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Sulfur-Substituted α-Alkyl Phenethylamines as Selective and Reversible MAO-A Inhibitors: Biological Activities, CoMFA Analysis, and Active Site Modeling

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A series of phenethylamine derivatives with various ring substituents and with or without *N*-methyl and/or C-α methyl or ethyl groups was synthesized and assayed for their ability reversibly to inhibit monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B). Several compounds showed potent and selective MAO-A inhibitory activity (IC_{50} in the submicromolar range) but none showed appreciable activity toward MAO-B. A three-dimensional quantitative structure−activity relationship study for MAO-A inhibition was performed on the series using comparative molecular field analysis (CoMFA). The resulting model gave a cross-validated q^2 of 0.72 and showed that in this series of compounds steric properties of the substituents were more important than electrostatic effects. Molecular modeling based on the recently published crystal structure of inhibitor-bound MAO-A provided detailed evidence for specific interactions of the ligands with the enzyme, supported by previous references and consistent with results from the CoMFA. On the basis of these results, structural determinants for selectivity of substituted amphetamines for MAO-A are discussed.

Introduction

The phenethylamine scaffold has served over the last century for the synthesis of perhaps thousands of derivatives with many different and often useful pharmacological activities. This privileged structure is present in the catecholamine neurotransmitters, and subtle structural variations lead to compounds that interact differentially with several biogenic amine target proteins. More specifically, many α-methylated derivatives (often referred to in the literature as "substituted amphetamines") have been described as receptor, transporter, or metabolic enzyme ligands.[1−3]

One of these biological targets is monoamine oxidase (MAO; EC 1.4.3.4), the major enzyme participating in the catabolism of monoamine neurotransmitters and related exogenous amines. MAO exists in two isoforms,[4] MAO-A and MAO-B, differing in their substrate preferences, inhibitor selectivity, tissue distribution, and molecular genetics.[5,6] Selective inhibitors of MAO-A are used in the therapy of depression and anxiety disorders, among others[7,8] whereas MAO-B inhibitors are useful in the treatment of Parkinson's[9] and Alzheimer's[10] diseases. The irreversible, selective MAO-A inhibitor clorgyline is structurally very similar to a phenethylamine, and the irreversible selective MAO-B inhibitor selegiline is a substituted phenethylamine. Furthermore, many amphetamine derivatives have been shown to be selective and reversible MAO-A inhibitors.[11−15] Some of the latter, however, also interact strongly with monoamine transporters or receptors.[1,3]

The multiple potential applications and the synthetic accessibility of phenethylamine derivatives have made them an attractive goal for structural modification and structure−activity studies. By contrast, their relative pharmacological promiscuity underscores the need to identify the structural determinants of their preference for different targets. In the present work we have synthesized and assessed a series of analogues with different ring substitution patterns and with or without *N*-methyl and/or C-α methyl or ethyl groups and assayed them for their ability to inhibit MAO-A and MAO-B. Finally, a three-dimensional quantitative structure−activity relationship study for MAO-A inhibition was performed on the series using comparative molecular field analysis (CoMFA), and the results compared with, and overlaid onto, the recently published crystal structure of clorgyline-bound MAO-A.[16]

Chemistry

The synthetic route used to obtain compounds **8a**−**g** and **9a**−**c** corresponds to a modification of a previously described procedure (Scheme 1).[17] Thiophenol **2** was prepared from 1,4-dimethoxybenzene (**1**) by chlorosulfonylation using chlorosulfonic acid, followed by reduction with zinc powder and 30% HCl, which gave better yields than the reported method using 25% H_2SO_4.[18] *S*-Alkylation with an alkyl halide was followed by formylation, typically using the Vilsmeier reaction,

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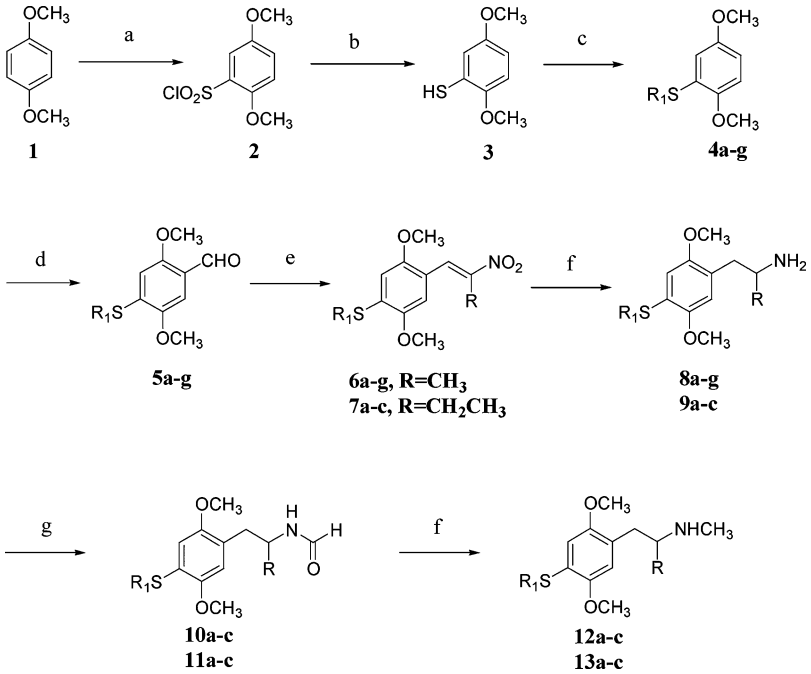
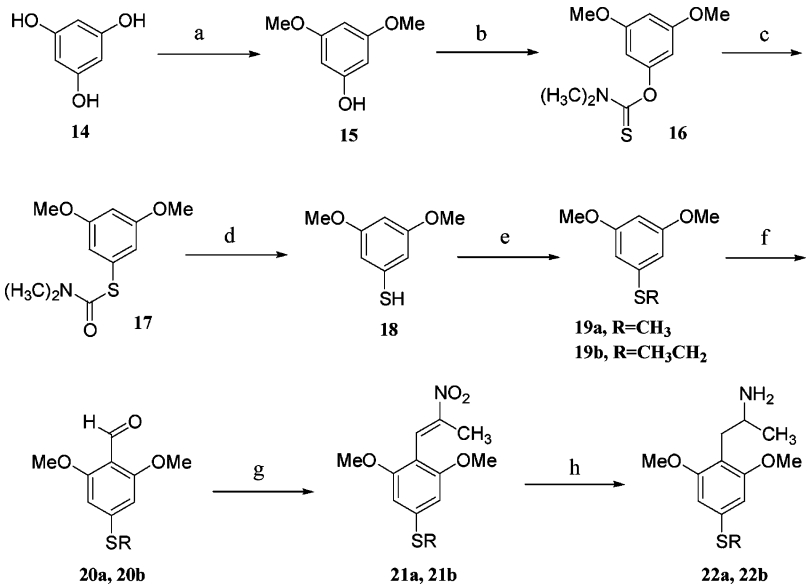
Scheme 1[a]



[a] Reagents: (a) $HOSO_2Cl/H_2O$; (b) Zn (dust)/HCl 30% v/v (60 °C); (c) KOH/R_1X (60 °C); (d) $POCl_3$/*N*-methylformanilide (40−50 °C); (e) RNO_2/base/reflux; (g) HCO_2Et/reflux; (f) $LiAlH_4$/THF/reflux.

Scheme 2[a]



[a] Reagents: (a) $MeOH/H_2SO_4$/reflux; (b) $NaH/(CH_3)_2NC(S)Cl$/reflux; (c) 285 °C (6 h); (d) KOH/MeOH/reflux; (e) KOH/RX (60 °C); (f) *n*-BuLi/TMEDA/DMF; (g) $CH_3CH_2NO_2$/Base/reflux; (h) $LiAlH_4$/THF/reflux.

which led in good yields to the series of aldehydes **5a**−**g**.

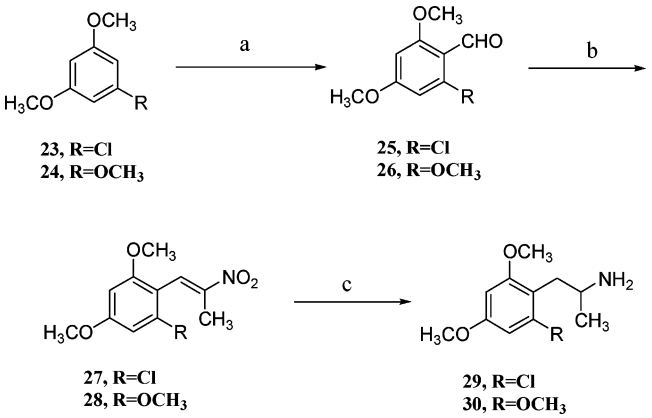
The expected 1,2,4,5-substitution pattern was confirmed by NMR spectrometry, which revealed two singlets in the aromatic region corresponding to a para orientation of the aromatic protons. A singlet near 10 ppm confirmed the presence of the aldehyde group.

All of the nitrostyrene intermediates were generated by Knoevenagel condensation of the aldehydes with the corresponding nitroalkanes. The conditions required to obtain the α-ethyl compounds (**7a**−**c**) were different from those used in the synthesis of the α-methyl (**6a**−**g**) analogues. That is, for the lower homologues ammonium acetate was used as the catalyst, whereas for the α-ethyl derivatives it was necessary to use *N*,*N*-dimethylethylenediamine (DMEDA) with toluene as the solvent. The final products **8a**−**g** and **9a**−**c** were isolated as their hydrochloride salts after reduction of the corresponding nitrostyrenes with $LiAlH_4$.

The *N*-methyl compounds (**12a**−**c** and **13a**−**c**) were readily obtained after treating the corresponding free amines with ethyl formate at reflux to produce the *N*-formamides, which were immediately reduced with $LiAlH_4$ without further purification. The final products were also isolated as their hydrochloride salts.

Scheme 2 shows the synthetic route developed to obtain a series of 2,4,6-ring-substituted phenethylamines. This synthesis of 2,4,6-substituted compounds

Scheme 3[a]



[a] Reagents: (a) $POCl_3$/*N*-methylformanilide (40−50 °C); (b) CH_3NO_2/base/reflux; (c) $LiAlH_4$/THF/reflux.

started with the *O*-methylation of phloroglucinol **14**, which behaves as its keto tautomer,[19] in methanol with H_2SO_4 and gave the three expected products of *O*-alkylation. Once these compounds were separated, the major product was determined to be the desired dimethylated **15**, obtained in 50% yield.

The formation of the sodium phenoxide with sodium hydride and subsequent addition of dimethylthiocarbamoyl chloride in DMF gave as a product *O*-(3,5-dimethoxyphenyl)dimethylthiocarbamate **16**. The next step was the Newman−Kwart[20,21] rearrangement to obtain the *S*-(3,5-dimethoxyphenyl)dimethylthiocarbamate **17**.

After base hydrolysis, the desired thiol **18** was obtained and the subsequent alkylations were carried out with the corresponding alkyl halide to obtain 5-alkylthio-1,3-dimethoxybenzenes **19a** and **19b**. Various approaches, including the Vilsmeier reaction (with *N*-methylformanilide and $POCl_3$), Cl_2CHOCH_3 and $SnCl_4$, and the Duff reaction, were attempted to install the desired aldehyde function between the methoxy groups (compounds **20a**,**b**). Unfortunately, all these reactions led to the undesired regiochemistry, with the aldehyde group located between the methoxy and alkylthio groups. Treatment with *n*-BuLi/DMF generated a mixture of both aldehydes, but the predominant product was the undesired regioisomer. Finally, reaction with *n*-BuLi/DMF using TMEDA solved the problem, providing up to an 80% yield of the desired aldehyde.

Condensation of the aldehydes with the corresponding nitroalkane and subsequent reduction with $LiAlH_4$ afforded the expected amines (**22a**,**b**), which were converted to their hydrochloride salts. Other compounds containing the 2,4,6 substitution pattern are shown in Scheme 3, starting with the formylation of the corresponding substrates 1,3-dimethoxy-5-chlorobenzene (**23**) and 1,3,5-trimethoxy-benzene (**24**). A series of reactions parallel to that employed for **22a**,**b** gave the products as hydrochloride salts.

