino)thiomethyl]-2,4,6-trimethylbenzene;
(5-hydroxy-2,4,6-trimethyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;
(2,4,5,6-tetrachloro-1,3-phenylene)bis(methylene) dicarbamimidothioate;
(2-methoxy-5-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;
(2-methyl-1,3-phenylene)bis(methylene) dicarbamimidothioate;
(4-methoxy-1,3-phenylene)bis(methylene) dicarbamimidothioate;
(5-methoxy-1,3-phenylene)bis(methylene) dicarbamimidothioate;
(4,6-dibromo-1,3-phenylene)bis(methylene) dicarbamimidothioate; and
(4,6-diisopropyl-1,3-phenylene)bis(methylene) dicarbamimidothioate.

6. The method of Claim 3 wherein the compound of formula (I) is a compound of formula (Ia) wherein:

Q is -C(R^{3a})=;

R¹ and R² are the same and selected from -R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and

$-R^6-C(=NR^4)N(R^4)R^5;$
 R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of hydrogen, alkyl, halo, $-R^6-OR^7$, $-R^6-CN$, $-R^6-C(O)OR^8$ and $-R^6-S-C(=NR^4)N(R^4)R^5$;
each R^4 and R^5 is independently hydrogen, alkyl, or $-OR^7$;
each R^6 is independently a direct bond or a straight or branched alkylene chain;
each R^7 is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
each R^8 is independently hydrogen or alkyl.

7. The method of Claim 6 wherein the compound of formula (Ia) is selected from the group consisting of:

1,3-di[(2-cyano-3-methylguanidino)methyl]-2,4,6-trimethylbenzene; and
2,2'-(1,3-phenylene)diacetimidamide.

8. The method of Claim 3 wherein the compound of formula (I) is a compound of formula (Ia) wherein:

Q is $-C(R^{3a})=$;
 R^1 and R^2 are each $-R^6-N(R^7)C(=NR^4)N(R^4)R^5$;
 R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of hydrogen, alkyl, halo, $-R^6-OR^7$, $-R^6-CN$, $-R^6-C(O)OR^8$ and $-R^6-S-C(=NR^4)N(R^4)R^5$;
each R^4 and R^5 is independently hydrogen, alkyl, or $-OR^7$;
each R^6 is independently a direct bond or a straight or branched alkylene chain;
each R^7 is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
each R^8 is independently hydrogen or alkyl.

9. The method of Claim 8 wherein the compound of formula (Ia) is N -(3-

guanidinomethyl-2,4,6-trimethylbenzyl)guanidine.

10. The method of Claim 2 wherein the compound of formula (I) is a compound of formula (Ia) wherein:

Q is -N=;

R¹ and R² are the same and are selected from the group consisting of

- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of

- hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,

- R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)R⁹, -S(O)OR⁹, -S(O)_pR⁸,

- S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

- R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is

- independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and

each R⁹ is alkyl.

11. The method of Claim 10 wherein the compound of formula (I) is a compound of formula (Ia) wherein:

Q is -N=;

R¹ and R² are each -R⁶-S-C(=NR⁴)N(R⁴)R⁵;

R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of hydrogen, alkyl, and halo;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain; and each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,

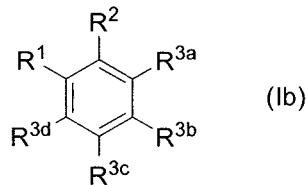
optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl.

12. The method of Claim 11 wherein the compound of formula (Ia) is selected from the group consisting of:

pyridine-2,6-diylbis(methylene) dicarbamimidothioate; and

(2,4,6-trimethylpyridine-3,5-diyl)bis(methylene) dicarbamimidothioate.

13. The method of Claim 1 wherein the compound of formula (I) is a compound of formula (Ib):



wherein:

R^1 and R^2 are each independently selected from the group consisting of

- $R^6-S-C(=NR^4)N(R^4)R^5$, - $R^6-C(O)-S-C(=NR^4)N(R^4)R^5$,
- $R^6-S-C(=NR^4)N(R^4)N(R^4)R^5$, - $R^6-O-C(=NR^4)N(R^4)R^5$,
- $R^6-C(O)-N=C[N(R^4)(R^5)]N(R^4)R^5$, - $R^6-C(=NR^4)N(R^4)R^5$, - $R^6-C(=NCN)N(R^4)R^5$,
- $R^6-N(R^7)C(=NCN)N(R^4)R^5$ and - $R^6-N(R^7)C(=NR^4)N(R^4)R^5$;

