Structure−Activity Relationship of New Growth Inhibitors of *Trypanosoma cruzi*

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Several drugs bearing the 4-phenoxyphenoxy skeleton and other closely related structures were designed, synthesized, and evaluated as antiproliferative agents against *Trypanosoma cruzi*, the etiologic agent of Chagas' disease. The new class of drugs was envisioned by modifying the nonpolar 4-phenoxyphenoxy moiety replacing selected aromatic protons by different groups via electrophilic aromatic substitution reactions as well as introducing a sulfur atom at the polar extreme. Of the designed compounds, sulfur-containing derivatives were shown to be potent antireplicative agents against *T. cruzi*. Among these drugs, 4-phenoxyphenoxyethyl thiocyanate (compound **56**) proved to be an extremely active growth inhibitor of the epimastigote forms of *T. cruzi* and displayed an IC_{50} of 2.2 μM. Under the same assay conditions, this drug was much more active than Nifurtimox, one of the drugs currently in clinical use to control this disease. This thiocyanate derivative was also a very active inhibitor against the intracellular form of the parasite at the nanomolar level. Other sulfur derivatives prepared also exhibited very potent antiproliferative action against *T. cruzi*. The presence of a sulfur atom at the polar extreme for this family of compounds seems to be very important for biological action because this atom was always associated with high inhibition values. 4-Phenoxyphenoxyethyl thiocyanate presents very good prospective not only as a lead drug but also as a potential chemotherapeutic agent.

Introduction

It has been estimated that around 16−18 million people are infected with *Trypanosoma cruzi*, the etiologic agent of American trypanosomiasis (Chagas' disease), that 2−3 million individuals have the clinical symptoms that characterize the chronic stage of Chagas' disease, and that 45 000 of them die each year.[1,2]

The parasite has a complex life cycle involving blood-sucking Reduviid insects and mammals.[3] It multiplies in the insect gut as an epimastigote form and is spread as a nondividing metacyclic trypomastigote from the insect feces by contamination of intact mucosa or wounds produced by the blood-sucking activity of the vector. In the mammalian host, *T. cruzi* multiplies intracellularly in the amastigote form and is subsequently released into the blood stream as a nondividing trypomastigote.[3] Transmission of Chagas' disease could also occur via the placenta or blood transfusion.[3] This latter mechanism is responsible for the occurrence of Chagas' disease in developed countries where the disease is not endemic.[4,5]

Two drugs, Nifurtimox (4-[(5-nitrofurfurylidene)-amino]-3-methylthiomorpholine 1,1-dioxide, **1**) and Benznidazole (*N*-benzyl-2-nitro-1-imidazoleacetamide, **2**) (Chart 1), have been shown to cure at least 50% of recent infections as demonstrated by the disappearance of symptoms and the negativization of parasitemia and serology.[6−8] However, results of treatment trials for acute infections have not been homogeneous in the different countries,[6,7] probably because of the different drug sensitivity of the distinct *T. cruzi* strains. In addition, both drugs produce serious side effects.[9] Treatment duration is another drawback as both drugs have to be given for prolonged periods. The usefulness of these drugs for parasitological cure in the indeterminate or chronic stage of the infections has also been questioned; after treatment, serology remains positive in most cases even when parasitemia is absent.[10] Gentian Violet (*N*-{4,4-bis[[4-(dimethylamino)phenyl]-methylene]-2,5-cyclohexadien-1-ylidene}-*N*-methylammonium chloride, **3**) is the only drug available as a

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

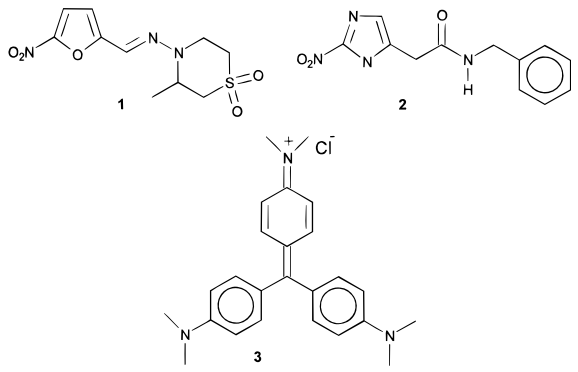

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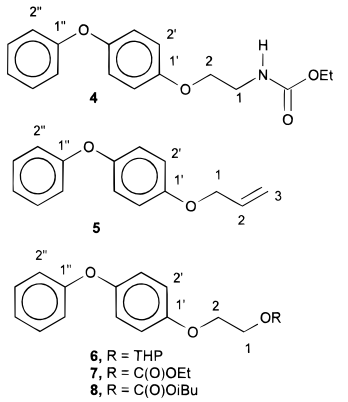
Chart 2. Chemical Structures of Fenoxycarb and Four Inhibitors of *T. cruzi* Proliferation Taken as Lead Drugs



chemoprophylactic agent to prevent blood transmission of Chagas' disease.[11] However, this drug is carcinogenic in animals, and safety concerns have been raised against its use (Chart 1).[12]

The above findings stress the need of having chemotherapeutic and chemoprophylactic agents that are effective against all strains of *T. cruzi* and with less or no side effects than those currently available.[12,13]

In the present study, we investigated the trypanostatic activity of the lead structures (compounds **4**−**8**) (Chart 2) which present a dual action, as juvenile hormone analogues of Chagas' disease vector *Triatoma infestans*[14,15] and as potent growth inhibitors of *T. cruzi* proliferation.[16] Juvenile hormones are crucial compounds for maintaining larval stages and maturation of the reproductive system in the female.[17] These compounds have been studied as a consequence of the finding that after treatment of the insects with the well-known insect growth regulator Fenoxycarb[18] (ethyl *N*-{2-[(4-phenoxyphenoxy)ethyl]}carbamate, **4**), they were more resistant to infection with *T. cruzi*.[19] Some modified structures having the 4-phenoxyphenoxy moiety were found later to be more active than Fenoxycarb against *T. cruzi* cells. Preliminary studies on the mode of action of these drugs have provided evidence that they could be inhibitors of the sterol biosynthetic pathway.[20,21] Very recently, we have found that this class of inhibitors blocks the sterol biosynthetic pathway at an early stage.[22] Since this pathway is different in *T. cruzi* from that present in mammalian cells,[23] we anticipate a lower toxicity of these compounds toward the host cells. It is interesting to note that sterol biosynthesis inhibitors have been postulated to be potential chemotherapeutic agents against Chagas' disease.[23−25]

Compound **6**, one of the representative members of our designed drugs and structurally related to Fenoxycarb, was a very effective agent against the intracellular form of the parasite,[26] and, as occurs with other ergosterol biosynthesis inhibitors,[25] it exhibited vanishing action to eradicate the nonproliferative trypomastigotes.[27]

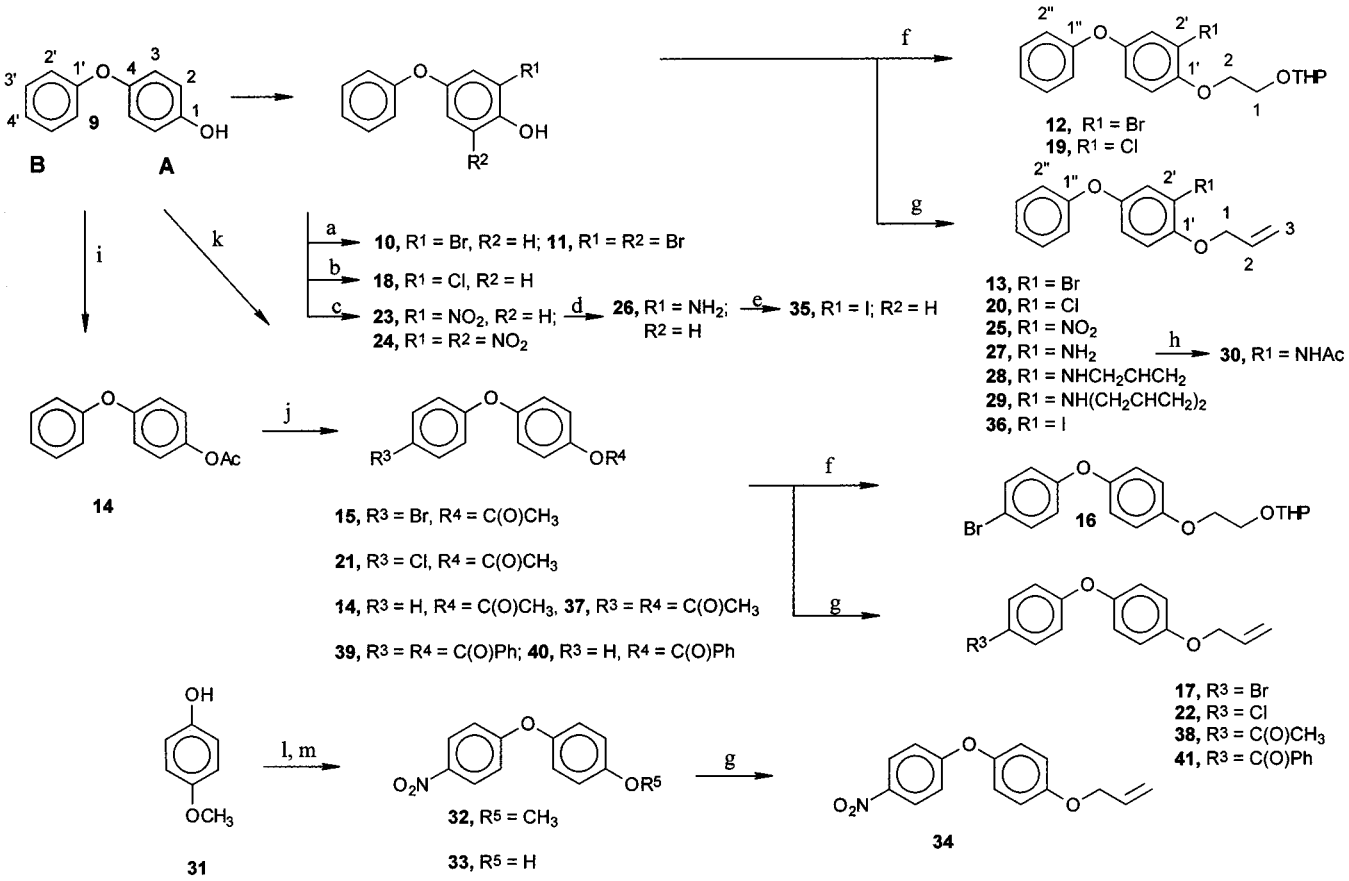
As part of our efforts to improve the antireplicative activity of these inhibitors against *T. cruzi*, and in order to investigate their structure−activity relationship, we prepared a series of new derivatives structurally related to our lead drugs (compounds **5**−**8**) and evaluated their biological activity (Chart 2).

Rationale

The presence of the 4-phenoxyphenoxy moiety at the nonpolar extreme of a number of selected drugs is crucial to maintain high growth inhibitory action against *T. cruzi*.[28−30] Replacement of the phenoxy group by a methoxy or a benzoyl groups accomplishes a dramatic impairing in the biological activity.[30] The design and synthesis of the new compounds in this work was encouraged by the potent antiparasitic activity shown by compounds **5**−**8**[16,28,29] taken as lead drugs. Therefore, a new set of related compounds possessing the 4-phenoxyphenoxy moiety and closely related frames and a sulfur derivative at the polar end of these drugs were designed, prepared, and evaluated against the epimastigote form of *T. cruzi* which is, by far, the preferred model to screen new drugs.

Then, bearing in mind that the 4-phenoxyphenoxy skeleton showed a marked influence in modulating biological activity, it seemed interesting to replace an aromatic hydrogen atom by different atoms or groups in order to see their influence on biological activity. Employing 4-phenoxyphenol as starting material, the more attractive positions to carry out this idea were the ortho position (C-2) to the phenol group at the A ring for being a favorite site for electrophilic aromatic substitution and the para position (C-4′) at the B ring by partial deactivation of the A ring with an electron-withdrawing group (Scheme 1). Accordingly, bromine, chorine, nitro, and iodine functions were selected as suitable units to be introduced at the aromatic ring. It was decided to use tetrahydropyranyl and allyl ethers as terminal polar ends due to the high activity previously presented by these groups.[30] Thus, treatment of 4-phenoxyphenol with bromine in toluene in the presence of *tert*-butylamine at low temperature led to a monobromo derivative at the ortho position (compound **10**) and a small amount of the dibromo derivative **11**.[31] Analysis of the ^{13}C NMR spectrum of **10** indicated the presence of 10 nonequivalent carbons. These data, together with the corresponding chemical shifts and the mass spectrum showing the pattern for monobromination, were quite in agreement with the substitution at C-2. Drugs **12** and **13** were straightforwardly prepared by treatment with bromoethyl tetrahydropyranyl ether and allyl ether, respectively, by a modified Williamson methodology.[32] On the other hand, the presence of an acetyl group at C-1 (compound **14**) deactivated the A ring in such a way that the preferred site for an electrophilic aromatic substitution was the C-4′ position. Therefore, treatment of acetate **14** with aqueous bromine gave rise to monobromo derivative **15**[33] that when treated under these modified Williamson conditions with the appropriate halides brought about acetyl cleavage producing drugs **16** and **17** in good yields, respectively. Monochlorophenol derivative **18** was successfully prepared in moderate yield treating phenol **9** with *N*-chlorosuccinimide in refluxing benzene.[34] This product was transformed into drugs **19** and **20** by reaction of the respective halides. The preparation of the chloro derivative at the C-4′ position (compound **21**) was achieved via the respective acetate **14** by treatment with 1-chlorobenzotriazole with moderate yield.[35] Transformation of **21** into **22** was carried out by treatment with allyl bromide. Phenol **9** reacted with 70% nitric

Scheme 1[a]



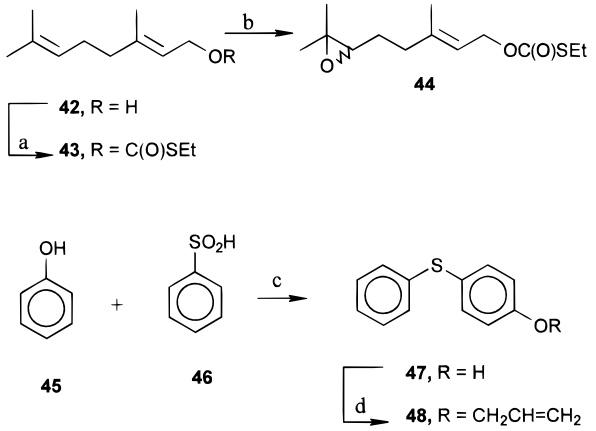
[a] Reagents: (a) Br_2/*t*-BuNH_2, toluene, −70 °C (45%); (b) NCS, benzene, reflux, 48 h (46%); (c) 70% HNO_3/AcOH, rt, 15 min (70%); (d) H_2, 10% Pd/C, EtOAc, 3 atm, rt, 1 h (92%); (e) H_2SO_4/H_2O, $NaNO_2$, 0 °C, i. NaI, CuCl, rt (20%); (f) $BrCH_2CH_2OTHP$, KOH/DMSO, rt (33% for **12**, 60% for **16**, 74% for **19**); (g) allyl bromide, KOH/DMSO, rt (88% for **13**, 81% for **17**, 75% for **20**, 68% for **22**, 17% for **25**, 65% for **27**, 80% for **34**, 54% for **36**, 38% for **38**, 79% for **41**); (h) Ac_2O/py, rt, overnight (63%); (i) Ac_2O/py, rt, 16 h (87%); (j) Br_2/H_2O, rt, 2 h (58% for **15**), 1-chlorobenzotriazole, CH_2Cl_2, rt, 6 d (49% for **21**); (k) S_2C, CH_3COCl, $AlCl_3$, −5 °C, 2 h (26% for **37**), S_2C, PhCOCl, $AlCl_3$, −5 °C, 2 h (15% for **40**); (l) 1-chloro-4-nitrobenzene, DMSO/KOH, CuCl, 70 °C, 16 h (45%); (m) CH_3CH_2SH, $AlCl_3$, 0 °C, 3 h (91%).

