Selective ET_A Antagonists. 5. Discovery and Structure−Activity Relationships of Phenoxyphenylacetic Acid Derivatives

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Received July 20, 1999

The fifth paper in this series describes the culmination of our investigations into the development of a potent and selective ET_A receptor antagonist for the treatment of diseases mediated by ET-1. Receptor site mapping of several ET_A antagonists prepared previously identified a common cationic binding site which prompted synthesis of phenoxyphenylacetic acid derivative **13a**, which showed good in vitro activity (IC_{50} 59 nM, rat aortic ET_A). Optimization of **13a** led to the identification of **27b**, which exhibited an IC_{50} of 4 nM. Although this did not translate into the expected in vivo potency, a compound of comparable in vitro activity, **27a** (RPR118031A), showed a far better pharmacokinetic profile and in vivo potency (75 μmol/kg) and was duly proposed and accepted as a development candidate.

Introduction

The endothelins (ETs) are a family of 21 amino acid peptides that are widely distributed throughout the body. The first endothelin discovered, endothelin-1 (ET-1),[1] is the most potent vasoconstrictor known to date and has been implicated in the pathophysiology of several disease states including hypertension, pulmonary hypertension, cerebral and myocardial ischaemia, renal failure, and atherosclerosis.[2] ET-1 exerts its effect through binding to two distinct receptor subtypes which have varying distributions through many cell types.[3] The ET_A subtype is found primarily on vascular smooth muscle where it mediates vasoconstriction and smooth muscle cell proliferation,[4] whereas the ET_B subtype is distributed in a variety of tissues and mediates both vasodilatation and vasoconstriction.[5]

Antagonism of binding of ET-1 to its receptors is thus seen as an attractive target for therapeutic purposes, and consequently a number of structurally diverse antagonists have been reported.[6] These include peptides such as the ET_A selective antagonist BQ123[7] **1** and the ET_B selective antagonist BQ788[8] **2** (Figure 1). These peptides have been instrumental in implicating endothelin receptors in hypertension and renal failure,[9] although the preferred mode of action—selective ET_A, selective ET_B, or mixed ET_A/ET_B antagonism—has still to be fully evaluated.[4,10] However, it is the more recent discovery of nonpeptidic antagonists that has led to exhaustive investigation of the pathophysiological role of endothelin in various disease states and the potential uses of orally active ET antagonists (Figure 1).[6] These include the ET_A selective PD156707[11] **3** and the mixed ET_A/ET_B antagonists such as Ro47-0203 (Bosentan)[12] **4**, SB209670[13] **5a**, and L-749,329[14] **5b**. Abbott Laboratories has recently disclosed some very potent ET_A selective antagonists, typified by **6a** and **6b**.[15]

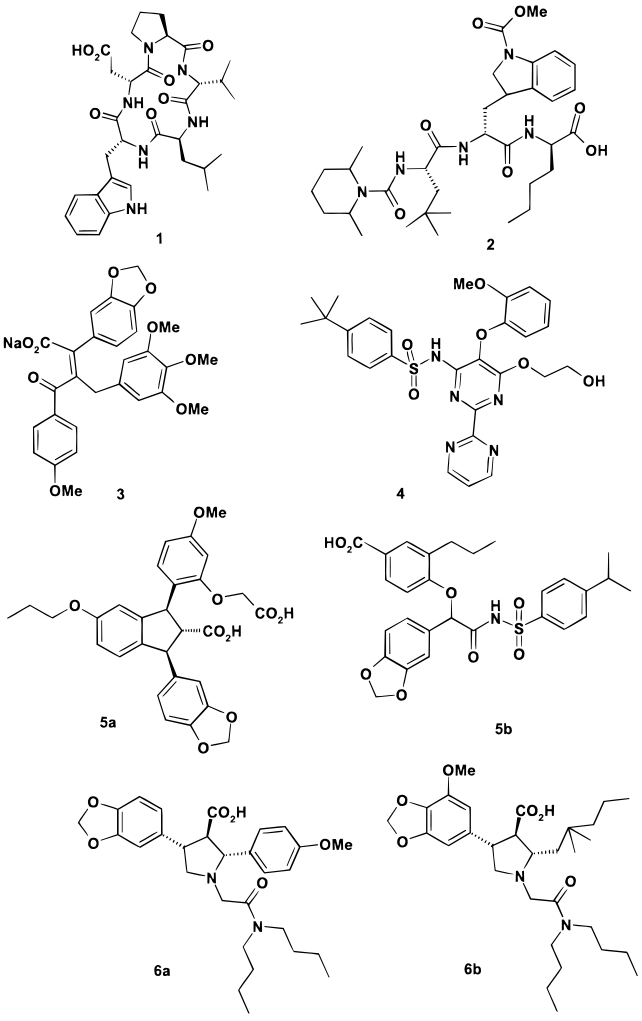

Figure 1. Selection of ET receptor antagonists.

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10.1021/jm990378b CCC: $19.00
Published on Web 02/11/2000

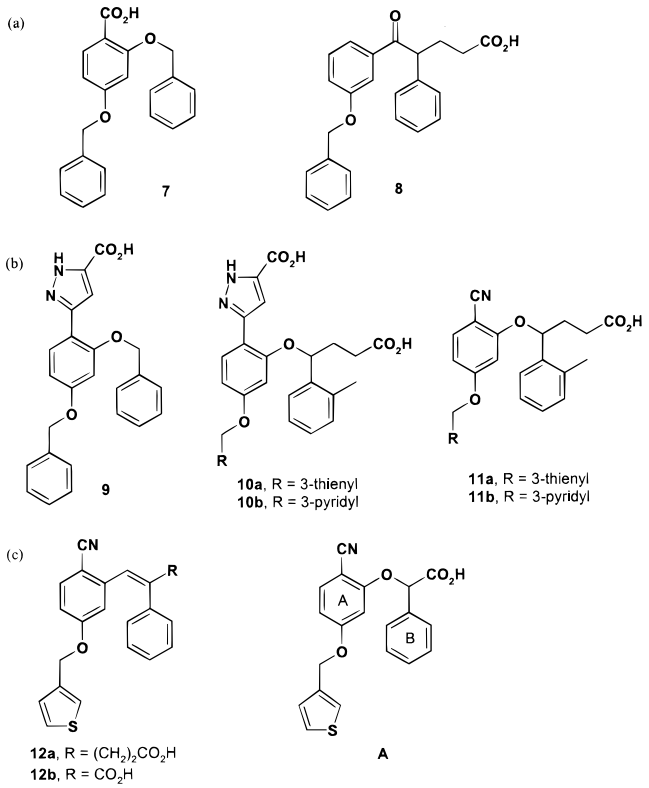


Figure 2. Representative examples of ET_A selective antagonists: (a) initial leads from screening the RPR corporate database; (b) hybrid structures of the initial leads; (c) third-generation structures.

Our work in this area was initiated by the discovery of two in-house leads, 2,4-dibenzyloxybenzoic acid[16] **7** and the 5-ketopentanoic acid derivative[17] **8** (Figure 2). Overlap of representative examples of these two series, namely **8** and **9**, identified common structural elements including a common cationic site accessed by the carboxylic acids. This led to the discovery of a more potent hybrid series, the 4-aryloxy-4-arylbutyric acid derivatives **10** and **11**.[18] Attempts to rigidify the butyric acid side chain by introduction of a vinyl linker, as in **12a**, led to a loss in potency.[19] However, during the course of the work it was found surprisingly that **12b**, the chain shortened analogue of **12a**, was in fact the most potent compound in the vinyl series. Further, it was shown that **12b** fitted well the simple receptor model derived from earlier members of the series.[19] With this knowledge it seemed likely that shortening the chain of the 4-aryloxy-4-arylbutyric acid derivatives could lead to highly potent analogues. This concept was explored further through superimposition studies, within the simple receptor model, of the prototype **A** with both **12b** (Figure 3a) and **11a** (Figure 3b). These studies, which clearly demonstrated that the putative cationic receptor site point could be accessed by this new class of compound, prompted us to pursue such structures and we were gratified to obtain our most potent ET_A antagonists to date. This paper outlines the synthesis and structure–activity relationship of these phenoxyphenylacetic acids. Also described is the in vitro functional pharmacology, the in vivo activities, and the pharmacokinetic profile which lead to the final selection of **27a** (RPR118031A) as a development candidate.

Chemistry

The preparation of compounds described in this paper is illustrated in Schemes 1–4. The physical properties of all compounds for which biological data is available are presented in Tables 1–4.

Compounds **13a–i** and **14d–f** were prepared by alkylation of the cyanophenol derivatives **18** with methyl α-bromoaryl acetates **16** and subsequent alkaline hydrolysis as shown in Scheme 1. The initial alkylation of 2,4-dihydroxybenzaldehyde gave almost exclusively salicylaldehyde derivatives **17**, presumably due to an intramolecular H-bond between the aldehyde carbonyl and the ortho phenolic proton making it less prone to deprotonation. A simple three-step, one-pot procedure led to the cyanophenol derivatives **18**. Compounds **16a–j** were prepared by one of two methods. Commercially available benzaldehydes underwent a carbene mediated conversion to the corresponding mandelic acids **20**,[20] which were then readily transformed to the required bromo esters **16** via esterification and bromination. Alternatively, commercially available phenylacetic acids were sequentially esterified and brominated to furnish **16**.

Compounds **13j–l, 14c,** and **15c–e** were prepared by the route shown in Scheme 2. Reaction of 2-fluoro-4-hydroxybenzonitrile with alkyl halides furnished compounds **22**. Fluoride displacement from **22** was accomplished by use of the dianion of mandelic acid derivatives **20** to give the target structures.

Compounds **14a,b,g–i** and **15a,b,f–l**, were prepared by the route outlined in Scheme 3. This approach is very similar to that described in Scheme 1 and allows the preparation of an advanced common intermediate **23**, obtained by rhodium catalyzed deallylation of the allyl analogue **24**,[21] which can then be coupled to a variety of alkyl halides. This convergent route for modification of the 5-substituent of ring A is particularly useful in cases where the alkyl halide is difficult to prepare.

Compounds **14c** and **15e** were resolved into their enantiomers, **26a** and **26b** respectively, via the (−)-ephedrine salt as shown in Scheme 4. Absolute stereochemistry was assigned from a single-crystal X-ray structure of **25a**, the ephedrine salt of **26a**. Preparation of the sodium salts **27a,b** is also described in this scheme.

