ChemPubSoc Europe

DOI: 10.1002/cmdc.201500100

CHEMMEDCHEM Full Papers

Aryloxyethyl Thiocyanates Are Potent Growth Inhibitors of *Trypanosoma cruzi* and *Toxoplasma gondii*

María N. Chao,[a] Carolina Exeni Matiuzzi,[a] Melissa Storey,[b] Catherine Li,[b] Sergio H. Szajnman,[a] Roberto Docampo,[b] Silvia N. J. Moreno,[b] and Juan B. Rodriguez*[a]

As a part of our project aimed at searching for new safe chemotherapeutic agents against parasitic diseases, several compounds structurally related to the antiparasitic agent WC-9 (4-phenoxyphenoxyethyl thiocyanate), which were modified at the terminal phenyl ring, were designed, synthesized, and evaluated as growth inhibitors against *Trypanosoma cruzi*, the etiological agent of Chagas disease, and *Toxoplasma gondii*, the parasite responsible of toxoplasmosis. Most of the synthetic analogues exhibited similar antiparasitic activity and were slightly more potent than our lead WC-9. For example, two trifluoromethylated derivatives exhibited ED_{50} values of 10.0 and 9.2 μM against intracellular *T. cruzi*, whereas they showed potent action against tachyzoites of *T. gondii* (ED_{50} values of 1.6 and 1.9 μM against *T. gondii*). In addition, analogues of WC-9 in which the terminal aryl group is in the *meta* position with respect to the alkyl chain bearing the thiocyanate group showed potent inhibitory action against both *T. cruzi* and *T. gondii* at the very low micromolar range, which suggests that a *para*-phenyl substitution pattern is not necessary for biological activity.

Introduction

Trypanosomatids have a strict requirement for specific endogenous sterols for survival and cannot use the abundant supply of cholesterol present in their mammalian hosts.[1–5] For that reason, ergosterol biosynthesis has become a valid target to control parasitic diseases caused by pathogenic trypanosomatids. It has been reported that ergosterol biosynthesis inhibitors with potent in vitro activity and special pharmacokinetic properties in mammals can induce radical parasitological cure in animal models of both acute and chronic experimental Chagas disease.[6,7] 4-Phenoxyphenoxyethyl thiocyanate (**1**; WC-9) is an interesting drug that presents ED_{50} values at the low nanomolar range against the clinically more relevant replicative form (amastigotes) of *Trypanosoma cruzi*,[8–10] the etiological agent of Chagas disease or American trypanosomiasis (Figure 1). WC-9 induces a dose-dependent effect of growth of the epimastigotes (EP strain).[11] Furthermore, the growth inhibitory effects of WC-9 are associated with depletion of parasitic endogenous sterols, in addition to ergosterol and its 24-ethyl analogue with no accumulation of sterol intermediates or precursors; this is indicative of obstruction of the biosynthetic pathway at the presqualene level.[11]

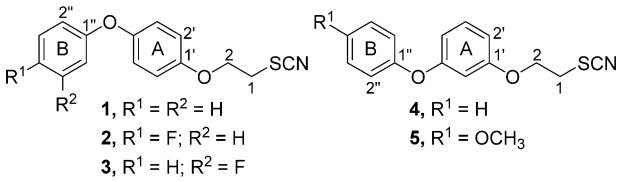


Figure 1. Chemical structure of WC-9 (**1**) and other closely related analogues.

Squalene synthase (SQS) is a crucial enzyme in isoprenoid biosynthesis that catalyzes the first committed step in ergosterol biosynthesis, for which reductive dimerization of two molecules of farnesyl pyrophosphate takes place to form squalene. It has been determined that the precise mode of action of WC-9 is as an inhibitor of the enzymatic activity of *T. cruzi* SQS[11] by employing highly purified glycosomes and mitochondrial membrane vesicles obtained from *T. cruzi* epimastigotes as the enzyme source.[12] WC-9 is a potent inhibitor of both glycosomal and mitochondrial *T. cruzi* SQS, with IC_{50} values of 88 and 129 nM. The dose–response curves for the activity of WC-9 against *Tc*SQS are consistent with noncompetitive inhibition with $K_i = IC_{50}$; these K_i values are two to three orders of magnitude lower than the K_M values of the substrates.[11]

An Apicompexan parasite such as *Toxoplasma gondii*, the agent responsible for toxoplasmosis, lacks the mevalonate pathway and uses a prokaryotic-type 1-deoxy-D-xylulose-5-phosphate (DOXP) pathway instead to make isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP).

[a] M. N. Chao, C. E. Matiuzzi, Dr. S. H. Szajnman, Prof. Dr. J. B. Rodriguez
Departamento de Química Orgánica and UMYMFOR (CONICET-FCEyN)
Facultad de Ciencias Exactas y Naturales
Universidad de Buenos Aires
Pabellón 2, Ciudad Universitaria, C1428EHA, Buenos Aires (Argentina)
E-mail: jbr@qo.fcen.uba.ar

[b] M. Storey, C. Li, Prof. Dr. R. Docampo, Prof. Dr. S. N. J. Moreno
Center for Tropical and Emerging Global Diseases and
Department of Cellular Biology
University of Georgia, Athens, GA, 30602 (USA)

Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cmdc.201500100: ^1H, ^{19}F, and ^{13}C NMR spectra of the target molecules and corresponding intermediates.

The DOXP pathway is localized to the apicoplast and is essential.[13] It has been demonstrated that *T. gondii* does not synthesize cholesterol but imports it from the host,[14] which suggests that inhibitors of the host SQS could potentially inhibit *T. gondii* growth. The fact that WC-9 and closely related analogues are growth inhibitors of *T. gondii* is in agreement with other work that has shown that mevalonate pathway inhibitors are active against Apicomplexan parasites such as *Babesia divergens*,[15] *Plasmodium falciparum*,[15,16] *Cryptosporidium parvum*,[17] and *T. gondii*;[18] this indicates that these parasites, which lack the mevalonate pathway, are dependent on the biosynthesis of the precursors of the isoprenoid pathway by the host. In this regard, it has recently been demonstrated that *T. gondii* acquires isoprenoid intermediates such as farnesyl diphosphate and/or geranylgeranyl diphosphate from the host cell produced by the mevalonate pathway.[19]

Rationale

To date, the crystal structure of *Tc*SQS with WC-9 is not available. However, the X-ray crystallographic structure of WC-9 bound to dehydrosqualene synthase from *Staphylococcus aureus* has been recently published.[20] This enzyme catalyzes dehydrosqualene formation, a metabolite that is further transformed into staphyloxanthin. It has been postulated that WC-9 might bind into the same hydrophobic S2 pocket in *Tc*SQS as it does in dehydrosqualene synthase and keeps the same polar interactions with the thiocyanate group.[20] Furthermore, it was recently shown that is possible to obtain crystals of WC-9 bound to human SQS, but all attempts to do so with *Tc*SQS were unsuccessful.[21]

On the basis of the chemical structure of WC-9, we conducted meticulous structure activity/biological activity relationship studies that led to the assumption that the phenoxyethyl thiocyanate moiety (colored in red in Figure 1) should be considered as the structure of the pharmacophore.[8–10,22–24] Although WC-9 is able to impair parasitemia in murine models of Chagas disease, the level of protection is not as efficient as that shown by ketoconazole, which is used as a positive control.[25] This lack of in vivo efficacy of WC-9 may be attributed to poor pharmacokinetic properties, which indeed should be improved. In this respect, the finding that structural variations in the B ring of WC-9 have a marked influence on biological activity encouraged us to follow this approach. As a matter of fact, the introduction of a fluorine atom in the B ring of WC-9 gives rise to compounds **2** and **3**, which have estimated log*P* values of 4.71 compared with a log*P* value of 4.51 for WC-9; this is indicative of better distribution between water/octanol. In fact, compounds **2** and **3** are both significantly more potent than WC-9 in in vitro assays (Figure 1).[23]

The question that arises is how is it possible to optimize the chemical structure of WC-9 without knowing the binding site at the target enzyme? The availability of this information would be very important for the rational design of more effective noncompetitive inhibitors structurally related to WC-9.

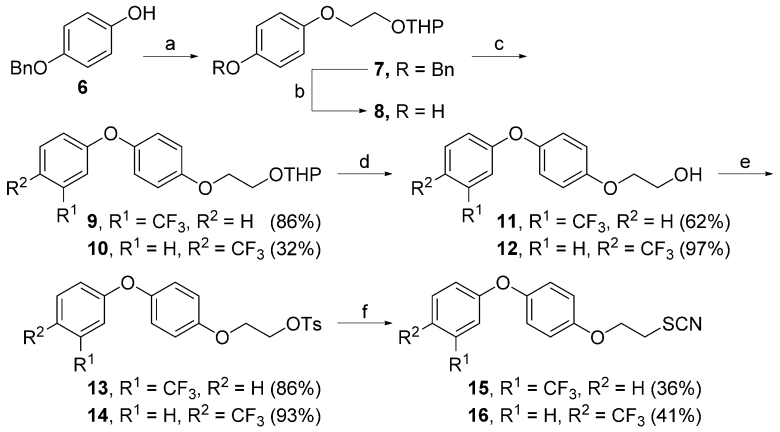
The Buchwald coupling reaction has proven to be a reliable method to prepare asymmetric substituted diaryl ethers and diaryl amines.[26] Certainly, a variety of WC-9 analogues bearing different substituents at either the A ring or the B ring have been prepared by employing this protocol,[24] which is a reliable alternative to obtain these types of compounds by avoiding the use of expensive and not always commercially available phenylboronic acids as starting materials.[27]

Results and Discussion

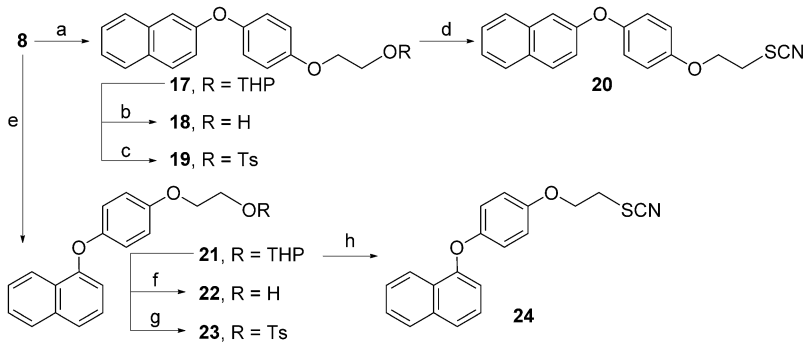
Therefore, following a classical approach, the structural variations considered were those that involved different substitutions on the B ring as well as the relative position of the B ring to the aliphatic chain. The introduction of an electron-withdrawing moiety into the B ring such as the trifluoromethyl group was the first structural modification considered. Then, by employing commercially available 4-(benzyloxy)phenol (**6**), this compound was converted into tetrahydropyranyl (THP) ether derivative **7** in 96% yield by treatment with 2-bromoethyl tetrahydro-2*H*-pyran-2-yl ether in a suspension of potassium hydroxide in dimethyl sulfoxide by following a slightly modified Williamson reaction.[28] Removal of the protecting benzyl (Bn) group was performed by treatment with hydrogen gas (0.3 MPa) at room temperature in the presence of palladium on charcoal to afford phenol **8** in 73% yield. Upon treatment with 1-iodo-3-(trifluoromethyl)benzene in the presence of 5% cuprous iodide, 10% picolinic acid, and potassium phosphate according to the Buchwald protocol, **8** was transformed into conveniently functionalized diaryl ether **9** in 86% yield. Buchwald coupling of **8** with 1-iodo-4-(trifluoromethyl)benzene gave **10** in 32% yield. Compound **9** was deprotected by treatment with pyridinium 4-toluenesulfonate (PPTS) in methanol to afford corresponding free alcohol **11** in 62% yield. Treatment of **11** with tosyl chloride (TsCl) in pyridine (py) gave tosylate **13** in 86% yield. Compound **13** was further transformed into thiocyanate **15** by treatment with potassium thiocyanate in DMF at 100 °C in 36% yield (Scheme 1). In a similar strategy, **10** was transformed into alcohol **12**, which was treated with tosyl chloride to give **14**. Compound **14** was finally transformed into **16** by treatment with potassium thiocyanate, as illustrated in Scheme 1.

To study the influence of the polarity of the terminal phenyl group, this ring was replaced by a naphthyl group to give compounds **20** and **24**, the estimated log*P* values of which were both 5.2 compared to 4.2 for the WC-9 molecule. Buchwald coupling of **8** with either 2-bromonaphthalene or 1-bromonaphthalene afforded diaryl ether derivative **17** or **21** in a low but reproducible yield of 18 or 32%, respectively. Following the general strategy, each tetrahydropyranyl protecting group present in **17** and **21** was cleaved by treatment with pyridinium 4-toluenesulfonate to afford corresponding free alcohols **18** and **22** in good yields. These alcohols were tosylated to give **19** and **23**. Upon treatment with potassium thiocyanate, in separate experiments, these compounds were converted into target molecules **20** and **24**, respectively, as illustrated in Scheme 2.

We recently described a pyridyl analogue of WC-9 in which the nitrogen atom occupies the 3′′-position.[24] To complete the



Scheme 1. *Reagents and conditions*: a) $Br(CH_2)_2OTHP$, KOH, DMSO, RT, 24 h, 96%; b) H_2, Pd/C, EtOAc, RT, 4 h, 73%; c) 1-iodo-3-(trifluoromethyl)benzene or 1-iodo-4-(trifluoromethyl)benzene, 5% CuI, 10% picolinic acid, K_3PO_4, DMSO, 90 °C, 36 h; d) PPTS, MeOH, RT, 24 h; e) TsCl, py, 0 °C, 4 h; f) KSCN, DMF, 80 °C, 48 h.

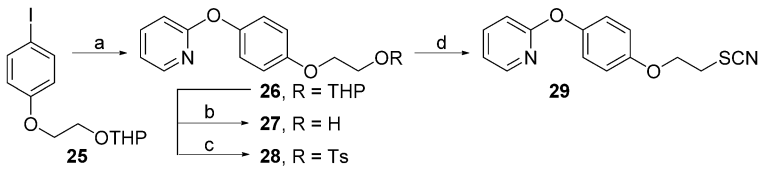


Scheme 2. *Reagents and conditions*: a) 2-Bromonaphthalene, 5% CuI, 10% picolinic acid, K_3PO_4, DMSO, 90 °C, 24 h, 18%; b) PPTS, MeOH, RT, 4 h, 97%; c) TsCl, py, RT, 4 h, 67%; d) KSCN, DMF, 100 °C, 3 h, 43%; e) 1-bromonaphthalene, 5% CuI, 10% picolinic acid, K_3PO_4, DMSO, 90 °C, 24 h, 29%; f) PPTS, MeOH, RT, 4 h, 92%;. g) TsCl, py, RT, 4 h, 91%; h) KSCN, DMF, 100 °C, 3 h, 43%.

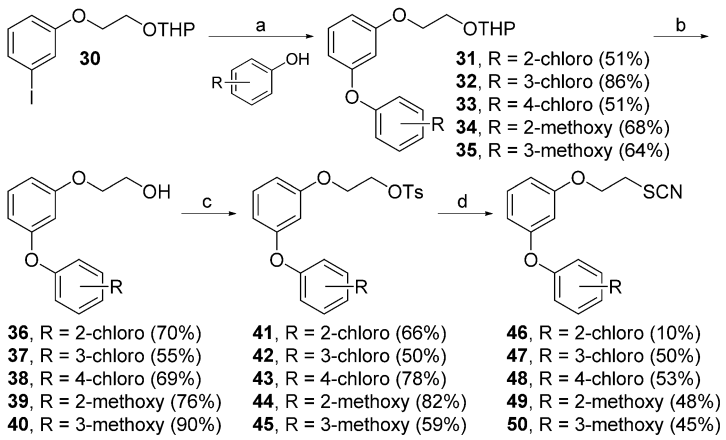
structure/activity analysis, it was decided to prepare the corresponding pyridyl derivative in which the nitrogen atom was placed at the C-2″ position to give target molecule **29**. Incorporation of the pyridyl unit was performed through Buchwald coupling between the already depicted 4-iodophenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (**25**) and 2-hydroxypyridine to produce tetrahydropyranyl derivative **26** in 48% yield. Once this adduct was at hand, similarly to the preparation of **16** and **17**, cleavage of the tetrahydropyranyl protecting group of **26** gave free alcohol **27** in 60% yield. Tosylation of **27** produced **28** in 90% yield, and further substitution of the tosylate group by the thiocyanate ion afforded **29** in 61% yield (Scheme 3).

At the present time, the optimal relative position of the terminal phenyl group of WC-9 is not conclusive. We recently demonstrated that analogues for which the phenyl group is in the C-3′ position exhibit antiparasitic activity almost of the same efficacy as those compounds bearing this group at the C-4′ position.[24] Therefore, compounds **46**–**50**, which are regioisomers of WC-9 bearing either a chlorine atom or a methoxy group at diverse positions of the terminal ring, were prepared. The synthetic strategy to obtain these compounds is presented in Scheme 4 and starts with already described 3-iodophenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (**30**) as the common starting material.[24] This compound was treated separately with 2-chlorophenol, 3-chlorophenol, 4-chlorophenol, 2-methoxyphenol, and 3-methoxyphenol under the usual Buchwald coupling procedure to give expected asymmetric diaryl ethers **31**–**35** in moderate to good yields. Then, following the general method in individual experiments, each of these compounds underwent cleavage of the tetrahydropyranyl ring to give **36**–**40**. Tosylation afforded **41**–**45**, and nucleophilic displacement of the tosylate group by treatment with potassium thiocyanate afforded the expected regioisomers of WC-9, that is, compounds **46**–**50** (Scheme 4).

Pyridyl regioisomer analogues of WC-9 such as **60**–**62** were other interesting structural variations considered as polar compounds (estimated $\log P = 2.82$) with the pharmacophore in the molecules intact. In this case, the synthesis of the compounds was not straightforward, particularly, for the preparation of **62**, as discussed below. Then, compound **30** was used as a committed starting material, which was separately treated with 2-hydroxypyridine, 3-hydroxypyridine, and 4-hydroxypyridine under Buchwald coupling reaction conditions to give rise to coupled products **51**–**53** in moderate yields. These compounds were easily deprotected by treatment with pyridinium 4-toluenesulfonate to



Scheme 3. *Reagents and conditions*: a) 2-Hydroxypyridine (1.2 equiv) 5% CuI, 10% picolinic acid, K_3PO_4, DMSO, 80 °C, 24 h, 48%; b) PPTS, MeOH, RT, 16 h, 60%; c) TsCl, py, 0 °C, then RT, 90%; d) KSCN, DMF, 100 °C, 61%.