Results and Discussion

In the present work, we have studied the influence on MAO inhibition by phenethylamine derivatives with different substituents on the aromatic ring, such as alkylthio, methoxy, and halide groups, as well as methyl and ethyl groups at the alpha side chain carbon. In addition, the effect of methylation of the amino group was evaluated. The pharmacological and CoMFA results for the compounds synthesized in this work are summarized in Table 1. As can be seen, some of these modifications, especially in the amphetamine (α-methyl) derivatives, generated potent and highly selective MAO-A inhibitors. Table 2 summarizes the results of our CoMFA analysis of another series of structurally similar MAO-A inhibitors.[11]

No effects on MAO-B were observed below 100 μM (the highest concentration tested) for any of the compounds. Therefore, the following discussion is based only on effect of the subject compounds as MAO-A inhibitors.

The statistical parameters from the CoMFA are listed in Table 5 and the residual plot for all 38 compounds is shown in Figure 1A. The unusually high contribution of steric (82%) versus electrostatic factors (18%) can be attributed to the nature of the analogue series under investigation. Whereas most studies have employed a variety of substituents with diverse electronic properties (charged groups, etc.), this work was concerned mostly with different *S*- and α-alkyl chain lengths, where steric effects are much more important than electrostatics. To lend support to the model, two test sets of seven compounds each were generated by random selection, and their IC_{50} values were predicted based upon the training set of the remaining 31 compounds. The residual plots for the combined test sets are shown in Figure 1B.

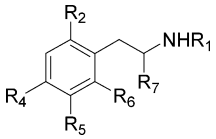
The CoMFA contour maps are shown in Figures 2A and 2B. The electrostatic contour plot is shown in Figure 2A. The blue contours illustrate regions where a positively charged group enhances activity and red contours describe regions where a negatively charged group enhances activity. In Figure 2B, the green contours represent regions where bulky groups are favorable, whereas yellow contours represent regions where steric effects are unfavorable.

Effects of Different Substituents on the Aromatic Ring. As reported in a previous study of similar compounds as MAO-A inhibitors,[11] potency was a function of the length of the carbon chain attached to the sulfur at the para position, as indicated by the green contours in Figure 2B, reaching a maximum with a linear three-carbon chain (**8a**−**c**; **9a**−**c**; **12a**−**c**, and **13a**−**c**). With more than three carbon atoms, or branching of the alkyl chain, the potency decreases (cf. **8d**−**e** and **8c** vs **8f**) consistent with the yellow contours outside of the green ones, suggesting that even though the enzyme is able to accommodate groups as long as *n*-butylthio, it has a low tolerance for branched substituents.

The compounds with the 2,4,5-substitution pattern were generally less potent, consistent with a prior report that substituents adjacent to the para position reduce the potency of *p*-alkylthio or alkoxy amphetamine derivatives as MAO-A inhibitors.[11] A similar trend had been observed in a series of analogues containing a *para*-dimethylamino substituent.[12,13]

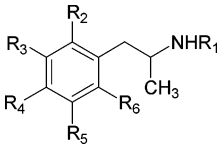
The inhibitory activity of compounds with the 2,4,6-trisubstitution pattern (**22a**−**b**, **29**, and **30**) was similar to that reported for their 4-monosubstituted analogues (cf. **22a** vs **32**; **22b** vs **33**; **30** vs **35**) and 15−45-fold higher than their counterparts having the 2,4,5-trisub-

Table 1. Structures of the Amphetamine Derivatives, Their Biological Activities (IC_{50} and pIC_{50}) and CoMFA Parameters (Predicted and Residuals) in MAO-A Inhibition



compd	R_1	R_2	R_4	R_5	R_6	R_7	IC_{50}[b]	$p(IC_{50})$[c]	predicted activity[d]	residuals (Δ)
8a	H	OCH_3	CH_3S	OCH_3	H	CH_3	5.2 ± 0.8	5.28	4.69	0.59
8b	H	OCH_3	CH_3CH_2S	OCH_3	H	CH_3	3.8 ± 0.2	5.42	5.35	0.08
8c	H	OCH_3	$CH_3CH_2CH_2S$	OCH_3	H	CH_3	2.4 ± 0.5	5.61	5.48	0.13
8d	H	OCH_3	$CH_3(CH_2)_3S$	OCH_3	H	CH_3	2.9 ± 0.6	5.53	5.65	−0.12
8e	H	OCH_3	$CH_3(CH_2)_4S$	OCH_3	H	CH_3	14.3 ± 0.5	4.84	5.11	−0.27
8f	H	OCH_3	$(CH_3)_2CHS$	OCH_3	H	CH_3	27.3 ± 1.2	4.56	4.84	−0.28
8g	H	OCH_3	$PhCH_2CH_2S$	OCH_3	H	CH_3	>100	3.00	4.30	−0.34
9a	H	OCH_3	CH_3S	OCH_3	H	CH_3CH_2	30.9 ± 1.7	4.51	4.66	−0.15
9b	H	OCH_3	CH_3CH_2S	OCH_3	H	CH_3CH_2	11.8 ± 2.1	4.93	4.64	0.29
9c	H	OCH_3	$CH_3CH_2CH_2S$	OCH_3	H	CH_3CH_2	7.6 ± 1.2	5.12	5.01	0.11
12a	CH_3	OCH_3	CH_3S	OCH_3	H	CH_3	1.8 ± 0.2	5.73	5.92	−0.19
12b	CH_3	OCH_3	CH_3CH_2S	OCH_3	H	CH_3	1.40 ± 0.07	5.84	6.13	−0.29
12c	CH_3	OCH_3	$CH_3CH_2CH_2S$	OCH_3	H	CH_3	0.30 ± 0.03	6.44	5.99	0.45
13a	CH_3	OCH_3	CH_3S	OCH_3	H	CH_3CH_2	15.5 ± 1.4	4.81	4.56	0.25
13b	CH_3	OCH_3	CH_3CH_2S	OCH_3	H	CH_3CH_2	4.5 ± 0.9	5.35	5.35	0
13c	CH_3	OCH_3	$CH_3CH_2CH_2S$	OCH_3	H	CH_3CH_2	1.40 ± 0.08	5.85	6.02	−0.17
22a	H	OCH_3	CH_3S	H	OCH_3	CH_3	0.30 ± 0.05	6.49	6.88	−0.39
22b	H	OCH_3	CH_3CH_2S	H	OCH_3	CH_3	0.080 ± 0.002	7.09	7.10	−0.01
29	H	OCH_3	OCH_3	H	Cl	CH_3	0.07 ± 0.01	7.15	6.93	0.22
30	H	OCH_3	OCH_3	H	OCH_3	CH_3	0.40 ± 0.08	6.34	6.28	0.06

Table 2. Additional Compounds Used in CoMFA Analyses[a,e]



compd	ring substituents	IC_{50}[b]	$p(IC_{50})$[c]	predicted activity[d]	residuals (Δ)
31	amphetamine (R2→R6 = H)	11	5.0	5.22	−0.22
32	4-CH_3S	0.2	6.7	6.39	0.31
33	4-CH_3CH_2S	0.1	7.0	6.89	0.11
34	4-$(CH_3)_2CH_2S$	0.4	6.4	6.74	−0.34
35	4-CH_3O	0.3	6.5	6.24	0.28
37	4-CH_3CH_2O	0.2	6.7	6.83	−0.13
38	4-Cl	4.0	5.4	5.03	0.37
39	2,4-$(OCH_3)_2$	0.6	6.2	5.75	−0.47
40	2,5-$(OCH_3)_2$	>100	3.0	3.68	−0.16
41	3,4-$(OCH_3)_2$	20	4.7	4.75	−0.05
42	4-CF_3-2,5-$(OCH_3)_2$	>100	3.0	3.4	−0.40
43	4-Br-2,5-$(OCH_3)_2$	100	4.0	3.64	0.36
44	4-I-2,5-$(OCH_3)_2$	43	4.4	3.99	0.41
45	4-CH_3−2,5-$(OCH_3)_2$	24	4.6	3.95	0.67
47	4-NO_2−2,5-$(OCH_3)_2$	>100	3.0	3.03	−0.03
48	4-NH_2−2,5-$(OCH_3)_2$	>100	3.0	3.83	−0.03
49	2-Br-4,5-$(OCH_3)_2$	9.3	5.0	5.35	−0.32
50	5-Br-2,4-$(OCH_3)_2$	13	4.9	5.15	−0.25

[a] Data from Scorza et al.[11] [b] Biological activity expressed in μM. [c] Expressed as the logarithm of $1/IC_{50}$ (μM) value. [d] Predicted from the CoMFA model. [e] The IC_{50} values were calculated from the inhibition versus −log concentration curves, with 5−8 concentrations of the compounds. Each concentration was tested in triplicate.

stitution pattern (**22a** vs **8a** and **22b** vs **8b**). When the 6-methoxy group of **30** was replaced by a chlorine (**29**), the potency increased 6-fold (IC_{50} = 71 nM) over the trimethoxy compound. The chlorine atom is larger, more electronegative, and more hydrophobic than the oxygen of the methoxy group, and one or more of these properties must be important for the increased potency of compound **29** over **30**. Further experiments are necessary to determine the role of these properties in the potency of amphetamine derivatives with the 2,4,6 substitution pattern. The electrostatic contour plots shown in Figure 2A emphasize this preference for electronegative groups as the large red contours in the ortho positions. By contrast, the blue contour shows areas where a high electron density provided by the substituent decreases activity, exemplified by the 5-methoxy group, which in addition to its unfavorable electrostatic properties, also shows a disfavored steric interaction.

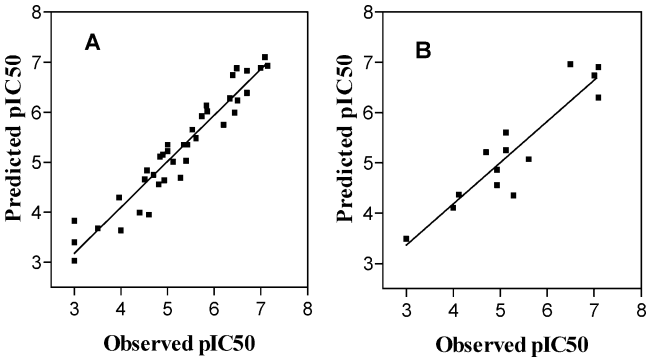


Figure 1. Plot of the predicted pIC_{50} vs the observed pIC_{50} values for the MAO-A CoMFA model. A. All compounds (n = 38, R^2 = 0.92, s = 0.31, p < 0.0001). B. Test set (n = 14, R^2 = 0.85, s = 0.44, p < 0.0001).

