Design and Synthesis of Aryloxyethyl Thiocyanate Derivatives as Potent Inhibitors of *Trypanosoma cruzi* Proliferation

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As a part of our project directed at the search of new chemotherapeutic agents against American trypanosomiasis (Chagas' disease), several drugs possessing the 4-phenoxyphenoxy skeleton and other closely related structures employing the thiocyanate moiety as polar end group were designed, synthesized, and evaluated as antiproliferative agents against *Trypanosoma cruzi*, the parasite responsible for this disease. These thiocyanate analogues were envisioned bearing in mind the potent activity shown by 4-phenoxyphenoxyethyl thiocyanate (compound **8**) taken as lead drug. This compound had previously proved to be an extremely active growth inhibitor against *T. cruzi* with IC_{50} values ranging from the very low micromolar level in epimastigotes to the low nanomolar level in the intracellular form of the parasite. Of the designed compounds, the ethyl thiocyanate drugs connected to nonpolar skeletons, namely, arylthio, 2,4-dichlorophenoxy, ortho-substituted aryloxy, and 2-methyl-4-phenoxyphenoxy (compounds **15**, **34**, **47**, **52**, **72**, respectively), were shown to be very potent antireplicative agents against *T. cruzi*. On the other hand, conformationally restricted analogues as well as branched derivatives at the aliphatic side chain were shown to be moderately active against *T. cruzi* growth. The biological activity of drugs bearing the thiocyanate group correlated quite well with the activity exhibited by their normal precursors, the tetrahydropyranyl ether derivatives, when bonded to the same nonpolar skeleton. Compounds having the tetrahydropyranyl moeity as polar end were proportionally much less active than sulfur-containing derivatives in all cases. Drugs **47** and **72** also resulted to be very active against the amastigote form of the parasite growing in myoblasts; however, they were slightly less active than the lead drug **8**. On the other hand, compounds **34** and **52** were almost devoid of activity against myoblasts. Surprisingly, the dithio derivative **15** was toxic for myoblasts.

Introduction

American trypanosomiasis (Chagas' disease), caused by the kinetoplastid protozoon *Trypanosoma cruzi*, is considered by the Word Health Organization to be one of the important tropical parasitic diseases worldwide together with malaria and schistosomiasis. This major health problem afflicts 16−18 million persons in Latin America, who are infected with *T. cruzi*.[1] At the present time, it was calculated that around of 2−3 million people present the typical symptoms that characterize the chronic stage of American trypanosomiasis producing 45 000 deaths yearly.[2] This illness is transmitted in rural areas to humans and other mammals by Reduviid bugs, for instance *Rhodnius prolixus* and *Triatoma infestans*,[3,4] as a consequence of the blood-sucking activity of Chagas' disease vectors on mammals when feeding in a cyclic process. The parasite occurs in three main morphological forms in a complex life cycle. It multiplies within the crop and midgut of Chagas' disease vectors as the epimastigote form, and it is released with the insect excrements as the nondividing highly infective metacyclic trypomastigotes that invade mammalian tissues via wounds provoked by blood-sucking action. The parasite proliferates intracellularly as the amastigote, the clinically more important form of the parasite, which is released as the nondividing bloodstream trypomastigote forms that invade other tissues.[3,4]

In the past few years a tremendous impetus in the study of *T. cruzi* biochemistry and physiology has been observed.[5] As a result of these studies, several crucial enzymes for parasite survival and not present in the host have been identified as potential targets for the design of new drugs.[6−11] However, the existing chemotherapy to control this parasitic infection is based on old and quite unspecific drugs associated with long-term treatments and severe side effects. Certainly, the only two drugs currently in use for clinical treatment of this disease, nifurtimox (4-([5-nitrofurfurylidene]amino)-3-methylthiomorpholine 1,1-dioxide) and benznidazole (*N*-benzyl-2-nitro-1-imidazoleacetamide), are able to cause negativization of parasitemia and serology in most of the cases.[12,13] However, they are not specific enough to all *T. cruzi* strains to warrant complete cure and hence the divergence of efficacy observed for both drugs in different endemic areas.[14−17] Due to the chemotherapy

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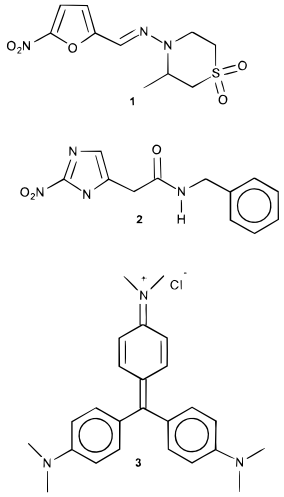
Chart 1. Current Drugs for Treatment of Chagas' Disease and Blood Sterilization

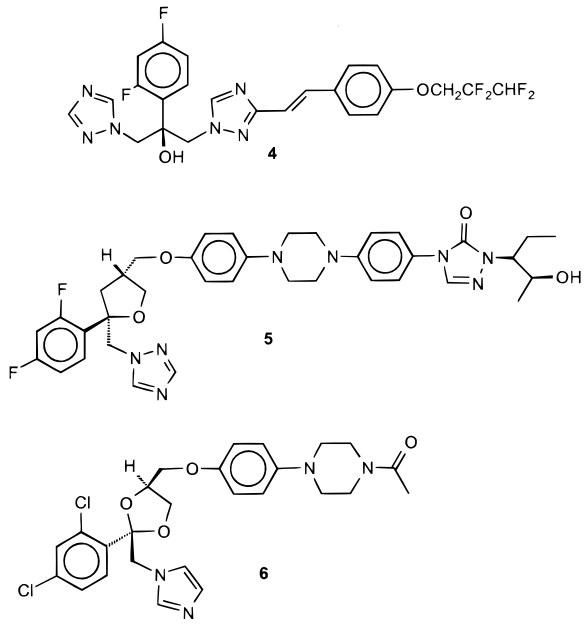


drawbacks, there is significant interest in developing novel chemotherapeutic approaches against Chagas' disease based on unique aspects of *T. cruzi* structure and metabolism. Moreover, the chronic stage of this disease leads to irreversible cardiac and digestive disorders and is the leading cause of heart disease in Latin America with close to 90 million people at risk. Many chagasic patients die from heart failure associated with cardiomyopathy during the chronic phase of the disease, while in the acute phase myocarditis occurs in near 60% of patients with an estimated 9% of mortality occurring in endemic areas.[18] In addition, the main way of transmission in large urban centers takes place by transfusion of infected blood or through the placenta. This kind of mechanism is responsible for the occurrence of Chagas' disease in countries where this illness is not endemic. In the past few years, this illness has been encountered, in the United States, as a consequence of transfusion of contaminated blood from immigrants.[19−21] For that reason, it is very important to have an efficient agent to eradicate the bloodstream trypomastigotes from blood banks. Crystal violet (*N*-{4-bis[[4-(dimethylamino)phenyl]methylene]-2,5-cyclohexadien-1-ylidene}-*N*-methylmethanaminium chloride), the only drug employed for blood sterilization and discovered for that purpose some decades ago,[22] cannot be considered as an ideal drug. In fact, this agent suffers from some disadvantages, since it was shown to be carcinogenic in in vivo assays[23] (Chart 1).

The above summary emphasizes the urgent need of new chemotherapeutic and chemoprophylactic agents that are specific and effective against all strains of the parasite with less or no toxicity than that produced by the drugs currently in use for clinical therapy.

Ergosterol biosynthesis proved to be an interesting target for the design of new drugs not only for fungi but also for different pathogenic parasites.[24] Sterol biosynthesis in parasites differs essentially compared with the mammalian host due to the final product in the latter biosynthetic pathway leads to cholesterol.[24] Depletion of endogenous sterols produces inhibition of growth of the parasite; therefore, selective inhibition of a crucial enzyme responsible of sterol biosynthesis of the parasite will slow *T. cruzi* growth. The blockage of this metabolic

Chart 2. Chemical Structures of Three Well-Known Sterol Biosynthesis Inhibitors That Are Effective Against *T. cruzi*



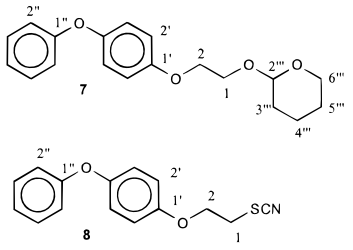
pathway has been extensively studied, and even some drugs resulted to be potential chemotherapeutic agents such as the bis triazole derivatives D0870 and SCH 56592 (compounds **4** and **5**, respectively) and the triazole derivative **6**, ketoconazole (Chart 2).[25−29]

We have reported that several compounds structurally related to the well-known insect growth regulator fenoxycarb[30] (*N*-{2-[(4-phenoxyphenoxy)ethyl]}ethyl carbamate) are very active trypanostatic agents. In fact, slight modifications on the fenoxycab side chain give drugs **7** and **8** and other closely related compounds, which are shown to be potent inhibitors against *T. cruzi* growth.[31−35] The molecule of fenoxycarb had been taken as lead structure on the basis that Chagas' disease vector treated with this compound was less susceptible to natural infection with *T. cruzi* than untreated controls.[36] These interesting results led to evaluate several modified structures, which had previously shown to be active on the Chagas' disease vector *Triatoma infestans*,[37,38] against the parasite establishing a good correlation between trypanostatic activity and juvenile hormone action[39] and suggesting a mechanism of infection control. There is strong evidence that the target of 4-phenoxyphenoxy derivatives is the ergosterol biosynthetic pathway. When *T. cruzi* epimastigotes are treated with the thiocyanate derivative **8**, an accumulation of low molecular weight metabolites from mevalonate to squalene is observed (Chart 3).[40]

Compounds **7** and **8** and other sulfur-containing derivatives were also effective agents against amastigotes,[32,41,42] the clinically more relevant form of the parasite, and as observed for other sterol biosynthesis inhibitors, they were devoid of capacity to eradicate the nondividing highly infective trypomastigotes.[43]

Bearing in mind the ultrapotent activity exhibited by drug **8** (4 times more active than nifurtimox in epimastigotes and significantly more active in amastigotes, under the same assays conditions),[32] a new set of related compounds having the aryloxyethyl thiocyanate moiety

Chart 3. Chemical Structures of Two Representative Inhibitors of *T. cruzi* Proliferation Structurally Related to Fenoxycarb Taken as Lead Drug



was designed, synthesized, and biologically evaluated against *T. cruzi* cells in order to establish a structure−activity relationship and to refine the inhibitory action already observed. It is important to point out that the tetrahydropyranyl derivatives related to drug **7** are the common intermediate for the preparation of thiocyanates, so it will be of interest to compare their biological activity with the final products, that is, the thiocyanate-containing drugs.

Rationale

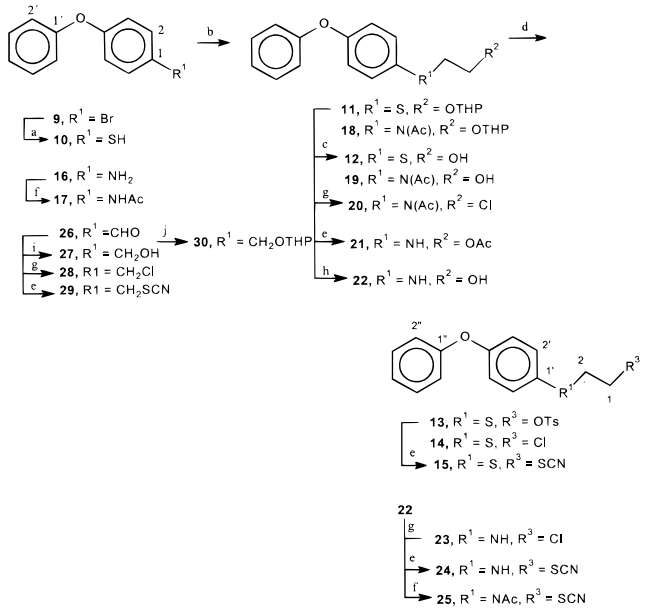
The introduction of a sulfur atom at the polar extreme in a series of 4-phenoxyphenoxyethyl derivatives and closely related compounds gives rise to extremely potent inhibitors against *T. cruzi* proliferation. The replacement of this sulfur atom by an oxygen atom brings about a dramatic impairing in the biological activity. On the other hand, the 4-phenoxyphenoxy unit is also very important to maintain high inhibitory values against *T. cruzi* growth, because replacement of the terminal phenoxy group by methoxy or benzoyl groups has a marked effect in the biological action producing moderately active drugs.[33,34] The preparation of the new drugs in the present study was motivated by the potent activity shown by the lead structure **8**. The incorporation of the thiocyanate moiety at the terminal aliphatic chain of 4-phenoxyphenoxy derivatives and closely related compounds gives rise to potent growth inhibitors of *T. cruzi*. Therefore a new set of related compounds possessing the aryloxyethyl thiocyanate moieties was designed, prepared, and evaluated against the epimastigote forms of *T. cruzi* which is the preferred form to test new drugs.

Bearing in mind the unusual biological activity exhibited by sulfur-containing derivatives at C-1, it was likely that minor modifications in the vicinity of this position would have a strong effect on the biological activity. The replacement of the oxygen atom between the phenyl group and the aliphatic side chain (C-2) by other heteroatoms (sulfur or nitrogen) was the first modification considered. The designed drugs **11** and **15** were straightforwardly prepared from 4-bromodiphenyl ether (compound **9**). This compound treated with metallic magnesium gave rise to the respective Grignard reagent that, on reaction with sulfur followed by reduction with lithium aluminum hydride,[44] produced the respective thiophenol **10** in theoretical yield. Compound **10** was transformed into the tetrahydropyranyl ether derivative **11** by treatment with 2-bromoethyl tetrahydro-2*H*-pyran-2-yl ether in a suspension of potassium hydroxide in dimethyl sulfoxide, via a modified Williamson procedure.[45] Cleavage of the tetrahydropyranyl group of **11** with pyridinium *p*-toluenesulfonate[46] produced alcohol **12**, which after treatment with tosyl chloride gave tosylate **13** and the undesired chloride derivative (compound **14**) as a side product. Tosylate **13** reacted with potassium thiocyanate in *N*,*N*-dimethylformamide at 100 °C to yield the desired thiocyanate derivative **15**.[47] The nitrogen-containing derivatives (compounds **18**, **24**, and **25**), replacing the oxygen atom at C-1′ by a nitrogen atom, were prepared following a similar synthetic approach employing 4-phenoxyaniline (**16**) as starting material. Attempts to alkylate the nitrogen atom of **16** with 2-bromoethyl tetrahydro-2*H*-pyran-2-yl ether were unsuccessful; however, the acetanilide derivative **17**, with a lower pK_a, was easily *N*-alkylated by treatment with 2-bromoethyl tetrahydro-2*H*-pyran-2-yl ether to afford compound **18** in almost quantitative yield. Removal of tetrahydropyranyl group with pyridinium *p*-toluenesulfonate gave alcohol **19**. The normal precursor to obtain thiocyanate derivatives was the corresponding tosylate because a good leaving group at C-1 has to be present; nonetheless an alkyl halide could be an alternate leaving group. Although **19** could not be tosylated under the usual conditions, this compound was transformed into the respective chloride (compound **20**) by treatment with triphenylphosphine in carbon tetrachloride.[48,49] Surprisingly, when **20** was treated with potassium thiocyanate in dimethylformamide it afforded acetate **21** instead of the expected thiocyanate derivative **25**. The formation of compound **21** can be rationalized by the anchimeric assistance of the neighbor acetate group. Hydrolysis of **21** with potassium carbonate led to **22** that reacted with triphenylphosphine in carbon tetrachloride to give **23** in good yield. Nucleophilic displacement with potassium thiocyanate afforded **24**. As preliminary biological assays had indicated that **18** exhibited similar inhibitory action as the parent drug **8**, it was of interest to prepare the acetylated analogue of **24**. Therefore, compound **24** reacted with acetic anhydride in pyridine to yield **25** (Scheme 1).