Scheme 4. *Reagents and conditions*: a) 5% CuI, 10% picolinic acid, K_3PO_4, DMSO, 80 °C, 24 h; b) PPTS, MeOH, RT, 16 h; c) TsCl, py, 0 °C, 6 h; d) KSCN, DMF, 100 °C, 6 h.

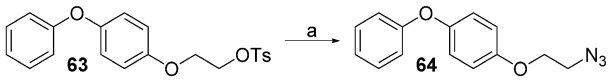
yield corresponding free alcohols **54**–**56**. Upon treatment with an excess amount of tosyl chloride, **54** and **55** were converted into tosylates **57** and **58**, respectively, whereas the corresponding tosylate of alcohol **56** could not be obtain owing to formation of a tosylpyridinium ion, which not only consumes the reagent but also forms an extremely polar species that hinders the reaction.[29] This problem was circumvented by the preparation of bromide **59**. Then, upon treatment with *N*-bromosuccinimide (NBS) and triphenylphosphine, **56** was converted into **69**.[30] Compounds **60**–**62** were obtained in good yields by treatment of tosylates **57** and **58** or bromide **59** with potassium thiocyanate (Scheme 5).

The group in WC-9 and other closely related analogues seems to be essential for biological activity. To study the influence of this group on biological action, its replacement with another electrophilic group such as the azido moiety was considered. Thus, treatment of tosylate **63** with sodium azide in DMF afforded compound **64** (Scheme 6).

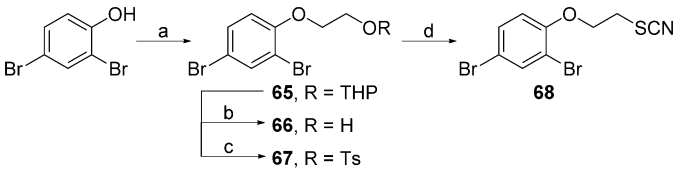
Previous biological data indicates that a simplified analogue of WC-9 (i.e., 2,4-dichlorophenoxyethyl thiocyanate), in which the aromatic skeleton is a 2,4-dichlorophenyl group instead of a 4-phenoxyphenyl moiety, exhibits anti-Chagasic activity similar to that of our lead compound WC-9.[9] Then, it would seem of interest to evaluate corresponding bromine analogue **68**. Thus, the reaction of 2,4-dibromophenol with bromoethyl tetrahydropyranyl ether afforded **65**, which after hydrolysis of the tetrahydropyranyl group followed by treatment with tosyl chloride and further nucleophilic attack of potassium thiocyanate led to compound **68** (Scheme 7).

Finally, as a part of the strategy to evaluate a very simple structure, pyridyl derivative **72** was considered as a polar and very simple structure having an estimated log*P* value of 1.32. This compound was prepared straightforwardly from 3-hydroxypyridine following the general method, as described in Scheme 8.

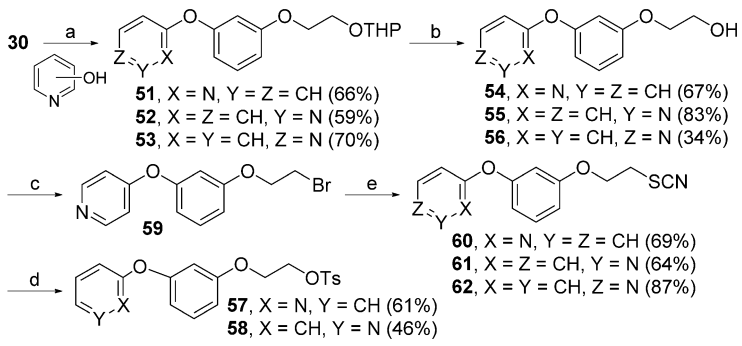
Biological evaluation of these new WC-9 analogues was very encouraging. Title compounds **15** and **16** were potent growth inhibitors of the intracellular



Scheme 6. *Reagents and conditions*: a) NaN_3, DMF, 100 °C, 6 h, 35%.

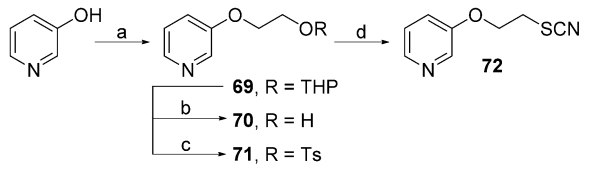


Scheme 7. *Reagents and conditions*: a) KOH, $BrCH_2CH_2OTHP$, DMSO, RT, 16 h, 46%; b) PPTS, MeOH, RT, 16 h, 70%; c) TsCl, py, 0 °C, 6 h, 84%; d) KSCN, DMF, 100 °C, 6 h, 75%.



Scheme 5. *Reagents and conditions*: a) 5% CuI, 10% picolinic acid, K_3PO_4, DMSO, 80 °C, 24 h; b) PPTS, MeOH, RT, 16 h; c) NBS, Ph_3P, CH_2Cl_2, 0 °C, 24%; d) TsCl, py, 0 °C, 6 h; e) KSCN, DMF, 100 °C, 6 h.

form of *T. cruzi*, which is the clinically more relevant replicative form of the parasite. Certainly, both of these compounds bearing an electron-withdrawing group at the C-3′′ and C-4′′ positions exhibited ED_{50} values quite similar to that of WC-9, used as a positive control, under the same assay conditions. Compounds **15** and **16** were also potent inhibitors of *T. gondii* (tachyzoites) growth, and possess ED_{50} values at the very low micromolar level (1.6 and 2.0 μM, respectively). The introduction of a naphthyl group as a terminal B ring of WC-9 to give **20** and **24** was not beneficial, as they were devoid of action against amastigotes of *T. cruzi*. Interestingly, **20** and **24** exhibited potent inhibitory action against tachyzoites of *T. gondii* with ED_{50} values of 2.3 and 2.9 μM, respectively. Surprisingly, in spite of having the pharmacophore moiety in the structure, pyridyl derivative **29** was devoid of antiparasitic activity against both *T. cruzi* and *T. gondii*. With the exception of **47**, which presented vanishing biological activity, regioisomers **46**–**50** bearing electron-donating groups at the terminal ring showed potent inhibitory action against *T. cruzi* and *T. gondii*;



Scheme 8. *Reagents and conditions*: a) KOH, $BrCH_2CH_2OTHP$, DMSO, RT, 16 h, 31%; b) PPTS, MeOH, RT, 16 h, 46%; c) TsCl, py, 0 °C, 6 h, 69%; d) KSCN, DMF, 100 °C, 6 h, 42%.

compounds **48** and **50** showed efficacy similar to that of WC-9. Interestingly, regioisomers **46**–**50** were all very potent growth inhibitors of tachyzoites of *T. gondii* and showed ED_{50} values of 2.1, 3.9, 2.8, and 4.0 μM, respectively, as shown in Table 1. Only pyridyl analogue **61** showed potent antiparasitic action with ED_{50} values of 7.5 and 3.7 μM against *T. cruzi* and *T. gondii*, respectively. The rest of the pyridyl derivatives, that is, **60** and **62**, were free of antiparasitic activity. Evidently, the relative position of the nitrogen atom in the B ring plays a key role in modulating the biological activity. Unexpectedly, dibromo derivative **68** was inactive as an antiparasitic agent on the basis of the results previously exhibited by the parent dichloro analogue.[9] Finally, simple pyridyl derivative **72** was also devoid of antiparasitic activity. These data are in agreement with our previous results[24] and confirm that the *para*-aryl substitution pattern of WC-9 is not necessary for effective biological activity. The results are presented in Table 1.

Conclusions

It can be concluded that most of the compounds studied behave as anti-*T. cruzi* agents as well as anti-*Toxoplasma* agents favoring the activity against *T. gondii*. The key reaction to access these compounds was the Buchwald coupling reaction, which has proven to be reliable not only to obtain WC-9 derivatives modified at the B ring but also to synthesize derivatives substituted at the A ring in the future. The promising biological activity observed for the target molecules together with the drug-like character of these compounds motivate new studies to find an optimized chemical structure with a known and precise mode of action. Efforts in this direction are currently being pursued in our laboratory.

Table 1. Biological activity of WC-9 analogues against *T. cruzi* (amastigotes), *T. gondii* (tachyzoites), and Vero cells.

Compound	ED_{50} [μM][a]			SI[b]	
	T. cruzi	*T. gondii*	Cytotoxicity	*T. cruzi*	*T. gondii*
15	10.0 ± 2.5	1.66 ± 0.35	> 50.0	> 5.0	> 31.1
16	9.2 ± 1.8	1.86 ± 0.38	> 50.0	5.4	> 26.7
20	> 10.0	2.25 ± 0.84	104.7 ± 7.8	> 10.4	46.5
24	> 10.0	2.87 ± 0.19	70.1 ± 7.6	> 7	24.4
29	> 10.0	> 10.0	> 200.0		
46	11.94 ± 0.38	2.13 ± 0.38	> 50.0	4.2	23.4
47	> 20.0	> 10.0	> 200.0		
48	6.27 ± 0.75	3.86 ± 0.28	98.4 ± 5.8	15.7	25.2
49	11.7 ± 2.52	2.79 ± 0.42	115.7 ± 39.8	9.9	41.5
50	8.75 ± 0.33	4.02 ± 0.27	96.2 ± 37.5	11.0	23.9
60	> 10.0	> 10.0	> 200.0		
61	7.49 ± 1.39	3.71 ± 0.92	124.0 ± 12.0	16.6	33.5
62	> 10.0	> 10.0	> 200.0		
64	> 10.0	> 10.0	> 200.0		
68	> 20.0	> 10.0	> 50.0		
71	> 10.0	> 10.0	> 200		
WC-9	5.0 ± 1.1	4.8 ± 0.41	82.6 ± 7.3	16.5	20.7
benznidazole	1.92 ± 0.55	–	–	–	–
atovaquone	–	0.032 ± 0.019	–	–	–

[a] Data are the mean ± SD of one experiment carried out in triplicate. [b] Selectivity index: $(ED_{50\,cytotox.})/(ED_{50\,parasite})$.

Experimental Section

General methods

The glassware used in air- and/or moisture-sensitive reactions was flame dried, and the reactions were performed under a dry argon atmosphere. Unless otherwise noted, chemicals were commercially available and were used without further purification. Anhydrous DMF and anhydrous dimethyl sulfoxide were used as supplied from Aldrich. Nuclear magnetic resonance spectra were obtained by using a Bruker AM-500 MHz spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. ^{13}C NMR spectra were fully decoupled. High-resolution mass spectra were recorded by using a Bruker micrOTOF-Q II spectrometer, which is a hybrid quadrupole time of flight mass spectrometer with MS–MS capability. Melting points were determined by using a Fisher–Johns apparatus. Column chromatography was performed with E. Merck silica gel plates (Kieselgel 60, 230–400 mesh). Analytical thin-layer chromatography was performed by employing 0.2 mm coated commercial silica gel plates (E. Merck, DC-Aluminum sheets, Kieselgel 60 F_{254}).

Syntheses

4-Benzyloxyphenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (7): A solution of 4-(benzyloxy)phenol (**6**; 5.00 g, 25.0 mmol) in DMSO (25 mL) was treated with KOH (2.81 g, 50.0 mmol). The mixture was stirred at room temperature for 5 min. Then, bromoethyl tetrahydropyranyl ether (6.27 g, 30.0 mmol) was added, and the mixture was stirred at room temperature overnight. The mixture was partitioned between H_2O (70 mL) and CH_2Cl_2 (70 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layer was washed with a saturated solution of NaCl (5 × 50 mL), dried ($MgSO_4$), and concentrated. The product was purified by column chromatography (hexane/EtOAc 19:1) to yield pure **7** (7.89 g, 96%) as a colorless oil: $R_f = 0.63$ (hexane/EtOAc 7:3); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.46$–1.88 (m, 6H, H-3‴, H-4‴, H-5‴), 3.45–3.61 (m, 1H, H-6‴$_a$), 3.70–4.05 (m, 3H, H-1, H-6‴$_b$), 4.05–4.18 (m, 2H, H-2), 4.72 (distorted (dist.) t, J = 3.2 Hz, 1H, H-2‴), 5.02 (s, 2H, PhCH_2O-), 6.87 (d, J = 9.3 Hz, 2H, H-3′), 6.92 (d, J = 9.3 Hz, 2H, H-2′), 7.24–7.47 ppm (m, 5H, aromatic H); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 19.4$ (C-4‴), 25.4 (C-5‴), 30.5 (C-3‴), 62.2 (C-6‴), 65.9 (C-1), 68.1 (C-2), 70.7 (PhCH_2O-), 99.0 (C-2‴), 115.7 (C-3′), 115.8 (C-2′, C-3′), 127.5 (C-2″), 127.9 (C-4″), 128.5 (C-3″), 137.3 (C-1″), 153.1 (C-1′), 153.3 ppm (C-4′); HRMS (ESI): *m/z*: calcd for $C_{20}H_{24}O_4Na$: 351.1572 $[M+Na]^+$; found: 351.1574.

4-Hydroxyphenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (8): A solution of **7** (8.150 g, 24.8 mmol) in EtOAc (40 mL) in the presence of 5% Pd/C (40 mg) was treated with H_2

(0.3 MPa). The mixture was stirred at room temperature for 4 h. The mixture was filtered off and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc 4:1) to produce pure **8** (4.301 g, 73%) as a colorless oil: R_f = 0.27 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.51–1.68 (m, 4H, H-4″, H-5″), 1.72–1.77 (m, 1H, H-3″a), 1.81–1.88 (m, 1H, H-3″b), 3.51–3.56 (m, 1H, H-6‴$_a$), 3.79 (ddd, J = 11.1, 6.4, 4.1 Hz, 1H, H-6‴$_b$), 3.92 (m, 1H, H-1$_a$), 4.03 (m, 1H, H-1$_b$), 4.11 (m, 2H, H-2), 4.71 (t, J = 3.7 Hz, 1H, H-2″), 6.75 (d, J = 9.1 Hz, 2H, H-3′), 6.81 ppm (d, J = 8.9 Hz, 2H, H-2′); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 19.3 (C-4″), 25.4 (C-5″), 30.5 (C-3″), 62.2 (C-6″), 66.0 (C-1), 68.1 (C-2), 99.0 (C-2″), 115.9 (C-2′), 116.0 (C-3′), 149.7 (C-4′), 153.0 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{13}H_{18}O_4Na$: 261.1103 $[M+Na]^+$; found: 261.1088.

4-[(3-Trifluoro)phenoxy]phenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (9): A mixture of **8** (1.50 g, 6.29 mmol), 1-iodo-3-(trifluoromethyl)benzene (2.06 g, 7.56 mmol), CuI (120 mg, 0.63 mmol), 2-picolinic acid (155 mg, 1.26 mmol), and K_3PO_4 (2.68 g, 12.6 mmol) under anhydrous conditions was evacuated and backfilled with argon (2×). Then, DMSO was added (15.0 mL), and the mixture was stirred vigorously at 80 °C for 36 h. The mixture was cooled to room temperature and partitioned between EtOAc (20 mL) and H_2O (20 mL). The aqueous layer was extracted with EtOAc (2× 20 mL). The combined organic phase was washed with brine (5× 50 mL), dried ($MgSO_4$), and concentrated. The product was purified by column chromatography (silica gel, hexane/EtOAc 19:1) to afford pure **9** (2.06 g, 86%) as a colorless oil: R_f = 0.64 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.53–1.68 (m, 4H, H-4‴, H-5‴), 1.72–1.78 (m, 1H, H-3‴$_a$), 1.81–1.87 (m, 1H, H-3‴$_b$), 3.53 (m, 1H, H-6‴$_a$), 3.82 (ddd, J = 11.2, 6.3, 4.2 Hz, 1H, H-6‴$_b$), 3.91 (ddd, J = 11.3, 8.2, 3.1 Hz, 1H, H-1$_a$), 4.07 (ddd, J = 11.1, 4.9, 4.3 Hz, 1H, H-1$_b$), 4.16 (m, 2H, H-2), 4.72 (t, J = 3.6 Hz, 1H, H-2‴), 6.94 (d, J = 9.3 Hz, 2H, H-2′), 7.98 (d, J = 9.3 Hz, 2H, H-3′), 7.09 (dd, J = 8.2, 2.1 Hz, 1H, H-6″), 7.16 (t, J = 1.9 Hz, 1H, H-2″), 7.28 (dt, J = 7.8, 0.7 Hz, 2H, H-4″), 7.39 ppm (t, J = 8.0 Hz, 2H, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 19.4 (C-4‴), 25.4 (C-5‴), 30.5 (C-3‴), 62.2 (C-6‴), 65.9 (C-1), 67.9 (C-2), 99.0 (C-2‴), 114.0 (q, J = 3.9 Hz, C-2″), 116.0 (C-2′), 118.9 (q, J = 3.8 Hz, C-4″), 120.4 (C-5″), 130.1 (C-6″), 149.1 (C-4′), 155.8 (C-1′), 160.0 ppm (C-1″); ^{19}F NMR (470.54 MHz, $CDCl_3$): δ = −62.71 ppm; HRMS (ESI): *m/z*: calcd for $C_{20}H_{21}O_4F_3Na$: 405.129 $[M+Na]^+$; found: 405.1285.

4-[(4-Trifluoro)phenoxy]phenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (10): A mixture of **8** (433 mg, 1.82 mmol), 1-iodo-4-(trifluoromethyl)benzene (594 mg, 2.18 mmol), CuI (34.6 mg, 0.36 mmol), 2-picolinic acid (44.8 mg, 0.36 mmol), and K_3PO_4 (773 g, 3.64 mmol) in DMSO (6.0 mL) was treated as described in the method for the preparation of **9** for 13 days. The residue was purified by column chromatography (silica gel, hexane/EtOAc 19:1) to give pure **10** (225 g, 32%) as a colorless oil: R_f = 0.60 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.53–1.67 (m, 4H, H-4‴, H-5‴), 1.73–1.79 (m, 1H, H-3‴$_a$), 1.82–1.88 (m, 1H, H-3‴$_b$), 3.54 (m, 1H, H-6‴$_a$), 3.82 (ddd, J = 11.2, 6.4, 4.4 Hz, 1H, H-6‴$_b$), 3.91 (ddd, J = 11.3, 8.2, 3.1 Hz, 1H, H-1$_a$), 4.07 (m, 1H, H-1$_b$), 4.16 (m, 2H, H-2), 4.72 (t, J = 3.6 Hz, 1H, H-2‴), 6.95 (d, J = 9.3 Hz, 2H, H-2′), 6.97 (m, 2H, H-2″), 6.99 (d, J = 9.3 Hz, 2H, H-3′), 7.56 ppm (d, J = 8.9 Hz, 2H, H-3″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 19.4 (C-4‴), 25.4 (C-5‴), 30.5 (C-3‴), 62.2 (C-6‴), 65.8 (C-1), 67.9 (C-2), 99.0 (C-2‴), 116.0 (C-2′), 116.8 (C-3′), 121.5 (C-2″), 127.0 (q, J = 3.8 Hz, C-3″), 148.8 (C-4′), 156.0 (C-1′), 161.5 ppm (C-1″); ^{19}F NMR (470.59 MHz, $CDCl_3$): δ = −61.66 ppm; HRMS (ESI): *m/z*: calcd for $C_{20}H_{21}F_3NaO_4$ 405.1290 $[M+Na]^+$; found: 405.1286.

