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Synthesis and Activity of Bivalent FKBP12 Ligands for the Regulated Dimerization of Proteins

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Abstract—The total synthesis and in vitro activities of a series of chemical inducers of dimerization (CIDs) is described. The use of small-molecule CIDs to control the dimerization of engineered FKBP12-containing fusion proteins has been demonstrated to have broad utility in biological research as well as potential medical applications in gene and cell therapies. The facility and flexibility of preparation make this new class of wholly synthetic compounds exceptionally versatile tools for the study of intracellular signaling events mediated by protein–protein interactions or protein localization. While some congeners possess potency comparable to or better than the first generation natural product-derived CID, FK1012, structure–activity relationships are complex and underscore the need for application-specific compound optimizations. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Introduction

In a seminal 1993 *Science* paper, Stuart Schreiber and long-time collaborator Gerald Crabtree, demonstrating a powerful union of chemistry and biology, described a method for inducing the dimerization of artificial intracellular protein receptors with cell permeable ligands.[1] This method provided a means of temporally controlling specific signal transduction pathways and gene expressions with small-molecules. Since their initial report, small-molecule induced protein dimerization has been utilized to study a wide range of intracellular signaling events which are naturally mediated by protein–protein interactions or protein localization. In this way, dose-dependent small-molecule control has been brought over signaling pathways initiated by the T-cell receptor,[1,2] erythropoietin receptor,[3] PDGF and insulin receptors,[4] c-kit receptor,[5] Fas,[6–10] Src kinase,[11] Sos,[12] Raf kinase,[13,14] ZAP kinase,[15] LMP1,[16] and FLICE.[17–19] Clustering of cadherin[20] and localization of proteins to the plasma membrane[9,11,12,15,16,21] and into or out of the nucleus[9,22] have also been effected. In addition, small-molecule controlled reconstitution of multidomain transcription factors has provided a direct means of regulating gene expression[9,10,21,23–25] and has thus enabled a medicinally important means of delivering therapeutic proteins via gene therapy. Toward this end, pharmacologic control of the production of human growth hormone in vivo has been achieved using an orally active small-molecule.[25,26]

The crux of the original Schreiber and Crabtree method was the use of a semi-synthetic dimer of the natural product FK506, aptly named FK1012.[1,27] By virtue of its bivalent affinity for FK506-binding protein (FKBP12), FK1012 is a chemical inducer of dimerization (CID) which is able to dimerize[28] or oligomerize fusion proteins containing one or more FKBP12 domains (Fig. 1).

To date, FK1012 has been the most widely utilized CID, although related systems based on the natural products cyclosporin (as a semi-synthetic dimer),[8,9,15] coumermycin,[13] and rapamycin[15,21,23,25,26] have also been reported. More recently, we have described a wholly synthetic

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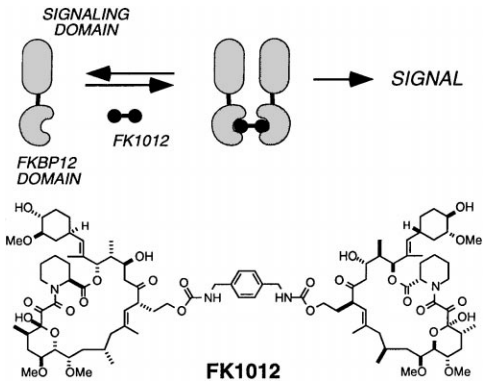


Figure 1. FK1012, a chemical inducer of dimerization (CID).

dimerizer, AP1510, derived from a simple non-macrocyclic FKBP12 ligand.[10] Despite having significantly weaker affinity for FKBP12, AP1510 proved to be comparable to FK1012 in activating Fas-mediated apoptosis and substantially better than FK1012 in activating gene expression.

While small-molecule regulated protein dimerization has already proven to be a versatile and general tool for research and medical applications, its performance in any particular context may be influenced by the nature of the CID employed. Apart from the traditional properties that affect drug efficacy, such as biological stability, cell permeability, and pharmacokinetics, some dimerization-initiated events appear to be especially sensitive to the spatial orientation of the signaling fusion proteins.[10,15] Thus, CID selection from a collection of compounds may be necessary for achieving optimal efficacy. Herein, we report synthetic details and structure–activity studies for one extended family of AP1510 congeners.

Results and Discussion

The X-ray crystal structure of a high-affinity pipecolyl α-ketoamide ligand in complex with FKBP12[29] provided the basis for the original design of wholly synthetic CIDs (Fig. 2). The solvent-exposed 'eastern' phenyl ring served as a convenient site for attachment of a dimerizing linker moiety, while the 'northwestern' phenethyl appendage served as a readily-modifiable stage for introducing additional hydrophilic or hydrophobic functionality. Thus, two series of symmetrical homodimerizers were prepared in which the phenethyl substituents and linker moieties were independently varied. Dimerizers were tested in three previously described assay systems; induction of Fas-mediated apoptosis and induction of gene transcription in transiently or stably transfected cells (Fig. 3).

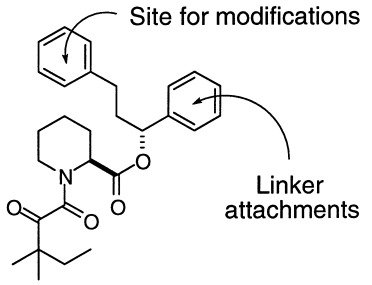


Figure 2. Prototypical synthetic ligand used as basis for synthetic CIDs.

A model synthetic dimerizer, **1a**, having a 10-atom bisamide linker, was prepared and tested in these assays (Table 1). Compound **1a** proved to be essentially inactive in all three assays, showing only very weak induction of transcription in the transiently transfected cells at high concentrations. The diaminoethyl portion of the linker of **1a** was replaced with a number of structurally diverse diamines in an attempt to provide greater flexibility between the monomeric units, but all compounds were devoid of activity in these assays (compounds and data not shown).

The finding that **2a**, the monomeric precursor of **1a**, exhibited a 240-fold lower affinity for FKBP12 than FK506 (Table 2), suggested that a tighter binding monomer might be critical for dimerizer activity. A number of closely related monomers (**2b–e**) were prepared in

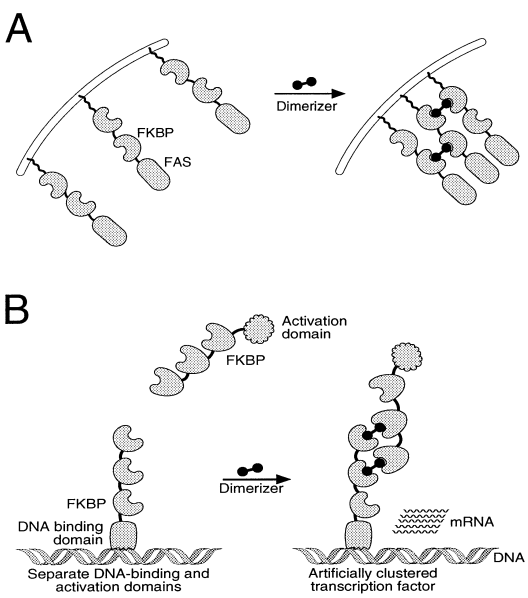
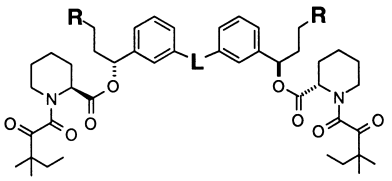
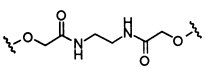
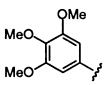
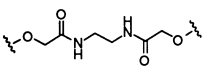
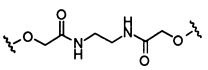
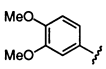
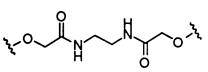
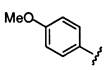
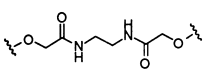
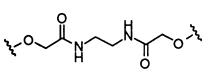
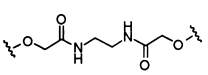
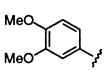
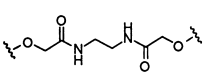
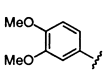
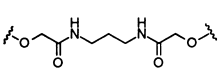
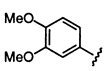
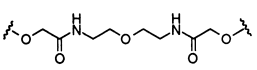
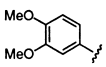
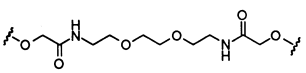
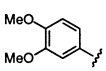
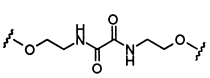


Figure 3. Schemes for obtaining dimerizer-dependent (A) apoptosis via Fas activation; and (B) regulation of gene expression.

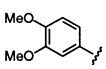
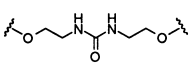
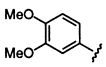
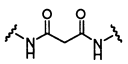
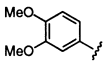
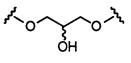
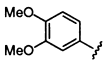
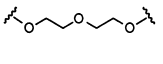
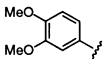
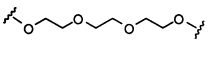
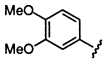
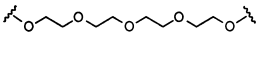
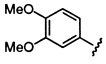
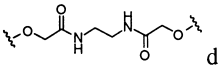
Table 1. In vitro cellular activities of synthetic dimerizers



Compd	R	L	Apoptosis IC_{50} (nM)	Transcription EC_{50} (nM)[a]/% expression[b]	
				transient	stable
1a (AP1932)			> 1000	≥500 (8%)	nc (1%)
1b (AP1930)			≥200	≥250 (50%)	nc (2%)
1c (AP1933)			≥500	≥500 (15%)	nc (1%)
1d (AP1510)			6	15 (100%)	20 (100%)
1e (AP22375)			400	≥300 (60%)	≥500 (23%)
1f (AP1539)			30	≥400 (40%)	nc (2%)
1g (AP1909)			1000	Nc (0%)	nc (1%)
1h[c] (AP22398)			60	≥300 (115%)	≥300 (120%)
1i (AP1908)			20	20 (35%)	nc (3%)
1j (AP1428)			10	15 (75%)	8 (9%)
1k (AP1427)			15	10 (10%)	nc (3%)
1l (AP1980)			80	70 (65%)	≥ 150 (50%)

(continued)

Table 1—*contd*

Compd	R	L	Apoptosis IC_{50} (nM)	Transcription EC_{50} (nM)[a]/% expression[b]	
				transient	stable
1m (AP1981)			6	15 (115%)	25 (110%)
1n (AP3358)			100	70 (50%)	nc (2%)
1o (1871)			700	≥150 (100%)	≥400 (53%)
1p (AP1592)			350	≥250 (85%)	≥400 (60%)
1q (AP1511)			200	≥150 (60%)	nc (2%)
1r (AP1578)			140	80 (25%)	nc (5%)
1s (AP1979)		 d	25	15 (100%)	20 (120%)

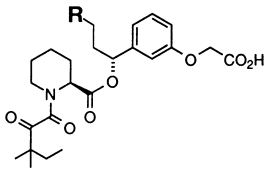
[a]EC_{50}s expressed as ≥ indicate the dimerizer concentration giving half-maximal response when maximal response was observed at the highest concentration tested (1μM); nc indicates no EC_{50} was calculable due to low expression levels.
[b]Peak levels of protein expression normalized to peak expression of **1d** (AP1510).
[c]L-Proline analogue.
[d]Para substituted linker attachment.

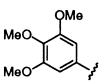
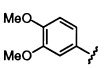
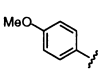
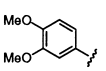
hopes of increasing affinity for FKBP12 by increasing the lipophilicity of the phenethyl appendage. In addition, the possibility that poor water solubility of **1a** might contribute to its inactivity led to the preparation of pyridine- and morpholine-containing monomers **2f** and **2g**, both of which were considered to have vastly improved aqueous solubility compared to **2a**. Of these monomers, only the dimethoxy analogue, **2d**, showed slightly (threefold) enhanced FKBP12 binding while the morpholino analogue, **2g**, was about fourfold weaker than **2a** (Table 2).