As a second variation, the replacement of the ethoxy unit in the lead drug **8** by a methylene group to give thiocyanate **29** was considered. This drug was easily prepared from 4-phenoxybenzaldehyde (compound **26**). On reaction with sodium borohydride,[50] **26** was converted into the alcohol **27**, which after treatment with triphenylphosphine in carbon tetrachloride−acetonitrile yielded the chloride **28**. Compound **28** reacted with potassium thiocyanate to yield the benzyl thiocyanate **29**. To correlate the biological activity of drug **29** with the tetrahydropyranyl ether analogue, compound **30** was easily prepared by treating alcohol **27** with 3,4-dihydro-2*H*-pyran in the presence of pyridinium *p*-toluenesulfonate (Scheme 2).

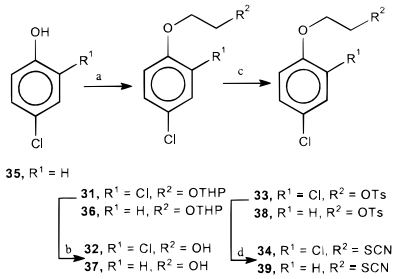
Previous biological assays had indicated that the tetrahydropyranyl ether **31**, in which the aromatic skeleton was a 2,4-dichlorophenyl group instead of a 4-phenoxyphenyl moiety, was 2-fold more active than its analogue **7**. Then, it was interesting to prepare the respective thiocyanate derivative from the readily available compound **31**, which after hydrolysis of the tetrahydropyranyl group followed by treatment with tosyl chloride and further nucleophilic attack of potassium thiocyanate led to drug **34**. To study the influence of

Scheme 1[a]



[a] Reagents: (a) i. Mg/I_2, THF, 65 °C, 15 min, then rt, 2 h, ii. S_8, 3 h, rt, iii. $LiAlH_4$, rt, 30 min (100%); (b) $BrCH_2CH_2OTHP$, KOH/DMSO, rt, 16 h (43% for **11**, 90% for **18**); (c) PPTs, MeOH, rt, (78% for **12**, 73% for **19**); (d) ClTs/py, rt, 4 h (85% for **13**, 9% for **14**); (e) KSCN, DMF, 100 °C, 5 h (100% for **15**, 95% for **21**, 39% for **24**, 13% for **29**); (f) Ac_2O/py, rt, 16 h (98% for **17**, 82% for **25**); (g) Ph_3P/Cl_4C, MeCN, rt, overnight (51% for **20**, 70% for **23**); (h) K_2CO_3, $MeOH-H_2O$, rt, 3 h; (i) $NaBH_4$, EtOH, rt, 2 h (84%); (j) PPTs, DHP, Cl_2CH_2, rt, (100%).

Scheme 2[a]

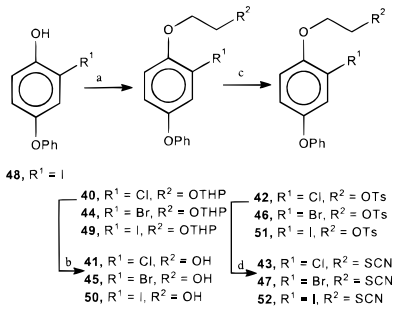


[a] Reagents: (a) $BrCH_2CH_2OTHP$, KOH/DMSO, rt, overnight (77%); (b) PPTs, MeOH, rt, (43% for **32**, 78% for **37**); (c) ClTs/py, rt, 4 h (53% for **33**, 92% for **38**); (d) KSCN, DMF, 100 °C, 5 h (70% for **34**, 63% for **39**).

the chlorine atom at C-2′ position on biological activity, the 4-phenyl group was envisioned. Therefore, employing 4-chlorophenol (compound **35**) as starting material, this compound was transformed into tetrahydropyranyl derivative **36**, which following a similar protocol as described for **34** was converted into thiocyanate **39** in good yield (Scheme 2).

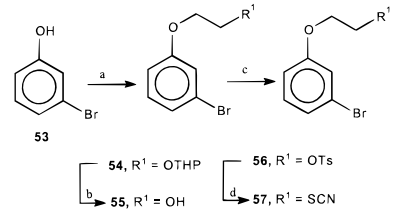
We have recently demonstrated[32] that the substitution of an ortho hydrogen atom of 4-phenoxyphenol by different groups exhibited a marked influence on biological activity. It has been found that the inhibitory potency increases as the substituent size increases. Then, it was reasonable to consider that the replacement in our lead drug **8** of the hydrogen atom at the C-2′ position by different halogen atoms would lead to more active drugs than **8**. For the above reasons, 4-phenoxyphenoxyethyl thiocyanates possessing chlorine, bromine, and iodine at C-2′ (drugs **43**, **47**, and **52**, respectively) were designed and synthesized. Consequently, using the halogen-containing derivatives 2-chloro-4-phenoxyphenoxyethyl and 2-bromo-4-phenoxyphenoxyethyl tetrahydropyranyl ethers (compounds **40** and **44**, respectively) as starting materials,[32] these compounds were converted into the desired thiocyanate derivatives **43** and **47** following a similar synthetic approach as depicted for compound **15**. The iodine derivative **52** was prepared from iodophenol **48**,[32] and this compound was converted into the tetrahydropyranyl derivative **49**, which was transformed into the desired drug employing a similar method for the preparation of **15** (Scheme 3).

Scheme 3[a]



[a] Reagents: (a) $BrCH_2CH_2OTHP$, KOH/DMSO, rt, overnight (68%); (b) PPTs, MeOH, rt, (42% for **41**, 64% for **45**, 59% for **50**); (c) ClTs/py, rt, 4 h (40% for **42**, 94% for **46**, 100% for **51**); (d) KSCN, DMF, 100 °C, 5 h (73% for **43**, 62% for **47**, 52% for **52**).

Scheme 4[a]



[a] Reagents: (a) $BrCH_2CH_2OTHP$, KOH/DMSO, rt, overnight (39%); (b) PPTs, MeOH, rt, (100%); (c) ClTs/py, rt, 4 h (75%); (d) KSCN, DMF, 100 °C, 5 h (54%).

Since halogen derivatives were very promising drugs it was decided to introduce a halogen atom at the meta position (C-3′). In this case, the designed drug was a simplified model of aryloxyethyl derivatives due to synthetic difficulties to carry out a substitution in 4-phenoxyphenoxy derivatives at this site. *m*-Bromophenol (**53**) was used as starting material. Following the usual synthetic methodology, **53** reacted with 2-bromoethyl tetrahydro-2*H*-pyran-2-yl ether to give **54**, which after cleavage of the protective group, tosylation and S_N2 reaction with the thiocyanate ion produced drug **57** (Scheme 4).

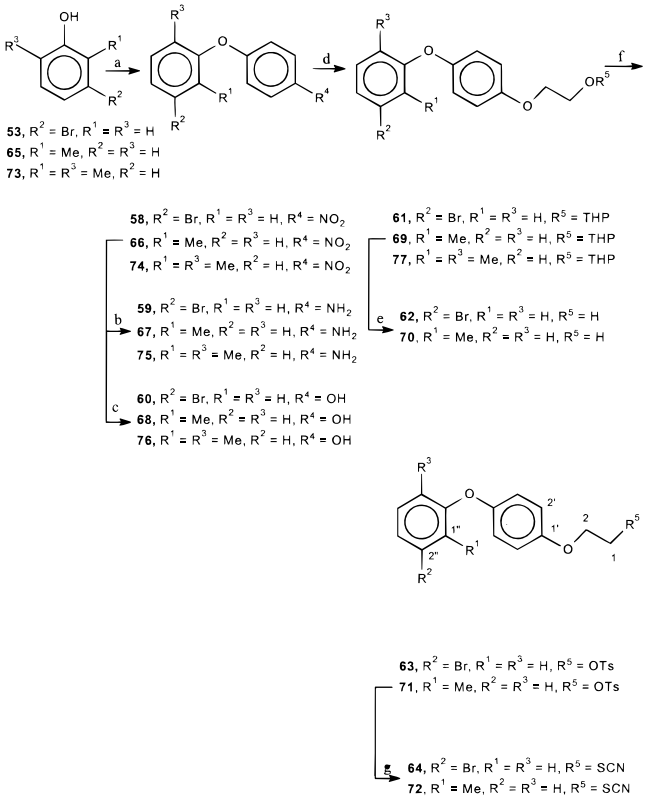
To study the influence of the relative spatial alignment of the phenyl groups on the biological activity, it was considered that the replacement of the hydrogen atom at the ortho position in the B ring (C-2″) would drive the phenyl groups to adopt a special conformation by van der Waals interactions. The synthesis of these kinds of 4-phenoxyphenoxy derivatives was not direct because the C-2″ is not activated for an electrophilic aromatic substitution. Therefore, the required phenol intermediates (compounds **60**, **68**, and **76**, respectively) to prepare the designed drugs were synthesized employing a nucleophilic aromatic substitution, an Ullmann

coupling reaction in this case, as the key step.[50] Thus, 3-bromophenol (compound **48**) was condensed with 4-nitrochlorobenzene in the presence of cuprous chloride to afford the nitro derivative **58** in good yield. This compound was reduced by catalytic hydrogenation employing palladium on charcoal as catalyst[51] to yield the aniline **59** in very good yield. On reaction with sodium nitrite in sulfuric acid in the presence of urea,[52] **59** was transformed into the phenol **60**. This modified Sandmeyer protocol occurred in moderate yield. Following the usual synthetic procedures the intermediate **60** led to compound **61** by treatment with 2-bromoethyl tetrahydro-2*H*-pyran-2-yl ether, which after tetrahydropyranyl cleavage, followed by tosylation and further nucleophilic displacement with potassium thiocyanate produced the desired thiocyanate **64** in good yield. The use of a group bigger than a bromine atom to replace the H-2″, namely a methyl unit, would give rise to stronger van der Waals forces than those present in compound **64** and its precursors. For that reason, it is quite reasonable to assume that the increment of the substituent size will lead to an increase in the torsion angles $\phi_{C2''-C1''-O1''-C4'}$, that is, a displacement out of the plane of one phenyl group with respect to the other one. Therefore, drugs **69** and **72** were synthesized starting from *o*-cresol via the phenol intermediate **70** employing the same synthetic strategy as depicted for the bromine derivatives **61** and **64**. Finally, the introduction of an extra methyl group at C-6″ was also considered in order to bring about strong van der Waals forces. Then, the preparation of compound **77** was successfully carried out employing 2,6-dimethylphenol as starting material; however, the respective Sandmeyer-type reaction to produce the corresponding phenol intermediate was not satisfactory in terms of the yield (Scheme 5).

Another interesting structural variation was the preparation of conformationally constrained 4-phenoxyphenoxy derivatives in order to investigate the influence of a specific restricted spatial disposition of both phenyl groups on biological activity. The skeleton of xanthone (compound **78**) would be a suitable template to prepare these rigid drugs. The C-2 and C-4 positions of the xanthone ring should be the more active sites for an electrophilic aromatic substitution reaction because they are para and ortho with respect to phenoxy group. However, reaction at the C-2 position would be more favorable than at C-4 due to absence of steric hindrances of the incoming electrophile. The nitration reaction at C-2 to form compound **79** was considered as the key step for the preparation of the tetrahydropyranyl and thiocyanate derivatives built on a rigid template because the nitro group can be readily converted into the corresponding phenol intermediate. The substitution of H-2 by a nitro group was satisfactory and carried out in detriment of the yield by adding 0.5 equiv of the nitrating agent (fuming nitric acid in concentrated sulfuric acid)[53] over a cold diluted solution of 1 equiv of xanthone in concentrated sulfuric acid. Xanthone was always in excess irrespective of the nitrating agent and the forming 2-nitroxanthone was less like to react with the NO_2^+ cation than the starting material **78**. Compound **79** was reduced by catalytic hydrogenation to form the rigid aniline **80** that on reaction with sodium nitrite in sulfuric acid at low temperature, and in the presence of urea, led to the hydroxy derivative **81**. Treatment of this compound with 2-bromoethyl tetrahydro-2*H*-pyran-2-yl ether afforded the conformationally constrained drug **82**. After the routine three synthetic steps, compound **82** was converted into the rigid thiocyanate **85** in good yield (Scheme 6).

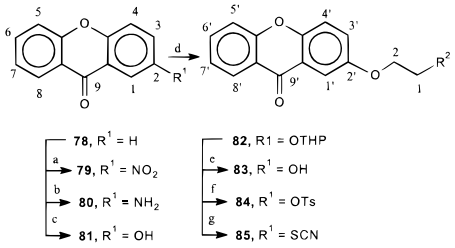
Since the presence of the thiocyanate group at the polar end of this family of drugs was hardly responsible for the ultrapotency observed, it would be predicted that slight modification in the aliphatic side chain would be a remarkable effect on biological activity. It was decided to attach a methyl group at the C-1 position of our lead drug **8**. The replacement of either the *pro-R* or *pro-S*

Scheme 5[a]



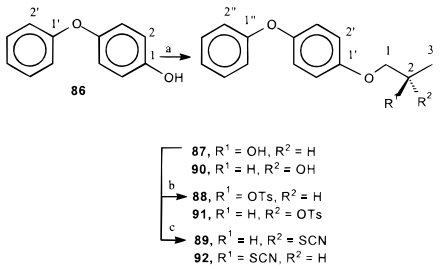
[a] Reagents: (a) 1-chloro-4-nitrobenzene, DMSO/KOH, CuCl, rt, 16 h (71% for **58**, 54% for **66**, 63% for **74**); (b) H_2, Pd/C 3 atm, rt, overnight (91% for **59**, 94% for **67**, 94% for **75**); (c) i. H_2SO_4/AcOH, ii. $NaNO_2$, H_2O, 0 °C, 20 min, iii. urea, H_2O, iv. H_2O/H_2SO_4, reflux (37% for **60**, 26% for **68**, 10% for **76**); (d) $BrCH_2CH_2OTHP$, KOH/DMSO, rt (60% for **61**, 60% for **69**, 54% for **77**); (e) PPTs, MeOH, rt (85% for **62**, 100% for **70**); (f) ClTs/py, rt (95% for **63**, 67% for **71**); (g) KSCN, DMF, 100 °C (71% for **64**, 50% for **72**).