acid in glacial acetic acid[36] to give mononitrophenol **23** as the main product in good yield and the 2,6-dinitro derivative **25** as a side product. Compound **23** on treatment with allyl bromide was transformed into drug **25**. The nitro compound **23** was reduced by catalytic hydrogenation employing palladium on charcoal as catalyst[37] to afford aminophenol **26**, which on reaction with allyl bromide gave rise to allyl ether **27** as the main product and the undesired *N*-alkyl products **28** and **29** as minor components. Compound **26** was converted into the amide **30** by treatment with acetic anhydride. Nitration at the C-4′ of 4-phenoxyphenol was performed employing a nucleophilic aromatic substitution as the key step. Then, 4-methoxyphenol (compound **31**) was condensed with 4-nitrochlorobenzene in the presence of cuprous ion[38] to give the mononitro derivative **32**. Demethylation of **32** by treatment with mercaptoethanol and aluminum chloride[39] gave free phenol **33**, which on reaction with allyl bromide led to **34** in good yields. The synthesis of the *o*-iodo derivative **36** was achieved employing aminophenol **26** as intermediate.[40] Then, on treatment with sodium nitrite in sulfuric acid followed by addition of sodium iodide in the presence of cuprous chloride and further reaction with allyl bromide, **26** was converted into drug **36** (Scheme 1). Acyl derivatives at the C-4′ position were carried out via Friedel−Crafts methodology employing 4-phenoxyphenol (**9**) as starting material. This compound when treated with either acetyl or benzoyl chloride in carbon disulfide using aluminum chloride as catalyst[41] led to the acylated product at the hydroxyl group as main products in both cases (compounds **14** and **40**, respectively) and the desired C-4′ acylated compounds **37** and **39** as minor products. On reaction with allyl bromide, these compounds were converted into drugs **38** and **41** (Scheme 1).

Since compounds with an isoprenic skeleton had presented potent inhibitory action against *T. cruzi* proliferation, it was decided to prepare two drugs bearing sulfur atoms at their polar ends using geraniol as the isoprenic source. Then, geraniol (compound **42**) was treated with ethyl chlorothiolformate to give **43** that after treatment with *m*-chloroperbenzoic acid led to epoxy derivative **44**. To investigate the influence of the oxygen atom between the phenyl groups on the biological activity, it was decided to replace it by a sulfur atom. Therefore, phenol (**45**) was treated with recently prepared benzenesulfinic acid (**46**) to afford **47** in moderate yield.[42] After reaction with allyl bromide, **47** was transformed into **48** (Scheme 2).

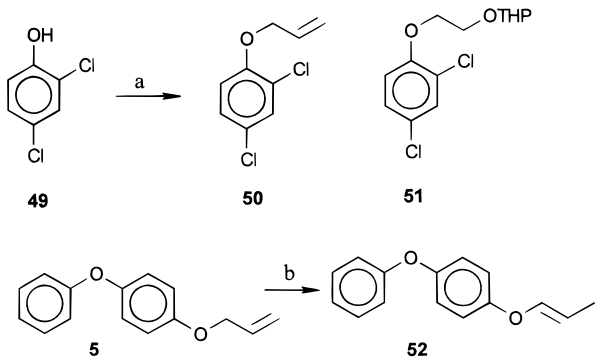
Some related modification was also contemplated by adding two extra chlorine atoms at the A ring and deleting the phenoxy group to determine the control of this phenoxy unit on biological activity. Then, 2,4-dichlorophenol (compound **49**) was converted into **50** and **51** in the usual way (Scheme 3).

Scheme 2[a]



[a] Reagents: (a) ClC(O)SEt/py, rt, 16 h (93%); (b) *m*-CPBA, Cl_2CH_2, 0 °C, 3 h (93%); (c) 60 °C, 1 h (19%); (d) allyl bromide, KOH/DMSO, rt, 3 h (96%).

Scheme 3[a]

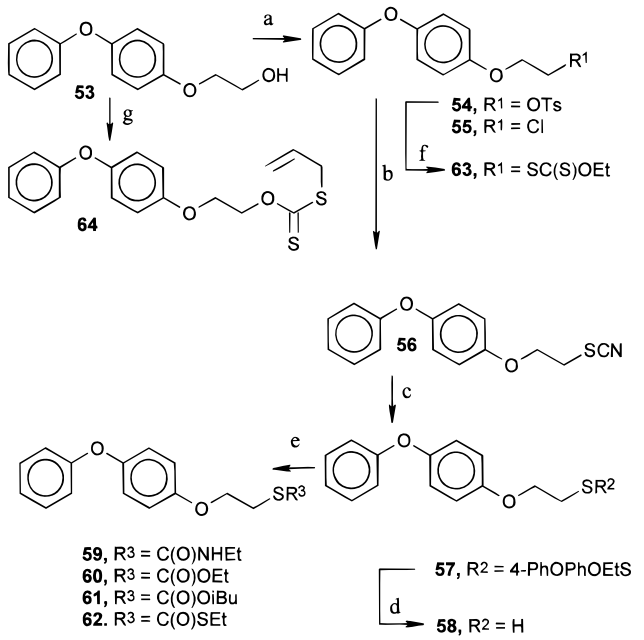


[a] Reagents: (a) allyl bromide, KOH/DMSO, rt, 3 h (73% for **50**), $BrCH_2CH_2OTHP$, KOH/DMSO, rt (28% for **51**); (b) *n*-BuLi, THF, 2 °C (28%).

As the allyl ether group is frequently found in drugs with high inhibitory action, it was interesting to study the biological activity of its isomer vinyl ether (compound **52**). This drug was easily obtained by treatment of **5** with *n*-butyllithium in tetrahydrofuran[43] (Scheme 3).

Another structural variation was the replacement of the oxygen atom at carbon-1 of the aliphatic chain by a sulfur atom, giving rise to a series of thiolcarbamate, thiolcarbonate, and xanthate derivatives, to study their influence on the biological activity. The synthesis of analogues of compounds **5**−**8** having a sulfur atom at the polar end was carried out employing as starting material the readily available alcohol **53**, which was straightforwardly prepared from 4-phenoxyphenol.[15] Therefore, alcohol **53** was treated with tosyl chloride to afford the expected tosylate **54** with good yield and the undesired chloride derivative (compound **57**) as a side product (Scheme 4). Tosylate **54** was transformed into the thiocyanate derivative **56** by treatment with potassium thiocyanate[44] in *N*,*N*-dimethylformamide at 100 °C. Thiocyanates are able to undergo thermal rearrangements under these conditions,[45] but no formation of the undesired isothiocyanate product was detected. Analysis of the ^{13}C NMR spectrum for compound **56** showed a signal corresponding to the thiocyanate group at 113.47 ppm, which agreed perfectly with the single formation of this compound.[46] Alkyl isothiocyanates

Scheme 4[a]

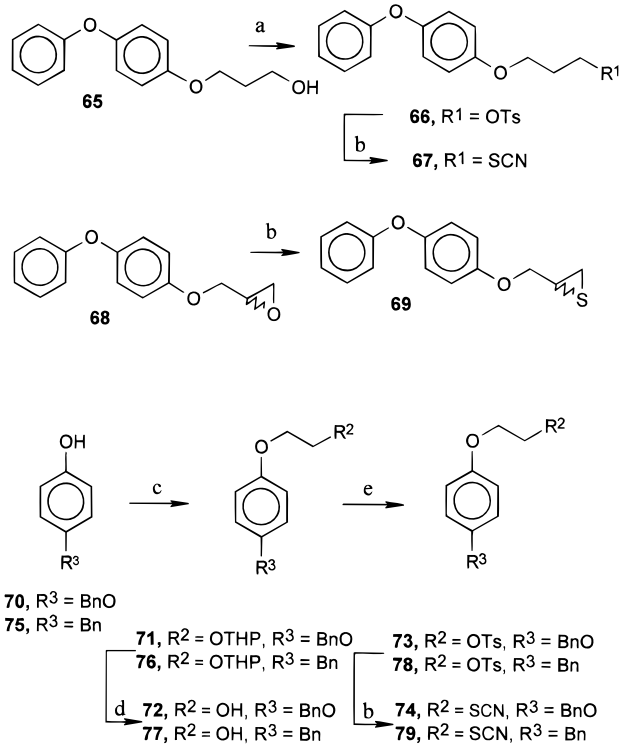


[a] Reagents: (a) ClTs/py, rt, 4 h (70% for **54**, 17% for **55**); (b) KSCN, DMF, 100 °C, 3 h (73%); (c) $NaOCH_3/CH_3OH$, rt, 2 h (98%); (d) Zn/AcOH, 11 °C, 1 h (91%); (e) EtNCO/py, rt, overnight (56% for **59**), ClCOOEt/py, rt, overnight (55% for **60**), ClCOO*i*-Bu/py, rt, overnight (40% for **61**), ClC(O)SEt/py, rt, overnight (44% for **62**); (f) KSC(S)OEt/DMSO, 90 °C, 2 h (86%); (g) i. DBU, S_2C, DMF, rt, 20 min, ii. allyl bromide, rt, 30 min (39%).

would show the respective peak at lower fields (∼130 ppm).[46] Saponification of **56** with sodium methoxide[45] gave rise to the disulfide derivative (compound **57**) as the main product and a small amount of the desired product, the mercaptane **58**. Treatment of this mixture of products with zinc in boiling acetic acid[47] led to pure compound **58** with excellent yield. Mercaptane **58** was the common intermediate for the preparation of thiolcarbonate and thiolcarbamate derivatives. Therefore, compound **58** reacted with ethyl isocyanate, ethyl chloroformate, isobutyl chloroformate, and ethyl chlorothiolformate to give compounds **59**, **60**, **61**, and **62**, respectively, in moderate yields. To study the influence of an extra sulfur atom, the preparation of xanthate derivatives was the second modification considered by replacing the oxygen atom of the carbonyl group by a sulfur atom. Two types of sulfur derivatives were prepared, the first with the sulfur atom on the same side of the aliphatic chain (carbon-1) and the second with it on the opposite position. Therefore, tosylate **54** was treated with potassium *O*-ethyl xanthate[32] to afford xanthate derivative **63** in good yield. On the other hand, on reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and carbon disulfide[48] followed by addition of allyl bromide, **55** was converted into xanthate **64** (Scheme 4).

Since preliminary biological assays had indicated the strong influence of a sulfur atom on biological activity, especially the thiocyanate group, it was decided to prepare a set of closely related compounds so as to find an optimal structure. It was interesting to assess the influence of the aliphatic chain length on biological activity by increasing it in one carbon. This transformation was carried out from the readily available alcohol **65**,[29] which was treated with tosyl chloride to

Scheme 5[a]



[a] Reagents: (a) ClTs/py, rt (60%); (b) KSCN, DMF, 100 °C, 3 h (87% for **67**, 47% for **69**); (c) $BrCH_2CH_2OTHP$, KOH/DMSO, rt (55% for **71**, 65% for **76**); (d) PPTs, MeOH, rt (82% for **72**, 77% for **77**); (e) ClTs/py, rt (82% for **73**, 63% for **78**); (f) KSCN, DMF, 100 °C (70% for **74**, 52% for **79**).

give **66**, followed by nucleophilic displacement with potassium thiocyanate to give **67**. An episulfide group was also attached to the same chain length by reaction of epoxide **68**[29] with potassium thiocyanate[49] to give **69** (Scheme 5). To study the influence of the spacial alignment of the terminal phenyl group, a slight modification at the aromatic skeleton was also considering by replacing the phenoxy moiety by a benzyloxy and benzyl group keeping the thiocyanate function as the polar end. Therefore, employing 4-(benzyloxy)phenol and 4-benzylphenol (compounds **70** and **75**, respectively) as starting materials, these compounds were transformed into tetrahydropyranyl derivatives **71** and **76**, which following a similar method as depicted for **56** were converted into thiocyanates **74** and **79** in good yields (Scheme 5).

Drug Screening

Biological assays on epimastigotes were performed as previously described.[30] *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 performed with each group that was tested.

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

compd	IC_{50} (μM)	compd	IC_{50} (μM)
1, Nifurtimox	8.6	**5**	221
12	67	**13**	182
16	85	**17**	>250
19	143	**20**	>250
22	>250	**25**	185
30	97	**34**	230
36	91	**38**	300
41	>330	**43**	298
44	>380	**48**	324
50	282	**51**	93
52	>440	**56**	2.2
59	17.0	**60**	15.1
61	19.1	**62**	37.7
63	41.9	**64**	96.1
67	3.5	**69**	3.9
71	121	**74**	8.1
76	282	**79**	13.4

To calculate percent inhibition, the following formula was used:

$$100 - \frac{(\Delta A_d \times 100)}{\Delta A_c} = \text{percent inhibition}$$

where ΔA_c and ΔA_d are the differences in the absorbance of control cultures and drug-treated cultures, respectively, at the beginning and at the end of the experiment. The maximum amount of solvent used (1% ethanol) did not have any significant effect on the epimastigote growth. The values of IC_{50} were estimated by linear and polynomial regression. The results are presented in Table 1.

Experiments on the intracellular form of the parasite were conducted on *T. cruzi*-infected L_6E_9 myoblasts as described before.[26]

Confluent cell myoblast cell monolayers were prepared on 0.9- × 0.9-cm coverslips in tissue culture chambers (three coverslips per treatment). Myoblasts was trypsinized and counted in a Neubauer hemacytometer. The same amount of cells was inoculated in each chamber. The monolayers were washed three times with phosphate-buffered saline (PBS) at 37 °C after 4 h. Some monolayers were exposed to a suspension of tissue culture-derived trypomastigotes in DMEM-10% FBS (1 mL/chamber). The final concentration of trypomastigotes was calculated based on a ratio of 8:1 parasites:L_6E_9 cells. The parasites were allowed to internalize within the myoblast for 24 h. At this time, a set *T. cruzi*-infected cultures was fixed and stained with Giemsa and was designated as the 24-h control culture. The media from the remaining slides were removed, and fresh DMEM-10% FBS alone (control) or containing drug **1** or **56** was added to the cultures. After a further 24 h of incubation at 37 °C, a set of *T. cruzi*-infected cultures (untreated control and drug-treated) was fixed and stained with Giemsa. Media were removed from other cultures, and again, fresh DMEM-10% FBS alone (control) or containing compound **1** or **56** was added to the cultures. Cultures were incubated (37 °C) for a further 24 h after which they were fixed and stained with Giemsa. Infection was assessed by the percentage of myoblasts with intracellular parasites and by the number of parasites present in 100 myoblasts.