R^{3a} , R^{3b} , R^{3c} and R^{3d} are each independently selected from the group consisting of

hydrogen, alkyl, halo, haloalkyl, - R^6-OR^7 , - R^6-CN , - R^6-NO_2 , - $R^6-N(R^8)_2$,

- $R^6-C(O)OR^8$, - $R^6-C(O)N(R^8)_2$, - $N(R^8)S(O)_tR^9$, - $S(O)_tOR^9$, - $S(O)_pR^8$,

- $S(O)_N(R^8)_2$, - $R^6-S-C(=NR^4)N(R^4)R^5$, - $R^6-O-C(=NR^4)N(R^4)R^5$,

- $R^6-C(=NR^4)N(R^4)R^5$, and - $R^6-N(R^7)-C(=NR^4)N(R^4)R^5$, wherein each t is

independently 1 or 2 and each p is 0, 1 or 2;

each R^4 and R^5 is independently hydrogen, alkyl, or - OR^7 ;

each R^6 is independently a direct bond or a straight or branched alkylene chain;

each R^7 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl.

substituted heteroarylalkyl;
 each R⁸ is independently hydrogen or alkyl; and
 each R⁹ is alkyl.

14. The method of Claim 13 wherein the compound of formula (I) is a compound of formula (Ib) wherein:

R¹ and R² are the same and selected from the group consisting of

- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of

- hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,
- R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,
- S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is

independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and

each R⁹ is alkyl.

15. The method of Claim 14 wherein the compound of formula (I) is a compound of formula (Ib) wherein:

R¹ and R² are the same and are -R⁶-S-C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN and -R⁶-C(O)OR⁸;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

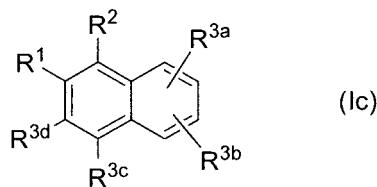
each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,

optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
each R⁸ is independently hydrogen or alkyl.

16. The method of Claim 15 wherein the compound of formula (Ib) is selected from the group consisting of:
(1,2-phenylene)bis(methylene) dicarbamimidothioate; and
(3,4,5,6-tetramethyl-1,2-phenylene)bis(methylene) dicarbamimidothioate.

17. The method of Claim 1 wherein the compound of formula (I) is a compound of formula (Ic):



wherein:

R¹ and R² are each independently selected from the group consisting of
 -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
 -R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of
 hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,
 -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,
 -S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is
 independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally

substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;
 each R⁸ is independently hydrogen or alkyl; and
 each R⁹ is alkyl.

18. The method of Claim 17 wherein the compound of formula (I) is a compound of formula (Ic) wherein:

R¹ and R² are the same and selected from the group consisting of

- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂, -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸, -S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and

each R⁹ is alkyl.

19. The method of Claim 18 wherein the compound of formula (I) is a compound of formula (Ic) wherein:

R¹ and R² are both -R⁶-S-C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN and -R⁶-C(O)OR⁸;

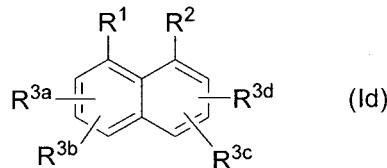
each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
 each R⁸ is independently hydrogen or alkyl.

20. The method of Claim 19 wherein the compound of formula (Ic) is naphthalene-1,2-diylbis(methylene) dicarbamimidothioate.

21. The method of Claim 1 wherein the compound of formula (I) is a compound of formula (Id):



wherein:

R¹ and R² are each independently selected from the group consisting of

- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of

hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,

-R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,

-S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

-R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is

independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

substituted heteroarylalkyl;
 each R⁸ is independently hydrogen or alkyl; and
 each R⁹ is alkyl.

22. The method of Claim 21 wherein the compound of formula (I) is a compound of formula (Id) wherein:

R¹ and R² are the same and selected from the group consisting of

- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of

- hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂,
- R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸,
- S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and

each R⁹ is alkyl.

23. The method of Claim 22 wherein the compound of formula (I) is a compound of formula (Id) wherein:

R¹ and R² are both -R⁶-S-C(=NR⁴)N(R⁴)R⁵;

R^{3a}, R^{3b}, R^{3c} and R^{3d} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, -R⁶-OR⁷, -R⁶-CN and -R⁶-C(O)OR⁸;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

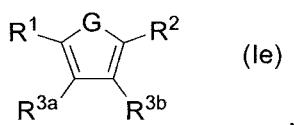
each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,

optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
each R⁸ is independently hydrogen or alkyl.

24. The method of Claim 23 wherein the compound of formula (Id) is naphthalene-1,8-diylbis(methylene) dicarbamimidothioate.