Results and Discussion

All test compounds were assayed in vitro for their ability to antagonize the binding of [^{125}I]ET-1 to rat aortic A10 cell membrane ET_A receptors.[16] The results are shown in Tables 1–4. A selection of the compounds described in this paper were screened against a rat cerebellum ET_B preparation,[16] and in all cases tested they caused less than 50% inhibition of the binding of [^{125}I]ET-1 at a concentration of 30 μM (data not shown). Functional activity of selected compounds was measured as the inhibition of ET-1 induced contraction of isolated rat aortic rings denuded of the endothelium (Table 5).[16] In all cases the compounds showed no agonist activity but antagonized the ET-1 induced contractions in a dose dependent manner; the dose–response curves of ET-1 were shifted to the right in a parallel fashion by increasing concentrations of compound with no significant reduction in the maximal response. In pithed rats

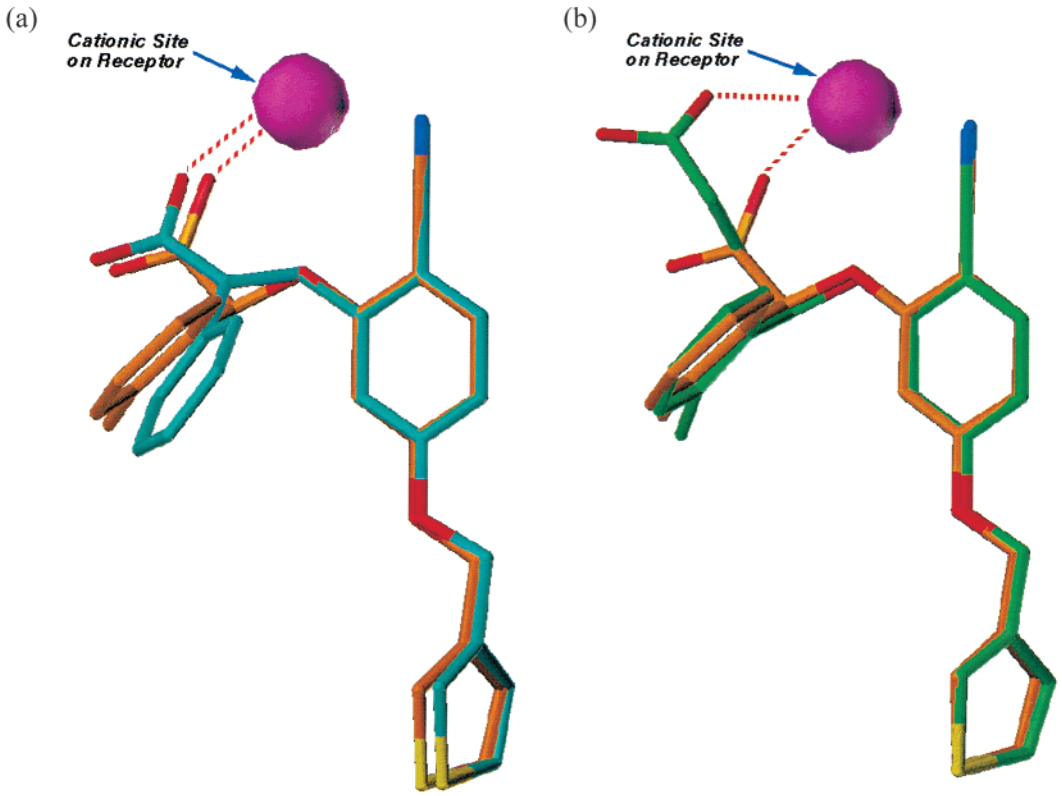
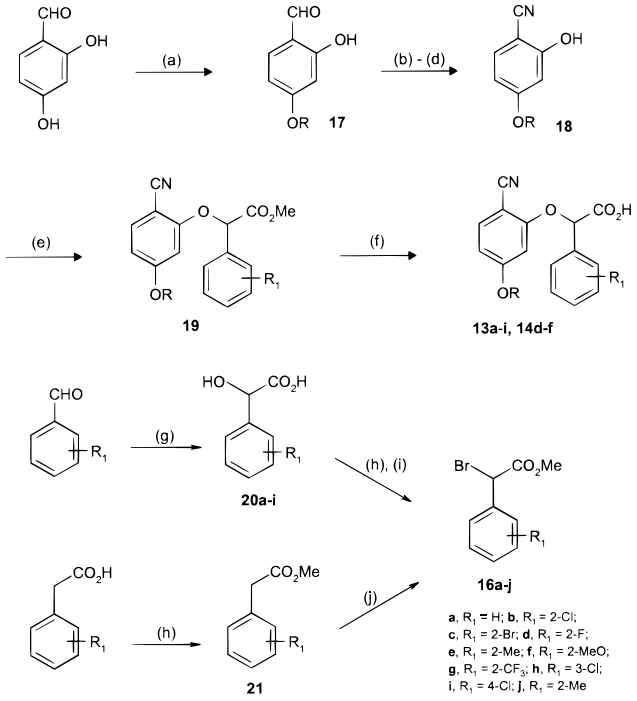


Figure 3. (a) Overlap of **12b** (cyan) and **A** (beige), showing the putative cationic site. (b) Overlap of **11** (green) and **A** (beige), showing the putative cationic site.

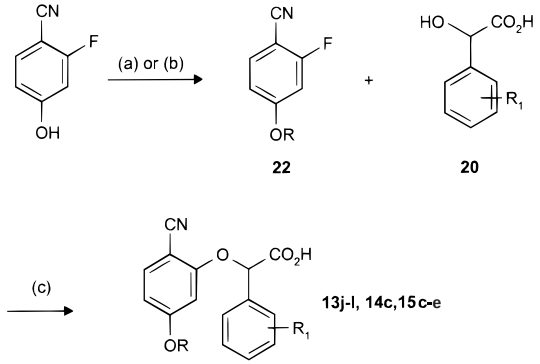
Scheme 1. Synthesis of 2-[(5-Aryl and 5-Heteroaryl)methoxy-2-cyano]phenoxyarylacetic Acids (Method A)[a]



[a] Reagents: (a) RCl, K_2CO_3, KI, $Bu_4NBr_{(cat)}$, MEK, reflux; (b) H_2N-OH·HCl, pyridine, EtOH, reflux; (c) Ac_2O, $NaOAc_{(cat)}$, reflux; (d) K_2CO_3, MeOH, THF, H_2O, rt; (e) **16a**−**j**, NaH, DMF, rt; (f) 1 M NaOH, dioxan, rt; (g) $CHBr_3$, KOH, LiCl, dioxan, H_2O, 10−15 °C; (h) MeOH, $H_2SO_{4(cat)}$, reflux; (i) $SOBr_2$, toluene, rt; (j) NBS, AIBN, $CHCl_3$, reflux.

pretreated with BQ788, to block ET_B receptors, selected compounds also showed a dose related rightward displacement of the ET-1 dose−response curves (Table 5). The pharmacokinetic profile of selected compounds is described in Table 6.

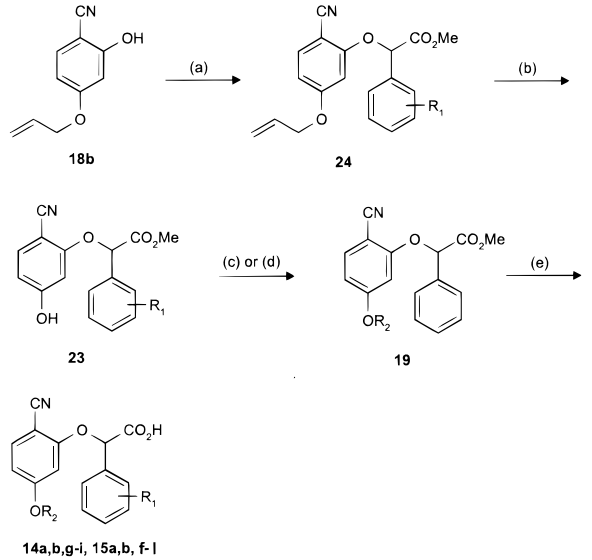
Scheme 2. Synthesis of [(5-Aryl and 5-Heteroaryl)methoxy-2-cyano]phenoxyarylacetic Acids (Method B)[a]



[a] Reagents: (a) RCl, K_2CO_3, DMF, rt; (b) ROH, PPh_3, DIAD, THF, rt; (c) NaH (2 equiv), DMSO, rt.

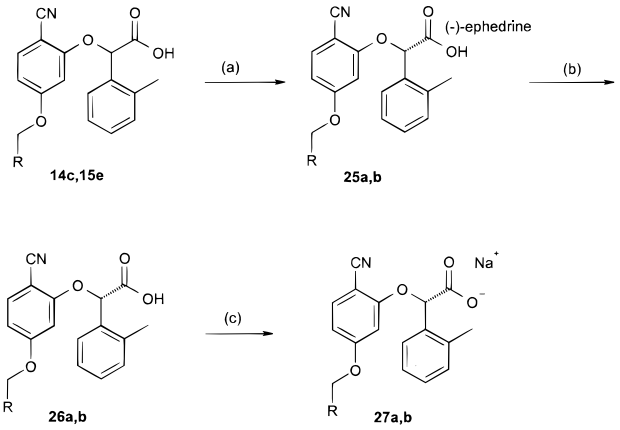
Compound **13a**, designed from the interaction site mapping model, had an IC_{50} of 59 nM in the ET_A receptor binding assay and was a functional ET-1 antagonist with a pK_b of 7.2 (see Table 5). The effect of substituents in the B-ring of **13a** is shown in Table 1. The effect of an ortho substituent was predominantly steric, with an optimum size being chloro (**13b**) or methyl (**13e**), giving a 3-fold increase in activity. These compounds also showed better functional activity, with pK_b values of 7.8 and 7.9, respectively. Smaller (**13d**) or larger (**13c,f,g**) groups led to a progressive loss in potency. Introduction of a meta (**13h**) or a para (**13i**) substituent was detrimental. The dramatic ortho effect

Scheme 3. Synthesis of [(5-Aryl and 5-Heteroaryl)methoxy-2-cyano]phenoxyarylacetic Acids (Method C)[a]



[a] Reagents: (a) **16**, NaH, DMF, rt; (b) $Rh(PPh_3)_3Cl_{(cat)}$, MeOH, DABCO, reflux; (c) R_2-Cl, NaH, DMF, rt; (d) R_2-OH, PPh_3, DIAD, THF, rt; (e) 1 M NaOH, dioxan, rt.