Scheme 6[a]



[a] Reagents: (a) fuming HNO_3/H_2SO_4, 0 °C, 40 min; (b) H_2, Pd/C 3 atm, rt, 6 h (91% overall yield from **78**, based on the number of equiv of HNO_3 employed); (c) i. H_2SO_4/AcOH, ii. $NaNO_2$, H_2O, 0 °C, 20 min, iii. urea, H_2O, iv. H_2O/H_2SO_4, reflux (36%); (d) $BrCH_2CH_2OTHP$, KOH/DMSO, rt (45%); (e) PPTs, MeOH, rt (100%); (f) ClTs/py, rt (78%); (g) KSCN, DMF, 100 °C (71%).

Scheme 7[a]



[a] Reagents: (a) KOH, DMSO, *S*-propylene oxide or *R*-propylene oxide, rt, 6 h (20% for **87**, 15% for **90**); (b) ClTs/py, rt (87% for **88**, 84% for **91**); (c) KSCN, DMF, 100 °C (58% for **89**, 57% for **92**).

Table 1. Growth Inhibition against *T. cruzi* (Epimastigotes)

compd	IC_{50} (μM)	compd	IC_{50} (μM)
11	291	**15**	0.87[a]
18	211	**19**	277
24	141	**25**	14.4
29	18.7	**30**	102
34	1.0[b]	**36**	>390
39	14.1	**43**	24.5
47	1.4[d]	**49**	45
52	1.8[e]	**54**	104
57	<4[c]	**61**	138
64	2.9	**69**	143
72	2.7[f]	**77**	>60
82	>60	**85**	54
89	25	**92**	>82
ketoconazole, **6**	3.2	**8**	2.2[g,32]

[a] $IC_{90} = 32\ \mu M$. [b] $IC_{90} = 30\ \mu M$. [c] $IC_{90} = 27\ \mu M$. [d] $IC_{90} = 18\ \mu M$. [e] $IC_{90} = 23\ \mu M$. [f] $IC_{90} = 3.5\ \mu M$. [g] $IC_{90} = 3.5\ \mu M$.

hydrogen atoms at C-1 by this function would lead to chiral compounds. Thus, regioselective ring opening of *S*-propylene oxide by treatment with 4-phenoxyphenol (compound **86**) in basic medium lead to optically pure alcohol **87**, which after reaction with tosyl chloride and further nucleophilic displacement with potassium thiocyanate afforded chiral thiocyante **89** in moderate yield. The enantiomer of **89** was prepared starting from *R*-propylene oxide employing the same synthetic sequence (Scheme 7).

Results and Discussion

The biological data on the epimastigote form of *T. cruzi* cells were very encouraging. Ketoconazole was used as positive control. The results are presented in Table 1.

Replacement of the Oxygen Atom at C-1′ by a Heteroatom. Replacement of the oxygen atom by a sulfur atom at the C-1′ position of lead drug **8** led to a significant improvement on the biological activity. On the other hand, when the substitution was made with a nitrogen atom at that position, an important decrease in the inhibitory action was observed. For instance, compound **15** exhibited a remarkably high biological activity on the epimastigote form of the parasite with an IC_{50} of 0.9 μM and was 2-fold more active than lead compound **8** (IC_{50} 2.2 μM).[32] This compound was able to produce 95% inhibition at a concentration of 35 μM. Contrary to it would be expected, the sulfur-containing tetrahydropyranyl ether derivative **12** was 2-fold less active than lead drug **7** (IC_{50} 138 μM).[33] Nitrogen-containing derivatives did not lead to an enhancement on biological activity. Thus, substitution of the oxygen at C-1′ by a nitrogen (compound **24**) produced a dramatic reduction in biological activity compared to our lead structure **8** with IC_{50} of 141 μM. The decrease in the inhibitory action was not so pronounced with *N*-acetylated derivatives; certainly, drug **25** exhibited an IC_{50} close to 15 μM, 10 times more active than **24**, while its normal tetrahydropyranyl precursor (compound **18**) was a moderate inhibitor of *T. cruzi* growth (IC_{50} > 200 μM).

Replacement of the Terminal Phenoxy Group by a Chlorine Atom. The replacement of the terminal phenoxy group and the H-1′ by chlorine atoms in our lead drug **8** produced a very active compound. As predicted by the biological activity previously observed for compound **31** (IC_{50} 93 μM),[32] being almost 50% more active than compound **7**, drug **34** proved to be an extremely potent trypanostatic agent being 2-fold more active than **8** with an IC_{50} of 1.0 μM. In addition at concentrations as low as 40 μM complete growth arrest took place. The presence of the chlorine atom at the ortho position with respect to the ether group seemed to be very important for biological activity. Removal of chlorine atom at C-1′ from compound **34** led to drug **39** that was 15 times less active than the dichloride derivative. Moreover, the precursor tetrahydropyranyl derivative **36** was almost devoid of inhibitory action.

Shortening the Aliphatic Side Chain and Elimination of the Oxygen Atom at C-1′. Although shortening of the aliphatic side chain and deleting the oxygen atom at C-1′ gave place to the very potent drug **29**, this compound was around 10 times less active than lead structure **8**. Unexpectedly, the introduction of the tetrahydropyranyl functionality (compound **30**) produced a slight improvement on biological activity (IC_{50} 102 μM) compared with drug **7**.

Introduction of a Halogen Atom at the C-2′ Position. Taking into account the increment on biological activity when the thiocyanate moiety replaces the tetrahydropyranyl group when bonded to the same nonpolar skeleton, and considering that the larger the substituent, the more active the drug, it was reasonably expected that an improvement on biological activity would occur by introducing different groups at C-2′.[32] With the exception of chlorine derivative **43**, which exhibited an IC_{50} of 25 μM, the introduction of a halogen atom at the ortho position in the 4-phenoxyphenoxy skeleton produced very active trypanostatic agents. The normal precursor for the preparation of **43** (drug **40**) had previously exhibited an IC_{50} of 93 μM, being one of the most active tetrahydropyranyl ether derivatives ever prepared.[32] Therefore, the introduction of either bromine or iodine into the lead structure brought about two very potent anti-*T. cruzi* agents exhibiting quite similar biological activities as compound **8**. However, the therapeutic index for drugs **47** and **52** was not as good as previously observed for compound **8**. These halogen-containing drugs presented IC_{90} values of 18 and 23 μM, respectively, data that are still far from those reported for **8** (IC_{90} of 3.5 μM).[32]

Elimination of the Terminal Phenoxy Moiety and Introduction of a Bromine Atom at the C-3′ Position. Replacement of a bromine atom at the meta position (C-3′) with respect to the phenol group together with elimination of the terminal phenoxy moiety was

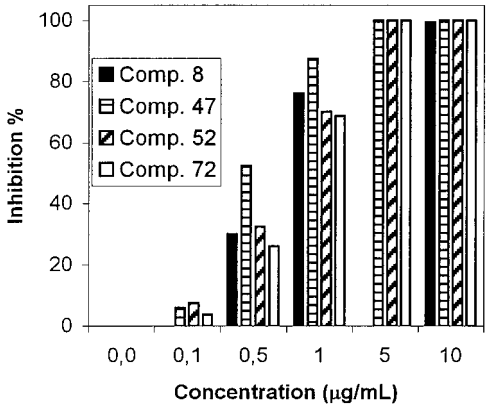


Figure 1. Dose−response graph for compounds **8**, **47**, **52**, and **72**.

very promising for biological activity. In fact, thiocyanate **57** was a very potent trypanostatic agent with an IC_{90} close to 27 μM, activity that correlates quite properly with the activity exhibited with its precursor, the tehydropyranyl ether **54**.

Structural Variations in the B Ring. Structural modifications at the C-2″ or C-3″ positions in the B ring to give thiocyanates **64** and **72** seemed not to have a significant effect on biological activity. In fact, both of these drugs exhibited almost the same inhibitory action as lead drug **8** presenting IC_{50} values of 2.9 and 2.7 μM, respectively. In addition, their precursors **61** and **69**, which showed IC_{50} values of 138 and 143 μM, respectively, were as active as lead compound **7** (IC_{50} 138 μM).[32] The above biological data are very meaningful for drug design because the introduction of different groups at C-2″ or C-3″ is not only somewhat difficult but also has no significant consequence on biological activity. Moreover, as we had previously demonstrated that substitutions at C-4″ produced an impairment on the growth inhibitory effect, it can be concluded that any modification in the B ring will not lead to an enhancement on biological activity.

Conformationally Rigid Aryloxyethyl Thiocyanates. Aryloxyethyl thiocyanates built on a rigid template did not present potent action in inhibiting the proliferation of *T. cruzi*. Accordingly, although conformationally constrained thiocyanate **85** was a rather active compound (IC_{50} 54 μM), its inhibitory action was far from that observed for other thiocyanates derivatives, namely the lead structure **8**. In addition, its precursor (compound **82**) showed very modest activity, which at a concentration of 60 μM merely a 25% inhibition was observed.

Branched Derivatives of Lead Drug 8. The introduction of a branched side chain at the proximity of the thiocyante moiety did not improve the biological activity. On the contrary, neither enantiomer was more active than **8**: the *R* isomer (compound **89**) was 10 times less active than **8**, while its antipode **92** was almost 30 times less active than our lead drug. A typical dose−response graph for the more active drugs such as compounds **8**, **47**, **52**, and **72** is illustrated in Figure 1.

The more promising drugs (compounds **15**, **34**, **47**, **52**, and **72**, respectively) were assayed against the intracellular form of the parasite employing compound **8** as positive control. Compound **15** proved to be toxic for myoblasts, while drugs **34** and **52** were devoid of activity against amastigotes. On the other hand, compounds **47** and **72** were highly active trypanostatic agents but to a lesser extent than **8** (IC_{50} 16.0 μM) exhibiting IC_{50} values of 64.5 and 41.7 μM, respectively, under the same assays conditions based on differential uracil incorporation[54] (see Table 2). In contrast to compound **15**, no toxicity to the host cells, as assessed by phase contrast microscopy observation of detachment, vacuolation, and rounding of the cells, was detected using the concentrations of compounds described.

Table 2. Growth Inhibition against Intracellular *T. cruzi*

compd	IC_{50} (μM)	compd	IC_{50} (μM)
8	16.0	**34**	>100
47	64.5	**52**	>100
72	41.7		

In conclusion, aryloxylethyl thiocyanate derivatives represent an interesting new family of drugs to control replication of *T. cruzi* cells that were rationally designed and synthesized. Slight modifications in the closeness to the polar end group produced a marked effect on inhibitory action. Work aimed at exploiting the potential usefulness of these thiocyanate derivatives as well as in vivo studies of the more promising drugs is currently in progress in our laboratory.

Experimental Section

The glassware used in air- and/or moisture-sensitive reactions was flamed-dried and the experiments were carried out under a dry nitrogen atmosphere. Unless otherwise noted, chemicals were commercially available and used without further purification.

Nuclear magnetic resonance spectra were recorded on Bruker AC-200 MHz and Bruker AM-500 spectrometers. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. The ^{1}H NMR spectra are referenced with respect to the residual $CHCl_3$ proton of the solvent $CDCl_3$ at 7.26 ppm. Coupling constants are reported in hertz (Hz). ^{13}C NMR spectra were fully decoupled and are referenced to the middle peak of the solvent $CDCl_3$ at 77.00 ppm. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet.

Melting points were determined using a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded using a Nicolet Magna 550 spectrometer. Low-resolution mass spectra were obtained on a VG TRIO 2 instrument at 70 eV (direct inlet). High-resolution mass spectrometry (HRMS) were conducted on a VG ZAB BEqQ spectrometer.

Column chromatography was performed employing E. Merck silica gel (Kieselgel 60, 230−400 mesh). Analytical thin-layer chromatography was performed employing 0.2-mm coated commercial silica gel plates (E. Merck, DC-aluminum sheets, Kieselgel 60 F_{254}) and was visualized by 254 nm UV or by immersion into an ethanolic solution of 5% H_2SO_4.

Elemental analyses were performed by UMYMFOR (Facultad de Ciencias Exactas y Naturales-CONICET) and Atlantic Microlab, Norcross, Ga. The results were within ±0.4% of the theoretical values except when otherwise stated.

4-Phenoxythiophenol (10). To a solution of 4-bromophenyl phenyl ether (**9**; 2.00 g, 8.0 mmol) in tetrahydrofuran (10 mL) were added metallic magnesium (297 mg, 12.2 mmol) and iodine (30 mg) and the mixture was refluxed for 15 min. The reaction mixture was allowed to cool to room temperature and was stirred for 2 h. The resulting dark solution was treated with sulfur (3.125 g) and the mixture was stirred for an additional 3 h. Then, the mixture was cooled to 0 °C and was treated with excess of lithium aluminum hydride (1.0 g). The reaction mixture was stirred for 30 min. The reaction was quenched with ethyl acetate (2.0 mL) and the mixture was

partitioned between methylene chloride (70 mL) and an aqueous saturated solution of sodium potassium tartrate (100 mL). The aqueous phase was extracted with methylene chloride (2 × 50 mL), and the combined organic layers were washed with water (2 × 100 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography eluting with hexanes−EtOAc (50:1) to afford 1.61 g (100% yield) of pure compound **10** as a syrup: R_f 0.71 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3447, 3063, 3038, 2567, 1490, 1242, 1170, 828, 760, 690; ^1H NMR ($CDCl_3$) δ 3.36 (s, 1 H, −S*H*), 6.85 (d, J = 8.7 Hz, 2 H, H-3), 6.91−7.50 (m, 5 H, aromatic protons), 7.21 (d, J = 8.7 Hz, 2 H, H-2); ^{13}C NMR ($CDCl_3$) δ 118.70 (C-2′), 119.55 (C-3), 123.28 (C-4′), 129.68 (C-2, C-3′), 132.55 (C-1), 155.75 (C-4), 156.97 (C-1′).