Effects of Different Chain Lengths on the α-Carbon Atom. The lengthening of the α-alkyl of the phenethylamine derivatives, from methyl (**8a**−**c** and **12a**−**c**) to ethyl (**9a**−**c** and **13a**−**c**), led to decreased inhibitory activity of these compounds at MAO-A. A similar trend, i.e. decreased potency, has been reported for an α-ethyl amiflamine analogue[13] and more recently for the α-ethyl analogue of the potent MAO-A inhibitor 4-methylthioamphetamine (**32**).[23]

Effects of *N*-Methylation. One of the most intriguing results obtained in the present work was the

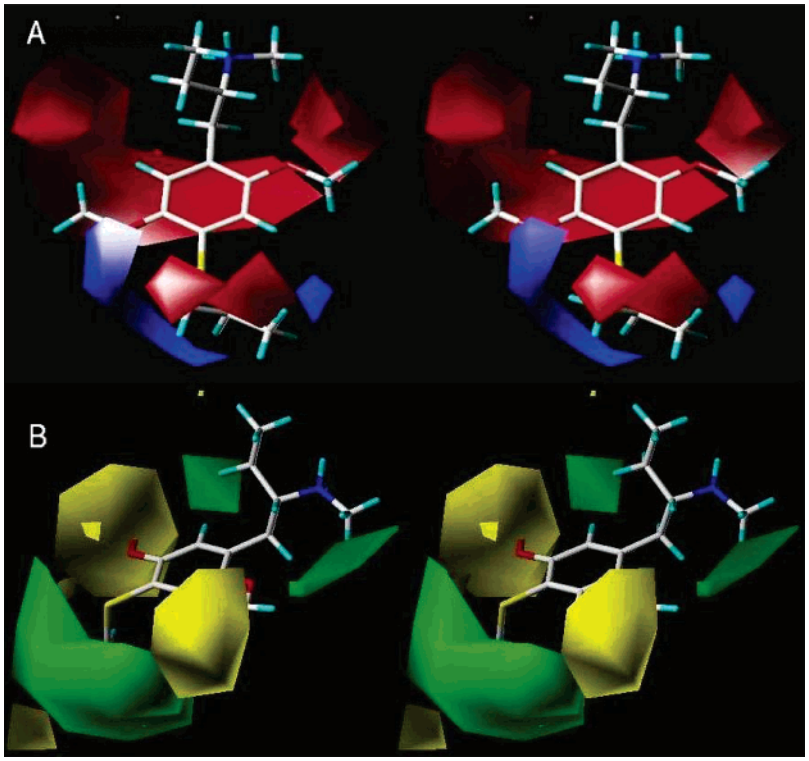


Figure 2. (A) CoMFA steric STDEV*COEFF contour plots of compound (S)-**13c**. Sterically favored areas (contribution level 60%) are represented by green polyhedra. Sterically disfavored areas (contribution level 30%) are represented by yellow polyhedra. (B) CoMFA electrostatic STDEV*COEFF contour plots of compound (S)-**13c**. Positive charge favored areas (contribution level 80%) are represented by blue polyhedra. Negative charge favored areas (contribution level 20%) are represented by red polyhedra.

Table 3. Effect of Preincubation on MAO-A Inhibition[a]

	percent inhibition of MAO-A	
compd	0 min preincubation time	30 min preincubation time
clorgyline [10^{-7}]	17.9 ± 0.2	75.0 ± 4.0
8c [10^{-7}]	15.7 ± 5.2	20.0 ± 3.8
22b [10^{-7}]	23.7 ± 5.2	33.0 ± 3.2

[a] Crude mitochondrial suspensions were preincubated at 37 °C for the times indicated, with each compound at a concentration that, without preincubation, did not produce total inhibition of the enzyme. Percent inhibition of deamination of 5-HT (100 μM) was determined by HPLC-ED. Clorgyline was used as a positive control. Values are means ± SD of triplicate determinations.

Table 4. Reversibility of MAO-A Inhibition as Demonstrated by Restoration of Inhibition after Repeated Washing

	percent MAO-A inhibition	
compd	before washing	after washing
clorgyline [10^{-4}]	100	100
8c [10^{-7}]	20 ± 1.2	0
22b [10^{-7}]	40 ± 5.3	0
29 [10^{-7}]	58 ± 3.1	0

[a] Crude mitochondrial suspensions were preincubated for 10 min with inhibitor, and then the preparation was washed three times by centrifugation and resuspension. MAO-A activity of the preparation and of the control experiments was measured by HPLC-ED with 5-HT (100 μM) as selective substrate. Each value is the mean ± SD of triplicate determinations.

unexpected increase in MAO-A inhibitor potency when the amines were *N*-methylated, as illustrated by the green contours in Figure 2B (cf. **8a**−**c** vs **12a**−**c** and **9a**−**c** vs **13a**−**c**). This increase in potency was fairly substantial in the case of the *n*-propylthio compounds (cf. **8c** = 2.45 μM vs **12c** = 0.36 μM and **9c** = 7.65 μM vs **13c** = 1.40 μM). These results are particularly interesting because they represent a trend opposite to that found for certain other amphetamine derivatives such as amphetamine itself,[27,28] 3,4-methylenedioxyamphetamine (**52**),[11] or **32**,[23] compared with their *N*-methyl derivatives, where *N*-methylation led to an approximately 3-fold loss in activity.

A very recent CoMFA on substituted amphetamine interactions with the human serotonin transporter indicated the presence of a sterically disfavored region near the 6- (or 2)-position and another region near the 3-position where an electronegative substituent is unfavorable.[29] Our results suggest that the opposite is the case for MAO-A inhibition. Similarly, the 2,5-dimethoxy-4-X substitution pattern is commonly acknowledged as a particularly favorable arrangement in substituted amphetamines with full or partial agonist activity at the 5-HT_2 receptor subtypes usually associated with hallucinogenesis,[3] whereas it seems to disfavor interaction with MAO-A.

Consequently, on the basis of the data shown here, we appear to be identifying structural determinants of the selectivity of substituted amphetamines for mechanistically different monoaminergic activities. In addition, our present finding that *N*-methylation may increase MAO-A inhibitory potency in some cases, and the observation that this structural change commonly leads to reduced hallucinogenic potency,[17] points to an additional design feature that might be exploited for the synthesis of selective amphetamine-based MAO-A inhibitors devoid of undesirable CNS side effects.

Time Dependency and Reversibility of the MAO-A Inhibition. Table 3 summarizes the results obtained when some of the most potent derivatives were preincubated with the enzyme. As can be seen, no

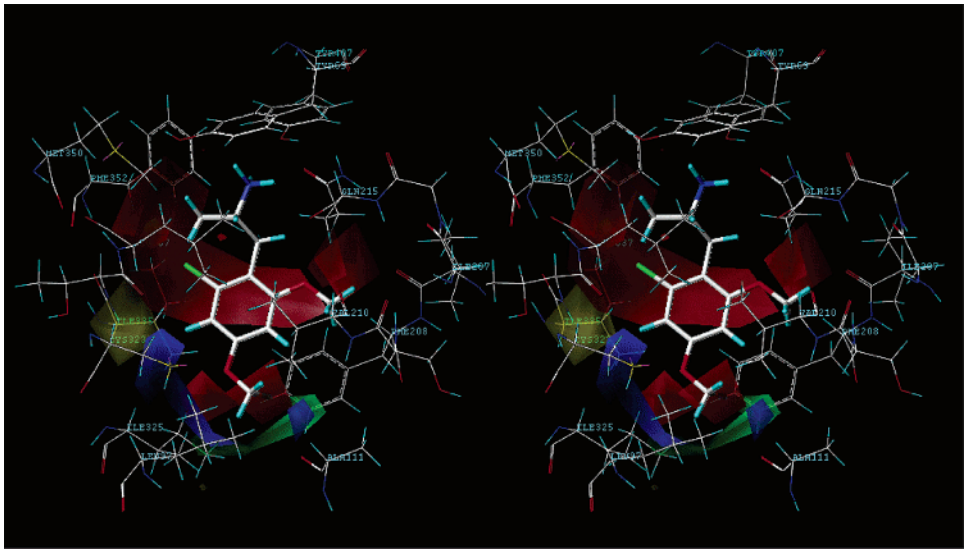


Figure 3. Superimposition of CoMFA (electrostatic and steric) contours with compound (*S*)-**29** onto minimized ligand binding domain derived from the crystal structure of MAO-A.[16]

significant changes were observed in MAO-A inhibition after different preincubation times (0 and 30 min), indicating that blockade of the enzyme was not time-dependent, and that the inhibition was not due to substrate competition, because the inhibitors were not metabolized by the enzyme, but rather resulted from a real blockade of enzymatic activity. Reversibility of the inhibition was assessed in a selected group of compounds by repeated washing of the preparation in the presence of the inhibitor (Table 4). Significant recovery of MAO-A activity was observed after the washing procedure, indicating that the in vitro MAO-A inhibition by these derivatives is reversible and fundamentally different from that produced by the suicide inhibitor clorgyline.

Enzyme Active Site Model. Sybyl 6.9 for Linux was also used for receptor modeling. The X-ray crystal structure (1O5W) has recently been published of MAO-A irreversibly bound to the MAO-A selective inhibitor clorgyline.[16] Compound **29** was chosen as the illustrative case due to its high potency and comparative similarity to clorgyline, which allowed superimposition of their respective aromatic rings. Clorgyline was then removed in silico, and the flavin cofactor was modified back to its precovalently inhibited state. Minimizations were then performed on the ensemble of the ligand (*S*)-**29** and enzyme residues within 9Å of the docked ligand using the MMFF94s force field and MMFF94 charges until convergence was reached. Although clorgyline appears to be protonated in the crystal structure, because of the lack of certainty regarding whether the protonated or unprotonated ligand initially binds, both forms were modeled using the same approach. The results were highly similar, without significant differences in the overall minimized structure. For illustrative purposes the protonated form of the ligand is shown in the figures. The CoMFA fields shown in Figure 3 were overlaid on the receptor at the same scale. Figure 4 was generated using PyMOL 0.95.[30]

Key features of the modeling results include logical interactions of the ligand with the putative binding site of the enzyme. Of particular note is the presence of Cys 323, which is ideally positioned to interact with oxygen or sulfur substituents in the para position of the aromatic ring of the inhibitors, either through hydrogen bonding or van der Waals interactions. This potential interaction is illustrated by the red electrostatic CoMFA field around the sulfur (see Figure 2A). Also noteworthy is Phe 208, which appears to interact with the aromatic ring of the ligand through a $\pi-\pi$ stacking interaction.

Several residues seem to be positioned to interact with the amine of the ligand side chain. It might be noted, however, that in contrast to monoamine GPCRs, there is no aspartate or glutamate nearby to form a salt bridge with the protonated amine. We speculate that a deamination mechanism involving abstraction of an N electron would be hindered by actual ionic protonation of the amine electron pair. Chief among potential residues that could hydrogen bond with the amino group are Gln 215 and Tyr 407, both of which are capable of hydrogen bonding through their side chain carbonyl and phenolic hydroxyl groups, respectively. Tyr 69 also appears to be near enough to interact with the amine through a $\pi-$cation interaction if it were protonated.

With respect to alkylthio substituents at the para-position, there appears to be a complementary "pocket" in the receptor created by hydrophobic residues Leu 97, Val 210, and Ala 111. The size of this space would seem to allow for a favorable interaction with modest length unbranched alkyl chains attached to sulfur, in accord with the green steric field of the CoMFA analysis, but would disfavor longer or branched substituents. The apparent absence of any direct interactions with methoxy groups in the 6-position indicates the possibility that there may be a bridging water molecule in actual bound inhibitor ensembles. An apparent hydrophilic pocket in that region is created by Gln 215, Tyr 444, Asn 181, and the backbone amide of Ile 207.

The yellow steric CoMFA contours located around both positions meta to the side chain can be rationalized as indications of disfavored interactions with residues in those areas of the enzyme binding site. One of the meta positions is relatively sterically hindered by Ile 335 and Thr 336 and the backbone connecting them. Thus, this meta position appears completely occluded. This occlusion also forces any alkyl attached to the para-

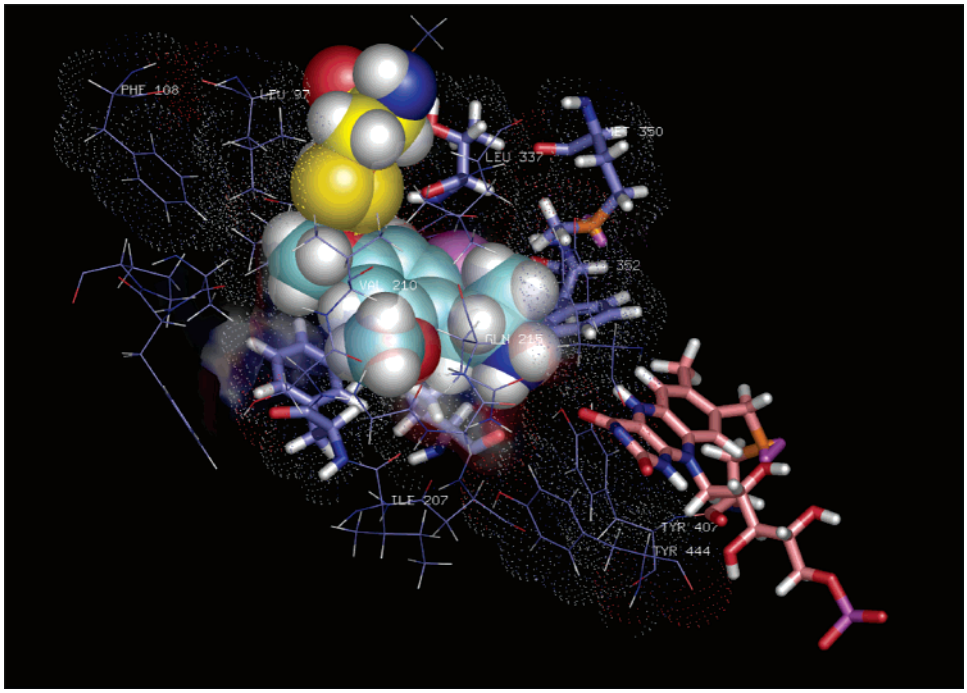


Figure 4. View of the complex of compound (*S*)-**29** cominimized into the binding pocket of the crystal structure of MAO-A. The orange structure to the lower right is the flavin cofactor, to indicate the relative position of the inhibitors in the enzyme active site. Cys 323 is represented as space-filling yellow spheres to show the proposed contact with the substituent at the para-position of the inhibitor ligand.