A dimerizer series was constructed from the above monomers (**2b–g**) in which the 10-atom bisamide linker of **1a** was held constant while the modifications to the phenethyl substituent were examined (Table 1, **1a–g**). In this series only two dimerizers exhibited significant activity in the Fas assay, the dimethoxyphenyl analogue **1d** (AP1510) and the pyridyl analogue **1f**. In both transcription assays, only **1d** showed activity at low nanomolar concentrations. The trimethoxyphenyl, monomethoxyphenyl and pyridyl compounds, **1b, 1e** and **1f**, respectively, all showed weak activity in the transient transcription assay, but with much higher EC50s and expression levels that were only half that of **1d** at the highest concentration tested (1 μM). In the stable transcription assay, **1e** was the only compound of the initial series other than **1d** that displayed even weak activity.

Although the slightly greater FKBP12 affinity of **2d** was commensurate with the superior cellular activity of its dimer **1d**, its affinity was only threefold better than the original model monomer **2a**. Furthermore, pyridyl analogue **2f** which proved to be reasonably potent in the Fas assay had equivalent FKBP12 affinity to the Fas-inactive analogs **1a** and **1c**. Even more striking, while **1f** was only fivefold less potent than **1d** in the Fas assay, it was at least 25-fold weaker in the transient transcription assay and all but devoid of activity in the stable transcription assay.

Table 2. Affinities of FKBP12 monomeric ligands



Compd	R	IC_{50} (nM)	Rel. affinity
FK506		2.5	0.004
2a		600	1.0
2b		820	1.4
2c		400	0.7
2d		180	0.3
2e		910	1.5
2f		650	1.1
2g		2480	4.1
2h[a]		1460	2.4

[a]L-Proline analogue.

Apparently, subtle structural variation in the FKBP12-binding region of the dimerizers can have profound effects on their cellular potencies which are not necessarily related to their FKBP12 affinities. More recent structural studies on a related series of synthetic dimerizers have revealed, in contrast to the observations for FK1012,[28] a close association of both of the bound FKBP12 domains with each monomer unit of the dimerizer, including parts of the phenethyl side chain.[30] Thus, alterations to this appendage which lead to differences in the binding of monomers to a single FKBP12 molecule may conceivably result in profoundly different binding properties within the tripartite complex. Relevant to this proposal, compound **1h** was prepared which is identical to **1d** except for a replacement of the six-membered ring pipecolyl core by the five-membered ring proline. This change was expected and found to result in an approximate loss of FKBP12 affinity by one order of magnitude (monomer **2h**, Table 2). As this structural change is buried more deeply in the FKBP12 binding pocket, it is less likely to result in additional perturbations in the ternary complex. Consistent with this notion, **1h** showed a general loss in activity in all assays, relative to **1d**, that was of similar magnitude as its loss in FKBP12 affinity.

A second series of dimerizers was examined in which the dimethoxyphenyl-containing monomer **2d** was held constant and the length and chemical nature of the linker moiety was varied (Table 1, **1i–s**). Compounds **1i, 1j**, and **1k** retained the basic **1d** bisamide linker although with varying lengths. A modest threefold decrease in efficacy for inducing apoptosis was observed for **1i**, relative to **1d**, otherwise no dramatic change in activity was seen for these compounds in the Fas assay. In contrast, none of the compounds showed any activity in the stable transcription assay. Mixed results were observed in the transient assay as only **1j** had activity comparable to **1d**. Thus, it appears that CID efficacy in the Fas assay is less sensitive to minor structural changes than are the transcription assays.

Different bisamide configurations in linkers of 10, 9 and five-atom lengths were installed in compounds **1l, 1m**, and **1n**. Compounds **1l** and **1m** share an ethoxyamino tether that was coupled to form an oxamide and a urea, respectively, and **1n** was derived from anilino monomers to yield a short 'retro' bisamide linked dimerizer. Despite the alteration in the arrangement of atoms of the linker, both **1l** and **1m** proved to be effective in inducing apoptosis as well as inducing transcriptional activation in both transient and stable systems. In fact, **1m** in all instances appeared to be slightly superior to **1d**. The shortest dimerizer, **1n**, proved to be only modestly effective in inducing apoptosis and ineffective at inducing transcriptional activation in the stable cell line, although, significant activity was observed in the transient transcription assay. A more radically altered set of compounds incorporating polyether linkers was also examined (**1o–r**). This set spanned the range of linker lengths from five atoms (~7.3 Å distance between aromatic rings) for **1o** to seven atoms for **1p**, 10-atoms for **1q**, and 13-atoms for **1r**. In all cases, the ability to induce apoptosis in the Fas assay was poor. A divergence of activities was seen in the ability of these dimers to induce transcriptional activation. In the transient transcription assay, **1o, 1p**, and **1q** induced transcriptional activation with potencies only 10- to 20-fold lower than **1d** while the longer-linked compound **1r** was able only to achieve one-fourth the level of expression as **1d**. The greater flexibility of five-atom linker of **1o** relative to the

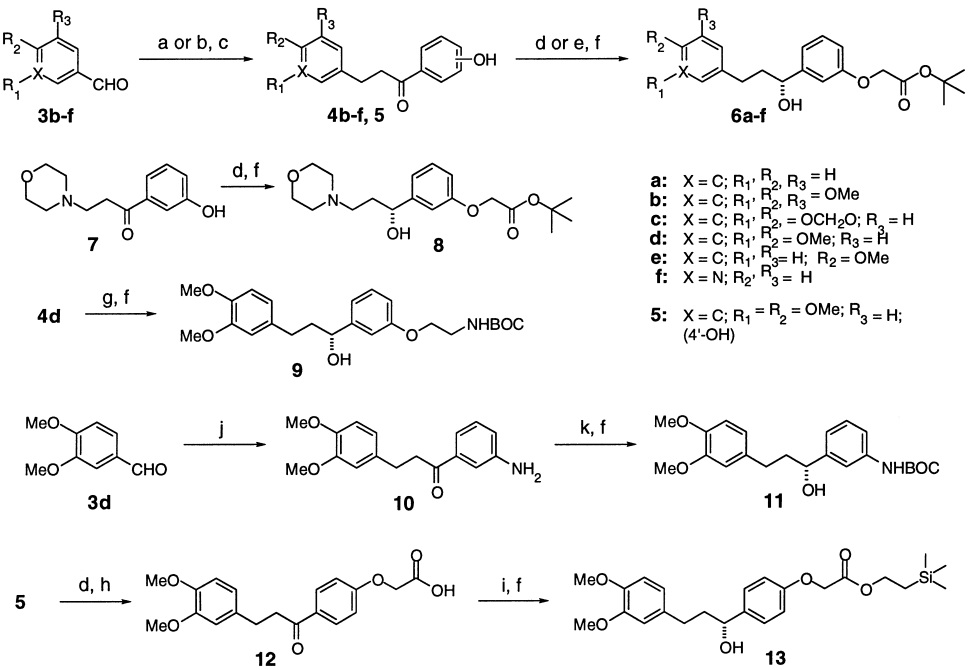
five-atom bisamide linker of **1n** may account for the dramatic difference in activities of these two compounds.

Finally, a regioisomeric linker was examined with the preparation of compound **1s** wherein the linker was attached to the para position of the phenyl ring as opposed to the meta position as in **1d**. Despite the geometric change, **1s** exhibited only fourfold weaker activity in the Fas assay and activity in both transcription assays that was essentially identical to that of **1d**.

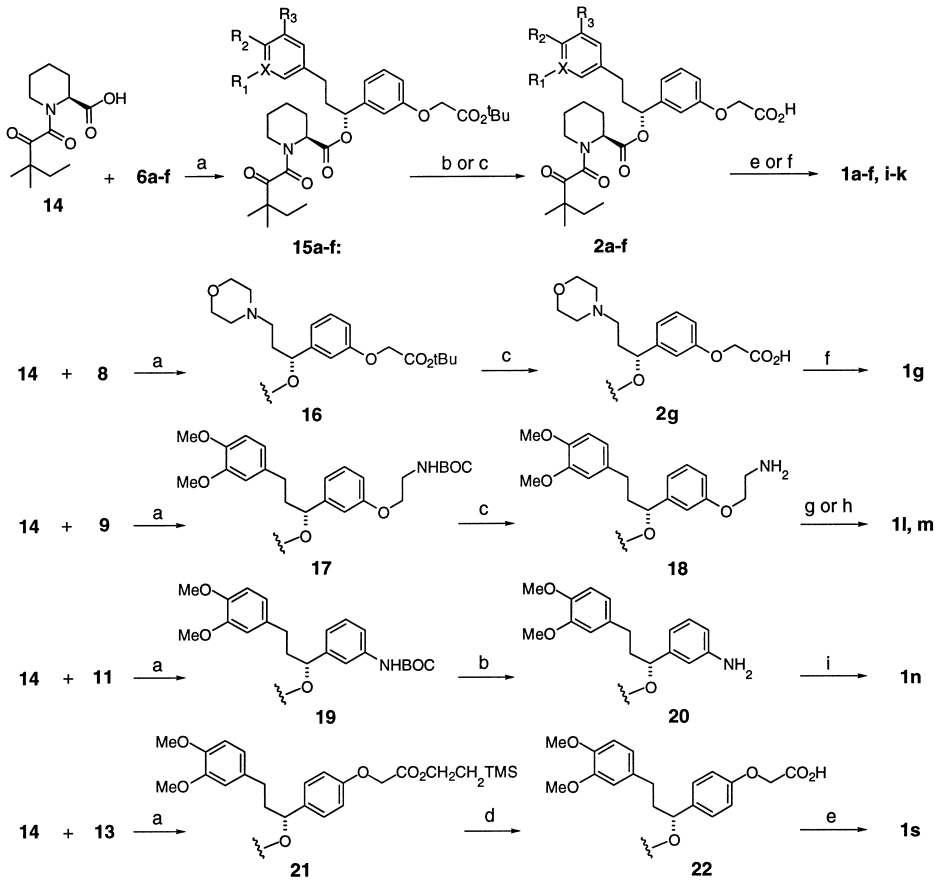
Chemistry

Dimerizers **1a–s** (Table 1) were prepared via two general routes. Both routes began with the elaboration of a homochiral benzylic carbinol (Scheme 1). In the first route, these carbinols were first esterified with the known pipecolic acid derivative **14**[29] and then subsequently dimerized via two-to-one coupling with a symmetrical bifunctional linker (Scheme 2). In the second route, the carbinol subunits were first dimerized and then coupled to the pipecolic acid moiety (Scheme 3).