Table 2. Growth Inhibition of Intracellular *T. cruzi* by **56**

drug **56**	% myoblasts with parasites	no. of parasites/ 100 myoblasts (%R)[a]
none (24 h)	26.0 ± 6.0	91.8 ± 8.25
none (48 h)	21.5 ± 1.5	239.5 ± 32.5
0.1 (μg/mL)	22.0 ± 2.0	218.0 ± 42.0 (9)
0.5 (μg/mL)	18.3 ± 4.8	98.0 ± 25.0 (59)
1.0 (μg/mL)	19.3 ± 4.8	69.3 ± 25.0 (71)
none (72 h)	27.5 ± 0.5	578.5 ± 7.5
0.1 (μg/mL)	15.5 ± 0.5	238.0 ± 59.0 (59)
0.5 (μg/mL)	12.5 ± 0.5	124.5 ± 29.3 (79)
1.0 (μg/mL)	15.0 ± 3.0	63.5 ± 10.5 (89)
none (24 h)	38.0 ± 2.0	85.0 ± 3.0
none (48 h)	31.5 ± 1.5	270.5 ± 6.8
1.0 (μg/mL)	20.5 ± 0.5	59.3 ± 4.3 (78)
2.5 (μg/mL)	20.3 ± 1.3	57.0 ± 2.0 (78)
5.0 (μg/mL)	19.8 ± 2.8	48.0 ± 3.5 (82)
none (72 h)	24.8 ± 4.8	733.5 ± 15.5
1.0 (μg/mL)	16.3 ± 0.8	85.5 ± 10.0 (88)
2.5 (μg/mL)	17.0 ± 0.0	76.3 ± 0.8 (90)
5.0 (μg/mL)	8.3 ± 2.3	28.0 ± 1.0 (96)

[a] % R, percent reduction compared to control.

Table 3. Growth Inhibition of Intracellular *T. cruzi* by Nifurtimox

1, nifurtimox	% myoblasts with parasites	no. of parasites/ myoblasts (%R)[a]
none (24 h)	34.50 ± 2.50	80.25 ± 1.25
none (48 h)	16.25 ± 3.75	155.0 ± 2.5
1.0 (μg/mL)	14.00 ± 0.01	64.50 ± 1.00 (58)
2.5 (μg/mL)	13.50 ± 0.01	34.75 ± 1.75 (78)
5.0 (μg/mL)	13.50 ± 3.00	27.00 ± 9.00 (83)
none (72 h)	20.00 ± 0.01	321.0 ± 21.5
1.0 (μg/mL)	12.50 ± 0.5	70.50 ± 15.75 (78)
2.5 (μg/mL)	7.00 ± 0.01	20.25 ± 2.25 (94)
5.0 (μg/mL)	6.75 ± 0.25	9.25 ± 1.25 (97)

[a] % R, percent reduction compared to control.

A minimum of 200 cells were screened in each culture. The results are presented in Tables 2 and 3.

Results and Discussion

Biological assays on the proliferation of the epimastigote form of *T. cruzi* of this family of compounds were very promising. Nifurtimox (compound **1**) and lead drug **5** were employed as positive controls.

Replacement of the hydrogen atoms at the ortho position of 4-phenoxyphenol by different functions produced a slight improvement on the biological activity. On the other hand, when the substitution was made at the C-4′ position an important impairing on the inhibitory action was observed, making an exception for drug **16**. Contrary to this, as was previously noticed,[30] in this study the tetrahydropyranyl ether was more active than the allyl ether compared with the same nonpolar residue. For example, the pairs of drugs **12** and **13**, **16** and **17**, **19** and **20** exhibited a variable degree of activities favoring the tetrahydropyranyl ethers. Compounds **12** and **16** proved to be very active compounds (IC_{50} of 67 and 85 μM, respectively) and more active than lead drug **6** (IC_{50} 138 μM).[30] From the analysis of Table 1, it can be deduced that increments in the atomic size of the substituent provoked improvements on biological activity. Thus, allyl ether **36** was found to be more active than **13**, and this compound was more active than **20** (IC_{50} of 91, 182, and >250 μM, respectively). Compound **20** exhibited almost the same inhibitory action as **5** (IC_{50} 221 μM). The acetamido derivative **30** was also a very active compound with an IC_{50} of 97 μM. The substitution at the B ring did not result in an increase in the antiproliferative action; for example, drugs **17**, **22**, **34**, **38**, and **41** presented vanishing inhibition values. All of them were less active than **5** and **6**.

The replacement of the oxygen atom between the phenyl groups by a sulfur (compound **48**) produced a dramatic reduction in biological activity as well as the isomerization of the allyl ether function (drug **52**). It is worthy to point out the inhibitory action shown when the terminal phenyl group was replaced by a chlorine atom in the case of drug **51** which was more active than the analogues **6** and **20**. In contrast, drug **50** was only moderately active.

Of the designed drugs, thiocyanate **56** was the most potent drug among the tested compounds. At concentrations as low as 37 μM, almost complete growth arrest took place. The biological activity exhibited for drug **56** was extremely high, with an IC_{50} of 2.2 μM, 4 times more active than Nifurtimox, which showed an IC_{50} of 8.6 μM under similar assay conditions. In addition, compound **56** was very active to control proliferation of amastigotes grown on L_6E_9 myoblasts. At concentrations as low as 0.37 μM, compound **56** was able to inhibit 50% of growth and to reduce the percentage of myoblasts containing amastigotes to one-half, while at a concentration of 18 μM, almost complete eradication of the parasites took place. In the range of concentrations used, this compound was not toxic to myoblasts and no changes in their normal morphology were determined (Table 2). Nifurtimox was also used as positive control in the amastigote form of the parasite. This drug exhibited a similar effect as **56** as a growth inhibitor of intracellular *T. cruzi* (Table 3).

The rest of the tested compounds presented remarkable action in inhibiting the proliferation of this parasite. Consequently, thiolcarbamate **59** and thiolcarbonate **60** were also very active compounds demonstrating similar inhibition values, with IC_{50} values of 17.0 and 15.1 μM, respectively. Isobutyl thiolcarbonate **61** even proved to be a very potent antiproliferative agent against this parasite and was slightly less active than **59** and **60**. The presence of two sulfur atoms, each one bonded to the carbonyl group, did not result in an increase of the biological activity, taking dithiolcarbonate **62** as an example. On the contrary, compound **60** was 3 times more active than **62**. It is worth pointing out the activity observed for thiolcarbonates **60** and **61** as compared with carbonates **7** and **8**, which had previously presented IC_{50} values close to 100 and 25 μM, respectively.[16] The growth inhibitory effect was more dramatic with the pair of drugs **7** and **60** than with the pair **8** and **61**. In the former case, the activity was increased by more than 6 times, while in the latter case, the activity was also increased but to a lesser extent.

Although xanthates **63** and **64** were not so active as the rest of this family of compounds, it is interesting to point out that the biological activity exhibited for *O*-ethyl xanthate **63**, in which the sulfur atom is at carbon-1, compared with the activity observed for its analogue **64**. Compound **63** is 2-fold more active than **64**. Thus, replacement of the carbonyl group by a thiocarbonyl unit did not produce any improvement in the biological activity, but when the sulfur atom is not

at carbon-1, the biological activity substantially decreased. The increment of chain length in **67** did not improve the biological activity. Although **67** was extremely active with an IC_{50} of 3.5 μM, it was less active than its analogue **56**. The presence of an episulfide at the polar extreme also produced a very active compound, as was the case of **69** with an IC_{50} of 3.9 μM. Compounds **74** and **79** were very active drugs, and the presence of the thiocyante group certainly improved the biological activity compared with their precursor tetrahydropyranyl ethers **71** and **76**, which were moderately active compounds.

The results presented in this work indicate the strong influence of the sulfur atom on the biological activity. The biological activity exhibited for thiocyanate **56** is quite encouraging. This drug was almost 4 times more active than the well-known trypanocidal agent Nifurtimox. Moreover, the presence of the thiocyanate moiety itself does not ensure ultrapotent inhibitory action; contrarily, the nonpolar residue bonded to this unit has a strong influence on biological activity.

In conclusion, compound **56** and closely related compounds in which the thiocyanate or episulfide group is present as polar ends represent an interesting example of a new class of drugs to control proliferation of *T. cruzi* cells that were rationally designed and prepared. Studies on the mechanism of action of this drug, as well as modifications in the skeleton of compound **56**, keeping the thiocyanate moiety, are currently being pursued in our laboratory.

Experimental Section

The glassware used in air- and/or moisture-sensitive reactions was flame-dried, and reactions were carried out under a dry nitrogen atmosphere. Unless otherwise noted, chemicals were commercially available and used without further purification. Solvents were distilled before use. Toluene and tetrahydrofuran were distilled from sodium/benzophenone ketyl, pyridine was distilled from calcium hydride and stored over potassium hydroxide pellets, dimethyl sulfoxide was distilled from calcium hydride and stored over freshly activated 3-Å molecular sieves, and methanol was distilled from magnesium methoxide and stored over 3-Å molecular sieves. Anhydrous *N*,*N*-dimethylformamide was used as supplied from Aldrich.

Nuclear magnetic resonance spectra were recorded using a Bruker AC-200 MHz spectrometer. 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. ^{13}C NMR spectra were fully decoupled and are referenced to the middle peak of the solvent $CDCl_3$ at 77.0 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). Positive ion fast atom bombardment mass spectra (FABMS) were obtained on a VG ZAB BEqQ spectrometer at an accelerating voltage of 8 kV and a resolution of 500. Thioglycerol was used as the sample matrix, and ionization was effected by a beam of cesium atoms.

Flash chromatography was performed according to the Still methodology[50] with 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). The results were within ±0.4% of the theoretical values except where otherwise stated.

2-Bromo-4-phenoxyphenol (10) and 2,6-Dibromo-4-phenoxyphenol (11). To a solution of 98% *tert*-butylamine (240 mg, 3.3 mmol) in anhydrous toluene (25 mL) cooled to −30 °C and under nitrogen atmosphere was added bromine (80 μL, 1.54 mmol) dropwise, and the mixture was stirred for 10 min. The mixture was cooled to −70 °C, and a solution of 4-phenoxyphenol (**9**) (611 mg, 3.3 mmol) in methylene chloride (10 mL) was carefully added. The reaction mixture was stirred for 2 h and then was allowed to warm to room temperature. The organic layer was washed with a saturated solution of sodium chloride (3 × 30 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane−CH_2Cl_2 (97:3) as eluent to afford 396 mg (45% yield) of pure compound **10** and 142 mg of the side product **11** as colorless oils. Compound **10**: R_f 0.37 (hexane−CH_2Cl_2, 7:3); ^{1}H NMR ($CDCl_3$) δ 5.51 (s, 1 H, O*H*), 6.93−7.28 (m, 7 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 109.96 (C-2), 116.48 (C-2′), 117.96 (C-6), 120.36 (C-5), 122.86 (C-4′), 123.05 (C-3), 129.69 (C-3′), 148.58 (C-4), 150.44 (C-1), 157.67 (C-1′); MS (*m*/*z*, relative intensity) 266 (M^+, 75), 264 (M^+, 80), 189 (9), 187 (9), 157 (34), 128 (21), 77 (64), 51 (100). Compound **11**: R_f 0.54 (hexane−CH_2Cl_2, 7:3); MS (*m*/*z*, relative intensity) 346 (M^+, 0.8), 344 (M^+, 1.5), 342 (M^+, 0.8), 266 (92), 264 (100), 157 (30), 128 (17), 109 (18), 84 (19), 76 (19), 49 (37), 43 (92).

2-(2-Bromo-4-phenoxyphenoxy)ethyl Tetrahydro-2*H*-pyran-2-yl Ether (12). A solution of **10** (115.6 mg, 0.44 mmol) in dimethyl sulfoxide (3 mL) was treated with potassium hydroxide (100 mg, 1.79 mmol). The mixture was stirred at room temperature for 5 min. Then, bromoethyl tetrahydropyranyl ether (180 mg, 0.86 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 a saturated solution of sodium chloride (5 × 50 mL) and dried ($MgSO_4$). The residue was purified by column chromatography (silica gel) eluting with hexane−CH_2Cl_2 (95:5) to give 58 mg (33% yield) of pure compound **12** as a colorless oil: R_f 0.55 (hexanes−EtOAc, 7:3); IR (film, cm^{-1}) 3067, 3040, 2941, 2872, 1589, 1485, 1454, 1265, 1217, 1126, 1078, 1036, 987, 901, 872, 816, 750, 692; ^{1}H NMR ($CDCl_3$) δ 1.53−1.91 (m, 6 H, H-3‴, H-4‴, H-5‴), 3.56 (m, 1 H, H-6‴a), 3.81−4.08 (m, 3 H, H-1, H-2, H-6‴b), 4.19 (m, 2 H, H-2), 4.78 (m, 1 H, H-2‴), 6.95−7.35 (m, 8 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.26 (C-4‴), 25.41 (C-5‴), 30.50 (C-3‴), 62.05 (C-6‴), 65.58 (C-1), 69.55 (C-2), 99.00 (C-2‴), 112.87 (C-2′), 114.70 (C-2″), 118.07 (C-5′), 119.10 (C-6′), 123.08 (C-4″), 124.43 (C-3′), 129.72 (C-3″), 150.95 (C-4′), 151.82 (C-1′), 157.70 (C-1″); MS (*m*/*z*, relative intensity) 394 (M^+, 7), 392 (M^+, 7), 266 (20), 264 (20), 129 (100), 85 (58). Anal. ($C_{19}H_{21}O_4Br$) C, H.

2-Bromo-4-phenoxyphenyl Prop-2-en-1-yl Ether (13). A solution of compound **10** (117 mg, 0,44 mmol) in dimethyl sulfoxide (5 mL) was treated with potassium hydroxide (100 mg, 1.8 mmol), and the mixture was stirred for 5 min. Then, allyl bromide (0.1 mL, 1.16 mmol) was added, and the mixture was stirred at room temperature for 5 h. The reaction was worked up as described for the preparation of compound **7**. The residue was purified by column chromatography (silica gel) using toluene−MeOH (0.1%) as eluent to obtain 118 mg (88% yield) of pure ether **13** as a colorless oil: R_f 0.88 (toluene−MeOH, 99:1); IR (film, cm^{-1}) 3070, 2922, 2868, 1589, 1483, 1284, 1265, 1215, 1188, 1040, 1016, 997, 928, 906, 752, 692; ^{1}H NMR ($CDCl_3$) δ 4.57 (dt, J = 5.0, 1.2 Hz, 2 H, H-1), 5.30 (dd, J = 10.5, 1.4 Hz, 1 H, H-3$_{cis\ to\ 2}$), 5.46 (dd, J = 17.2, 1.6 Hz, 1 H, H-3$_{trans\ to\ 2}$), 6.05 (ddt, J = 17.2, 10.1, 5.3 Hz, 1 H, H-2), 6,83−7.35 (m, 8 H, aromatic protons); ^{13}C NMR ($CDCl_3$)

δ 70.40 (C-1), 112.79 (C-2′), 114.50 (C-2″), 117.75 (C-3), 118.10 (C-5′), 119.00 (C-6′), 123.09 (C-4″), 124.43 (C-3′), 129.72 (C-3″), 132.69 (C-2), 150.95 (C-4′), 151.34 (C-1′), 157.62 (C-1″); MS (*m*/*z*, relative intensity) 306 (M^+, 51), 304 (M^+, 52), 265 (100), 263 (91), 219 (15), 156 (20), 128 (95), 77 (90). Anal. ($C_{15}H_{13}O_2Br$) C, H.

