Aryloxyethyl Thiocyanates are Potent Growth Inhibitors of Trypanosoma cruzi and Toxoplasma gondii

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Abstract

As a part of our project aimed at searching new safe chemotherapeutic agents against parasitic diseases, several compounds structurally related to the antiparasitic agent WC-9 (4-phenoxyphe-noxyethyl 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 being slightly more potent than our lead WC-9. For example, the trifluoromethyl derivatives 15 and 16 exhibited ED₅₀ values of 10.0 μM and 9.2 μM, respectively, against intracellular T. cruzi, whereas they showed potent action against tachyzoites of T. gondii (ED₅₀ values 1.6 μM and 1.9 μM against T. gondii, respectively). In addition, the WC-9 analogues 48 and 61, in which the terminal aryl group was meta 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 suggesting that para-phenyl substitution pattern is not necessarily required for biological activity.

Graphical Abstract

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

**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 (compound 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] In addition, the growth inhibitory effects of WC-9 are associated with a depletion of the parasite endogenous sterols, ergosterol and its 24-ethyl analogue with no accumulation of sterol intermediates or precursors indicating a blockade of the biosynthetic pathway at a pre-squalene level.[11]

Squalene synthase (SQS) is a crucial enzyme in isoprenoid biosynthesis, which catalyzes the first committed step in ergosterol biosynthesis, where a 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 an inhibitor of the enzymatic activity of *T cruzi* SQS,[11] employing as enzyme source highly purified glycosomes and mitochondrial membrane vesicles obtained from *T. cruzi* epimastigotes.[12] WC-9 is a potent inhibitor of both glycosomal and mitochondrial *T. cruzi* SQS, with IC$_{50}$ values of 88 nM and 129 nM. The dose-response curves for the activity of WC-9 against *Tc*SQS were consistent with non-competitive inhibition with $K_i = IC_{50}$; these $K_i$ values are two to three orders of magnitude lower that the $K_m$ of the substrates.[11]

Apicomplexan parasite such as *Toxoplasma gondii*, the responsible agent of toxoplasmosis, lacks the mevalonate pathway and uses a prokaryotic-type 1-deoxy-D-xylulose-5-phosphate (DOXP) pathway instead to make IPP and DMAPP. The DOXP pathway localizes to the apicoplast and is essential.[13] It has been demonstrated that *T. gondii* does not synthesize cholesterol and imports it from the host,[14] suggesting that inhibitors of the host SQS could potentially inhibit *T. gondii* growth. The fact that WC-9 and closely related analogues were growth inhibitor of *T. gondii* is quite in agreement with other authors 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]* indicating that these parasites, which lack the mevalonate pathway, are dependent on host biosynthesis of precursors of the isoprenoid pathway. In this regard, it has recently been demonstrated that *T. gondii* acquires isoprenoid intermediates like farnesyl diphosphate and/or geranylgeranyl diphosphate from the host cell produced by the mevalonate pathway.[19]
Rationale

To date the crystal structure of TcSQS with WC-9 is not available. However, the X-ray crystallographic structure of WC-9 bound to dehydrosqualene synthase (CrtM) 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 TcSQS as it does in dehydrosqualene synthase keeping the same polar interactions with the thiocyanate group.\[^{20}\] Besides, lately it was possible to obtain crystals of WC-9 bound to human SQS but all the attempts to do so with TcSQS were unsuccessful.\[^{21}\]

Based on WC-9 chemical structure, we have conducted a meticulous structure activity / biological activity relationship studies that lead 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 ketoconazole, 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 at the B ring of WC-9 had a marked influence on biological activity encouraged us to follow this approach. As a matter of fact, the introduction of a fluorine atom at the B ring of WC-9 gives rise to compounds 2 and 3, which have estimated log P values of 4.71 versus log P of 4.51 for WC-9, indicating a better distribution between water/ octanol. In fact, both of these compounds, 2 and 3, are 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 in order to design rationally more effective non-competitive inhibitors structurally related to WC-9.

The Buchwald coupling reaction has proven to be a reliable method to prepare asymmetric substituted diaryl ethers or even diaryl amines.\[^{26}\] Certainly, a variety of WC-9 analogues bearing different substituents either at the A ring or B ring has been prepared employing this protocol,\[^{24}\] which is a reliable alternate method to get these type of compounds 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 at the B ring as well as the relative position of the B ring to the aliphatic chain. The introduction of an electron withdrawing moiety at the B ring such as the trifluoromethyl group was the first structural modification considered. Then, employing commercially available 4-(benzyl oxy)phenol (6), this compound was converted into the tetrahydropyranyl ether derivative 7 in 96% yield by treatment with 2-bromoethyl tetrahydro-2H-pyran-2-yl ether in a suspension of potassium hydroxide in dimethyl...
sulfoxide, following to a slightly modified Williamson reaction. Removal of the protecting benzyl group was carried out by treatment with hydrogen at 3 atm and room temperature, in the presence of palladium on charcoal, to afford phenol 8 in 73% yield, which on 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 produced the conveniently functionalized diaryl ether 9 in 86% yield. Buchwald coupling reaction between 8 and 1-iodo-4-(trifluoromethyl)benzene gave 10 in 32% yield. Compound 9 was deprotected by treatment with pyridinium p-toluenesulfonate in methanol to afford the corresponding free alcohol 11 in 62% yield, which, in turned, was treated with tosyl chloride in pyridine to give tosylate 13 in 86% yield. 13 was further transformed into the thiocyanate derivative 15 by treatment with potassium thiocyanate in N,N-dimethylformamide at 100 °C in 36% yield (Scheme 2). In a similar strategy, 10 was transformed into alcohol 12, which was reacted with tosyl chloride to give 14, which was finally transformed into the title compound 16 by treatment with potassium thiocyanate as illustrated in Scheme 2.

In order to study the influence of the polarity of the terminal phenyl group, it was conceived the replacement of this ring by a naphtyl group giving rise to title compounds 20 and 24, whose estimated log P values were both 5.2 versus 4.2 corresponding to the WC-9 molecule. Buchwald coupling reaction of 8 either with 2-bromonaphtalene or 1-bromonaphtalene afforded the diaryl ether derivatives 17 and 21 in low but reproducible yields of 18% and 32%, respectively. Following the general strategy each tetrahydropyranyl protecting group present in 17 and 21 was cleaved by treatment with pyridinium p-toluenesulfonate affording the corresponding free alcohols 18 and 22 in good yields, which were tosylated to give 19 and 23. On treatment with potassium thiocyanate, in separate experiments, these compounds were converted into the target molecules 20 and 24, respectively, as illustrated in Scheme 2.

We have recently described a pyridyl analogue of WC-9 where the nitrogen atom occupied the 3″ position. In order to complete the structure / activity analysis it was decided to prepare the corresponding pyridyl derivative where the nitrogen atom was placed at the C-2″ position giving rise to the target molecule 29. The incorporation of the pyridyl unit was carried out through a Buchwald coupling reaction between the already depicted 4-iodophenoxyethyl tetrahydro-2H-pyran-2-yl ether (25) with 2-hydrozypyridine to produce tetrahydro pyranyl derivative 26 in 48% yield. Once this adduct was at hand, and similarly to the preparation of 16 and 17, cleavage of tetrahydropyranyl protecting group of 26 to give free alcohol 27, followed by tosylation to produce 28, and further substitution of the tosylate group by the thiocyanate ion afforded the title compound 29 in reaction yields of 60%, 90%, and 61%, respectively (Scheme 3).

At the present time it is not conclusive which one is the optimal relative position of terminal phenyl of WC-9. We have recently demonstrated that analogues where the phenyl group was at the C-3′ position exhibited antiparasitic activity almost of the same efficacy as those compounds bearing this group at the C-4′ position. Therefore, it was conceived several regioisomers of WC-9 bearing different either chlorine or a methoxy group at diverse positions of the terminal ring such as 46–50. The synthetic strategy to obtain these
compounds is presented in Scheme 4 employing the already described 3-iodophenoxyethyl tetrahydro-2H-pyran-2-yl ether (30) as a common starting material.[24] This compound was reacted with five substituted phenols like 2-chloro, 3-chloro, 4-chloro, 2-methoxy, and 3-methoxyphenol under the usual Buchwald coupling procedures giving rise to the expected asymmetric diaryl ethers 31–35 in a range from moderate to good yields. Then, following the general method in individual experiments, each of these compounds suffered from tetrahydropyranyl cleavage to give 36–40, further tosylation to form tosylates 41–45 and nucleophilic displacement of the tosylate group by treatment with potassium thiocyanate to afford the expected regioisomers of WC-9, that is, compounds 46–50, respectively (Scheme 4).

Pyridyl regioisomers analogues of WC-9 such as 60–62 were other interesting structural variations considered yielding polar compounds (estimated log P = 2.82) and keeping the pharmacophore into the molecules. In this case, the synthesis of the title compounds was not straightforward, particularly, for the preparation of 62 as will be discussed later. Then, compound 30 was used as a committed starting material, which, on separate experiments, was reacted with 2-hydroxy-, 3-hydroxy-, and 4-hydroxypyridine under Buchwald coupling reaction conditions to give rise to coupled products 51–53 in moderate yields, which were easily deprotected by treatment with pyridinium p-toluenesulfonate to yield the corresponding free alcohols 54–56. On treatment with excess of tosyl chloride 54 and 55 were converted into tosylates 57 and 58, respectively; while the corresponding tosylate of alcohol 56 could not be obtain due to formation of a toslypyridinium ion, which not only consumes reagent, but also forms an extremely polar species that hinders the reaction.[29] This problem was circumvented by the preparation of the bromide derivative 59. Then, on treatment with N-bromosuccinimide and triphenylphosphine 56 was converted into 69.[30] The title compounds 60–62 were obtained by treatment of tosylates 57 and 58, or bromine 59 with potassium thiocyanate in good yields (Scheme 5).

The thiocyanate group in WC-9 and other closely related analogues seems to be essential for biological activity. In order to study the influence of this group on biological action it was considered to replace it by other electrophilic group such as the azido moiety. Thus, the already described tosylate 63, treated with sodium azide in N,N-dimethylformamide afforded the title compound 64 (Scheme 6).

Previous biological data had indicated that a simplified analogue of WC-9 (2,4-dichlorophenoxyethyl thiocyanate), in which the aromatic skeleton was a 2,4-dichlorophenyl group instead of a 4-phenoxyphenyl moiety, exhibited similar anti Chagasic activity as our lead compound WC-9.[9] Then, it would seem of interest to evaluate the corresponding bromine analogue 68. Thus, synthesis of Williamson between 2,4-dibromophenol and 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 the title compound 68 (Scheme 7).

