Paths of analysis*

C38

Synthia

March 3, 2022

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: FGI, FGI with protections

Max. paths returned: 5

Max. iterations: 300

Commercial:

1. Max. molecular weight - 1000 g/mol
2. Max. price - 1000 $/g

Published:

1. Max. molecular weight - 1000 g/mol
2. Popularity - 10

My Stockroom:

1. Max. molecular weight - 1000 g/mol

Reaction scoring formula: TUNNEL_COEF*FGI_COEF*STEP*20+1000000*(CONFLICT+NON_SELECTIVITY+FILTERS+PROTECT)

Chemical scoring formula: SMALLER^ 3,SMALLER^ 1.5

Min. search width: 400

Max. reactions per product: 60

Strategies: none selected

*The results stated herein were generated using the proprietary platform owned and maintained by Grzybowski Scientific Inventions, Inc., a subsidiary of Merck KGaA, Darmstadt Germany. The results are provided on an as is basis, and shall be used solely in connection with the rights afforded in the license agreement and for no other purpose.

FGI Coeff: 0

JSON Parameters: {}

2 Paths

3 paths found. *Paths are sorted by score. Reactions are sorted in appearance order for each path.*

2.1 Path 1

Score: `576.15`

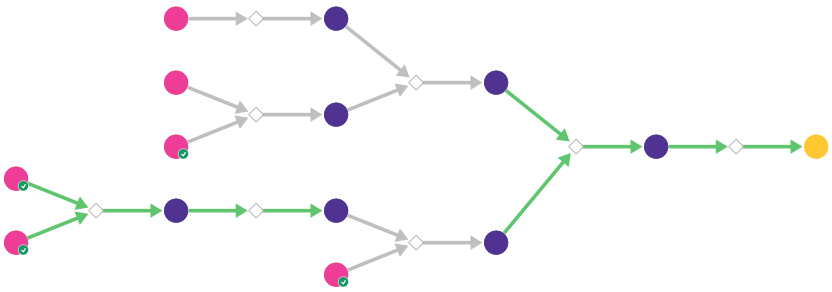
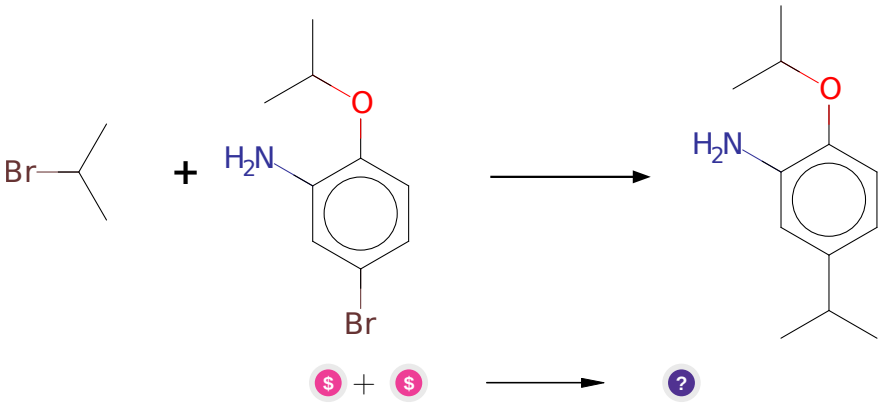


Figure 1: Outline of path 1

2.1.1 Photoredox Cross-Electrophile Coupling of Unactivated Alkyl Bromides



Substrates:

1. 2-Bromopropane - *available at Sigma-Aldrich*

2. 5-Bromo-2-isopropoxyaniline - *available at Sigma-Aldrich*

Products:

1. CC(C)Oc1ccc(C(C)C)cc1N

Typical conditions: [Ir]-photocat.[Ni]-cat.TTMSS.base.blue light

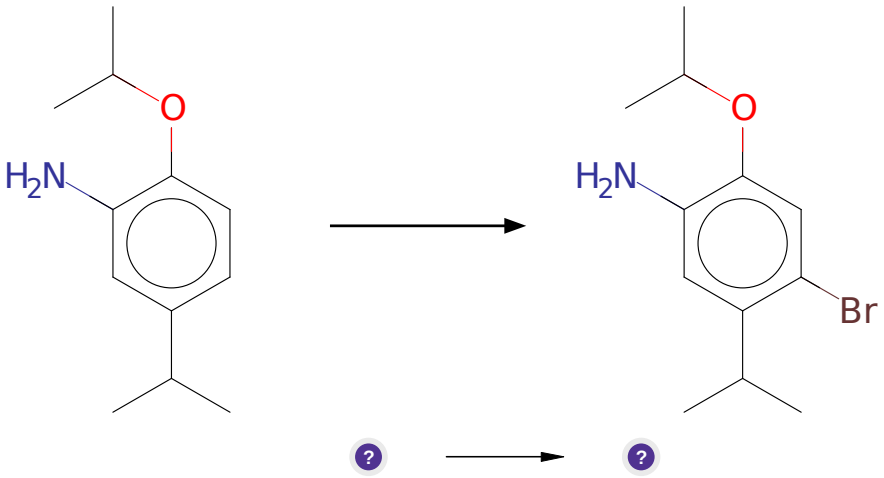
Protections: none

Yield: good

Reference: *10.1021/jacs.6b04818* and *10.1016/j.bbrc.2020.04.028* and *10.1021/acsmedchemlett.8b00183*

Retrosynthesis ID: 31016940

2.1.2 Bromination of aromatic compounds



Substrates:

1. CC(C)Oc1ccc(C(C)C)cc1N

Products:

1. CC(C)Oc1cc(Br)c(C(C)C)cc1N

Typical conditions: Br2.Fe

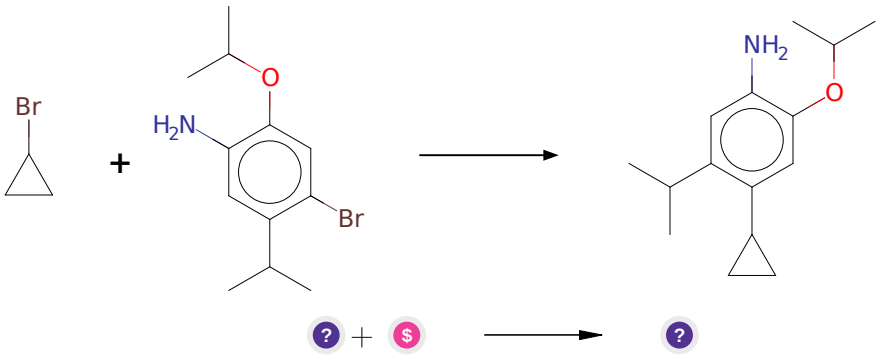
Protections: none

Yield: good

Reference: *10.1021/acs.accounts.6b00120*

Retrosynthesis ID: 7777000

2.1.3 Photoredox Cross-Electrophile Coupling of Unactivated Alkyl Bromides



Substrates:

1. CC(C)Oc1cc(Br)c(C(C)C)cc1N
2. Bromocyclopropane - *available at Sigma-Aldrich*

Products:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1N

Typical conditions: [Ir]-photocat.[Ni]-cat.TTMSS.base.blue light

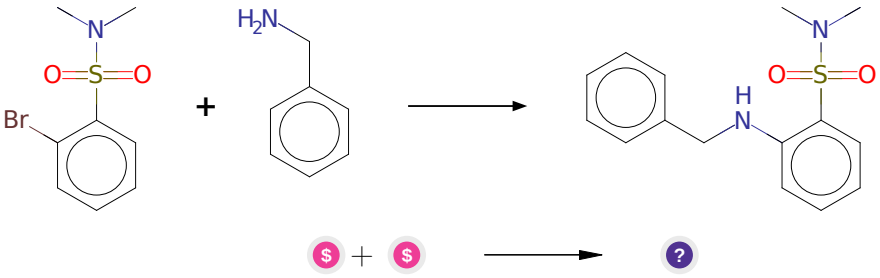
Protections: none

Yield: good

Reference: *10.1021/jacs.6b04818* and *10.1016/j.bbrc.2020.04.028* and *10.1021/acsmedchemlett.8b00183*

Retrosynthesis ID: 31016940

2.1.4 Amination of aryl bromides



Substrates:

1. 2-Bromo-N,N-dimethylbenzenesulphonamide 1g pack - *Combi-Blocks*

2. Benzylamine - *available at Sigma-Aldrich*

Products:

1. CN(C)S(=O)(=O)c1ccccc1NCc1ccccc1

Typical conditions: Pd.ligand.base or CuI.ligand.base

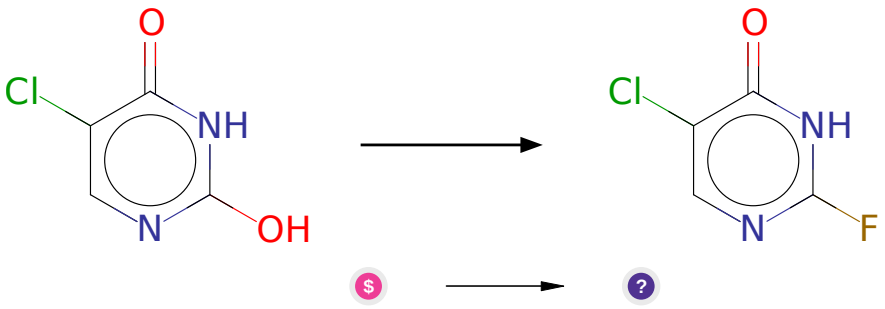
Protections: none

Yield: good

Reference: *10.1021/ja903049z* and *10.1021/jo060945k* and *10.1021/jo060190h* and *10.1039/B923255A* and *10.1021/jm8003625* and *10.1021/jo9006738*

Retrosynthesis ID: 28544

2.1.5 Synthesis of haloarenes via triflates



Substrates:

1. 5-chloro-uracil - *Combi-Blocks*

Products:

1. O=c1[nH]c(F)ncc1Cl

Typical conditions: 1.Tf2O 2. [Pd].MX

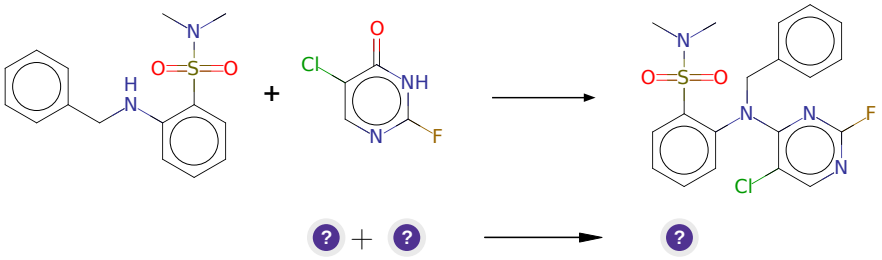
Protections: none

Yield: moderate

Reference: *10.1016/j.tetasy.2012.04.008* and WO2007/136577 (p46) and *10.1021/ol202098h* and *10.1021/ol402859k* and *10.1021/jacs.5b09308*

Retrosynthesis ID: 23940

2.1.6 Amination of pyridones



Substrates:

1. CN(C)S(=O)(=O)c1ccccc1NCc1ccccc1
2. O=c1[nH]c(F)ncc1Cl

Products:

1. CN(C)S(=O)(=O)c1ccccc1N(Cc1ccccc1)c1nc(F)ncc1Cl

Typical conditions: 1.PCl5.2.amine

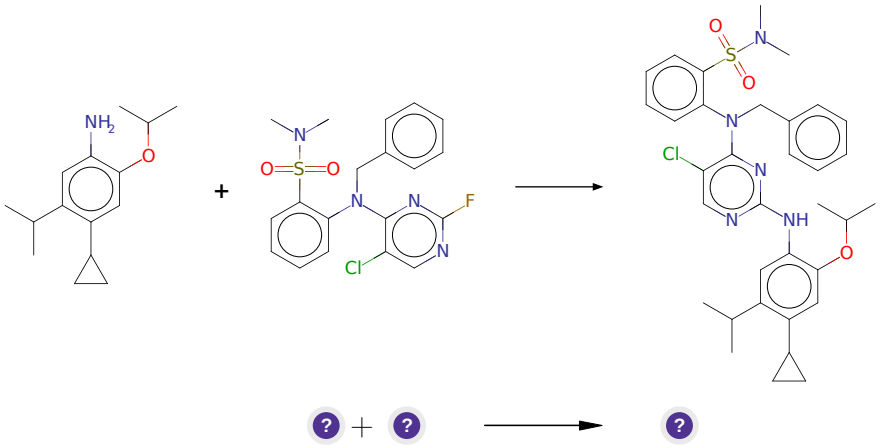
Protections: none

Yield: moderate

Reference: *10.1021/jm300780p* AND *10.3390/molecules170910902* AND *10.1021/jm00392a017*