4-Phenoxyphenyl Acetate (14). A solution of 4-phenoxyphenol (1.69 g, 9.1 mmol) in pyridine (5 mL) was treated with acetic anhydride (0.9 mL). The reaction mixture was stirred at room temperature for 16 h. The mixture was partitioned between methylene chloride (30 mL) and 10% HCl solution (20 mL), and the mixture was stirred for 1 h. The organic phase was washed with 10% HCl (3 × 30 mL) and water to pH = 7 and dried ($MgSO_4$), and the solvent was evaporated to afford 1.80 g (87% yield) of pure acetate **14** as a colorless oil that was used in the next step without further purification: R_f 0.52 (CH_2Cl_2−hexane, 7:3); MS (*m*/*z*, relative intensity) 228 (M^+, 8), 186 (100), 157 (10), 129 (12), 109 (15).

4-(4-Bromophenoxy)phenyl Acetate (15). A suspension of acetate **14** (666 mg, 2.9 mmol) in water (10 mL) was treated with bromine (0.19 mL, 3.7 mmol). The reaction mixture was stirred at room temperature for 2 h. Then, the reaction was quenched with a 1.0 M aqueous solution of sodium bisulfite (4 mL), and the mixture was extracted with methylene chloride (3 × 20 mL). The combined organic layers were washed with brine (2 × 15 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing toluene−MeOH (0.1%) as eluent to afford 577 mg (58% yield) of pure compound **15** as a colorless oil: R_f 0.47 (toluene−MeOH, 9:1); IR (film, cm^{-1}) 3075, 1772, 1585, 1500, 1488, 1373, 1253, 1186, 1078, 1017, 909, 830; MS (*m*/*z*, relative intensity) 308 (M^+, 6), 306 (M^+, 6), 266 (52), 264 (57), 157 (23), 128 (12), 41 (100).

2-[4-(4-Bromophenoxy)phenoxy]ethyl Tetrahydro-2*H*-pyran-2-yl Ether (16). Compound **15** (98 mg, 0.32 mmol) in dimethyl sulfoxide (5 mL) was treated with potassium hydroxide (1.3 mmol). The suspension was stirred for 30 min at room temperature. Then, bromoethyl tetrahydropyranyl ether (130 mg, 0.6 mmol) was added; the reaction mixture was stirred at room temperature overnight. The reaction was worked up as described for the preparation of compound **12**. The residue was purified by column chromatography (silica gel) eluting with hexane−CH_2Cl_2 (3:2) to afford 75 mg (60% yield) of pure compound **16** as a colorless oil: R_f 0.37 (hexanes−EtOAc, 2:3); IR (film, cm^{-1}) 3073, 3045, 2941, 2872, 1639, 1608, 1580, 1504, 1481, 1456, 1352, 1279, 1227, 1163, 1140, 1126, 1068, 1034, 928, 908, 872, 824, 758, 714, 569, 517, 500; ^{1}H NMR ($CDCl_3$) δ 1.55−1.90 (m, 6 H, H-3‴, H-4‴, H-5‴), 3.56 (m, 1 H, H-6‴a), 3.78−4.08 (m, 3 H, H-1, H-6‴b), 4.10−4.17 (m, 2 H, H-2), 4.71 (distorted t, J = 3.4 Hz, 1 H, H-2‴), 6.81 (d, J = 8.9 Hz, 2 H, H-2″, H-6″), 6.93 (m *AB*, 4 H, H-2′, H-3′, H-5′, H-6′), 7.37 (d, J = 8.9 Hz, 2 H, H-3″, H-5″); ^{13}C NMR ($CDCl_3$) δ 19.35 (C-4‴), 25.39 (C-5‴), 30.49 (C-3‴), 62.17 (C-6‴), 65.84 (C-1), 67.97 (C-2), 98.99 (C-2‴), 114.71 (C-4″), 115.89 (C-2′), 119.20 (C-3′), 120.76 (C-2″), 132.44 (C-3″), 149.77 (C-4′), 155.51 (C-1′), 157.72 (C-1″); MS (*m*/*z*, relative intensity) 394 (M^+, 9), 392 (M^+, 9), 266 (16), 264 (16), 157 (12), 155 (10), 129 (100). Anal. ($C_{19}H_{21}O_4Br$) C, H.

4-(4-Bromophenoxy)phenyl Prop-2-en-1-yl Ether (17). Compound **15** (156 mg, 0.51 mmol) in dimethyl sulfoxide (5 mL) was treated with potassium hydroxide (100 mg, 1.8 mmol), and the mixture was stirred for 30 min. Then, allyl bromide (0.1 mL) was added, and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched as depicted for the preparation of compound **12**. The residue was purified by column chromatography (silica gel) using toluene−MeOH (0.1%) as eluent to obtain 126 mg (81% yield) of pure compound **17** as a colorless oil: R_f 0.93 (toluene−MeOH, 9:1); IR (film, cm^{-1}) 3058, 3086, 2916, 2866, 1884, 1647, 1578, 1504, 1483, 1427, 1404, 1300, 1290, 1244, 1219, 1194, 1097, 1016, 997, 935, 843, 825, 814; ^{1}H NMR ($CDCl_3$) δ 4.51 (dt, J = 5.2, 1.5 Hz, 2 H, H-1), 5.29 (dq, J = 10.4, 1.3 Hz, 1 H, H-3$_{cis\ to\ 2}$), 5.41 (dq, J = 17.2, 1.3 Hz, 1 H, H-3$_{trans\ to\ 2}$), 6.05 (ddt, J = 17.2, 10.4, 5.2 Hz, 1 H, H-2), 6.81 (d, J = 8.9 Hz, 2 H, H-2“, H-6”), 6.91 (m *AB*, 4 H, H-2′, H-3′, H-5′, H-6′), 7.37 (d, J = 8.9 Hz, 2 H, H-3“, H-5”); ^{13}C NMR ($CDCl_3$) δ 69.30 (C-1), 114.74 (C-4″), 115.90 (C-2′), 117.68 (C-3), 119.25 (C-3′), 120.76 (C-2″), 132.47 (C-3″), 133.23 (C-2), 149.78 (C-4′), 155.17 (C-1′), 157.70 (C-1″); MS (*m*/*z*, relative intensity) 306 (M^+, 27), 304 (M^+, 29), 265 (57), 263 (59), 185 (29), 157 (34), 155 (39), 128 (100). Anal. ($C_{15}H_{13}O_2Br$) C, H.

2-Chloro-4-phenoxyphenol (18). A solution of 4-phenoxyphenol (910 mg, 4.9 mmol) in benzene (20 mL) was treated with *N*-chlorosuccinimide (570 mg, 4.3 mmol). The reaction mixture was refluxed for 48 h. Then, the mixture was allowed to cool to room temperature and was partitioned between water (100 mL) and methylene chloride (100 mL). The aqueous phase was extracted with methylene chloride (2 × 70 mL). The combined organic layers were washed with a saturated solution of sodium chloride (2 × 100 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane−CH_2Cl_2 (2:1) to give 493 mg (46% yield) of pure compound **18** as a colorless oil: R_f 0.48 (hexane−CH_2Cl_2, 1:1); MS (*m*/*z*, relative intensity) 222 (M^+, 26), 220 (M^+, 67), 186 (100), 157 (40), 129 (30), 109 (46).

2-(2-Chloro-4-phenoxyphenoxy)ethyl Tetrahydro-2*H*-pyran-2-yl Ether (19). Phenol **18** (235 mg, 1.06 mmol) in dimethyl sulfoxide (5 mL) was treated with potassium hydroxide (250 mg, 4.5 mmol). The suspension was stirred for 5 min. Then, bromoethyl tetrahydropyranyl ether (440 mg, 2.1 mmol) was stirred at room temperature overnight. The reaction mixture was worked up as described for compound **12**. The residue was purified by column chromatography (silica gel) employing hexane−CH_2Cl_2 (7:3) as eluent to afford 272 mg (74% yield) of pure compound **19** as a colorless oil: R_f 0.48 (hexanes−EtOAc, 1:1); IR (film, cm^{-1}) 3067, 3042, 2943, 2874, 1589, 1487, 1454, 1263, 1217, 1140, 1126, 1078, 1036, 912, 872, 816, 752, 692; ^{1}H NMR ($CDCl_3$) δ 1.50−1.82 (m, 6 H, H-3‴, H-4‴, H-5‴), 3.54 (m, 1 H, H-6‴a), 3.80−4.15 (m, 3 H, H-1, H-6‴b), 4.20 (t, J = 5.0 Hz, 2 H, H-2), 4.76 (t, J = 3.2 Hz, 1 H, H-2‴), 6.90−7.36 (m, 8 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.27 (C-4‴), 25.41 (C-5‴), 30.40 (C-3‴), 62.07 (C-6‴), 65.61 (C-1), 69.51 (C-2), 98.99 (C-2‴), 115.14 (C-2″), 118.12 (C-5′),* 118.33 (C-6′),* 121.46 (C-3′), 123.10 (C-4″), 124.00 (C-2′), 129.72 (C-3″), 150.81 (C-4′), 150.90 (C-1′), 157.61 (C-1″); MS (*m*/*z*, relative intensity) 350 (M^+, 7), 348 (M^+, 21), 222 (12), 220 (41), 209 (29), 207 (27), 129 (95), 127 (13), 109 (39), 107 (48), 85 (100), 83 (54), 73 (63). Anal. ($C_{19}H_{21}O_4Cl$) C, H.

2-Chloro-4-phenoxyphenyl Prop-2-en-1-yl Ether (20). A solution of compound **18** (135 mg, 0.69 mmol) in dimethyl sulfoxide (5 mL) was treated with potassium hydroxide (130 mg, 2.3 mmol). The mixture was stirred for 5 min at room temperature. Then, allyl bromide (100 μL, 1.2 mmol) was added, and the reaction mixture was stirred for 5 h. The reaction mixture was treated according to the general procedure described for the preparation of **12**. The product was purified by column chromatography eluting with toluene−MeOH (0.02%) to give 135 mg (75% yield) of pure ether **20** as a colorless oil: R_f 0.88 (toluene−MeOH, 99:1); IR (film, cm^{-1}) 3072, 3042, 2986, 2918, 2877, 1589, 1485, 1269, 1215, 1053, 1020, 997, 922, 754, 690; ^{1}H NMR ($CDCl_3$) δ 4.58 (d, J = 5.0 Hz, 2 H, H-1), 5.31 (d, J = 10.5 Hz, 1 H, H-3$_{cis\ to\ 2}$), 5.46 (d, J = 17.2 Hz, 1 H, H-3$_{trans\ to\ 2}$), 6.07 (ddt, J = 17.2, 10.2, 5.2 Hz, 1 H, H-2), 6.85−7.36 (m, 8 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 70.35 (C-1), 114.85 (C-2″), 117.80 (C-3), 118.15 (C-6′),* 118.22 (C-5′),* 121.44 (C-3′), 123.11 (C-4″), 123.82 (C-2′), 129.72 (C-3″), 132.74 (C-2), 150.41 (C-4′), 150.72 (C-1′), 157.55 (C-1″); MS (*m*/*z*, relative intensity) 262 (M^+, 28), 260 (M^+, 79), 221 (56), 219 (100). Anal. ($C_{15}H_{13}O_2Cl$) C, H.

4-(4-Chlorophenoxy)phenyl Acetate (21). A solution of **14** (264 mg, 1.15 mmol) in methylene chloride (10 mL) was treated with 1-chlorobenzotriazole (180 mg, 1.15 mmol). The reaction mixture was stirred at room temperature for 6 days. The solvent was evaporated, and the residue was purified by column chromatography (silica gel) using toluene−MeOH (0.1%) as eluent to yield 148 mg (49% yield) of pure compound **21** as a colorless oil: R_f 0.92 (hexanes−EtOAc, 7:3); IR (film,

cm^{-1}) 3099, 3069, 3045, 1759, 1591, 1482, 1350, 1253, 1210, 1186, 1090, 1011, 836, 770; MS (*m*/*z*, relative intensity) 264 (M^+, 8), 262 (M^+, 22), 228 (38), 222 (51), 220 (81), 186 (100), 157 (31), 129 (23), 109 (33).

4-(4-Chlorophenoxy)phenyl Prop-2-en-1-yl Ether (22). To a solution of **21** (90 mg, 0.34 mmol) in dimethyl sulfoxide (5 mL) was added potassium hydroxide (100 mg, 1.8 mmol). The mixture was stirred for 20 min. Then, allyl bromide (100 μL, 1.2 mmol) was added, and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched as depicted for compound **12**. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (0.5%) to give 61 mg (68% yield) of pure ether **22** as a colorless oil: R_f 0.47 (hexanes−EtOAc, 49:1); IR (film, cm^{-1}) 3078, 2856, 1755, 1591, 1504, 1485, 1425, 1227, 1090, 1009, 926, 874, 845, 825; ^{1}H NMR ($CDCl_3$) δ 4.52 (dt, J = 5.3, 1.4 Hz, 2 H, H-1), 5.29 (dq, J = 10.5, 1.4 Hz, 1 H, H-3$_{cis\ to\ 2}$), 5.41 (dq, J = 17.2, 1.4 Hz, 1 H, H-3$_{trans\ to\ 2}$), 6.06 (ddt, J = 17.2, 5.3, 1.4 Hz, 1 H, H-2), 6.86 (d, J = 8.9 Hz, 2 H, H-2", H-6"), 6,93 (m *AB*, 4 H, H-2′, H-3′, H-5′, H-6′), 7.24 (d, J = 8.9 Hz, 2 H, H-3", H-5"); ^{13}C NMR ($CDCl_3$) δ 69.33 (C-1), 115.91 (C-2′), 117.69 (C-3), 118.85 (C-3′), 120.69 (C-2″), 129.53 (C-3″), 133.25 (C-2), 149.96 (C-4′), 155.14 (C-1′), 157.13 (C-1″); MS (*m*/*z*, relative intensity) 262 (M^+, 28), 260 (M^+, 79), 221 (56), 219 (100), 128 (24), 127 (27). Anal. ($C_{15}H_{13}O_2Cl$) C, H.

2-Nitro-4-phenoxyphenol (23) and 2,4-Dinitro-4-phenoxyphenol (24). To a solution of 4-phenoxyphenol (541 mg, 2.9 mmol) in glacial acetic acid (15 mL) was added dropwise 70% nitric acid (180 mg, 2.9 mmol) with vigorous stirring. The mixture was stirred at room temperature for 15 min. The reaction mixture was poured into an aqueous saturated solution of sodium bicarbonate (40 mL). The mixture was extracted with methylene chloride (3 × 30 mL), the combined organic layers were washed with water (2 × 20 mL) and dried ($MgSO_4$), the solvent was evaporated. The residue was purified by column chromatography (silica gel) using hexanes−EtOAc (9:1) as eluent to afford 471 mg (70% yield) of pure mononitro derivative **23** and 64 mg of dinitro derivative **24** as yellow solids. Compound **23**: R_f 0.62 (hexanes−EtOAc, 7:3); mp 54−55 °C; IR (KBr, cm^{-1}) 3343, 3092, 3079, 3059, 1630, 1591, 1544, 1472, 1432, 1313, 1240, 1161, 949, 791, 850; MS (*m*/*z*, relative intensity) 231 (M^+, 100), 196 (8), 128 (25), 77 (70), 51 (72). Compound **24**: R_f 0.03 (hexanes−EtOAc, 7:3); mp 129−130 °C; IR (KBr, cm^{-1}) 3093, 1645, 1591, 1548, 1494, 1422, 1349, 1313, 1253, 1192, 1084, 993, 927, 842; MS (*m*/*z*, relative intensity) 276 (M^+, 17), 197 (3), 183 (3), 172 (5), 91 (15), 63 (19), 51 (100).