Scheme 4. Synthesis of Pure Enantiomers and Sodium Salts of Selected Compounds[a]



[a] Reagents: (a) (−)-ephedrine, ether, rt; (b) 2 M HCl, ethyl acetate, rt; (c) 0.1 M NaOH, dioxan, rt.

indicates a subtle reliance on torsion angle for optimal interaction with the receptor. The loss of activity with all other substituents suggests a limited amount of space in this region of the ligand upon binding. Replacement of the phenyl group by a variety of heteroaromatic isosteres was not fruitful (**13j**−**l**). This could be due to a simple hydrophobic interaction being required at this site or inability to attain the optimal conformation of the aryl group upon introduction of a heteroatom. In general, the SAR at this position appeared to mirror that of the phenoxybutyric acid series.[18]

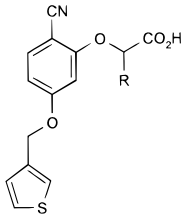
Replacement of the 3-thienyl group by aromatic groups is summarized in Table 2. A simple phenyl group (**14a**) led to a 3-fold loss in potency, as was seen in the phenoxybutyric acids. Steric crowding of the point of attachment (**14b**) was not tolerated. Introduction of a 3,4-methylenedioxy substituent, however, gave a slight increase in potency (compounds **14c**−**f**). These structures also showed improved functional activity (pK_b values of 7.4−8.0) and were orally bioavailable (e.g. 76% for **14e**), as shown in Table 5. Moving this substituent around the phenyl ring (**14g**) or changing it to an ethylenedioxy group (**14i**) gave essentially inactive structures, as did replacement of this fused group by methoxy substituents (**14h**). The sharp SAR around this position suggests a demanding steric restriction that can be satisfied by the 3,4-methylenedioxy group but not by the other groups considered. Alternatively, the lone pairs of the methylenedioxy group may interact directly with a site on the receptor, in a way that is not possible via the other groups.

The effect of replacing the thien-3-yl group of **13b** or **13e** by other heteroaromatic rings is summarized in Table 3. A variety of five-membered heterocycles (**15a**−**c**) were introduced with no increase in potency. Introduction of a 2- (**15d**) or 3-pyridyl group (**15g**) gave a drop in activity. However, use of a 4-pyridyl group (**15e,f**) gave at least a 2-fold increase in potency, when compared to the analogous thienyl containing compounds, but oral bioavailability was negligible (data not shown). This is reflected in the large drop in in vivo potency when the compounds were administered by the oral route rather than iv (see Table 6). The poor oral bioavailability is attributed to extensive oxidative metabolic cleavage of the pyridylmethoxy group. Attempts to prevent this by varying the heterocycle (**15i**−**l**) were unsuccessful. Although the benzoxazole derivatives **15j,k**, prepared to mimic the methylenedioxyphenyl group of **14c**−**f**, maintained in vitro potency and functional activity (pK_b values of 7.5 and 7.8 for **15j** and **15k**, respectively), oral potency was again very poor (see Table 6).

An alternative means of preventing metabolism was thought to be variation of the linker group to ring A, but this was also unsuccessful; ethoxy, methylthio, alkyl, alkenyl, and alkynyl linkers all abolished activity. Replacement of the nitrile function with groups such as acid, ester, aldehyde, amide, and glycineamide led to loss of activity, as did replacement of the carboxylic acid.

The ET_A activity was found to reside in the (*S*)-enantiomer, as shown by the activities of **26a** and **26b** in Table 4. The in vitro activity of **26a** was 6 nM compared to the value of 12 nM for the racemate **14c**. The (*S*)-enantiomer of **15e**, compound **26b**, also showed a 2-fold increase in potency from 9 to 5 nM. The corresponding (*R*)-enantiomers were almost 20-fold less active (data not shown), as might be expected from the receptor site mapping. A corresponding increase in functional activity was also observed, **26b** having a pK_b value of 8.3 (see Table 5). The respective sodium salts were prepared to increase solubility and, in the case of **26a**, to raise the melting point to an acceptable level for formulation. These salts, **27a** and **27b**, retained in vitro and functional activity and showed in vivo activity of 44-fold and 90-fold shifts, respectively, in dose−response curves when given iv. Unfortunately, a dramatic loss in activity was seen upon oral administration of **27b**, which ties in with the pharmacokinetic data observed in Table 6. It was gratifying, however, to observe a negligible loss in potency and a long duration of action upon oral administration of **27a** (see Table 6). In fact, the oral activity seen after 5 h with **27a** was

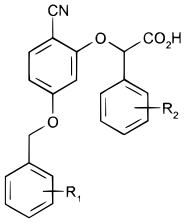
Table 1. Physical Properties and in Vitro Activity of [2-Cyano-5-(thien-3-yl)methoxy]phenoxyarylacetic Acids



cmpd[a,b]	R	mp (°C)	formula	analysis[c]	inhibition of ET-1 binding to ET_A IC_{50} (nM)[d]
13a	Ph	63−8	$C_{20}H_{15}NO_4S$	C, H, N	59, 70
13b	2-Cl−Ph	68−70	$C_{20}H_{14}ClNO_4S$	C, H, N	11, 17
13c	2-Br−Ph	89−98	$C_{20}H_{14}BrNO_4S$, $0.5H_2O$	C, H, N	51, 44
13d	2-F−Ph	159−61	$C_{20}H_{14}FNO_4S$	C, H, N, S	22, 21
13e	2-Me−Ph	120−2	$C_{21}H_{17}NO_4S$	C, H, N, S	16, 20
13f	2-MeO−Ph	118−20	$C_{21}H_{17}NO_5S$, $0.75H_2O$	C, H, N, S	529
13g	2-CF_3−Ph	28−30	$C_{21}H_{14}F_3NO_4S$	C, H, N	53, 42
13h	3-Cl−Ph	134−6	$C_{20}H_{14}ClNO_4S$, $0.5C_4H_{10}O$	C, H, N, S	98
13i	4-Cl−Ph	158−60	$C_{20}H_{14}ClNO_4S$	C, H, N, Cl	504
13j[e]	fur-3-yl	100−2	$C_{18}H_{13}NO_5S$, $0.5H_2O$	C, H, N	2850
13k[e]	fur-2-yl	85−7	$C_{18}H_{13}NO_5S$	C, H, N	2400
13l[e,f]	thiophen-3-yl	179−80	$C_{19}H_{14}N_2O_4S$	C, H, N, S	531, 630

[a] All compounds prepared according to method A unless otherwise stated. [b] ^1H NMR spectra were consistent with the assigned structures. [c] ±0.4%. [d] Data from binding assays was corrected for nonspecific binding and expressed as a percentage of total [^{125}I]-ET-1 binding in the presence of vehicle. IC_{50} values were obtained by curve fitting. In a minority of cases, when duplicate IC_{50} values were not obtained, the results of IC_{50} measurements were confirmed by retesting a single concentration selected to fall on the concentration−response curve. [e] Prepared by method B. [f] Thiophen-3-ylmethoxy replaced by pyrid-4-ylmethoxy.

Table 2. Physical Properties and in Vitro Activities of [5-(Aryl)methoxy-2-cyano]phenoxyarylacetic Acids



cmpd[a]	R_1	R_2	method	mp (°C)	formula	analysis[b]	ET_A IC_{50} (nM)[c]
14a	H	2-CH_3	C	128−30	$C_{23}H_{19}NO_4$	C, H, N	49, 39
14b	2,6-$(CH_3)_2$	2-CH_3	C	193−5	$C_{25}H_{23}NO_4$	C, H, N	857
14c	3,4-OCH_2O-	2-CH_3	B	125−6	$C_{24}H_{19}NO_6$	C, H, N	12, 14
14d	3,4-OCH_2O-	2-CF_3	A	137−8	$C_{24}H_{16}F_3NO_6$	C, H, N	14, 16
14e	3,4-OCH_2O-	2-Cl	A	144−5	$C_{23}H_{16}ClNO_6$	C, H, N	11, 14
14f	3,4-OCH_2O-	H	A	127−8	$C_{23}H_{17}NO_6$, $0.75H_2O$	C, H, N	25, 41
14g	2,3-OCH_2O-	2-CH_3	C	178−80	$C_{24}H_{19}NO_6$	C, H, N	3000, 2850
14h	3,4,5-$(OCH_3)_3$	2-CH_3	C	67−9	$C_{26}H_{25}NO_7$	C, H, N	>3000
14i	3,4-$O(CH_2)_2O$-	2-CH_3	C	153−5	$C_{25}H_{21}NO_6$	C, H, N	1230, 1500

[a] ^1H NMR spectra consistent with assigned structures. [b] ±0.4%. [c] See footnote d, Table 1.

still substantially higher than the maximal response to **27b**. This is attributed to the high bioavailability (84%) and low clearance (0.4 L h^{-1} kg^{-1}) observed for **27a**.

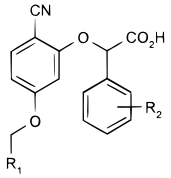
Conclusion

Overlap of representative examples from two earlier series of selective ET_A receptor identified a prototype structure **A**, which was found to overlay well with compounds from both the earlier series and was found to elicit an increase in potency when prepared (**13a**). Extensive investigation of the SAR around **13a** led to more potent analogues, namely **14c** and **15e**. The potency was further improved by identifying the active enantiomers **26a** and **26b**, respectively. The physical characteristics of these compounds were improved through formation of the sodium salts **27a** (RPR118031A) and **27b** (RPR117820A), which were found to be pharmaceutically acceptable forms. Although the latter was the more potent by iv dosing in an animal model, it suffered from poor oral bioavailability which resulted in no oral effect. The former compound, on the other hand, exhibited a good pharmacokinetic profile, and this led to a long duration of action when administered orally. The excellent properties of RPR118031A set it apart from others in the large series of endothelin antagonists described in this series of papers, and it was duly proposed and accepted as a development candidate.

Experimental Section

Melting points were determined using an Electrothermal apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian VXR 400 instrument. Where analyses are indicated by the symbols of the elements, results were within 0.4% of the theoretical values. Flash chromatography was performed using "Sorbsil" (Crosfield) silica gel, mesh size 40−60 μm supplied by Rhone Poulenc. Chiral HPLC experiments were performed using a Chiralpak AD column.