2-(4-Phenoxyphenylthio)ethyl Tetrahydro-2*H*-pyran-2-yl Ether (11). To a solution of thiophenol **10** (1,046 g, 5.2 mmol) in dimethyl sulfoxide (5.0 mL) was added potassium hydroxide (1.165 g, 20.4 mmol). The mixture was stirred at room temperature for 5 min. Then, bromoethyl tetrahydropyranyl ether (1.30 g, 6.2 mmol) was added and the reaction mixture was stirred at room temperature overnight. The mixture was partitioned between water (50 mL) and methylene chloride (50 mL). The aqueous phase was extracted with methylene chloride (2 × 30 mL). The combined organic layers were washed with saturated solution of sodium chloride (5 × 50 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing a mixture of hexanes−EtOAc (19:1) as eluent to yield 739 mg (43% yield) of pure compound **11** as a colorless oil: R_f 0.49 (hexanes−EtOAc, 17:3); IR (film, cm^{-1}) 2942, 2877, 1590, 1498, 1354, 1238, 1122, 1032, 974, 870; ^1H NMR ($CDCl_3$) δ 1.52−1.86 (m, 6 H, H-3‴, H-4‴, H-5‴), 3.09 (t, J = 6.8 Hz, 2 H, H-2), 3.50 (m, 1 H, H-6‴$_a$), 3.64 (m, 1 H, H-6‴$_b$), 3.73−4.03 (m, 2 H, H-1), 4.61 (distorted t, J = 3.2 Hz, 1 H, H-2‴), 6.92 (d, J = 8.8 Hz, 2 H, H-3′), 6.91−7.39 (m, 5 H, aromatic protons) 7.37 (d, J = 8.7 Hz, 2 H, H-2′); ^{13}C NMR ($CDCl_3$) δ 19.37 (C-4‴), 25.37 (C-5‴), 30.51 (C-3‴), 34.76 (C-2), 62.18 (C-6‴), 66.43 (C-1), 98.87 (C-2‴), 118.91 (C-2″), 119.26 (C-3′), 123.42 (C-4″), 129.74 (C-2′, C-3″), 132.28 (C-1′), 156.32 (C-4′), 156.94 (C-1″); MS (*m*/*z*, relative intensity) 330 (M^+, 1), 250 (19), 248 (20), 141 (20), 85 (100); HRMS calcd for ($C_{19}H_{22}O_3S$) 330.1290, found 330.1289. Anal. ($C_{19}H_{22}O_3S$) C, H.

2-(4-Phenoxyphenylthio)ethanol (12). To a solution of compound **11** (720 mg, 2.2 mmol) in methanol (30 mL) was added pyridinium *p*-toluenesulfonate (30 mg). The reaction mixture was stirred at room temperature for 14 h. The mixture was partitioned between water (70 mL) and methylene chloride (70 mL). The aqueous phase was extracted with methylene chloride (2 × 30 mL) and the combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$), and the solvent was evaporated to afford 420 mg (78% yield) of pure alcohol **12** as a colorless oil that was use in the next step without further purification: R_f 0.14 (hexanes−EtOAc, 17:3); IR (film, cm^{-1}) 3385, 3063, 2947, 2878, 1582, 1483, 1238, 1167, 1045, 756, 692; MS (*m*/*z*, relative intensity) 246 (M^+, 100), 215 (43), 202 (14), 181 (25), 77 (50).

2-(4-Phenoxyphenylthio)ethyl 4-Toluenesulfonate (13) and 2-(4-Phenoxyphenylthio)ethyl Chloride (14). To a solution of alcohol **12** (400 mg, 1.6 mmol) in pyridine (5 mL) cooled at 0 °C was added *p*-toluenesulfonyl chloride (389 mg, 5.0 mmol) portionwise, and the mixture was stirred at room temperature for 4 h. Then, 5% HCl (50 mL) was added and the reaction mixture was stirred for an additional hour. The mixture was extracted with methylene chloride (50 mL) and the organic layer was washed with 5% HCl (3 × 50 mL) and water (3 × 50 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated to give 550 mg (85% yield) of pure tosylate **13** as a colorless oil and 39 mg of chloride **14** as a colorless oil. Compound **13**: R_f 0.68 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 2939, 2870, 1584, 1484, 1238, 1132, 1032, 868, 756, 692; MS (*m*/*z*, relative intensity) 400 (M^+, 18), 278 (20), 201 (73), 77 (100). Compound **14**: MS (*m*/*z*, relative intensity) 266 (M^+, 37), 264 (M^+, 100), 215 (27), 201 (34), 108 (10), 129 (18), 181 (12), 77 (77).

2-(4-Phenoxyphenylthio)ethyl Thiocyanate (15). To a solution of tosylate **13** (530 mg, 1.3 mmol) in anhydrous *N*,*N*-dimethylformamide (5 mL) was added potassium thiocyanate (520 mg, 5.4 mmol). The reaction mixture was heated at 100 °C for 5 h. The mixture was allowed to cool to room temperature and water (50 mL) was added. The aqueous phase was extracted with methylene chloride (2 × 50 mL) and the combined organic layers were washed with an aqueous saturated solution of sodium chloride (5 × 50 mL) and water (2 × 50 mL). The solvent was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel) using a mixture of hexanes−EtOAc (24:1) as eluent to afford 380 mg (100% yield) of pure compound **15** as a yellow pale oil: R_f 0.58 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3061, 2924, 2853, 2154, 1582, 1485, 1240, 1167, 868, 756, 692; ^1H NMR (500 MHz, $CDCl_3$) δ 3.08 (m, 2 H, H-1), 3.20 (m, 2 H, H-2), 6.96 (d, J = 8.8 Hz, 2 H, H-3′), 6.97−7.42 (m, 5 H, aromatic protons), 7.40 (d, J = 8.8 Hz, 2 H, H-2′); ^{13}C NMR ($CDCl_3$) δ 33.26 (C-1), 35.44 (C-2), 119.23 (C-2″), 119.42 (C-3′), 123.93 (C-4″), 129.87 (C-3″), 132.98 (C-1′), 134.05 (C-2′), 156.34 (C-4′), 157.80 (C-1″); MS (*m*/*z*, relative intensity) 287 (M^+, 83), 274 (3), 215 (20), 201 (96), 77 (100); HRMS calcd for ($C_{15}H_{13}ONS_2$) 287.0439, found 287.0441. Anal. ($C_{15}H_{13}ONS_2$) C, H.

***N*-(4-Phenoxyphenyl)acetamide (17).** A solution of 4-phenoxyaniline (**16**; 2.00 g, 10.8 mmol) in anhydrous pyridine (3 mL) was treated with acetic anhydride (2 mL). The reaction mixture was stirred at room temperature overnight. Then, 5% hydrochloric acid (20 mL) was added and the mixture was stirred for 1 h. The aqueous phase was extracted with methylene chloride (2 × 50 mL). The combined organic layers were washed with 5% HCl (3 × 50 mL), and water (2 × 50 mL). The solvent was dried ($MgSO_4$) and evaporated to afford 2.408 g (98% yield) of pure amide **17** as a brown solid: mp 128−129 °C; IR (KBr, cm^{-1}) 3290, 3258, 3194, 3136, 3067, 1661, 1607, 1549, 1549, 1506, 1489, 1406, 1373, 1315, 1244, 856, 831, 754, 691; MS (*m*/*z*, relative intensity) 227 (M^+, 66), 185 (100), 156 (11), 108 (75).

***N*-Acetyl-*N*-(4-phenoxyphenyl)aminoethyl Tetrahydro-2*H*-pyran-2-yl Ether (18).** A solution of acetate **17** (3.405 g, 15 mmol) in dimethyl sulfoxide (5 mL) was treated with potassium hydroxide (1.7 g, 30 mmol). The mixture was stirred at room temperature for 5 min. Then, bromoethyl tetrahydropyranyl ether (3.923 g, 15.75 mmol) was added, and the solution was stirred at room temperature overnight. The reaction was worked up as depicted for **11**. The product was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (7:3) to afford 4.801 g (90% yield) of pure compound **18** as a yellow oil: IR (film, cm^{-1}) 3292, 3065, 2941, 2870, 1663, 1506, 1489, 1406, 1240, 1072, 1036, 872, 754, 692; ^1H NMR ($CDCl_3$) δ 1.52−1.89 (m, 6 H, H-3‴, H-4‴, H-5‴), 1.87 (s, 3 H, COC*H*$_3$), 3.53 (m, 1 H, H-6‴$_a$), 3.63 (m, 1 H, H-6‴$_b$), 3.60−4.00 (m, 4 H, H-1, H-2), 4.56 (m, 1 H, H-2‴), 6.95−7.41 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.37 (C-4‴), 22.73 (CO*C*H3), 25.34 (C-5‴), 30.51 (C-3‴), 48.92 (C-2), 62.17 (C-6‴), 64.49 (C-1), 98.64 (C-2‴), 119.02 (C-2″), 119.30 (C-3′), 121.56 (C-2′), 123.86 (C-4″), 129.85 (C-3″), 138.07 (C-1′), 156.32 (C-4′), 156.89 (C-1″); MS (*m*/*z*, relative intensity) 355 (M^+, 5), 254 (10), 227 (89), 198 (20), 185 (100), 108 (65), 43 (77); HRMS calcd for $C_{21}H_{25}O_4N$ 355.1799, found 355.1791 Anal. ($C_{21}H_{25}O_4N$) C, H.

***N*-Acetyl-*N*-(4-phenoxyphenyl)aminoethanol (19).** To a solution of compound **18** (3.834 g, 10.8 mmol) in methanol (100 mL) was added pyridinium 4-toluenesulfonate (200 mg). The mixture was stirred at room temperature for 4 days. The reaction was worked up as described for **12**. The residue was purified by column chromatography (silica gel) employing a mixture of hexanes−EtOAc (7:3) as eluent to give 2.155 g (73% yield) of pure alcohol **19** as a white solid and 900 mg of unreacted material: mp 90−92 °C; MS (*m*/*z*, relative intensity) 271 (M^+, 21), 227 (8), 198 (100), 43 (85).

***N*-Acetyl-(4-phenoxyphenyl)-2-chloroethylamine (20).** To a solution of triphenylphosphine (900 mg, 3.4 mmol) in carbon tetrachloride (20 mL) and acetonitrile (5 mL) was added alcohol **19** (650 mg, 2.4 mmol). The reaction mixture was

stirred at room temperature overnight. The solvent was evaporated and the residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (7:3) to afford 355 mg (51% yield) of pure chloride **20** as a pale yellow oil: R_f 0.52 (hexanes−EtOAc, 1:1); MS (*m*/*z*, relative intensity) 291 (M^+, 2), 289 (M^+, 6), 271 (20), 247 (5), 211 (10), 198 (100).

(4-Phenoxyphenyl)aminoethyl Acetate (21). A mixture of chloride **20** (154 mg, 0.53 mmol) and potassium thiocyanate (500 mg, 5.1 mmol) in *N*,*N*-dimethylformamide (3 mL) was stirred at 100 °C for 6 h. The mixture was treated as depicted for **15**. The product was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (9:1) to afford 130 mg (95% yield) of pure acetate **21** as a colorless oil: R_f 0.56 (hexanes−EtOAc, 7:3); MS (*m*/*z*, relative intensity) 271 (M^+, 24), 211 (13), 198 (100).

2-[(4-Phenoxyphenyl)amino]ethanol (22). A solution of acetate **21** (250 mg, 0.93 mmol) in methanol−water (10:3) (13 mL) was treated with potassium carbonate. The reaction mixture was stirred at room temperature for 3 h. The mixture was partitioned between water (50 mL) and methylene chloride (70 mL). The aqueous phase was extracted with methylene chloride (2 × 50 mL). The combined organic layers were washed with brine (3 × 70 mL), dried ($MgSO_4$), and the solvent was evaporated to afford 200 mg (87% yield) of pure amino alcohol **22** as a white solid: R_f 0.24 (hexanes−EtOAc, 7:3); MS (*m*/*z*, relative intensity) 229 (M^+, 29), 198 (100).

(2-Chloroethyl)(4-phenoxyphenyl)amine (23). To a solution of triphenylphosphine (400 mg, 1.5 mmol) in carbon tetrachloride (20 mL) and acetonitrile (5 mL) was added amino alcohol **22** (200 mg, 0.87 mmol). The mixture was stirred at room temperature for 16 h. Then, the solvent was evaporated and the residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (9:1) to give 152 mg (70% yield) of pure compound **23** as a colorless oil: IR (film, cm^{-1}) 2957, 2835, 1589, 1508, 1489, 1233, 868, 835, 754, 692; MS (*m*/*z*, relative intensity) 249 (M^+, 10), 247 (M^+, 31), 198 (100).

4-Phenoxyphenylaminoethyl Thiocyanate (24). A solution of compound **23** (150 mg, 0.6 mmol) in anhydrous dimethylformamide (3 mL) was treated with potassium thiocyanate (200 mg, 2.1 mmol). The mixture was stirred at 100 °C for 6 h. the reaction was worked up as depicted for **15**. The residue was purified by column chromatography (silica gel) employing hexanes−EtOAc (19:1) as eluent to afford 63 mg (39% yield) of pure compound **24** as a white solid and 72 mg of unreacted chloride **23**: R_f 0.09 (EtOAc); IR (KBr, cm^{-1}) 2918, 2851, 2156, 1491, 1244, 1171, 1094, 1032, 827, 667; ^{1}H NMR ($CDCl_3$) δ 3.26 (t, J = 6.7 Hz, 2 H, H-1), 4.04 (t, J = 6.7 Hz, 2 H, H-2), 7.01 (d, J = 8.8 Hz, 2 H, H-2′), 7.02−7.32 (m, 5 H aromatic protons), 7.34 (d, J = 8.6 Hz, 2 H, H-3′); ^{13}C NMR ($CDCl_3$) δ 26.83 (C-1), 54.39 (C-2), 118.75 (C-2″), 119.32 (C-3′), 123.27 (C-4″), 125.19 (C-2′), 129.66 (C-3″), 135.72 (C-1′), 154.45 (C-4′), 157.05 (C-1″); MS (*m*/*z*, relative intensity) 270 (M^+, 100), 243 (4), 215 (9), 210 (10), 198 (16), 84 (74); HRMS calcd for ($C_{15}H_{14}ON_2S$) 270.0826, found 270.0827. Anal. ($C_{15}H_{14}ON_2S\cdot H_2O$) C, H.

***N*-Acetyl-(4-phenoxyphenyl)-2-thiocyanoethylamine (25).** A solution of compound **24** (30 mg, 0.11 mmol) in pyridine (3 mL) was treated with acetic anhydride (2 mL). The reaction mixture was treated as depicted for **17**. The product was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (4:1) to afford 28 mg (82% yield) of pure compound **25** as a colorless oil: R_f 0.55 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 3 H, C(O)CH_3); 3.20 (t, J = 6.9 Hz, 2 H, H-2), 4.03 (t, J = 6.8 Hz, 2 H, H-1), 7.02−7.43 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.84 (C-1), 27.41 (C(O)-*C*H$_3$), 52.53 (C-2), 118.67 (C-2″), 119.33 (C-3′), 123.75 (C-4″), 126.03 (C-2′), 129.85 (C-3″), 155.70 (C-4′), 156.68 (C-1″); MS (*m*/*z*, relative intensity) 312 (M^+, 17), 297 (7), 270 (10), 198 (90), 43 (100); HRMS calcd for ($C_{17}H_{16}O_2N_2S$) 312.0933, found 312.0929.

4-Phenoxyphenylmethanol (27). A solution of 4-phenoxybenzaldehyde (**26**; 1.00 g, 5.2 mmol) in absolute ethanol (20 mL) was treated with sodium borohydride (210 mg) and the mixture was stirred at room temperature for 2 h. The reaction was quenched by careful addition of 5% HCl (2 mL). The mixture was partitioned between water (50 mL) and methyene chloride (70 mL). The organic layer was washed with water (3 × 50 mL), dried ($MgSO_4$), and the solvent was evaporated to afford 876 mg (84% yield) of pure alcohol **27** as a white solid: mp 94−96 °C; R_f 0.61 (hexanes−EtOAc, 3:2); IR (KBr, cm^{-1}) 3358, 3059, 2930, 2881, 1590, 1526, 1489, 1245, 1005, 845, 697; MS (*m*/*z*, relative intensity) 200 (M^+, 100), 183 (18), 171 (19), 153 (21), 107 (44), 94 (54), 77 (66).