Table 5. Statistics from MAO-A CoMFA Model

q^2 [a]	N [b]	n [c]	R^2 [d]	F	steric	electrostatic
0.724	4	38	0.92	410.3	0.823	0.177

[a] Cross-validated correlation coefficient. [b] Optimal number of principal components. [c] Number of compounds. [d] Fitted correlation coefficient

substituent to adopt an anti orientation with respect to this meta position. The other meta position also appears sterically encumbered by a cluster of residues that includes Leu 97, Ala 111, Phe 208, and Val 210. Nevertheless, we speculate that the alkyl attached to the para substituent projects into a groove formed within the intersection of these residues. Flanking meta substituents on both sides of the para-substituent would not only protrude into these sterically restricted areas, but would also force its attached alkyl chain out of plane, with no apparent space for accommodation by the enzyme binding site. In the case of 2,4,6-trisubstituted compounds, no such interference would occur, possibly explaining their generally higher potency. In this regard it is interesting to note the marked difference in activities of compounds **39** and **41** (Table 2).

Figure 4 shows more dramatically the interactions between (*S*)-**29** and the putative active site of MAO-A. The thiol group of Cys 323 (represented as space-filling spheres that include the lone pairs on sulfur) is shown optimally positioned to interact with the substituent (in this case, a methoxy) in the 4 position of the ligand. The greater lipophilicity and softness of sulfur would suggest that sulfur−sulfur interactions might be stronger than sulfur−oxygen interactions. On the basis of this reasoning, the effect on potency is predictable in going from **35** to **32** or **22a** to **30**. Also, the many hydrophobic residues surrounding the binding pocket can be more clearly seen in this representation, above and below the plane of the ligand, as well as to the left in the pocket suited for interaction with alkyl chains of the 4-substituent, and at the top of the figure in the area occupied by the *o*-chlorine and α-methyl group on the side chain.

Experimental Section

Enzymatic Assays. The effects of the different compounds on MAO-A or MAO-B activity, as well as time-dependency and reversibility studies, were carried out using a crude rat brain mitochondrial suspension from male Sprague−Dawley rats weighing 180−220 g, with 5-HT (100 μM) and 4-dimethylaminophenethylamine (DMAPEA, 5 μM) used as selective substrates for MAO-A and MAO-B,[22] respectively, and detecting these compounds and their deaminated metabolites with HPLC and electrochemical detection (HPLC-ED) as described previously.[23] The IC_{50} values were determined from plots of percent inhibition, calculated in relation to a sample of the enzyme treated under the same conditions without inhibitors, versus −log [I]. The protein content was determined according to Lowry et al.[24]

Chromatographic Conditions. A C_{18} reverse phase column (ODS 250 mm × 4.0 mm, LichroCART, USA), an amperometric detector (Merck-Recipe L3500A), and a two channel recorder (BAS) were used to analyze the reaction mixtures. All other conditions were as previously described.[11]

Statistical Analysis. IC_{50} values are given as the mean ± SD of at least two independent experiments, each in triplicate. Statistical significance was determined using Student's *t*-test. In all cases the significance level was found to be $P < 0.05$.

CoMFA Analysis. The analysis was performed on 38 analogues taken both from this work (Table 1) and from Scorza et al.[11] (Table 2) using the Sybyl 6.9[25] software package for Linux running on an AMD Athlon XP processor. For all modeling purposes, the more potent (*S*) enantiomer was used, in accordance with previous studies of MAO-A inhibition by amphetamines that have consistently shown that the (*S*) isomer was more potent than its antipode.[23,26,27] Structures were minimized using the MMFF94S force field and MMFF94 charges, with amino groups protonated, and a dielectric constant of 70. Enzyme inhibition data were converted to pIC_{50} values. Sybyl standard parameters were used, with steric and dielectric cutoff values of 15 and 10 kcal/mol, respectively, and

a distance dependent dielectric function. Partial least squares (PLS) calculations were performed: five cross-validated (four groups) and one non-cross-validated. The highest R^2 (0.92) and q^2 (0.72) values were obtained for four components with a standard deviation of 0.31.

Chemistry. All reagents were commercially available and were used without further purification unless otherwise indicated. Anhydrous THF was obtained by distillation from benzophenone−sodium under nitrogen immediately before use. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded with either a 500 MHz Varian DRX-500s or a 300 MHz Bruker ARX-300 NMR spectrometer. Chemical shifts are reported in δ values (ppm) relative to an internal reference (0.03%, v/v) of tetramethylsilane (TMS) in $CDCl_3$, except were noted. Chemical ionization mass spectra (CIMS), with isobutene as a carrier gas, were obtained with a Finnigan 4000 spectrometer. Elemental analyses were performed by the Purdue University Microanalyses Laboratory and are within ±0.4% of the calculated values unless otherwise noted. Thin-layer chromatography was performed using J. T. Baker flex silica gel IB2-F, plastic-baked sheets with fluorescent indicator, visualizing with UV light at 254 nm and 3:2 hexane/ethyl acetate as the developing solvent unless otherwise noted. Column chromatography was carried out with silica gel 60, 230−400 mesh (J. T. Baker). All reactions were carried out under an inert atmosphere of argon unless otherwise indicated. Compounds **1**, **14**, **23** and **24** were commercially available. In a few instances intermediates had been previously reported, but without NMR data. NMR data have now been provided for those compounds.

Chemistry. 2,5-Dimethoxybenzenesulfonyl Chloride (2). This compound was prepared from **1** in 68.3% yield by a modification of the method of Shulgin and Shulgin,[17] mp 110−113 °C (lit.[17] mp 115−117 °C; 109−112 °C[18]).

2,5-Dimethoxybenzenethiol (3). This compound was obtained as a colorless oil in a much improved 99% yield by a modification of the method of Shulgin and Shulgin,[17] using 30% v/v HCl instead of the reported H_2SO_4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (d, 1H, J = 3.0 Hz, ArH), 6.78 (d, 1H, J = 9.0 Hz, ArH), 6.65 (dd, 1H, J = 9.0 Hz, J' = 3.0 Hz, ArH), 3.92 (s, 1H, SH), 3.84 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3).

General Procedure for the Alkylation of 2,5-Dimethoxy-benzenethiol. To a nitrogen-flushed 250 mL flask containing a solution of KOH (20 mmol) in 50 mL of MeOH was added **3** (10 mmol). The mixture was allowed to stir for 1 h before adding the corresponding alkyl halide (20 mmol). The reaction was heated at reflux for 30 min, cooled, and poured into 200 mL of water. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), dried with anhydrous Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. Bulb-to-bulb distillation generally gave the products as colorless oils.

1,4-Dimethoxy-2-methylthiobenzene (4a). This compound was prepared in 99% yield using the general procedure given above, but 20 mmol of Me_2SO_4 was used as alkylating agent. Bulb-to-bulb distillation (80−85 °C/0.1 Torr)(lit.[31] bp 86−88 °C/0.04 mm) gave the desired product, which solidified; mp 33−34 °C (lit.[31] mp 33−34 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (d, 1H, J = 9.0 Hz, ArH), 6.75 (d, 1H, J = 3.0 Hz, ArH), 6.64 (dd, 1H, J = 6.0 Hz, J' = 3.0 Hz, ArH), 3.85 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3S).

1,4-Dimethoxy-2-ethylthiobenzene (4b). This compound was obtained in 99% yield as a colorless oil.[17,32]

1,4-Dimethoxy-2-*n*-propylthiobenzene (4c). This compound was obtained in 99% yield using the reported procedure of Shulgin and Shulgin.[17] ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (d, 1H, J = 3.0 Hz, ArH), 6.73 (d, 1H, J = 9.0 Hz, ArH), 6.63 (dd, 1H, J = 6.0 Hz, J' = 3.0 Hz, ArH), 3.80 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 2.84 (t, 2H, J = 7.0 Hz, $CH_3CH_2\mathit{CH_2}S$), 1.67 (sextuplet, 2H, J = 7.0 Hz, $CH_3\mathit{CH_2}CH_2S$), 1.02 (t, 3H, J = 7.0 Hz, $\mathit{CH_3}CH_2CH_2S$).

1,4-Dimethoxy-2-*n*-butylthiobenzene (4d). This compound was obtained in 96% yield as a colorless oil that solidified upon standing. The compound was purified by bulb-to-bulb distillation (105−110 °C/0.1 Torr) (lit.[33] bp 130−132 °C/0.4 mm) and had mp 36−37 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 (d, 1H, J = 3.0 Hz, ArH), 6.77 (d, 1H, J = 9.0 Hz, ArH), 6.67 (dd, 1H, J = 6.0 Hz, J' = 3.0 Hz, ArH), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.89 (t, 2H, J = 7.0 Hz, $CH_3(CH_2)_2\mathit{CH_2}S$), 1.67 (quintuplet, 2H, J = 7.0 Hz, $CH_3CH_2\mathit{CH_2}CH_2S$), 1.48 (sextuplet, 2H, J = 7.0 Hz, $CH_3\mathit{CH_2}(CH_2)_2S$), 0.93 (t, 3H, J = 7.0 Hz, $\mathit{CH_3}(CH_2)_3S$).

1,4-Dimethoxy-2-*n*-pentylthiobenzene (4e). This compound was obtained in 99% yield as a colorless oil that solidified upon standing. It was purified by bulb to bulb distillation (105−110 °C/0.1 Torr) (lit.[34] 139−142 °C/0.8 Torr) and had mp 38−39 °C (lit.[34] mp 38−39 °C).

1,4-Dimethoxy-2-*i*-propylthiobenzene (4f). This compound was obtained in 99% yield as a colorless oil, using the reported procedure of Shulgin and Shulgin.[17] The material was purified by bulb to bulb distillation (75−80 °C/0.05 Torr) (lit.[17] 110−110 °C/0.2 mm/Hg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (d, 1H, J = 3.0 Hz, ArH), 6.81 (d, 1H, J = 9.0 Hz, ArH), 6.75 (dd, 1H, J = 6.0 Hz, J' = 3.0 Hz, ArH), 3.86 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.50 (m, 1H, $(CH_3)_2\mathit{CH}S$), 1.32 (d, 6H, J = 7.0 Hz, $(\mathit{CH_3})_2CHS$).

1,4-Dimethoxy-2-(2-phenethyl)thiobenzene (4g). This product was obtained in 98% yield using 1-bromo-2-phenylethane as the alkylating agent. The colorless oil was purified by bulb-to-bulb distillation (95−100 °C/0.1 Torr). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (m, 3H, Ar(1)H), 7.30 (m, 5H, Ar(2)H), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.30 (t, 2H, J = 7.0 Hz, Ar(2)$CH_2\mathit{CH_2}S$), 3.05 (t, 2H, J = 7.0 Hz, Ar(2)$\mathit{CH_2}CH_2S$). HREIMS *m/z* calcd for $C_{16}H_{18}O_2S$ (M) 274.1028, found 274.1031.