Finally, as a part of the strategy to evaluate very simple structure, the 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. The title compounds 15 and 16 were potent growth inhibitors of the intracellular 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 the C-4″ positions exhibited ED$_{50}$ values quite similar compared to 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 possessing ED$_{50}$ values at the very low micromolar level (1.6 μM and 2.0 μM, respectively). The introduction of a naphtyl group as a terminal B ring of WC-9 was not beneficial for the anti-*T. cruzi* activity giving rise to 20 and 24, which are 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 μM and 2.9 μM, respectively. Surprisingly, in spite of having the pharmacopore 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, the regioisomers of WC-9 bearing electron-donor groups at the terminal ring 46–50 showed potent inhibitory action against *T. cruzi* and *T. gondii* being 48 and 50 those with similar efficacy compared with WC-9. Interestingly, all of them were very potent growth inhibitors of tachyzoites of *T. gondii* showing ED$_{50}$ values of 2.1 μM, 3.9 μM, 2.8 μM and 4.0 μM, respectively, as shown in Table 1. Only the pyridyl analogues of the regioisomer of WC-9 61 showed potent antiparasitic action having ED$_{50}$ values of 7.5 μM and 3.7 μM against *T. cruzi* and *T. gondii*, respectively. The rest of these pyridyl derivatives, that is, 60 and 62, are free of antiparasitic activity. Evidently, the relative position of the nitrogen atom at the B ring plays a key role in modulating the biological activity. Unexpectedly, the dibromo derivative 68 was inactive as an antiparasitic agent based on the results previously exhibited by the parent dichloro analogue. Finally, the simple pyridyl derivative 72 was devoid of antiparasitic activity as well. These data were in agreement with our previous results confirming that the paraaryl substitution pattern of WC-9 would not be necessarily required for an effective biological activity. The results are presented in Table 1.

**Conclusions**

It can be concluded that, most of the title compounds behave as anti-*T. cruzi* agents as well as anti-*Toxoplasma* agents favoring the latter ones. 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 substituted derivatives at the A ring in the future. The promising biological activity observed of the target molecules together with the drug-like character of these compounds motivate new studies to find an optimized chemical structure knowing the precise mode of action. Efforts in these aspects are currently being pursued in our laboratory.
Experimental Section

The glassware used in air and/or moisture sensitive reactions was flame-dried and carried out under a dry argon atmosphere. Unless otherwise noted, chemicals were commercially available and were used without further purification. Anhydrous $N,N$-dimethylformamide and anhydrous dimethyl sulfoxide were used as supplied from Aldrich.

Nuclear magnetic resonance spectra were obtained using a Bruker AM-500 MHz spectrometer. Chemical shifts are reported in parts per million ($\delta$) relative to tetramethylsilane. Coupling constants are reported in Hertz. $^{13}$C NMR spectra were fully decoupled. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet.

High-resolution mass spectra were performed 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 using a Fisher-Johns apparatus and are uncorrected.

Column chromatography was performed with E. Merck silica gel plates (Kieselgel 60, 230–400 mesh). Analytical thin layer chromatography was performed employing 0.2 mm coated commercial silica gel plates (E. Merck, DC-Aluminum sheets, Kieselgel 60 F$_{254}$).

4-Benzylxoxyphenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (7)

A solution of 4-(benzylxy)phenol (6; 5.00 g, 25.0 mmol) in dimethyl sulfoxide (25 mL) was treated with potassium hydroxide (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 reaction mixture was stirred at room temperature overnight. The mixture was partitioned between water (70 mL) and methylene chloride (70 mL). The aqueous phase was extracted with methylene chloride (2 × 40 mL). The combined organic layers were washed with a saturated solution of sodium chloride (5 × 50 mL), dried (MgSO$_4$), and the solvent was evaporated. The product was purified by column chromatography eluting with hexane–EtOAc (19:1) to yield 7.89 g (96% yield) of pure compound 7 as a colorless oil: $R_f$ 0.63 (hexane–EtOAc, 7:3); $^1$H 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 (dist. t, $J$ = 3.2 Hz, 1H, H-2‴), 5.02 (s, 2H, PhCH$_2$O-), 6.87 (d, $J$ = 9.3 Hz, 2H, H-3′′), 6.92 (d, $J$ = 9.3 Hz, 2H, H-2′′), 7.24–7.47 (m, aromatic protons); $^{13}$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$_2$O–), 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 (C-4′). HRMS (ESI) calcd. for C$_{20}$H$_{24}$O$_4$Na [M+Na]+ 351.1572; found 351.1574.

4-Hydroxyphenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (8)

A solution of 7 (8.150 g, 24.8 mmol) in ethyl acetate (40 mL) in the presence of 5% palladium on charcoal (40 mg) was treated with hydrogen at 3 atm. The reaction was stirred at room temperature for 4 h. The mixture was filtered off and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (4:1) as eluant to produce 4.301 g (73% yield) of pure 8 as a colorless oil: $R_f$ 0.27 (hexane–
4-[(3-Trifluoro)phenoxy]phenoxyethyl Tetrahydro-2\(\text{H}\)-pyran-2-yl Ether (9)

A mixture of compound 8 (1.50 g, 6.29 mmol), 1-iodo-3-(trifluoromethyl)benzene (2.06 g, 7.56 mmol), copper(II) iodide (120 mg, 0.63 mmol), 2-picolinic acid, (155 mg, 1.26 mmol), potassium phosphate tribasic (773 g, 3.64 mmol) in dimethyl sulfoxide (6.0 mL), and potassium phosphate tribasic (2.68 g, 12.6 mmol) under anhydrous conditions was evacuated and backfilled with argon. This sequence was repeated twice. Then, dimethyl sulfoxide was added (15.0 mL) and the reaction mixture was stirred vigorously at 80 °C for 36 h. The mixture was cooled to room temperature and partitioned between ethyl acetate (20 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine (5 × 50 mL), dried (MgSO\(_4\)) and the solvent was evaporated. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (19:1) as eluent to afford 2.06 g (86% yield) of pure 9 as a colorless oil: \(R_t 0.64\) (hexane–EtOAc; 7:3); \(^1\text{H} \text{NMR (500.13 MHz, CDCl}_3\) \(\delta 1.53–1.68\) (m, 4H, H-4\(\text{″}\), H-5\(\text{″}\)), 1.72–1.78 (m, 1H, H-3\(\text{‴}\)), 1.81–1.87 (m, 1H, H-3\(\text{‴}\)), 3.53 (m, 1H, H-6\(\text{‴}\)), 3.82 (ddd, \(J = 11.2, 6.3, 4.2\) Hz, 1H, H-6\(\text{‴}\)), 3.91 (ddd, \(J = 11.3, 8.2, 3.1\) Hz, 1H, H-1\(\text{‴}\)), 4.07 (ddd, \(J = 11.1, 4.9, 4.3\) Hz, 1H, H-1\(\text{‴}\)), 4.16 (m, 2H, H-2), 4.72 (t, \(J = 3.6\) Hz, 1H, H-2\(\text{″}\)), 6.94 (d, \(J = 9.3\) Hz, 2H, H-3\(\text{″}\)), 7.98 (d, \(J = 9.3\) Hz, 2H, H-3\(\text{‴}\)), 7.09 (dd, \(J = 8.2, 2.1\) Hz, 1H, H-6\(\text{″}\)), 7.16 (t, \(J = 1.9\) Hz, 1H, H-2\(\text{″}\)), 7.28 (dt, \(J = 7.8, 0.7\) Hz, 2H, H-4\(\text{″}\)), 7.39 (t, \(J = 8.0\) Hz, 2H, H-5\(\text{″}\)); \(^{13}\text{C} \text{NMR (125.77 MHz, CDCl}_3\) \(\delta 19.4\) (C-4\(\text{″}\)), 25.4 (C-5\(\text{″}\)), 30.5 (C-3\(\text{‴}\)), 62.2 (C-6\(\text{‴}\)), 65.9 (C-1), 67.9 (C-2), 99.0 (C-2\(\text{″}\)), 116.0 (C-3\(\text{‴}\)), 149.1 (C-4\(\text{″}\)), 155.8 (C-1\(\text{‴}\)), 160.0 (C-1\(\text{″}\)); \(^3\text{F} \text{NMR (470.54 MHz, CDCl}_3\) \(\delta -62.71\). HRMS (ESI) calcd. for C\(_{20}\)H\(_{21}\)O\(_3\)F\(_3\)Na [M+Na\(^+\)] 405.129; found 405.1285.

4-[(4-Trifluoro)phenoxy]phenoxyethyl Tetrahydro-2\(\text{H}\)-pyran-2-yl Ether (10)

A mixture of compound 8 (433 mg, 1.82 mmol), 1-iodo-4-(trifluoromethyl)benzene (594 mg, 2.18 mmol), copper(I) iodide (34.6 mg, 0.36 mmol), 2-picolinic acid, (44.8 mg, 0.36 mmol), and potassium phosphate tribasic (773 g, 3.64 mmol) in dimethyl sulfoxide (6.0 mL) was treated as described for the preparation of 9 for 13 days. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (19:1) as eluent to give 225 g (32% yield) of pure 10 as a colorless oil: \(R_t 0.60\) (hexane–EtOAc; 7:3); \(^1\text{H} \text{NMR (500.13 MHz, CDCl}_3\) \(\delta 1.53–1.67\) (m, 4H, H-4\(\text{″}\), H-5\(\text{″}\)), 1.73–1.79 (m, 1H, H-3\(\text{‴}\)), 1.82–1.88 (m, 1H, H-3\(\text{‴}\)), 3.54 (m, 1H, H-6\(\text{‴}\)), 3.82 (ddd, \(J = 11.2, 6.4, 4.4\) Hz, 1H, H-6\(\text{‴}\)), 3.91 (ddd, \(J = 11.3, 8.2, 3.1\) Hz, 1H, H-1\(\text{‴}\)), 4.07 (m, 1H, H-1\(\text{‴}\)), 4.16 (m, 2H, H-2), 4.72 (t, \(J = 3.6\) Hz, 1H, H-2\(\text{″}\)), 6.95 (d, \(J = 9.3\) Hz, 2H, H-2\(\text{″}\)), 6.97 (m, 2H, H-2\(\text{‴}\)), 6.99 (d, \(J = 9.3\) Hz, 2H, H-3\(\text{‴}\)), 7.56 (d, \(J = 8.9\) Hz, 2H, H-3\(\text{″}\)); \(^{13}\text{C} \text{NMR (125.77 MHz, CDCl}_3\) \(\delta 19.4\) (C-4\(\text{″}\)), 25.4 (C-5\(\text{″}\)), 30.5 (C-3\(\text{‴}\)), 62.2 (C-6\(\text{‴}\)), 65.8 (C-1), 67.9 (C-2), 99.0 (C-2\(\text{″}\)), 116.0 (C-3\(\text{‴}\)), 116.8
4-[(3-Trifluoro)phenoxy]phenoxyethyl 4-Toluenesulfonate (13)

To a solution of alcohol 11 (922 mg, 3.09 mmol) in pyridine (5.0 mL) was added with p-toluenesulfonyl chloride (1.72 g, 9.02 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. Then, 5% HCl (50 mL) was added and the reaction mixture was stirred for an additional hour. The mixture was extracted with methylene chloride (50 mL), dried (MgSO₄), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing a mixture of hexane-EtOAc (19:1) as eluent to afford 1.29 g of tosylate 13 (86% yield) as a colorless oil: Rf 0.30 (hexane–EtOAc, 7:3); ¹H NMR (500.13 MHz, CDCl₃) δ 2.03 (t, J = 5.5 Hz, 1H, -OH), 3.99 (m, 2H, H-2), 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 (t, J = 8.0 Hz, 2H, H-5‴); ¹³C NMR (125.77 MHz, CDCl₃) 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 (C-1‴). HRMS (ESI) calcd. for C₁₅H₁₃O₃F₃Na [M + Na]⁺ 321.0714; found 321.0703.