2-Nitro-4-phenoxyphenyl Prop-2-en-1-yl Ether (25). To a solution of compound **23** (114 mg, 0.5 mmol) in dimethyl sulfoxide (3 mL) was added potassium hydroxide (100 mg, 1.8 mmol). The mixture was stirred at room temperature for 5 min. Then, allyl bromide (100 μL, 1.2 mmol) was added, and the reaction mixture was stirred overnight. After the usual workup, the residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (3:2) to afford 23 mg (17% yield) of pure compound **25** as a yellow oil: R_f 0.62 (hexane−CH_2Cl_2, 2:3); IR (film, cm^{-1}) 3080, 2924, 2870, 1591, 1529, 1500, 1423, 1356, 1271, 1217, 1153, 993, 949, 841, 756, 692; ^{1}H NMR ($CDCl_3$) δ 4.66 (dt, J = 5.0, 1.5 Hz, 2 H, H-3), 5.35 (dq, J = 10.5, 1.4 Hz, 1 H, H$_{cis\ to\ 2}$), 5.47 (dq, J = 17.1, 1.5 Hz, 1 H, H-3$_{trans\ to\ 2}$), 6.04 (ddt, J = 17.3, 10.3, 5.0 Hz, 1 H, H-2), 6.98−7.40 (m, 7 H, aromatic protons), 7.48 (d, J = 2.9 Hz, 1 H, H-3′); ^{13}C NMR ($CDCl_3$) δ 70.83 (C-1), 115.76 (C-3′), 116.63 (C-6′), 118.42 (C-3), 118.70 (C-2″), 123.99 (C-4″), 124.43 (C-5′), 130.04 (C-3″), 131.90 (C-2′), 137.02 (C-2), 147.80 (C-1′), 156.69 (C-4′), 159.26 (C-1″); MS (*m*/*z*, relative intensity) 271 (M^+, 62), 230 (43), 171 (12), 144 (18), 131 (25), 77 (100). Anal. ($C_{15}H_{13}O_4N$) C, H, N.

2-Amino-4-phenoxyphenol (26). A solution of **23** (1.212 g, 5.2 mmol) in ethyl acetate (50 mL) in the presence of 10% palladium on charcoal (50 mg) was treated with hydrogen under 3 atm at room temperature for 1 h. Then the reaction mixture was filtered, and the solvent was evaporated to afford 973 mg (92% yield) of compound **26** as a brown crystal that was used in the next step without further purification: R_f 0.37 (hexanes−EtOAc, 3:2); mp 107−108 °C; IR (KBr, cm^{-1}) 3383, 3314, 1597, 1539, 1489, 1223, 1080, 876, 844, 781; MS (*m*/*z*, relative intensity) 201 (M^+, 100), 183 (10), 172 (11), 156 (10), 144 (13), 128 (18), 96 (24).

2-Amino-4-phenoxyphenyl Prop-2-en-1-yl Ether (27), 2-(Prop-2-en-1-ylamino-4-phenoxyphenyl Prop-2-en-1-yl Ether (28), and 2-(Diprop-2-en-1-ylamino-4-phenoxyphenyl Prop-2-en-1-yl Ether (29). Compound **26** (760 mg, 3.8 mmol) was treated with potassium hydroxide (425 mg, 7.6 mmol) and allyl bromide (320 μL, 3.8 mmol) following the method of preparation described for **13**. After the usual workup, the residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (99:1) to yield 600 mg (65% yield) of pure **27**, 350 mg of compound **28**, and 100 mg of **29** as colorless oils. Compound **27**: R_f 0.84 (hexanes−EtOAc, 7:3); IR (film, cm^{-1}) 3477, 3391, 3078, 3038, 2925, 2859, 1622, 1589, 1516, 1496, 1303, 1217, 1024, 971, 931, 865, 752, 698; MS (*m*/*z*, relative intensity) 241 (M^+, 13), 200 (100). Compound **28**: R_f 0.75 (hexanes−EtOAc, 7:3); IR (film, cm^{-1}) 3430, 3087, 2966, 2931, 2859, 1610, 1600, 1516, 1489, 1454, 1230, 1222, 1173, 1018, 1000, 929, 858, 760, 693. MS (*m*/*z*, relative intensity) 281 (M^+, 17), 240 (100), 162 (14), 146 (87). Compound **29**: R_f 0.60 (hexanes−EtOAc, 7:3); IR (film, cm^{-1}) 3084, 3071, 3018, 2978, 2932, 2852, 1642, 1591, 1501, 1489, 1457, 1217, 1171, 1115, 1171, 994, 966, 921, 757, 693; MS (*m*/*z*, relative intensity) 321 (M^+, 12), 280 (100), 238 (12), 212 (24), 186 (11), 146 (24).

2-Acetamido-4-phenoxyphenyl Prop-2-en-1-yl Ether (30). To a solution of **27** (116 mg, 0.48 mmol) in pyridine (3 mL) was added acetic anhydride (1.0 mL). The reaction mixture was stirred at room temperature overnight. The reaction was quenched as depicted for compound **14**. The residue was purified by column chromatography (silica gel) employing hexanes−EtOAc (7:3) as eluent to give 85 mg (63% yield) of pure compound **30** as a white solid: R_f 0.47 (hexanes−EtOAc, 7:3); mp 79−80 °C; IR (KBr, cm^{-1}) 3310, 1666, 1589, 1599, 1537, 1491, 1429, 1376, 1261, 1217, 1175, 1122, 1076, 1024, 995, 924, 889, 814; ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3 H, C*H*$_3$C(O)NH), 4.43 (dt, J = 5.4, 1.2 Hz, 2 H, H-1), 5.28 (dq, J = 10.5, 1.3 Hz, 1 H, H-3$_{cis\ to\ 2}$), 5.35 (dq, J = 17.4, 1.5 Hz, 1 H, H-3$_{trans\ to\ 2}$), 6.02 (ddt, J = 17.4, 10.5, 5.4 Hz, 1 H, H-2), 6.61 (dd, J = 8.8, 2.8 Hz, 1 H, H-5′), 6.77 (d, J = 8.9 Hz, 1 H, H-6′), 6.90 (m, 2 H, H-2″, H-6"), 6.99 (dt, J = 7.03, 1.2 Hz, 1 H, H-4″), 7.23 (m, 2 H, H-3″, H-5″), 7.74 (s broad, 1 H, N*H*), 8.12 (d, J = 2.5 Hz, 1 H, H-3′); ^{13}C NMR ($CDCl_3$) δ 25.00 (*C*H$_3$C(O)NH), 70.20 (C-1), 110.55 (C-3′), 112.14 (C-5′), 113.97 (C-6′), 117.98 (C-3), 118.41 (C-2″), 122.65 (C-4″), 129.04 (C-2′), 129.63 (C-3″), 132.93 (C-2), 142.97 (C-1′), 150.68 (C-4′), 158.20 (C-1″), 168.13 (C═O); MS (*m*/*z*, relative intensity) 283 (M^+, 20), 242 (40), 200 (100), 85 (42), 83 (60). Anal. ($C_{17}H_{17}O_3N$): C, H.

4-(4-Nitrophenoxy)phenyl Methyl Ether (32). A solution of 4-methoxyphenol (**31**) (2.160 g, 17 mmol) in dimethyl sulfoxide (5 mL) was treated with potassium hydroxide (960 mg, 17 mmol). The reaction mixture was stirred for 5 min. Then, 1-chloro-4-nitrobenzene (2.741 g, 17 mmol) and cuprous chloride (10 mg) were added, and the reaction mixture was stirred at 70 °C for 16 h. The mixture was poured into water (50 mL) and was extracted with methylene chloride (3 × 30 mL). The combined organic layers were washed with brine (5 × 70 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using hexane−CH_2Cl_2 (7:3) as eluent to give 1.942 g (45% yield) of pure compound **32** as a green solid: R_f 0.44 (hexane−CH_2Cl_2, 1:1); mp 111−112 °C; IR (KBr, cm^{-1}) 3112, 3016, 2850, 1610, 1585, 1507, 1487, 1455, 1343, 1298, 1239, 1198, 1186, 1163, 1110, 1102, 1031, 879, 843, 748, 712, 689, 652, 536; MS (*m*/*z*, relative intensity) 245 (M^+, 100), 230 (36), 156 (10), 128 (33).

4-(4-Nitrophenoxy)phenol (33). To a mixture of aluminum chloride (1.101 g) in mercaptoethanol (7.5 mL) was added dropwise **32** (305 mg, 1.24 mmol) in mercaptoethanol (3 mL) keeping the reaction temperature below 0 °C. The reaction mixture was stirred at 0 °C for 3 h. The mixture was poured

into 10% hydrochloric acid (30 mL) and was extracted with methylene chloride (3 × 30 mL). The combined organic layers were washed with brine (3 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography eluting with Cl_2CH_2-hexane (4:1) to give 260 mg (91% yield) of pure phenol **33** as a yellow solid: R_f 0.14 (CH_2Cl_2-hexane, 3:2); mp 175−176 °C; MS (*m*/*z*, relative intensity) 231 (M^+, 100), 185 (8), 157 (28), 128 (25).

4-(4-Nitrophenoxy)phenyl Prop-2-en-1-yl Ether (34). A solution of phenol **33** (121 mg, 0.52 mmol) in dimethyl sulfoxide (3 mL) was treated as depicted for **13**. After the usual workup, the product was purified by column chromatography (silica gel) eluting with hexane−CH_2Cl_2 (9:1) to afford 113 mg (80% yield) of pure **34** as a yellow oil: R_f 0.5 (hexanes−EtOAc, 8:2); IR (film, cm^{-1}) 3110, 3089, 2931, 2869, 1610, 1591, 1507, 1493, 1424, 1342, 1255, 1232, 1192, 1168, 1111, 1024, 1011, 998, 933, 879, 840, 752, 692; ^1H NMR ($CDCl_3$) δ 4.58 (dt, J = 5.2, 1.5 Hz, 2 H, H-1), 5.32 (dq, J = 10.5, 1.4 Hz, H-3$_{cis\ to\ 2}$), 5.44 (dq, J = 17.2, 1.4 Hz, H-3$_{trans\ to\ 2}$), 6.08 (ddt, J = 17.2, 10.5, 5.3 Hz, 1 H, H-2), 6.97 (d, J = 9.2 Hz, 2 H, H-2′, H-6′), 7.03 (m *AB*, 4 H, H-2, H-3, H-5, H-6), 8.18 (d, J = 9.3 Hz, 2 H, H-3“, H-5”); ^{13}C NMR ($CDCl_3$) δ 69.31 (C-1), 116.20 (C-2′), 116.42 (C-2″), 117.85 (C-3), 121.72 (C-3′), 125.86 (C-3″), 133.04 (C-2), 147.97 (C-4′), 156.19 (C-1′), 164.06 (C-1″); MS (*m*/*z*, relative intensity) 271 (M^+, 5), 264 (18), 230 (100), 184 (10), 128 (37). Anal. ($C_{15}H_{13}O_4N\cdot{}^1/_2H_2O$) C, H, N.

2-Iodo-4-phenoxyphenol (35). To a suspension of aminophenol **26** (312 mg, 1.35 mmol), water (1.4 mL), and concentrated sulfuric acid (90 μL) cooled to 0 °C was added dropwise sodium nitrite (97 mg, 1.35 mmol) in water (1.0 mL). The reaction mixture was stirred for 20 min at 0 °C. Then, concentrated sulfuric acid (30 μL) was added. The mixture was poured into an aqueous solution of sodium iodide (6.0 M, 0.3 mL), and the mixture was stirred for 10 min at 0 °C. Then, cuprous chloride (10 mg) was added, and the reaction mixture was heated at 75−80 °C until evolution of nitrogen ceased. The mixture was allowed to cool to room temperature and was extracted with methylene chloride (3 × 20 mL). The combined organic layers were washed with a saturated solution of sodium bisulfite (2 × 30 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using hexane−CH_2Cl_2 (3:2) as eluent to afford 128 mg (30% yield) of pure iodophenol **35** as a colorless oil: R_f 0.53 (hexane−CH_2Cl_2, 1:1); IR (film, cm^{-1}) 3501, 3073, 3052, 2924, 2852, 1505, 1588, 1476, 1405, 1255, 1218, 1034, 896, 749, 691; MS (*m*/*z*, relative intensity) 312 (M^+, 13), 157 (6), 128 (11), 92 (11), 77 (100).

2-Iodo-4-phenoxyphenyl Prop-2-en-1-yl Ether (36). Compound **35** (125 mg, 0.4 mmol) in dimethyl sulfoxide (5 mL) was treated with potassium hydroxide and allyl bromide as depicted for compound **13**. After the usual workup, the residue was purified by column chromatography (silica gel) eluting with hexane−CH_2Cl_2 (3:2) to give 76 mg (54% yield) of pure compound **36** as a colorless oil: R_f 0.75 (hexane−CH_2Cl_2, 1:1); IR (film, cm^{-1}) 3065, 2924, 2854, 1587, 1479, 1423, 1265, 1215, 1034, 995, 928, 895, 750, 692; ^1H NMR ($CDCl_3$) δ 4.57 (dd, J = 4.9, 1.2 Hz, 2 H, H-1), 5.31 (dt, J = 10.5, 1.4 Hz, 1 H, H-3$_{cis\ to\ 2}$), 5.51 (dt, J = 17.2, 1.5 Hz, 1 H, H-3$_{trans\ to\ 2}$), 6.07 (ddt, J = 17.2, 10.5, 4.9 Hz, 1 H, H-2), 6.77 (d, J = 8.9 Hz, 1 H, H-6′), 6.93−7.11 (m, 4 H, aromatic protons), 7.26−7.35 (m, 2 H, aromatic protons), 7.47 (d, J = 2.9 Hz, 1 H, H-3′); ^{13}C NMR ($CDCl_3$) δ 70.44 (C-1), 86.73 (C-2′), 113.09 (C-3), 117.68 (C-6′), 117.99 (C-2″), 120.12 (C-5′), 123.01 (C-4″), 129.72 (C-3′), 130.40 (C-3″), 132.65 (C-2), 151.06 (C-4′), 153.69 (C-1″), 157.77 (C-1′); MS (*m*/*z*, relative intensity) 352 (M^+, 43), 311 (16), 156 (7), 128 (33), 77 (100). Anal. ($C_{15}H_{13}O_2I$) C, H.