4-[(3-Trifluoro)phenoxy]phenoxyethanol (11): A solution of **9** (1.96 g, 5.13 mmol) in MeOH (50 mL) was treated with PPTS (30 mg). The mixture was stirred at room temperature overnight. Then, H_2O (70 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with brine (3×50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc 17:1) to give pure alcohol **11** (944.0 mg, 62%) as a colorless oil: R_f = 0.30 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.03 (t, J = 5.5 Hz, 1H, -O*H*), 3.99 (m, 2H, H-1), 4.01 (t, J = 4.5 Hz, 2H, H-2), 6.94 (d, J = 9.1 Hz, 2H, H-2′), 7.00 (d, J = 9.1 Hz, 2H, H-3′), 7.10 (dd, J = 8.3, 2.4 Hz, 1H, H-6″), 7.17 (t, J = 1.9 Hz, 1H, H-2″), 7.29 (d, J = 7.7 Hz, 2H, H-4″), 7.40 ppm (t, J = 8.0 Hz, 2H, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 61.5 (C-1), 69.7 (C-2), 114.1 (q, J = 3.9 Hz, C-2″), 115.9 (C-2′), 119.0 (q, J = 3.8 Hz, C-4″), 120.5 (C-5″), 130.2 (C-6″), 149.5 (C-4′), 155.5 (C-1′), 158.8 ppm (C-1″); HRMS (ESI): *m/z*: calcd for $C_{15}H_{13}O_3F_3Na$: 321.0714 $[M+Na]^+$; found: 321.0703.

4-[(4-Trifluoro)phenoxy]phenoxyethanol (12): A solution of **10** (229 mg, 0.60 mmol) in MeOH (10 mL) was treated with PPTS (30 mg) as described in the method for the preparation of **11**. Purification by column chromatography (silica gel, hexane/EtOAc 17:1) afforded pure alcohol **12** (174 mg, 97%) as a white solid: R_f = 0.20 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 3.99 (m, 2H, H-1), 4.10 (t, J = 4.5 Hz, 2H, H-2), 6.94 (d, J = 9.1 Hz, 2H, H-2′), 6.98 (d, J = 8.5 Hz, 2H, H-2″), 7.01 (d, J = 9.1 Hz, 2H, H-3′), 7.54 ppm (d, J = 8.6 Hz, 2H, H-3″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 61.5 (C-1), 69.7 (C-2), 115.8 (C-2′), 116.9 (C-3′), 121.6 (C-2″), 127.0 (q, J = 3.7 Hz, C-3″), 149.1 (C-4′), 155.7 (C-1′), 161.4 ppm (C-1″); ^{19}F NMR (470.54 MHz, $CDCl_3$): δ = −61.68 ppm; HRMS (ESI): *m/z*: calcd for $C_{15}H_{13}F_3NaO_3$ 321.0714 $[M+Na]^+$; found: 321.0719.

4-[(3-Trifluoro)phenoxy]phenoxyethyl 4-toluenesulfonate (13): TsCl (1.72 g, 9.02 mmol) was added to a solution of alcohol **11** (922 mg, 3.09 mmol) in pyridine (5.0 mL) at 0 °C. The mixture was stirred at room temperature for 4 h. Then, 5% HCl (50 mL) was added, and the mixture was stirred for an additional 1 h. The mixture was extracted with CH_2Cl_2 (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 concentrated. The product was purified by column chromatography (silica gel, hexane/EtOAc 19:1) to afford tosylate **13** (1.29 g, 86%) as a colorless oil: R_f = 0.50 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.45 (s, 3H, PhC*H*$_3$), 4.16 (m, 2H, H-1), 4.38 (m, 2H, H-2), 6.81 (d, J = 9.1 Hz, 2H, H-2′), 6.96 (d, J = 9.1 Hz, 2H, H-3′), 7.08 (dd, J = 8.2, 2.3 Hz, 1H, H-6″), 7.15 (t, J = 1.9 Hz, 1H, H-2″), 7.29 (d, J = 7.7 Hz, 2H, H-4″), 7.35 (d, J = 8.0 Hz, 2H, H-3‴), 7.40 (t, J = 8.0 Hz, 2H, H-5″), 7.83 ppm (d, J = 8.3 Hz, 2H, H-2‴); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 21.6 (*C*H$_3$), 66.0 (C-1), 68.0 (C-2), 114.2 (q, J = 3.9 Hz, C-2″), 116.0 (C-2′), 119.1 (q, J = 3.9 Hz, C-4″), 120.6 (C-6″), 121.1 (C-3′), 128.0 (C-2‴), 129.9 (C-3‴), 130.2 (C-5″), 132.1 (q, J = 32.6 Hz, C-3″), 132.9 (C-4‴), 145.0 (C-1‴), 149.7 (C-4′), 154.8 (C-1′), 158.7 ppm (C-1″); ^{19}F NMR (470.59 MHz, $CDCl_3$): δ = −62.71 ppm (s); HRMS (ESI): *m/z*: calcd for $C_{22}H_{19}F_3NaO_5S$ 475.0803 $[M+Na]^+$; found: 475.0775.

4-[(4-Trifluoro)phenoxy]phenoxyethyl 4-toluenesulfonate (14): TsCl (352 mg, 1.84 mmol) was added to a solution of alcohol **12** (176 mg, 0.59 mmol) in pyridine (3.0 mL) at 0 °C. The mixture was treated as detailed in the method for the preparation of **13** to afford pure tosylate **14** (249 mg, 93%) as a colorless oil: R_f = 0.50 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.45 (s, 3H, PhC*H*$_3$), 4.16 (m, 2H, H-1), 4.38 (m, 2H, H-2), 6.81 (d, J = 9.1 Hz, 2H, H-2′), 6.966 (d, J = 8.5 Hz, 2H, H-2″), 6.970 (d, J = 9.1 Hz, 2H, H-3′),

7.36 (d, J=8.0 Hz, 2H, H-3‴), 7.54 (d, J=8.6 Hz, 2H, H-3″), 7.83 ppm (d, J=8.3 Hz, 2H, H-2‴); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=21.7 ($PhCH_3$) 66.0 (C-1), 68.0 (C-2), 116.0 (C-2′), 116.9 (C-3′), 121.5 (C-2″), 127.0 (q, J=3.8 Hz, C-3″), 128.0 (C-2‴), 129.9 (C-3‴), 132.9 (C-4‴), 145.0 (C-1‴), 149.4 (C-4′), 155.0 (C-1′), 161.3 ppm (C-1″); ^{19}F NMR (470.54 MHz, $CDCl_3$): δ=−61.69 ppm; HRMS (ESI): m/z: calcd for $C_{22}H_{19}O_5F_3SNa$: 475.0803 $[M+Na]^+$; found: 475.0809.

4-[(3-Trifluoro)phenoxy]phenoxyethyl thiocyanate (15): A solution of tosylate **13** (1.290 g, 2.85 mmol) in anhydrous DMF (10 mL) was treated with KSCN (1.390 g, 14.3 mmol). The mixture was heated at 100 °C for 48 h. The mixture was allowed to cool to room temperature and H_2O (20 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (2×30 mL), and the combined organic layer was washed with brine (5×30 mL) and H_2O (2×30 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc 19:1) to give pure **15** (346 mg, 36%) as a colorless oil: R_f=0.51 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ=3.35 (t, J=5.8 Hz, 2H, H-1), 4.33 (t, J=5.8 Hz, 2H, H-2), 6.95 (d, J=9.1 Hz, 2H, H-2′), 7.01 (d, J=9.1 Hz, 2H, H-3′), 7.11 (dd, J=8.2, 2.3 Hz, 1H, H-6″), 7.18 (t, J=2.0 Hz, 1H, H-2″), 7.30 (d, J=7.7 Hz, 2H, H-4″), 7.41 ppm (t, J=8.0 Hz, 2H, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=33.2 (C-1), 66.4 (C-2), 111.6 (*SCN*), 114.3 (q, J=3.9 Hz, C-2″), 116.1 (C-2′), 119.2 (q, J=3.8 Hz, C-4″), 120.6 (C-5″), 123.7 (q, J=272.4 Hz, *CF*$_3$), 130.2 (C-6″), 132.1 (q, J=32.6 Hz, C-3″), 150.1 (C-4′), 154.6 (C-1′), 158.6 ppm (C-1″); ^{19}F NMR (470.54 MHz, $CDCl_3$): δ=−62.70 ppm; HRMS (ESI): m/z: calcd for $C_{16}H_{12}O_2NSF_3Na$: 362.0439 $[M+Na]^+$; found: 362.0428.

4-[(4-Trifluoro)phenoxy]phenoxyethyl thiocyanate (16): A solution of tosylate **14** (249 mg, 0.55 mmol) in anhydrous DMF (4 mL) was treated with KSCN (266 mg, 2.73 mmol). The mixture was heated at 100 °C for 48 h. The reaction was worked up as detailed in the method for the preparation of **15**. The residue was purified by column chromatography (silica gel, hexane/EtOAc 19:1) to give pure **16** (76 mg, 41%) as a colorless oil: R_f=0.53 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ=3.35 (t, J=5.8 Hz, 2H, H-1), 4.33 (t, J=5.8 Hz, 2H, H-2), 6.95 (d, J=9.2 Hz, 2H, H-2′), 6.99 (d, J=8.4 Hz, 2H, H-2″), 7.03 (d, J=9.2 Hz, 2H, H-3′), 7.55 ppm (d, J=8.4 Hz, 2H, H-3″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=33.2 (C-1), 66.4 (C-2), 111.6 (*SCN*), 116.1 (C-2′), 117.0 (C-3′), 121.6 (C-2″), 127.1 (q, J=3.8 Hz, C-3″), 149.7 (C-4′), 154.8 (C-1′), 161.2 ppm (C-1″); ^{19}F NMR (470.54 MHz, $CDCl_3$): δ=−61.70 ppm; HRMS (ESI): m/z: calcd for $C_{16}H_{12}O_2NSF_3Na$: 362.0439 $[M+Na]^+$; found: 362.0419.

β-Naphthyloxyphenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (17): A mixture of **8** (889 mg, 3.73 mmol), 2-bromonaphthalene (111 mg, 0.54 mmol), CuI (79 mg, 0.42 mmol), 2-picolinic acid (91.5 mg, 0.74 mmol), and K_3PO_4 (1.53 g, 7.22 mmol) in DMSO (6 mL) was treated as detailed in the method for the preparation of **9**. The residue was purified by column chromatography (silica gel, hexane/EtOAc 9:1) to afford pure **17** (244 mg, 18%) as a colorless oil: R_f=0.55 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ=1.53–1.68 (m, 4H, H-4‴, H-5‴), 1.73–1.79 (m, 1H, H-3‴$_a$), 1.85 (m, 1H, H-3‴$_b$), 3.55 (m, 1H, H-6‴$_a$), 3.83 (ddd, J=11.1, 6.4, 4.3 Hz, 1H, H-6‴$_b$), 3.92 (ddd, J=10.5, 8.9, 2.2 Hz, 1H, H-1$_a$), 4.07 (m, 1H, H-1$_b$), 4.17 (m, 2H, H-2), 4.73 (t, J=3.5 Hz, 1H, H-2‴), 6.96 (d, J=9.1 Hz, 2H, H-2′), 7.04 (d, J=9.0 Hz, 2H, H-3′), 7.18 (d, J=1.9 Hz, 1H, H-1″), 7.24 (dd, J=9.0, 2.5 Hz, 1H, H-3″), 7.37 (m, 1H, H-6″), 7.43 (ddd, J=7.9, 7.1, 0.8 Hz, 1H, H-7″), 7.66 (d, J=8.2 Hz, 1H, H-8″), 7.799 (d, J=8.2 Hz, 1H, H-4″), 7.804 ppm (d, J=9.1 Hz, 1H, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=19.4 (C-4‴), 25.4 (C-5‴), 30.5 (C-3‴), 62.2 (C-6‴), 65.9 (C-1), 68.0 (C-2), 99.0 (C-2‴), 112.2 (C-1″), 115.9 (C-2′), 119.3 (C-3″), 121.0 (C-3′), 124.3 (C-6″), 126.5 (C-8″), 127.0 (C-7″), 127.7 (C-5″), 129.8 (C-4″), 129.8 (C-10″), 134.3 (C-9″), 150.2 (C-4′), 155.4 (C-1′), 156.4 ppm (C-2″); HRMS (ESI): m/z: calcd for $C_{23}H_{24}NaO_4$ 387.1572 $[M+Na]^+$; found: 387.1558.

β-Naphthyloxyphenoxyethanol (18): A solution of **17** (358 mg, 0.98 mmol) in MeOH (10 mL) was treated with PPTS (20 mg) as described in the method for the preparation of **11**. The residue was purified by column chromatography (silica gel, hexane/EtOAc 17:1) to yield alcohol **18** (266 mg, 97%) as a white solid: R_f=0.22 (hexane/EtOAc); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ=3.99 (dist.t, J=4.2 Hz, 2H, H-1), 4.10 (dist.t, J=4.5 Hz, 2H, H-2), 6.95 (d, J=9.0 Hz, 2H, H-2′), 7.05 (d, J=9.2 Hz, 2H, H-3′), 7.18 (d, J=2.4 Hz, 1H, H-1″), 7.25 (dd, J=9.0, 2.6 Hz, H-3″), 7.40 (ddd, J=8.1, 6.8, 1.3 Hz, 1H, H-6″), 7.43 (ddd, J=8.2, 6.8, 1.3 Hz, 1H, H-7″), 7.66 (dd, J=8.1, 0.7 Hz, 1H, H-8″), 7.80 (d, J=8.2 Hz, 1H, H-4″), 7.81 ppm (d, J=9.0 Hz, 1H, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=61.6 (C-1), 69.7 (C-2), 112.4 (C-1″), 115.7 (C-2′), 119.4 (C-3″), 121.0 (C-3′), 124.4 (C-6″), 126.5 (C-8″), 127.0 (C-7″), 127.7 (C-5″), 129.8 (C-4″), 129.8 (C-10″), 134.3 (C-9″), 150.5 (C-4′), 155.1 (C-1′), 156.3 ppm (C-2″); HRMS (ESI): m/z: calcd for $C_{18}H_{17}O_3$ 281.1178 $[M+H]^+$; found: 281.1166.

β-Naphthyloxyphenoxyethyl 4-toluenesulfonate (19): A solution of alcohol **18** (286 mg, 1.02 mmol) in pyridine (5 mL) was treated with TsCl (547 mg, 2.87 mmol) at 0 °C as described in the method for the preparation of **13**.Purification of the crude compound by column chromatography afforded tosylate **19** (295 mg, 67%) as a white solid: R_f=0.50 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ=2.45 (s, 3H, *CH*$_3$), 4.16 (m, 2H, H-1), 4.38 m, 2H, H-2), 6.81 (d, J=9.1 Hz, 2H, H-2′), 7.00 (d, J=9.1 Hz, 2H, H-3′), 7.17 (d, J=2.5 Hz, 1H, H-1″), 7.23 (dd, J=8.8, 2.6 Hz, 1H, H-3″), 7.36 (d, J=8.0 Hz, 2H, H-3‴), 7.38 (ddd, J=8.0, 6.8, 1.2 Hz, 1H, H-6″), 7.44 (ddd, J=8.1, 6.9, 1.3 Hz, 1H, H-7″), 7.66 (dd, J=8.2, 0.5 Hz, 1H, H-8″), 7.80 (d, J=8.1 Hz, 1H, H-4″), 7.81 (d, J=9.0 Hz, 1H, H-5″), 7.84 ppm (d, J=8.3 Hz, 2H, H-2‴); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=21.7 (*CH*$_3$), 66.1 (C-1), 68.1 (C-2), 112.5 (C-1″), 115.8 (C-2′), 119.4 (C-3″), 120.9 (C-3′), 124.5 (C-6″), 126.5 (C-8″), 127.0 (C-7″), 127.7 (C-5″), 128.1 (C-2‴), 129.8 (C-4″), 129.9 (C-10″), 129.9 (C-3‴), 132.9 (C-4‴), 134.3 (C-9″), 145.0 (C-1‴), 150.8 (C-4′), 154.4 (C-1′), 158.9 ppm (C-2″); HRMS (ESI): m/z: calcd for $C_{25}H_{22}O_5SNa$: 457.1086 $[M+Na]^+$; found: 457.1077.

β-Naphthyloxyphenoxyethyl thiocyanate (20): A solution of **19** (295 mg, 0.68 mmol) in anhydrous DMF (5 mL) was treated with KSCN (350 mg, 3.60 mmol) as detailed in the method for the preparation of **15**. The residue was purified by column chromatography (silica gel, hexane/EtOAc 9:1) to give pure **20** (93.3 mg, 43%) as a white solid: R_f=0.52 (hexane/EtOAc 7:3); m.p. 81–82 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ=3.35 (t, J=5.8 Hz, 2H, H-1), 4.32 (t, J=5.8 Hz, 2H, H-2), 6.95 (d, J=9.1 Hz, 2H, H-2′), 7.06 (d, J=9.1 Hz, 2H, H-3′), 7.20 (d, J=2.4 Hz, 1H, H-1″), 7.24 (dd, J=8.9, 2.5 Hz, 1H, H-3″), 7.38 (ddd, J=8.1, 6.9, 1.3 Hz, 1H, H-6″), 7.43 (ddd, J=8.1, 6.9, 1.3 Hz, 1H, H-7″), 7.67 (d, J=8.2 Hz, 1H, H-8″), 7.81 (d, J=7.7 Hz, 1H, H-4″), 7.82 ppm (d, J=8.9 Hz, 1H, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=33.4 (C-1), 66.4 (C-2), 111.8 (SCN), 112.6 (C-1″), 115.9 (C-2′), 121.0 (C-3′), 124.5 (C-6″), 126.5 (C-8″), 127.0 (C-7″), 127.7 (C-5″), 129.83 (C-4″), 129.87 (C-5″a), 134.3 (C-8″a), 151.1 (C-4′), 154.1 (C-1′), 156.0 ppm (C-2″); HRMS (ESI): m/z: calcd for $C_{19}H_{15}O_2NSNa$: 344.0721 $[M+Na]^+$; found: 344.0711.