4-[(4-Trifluoro)phenoxy]phenoxyethanol (12)

A solution of compound 10 (229 mg, 0.60 mmol) in methanol (10 mL) was treated with pyridinium 4-toluenesulfonate (30 mg) as described for the preparation of 11. Purification by column chromatography (silica gel) eluting with hexane–EtOAc (17:1) afforded 174 mg (97% yield) of pure alcohol 12 as a white solid: Rf 0.20 (hexane–EtOAc, 7:3); ¹H NMR (500.13 MHz, CDCl₃) δ 3.99 (m, 2H, H-2), 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 (d, J = 8.6 Hz, 2H, H-3‴); ¹³C NMR (125.77 MHz, CDCl₃) 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 (C-1″); ¹⁹F NMR (470.54 MHz, CDCl₃) δ −61.68. HRMS (ESI) calc. for C₁₅H₁₃O₃F₃Na [M + Na]⁺ 321.0714; found 321.0719.

4-[(3-Trifluoro)phenoxy]phenoxyethanol (11)

A solution of compound 9 (1.96 g, 5.13 mmol) in methanol (50 mL) was treated with pyridinium 4-toluenesulfonate (30 mg). The reaction mixture was stirred at room temperature overnight. Then, water (70 mL) was added, and the mixture was extracted with methylene chloride (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL), dried (MgSO₄), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (17:1) to give 944.0 mg (62% yield) of pure alcohol 11 as a colorless oil: Rf 0.30 (hexane–EtOAc, 7:3); ¹H NMR (500.13 MHz, CDCl₃) δ 2.03 (t, J = 5.5 Hz, 1H, -OH), 3.99 (m, 2H, H-2), 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 (t, J = 8.0 Hz, 2H, H-5‴); ¹³C NMR (125.77 MHz, CDCl₃) 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 (C-1‴). HRMS (ESI) calcd. for C₁₅H₁₃O₃F₃Na [M + Na]⁺ 321.0714; found 321.0703.
Hz, 2H, H-3″), 7.40 (t, J = 8.0 Hz, 2H, H-5″), 7.83 (d, J = 8.3 Hz, 2H, H-2″); 13C NMR (125.77 MHz, CDCl3) δ 21.6 (CH3), 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 (C-1″). 19F NMR (470.59 MHz, CDCl3) δ −62.71 (s). HRMS (ESI) calc for C22H19F3NaO5S [M+Na]+ 475.0803; found 475.0775.

4-[(4-Trifluoro)phenoxy]phenoxyethyl 4-Toluenesulfonate (14)

A solution of tosylate 13 (249 mg, 0.55 mmol) in anhydrous N,N-dimethylformamide (4 mL) was treated with potassium thiocyanate (266 mg, 2.73 mmol). The reaction mixture was heated at 100 °C for 48 h. The reaction was work-up as depicted for the preparation of 15. The residue was purified by column chromatography (silica gel) employing a mixture of hexane–EtOAc (19:1) as eluent to give 76 mg (41% yield) of pure compound 16 as a colorless oil.
colorless oil: Rf 0.53 (hexane–AcOEt, 7:3); 1H NMR (500.13 MHz, CDCl3) 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 (d, J = 8.4 Hz, 2H, H-3″); 13C NMR (125.77 MHz, CDCl3) 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 (C-1″); 19F NMR (470.54 MHz, CDCl3) δ –61.70. HRMS (ESI) calc'd for C16H12O2NSF3Na [M + Na]+ 362.0439; found 362.0419.

β-Naphtyloxyphenoxyethanol (18)

A solution of 17 (358 mg, 0.98 mmol) in methanol (10 mL) was treated with pyridinium p-toluenesulfonate (20 mg) according to the general procedure. After the usual work-up, evaporation of the solvent yielded 266 mg of alcohol 18 (97% yield) as a white solid: Rf 0.22 (hexane–EtOAc); 1H NMR (500.13 MHz, CDCl3) 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 (dd, J = 8.1, 6.8, 1.3 Hz, 1H, H-6″), 7.43 (dd, 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 (d, J = 9.0 Hz, 1H, H-5″); 13C NMR (125.77 MHz, CDCl3) 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 (C-2″). HRMS (ESI) calc'd for C18H17O3 [M +H]+ 281.1178; found 281.1166.

β-Naphtyloxyphenoxyethyl 4-Toluenesulfonate (19)

A solution of alcohol 18 (286 mg, 1.02 mmol) in pyridine (5 mL) was treated with tosyl chloride (547 mg, 2.87 mmol) at 0 °C as depicted in the general procedure. Purification of
the crude compound by column chromatography afforded 295 mg (67% yield) of tosylate 19 as a white solid: $R_f$ 0.50 (hexane–EtOAc, 7:3); $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 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 (ddd, $J = 8.2$, 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 (d, $J = 8.3$ Hz, 2H, H-2*); $^{13}$C NMR (125.77 MHz, CDCl$_3$) $\delta$ 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-3*), 132.9 (C-4*), 134.3 (C-9*), 154.0 (C-6*), 150.8 (C-4*), 154.4 (C-1*), 158.9 (C-2*). HRMS (ESI) calc. for C$_{25}$H$_{22}$O$_5$Na [M+Na]$^+$ 457.1086; found 457.1077.

**β-Naphtyloxyphenylethyl Thiocyanate (20)**

A solution of 19 (295 mg, 0.68 mmol) in anhydrous N,N-dimethylformamide (5 mL) was treated with potassium thiocyanate (350 mg, 3.60 mmol) according to the general procedure. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (9:1) as eluent to give 93.3 mg (43% yield) of pure 20 as a white solid: $R_f$ 0.52 (hexane–EtOAc, 7:3); mp 81–82 °C; $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 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 (d, $J = 8.9$ Hz, 1H, H-5*); $^{13}$C NMR (125.77 MHz, CDCl$_3$) $\delta$ 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 (C-2*). HRMS (ESI) calc. for C$_{19}$H$_{13}$O$_2$NSNa [M + Na]$^+$ 344.0721; found 344.0711.

**α-Naphtyloxyphenylethyl Tetrahydro-2H-pyran-2-yl Ether (21)**

A mixture of 8 (724 mg, 3.04 mmol), 1-bromonaphthalene (840 mg, 4.08 mmol), copper (I) iodide (60.7 mg, 0.32 mmol), 2-picolinic acid (75.8 mg, 0.62 mmol) and potassium phosphate tribasic (1.33 g, 6.24 mmol) in dimethyl sulfoxide (6 mL) was treated as usual for 48 h. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (9:1) as eluent to give 322 mg (29% yield) of pure 21 as a colorless oil: $R_f$ 0.56 (hexane–EtOAc, 7:3); $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 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”), 4.02 (ddd, $J = 11.1$, 5.0, 4.3 Hz, 1H, H-1”), 4.16 (m, 2H, H-2”), 4.70 (t, $J = 3.8$ Hz, 1H, H-2”), 6.79 (ddd, $J = 7.6$, 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 (d, $J = 8.5$ Hz, 1H, H-8”), $^{13}$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”), 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-7”), 134.7 (C-10”), 149.7 (C-4”), 153.1 (C-1”), 155.2 (C-1”). HRMS (ESI) calc. for C$_{23}$H$_{24}$O$_4$Na [M+Na]$^+$ 387.1572; found 387.1563.
α-Naphtyloxyphenylethanol (22)

A solution of 21 (322 mg, 0.89 mmol) in methanol (10 mL) was treated with pyridinium p-toluene sulfonate (20 mg) according to the general method to afford 229 mg (92% yield) of 22 as a colorless oil: Rf 0.24 (hexane–EtOAc, 7:3); 1H NMR (500.13 MHz, CDCl3) 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-1), 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 (dd, J = 8.0, 1.5 Hz, 1H, H-8″); 13C NMR (125.77 MHz, CDCl3) 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 (C-1′). HRMS (ESI) calcd for C18H16O3Na [M+Na]+ 303.0997; found 303.1005.

α-Naphtyloxyphenylethyl 4-Toluenesulfonate (23)

To a solution of alcohol 22 (229 mg, 0.82 mmol) in pyridine (5 mL) was added p-toluenesulfonyl chloride (517 mg, 2.71 mmol) at 0 °C. After the usual work up, purification of the product afforded 323 mg (91% yield) of tosylate 23 as a white solid: Rf 0.48 (hexane–EtOAc, 7:3); 1H NMR (500.13 MHz, CDCl3) δ 2.45 (s, 3H, C-1), 66.4 (C-2), 111.7 (C-1′), 120.6 (C-3″), 122.5 (C-4″), 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 (C-1′). HRMS (ESI) calcd for C25H22O5Na [M+Na]+ 457.1086; found 457.1082.

α-Naphtyloxyphenylethyl Thiocyanate (24)

A solution of tosylate 23 (323 mg, 1.03 mmol) in N,N-dimethylformamide (6 mL) was treated with potassium thiocyanate (581 mg, 5.98 mmol) following the general procedure. The residue was purified by column chromatography (silica gel) employing a mixture of hexane–EtOAc (19:1) as eluent to afford 140 mg (43% yield) of pure 24 as a white solid: Rf 0.54 (hexane–AcOEt, 7:3); mp 95–96 °C; 1H NMR (500.13 MHz, CDCl3) 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 (dd, J = 8.0, 1.5 Hz, 1H, H-8″); 13C NMR (125.77 MHz, CDCl3) δ 33.3 (C-1′), 66.4 (C-2′), 111.7 (SCN), 111.8 (C-2″), 116.0 (C-2′), 120.5 (C-3′), 122.0 (C-4″), 122.8 (C-8″), 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 (C-1′). HRMS (ESI) calcd for C19H15O2NSNa [M+Na]+ 344.0721; found 344.0702.

4-(Pyridin-2-ylxyloxy)phenoxyethy Tetrahydro-2H-pyran-2-yl Ether (26)

A mixture of 25 (1.40 g, 4.02 mmol), 2-hydroxy pyridine (450 mg, 4.73 mmol), copper (I) iodide (73.3 mg, 0.38 mmol), 2-picolinic acid (91.0 mg, 0.74 mmol), and potassium phosphate tribasic (1.74 g, 8.20 mmol) in methyl sulfoxide (6 mL) was treated according to the general procedure for 8 days. The product was purified by column chromatography.