25. The method of Claim 1 wherein the compound of formula (I) is a compound of formula (Ie):



wherein:

G is -O- or -S-;

R¹ and R² are each independently selected from the group consisting of

- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂, -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)R⁹, -S(O)OR⁹, -S(O)_pR⁸, -S(O)N(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and
each R⁹ is alkyl.

26. The method of Claim 25 wherein the compound of formula (I) is a compound of formula (Ie) wherein:

G is -O- or -S-;

R¹ and R² are the same and selected from the group consisting of

- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂, -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸, -S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and

each R⁹ is alkyl.

27. The method of Claim 26 wherein the compound of formula (I) is a compound of formula (Ie) wherein:

G is -S-;

R¹ and R² are the same and selected from -R⁶-S-C(=NR⁴)N(R⁴)R⁵ and -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵;

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, -R⁶-OR⁷, -R⁶-CN and -R⁶-C(O)OR⁸;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

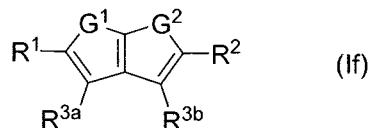
each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and

each R⁸ is independently hydrogen or alkyl.

28. The method of Claim 27 wherein the compound of formula (Ie) is selected from the group consisting of:

2-(5-carbamimidoylsulfanecarbonyl-3,4-dichlorothiophene-2-carbonyl)isothiourea;
 thiophene-2,5-diylbis(methylene) dicarbamimidothioate;
 (3,4-diphenylthiophene-2,5-diyl)bis(methylene) dicarbamimidothioate;
 and
 (3,4-dimethylthiophene-2,5-diyl)bis(methylene) dicarbamimidothioate.

29. The method of Claim 1 wherein the compound of formula (If) is a compound of formula (If):



wherein:

G¹ and G² are both -O-;

or G¹ and G² are both -S-;

R¹ and R² are each independently selected from the group consisting of

- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂, -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)₂R⁹, -S(O)₂OR⁹, -S(O)_pR⁸, -S(O)N(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,

-R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is independently 1 or 2 and each p is 0, 1 or 2;
 each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;
 each R⁶ is independently a direct bond or a straight or branched alkylene chain;
 each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl;
 each R⁸ is independently hydrogen or alkyl; and
 each R⁹ is alkyl.

30. The method of Claim 29 wherein the compound of formula (I) is a compound of formula (If) wherein:

G¹ and G² are both -O-;

or G¹ and G² are both -S-;

R¹ and R² are the same and selected from the group consisting of

-R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
 -R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
 -R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂, -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸, -S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl;

each R⁸ is independently hydrogen or alkyl; and

each R⁹ is alkyl.

31. The method of Claim 30 wherein the compound of formula (I) is a compound of formula (If) wherein:

G¹ and G² are both -S-;

R¹ and R² are the same and selected from -R⁶-S-C(=NR⁴)N(R⁴)R⁵ and -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵;

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, -R⁶-OR⁷, -R⁶-CN and -R⁶-C(O)OR⁸;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

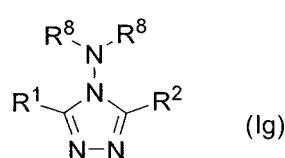
each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and

each R⁸ is independently hydrogen or alkyl.

32. The method of Claim 31 wherein the compound of formula (If) is (3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl)bis(methylene) dicarbamimidothioate.

33. The method of Claim 1 wherein the compound of formula (I) is a compound of formula (Ig):



wherein:

R¹ and R² are each independently selected from the group consisting of

- R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
- R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
- R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;
each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and
each R⁸ is independently hydrogen or alkyl.

34. The method of Claim 33 wherein the compound of formula (I) is a compound of formula (Ig) wherein:

R¹ and R² are the same and selected from the group consisting of

-R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(O)-S-C(=NR⁴)N(R⁴)R⁵,
-R⁶-S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵,
-R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
-R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and

each R⁸ is independently hydrogen or alkyl.

35. The method of Claim 34 wherein the compound of formula (I) is a compound of formula (Ig) wherein:

R¹ and R² are both -R⁶-S-C(=NR⁴)N(R⁴)R⁵;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

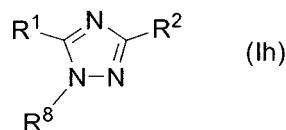
R⁶ is a direct bond or a straight or branched alkylene chain;

R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and

each R⁸ is independently hydrogen or alkyl.

36. The method of Claim 35 wherein the compound of formula (Ig) is (4-amino-4*H*-1,2,4-triazole-3,5-diyil)bis(methylene) dicarbamimidothioate.