4-(4-Acetoxyphenoxy)phenyl Acetate (37). A suspension of anhydrous aluminum chloride (660 mg) in carbon disulfide (5 mL) was cooled to −5 °C under nitrogen atmosphere. Then, 4-phenoxyphenol (810 mg, 4.34 mmol) was added followed by careful addition of acetyl chloride (0.33 mL, 4.7 mmol), keeping the reaction temperature below −5 °C. The mixture was stirred for 2 h at room temperature. The mixture was poured into ice (5 g), and concentrated hydrochloric acid (5 mL) was added. The resulting mixture was extracted with methylene chloride (3 × 20 mL). The combined organic layers were washed with water (3 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (9:1) to afford 257 mg (26% yield) of pure compound **37** and 553 mg of undesired 4-phenoxyphenyl acetate (**14**): R_f 0.21 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3350, 3072, 3006, 1756, 1683, 1611, 1525, 1504, 1366, 1254, 1181, 1009, 916, 850, 830, 592; MS (*m*/*z*, relative intensity) 270 (M^+, 11), 228 (75), 213 (100), 186 (30), 157 (10).

4-(4-Acetylphenoxy)phenyl Prop-2-en-1-yl Ether (38). A solution of **37** (158 mg, 0.58 mmol) in dimethyl sulfoxide (3 mL) was treated with potassium hydroxide and allyl bromide according to the protocol described for compound **13**. After the usual workup, the residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to afford 60 mg (38% yield) of pure compound **38** as a white solid: R_f 0.77 (hexanes−EtOAc, 7:3); mp 54−55 °C; ^1H NMR ($CDCl_3$) δ 2.55 (s, 3 H, −C(O)CH_3), 4.54 (d, J = 5.3 Hz, 2 H, H-1), 5.30 (dd, J = 10.5, 1.3 Hz, 1 H, H-3$_{cis\ to\ 2}$), 5.42 (dd, J = 17.2, 1.4 Hz, 1 H, H-3$_{trans\ to\ 2}$), 6.08 (ddt, J = 17.2, 10.5, 5.3 Hz, 1 H, H-2), 6.94 (d, J = 8.7 Hz, 2 H, H-2′, H-6′), 6,95 (m *AB*, 4 H, H-2, H-3, H-5, H-6), 7.91 (d, J = 8.7, 1.9 Hz, 2 H, H-3′, H-5′); ^{13}C NMR ($CDCl_3$) δ 26.34 (CH_3C(O)), 69.27 (C-1), 115.98 (C-2′), 116.40 (C-2″), 117.74 (C-3), 121.55 (C-3′), 130.51 (C-3″), 131.45 (C-4″), 133.14 (C-2), 148.65 (C-1′), 155.69 (C-4′), 162.82 (C-1″); MS (*m*/*z*, relative intensity) 268 (M^+, 54), 227 (68), 157 (14), 91 (17), 76 (14), 43 (100). Anal. ($C_{16}H_{16}O_3$) C, H.

4-(4-Benzoylphenoxy)phenyl Benzoate (39) and 4-Phenoxyphenyl Benzoate (40). To a mixture of anhydrous aluminum chloride (690 mg, 4.9 mmol) in carbon disulfide (10 mL) was added 4-phenoxyphenol (890 g, 4.8 mmol) at −5 °C. Then, benzoyl chloride (0.6 mL, 5.1 mmol) was added. The reaction mixture was stirred for 2 h at −5 °C, and the reaction was quenched as depicted for **37**. The residue was purified by column chromatography (silica gel) using hexanes−EtOAc (19:1) as eluent to afford 283 mg (15% yield) of pure benzoyl derivative **39** and 1.050 g of benzoate **40** as white solids. Compound **39**: R_f 0.47 (hexanes−EtOAc, 4:1); mp 130−131 °C; IR (KBr, cm^{-1}) 3098, 3072, 3045, 3012, 1743, 1644, 1604, 1505, 1452, 1439, 1320, 1273, 1187, 1068, 942, 705; MS (*m*/*z*, relative intensity) 394 (M^+, 13), 106 (13), 105 (100). Compound **40**: R_f 0.67 (hexanes−EtOAc, 4:1); mp 99−100 °C; IR (KBr, cm^{-1}) 5065, 3038, 1737, 1590, 1488, 1454, 1318, 1267, 1246, 1190, 1069, 1029, 870, 791, 711.

4-(4-Benzoylphenoxy)phenyl Prop-2-en-1-yl Ether (41). A solution of **39** (149 mg, 0.37 mmol) in dimethyl sulfoxide (3.0 mL) was treated with potassium hydroxide and allyl following the methodology described for **13**. After the usual workup, the product was purified by column chromatography (silica gel) eluting with CH_2Cl_2-hexane (3:2) to afford 99 mg (79% yield) of pure **41** as a white solid: R_f 0.67 (hexanes−EtOAc, 4:1); mp 95−96 °C; IR (KBr, cm^{-1}) 3063, 2914, 2866, 1644, 1600, 1508, 1444, 1291, 1244, 1146, 1113, 1021, 931, 842, 818, 801, 732, 692, 682; ^1H NMR ($CDCl_3$) δ 4.53 (dt, J = 5.2, 1.2 Hz, 2 H, H-3), 5.29 (dd, J = 10.5, 1.3 Hz, 1 H, H-3$_{cis\ to\ 2}$), 5.42 (dd, J = 17.2, 1.2 Hz, 1 H, H-3$_{trans\ to\ 2}$), 6.07 (ddt, J = 17.2, 10.5, 5.3 Hz, 1 H, H-2), 6.91−7.05 (m, 6 H, aromatic protons), 7.41 (m, 3 H, aromatic protons), 7.73−7.83 (m, 4 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 69.26 (C-1), 115.99 (C-2′), 116.26 (C-2″), 117.67 (C-3), 121.54 (C-3′), 128.16 (C-3‴), 129.70 (C-3″), 131.43 (C-4″), 131.96 (C-2‴), 132.39 (C-4‴), 133.14 (C-2), 138.04 (C-1‴), 148.74 (C-1′), 155.67 (C-4′), 162.47 (C-1″), 195.30 (C═O); MS (*m*/*z*, relative intensity) 330 (M^+, 51), 289 (76), 152 (15), 105 (100). Anal. ($C_{22}H_{18}O_3$) C, H.

***S*-Ethyl 3,7-Dimethylocta-2,6-dien-1-yl Thiolcarbonate (43).** A solution of geraniol (**42**) (1.540 g, 10 mmol) was treated with ethyl chlorothiolformate (1.25 mL, 12 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was quenched as depicted for compound **14**. The product was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to afford 2.254 g (93%

yield) of pure thiolcarbonate **43** as a colorless oil: R_f 0.68 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 2968, 2932, 1709, 1449, 1377, 1271, 1136, 972, 924, 677; ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.4 Hz, 3 H, SCH_2CH_3), 1.59 (s, 3 H, Me at C-7), 1.67 (s, 3 H, H-8), 1.71 (s, 3 H, Me at C-3), 1.99−2.14 (m, 4 H, H-4, H-5), 2.86 (q, J = 7.4 Hz, 2 H, SCH_2CH_3), 4.71 (d, J = 7.2 Hz, 2 H, H-1), 5.07 (m, 1 H, H-6), 5.35 (dt, J = 7.3, 1.1 Hz, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 15.00, 16.45, 17.65, 25.30, 25.61 (C-8), 26.21, 39.48, 63.96, 117.76, 123.63, 131.84, 143.20, 171.00; MS (*m*/*z*, relative intensity) 136 (35), 95 (11), 93 (27), 81 (43), 69 (100). Anal. ($C_{13}H_{22}O_2S$) C, H.

***S*-Ethyl 3,7-Dimethyl-6,7-epoxyoct-2-en-1-yl Thiolcarbonate (44).** To a solution of thiolcarbonate **43** (900 mg, 3.71 mmol) in methylene chloride (30 mL) was added dropwise *m*-chloroperoxybenzoic acid (900 mg) in methylene chloride (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. The mixture was allowed to room temperature, the organic phase was extracted with an aqueous saturated solution of sodium bicarbonate (3 × 50 mL) and water (2 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (4:1) to give 887 mg (93% yield) of pure epoxide **44** as a colorless oil: R_f 0.30 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 2963, 2930, 1709, 1456, 1377, 1271, 1138, 972, 924, 874, 818, 679; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H, H-8), 1.29 (s, 3 H, Me at C-7), 1.30 (t, J = 7.4 Hz, 3 H, SCH_2CH_3), 1.73 (s, 3 H, Me at 3), 2.20 (m, 2 H, H-4), 2.68 (t, J = 6.2 Hz, 1 H, H-6), 2.85 (q, J = 7.4 Hz, 2 H, SCH_2CH_3), 4.72 (d, J = 7.2 Hz, 2 H, H-1), 5.40 (dt, J = 7.3, 1.1 Hz, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 14.99, 16.44, 18.71, 24.78, 25.31, 27.01, 36.17, 58.33, 63.76, 63.84, 118.40, 142.28, 171.03; MS (*m*/*z*, relative intensity) 172 (4), 153 (12), 135 (16), 109 (17), 95 (35), 81 (76), 71 (82), 49 (83), 43 (100). Anal. ($C_{13}H_{22}O_3S$) C, H.

4-Hydroxyphenyl Phenyl Sulfide (47). A mixture of phenol (**45**; 600 mg, 6.4 mmol) and benzensulfinic acid (**46**; 1.605 g, 11.3 mmol) was heated to 60 °C, and the reaction mixture was stirred at this temperature for 1 h. The mixture was partitioned between an aqueous saturated solution of potassium carbonate (100 mL) and methylene chloride (100 mL). The organic layer was washed with water (3 × 70 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with toluene−EtOAc (49:1). The more polar residue was repurified by column chromatography eluting with hexanes−EtOAc (4:1) to give 250 mg (19% yield) of pure compound **47** as a colorless oil: R_f 0.45 (toluene−EtOAc, 9:1); IR (film, cm^{-1}) 3370, 3059, 1701, 1599, 1492, 1448, 1362, 1261, 1177, 1106, 1027, 835, 740, 692, 535; MS (*m*/*z*, relative intensity) 202 (M^+, 100), 183, 173, 141. Anal. ($C_{12}H_{10}OS \cdot {}^1/_3EtOAc$) C, H.

4-(Phenylthio)phenyl Prop-2-en-1-yl Ether (48). A solution of compound **47** (100 mg, 0.5 mmol) in dimethyl sulfoxide (3 mL) was treated with allyl bromide following the general procedure. The residue was purified by column chromatography (silica gel) employing hexanes−EtOAc (19:1) as eluent to afford 119 mg (96% yield) of pure allyl ether **48** as a colorless oil: R_f 0.63 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3073, 3019, 2916, 2868, 2541, 1891, 1593, 1493, 1285, 1242, 1173, 1024, 928, 739, 691, 532; ^1H NMR ($CDCl_3$) δ 4.55 (d, J = 5.2 Hz, 2 H, H-1), 5.30 (d, J = 10.5 Hz, 1 H, H-3_{cis}), 5.42 (d, J = 17.2 Hz, 1 H, H-3_{trans}), 6.06 (ddt, J = 17.2, 10.4, 5.1 Hz, 1 H, H-2), 6.91 (d, J = 8.8 Hz, 2 H, H-2′, H-6′), 7.19 (m, 5 H, aromatic protons), 7.40 (d, J = 8.7 Hz, 2 H, H-3′, H-5′); ^{13}C NMR ($CDCl_3$) δ 68.86 (C-1), 115.79 (C-2′), 117.81 (C-3), 124.73 (C-4′), 125.77 (C-4″), 128.32 (C-3″), 128.87 (C-2″), 132.93 (C-2), 135.13 (C-3′), 138.42 (C-1″), 158.77 (C-1′); MS (*m*/*z*, relative intensity) 242 (M^+, 38), 201 (100), 171 (8), 129 (17). Anal. ($C_{15}H_{14}OS$) C, H.

2,4-Dichlorophenyl Prop-2-en-1-yl Ether (50). Compound **50** was obtained as described for compound **13** from 2,4-dichlorophenol (compound **49**; 1.635 g, 10 mmol). After the usual treatment the residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to afford 1.502 g (74% yield) of pure allyl ether **50** as a colorless oil: R_f 0.63 (hexanes−EtOAc, 9:1); IR (film, cm^{-1}) 3084, 2922, 2870, 2540, 1572, 1483, 1288, 1253, 1105, 1016, 802, 754, 660, 559; ^1H NMR ($CDCl_3$) δ 4.58 (d, J = 5.1 Hz, 2 H, H-1), 5.32 (dd, J = 10.5, 1.2 Hz, 1 H, H-3_{cis}), 5.45 (dd, J = 17.3, 1.5 Hz, 1 H, H-3_{trans}), 6.03 (ddt, J = 17.2, 10.5, 1.5 Hz, 1 H, H-2), 6.83 (d, J = 8.8 Hz, 1 H, H-5′), 7.15 (dd, J = 8.8, 2.5 Hz, 1 H, H-4′), 7.36 (d, J = 2.5 Hz, 1 H, H-3′); ^{13}C NMR ($CDCl_3$) δ 70.02 (C-1), 114.59 (C-6′), 118.08 (C-3), 123.98 (C-2′), 125.91 (C-4′), 127.46 (C-5′), 130.02 (C-3′), 132.30 (C-2), 152.97 (C-1′); MS (*m*/*z*, relative intensity) 202, 204, 206 (M^+, 37, 23, 4), 169 (6), 167 (18), 166 (3), 164 (15), 162 (24), 137 (4), 135 (23), 133 (39), 41 (100). Anal. ($C_9H_8OCl_2$) C, H.

2,4-Dichlorophenoxyethyl Tetrahydro-2*H*-pyran-2-yl Ether (51). To a suspension of 2,4-dichlorophenol (820 mg, 5 mmol) and potassium hydroxide (1.100 g, 20 mmol) in dimethyl sulfoxide (3 mL) was added bromoethyl tetrahydropyranyl ether (2.090 g, 10 mmol) following the method described for **13**. After the usual treatment the product was purified by column chromatography (silica gel) employing hexanes−EtOAc (9:1) as eluent to give 407 mg (28% yield) of pure compound **51** as a colorless oil: R_f 0.43 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 2943, 2871, 1585, 1480, 1292, 1265, 1080, 1015, 802, 739; ^1H NMR ($CDCl_3$) δ 1.52−1.84 (m, 6 H, H-3″, H-4″, H-5″), 3.51 (m, 1 H, H-6″$_a$), 3.85 (m, 2 H, H-1), 4.04 (m, 1 H, H-6″$_b$), 4.17 (distorted t, J = 4.7 Hz, 2 H, H-2), 4.72 (m, 1 H, H-2″), 6.87 (d, J = 8.8 Hz, 1 H, H-5′), 7.14 (dd, J = 8.8, 2.5 Hz, 1 H, H-4′), 7.34 (d, J = 2.5 Hz, 1 H, H-3′); ^{13}C NMR ($CDCl_3$) δ 19.19 (C-4″), 25.33 (C-3″), 30.40 (C-5″), 61.98 (C-1), 65.39 (C-2″), 69.07 (C-2), 98.94 (C-6″), 114.61 (C-6′), 123.92 (C-2′), 125.84 (C-4′), 127.40 (C-5′), 129.85 (C-3′), 153.36 (C-1′); MS (*m*/*z*, relative intensity) 290, 292, 294 (M^+, 13, 9, 1), 129 (79), 85 (100). Anal. ($C_{13}H_{16}O_3Cl_2$) C, H.