Retrosynthesis ID: 14895

2.1.7 Nucleophilic aromatic substitution



Substrates:

1. CN(C)S(=O)(=O)c1ccccc1N(Cc1ccccc1)c1nc(F)ncc1Cl
2. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1N

Products:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1Nc1ncc(Cl)c(N(Cc2ccccc2)c2ccccc2S(=O)(=O)N(C)C)n1

Typical conditions: Solvent

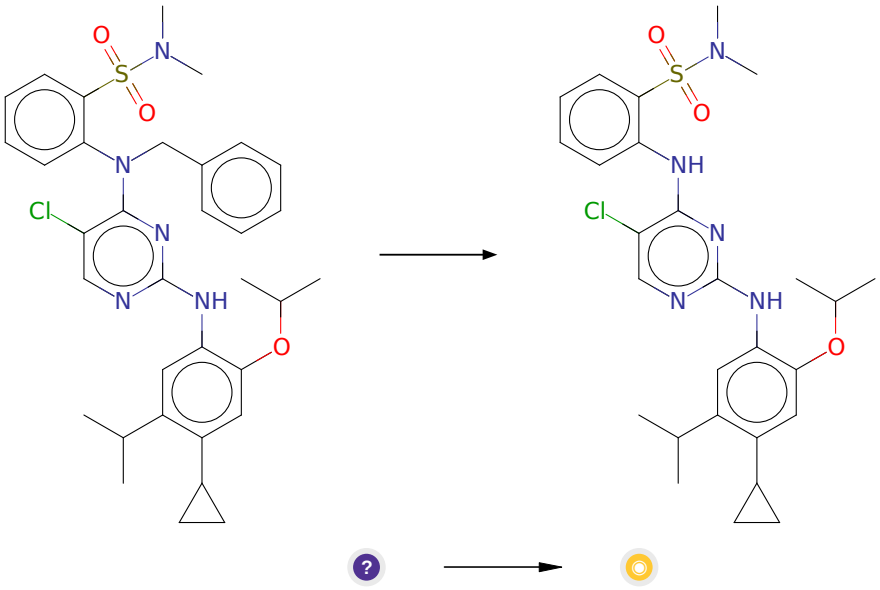
Protections: none

Yield: good

Reference: *10.1002/9781118093559.ch4*

Retrosynthesis ID: 49476

2.1.8 Debenzylation



Substrates:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1Nc1ncc(Cl)c(N(Cc2ccccc2)c2ccccc2S(=O)(=O)N(C)C)n1

Products:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1Nc1ncc(Cl)c(Nc2ccccc2S(=O)(=O)N(C)C)n1

Typical conditions: H2. Pd/C or Pd(OH)2

Protections: none

Yield: good

Reference: DOI: *10.1002/1521-3773(20020603)41:11<1895::AID-ANIE1895>3.0.CO;2-3* and *10.1021/jo400589j* and *10.1021/jm8012932* (SI,page S6) and *10.1080/00397911.2016.1261164*

Retrosynthesis ID: 9995661

2.2 Path 2

Score: 639.39

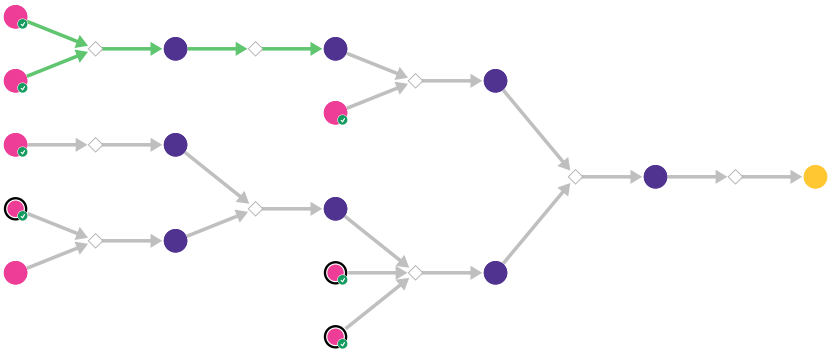
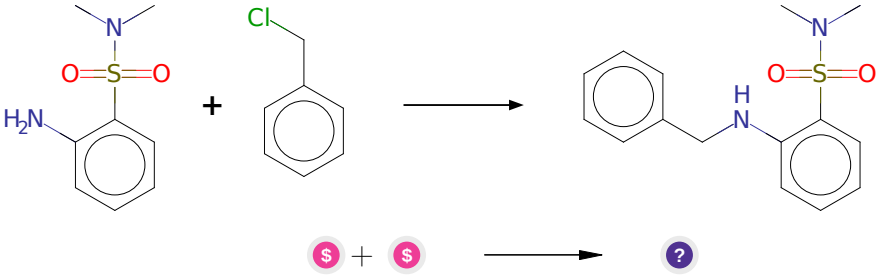


Figure 2: Outline of path 2

2.2.1 Alkylation of amines with alkyl chlorides (PTC conditions)



Substrates:

1. a-Chlorotoluene - *available at Sigma-Aldrich*
2. 2-Amino-N,N-dimethylbenzenesulfonamide - *Combi-Blocks*

Products:

1. CN(C)S(=O)(=O)c1ccccc1NCc1ccccc1

Typical conditions: NaOH.water.PTC-catalyst

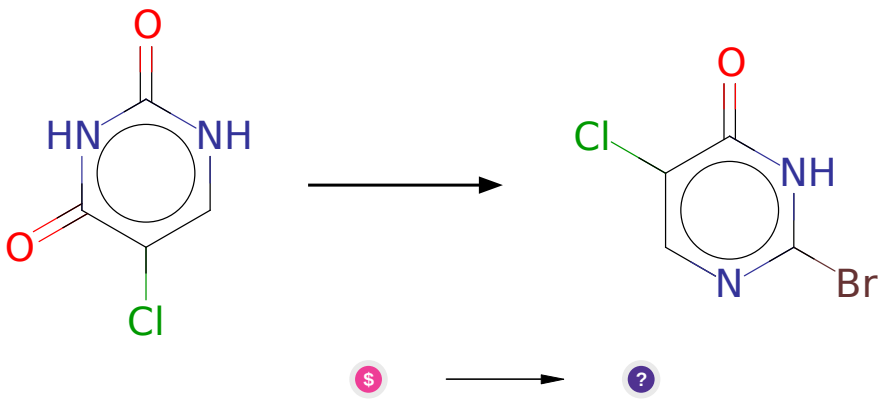
Protections: none

Yield: moderate

Reference: *10.1080/00397911.2013.828077* and *10.1002/ejoc.201200202* and *10.1080/10799893.2019.1585453* and *10.1248/cpb.c14-00754*

Retrosynthesis ID: 4785

2.2.2 Synthesis of halopyrimidines



Substrates:

1. 5-Chlorouracil - *available at Sigma-Aldrich*

Products:

1. O=c1[nH]c(Br)ncc1Cl

Typical conditions: POCl3.or.POBr3 or Ph3P.NBS/NCS

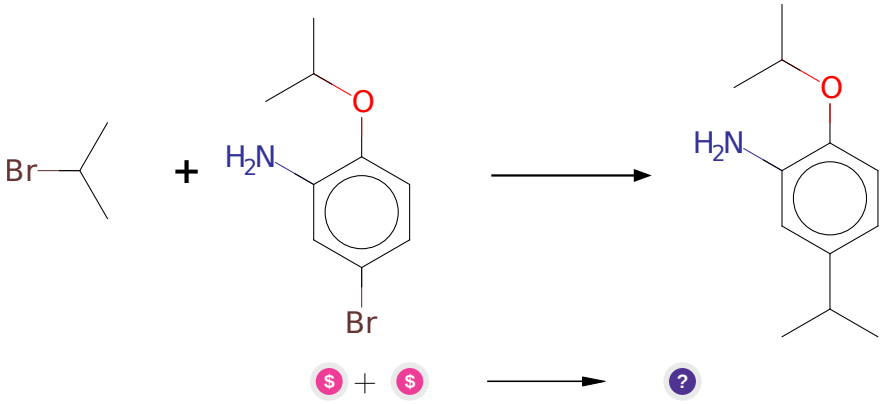
Protections: none

Yield: moderate

Reference: *10.1002/1522-2675(20010516)84:5<1112::AID-HLCA1112>3.0.CO;2-8* and *10.1039/c5dt02185e* and *10.1016/j.molstruc.2012.07.010* and *10.1021/jo01293a022* and *10.1002/ejoc.200400209*

Retrosynthesis ID: 28914

2.2.3 Photoredox Cross-Electrophile Coupling of Unactivated Alkyl Bromides



Substrates:

1. 2-Bromopropane - *available at Sigma-Aldrich*
2. 5-Bromo-2-isopropoxyaniline - *available at Sigma-Aldrich*

Products:

1. CC(C)Oc1ccc(C(C)C)cc1N

Typical conditions: [Ir]-photocat.[Ni]-cat.TTMSS.base.blue light

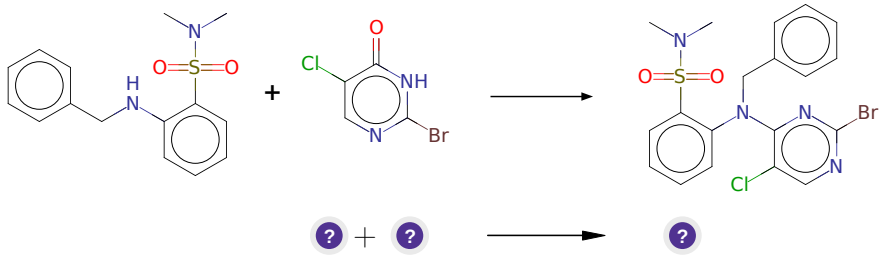
Protections: none

Yield: good

Reference: *10.1021/jacs.6b04818* and *10.1016/j.bbrc.2020.04.028* and *10.1021/acsmedchemlett.8b00183*

Retrosynthesis ID: 31016940

2.2.4 Amination of pyridones



Substrates:

1. CN(C)S(=O)(=O)c1ccccc1NCc1ccccc1
2. O=c1[nH]c(Br)ncc1Cl

Products:

1. CN(C)S(=O)(=O)c1ccccc1N(Cc1ccccc1)c1nc(Br)ncc1Cl

Typical conditions: 1.PCl5.2.amine

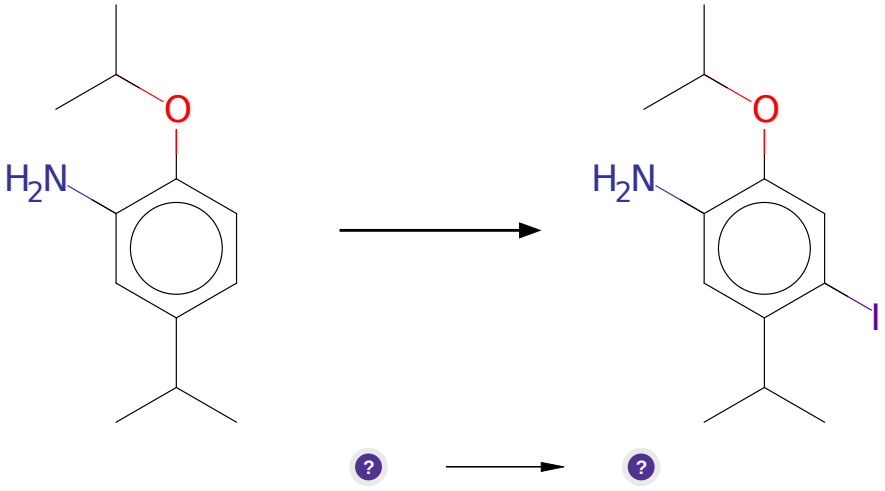
Protections: none

Yield: moderate

Reference: *10.1021/jm300780p* AND *10.3390/molecules170910902* AND *10.1021/jm00392a017*