4-Phenoxyphenylmethyl Chloride (28). To a solution of triphenylphosphine (450 mg, 1.71 mmol) in carbon tetrachloride−acetonitrile (1:1, 20 mL) was added alcohol **23** (314 mg, 1.6 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was suspended in hexane (50 mL) and filtered off and the solvent was evaporated. The chloride **24** resulted to be unstable and was used in the next step without further purification.

4-Phenoxyphenylmethyl Thiocyanate (29). The above extract was dissolved in anhydrous dimethylformamide (3 mL) and was treated with potassium thiocyanate (500 mg, 5.1 mmol). The mixture was stirred at 100 °C for 3 h. The reaction was quenched as depicted for **15**. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc to give 50 mg of pure compound **25** (13% yield) as a yellow pale solid: mp 52−53 °C; IR (film, cm^{-1}) 3056, 2995, 2933, 2154, 1595, 1516, 1493, 1460, 1430, 1239, 1110, 1076; ^{1}H NMR ($CDCl_3$) δ 4.15 (s, 2 H, H-1), 6.97−7.39 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 38.01 (C-1), 118.86 (C-3′), 119.45 (C-2″), 123.88 (C-4″), 128.67 (C-1′), 129.87 (C-3″), 130.50 (C-2′), 156.38 (C-4′), 158.15 (C-1″); MS (*m*/*z*, relative intensity) 241 (M^+, 4), 183 (100), 155 (10), 91 (22), 77 (40); HRMS calcd for $C_{14}H_{11}ONS$ 241.0561, found 241.0569. Anal. ($C_{14}H_{11}ONS\cdot 0.1C_6H_{14}$) C, H, N, S.

(±)-4-Phenoxyphenylmethyl Tetrahydro-2*H*-pyran-2-yl Ether (30). To a solution of alcohol **27** (158 mg, 0.79 mmol) in anhydrous methylene chloride (50 mg) were added pyridinium 4-toluenesulfonate (20 mg) and 3,4-dihydro-2*H*-pyran (1 mL). The reaction mixture was stirred at room temperature overnight. The organic phase was washed with water (3 × 50 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to give 224 mg (100% yield) of pure compound **30** as a colorless oil: R_f 0.41 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 2943, 2869, 1589, 1508, 1489, 1238, 1134, 1038, 871, 692; ^{1}H NMR ($CDCl_3$) δ 1.56−1.88 (m, 6 H, H-3‴, H-4‴, H-5‴), 3.51−3.59 (m, 1 H, H-6‴$_a$), 3.87−3.96 (m, 1 H, H-6‴$_b$), 4.46 (d, J = 11.8 Hz, 1 H, H-1$_a$), 4.72 (distorted t, J = 3.4 Hz, 1 H, H-2‴), 4.75 (d, J = 11.9 Hz, 1 H, H-1$_b$); ^{13}C NMR ($CDCl_3$) δ 19.34 (C-4‴), 25.47 (C-5‴), 30.57 (C-3‴), 62.13 (C-6‴), 68.38 (C-1), 97.73 (C-2‴), 118.76 (C-3′), 118.79 (C-2″), 123.16 (C-4″), 129.42 (C-1′), 129.67 (C-3″), 133.18 (C-2′), 156.69 (C-4′), 157.29 (C-1″); MS (*m*/*z*, relative intensity) 284 (M^+, 37), 183 (100), 85 (72). Anal. ($C_{18}H_{20}O_3$) C, H.

2,4-Dichlorophenoxyethanol (32). A solution of compound **31** (746 mg, 2.6 mmol) in methanol (30 mL) was treated with pyridinium 4-toluenesulfonate (20 mg). The mixture was stirred at room temperature overnight. The reaction was worked up as described for **12**. The residue was purified by column chromatography eluting with hexanes−EtOAc (9:1) to afford 230 mg (43% yield) of pure compound **32** as a colorless oil: R_f 0.14 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3238, 2932, 1487, 1389, 1267, 1107, 1063, 930, 829, 799; MS (*m*/*z*, relative intensity) 210 (M^+, 5), 208 (M^+, 27), 206 (M^+, 42), 166 (18), 164 (97), 162 (100)

2,4-Dichlorophenoxyethyl 4-Toluenesulfonate (33). To a solution of alcohol **31** (230 mg, 1.1 mmol) in pyridine (3 mL) was added portionwise tosyl chloride (254 mg, 1.3 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. The reaction was quenched as depicted for compound **11**. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (9:1) to yield 190 mg (53% yield) of pure tosylate **33** as a colorless oil: IR (film, cm^{-1}) 1599,

1481, 1452, 1356, 1294, 1190, 1032, 930, 812, 665; MS (*m/z*, relative intensity) 362 (M^+, 5) 360 (M^+, 8), 199 (86), 155 (48), 91 (100).

2,4-Dichlorophenoxyethyl Thiocyanate (34). A solution of compound **33** (178 mg, 0.5 mmol) in dimethylformamide (2 mL) was treated with potassium thiocyanate (300 mg, 3.1). The mixture was stirred at 100 °C for 6 h and was worked up as depicted for **15**. The residue was purified by column chromatography (silica gel) employing hexanes−EtOAc (9:1) as eluent to afford 90 mg (70% yield) of pure compound **34** as a colorless oil: IR (film, cm^{-1}) 3074, 2933, 2880, 2156, 1585, 1483, 1389, 1288, 1250, 1105, 1063, 1024, 870, 804, 731; ^{1}H NMR ($CDCl_3$) δ 3.37 (t, J = 5.9 Hz, 2 H, H-1), 4.34 (t, J = 5.9 Hz, 2 H, H-2), 6.88 (d, J = 8.8 Hz, 1 H, H-6′), 7.21 (dd, J = 8.8, 2.5 Hz, 1 H, H-5′), 7.39 (d, J = 2.5 Hz, 1 H, H-3′); ^{13}C NMR ($CDCl_3$) δ 32.99 (C-1), 67.30 (C-2), 114.97 (C-6′), 124.24 (C-2′), 127.07 (C-4′), 127.64 (C-5′), 130.15 (C-3′); 152.19 (C-1′); MS (*m/z*, relative intensity) 251 (M^+, 3), 249 (M^+, 12), 247 (M^+, 17), 166 (1), 164 (8), 162 (12), 137 (2), 135 (9), 133 (15), 86 (100). Anal. Calcd for ($C_9H_7ONCl_2S$: C 43.57, H 2.84, N 5.64, S 12.92. Found: C 43.80, H 2.31, N 5.39, S 12.53.

4-Chlorophenylethyl Tetrahydro-2*H*-pyran-2-yl Ether (36). A solution of 4-chlorophenol (**35**; 386 mg, 3.0 mmol) in dimethyl sulfoxide (3 mL) was treated with potassium hydroxide (350 mg, 6.2 mmol) and bromoethyl tetrahydropyranyl ether (650 mg, 3.1 mmol). The mixture was stirred at room temperature overnight. After the usual workup, the residue was purified by column chromatography (silica gel) using hexanes−EtOAc (19:1) as eluent to afford 592 mg (77% yield) of pure compound **36** as a yellow oil: IR (film, cm^{-1}) 2943, 2874, 1597, 1492, 1456, 1284, 1248, 1140, 1080, 1036, 989, 824, 667; ^{1}H NMR ($CDCl_3$) δ 1.55−1.81 (m, 6 H, H-3″, H-4″, H-5″), 3.55 (m, 1 H, H-6″$_a$), 3.77−4.03 (m, 3 H, H-1, H6″$_b$), 4.06−4.15 (m, 2 H, H-2), 4.69 (distorted t, J = 3.5 Hz, 1 H, H-2″), 6.85 (d, J = 8.9 Hz, 2 H, H-2′), 7.21 (d, J = 8.9 Hz, 2 H, H-3′); ^{13}C NMR ($CDCl_3$) δ 19.32 (C-4″), 25.36 (C-5″), 30.45 (C-3″), 62.15 (C-6″), 65.72 (C-1), 67.75 (C-2), 98.99 (C-2″), 115.98 (C-2′), 125.63 (C-4′), 129.19 (C-3′), 157.52 (C-1′); MS (*m/z*, relative intensity) 258 (M^+, 5), 256 (M^+, 14), 129 (64), 85 (100), 73 (58). Anal. ($C_{13}H_{17}O_3Cl$) C, H.

4-Chlorophenoxyethanol (37). To a solution of compound **36** (500 mg, 2.0 mmol) in methanol (20 mL) was added pyridinium 4-toluenesulfonate (30 mg). The mixture was stirred at room temperature for 16 h. The reaction was quenched as depicted for compound **12**. The product was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (9:1) to afford 260 mg (78% yield) of pure alcohol **37** as a colorless oil: IR (film, cm^{-1}) 3370, 2934, 2876, 1597, 1493, 1452, 1287, 1246, 1092, 1053, 916, 824, 667; MS (*m/z*, relative intensity) 174 (M^+, 20) 172 (M^+, 63), 130 (46), 128 (100).

4-Chlorophenoxyethyl 4-Toluenesulfonate (38). A solution of alcohol **37** (195 mg, 1.13 mmol) in pyridine (3 mL) was treated with tosyl chloride (300 mg, mmol) according to the general procedure. The product was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to afford 301 mg (92% yield) of pure tosylate **38** as a colorless oil: MS (*m/z*, relative intensity) 328 (M^+, 1), 326 (M^+, 3), 199 (35), 172 (19), 155 (26), 128 (97), 91 (100).

4-Chlorophenoxyethyl Thiocyanate (39). A solution of tosylate **38** (250 mg, 0.77 mmol) in dimethylformamide (3 mL) was treated with potassium thiocyanate (500 mg, 5.1 mmol) according to the method of preparation of **15**. After the usual workup, the product was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to afford 105 mg (63% yield) of pure compound **39** as a colorless oil: IR (film, cm^{-1}) 2941, 2878, 2156, 1597, 1491, 1464, 1283, 1244, 1171, 1092, 1030, 824, 664; ^{1}H NMR ($CDCl_3$) δ 3.30 (t, J = 5.8 Hz, 2 H, H-1), 4.26 (t, J = 5.8 Hz, 2 H, H-2), 6.85 (d, J = 9.0 Hz, 2 H, H-2′), 7.25 (d, J = 9.0 Hz, 2 H, H-3′); ^{13}C NMR ($CDCl_3$) δ 33.07 (C-1), 66.12 (C-2), 115.94 (C-2′), 126.66 (C-4′), 129.45 (C-3′), 156.37 (C-1′); MS (*m/z*, relative intensity) 215 (M^+, 10), 213 (M^+, 28), 128 (13), 99 (17), 86 (100). Anal. (C_9H_8ONSCl) C, H.

2-Chloro-4-phenoxyphenoxyethanol (41). A solution of compound **40** (635 mg, 1.8 mmol) in methanol (20 mL) was treated with pyridinium *p*-toluenesulfonate (30 mg). The mixture was treated as described for the preparation of compound **12**. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (9:1) to afford 200 mg (42% yield) of pure compound **41** as a colorless oil: IR (film, cm^{-1}) 3385, 3076, 2941, 1596, 1491, 1266, 1216, 1057, 913, 758, 695; MS (*m/z*, relative intensity) 266 (M^+, 20), 264 (M^+, 60), 222 (26), 220 (96), 84 (49), 77 (60), 49 (100).

2-Chloro-4-phenoxyphenoxyethyl 4-Toluenesulfonate (42). A solution of alcohol **41** (180 mg, 0.68 mmol) in pyridine (3 mL) was treated with tosyl chloride (250 mg, 1.3 mmol). After the usual treatment the residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to give 113 mg (40% yield) of pure **42** as a colorless oil: MS (*m/z*, relative intensity) 420 (M^+, 6), 418 (M^+, 15), 221 (4), 219 (10), 199 (100), 155 (31), 91 (86), 77 (47).

2-Chloro-4-phenoxyphenoxyethyl Thiocyanate (43). To a solution of tosylate **42** (120 mg, 0.29 mmol) in dimethylformamide (3 mL) was added potassium thiocyanate (300 mg, mmol). The reaction was heated at 100 °C with vigorous stirring for 6 h. The reaction was quenched as depicted for **15**. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (9:1) to afford 65 mg (73% yield) of pure compound **43** as a colorless oil: IR (film, cm^{-1}) 2918, 2850, 2156, 1481, 1217, 1055, 1024, 924, 876, 824, 961; ^{1}H NMR ($CDCl_3$) δ 3.38 (t, J = 5.9 Hz, 2 H, H-1), 4.34 (t, J = 5.9 Hz, 2 H, H-2), 6.91−7.38 (m, 8 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 33.26 (C-1), 68.10 (C-2), 116.06 (C-2′), 118.26 (C-5′), 118.51 (C-6′), 121.38 (C-3′), 123.49 (C-4″), 124.63 (C-2″), 129.84 (C-3″), 149.64 (C-4′), 152.09 (C-1′), 157.16 (C-1″); MS (*m/z*, relative intensity) 307 (M^+, 7), 305 (M^+, 20), 221 (13), 219 (36), 86 (42), 77 (100). Anal. ($C_{15}H_{12}O_2NSCl$) C, H.

2-Bromo-2-phenoxyphenylethanol (45). Compound **45** was prepared from **44** (510 mg, 1.3 mmol) following the method of preparation described for **12**. Purification by column chromatography eluting with hexanes−EtOAc (17:1) gave 256 mg (64% yield) of pure alcohol **45** as a colorless oil: R_f 0.20 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3391, 2930, 2858, 1589, 1490, 1457, 1217, 1047, 870, 750; MS (*m/z*, relative intensity) 310 (M^+, 93), 308 (M^+, 100), 266 (68), 264 (69), 157 (25), 77 (75).

2-Bromo-4-phenoxyphenylethyl 4-Toluenesulfonate (46). Alcohol **45** (220 mg, 0.71 mmol) was treated with tosyl chloride according to the general procedure. After the usual workup, 310 mg (94% yield) of pure product as colorless oil were isolated that were used in the next step without further purification: R_f 0.30 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3067, 2953, 2876, 1589, 1496, 1360, 1267, 1215, 1020, 910, 814, 754, 692; MS (*m/z*, relative intensity) 464 (M^+, 6), 462 (M^+, 6), 310 (15), 308 (13), 266 (33), 264 (33), 199 (86), 155 (32), 91 (73), 77 (100).