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4-(Pyridin-2-yloxy)phenoxyethanol (27)

A solution of 26 (607 mg, 1.92 mmol) in methanol (10 mL) was treated with pyridinium p-toluenesulfonate (20 mg) and the mixture was stirred at room temperature for 4 h. After the usual work up, the product was purified by column chromatography (silica gel) employing a method. The product was purified by column chromatography (silica gel) employing a mixture of hexane–EtOAc (3:7) to give 607 mg (48% yield) of pure 26 as a colorless oil: \( R_f \) 0.09 (hexane–EtOAc, 1:1); \(^1\)H NMR (500.13 MHz, CDCl\(_3\)) \( \delta \) 1.52–1.65 (m, 4H, H-4‴), 1.72–1.78 (m, 1H, H-3‴), 1.81–1.86 (m, 1H, H-3″), 3.54 (m, 1H, H-6‴), 3.84 (ddd, \( J = 11.2, 6.4, 4.4 \) Hz, 1H, H-6″), 3.91 (ddd, \( J = 11.2, 8.2, 3.0 \) Hz, 1H, H-1‴), 4.07 (ddd, \( J = 11.2, 4.8, 4.2 \) Hz, 1H, H-1″), 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 (ddd, \( J = 9.2, 6.6, 2.1 \) Hz, 1H, H-5″); \(^{13}\)C NMR (125.77 MHz, CDCl\(_3\)) \( \delta \) 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-3′), 127.4 (C-3″), 133.7 (C-4′), 138.2 (C-5″), 139.8 (C-3′), 158.6 (C-1′), 162.6 (C-1″). HRMS (ESI) calcd. for C\(_{18}\)H\(_{21}\)NO\(_4\)Na [M+Na\(^+\)] + 338.1368; found 338.1365.

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 tosyl chloride (352 mg, 1.85 mmol) at 0 °C. The reaction was quenched as depicted for the preparation of 13 to afford 183 mg (90% yield) of pure 28 as a white solid: \( R_f \) 0.39 (AcOEt); \(^1\)H NMR (500.13 MHz, CDCl\(_3\)) \( \delta \) 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, \( J = 9.3, 0.7 \) 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 (ddd, \( J = 9.2, 6.6, 2.2 \) Hz, 1H, H-5″); \(^{13}\)C NMR (125.77 MHz, CDCl\(_3\)) \( \delta \) 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 (C-1″). HRMS (ESI) calcd. for C\(_{20}\)H\(_{20}\)NO\(_2\)S [M+H\(^+\)] + 323.0974; found 323.0978.

4-(Pyridin-2-yloxy)phenoxyethyl Thiocyanate (29)

A solution of compound 28 (136 mg, 0.35 mmol) in anhydrous N,N-dimethylformamide (2 mL) was treated with potassium thiocyanate (200 mg, 2.06 mmol) according to the general method. The product was purified by column chromatography (silica gel) employing a
mixture of hexane-EtOAc (1:1) as eluent to yield 56.9 mg (61% yield) of thiocyanate 29 as a white solid: \( R_f 0.38 \) (AcOEt); \(^1^H\) 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\( ^\prime \)), 6.65 (d, \( J = 9.3, 0.7 \) Hz, 1H, H-6\( ^\prime \)), 7.02 (d, \( J = 9.0 \) Hz, 2H, H-2\( ^\prime \)), 7.33 (d, \( J = 9.0 \) Hz, 2H, H-3\( ^\prime \)), 7.31 (ddd, \( J = 7.0, 1.8, 0.7 \) Hz, 1H, H-3\( ^\prime \)), 7.39 (ddd, \( J = 9.2, 6.6, 2.1 \) Hz, 1H, H-5\( ^\prime \)); \(^1^C\) NMR (125.77 MHz, CDCl\(_3\)) \( \delta \) 33.1 (C-1), 66.2 (C-2), 105.9 (C-6\( ^\prime \)), 111.6 (SCN), 115.3 (C-2\( ^\prime \)), 121.9 (C-4\( ^\prime \)), 127.9 (C-3\( ^\prime \)), 134.8 (C-4\( ^\prime \)), 138.1 (C-5\( ^\prime \)), 139.9 (C-3\( ^\prime \)), 157.6 (C-1\( ^\prime \)), 162.6 (C-1\( ^\prime \)). HRMS (ESI) calcd. for \( \text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_2\text{S} [\text{M}+\text{H}]^+ \) 273.0698; found 270.03.

### 3-(2-Chlorophenoxy)phenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (31)

A mixture of compound 30 (927 mg, 2.6 mmol), 2-chlorophenol (411 mg, 3.2 mmol), copper (I) iodide (50.6 mg, 0.27 mmol), 2-picolinic acid, (65.5 mg, 0.53 mmol), and potassium phosphate tribasic (1.129 g, 5.3 mmol) was evacuated and back-filled with argon as described for the preparation of 9. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (24:1) as eluent to afford 475 mg (51% yield) of pure 31 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\( ^\prime \), H-5\( ^\prime \)), 1.70–1.76 (m, 1H, H-3\( ^\prime \)), 1.79–1.86 (m, 1H, H-3\( ^\prime \)), 3.52 (m, 1H, H-6\( ^\prime \)), 3.80 (ddd, \( J = 11.2, 6.4, 4.2 \) Hz, 1H, H-6\( ^\prime \)), 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\( ^\prime \)), 6.54 (m, 2H, H-4\( ^\prime \), H-6\( ^\prime \)), 6.55 (t, \( J = 2.3 \) Hz, 1H, H-2\( ^\prime \)), 7.02 (dt, \( J = 8.0, 1.5 \) Hz, 1H, H-6\( ^\prime \)), 7.09 (dt, \( J = 7.7, 1.5 \) Hz, 1H, H-4\( ^\prime \)), 7.21 (t, \( J = 8.0 \) Hz, 1H, H-5\( ^\prime \)), 7.22 (m, 1H, H-5\( ^\prime \)), 7.45 (dd, \( J = 8.0, 1.6 \) Hz, 1H, H-3\( ^\prime \)); \(^1^C\) NMR (125.77 MHz, CDCl\(_3\)) \( \delta \) 19.4 (C-4\( ^\prime \)), 25.4 (C-5\( ^\prime \)), 30.5 (C-3\( ^\prime \)), 62.2 (C-6\( ^\prime \)), 65.7 (C-1), 67.6 (C-2), 99.0 (C-2\( ^\prime \)), 104.8 (C-2\( ^\prime \)), 109.6 (C-6), 110.2 (C-4\( ^\prime \)), 121.2 (C-6\( ^\prime \)), 124.8 (C-4\( ^\prime \)), 126.0 (C-2\( ^\prime \)), 127.9 (C-5\( ^\prime \)), 130.1 (C-3\( ^\prime \)), 130.8 (C-5\( ^\prime \)), 152.2 (C-1\( ^\prime \)), 158.1 (C-3\( ^\prime \)), 160.2 (C-1\( ^\prime \)). HRMS (ESI) calcd. for \( \text{C}_{19}\text{H}_{19}\text{O}_4\text{ClNa} [\text{M}+\text{Na}]^+ \) 371.1026; found 371.1023.

### 3-(2-Chlorophenoxy)phenoxyethanol (36)

A solution of compound 31 (475 mg, 1.4 mmol) in methanol (75 mL) was treated with pyridinium 4-toluenesulfonate (30 mg) at 0 °C. The reaction mixture was stirred at room temperature overnight. After the usual work up, the residue was purified by column chromatography eluting with hexane–EtOAc (4:1) to give 252 mg (70% yield) of pure alcohol 36 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\( ^\prime \)), 6.56 (ddd, \( J = 8.1, 2.3, 0.9 \) Hz, 1H, H-6\( ^\prime \)), 6.66 (ddd, \( J = 8.2, 2.3, 0.8 \) Hz, 1H, H-2\( ^\prime \)), 7.03 (dd, \( J = 8.1, 1.5 \) Hz, 1H, H-6\( ^\prime \)), 7.10 (ddd, \( J = 7.7, 7.5, 1.5 \) Hz, 1H, H-4\( ^\prime \)), 7.22 (t, \( J = 8.0 \) Hz, 1H, H-5\( ^\prime \)), 7.24 (m, 1H, H-5\( ^\prime \)), 7.46 (dd, \( J = 8.0, 1.6 \) Hz, 1H, H-3\( ^\prime \)); \(^1^C\) NMR (125.77 MHz, CDCl\(_3\)) \( \delta \) 61.4 (C-1), 67.3 (C-2), 104.5 (C-2\( ^\prime \)), 109.3 (C-6\( ^\prime \)), 110.3 (C-4\( ^\prime \)), 121.3 (C-6\( ^\prime \)), 125.0 (C-4\( ^\prime \)), 126.1 (C-2\( ^\prime \)), 128.0 (C-5\( ^\prime \)), 130.3 (C-3\( ^\prime \)), 130.8 (C-5\( ^\prime \)), 152.2 (C-1\( ^\prime \)), 158.1 (C-3\( ^\prime \)), 160.3 (C-1\( ^\prime \)). HRMS (ESI) calcd. for \( \text{C}_{14}\text{H}_{14}\text{O}_3\text{Cl} [\text{M}+\text{H}]^+ \) 265.0631; found 265.0633.

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**3-(2-Chlorophenoxy)phenoxyethyl 4-Toluenesulfonate (41)**

A solution of alcohol 36 (253 mg, 0.95 mmol) in pyridine (3 mL) was treated with p-toluenesulfonyl chloride (546 mg, 2.9 mmol) according to the general method. The product was purified by column chromatography (silica gel) employing a mixture of hexane–EtOAc (9:1) as eluent to afford 226 mg (66% yield) of tosylate 41 as a colorless oil. Rf 0.25 (hexane–EtOAc, 4:1); ¹H NMR (500.13 MHz, CDCl₃) δ 2.44 (s, 3H, CH₃), 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 (d, J = 8.4 Hz, 2H, H-2″); ¹³C NMR (125.77 MHz, CDCl₃) δ 21.6 (CH₃), 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-2″), 159.3 (C-1″). HRMS (ESI) calcd for C₂₁H₁₇O₅NSClNa [M+Na]⁺ 441.0539; found 441.0547.

**3-(2-Chlorophenoxy)phenoxyethyl Thiocyanate (46)**

A solution of tosylate 41 (226 mg, 0.54 mmol) in anhydrous N,N-dimethylformamide (3 mL) was treated with potassium thiocyanate (262 mg, 2.7 mmol). The reaction mixture was heated at 100 °C for 3 h. After the usual work up, the residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (19:1) to give 15.8 mg (10% yield) of pure 46 as a colorless oil: Rf 0.38 (hexane–EtOAc, 4:1); ¹H NMR (500.13 MHz, CDCl₃) δ 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 (ddd, 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-5″), 7.24 (m, 1H, H-5″), 7.47 (dd, J = 8.0, 1.6 Hz, 1H, H-3″); ¹³C NMR (125.77 MHz, CDCl₃) δ 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 (C-1″). HRMS (ESI) calcd for C₁₃H₁₂O₂NSClNa [M+Na]⁺ 328.0175; found 328.0169.