Retrosynthesis ID: 14895

2.2.5 Iodination of aromatic compounds



Substrates:

1. CC(C)Oc1ccc(C(C)C)cc1N

Products:

1. CC(C)Oc1cc(I)c(C(C)C)cc1N

Typical conditions: I2 or other iodinating agent e.g. NIS

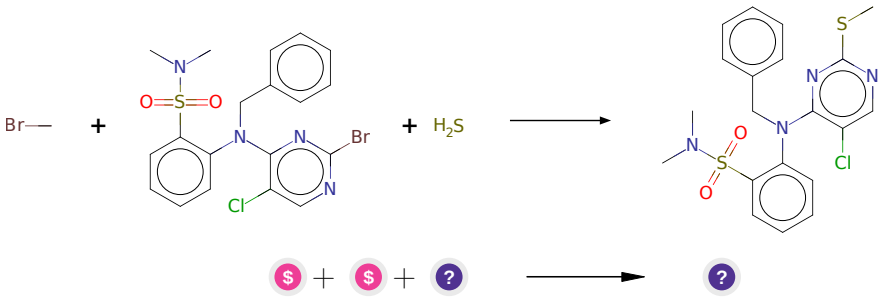
Protections: none

Yield: good

Reference: DOI: *10.1039/C5SC00964B* and *10.1016/j.tetlet.2005.05.117* and *10.1007/s11178-005-0256-1*

Retrosynthesis ID: 10697

2.2.6 One pot synthesis of aryl-alkyl sulfides



Substrates:

1. Hydrogen sulfide - *available at Sigma-Aldrich*
2. Methyl bromide - *available at Sigma-Aldrich*
3. CN(C)S(=O)(=O)c1ccccc1N(Cc1ccccc1)c1nc(Br)ncc1Cl

Products:

1. CSc1ncc(Cl)c(N(Cc2ccccc2)c2ccccc2S(=O)(=O)N(C)C)n1

Typical conditions: nBuLi.THF.-78C.then.S.then AlkBr.to.rt

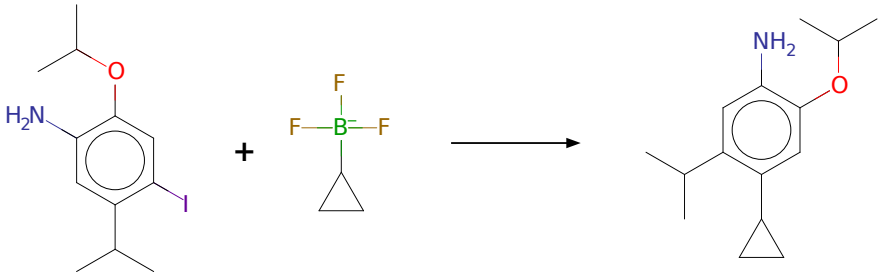
Protections: none

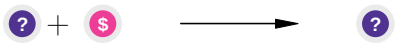
Yield: good

Reference: *10.1021/jo049758h*

Retrosynthesis ID: 5320

2.2.7 Suzuki coupling of cyclopropanotrifluoroboranes and aryl iodides





Substrates:

1. CC(C)Oc1cc(I)c(C(C)C)cc1N
2. Potassium cyclopropyltrifluoroborate - *available at Sigma-Aldrich*

Products:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1N

Typical conditions: K3PO4.Pd(OAc)2.ruphos.H2O.toluene.110C

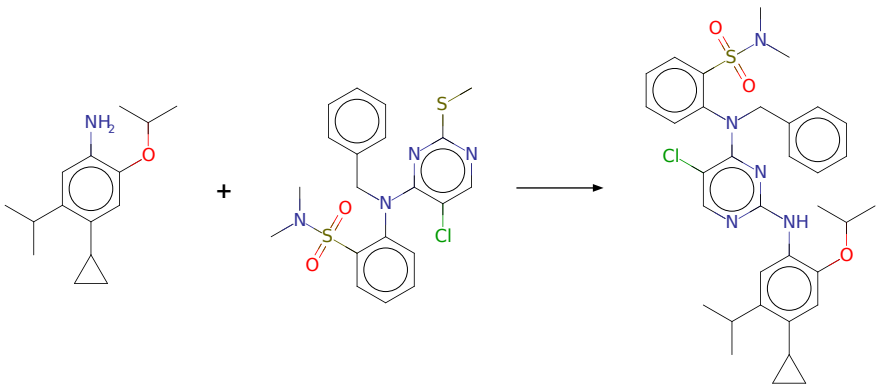
Protections: none

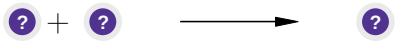
Yield: good

Reference: *10.1002/ejoc.201100119* and WO2014006066 p.26 and WO2014184275 p.107

Retrosynthesis ID: 31016521

2.2.8 Substiution of 2-thiomethylpyrimidines with amines





Substrates:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1N
2. CSc1ncc(Cl)c(N(Cc2ccccc2)c2ccccc2S(=O)(=O)N(C)C)n1

Products:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1Nc1ncc(Cl)c(N(Cc2ccccc2)c2ccccc2S(=O)(=O)N(C)C)n1

Typical conditions: K2CO3.DMF

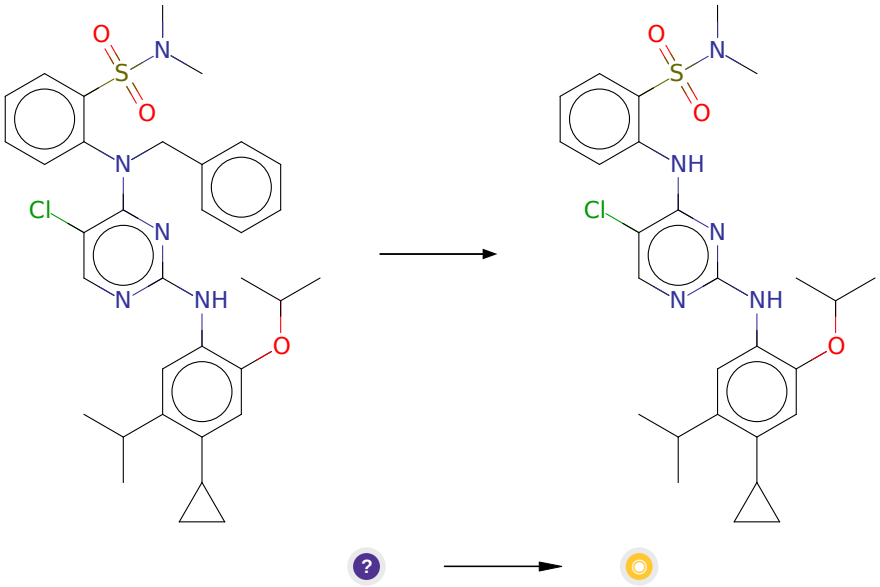
Protections: none

Yield: good

Reference: *10.1021/jm980222w* AND *10.1016/j.cclet.2014.10.007* AND *10.1002/jhet.5570280520* AND *10.1080/00397910701396930*