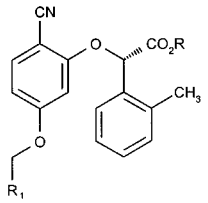
Table 3. Physical Properties and in Vitro Activities of [5-(Heteroaryl)methoxy-2-cyano]phenoxyarylacetic Acids

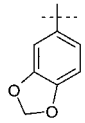
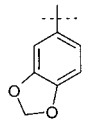


compd[a]	R_1	R_2	method	mp (°C)	formula	analysis[b]	ET_A IC_{50} (nM)[c]
13e	thiophen-3-yl	2-CH_3	A	120−2	$C_{20}H_{15}NO_4S$	C, H, N	16, 20
15a	fur-3-yl	2-CH_3	C	141−3	$C_{21}H_{17}NO_5$	C, H, N	68
15b	isothiazol-3-yl	2-CH_3	C	165−7	$C_{20}H_{17}N_2O_4S$, 0.5H_2O	C, H, N, S	220
15c	thiazol-5-yl	2-CH_3	B	226−7	$C_{20}H_{16}N_2O_4S$, H_2O	C, H, N	28, 30
15d	pyrid-2-yl	2-CH_3	B	189−91	$C_{22}H_{18}N_2O_4$	C, H, N	>3000
15e	pyrid-4-yl	2-CH_3	B	193−4	$C_{22}H_{18}N_2O_4$	C, H, N	8, 9
15f	pyrid-4-yl	2-Cl	C	225−6	$C_{21}H_{15}ClN_2O_4$	C, H, N	6, 6
15g	pyrid-3-yl	2-CH_3	C	201−2	$C_{22}H_{18}N_2O_4$, 0.2H_2O	C, H, N	30
15h	4-F-pyrid-4-yl	2-CH_3	C	178−9	$C_{22}H_{17}FN_2O_4$	C, H, N	22, 23
15i	pyridazin-4-yl	2-Cl	C	203−5	$C_{20}H_{14}ClN_3O_4$	C, H, N	44, 43
15j	benzoxazol-6-yl	2-Cl	C	172−8	$C_{23}H_{15}ClN_2O_5$, 0.5H_2O	C, H, N	8, 9
15k	benzoxazol-6-yl	2-CH_3	C	207−9	$C_{24}H_{18}N_2O_5$, 0.5H_2O	C, H, N	6, 6
15l	benzoxazol-5-yl	2-CH_3	C	189−91	$C_{24}H_{18}N_2O_5$, 0.5H_2O	C, H, N	64, 75

[a−c] See footnotes in Table 2.

Table 4. Physical Properties and in Vitro Activities of Enantiomerically Pure Acids and Their Corresponding Salts



Compd[a]	R_1	R	mp(°C)	Formula	Analysis[b]	ET_A IC_{50} (nM)[c]
26a		H	53-7	$C_{24}H_{19}NO_6$	C,H,N	6, 9
26b		H	228-30	$C_{22}H_{18}N_2O_4$	C,H,N	3, 5
27a		Na	212-4	$C_{24}H_{18}NNaO_6$	C,H,N	6, 7
27b		Na	180-3	$C_{22}H_{17}N_2NaO_4$	C,H,N	4, 5

[a−c] See footnotes in Table 2.

Molecular Modeling. All structures were initially created using Concord 3D builder (distributed by Tripos Inc., 1699 Hanley Road, Suite 303, St. Louis, MO 63144). The remaining modeling was carried out within Chem-X (developed and distributed by Chemical Design Ltd., Roundway House, Cromwell Park, Chipping Norton, Oxfordshire, OX7 5SR U.K.). Charges were first set using the Gasteiger method, and conformational analysis and energy calculations were carried out using the default Chem-X force field.

Pharmacology. (a) Receptor Preparation. ET_A receptors from the rat aortic smooth muscle cell line A10 cells (ATCC number: CRL-1476) and ET_B receptors from rat cerebellum were prepared as described previously.[18]

(b) ET_A Binding Assays. ET_A binding assays were performed in Millipore 0.22 mm 96-well Multiscreen plates and consisted of 20 pM [^{125}I] ET-1, test compound or vehicle, and A10 cells in a final volume of 250 mL. Nonspecific binding was measured using 500 nM unlabeled ET-1. [^{125}I] ET-1 was prepared in CO_2 independent tissue culture medium (Life Technologies) containing 0.1% w/v BSA, and test compounds and unlabeled ET-1 were prepared in the same, supplemented with dimethyl sulfoxide at 5% v/v final assay concentration. A10 cells which were stored at −20 °C in 50 mM Hepes buffer pH 7.3 were resuspended in CO_2 independent tissue culture medium immediately before use. Reactions were started by the addition of cells and allowed to proceed for 2 h at 37 °C before being terminated by vacuum filtration. The filters were

Table 5. In Vitro Functional Activities and in Vivo Data of the Most Active Antagonists

		pithed rat[a−c]		
compd	pK_b[a]	iv (25 μmol/kg)	po (75 μmol/kg)[d]	po (75 μmol/kg)[e]
13a	7.24 ± 0.3	4.45 (3.2, 6.2)	nd	nd
13b	7.76 ± 0.4	nd	nd	nd
13e	7.9 ± 0.2	19 (11, 34)	nd	nd
14c	7.9 ± 0.3	23 (15, 35)	26 (13, 53)	15 (8, 28)
14d	7.4 ± 0.2	9.0 (5.6, 14.4)	nd	nd
14e	8.0 ± 0.5	13.8 (8.3, 22.9)	19	10
14f	7.4 ± 0.4	7.6 (5.0, 11.3)	nd	nd
15e	7.6 ± 0.3	49 (34, 71)	8 (3.6, 19)	nd
15f	7.7 ± 0.2	46.8 (28.1, 77.8)	2.7 (1.1, 6.9)	1.7 (1.2, 2.5)
15j	7.5	nd	nd	nd
15k	7.8 ± 0.4	63 (42, 95)	ns	3.1 (1.6, 6.0)
26a	nd	nd	nd	nd
26b	8.3 ± 0.3	90 (56, 144)	5.9 (3.2, 11.2)	7.7 (2.1, 11)
27a	8.1 ± 0.3	45 (29, 69)	34 (13, 89)	55 (28, 105)
27b	nd	85	9	13

[a] All determinations were carried out in duplicate. [b] Degree of rightward shift of the ET-1 dose−response curve upon administration of compound. [c] Values in parentheses are 95% confidence limits. [d] After 1.5 h. [e] After 3 h.

Table 6. Pharmacokinetic Data of Selected Compounds[a]

compd	bioavailability (%)	Cp_{max} (μg/mL)	T_{max} (h)	$t^1/_2$ (h)	solubility (mg/mL)
13b	129	62	0.5	5.0	1.19
14e	76	22	1.0	6.3	1.68
27a	84	5.9	1.0	2.8	>20
27a[b]	89	30.1	0.5	7.4	
27b	9	0.29	2.0	0.2	

[a] Results obtained in male Sprague−Dawley rats dosed at 10 mg/kg po, unless otherwise stated. [b] Results from male Beagle dogs dosed at 10 mg/kg po.

then washed twice in ice cold 50 mM Tris buffer pH 7.4 and collected for g-counting.

(c) ET_B Binding Assays. ET_B binding assays were performed as previously described.[18]

(d) Functional Assays. Functional assays were carried out as previously described.[16]

(e) In Vivo Pharmacology. In vivo pharmacology was carried out as previously described.[22]

(f) Pharmacokinetics in the Rat. Pharmacokinetics were carried out as previously described[18]

Chemistry. General Method A. [*R,S*]-[2-Cyano-5-(thien-3-yl)methoxy]phenoxyphenylacetic Acid 13a. (i) 2-Hydroxy-4-(thien-3-yl)methoxybenzaldehyde 17a. A solution of 2,4-dihydroxybenzaldehyde (26.22 g, 189 mmol) in butan-2-one (500 mL) was treated with K_2CO_3 (26.34 g, 190 mmol), KI (31.80 g, 191.5 mmol), tetrabutylammonium bromide (5.61 g, 23.2 mmol), and 3-chloromethylthiophene (25.26 g, 190 mmol), and the reaction mixture was refluxed for 24 h. The solid was filtered off, and the organics were concentrated to dryness. The residue was partitioned between ethyl acetate and H_2O (500 mL each), the layers were separated, and the organics were dried over $MgSO_4$, filtered, and concentrated to leave a yellow oil. Flash chromatography (20% ethyl acetate in pentanes) furnished 18.00 g (41%) of **17a** as a white solid, mp 83−5 °C. ^{1}H NMR ($CDCl_3$): δ 11.48 (s, 1H), 9.73 (s, 1H), 7.45 (d, J = 8 Hz, 1H), 7.37 (dd, J = 5, 3 Hz, 1H), 7.34 (m, 1H), 7.14 (dd, J = 5, 2 Hz, 1H), 6.61 (dd, J = 8, 3 Hz, 1H), 6.51 (d, J = 3 Hz, 1H), 5.12 (s, 2H).

(ii) 2-Hydroxy-4-(thien-3-yl)methoxybenzonitrile 18a. A solution of **17a** (8.0 g, 34.0 mmol) in EtOH (250 mL) was treated with hydroxylamine hydrochloride (2.67 g, 38.0 mmol) and pyridine (2.51 mL, 32.0 mmol), and the reaction mixture was refluxed for 1 h. The reaction mixture was concentrated to ~50 mL and diluted with H_2O (100 mL) and extracted with ethyl acetate (150 mL). The organic layers were washed with 2 M HCl and brine (50 mL each), dried over $MgSO_4$, filtered, and stripped. The residual solid was triturated with pentanes to furnish 8.10 g (96%) of 2-hydroxy-4-(thien-3-yl)methoxybenzaldehyde oxime as a pale blue solid. A stirred solution of the oxime (8.10 g, 32.5 mmol) and sodium acetate (0.11 g, mmol) in acetic anhydride (30 mL) was refluxed for 1.5 h. The solution was treated with H_2O (300 mL) and stirred for 1 h to give a brown solid, which was filtered, washed with H_2O, and dried to give 8.62 g (97%) of 2-acetoxy-4-(thien-3-yl)methoxybenzonitrile as a light brown solid. A solution of the acetoxy compound (8.62 g, 31.6 mmol) in MeOH/THF (45/35 mL) was treated with 1 M K_2CO_3 (35 mL) and stirred at room temperature for 1.5 h. The solution was diluted with H_2O (40 mL) and brought to pH 1 with 2 M HCl. The solution was then extracted with ethyl acetate (2 × 100 mL), the combined organics were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and evaporated to give a tan solid. This was washed with pentane/ether (1/1) to give 6.63 g (93%)of **18a** as a light fawn solid, mp 140−2 °C. ^{1}H NMR ($CDCl_3$): δ 10.33 (s, 1H), 7.36 (d, J = 9 Hz, 1H), 7.34 (m, 2H), 7.13 (dd, J = 6, 2 Hz, 1H), 6.59 (d, J = 3 Hz, 1H), 6.48 (dd, J = 9, 3 Hz, 1H), 5.06 (s, 2H).