**3-(3-Chlorophenoxy)phenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (32)**

A mixture of compound 30 (959 mg, 2.7 mmol), 3-chlorophenol (708 mg, 5.5 mmol), copper (I) iodide (52.4 mg, 0.27 mmol), 2-picolinic acid, (67.8 mg, 0.55 mmol), and potassium phosphate tribasic (1.169 g, 5.5 mmol) under the conditions depicted for the preparation of 9. The reaction mixture was stirred vigorously at 90 °C for 21 days. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (24:1) as eluent to afford 826 mg (86% yield) of pure 32 as a colorless oil: Rf 0.76 (hexane–EtOAc; 3:2); ¹H NMR (500.13 MHz, CDCl₃) δ 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 (t, J = 8.2 Hz, 2H, H-5″, H-5″); ¹³C NMR (125.77 MHz, CDCl₃) δ 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″).
3-(3-Chlorophenoxy)phenoxyethyl 4-Toluenesulfonate (42)

A solution of compound 32 (581 mg, 1.7 mmol) in methanol (75 mL) was treated with pyridinium p-toluenesulfonate (30 mg). The reaction mixture was stirred at room temperature overnight and was quenched as described for the preparation of 6. The product was purified by column chromatography eluting with hexane–EtOAc (86:14) to give 302 mg (50% yield) of pure alcohol 37R as a colorless oil: Rf 0.14 (hexane–EtOAc; 4:1); 1H NMR (500.13 MHz, CDCl3) δ 3.98 (m, 2H, H-2), 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 (dt, J = 8.2, 2.6 Hz, 2H, H-5′, H-5″); 13C NMR (125.77 MHz, CDCl3) δ 61.4 (C-1), 69.2 (C-3′), 105.0 (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 (C-1′). HRMS (ESI) calcd for C14H13O3ClNa [M+Na]+ 287.0451; found 287.0441.

3-(3-Chlorophenoxy)phenoxyethanol (37)

To a solution of compound 32 (581 mg, 1.7 mmol) in methanol (75 mL) was added pyridinium p-toluenesulfonate (30 mg). The reaction mixture was stirred at room temperature overnight and was quenched as described for the preparation of 6. The product was purified by column chromatography eluting with hexane–EtOAc (86:14) to give 302 mg (50% yield) of pure alcohol 37 as a colorless oil: Rf 0.14 (hexane–EtOAc; 4:1); 1H NMR (500.13 MHz, CDCl3) δ 2.43 (s, 3H, C-2), 4.12 (m, 2H, H-1), 4.36 (m, 2H, H-2), 6.42 (t, J = 2.3 Hz, 1H, H-2′), 6.57 (dd, 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′), 6.68 (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 (d, J = 8.3 Hz, 2H, H-2″); 13C NMR (125.77 MHz, CDCl3) δ 21.6 (CH3), 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 (C-1′). HRMS (ESI) calcd for C21H16O3SNaClNa [M+Na]+ 441.0539; found 441.0543.

3-(3-Chlorophenoxy)phenoxyethyl Thiocyanate (47)

To a solution of compound 32 (581 mg, 1.7 mmol) in methanol (75 mL) was added pyridinium p-toluenesulfonate (30 mg). The reaction mixture was stirred at room temperature overnight and was quenched as described for the preparation of 6. The product was purified by column chromatography eluting with hexane–EtOAc (86:14) to give 302 mg (50% yield) of pure alcohol 37 as a colorless oil: Rf 0.14 (hexane–EtOAc; 4:1); 1H NMR (500.13 MHz, CDCl3) δ 3.98 (m, 2H, H-2), 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 (dt, J = 8.2, 2.6 Hz, 2H, H-5′, H-5″); 13C NMR (125.77 MHz, CDCl3) δ 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 (C-1′). HRMS (ESI) calcd for C_{15}H_{22}O_2SNa \[M+Na\]^+ 328.0175; found 328.0177.

### 3-(4-Chlorophenoxy)phenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (33)

A mixture of compound 30 (810 mg, 2.3 mmol), 4-chlorophenol (598 mg, 4.6 mmol), copper (I) iodide (44.4 mg, 0.23 mmol), 2-picolinic acid, (57.4 mg, 0.47 mmol), and potassium phosphate tribasic (987 mg, 4.6 mmol) was treated according to the general procedure and stirred at room temperature overnight and was quenched as described for the preparation of pyridinium 4-toluenesulfonate (30 mg). The reaction mixture was stirred at 90 °C for 19 days. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (24:1) as eluent to afford 417 mg of pure alcohol (69% yield) of pure alcohol was purified by column chromatography eluting with hexane–EtOAc (9:1) to give 219 mg (78% yield) of pure 33 as a colorless oil: R_f 0.34 (hexane–EtOAc: 3:2); ^1H NMR (500.13 MHz, CDCl_3) δ 1.52–1.69 (m, 4H, H-4‴), 6.41 (t, J = 8.2, 2.2, 0.7 Hz, 1H, H-6‴), 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 (d, J = 9.1 Hz, 2H, H-2″); ^13C NMR (125.77 MHz, CDCl_3) δ 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-3′), 129.7 (C-1″), 155.7 (C-1‴), 158.0 (C-1′), 160.3 (C-3′). HRMS (ESI) calcd for C_{19}H_{20}O_4ClNa [M+Na]^+ 371.1026; found 371.1002.

### 3-(4-Chlorophenoxy)phenoxyethanol (38)

A solution of compound 33 (417 mg, 1.2 mmol) in methanol (75 mL) was treated with pyridinium 4-toluenesulfonfate (30 mg). The reaction mixture was stirred at room temperature overnight and was quenched as described for the preparation of 11. The product was purified by column chromatography eluting with hexane–EtOAc (9:1) to give 219 mg (69% yield) of pure alcohol 38 as a colorless oil: R_f 0.11 (hexane–EtOAc: 8:2); ^1H NMR (500.13 MHz, CDCl_3) δ 1.98 (t, J = 6.3, 1H, -OH), 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 (d, J = 9.0 Hz, 2H, H-2″); ^13C NMR (125.77 MHz, CDCl_3) δ 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 (C-3′). HRMS (ESI) calcd for C_{14}H_{13}O_3ClNa [M+Na]^+ 287.0451; found 287.0450.

### 3-(4-Chlorophenoxy)phenoxyethyl 4-Toluenesulfonate (43)

To a solution of 8 (219 mg, 0.83 mmol) in pyridine (3 mL) was added p-toluenesulfonyl chloride (474 mg, 2.48 mmol) following the method of preparation described for 12. The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (47:3) to give 269 mg (78% yield) of pure 13 as a colorless oil: R_f 0.25 (hexane–EtOAc, 4:1); ^1H NMR (500.13 MHz, CDCl_3) δ 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 (d, J = 8.4 Hz, 2H, H-2″); ^13C NMR (125.77 MHz, CDCl_3) δ 21.6 (CH_3), 65.5 (C-1), 67.9 (C-2), 105.6 (C-2″),

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3-(4-Chlorophenoxy)phenoxyethyl Thiocyanate (48)

To a solution of 13 (269 mg, 0.64 mmol) in N,N-dimethylformamide (3 mL) was added potassium thiocyanate (319 mg, 3.2 mmol). The reaction mixture was treated according to the general method. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (24:1) to afford 104 mg (53% yield) of pure alcohol as a colorless oil: Rf 0.18 (hexane–EtOAc; 4:1); 1H NMR (500.13 MHz, CDCl3) δ 3.32 (t, J = 5.8 Hz, 2H, H-1), 4.29 (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 (d, J = 9.0 Hz, 2H, H-2′); 13C NMR (125.77 MHz, CDCl3) δ 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 (C-3′′′). HRMS (ESI) calcd for C15H13O2NSCl [M+H]+ 306.0356; found 306.0365.

3-(2-Methoxyphenoxy)phenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (34)

To a mixture of compound 30 (939 mg, 2.7 mmol), 2-methoxyphenol (670 mg, 5.4 mmol), copper (I) iodide (51.4 mg, 0.27 mmol), 2-picolinic acid, (66.4 mg, 0.54 mmol), and potassium phosphate tribasic (1.148 g, 5.4 mmol) was added dimethyl sulfoxide (3 mL) and the reaction mixture was stirred at 90 °C for 3 days according to the general method. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (47:3) as eluent to afford 628 mg (68% yield) of pure 34 as a colorless oil: Rf 0.35 (hexane–EtOAc; 4:1); 1H NMR (500.13 MHz, CDCl3) δ 1.50–1.65 (m, 4H, H-4′′′, H-5′′′), 1.70–1.76 (m, 1H, H-3′′′), 1.79–1.85 (m, 1H, H-3′′′′), 3.51 (m, 1H, H-6′′′′), 3.79 (ddd, J = 11.0, 6.5, 4.4 Hz, 1H, H-6′′′′), 3.84 (s, 3H, OCH3), 3.88 (ddd, J = 11.3, 8.2, 3.1 Hz, 1H, H-1′′′), 4.02 (m, 1H, H-1′′′′), 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 (t, J = 8.1 Hz, 1H, H-5′′′′); 13C NMR (125.77 MHz, CDCl3) δ 19.4 (C-4′′′′), 25.4 (C-5′′′′), 30.5 (C-3′′′′), 56.0 (OCH3), 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 (C-3′′′′). HRMS (ESI) calcd. for C20H21O3NSNa [M + Na]+ 367.1521; found 367.1515.

3-(2-Methoxyphenoxy)phenoxyethanol (39)

A solution of compound 34 (611 mg, 1.8 mmol) in methanol (10 mL) was treated with pyridinium 4-toluenesulfonate (30 mg). The reaction mixture was stirred at room temperature overnight and was quenched as described for the preparation of 11. The product was purified by column chromatography eluting with hexane-EtOAc (87:13) to give 349 mg (76% yield) of pure alcohol 39 as a colorless oil: Rf 0.08 (hexane–EtOAc; 4:1); 1H NMR (500.13 MHz, CDCl3) δ 2.00 (t, J = 6.2, 1H, -OH), 3.84 (s, 3H, OCH3), 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-5).
3-(2-Methoxyphenoxy)phenoxyethyl Thiocyanate (49)

To a solution of 39 (349 mg, 1.08 mmol) in pyridine (3 mL) was added p-toluenesulfonyl chloride (767 mg, 4.02 mmol) following the method of the preparation described for 12. The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (9:1) as eluent to afford 505 mg (64% yield) of pure 49 as a colorless oil: Rf 0.22 (hexane–EtOAc, 4:1); mp 92 °C; 1H NMR (500.13 MHz, CDCl3) δ 2.44 (s, 3H, C–O), 3.83 (s, 3H, OCH3), 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 (ddd, 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'm), 7.80 (d, J = 8.3 Hz, 2H, H-2'm), 13C NMR (125.77 MHz, CDCl3) δ 21.6 (PhCH3), 56.0 (OCH3), 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 (C-3'). HRMS (ESI) calcd. for C22H22O3S [M+H]+ 415.1215; found 415.1219.