Retrosynthesis ID: 14935

2.2.9 Debenzylation



Substrates:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1Nc1ncc(Cl)c(N(Cc2ccccc2)c2ccccc2S(=O)(=O)N(C)C)n1

Products:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1Nc1ncc(Cl)c(Nc2ccccc2S(=O)(=O)N(C)C)n1

Typical conditions: H2. Pd/C or Pd(OH)2

Protections: none

Yield: good

Reference: DOI: *10.1002/1521-3773(20020603)41:11<1895::AID-ANIE1895>3.0.CO;2-3* and *10.1021/jo400589j* and *10.1021/jm8012932* (SI,page S6) and *10.1080/00397911.2016.1261164*

Retrosynthesis ID: 9995661

2.3 Path 3

Score: `741.80`

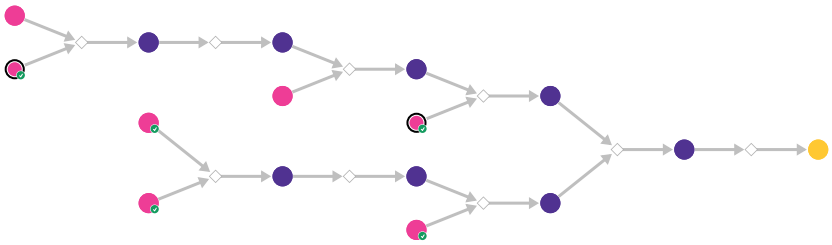
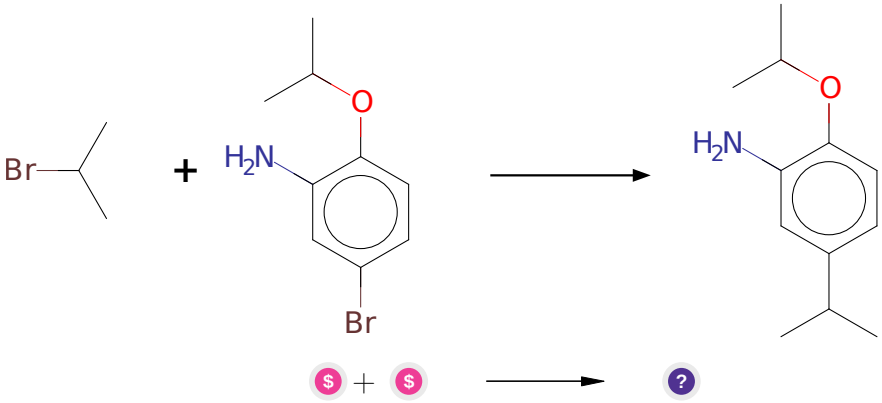


Figure 3: Outline of path 3

2.3.1 Photoredox Cross-Electrophile Coupling of Unactivated Alkyl Bromides



Substrates:

1. 2-Bromopropane - *available at Sigma-Aldrich*
2. 5-Bromo-2-isopropoxyaniline - *available at Sigma-Aldrich*

Products:

1. CC(C)Oc1ccc(C(C)C)cc1N

Typical conditions: [Ir]-photocat.[Ni]-cat.TTMSS.base.blue light

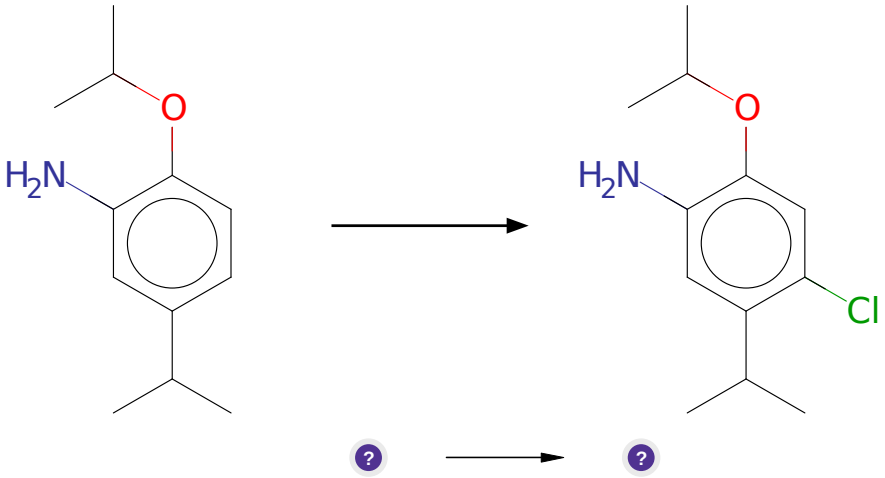
Protections: none

Yield: good

Reference: *10.1021/jacs.6b04818* and *10.1016/j.bbrc.2020.04.028* and *10.1021/acsmedchemlett.8b00183*

Retrosynthesis ID: 31016940

2.3.2 Chlorination of aromatic compounds



Substrates:

1. CC(C)Oc1ccc(C(C)C)cc1N

Products:

1. CC(C)Oc1cc(Cl)c(C(C)C)cc1N

Typical conditions: Cl2 or other chlorinating agent like NCS

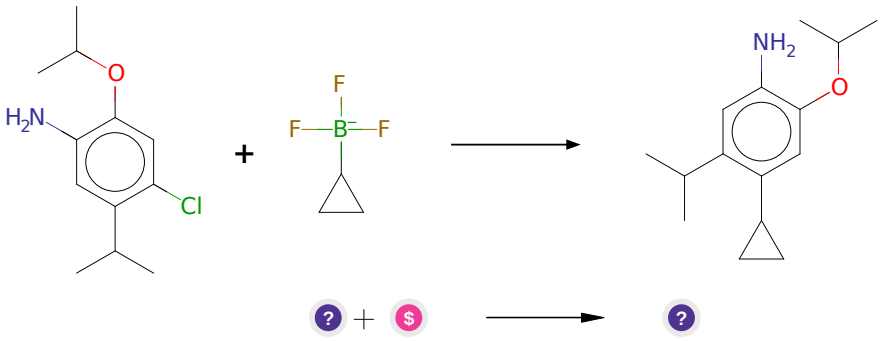
Protections: none

Yield: moderate

Reference: DOI: *10.1007/s11178-005-0256-1*

Retrosynthesis ID: 11125

2.3.3 Suzuki coupling of cyclopropanotrifluoroboranes and aryl chlorides



Substrates:

1. CC(C)Oc1cc(Cl)c(C(C)C)cc1N
2. Potassium cyclopropyltrifluoroborate - *available at Sigma-Aldrich*

Products:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1N

Typical conditions: K2CO3.Pd(OAc)2.H2O.100C

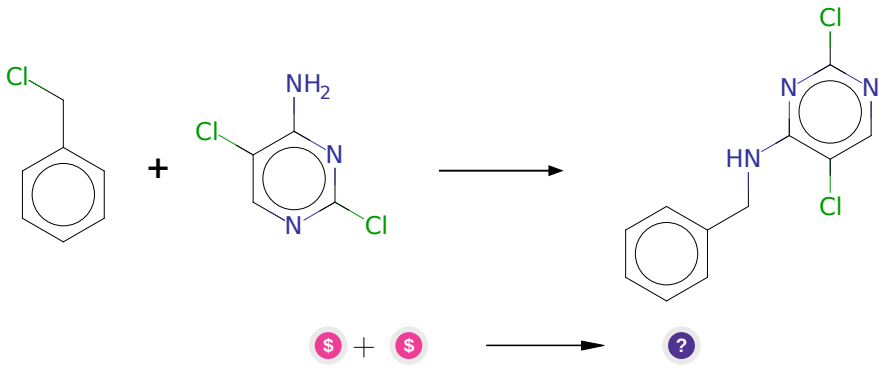
Protections: none

Yield: good

Reference: *10.1021/jo801269m* and WO2012101066 p.177 and WO2011/55115 p.72

Retrosynthesis ID: 31016519

2.3.4 Alkylation of amines with alkyl chlorides (PTC conditions)



Substrates:

1. 2,5-Dichloropyrimidin-4-amine - *Combi-Blocks*
2. a-Chlorotoluene - *available at Sigma-Aldrich*

Products:

1. Clc1ncc(Cl)c(NCc2ccccc2)n1

Typical conditions: NaOH.water.PTC-catalyst

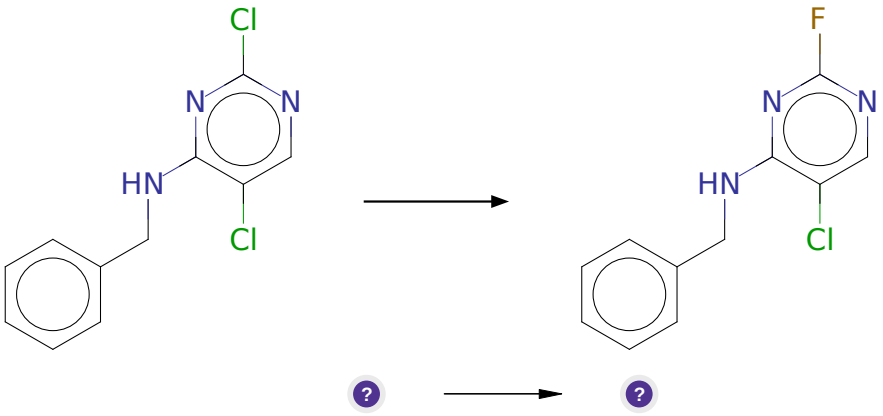
Protections: none

Yield: moderate

Reference: *10.1080/00397911.2013.828077* and *10.1002/ejoc.201200202* and *10.1080/10799893.2019.1585453* and *10.1248/cpb.c14-00754*

Retrosynthesis ID: 4785

2.3.5 Nucleophilic aromatic substitution



Substrates:

1. Clc1ncc(Cl)c(NCc2ccccc2)n1

Products:

1. Fc1ncc(Cl)c(NCc2ccccc2)n1

Typical conditions: CsF.DMF

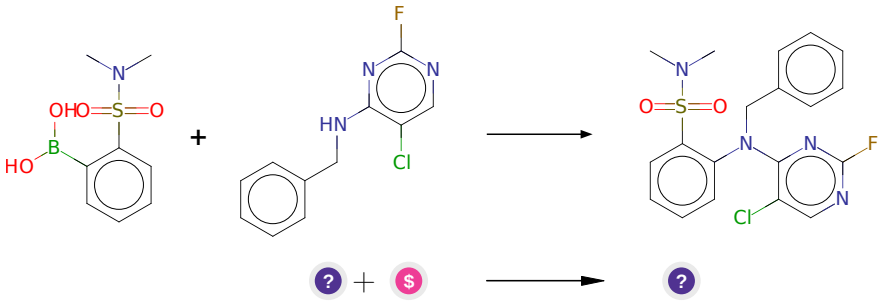
Protections: none

Yield: moderate

Reference: *10.1016/j.tetlet.2015.09.057* and *10.1016/j.cattod.2012.02.063* and *10.1016/j.ejmech.2015.01.034*

Retrosynthesis ID: 29650

2.3.6 Chan-Lam Coupling



Substrates:

1. Fc1ncc(Cl)c(NCc2ccccc2)n1
2. 2-(N,N-DIMETHYLSULPHAMOYL)BENZENEBORONIC ACID - *Combi-Blocks*

Products:

1. CN(C)S(=O)(=O)c1ccccc1N(Cc1ccccc1)c1nc(F)ncc1Cl

Typical conditions: Cu(II)Ac.DCM

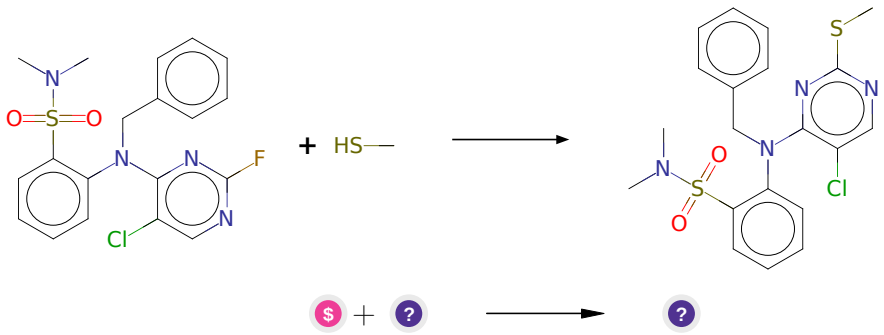
Protections: none

Yield: good

Reference: *10.5012/bkcs.2012.33.5.1785* and *10.1039/C8GC02611D* and *10.1055/s-2008-1032184*

Retrosynthesis ID: 31015959

2.3.7 Nucleophilic aromatic substitution



Substrates:

1. Methanethiol - *available at Sigma-Aldrich*

2. CN(C)S(=O)(=O)c1ccccc1N(Cc1ccccc1)c1nc(F)ncc1Cl

Products:

1. CSc1ncc(Cl)c(N(Cc2ccccc2)c2ccccc2S(=O)(=O)N(C)C)n1

Typical conditions: NaH.THF.0-80 C or K2CO3.DMF.110 C

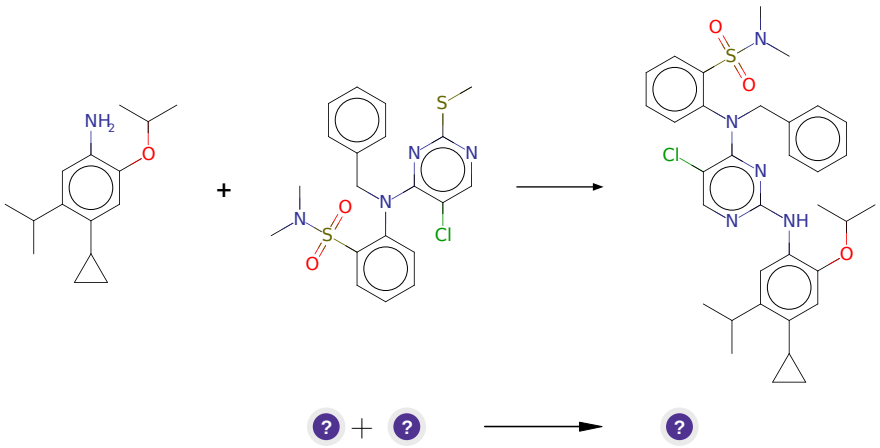
Protections: none

Yield: good

Reference: *10.1016/j.tetlet.2015.10.008* p. 6479, 6483 and *10.1016/j.ejmech.2016.06.056* p. 82, 85

Retrosynthesis ID: 49475

2.3.8 Substiution of 2-thiomethylpyrimidines with amines



Substrates:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1N
2. CSc1ncc(Cl)c(N(Cc2ccccc2)c2ccccc2S(=O)(=O)N(C)C)n1

Products:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1Nc1ncc(Cl)c(N(Cc2ccccc2)c2ccccc2S(=O)(=O)N(C)C)n1

Typical conditions: K2CO3.DMF

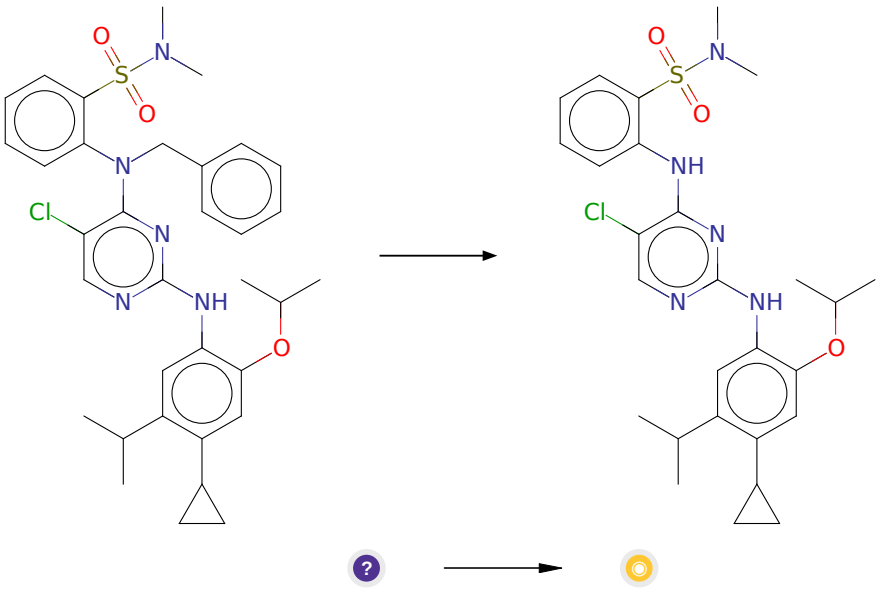
Protections: none

Yield: good

Reference: *10.1021/jm980222w* AND *10.1016/j.cclet.2014.10.007* AND *10.1002/jhet.5570280520* AND *10.1080/00397910701396930*

Retrosynthesis ID: 14935

2.3.9 Debenzylation



Substrates:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1Nc1ncc(Cl)c(N(Cc2ccccc2)c2ccccc2S(=O)(=O)N(C)C)n1

Products:

1. CC(C)Oc1cc(C2CC2)c(C(C)C)cc1Nc1ncc(Cl)c(Nc2ccccc2S(=O)(=O)N(C)C)n1

Typical conditions: H2. Pd/C or Pd(OH)2

Protections: none

Yield: good

Reference: DOI: *10.1002/1521-3773(20020603)41:11<1895::AID-ANIE1895>3.0.CO;2-3* and *10.1021/jo400589j* and *10.1021/jm8012932* (SI,page S6) and *10.1080/00397911.2016.1261164*

Retrosynthesis ID: 9995661