α-Naphthyloxyphenylethyl tetrahydro-2*H*-pyran-2-yl ether (21): A mixture of **8** (724 mg, 3.04 mmol), 1-bromonaphthalene (840 mg, 4.08 mmol), CuI (60.7 mg, 0.32 mmol), 2-picolinic acid (75.8 mg, 0.62 mmol), and K_3PO_4 (1.33 g, 6.24 mmol) in DMSO (6 mL) was

treated as described in the method for the preparation of **9** for 48 h. The residue was purified by column chromatography (silica gel, hexane/EtOAc 9:1) to give pure **21** (322 mg, 29%) as a colorless oil: R_f = 0.56 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.51–1.68 (m, 4H, H-4‴, H-5‴), 1.72–1.78 (m, 1H, H-3‴$_a$), 1.81–1.89 (m, 1H, H-3‴$_b$), 3.55 (m, 1H, H-6‴$_a$), 3.83 (ddd, J = 11.1, 6.4, 4.3 Hz, 1H, H-6‴$_b$), 3.90 (m, 1H, H-1$_a$), 4.02 (ddd, J = 11.1, 5.0, 4.3 Hz, 1H, H-1$_b$), 4.16 (m, 2H, H-2), 4.70 (t, J = 3.8 Hz, 1H, H-2‴), 6.79 (dd, J = 7.6, 0.8 Hz, 1H, H-2″), 6.94 (d, J = 9.2 Hz, 2H, H-2′), 7.02 (d, J = 9.2 Hz, 2H, H-3′), 7.33 (t, J = 7.8 Hz, 1H, H-3″), 7.52 (m, 2H, H-6″, H-7″), 7.58 (d, J = 8.6 Hz, 1H, H-4″), 7.85 (dd, J = 7.4, 1.9 Hz, 1H, H-5″), 8.24 ppm (d, J = 8.5 Hz, 1H, H-8″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 19.4 (C-4‴), 25.4 (C-5‴), 30.5 (C-3‴), 62.2 (C-6‴), 65.9 (C-1), 68.1 (C-2), 99.0 (C-2‴), 111.3 (C-2″), 116.0 (C-2′), 120.5 (C-3′), 122.0 (C-4″), 122.4 (C-8″), 125.7 (C-3″), 126.2 (C-7″), 126.5 (C-9″), 126.7 (C-6″), 127.6 (C-5″), 134.7 (C-10″), 149.7 (C-4′), 153.1 (C-1‴), 155.2 ppm (C-1′); HRMS (ESI): m/z: calcd for $C_{23}H_{24}O_4Na$: 387.1572 $[M+Na]^+$; found: 387.1563.

α-Naphthyloxyphenylethanol (22): A solution of **21** (322 mg, 0.89 mmol) in MeOH (10 mL) was treated with PPTS (20 mg) as described in the method for the preparation of **11** to afford **22** (229 mg, 92%) as a colorless oil: R_f = 0.24 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 3.98 (dist. t, J = 4.3 Hz, 2H, H-1), 4.09 (dist. t, J = 4.1 Hz, 2H, H-2), 6.80 (d, J = 7.5 Hz, 1H, H-2″), 6.93 (d, J = 9.0 Hz, 2H, H-2′), 7.03 (d, J = 9.0 Hz, 2H, H-3′), 7.34 (t, J = 7.9 Hz, 1H, H-3″), 7.52 (m, 2H, H-6″, H-7″), 7.56 (d, J = 8.3 Hz, 1H, H-4″), 7.86 (dd, J = 7.3, 1.6 Hz, 1H, H-5″), 8.28 ppm (dd, J = 8.0, 1.5 Hz, 1H, H-8″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 61.5 (C-1), 69.7 (C-2), 111.5 (C-2″), 115.7 (C-2′), 120.6 (C-3′), 122.0 (C-4″), 122.5 (C-8″), 125.7 (C-3″), 125.8 (C-7″), 126.4 (C-9″), 126.6 (C-6″), 127.7 (C-5″), 134.8 (C-10″), 151.1 (C-4′), 154.3 (C-1‴), 154.9 ppm (C-1′); HRMS (ESI): m/z: calcd for $C_{18}H_{16}O_3Na$: 303.0997 $[M+Na]^+$; found: 303.1005.

α-Naphthyloxyphenylethyl 4-toluenesulfonate (23): TsCl (517 mg, 2.71 mmol) was added to a solution of alcohol **22** (229 mg, 0.82 mmol) in pyridine (5 mL) at 0 °C. The mixture was treated as detailed in the method for the preparation of **13.** Purification of the product afforded tosylate **23** (323 mg, 91%) as a white solid: R_f = 0.48 (hexane/EtOAc 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.45 (s, 3H, CH_3), 4.15 (m, 2H, H-1), 4.37 (m, 2H, H-2), 6.788 (d, J = 6.8 Hz, 1H, H-2″), 6.790 (d, J = 9.1 Hz, 2H, H-2′), 6.98 (d, J = 9.1 Hz, 2H, H-3′), 7.33 (t, J = 8.2 Hz, 1H, H-3″), 7.35 (d, J = 8.0 Hz, 2H, H-3‴), 7.52 (m, 2H, H-6″, H-7″), 7.57 (d, J = 8.3 Hz, 1H, H-4″), 7.83 (d, J = 8.4 Hz, 2H, H-2‴), 7.86 (dd, J = 7.3, 1.8 Hz, 1H, H-5″), 8.26 ppm (dd, J = 7.7, 1.3 Hz, 1H, H-8″); HRMS (ESI): m/z: calcd for $C_{25}H_{22}O_5SNa$: 457.1086 $[M+Na]^+$; found: 457.1082.

α-Naphthyloxyphenylethyl thiocyanate (24): A solution of tosylate **23** (323 mg, 1.03 mmol) in DMF (6 mL) was treated with KSCN (581 mg, 5.98 mmol) as described in the method for the preparation of **15**. The residue was purified by column chromatography (silica gel, hexane/EtOAc 19:1) to afford pure **24** (140 mg, 43%) as a white solid: R_f = 0.54 (hexane/EtOAc 7:3); m.p. 95–96 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 3.35 (t, J = 5.8 Hz, 2H, H-1), 4.32 (t, J = 5.8 Hz, 2H, H-2), 6.83 (d, J = 7.6 Hz, 1H, H-2″), 6.93 (d, J = 9.1 Hz, 2H, H-2′), 7.04 (d, J = 9.1 Hz, 2H, H-3′), 7.35 (t, J = 7.9 Hz, 1H, H-3″), 7.52 (m, 2H, H-6″, H-7″), 7.58 (d, J = 8.2 Hz, 1H, H-4″), 7.87 (dd, J = 7.4, 1.9 Hz, 1H, H-5″), 8.26 ppm (dd, J = 8.0, 1.5 Hz, 1H, H-8″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 33.3 (C-1), 66.4 (C-2), 111.7 (S*C*N), 111.8 (C-2″), 116.0 (C-2′), 120.5 (C-3′), 122.0 (C-4″), 122.8 (C-8″), 125.7 (C-3″), 125.9 (C-7″), 126.4 (C-9″), 126.6 (C-6″), 127.7 (C-5″), 134.9 (C-10″), 151.8 (C-4′), 153.9 (C-1‴), 154.0 ppm (C-1′); HRMS (ESI): m/z: calcd for $C_{19}H_{15}O_2NSNa$: 344.0721 $[M+Na]^+$; found: 344.0702.

4-(Pyridin-2-yloxy)phenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (26): A mixture of **25** (1.40 g, 4.02 mmol), 2-hydroxypyridine (450 mg, 4.73 mmol), CuI (73.3 mg, 0.38 mmol), 2-picolinic acid (91.0 mg, 0.74 mmol), and K_3PO_4 (1.74 g, 8.20 mmol) in DMSO (6 mL) was treated as described in the method for the preparation of **9** for 8 days. The product was purified by column chromatography (silica gel, hexane/EtOAc 3:7) to give pure **26** (607 mg, 48%) as a colorless oil: R_f = 0.09 (hexane/EtOAc 1:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.52–1.65 (m, 4H, H-4‴, H-5‴), 1.72–1.78 (m, 1H, H-3‴$_a$), 1.81–1.86 (m, 1H, H-3‴$_b$), 3.54 (m, 1H, H-6‴$_a$), 3.84 (ddd, J = 11.2, 6.4, 4.4 Hz, 1H, H-6‴$_b$), 3.91 (ddd, J = 11.2, 8.2, 3.0 Hz, 1H, H-1$_a$), 4.07 (ddd, J = 11.2, 4.8, 4.2 Hz, 1H, H-1$_b$), 4.18 (m, 2H, H-2), 4.72 (t, J = 3.6 Hz, 1H, H-2‴), 6.22 (dt, J = 6.7, 0.9 Hz, 1H, H-4″), 6.64 (d, J = 9.2 Hz, 1H, H-6″), 7.02 (d, J = 9.0 Hz, 2H, H-2′), 7.28 (d, J = 9.0 Hz, 2H, H-3′), 7.32 (dd, J = 6.8, 2.1 Hz, 1H, H-3″), 7.39 ppm (ddd, J = 9.2, 6.6, 2.1 Hz, 1H, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 19.2 (C-4‴), 25.3 (C-5‴), 30.4 (C-3‴), 62.1 (C-6‴), 65.6 (C-1), 67.7 (C-2), 98.9 (C-2‴), 105.7 (C-6″), 115.1 (C-2′), 121.6 (C-4″), 127.4 (C-3′), 133.7 (C-4′), 138.2 (C-5″), 139.8 (C-3″), 158.6 (C-1′), 162.6 ppm (C-1″); HRMS (ESI): m/z: calcd for $C_{18}H_{21}NO_4Na$: 338.1368 $[M+Na]^+$; found: 338.1365.

4-(Pyridin-2-yloxy)phenoxyethanol (27): A solution of **26** (607 mg, 1.92 mmol) in MeOH (10 mL) was treated with PPTS (20 mg), and the mixture was stirred at room temperature for 4 h. The mixture was worked up as described in the method for the preparation of **11**. The product was purified by column chromatography (silica gel, EtOAc) to afford pure alcohol **27** (266 mg, 60%) as a white solid: R_f = 0.09 (EtOAc); m.p. 150 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 3.99 (m, 2H, H-1), 4.13 (dist. t, J = 4.6 Hz, 2H, H-2), 6.22 (dt, J = 6.7, 1.4 Hz, 1H, H-4″), 6.65 (dq, J = 9.3, 0.7 Hz, 1H, H-6″), 7.02 (d, J = 9.0 Hz, 2H, H-2′), 7.31 (d, J = 8.9 Hz, 2H, H-3′), 7.32 (ddd, J = 6.5, 2.2, 0.6 Hz, 1H, H-3″), 7.39 ppm (ddd, J = 9.2, 6.6, 2.2 Hz, 1H, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 61.4 (C-1), 69.5 (C-2), 105.8 (C-6″), 115.2 (C-2′), 121.9 (C-4″), 127.7 (C-3′), 138.2 (C-5″), 139.8 (C-3″), 158.4 (C-1′), 163.8 (C-1″), 105.7 (C-6″), 115.1 (C-2′), 121.6 (C-4″), 127.4 (C-3′), 133.7 (C-4′), 138.2 (C-5″), 139.8 (C-3″), 158.6 (C-1′), 162.6 ppm (C-1″); HRMS (ESI): m/z: calcd for $C_{13}H_{14}NO_3$ 232.0974 $[M+H]^+$; found: 232.0978.

4-(Pyridin-2-yloxy)phenoxyethyl 4-toluenesulfonate (28): A solution of alcohol **27** (122 mg, 0.53 mmol) in pyridine (2 mL) was treated with TsCl (352 mg, 1.85 mmol) at 0 °C. The reaction was quenched as detailed in the method for the preparation of **13** to afford pure **28** (183 mg, 90%) as a white solid: R_f = 0.39 (EtOAc); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.46 (s, 3H, CH_3), 4.18 (m, 2H, H-1), 4.39 (m, 2H, H-2), 6.22 (dt, J = 6.7, 1.3 Hz, 1H, H-4″), 6.64 (dq, J = 9.3, 0.6 Hz, 1H, H-6″), 6.88 (d, J = 8.9 Hz, 2H, H-2′), 7.27 (d, J = 8.9 Hz, 2H, H-3′), 7.30 (ddd, J = 6.9, 2.0, 0.5 Hz, 1H, H-3″), 7.36 (d, J = 7.9 Hz, 2H, H-3‴), 7.39 (ddd, J = 9.0, 6.6, 2.3 Hz, 1H, H-5″), 7.83 ppm (d, J = 8.4 Hz, 2H, H-2‴); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 21.7 (*C*H$_3$), 65.8 (C-1), 67.9 (C-2), 105.8 (C-6″), 115.2 (C-2′), 121.8 (C-4″), 127.7 (C-3′), 128.0 (C-2‴), 129.9 (C-3‴), 134.5 (C-4′), 132.8 (C-4‴), 138.1 (C-5″), 139.8 (C-3″), 145.1 (C-1‴), 157.8 (C-1′), 162.6 ppm (C-1″); HRMS (ESI): m/z: calcd for $C_{20}H_{20}N_2O_5S$ 386.1062 $[M+H]^+$; found: 386.1055.

4-(Pyridin-2-yloxy)phenoxyethyl thiocyanate (29): A solution of **28** (136 mg, 0.35 mmol) in anhydrous DMF (2 mL) was treated with KSCN (200 mg, 2.06 mmol) as described in the method for the preparation of **15**. The product was purified by column chromatog-

raphy (silica gel, hexane/EtOAc 1:1) to yield thiocyanate **29** (56.9 mg, 61%) as a white solid: $R_f = 0.38$ (EtOAc); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.36$ (t, $J = 5.8$ Hz, 2H, H-1), 4.36 (t, $J = 5.8$ Hz, 2H, H-2), 6.23 (dt, $J = 6.7$, 1.3 Hz, 1H, H-4″), 6.65 (dq, $J = 9.3$, 0.7 Hz, 1H, H-6″), 7.02 (d, $J = 9.0$ Hz, 2H, H-2′), 7.33 (d, $J = 9.0$ Hz, 2H, H-3′), 7.31 (ddd, $J = 7.0$, 1.8, 0.7 Hz, 1H, H-3″), 7.39 ppm (ddd, $J = 9.2$, 6.6, 2.1 Hz, 1H, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 33.1$ (C-1), 66.2 (C-2), 105.9 (C-6″), 111.6 (SCN), 115.3 (C-2′), 121.9 (C-4″), 127.9 (C-3′), 134.8 (C-4′), 138.1 (C-5″), 139.9 (C-3″), 157.6 (C-1′), 162.6 ppm (C-1″); HRMS (ESI): *m/z*: calcd for $C_{14}H_{13}N_2O_2S$ 273.0698 $[M+H]^+$; found: 273.0703.

3-(2-Chlorophenoxy)phenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (31): A mixture of **30** (927 mg, 2.6 mmol), 2-chlorophenol (411 mg, 3.2 mmol), CuI (50.6 mg, 0.27 mmol), 2-picolinic acid (65.5 mg, 0.53 mmol), and K_3PO_4 (1.129 g, 5.3 mmol) was evacuated and backfilled with argon as detailed in the method for the preparation of **9**. The product was purified by column chromatography (silica gel, hexane/EtOAc 24:1) to afford pure **31** (475 mg, 51%) as a colorless oil: $R_f = 0.47$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.50$–1.65 (m, 4H, H-4‴, H-5‴), 1.70–1.76 (m, 1H, H-3‴$_a$), 1.79–1.86 (m, 1H, H-3‴$_b$), 3.52 (m, 1H, H-6‴$_a$), 3.80 (ddd, $J = 11.2$, 6.4, 4.2 Hz, 1H, H-6‴$_b$), 3.88 (ddd, $J = 11.2$, 8.2, 3.1 Hz, 1H, H-1$_a$), 4.07 (m, 1H, H-1$_b$), 4.12 (m, 2H, H-2), 4.69 (t, $J = 3.6$ Hz, 1H, H-2‴), 6.54 (m, 2H, H-4′, H-6′), 6.55 (t, $J = 2.3$ Hz, 1H, H-2′), 7.02 (dt, $J = 8.0$, 1.5 Hz, 1H, H-6″), 7.09 (dt, $J = 7.7$, 1.5 Hz, 1H, H-4″), 7.21 (t, $J = 8.0$ Hz, 1H, H-5′), 7.22 (m, 1H, H-5″), 7.45 ppm (dd, $J = 8.0$, 1.6 Hz, 1H, H-3″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 19.4$ (C-4‴), 25.4 (C-5‴), 30.5 (C-3‴), 62.2 (C-6‴), 65.7 (C-1), 67.6 (C-2), 99.0 (C-2‴), 104.8 (C-2′), 109.6 (C-6′), 110.2 (C-4′), 121.2 (C-6″), 124.8 (C-4″), 126.0 (C-2″), 127.9 (C-5″), 130.1 (C-3″), 130.8 (C-5′), 152.2 (C-1″), 158.1 (C-3′), 160.2 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{19}H_{21}O_4ClNa$: 371.1026 $[M+Na]^+$; found: 371.1023.

3-(2-Chlorophenoxy)phenoxyethanol (36): A solution of **31** (475 mg, 1.4 mmol) in MeOH (75 mL) was treated with PPTS (30 mg) at 0 °C. The mixture was treated as described in the method for the preparation of **11**. The residue was purified by column chromatography (hexane/EtOAc 4:1) to give pure alcohol **36** (252 mg, 70%) as a colorless oil: $R_f = 0.05$(hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.95$ (dist.t, $J = 4.5$ Hz, 2H, H-1), 4.06 (dist.t, $J = 4.5$ Hz, 2H, H-2), 6.54 (t, $J = 2.2$ Hz, 1H, H-4′), 6.56 (ddd, $J = 8.1$, 2.3, 0.9 Hz, 1H, H-6′), 6.66 (ddd, $J = 8.2$, 2.3, 0.8 Hz, 1H, H-2′), 7.03 (dd, $J = 8.1$, 1.5 Hz, 1H, H-6″), 7.10 (ddd, $J = 7.7$, 7.5, 1.5 Hz, 1H, H-4″), 7.22 (t, $J = 8.0$ Hz, 1H, H-5′), 7.24 (m, 1H, H-5″), 7.46 ppm (dd, $J = 8.0$, 1.6 Hz, 1H, H-3″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 61.4$ (C-1), 67.3 (C-2), 104.5 (C-2′), 109.3 (C-6′), 110.3 (C-4′), 121.3 (C-6″), 125.0 (C-4″), 126.1 (C-2″), 128.0 (C-5″), 130.3 (C-3″), 130.8 (C-5′), 152.2 (C-1″), 158.1 (C-3′), 160.3 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{14}H_{14}O_3Cl$ 265.0631 $[M+H]^+$; found: 265.0633.