4-Phenoxyphenyl Prop-1-en-1-yl Ether (52). To a solution of compound **6** (326 mg, 1.4 mmol) in anhydrous tetrahydrofuran (7 mL) was added dropwise a 2.0 M solution of *n*-butyllithium (1.12 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 1 h. Then, a saturated solution of ammonium chloride (20 mL) was added. The mixture was extracted with methylene chloride (3 × 15 mL). The combined layers were washed with water (2 × 20 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane−CH_2Cl_2 (9:1) to afford 63 mg (20% yield) of pure compound **52** as a colorless oil: R_f 0.5 (hexane−CH_2Cl_2, 4:1); IR (film, cm^{-1}) 3043, 2922, 2865, 1700, 1588, 1504, 1219, 1110, 1021, 843, 751, 691; ^1H NMR ($CDCl_3$) δ 1.72 (dd, J = 6.7, 1.7 Hz, 3 H, H-3), 4.85 (m, 1 H, H-2), 6.33 (dd, J = 6.4, 1.7 Hz, 1 H, H-1), 6.93−7.34 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 9.33 (C-3), 107.21 (C-2), 117.36 (C-2″), 117.96 (C-2′), 120.56 (C-3′), 122.73 (C-4″), 129.66 (C-3″), 141.33 (C-1), 153.70 (C-1′), 158.15 (C-1″); MS (*m*/*z*, relative intensity) 226 (M^+, 100), 197 (23), 186 (55), 170 (10), 157 (14), 141 (6), 129 (18), 115 (13), 109 (17), 91 (6), 77 (37), 63 (8), 51 (25). Anal. ($C_{15}H_{14}O_2$) C, H.

4-Phenoxyphenoxyethyl 4-Toluenesulfonate (54) and 4-Phenoxyphenoxyethyl Chloride (55). A solution of alcohol **53** (960 mg, 4.17 mmol) in pyridine (5 mL) was treated with *p*-toluenesulfonyl chloride (954 mg, 5.0 mmol), 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 H_2O (3 × 50 mL). The organic phase was dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexanes−EtOAc (9:1) as eluent to afford 1.068 mg of tosylate **54** (70% yield) and 210 mg of chloride **55** (17% yield) as colorless oils. Compound **54**: R_f 0.16 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3070, 2955, 2926, 1589, 1504, 1360, 1223, 1190, 932, 777, 553; MS (*m*/*z*, relative intensity) 384 (M^+, 10), 248 (7), 199 (53), 185 (15), 155 (28), 91 (56), 49 (100). Compound **55**: R_f 0.59 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3064, 2962, 2927, 2866, 1589, 1504, 1220, 1039, 841, 756, 513; MS (*m*/*z*,

relative intensity) 250 (23), 248 (M^+, 64), 185 (61), 129 (34), 84 (62), 79 (68), 49 (100).

4-Phenoxyphenoxyethyl Thiocyanate (56). A solution of tosylate **54** (1.068 mg, 2.89 mmol) in anhydrous dimethylformamide (5 mL) was treated with potassium thiocyanate (1.966 mg, 20.23 mmol). The reaction mixture was heated at 100 °C for 3 h. The mixture was allowed to cool to room temperature, and water (70 mL) was added. The aqueous phase was extracted with methylene chloride (2 × 50 mL), and the combined organic layers were washed with brine (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) eluting with hexanes−EtOAc (4:1) to give 573 mg (73% yield) of pure compound **56** as a white solid: R_f 0.27 (hexanes−EtOAc, 4:1); mp 52 °C (EtOH−H_2O); IR (film, cm^{-1}) 3051, 2936, 2869, 2156, 1504, 1228; ^1H NMR ($CDCl_3$) δ 3.33 (t, J = 5.8 Hz, 2 H, H-1), 4.30 (t, J = 5.8 Hz, 2 H, H-2), 6.87−7.09 (m, 7 H, aromatic protons), 7.25−7.34 (m, 2 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 33.23 (C-1), 66.37 (C-2), 113.47 (S*C*N), 115.86 (C-2″), 117.78 (C-2′), 120.63 (C-3′), 122.65 (C-4″), 129.58 (C-3″), 151.16 (C-4′),153.89 (C-1′), 158.01 (C-1″); MS (*m*/*z*, relative intensity) 271 (M^+, 100), 185 (86). Anal. ($C_{15}H_{13}O_2NS$) C, H, N, S.

4-Phenoxyphenoxyethyl Disulfide (57) and 4-Phenoxyphenoxyethyl Mercaptane (58). Thiocyanate **56** (297 mg, 1.1 mmol) was treated with a 1.0 M solution of sodium methoxide in anhydrous methanol (5 mL). The reaction mixture was stirred at room temperature for 2 h. The mixture was partitioned between water (70 mL) and methylene chloride (70 mL). The organic layer was washed with water (5 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated to afford 265 mg of a 2:1 mixture of **57** and **58** favoring the disulfide. The residue was dissolved in glacial acetic acid, and zinc (642 mg, 9.8 mmol) was added. The reaction mixture was refluxed for 1 h. The mixture was allowed to cooled to room temperature and was partitioned between water (50 mL) and methylene chloride (70 mL). The organic phase was washed with water (2 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated to yield 245 mg (91% yield) of pure sulfide **58** as a white solid. This compound was used without further purification. To characterize both components, 100 mg of the mixture **57**/**58**, in an independent experiment, could be resolved by column chromatography (silica gel) eluting with hexane−*i*-PrOH (1%) to afford 61 mg of disulfide **57** as a white solid and 30 mg of pure compound **58**. Compound **57**: R_f 0.58 (hexanes−EtOAc, 4:1); mp 68−69 °C (MeOH−EtOAc); IR (film, cm^{-1}) 3042, 2922, 2868, 1589, 1504, 1487, 1215, 1020, 841, 752, 528; MS (*m*/*z*, relative intensity) 279 (1), 260 (11), 246 (20), 186 (100), 75 (80); FABMS (*m*/*z*, relative intensity) 490 (53), 503 (100). Anal. ($C_{28}H_{26}O_4S_2$·EtOAc) C, H. Compound **58**: R_f 0.64 (hexanes−EtOAc, 4:1); mp 45 °C (MeOH); IR (film, cm^{-1}) 3041, 2931, 2868, 1589, 1504, 1490, 1220, 843; MS (*m*/*z*, relative intensity) 246 (M^+, 30), 185 (100).

***S*-(4-Phenoxyphenoxyethyl) *N*-Ethylthiolcarbamate (59).** Compound **58** (70 mg, 0.28 mmol) in pyridine (3 mL) was treated with ethyl isocyanate (0.1 mL) and 4-(dimethylamino)pyridine (10 mg). The reaction mixture was stirred for 4 h. The mixture was partitioned between methylene chloride (50 mL) and 10% HCl (50 mL). The organic phase was washed with 10% HCl (4 × 50 mL) and water (3 × 50 mL). Then, the organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography employing hexanes−ethyl acetate (4:1) as eluent to give 50 mg (56% yield) of pure thiolcarbamate **59** as a white solid: R_f 0.21 (hexanes−EtOAc, 4:1); mp 86−87 °C; IR (film, cm^{-1}) 2978, 2935, 2874, 1655, 1589, 1507, 1489, 1221, 845; ^1H NMR ($CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3 H, $-CH_2CH_3$), 3.28 (t, J = 6.5 Hz, 2 H, H-1), 3.34 (m, 2 H, $-CH_2CH_3$), 4.13 (t, J = 6.5 Hz, 2 H, H-2), 5.47 (broad s, 1 H, −N*H*), 6.87−7.07 (m, 7 H, aromatic protons), 7.29 (m, 2 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.87 (CH_2CH_3), 29.05 (C-1), 36.48 (CH_2CH_3), 67.93 (C-2), 115.73 (C-2″), 117.66 (C-2′), 120.68 (C-3′), 122.44 (C-4″), 129.54 (C-3″), 150.46 (C-4′), 154.69 (C-1′), 158.34 (C-1″); MS (*m*/*z*, relative intensity) 317 (M^+, 10), 186 (100), 132 (86). Anal. ($C_{17}H_{19}O_3NS$) C, H, N, S.

***S*-(4-Phenoxyphenoxyethyl) Ethyl Thiolcarbonate (60).** Mercaptane **58** (72 mg, 0.29 mmol) in pyridine (3 mL) was treated with ethyl chloroformate (0.1 mL). The reaction mixture was stirred at room temperature overnight. The mixture was partitioned between methylene chloride (50 mL) and 10% HCl (50 mL). The organic phase was washed with 10% HCl (4 × 50 mL) and water (3 × 50 mL). The organic layers were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with toluene−ethyl acetate (99:1) to afford 51 mg (55% yield) of pure thiolcarbonate **60** as a colorless oil: R_f 0.52 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3038, 2984, 2930, 1719, 1604, 1146, 864; ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.0 Hz, 3 H, $-CH_2CH_3$), 3.22 (t, J = 6.6 Hz, 2 H, H-1), 4.15 (t, J = 6.6 Hz, 2 H, H-2), 4.29 (q, J = 7.0 Hz, 2 H, $-CH_2CH_3$), 6.86−7.07 (m, 7 H, aromatic protons), 7.25−7.33 (m, 2 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.24 (CH_2CH_3), 30.08 (C-1), 63.77 (CH_2CH_3), 67.20 (C-2), 115.74 (C-2″), 117.69 (C-2′), 120.69 (C-3′), 122.48 (C-4″), 129.56 (C-3″), 150.58 (C-4′),154.56 (C-1′), 158.32 (C-1″), 170.52 (C═O); MS (*m*/*z*, relative intensity) 318 (M^+, 6), 186 (18), 133 (28), 84 (50), 49 (100). Anal. ($C_{17}H_{18}O_4S$) C, H.

***S*-(4-Phenoxyphenoxyethyl) Isobutyl Thiolcarbonate (61).** A solution of mercaptane **58** (30 mg, 0.12 mmol) in pyridine (2 mL) was treated with isobutyl chloroformate (0.1 mL), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was worked up as described for compound **60** and purified by column chromatography (silica gel) eluting with toluene−hexanes−ethyl acetate (50:50:0.75) to give 14 mg (40% yield) of isobutyl thiolcarbonate **61** as a colorless oil: R_f 0.43 (hexanes−EtOAc, 19:1); IR (film, cm^{-1}) 2962, 1717, 1506, 1223, 1142, 841, 754; ^1H NMR ($CDCl_3$) δ 0.94 (d, J = 6.8 Hz, 6 H, $-CH(CH_3)_2$), 1.98 (m, 1 H, $-CH(CH_3)_2$), 3.23 (t, J = 6.5 Hz, 2 H, H-1), 4.02 (d, J = 6.6 Hz, 2 H, $-CH_2CH$), 4.15 (t, J = 6.5 Hz, 2 H, H-2), 6.86−7.11 (m, 7 H, aromatic protons), 7.25−7.33 (m, 2 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 18.90 ($-CH(CH_3)_2$), 27.87 ($-CH(CH_3)_2$), 30.14 (C-1), 67.29 (C-2), 73.72 ($-CH_2CH$), 115.79 (C-2″), 117.73 (C-2′), 120.72 (C-3′), 122.52 (C-4″), 129.59 (C-3″), 150.63 (C-4′), 154.61 (C-1′), 158.34 (C-1″), 170.71 (C═O); MS (*m*/*z*, relative intensity) 346 (M^+, 12), 186 (75), 149 (21), 105 (29), 57 (100). Anal. ($C_{19}H_{22}O_4S$) C, H.

4-Phenoxyphenoxyethyl Ethyl Dithiolcarbonate (62). To a solution of mercaptane **58** (66 mg, 0.27 mmol) in pyridine (3 mL) was added ethyl chlorothiolformate (0.1 mL), and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was worked up as described for **60** and purified by column chromatography using hexanes−ethyl acetate (97:3) as eluent to afford 40 mg (44% yield) of dithiolcarbonate **62** as a pale yellow oil: R_f 0.42 (hexanes−EtOAc, 19:1); IR (film, cm^{-1}) 3044, 2972, 2932, 2874, 1747, 1647, 1506, 1244, 872, 739; ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.4 Hz, 3 H, $-CH_2CH_3$), 2.99 (q, J = 7.4 Hz, 2 H, $-CH_2CH_3$), 3.35 (t, J = 6.4 Hz, 2 H, H-1), 4.11 (t, J = 6.5 Hz, 2 H, H-2), 6.84−7.04 (m, 7 H, aromatic protons), 7.25−7.32 (m, 2 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.89 (CH_2CH_3), 25.30 (CH_2CH_3), 29.56 (C-1), 67.18 (C-2), 115.78 (C-2″), 117.72 (C-2′), 120.71 (C-3′), 122.53 (C-4″), 129.58 (C-3″), 150.66 (C-4′), 154.51 (C-1′), 158.31 (C-1″), 189.20 (C═O); MS (*m*/*z*, relative intensity) 334 (M^+, 16), 260 (7), 246 (18), 186 (39), 149 (67), 89 (54), 75 (100). Anal. ($C_{17}H_{18}O_3S_2$) C, H.

4-Phenoxyphenoxyethyl *O*-Ethyl Xanthate (63). A solution of tosylate **54** (38 mg, 0.105 mmol) in dimethyl sulfoxide (2 mL) was treated with potassium *O*-ethyl xanthate (87 mg, 0.52 mmol). The reaction mixture was stirred at 90 °C for 2 h. Then, the mixture was allowed to cool to room temperature and was partitioned between water (50 mL) and methylene chloride (50 mL). The aqueous phase was extracted with methylene chloride (3 × 40 mL). The combined organic layers were washed with brine (5 × 50 mL) and water (2 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel)

using hexanes−EtOAc (9:1) as eluent to give 30 mg (86% yield) of pure xanthate **63** as a colorless oil: R_f 0.56 (hexanes−EtOAc, 9:1); IR (film, cm^{-1}) 2994, 2933, 1589, 1504, 1489, 1221, 1111, 1051, 842, 756, 692; ^1H NMR ($CDCl_3$) δ 1.42 (t, J = 7.0 Hz, 3 H, $-CH_2CH_3$), 3.53 (t, J = 6.5 Hz, 2 H, H-1), 4.20 (t, J = 6.5 Hz, 2 H, H-2), 4.67 (q, J = 7.0 Hz, 2 H, $-CH_2CH_3$), 6.85−7.07 (m, 7 H, aromatic protons), 7.25−7.33 (m, 2 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 13.78 ($-CH_2CH_3$), 34.98 (C-1), 66.30 (C-2), 70.25 ($-CH_2CH_3$), 115.81 (C-2″), 117.71 (C-2′), 120.70 (C-3′), 122.52 (C-4″), 129.58 (C-3″), 150.63 (C-4′), 154.56 (C-1′), 158.31 (C-1″), 214.27 (C=S); MS (*m*/*z*, relative intensity) 334 (M^+, 1), 248 (70), 185 (79), 149 (43), 129 (50), 77 (100). Anal. ($C_{17}H_{18}O_3S_2$) C, H.