The syntheses of the carbinol subunits **6b–f, 9**, and **13** (Scheme 1) were achieved by the Claisen–Schmidt condensation of an appropriate aromatic aldehyde with a 3′- or 4′-hydroxyacetophenone. The product chalcones were then regioselectively reduced via hydrogenation with Lindlar catalyst to afford the 1,3-diphenylpropanones **4b–f** and **5**. A 'prelinker' *tert*-butylacetate unit was then emplaced by alkylation of the resultant phenols with *tert*-butyl bromoacetate. In the case of alcohol **9**, the intermediate **4d** was alkylated instead with *N*-BOC-bromoethanamine.[31] Finally, the enantioselective reduction of these *O*-alkylated propanones was achieved using (+)-β-chlorodiisopinocamphenylborane ((+)-DIP-Chloride™)[32] to provide alcohols **6b–f**, and **9** in 97–98% enantiomeric excess. Alcohol **6a**, was prepared by regiospecific alkylation of the known (1*R*)-3-phenyl-(3-hydroxyphenyl)-propan-1-ol (98% ee) with *tert*-butyl bromoacetate.[29] Alcohol **8** was prepared from the Mannich base **7** by alkylation with *tert*-butyl bromoacetate followed by enantioselective reduction to afford **8** in 95% ee. Alcohol **11** was prepared from 3′-nitroacetophenone in a similar manner to **6b–f**, however, the resulting aniline **10**, rather than being alkylated with a prelinker subunit, was protected as its BOC derivative and reduced with (+)-DIP-Chloride™ to afford the desired alcohol in 98% ee. Due to the expected acid instability of the 4′-alkoxy substituted carbinol derivative, we chose to exchange the *tert*-butyl ester protecting



Scheme 1. Reagents and conditions: (a) 3′-Hydroxyacetophenone or 4′-hydroxyacetophenone, KOH, H_2O/EtOH, 0 °C; (b) 3′-hydroxy acetophenone, piperidine, reflux; (c) H_2, Lindlar catalyst, MeOH; (d) *tert*-butyl bromoacetate, K_2CO_3, DMF, 0 °C; (f) (+)-DIP-Chloride™, THF, −20 °C; (g) $BrCH_2CH_2NHBOC$, NaI, K_2CO_3, DMF, 60 °C; (h) TFA, CH_2Cl_2, 0 °C; (i). $TMSCH_2CH_2OH$, DCC, DMAP, CH_2Cl_2, 0 °C; (j) i. 3′-nitroacetophenone, KOH, H_2O/EtOH, 0 °C; ii. H_2, Lindlar catalyst, MeOH; (k) $(BOC)_2O$, DIEA, CH_2Cl_2.

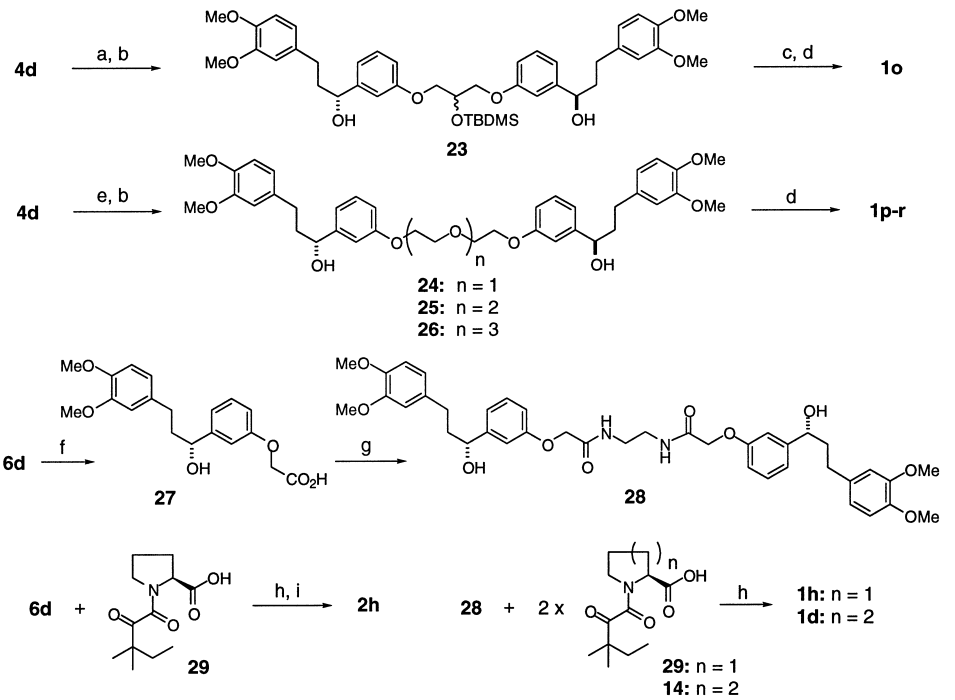


Scheme 2. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 °C; (b) TFA, CH_2Cl_2, 0 °C; (c) HCl, CH_2Cl_2, 0 °C; (d) TBAF, DMF, 0 °C; (e) i. *N,N′*-disuccinimidyl carbonate, pyridine, CH_3CN, 0 °C; ii. diamine-2HCl, TEA, CH_3CN, 0 °C; (f) diamine, DCC, DMAP, CH_2Cl_2, 0 °C; (g) CDI, TEA, CH_2Cl_2, 0 °C; (h) oxalyl chloride, TEA, CH_2Cl_2, 0 °C; (i) malonic acid, BOP, DIEA, CH_2Cl_2, 0 °C.

group of **5** with a fluoride-cleavable trimethylsilylethyl ester. Enantioselective reduction of this intermediate then afforded alcohol **13** with a 98% ee.

Coupling of alcohols **6a–f, 8, 9, 11**, and **13** to pipecolyl acid **14** (Scheme 2) afforded esters **15a–f, 16, 17, 19**, and **21**. Acidolysis of the *tert*-butyl ester protecting groups of **15a–f** and **16** afforded the corresponding acids **2a–f** and **2g**, while tetrabutylammonium fluoride treatment of **21** removed the trimethylsilylethyl protecting group to provide acid **22**. The removal of BOC protecting group of **17** and **19** afforded the corresponding amines **18** and **20**. Dimerization of the monomeric acids **2a–g** and **22** with ethylenediamine via either the corresponding succinimidyl esters or by DCC coupling afforded the desired dimerizers **1a–g** and **1s**, whereas dimerization of **2d** with 1,3-diaminopropane, 2,2′-oxybis(ethylamine), and 2,2′-(ethylenedioxy)bis(ethyl amine) afforded dimers **1i–k**. Dimerization of **18** with either 1,1′-carbonyldiimidazole or oxalyl chloride afforded urea **1l** and oxamide **1m**, respectively. Finally, the aniline **20** was dimerized by BOP coupling with malonic acid to form the diamide **1n**.

Dimerizers **1o–r** and **1h** were prepared via the DCC coupling of acids **14** or **29** with diols **23–26** and **28** (Scheme 3). Diol **23** was prepared from the phenolic propanone **4d** by treatment with epibromohydrin followed by TBDMS ether protection of the resulting carbinol. The protected bis-propanone was enantioselectively reduced with (+)-DIP-Chloride® to afford the desired diol in 97% diastereomeric excess. Diols **24–26** of 95% de were prepared in a similar manner by treatment of **4d** with the appropriate bis-iodoethyl ether followed by enantioselective reduction. Coupling of **23–26** with **14** afforded dimers **1o–r** after HF deprotection of the silyl ether intermediate for **1o**. The final diol, **28**, was prepared by base hydrolysis of alcohol **6d** to afford acid **27**. The acid **27** was recrystallized to >99% ee. Single crystal X-ray analysis confirmed the expected absolute configuration. Dimerization of **27** with ethylenediamine/PyBOP afforded diol **28** which



Scheme 3. Reagents and conditions: (a) i. epibromohydrin, KO*t*-Bu, DMF, 100 °C; ii. TBDMS-Cl, imidazole, DMF, 0 °C; (b) (+)-DIP-Chloride©, THF, −20 °C; (c) 2 equiv **14**, DCC, DMAP, CH_2Cl_2, 0 °C; (d) 49% HF, CH_3CN. (e) diiodide, NaH, DMF; (f) 6 N NaOH, MeOH; (g) ethylenediamine, PyBOP, THF, TEA, 0 °C; (h) DCC, DMAP, CH_2Cl_2, 0 °C; (i) TFA, CH_2Cl_2, 0 °C.

was then coupled to either acid **14** or **29** to afford dimers **1d** and **1h**, respectively. The monomeric acid **2h** was prepared for binding studies by DCC coupling of acid **29** and alcohol **6d** followed by acidolysis deprotection.

Conclusions

AP1510 (**1d**) has previously been shown to be a versatile synthetic CID for regulating intracellular protein–protein interactions.[10] In this report we have detailed synthetic routes to an extended family of AP1510 congeners and examined the activities of these dimerizers in two types of cell-based assays; induction of Fas-mediated apoptosis and activation of gene expression. The dimerizers of this study differ structurally from AP1510 at one of two sites. Variations to the length and character of the linker were examined as were variations within the phenethyl side chain portion of the FKBP12 binding domain.

While clear structure–activity relationships are as yet difficult to precisely define, it is apparent that FKBP12 affinity is not the only determining factor and that CID efficacy is application-dependent and sensitive to even modest molecular changes. These subtle structural variations presumably lead to differences in the relative spatial orientations of the two binding sites, differences in potentials for hydrophobic collapse, or differences in entropic costs for binding. Multiple FKBP12 domains may result in complexes stabilized by avidity effects, and these effects may be more or less sensitive to dimerizer structural changes than is single FKBP12 affinity. The observation that some CIDs behave as 'partial agonists' in the transcription assay, having sub-maximal plateau expression levels, suggests that some compounds may produce a significant population of signalling-incompetent complexes. Similarly, on- and off-rates may play a role in multi-receptor dimerization where remodeling of initially-formed, non-productive protein conformations might be required to achieve the biological response. In support of this supposition is the observation that some compounds of very poor efficacy in stably transfected cells show much greater potency in transiently transfected cells—presumably compensated by the higher target protein concentrations in the latter. Possible differences in cellular permeability or partitioning could also account for some variation in compound efficacies.

The ability to readily modify the wholly-synthetic AP1510 family of CIDs should facilitate application-dependent compound optimizations and better our understanding of the geometric and kinetic factors which influence CID activity.

Experimental

General methods. All reagents and solvents were obtained from commercial sources and used without further purification. All melting points were measured on a Laboratory Devices MEL-TEMP II apparatus and are uncorrected. All IR spectra were recorded on a Perkin-Elmer 1600 Series FTIR and ^{1}H, ^{19}F, and ^{13}C NMR spectra on a Bruker ARX-300 instrument. Chemical shifts are reported downfield from tetramethylsilane and in cases where a mixture of keto-amide rotamers is present, only the chemical shifts of the major rotamer are reported. Low resolution mass spectra (LRMS) were obtained on a Micromass Platform II quadrupole mass spectrometer operating in electrospray mode while high resolution mass spectra (HRMS) were obtained on a JEOL SX-102A mass spectrometer using fast atom bombardment (FAB). Data for HRMS were recorded at a mass resolution of 10,000 and internally calibrated using reference ions from poly(ethylene glycol) or poly(propylene glycol) as appropriate. Flash chromatography was performed on silica gel (Merck, 230–400 mesh). Analytical TLC was performed on silica gel 60 F_{254} plates (Merck). Chiral HPLC was performed on Chiral Technologies Inc. (Exton, PA) analytical columns.

General procedure A. A solution of aldehyde **3** (600 mmol) and acetophenone (600 mmol) in EtOH (200 mL) was cooled to 0 °C and treated with a cold (~10 °C) solution of aqueous KOH (1 L, 2400 mmol). The resulting solution was allowed to warm to room temperature and stir for 16 h at room temperature. The resulting slurry was then poured onto ice (1 L) containing 12 N HCl (200 mL) resulting in a yellowish precipitate. The aqueous portion was decanted and the solids triturated with water (4×500 mL) then dissolved in EtOAc (1 L). The organic extract was washed with brine (2×200 mL), dried over Na_2SO_4, filtered, and concentrated to afford chalcone product.

General procedure B. A solution of chalcone (90 mmol) and Lindlar catalyst (5% Pd, 2.5 g) in MeOH (100 mL) was hydrogenated at 40–50 psi pressure of H_2 in a Parr hydrogenator for 6 h. The reaction mixture was then filtered and the filtered solids dissolved in hot MeOH (400 mL). The methanolic solution was filtered while hot and the combined filtrates cooled and refiltered through a pad of Celite to remove small amounts of remaining catalyst. The filtrate was concentrated to a solid and filtered with the aid of EtOAc (100 mL) or otherwise indicated solvent.

General procedure C. A solution of phenol **4** (8.0 mmol) and K_2CO_3 (2.21 g, 16.0 mmol) in acetone (25 mL) was treated with *tert*-butyl bromoacetate (1.3 mL, 8.8 mmol) and allowed to stir at room temperature for 20 h. After this time the reaction mixture was filtered, concentrated, and flash chromatographed to afford product.