3-(2-Chlorophenoxy)phenoxyethyl 4-toluenesulfonate (41): A solution of alcohol **36** (253 mg, 0.95 mmol) in pyridine (3 mL) was treated with TsCl (546 mg, 2.9 mmol) as detailed in the method for the preparation of **13**. The product was purified by column chromatography (silica gel, hexane/EtOAc 9:1) to afford tosylate **41** (226 mg, 66%) as a colorless oil: $R_f = 0.25$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 2.44$ (s, 3H, CH_3), 4.11 (m, 2H, H-1), 4.35 (m, 2H, H-2), 6.39 (t, $J = 2.3$ Hz, 1H, H-2′), 6.53 (m, 2H, H-4′, H-6′), 7.00 (dd, $J = 8.1$, 1.5 Hz, 1H, H-6″), 7.11 (dt, $J = 7.7$, 1.5 Hz, 1H, H-4″), 7.18 (t, $J = 8.2$ Hz, 1H, H-5′), 7.24 (ddd, $J = 8.1$, 7.5, 1.6 Hz, 1H, H-5″), 7.32 (d, $J = 8.0$ Hz, 2H, H-3‴), 7.46 (dd, $J = 8.0$, 1.6 Hz, 1H, H-3″), 7.81 ppm (d, $J = 8.4$ Hz, 2H, H-2‴); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 21.6$ (CH_3), 65.5 (C-1), 68.0 (C-2), 104.6 (C-2′), 109.2 (C-6′), 110.6 (C-4′), 121.2 (C-6″), 125.0 (C-4″), 127.99 (C-5″), 128.02 (C-2‴), 129.8 (C-3‴), 130.2 (C-3″), 130.9 (C-5′), 132.9 145.0 (C-1‴), 152.0 (C-1″), 158.2 (C-3′), 159.3 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{21}H_{19}O_5SClNa$: 441.0539 $[M+Na]^+$; found: 441.0547.

3-(2-Chlorophenoxy)phenoxyethyl thiocyanate (46): A solution of tosylate **41** (226 mg, 0.54 mmol) in anhydrous DMF (3 mL) was treated with KSCN (262 mg, 2.7 mmol). The mixture was heated at 100 °C for 3 h. The reaction was worked up as detailed in the method for the preparation of **15**. The residue was purified by column chromatography (silica gel, hexane/EtOAc 19:1) to give pure **46** (15.8 mg, 10%) as a colorless oil: $R_f = 0.38$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.32$ (t, $J = 5.8$ Hz, 2H, H-1), 4.29 (t, $J = 5.8$ Hz, 2H, H-2), 6.55 (t, $J = 2.3$ Hz, 1H, H-3′), 6.57 (ddd, $J = 8.2$, 2.1, 0.8 Hz, 1H, H-4′), 6.67 (ddd, $J = 8.3$, 2.4, 0.7 Hz, 1H, H-6′), 7.03 (dd, $J = 8.2$, 1.5 Hz, 1H, H-6″), 7.11 (dt, $J = 7.7$, 1.4 Hz, 1H, H-4″), 7.24 (t, $J = 8.2$ Hz, 1H, H- H-5′), 7.24 (m, 1H, H-5″), 7.47 ppm (dd, $J = 8.0$, 1.6 Hz, 1H, H-3″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 33.2$ (C-1), 65.9 (C-2), 104.6 (C-2′), 109.3 (C-6′), 110.8 (C-4′), 111.6 (SCN), 121.4 (C-6″), 125.1 (C-4″), 126.2 (C-2″), 128.0 (C-5″), 130.4 (C-5′), 130.9 (C-5′), 151.9 (C-1″), 158.4 (C-3′), 159.1 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{15}H_{12}O_2NSClNa$: 328.0175 $[M+Na]^+$; found: 328.0169.

3-(3-Chlorophenoxy)phenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (32): A mixture of **30** (959 mg, 2.7 mmol), 3-chlorophenol (708 mg, 5.5 mmol), CuI (52.4 mg, 0.27 mmol), 2-picolinic acid (67.8 mg, 0.55 mmol), and K_3PO_4 (1.169 g, 5.5 mmol) as detailed in the method for the preparation of **9**. The mixture was stirred vigorously at 90 °C for 21 days. The product was purified by column chromatography (silica gel, hexane/EtOAc 24:1) to afford pure **32** (826 mg, 86%) as a colorless oil: $R_f = 0.76$ (hexane/EtOAc 3:2); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.52$–1.65 (m, 4H, H-4‴, H-5‴), 1.72–1.76 (m, 1H, H-3‴$_a$), 1.81–1.84 (m, 1H, H-3‴$_b$), 3.55 (m, 1H, H-6‴$_a$), 3.80 (ddd, $J = 10.7$, 6.6, 3.8 Hz, 1H, H-6‴$_b$), 3.91 (ddd, $J = 11.1$, 8.7, 2.4 Hz, 1H, H-1$_a$), 4.07 (m, 1H, H-1$_b$), 4.12 (m, 2H, H-2), 4.72 (t, $J = 3.3$ Hz, 1H, H-2‴), 6.61 (t, $J = 2.3$ Hz, 1H, H-2′), 6.72 (m, 2H, H-4′, H-6′), 6.90 (dd, $J = 8.0$, 1.3 Hz, 1H, H-6″), 7.00 (t, $J = 2.0$ Hz, 1H, H-2″), 7.09 (m, 1H, H-4″), 7.25 ppm (t, $J = 8.2$ Hz, 2H, H-5′, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 19.2$ (C-4‴), 25.3 (C-5‴), 30.4 (C-3‴), 62.3 (C-6‴), 65.8 (C-1), 67.5 (C-2), 99.1 (C-2‴), 106.1 (C-2′), 110.2 (C-6′), 111.6 (C-4′), 116.8 (C-6″), 118.9 (C-2″), 123.2 (C-4″), 130.2 (C-5″), 130.4 (C-5′), 134.6 (C-3″), 157.4 (C-1‴), 158.0 (C-3′), 160.2 ppm (C-1′).

3-(3-Chlorophenoxy)phenoxyethanol (37): A solution of **32** (581 mg, 1.7 mmol) in MeOH (75 mL) was treated with PPTS (30 mg). The mixture was stirred at room temperature overnight and was quenched as described in the method for the preparation of **11**. The product was purified by column chromatography (hexane/EtOAc 86:14) to give pure alcohol **37** (302 mg, 55%) as a colorless oil: $R_f = 0.14$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.98$ (m, 2H, H-1), 4.09 (t, $J = 4.1$ Hz, 2H, H-2), 6.62 (t, $J = 2.3$ Hz, 1H, H-2′), 6.65 (dd, $J = 8.1$, 1.6 Hz, 1H, H-4′), 6.74 (dd, $J = 8.2$, 2.1 Hz, 1H, H-6′), 6.93 (dd, $J = 8.3$, 1.6 Hz, 1H, H-6″), 7.03 (t, $J = 2.1$ Hz, 1H, H-2″), 7.11 (dd, $J = 7.9$, 0.7 Hz, 1H, H-4″), 7.28 ppm (dt, $J = 8.2$, 2.6 Hz, 2H, H-5′, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 61.4$ (C-1), 69.3 (C-2), 105.9 (C-2′), 110.0 (C-6′), 111.8 (C-4′), 117.0 (C-6″), 119.1 (C-2″), 123.4 (C-4″), 130.4 (C-5″), 130.5 (C-5′), 135.0 (C-3″), 157.6 (C-1″), 157.9 (C-3′), 160.0 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{14}H_{13}O_3ClNa$: 287.0451 $[M+Na]^+$; found: 287.0441.

3-(3-Chlorophenoxy)phenoxyethyl 4-toluenesulfonate (42): TsCl (796 mg, 4.18 mmol) was added to a solution of **37** (368 mg,

1.39 mmol) in pyridine (3 mL) as described in the method for the preparation of **13**. The product was purified by column chromatography (silica gel, hexane/EtOAc 97:3) to give pure **42** (290 mg, 50%) as a colorless oil: $R_f = 0.19$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 2.43$ (s, 3H, CH_3), 4.12 (m, 2H, H-1), 4.36 (m, 2H, H-2), 6.42 (t, $J = 2.3$ Hz, 1H, H-2′), 6.57 (ddd, $J = 8.3$, 2.4, 0.7 Hz, 1H, H-4′), 6.61 (ddd, $J = 8.2$, 2.3, 0.8 Hz, 1H, H-6′), 6.88 (ddd, $J = 8.3$, 2.4, 0.9 Hz, 1H, H-6″), 6.97 (t, $J = 2.2$ Hz, 1H, H-2″), 7.08 (ddd, $J = 8.0$, 1.9, 0.9 Hz, 1H, H-4″), 7.24 (m, 2H, H-5′, H-5″), 7.32 (d, $J = 8.0$ Hz, 2H, H-3‴), 7.81 ppm (d, $J = 8.3$ Hz, 2H, H-2‴); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 21.6$ (CH_3), 65.5 (C-1), 67.9 (C-2), 106.0 (C-2′), 109.8 (C-6′), 112.1 (C-4′), 116.9 (C-6″), 119.0 (C-2″), 123.5 (C-4″), 128.0 (C-2‴), 129.8 (C-3‴), 130.4 (C-5″), 130.5 (C-5′), 132.8 (C-4‴), 135.0 (C-3″), 145.0 (C-1‴), 157.5 (C-1″), 157.9 (C-3′), 159.4 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{21}H_{19}O_5SClNa$: 441.0539 $[M+Na]^+$; found: 441.0543.

3-(3-Chlorophenoxy)phenoxyethyl thiocyanate (47): KSCN (293 mg, 3.0 mmol) was added to a solution of **12** (252 mg, 0.60 mmol) in DMF (3 mL). The mixture was treated as described in the method for the preparation of **15**. The product was purified by column chromatography (silica gel, hexane/EtOAc 91:9) to afford **47** (92.3 mg, 50%) as a colorless oil: $R_f = 0.36$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.33$ (t, $J = 5.8$ Hz, 2H, H-1), 4.30 (t, $J = 5.8$ Hz, 2H, H-2), 6.59 (t, $J = 2.3$ Hz, 1H, H-2′), 6.66 (ddd, $J = 8.2$, 2.3, 0.8 Hz, 1H, H-4′), 6.71 (ddd, $J = 8.3$, 2.4, 0.7 Hz, 1H, H-6′), 6.91 (ddd, $J = 8.3$, 2.4, 0.9 Hz, 1H, H-6″), 7.00 (t, $J = 2.1$ Hz, 1H, H-2″), 7.09 (ddd, $J = 8.0$, 1.9, 0.9 Hz, 1H, H-4″), 7.30 ppm (m, 2H, H-5′, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 33.2$ (C-1), 65.9 (C-2), 106.1 (C-2′), 109.9 (C-6′), 111.6 (SCN), 112.4 (C-4′), 117.0 (C-6″), 119.1 (C-2″) 123.6 (C-4″), 130.5 (C-5″), 130.6 (C-5′), 135.1 (C-3″), 157.7 (C-1″), 157.8 (C-3′), 159.2 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{15}H_{12}O_2SNClNa$: 328.0175 $[M+Na]^+$; found: 328.0177.

3-(4-Chlorophenoxy)phenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (33): A mixture of **30** (810 mg, 2.3 mmol), 4-chlorophenol (598 mg, 4.6 mmol), CuI (44.4 mg, 0.23 mmol), 2-picolinic acid (57.4 mg, 0.47 mmol), and K_3PO_4 (987 mg, 4.6 mmol) was treated as described in the method for the preparation of **9** and was stirred at 90 °C for 19 days. The product was purified by column chromatography (silica gel, hexane/EtOAc 24:1) to afford pure **33** (417 mg, 51%) as a colorless oil: $R_f = 0.34$ (hexane/EtOAc 3:2); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.52$–1.69 (m, 4H, H-4‴, H-5‴), 1.73–1.79 (m, 1H, H-3‴$_a$), 1.82–1.88 (m, 1H, H-3‴$_b$), 3.55 (m, 1H, H-6‴$_a$), 3.82 (ddd, $J = 11.2$, 6.4, 4.1 Hz, 1H, H-6‴$_b$), 3.91 (ddd, $J = 11.2$, 8.3, 3.0 Hz, 1H, H-1$_a$), 4.06 (m, 1H, H-1$_b$), 4.14 (m, 2H, H-2), 4.72 (t, $J = 3.6$ Hz, 1H, H-2‴), 6.60 (m, 2H, H-2′, H-4′), 6.79 (d, $J = 9.0$ Hz, 1H, H-6′), 6.97 (d, $J = 9.0$ Hz, 2H, H-3″), 7.21 (d, $J = 8.9$ Hz, 1H, H-6′), 7.22 (t, $J = 8.5$ Hz, 1H, H-5′), 7.31 ppm (d, $J = 9.1$ Hz, 2H, H-2″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 19.4$ (C-4‴), 25.4 (C-5‴), 30.5 (C-3‴), 62.2 (C-6‴), 65.7 (C-1), 67.6 (C-2), 99.0 (C-2‴), 105.7 (C-2′), 109.9 (C-6′), 111.2 (C-4′), 120.2 (C-2″), 128.3 (C-4″), 129.5 (C-5′), 129.7 (C-3″), 155.7 (C-1″), 158.0 (C-1′), 160.3 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{19}H_{21}O_4ClNa$: 371.1026 $[M+Na]^+$; found: 371.1002.

3-(4-Chlorophenoxy)phenoxyethanol (38): A solution of **33** (417 mg, 1.2 mmol) in MeOH (75 mL) was treated with PPTS (30 mg). The mixture was stirred at room temperature overnight and was quenched as described in the method for the preparation of **11**. The product was purified by column chromatography (hexane/EtOAc 9:1) to give pure alcohol **38** (219 mg, 69%) as a colorless oil: $R_f = 0.11$ (hexane/EtOAc 8:2); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.98$ (t, $J = 6.3$, 1H, -O*H*), 3.95 (dt, $J = 6.0$, 4.6 Hz, 2H, H-1), 4.05 (dist.t, $J = 4.5$ Hz, 2H, H-2), 6.56 (t, $J = 2.3$ Hz, 1H, H-2′), 6.60 (ddd, $J = 8.1$, 2.2, 0.7 Hz, 1H, H-4′), 6.68 (ddd, $J = 8.3$, 2.4, 0.7 Hz, 1H, H-6′), 6.95 (d, $J = 9.0$ Hz, 2H, H-3″), 7.23 (t, $J = 8.2$ Hz, 1H, H-5′), 7.29 ppm (d, $J = 9.0$ Hz, 2H, H-2″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 61.4$ (C-1), 69.3 (C-2), 105.5 (C-2′), 109.6 (C-6′), 111.4 (C-4′), 120.4 (C-2″), 128.5 (C-4″), 129.7 (C-5′), 130.3 (C-3″), 155.6 (C-1‴), 158.2 (C-1′), 160.0 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{14}H_{13}O_3ClNa$: 287.0451 $[M+Na]^+$; found: 287.0450.

3-(4-Chlorophenoxy)phenoxyethyl 4-toluenesulfonate (43): TsCl (474 mg, 2.48 mmol) was added to a solution of **8** (219 mg, 0.83 mmol) in pyridine (3 mL) as described in the method for the preparation of **13**. The product was purified by column chromatography (silica gel, hexane/EtOAc 47:3) to give pure **43** (269 mg, 78%) as a colorless oil: $R_f = 0.25$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 2.43$ (s, 3H, CH_3), 4.11 (m, 2H, H-1), 4.35 (m, 2H, H-2), 6.41 (t, $J = 2.3$ Hz, 1H, H-2′), 6.55 (ddd, $J = 8.3$, 2.4, 0.7 Hz, 1H, H-4′), 6.58 (ddd, $J = 8.2$, 2.2, 0.7 Hz, 1H, H-6′), 6.93 (d, $J = 9.0$ Hz, 2H, H-3″), 7.20 (t, $J = 8.3$ Hz, 1H, H-5′), 7.30 (d, $J = 9.0$ Hz, 2H, H-2″), 7.33 (d, $J = 8.0$ Hz, 2H, H-3‴), 7.81 ppm (d, $J = 8.4$ Hz, 2H, H-2‴); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 21.6$ (CH_3), 65.5 (C-1), 67.9 (C-2), 105.6 (C-2′), 109.5 (C-6′), 111.6 (C-4′), 120.3 (C-2″), 128.0 (C-2‴), 128.5 (C-4″), 129.7 (C-5′), 129.8 (C-3‴), 130.3 (C-3″), 132.8 (C-4‴), 145.0 (C-1‴), 155.5 (C-1″), 158.1 (C-1′), 159.3 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{21}H_{20}O_5ClS$ 419.0720 $[M+H]^+$; found: 419.0717.

3-(4-Chlorophenoxy)phenoxyethyl thiocyanate (48): KSCN (319 mg, 3.2 mmol) was added to a solution of **43** (269 mg, 0.64 mmol) in DMF (3 mL). The mixture was treated as detailed in the method for the preparation of **15**. The product was purified by column chromatography (silica gel, hexane/EtOAc 24:1) to afford **48** (104 mg, 53%) as a colorless oil: $R_f = 0.18$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.32$ (t, $J = 5.8$ Hz, 2H, H-1), 4.29 (t, $J = 5.8$ Hz, 2H, H-2), 6.56 (t, $J = 2.3$ Hz, 1H, H-2′), 6.62 (dd, $J = 7.9$, 2.0 Hz, 1H, H-4′), 6.68 (dd, $J = 8.3$, 2.4 Hz, 1H, H-6′), 6.96 (d, $J = 9.0$ Hz, 2H, H-3″), 7.25 (t, $J = 8.3$ Hz, 1H, H-5′), 7.30 ppm (d, $J = 9.0$ Hz, 2H, H-2″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 33.2$ (C-1), 65.9 (C-2), 105.6 (C-2′), 109.6 (C-6′), 111.6 (SCN), 111.9 (C-4′), 120.4 (C-2″), 128.6 (C-4″), 129.8 (C-5′), 130.5 (C-3″), 155.4 (C-1‴), 158.3 (C-1′), 159.2 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{15}H_{13}O_2NSCl$ 306.0356 $[M+H]^+$; found: 306.0365.