(iii) [*R,S*]-Methyl [2-Cyano-5-(thien-3-yl)methoxy]phenoxyphenylacetate 19a. A solution of **18a** (1.0 g, 4.32 mmol) in DMF (14 mL) was treated with NaH (0.19 g of 60%, 4.75 mmol). The reaction mixture was stirred at room temperature for 10 min, and the brown solution was treated with methyl α-bromophenylacetate **16a** (1.02 g, 4.45 mmol). The reaction mixture was stirred at room temperature for 1 h before being diluted with H_2O (30 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organics were washed with brine (2 × 30 mL), dried over $MgSO_4$, filtered, and concentrated to give a pale fawn solid. Recrystallization from cyclohexane/ethyl acetate gave 0.91 g (56%) of **19a** as a colorless solid, mp 112−4 °C. ^{1}H NMR ($CDCl_3$): δ 7.63 (dd, J = 7, 2 Hz, 2H), 7.52 (d, J = 8 Hz, 1H), 7.43 (m, 3H), 7.37 (dd, J = 5, 3 Hz, 1H), 7.32 (m, 1H), 7.12 (dd, J = 4, 2 Hz, 1H), 6.64 (dd, J = 8, 3 Hz, 1H), 6.46 (d, J = 3 Hz, 1H), 5.66 (s, 1H), 5.07 (s, 2H), 3.72 (s, 3H). Anal. ($C_{21}H_{17}NO_4S$) C, H, N, S.

(iv) [*R,S*]-[2-Cyano-5-(thien-3-yl)methoxy]phenoxyphenylacetic Acid 13a. A solution of **19a** (0.60 g, 1.58 mmol) in dioxan (17 mL) was treated with 1 M NaOH (4.75 mL) and stirred at room temperature for 1 h. The solution was brought to pH 7 with 2 M HCl, evaporated, and diluted with H_2O (10 mL) to give a yellow precipitate. The suspension was brought to pH 1 with 2 M HCl and extracted with ethyl acetate (25 mL). The organics were washed with water, dried over $MgSO_4$, filtered, and dried to give a yellow foam. Trituration with pentane gave 0.44 g (76%) of **13a** as a yellow solid, mp 63−8 °C. ^{1}H NMR ($CDCl_3$): δ 7.58 (dd, J = 8, 3 Hz, 2H), 7.45 (d, J = 9 Hz, 1H), 7.35 (m, 3H), 7.31 (dd, J = 4, 2 Hz, 1H), 7.24 (m, 1H), 7.06 (dd, J = 4, 2 Hz, 1H), 6.58 (dd, J = 9, 2 Hz, 1H), 6.47 (d, J = 3 Hz, 1H), 5.65 (s, 1H), 5.01 (s, 2H). IR (KBr): 3424(bm), 2229(m), 1740(m), 1610(s) cm^{-1}. Anal. ($C_{20}H_{15}NO_4S$) C, H, N.

Also prepared by this method were the following compounds:

[*R,S*]-(2-Chloro)phenyl-[2-cyano-5-(thien-3-yl)methoxy]phenoxyacetic Acid 13b. Obtained as a white solid, mp 85−7 °C (trituration with pentane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 7.74 (m, 1H), 7.48 (d, J = 9 Hz, 1H), 7.41 (m, 1H), 7.32 (m, 4H), 7.10 (dd, J = 4, 2 Hz, 1H), 6.62 (dd, J = 9, 3 Hz, 1H), 6.54 (d, J = 3 Hz, 1H), 6.70 (s, 1H), 5.05 (s, 2H). Anal. ($C_{20}H_{14}ClNO_4$, $0.5C_4H_8O$) C, H, N.

[*R,S*]-(2-Bromo)phenyl-[2-cyano-5-(thien-3-yl)methoxy]phenoxyacetic Acid 13c. Obtained as a white solid, mp 89−98 °C (trituration with pentane). ^{1}H NMR ($CDCl_3$): δ 7.74 (dd, J = 9, 2 Hz, 1H), 7.62 (dd, 1H, J = 9, 1 Hz, 1H), 7.49 (d, J = 9 Hz, 1H), 7.49 (td, J = 8, 1 Hz, 1H), 7.35 (m, 1H), 7.28 (m, 2H), 7.10 (dd, J = 5, 1 Hz, 1H), 6.63 (dd, J = 9, 3 Hz, 1H), 6.52 (d, J = 3 Hz, 1H), 6.21 (s, 1H), 5.07 (dd, J = 12, 4 Hz, 2H). Anal. ($C_{20}H_{14}BrNO_4S$, $0.5H_2O$) C, H, N.

[*R,S*]-[2-Cyano-5-(thien-3-yl)methoxy]phenoxy-(2-fluoro)phenylacetic Acid 13d. Obtained as a yellow solid, mp 159−161 °C (trituration with pentane). ^{1}H NMR ($CDCl_3$): δ 7.68 (td, J = 8, 2 Hz, 1H), 7.48 (d, J = 9 Hz, 1H), 7.35 (m, 3H), 7.20 (t, J = 8 Hz, 1H), 7.11 (m, 2H), 6.62 (dd, J = 9, 2 Hz, 1H), 6.54 (d, J = 2 Hz, 1H), 6.04 (s, 1H), 5.05 (s, 2H). Anal. ($C_{20}H_{14}FNO_4S$) C, H, N, S.

[*R,S*]-[2-Cyano-5-(thien-3-yl)methoxy]phenoxy-(2-methyl)phenylacetic Acid 13e. Obtained as a white solid, mp 109−110 °C (flash chromatography with ethyl acetate followed by trituration with diethyl ether). ^{1}H NMR ($CDCl_3$): δ 7.64 (dd, J = 8, 2 Hz, 1H), 7.50 (d, J = 9 Hz, 1H), 7.33 (dd, J = 5, 3 Hz, 1H), 7.29 (m, 3H), 7.22 (td, J = 7, 3 Hz, 1H), 7.09 (dd, J = 6, 2 Hz, 1H), 6.62 (dd, J = 9, 2 Hz, 1H), 6.43 (d, J = 2 Hz, 1H), 5.85 (s, 1H), 5.05 (s, 2H), 2.50 (s, 3H). Anal. ($C_{21}H_{17}NO_4S$) C, H, N, S.

[*R,S*]-[2-Cyano-5-(thien-3-yl)methoxy]phenoxy-(2-methoxy)phenylacetic Acid 13f. Obtained as a yellow solid, mp 118−20 °C (trituration with pentane). ^{1}H NMR ($CDCl_3$): δ 7.61 (dd, J = 8, 3 Hz, 1H), 7.47 (d, J = 9 Hz, 1H), 7.47 (m, 2H), 7.40 (m, 1H), 7.11 (dd, J = 5, 1 Hz, 1H), 7.03 (t, J = 8 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 6.60 (m, 2H), 6.16 (s, 1H), 5.04 (dd, J = 12, 3 Hz, 2H), 3.92 (s, 3H). Anal. ($C_{21}H_{17}NO_5S$, $0.75H_2O$) C, H, N, S.

[*R,S*]-[2-Cyano-5-(thien-3-yl)methoxy]phenoxy-(2-trifluoromethyl)phenylacetic Acid 13g. Obtained as a white solid, mp 39−40 °C (trituration with diethyl ether/pentane). ^{1}H NMR ($CDCl_3$): δ 7.95 (d, J = 8 Hz, 1H), 7.72 (d, J = 8 Hz, 1H), 7.65 (t, J = 8 Hz, 1H), 7.54 (d, J = 7 Hz, 1H), 7.50 (d, J = 10 Hz, 1H), 7.35 (dd, J = 5, 3 Hz, 1H), 7.30 (m, 1H), 7.10 (dd, J = 6, 2 Hz, 1H), 6.64 (dd, J = 9, 2 Hz, 1H), 6.54 (d, J = 2 Hz, 1H), 6.09 (s, 1H), 5.06 (dd, J = 12, 3 Hz, 2H). Anal. ($C_{21}H_{14}F_3NO_4S$) C, H, N.

[*R,S*]-(3-Chloro)phenyl-[2-cyano-5-(thien-3-yl)methoxy]phenoxyacetic Acid 13h. Obtained as a white solid, mp 134−6 °C (flash chromatography with ethyl acetate followed by trituration with diethyl ether/pentane). ^{1}H NMR ($CDCl_3$): δ 7.60 (m, 1H), 7.54 (dt, J = 7, 1 Hz, 1H), 7.52 (d, J = 9 Hz, 1H), 7.35 (m, 3H), 7.29 (dd, J = 4, 1 Hz, 1H), 7.09 (dd, J = 6, 2 Hz, 1H), 6.65 (dd, J = 9, 2 Hz, 1H), 6.44 (d, J = 3 Hz, 1H), 5.52 (s, 1H), 5.06 (m, 2H), 3.49 (q, J = 7 Hz, 2H), 1.20 (t, J = 7 Hz, 3H). Anal. ($C_{20}H_{14}ClNO_4S$, $0.5C_4H_{10}O$) C, H, N.

[*R,S*]-(4-Chloro)phenyl-[2-cyano-5-(thien-3-yl)methoxy]phenoxyacetic Acid 13i. Obtained as a cream solid, mp 158−60 °C (trituration with pentane). ^{1}H NMR ($CDCl_3$): δ 7.55 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 1H), 7.38 (m, 4H), 7.08 (d, J = 3 Hz, 1H), 6.66 (dd, J = 9, 2 Hz, 1H), 6.44(s, 1H), 5.63 (s, 1H), 5.08 (s, 2H). Anal. ($C_{20}H_{14}ClNO_4S$) C, H, N, S.