2-Bromo-4-phenoxyphenoxyethyl Thiocyanate (47). Compound **46** (273 mg, 0.60 mmol) was treated with potassium thiocyanate as depicted for compound **13**. Purification by column chromatography (silica gel) employing hexanes−EtOAc (9:1) as eluent afforded 130 mg (62% yield) of pure **47** as a colorless oil: R_f 0.36 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3067, 2934, 2877, 2156, 1587, 1483, 1265, 1215, 1070, 1043, 1022, 910, 874, 756, 699; ^{1}H NMR ($CDCl_3$) δ 3.37 (t, J = 5.9 Hz, 2 H, H-1), 4.33 (t, J = 5.9 Hz, 2 H, H-2), 6.88−7.37 (m, 8 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 33.26 (C-1), 67.98 (C-2), 113.40 (C-2′), 115.60 (C-2″), 118.43 (C-5′), 119.01 (C-6′), 123.46 (C-4″), 124.34 (C-3′), 129.83 (C-3″), 150.59 (C-4′), 152.28 (C-1′), 157.24 (C-1″); MS (*m/z*, relative intensity) 351 (M^+, 69), 349 (M^+, 66), 265 (60), 263 (61), 128 (19), 86 (32), 77 (100). Anal. ($C_{15}H_{12}O_2NSBr$) C, H.

2-Iodo-4-phenoxyphenoxyethyl Tetrahydro-2*H*-pyran-2-yl Ether (49). Iodophenol **48** (225 mg, 0.72 mmol) was treated with bromoethyl tetrahydropyranyl ether as depicted for compound **11**. The residue was purified by column chromatography (silica gel) employing a mixture of hexanes−EtOAc (19:1) as eluant to afford 216 mg (68% yield) of pure

compound **49** as a colorless oil: R_f 0.45 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3063, 2941, 1872, 1587, 1479, 1456, 1265, 1219, 1140, 1034, 891, 814, 750, 692; ^1H NMR ($CDCl_3$) δ 1.50−1.80 (m, 6 H, H-3‴, H-4‴, H-5‴), 3.56 (m, 1 H, H-6‴$_a$), 3.83−4.07 (m, 3 H, H-1, H-6‴$_b$), 4.17 (distorted t, J = 4.7 Hz, 2 H, H-2), 4.80 (distorted t, J = 3.1 Hz, 1 H, H-2‴), 6.82 (d, J = 8.9 Hz, 1 H, H-6′), 6.92−7.09 (m, 4 H, aromatic protons), 7.25−7.34 (m, 2 H, aromatic protons), 7.46 (d, J = 2.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.22 (C-4‴), 25.40 (C-5‴), 30.50 (C-3‴), 62.05 (C-6‴), 65.60 (C-1), 69.53 (C-2), 86.74 (C-2′), 99.02 (C-2‴), 113.07 (C-6′), 117.91 (C-2″), 120.18 (C-5′), 122.95 (C-4″), 129.67 (C-3′), 130.35 (C-3″), 151.02 (C-4′), 154.14 (C-1″), 157.80 (C-1′); MS (*m*/*z*, relative intensity) 440 (M^+, 10), 356 (2), 312 (23), 129 (100); HRMS calcd for ($C_{19}H_{21}O_4I$) 440.0485, found 440.0483. Anal. ($C_{19}H_{21}IO_4$) C, H.

2-Iodo-4-phenoxyphenoxyethanol (50). Compound **49** (190 mg, 0.43 mmol) was treated with pyridinium 4-toluenesulfonate as depicted for the preparation of **12** to give 91 mg (59% yield) of pure alcohol **50** as a colorless oil: R_f 0.16 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3366, 3065, 3034, 2936, 2874, 1475, 1456, 1265, 1217, 1074, 1043, 889, 816, 750, 692; MS (*m*/*z*, relative intensity) 356 (M^+, 59), 312 (97), 264 (12), 230 (16), 220 (20), 186 (30), 77 (100).

2-Iodo-4-phenoxyphenoxyethyl 4-Toluenesulfonate (51). Alcohol **50** (80 mg, 0.22 mmol) was treated with tosyl chloride as described for the preparation of **13** affording 119 mg (100% yield) of pure tosylate **51** as a colorless oil: R_f 0.35 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 2924, 2872, 1477, 1456, 1267, 1217, 1176, 1022, 928, 891, 816, 777; MS (*m*/*z*, relative intensity) 510 (M^+, 16), 311 (13), 199 (100), 155 (34), 91 (82).

2-Iodo-4-phenoxyphenoxyethyl 4-Thiocyanate (52). Compound **51** (110 mg, 0.22 mmol) was treated with potassium thiocyanate as depicted for **15**. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to give 45 mg (52% yield) of pure compound **52** as a colorless oil: R_f 0.31 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3063, 3040, 2926, 2876, 2154, 1585, 1481, 1387, 1267, 1215, 1070, 1038, 878, 816, 773, 692; ^1H NMR ($CDCl_3$) δ 3.39 (t, J = 5.9 Hz, 2 H, H-1), 4.31 (t, J = 5.9 Hz, 2 H, H-2), 6.81 (d, J = 8.9 Hz, 1 H, H-6′), 6.93−7.13 (m, 4 H, aromatic protons), 7.29−7.37 (m, 2 H, aromatic protons), 7.46 (d, J = 2.8 Hz, 1 H, H-3′); ^{13}C NMR ($CDCl_3$) δ 33.31 (C-1), 67.90 (C-2), 87.04 (C-2′), 113.80 (C-6′), 118.28 (C-2″), 120.11 (C-5′), 123.33 (C-4″), 129.80 (C-3′), 130.31 (C-3″), 152.17 (C-4′), 152.94 (C-1″), 157.39 (C-1′); MS (*m*/*z*, relative intensity) 397 (M^+, 69), 311 (45), 128 (74), 77 (100). Anal. ($C_{15}H_{12}O_2NSI$) C, H.

3-Bromophenoxyethyl Tetrahydro-2*H*-pyran-2-yl Ether (54). Compound **54** was prepared from 3-bromophenol (**53**; 500 mg, 2.89 mmol) according to the method of preparation for compound **11**. The residue was purified by column chromatography (silica gel) employing hexanes−EtOAc (9:1) as eluent to yield 336 mg (39% yield) of pure compound **54** as a colorless oil: R_f 0.34 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 2941, 2871, 1591, 1572, 1476, 1067, 1034, 991, 872, 772, 681; ^1H NMR ($CDCl_3$) δ 1.54−1.87 (m, 6 H, H-3″, H-4″, H-5″), 3.42−3.57 (m, 1 H, H-6″$_a$), 3.74−4.08 (m, 3 H, H-1, H-6″$_b$), 4.13 (t, J = 4.6 Hz, 2 H, H-2), 4.69 (distorted t, J = 3.2 Hz, 1 H, H-2″), 6.80−7.20 (m, 5 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.29 (C-4″), 25.38 (C-5″), 30.46 (C-3″), 62.13 (C-6″), 65.68 (C-1), 67.71 (C-2), 98.97 (C-2″), 113.74 (C-6′), 118.06 (C-2′), 122.69 (C-3′), 123.89 (C-4′), 130.41 (C-5′), 158.70 (C-1′); MS (*m*/*z*, relative intensity) 302 (M^+, 25), 300 (M^+, 28), 200 (10), 174 (16), 172 (18), 129 (35), 101 (66), 85 (100). Anal. ($C_{12}H_{15}BrO_2$) C, H.

3-Bromophenoxyethanol (55). Alcohol **55** was prepared from ether **54** (233 mg, 0.77 mmol) as described for **12**. Evaporation of the solvent afforded 170 mg (100% yield) of pure alcohol **55** (colorless oil) that was used as such in the next step: R_f 0.08 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3356, 2934, 2874, 1589, 1574, 1476, 1287, 1231, 1051, 928, 768, 681; MS (*m*/*z*, relative intensity) 218 (M^+, 22), 216 (M^+, 24), 174 (95), 172 (100), 157 (18), 155 (17), 93 (31).

3-Bromophenoxyethyl 4-Toluenesulfonate (56). Alcohol **55** (160 mg, 0.74 mmol) was treated with tosyl chloride described for **13**. Evaporation of the solvent of the solvent yielded 205 mg (75% yield) of pure tosylate **56** as a colorless oil: R_f 0.29 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3067, 2953, 1591, 1574, 1476, 1456, 1360, 1177, 1096, 1074, 1022, 928, 816, 775, 664; MS (*m*/*z*, relative intensity) 372 (M^+, 24), 370 (M^+, 23), 199 (100), 155 (84), 91 (87).

3-Bromophenoxyethyl Thiocyanate (57). Tosylate **56** (200 mg, 0.43 mmol) reacted with potassium thiocyanate as depicted for **13**. Purification by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) afforded 60 mg (54% yield) of pure compound **57** as a colorless oil: R_f 0.47 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 2924, 2853, 2156, 1589, 1474, 1283, 1227, 1067, 1030, 901, 860, 679; ^1H NMR ($CDCl_3$) δ 3.30 (t, J = 5.8 Hz, 2 H, H-1), 4.28 (t, J = 5.8 Hz, 2 H, H-2), 6.85 (dt, J = 6.3, 2.9 Hz, 1 H, H-6′), 7.07−7.20 (m, 3 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 33.06 (C-1), 66.01 (C-2), 113.50 (C-6′), 118.03 (C-5′), 122.87 (C-3′), 124.87 (C-4′), 130.69 (C-5′), 158.48 (C-1′); MS (*m*/*z*, relative intensity) 259 (M^+, 99), 257 (M^+, 100), 201 (6), 199 (7), 187 (10), 185 (11), 174 (27), 172 (28), 157 (20), 155 (20), 145 (20), 143 (21), 86 (89). Anal. (C_9H_8-ONSBr) C, H.

3-Bromophenyl 4-Nitrophenyl Ether (58). A solution of 3-bromophenol (**53**; 1.73 g, 10 mmol) in dimethyl sulfoxide (10 mL) was treated with potassium hydroxide (600 mg, 11 mmol). The mixture was stirred at room temperature for 10 min. Then, 4-chloronitrobenzene (1.57 g, 10 mmol) and cuprous chloride (50 mg) were added and the mixture was stirred at room temperature overnight. The reaction was worked up as depicted for **11**. The product was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (50:1) to afford 2.099 g (71% yield) of pure compound **58** as a colorless oil: R_f 0.20 (hexanes−EtOAc, 19:1); IR (film, cm^{-1}) 1580, 1516, 1489, 1341, 1240, 1111, 1061, 895, 847, 775, 750, 671; MS (*m*/*z*, relative intensity) 295 (M^+, 100), 293 (M^+, 92), 265 (14), 263 (13), 168 (54), 157 (16), 155 (19), 139 (41), 128 (33).

4-(3-Bromophenoxy)aniline (59). A solution of compound **58** (1.5 g, 5.1 mmol) in ethyl acetate (50 mL) in the presence of palladium on charcoal (100 mg) was treated with hydrogen at 3 atm, and the mixture was stirred at room temperature overnight. The mixture was filtered, and the solvent was evaporated to give 1.220 g (91% yield) of pure amine **59** as a pale yellow oil that was used as such in the next step: R_f 0.61 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 2824, 2594, 2575, 1570, 1504, 1485, 1246, 1198, 831, 779, 692; MS (*m*/*z*, relative intensity) 265 (M^+, 5), 263 (M^+, 5), 185 (100), 156 (17), 108 (99), 80 (69).

4-(3-Bromophenoxy)phenol (60). To a solution of amine **59** (1.00 g, 3.8 mmol) in glacial acetic acid (12 mL) was added sulfuric acid (3.6 mL). The mixture was cooled at 0 °C, and a solution of sodium nitrite (350 mg, 5.2 mmol) in water (2 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 20 min. Then, urea (120 mg) and cold water (12 mL) was added. This mixture was kept at 0 °C and was carefully added to a boiling mixture of water (25 mL) and concentrated sulfuric acid (6 mL). After the addition was complete the reaction was stirred for an additional 10 min at the boiling temperature. The mixture was allowed to cool and was partitioned between water (100 mL) and methylene chloride (70 mL). The aqueous phase was extracted with methylene chloride 2 × 70 mL), and the combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography eluting with hexanes−EtOAc (9:1) to yield 374 mg (37% yield) of pure phenol **60** as a colorless oil: R_f 0.32 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3377, 1592, 1508, 1489, 1362, 1217, 1096, 1070, 847, 815, 692; MS (*m*/*z*, relative intensity) 266 (M^+, 11), 264 (M^+, 12), 186 (100), 157 (21), 129 (14), 109 (25).

4-(3-Bromophenoxy)phenoxyethyl Tetrahydro-2*H*-pyran-2-yl Ether (61). Phenol **60** (359 mg, 1.36 mmol) was condensed with bromoethyl tetrahydropyranyl ether (358 mg, 1.7 mmol) as described for **11**. The product was purified by column chromatography (silica gel) employing hexanes−EtOAc (19:1) as eluent to afford 320 mg (60% yield) of pure compound **61** as a colorless oil: R_f 0.24 (hexanes−EtOAc, 10:1); ^1H NMR

($CDCl_3$) δ 1.50−1.91 (m, 6 H, H-3‴, H-4‴, H-5‴), 3.54 (m, 1 H, H-6‴$_a$), 3.74−3.95 (m, 3 H, H-1, H-6‴$_b$), 3.98−4.15 (m, 2 H, H-2), 4.69 (distorted t, J = 3.3 Hz, 1 H, H-2‴), 6.77−7.38 (m, 8 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.25 (C-4‴), 25.32 (C-3‴), 30.40 (C-5‴), 62.01 (C-6‴), 65.75 (C-1), 67.86 (C-2), 98.84 (C-2‴), 115.73 (C-6″), 117.52 (C-2′), 120.57 (C-3′), 122.31 (C-2″), 125.49 (C-3″), 129.45 (C-4″), 132.36 (C-5″), 155.11 (C-4′), 157.64 (C-1′), 158.35 (C-1″); MS (*m*/*z*, relative intensity) 394 (M^+, 9) 392 (M^+, 10), 266 (9), 264 (9), 129 (100), 85 (70); HRMS calcd for ($C_{19}H_{21}O_4Br$) 392.0623, found 392.0619.

4-(3-Bromophenoxy)phenoxyethanol (62). Compound **61** (302 mg, 0.77 mmol) was reacted with pyridinium 4-toluenesulfonate according to the procedure of **12** and was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (9:1) to give 203 mg (85% yield) of pure alcohol **62** as a white solid: mp 49−50 °C; R_f 0.44 (hexanes−EtOAc, 4:1); IR (KBr, cm^{-1}) 3292, 2930, 2872, 1587, 1506, 1491, 1248, 1221, 1107, 1074, 1053, 891; MS (*m*/*z*, relative intensity) 310 (M^+, 16), 308 (M^+, 17), 266 (19), 264 (22), 230 (100), 186 (98).