37. The method of Claim 1 wherein the compound of formula (I) is a compound of formula (Ih):



wherein:

R^1 and R^2 are each independently selected from the group consisting of

- R^6 -S-C(=NR⁴)N(R⁴)R⁵, - R^6 -C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R^6 -S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, - R^6 -O-C(=NR⁴)N(R⁴)R⁵,
- R^6 -C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, - R^6 -C(=NR⁴)N(R⁴)R⁵, - R^6 -C(=NCN)N(R⁴)R⁵,
- R^6 -N(R⁷)C(=NCN)N(R⁴)R⁵ and - R^6 -N(R⁷)C(=NR⁴)N(R⁴)R⁵;

each R^4 and R^5 is independently hydrogen, alkyl, or -OR⁷;

each R^6 is independently a direct bond or a straight or branched alkylene chain;

each R^7 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and

R^8 is independently hydrogen or alkyl.

38. The method of Claim 37 wherein the compound of formula (I) is a compound of formula (Ih) wherein:

R^1 and R^2 are the same and selected from the group consisting of

- R^6 -S-C(=NR⁴)N(R⁴)R⁵, - R^6 -C(O)-S-C(=NR⁴)N(R⁴)R⁵,
- R^6 -S-C(=NR⁴)N(R⁴)N(R⁴)R⁵, - R^6 -O-C(=NR⁴)N(R⁴)R⁵,
- R^6 -C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, - R^6 -C(=NR⁴)N(R⁴)R⁵, - R^6 -C(=NCN)N(R⁴)R⁵,
- R^6 -N(R⁷)C(=NCN)N(R⁴)R⁵ and - R^6 -N(R⁷)C(=NR⁴)N(R⁴)R⁵;

each R^4 and R^5 is independently hydrogen, alkyl, or -OR⁷;

each R^6 is independently a direct bond or a straight or branched alkylene chain;

each R^7 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl,

optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and

R^8 is independently hydrogen or alkyl.

39. The method of Claim 38 wherein the compound of formula (I) is a compound of formula (Ih) wherein:

R^1 and R^2 are both $-R^6-S-C(=NR^4)N(R^4)R^5$;

each R^4 and R^5 is independently hydrogen, alkyl, or $-OR^7$;

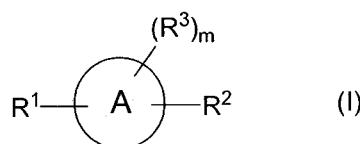
R^6 is a direct bond or a straight or branched alkylene chain;

R^7 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl; and

R^8 is independently hydrogen or alkyl.

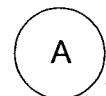
40. The method of Claim 39 wherein the compound of formula (Ih) is $(1H-1,2,4-triazole-3,5-diyl)bis(methylene)$ dicarbamimidothiodate.

41. A method of treating an iron disorder in a mammal by the inhibition of DMT1 in the mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (I):



wherein:

m is 0, 1, 2, 3, or 4;



is aryl or heteroaryl;

R^1 and R^2 are each independently selected from the group consisting of

$-R^6-S-C(=NR^4)N(R^4)R^5$, $-R^6-C(O)-S-C(=NR^4)N(R^4)R^5$,
 $-R^6-S-C(=NR^4)N(R^4)N(R^4)R^5$, $-R^6-O-C(=NR^4)N(R^4)R^5$,

-R⁶-C(O)-N=C[N(R⁴)(R⁵)]N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NCN)N(R⁴)R⁵,
-R⁶-N(R⁷)C(=NCN)N(R⁴)R⁵ and -R⁶-N(R⁷)C(=NR⁴)N(R⁴)R⁵;

each R³ is independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, optionally substituted aryl, -R⁶-OR⁷, -R⁶-CN, -R⁶-NO₂, -R⁶-N(R⁸)₂, -R⁶-C(O)OR⁸, -R⁶-C(O)N(R⁸)₂, -N(R⁸)S(O)_tR⁹, -S(O)_tOR⁹, -S(O)_pR⁸, -S(O)_tN(R⁸)₂, -R⁶-S-C(=NR⁴)N(R⁴)R⁵, -R⁶-O-C(=NR⁴)N(R⁴)R⁵, -R⁶-C(=NR⁴)N(R⁴)R⁵, and -R⁶-N(R⁷)-C(=NR⁴)N(R⁴)R⁵, wherein each t is independently 1 or 2 and each p is 0, 1 or 2;

each R⁴ and R⁵ is independently hydrogen, alkyl, or -OR⁷;

each R⁶ is independently a direct bond or a straight or branched alkylene chain;

each R⁷ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R⁸ is independently hydrogen or alkyl; and

each R⁹ is alkyl;

as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.