[*R,S*]-[5-(Benzo(1,3)dioxol-5-yl)methoxy-2-cyano]phenoxy-(2-trifluoromethyl)phenylacetic Acid 14d. Obtained as a white solid, mp 137−8 °C (flash chromatography with 5% MeOH in CH_2Cl_2 followed by trituration with diisopropyl ether/pentane). ^{1}H NMR ($CDCl_3$): δ 7.94 (d, J = 9 Hz, 1H), 7.72 (d, J = 9 Hz, 1H), 7.74 (t, J = 8 Hz, 1H), 7.53 (t, J = 8 Hz, 1H), 7.48 (d, J = 9 Hz, 1H), 6.82 (m, 3H), 6.63 (dd, J = 9, 3 Hz, 1H), 6.52 (d, J = 3 Hz, 1H), 6.18 (s, 1H), 5.97 (s, 2H), 4.93 (dd, J = 12, 3 Hz, 2H). Anal. ($C_{24}H_{16}F_3NO_6$) C, H, N.

[*R,S*]-[5-(Benzo(1,3)dioxol-5-yl)methoxy-2-cyano]phenoxy-(2-chloro)phenylacetic Acid 14e. Obtained as a cream solid, mp 144−5 °C (flash chromatography with 4:1 pentane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 7.70 (m, 1H), 7.47 (d, J = 9 Hz, 1H), 7.41 (m, 1H), 7.30 (m, 2H), 6.84 (m, 1H), 6.80 (t, J = 7 Hz, 2H), 6.60 (dd, J = 9, 2 Hz, 1H), 6.51 (m, 1H), 6.28 (s, 1H), 5.98 (s, 2H), 4.92 (dd, J = 12, 4 Hz, 2H). Anal. ($C_{23}H_{16}ClNO_6$) C, H, N.

[*R,S*]-[5-(Benzo(1,3)dioxol-5-yl)methoxy-2-cyano]phenoxyphenylacetic Acid 14f. Obtained as a cream solid, mp 127−8 °C (flash chromatography with a solvent gradient of 20% to 30% ethyl acetate in pentane). ^{1}H NMR ($CDCl_3$): δ 7.61 (m, 2H), 7.50 (d, J = 9 Hz, 1H), 7.41 (m, 3H), 6.84 (m, 1H), 6.80 (m, 2H), 6.61 (dd, J = 9, 3 Hz, 1H), 6.44 (d, J = 3 Hz, 1H), 5.97 (s, 2H), 5.66 (s, 1H), 4.92 (s, 2H). Anal. ($C_{23}H_{17}NO_6$, $0.6H_2O$) C, H, N.

General Method B. [*R,S*]-[2-Cyano-5-(thien-3-yl)-methoxy]phenoxyfuran-3-ylacetic Acid 13j. A solution of α-hydroxyfuran-3-ylacetic acid[23] (0.35 g, 2.46 mmol) in DMSO (8 mL) was treated with NaH (60% dispersion, 0.20 g, 5.00 mmol) and stirred at room temperature for 5 min. A solution of 2-fluoro-4-(thien-3-yl)methoxybenzonitrile **22a**[18] (0.57 g, 2.45 mmol) in DMSO (2 mL) was then added dropwise. The reaction mixture was stirred at room temperature for 3h before quenching with H_2O (50 mL) and washing with ethyl acetate (2 × 50 mL). The aqueous layer was acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 50 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography, eluting with a solvent gradient of 1:1 pentane/ethyl acetate to ethyl acetate, gave 0.40 g (46%) of **13j** as a white solid, mp 100−2 °C. ^{1}H NMR ($CDCl_3$): δ 7.68 (s, 1H), 7.52 (d, J = 9 Hz, 1H), 7.45 (m, 1H), 7.37 (dd, J = 5, 3 Hz, 1H), 7.42 (m, 1H), 7.11 (d, J = 7 Hz, 1H), 6.66 (dd, J = 9, 3 Hz, 1H), 6.61 (m, 1H), 6.49 (d, J = 3 Hz, 1H), 5.69 (s, 1H), 5.08 (s, 2H). Anal. ($C_{18}H_{13}NO_5S$) C, H, N.

The following compounds were similarly prepared:

[*R,S*]-[2-Cyano-5-(thiophen-3-yl)methoxy]phenoxyfuran-2-ylacetic Acid 13k. Obtained as a brown solid, mp 85−7 °C (flash column with solvent gradient of 2% to 20% MeOH in CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 7.47 (d, J = 8 Hz, 1H), 7.44 (m, 1H), 7.35 (dd, J = 5, 3 Hz, 1H), 7.32 (m, 1H), 7.11 (dd, J = 5, 1 Hz, 1H), 6.63 (dd, J = 9, 3 Hz, 1H), 6.59 (d, J = 3 Hz, 1H), 6.56 (d, J = 3 Hz, 1H), 6.38 (m, 1H), 5.73 (s, 1H), 5.06 (s, 2H). Anal. ($C_{18}H_{13}NO_5S$) C, H, N.

[*R,S*]-[2-Cyano-5-(pyrid-4-yl)methoxy]phenoxythien-3-ylacetic Acid 13l. Obtained as a white solid, mp 179−80 °C (recrystallized from ethyl acetate/cyclohexane). ^{1}H NMR ($CDCl_3$): δ 8.64 (d, J = 6 Hz, 2H), 7.60 (m, 1H), 7.53 (d, J = 8 Hz, 1H), 7.34 (m, 4H), 6.62 (dd, J = 8, 2 Hz, 1H), 6.55 (d, J = 2 Hz, 1H), 5.76 (s, 1H), 5.12 (s, 2H). IR (KBr): 3433.3 (m), 2219.8 (m), 1722.2 (m), 1606.2 (s) cm^{-1}. Anal. ($C_{19}H_{14}N_2O_4S$) C, H, N.

[*R,S*]-[5-(Benzo(1,3)dioxol-5-yl)methoxy-2-cyano]phenoxy-(2-methyl)phenylacetic Acid 14c. Obtained as a white solid, mp 124−5 °C (flash column with solvent gradient of 1:1 ethyl acetate/pentane to ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 7.63 (dd, J = 7, 3 Hz, 1H), 7.49 (d, J = 9 Hz, 1H), 7.38 (m, 2H), 7.21 (dd, J = 7, 3 Hz, 1H), 6.84 (s, 1H), 6.80 (m, 2H), 6.60 (dd, J = 9, 3 Hz, 1H), 6.42 (d, J = 3 Hz, 1H), 5.97 (s, 2H), 5.84 (s, 1H), 4.91 (s, 2H), 2.50 (s, 3H). Anal. ($C_{24}H_{19}NO_6$) C, H, N.

[*R,S*]-[2-Cyano-5-(thiazol-5-yl)methoxy]phenoxy-(2-methyl)phenylacetic Acid 15c. Obtained as a white solid, mp 226−7 °C (recrystallized from ethyl acetate/cyclohexane). ^{1}H NMR (DMSO-d_6): δ 9.15 (s, 1H), 8.04 (s, 1H), 7.70 (d, J = 9 Hz, 1H), 7.51 (dd, J = 9, 2 Hz, 1H), 7.28 (m, 3H), 6.94 (d, J = 3 Hz, 1H), 6.82 (dd, J = 9, 3 Hz, 1H), 6.26 (s, 1H), 5.49 (s, 2H), 2.46 (s, 3H). IR (KBr) 3433.2 (m), 2219.8 (m), 1732.7 (m), 1609.7 (s) cm^{-1}. Anal. ($C_{20}H_{16}N_2O_4S$, H_2O) C, H, N.

[*R,S*]-[2-Cyano-5-(pyrid-2-yl)methoxy]phenoxy-(2-methyl)phenylacetic Acid 15d. Obtained as a yellow solid, mp 189−91 °C (recrystallized from ^{i}PrOH). ^{1}H NMR (DMSO-d_6): δ 8.60 (d, J = 5 Hz, 1H), 7.85 (td, J = 8, 2 Hz, 1H), 7.68 (d, J = 8 Hz, 1H), 7.52 (t, J = 8 Hz, 2H), 7.38 (dd, J = 8, 6 Hz, 1H), 7.27 (m, 3H), 6.97 (d, J = 3 Hz, 1H), 6.80 (dd, J = 8, 2 Hz, 1H), 6.25 (s, 1H), 5.26 (dd, J = 14, 3 Hz, 2H), 2.47 (s, 3H). Anal. ($C_{22}H_{18}N_2O_4$) C, H, N.

[*R,S*]-[2-Cyano-5-(pyrid-4-yl)methoxy]phenoxy-(2-methyl)phenylacetic Acid 15e. Obtained as a yellow solid, mp 193−4 °C (flash chromatography with a solvent gradient of 0−20% MeOH in ethyl acetate). ^{1}H NMR (DMSO-d_6): δ 8.60 (dd, J = 6, 2 Hz, 2H), 7.69 (d, J = 8 Hz, 1H), 7.49 (m, 1H), 7.43 (d, J = 6 Hz, 2H), 7.27 (m, 3H), 6.96 (d, J = 3 Hz, 1H), 6.88 (dd, J = 8, 2 Hz, 1H), 6.25 (s, 1H), 5.28 (m, 2H), 2.46 (s, 3H). Anal.($C_{22}H_{18}N_2O_4$) C, H, N.

General Method C. [*R,S*]-(5-Benzyloxy-2-cyano)phenoxy-(2-methyl)phenylacetic Acid 14a. (i) 4-Allyloxy-2-hydroxybenzonitrile 18b. This was prepared as for **18a** and obtained as a white solid (recrystallization from diisopropyl ether). ^{1}H NMR ($CDCl_3$): δ 7.36 (d, J = 9 Hz, 1H), 6.52 (d, J = 3 Hz, 1H), 6.44 (dd, J = 9, 3 Hz, 1H), 6.01 (ddt, J = 17, 10, 5 Hz, 1H), 5.41 (dd, J = 17, 2 Hz, 1H), 5.31 (dd, J = 10, 2 Hz, 1H), 4.52 (dt, J = 5, 2 Hz, 2H).

(ii) [R,S]-Methyl (5-Allyloxy-2-cyano)phenoxy-(2-methyl)phenylacetate 24a. This was prepared by alkylation of **18b** following the method for **19a** and obtained as a white solid, mp 87−90 °C (trituration with diisopropyl ether). ^{1}H NMR ($CDCl_3$): δ 7.65 (m, 1H), 7.50 (d, J = 9 Hz, 1H), 7.28 (m, 2H), 7.23 (m, 1H), 6.56 (dd, J = 9, 2 Hz, 1H), 6.40 (d, J = 2 Hz, 1H), 6.00 (ddt, J = 17, 10, 5 Hz, 1H), 5.86 (s, 1H), 5.90 (dd, J = 17, 2 Hz, 1H), 5.33 (dd, J = 10, 2 Hz, 1H), 4.53 (dt, J = 5, 2 Hz, 2H), 3.75 (s, 3H), 2.51 (s, 3H).