4-(3-Bromophenoxy)phenoxyethyl 4-Toluenesulfonate (63). Alcohol **62** (178 mg, 0.58 mmol) was treated with 4-toluenesulfonyl chloride as depicted for **13** affording 254 mg (95% yield) of pure tosylate **63** as a colorless oil: IR (film, cm^{-1}) 2924, 2874, 1597, 1504, 1484, 1362, 1228, 1177, 1022, 934, 821, 777, 664; MS (*m*/*z*, relative intensity) 464 (M^+, 10), 462 (M^+, 10), 384 (31), 199 (100), 155 (47), 91 (87)

4-(3-Bromophenoxy)phenoxyethyl Thiocyanate (64). Tosylate **63** (219 mg, 0.47 mmol) was reacted with potassium thiocyanate as described for **15**. The product was purified by column chromatography employing hexanes−EtOAc (19:1) to afford 116 mg (71% yield) of pure compound **57** as a colorless oil: R_f 0.38 (hexanes−EtOAc, 3:1); IR (film, cm^{-1}) 2934, 2870, 2156, 1587, 1503, 1489, 1219, 1070, 1032, 866, 842, 827, 692; ^{1}H NMR ($CDCl_3$) δ 3.31 (t, J = 5.8 Hz, 2 H, H-1), 4.29 (t, J = 5.8 Hz, 2 H, H-2), 6.80−7.09 (m, 6 H, aromatic protons), 7.27−7.41 (m, 2 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 33.29 (C-1), 66.41 (C-2), 115.94 (C-6″), 117.86 (C-2′), 120.69 (C-3′), 122.69 (C-2″), 125.63 (C-3″), 129.61 (C-4″), 132.52 (C-5″), 153.92 (C-4′), 157.37 (C-1′), 158.07 (C-1″); MS (*m*/*z*, relative intensity) 351 (M^+, 18), 349 (M^+, 18), 271 (50), 265 (14), 263 (16), 185 (100), 157 (17), 155 (15), 129 (38); HRMS calcd for ($C_{15}H_{12}O_2NSBr$) 348.9772, found 348.9779.

2-Methylphenyl 4-Nitrophenyl Ether (66). A mixture of *o*-cresol (**65**; 2.60 g, 24 mmol) and 4-chloronitrobenzene (3.78 g, 24 mmol) was treated as depicted for **58**. The product was purified by column chromatography (silica gel) eluting with hexane to afford 3.024 g (54% yield) of pure compound **66** as a colorless oil: R_f 0.43 (hexanes−EtOAc, 4:1); MS (*m*/*z*, relative intensity) 229 (M^+, 100), 212 199, 182 168 153 91.

4-(2-Methylphenoxy)aniline (67). Compound **66** (2.891 g, 12.6 mmol) was reacted with hydrogen as depicted for **59** affording 2.365 g (94% yield) of pure aniline **67** as a colorless oil that was used as such in the next step: R_f 0.13 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3441, 3371, 2934, 2859, 1629, 1521, 1489, 1242, 1204, 1109, 875, 837, 748; MS (*m*/*z*, relative intensity) 199 (M^+, 100), 108 (81), 93 (81).

4-(2-Methylphenoxy)phenol (68). Compound **68** was prepared following a similar protocol depicted for **60** starting from aniline **67** (1.60 g, 8.0 mmol) and was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (24:1) to yield 417 mg (26% yield) of pure phenol **68** as a colorless oil: R_f 0.59 (hexanes−EtOAc, 3:1); IR (film, cm^{-1}) 3350, 1510, 1495, 1468, 1233, 1112, 828, 774; MS (*m*/*z*, relative intensity) 200 (M^+, 100), 107 (70), 94 (50), 90 (50), 65 (70).

4-(2-Methylphenoxy)phenoxyethyl Tetrahydro-2*H*-pyran-2-yl Ether (69). Phenol **68** (505 mg, 2.5 mmol) was condensed with bromoethyl tetrahydropyranyl ether according to the procedure of **13** and was purified by column chromatography (silica gel) employing hexanes−EtOAc (97:3) as eluent to give 584 mg (60% yield) of pure ether **69** as a colorless oil: R_f 0.62 (hexanes−EtOAc, 3:1); IR (film, cm^{-1}) 3059, 2954, 2881, 1597, 1506, 1493, 1453, 1215, 1196, 1045, 986, 828, 775; ^{1}H NMR ($CDCl_3$) δ 1.52−1.86 (m, 6 H, H-3‴, H-4‴, H-5‴), 2.27 (s, 3 H, Ph*Me*), 3.53 (m, 1 H, H-6‴$_a$), 3.75−3.94 (m, 3 H, H-1, H-6‴$_b$), 3.99−4.15 (m, 2 H, H-2), 4.71 (distorted t, J = 3.2 Hz, 1 H, H-2‴), 6.77−7.24 (m, 8 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 16.16 (Ph*Me*), 19.37 (C-4‴), 25.42 (C-3‴), 30.52 (C-5‴), 62.17 (C-6‴), 65.90 (C-1), 68.04 (C-2), 98.99 (C-2‴), 115.82 (C-6″), 118.11 (C-2′), 119.17 (C-4″), 123.09 (C-3′), 126.92 (C-5″), 129.24 (C-2″), 131.26 (C-3″), 151.29 (C-4′), 154.62 (C-1′), 155.75 (C-1″); MS (*m*/*z*, relative intensity) 328 (M^+, 1), 256 (7), 129 (40), 85 (100); HRMS calcd for ($C_{20}H_{24}O_4$) 328.1675, found 328.1680.

4-(2-Methylphenoxy)phenoxyethanol (70). Ether **69** (405 mg, 1.2 mmol) was treated as described for the preparation of **12**. After the usual workup and evaporation of the solvent afforded 333 mg (100% yield) of pure alcohol **70** as a colorless oil: R_f 0.19 (hexanes−EtOAc, 3:1); IR (film, cm^{-1}) 3362, 2934, 2868, 1585, 1506, 1460, 1299, 1229, 1203, 1118, 1088, 1052, 880, 834, 762; MS (*m*/*z*, relative intensity) 244 (M^+, 35), 200 (38), 172 (24), 128 (100).

4-(2-Methylphenoxy)phenoxyethyl 4-Toluenesulfonate (71). Alcohol **70** (207 mg, 0.85 mmol) was treated with tosyl chloride as depicted for **13**. The product was purified by column chromatography (silica gel) using hexanes−EtOAc (9:1) as eluent to afford 227 (67% yield) of pure tosylate **71** as a colorless oil and 30 mg of unreacted alcohol **70**: R_f 0.32 (hexanes−EtOAc, 3:1); IR (film, cm^{-1}) 2928, 1510, 1492, 1456, 1365, 1233, 1172, 1027930, 822, 774, 665; MS (*m*/*z*, relative intensity) 398 (M^+, 28), 199 (100), 155 (40), 91 (95).

4-(2-Methylphenoxy)phenoxyethyl Thiocyanate (72). Tosylate **71** (196 mg, 0.68 mmol) was treated with potassium thiocyanate as depicted for **15**. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (93:7) to afford 97 mg (50% yield) of pure thiocyanate **72** as a colorless oil: R_f 0.12 (hexanes−EtOAc, 9:1); IR (film, cm^{-1}) 3067, 2927, 2869, 2161, 1588, 1512, 1471, 1301, 1235, 1207, 1120, 1044, 880, 833, 763; ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3 H, Ph*Me*), 3.29 (t, J = 5.8 Hz, 2 H, H-1), 4.26 (t, J = 5.8 Hz, 2 H, H-2), 6.81 (dd, J = 7.9, 1.3 Hz, 1 H), 6.87 (m*AB*, 4 H, H-2, H-3), 6.97−7.24 (m, 3 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 16.08 (Ph*Me*), 33.28 (C-1), 66.47 (C-2), 115.88 (C-6″), 118.43 (C-2′), 119.04 (C-4″), 123.38 (C-3′), 126.97 (C-5″), 129.24 (C-2″), 131.31 (C-3″), 152.12 (C-4′), 153.28 (C-1′), 155.27 (C-1″); MS (*m*/*z*, relative intensity) 285 (M^+, 34), 213 (35), 199 (38) 86 (100); HRMS calcd for ($C_{16}H_{15}O_2NS$) 285.0824, found 285.0829. Anal. Calcd for $C_{16}H_{15}O_2NS$: C 67.34, H 5.30, N 4.91, S 11.23. Found: C 66,27, H 5.14, N 5.03, S 11.17.

2,6-Dimethylphenyl 4-Nitrophenyl Ether (74). 2,6-Dimethylphenol (**73**; 3.30 g, 25 mmol) was reacted with 4-chloronitrobenzene (3.87, 22 mmol) according to the method of preparation of **58**. The product was purified by column chromatography (silica gel) eluting with hexane−Cl_2CH_2 (24:1) to yield 3.356 g (63% yield) of pure compound **74** as a green solid: R_f 0.56 (hexane−CH_2Cl_2, 1:1); mp 51−52 °C; IR (KBr, cm^{-1}) 3448, 2927, 1605, 1529, 1488, 1342, 1237, 1178, 1107, 851, 786, 757; MS (*m*/*z*, relative intensity) 243 (M^+, 100), 226 (16), 196 (17), 105 (43), 77 (45).

4-Aminophenyl 2,6-Dimethylphenyl Ether (75). Nitro derivative **74** (1.95 g, 8.02 mmol) was hydrogenated as depicted for **59** affording 1.60 g (94% yield) of pure compound **74** as a white solid: mp 88−90 °C; R_f 0.20 (hexanes−EtOAc, 4:1); IR (KBr, cm^{-1}) 3434, 3368, 3348, 3230, 3059, 2953, 2921, 1637, 1506, 1473, 1274, 1216, 1091, 867, 841, 782; MS (*m*/*z*, relative intensity) 213 (M^+, 100), 108 (42), 93 (57).

2,6-Dimethylphenoxyphenol (76). Amino derivative **75** (1.30 g, 6.10 mmol) was treated as described for the preparation of **60**. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to afford 125 mg (10% yield) of pure phenol **76** as a colorless oil: R_f 0.26 (hexanes−EtOAc, 4:1); MS (*m*/*z*, relative intensity) 214 (M^+, 100), 121 (55).

2,6-Dimethylphenoxyphenyl Tetrahydro-2*H*-pyran-1-yl Ether (77). Compound **76** (110 mg, 0.51 mmol) was treated with bromoethyl tetrahydropyranyl ether as described for **11**. The product was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to afford 94 mg (54% yield) of pure compound **77** as a colorless oil: R_f 0.43 (hex-

anes−EtOAc, 4:1); ^{1}H NMR ($CDCl_3$) δ 1.53−1.85 (m, 6 H, H-3‴, H-4‴, H-5‴), 2.12 (s, 6 H, Ph*Me*), 3.51 (m, 1 H, H-6‴$_a$), 3.75−4.00 (m, 3 H, H-1, H-6‴$_b$), 4.02−4.12 (m, 2 H, H-2), 4.69 (distorted t, J = 2.9 Hz, 1 H, H-2‴), 6.65 (d, J = 9.2 Hz, 2 H, H-2), 6.82 (d, J = 9.1 Hz, 2 H, H-3), 7.05 (m, 3 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 16.29 (Ph*Me*), 19.33 (C-4‴), 25.39 (C-3‴), 30.48 (C-5‴), 62.12 (C-2‴), 65.90 (C-1), 68.05 (C-2), 98.93 (C-2‴), 115.14 (C-2′), 115.77 (C-3′), 124.81 (C-4″), 128.91 (C-3″), 131.50 (C-2″), 151.53 (C-4′), 152.11 (C-1′), 153.39 (C-1″); MS (*m*/*z*, relative intensity) 342 (M^+, 26), 214 (32), 129 (100); HRMS calcd for ($C_{21}H_{26}O_4$) 342.1831, found 342.1834.

2-Nitroxanthone (79). To a solution of xanthone (**78**; 5.00 g, 25.5 mmol) in concentrated sulfuric acid (14 mL) cooled at 0 °C was added dropwise fuming nitric acid (0.9 mL, 12.8 mmol) in concentrated sulfuric acid (3 mL). The reaction mixture was stirred at 0 °C for 40 min. The mixture was poured onto crushed ice. The solid was filtered off and was washed with cold water until pH 7. The residue was used as such in the next step without further purification. An analytical sample was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (4:1) as eluent to afford pure compound **79** as a white solid: mp 195−198 °C; R_f 0.50 (toluene); IR (KBr, cm^{-1}) 1668, 1614, 1533, 1462, 1348, 833, 770, 746, 669; ^{1}H NMR ($CDCl_3$) δ 7.34−7.58 (m, 3 H, H-5, H-7), 7.64 (d, J = 9.1 Hz, 1 H, H-4), 7.81 (m, 1 H, H-6), 8.35 (dd, J = 8.0, 1.6 Hz, 1 H, H-8), 8.55 (dd, J = 9.2, 2.8 Hz, 1 H, H-3), 9.21 (d, J = 2.8 Hz, 1 H, H-1); ^{13}C NMR ($CDCl_3$) δ 118.21 (C-5), 119.66 (C-4), 121.43 (C-8$_a$), 123.56 (C-7), 123.92 (C-9$_a$), 125.27 (C-4), 126.75 (q), 126.97 (C-3), 129.01 (C-8), 135.89 (C-6), 155.88 (C-5$_a$), 159.20 (C-4$_a$); MS (*m*/*z*, relative intensity) 241 (M^+, 36), 196 (100), 168 (49), 139 (88).

2-Aminoxanthone (80). A suspension of compound **79** in ethyl acetate (100 mL) in the presence of palladium on charcoal as catalyst (200 mg) was treated with hydrogen at 3 atm in a Parr apparatus. The mixture was shaken at room temperature for 6 h. The mixture was filtered and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexanes−EtOAc as eluent to afford 2.465 g (46% yield from xanthone, 91% yield taken the equivalents of nitric acid used) of pure compound **80** as a yellow solid: mp 190−192 °C; IR (KBr, cm^{-1}) 3412, 3321, 1641, 1618, 1593, 1491, 1466, 1327, 1209, 1147, 881, 756, 625; R_f 0.72 (hexanes−EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.18 (dd, J = 8.8, 2.8 Hz, 1 H, H-3), 7.32−7.55 (m, 3 H, H-1, H-7, H-5), 7.37 (d, J = 8.9 Hz, 1 H, H-4), 7.72 (m, 1 H, H-6), 8.29 (dd, J = 8.0, 1.5 Hz, 1 H, H-8), 8.48 (s, 1 H, H-); ^{13}C NMR ($CDCl_3$−CD_3OD, 20%) δ 108.45 (C-1), 117.78 (C-5), 118.67 (C-4), 120.85 (C-8$_a$), 121.82 (C-9$_a$), 123.27 (C-7), 124.08 (C-3), 126.13 (C-8), 134.43 (C-6), 143.24 (C-2), 156.07 (C-5$_a$), 168.52 (C-4$_a$), 177.80 (C-9); MS (*m*/*z*, relative intensity) 211 (M^+, 59), 196 (15), 69 (100).