3-(2-Methoxyphenoxy)phenoxyethyl Thiocyanate (49)

To a solution of 44 (449 mg, 1.08 mmol) in N,N-dimethylformamide (3 mL) was added potassium thiocyanate (526 mg, 5.4 mmol). The reaction mixture was treated according to the general procedure. The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (93:7) to afford 156 mg (48% yield) of pure 49 as a colorless oil: Rf 0.22 (hexane–EtOAc, 4:1); 1H NMR (500.13 MHz, CDCl3) δ 3.13 (t, J = 5.9 Hz, 2H, H-1), 3.84 (s, 3H, OCH3), 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 (t, J = 8.2 Hz, 1H, H-5'″), 13C NMR (125.77 MHz, CDCl3) δ 33.3 (C-1), 56.0 (OCH3), 65.8 (C-2'), 103.9 (C-2''), 108.5 (C-6''), 110.2 (C-4''), 111.7 (SCN), 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 (C-3''). HRMS (ESI) calcd. for C16H15O3NS [M+Na]+ 324.0670; found 324.0660.

3-(3-Methoxyphenoxy)phenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (35)

To a mixture of compound 30 (800 mg, 2.3 mmol), 3-methoxyphenol (570 mg, 4.6 mmol), copper (I) iodide (43.8 mg, 0.23 mmol), 2-picolinic acid (56.6 mg, 0.46 mmol), and potassium phosphate tribasic (978 mg, 4.6 mmol) was added dimethyl sulfoxide (3.0 mL) and the reaction mixture was stirred at 90 °C for 5 days according to the general procedure. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (49:1) as eluent to afford 505 mg (64% yield) of pure 35 as a colorless oil: Rf 0.46 (hexane–EtOAc; 4:1); 1H NMR (500.13 MHz, CDCl3) δ 1.53–1.68 (m, 4H, H-4'', H-5'″), 1.73–1.79
3-(3-Methoxyphenoxy)-phenoxyethyl 4-Toluenesulfonate (45)

A solution of compound 5 (852 mg, 2.5 mmol) in methanol (10 mL) was treated with pyridinium 4-toluenesulfonate (30 mg). The reaction mixture was stirred at room temperature overnight and was quenched as described for the preparation of 11. The product was purified by column chromatography eluting with hexane–EtOAc (23:2) to give 582 mg (90% yield) of pure alcohol 45 as a colorless oil: \( R_f \) 0.10 (hexane–EtOAc; 4:1); \( ^1{H} \) NMR (500.13 MHz, CDCl\(_3\)) \( \delta \) 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 (dd, \( J = 8.2, 2.4, 0.6 \) Hz, 1H, aromatic proton), 6.57 (m, 2H, aromatic proton), 6.61 (dd, \( J = 8.2, 2.2, 0.7 \) 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 (d, \( J = 8.3 \) Hz, 2H, H-2‴); \( ^{13}C \) NMR (125.77 MHz, CDCl\(_3\)) \( \delta \) 21.6 (Ph\(_2\)C), 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‴), 130.1 (C-5′″), 130.2 (C-5″), 158.1 (C-4‴), 158.3 (C-3‴), 159.9 (C-1″), 160.9 (C-3″). HRMS (ESI) calcd. for C\(_{15}\)H\(_{17}\)O\(_3\)Na [M+Na]\(^+\) 383.0946; found 383.0941.

3-(3-Methoxyphenoxy)-phenoxyethyl 4-Toluenesulfonate (45)

To a solution of 36 (582 mg, 2.24 mmol) in pyridine (3 mL) was added \( p \)-toluenesulfonyl chloride (1.28 g, 6.71 mmol) following the general method. The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (4:1) to give 209 mg (59% yield) of pure alcohol 45 as a colorless oil: \( R_f \) 0.02 (hexane–EtOAc; 4:1); \( ^1{H} \) NMR (500.13 MHz, CDCl\(_3\)) \( \delta \) 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 (dd, \( J = 8.2, 2.4, 0.6 \) Hz, 1H, aromatic proton), 6.57 (m, 2H, aromatic proton), 6.61 (dd, \( J = 8.2, 2.2, 0.7 \) 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 (d, \( J = 8.3 \) Hz, 2H, H-2‴); \( ^{13}C \) NMR (125.77 MHz, CDCl\(_3\)) \( \delta \) 21.6 (Ph\(_2\)C), 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‴), 130.1 (C-5′″), 130.2 (C-5″), 158.1 (C-4‴), 158.3 (C-3‴), 159.9 (C-1″), 160.9 (C-3″). HRMS (ESI) calcd. for C\(_{15}\)H\(_{17}\)O\(_3\)Na [M+Na]\(^+\) 383.0946; found 383.0941.

3-(3-Methoxyphenoxy)-phenoxyethyl Thiocyanate (50)

To a solution of 15 (339 mg, 0.82 mmol) in \( N,N \)dimethylformamide (3 mL) was added potassium thiocyanate (397 mg, 4.1 mmol). The reaction mixture was treated according to the general procedure. The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (19:1) to afford 112 mg (45% yield) of 50 as a colorless oil: \( R_f \)
3-(3-Pyridyloxy)phenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (51)

A mixture of compound 30 (1.051 g, 3.0 mmol), 2-hydroxyypyridine (861 mg, 9.0 mmol), copper(I) iodide (57.5 mg, 0.30 mmol), 2-picolinic acid (74.3 mg, 0.60 mmol), and potassium phosphate tribasic (1.928 g, 9.0 mmol) in dimethyl sulfoxide (3.0 mL) was stirred vigorously at 90 °C for 13 days according to the general procedure. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (2:3) as eluent to afford 484 mg (59% yield) of pure 51 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\(^{\alpha}\), H-5\(^{\alpha}\)), 1.73–1.79 (m, 1H, H-3\(^{\alpha}\)), 1.82–1.88 (m, 1H, H-3\(^{\beta}\)), 3.56 (m, 1H, H-6\(^{\alpha}\)), 3.85 (ddd, \( J = 11.3, 6.2, 4.2 \) Hz, 1H, H-6\(^{\beta}\)), 3.92 (ddd, \( J = 11.3, 8.3, 3.1 \) Hz, 1H, H-1\(_{\beta}\)), 4.08 (ddd, \( J = 11.3, 5.0, 4.2 \) Hz, 1H, H-1\(_{\alpha}\)), 4.20 (m, 2H, H-2), 4.72 (t, \( J = 3.6 \) Hz, 1H, H-2\(^{\alpha}\)), 6.25 (dt, \( J = 6.7, 1.3 \) Hz, 1H, H-4\(^{\beta}\)), 6.68 (dq, \( J = 9.3, 0.7 \) Hz, 1H, H-6\(^{\beta}\)), 6.97–7.03 (m, 3H, aromatic protons), 7.34 (ddd, \( J = 6.9, 2.1, 0.7 \) Hz, 1H, H-3\(^{\beta}\)), 7.39–7.43 (m, 2H, aromatic protons); \(^{13}\)C NMR (125.77 MHz, CDCl\(_3\)) \( \delta \) 19.3 (C-4\(^{\beta}\)), 25.4 (C-5\(^{\beta}\)), 30.5 (C-3\(^{\alpha}\)), 62.2 (C-6\(^{\beta}\)), 65.7 (C-1), 67.7 (C-2), 99.0 (C-2\(^{\alpha}\)), 105.8 (C-2\(^{\beta}\)), 113.2 (C-6\(^{\alpha}\)), 115.1 (C-4\(^{\alpha}\)), 118.8 (C-6\(^{\beta}\)), 122.0 (C-4\(^{\beta}\)), 130.1 (C-5\(^{\beta}\)), 137.8 (C-5\(^{\alpha}\)), 139.8 (C-3\(^{\alpha}\)), 141.9 (C-1\(^{\alpha}\)), 159.5 (C-3\(^{\beta}\)), 162.4 (C-1\(^{\beta}\)). HRMS (ESI) calcd. for C\(_{18}\)H\(_{26}\)O\(_4\)NNa [M+Na]+ 338.1368; found 338.1368.

3-(3-Pyridyloxy)phenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (52)

A mixture of compound 30 (900 mg, 2.6 mmol), 3-hydroxyypyridine (491 mg, 5.2 mmol), copper(I) iodide (49.2 mg, 0.26 mmol), 2-picolinic acid (63.6 mg, 0.52 mmol), and potassium phosphate tribasic (1.10 g, 5.2 mmol) in dimethyl sulfoxide (3.0 mL) was stirred at 90 °C for 3 days. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (83:17) as eluent to afford 484 mg (59% yield) of pure 52 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\(^{\alpha}\), H-5\(^{\alpha}\)), 1.71–1.76 (m, 1H, H-3\(^{\alpha}\)), 1.79–1.85 (m, 1H, H-3\(^{\beta}\)), 3.52 (m, 1H, H-6\(^{\alpha}\)), 3.80 (ddd, \( J = 11.2, 6.4, 4.1 \) Hz, 1H, H-6\(^{\beta}\)), 3.89 (ddd, \( J = 11.2, 8.2, 3.1 \) Hz, 1H, H-1\(_{\beta}\)), 4.04 (m, 1H, H-1\(_{\alpha}\)), 4.13 (m, 2H, H-2), 4.69 (t, \( J = 3.7 \) Hz, 1H, H-2\(^{\alpha}\)), 6.60 (m, 2H, aromatic protons), 6.73 (ddd, \( J = 8.3, 2.2, 0.9 \) Hz, 1H, H-6\(^{\beta}\)), 7.23–7.32 (m, 3H, H-5\(^{\alpha}\), H-6\(^{\alpha}\)), 8.37 (d, \( J = 3.7 \) Hz, 1H, H-4\(^{\beta}\)), 8.41 (d, \( J = 2.4 \) Hz, 1H, H-2\(^{\beta}\)); \(^{13}\)C NMR (125.77 MHz, CDCl\(_3\)) \( \delta \) 19.4 (C-4\(^{\alpha}\)), 25.4 (C-5\(^{\beta}\)), 30.5 (C-3\(^{\alpha}\)), 62.2 (C-6\(^{\beta}\)), 65.7 (C-1), 67.6 (C-2), 99.0 (C-2\(^{\alpha}\)), 105.8 (C-2\(^{\beta}\)), 110.3 (C-6\(^{\alpha}\)), 111.2 (C-4\(^{\alpha}\)), 124.1 (C-6\(^{\beta}\)), 125.6 (C-5\(^{\beta}\)), 130.4 (C-5\(^{\alpha}\)), 141.6 (C-2\(^{\alpha}\)), 144.4 (C-4\(^{\beta}\)), 153.7 (C-1\(^{\alpha}\)), 157.5 (C-1\(^{\beta}\)), 160.4 (C-3\(^{\alpha}\)).
3-(4-Pyridyloxy)phenoxyethyl Tetrahydro-2H-pyran-2-yl Ether (53)

A mixture of compound 30 (795 mg, 2.3 mmol), 4-hydroxypyridine (436 mg, 4.6 mmol), copper (I) iodide (43.7 mg, 0.23 mmol), 2-picolinic acid, (56.5 mg, 0.46 mmol), and potassium phosphate tribasic (976 mg, 4.6 mmol) in dimethyl sulfoxide (3.0 mL) was stirred at 90 °C for 2 days. The product was purified by column chromatography (silica gel) employing CH₂Cl₂–MeOH (97:3) as eluent to afford 508 mg (70% yield) of 53 as a colorless oil: R₇ 0.14 (CH₂Cl₂–MeOH, 19:1); ¹H NMR (500.13 MHz, CDCl₃) δ 1.51–1.65 (m, 4H, H-4‴), 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 (dd, J = 11.3, 6.4, 4.0 Hz, 1H, H-6‴b), 3.89 (dd, 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 (d, J = 7.8 Hz, 2H, H-3′); ¹³C NMR (125.77 MHz, CDCl₃) δ 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 (C-1″).