General Procedure for the Formylation of 1,4-Dimethoxy-2-alkylthiobenzenes (5a−g). Phosphorus oxychloride (60 mmol) was mixed with *N*-methylformanilide (60 mmol) and heated to 40−50 °C for 5−10 min with gentle manual shaking, until a color change occurred. The corresponding alkylbenzene **4a**−**g** was added (20 mmol) in one portion. The reaction was exothermic, and the color changed from orange to dark red. The mixture was heated for 15 min keeping the temperature under 70 °C, and then 100 g of crushed ice was added. The mixture was magnetically stirred for 1 h. The solids were filtered, washed with cold water, and the products were recrystallized from ethanol.

2,5-Dimethoxy-4-methylthiobenzaldehyde (5a). This compound was obtained as a yellow powder in 73% yield, mp 98−100 °C (lit.[31] mp 99−100 °C; 97.5−98.5 °C[18]).

2,5-Dimethoxy-4-ethylthiobenzaldehyde (5b). The product was obtained as amber crystals in 88% yield, mp 87−88 °C (lit.[32] mp 86−88 °C; 87−88 °C[17]).

2,5-Dimethoxy-4-*n*-propylthiobenzaldehyde (5c). The product was obtained as a yellow powder in 99% yield, mp 78−79 °C (lit.[17] mp 76−77 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.42 (s, 1H, CHO), 7.31 (s, 1H, ArH), 6.83 (s, 1H, ArH), 3.98 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.00 (t, 2H, J = 7.0 Hz, $CH_3CH_2\mathit{CH_2}S$), 1.85 (sextuplet, 2H, J = 7.0 Hz, $CH_3\mathit{CH_2}CH_2S$), 1.17 (t, 3H, J = 7.0 Hz, $\mathit{CH_3}CH_2CH_2S$).

2,5-Dimethoxy-4-*n*-butylthiobenzaldehyde (5d). The product was obtained as a yellow powder in 86% yield, mp 72−73 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.37 (s, 1H, CHO), 7.27 (s, 1H, ArH), 6.78 (s, 1H, ArH), 3.93 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 2.97 (t, 2H, J = 7.0 Hz, $CH_3(CH_2)_2\mathit{CH_2}S$), 1.75 (quintuplet, 2H, J = 7.0 Hz, $CH_3CH_2\mathit{CH_2}CH_2S$), 1.54 (sextuplet, 2H, J = 7.0 Hz, $CH_3\mathit{CH_2}(CH_2)_2S$), 0.98 (t, 3H, J = 7.0 Hz, $\mathit{CH_3}(CH_2)_3S$). HREIMS *m/z* calcd for $C_{13}H_{18}O_3S$ (M) 254.0977, found 254.0975.

2,5-Dimethoxy-4-*n*-pentylthiobenzaldehyde (5e). The product was obtained as a yellow powder in 99% yield, mp 104−105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.36 (s, 1H, CHO), 7.25 (s, 1H, ArH), 6.77 (s, 1H, ArH), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 2.96 (t, 2H, J = 7.0 Hz, $CH_3(CH_2)_3\mathit{CH_2}S$), 1.76 (quintuplet, 2H, J = 7.0 Hz, $CH_3(CH_2)_2\mathit{CH_2}CH_2S$), 1.49 (quintuplet, 2H, J = 7.0 Hz, $CH_3CH_2\mathit{CH_2}(CH_2)_2S$), 1.38 (sextuplet, 2H, J = 7.0 Hz, $CH_3\mathit{CH_2}(CH_2)_3S$), 0.98 (t, 3H, J = 7.0 Hz, $\mathit{CH_3}(CH_2)_4S$). HREIMS *m/z* calcd for $C_{14}H_{20}O_3S$ (M) 268.1133, found 268.1131.

2,5-Dimethoxy-4-*i*-propylthiobenzaldehyde (5f). The product was obtained as a yellow powder in 78% yield, mp 89−90 °C (lit.[17] mp87.5−89 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.38 (s, 1H, CHO), 7.27 (s, 1H, ArH), 6.88 (s, 1H, ArH), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.61 (m, 1H, $(CH_3)_2CH$S), 1.41 (d, 6H, J = 7.0 Hz, $(CH_3)_2$CHS).

2,5-Dimethoxy-4-(2-phenethyl)thiobenzaldehyde (5g). The product was obtained as a yellow powder in 90% yield, mp 102−105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.42 (s, 1H, CHO), 7.40 (m, 2H, Ar(1)H), 7.32 (m, 5H, Ar(2)H), 3.95 (s, 6H, 2 × OCH_3), 3.29 (t, 2H, J = 7.0 Hz, Ar(2)CH_2CH_2S), 3.09 (t, 2H, J = 7.0 Hz, Ar(2)CH_2CH_2S). HREIMS *m/z* calcd for $C_{17}H_{18}O_3S$ (M) 302.0977, found 302.0972.

General Procedure for the Preparation of Arylnitropropenes (6a−g). A mixture of the corresponding aldehyde **5a−g** (10.0 mmol) in 50 mL of nitroethane was heated to 60 °C, and then anhydrous NH_4OAc (6.0 mmol) was added in one portion. The reaction was heated at reflux with stirring for 3−5 h. After cooling to room temperature, removal of the excess nitroethane in vacuo gave a red oil, which upon addition of ethanol (10 mL) spontaneously crystallized. The product was recrystallized from 20 mL of boiling ethanol.

1-(2,5-Dimethoxy-4-methylthiophenyl)-2-nitro-1-propene (6a). The product was obtained in 73% yield as orange crystals, mp 134−136 °C (lit.[31] mp 137−138 °C; 137−138 °C[17]). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (s, 1H, ArCH), 6.78 (s, 1H, ArH), 6.73 (s, 1H, ArH), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.50 (s, 3H, SCH_3), 2.42 (s, 3H, CH_3CNO_2).

1-(2,5-Dimethoxy-4-ethylthiophenyl)-2-nitro-1-propene (6b). The product was obtained in 85% yield as orange needles, mp 110−111 °C (lit.[17] mp 112−113 °C; 110−111 °C[32]).

1-(2,5-Dimethoxy-4-*n*-propylthiophenyl)-2-nitro-1-propene (6c). The product was obtained in 69% yield as orange needles, mp 83−85 °C (lit.[17] mp 83−84 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (s, 1H, ArCH), 6.73 (s, 1H, ArH), 6.71 (s, 1H, ArH), 3.79 (s, 6H, 2 × OCH_3), 2.86 (t, 2H, J = 7.0 Hz, $CH_3CH_2CH_2$S), 2.34 (s, 3H, CH_3CNO_2), 1.68 (sextuplet, 2H, J = 7.0 Hz, $CH_3CH_2CH_2$S), 1.01 (t, 3H, J = 7.0 Hz, $CH_3CH_2CH_2$S).

1-(2,5-Dimethoxy-4-*n*-butylthiophenyl)-2-nitro-1-propene (6d). The product was obtained in 90% yield as orange needles, mp 64−65 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (s, 1H, ArCH), 6.81 (s, 1H, ArH), 6.78 (s, 1H, ArH), 3.87 (s, 6H, 2 × OCH_3), 2.96 (t, 2H, J = 7.0 Hz, $CH_3(CH_2)_2CH_2$S), 2.43 (s, 3H, CH_3CNO_2), 1.70 (quintuplet, 2H, J = 7.0 Hz, $CH_3CH_2CH_2CH_2$S), 1.52 (sextuplet, 2H, J = 7.0 Hz, $CH_3CH_2(CH_2)_2$S), 0.97 (t, 3H, J = 7.0 Hz, $CH_3(CH_2)_3$S). HREIMS *m/z* calcd for $C_{15}H_{21}NO_4S$ (M) 311.1191, found 311.1183.

1-(2,5-Dimethoxy-4-*n*-pentylthiophenyl)-2-nitro-1-propene (6e). The product was obtained in 71% yield as yellow crystals, mp 63−65 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (s, 1H, ArCH), 6.81 (s, 1H, ArH), 6.79 (s, 1H, ArH), 3.87 (s, 6H, 2 × OCH_3), 2.95 (t, 2H, J = 7.0 Hz, $CH_3(CH_2)_3CH_2$S), 2.43 (s, 3H, CH_3CNO_2), 1.73 (quintuplet, 2H, J = 7.0 Hz, $CH_3(CH_2)_2CH_2CH_2$S), 1.47 (quintuplet, 2H, J = 7.0 Hz, $CH_3CH_2CH_2(CH_2)_2$S), 1.37 (sextuplet, 2H, J = 7.0 Hz, $CH_3CH_2(CH_2)_3$S), 0.93 (t, 3H, J = 7.0 Hz, $CH_3(CH_2)_4$S). HREIMS *m/z* calcd for $C_{16}H_{23}NO_4S$ (M) 325.1348, found 325.1338.

1-(2,5-Dimethoxy-4-*i*-propylthiophenyl)-2-nitro-1-propene (6f). The product was obtained in 85% yield as orange needles, mp 99−100 °C (lit.[17] mp 99−100 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H, ArCH), 6.92 (s, 1H, ArH), 6.80 (s, 1H, ArH), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.59 (m, 1H, $(CH_3)_2CH$S), 2.43 (s, 3H, CH_3CNO_2), 1.37 (d, 6H, J = 7.0 Hz, $(CH_3)_2$CHS).

1-(2,5-Dimethoxy-4-(2-phenylethylthiophenyl)-2-nitro-1-propene (6g). The product was obtained in 85% yield as a light yellow powder, mp 112−114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (s, 1H, ArCH), 7.38 (m, 2H, Ar(2)H), 7.31 (m, 3H, Ar(2)H), 6.89 (s, 1H, Ar(1)H), 6.85 (s, 1H, Ar(1)H), 3.94 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.25(t, 2H, J = 7.0 Hz, Ar(2)CH_2CH_2S), 3.08 (t, 2H, J = 7.0 Hz, Ar(2)CH_2CH_2S), 2.47 (s, 3H, CH_3CHNO_2). HREIMS *m/z* calcd for $C_{19}H_{21}NO_4S$ (M) 359.1191, found 359.1189.

General Procedure for the Preparation of Arylnitrobutenes (7a−c). A mixture of the corresponding aldehyde **5a−c** (10.0 mmol), 16.0 mmol of nitropropane, and 2.9 mmol of DMEDA in 100 mL of toluene was heated at reflux under a Dean−Stark trap for 48 h. After cooling to room temperature, removal of the solvent in vacuo gave the product, which was recrystallized from 20 mL of boiling ethanol.

1-(2,5-Dimethoxy-4-methylthiophenyl)-2-nitro-1-butene (7a). The product was obtained in 50% yield as orange cotton-like crystals, mp 98−100 °C (lit.[35] mp 103−105 °C).[35] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (s, 1H, ArCH), 6.91 (s, 1H, ArH), 6.79 (s, 1H, ArH), 3.88 (s, 6H, 2 × OCH_3), 2.86 (q, 2H, J = 7.0 Hz, $CH_3CH_2CNO_2$), 2.49 (s, 3H, CH_3S), 1.29 (t, 3H, J = 7.0 Hz, $CH_3CH_2CNO_2$).

1-(2,5-Dimethoxy-4-ethylthiophenyl)-2-nitro-1-butene (7b). The product was obtained in 54% yield as orange crystals, mp 75−78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H, ArCH), 6.81 (s, 1H, ArH), 6.80 (s, 1H, ArH), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 2.98 (q, 2H, J = 7.0 Hz, CH_3CH_2S), 2.86 (q, 2H, J = 7.0 Hz, $CH_3CH_2CNO_2$), 1.38 (t, 3H, J = 7.0 Hz, CH_3CH_2S), 1.29 (t, 3H, J = 7.0 Hz, $CH_3CH_2CNO_2$).