General procedure D. A 60% mineral oil suspension of NaH (4.2 g, 105 mmol) in anhydrous DMF (125 mL) was cooled to 5 °C in an ice bath and phenol **2** (90 mmol) was added portionwise. The resulting yellow solution was stirred for 15 min followed by addition of *tert*-butyl bromoacetate (16.2 mL, 110 mmol). The reaction mixture was stirred at 5 °C for 15 min, allowed to warm to room temperature, and partitioned between EtOAc (200 mL) and water (200 mL). The organic phase was washed with brine (4×200 mL), dried over Na_2SO_4, filtered, and concentrated to afford crude product which was purified by flash chromatography.

General procedure E. A solution of ketone (90 mmol) in THF (50 mL) at −20 °C was treated with a solution of (+)-DIP-Chloride® (43.3 g, 135 mmol) in THF (100 mL) at −20 °C. The resulting mixture was allowed to stand in a −10 °C freezer for 16 h after which time the mixture was concentrated and treated with diethyl ether (300 mL) followed by diethanolamine (77.6 mL, 810 mmol). The viscous mixture was allowed to stir at room temperature for 6 h after which time it was filtered through a pad of Celite with the aid of EtOAc. The filtrate was concentrated and the crude material flash chromatographed to afford product.

General procedure F. A solution of alcohol (1.0 mmol), carboxylic acid (1.1 mmol), and DMAP (0.11 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was treated with DCC (1.1 mmol). The mixture was allowed to warm to room temperature and stir for 2 h after which time it was diluted with EtOAc (4 mL) and filtered through a plug of Celite. The filtrate was concentrated and the crude material flash chromatographed to afford product.

General procedure G. A solution of *tert*-butyl ester (0.4 mmol), in CH_2Cl_2 (6.0 mL) at 0 °C was treated with TFA (2.0 mL). The mixture was allowed to warm to room temperature and stir for 2 h after which time it was diluted with benzene (25 mL) and concentrated. The crude material was then flash chromatographed to afford product.

General procedure H. A solution of substrate (0.4 mmol), in CH_2Cl_2 (20.0 mL) at 0 °C was purged with a slow stream of hydrogen chloride for 5 min. The mixture was allowed to warm to room temperature and stir for 2 h after which time it was diluted with benzene (25 mL) and concentrated. The crude material was then flash chromatographed to afford product.

General procedure I. A solution of carboxylic acid (0.70 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was treated with DCC (148 mg, 0.70 mmol) followed by DMAP (8.6 mg, 0.07 mmol). The suspension was allowed to stir for 5 min after which time a solution of CH_2Cl_2 (100 μL) containing ethylenediamine (18.7 uL, 0.28 mmol) was added. The reaction was allowed to warm to room temperature and stir for 5 h, after which time it was diluted with EtOAc (5 mL), filtered through a plug of glass wool, concentrated, and flash chromatographed to afford product.

General procedure J. A solution of carboxylic acid (2.90 mmol) in CH_3CN (30 mL) was treated with disuccinimidyl carbonate (1.12 g, 4.37 mmol) followed by pyridine (704 μL, 8.70 mmol) and allowed to stir for 24 h. The reaction mixture was diluted with EtOAc (200 mL), washed with brine (2×200 mL), dried over Na_2SO_4, filtered, concentrated, and flash chromatographed (75% EtOAc/hexane) to afford crude product. A solution of the semi-pure succinimidyl ester (2.50 mmol) in CH_3CN (25 mL) was treated with either ethylenediamine dihydrochloride (150 mg, 1.125 mmol) or ethylenediamine (75.2 μL, 1.125 mmol) followed by triethylamine (1.74 mL, 12.5 mmol or 349 μL, 2.5 mmol) and allowed to stir for 4 h. The reaction mixture was then diluted with EtOAc (200 mL), washed with brine (2×100 mL), dried over Na_2SO_4, filtered, concentrated, and flash chromatographed to afford product.

General procedure K. A solution of diol (0.40 mmol), acid (1.00 mmol), and DMAP (12 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was treated with DCC (206 mg, 1.00 mmol). The mixture was allowed to warm to room temperature and stir for 2 h after which time it was diluted with EtOAc (4 mL) and filtered through a plug of Celite. The filtrate was concentrated and the crude material flash chromatographed to afford product.

General procedure L. A solution the bis-ketone (1.0 mmol) in THF (10 mL) at −20 °C was treated with a solution of (+)-DIP-Chloride® (1.28 g, 4.0 mmol) in THF (15 mL) at −20 °C. The resulting mixture was allowed to stand in a −10 °C freezer for 16 h after which time the mixture was concentrated and treated with diethyl ether (30 mL) followed by diethanolamine (2.3 mL, 24 mmol). The viscous mixture was allowed to stir at room temperature for 6 h after which time it was filtered through a pad of Celite with the aid of EtOAc. The filtrate was concentrated and the crude material flash chromatographed to afford product.

General procedure M. A 60% mineral oil suspension of NaH (1.4 g, 35.0 mmol) in anhydrous DMF (25 mL) was cooled to 5 °C in an ice bath and **4d** (10 g, 35 mmol) added portionwise. The resulting yellow solution was stirred for 15 min followed by addition of the bis-iodoethyl ether (14 mmol). The reaction mixture was allowed to warm to room temperature and stir for 16 h then partitioned between EtOAc (200 mL) and water (250 mL). The organic phase was washed with brine (3×200 mL), dried over Na_2SO_4, filtered, and concentrated to afford crude product which was purified by flash chromatography.

1-(3-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-1-propanone (4b). General procedure A was used for the reaction of 3,4,5-trimethoxybenzaldehyde and 3′-hydroxyacetophenone. The crude solids were treated with EtOAc (50 mL) followed by hexane (50 mL) then filtered to afford product (9.22 g, 59%) as a yellow solid: mp 173–174 °C; TLC (EtOAc/hexane, 2/3) R_f = 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) 9.80 (s, 1H), 7.82 (d, J = 15.6 Hz, 1H), 7.70–7.63 (m, 2H), 7.48 (s, 1H), 7.39 (t, J = 7.9 Hz, 1H) 7.23 (s, 2H) 7.08 (d, J = 7.6 Hz, 1H), 3.87 (s, 6H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 189.5, 158.1, 153.5, 144.7, 140.1, 139.5, 130.6, 130.1, 121.8, 120.5, 119.9, 115.0, 106.9, 60.5, 56.5. LRMS (ES+): $(M+H)^+$ 315.

General procedure B was used for the reduction of the above chalcone. Solids were chromatographed (40% then 50% EtOAc/hexane) to afford product (1.37 g, 68%) as a colorless solid: mp 138–139 °C; TLC (EtOAc/hexane, 2:3) R_f = 0.28; IR (neat) 3395, 2940, 1680, 1590, 1505, 1455, 1240, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.54–7.52 (m, 2H), 7.34 (app t, J = 8.1 Hz, 1H), 7.10 (dd, J = 7.9, 2.2 Hz, 1H), 6.48 (s, 2H), 6.08 (s, 1H), 3.85 (s, 9H), 3.30 (t, J = 7.3 Hz, 2H), 3.02 (t, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 200.0, 156.7, 153.6, 138.7, 137.4, 136.7, 130.3, 120.9, 115.0, 105.8, 61.3, 56.5, 41.0, 31.0; LRMS (CI+): $(M+H)^+$ 317, $(M+NH_4)^+$ 334.

3-(1,3-Benzodioxol-5-yl)-1-(3-hydroxyphenyl)-1-propanone (4c). General procedure A was used for the reaction of 3,4-(methylenedioxy)benzaldehyde and 3′-hydroxyacetophenone. The crude solids were filtered with the aid of EtOAc (50 mL) to afford 7.0 g of yellow solids. The solids were recrystallized from EtOAc to afford product (4.6 g, 34%) as a yellow solid: mp 184–185 °C; TLC (EtOAc/hexane, 3/7) R_f = 0.26; ^{1}H NMR (CD_3OD, 300 MHz) 7.60 (d, J = 15.6 Hz, 1 H), 7.44–7.42 (m, 2 H), 7.32 (s, 1 H), 7.27–7.12 (m, 2 H), 7.10 (d, J = 6.5 Hz, 1 H), 6.94 (dd, J = 8.1, 2.5 Hz, 1 H), 6.78 (d, J = 8.0 Hz, 1 H), 5.92 (s, 2 H); ^{13}C NMR (CD_3OD, 75 MHz) 192.8, 159.5, 152.0, 150.4, 146.6, 131.2, 127.1, 121.6, 121.3, 116.2, 110.0, 108.2, 105.7, 103.5; LRMS (ES+): $(M+H)^+$ 269, $(M+NH_4)^+$ 286.

General procedure B was used for the reduction of the above chalcone. Recrystallization of solids from

EtOAc/hexane afforded product (4.10 g, 41%) as a colorless solid: TLC (EtOAc/hexane, 3/7) R_f=0.40; mp 146–147 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 9.73 (s, 1H), 7.43 (d, J=7.8 Hz, 1H), 7.34–7.29 (m, 2H), 7.02 (d, J=8.0 Hz, 1H), 6.88 (m, 1H), 6.80 (d, J=7.9 Hz, 1H), 6.71 (d, J=7.9 Hz, 1H), 5.96 (s, 2H), 3.26 (t, J=7.6 Hz, 2H), 2.84 (t, J=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.4 158.0, 147.5, 145.7, 138.4, 135.4, 130.1, 121.5, 120.5, 119.3, 114.4, 109.2, 108.4, 101.0, 40.2, 29.7; LRMS (ES−): $(M-H)^-$ 269.

3-(3,4-Dimethoxyphenyl)-1-(3-hydroxyphenyl)-1-propanone (4d). General procedure A was used for the reaction of 3,4-dimethoxybenzaldehyde and 3′-hydroxyacetophenone. Filtration afforded product (155 g, 91%) as a yellow colored solid: mp 138–139 °C; TLC (EtOAc/hexane, 1/1) R_f=0.35; ^{1}H NMR (DMSO-d_6, 300 MHz) 9.85 (br s, 1H), 7.71 (d, J=6.6 Hz, 2H), 7.61 (d, J=7.7 Hz, 1H), 7.53 (d, J=1.7 Hz, 1H), 7.47 (d, J=1.7 Hz, 1H), 7.39–7.34 (m, 2H), 7.07–7.00 (m, 2H), 3.87 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) 189.4, 158.2, 151.6, 149.4, 144.7, 139.7, 130.1, 127.9, 124.2, 120.4, 120.2, 119.7, 115.0, 112.0, 111.2, 56.1, 56.0; LRMS (ES+) $(M+H)^+$ 285.

General procedure B was used for the reduction of the above chalcone. Recrystallization from EtOAc afforded product (19.1 g, 76%) as a colorless solid: mp 132–134 °C; TLC (EtOAc/hexane, 1/1) R_f=0.42; ^{1}H NMR (DMSO-d_6, 300 MHz) 9.73 (s, 1H), 7.43 (d, J=7.8 Hz, 1H), 7.33–7.28 (m, 2H), 7.02 (dd, J=8.0, 1.9 Hz, 1H), 6.88–6.74 (m, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.20 (t, J=7.4 Hz, 2H), 2.86 (t, J=7.5 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) 199.6, 158.0, 149.0, 147.5, 138.5, 134.1, 130.1, 120.5, 119.3, 114.5, 112.9, 112.3, 55.9, 55.8, 40.2, 29.6; LRMS (ES+) $(M+NH_4)^+$ 304.