(iii) [*R,S*]-Methyl (2-Cyano-5-hydroxy)phenoxy-(2-methyl)phenylacetate 23a. A solution of **24a** (17.9 g, 53.0 mmol) in MeOH was treated with DABCO (11.9 g, 106 mmol) and Wilkinsons catalyst (2.45 g, 2.65 mmol) and stirred at reflux for 2 h. The reaction mixture was concentrated to a brown oil, which was dissolved in ethyl acetate (500 mL) and washed successively with 2 M HCl, H_2O, and brine (200 mL each), dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (1:1 ethyl acetate/pentane) then trituration with pentane gave 9.5 g (60%) of **23a** as a white solid, mp 118−21 °C. ^{1}H NMR ($CDCl_3$): δ 7.61 (dd, J = 8, 2 Hz, 1H), 7.39 (d, J = 9 Hz, 1H), 7.27 (m, 1H), 7.21 (td, J = 8, 2 Hz, 2H), 6.52 (dd, J = 8, 2 Hz, 1H), 6.37 (d, J = 2 Hz, 1H), 5.86 (s, 1H), 3.73 (s, 3H), 2.49 (s, 3H). Anal. ($C_{17}H_{15}NO_4$) C, H, N.

(iv) [*R,S*]-Methyl (5-Benzyloxy-2-cyano)phenoxy-(2-methyl)phenylacetate 19b. This was prepared by alkylation of **23a** following the method for **19a** and obtained as an off-white solid, mp 134−6 °C (trituration with pentane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 7.64 (m, 1H), 7.51 (d, J = 8 Hz, 1H), 7.39 (m, 5H), 7.30 (m, 2H), 7.21 (m, 1H), 6.63 (d, J = 8 Hz, 1H), 6.46 (s, 1H), 5.83 (s, 1H), 5.06 (s, 2H), 3.72 (s, 3H), 2.49 (s, 3H).

(v) [*R,S*]-(5-Benzyloxy-2-cyano)phenoxy-(2-methyl)-phenylacetic Acid 14a. This was prepared by hydrolysis of **19b** following the method for **13a** and obtained as a white solid, mp 128−30 °C (flash chromatography with 5% MeOH in CH_2Cl_2 then trituration with diethyl ether/pentane). ^{1}H NMR ($CDCl_3$): δ 7.63 (dd, J = 7, 3 Hz, 1H), 7.50 (d, J = 9 Hz, 1H), 7.34 (m, 5H), 7.28 (m, 2H), 7.22 (td, J = 6, 2 Hz, 1H),

6.63 (dd, $J = 9$, 3 Hz, 1H), 6.44 (d, $J = 3$ Hz, 1H), 5.84 (s, 1H), 5.03 (s, 2H), 2.49 (s, 3H). Anal.$C_{23}H_{19}NO_4$) C, H, N.

Also prepared by this method were the following compounds:

[*R,S*]-[2-Cyano-5-(2,6-dimethyl)benzyloxy]phenoxy-(2-methyl)phenylacetic Acid 14b. Obtained as a white solid, mp 189−91 °C (trituration with pentane). ^{1}H NMR ($CDCl_3$): δ 7.67 (m, 1H), 7.54 (d, $J = 8$ Hz, 1H), 7.23 (m, 4H), 7.08 (d, $J = 7$ Hz, 2H), 6.70 (d, $J = 9$ Hz, 1H), 6.55 (s, 1H), 5.81 (s, 1H), 5.04 (s, 2H), 2.53 (s, 3H), 2.38 (s, 6H). Anal. ($C_{25}H_{23}NO_4$) C, H, N.

[*R,S*]-[5-(Benzo(1,3)dioxol-4-yl)methoxy-2-cyano]phenoxy-(2-methyl)phenylacetic Acid 14g. Obtained as a white solid, mp 178−80 °C (trituration with diethyl ether). ^{1}H NMR (DMSO-d_6): δ 7.69 (d, $J = 8$ Hz, 1H), 7.52 (d, $J = 8$ Hz, 1H), 7.28 (m, 3H), 6.94 (m, 4H), 6.80 (d, $J = 9$ Hz, 1H), 6.26 (s, 1H), 6.07 (s, 2H), 5.11 (s, 2H), 2.46 (s, 3H). Anal. $C_{24}H_{19}NO_6$) C, H, N.

[*R,S*]-[2-Cyano-5-(3,4,5-trimethoxy)benzyloxy]phenoxy-(2-methyl)phenylacetic Acid 14h. Obtained as a white solid, mp 67−9 °C (trituration with pentane). ^{1}H NMR (DMSO-d_6): δ 7.64 (d, $J = 8$ Hz, 1H), 7.51 (d, $J = 8$ Hz, 1H), 7.24 (m, 3H), 6.64, d, $J = 9$ Hz, 1H), 6.60 (s, 2H), 6.46 (s, 1H), 5.83 (s, 1H), 4.94 (s, 2H), 3.95 (s, 9H), 2.48 (s, 3H). Anal. ($C_{26}H_{25}NO_7$) C, H, N.

[*R,S*]-[2-Cyano-5-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-methoxy]phenoxy-(2-methyl)phenylacetic Acid 14i. Obtained as a white solid, mp 153−5 °C (trituration with diethyl ether). ^{1}H NMR ($CDCl_3$): δ 7.66 (m, 1H), 7.48 (d, $J = 9$ Hz, 1H), 7.21 (m, 3H), 6.91 (s, 1H), 6.88 (s, 2H), 6.60 (d, $J = 9$ Hz, 1H), 6.53 (s, 1H), 5.79 (s, 1H), 4.95 (s, 2H), 4.28 (s, 4H), 2.51 (s, 3H). Anal. ($C_{25}H_{21}NO_6$) C, H, N.

[*R,S*]-[2-Cyano-5-(fur-3-yl)methoxy]phenoxy-(2-methyl)phenylacetic Acid 15a. Obtained as a white solid, mp 132−4 °C (flash chromatography with 5% MeOH in CH_2Cl_2 then trituration with pentane). ^{1}H NMR ($CDCl_3$): δ 7.64 (dd, $J = 7$, 2 Hz, 1H), 7.51 (d, $J = 7$ Hz, 1H), 7.47 (s, 1H), 7.42 (t, $J = 3$ Hz, 1H), 7.27 (m, 3H), 6.62 (dd, $J = 7$, 2 Hz, 1H), 6.44 (d, $J = 2$ Hz, 1H), 6.43 (d, $J = 3$ Hz, 1H), 5.86 (s, 1H), 4.92 (s, 2H), 2.51 (s, 3H). Anal. ($C_{21}H_{17}NO_5$) C, H, N.

[*R,S*]-[2-Cyano-5-(isothiazol-3-yl)methoxy]phenoxy-(2-methyl)phenylacetic Acid 15b. Obtained as a light gray solid, mp 165−7 °C (trituration with pentane). ^{1}H NMR (DMSO-d_6): δ 9.12 (d, $J = 5$ Hz, 1H), 7.68 (d, $J = 8$ Hz, 1H), 7.50 (dd, $J = 7$, 2 Hz, 1H), 7.48 (d, $J = 5$ Hz, 1H), 7.28 (m 3H), 6.95 (d, $J = 3$H, 1H), 6.80 (dd, $J = 8$, 2 Hz, 1H), 6.24 (s, 1H), 5.84 (s, 2H), 2.46 (s, 3H). Anal. ($C_{20}H_{16}N_2O_4S$, $0.5H_2O$) C, H, N, S.

[*R,S*]-(2-Chloro)phenyl-[2-cyano-5-(pyrid-4-yl)methoxy]phenoxyacetic Acid 15f. Obtained as a white solid, mp 225−6 °C (recrystallization with ^{i}PrOH). ^{1}H NMR (DMSO-d_6): δ 8.59 (dd, $J = 7$, 2 Hz, 2H), 7.68 (d, $J = 9$ Hz, 1H), 7.59 (m, 1H), 7.53 (m, 1H), 7.43 (m, 4H), 6.91 (d, $J = 2$ Hz, 1H), 6.79 (dd, $J = 9$, 2 Hz, 1H), 6.33 (s, 1H), 5.28 (s, 2H). Anal. ($C_{21}H_{15}ClN_2O_4$) C, H, N.

[*R,S*]-[2-Cyano-5-(pyrid-3-yl)methoxy]phenoxy-(2-methyl)phenylacetic Acid 15g. Obtained as a white solid (recrystallization with MeOH/ethyl acetate). ^{1}H NMR (DMSO-d_6): δ 8.70 (s, 1H), 8.59 (d, $J = 8$ Hz, 1H), 7.91 (d, $J = 8$ Hz, 1H), 7.68 (d, $J = 9$ Hz, 1H), 7.47 (m, 2H), 7.26 (m, 3H), 6.94 (s, 1H), 6.82 (d, $J = 9$ Hz, 1H), 6.12 (s, 1H), 5.23 (s, 2H), 2.46 (s, 3H). Anal. ($C_{22}H_{18}N_2O_4$, $0.2H_2O$) C, H, N.

[*R,S*]-[2-Cyano-5-(2-fluoropyrid-4-yl)methoxy]phenoxy-(2-methyl)phenylacetic Acid 15h. Obtained as a white solid, mp 178−9 °C (recrystallization with pentane/ethyl acetate). ^{1}H NMR (DMSO-d_6): δ 8.27 (d, $J = 5$ Hz, 1H), 7.72 (d, $J = 8$ Hz, 1H), 7.49 (dd, $J = 8$, 3 Hz, 1H), 7.39 (d, $J = 6$ Hz, 1H), 7.28 (m, 3H), 7.23 (s, 1H), 6.98 (d, $J = 3$ Hz, 1H), 6.79 (dd, $J = 9$, 3 Hz, 1H), 6.25 (s, 1H), 5.34 (s, 2H), 2.45 (s, 3H). Anal. ($C_{22}H_{17}FN_2O_4$) C, H, N.

[*R,S*]-(2-Chloro)phenyl-[2-cyano-5-(pyridazin-4-yl)-methoxy]phenoxyacetic Acid 15i. Obtained as a white solid, mp 203−5 °C (trituration with diethyl ether). ^{1}H NMR (DMSO-d_6): δ 9.32 (s, 1H), 9.26 (d, $J = 7$ Hz, 1H), 7.73 (m, 2H), 7.57 (m, 2H), 7.44 (m, 2H), 6.97 (s, 1H), 6.82 (s, $J = 9$ Hz, 1H), 6.37 (s, 1H), 5.38 (s, 2H). Anal. ($C_{20}H_{14}ClN_3O_4$) C, H, N.