3-(2-Pyridyloxy)phenoxyethanol (54)

A solution of compound 51 (575 mg, 1.82 mmol) in methanol (10 mL) was treated with pyridinium 4-toluenesulfonate (30 mg). After the usual work up, the residue was purified by column chromatography eluting with CH₂Cl₂–methanol (49:1) to give 281 mg (67% yield) of pure alcohol 54 as white solid: R₇ 0.12 (EtOAc); mp 95 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 1.72–1.78 (m, 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-3‴, 6.66 (dq, J = 9.2, 0.7 Hz, 1H, H-6‴), 6.96–7.00 (m, 3H, aromatic protons), 7.33 (ddd, J = 6.9, 2.1, 0.7 Hz, 1H, H-3‴), 7.38–7.42 (m, 2H, aromatic protons); ¹³C NMR (125.77 MHz, CDCl₃) δ 61.4 (C-1), 69.5 (C-2), 105.8 (C-2′), 113.2 (C-6′), 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 (C-1′).

3-(3-Pyridyloxy)phenoxyethanol (55)

A solution of compound 52 (477 mg, 1.51 mmol) in methanol (3 mL) was treated with pyridinium 4-toluenesulfonate (30 mg). The reaction mixture was stirred at room temperature overnight and was quenched as described for the preparation of 13. The product was purified by column chromatography eluting with hexane–EtOAc (1:1) to give 290 mg (83% yield) of pure alcohol 55 as a colorless oil: R₇ 0.14 (hexane–EtOAc, 1:1); ¹H NMR (500.13 MHz, CDCl₃) δ 2.07 (br s, 1H, OH), 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 (dd, 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 protons), 8.38 (ddd, J = 4.5, 1.4 Hz, 1H, H-4″), 8.42 (d, J = 2.7 Hz, 1H, H-2″); ¹³C NMR (125.77 MHz, CDCl₃) δ 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 (C-3″).

3-(4-Pyridyloxy)phenoxyethanol (56)

A solution of 53 (617 mg, 1.96 mmol) in methanol (3 mL) was treated with pyridinium 4-toluenesulfonate (30 mg). The reaction mixture was stirred at room temperature overnight...
and was quenched as described for the preparation of 13. The product was purified by column chromatography eluting with CH₂Cl₂–MeOH (97:3) to give 156 mg (34% yield) of alcohol 56 as white solid: Rₜ 0.45 (EtOAc–MeOH, 3:2); mp 117 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 2.02 (t, J = 6.2 Hz, 1H, -OH), 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 (d, J = 7.8 Hz, 2H, H-3″); ¹³C NMR (125.77 MHz, CDCl₃) δ 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 (C-3″).

3-(2-Pyridyloxy)phenoxyethyl 4-Toluenesulfonate (57)

To a solution of 54 (284 mg, 1.22 mmol) in pyridine (3 mL) was added p-toluenesulfonyl chloride (702 mg, 3.68 mmol) and the mixture was stirred at room temperature for 4 h. After the usual treatment, the residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (35:75) to give 289 mg (61% yield) of pure compound as white solid: Rₜ 0.44 (EtOAc); mp 157 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 2.44 (s, 3H, PhC–O); 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, 0.9 Hz, 1H, H-3″), 7.34–7.41 (m, 2H, aromatic protons), 7.36 (d, J = 8.1 Hz, 2H, H-3″), 7.82 (d, J = 8.3 Hz, 2H, H-2″); ¹³C NMR (125.77 MHz, CDCl₃) δ 21.6 (PhCH₃), 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 (C-1′).

3-(3-Pyridyl-3-yloxy)phenoxyethyl 4-Toluenesulfonate (58)

To a solution of 55 (402 mg, 1.74 mmol) in pyridine (3 mL) was added p-toluenesulfonyl chloride (994 mg, 5.21 mmol) following the method of the preparation described for 13. The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (3:2) to give 305 mg (46% yield) of pure compound as a colorless oil; Rₜ 0.69 (EtOAc); ¹H NMR (500.13 MHz, CDCl₃) δ 2.44 (s, 3H, PhC–O), 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 protons), 7.29 (m, 3H, aromatic protons), 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 (d, J = 1.9 Hz, 1H, H-2′′); ¹³C NMR (125.77 MHz, CDCl₃) δ 21.7 (PhCH₃), 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-3′), 159.4 (C-3′′). HRMS (ESI) calcd. for C₂₀H₂₀O₅NS [M+H]+ 386.1062; found 386.1055.

3-(4-Pyridyloxy)phenoxyethyl Bromide (59)

To a mixture of alcohol 56 (153 mg, 0.62 mmol) in methylene chloride (10 mL) at 0 °C was added triphenyl phosphine (191 mg, 0.73 mmol) and N-bromosuccinimide (129 mg, 0.73 mmol). The reaction mixture was stirred at room temperature for 2h. The reaction was quenched by addition of water (25 mL). Then, the mixture was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were washed with brine (3 × 50 mL), dried (Na₂SO₄),
and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with CH$_2$Cl$_2$–MeOH (24:1) to give 45.9 mg (24% yield) of pure 59 as white solid: $R_f$ 0.34 (EtOAc–MeOH, 3:2); mp 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 (d, $J = 7.8$ Hz, 2H, H-3″).

3-(2-Pyridyloxy)phenoxyethyl Thiocyanate (60)

To a solution of 57 (288 mg, 0.75 mmol) in N,N-dimethylformamide (3 mL) was added potassium thiocyanate (363 mg, 3.7 mmol). The reaction mixture was treated according to the general procedure. The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (65:35) to afford 141 mg (69% yield) of 60 as white solid: $R_f$ 0.26 (EtOAc); mp 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 protons), 7.33 (ddd, $J = 6.9$, 2.1, 0.7 Hz, 1H, H-3″), 7.39–7.44 (m, 2H, aromatic protons); $^{13}$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 (C-1″). HRMS (ESI) calcd. for C$_{14}$H$_{12}$O$_2$N$_2$Na [M+Na]$^+$ 295.0517; found 295.0516.

3-(3-Pyridyl-3-xyloxy)phenoxyethyl Thiocyanate (61)

To a solution of 58 (245 mg, 0.64 mmol) in N,N-dimethylformamide (3 mL) was added potassium thiocyanate (309 mg, 3.2 mmol). The reaction mixture was treated according to the general procedure. The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (65:35) to afford 73.5 mg (64% yield) of 61 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 protons), 8.38 (dd, $J = 4.6$, 1.4 Hz, 1H, H-4″), 8.42 (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 (C-3″). HRMS (ESI) calcd. for C$_{14}$H$_{12}$O$_2$N$_2$S [M+H]$^+$ 273.0698; found 273.0702.

3-(4-Pyridyloxy)phenoxyethyl Thiocyanate (62)

To a solution of 57 (45.9 mg, 0.16 mmol) in N,N-dimethylformamide (3.0 mL) was added potassium thiocyanate (75.8 mg, 0.78 mmol). The reaction mixture was treated according to the general procedure. The product was purified by column chromatography (silica gel) eluting with CH$_2$Cl$_2$–MeOH (24:1) to afford 37.0 mg (87% yield) of 62 as white solid: $R_f$ 0.67 (EtOAc–MeOH, 3:2); mp 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 (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″), 144.3 (C-3″), 162.3 (C-3″).
159.0 (C-1′), 179.0 (C-1″). HRMS (ESI) calcd. for C_{14}H_{13}O_{2}N_{2}S [M+H]^+ 273.0698; found 273.0704.

4-Phenoxyphenoxyethyl Azide (64)

To a solution of 63 (252 mg, 0.66 mmol) in N,N-dimethylformamide (3 mL) was added sodium azide (213 mg, 3.28 mmol). The reaction mixture was heated at 100 °C for 3 h. The mixture was allowed to cool to room temperature and water (20 mL) was added. The aqueous phase was extracted with methylene chloride (2 × 30 mL) and the combined organic layers were washed with brine (5 × 30 mL) and water (2 × 30 mL). The solvent was dried (Na$_2$SO$_4$) and evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane to give 59.5 mg (35% yield) of pure 64 as a colorless oil: R$_f$ 0.44 (hexane–EtOAc, 4:1); $^1$H NMR (500.13 MHz, CDCl$_3$) δ 3.60 (t, J = 5.0 Hz, 2H, H-1), 6.91 (d, J = 9.1 Hz, 2H, H-2′), 6.95 (m, 2H, aromatic protons), 6.99 (d, J = 9.2 Hz, 2H, H-3′), 7.05 (tt, J = 7.4, 1.1 Hz, 1H, H-4″), 7.30 (m, 2H, aromatic protons); $^{13}$C NMR (125.77 MHz, CDCl$_3$) δ 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 (C-1″). HRMS (ESI) calcd for C$_{14}$H$_{13}$O$_2$N$_3$Na [M+Na]$^+$ 278.0905; 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 dimethyl sulfoxide (5 mL) was treated with potassium hydroxide (668 mg, 11.9 mmol) and bromoethyl tetrahydropyranyl ether (1.24 g, 5.95 mmol) according to the general method. The residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (19:1) to afford 293 mg (46% yield) of pure 65 as a colorless oil: R$_f$ 0.43 (hexane–EtOAc, 4:1); $^1$H NMR (500.13 MHz, CDCl$_3$) δ 1.51–1.63 (m, 4H, H-4), 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-1a), 4.07 (m, 1H, H-1b), 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 (d, J = 2.4 Hz, 1H, H-2′); $^{13}$C NMR (125.77 MHz, CDCl$_3$) δ 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 (C-1′). HRMS (ESI) calcd for C$_{13}$H$_{10}$O$_3$Br$_2$Na [M+Na]$^+$ 400.9364; found 400.9370.

2,4-Dibromophenoxyethanol (66)

A solution of compound 65 (1.04 g, 2.74 mmol) in methanol (10 mL) was treated with pyridinium 4-toluenesulfonate (30 mg). The reaction mixture was stirred at room temperature overnight and quenched as described for the preparation of 6. The product was purified by column chromatography eluting with hexane–EtOAc (43:7) to give 568 mg (70% yield) of pure alcohol 66 as white solid: R$_f$ 0.14 (hexane–EtOAc; mp 59 °C; 4:1); $^1$H NMR (500.13 MHz, CDCl$_3$) δ 2.15 (t, J = 6.5 Hz, 1H, OH), 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 (d, J = 2.4 Hz, 1H, H-2′); $^{13}$C NMR (125.77 MHz, CDCl$_3$) δ 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 (C-1″). HRMS (ESI) calcd for C$_{6}$H$_{8}$O$_2$Br$_2$Na [M + Na]$^+$ 316.8789; found 316.8773.