Prop-2-en-1-yl *O*-(4-Phenoxyphenoxyethyl) Xanthate (64). A solution of alcohol **53** (70 mg, 0.28 mmol) in anhydrous dimethylformamide (2 mL) was treated with carbon disulfide (1 mL) and DBU (20 mg). The mixture was stirred at room temperature for 20 min, and allyl bromide (100 μL) was added. The reaction mixture was stirred for 30 min. 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 brine (5 × 50 mL) and water (2 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography employing hexanes−EtOAc (19:1) as eluent to give 40 mg (39% yield) of pure xanthate **64** as a yellow oil: R_f 0.51 (hexanes−EtOAc, 9:1); IR (film, cm^{-1}) 2994, 2933, 1589, 1504, 1489, 1221, 1111, 1051, 842, 756, 692; ^1H NMR ($CDCl_3$) δ 3.78 (dt, J = 7.0, 1.0 Hz, $SCH_2CH=CH_2$), 4.30 (t, J = 4.6 Hz, 2 H, H-2), 4.92 (t, J = 4.6 Hz, 2 H, H-1), 5.16 (dd, J = 10.1, 1.1 Hz, H-3‴$_{cis}$), 5.33 (dq, J = 17.0, 1.2 Hz, 1 H, H-3‴$_{trans}$), 5.93 (ddt, J = 17.0, 7 Hz, 1 H, H-2‴), 6.87−7.08 (m, 7 H, aromatic protons), 7.24−7.33 (m, 2 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 38.90 (C-1), 65.92 (C-2), 71.51 ($-OCH_2CH=CH_2$), 115.85 (C-2″), 117.77 (C-2′), 119.05 ($-OCH_2CH=CH_2$), 120.73 (C-3′), 122.58 (C-4″), 129.61 (C-3″), 131.55 ($-OCH_2CH=CH_2$), 150.80 (C-4′), 154.57 (C-1′), 156.24 (C-1″); MS (*m*/*z*, relative intensity) 346 (M^+, 1), 248 (12), 185 (20), 161 (63), 77 (70), 41 (100). Anal. ($C_{18}H_{18}O_3S_2$) C, H.

3-(4-Phenoxyphenoxy)propyl 4-Toluenesulfonate (66). A solution of alcohol **65** (570 mg, 0.23 mmol) in anhydrous pyridine (5 mL) was treated with tosyl chloride (530 mg) at 0 °C. The mixture was stirred at room temperature overnight. The reaction was quenched as described for **54**. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (4:1) as eluent to yield 550 mg (60% yield) of pure tosylate **66** as a colorless oil: R_f 0.27 (hexanes−EtOAc, 4:1).

3-(4-Phenoxyphenoxy)propyl Thiocyanate (67). To a solution of tosylate **66** (158 mg, 0.4 mmol) in anhydrous *N*,*N*-dimethylformamide (3 mL) was added potassium thiocyanate (400 mg, 4.1 mmol). The reaction mixture was treated as described for **56**. After the usual workup, the product was purified by column chromatography (silica gel) employing hexanes−EtOAc as eluent to afford 100 mg (87% yield) of pure compound **67** as a colorless oil: R_f 0.46 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 2924, 2871, 2154, 1589, 1504, 1489, 1219, 1043, 872, 843, 752, 692; ^1H NMR ($CDCl_3$) δ 2.30 (p, J = 6.6 Hz, 2 H, H-2), 3.19 (t, J = 6.9 Hz, 2 H, H-1), 4.10 (t, J = 5.7 Hz, 2 H, H-3), 6.82−7.33 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 31.37 (C-1), 36.39 (C-2), 65.18 (C-3), 115.52 (C-2″), 117.73 (C-2′), 120.71 (C-3′), 122.55 (C-4″), 129.58 (C-3″), 154.57 (C-1′), 158.26 (C-1″); MS (*m*/*z*, relative intensity) 285 (M^+, 47), 197 (6), 186 (50), 129 (33), 85 (51), 77 (83), 41 (100). Anal. ($C_{16}H_{15}O_2NS$) C, H, N.

4-Phenoxyphenyl 2,3-Episulfoprop-1-yl Ether (69). A solution of epoxide **68** (186 mg, 0.77 mmol) in *N*,*N*-dimethylformamide (3 mL) was treated with potassium thiocyanate (500 mg), and the mixture was stirred at 100 °C for 3 h. The mixture was worked up as depicted for **56**, and the residue was purified by column chromatography eluting with hexanes−EtOAc (9:1) to afford 93 mg (47% yield) of pure compound **69** as a white solid: R_f 0.38 (hexanes−EtOAc, 9:1); mp 60 °C; IR (KBr, cm^{-1}) 3070, 2872, 1593, 1508, 1302, 1244, 1105, 1034, 839, 773, 743, 613; ^1H NMR ($CDCl_3$) δ 2.33 (dd, J = 5.2, 1.4 Hz, 1 H, H-3$_a$), 2.62 (d, J = 6.2 Hz, 1 H, H-3$_b$), 3.28 (m, 1 H, H-2), 3.92 (dd, J = 10.2, 6.9 Hz, 1 H, H-1$_a$), 4.19 (dd, J = 10.2, 5.4 Hz, 1 H, H-1$_b$), 6.867.36 (m, 9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 23.92 (C-3), 31.44 (C-2), 73.31 (C-1), 115.98 (C-2″), 117.83 (C-2′), 120.78 (C-3′), 122.63 (C-4″), 129.69 (C-3″), 150.85 (C-4′), 154.73 (C-1′), 158.37 (C-1″); MS (*m*/*z*, relative intensity) 258 (M^+, 35), 185 (19), 129 (18), 83 (20), 73 (100). Anal. ($C_{15}H_{14}O_2S$) C, H.

2-[4-(Benzyloxy)phenoxy]ethyl Tetrahydro-2*H*-pyran-2-yl Ether (71). A solution of 4-(benzyloxy)phenol (**70**; 2.00 g, 9.9 mmol) in dimethyl sulfoxide (5 mL) was treated with bromoethyl tetrahydropyranyl ether as depicted for **13**. After the usual workup, the product was purified by column chromatography eluting with hexanes−EtOAc (4:1) to yield 1.786 g (55% yield) of pure compound **71** as a colorless oil: R_f 0.39 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3051, 2943, 2872, 1508, 1454, 1231, 1034, 826, 737, 525; ^1H NMR ($CDCl_3$) δ 1.53−1.87 (m, 6 H, H-3‴, H-4‴, H-5‴), 3.51 (m, 1 H, H-6‴a), 3.46−4.00 (m, 3 H), 4.03−4.12 (m, 2 H), 4.67 (distorted t, J = 3.3 Hz, 1 H, H-2‴), 5.00 (s, 2 H, $PhCH_2O$), 6.87 (m *AB*, 4 H, H), 7.24−7.42 (m, 5 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.32 (C-4‴), 25.39 (C-5‴), 30.48 (C-3‴), 62.11 (C-6‴), 65.89 (C-1), 68.08 (C-2), 70.65 ($PhCH_2$), 98.91 (C-2‴), 115.76 (C-2′, C-3′), 127.39 (C-4″),* 127.78 (C-2″),* 128.46 (C-3″), 137.29 (C-1″), 153.07 (C-1′); MS (*m*/*z*, relative intensity) 328 (M^+, 20), 129 (77), 91 (99), 85 (100). Anal. ($C_{20}H_{24}O_4$) C, H.

2-[4-(Benzyloxy)phenyl]ethanol (72). A solution of compound **71** (1.496 g, 4.6 mmol) in methanol (30 mL) was treated with pyridinium 4-toluenesulfonate (30 mg). The reaction mixture was stirred at room temperature overnight. Then, water (50 mL) was added, and the mixture was extracted with methylene chloride (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography eluting with hexanes−EtOAc (7:3) to give 919 mg (82% yield) of pure alcohol **72** as a white solid: R_f 0.10 (hexanes−EtOAc, 4:1); mp 103 °C; IR (KBr, cm^{-1}) 3491, 2961, 2914, 1612, 1512, 1454, 1250, 1055, 903, 802, 729, 698, 604; MS (*m*/*z*, relative intensity) 244 (M^+, 55), 153 (21), 109 (63), 91 (100). Anal. ($C_{15}H_{16}O_3$) C, H.

2-[4-(Benzyloxy)phenyl]ethyl 4-Toluenesulfonate (73). A solution of alcohol **72** (909 mg, 3.72 mmol) in anhydrous pyridine (3 mL) was treated with tosyl chloride (850 mg, 4.46 mmol) at 0 °C. The mixture was stirred at room temperature for 5 h. The reaction mixture was worked up as described for **54**. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (19:1) to afford 1.217 g (82% yield) of pure tosylate **73** as a white solid: R_f 0.74 (hexane−EtOAc); mp 90−92 °C; MS (*m*/*z*, relative intensity) 398 (M^+, 14), 199 (41), 155 (16), 91 (100). Anal. ($C_{22}H_{22}O_5S$) C, H.

2-[4-(Benzyloxy)phenyl]ethyl Thiocyanate (74). A solution of compound **73** in *N*,*N*-dimethylformamide (5 mL) was treated with potassium thiocyanate (610 mg). The reaction mixture was stirred at 100 °C for 3 h. The reaction was quenched as depicted for **56**. The residue was purified by column chromatography (silica gel) using hexane−CH_2Cl_2 (7:3) as eluent to afford a 70% yield of pure thiocyanate **74** as a white solid: R_f 0.33 (hexanes−EtOAc, 1:1); mp 78 °C; IR (KBr, cm^{-1}) 2928, 2882, 2156, 1516, 1464, 1402, 1296, 1242, 1045, 833, 737, 694; ^1H NMR ($CDCl_3$) δ 3.30 (t, J = 5.9 Hz, 2 H, H-1), 4.26 (t, J = 5.9 Hz, 2 H, H-2), 5.02 (s, 2 H, $PhCH_2O$), 6.89 (m *AB*, 4 H, H-2′, H-3′), 7.31−7.44 (m, 5 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 33.26 (C-1), 66.55 (C-2), 70.57 ($PhCH_2O$), 115.51 (C-2′),* 115.89 (C-3′),* 127.34 (C-2″), 127.82 (C-4″), 128.45 (C-3″), 137.03 (C-1″), 152.04 (C-4′), 153.69 (C-1′); MS (*m*/*z*, relative intensity) 285 (M^+, 70), 186 (64), 185 (48), 129 (25), 77 (100). Anal. ($C_{16}H_{15}O_2NS$): C, H, N.

2-(4-Benzylphenoxy)ethyl Tetrahydro-2*H*-pyran-2-yl Ether (76). 4-Benzylphenol (**75**; 867 mg, 4.7 mmol) was treated with potassium hydroxide (655 mg, 11.7 mmol) and bromoethyl tetrahydropyranyl ether (1.360 g, 6.5 mmol) as

described for **13**. After the usual workup, the product was purified by column chromatography eluting with hexanes−EtOAc (19:1) to afford 966 mg (65% yield) of pure compound **76** as a colorless oil: R_f 0.24 (hexanes−EtOAc, 19:1); IR (film, cm^{-1}) 3028, 2941, 2872, 1612, 1510, 1454, 1246, 1126, 1034, 729, 698; ^{1}H NMR ($CDCl_3$) δ 1.54−1.80 (m, 6 H), 3.54 (m, 1 H, H-6‴a), 3.77−4.02 (m, 3 H), 3.91 (s, 2 H, PhCH_2), 4.04−4.15 (m, 2 H), 4.69 (distorted t, J = 3.3 Hz, 1 H, H-2‴), 6.85 (d, J = 8.6 Hz, 2 H, H-2′), 7.08 (d, J = 8.6 Hz, 2 H, H-3′), 7.14−7.25 (m, 5 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.30 (C-4‴), 25.39 (C-5‴), 30.46 (C-3‴), 40.99 (PhCH_2), 62.07 (C-6‴), 65.80 (C-1), 67.42 (C-2), 98.88 (C-2‴), 114.69 (C-2′), 125.89 (C-4″), 128.34 (C-2″), 128.75 (C-3″), 129.75 (C-3′), 133.36 (C-4′), 141.51 (C-1″), 157.28 (C-1′); MS (*m*/*z*, relative intensity) 318 (M^+, 18), 184 (23), 129 (81), 85 (100). Anal. ($C_{20}H_{24}O_3$) C, H.

2-(4-Benzylphenoxy)ethanol (77). To a solution of compound **76** (966 mg, 3.04 mmol) in methanol (30 mL) was added pyridinium *p*-toluenesulfonate (50 mg). The reaction mixture was stirred at room temperature overnight. The mixture was partitioned between water (50 mL), methylene chloride (50 mL). The aqueous phase was extracted with methylene chloride (2 × 30 mL), the combined organic layers were washed with brine (2 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated to afford 536 mg (77% yield) of pure alcohol **77** as a white solid. This alcohol was used in the next step without further purification: R_f 0.11 (hexanes−EtOAc, 4:1); mp 64−65 °C; IR (KBr, cm^{-1}) 3491, 2961, 2914, 1612, 1512, 1454, 1250, 1055, 903, 802, 729, 698, 604; MS (*m*/*z*, relative intensity) 228 (M^+, 100), 184 (76), 183 (74), 165 (32), 106 (39), 91 (49).

2-(4-Benzylphenoxy)ethyl 4-Toluenesulfonate (78). Alcohol **77** (500 mg, 2.19 mmol) in pyridine (5 mL) was treated with tosyl chloride (500 mg, mmol) as depicted for **54**. The residue was purified by column chromatography (silica gel) eluting with hexanes−EtOAc (85:15) to afford 528 mg (63% yield) of pure tosylate **78** as a white solid: R_f 0.27 (hexanes−EtOAc, 4:1); mp 49−51 °C; IR (KBr, cm^{-1}) 3028, 3924, 1610, 1599, 1510, 1494, 1454, 1358, 1073, 1020, 922, 813, 781, 734. Anal. ($C_{22}H_{22}O_4S$) C, H.

2-(4-Benzylphenoxy)ethyl Thiocyanate (79). To a solution of tosylate **78** (286 mg, 0.74 mmol) was added potassium thiocyanate (363 mg, mmol). The solution was stirred at 100 °C for 3 h. After the usual workup, the product was purified by column chromatography employing hexanes−EtOAc (19:1) as eluent to give 104 mg (52% yield) of pure thiocyanate **79** as a colorless oil: R_f 0.36 (hexanes−EtOAc, 4:1); IR (film, cm^{-1}) 3028, 2918, 2872, 2154, 1611, 1508, 1242, 1177, 1030, 729, 698, 602; ^{1}H NMR ($CDCl_3$) δ 3.25 (t, J = 5.9 Hz, 2 H, H-1), 3.91 (s, 2 H, PhCH_2), 4.24 (t, J = 5.9 Hz, 2 H, H-2), 6.83 (d, J = 8.6 Hz, 2 H, H-2′), 7.11 (d, J = 8.6 Hz, 2 H, H-3′), 7.17−7.30 (m, 5 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 33.28 (C-1), 40.99 (PhCH_2), 65.89 (C-1), 114.72 (C-2′), 126.02 (C-4″), 128.41 (C-2″), 128.75 (C-3″), 130.01 (C-3′), 132.52 (C-4′), 141.25 (C-1″), 156.18 (C-1′); MS (*m*/*z*, relative intensity) 269 (M^+, 50), 242 (19), 182 (64), 91 (100). Anal. ($C_{16}H_{15}NOS$) C, H, N.

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Supporting Information Available: NMR spectral data for compounds **11**, **14**, **15**, **18**, **21**, **23**, **24**, **26**−**29**, **32**, **33**, **35**, **37**, **39**, **40**, **47**, **54**, **55**, **58**, **66**, **72**, **73**, **77**, and **78** and a table of data needed to calculate percent inhibition (11 pages). Ordering information is given on any current masthead page.

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