1-(2,5-Dimethoxy-4-*n*-propylthiophenyl)-2-nitro-1-butene (7c). The product was obtained in 55% yield as orange cotton-like crystals, mp 55−56 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H, ArCH), 6.80 (s, 1H, ArH), 6.79 (s, 1H, ArH), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 2.93 (t, 2H, J = 7.0 Hz, $CH_3CH_2CH_2$S), 2.85 (q, 2H, J = 7.0 Hz, $CH_3CH_2CNO_2$), 1.82−1.69 (m, 2H, $CH_3CH_2CH_2$S), 1.29 (t, 3H, J = 7.0 Hz, $CH_3CH_2CH_2$S), 1.08 (t, 3H, J = 7.0 Hz, $CH_3CH_2CNO_2$). HREIMS *m/z* calcd for $C_{15}H_{21}NO_4S$ (M) 311.1191, found 311.1194.

General Procedure for the Preparation of 8a−g and 9a−c. A 1 L three-neck flask was flushed with argon and then charged with freshly distilled THF (200 mL) and $LiAlH_4$ (50.0 mmol). The mixture was heated to 60 °C with very good stirring for 30 min. A solution of the correspondent arylnitroalkene **6a−g**, **7a−c** (10 mmol) in THF (50 mL) was added dropwise over a 30 min period. Heating at reflux was continued for 36 h, while maintaining a static pressure of argon. The mixture was cooled to room temperature and the excess hydride destroyed by careful dropwise addition of a solution of 1.9 mL of distilled water in 50 mL of THF. Aqueous (15% w/v) NaOH (1.9 mL) was added, followed by 5.7 mL of water. The mixture was stirred for 30 min and then filtered to remove the precipitated salts, and the filter cake was washed with THF (4 × 100 mL) and dried with $MgSO_4$ and the solvent evaporated under reduced pressure. In all cases the amine was obtained as a yellow oil that was purified by bulb-to-bulb distillation. The product was taken up into a minimal quantity of 2-propanol and converted to the hydrochloride by neutralizing to pH 5.5−6.0 with concentrated HCl dissolved in 2-propanol. The solution was diluted with anhydrous ether, which resulted in the formation of white crystals.

1-(2,5-Dimethoxy-4-methylthiophenyl)-2-aminopropane Hydrochloride (8a). This compound was obtained in 78% yield by the method of Nichols et al.[31] as white crystals, mp 200−202 °C (lit.[31] mp 204−205 °C; 200−201 °C[31]). ^{1}H NMR (300 MHz, D_2O): δ 6.93 (s, 1H, ArH), 6.91 (s, 1H, ArH), 3.84 (s, 6H, 2 × OCH_3), 3.63 (sextuplet, 1H, J = 7.0 Hz, $ArCH_2(CH_3)CHNH_2$), 2.92 (d, 2H, J = 7.0 Hz, $ArCH_2$), 2.47 (s, 3H, CH_3S), 1.28 (d, 3H, J = 7.0 Hz, $ArCH_2(CH_3)CHNH_2$). Anal. ($C_{12}H_{20}ClNO_2S$) C, H, N, S.

1-(2,5-Dimethoxy-4-ethylthiophenyl)-2-aminopropane Hydrochloride (8b). The product was obtained in 71% yield as white crystals, mp 127−129 °C (lit.[17] mp 128−130 °C; 127−129 °C[32]). Anal. ($C_{13}H_{22}ClNO_2S$) C, H, N, S.

1-(2,5-Dimethoxy-4-*n*-propylthiophenyl)-2-aminopropane Hydrochloride (8c). The product was obtained in 89% yield as white crystals, mp 135−142 °C. ^{1}H NMR (300 MHz, D_2O): δ 6.84 (s, 1H, ArH), 6.80 (s, 1H, ArH), 3.75 (s, 3H, 2 × OCH_3), 3.57 (sextuplet, 1H, J = 7.0 Hz, $ArCH_2(CH_3)CHNH_2$), 2.83−2.71 (m, 4H, $CH_3CH_2CH_2$S and $ArCH_2$), 1.55 (sextuplet, 2H, J = 7.0 Hz, $CH_3CH_2CH_2$S), 1.22 (d, 3H, J = 7.0 Hz, $ArCH_2$-

(CH_3)CHNH$_2$), 0.90 (t, 3H, J = 7.0 Hz, CH_3CH$_2$CH$_2$S. Anal. ($C_{14}H_{24}ClNO_2S$) C, H, N, S.

1-(2,5-Dimethoxy-4-*n*-butylthiophenyl)-2-aminopropane Hydrochloride (8d). The product was obtained in 62% yield as white crystals, mp 117−118 °C. ^{1}H NMR (300 MHz, D$_2$O): δ 6.96 (s, 1H, ArH), 6.86 (s, 1H, ArH), 3.78 (s, 6H, 2 × OCH$_3$), 3.57 (sextuplet, 1H, J = 7.0 Hz, ArCH$_2$(CH$_3$)CHNH$_2$), 2.90 (t, 2H, J = 7.0 Hz, CH$_3$CH$_2$CH$_2$$CH_2$S), 2.86 (d, 2H, J = 7.0 Hz, ArCH$_2$), 1.52 (quintuplet, 2H, J = 7.0 Hz, CH$_3$CH$_2$$CH_2$-CH$_2$S), 1.35 (sextuplet, 2H, J = 7.0 Hz, CH$_3$$CH_2CH_2CH_2$S), 1.22 (d, 3H, J = 7.0 Hz, ArCH$_2$(CH_3)CHNH$_2$), 0.82 (t, 3H, J = 7.0 Hz, CH_3CH$_2$CH$_2$CH$_2$S. Anal. ($C_{15}H_{26}ClNO_2S$) C, H, N, S.

1-(2,5-Dimethoxy-4-*n*-pentylthiophenyl)-2-aminopropane Hydrochloride (8e). The product was obtained in 68% yield as white crystals, mp 115−116 °C. ^{1}H NMR (300 MHz, D$_2$O): δ 6.92 (s, 1H, ArH), 6.86 (s, 1H, ArH), 3.77 (s, 6H, 2 × OCH$_3$), 3.59 (sextuplet, 1H, J = 7.0 Hz, ArCH$_2$(CH$_3$)CHNH$_2$), 2.87 (t, 2H, J = 7.0 Hz, CH$_3$(CH$_2$)$_3$$CH_2$S), 2.86 (d, 2H, J = 7.0 Hz, ArCH$_2$), 1.53 (quintuplet, 2H, J = 7.0 Hz, CH$_3$(CH$_2$)$_2$$CH_2$-CH$_2$S), 1.36−1.17 (m, 4H, CH$_3$$CH_2$(CH$_2$)$_3$S and CH$_3CH_2$$CH_2$-(CH$_2$)$_3$S), 1.23 (d, 3H, J = 7.0 Hz, ArCH$_2$(CH_3)CHNH$_2$), 0.78 (t, 3H, J = 7.0 Hz, CH_3(CH$_2$)$_4$S). Anal. ($C_{16}H_{28}ClNO_2S$) C, H, N, S.

1-(2,5-Dimethoxy-4-*i*-propylthiophenyl)-2-aminopropane Hydrochloride (8f). The product was obtained in 76% yield as white crystals, mp 143−145 °C (lit.[17] 146−147 °C). ^{1}H NMR (300 MHz, D$_2$O): δ 7.05 (s, 1H, ArH), 6.90 (s, 1H, ArH), 3.78 (s, 6H, 2 × OCH$_3$), 3.60 (sextuplet, 1H, J = 7.0 Hz, ArCH$_2$(CH$_3$)CHNH$_2$), 3.46 (m, 1H, (CH$_3$)$_2$$CH$S), 2.88 (d, 2H, J = 7.0 Hz, ArCH$_2$), 1.25 (d, 3H, J = 7.0 Hz, ArCH$_2$(CH_3)-CHNH$_2$), 1.18 (d, 6H, J = 7.0 Hz, (CH_3)$_2$CHS). Anal. ($C_{14}H_{24}$-$ClNO_2S$) C, H, N, S.

1-(2,5-Dimethoxy-4-(2-phenylethylthio)phenyl)-2-aminopropane Hydrochloride (8g). The product was obtained in 30% yield as white crystals, mp 134−136 °C. ^{1}H NMR (300 MHz, D$_2$O): δ 7.34 (m, 2H, Ar(2)H), 7.25 (m, 3H, Ar(2)H), 6.95 (s, 1H, Ar(1)H), 6.89 (s, 1H, Ar(1)H), 3.85 (s, 3H, OCH$_3$), 3.82 (s, 3H, OCH$_3$), 3.64 (sextuplet, 1H, J = 7.0 Hz, ArCH$_2$(CH$_3$)CHNH$_2$), 3.25 (t, 2H, J = 7.0 Hz, Ar(2)CH$_2$$CH_2$S), 2.96−2.88 (m, 4H, Ar(2)CH_2CH$_2$S and Ar(1)CH_2), 1.30 (d, 3H, J = 7.0 Hz, ArCH$_2$(CH_3)CHNH$_2$). Anal. ($C_{19}H_{26}ClNO_2S$) C, H, N, S.

1-(2,5-Dimethoxy-4-methylthiophenyl)-2-aminobutane Hydrochloride (9a). The product was obtained in 60% yield as white crystals, mp 223−224 °C (lit.[35] 220−221 °C). ^{1}H NMR (500 MHz, D$_2$O): δ 6.94 (s, 1H, ArH), 6.91 (s, 1H, ArH), 3.84 (s, 3H, 2 × OCH$_3$), 3.46 (m, 1H, CH$_3$-CH$_2$$CHNH_2$), 3.03−2.84 (dd, dd, 2H, J = 7.0 Hz, ArCH$_2$), 2.47 (s, 3H, CH$_3$S), 1.66 (m, 2H, CH$_3$$CH_2$CHNH$_2$), 1.01 (t, 3H, J = 7.0 Hz, CH_3CH$_2$CHNH$_2$). Anal. ($C_{13}H_{22}ClNO_2S$) C, H, N, S.

1-(2,5-Dimethoxy-4-ethylthiophenyl)-2-aminobutane Hydrochloride (9b). The product was obtained in 63% yield as white crystals, mp 177−182 °C. ^{1}H NMR (300 MHz, D$_2$O): δ 6.87 (s, 1H, ArH), 6.80 (s, 1H, ArH), 3.75 (s, 6H, 2 × OCH$_3$), 3.38 (m, 1H, CH$_3$CH$_2$$CHNH_2$), 2.92−2.72 (m, 4H, CH$_3$$CH_2$S and ArCH$_2$), 1.59 (m, 2H, CH$_3$$CH_2$CHNH$_2$), 1.17 (t, 3H, J = 7.0 Hz, CH_3CH$_2$S), 0.94 (t, 3H, J = 7.0 Hz, CH_3CH$_2$CHNH$_2$). HREIMS *m/z* calcd for $C_{14}H_{19}NO_4S$ (M) 297.1035, found 297.1027. Anal. ($C_{14}H_{24}ClNO_2S$) C, H, N, S.

1-(2,5-Dimethoxy-4-*n*-propylthiophenyl)-2-aminobutane Hydrochloride (9c). The product was obtained in 60% yield as white crystals, mp 174−177 °C. ^{1}H NMR (300 MHz, D$_2$O): δ 6.99 (s, 1H, ArH), 6.89 (s, 1H, ArH), 3.80 (s, 3H, 2 × OCH$_3$), 3.42 (m, 1H, CH$_3$CH$_2$$CHNH_2$), 3.00−2.79 (m, 4H, Ar$CH_2$ and CH$_3$CH$_2$$CH_2$S), 1.69−1.54 (m, 4H, CH$_3$$CH_2$-CHNH$_2$ and CH$_3$$CH_2CH_2$S), 0.97 (t, 3H, J = 7.0 Hz, CH_3CH$_2$-CH$_2$S), 0.93 (t, 3H, J = 7.0 Hz, CH_3CH$_2$CHNH$_2$). Anal. ($C_{15}H_{26}ClNO_2S$) C, H, N, S.