1-(3-Hydroxyphenyl)-3-(4-methoxyphenyl)-1-propanone (4e). General procedure A was used for the reaction of 4-methoxybenzaldehyde and 3′-hydroxyacetophenone. Filtration afforded product (83 g, 88%) as a yellow solid: TLC (EtOAc/hexane, 2/3) R_f=0.40; IR (neat) 3360, 1565, 1510, 1255, 1170 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) 9.84 (s, 1 H), 7.90 (d, J=8.7 Hz, 2 H), 7.77 (s, 2 H), 7.68 (d, J=7.6 Hz, 1 H), 7.54 (s, 1 H), 7.44 (d, J=7.9 Hz, 1 H), 7.13 (dd, J=8.1, 2.3 Hz, 1 H), 3.88 (s, 3 H); ^{13}C NMR (DMSO-d_6, 75 MHz) 189.4, 161.7, 158.1, 144.2, 139.7, 131.1, 130.1, 127.7, 120.4, 120.1, 119.8, 115.0, 114.8, 55.7; LRMS (ES+): $(M+H)^+$ 255; (ES−): $(M-H)^-$ 253.

General procedure B was used for the reduction of the above chalcone. Solids were chromatographed (40% EtOAc/hexane) to afford product (23.4 g, 46%) as a colorless solid: mp 91.5–92 °C; TLC (EtOAc/hexane, 2/3) R_f=0.50; IR (neat) 3415, 1665, 1595, 1510, 1450, 1245, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.53–7.48 (m, 2 H), 7.31 (t, J=7.9 Hz, 1 H), 7.13 (d, J=8.4 Hz, 1 H), 7.07 (dd, J=7.9, 1.7 Hz, 1 H), 6.82 (d, J=8.5 Hz, 1 H), 6.23 (s, 1 H), 3.77 (s, 3 H), 3.24 (t, J=7.2 Hz, 2 H), 2.99 (t, J=7.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 200.2, 158.0, 156.4, 138.2, 133.2, 129.9, 129.4, 120.7, 114.6, 114.0, 55.3, 40.8, 29.4; LRMS (ES+): $(M+H)^+$ 257; (ES−): $(M-H)^-$ 255.

1-(3-Hydroxyphenyl)-3-(3-pyridinyl)-1-propanone (4f). A mixture of 3′-hydroxyacetophenone (5.0 g, 36.7 mmol), 3-pyridinecarboxaldehyde (3.93 g, 36.7 mmol), and piperdine (7.26 mL, 73.4 mL) in EtOH (30 mL) was heated at reflux for 48 h. After this time the reaction mixture was concentrated and the residue flash chromatographed (5% then 10% MeOH/CH_2Cl_2) to afford crude product which was triturated with a 40% EtOAc/hexane solution to afford chalcone product (3.44 g, 33%) as a solid: TLC (MeOH/$CHCl_3$, 5/95) R_f=0.32; ^{1}H NMR (DMSO-d_6, 300 MHz) 9.78 (s, 1 H), 9.01 (s, 1 H), 8.61 (d, J=3.9 Hz, 1 H), 8.35 (d, J=8.0 Hz, 1 H), 7.99 (d, J=15.8 Hz, 1 H), 7.74 (d, J=15.8 Hz, 1 H), 7.65 (d, J=7.7 Hz, 1 H), 7.51–7.47 (m, 2 H), 7.38 (t, J=7.9 Hz, 1 H), 7.08 (dd, J=8.0, 2.3 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 75 MHz) 189.3, 158.1, 151.3, 150.7, 140.7, 139.0, 135.4, 131.0, 130.2, 124.5, 124.3, 120.9, 120.1, 115.1; LRMS (ES+): $(M+H)^+$ 226, (ES−): $(M-H)^-$ 224.

A mixture of the above chalcone (9.0 g, 40.0 mmol) and Lindlar catalyst (5% Pd, 2.25 g) in MeOH (225 mL) was hydrogenated in a Parr hydrogenator under H_2 at 40 psi for 16 h. The mixture was filtered through Celite and the filtrate concentrated to afford a residue which was chromatographed (50% then 60% EtOAc/hexane) to afford product (4.5 g, 50%) as a colorless oil: TLC (MeOH/$CHCl_2$, 5/95) R_f=0.29; IR (neat) 2930, 1680, 1585, 1450, 1295, 1175 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) 9.73 (s, 1 H), 8.50 (s, 1 H), 8.39 (d, J=4.2 Hz, 1 H), 7.71 (d, J=7.8 Hz, 1 H), 7.42 (d, J=7.6 Hz, 1 H), 7.32–7.27 (m, 3 H), 7.00 (dd J=8.0, 2.3 Hz, 1 H), 3.35–3.32 (obs m, 2 H), 2.93 (t, J=7.3 Hz, 2 H); ^{13}C NMR (DMSO-d_6, 75 MHz) 199.1, 158.0, 149.9, 147.3, 138.3, 137.0, 136.5, 130.1, 123.8, 120.6, 119.3, 114.4, 39.4, 27.0; LRMS (ES+): $(M+H)^+$ 228.

3-(3,4-Dimethoxyphenyl)-1-(4-hydroxyphenyl)-1-propanone (5). General procedure A was used for the reaction of 3,4-dimethoxybenzaldehyde and 4′-hydroxyacetophenone. Filtration afforded product (36.5 g, 64%) as a yellow colored solid: mp 201–203 °C; TLC (EtOAc/hexane, 2/3) R_f=0.28; ^{1}H NMR (DMSO-d_6, 300 MHz) 10.34 (s, 1H), 8.07 (d, J=8.6 Hz, 2H), 7.79 (d, J=15.5 Hz, 1H), 7.63 (d, J=15.5 Hz, 1 H), 7.51 (s, 1 H), 7.35 (dd, J=13.8, 8.3 Hz, 1 H), 7.01 (d, J=8.3 Hz, 1 H), 6.90 (d, J=8.6 Hz, 2 H), 3.86 (s, 3 H), 3.81 (s, 3 H); ^{13}C

NMR (DMSO-d_6, 75 MHz) 187.0, 162.0, 151.0, 149.0, 143.1, 131.0, 129.3, 127.7, 123.6, 119.7, 115.3, 111.6, 110.6, 55.7, 55.6; LRMS (ES+): $(M+H)^+$ 285; (ES−): $(M-H)^-$ 283.

General procedure B was used for the reduction of the above chalcone. Obtained product (500 mg, 50%) as a colorless solid: mp 140–141 °C; TLC (EtOAc/hexane, 2/3) R_f=0.31; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.89 (d, J=8.7 Hz, 2 H), 6.92–6.77 (m, 6 H), 3.84 (m, 6 H), 3.24 (d, J=7.2 Hz, 2 H), 3.00 (t, J=7.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.3, 161.2, 149.3, 147.8, 134.4, 131.2, 130.1, 120.7, 115.9, 112.4, 111.9, 56.4, 56.3, 40.7, 30.6; LRMS (ES+): $(M-H)^-$ 285.

(*R*)-1,1-Dimethylethyl [3-(1-hydroxy-3-phenylpropyl)-phenoxy]acetate (6a). (1*R*)-3-Phenyl-1-(3-hydroxyphenyl)-propan-1-ol (98% ee, 1.7 g, 7.46 mmol) was added to a suspension of NaH (60% dispersion in mineral oil, 358 mg, 8.95 mmol) in DMF (50 mL) and treated with *tert*-butyl bromoacetate (2.4 mL, 14.9 mmol). The resulting mixture was stirred at 40 °C for 16 h then quenched with water (50 mL) and extracted with EtOAc (250 mL). The organic layer was washed with brine (2×100 mL), dried over Na_2SO_4, filtered, and concentrated to an oil residue. Chromatography (20% EtOAc/hexane) afforded product (1.64 g, 64%) as a colorless oil (98% ee by Chiralcel OD HPLC, 25% *i*-PrOH/hexane, retention time 42.2 min for the *R*-enantiomer and 30.6 min for the *S*-enantiomer): TLC (EtOAc/hexane, 1/4) R_f=0.26; IR (neat) 3520, 2930, 1745, 1600, 1490, 1455, 1370, 1230, 1150, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.22–6.71 (m, 9 H), 4.58 (t, 1 H), 4.44 (s, 2 H), 2.68–2.59 (m, 2 H), 2.05-1.93 (m, 2 H), 1.41 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.4, 158.6, 146.8, 142.1, 130.0, 128.8, 128.7, 126.2, 119.5, 114.1, 112.6, 82.7, 74.1, 66.1, 40.8, 32.4, 28.4; HRMS (FAB): $(M+Na)^+$ calcd: 365.1729, recorded: 365.1721.

(*R*)-1,1-Dimethylethyl [3-[1-hydroxy-3-(3,4,5-trimethoxyphenyl)propyl]-phenoxy]acetate (6b). General procedure C was used for the alkylation of **4b**. The crude product was chromatographed (50% EtOAc/hexane) to afford product (3.30 g, 96%) as a colorless solid that may be recystallized from EtOAc: mp 99–100 °C; TLC (EtOAc/hexane, 2/3) R_f=0.47; IR (neat) 2955, 1750, 1684, 1590, 1455, 1230, 1150, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.59 (d, J=7.7 Hz, 1H), 7.49 (s, 1H), 7.39 (t, J=7.9 Hz, 1H), 7.14 (dd, J=8.2, 2.6 Hz, 1H), 6.47 (s, 2H), 4.58 (s, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 3.28 (t, J=7.3 Hz, 2H), 3.01 (t, J=7.8 Hz, 2H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.1 168.0, 158.5, 153.6, 138.6, 137.4 136.8, 130.1, 121.8, 120.4, 113.6, 105.8, 83.0, 66.1, 61.2, 56.5, 41.0, 31.0, 28.4; LRMS (ES+): (M+NH4)$^+$ 448, $(M+Na)^+$ 453.

General procedure E was used for the reduction of the above ketone. The crude product was chromatographed (50% then 100% EtOAc/hexane) to afford product (1.3 g, 99%) as a colorless oil (98% ee by Chiralcel OD HPLC, 20% i-PrOH/hexane, retention time 46.4 min for the *R*-enantiomer and 40.0 min for the *S*-enantiomer): TLC (EtOAc/hexane, 2/3) R_f=0.26; IR (neat) 3500, 2940, 1750, 1590, 1455, 1240, 1150, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.28 (t, J=7.8 Hz, 1 H), 6.96 (m, 2 H), 6.82 (m, 1 H), 6.41 (s, 2 H), 4.69 (t, J=6.2 Hz, 1 H), 4.52 (s, 2 H), 3.85 (s, 6 H), 3.83 (s, 3 H), 2.65 (m, 2 H), 2.05 (m, 2 H), 1.50 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.4, 158.6, 153.5, 146.8, 137.9, 136.6, 130.0, 119.5, 114.0, 112.7, 105.7, 82.8, 74.1, 66.0, 61.2, 56.5, 40.8, 32.8, 28.4; LRMS (ES+): (M+NH4)$^+$ 450; HRMS (FAB): $(M+Na)^+$ calcd: 455.2046, recorded: 455.2063.

(*R*)-1,1-Dimethylethyl [3-[3-(1,3-benzodioxol-5-yl)-1-hydroxypropyl]-phenoxy]acetate (6c). General procedure D was used for the alkylation of **4c**. The crude product was chromatographed (20% then 30% EtOAc/hexane) to afford product (5.04 g, 89%) as a waxy solid: mp 61–62 °C; IR (neat) 2980, 1750, 1685, 1490, 1445, 1245, 1155, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.58 (dd, J=6.7, 1.1 Hz, 1H), 7.48 (s, 1H), 7.39 (t, J=8.0 Hz, 1H), 7.17–7.13 (m, 1H), 6.89–6.69 (m, 4H), 5.94 (s, 2H), 4.58 (s, 2H), 3.25 (t, J=7.8 Hz, 2H), 2.99 (t, J=7.8 Hz, 2H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.0 168.0, 158.5, 148.1, 146.3, 138.6, 135.4, 130.1, 121.8, 121.5, 120.6, 113.4, 109.3, 108.7, 101.2, 83.0, 66.1, 41.1, 20.3, 28.4; LRMS (ES+): $(M+NH_4)^+$ 402.