2-Hydroxyxanthone (81). A solution of compound **80** (770 mg, 3.65 mmol) in glacial acetic acid (10 mL) was treated as described for the preparation of **60** to afford 280 mg (36% yield) of pure compound **81** as a red solid: R_f 0.10 (hexanes−EtOAc, 3:2); mp 176−177 °C; IR (KBr, cm^{-1}) 3312, 1659, 1628, 1487, 1460, 1348, 1237, 1153, 1109, 876, 821, 788, 757, 626; ^{1}H NMR ($CDCl_3$) δ 7.32−7.61 (m, 6 H, aromatic protons), 7.73 (m, 1 H, H-6), 8.28 (dd, J = 8.0, 1.5 Hz, H, H-8); ^{13}C NMR ($CDCl_3$) δ 108.69 (C-1), 117.72 (C-5), 118.97 (C-4), 120.58 (C-8$_a$), 121.70 (C-9$_a$), 123.38 (C-7), 124.47 (C-3), 126.00 (C-8), 134.56 (C-6), 150.09 (C-4$_a$), 153.37 (C-2), 156.02 (C-5$_a$); MS (*m*/*z*, relative intensity) 212 (M^+, 54), 184 (9), 69 (46), 55 (85), 43 (100).

2-[2-(Tetrahydro-2*H*-pyran-2-yl)oxyeth-1-yl]xanthone (82). A solution of phenol **81** (270 mg, 1.3 mmol) in methyl sulfoxide (3 mL) was treated as depicted for **11**. The product was purified by column chromatography eluting with hexanes−EtOAc (19:1) to afford 200 mg (45% yield) of pure compound **82** as a white solid: mp 92−93 °C; R_f 0.42 (hexanes−EtOAc, 3:2); ^{1}H NMR ($CDCl_3$) δ 1.55−1.81 (m, 6 H, H-3″, H-4″, H-5″), 3.53 (m, 1 H, H-6″$_a$), 3.80−3.97 (m, 2 H, H-6″$_b$, H-1$_a$), 4.10 (dt, J = 11.3, 4.5 Hz, 1 H, H-1$_b$), 4.27 (t, J = 5.4 Hz, 2 H, H-2), 4.72 (t, J = 3.3 Hz, 1 H, H-2″), 7.32−7.41 (m, 3 H, aromatic protons), 7.47 (d, J = 8.0 Hz, 1 H, H-4′), 7.68 (dd, J = 7.0, 1.6 Hz, 1 H, H-5′), 7.73 (d, J = 2.4 Hz, 1 H, H-1′), 8.34 (dd, J = 8.0, 1.7 Hz, 1 H, H-8′); ^{13}C NMR ($CDCl_3$) δ 19.35 (C-4″), 25.43 (C-3″), 30.53 (C-5″), 62.20 (C-2″), 65.73 (C-1), 68.22 (C-2), 99.02 (C-2″), 107.04 (C-1′), 117.94 (C-5′), 119.31 (C-4′), 121.31 (C-8$_a$′), 122.13 (C-9$_a$′), 123.68 (C-7′), 125.32 (C-3′), 126.70 (C-8′), 134.53 (C-6′), 151.06 (C-4$_a$′), 155.35 (C-2′), 156.15 (C-5$_a$′); MS (*m*/*z*, relative intensity) 340 (M^+, 9), 240 (26), 225 (20), 212 (62), 155 (11), 139 (21), 129 (26), 85 (80), 73 (74), 41 (100); HRMS calcd for ($C_{20}H_{20}O_5$) 340.1311, found 340.1315.

2-(2-Hydroxyeth-1-yl)xanthone (83). The tetrahydropyranyl group of compound **82** (150 mg, 0.44 mmol) was cleaved as described for **12** to give 112 mg (100% yield) of pure alcohol **83** as a white solid: mp 119−120 °C; IR (KBr, cm^{-1}) 3428, 2943, 1651, 1617, 1488, 1467, 1326, 1219, 1151, 1074, 1049, 919, 753; ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 1 H, −O*H*), 4.02 (distorted t, J = 4.5 Hz, 2 H, H-1), 4.22 (distorted t, J = 4.5 Hz, 2 H, H-2), 7.36−7.51 (m, 4 H, aromatic protons), 7.68−7.76 (m, 2 H, H-2), 8.24 (dd, J = 8.0, 1.7 Hz, 1 H, H-8′); ^{13}C NMR ($CDCl_3$) δ 61.34 (C-1), 69.94 (C-2), 106.95 (C-1′), 117.94 (C-5′), 119.53 (C-4′), 121.23 (C-8$_a$′), 122.12 (C-9$_a$′), 123.76 (C-7′), 125.05 (C-3′), 126.67 (C-8′), 134.65 (C-6′), 151.17 (C-4$_a$′), 155.00 (C-2′), 156.13 (C-5$_a$′), 177.02 (C-9′); MS (*m*/*z*, relative intensity) 256 (M^+, 31), 225 (17), 212 (100), 197 (7), 184 (24), 155 (10).

2-[2-(4-Toluenesulfonyloxy)eth-1-yl]xanthone (84). Alcohol **83** (100 mg, 0.39 mmol) was treated with tosyl chloride (110 mg, 0.58 mmol) as described for **13** to afford 125 mg of pure tosylate **84** (78% yield) as a white solid: IR (KBr, cm^{-1}) 2967, 2941, 1662, 1619, 1495, 1473, 1222, 1175, 1148, 1071, 1029; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3 H, Ph*Me*), 4.25 (m, 2 H, H-2), 4.40 (m, 2 H, H-1), 7.19−7.25 (m, 1 H, aromatic protons), 7.34 (d, J = 8.2 Hz, 2 H, H-3″), 7.38−7.57 (m, 4 H, aromatic protons), 7.83 (d, J = 8.2 Hz, 2 H, H-2″), 7.67−7.75 (m, 2 H, H-), 8.31 (dd, J = 8.0, 1.6 Hz, 1 H, H-8′); ^{13}C NMR ($CDCl_3$) δ 21.56 (Ph*Me*), 66.03 (C-1), 67.93 (C-2), 106.84 (C-1′), 117.91 (C-5′), 119.52 (C-4′), 121.12 (C-8$_a$′), 121.93 (C-9$_a$′), 123.78 (C-7′), 124.98 (C-3′), 126.57 (C-8′), 127.96 (C-2″), 129.85 (C-3″), 134.65 (C-6′), 144.97 (C-1″), 151.20 (C-4$_a$′), 154.27 (C-2′), 156.03 (C-5$_a$′), 176.77 (C-9′); MS (*m*/*z*, relative intensity) 410 (M^+, 26), 211 (22), 199 (96), 155 (52), 91 (100).

2-(2-Thiacyanoeth-1-yl)xanthone (85). A solution of tosylate **84** (114 mg, 0.28 mmol) in dimethylformamide (3 mL) was treated with potassium thiocyanate (300 mg, 3.1 mmol) as depicted for **15**. After the usual treatment, the product was purified by column chromatography employing a mixture of hexanes−EtOAc (19:1) as eluent to afford 59 mg (71% yield) of pure thiocyanate **75** as a white solid: mp 140−141 °C; IR (KBr, cm^{-1}) 2924, 2852, 2153, 1647, 1616, 1495, 1465, 1320, 1235, 1219, 1161, 1028, 888, 755; ^{1}H NMR ($CDCl_3$) δ 3.40 (t, J = 5.7 Hz, 2 H, H-1), 4.46 (t, J = 5.7 Hz, 2 H, H-2), 7.36−7.52 (m, 4 H, aromatic protons), 7.70−7.78 (m, 2 H, aromatic protons), 8.31 (dd, J = 9.0, 1.6 Hz, 1 H, H-8′); ^{13}C NMR ($CDCl_3$) δ 33.12 (C-1), 66.46 (C-2), 106.92 (C-1′), 117.89 (C-5′), 119.69 (C-4′), 121.05 (C-8$_a$′), 121.95 (C-9$_a$′), 123.74 (C-7′), 124.94 (C-3′), 126.48 (C-8′), 134.64 (C-6′), 151.63 (C-4$_a$′), 154.04 (C-2′), 155.97 (C-5$_a$′), 176.66 (C-9′); MS (*m*/*z*, relative intensity) 297 (M^+, 82), 274 (24), 211 (100), 184 (25), 155 (47); HRMS calcd for ($C_{16}H_{11}O_3NS$) 297.0460, found 297.0459.

(*S*)-1-(4-Phenoxyphenoxy)propan-2-ol (87). A solution of 4-phenoxyphenol (**86**; 1.0 g, 5.4 mmol) in methyl sulfoxide (3 mL) was treated with *S*-propylene oxide (320 mg, 0.4 mL, 5.5 mmol) and the mixture was stirred at room temperature for 6 h. The reaction mixture was quenched as depicted for **11**, and the residue was purified by column chromatography employing a mixture of hexanes−EtOAc (19:1) as eluent to give 266 mg (20% yield) of alcohol **87** as a white solid: R_f 0.51 (toluene-EtOAc, 4:1); mp 67−69 °C; $[\alpha]_D$ +18.2 (*c* 1.0, $CHCl_3$).

(*S*)-1-(4-Phenoxyphenoxy)propan-2-yl 4-Toluenesulfonate (88). Alcohol **87** (266 mg, 1.09 mmol) was treated with tosyl chloride as depicted for **13**. After the usual workup, 283 mg (87% yield) of pure tosylate **88** were obtained as a colorless oil: R_f 0.67 (toluene−EtOAc, 4:1); $[\alpha]_D$ −26.1 (*c* 1.7, chloroform); mp 102−104 °C; IR (KBr, cm^{-1}) 3065, 2984, 2926, 2874, 1597, 1504, 1489, 1364, 1225, 1190, 1045, 928, 903, 768, 665, 555; MS (*m*/*z*, relative intensity) 398 (M^+, 26), 213 (33), 185 (23), 155 (100), 91 (83).

(*R*)-1-(4-Phenoxyphenoxy)propan-2-yl Thiocyanate (89). Compound **88** (283 mg, 0.71 mmol) was reacted with potassium thiocyanate according to the method of preparation of **15** and was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to afford 117 mg (58% yield) of pure **89** as a colorless oil: $[\alpha]_D$ −28.5 (*c* 1.0, chloroform); IR (film, cm^{-1}) 3063, 2974, 2934, 2870, 2153, 1589, 1504, 1489, 1390, 1219, 1022, 843, 750, 692, 511; ^{1}H NMR ($CDCl_3$) δ 1.62 (d, J = 6.9 Hz, 3 H, H-3), 3.63 (m, 1 H, H-2), 4.11 (d, J = 6.1 Hz, 2 H, H-1), 6.86−7.09 (m, 7 H, aromatic protons), 7.26−7.34 (m, 2 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 18.14 (C-3), 43.51 (C-2), 71.42 (C-1), 115.89 (C-2″), 117.82 (C-2′), 120.70 (C-3′), 122.69 (C-4″), 129.62 (C-3″), 151.18 (C-4′), 154.06 (C-1′), 158.13 (C-1″); MS (*m*/*z*, relative intensity) 285 (M^+, 6), 272 (11), 251 (3), 186 (23), 87 (100); HRMS calcd for ($C_{16}H_{15}O_2NS$) 285.0824, found 285.0828. Anal. ($C_{16}H_{15}O_2NS$) C, H, N, S.

(*R*)-1-(4-Phenoxyphenoxy)propan-2-ol (90). 4-Phenoxyphenol (**86**; 900 mg, 4.8 mmol) was treated with *R*-propylene oxide (280 mg, 0.35 mL, 4.8 mmol) as depicted for **87**. The product was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to yield 175 mg (15% yield) of pure alcohol **90** as a white solid: R_f 0.51 (toluene−EtOAc, 4:1); mp 69−71 °C; $[\alpha]_D$ −19.0 (*c* 1.0, $CHCl_3$).

(*R*)-1-(4-Phenoxyphenoxy)propan-2-yl 4-Toluenesulfonate (91). Alcohol **90** (132 mg, 0.5 mmol) was transformed into tosylate **91** (colorless oil) in quantitative yield as depicted for **88**: $[\alpha]_D$ + 26.2 (*c* 1.0, chloroform); mp 101−103 °C.

(*S*)-1-(4-Phenoxyphenoxy)propan-2-yl Thiocyanate (92). Compound **92** was obtained from compound **91** (152.2 mg, 0.38 mmol) in 55% yield as depicted for **89**: $[\alpha]_D$ +28.4 (*c* 0.3, chloroform); HRMS calcd for ($C_{16}H_{15}O_2NS$) 285.0824, found 285.0821. Anal. ($C_{16}H_{15}O_2NS$) C, H, N, S.

Drug Screening. Biological assays on epimastigotes were performed as previously described.[32]

T. cruzi epimastigotes (Y strain) were grown in 20-mL screw-cap tubes at 28 °C in a liquid medium containing brain−heart infusion (37 g/L), hemin chlorohydrate (20 mg/L) (dissolved in 50% triethanolamine) and 10% newborn calf serum. The initial inoculum contained (2−3) × 10^6 cells/mL (as determined by counting in a Neubauer chamber) in a final volume of 1 mL. The concentration of cells was determined by measuring the absorbance of the culture medium containing parasites at 600 nm against a blank with culture medium alone. Each drug was tested at four different concentrations (1, 10, 50 and 100 μg/mL) each one in quadruplicate. Drugs were dissolved in ethanol. A control without drug was done with each group that was tested.

To calculate percent inhibition, the following formula was used: $100 - [(\Delta A_d \times 100)/\Delta A_c]$ = percent inhibition, where ΔA_c and ΔA_d are the differences in the absorbance of control cultures and drug-treated cultures, respectively, at the beginning and end of the experiment. The maximum amount of solvent used (1% ethanol) did not have any significant effect on the epimastigotes growth. The values of IC_{50} were estimated by linear and polynomial regression.

Experiments on the intracellular form of the parasite were conducted on *T. cruzi*-infected L_6E_9 myoblasts (Y strain) as described before.[54] L_6E_9 myoblasts were exposed to 2000 rads of γ radiation and plated on 75-cm^2 flasks at a density of 1.2 × 107 cells/flask in DMEM containing 20% fetal calf serum in a total volume of 10 mL. After 24 h of incubation at 35 °C, the cells were exposed to a suspension of 5 × 10^7 trypomastigotes/flask in DMEM containing 20% fetal calf serum for 2 h, then cultures were washed twice with Dulbecco′ PBS and the culture medium was replaced. Different concentrations of drugs were added to the cultures that were labeled with 1.0 μCi of [*5,6*-^{3}H]uracil and incubated for an additional 72 h. Incorporation of of [^{3}H]uracil was measured, the percent inhibition of [^{3}H]uracil incorporation (parasite proliferation) was calculated employing the following formula: inhibition percent = $[(A - B)/A] \times 100$, where A is the mean counts per minute of infected control-treated myoblasts and B is the mean counts per minute of infected drug-treated myoblasts.

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Supporting Information Available: NMR spectral data for compounds **12**−**14**, **17**, **19**−**23**, **27, 28**, **32**, **33**, **35**, **37**, **38**, **41**, **42**, **45**, **46**, **50**, **51**, **55**, **56**, **58**−**60**, **62**, **63**, **66**, **68**, **70**, **71**, **74**−**76**, **87,** and **88** and tables of data needed to calculate percent inhibition. This material is available free of charge via the Internet at http://pubs.acs.org.

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