3-(2-Methoxyphenoxy)phenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (34): DMSO (3.0 mL) was added to a mixture of **30** (939 mg, 2.7 mmol), 2-methoxyphenol (670 mg, 5.4 mmol), CuI (51.4 mg, 0.27 mmol), 2-picolinic acid (66.4 mg, 0.54 mmol), and K_3PO_4 (1.148 g, 5.4 mmol), and the mixture was stirred at 90 °C for 3 days as described in the method for the preparation of **9**. The product was purified by column chromatography (silica gel, hexane/EtOAc 47:3) to afford pure **34** (628 mg, 68%) as a colorless oil: $R_f = 0.35$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.50$–1.65 (m, 4H, H-4‴, H-5‴), 1.70–1.76 (m, 1H, H-3‴$_a$), 1.79–1.85 (m, 1H, H-3‴$_b$), 3.51 (m, 1H, H-6‴$_a$), 3.79 (ddd, $J = 11.0$, 6.5, 4.4 Hz, 1H, H-6‴$_b$), 3.84 (s, 3H, OCH_3), 3.88 (ddd, $J = 11.3$, 8.2, 3.1 Hz, 1H, H-1$_a$), 4.02 (m, 1H, H-1$_b$), 4.10 (m, 2H, H-2), 4.69 (t, $J = 3.6$ Hz, 1H, H-2‴), 6.53–6.55 (m, 2H, H-2′, H-4′), 6.62 (ddd, $J = 8.2$, 2.3, 0.6 Hz, 1H, H-6′), 6.92 (dt, $J = 7.7$, 1.4 Hz, 1H, H-6″), 7.00 (ddd, $J = 8.1$, 4.9, 1.5 Hz, 2H, H-3″, H-5″), 7.13 (dt, $J = 7.8$, 1.5 Hz, 1H, H-4″), 7.17 ppm (t, $J = 8.1$ Hz, 1H, H-5′); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 19.4$ (C-4‴), 25.4 (C-5‴), 30.5 (C-3‴), 56.0 (OCH_3), 62.2 (C-6‴), 65.7 (C-1), 67.4 (C-2), 99.0 (C-2‴), 104.0 (C-2′), 108.7 (C-6′), 109.6 (C-4′), 112.8 (C-3″), 121.1 (C-6″), 121.3 (C-5″), 124.9 (C-4″), 129.8 (C-5′), 144.8 (C-1″), 151.5 (C-2″), 159.1 (C-1′), 160.1 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{20}H_{24}O_5Na$: 367.1521 $[M+Na]^+$; found: 367.1515.

3-(2-Methoxyphenoxy)phenoxyethanol (39): A solution of **34** (611 mg, 1.8 mmol) in MeOH (10 mL) was treated with PPTS (30 mg). The mixture was stirred at room temperature overnight and was quenched as described in the method for the preparation of **11**. The product was purified by column chromatography (hexane/EtOAc 87:13) to give pure alcohol **39** (349 mg, 76%) as a colorless oil: R_f = 0.08 (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.00 (t, J = 6.2, 1H, -O*H*), 3.84 (s, 3H, OCH_3), 3.94 (m, 2H, H-1), 4.04 (t, J = 4.5 Hz, 2H, H-2), 6.52–6.55 (m, 2H, H-2′, H-4′), 6.61 (ddd, J = 8.3, 2.3, 0.7 Hz, 1H, H-6′), 6.93 (dt, J = 7.7, 1.4 Hz, 1H, H-6″), 7.00 (td, J = 8.1, 1.4 Hz, 2H, H-3″, H-5″), 7.15 (dt, J = 7.8, 1.4 Hz, 1H, H-4″), 7.18 ppm (t, J = 8.1 Hz, 1H, H-5′); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 56.0 (OCH_3), 61.4 (C-1), 69.2 (C-2), 103.8 (C-2′), 108.5 (C-6′), 109.7 (C-4′), 112.8 (C-3″), 121.1 (C-6″), 121.4 (C-5″), 125.1 (C-4″), 130.0 (C-5′), 144.6 (C-1″), 151.5 (C-2″), 159.3 (C-1′), 160.0 ppm (C-3′).

3-(2-Methoxyphenoxy)phenoxyethyl 4-toluenesulfonate (44): TsCl (767 mg, 4.02 mmol) was added to a solution of **39** (349 mg, 1.34 mmol) in pyridine (3 mL) as described in the method for the preparation of **13**. The product was purified by column chromatography (silica gel, hexane/EtOAc 9:1) to give pure **44** (456 mg, 82%) as a white solid: R_f = 0.13 (hexane/EtOAc 4:1); m.p. 92 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.44 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.09 (m, 2H, H-1), 4.33 (m, 2H, H-2), 6.38 (t, J = 2.4 Hz, 1H, H-2′), 6.47 (ddd, J = 8.3, 2.4, 0.8 Hz, 1H, H-4′), 6.52 (ddd, J = 8.2, 2.3, 0.8 Hz, 1H, H-6′), 6.93 (ddd, J = 7.8, 7.4, 1.4 Hz, 1H, H-6″), 6.98 (dd, J = 7.9, 1.8 Hz, 1H, H-3″), 7.01 (dd, J = 8.2, 1.4 Hz, 1H, H-5″), 7.14 (t, J = 8.2 Hz, 1H, H-4″), 7.15 (ddd, J = 8.1, 7.1, 2.0 Hz, 1H, H-5′), 7.32 (d, J = 8.0 Hz, 2H, H-3‴), 7.80 ppm (d, J = 8.3 Hz, 2H, H-2‴); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 21.6 (PhCH_3), 56.0 (OCH_3), 65.4 (C-1), 68.0 (C-2), 103.9 (C-2′), 108.3 (C-6′), 110.0 (C-4′), 112.8 (C-3″), 121.1 (C-6″), 121.4 (C-5″), 125.1 (C-4″), 128.0 (C-2‴), 129.8 (C-3‴), 130.0 (C-5′), 132.8 (C-4‴), 144.6 (C-1″), 144.9 (C-1‴), 151.5 (C-2″), 159.3 (C-1′), 160.0 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{22}H_{23}O_6S$ 415.1215 $[M+H]^+$; found: 415.1219.

3-(2-Methoxyphenoxy)phenoxyethyl thiocyanate (49): KSCN (526 mg, 5.4 mmol) was added to a solution of **44** (449 mg, 1.08 mmol) in DMF (3 mL). The mixture was treated as described in the method for the preparation of **15**. The product was purified by column chromatography (silica gel, hexane/EtOAc 93:7) to afford **49** (156 mg, 48%) as a colorless oil: R_f = 0.22 (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 3.31 (t, J = 5.9 Hz, 2H, H-1), 3.84 (s, 3H, OCH_3), 4.27 (t, J = 5.9 Hz, 2H, H-2), 6.53 (t, J = 2.3 Hz, 1H, H-2′), 6.56 (ddd, J = 8.2, 2.3, 0.8 Hz, 1H, H-4′), 6.61 (ddd, J = 8.2, 2.4, 0.7 Hz, 1H, H-6′), 6.94 (dt, J = 7.7, 1.4 Hz, 1H, H-6″), 7.00 (m, 2H, H-3″, H-5″), 7.15 (ddd, J = 8.1, 7.4, 1.7 Hz, 1H, H-4″), 7.19 ppm (t, J = 8.2 Hz, 1H, H-5′); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 33.3 (C-1), 56.0 (OCH_3), 65.8 (C-2), 103.9 (C-2′), 108.5 (C-6′), 110.2 (C-4′), 111.7 (S*C*N), 112.9 (C-3″), 121.1 (C-6″), 121.5 (C-5″), 125.2 (C-4″), 130.1 (C-5′), 144.4 (C-1″), 151.5 (C-2″), 158.9 (C-1′), 159.4 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{16}H_{15}O_3NS$ 324.0670 $[M+Na]^+$; found: 324.0660.

3-(3-Methoxyphenoxy)phenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (35): DMSO (3.0 mL) was added to a mixture of **30** (800 mg, 2.3 mmol), 3-methoxyphenol (570 mg, 4.6 mmol), CuI (43.8 mg, 0.23 mmol), 2-picolinic acid (56.6 mg, 0.46 mmol), and K_3PO_4 (978 mg, 4.6 mmol), and the mixture was stirred at 90 °C for 5 days as described in the method for the preparation of **9**. The product was purified by column chromatography (silica gel, hexane/EtOAc 49:1) to afford pure **35** (505 mg, 64%) as a colorless oil: R_f = 0.46 (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.53–1.68 (m, 4H, H-4‴, H-5‴), 1.73–1.79 (m, 1H, H-3‴$_a$), 1.82–1.89 (m, 1H, H-3‴$_b$), 3.55 (m, 1H, H-6‴$_a$), 3.81 (s, 3H, OCH_3), 3.82 (ddd, J = 11.0, 6.5, 4.2 Hz, 1H, H-6‴$_b$), 3.91 (ddd, J = 11.3, 8.2, 3.1 Hz, 1H, H-1$_a$), 4.06 (m, 1H, H-1$_b$), 4.14 (m, 2H, H-2), 4.72 (t, J = 3.6 Hz, 1H, H-2‴), 6.60–6.64 (m, 4H, aromatic H), 6.68 (ddd, J = 8.3, 2.3, 0.8 Hz, 1H, H-6′), 6.71 (ddd, J = 8.3, 2.2, 0.9 Hz, 1H, H-6″), 7.24 (t, J = 8.5 Hz, 1H, H-5′), 7.25 ppm (t, J = 8.1 Hz, 1H, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 19.3 (C-4‴), 25.4 (C-5‴), 30.5 (C-3‴), 55.3 (OCH_3), 62.2 (C-6‴), 65.7 (C-1), 67.5 (C-2), 99.0 (C-2‴), 105.0 (C-2′), 105.8 (C-2″), 109.0 (C-6′), 109.7 (C-4′), 111.1 (C-4″), 111.3 (C-6″), 130.0 (C-5′), 130.1 (C-5″), 158.1 (C-1″), 158.2 (C-3″), 160.2 (C-1′), 160.9 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{20}H_{24}O_5Na$: 367.1521 $[M+Na]^+$; found: 367.1516.

3-(3-Methoxyphenoxy)phenoxyethanol (40): A solution of **5** (852 mg, 2.5 mmol) in MeOH (10 mL) was treated with PPTS (30 mg). The mixture was stirred at room temperature overnight and was quenched as described in the method for the preparation of **11**. The product was purified by column chromatography (hexane/EtOAc 23:2) to give pure alcohol **40** (582 mg, 90%) as a colorless oil: R_f = 0.10 (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.01 (br s, 1H, O*H*), 3.94 (dist. t, J = 4.4 Hz, 2H, H-1), 3.78 (s, 3H, OCH_3), 4.04 (t, J = 4.5 Hz, 2H, H-2), 6.59 (m, 2H, aromatic H), 6.62 (m, 2H, aromatic H), 6.67 (dd, J = 8.1, 2.2 Hz, 2H, H-6′, H-6″), 7.22 ppm (t, J = 8.1 Hz, 2H, H-5′, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 61.4 (C-1), 69.2 (C-2), 105.1 (C-2′), 105.5 (C-2″), 109.1 (C-6′), 109.4 (C-4′), 111.2 (C-4″), 111.5 (C-6″), 130.1 (C-5′), 130.2 (C-5″), 158.1 (C-1″), 158.3 (C-3″), 159.9 (C-1′), 160.9 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{15}H_{17}O_4Na$: 283.0946 $[M+Na]^+$; found: 283.0941.

3-(3-Methoxyphenoxy)phenoxyethyl 4-toluenesulfonate (45): TsCl (1.28 g, 6.71 mmol) was added to a solution of **36** (582 mg, 2.24 mmol) in pyridine (3 mL) following the method for the preparation of **13**. The product was purified by column chromatography (silica gel, hexane/EtOAc 4:1) to give pure **45** (209 mg, 59%) as a colorless oil: R_f = 0.22 (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.43 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.10 (m, 2H, H-1), 4.35 (m, 2H, H-2), 6.43 (t, J = 2.4 Hz, 1H, H-2′), 6.53 (ddd, J = 8.2, 2.4, 0.6 Hz, 1H, aromatic H), 6.57 (m, 2H, aromatic H), 6.61 (ddd, J = 8.2, 2.2, 0.7 Hz, 1H, H-6′), 6.67 (dd, J = 8.1, 2.2 Hz, 1H, H-6″), 7.19 (t, J = 8.2 Hz, 1H, H-5′), 7.23 (t, J = 8.1 Hz, 1H, H-5″), 7.32 (d, J = 8.0 Hz, 2H, H-3‴), 7.81 ppm (d, J = 8.3 Hz, 2H, H-2‴); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 21.6 (PhCH_3), 55.4 (OCH_3), 65.5 (C-1), 68.0 (C-2), 105.1 (C-2′), 105.6 (C-2″), 109.1 (C-6′), 109.2 (C-4′), 111.2 (C-4″), 111.8 (C-6″), 128.0 (C-2‴), 129.8 (C-3‴), 130.15 (C-5′), 130.18 (C-5″), 132.8 (C-4‴), 145.0 (C-1‴), 158.1 (C-1″), 158.2 (C-3″), 159.2 (C-1′), 160.9 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{22}H_{23}O_6SNa$: 437.1035 $[M+Na]^+$; found: 437.1031.

3-(3-Methoxyphenoxy)phenoxyethyl thiocyanate (50): KSCN (397 mg, 4.1 mmol) was added to a solution of **15** (339 mg, 0.82 mmol) in DMF (3 mL). The mixture was treated as detailed in the method for the preparation of **15**. The product was purified by column chromatography (silica gel, hexane/EtOAc 19:1) to afford **50** (112 mg, 45%) as a colorless oil: R_f = 0.31 (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 3.32 (t, J = 5.8 Hz, 2H, H-1), 3.79 (s, 3H, OCH_3), 4.28 (t, J = 5.8 Hz, 2H, H-2), 6.58–6.62 (m, 3H, aromatic H), 6.65–6.69 (m, 3H, aromatic H), 7.24 ppm (dt, J = 8.2, 3.5 Hz, 2H, H-5′, H-5″); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 33.2 (C-1), 55.4 (OCH_3), 65.8 (C-2), 105.2 (C-2′), 105.6 (C-2″), 109.2 (C-6′), 109.4 (C-4′), 111.3 (C-4″), 111.7 (S*C*N), 112.1 (C-6″), 130.2 (C-5′), 130.4 (C-5″), 157.9 (C-1″), 158.4 (C-3″), 159.0 (C-1′), 161.0 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{16}H_{15}O_3NSNa$: 324.0670 $[M+Na]^+$; found: 324.0661.

3-(2-Pyridyloxy)phenoxyethyl Tetrahydro-2*H*-pyran-2-yl Ether (51): A mixture of **30** (1.051 g, 3.0 mmol), 2-hydroxypyridine (861 mg, 9.0 mmol), CuI (57.5 mg, 0.30 mmol), 2-picolinic acid (74.3 mg, 0.60 mmol), and K_3PO_4 (1.928 g, 9.0 mmol) in DMSO (3.0 mL) was treated as described in the method for the preparation of **9.** The product was purified by column chromatography (silica gel, hexane/EtOAc 2:3) to afford **51** (625 mg, 66%) as a colorless oil: $R_f = 0.49$ (EtOAc); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.53$–1.68 (m, 4H, H-4‴, H-5‴), 1.73–1.79 (m, 1H, H-3‴$_a$), 1.82–1.88 (m, 1H, H-3‴$_b$), 3.56 (m, 1H, H-6‴$_a$), 3.85 (ddd, $J = 11.3$, 6.2, 4.2 Hz, 1H, H-6‴$_b$), 3.92 (ddd, $J = 11.3$, 8.3, 3.1 Hz, 1H, H-1$_a$), 4.08 (ddd, $J = 11.3$, 5.0, 4.2 Hz, 1H, H-1$_b$), 4.20 (m, 2H, H-2), 4.72 (t, $J = 3.6$ Hz, 1H, H-2‴), 6.25 (dt, $J = 6.7$, 1.3 Hz, 1H, H-4″), 6.68 (dq, $J = 9.3$, 0.7 Hz, 1H, H-6′), 6.97–7.03 (m, 3H, aromatic H), 7.34 (ddd, $J = 6.9$, 2.1, 0.7 Hz, 1H, H-3″), 7.39–7.43 ppm (m, 2H, aromatic H); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 19.3$ (C-4‴), 25.4 (C-5‴), 30.5 (C-3‴), 62.2 (C-6‴), 65.7 (C-1), 67.7 (C-2), 99.0 (C-2‴), 105.8 (C-2′), 113.2 (C-6′), 115.1 (C-4′), 118.8 (C-6″), 122.0 (C-4″), 130.1 (C-5′), 137.8 (C-5″), 139.8 (C-3″), 141.9 (C-1″), 159.5 (C-3′,), 162.4 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{18}H_{22}O_4NNa$: 338.1368 $[M+Na]^+$; found: 338.1368.

3-(3-Pyridyloxy)phenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (52): A mixture of **30** (900 mg, 2.6 mmol), 3-hydroxypyridine (491 mg, 5.2 mmol), CuI (49.2 mg, 0.26 mmol), 2-picolinic acid (63.6 mg, 0.52 mmol), and K_3PO_4 (1.100 g, 5.2 mmol) in DMSO (3.0 mL) was stirred at 90 °C for 3 days. The product was purified by column chromatography (silica gel, hexane/EtOAc 83:17) to afford pure **52** (484 mg, 59%) as a colorless oil: $R_f = 0.09$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.50$–1.65 (m, 4H, H-4‴, H-5‴), 1.71–1.76 (m, 1H, H-3‴$_a$), 1.79–1.85 (m, 1H, H-3‴$_b$), 3.52 (m, 1H, H-6‴$_a$), 3.80 (ddd, $J = 11.2$, 6.4, 4.1 Hz, 1H, H-6‴$_b$), 3.89 (ddd, $J = 11.2$, 8.2, 3.1 Hz, 1H, H-1$_a$), 4.04 (m, 1H, H-1$_b$), 4.13 (m, 2H, H-2), 4.69 (t, $J = 3.7$ Hz, 1H, H-2‴), 6.60 (m, 2H, aromatic H), 6.73 (ddd, $J = 8.3$, 2.2, 0.9 Hz, 1H, H-6′), 7.23–7.32 (m, 3H, H-5″, H-6″), 8.37 (d, $J = 3.7$ Hz, 1H, H-4″), 8.41 ppm (d, $J = 2.4$ Hz, 1H, H-2″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 19.4$ (C-4‴), 25.4 (C-5‴), 30.5 (C-3‴), 62.2 (C-6‴), 65.7 (C-1), 67.6 (C-2), 99.0 (C-2‴), 105.8 (C-2′), 110.3 (C-6′), 111.2 (C-4′), 124.1 (C-6″), 125.6 (C-5″), 130.4 (C-5′), 141.6 (C-2″), 144.4 (C-4″), 153.7 (C-1″), 157.5 (C-1′), 160.4 ppm (C-3′).