General procedure E was used for the reduction of the above ketone. The crude product was chromatographed (20% then 25% EtOAc/hexane) to afford product (3.84 g, 96%) as a colorless oil (94% ee by Chiralcel OD HPLC, 35% *i*-PrOH/hexane, retention time 11.3 min for the *R*-enantiomer and 8.7 min for the *S*-enantiomer): TLC (EtOAc/hexane, 3/7) R_f=0.31; IR (neat) 3440, 1750, 1490, 1440, 1245, 1150, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.30–7.24 (m, 1 H), 6.98–6.93 (m, 2H), 6.82 (dd, J=8.2, 2.5 Hz, 1H), 6.75–6.64 (m, 3H), 5.93 (s, 2H), 4.67–4.63 (m, 1H), 4.53 (s, 2H), 2.68–2.60 (m, 2H), 2.10–1.95 (m, 3H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.4, 158.5, 148.0, 146.9, 146.0, 136.0, 130.0, 121.5, 119.5, 114.1, 112.5, 109.3, 108.5, 101.1, 82.7, 73.9, 66.1, 41.1, 32.1, 28.4; LRMS (ES+): $(M+NH_4)^+$ 404, $(M+Na)^+$ 409; HRMS (FAB): $(M+)^+$ calcd: 386.1728, measured: 386.1716.

(*R*)-1,1-Dimethylethyl [3-[3-(3,4-dimethoxyphenyl)-1-hydroxypropyl]phenoxy]-acetate (6d). General procedure C was used for the alkylation of **4d**. The crude product was chromatographed (30% EtOAc/hexane) to afford product (34.5 g, 99%) as a waxy solid: mp 56–56.5 °C;

TLC (EtOAc/hexane, 1/1) $R_f = 0.65$; IR (neat) 2975, 1750, 1685, 1590, 1515, 1445, 1370, 1260, 1235, 1155, 1080, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.57 (d, $J = 7.7$ Hz, 1H), 7.47 (d, $J = 2.3$ Hz, 1H), 7.39 (t, $J = 8.0$ Hz, 1H), 7.12 (dd, $J = 8.0$, 2.3 Hz, 1H), 6.82–6.77 (m, 3H), 4.56 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.25 (t, $J = 7.9$ Hz, 2H), 3.00 (t, $J = 7.8$ Hz, 2H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.2, 168.0, 158.6, 149.4, 147.9, 138.7, 134.2, 130.1, 121.8, 120.6, 113.6, 112.3, 111.9, 83.0, 66.1, 56.4, 56.3, 41.1, 30.2, 28.4; LRMS (ES+): $(M + NH_4)^+$ 418, $(M + Na)^+$ 423.

General procedure E was used for the reduction of the above ketone. The crude product was chromatographed (30%, then 40% EtOAc/hexane) to afford product (29.0 g, 82%) as a clear colorless oil (98% ee by Chiralcel OD HPLC, 25% *i*-PrOH/hexane, retention time 44.4 min for the *R*-enantiomer and 35.7 min for the *S*-enantiomer): TLC (EtOAc/hexane, 1/1) $R_f = 0.45$; IR (neat) 3515, 2935, 1750, 1590, 1515, 1450, 1260, 1235, 1150, 1080, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.28–7.23 (m, 1H), 6.98–6.92 (m, 2H), 6.82–6.71 (m, 4H), 4.68–4.64 (m, 1H), 4.52 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.70–2.61 (m, 2H), 2.10–1.97 (m, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.4, 158.6, 149.3, 147.7, 146.9, 134.8, 130.0, 120.6, 119.5, 114.0, 112.6, 112.2, 111.8, 82.7, 74.1, 66.1, 56.3, 56.2, 41.0, 32.0, 28.4; LRMS (ES+): $(M + NH_4)^+$ 402; HRMS (FAB): $(M)^+$ calcd: 402.2042, recorded: 402.2041; $(M + Na)^+$ calcd: 425.1940, recorded: 425.1941.

(*R*)-1,1-Dimethylethyl [3-[1-hydroxy-3-(4-methoxyphenyl)-propyl]phenoxy]-acetate (6e). General procedure C was used for the alkylation of **4e**. The crude product was chromatographed (20% then 30% EtOAc/hexane) to afford product (13.1 g, 91%) as an oil: TLC (EtOAc/hexane, 1/1) $R_f = 0.70$; IR (neat) 2980, 1750, 1685, 1515, 1245, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.56 (d, $J = 7.7$ Hz, 1H), 7.45 (s, 1H), 7.35 (t, $J = 8.0$ Hz, 1H), 7.16–7.10 (m, 3H), 6.85 (d, $J = 2.7$ Hz, 1H), 4.55 (s, 2H), 3.77 (s, 3H), 3.23 (t, $J = 7.3$ Hz, 2H), 2.99 (t, $J = 7.8$ Hz, 2H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.2, 168.0, 158.6, 138.7, 133.6, 130.1, 129.7, 121.9, 120.5, 113.6, 83.0, 66.1, 55.7, 41.1, 29.7, 28.4; LRMS (ES+): $(M + H)^+$ 257; (ES−): $(M - H)^-$ 255.

General procedure E was used for the reduction of the above ketone. The crude product was chromatographed (40% EtOAc/hexane) to afford product (5.76 g, 57%) as an oil (98% ee by Chiralcel OD HPLC, 40% *i*-PrOH/hexane, retention time 13.4 min for the *R*-enantiomer and 10.7 min for the *S*-enantiomer): TLC (EtOAc/hexane, 3/7) $R_f = 0.45$; IR (neat) 3500, 2935, 1750, 1610, 1510, 1245, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.27–7.22 (m, 2H), 7.09 (d, $J = 8.6$ Hz, 2H), 6.95–6.90 (m, 2H), 6.83–6.77 (m, 3H), 4.66–4.60 (m, 1H), 4.50 (s, 2H), 3.77 (s, 3H), 2.68–2.59 (m, 3H), 2.07–1.94 (m, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.0, 158.2, 157.8, 146.5, 133.8, 129.5, 129.3, 119.1, 113.9, 113.7, 112.2, 82.3, 73.6, 65.7, 55.3, 40.7, 31.1, 28.0; LRMS (ES+): $(M + NH_4)^+$ 390; HRMS (FAB): $(M)^+$ calcd: 372.1937, recorded: 372.1949.

(*R*)-1,1-Dimethylethyl [3-[1-hydroxy-3-(3-pyridinyl)propyl]-phenoxy]-acetate (6f). General procedure D was used for the alkylation of **4f**. The crude product was chromatographed (20% then 30% EtOAc/hexane) to afford product (5.04 g, 89%) as an oil: TLC (EtOAc/hexane, 3/1) $R_f = 0.30$, ($MeOH/CHCl_3$, 5/95) $R_f = 0.32$; IR (neat) 2980, 1750, 1685, 1585, 1440, 1370, 1225, 1155, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 8.53 (d, $J = 1.6$ Hz, 1H), 8.45 (d, $J = 4.0$ Hz, 1H), 7.58–7.54 (m, 2H), 7.46 (s, 1H), 7.37 (d, $J = 8.0$ Hz, 1H), 7.21 (dd, $J = 7.8$, 4.8 Hz, 1H), 7.13 (dd, $J = 8.2$, 2.6 Hz, 1H), 4.56 (s, 2H), 3.29 (t, $J = 7.4$ Hz, 2H), 3.07 (t, $J = 7.4$ Hz, 2H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 198.3, 168.0, 158.6, 150.4, 148.1, 138.4, 136.9, 136.4, 130.2, 123.7, 121.8, 120.6, 113.5, 83.0, 66.1, 40.2, 28.4, 27.5; LRMS (ES+): $(M + H)^+$ 342.

General procedure E was used for the reduction of the above ketone. The crude product was chromatographed (50% then 80% EtOAc/hexane) to afford product (3.6 g, 78%) as a colorless oil (97.5% ee by Chiralcel OD HPLC, 20% *i*-PrOH/hexane, retention time 77 min for the *R*-enantiomer and 53 min for the *S*-enantiomer): TLC (EtOAc/hexane, 3/1) $R_f = 0.20$, ($MeOH/CH_2Cl_2$, 5/95) $R_f = 0.32$; IR (neat) 3265, 2980, 1755, 1585, 1480, 1445, 1370, 1225, 1150, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 8.40–8.10 (m, 2H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.27–7.17 (m, 2H), 6.95–6.92 (m, 2H), 6.81–6.78 (m, 1H), 4.66–4.57 (m, 1H), 4.50 (s, 2H), 3.03 (br s, 1H), 2.75–2.67 (m, 2H), 2.10–1.97 (m, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.0, 158.2, 149.7, 147.1, 146.5, 137.3, 136.1, 129.6, 123.4, 119.0, 113.7, 112.1, 82.4, 73.0, 65.7, 40.1, 29.1, 28.1; LRMS (CI+): $(M + H)^+$ 344; HRMS (FAB): $(M)^+$ calcd: 343.1784, recorded: 343.1773.

1-(3-Hydroxyphenyl)-3-(4-morpholinyl)-1-propanone (7). A solution of morpholine (1.0 mL, 11.5 mmol) in EtOH (10 mL) was treated with 3′-hydroxyacetophenone (1.56 g, 11.5 mmol) and paraformaldehyde (340 mg, 11.5 mmol) followed by acetic acid (1.3 mL, 23 mmol). The resulting mixture was heated at reflux for 16 h then cooled and concentrated. The residue was then diluted with a 5% aqueous HCl solution (10 mL), washed with diethyl ether (2×10 mL) followed by neutralization by addition of solid $NaHCO_3$. The neutralized aqueous solution was extracted with diethyl ether (2×10 mL) which was then dried over Na_2SO_4, filtered, and concentrated to a residue. The residue was chromatographed

(5% MeOH/CH_2Cl_2) to afford product (680 mg, 25%) as a brownish oil: TLC (MeOH/$CHCl_3$, 5/95) R_f = 0.22; IR (neat) 2960, 2855, 1685, 1585, 1450, 1360, 1275, 1115, 995, 865 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.48 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 2.0 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H),7.05 (m, 1H), 3.75 (t, J = 4.7 Hz, 4H), 3.25 (t, J = 7.3 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H), 2.57 (t, J = 4.5 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.0, 156.8, 138.1, 123.0, 121.1, 120.1, 114.7, 66.6, 53.6, 53.5, 35.7; LRMS (ES−): $(M-H)^-$ 234.

(*R*)-1,1-Dimethylethyl [3-[1-hydroxy-3-(4-morpholinyl)-propyl]phenoxy]acetate (8). General procedure C was used for the alkylation of **7**. The crude product was chromatographed (1% MeOH/EtOAc) to afford product (10.5 g, 67%) as an oil: TLC (MeOH/$CHCl_3$, 5/95) R_f = 0.39; IR (neat) 2975, 1750, 1685, 1585, 1445, 1370, 1225, 1155, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.57 (d, J = 7.7 Hz, 1H), 7.46 (s, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 4.57 (s, 2H), 3.71 (t, J = 4.7 Hz, 4H), 3.15 (t, J = 7.3 Hz, 2H), 2.82 (t, J = 7.3 Hz, 2H), 2.50 (t, J = 4.6 Hz, 4H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 198.8, 168.0, 158.6, 138.7, 130.1, 121.8, 120.5, 113.6, 83.0, 67.3, 66.1, 54.1, 54.0, 36.5, 28.4; LRMS (ES+): $(M+H)^+$ 350.