General Procedure for the Preparation of *N*-Formyl Derivatives (10a−c and 11a−c). 10 mmol of the corresponding hydrochloride was dissolved in 30% w/v NaOH (100 mL) and extracted with CH$_2$Cl$_2$ (3 × 50 mL), the extract was dried with anhydrous MgSO$_4$, and the solvent was evaporated under reduced pressure. The free amine was dissolved in 15 mL of ethyl formate and heated at reflux overnight. After cooling the reaction mixture to room temperature, the excess ethyl formate was removed under reduced pressure to afford the crystalline product, which was recrystallized from 20 mL of boiling MeOH. The products were sufficiently pure to carry on to the next step.

***N*-Formyl-1-(2,5-dimethoxy-4-methylthiophenyl)-2-aminopropane (10a).** The product was obtained in 84% yield as white crystals, mp 142−144 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.05 (s, 1H, *N*−*CHO*), 6.78 (s, 1H, ArH), 6.65 (s, 1H, ArH), 4.27 (m, 1H, ArCH$_2$(CH$_3$)CHNH$_2$), 3.83 (s, 3H, 2 × OCH$_3$), 2.75 (d, 2H, J = 7.0, ArCH$_2$), 2.45 (s, 3H, CH_3S), 1.20 (d, 3H, J = 7.0 Hz, ArCH$_2$(CH_3)CHNH$_2$). HREIMS *m/z* calcd for $C_{13}H_{19}NO_3S$ (M) 269.1086, found 269.1089.

***N*-Formyl-1-(2,5-dimethoxy-4-ethylthiophenyl)-2-aminopropane (10b).** The product was obtained in 77% yield as white crystals, mp 130−134 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.00 (s, 1H, *N*-CHO), 6.76 (s, 1H, ArH), 6.68 (s, 1H, ArH), 4.22 (m, 1H, ArCH$_2$(CH$_3$)CHNH$_2$), 3.80 (s, 3H, 2 × OCH$_3$), 2.78−2.64 (m, 4H, CH$_3$$CH_2$S and ArCH$_2$), 1.34 (d, 3H, J = 7.0 Hz, ArCH$_2$(CH_3)CHNH$_2$), 1.30 (t, 3H, J = 7.0 Hz, CH_3CH$_2$S). HREIMS *m/z* calcd for $C_{14}H_{21}NO_3S$ (M) 283.1242, found 283.1247.

***N*-Formyl-1-(2,5-dimethoxy-4-*n*-propylthiophenyl)-2-aminopropane (10c).** The product was obtained in 86% yield as white crystals, mp 120−123 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.98 (s, 1H, *N*-CHO), 6.78 (s, 1H, ArH), 6.59 (s, 1H, ArH), 4.19 (m, 1H, ArCH$_2$(CH$_3$)CHNH$_2$), 3.75 (s, 3H, OCH$_3$), 3.77 (s, 3H, OCH$_3$), 2.80−2.60 (m, 4H, CH$_3$CH$_2$$CH_2$S and ArCH$_2$), 1.60 (sextuplet, 2H, J = 7.0 Hz, CH$_3$$CH_2CH_2$S), 1.14 (d, 3H, J = 7.0 Hz, ArCH$_2$(CH_3)CHNH$_2$), 0.96 (t, 3H, J = 7.0 Hz, CH_3CH$_2$CH$_2$S). HREIMS *m/z* calcd for $C_{15}H_{23}NO_3S$ (M) 297.1399, found 297.1402.

***N*-Formyl-1-(2,5-dimethoxy-4-methylthiophenyl)-2-aminobutane (11a).** The product was obtained in 75% yield as white crystals, mp 147−148 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.09 (s, 1H, *N*-CHO), 6.76 (s, 1H, ArH), 6.66 (s, 1H, ArH), 4.14 (m, 1H, ArCH$_2$(CH$_3$)CHNH$_2$), 3.85 (s, 3H, OCH$_3$), 3.83 (s, 3H, OCH$_3$), 2.82−2.76 (m, 2H, ArCH$_2$), 2.44 (s, 3H, SCH$_3$), 1.59 (m, 2H, CH$_3$$CH_2$CHNH$_2$), 0.98 (t, 3H, J = 7.0 Hz, CH_3CH$_2$CHNH$_2$). HREIMS *m/z* calcd for $C_{14}H_{21}NO_3S$ (M) 283.1242, found 283.1246.

***N*-Formyl-1-(2,5-dimethoxy-4-ethylthiophenyl)-2-aminobutane (11b).** The product was obtained in 86% yield as white crystals, mp 128−132 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.01 (s, 1H, *N*-CHO), 6.77 (s, 1H, ArH), 6.61 (s, 1H, ArH), 4.09 (m, 1H, CH$_3$CH$_2$$CHNH_2$), 3.76 (s, 3H, OCH$_3$), 3.73 (s, 3H, OCH$_3$), 2.84 (cuad, 3H, J = 7.0 Hz, CH$_3$$CH_2$S), 2.77−2.57 (m, 2H, ArCH$_2$), 1.51 (m, 2H, CH$_3$$CH_2$CHNH$_2$), 1.22 (t, 3H, J = 7.0 Hz, CH_3CH$_2$S), 0.90 (t, 3H, J = 7.0 Hz, CH_3CH$_2$-CHNH$_2$). HREIMS *m/z* calcd for $C_{15}H_{23}NO_3S$ (M) 297.1399, found 297.1395.

***N*-Formyl-1-(2,5-dimethoxy-4-*n*-propylthiophenyl)-2-aminobutane (11c).** The product was obtained in 91% yield as white crystals, mp 117−119 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.04 (s, 1H, *N*-CHO), 6.79 (s, 1H, ArH), 6.64 (s, 1H, ArH), 4.10 (m, 1H, CH$_3$CH$_2$$CHNH_2$), 3.80 (s, 3H, OCH$_3$), 3.76 (s, 3H, OCH$_3$), 3.00−2.79 (m, 4H, Ar$CH_2$ and CH$_3$CH$_2$$CH_2$S), 1.68−1.58 (m, 4H, CH$_3$$CH_2$CHNH$_2$ and CH$_3$$CH_2CH_2$S), 0.98−0.92 (m, 6H, CH_3CH$_2$CH$_2$S and CH_3CH$_2$CHNH$_2$). HREIMS *m/z* calcd for $C_{16}H_{25}NO_3S$ (M) 311.1555, found 311.1557.

General Procedure for the Reduction of the *N*-Formamides (10a−c and 11a−c). The *N*-methylamines were prepared from the corresponding formamides **10a−c** and **11a−c)** using the same quantities and procedures described above for the preparation of primary amines **8a−g** and **9a−c**.

***N*-Methyl-1-(2,5-dimethoxy-4-methylthiophenyl)-2-aminopropane Hydrochloride (12a).** The product was obtained in 77% yield as white crystals, mp 130−131 °C. ^{1}H NMR (500 MHz, D$_2$O): δ 6.93 (s, 1H, ArH), 6.91 (s, 1H, ArH), 3.84 (s, 6H, 2 × OCH$_3$), 3.52 (m, 1H, ArCH$_2$(CH$_3$)CHNH$_2$), 3.03−2.87 (dd, dd, 2H, J = 7.0 Hz, ArCH_2), 2.68 (s, 3H, NCH$_3$), 2.46 (s, 3H, CH$_3$S), 1.24 (d, 3H, J = 7.0 Hz, ArCH$_2$(CH_3)-CHNH$_2$). Anal. ($C_{13}H_{22}ClNO_2S$) C, H, N, S.

***N*-Methyl-1-(2,5-dimethoxy-4-ethylthiophenyl)-2-aminopropane Hydrochloride (12b).** The product was obtained in 88% yield as white crystals, mp 130−134 °C. ^{1}H NMR (300 MHz, D_2O): δ 6.96 (s, 1H, ArH), 6.87 (s, 1H, ArH), 3.78 (s, 6H, 2 × OCH_3), 3.48 (m, 1H, $ArCH_2(CH_3)CHNH_2$), 3.00−2.79 (m, 4H, $ArCH_2$ and CH_3CH_2S), 2.64 (s, 3H, NCH_3), 1.21−1.17 (m, 6H, $ArCH_2(CH_3)CHNH_2$ and CH_3CH_2S). Anal. ($C_{14}H_{24}ClNO_2S$) C, H, N, S.

***N*-Methyl-1-(2,5-dimethoxy-4-*n*-propylthiophenyl)-2-aminopropane Hydrochloride (12c).** The product was obtained in 67% yield as white crystals, mp 124−125 °C. ^{1}H NMR (300 MHz, D_2O): δ 6.88 (s, 1H, ArH), 6.82 (s, 1H, ArH), 3.76 (s, H, 2 × OCH_3), 3.47 (sextuplet, 1H, J = 7.0 Hz, $ArCH_2(CH_3)CHNH_2$), 2.97−2.74 (m, 4H, $ArCH_2$ and $CH_3CH_2CH_2S$), 2.63 (s, 3H, NCH_3), 1.54 (sextuplet, 2H, J = 7.0 Hz, $CH_3CH_2CH_2S$), 1.17 (d, 3H, J = 7.0 Hz, $ArCH_2(CH_3)CHNH_2$), 0.90 (t, 3H, J = 7.0 Hz, $CH_3CH_2CH_2S$). Anal. ($C_{15}H_{26}ClNO_2S$) C, H, N, S.

***N*-Methyl-1-(2,5-dimethoxy-4-methylthiophenyl)-2-aminobutane Hydrochloride (13a).** The product was obtained in 71% yield as white crystals, mp 152−154 °C. ^{1}H NMR (500 MHz, D_2O): δ 6.93 (s, 1H, ArH), 6.91 (s, 1H, ArH), 3.84 (s, 3H, 2 × OCH_3), 3.40 (m, 1H, $CH_3CH_2CHNH_2$), 2.98 (d, 2H, J = 7.0 Hz, $ArCH_2$), 2.68 (s, 3H, NCH_3), 2.46 (s, 3H, CH_3S), 1.67 (m, 2H, $CH_3CH_2CHNH_2$), 0.99 (t, 3H, J = 7.0 Hz, $CH_3CH_2CHNH_2$). Anal. ($C_{14}H_{24}ClNO_2S$) C, H, N, S.

***N*-Methyl-1-(2,5-dimethoxy-4-ethylthiophenyl)-2-aminobutane Hydrochloride (13b).** The product was obtained in 92% yield as white crystals, mp 137−139 °C. ^{1}H NMR (300 MHz, D_2O): δ 7.10 (s, 1H, ArH), 7.04 (s, 1H, ArH), 3.95 (s, 6H, 2 × OCH_3), 3.52 (m, 1H, $CH_3CH_2CHNH_2$), 3.10 (m, 4H, CH_3CH_2S and $ArCH_2$), 2.82 (s, 3H, NCH_3), 1.79 (m, 2H, $CH_3CH_2CHNH_2$), 1.36 (t, 3H, J = 7.0 Hz, CH_3CH_2S), 1.10 (t, 3H, J = 7.0 Hz, $CH_3CH_2CHNH_2$). Anal. ($C_{15}H_{26}ClNO_2S$) C, H, N, S.

***N*-Methyl-1-(2,5-dimethoxy-4-*n*-propylthiophenyl)-2-aminobutane Hydrochloride (13c).** The product was obtained in 84% yield as white crystals, mp 134−137 °C. ^{1}H NMR (300 MHz, D_2O): δ 6.94 (s, 1H, ArH), 6.85 (s, 1H, ArH), 3.78 (s, 6H, 2 × OCH_3), 3.36 (quintuplet, 1H, J = 7.0 Hz, $CH_3CH_2CHNH_2$), 2.92−2.85 (m, 4H, $ArCH_2$ and $CH_3CH_2CH_2S$), 2.65 (s, 3H, NCH_3), 1.66−1.53 (m, 4H, $CH_3CH_2CHNH_2$ and $CH_3CH_2CH_2S$), 0.94 (m, 6H, $CH_3CH_2CH_2S$ and $CH_3CH_2CHNH_2$). Anal. ($C_{16}H_{28}ClNO_2S$) C, H, N, S.