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2,4-Dibromophenoxyethyl 4-Toluenesulfonate (67)

To a solution of 66 (568 mg, 1.92 mmol) in pyridine (3 mL) was added p-toluenesulfonyl chloride (1.10 g, 5.76 mmol) following the method of the preparation described for 11. The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (9:1) to give 725 mg (84% yield) of pure 67 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 (dd, \( J = 8.5, 2.4 \) Hz, 1H, H-5'), 7.66 (d, \( J = 2.4 \) Hz, 1H, H-2'), 7.84 (d, \( J = 8.3, 2.4 \) Hz, H-3'); \(^{13}\)C NMR (125.77 MHz, CDCl\(_3\)) \( \delta \) 21.7 (PhCH\(_3\)), 62.2 (C-6), 76.6 (C-5'), 111.5 (SBr), 113.4 (C-2'), 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 (C-1'). HRMS (ESI) calcd. for C\(_{15}\)H\(_{14}\)O\(_4\)SBr\(_2\)Na \([M+Na]^+\) 470.8877; found 470.8864.

2,4-Dibromophenoxyethyl Thiocyanate (68)

To a solution of 67 (725 mg, 1.61 mmol) in N,N-dimethylformamide (3 mL) was added potassium thiocyanate (782 mg, 8.05 mmol). The reaction mixture was treated according to the general procedure. The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (23:2) to afford 405 mg (75% yield) of pure 68 as white solid; \( R_f 0.34 \) (hexane–EtOAc, 4:1); \(^1\)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 (d, \( J = 2.4 \) Hz, 1H, H-2'); \(^{13}\)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'), 131.2 (C-3'), 132.6 (C-4'), 135.7 (C-3'), 145.0 (C-1'), 153.6 (C-1'). HRMS (ESI) calcd for C\(_9\)H\(_7\)N\(_2\)SBr\(_2\)Na \([M+Na]^+\) 357.8513; found 357.8508.

3-Pyridloxyethyl Tetrahydro-2H-pyran-2-yl Ether (69)

A solution of 3-hydroxypyridine (1 g, 10.5 mmol) in dimethyl sulfoxide (5 mL) was treated with potassium hydroxide (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; the reaction mixture was stirred at room temperature overnight. The mixture was partitioned between methylene chloride (30 mL) and water (30 mL). The aqueous phase was extracted with methylene chloride (2 × 70 mL). The combined organic layers were washed with a saturated solution of sodium chloride (2 × 100 mL) and dried (Na\(_2\)SO\(_4\)), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (7:3) to afford 736 mg (31% yield) of pure 69 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'''), 3.83 (dd, \( J = 11.4, 6.3, 3.9 \) Hz, 1H, H-6''''b), 3.89 (dd, \( J = 11.2, 8.1, 3.2 \) Hz, 1H, H-1'''), 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 protons), 8.24 (dd, \( J = 4.4, 1.5 \) Hz, 1H, H-4'), 8.34 (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 (C-1'). HRMS (ESI) calcd. for C\(_9\)H\(_{18}\)O\(_3\)N \([M+H]^+\) 224.1287; found 224.1291.
3-Pyridyloxyethanol (70)

A solution of compound 69 (725 mg, 3.25 mmol) in methanol (3 mL) was treated with 4-toluenesulfonic acid (30 mg). The reaction mixture was stirred at room temperature overnight and was quenched as usual. The product was purified by column chromatography eluting with hexane–EtOAc (3:7) to give 304 mg (67% yield) of pure alcohol 70 as a yellow oil; \( R_f = 0.19 \) (EtOAc); \(^1\)H NMR (500.13 MHz, CDCl\(_3\)) \( \delta \) 2.34 (br s, 1H, OH), 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 protons), 8.24 (t, \( J = 3.0 \) Hz, 1H, H-4'), 8.34 (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 (C-1'). HRMS (ESI) calcd. for C\(_7\)H\(_{10}\)O\(_2\)N [M+H]\(^+\) 140.0712; found 140.0710.

3-Pyridyloxyethyl 4-Toluenesulfonate (71)

To a solution of 70 (303 mg, 2.18 mmol) in pyridine (3 mL) was added \( p \)-toluenesulfonyl chloride (1.25 g, 6.54 mmol) following the method of the preparation described for 13. The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (13:7) to give 441 mg (69% yield) of pure 71 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 protons), 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 (dd, \( J = 4.7, 1.3 \) Hz, 1H, H-4'). HRMS (ESI) calcd. for C\(_{14}\)H\(_{16}\)O\(_4\)NS [M+H]\(^+\) 294.0800; found 294.0798.

3-Pyridyloxyethyl Thiocyanate (72)

To a solution of 71 (413 mg, 1.41 mmol) in N,N-dimethylformamide (3 mL) was added potassium thiocyanate (683 mg, 7.04 mmol). The reaction mixture was treated according to the general procedure. The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (7:3) to afford 107 mg (42% yield) of 72 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 protons), 8.30 (dd, \( J = 4.0, 2.0 \) Hz, 1H, H-4'), 8.35 (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 (C-1'). HRMS (ESI) calcd. for C\(_8\)H\(_5\)ON\(_2\)SNa [M+Na]\(^+\) 203.0255; found 203.0255.

Drug Screening

**T. cruzi amastigote assays**

These experiments were done as reported using tdTomato labeled trypomastigotes\(^{[31]}\) with the modifications described by Recher et al., 2013.\(^{[32]}\) \( ED_{50} \) values were determined by non-linear regression analysis using SigmaPlot.

**T. gondii tachyzoites assays**

Experiments on *T. gondii* tachyzoites were carried out as described previously\(^{[33]}\) using *T. gondii* tachyzoites expressing red fluorescent protein\(^{[34]}\) with the modifications described by Recher et al., 2013.\(^{[32]}\) Plates were read with covered lids, and both excitation (544 nm) and emission (590 nm) were read from the bottom.
Cytotoxicity for Vero cells

The cytotoxicity was tested using the Alamar Blue™ assay as described by Recher et al., 2013.[32]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Figure 1.
Chemical structure of WC-9 (compound 1) and other closely related analogues.
Scheme 1.
Reagents and conditions: a) Br(CH₂)₂OTHP, KOH, DMSO, rt, 24 h, 96%; b) H₂, Pd/C, EtOAc, rt, 4 h, 73%; c) 1-iodo-3-(trifluoromethyl)benzene or 1-iodo-4-(trifluoromethyl)benzene, 5% CuI, 10% picolinic acid, K₃PO₄, DMSO, 90 °C, 36 h; d) PPTS, MeOH, rt, 24 h; e) TsCl, Py, 0 °C, 4 h; e) KSCN, DMF, 80 °C, 48 h.
Scheme 2.
Reagents and conditions: a) 2-bromonaphtalene, 5% CuI, 10% picolinic acid, K3PO4, DMSO, 90 °C, 24 h, 18%; b) PPTS, MeOH, rt, 4 h, 97%; c) ClTs, py, rt, 4 h, 67%; d) KSCN, DMF, 100 °C, 3 h, 43%; e) 1-bromonaphtalene, 5% Cul, 10% picolinic acid, K3PO4, DMSO, 90 °C, 24 h, 29%; f) PPTS, MeOH, rt, 4 h, 92%; g) ClTs, py, rt, 4 h, 91%; h) KSCN, DMF, 100 °C, 3 h, 43%.
Scheme 3.
Reagents and conditions: a) 2-hydroxypyridine (1.2 equiv.) 5% CuI, 10% picolinic acid, \( \text{K}_3\text{PO}_4 \), DMSO, 80 °C, 24 h, 48%; b) PPTs, MeOH, rt, 16 h, 60%; c) CITs, py, 0 °C, then, rt, 90%; d) KSCN, DMF, 100 °C, 61%.
Scheme 4.
Reagents and conditions: a) 5% CuI, 10% picolinic acid, K$_3$PO$_4$, DMSO, 80 °C, 24 h; b) PPTs, MeOH, rt, 16 h; c) CITs, py, 0 °C, 6 h; d) KSCN, DMF, 100 °C, 6 h.
Scheme 5.
Reagents and conditions: a) 5% CuI, 10% picolinic acid, K$_3$PO$_4$, DMSO, 80 °C, 24 h; b) PPTs, MeOH, rt, 16 h; c) NBS, PPh$_3$, CH$_2$Cl$_2$, 0° C, 24%; d) ClTs, py, 0 °C, 6 h; e) KSCN, DMF, 100 °C, 6 h.
Scheme 6.
Reagents and conditions: a) NaN₃, DMF, 100 °C, 6 h, 35%.
Scheme 7.
Reagents and conditions: a) KOH, BrCH₂CH₂OTHP, DMSO, rt, 16 h, 46%; b) PPTs, MeOH, rt, 16 h, 70%; c) ClTs, py, 0 °C, 6 h, 84%; d) KSCN, DMF, 100 °C, 6 h, 75%.
Scheme 8.
Reagents and conditions: a) KOH, BrCH$_2$CH$_2$OTHP, DMSO, rt, 16 h, 31%; b) PPTs, MeOH, rt, 16 h, 46%; CITS, py, 0 °C, 6 h, 69%; d) KSCN, DMF, 100 °C, 6 h, 42%.
Table 1

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

<table>
<thead>
<tr>
<th>Compound</th>
<th><em>T. cruzi</em> ED₅₀ (µM)</th>
<th><em>T. gondii</em> ED₅₀ (µM)</th>
<th>Cytotoxicity ED₅₀ (µM)</th>
<th>SI (<em>T. cruzi</em>)</th>
<th>SI (<em>T. gondii</em>)</th>
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<td>15</td>
<td>10.0 ± 2.5</td>
<td>1.66 ± 0.35</td>
<td>&gt; 50.0</td>
<td>&gt; 5.0</td>
<td>&gt; 31.1</td>
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<td>16</td>
<td>9.2 ± 1.8</td>
<td>1.86 ± 0.8</td>
<td>&gt; 50.0</td>
<td>5.4</td>
<td>&gt; 26.7</td>
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<tr>
<td>20</td>
<td>&gt; 10.0</td>
<td>2.25 ± 0.84</td>
<td>104.7 ± 7.8</td>
<td>&gt; 10.4</td>
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<tr>
<td>24</td>
<td>&gt; 10.0</td>
<td>2.87 ± 0.19</td>
<td>70.1 ± 7.6</td>
<td>&gt; 7</td>
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<tr>
<td>46</td>
<td>11.94 ± 0.38</td>
<td>2.13 ± 0.38</td>
<td>&gt; 50.0</td>
<td>4.2</td>
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<tr>
<td>47</td>
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<td>&gt; 200.0</td>
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<td>48</td>
<td>6.27 ± 0.75</td>
<td>3.86 ± 0.28</td>
<td>98.4 ± 5.8</td>
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<td>50</td>
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<td>4.02 ± 0.27</td>
<td>96.2 ± 37.5</td>
<td>11.0</td>
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<td>61</td>
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<td>WC-9</td>
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<td>82.6 ± 7.3</td>
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‡ Data are from one experiment in triplicate expressed as means ± S.D.