General procedure E (3.0 eq of (+)-DIP-Chloride™) was used for the reduction of the above ketone. The crude product was chromatographed (5% MeOH/EtOAc) to afford 270 mg (27%) of an oil that solidified to a waxy solid on standing (+97% de by comparative integration of ^{19}F NMR resonances of the (+)MPTA ester of chiral and racemic material: TLC (MeOH/CH_2Cl_2, 5/95) R_f = 0.33; IR (neat) 2955, 1750, 1585, 1455, 1370, 1225, 1155, 1120, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.57 (d, J = 7.9 Hz, 1H), 6.97 (m, 2H), 6.78 (d, J = 8.1 Hz, 1H), 4.91 (t, J = 5.7 Hz, 1H), 4.52 (s, 2H), 3.75 (t, J = 4.6 Hz, 4H), 2.70–2.40 (m, 6H), 1.85 (m, 2H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.5, 158.5, 147.0, 129.7, 119.1, 113.5, 112.4, 83.0, 67.3, 66.1, 54.1, 54.0, 36.5, 28.4; LRMS (ES+): $(M+H)^+$ 352. HRMS (FAB): $(M+H)^+$ calcd: 352.2124, recorded: 352.2124.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[3-[3-[1-hydroxy-3-(3,4-dimethoxyphenyl)-propyl]phenoxy]ethylamine (9). A solution of **4d** (5.0 g, 17.5 mmol) in DMF (25 mL) was treated with K_2CO_3 (7.2 g, 52 mmol), sodium iodide (130 mg, 0.87 mmol), and *N*-*tert*-butoxycarbonyl-2-bromoethanamine (4.7 g, 19.3 mmol) and heated at 60 °C for 48 h. The reaction mixture was then diluted with water (125 mL) and extracted with EtOAc (3×50 mL). The combined organic extracts were then washed with a 5% aqueous NaOH solution (2×50 mL) followed by water (2×50 mL) and brine (2×50 mL). The organic layer was then dried over Na_2SO_4, filtered, concentrated, and chromatographed (30% EtOAc/hexane) to afford product (3.8 g, 51%) as an oil: TLC (EtOAc/hexane, 1/1) R_f = 0.50; IR (neat) 2975, 1750, 1680, 1600, 1515, 1455, 1370, 1260, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.93 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 6.78–6.77 (m, 3H), 4.57 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.22 (t, J = 7.2 Hz, 2H), 2.99 (t, J = 7.9 Hz, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 198.2, 167.7, 162.1, 149.3, 147.8, 134.4, 131.1, 130.6, 120.6, 114.7, 112.3, 111.8, 83.1, 65.9, 56.3, 56.2, 40.7, 30.3, 28.4; LRMS (ES+): $(M+H)^+$ 401, $(M+NH_4)^+$ 418.

General procedure E was used for the reduction of the above ketone. The crude product was chromatographed (30% then 50% EtOAc/hexane) to afford product (970 mg, 39%) as an oil (99% ee by Chiralcel OD HPLC, 12.5% *i*-PrOH/hexane, retention time 56 min for the *R*-enantiomer and 52 min for the *S*-enantiomer): TLC (EtOAc/hexane, 1/1) R_f = 0.25; IR (neat) 3375, 2935, 1700, 1515, 1260, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.27–7.22 (m, 1H), 6.94–6.91 (m, 2H), 6.81–6.71 (m, 4H), 5.02 (br s, 1H), 4.67–4.63 (m, 1H), 4.01 (t, J = 5.1 Hz, 2H), 3.85 (s, 6H), 3.79–3.67 (m, 2H), 2.73–2.56 (m, 2H), 2.15–1.93 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.8, 155.9, 148.9, 147.3, 146.6, 134.4, 129.6, 120.2, 118.7, 113.5, 112.1, 111.9, 111.4, 79.6, 73.7, 67.2, 56.0, 55.8, 40.6, 40.2, 31.7, 28.4; LRMS (ES+): $(M+Na)^+$ 454; (ES−): $(M-H)^-$ 430; HRMS (FAB): $(M)^+$ calcd: 431.2308, recorded: 431.2301.

1-(3-Aminophenyl)-3-(3,4-dimethoxyphenyl)-1-propanone (10). General procedure A was used for the reaction of 3,4,-dimethoxybenzaldehyde and 3′-nitroacetophenone. The crude solids were filtered with the aid of EtOAc (50 mL) to afford 7.0 g of yellow solids. The solids were recrystallized from ethyl ether/EtOAc to afford product (4.7 g, 60%) as a orange colored solid: mp 158–159.5 °C; TLC (EtOAc/hexane, 1/1) R_f = 0.41; IR (neat) 1660, 1590, 1510, 1350, 1260, 1140, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 8.83 (t, J = 1.9 Hz, 1H), 8.43 (ddd, J = 8.1, 2.2, 1.0 Hz, 1H), 8.34 (dt, J = 7.7, 1.3 Hz, 1H), 7.85 (d, J = 15.5 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.38 (d, J = 15.5 Hz, 1H), 7.28 (dd, J = 2.0, 8.4 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 188.4, 152.5, 149.8, 148.8, 147.4, 140.3, 134.5, 130.2, 127.8, 127.2, 124.2, 123.6, 119.0, 111.6, 110.8, 56.5; HRMS (FAB): $(M)^+$ calcd: 313.0950, recorded: 313.0943.

General procedure B was used for the reduction of the above nitrochalcone. The crude product was chromatographed (25% then 50% EtOAc/hexane) to afford product (1.2 g, 64%) as a pale-yellow oil which solidified on standing: TLC (EtOAc/hexane, 1/1) R_f = 0.25; IR (neat) 3548, 3368, 2934, 1678, 1602, 1515, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.32–7.17 (m, 3H), 6.85–6.77

(m, 4H), 3.85 (s, 3H), 3.84 (s, 3H), 3.75 (br s, 2H), 3.22 (t, $J=7.2$ Hz, 2H), 2.99 (t, $J=7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 200.0, 149.4, 147.8, 147.2, 138.5, 134.5, 129.8, 120.6, 119.9, 118.7, 114.3, 112.4, 111.9, 56.4, 56.3, 41.1, 30.3; HRMS (FAB): $(M+Na)^+$ calcd: 308.1263, recorded: 308.1255.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-1-(3-aminophenyl)-3-(3,4-dimethoxyphenyl) propan-1-ol (11). A solution of aniline **10** (440 mg, 1.54 mmol) in CH_2Cl_2 (10 mL) was treated with di-*tert*-butyl dicarbonate (354 mg, 1.62 mmol) followed by DIEA (536 μL, 2.08 mmol). The reaction was stirred at room temperature for 16 h after which time the mixture was concentrated and chromatographed (30% to 50% EtOAc/hexane) to afford product (290 mg, 97% based on recovered **10** as a colorless solid: mp 133–134 °C; TLC (EtOAc/hexane, 1/1) $R_f=0.55$; IR (neat) 3340, 2975, 1725, 1685, 1590, 1515, 1235, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.93 (d, $J=1.5$ Hz, 1H), 7.62–7.59 (m, 2H), 7.36 (t, $J=7.9$ Hz, 1H), 6.79–6.76 (m, 3H), 6.64 (br s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.26 (t, $J=7.2$ Hz, 2H), 3.00 (t, $J=7.2$ Hz, 2H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.5, 153.0, 149.4, 147.9, 139.4, 138.1, 134.3, 129.6, 123.3, 123.0, 120.7, 118.3, 112.4, 111.9, 81.3, 56.4, 41.2, 30.3, 28.7; LRMS (ES+): $(M+NH_4)^+$ 403, $(M+Na)^+$ 408; (ES−): M^- 384.

General procedure E was used for the reduction of the above ketone. The crude product was chromatographed (30%, then 50% EtOAc/hexane) to afford product (32 mg, 86%) as a colorless oil (98% ee by Chiralcel OD HPLC, 20% *i*-PrOH /hexane, retention time 12.3 min for the *R*-enantiomer and 14.1 min for the *S*-enantiomer): TLC (EtOAc/hexane, 1/1) $R_f=0.38$; IR (neat) 3338, 2934, 1723, 1609, 1517, 1159 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.38 (s, 1H), 7.21 (m, 1H), 7.01–6.98 (m, 1H), 6.78–6.68 (m, 3H), 6.56 (s, 1H), 4.63 (dd, $J=7.4$, 5.5 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.68–2.55 (m, 2H), 2.08–1.95 (m, 2H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 152.7, 148.8, 147.2, 145.7, 138.5, 134.4, 129.0, 120.5, 120.2, 117.7, 116.1, 111.8, 111.3, 80.5, 73.7, 55.8, 40.6, 31.6, 28.3; LRMS (ES+): $(M+Na)^+$ 410; HRMS (FAB): $(M+Na)^+$ calcd: 410.1943, recorded: 410.1937.

[4-[3-(3,4-Dimethoxyphenyl)-1-propanone]phenoxy]acetic acid (12). General procedure C was used for the alkylation of **5**. The crude product was chromatographed (30% EtOAc/hexane) to afford product (10.1 g, 91%) as an oil: TLC (EtOAc/hexane, 3/7) $R_f=0.29$; IR (neat) 2975, 1750, 1680, 1600, 1515, 1455, 1370, 1260, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.93 (d, $J=8.8$ Hz, 2H), 6.91 (d, $J=8.9$ Hz, 2H), 6.78–6.77 (m, 3H), 4.57 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.22 (t, $J=7.2$ Hz, 2H), 2.99 (t, $J=7.9$ Hz, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 198.2, 167.7, 162.1, 149.3, 147.8, 134.4, 131.1, 130.6, 120.6, 114.7, 112.3, 111.8, 83.1, 65.9, 56.3, 56.2, 40.7, 30.3, 28.4; LRMS (ES+): $(M+H)^+$ 401, $(M+NH_4)^+$ 418.

A solution of the above *tert*-butyl ester (2.0 g, 4.99 mmol) in CH_2Cl_2 (8 mL) was treated with TFA (4.0 mL) and the mixture stirred at room temperature for 6 h. The reaction mixture was diluted with benzene (50 mL) and concentrated to a solid which was filtered with the aid of benzene to afford product (1.69 g, 98%) as a solid: ^{1}H NMR (DMSO-d_6, 300 MHz) 7.96 (d, $J=8.9$ Hz, 1H), 7.01 (d, $J=8.9$ Hz, 2H), 6.89–6.75 (m, 3H), 4.79 (s, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 3.27 (d, $J=7.3$ Hz, 1H), 2.86 (d, $J=7.6$ Hz, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) 198.1, 170.1, 161.9, 148.9, 147.3, 134.1, 130.5, 128.7, 120.4, 114.7, 112.7, 112.2, 64.8, 55.9, 55.7, 39.8, 29.7; LRMS (ES−): $(M-H)^-$ 343.

(*R*)-Trimethylsilylethyl [4-[3-(3,4-dimethoxyphenyl)-1-hydroxypropyl]-phenoxy]acetate (13). General procedure F was used for the coupling of acid **12** with 2-(trimethylsilyl)ethanol. The crude product was chromatographed (30% EtOAc/hexane) to afford product (3.2 g, 99%) as a colorless oil: TLC (EtOAc/hexane, 3/7) $R_f=0.53$; IR (neat) 2955, 1755, 1675, 1600, 1515, 1250, 1165, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.95 (d, $J=8.9$ Hz, 2H), 6.93 (d, $J=8.9$ Hz, 2H), 6.83–6.77 (m, 3H), 4.66 (s, 2H), 4.32 (t, $J=8.5$ Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.23 (t, $J=7.3$ Hz, 2H), 3.00 (t, $J=8.0$ Hz, 2H), 1.03 (td $J=4.7$, 2.9 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.4, 169.9, 163.1, 150.5, 149.0, 135.6, 132.4, 131.9, 121.7, 115.9, 113.5, 113.0, 66.9, 65.6, 57.5, 57.4, 41.9, 31.5, 18.9, 0.0; LRMS (ES+): $(M+H)^+$ 445, $(M+NH_4)^+$ 467.