3,5-Dimethoxyphenol (15). Concentrated H_2SO_4 (0.41 mol) was added dropwise to a stirred solution of phloroglucinol **14** (0.32 mol) in absolute MeOH (200 mL). The reaction was exothermic, and the temperature was kept below 80 °C during the addition. The mixture was heated at reflux with stirring for 24 h and was then allowed to cool to room temperature. Excess MeOH was removed by rotary evaporation, and the black residue was purified by vacuum distillation (120−130 °C/0.1 Torr) to afford a colorless oil. The distilled oil was a mixture of the three *O*-methyl derivatives. The monomethyl compound was removed by suspending the mixture in 10% K_2CO_3 and extracting with toluene (3 × 75 mL). The toluene extracts were concentrated, and the desired product was obtained by column chromatography over silica, eluting with ethyl acetate:hexane (1:4), to yield a colorless oil (47%) that solidified on standing; mp: 38−40 °C (lit.[19] mp 35−38 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.08 (t, 1H, J = 2.0 Hz, ArH), 6.03 (d, 2H, J = 2.0 Hz, ArH), 5.53 (bs., 1H, ArOH), 3.74 (s, 6H, 2 × OCH_3).

***O*-(3,5-Dimethoxyphenyl)dimethyl thiocarbamate (16).** This product was prepared by a reported procedure.[36] It was obtained in 47% yield as a white powder; mp 76−77 °C (lit.[36] m.p 77−78 °C).^{1}H NMR (300 MHz, $CDCl_3$): δ 6.36 (t, 1H, J = 2.0 Hz, ArH), 6.25 (d, 2H, J = 2.0 Hz, ArH), 3.77 (s, 6H, 2 × OCH_3), 3.45 (s, 3H, CH_3N), 3.32 (s, 3H, CH_3N).

***S*-(3,5-Dimethoxyphenyl)dimethyl thiocarbamate (17).** This product was prepared by the reported method.[36] It was obtained in 100% yield as a light-yellow crystals; mp 36−38 °C, lit.,[36] mp 36−38 °C).^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (d, 2H, J = 2.0 Hz, ArH), 6.48 (t, 1H, J = 2.0 Hz, ArH), 3.78 (s, 6H, 2 × OCH_3), 3.05 (s, 6H, $(CH_3)_2N$).

3,5-Dimethoxybenzenethiol (18). The product was obtained in 99% yield as a colorless oil, by the reported procedure.[36] The product was purified by bulb-to-bulb distillation (80−85 °C/0.1 Torr). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.43 (d, 2H, J = 2.0 Hz, ArH), 6.27 (t, 1H, J = 2.0 Hz, ArH), 3.76 (s, 6H, 2 × OCH_3), 3.50 (s, 1H, SH).

1,3-Dimethoxy-5-methylthiobenzene (19a). The product was obtained from **18** in 98% yield as a colorless oil, by a modification of the literature method,[36] using Me_2SO_4 instead of the reported iodomethane. The material was purified by bulb-to-bulb distillation (80−85 °C/0.03 Torr). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.40 (d, 2H, J = 2.0 Hz, ArH), 6.23 (t, 1H, J = 2.0 Hz, ArH), 3.76 (s, 6H, 2 × OCH_3), 2.45 (s, 3H, CH_3S).

1,3-Dimethoxy-5-ethylthiobenzene (19b). The product was obtained in 80% yield as a colorless oil, using the same procedure described for **19a** but with ethyl bromide as the alkylation agent. The product was purified by bulb-to-bulb distillation (80−85 °C/0.1 Torr). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.48 (d, 2H, J = 2.0 Hz, ArH), 6.28 (t, 1H, J = 2.0 Hz, ArH), 3.79 (s, 6H, 2 × OCH_3), 2.95 (q, 2H, J = 7.0 Hz, CH_3CH_2S), 1.34 (t, 3H, J = 7.0 Hz, CH_3CH_2S). HREIMS *m/z* calcd for $C_{10}H_{14}O_2S$ (M) 198.0715, found 198.0714.

General Procedure for the Preparation of Aldehydes 20a and 20b. To a stirred solution of the precursor **19a** or **19b** in dry Et_2O (30 mL) at −78 °C and under argon was added TMEDA (10.0 mmol). To this mixture was added *n*-BuLi 2.5 M in hexane (600 mmol) dropwise over 30 min. The mixture was allowed to warm to room temperature and stirred for 1 h, and then dry DMF (20.0 mmol) was added dropwise. The mixture was stirred for an additional 1 h and was then poured into 5% v/v H_2SO_4 (100 mL). The two layers were separated, and the aqueous layer was extracted with Et_2O (3 × 75 mL). The organic layers were combined and dried with anhydrous Na_2SO_4, and the solvent was evaporated. The product was crystallized from MeOH.

2,6-Dimethoxy-4-methylthiobenzaldehyde (20a). The product was obtained in 60% yield as light yellow crystals, mp 81−82 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.40 (s, 1H, CHO), 6.40 (s, 2H, ArH), 3.90 (s, 6H, 2 × OCH_3), 2.54 (s, 3H, CH_3S). ESIMS 213 (MH^+). Anal. ($C_{10}H_{12}O_3S$) C, H, S.

2,6-Dimethoxy-4-ethylthiobenzaldehyde (20b). This compound was obtained in 87% yield as light yellow crystals, mp 85−86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.40 (s, 1H, CHO), 6.43 (s, 2H, ArH), 3.89 (s, 6H, 2 × OCH_3), 3.05 (q, 2H, J = 7.0 Hz, CH_3CH_2S), 1.40 (t, 3H, J = 7.0 Hz, CH_3CH_2S). HREIMS *m/z* calcd for $C_{11}H_{14}O_3S$ (M) 226.0664, found 226.06671.

1-(2,6-Dimethoxy-4-methylthiophenyl)-2-nitropropene (21a). This compound was obtained in 80% yield as light orange cotton-like needles, with the procedure used for the preparation of arylnitroethanes **6a**−**g**; mp 147−149 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (s, 1H, $ArCHCNO_2$), 6.52 (s, 2H, ArH), 3.90 (s, 6H, 2 × OCH_3), 2.60 (s, 3H, CH_3S), 2.15 (s, 3H, CH_3CNO_2). HREIMS *m/z* calcd for $C_{12}H_{15}NO_4S$ (M) 269.0722, found 269.0723.

1-(2,6-Dimethoxy-4-ethylthiophenyl)-2-nitropropene (21b). This compound was obtained in 82% yield as light orange cotton-like needles, with the procedure used for the preparation of arylnitroethanes **6a**−**g**; mp 77−78 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (s, 1H, $ArCHCNO_2$), 6.52 (s, 2H, ArH), 3.84 (s, 6H, 2 × OCH_3), 3.01 (q, 2H, J = 7.0 Hz, CH_3CH_2S), 2.10 (s, 3H, CH_3CNO_2), 1.39 (t, 3H, J = 7.0 Hz, CH_3CH_2S). HREIMS *m/z* calcd for $C_{13}H_{17}NO_4S$ (M) 283.0878, found 283.0874.

1-(2,6-Dimethoxy-4-methylthiophenyl)-2-aminopropane Hydrochloride (22a). This compound was obtained in 58% yield as white crystals, with the procedure used for the preparation of **8 a**−**g**; mp 248−246 °C. ^{1}H NMR (300 MHz, D_2O): δ 6.62 (s, 2H, ArH), 3.80 (s, 6H, 2 × OCH_3), 3.50 (sextuplet, 1H, J = 7.0 Hz, $CHNH_2$), 2.85 (d, 2H, J = 7.0 Hz, $ArCH_2$), 2.50 (s, 3H, CH_3S), 1.22 (d, 3H, J = 7.0 Hz, $ArCH_2(CH_3)CHNH_2$). Anal. ($C_{13}H_{17}NO_4S$) C, H, N, S.

1-(2,6-Dimethoxy-4-ethylthiophenyl)-2-aminopropane Hydrochloride (22b). This compound was obtained in 48% yield as white crystals, with the procedure used for the preparation of **8 a**−**g**; mp 165−166 °C. ^{1}H NMR (300 MHz, D_2O): δ 6.65 (s, 2H, ArH), 3.77 (s, 6H, 2 × OCH_3), 3.49 (sextuplet, 1H, J = 7.0 Hz, CHNH$_2$), 2.98 (q, 2H, J = 7.0 Hz, CH_3CH_2S), 2.84 (d, 2H, J = 7.0 Hz, ArCH_2), 1.23 (t, 3H, J = 7.0 Hz, CH_3CH$_2$S), 1.22 (d, 3H, J = 7.0 Hz, ArCH$_2$(CH_3)-CHNH$_2$). Anal. ($C_{13}H_{23}ClNO_2S$) C, H, N, S.

2-Chloro-4,6-dimehoxybenzaldehyde (25). This compound was obtained from **23** in 78% yield as light yellow crystals, by the reported procedure;[37] mp 78−80 °C, (lit.[37] mp 79−80 °C).

1-(2-Chloro-4,6-dimethoxyphenyl)-2-nitro-1-propene (27). This compound was obtained from **25** in 82% yield as orange crystals, with the procedure described for the preparation of **6a**−**g**; mp 121−124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (s, 1H, ArCH), 6.61 (d, 1H, J = 2.0 Hz, ArH), 6.40 (d, 1H, J = 2.0 Hz, ArH), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.10 (s, 3H, CH_3CNO_2). HREIMS *m/z* calcd for $C_{11}H_{12}ClNO_4$ (M) 257.0455, found 257.0458.

1-(2-Chloro-4,6-dimethoxyphenyl)-2-aminopropane Hydrochloride (29). This compound was obtained from **27** in 45% yield as white crystals, by the procedure described for the preparation of **8a**−**g**, mp 190−193 °C. ^{1}H NMR (300 MHz, D_2O): δ 6.70 (d, 1H, J = 2.0 Hz, ArH), 6.52 (d, 1H, J = 2.0 Hz, ArH), 3.80 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.57 (sextuplet, 1H, ArCH$_2$(CH_3)CHNH$_2$), 2.98 (d, 2H, J = 7.0 Hz, ArCH$_2$), 1.30 (d, 3H, J = 7.0 Hz, CH_3CNH$_2$). Anal. ($C_{11}H_{17}Cl_2NO_2$) C, H, N.

2,4,6-Trimethoxybenzaldehyde (26). This compound was obtained from **24** in 85% yield as light yellow crystals, using the procedure described by Shulgin and Shulgin,[17] mp 119−121 °C (lit.[17] mp 115−116 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.40 (s, 1H, CHO), 6.60 (s, 2H, ArH), 3.90 (s, 6H, 2 × OCH_3), 3.85 (s, 3H, OCH_3).

1-(2,4,6-Trimethoxyphenyl)-2-nitro-1-propene (28). This compound was obtained from **26** in 82% yield as orange crystals, using the procedure described by Shulgin and Shulgin;[17] mp 144−147 °C (lit.[17] mp 147−148 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H, ArCH), 6.15 (s, 2H, ArH), 3.85 (s, 3H, OCH_3), 3.80 (s, 6H, 2 × OCH_3), 2.10 (s, 3H, CH_3CNO_2).

1-(2,4,6-Trimethoxyphenyl)-2-aminopropane Hydrochloride (30). This compound was obtained from **28** in 45% yield as white crystals, using the procedure described by Shulgin and Shulgin;[17] mp 208−212 °C, (lit.[17] mp 207−208 °C). ^{1}H NMR (300 MHz, D_2O): δ 6.30 (s, 2H, ArH), 3.80 (s, 3H, OCH_3), 3.75 (s, 6H, 2 × OCH_3), 3.49 (sextuplet, 1H, CH$_2$(CH_3)-CHNH$_2$), 2.80 (d, 2H, J = 7.0 Hz, ArCH$_2$), 1.20 (d, 3H, J = 7.0 Hz, CH$_2$(CH_3)CHNH$_2$). Anal. ($C_{12}H_{20}ClNO_3$) C, H, N.

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Supporting Information Available: Elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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