3-(4-Pyridyloxy)phenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (53): A mixture of **30** (795 mg, 2.3 mmol), 4-hydroxypyridine (436 mg, 4.6 mmol), CuI (43.7 mg, 0.23 mmol), 2-picolinic acid (56.5 mg, 0.46 mmol), and K_3PO_4 (976 mg, 4.6 mmol) in DMSO (3.0 mL) was stirred at 90 °C for 2 days. The product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 97:3) to afford **53** (508 mg, 70%) as a colorless oil: $R_f = 0.14$ (CH_2Cl_2/MeOH 19:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.51$–1.65 (m, 4H, H-4‴, H-5‴), 1.72–1.78 (m, 1H, H-3‴$_a$), 1.79–1.86 (m, 1H, H-3‴$_b$), 3.54 (m, 1H, H-6‴$_a$), 3.84 (ddd, $J = 11.3$, 6.4, 4.0 Hz, 1H, H-6‴$_b$), 3.89 (ddd, $J = 11.3$, 8.3, 3.1 Hz, 1H, H-1$_a$), 4.10 (m, 1H, H-1$_b$), 4.21 (m, 2H, H-2), 4.70 (t, $J = 3.7$ Hz, 1H, H-2‴), 6.49 (d, $J = 7.7$ Hz, 2H, H-2″), 6.91 (m, 2H, H-2′, H-4′), 7.00 (ddd, $J = 8.3$, 2.1, 0.6 Hz, 1H, H-6′), 7.41 (t, $J = 8.5$ Hz, 1H, H-5′), 7.59 ppm (d, $J = 7.8$ Hz, 2H, H-3″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 19.4$ (C-4‴), 25.3 (C-5‴), 30.5 (C-3‴), 62.4 (C-6‴), 65.7 (C-1), 68.0 (C-2), 99.2 (C-2‴), 109.9 (C-2″), 114.4 (C-2′), 114.9 (C-6′), 119.0 (C-4′), 131.0 (C-5′), 139.0 (C-3″), 144.2 (C-3′), 159.4 (C-1′), 179.1 ppm (C-1″).

3-(2-Pyridyloxy)phenoxyethanol (54): A solution of **51** (575 mg, 1.82 mmol) in MeOH (10 mL) was treated with PPTS (30 mg) as described in the method for the preparation of **11.** The residue was purified by column chromatography (CH_2Cl_2/MeOH 49:1) to give pure alcohol **54** (281 mg, 67%) as a white solid: $R_f = 0.12$ (EtOAc); m.p. 95 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 2.04$ (br s, 1H, OH), 3.97 (dist. t, $J = 4.5$ Hz, 2H, H-1), 4.12 (dist. t, $J = 4.6$ Hz, 2H, H-2), 6.24 (dt, $J = 6.7$, 1.3 Hz, 1H, H-4″), 6.66 (dq, $J = 9.2$, 0.7 Hz, 1H, H-6′), 6.96–7.00 (m, 3H, aromatic H), 7.33 (ddd, $J = 6.9$, 2.1, 0.7 Hz, 1H, H-3″), 7.38–7.42 ppm (m, 2H, aromatic H); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 61.4$ (C-1), 69.5 (C-2), 105.8 (C-2′), 113.2 (C-6′), 115.0 (C-4′), 119.1 (C-6″), 122.0 (C-4″), 130.2 (C-5′), 137.8 (C-5″), 139.9 (C-3″), 142.0 (C-1″), 159.2 (C-3′,), 162.3 ppm (C-1′).

3-(3-Pyridyloxy)phenoxyethanol (55): A solution of **52** (477 mg, 1.51 mmol) in MeOH (3 mL) was treated with PPTS (30 mg). The mixture was stirred at room temperature overnight and was quenched as described in the method for the preparation of **13**. The product was purified by column chromatography (hexane/EtOAc 1:1) to give pure alcohol **55** (290 mg, 83%) as a colorless oil: $R_f = 0.14$ (hexane/EtOAc 1:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 2.07$ (br s, 1H, O*H*), 3.96 (m, 2H, H-1), 4.01 (t, $J = 4.5$ Hz, 2H, H-2), 6.60 (t, $J = 2.3$ Hz, 1H, H-2′), 6.62 (ddd, $J = 8.1$, 2.3, 0.7 Hz, 1H, H-4′), 6.72 (ddd, $J = 8.3$, 2.4, 0.6 Hz, 1H, H-6′), 7.24–7.33 (m, 3H, aromatic H), 8.38 (dd, $J = 4.5$, 1.4 Hz, 1H, H-4″), 8.42 ppm (d, $J = 2.7$ Hz, 1H, H-2″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 61.3$ (C-1), 69.3 (C-2), 105.6 (C-2′), 110.1 (C-6′), 111.4 (C-4′), 124.1 (C-6″), 125.8 (C-5″), 130.5 (C-5′), 141.6 (C-2″), 144.6 (C-4″), 153.6 (C-1″), 157.6 (C-1′), 160.1 ppm (C-3′).

3-(4-Pyridyloxy)phenoxyethanol (56): A solution of **53** (617 mg, 1.96 mmol) in MeOH (3 mL) was treated with PPTS (30 mg). The mixture was stirred at room temperature overnight and was quenched as described in the method for the preparation of **11**. The product was purified by column chromatography (CH_2Cl_2/MeOH 97:3) to give alcohol **56** (156 mg, 34%) as a white solid: $R_f = 0.45$ (EtOAc/MeOH 3:2); m.p. 117 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 2.02$ (t, $J = 6.2$ Hz, 1H, -O*H*), 4.02 (m, 2H, H-1), 4.15 (t, $J = 4.5$ Hz, 2H, H-2), 6.49 (d, $J = 7.8$ Hz, 2H, H-2″), 6.90 (t, $J = 2.3$ Hz, 1H, H-2′), 6.95 (ddd, $J = 7.9$, 2.2, 0.7 Hz, 1H, H-4′), 6.99 (ddd, $J = 8.4$, 2.4, 0.7 Hz, 1H, H-6′), 7.43 (t, $J = 8.2$ Hz, 1H, H-5′), 7.59 ppm (d, $J = 7.8$ Hz, 2H, H-3″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 61.3$ (C-1), 69.7 (C-2), 109.7 (C-2″), 114.2 (C-2′), 115.2 (C-6′), 119.0 (C-4′), 131.2 (C-5′), 138.9 ppm (C-3″).

3-(2-Pyridyloxy)phenoxyethyl 4-toluenesulfonate (57): TsCl (702 mg, 3.68 mmol) was added to a solution of **54** (284 mg, 1.22 mmol) in pyridine (3 mL), and the mixture was stirred at room temperature for 4 h, and quenched as described in the method for the preparation of **13**. The residue was purified by column chromatography (silica gel, hexane/EtOAc 35:75) to give pure **57** (289 mg, 61%) as a white solid: $R_f = 0.44$ (EtOAc); m.p. 157 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 2.44$ (s, 3H, PhC*H*$_3$), 4.17 (m, 2H, H-1), 4.37 (m, 2H, H-2), 6.24 (dt, $J = 6.7$, 1.3 Hz, 1H, H-4″), 6.65 (dq, $J = 9.3$, 0.6 Hz, 1H, H-6′), 6.82 (t, $J = 2.2$ Hz, 1H, H-2′), 6.86 (ddd, $J = 8.4$, 2.5, 0.8 Hz, 1H, H-6″), 6.96 (ddd, $J = 6.9$, 2.1, 0.7 Hz, 1H, H-5′), 7.30 (ddd, $J = 7.9$, 2.0, 0.9 Hz, 1H, H-3″), 7.34–7.41 (m, 2H, aromatic H), 7.36 (d, $J = 8.1$ Hz, 2H, H-3‴), 7.82 ppm (d, $J = 8.3$ Hz, 2H, H-2‴); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 21.6$ (Ph*C*H$_3$), 65.7 (C-1), 67.9 (C-2), 105.9 (C-2′), 113.3 (C-6′), 114.9 (C-4′), 119.4 (C-6″), 122.0 (C-4″), 128.0 (C-2‴), 129.9 (C-3‴), 130.2 (C-5′), 137.8 (C-5″), 139.9 (C-3″), 142.0 (C-1″), 145.0 (C-1‴), 158.6 (C-3′,), 162.3 ppm (C-1′).

3-(3-Pyridyl-3-yloxy)phenoxyethyl 4-toluenesulfonate (58): TsCl (994 mg, 5.21 mmol) was added to a solution of **55** (402 mg, 1.74 mmol) in pyridine (3 mL) as described in the method for the preparation of **13**. The product was purified by column chromatog-

raphy (silica gel, hexane/EtOAc 3:2) to give pure **58** (305 mg, 46%) as a colorless oil: $R_f = 0.69$ (EtOAc); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 2.44$ (s, 3H, PhCH_3), 4.13 (m, 2H, H-1), 4.36 (m, 2H, H-2), 6.45 (t, $J = 2.3$ Hz, 1H, H-2′), 6.60 (m, 2H, aromatic H), 7.29 (m, 3H, aromatic H), 7.33 (d, $J = 8.1$ Hz, 2H, H-3‴), 7.81 (d, $J = 8.3$ Hz, 2H, H-2‴), 8.38 (dd, $J = 4.1$, 1.5 Hz, 1H, H-4″), 8.40 ppm (d, $J = 1.9$ Hz, 1H, H-2″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 21.7$ (PhCH_3), 65.8 (C-1), 67.9 (C-2), 105.7 (C-2′), 109.9 (C-6′), 111.7 (C-4′), 124.1 (C-6″), 125.7 (C-5″), 128.0 (C-2‴), 129.9 (C-3‴), 130.5 (C-5′), 132.8 (C-4‴), 141.6 (C-2″), 144.6 (C-4″), 145.0 (C-1‴), 153.5 (C-1″), 157.5 (C-1′), 159.4 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{20}H_{20}O_5NS$ 386.1062 $[M+H]^+$; found: 386.1055.

3-(4-Pyridyloxy)phenoxyethyl bromide (59): Ph_3P (191 mg, 0.73 mmol) and NBS (129 mg, 0.73 mmol) were added to a mixture of alcohol **56** (153 mg, 0.62 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of H_2O (25 mL). Then, the mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic layer was washed with brine (3×50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 24:1) to give pure **59** (45.9 mg, 24%) as a white solid: $R_f = 0.34$ (EtOAc/MeOH 3:2); m.p. 68 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.67$ (t, $J = 6.1$ Hz, 2H, H-1), 4.35 (t, $J = 6.1$ Hz, 2H, H-2), 6.50 (d, $J = 7.8$ Hz, 2H, H-2‴), 6.90 (t, $J = 2.3$ Hz, 1H, H-2′), 6.97 (m, 2H, H-4′, H-6′), 7.44 (t, $J = 8.2$ Hz, 1H, H-5′), 7.59 ppm (d, $J = 7.8$ Hz, 2H, H-3″).

3-(2-Pyridyloxy)phenoxyethyl thiocyanate (60): KSCN (363 mg, 3.7 mmol) was added to a solution of **57** (288 mg, 0.75 mmol) in DMF (3 mL). The mixture was treated as described in the method for the preparation of **15.** The product was purified by column chromatography (silica gel, hexane/EtOAc 45:65) to afford **60** (141 mg, 69%) as a white solid: $R_f = 0.26$ (EtOAc); m.p. 142 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.35$ (t, $J = 5.8$ Hz, 2H, H-1), 4.35 (t, $J = 5.8$ Hz, 2H, H-2), 6.24 (dt, $J = 6.7$, 1.3 Hz, 1H, H-4″), 6.66 (dq, $J = 9.2$, 0.6 Hz, 1H, H-6′), 6.98–7.02 (m, 3H, aromatic H), 7.33 (ddd, $J = 6.9$, 2.1, 0.7 Hz, 1H, H-3″), 7.39–7.44 ppm (m, 2H, aromatic H); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 33.1$ (C-1), 66.0 (C-2), 106.0 (C-2′), 111.6 (SCN), 113.3 (C-6′), 115.0 (C-4′), 119.8 (C-6″), 122.0 (C-4″), 130.4 (C-5′), 137.8 (C-5″), 139.9 (C-3″), 142.1 (C-1″), 158.3 (C-3′,), 162.3 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{14}H_{12}O_2N_2SNa$: 295.0517 $[M+Na]^+$; found: 295.0516.

3-(3-Pyridyn-3-yloxy)phenoxyethyl thiocyanate (61): KSCN (309 mg, 3.2 mmol) was added to a solution of **58** (245 mg, 0.64 mmol) in DMF (3 mL). The mixture was treated according to the method for the preparation of **15**. The product was purified by column chromatography (silica gel, hexane/EtOAc 65:35) to afford **61** (73.5 mg, 64%) as a colorless oil: $R_f = 0.26$ (hexane/EtOAc 1:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.33$ (t, $J = 5.9$ Hz, 2H, H-1), 4.33 (t, $J = 5.8$ Hz, 2H, H-2), 6.61 (t, $J = 2.3$ Hz, 1H, H-2′), 6.65 (ddd, $J = 8.2$, 2.3, 0.7 Hz, 1H, H-4′), 6.72 (ddd, $J = 8.3$, 2.3, 0.6 Hz, 1H, H-6′), 7.27–7.34 (m, 3H, aromatic H), 8.38 (dd, $J = 4.6$, 1.4 Hz, 1H, H-4″), 8.42 ppm (d, $J = 2.7$ Hz, 1H, H-2″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 33.2$ (C-1), 65.9 (C-2), 105.8 (C-2′), 110.0 (C-6′), 111.6 (SCN), 112.0 (C-4′), 124.1 (C-6″), 125.8 (C-5″), 130.7 (C-5′), 141.7 (C-2″), 144.7 (C-4″), 153.4 (C-1″), 157.7 (C-1′), 159.2 ppm (C-3′); HRMS (ESI): *m/z*: calcd for $C_{14}H_{13}O_2N_2S$ 273.0698 $[M+H]^+$; found: 273.0702.

3-(4-Pyridyloxy)phenoxyethyl thiocyanate (62): KSCN (75.8 mg, 0.78 mmol) was added to a solution of **57** (45.9 mg, 0.16 mmol) in DMF (3.0 mL). The mixture was treated as described in the method for the preparation of **15**. The product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 24:1) to afford **62** (37.0 mg, 87%) as a white solid: $R_f = 0.67$ (EtOAc/MeOH 3:2); m.p. 52 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.37$ (t, $J = 5.7$ Hz, 2H, H-1), 4.39 (t, $J = 5.7$ Hz, 2H, H-2), 6.49 (d, $J = 7.8$ Hz, 2H, H-2″), 6.93 (t, $J = 2.3$ Hz, 1H, H-2′), 7.00 (m, 2H, H-4′, H-6′), 7.46 (t, $J = 8.2$ Hz, 1H, H-5′), 7.60 ppm (d, $J = 7.8$ Hz, 2H, H-3″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 33.0$ (C-1), 66.3 (C-2), 109.9 (C-2″), 111.4 (SCN), 113.9 (C-2′), 115.9 (C-6′), 119.0 (C-4′), 131.3 (C-5′), 138.9 (C-3″), 144.3 (C-3′), 159.0 (C-1′), 179.0 ppm (C-1″); HRMS (ESI): *m/z*: calcd for $C_{14}H_{13}O_2N_2S$ 273.0698 $[M+H]^+$; found: 273.0704.

4-Phenoxyphenoxyethyl azide (64): NaN_3 (213 mg, 3.28 mmol) was added to a solution of **63** (252 mg, 0.66 mmol) in DMF (3 mL). The mixture was heated at 100 °C for 3 h. The mixture was allowed to cool to room temperature and H_2O (20 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (2×30 mL), and the combined organic layer was washed with brine (5×30 mL) and H_2O (2×30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (silica gel, hexane) to give pure **64** (59.5 mg, 35%) as a colorless oil: $R_f = 0.44$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.60$ (t, $J = 5.0$ Hz, 2H, H-1), 4.14 (t, $J = 5.0$ Hz, 2H, H-2), 6.91 (d, $J = 9.1$ Hz, 2H, H-2′), 6.95 (m, 2H, aromatic H), 6.99 (d, $J = 9.2$ Hz, 2H, H-3′), 7.05 (tt, $J = 7.4$, 1.1 Hz, 1H, H-4″), 7.30 ppm (m, 2H, aromatic H); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 50.2$ (C-1), 67.5 (C-2), 115.7 (C-2″), 117.7 (C-2′), 120.8 (C-3′), 122.6 (C-4″), 129.6 (C-3″), 150.8 (C-4′), 154.4 (C-1′), 158.3 ppm (C-1″); HRMS (ESI): *m/z*: calcd for $C_{14}H_{13}O_2N_3Na$: 278.0905 $[M+Na]^+$; found: 278.0892.

2,4-Dibromophenoxyethyl tetrahydro-2*H*-pyran-2-yl ether (65): A solution of 2,4-dibromophenol (1.5 g, 5.95 mmol) in DMSO (5 mL) was treated with KOH (668 mg, 11.9 mmol) and bromoethyl tetrahydropyranyl ether (1.24 g, 5.95 mmol) as described in the method for the preparation of **7**. The residue was purified by column chromatography (silica gel, hexane/EtOAc 19:1) to afford pure **65** (293 mg, 46%) as a colorless oil: $R_f = 0.43$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.51$–1.63 (m, 4H, H-4‴, H-5‴), 1.71–1.77 (m, 1H, H-3‴$_a$), 1.80–1.84 (m, 1H, H-3‴$_b$), 3.53 (m, 1H, H-6‴$_a$), 3.86 (ddd, $J = 11.0$, 5.9, 5.1 Hz, 1H, H-6‴$_b$), 3.92 (ddd, $J = 11.3$, 8.5, 2.9 Hz, 1H, H-1$_a$), 4.07 (m, 1H, H-1$_b$), 4.19 (m, 2H, H-2), 4.77 (t, $J = 3.6$ Hz, 1H, H-2‴), 6.82 (d, $J = 8.8$ Hz, 1H, H-6′), 7.35 (dd, $J = 8.7$, 2.4 Hz, 1H, H-5′), 7.66 ppm (d, $J = 2.4$ Hz, 1H, H-2′); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 19.2$ (C-4‴), 25.4 (C-5‴), 30.5 (C-3‴), 62.1 (C-6‴), 65.4 (C-1), 69.1 (C-2), 99.0 (C-2‴), 113.1 (C-4′), 113.2 (C-2′), 114.8 (C-6′), 131.1 (C-5′), 135.5 (C-3′), 154.8 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{13}H_{16}O_3Br_2Na$: 400.9364 $[M+Na]^+$; found: 400.9370.