[*R,S*]-[5-(Benzoxazol-6-yl)methoxy-2-cyano]phenoxy-(2-chloro)phenylacetic Acid 15j. Obtained as a buff solid, mp 175−8 °C (flash chromatography with 14:1 CH_2Cl_2/MeOH). ^{1}H NMR (DMSO-d_6): δ 8.78 (s, 1H), 7.89 (s, 1H), 7.83 (d, $J = 9$ Hz, 1H), 7.69 (d, $J = 8$ Hz, 1H), 7.60 (m, 1H), 7.54 (m, 1H), 7.50 (dd, $J = 8$, 2 Hz, 1H), 7.44 (m, 2H), 6.92 (d, $J = 3$ Hz, 1H), 7.83 (dd, $J = 9$, 2 Hz, 1H), 6.32 (s, 1H), 5.32 (s, 2H). Anal. ($C_{23}H_{15}ClN_2O_5$, $0.5H_2O$) C, H, N.

[*R,S*]-[5-(Benzoxazol-6-yl)methoxy-2-cyano]phenoxy-(2-methyl)phenylacetic Acid 15k. Obtained as a cream solid, mp 207−9 °C (flash chromatography with 29:1 CH_2Cl_2/MeOH). ^{1}H NMR ($CDCl_3$): δ 8.17 (s, 1H), 7.82 (d, $J = 8$ Hz, 1H), 7.66 (m, 2H), 7.50 (d, $J = 8$ Hz, 1H), 7.42 (d, $J = 8$ Hz, 1H), 7.25 (t, $J = 4$ Hz, 2H), 7.19 (t, $J = 4$ Hz, 1H), 6.64 (dd, $J = 8$, 2 Hz, 1H), 6.56 (d, $J = 2$ Hz, 1H), 5.79 (s, 1H), 5.20 (dd, $J = 11$, 2 Hz, 2H), 2.50 (s, 3H). Anal. ($C_{24}H_{18}N_2O_5$, $0.5H_2O$) C, H, N.

[*R,S*]-[5-(Benzoxazol-5-yl)methoxy-2-cyano]phenoxy-(2-methyl)phenylacetic Acid 15l. Obtained as a white solid, mp 189−91 °C (recrystallization from ethyl acetate). ^{1}H NMR (DMSO-d_6): δ 8.39 (s, 1H), 7.92 (s, 1H), 7.81 (d, $J = 8$ Hz, 1H), 7.69 (d, $J = 8$ Hz, 1H), 7.55 (dd, $J = 7$, 2 Hz, 1H), 7.50 (m, 1H), 7.26 (m, 3H), 6.94 (d, $J = 3$ Hz, 1H), 6.82 (dd, $J = 9$, 3 Hz, 1H), 6.22 (s, 1H), 5.31 (s, 2H), 2.46 (s, 3H). Anal. ($C_{24}H_{18}N_2O_5$, $0.5H_2O$) C, H, N.

General Procedure for Resolution of Enantiomers and Subsequent Formation of Sodium Salts. (i) (+)-[5-(Benzo(1,3)dioxol-5-yl)methoxy-2-cyano]phenoxy-(2-methyl)phenylacetic Acid, (−)-Ephedrine Salt 25a. A suspension of **14c** (48.8 g, 117 mmol) in diethyl ether (500 mL) and ethyl acetate (150 mL) was treated dropwise with a solution of (−)-ephedrine (19.3 g, 117 mmol) in diethyl ether (150 mL) at room temperature. The reaction mixture was allowed to stand overnight, and the biege solid formed was isolated by filtration. Two recrystallizations from ethyl acetate gave 25.95 g (38%) of **25a** as a white solid, mp 170−3 °C. Chiral HPLC indicated a de of >99.9%. ^{1}H NMR (DMSO-d_6): δ 7.59 (d, $J = 8$ Hz, 1H), 7.54 (t, $J = 4$ Hz, 1H), 7.33 (m, 4H), 7.26 (m, 1H), 7.17 (m, 3H), 7.01 (d, $J = 2$ Hz, 1H), 6.93 (td, $J = 8$, 3 Hz, 1H), 6.91 (d, $J = 8$ Hz, 1H), 6.70 (d, $J = 3$ Hz, 1H), 6.66 (dd, $J = 9$, 3 Hz, 1H), 6.02 (s, 2H), 5.57 (bs, 1H), 5.01 (m, 3H), 3.23 (m, 1H), 2.54 (s, 3H), 2.52 (m, 1H), 2.46 (s, 3H), 0.85 (d, $J = 7$ Hz, 3H). Anal. ($C_{34}H_{34}N_2O_7$) C, H, N.

Also prepared by this method was the following compound:

(+)-(2-Cyano-5-(pyrid-4-yl)methoxy)phenoxy-(2-methyl)phenylacetic Acid, (−)-Ephedrine Salt 25b. A solution of **15e** (16.1 g, 43.0 mmol) in EtOH (130 mL) was treated with (−)-ephedrine (8.05 g, 48.7 mmol) and stirred at room temperature for 1 h. The reaction mixture was allowed to stand overnight, and the solid was filtered off. Recrystallization from EtOH gave 9.9 g (43%) of **25b** as a white solid, mp 172−4 °C. Chiral HPLC indicated a de of 99.5%.

(ii) (+)-[5-(Benzo(1,3)dioxol-5-yl)methoxy-2-cyano]phenoxy-(2-methyl)phenylacetic Acid 26a. A suspension of **25a** (22.4 g, 38.4 mmol) in ethyl acetate (1 L) was treated with 2 M HCl (500 mL) and stirred vigorously at room temperature for 1 h. The organic layer was separated, washed with 2 M HCl and brine (200 mL each), dried over $MgSO_4$, filtered, and concentrated to a yellow oil. Trituration with ether/pentane gave 15.5 g (97%) of **26a** as a white glassy foam, mp 53−7 °C. Chiral HPLC indicated an ee of 99.4%. Optical rotation of (+) 0.57 ($c = 0.485$ g/100 mL, MeOH). ^{1}H NMR ($CDCl_3$): δ 7.63 (dd, $J = 7$, 3 Hz, 1H), 7.50 (d, $J = 8$ Hz, 1H), 7.28 (m, 2H), 7.22 (td, $J = 7$, 3 Hz, 1H), 6.82 (m, 3H), 6.61 (dd, $J = 9$, 2 Hz, 1H), 6.43 (d, $J = 2$ Hz, 1H), 5.98 (s, 2H), 5.84 (s, 1H), 4.92 (s, 2H), 2.50 (s, 3H). Anal. ($C_{24}H_{19}NO_6$) C, H, N.

Also prepared by this method was the following compound:

(+)-(2-Cyano-5-(pyrid-4-yl)methoxy)phenoxy-(2-methyl)phenylacetic Acid 26b. A mixture of **25b** (17.3 g, 32.0 mmol) in H_2O (1.7 L) was treated with 1 M HCl (32 mL). The pH of the reaction mixture was adjusted to 4.5 with 1 M NaOH and stirred for 20 min. Filtration and drying gave 10.8 g (90%)

of **26b** as a white solid, mp 228−30 °C. Chiral HPLC indicated an ee of 99.9%. ^{1}H NMR (DMSO-d_6): δ 8.60 (dd, J = 6, 2 Hz, 2H), 7.71 (d, J = 8 Hz, 1H), 7.50 (dd, J = 7, 2 Hz, 1H), 7.44 (d, J = 6 Hz, 2H), 7.28 (m, 3H), 6.98 (d, J = 3 Hz, 1H), 6.79 (dd, J = 9, 3 Hz, 1H), 6.26 (s, 1H), 5.28 (s, 2H), 2.45 (s, 3H). Anal. ($C_{22}H_{18}N_2O_4$) C, H, N.

(iii) (+)-[5-(Benzo(1,3)dioxol-5-yl)methoxy-2-cyano]-phenoxy-(2-methyl)phenylacetic Acid, Sodium Salt 27a. A suspension of **26a** (13.5 g, 32.3 mmol) in H_2O (50 mL) was treated with 0.1 M NaOH (323 mL) and stirred at room temperature for 1 h. The reaction mixture was filtered, and the filtrate was concentrated to constant weight. Recrystallization from ^{n}BuOH gave 8.15 g (57%) of **27a** as a white solid, mp 212−4 °C. Chiral HPLC indicated an ee of >99.9%. ^{1}H NMR (DMSO-d_6): δ 7.59 (d, J = 9 Hz, 1H), 7.54 (t, J = 6 Hz, 1H), 7.15 (m, 3H), 7.04 (d, J = 2 Hz, 1H), 6.98 (dd, J = 8, 2 Hz, 1H), 6.93 (d, J = 8 Hz, 1H), 6.65 (m, 2H), 6.02 (s, 2H), 5.43 (s, 1H), 5.01 (dd, J = 17, 13 Hz, 2H), 2.46 (s, 3H). Anal. ($C_{24}H_{18}NNaO_6$) C, H, N.

Also prepared by this method was the following compound:

(+)-2-(2-Cyano-5-(pyrid-4-yl)methoxy)phenoxy-2-(2-methyl)phenylacetic Acid, Sodium Salt 27b. Obtained as a white solid, mp 180−3 °C. Chiral HPLC indicated >99.9% ee. ^{1}H NMR (DMSO-d_6): δ 8.60 (d, J = 5 Hz, 2H), 7.61 (d, J = 8 Hz, 1H), 7.54 (m, 1H), 7.43 (m, 2H), 7.14 (m, 3H), 6.72 (d, J = 3 Hz, 1H), 6.66 (dd, J = 8, 3 Hz, 1H), 5.43 (s, 1H), 5.22 (dd, J = 16, 12 Hz, 2H), 2.46 (s, 3H). Anal. ($C_{22}H_{17}N_2NaO_4$) C, H, N.

Acknowledgment. The authors thank the following people for their contributions to the work described herein: Joanne Allen, Adnan Al-Shaar, Mark Birrell, Roman Brazdil, Clive Brealey, Devnandan Chatterjee, Shelly Darnborough, Declan Flynn, Brian Pedgrift, Robert Petheram, Jeffrey Philips, Anne White, and Melanie Wong.

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JM990378B