2,4-Dibromophenoxyethanol (66): A solution of **65** (1.04 g, 2.74 mmol) in MeOH (10 mL) was treated with PPTS (30 mg). The mixture was stirred at room temperature overnight and was quenched as described in the method for the preparation of **6**. The product was purified by column chromatography (hexane/EtOAc 43:7) to give pure alcohol **66** (568 mg, 70%) as a white solid: $R_f = 0.14$ (hexane/EtOAc 4:1); m.p. 59 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 2.15$ (t, $J = 6.5$ Hz, 1H, O*H*), 3.99 (dt, $J = 6.2$, 4.6 Hz, 2H, H-1), 4.12 (t, $J = 4.5$ Hz, 2H, H-2), 6.80 (d, $J = 8.7$ Hz, 1H, H-6′), 7.38 (dd, $J = 8.7$, 2.4 Hz, 1H, H-5′), 7.68 ppm (d, $J = 2.4$ Hz, 1H, H-2′); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 61.2$ (C-1), 71.0 (C-2), 113.4 (C-4′), 113.6 (C-2′), 114.9 (C-6′), 131.3 (C-5′), 135.6 (C-3′), 154.3 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_8H_8O_2Br_2Na$: 316.8789 $[M+Na]^+$; found: 316.8773.

2,4-Dibromophenoxyethyl 4-toluenesulfonate (67): TsCl (1.10 g, 5.76 mmol) was added to a solution of **66** (568 mg, 1.92 mmol) in

pyridine (3 mL) as described in the method for the preparation of **13**. The product was purified by column chromatography (silica gel, hexane/EtOAc 9:1) to give pure **67** (725 mg, 84%) as a colorless oil: $R_f = 0.33$ (hexane/EtOAc 4:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta =$ 2.44 (s, 3H, PhCH_3), 4.22 (m, 2H, H-1), 4.42 (m, 2H, H-2), 6.71 (d, $J =$ 8.8 Hz, 1H, H-6′), 7.350 (d, $J = 8.7$, 2H, H-3″), 7.353 (dd, $J = 8.5$, 2.4 Hz, 1H, H-5′), 7.66 (d, $J = 2.4$ Hz, 1H, H-2′), 7.84 ppm (d, $J = 8.3$, 2H, H-3″); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 21.7$ (PhCH_3), 66.8 (C-1), 67.6 (C-2), 113.4 (C-4′), 114.0 (C-2′), 114.8 (C-6′), 128.0 (C-2″), 129.9 (C-3″), 131.2 (C-5′), 132.6 (C-4″), 135.7 (C-3′), 145.0 (C-1″), 153.8 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{15}H_{14}O_4SBr_2Na$: 470.8877 $[M+Na]^+$; found: 470.8864.

2,4-Dibromophenoxyethyl thiocyanate (68): KSCN (782 mg, 8.05 mmol) was added to a solution of **67** (725 mg, 1.61 mmol) in DMF (3 mL). The mixture was treated as described in the method for the preparation of **15**. The product was purified by column chromatography (silica gel, hexane/EtOAc 23:2) to afford **68** (405 mg, 75%) as a white solid: $R_f = 0.34$ (hexane/EtOAc 4:1); m.p. 85 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.39$ (t, $J = 5.9$ Hz, 2H, H-1), 4.34 (t, $J = 5.9$ Hz, 2H, H-2), 6.81 (d, $J = 8.7$ Hz, 1H, H-6′), 7.40 (dd, $J = 8.7$, 2.4 Hz, 1H, H-5′), 7.70 ppm (d, $J = 2.4$ Hz, 1H, H-2′); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 33.0$ (C-1), 67.3 (C-2), 111.5 (SCN), 113.5 (C-4′), 114.5 (C-2′), 115.1 (C-6′), 131.4 (C-5′), 135.9 (C-3′), 153.6 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_9H_7ONSBr_2Na$: 357.8513 $[M+Na]^+$; found: 357.8508.

3-Pyridyloxyethyl tetrahydro-2*H*-pyran-2-yl ether (69): A solution of 3-hydroxypyridine (1 g, 10.5 mmol) in DMSO (5 mL) was treated with KOH (1.18 g, 21.0 mmol). The suspension was stirred for 30 min at room temperature. Then, bromoethyl tetrahydropyranyl ether (2.20 g, 10.5 mmol) was added, and the mixture was stirred at room temperature overnight. The mixture was partitioned between CH_2Cl_2 (30 mL) and H_2O (30 mL). The aqueous phase was extracted with CH_2Cl_2 (2×70 mL). The combined organic layer was washed with a saturated solution of NaCl (2×100 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc 7:3) to afford pure **69** (736 mg, 31%) as a yellow oil: $R_f = 0.26$ (hexane/EtOAc 1:1); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta =$ ^{1}H NMR (500.13 MHz, $CDCl_3$) $\delta =$ 1.52–1.65 (m, 4H, H-4‴, H-5‴), 1.71–1.77 (m, 1H, H-3‴$_a$), 1.81–1.85 (m, 1H, H-3‴$_b$), 3.53 (m, 1H, H-6‴$_a$), 3.83 (ddd, $J = 11.4$, 6.3, 3.9 Hz, 1H, H-6‴$_b$), 3.89 (ddd, $J = 11.2$, 8.1, 3.2 Hz, 1H, H-1$_a$), 4.08 (ddd, $J =$ 11.4, 5.2, 4.0 Hz, 1H, H-1$_b$), 4.12 (m, 2H, H-2), 4.71 (t, $J = 3.6$ Hz, 1H, H-2‴), 7.23 (m, 2H, aromatic H), 8.24 (dd, $J = 4.4$, 1.5 Hz, 1H, H-4′), 8.34 ppm (t, $J = 2.7$ Hz, 1H, H-2′); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta =$ 19.3 (C-4″), 25.3 (C-5″), 30.4 (C-3″), 62.2 (C-6″), 65.7 (C-1), 67.7 (C-2), 99.1 (C-2‴), 121.2 (C-6′), 123.9 (C-5′), 138.0 (C-2′), 142.5 (C-4′), 154.9 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_{12}H_{18}O_3N$ 224.1287 $[M+H]^+$; found: 224.1291.

3-Pyridyloxyethanol (70): A solution of **69** (725 mg, 3.25 mmol) in MeOH (3 mL) was treated with PTSA (30 mg). The mixture treated as detailed in the method for the preparation of **11**. The product was purified by column chromatography (hexane/EtOAc 3:7) to give pure alcohol **70** (304 mg, 67%) as a yellow oil: $R_f = 0.19$ (EtOAc); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 2.34$ (br s, 1H, O*H*), 4.00 (dist. t, $J = 4.8$ Hz, 2H, H-1), 4.14 (dist. t, $J = 4.1$ Hz, 2H, H-2), 7.23 (m, 2H, aromatic H), 8.24 (t, $J = 3.0$ Hz, 1H, H-4′), 8.34 ppm (t, $J =$ 1.8 Hz, 1H, H-2′); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 61.3$ (C-1), 69.6 (C-2), 121.2 (C-6′), 123.9 (C-5′), 138.0 (C-2′), 142.5 (C-4′), 154.9 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_7H_{10}O_2N$ 140.0712 $[M+H]^+$; found: 140.0710.

3-Pyridyloxyethyl 4-toluenesulfonate (71): TsCl (1.25 g, 6.54 mmol) was added to a solution of **70** (303 mg, 2.18 mmol) in pyridine (3 mL) as described in the method for the preparation of **13**. The product was purified by column chromatography (silica gel, hexane/EtOAc 13:7) to give pure **71** (441 mg, 69%) as a colorless oil: $R_f = 0.48$ (EtOAc); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 2.45$ (s, 3H, PhCH_3), 4.21 (m, 2H, H-1), 4.40 (m, 2H, H-2), 7.24 (m, 2H, aromatic H), 7.35 (d, $J = 8.0$, 2H, H-3″), 7.82 (d, $J = 8.4$, 2H, H-3″), 8.22 (d, $J = 3.0$ Hz, 1H, H-2′), 8.25 ppm (dd, $J = 4.7$, 1.3 Hz, 1H, H-4′); HRMS (ESI): *m/z*: calcd for $C_{14}H_{16}O_4NS$ 294.0800 $[M+H]^+$; found: 294.0798.

3-Pyridyloxyethyl thiocyanate (72): KSCN (683 mg, 7.04 mmol) was added to a solution of **71** (413 mg, 1.41 mmol) in DMF (3 mL). The mixture was treated as detailed in the method for the preparation of **15**. The product was purified by column chromatography (silica gel, hexane/EtOAc 7:3) to afford **72** (107 mg, 42%) as a colorless oil: $R_f = 0.38$ (EtOAc); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.37$ (t, $J = 5.8$ Hz, 2H, H-1), 4.38 (t, $J = 5.8$ Hz, 2H, H-2), 7.25 (m, 2H, aromatic H), 8.30 (dd, $J = 4.0$, 2.0 Hz, 1H, H-4′), 8.35 ppm (m, 1H, H-2′); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 33.1$ (C-1), 66.1 (C-2), 111.4 (SCN), 121.5 (C-6′), 124.0 (C-5′), 137.9 (C-2′), 143.3 (C-4′), 154.1 ppm (C-1′); HRMS (ESI): *m/z*: calcd for $C_8H_8ON_2SNa$: 203.0255 $[M+Na]^+$; found: 203.0255.

Drug screening

***T. cruzi* amastigote assays**: These experiments were done as reported by using tdTomato labeled trypomastigotes[31] with the modifications described by Recher et al.[32] ED_{50} values were determined by nonlinear regression analysis by using SigmaPlot.

***T. gondii* tachyzoites assays**: Experiments on *T. gondii* tachyzoites were performed as described previously[33] by using *T. gondii* tachyzoites expressing red fluorescent protein[34] with the modifications described by Recher et al.[32] Plates were read with covered lids, and both excitation (544 nm) and emission (590 nm) were read from the bottom.

Cytotoxicity toward Vero cells: The cytotoxicity was tested by using the Alamar Blue assay, as described by Recher et al.[32]

Acknowledgements

This work was supported by grants from the National Research Council of Argentina (PIP 0797), Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT) (PICT 2012 #0457), and the Universidad de Buenos Aires (20020130100223BA) to J.B.R., the Bunge & Born Foundation to S.H.S, and the US National Institutes of Health to R.D. (AI-107663) and S.N.J.M. (AI-102254).

Keywords: antiparasitic agents · biological activity · chemotherapeutic agents · inhibitors · structure–activity relationships

[1] J. A. Urbina, *Parasitology* **1997**, *114*, S91 – S99.
[2] J. A. Urbina, *Curr. Pharm. Des.* **2002**, *8*, 287 – 295.
[3] F. S. Buckner, J. A. Urbina, *Int. J. Parasitol. Drugs Drug Resist.* **2012**, *2*, 236 – 242.
[4] G. I. Lepesheva, F. Villalta, M. R. Waterman, *Adv. Parasitol.* **2011**, *75*, 65 – 87.

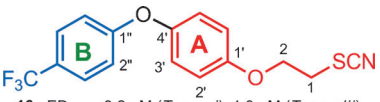
[5] R. Docampo, G. Schmuñis, *Parasitol. Today* **1997**, *13*, 129 – 130.
[6] J. A. Urbina, J. L. Concepción, S. Rancel, G. Bisbal, R. Lira, *Mol. Biochem. Parasitol.* **2002**, *125*, 35 – 45.
[7] J. A. Urbina, G. Payares, J. Molina, C. Sanoja, A. Liendo, K. Lazardi, M. M. Piras, R. Piras, N. Perez, P. Wincker, J. F. Ryley, *Science* **1996**, *273*, 969 – 971.
[8] G. M. Cinque, S. H. Szajnman, L. Zhong, R. Docampo, A. J. Schvartzapel, J. B. Rodriguez, E. G. Gros, *J. Med. Chem.* **1998**, *41*, 1540 – 1554.
[9] S. H. Szajnman, W. Yan, B. N. Bailey, R. Docampo, E. Elhalem, J. B. Rodriguez, *J. Med. Chem.* **2000**, *43*, 1826 – 1840.
[10] E. Elhalem, B. N. Bailey, R. Docampo, I. Ujváry, S. H. Szajnman, J. B. Rodriguez, *J. Med. Chem.* **2002**, *45*, 3984 – 3999.
[11] J. A. Urbina, J. L. Concepcion, A. Montalvetti, J. B. Rodriguez, R. Docampo, *Antimicrob. Agents Chemother.* **2003**, *47*, 2047 – 2050.
[12] J. L. Concepcion, D. Gonzalez-Pacanowska, J. A. Urbina, *Arch. Biochem. Biophys.* **1998**, *352*, 114 – 120.
[13] S. C. Nair, C. F. Brooks, C. D. Goodman, A. Sturm, G. I. McFadden, S. Sundriyal, J. L. Anglin, Y. Song, S. N. Moreno, B. Striepen, *J. Exp. Med.* **2011**, *208*, 1547 – 1559.
[14] I. Coppens, A. P. Sinai, K. A. Joiner, *J. Cell Biol.* **2000**, *149*, 167 – 180.
[15] P. Grellier, A. Valentin, V. Millerioux, J. Schrevel, D. Rigomier, *Antimicrob. Agents Chemother.* **1994**, *38*, 1144 – 1148.
[16] B. Pradines, M. Torrentino-Madamet, A. Fontaine, M. Henry, E. Baret, J. Mosnier, S. Briolant, R. Fusai, C. Rogier, *Antimicrob. Agents Chemother.* **2007**, *51*, 2654 – 2655.
[17] K. Bessoff, A. Sateriale, K. K. Lee, C. D. Huston, *Antimicrob. Agents Chemother.* **2013**, *57*, 1804 – 1814.
[18] E. Cortez, A. C. Stumbo, M. Olieveira, H. S. Barbosa, L. Carvalho, *Int. J. Antimcrob. Agents* **2009**, *33*, 185 – 186.
[19] Z. H. Li, S. Ramakrishnan, B. Striepen, S. N. Moreno, *PLoS Pathog.* **2013**, *9*, e1003665.
[20] F. Y. Lin, Y. L. Liu, K. Li, R. Cao, W. Zhu, J. Axelson, R. Pang, E. Oldfield, *J. Med. Chem.* **2012**, *55*, 4367 – 4372.
[21] N. Shang, Q. Li, T. P. Ko, H. C. Chan, J. Li, Y. Zheng, C. H. Huang, F. Ren, C. C. Chen, Z. Zhu, M. Galizzi, Z. H. Li, C. A. Rodrigues-Poveda, D. Gonzalez-Pacanowska, P. Veiga-Santos, T. M. de Carvalho, W. de Souza, J. A. Urbina, A. H. Wang, R. Docampo, K. Li, Y. L. Liu, E. Oldfield, R. T. Guo, *PLoS Pathog.* **2014**, *10*, e1004114.
[22] A. J. Schvartzapel, L. Zhong, R. Docampo, J. B. Rodriguez, E. G. Gros, *J. Med. Chem.* **1997**, *40*, 2314 – 2322.
[23] G. García Liñares, S. Gismondi, N. Osa Codesido, S. N. J. Moreno, R. Docampo, J. B. Rodriguez, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5068 – 5071.
[24] P. D. Elicio, M. N. Chao, M. Galizzi, C. Li, S. H. Szajnman, R. Docampo, S. N. J. Moreno, J. B. Rodriguez, *Eur. J. Med. Chem.* **2013**, *69*, 480 – 489.
[25] G. E. G. Linares, E. L. Ravaschino, J. B. Rodriguez, *Curr. Med. Chem.* **2006**, *13*, 335 – 360.
[26] a) D. Maiti, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 17423 – 17429; b) B. Bhayana, B. P. Fors, S. L. Buchwald, *Org. Lett.* **2009**, *11*, 3954 – 3957; c) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552 – 13554.
[27] a) D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett.* **1998**, *39*, 2937 – 2940; b) D. M. T. Chan, K. L. Monaco, R.-P. Wang, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933 – 2936.
[28] A. J. Schvartzapel, L. Fichera, M. Esteva, J. B. Rodriguez, E. G. Gros, *Helv. Chim. Acta* **1995**, *78*, 1207 – 1214.
[29] J. A. H. Inkster, K. Liu, S. Ait-Mohand, P. Schaffer, B. Guérin, T. J. Ruth, T. Storr, *Chem. Eur. J.* **2012**, *18*, 11079 – 11087.
[30] B. Imperiali, R. S. Roy, *J. Org. Chem.* **1995**, *60*, 1891 – 1894.
[31] A. M. Canavaci, J. M. Bustamante, A. M. Padilla, C. M. Pereza Brandan, L. J. Simpson, D. Xu, C. L. Boehlke, R. L. Tarleton, *PLoS Neglected Trop. Dis.* **2010**, *4*, e740.
[32] M. Recher, A. P. Barboza, Z.-H. Li, M. Galizzi, M. Ferrer-Casal, S. H. Szajnman, R. Docampo, S. N. Moreno, J. B. Rodriguez, *Eur. J. Med. Chem.* **2013**, *60*, 431 – 440.
[33] M. J. Gubbels, C. Li, B. Striepen, *Antimicrob. Agents Chemother.* **2003**, *47*, 309 – 316.
[34] S. Agrawal, G. G. van Dooren, W. L. Beatty, B. Striepen, *J. Biol. Chem.* **2009**, *284*, 33683 – 33691.

Received: March 4, 2015
Published online on ■■ ▮▮, 0000

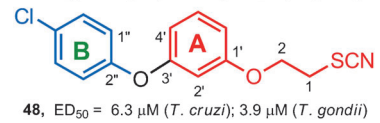
*M. N. Chao, C. E. Matiuzzi, M. Storey, C. Li, S. H. Szajnman, R. Docampo, S. N. J. Moreno, J. B. Rodriguez**

■■ – ■■

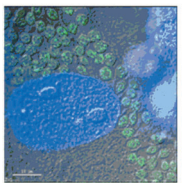
Aryloxyethyl Thiocyanates Are Potent Growth Inhibitors of *Trypanosoma cruzi* and *Toxoplasma gondii*



16, ED_{50} = 9.2 μM (*T. cruzi*); 1.9 μM (*T. gondii*)



48, ED_{50} = 6.3 μM (*T. cruzi*); 3.9 μM (*T. gondii*)



T. cruzi amastigotes (marked with GFP) inside a cell

Finding the WC: WC-9 is a well-known antichagasic agent targeting squalene synthase. We describe the design, synthesis, and biological evaluation of WC-9 analogues bearing the aryloxy moiety bonded either at the C-4′ or the C-3′ position of the A ring. Some of the analogues are effective growth inhibitors of both *Trypanosoma cruzi* and *Toxoplasma gondii*, the etiologic agents of Chagas disease and toxoplasmosis, respectively.