General procedure E was used for the reduction of the above ketone. The crude product was chromatographed (30%, EtOAc/hexane) to afford product (455 mg, 91%) as a clear colorless oil (98% ee by Chiralcel OD HPLC, 30% *i*-PrOH/hexane, retention time 23.6 min for the *R*-enantiomer and 17.9 min for the *S*-enantiomer): TLC (EtOAc/hexane, 3/7) $R_f=0.28$; IR (neat) 3525, 2950, 1755, 1610, 1515, 1250, 1175, 1030, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.25–7.21 (m, 2H), 6.86–6.83 (m, 2H), 6,74 (d, $J=8.4$ Hz, 1H), 6.69–6.66 (m, 2H), 4.61–4.55 (m, 3H), 4.29–4.23 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 2.66–2.50 (m, 2H), 2.10–1.89 (m, 2H), 1.72 (br s, 1H), 1.01–0.96 (m, 2H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.6, 158.9, 150,4, 148.8, 139.4, 135.9, 128.8, 121.7, 116.2, 113.3, 112.9, 74.9, 67.2, 65.3, 57.5, 57.4, 42.1, 33.2, 18.9, 0.00; LRMS (ES+): $(M+Na)^+$ 469; HRMS(FAB): $(M)^+$ calcd: 446.2125, recorded: 446.2120; $(M+Na)^+$ calcd: 469.2022, recorded: 469.2045.

(2*S*)-1-(3,3,-Dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylic acid (14). The title compound was prepared as previously described.[29]

(1*R*)-1-[3-[2-(1,1-Dimethylethoxy)-2-oxoethoxy]phenyl]-3-phenyl-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (15a). General procedure F was used for the coupling of alcohol **6a** and acid **14**. The crude product was chromatographed (20% EtOAc/hexane) to afford product (470 mg, 82%) as a colorless oil: TLC (EtOAc/hexane, 1/4) $R_f = 0.45$; IR (neat) 2955, 1750, 1645, 1445, 1225, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.50–6.90 (m, 9H), 5.93 (t, $J = 6.0$ Hz, 1H), 5.46 (d, $J = 3.4$ Hz, 1H), 4.67 (s, 2H), 3.50 (d, $J = 12.9$ Hz, 1H), 3.32 (td, $J = 12.5$, 3.0 Hz, 1H), 2.75 (m, 2H), 2.53 (d, $J = 13.6$ Hz, 1H), 2.41 (m, 1H), 2.22 (m, 1H), 1.97–1.71 (m, 7H), 1.62 (s, 9H), 1.38 (s, 3H), 1.35 (s, 3H), 1.03 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3, 175.0, 170.0, 168.0, 167.5, 158.5, 141.7, 141.2, 130.2, 128.9, 128.7, 126.5, 120.2, 114.7, 113.6, 82.8, 66.1, 51.6, 47.1, 44.5, 38.2, 32.9, 32.0, 28.4, 26.8, 25.3, 24.0, 23.4, 21.6, 9.2; HRMS (FAB): $(M + Na)^+$ calcd: 602.3094, recorded: 602.3090.

(1*R*)-1-[3-[2-(1,1-Dimethylethoxy)-2-oxoethoxy]phenyl]-3-(3,4,5-trimethoxyphenyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (15b). General procedure F was used for the coupling of alcohol **6b** and acid **14**. The crude product was chromatographed (20% then 30% EtOAc/hexane) to afford product (776 mg, 78%) as a colorless oil: TLC (EtOAc/hexane, 2/3) $R_f = 0.49$; IR (neat) 2940, 1745, 1645, 1590, 1455, 1240, 1150, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.30–6.80 (m, 4H), 6.37 (s, 2H), 5.82 (t, $J = 6.1$ Hz, 1H), 5.33 (d, $J = 5.2$ Hz, 1H), 4.54 (s, 2H), 3.85 (s, 6H), 3.83 (s, 3H), 3.38 (d, $J = 12.6$ Hz, 1H), 3.16 (td, $J = 12.8$, 3.1 Hz, 1H), 2.60 (m, 2H), 2.45–2.05 (m, 3H), 1.70 (m, 6H), 1.50 (s, 9H), 1.45 (m, 2H), 1.25 (s, 3H), 1.23 (s, 3H), 0.90 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.2, 175.1, 170.1, 168.2, 167.6, 158.5, 153.6, 141.7, 137.0, 130.1, 120.9, 120.2, 114.6, 113.7, 105.7, 82.7, 66.2, 61.2, 56.5, 51.7, 47.1, 44.6, 38.2, 32.9, 32.4, 28.4, 26.8, 25.3, 23.9, 23.5, 21.6, 9.1; HRMS (FAB): $(M)^+$ calcd: 669.3513, meas: 669.349; $(M + Na)^+$ calcd: 692.3411, recorded: 692.3401.

(1*R*)-1-[3-[2-(1,1-Dimethylethoxy)-2-oxoethoxy]phenyl]-3-(1,3-benzodioxol-5-yl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (15c). General procedure F was used for the coupling of alcohol **6c** acid and **14**. The crude product was chromatographed (20% then 30% EtOAc/hexane) to afford product (556 mg, 69%) as a colorless oil: TLC (EtOAc/hexane, 3/7) $R_f = 0.49$; IR (neat) 2970, 1745, 1700, 1640, 1490, 1440, 1245, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.32–7.26 (m, 1H), 6.99–6.84 (m, 6H), 5.93 (s, 2H). 5.80–76 (m, 1H), 5.33 (d, $J = 4.9$ Hz, 1H), 4.55 (s, 2H), 3.38 (d, $J = 12.9$ Hz, 1H), 3.16 (td, $J = 12.3$, 3.1 Hz, 1H), 2.63–2.50 (m, 2H), 2.38 (d, $J = 13.7$ Hz, 1H), 2.26–2.16 (m, 1H), 2.09–2.04 (m, 1H), 1.81–1.57 (m, 7H), 1.51 (s, 9H), 1.26, (s, 3H), 1.23 (s, 3H), 0.91 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.2, 170.0, 168.3, 167.6, 158.5, 148.1, 146.2, 141.7, 135.0, 130.1, 121.5, 120.2, 114.9, 113.6, 109.2, 108.6, 101.2, 82.7, 66.2, 51.7, 47.1, 44.5, 38.3, 32.9, 31.6, 28.4, 26.8, 25.3, 23.8, 23.5, 21.6, 9.1; HRMS (FAB): $(M + Na)^+$ calcd: 646.2992, recorded: 646.3021.

(1*R*)-1-[3-[2-(1,1-Dimethylethoxy)-2-oxoethoxy]phenyl]-3-(3,4-dimethoxyphenyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (15d). General procedure F was used for the coupling of alcohol **6d** and acid **14**. The crude product was chromatographed (25% then 30% EtOAc/hexane) to afford product (993 mg, 78%) as a colorless oil: TLC (EtOAc/hexane, 3/7) $R_f = 0.28$; IR (neat) 2940, 1735, 1645, 1515, 1455, 1225, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.20–7.17 (m, 2H), 6.91–6.69 (m, 5H), 5.73–5.68 (m, 1H). 5.24 (br s, 1H), 4.46 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.29 (d, $J = 13.2$ Hz, 1H), 3.07 (td, $J = 12.7$, 3.0 Hz, 1H), 2.52–2.44 (m, 2H), 2.29 (d, $J = 13.6$ Hz, 1H), 2.20–2.13 (m, 1H), 2.04–1.95 (m, 1H), 1.71–1.51 (m, 7H), 1.41 (s, 9H), 1.16, (s, 3H), 1.14 (s, 3H), 0.82 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.2, 170.1, 168.3, 167.6, 158.5, 149.3, 147.8, 141.8, 133.9, 130.1, 120.5, 120.3, 114.7, 113.7, 112.2, 111.7, 82.7, 66.2, 56.2, 51.7, 47.1, 44.6, 38.3, 32.9, 31.6, 28.8, 26.8, 25.3, 23.8, 23.5, 21.6, 9.1; HRMS (FAB): $(M + Na)^+$ calcd: 662.3305, recorded: 662.3301.

(1*R*)-1-[3-[2-(1,1-Dimethylethoxy)-2-oxoethoxy]phenyl]-3-(4-methoxyphenyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (15e). General procedure F was used for the coupling of alcohol **6e** and acid **14**. The crude product was flash chromatographed (25% EtOAc/hexane) to afford product (72 mg, 87%) as a colorless foam: TLC (EtOAc/hexane, 2/8) $R_f = 0.35$; IR (neat) 2970, 1750, 1645, 1515, 1440, 1250, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.29–7.22 (m, 1H), 7.06–6.79 (m, 7H), 5.79–5.74 (m, 1H), 5.30 (d, $J = 5.0$ Hz, 1H), 4.52 (s, 2H), 3.78 (s, 3H), 3.36 (d, $J = 13.3$ Hz, 1H), 3.15 (td, $J = 12.7$, 3.0, 1H), 2.63–2.48 (m, 2H), 2.35 (d, $J = 13.6$ Hz, 1H), 2.27–2.17 (m, 1H), 2.08–1.98 (m, 1H), 1.79–1.55 (m, 7H), 1.48 (s, 9H), 1.23 (s, 3H), 1.20 (s, 3H), 0.89 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 207.8, 169.7, 167.9, 167.3, 158.2, 141.4, 132.8, 129.7, 129.3, 119.9, 114.3, 113.9, 113.2, 82.3, 65.8, 55.3, 51.3, 46.7, 44.2, 38.0, 32.5, 30.7, 28.1, 26.4, 25.0, 24.5, 23.6, 23.1, 21.2, 8.8; LRMS (ES+): $(M + NH_4)^+$ 627; $(M + Na)^+$ 632.

(1*R*)-1-[3-[2-(1,1-Dimethylethoxy)-2-oxoethoxy]phenyl]-3-(3-pyridinyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (15f). General procedure F was used for the coupling of alcohol **6f** and acid **14**.

The crude product was chromatographed (20–60% EtOAc/hexane) to afford product (860 mg, 96%) as a colorless oil: TLC (EtOAc/hexane, 1/1) $R_f = 0.36$; IR (neat) 2970, 1750, 1700, 1645, 1440, 1225, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 8.46 (m, 2H), 7.50–6.80 (m, 6H), 5.80 (t, $J = 6.1$ Hz, 1H), 5.32 (d, $J = 5.0$ Hz, 1H), 4.54 (s, 2H), 3.38 (d, $J = 12.8$ Hz, 1H), 3.14 (td, $J = 12.6$, 3.0 Hz, 1H) 2.60 (m, 2H), 2.36 (d, $J = 13.7$ Hz, 1H), 2.25 (m, 1H), 2.10 (m, 1H), 1.75 (m, 4H), 1.49 (s, 9H), 1.45 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H), 0.90 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.2, 175.1, 170.0, 168.2, 167.7, 158.6, 150.2, 148.1, 141.3, 136.6, 130.2, 123.8, 120.1, 115.0, 113.6, 107.9, 82.8, 66.1, 51.7, 47.1, 44.6, 39.2, 37.8, 34.4, 33.0, 29.2, 28.4, 26.7, 25.3, 23.9, 23.5, 21.6, 21.4, 9.1; LRMS (ES+): $(M+H)^+$ 581, $(M+Na)^+$ 603; (ES−): $(M+H)^+$ 579.

(1*R*)-1-[3-[2-(1,1-Dimethylethoxy)-2-oxoethoxy]phenyl]-3-(4-morpholinyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (16). General procedure F was used for the coupling of alcohol **8** and acid **14**. The crude product was chromatographed (75% EtOAc/hexane) to afford product (831 mg, 72%) as a colorless oil: TLC (EtOAc) $R_f = 0.47$; IR (neat) 2970, 1750, 1645, 1445, 1225, 1150, 990 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.31–7.27 (m, 1H), 6.99 (d, $J = 7.9$ Hz, 1H), 6.93–6.90 (m, 1H), 6.84 (dd, $J = 8.2$, 2.5 Hz, 1H), 5.89 (t, $J = 6.9$ Hz, 1H), 5.29 (d, $J = 4.9$ Hz, 1H), 4.54 (s, 2H), 3.71 (t, $J = 4.4$ Hz, 4H), 3.36 (d, $J = 13.1$ Hz, 1H), 3.13 (td, $J = 12.7$, 2.9 Hz, 1H), 2.42–2.30 (m, 2H), 2.18–2.11 (m, 1H), 2.00–1.91 (m, 1H), 1.79–1.57 (m, 7H), 1.51 (s, 9H), 1.24 (s, 3H), 1.22 (s, 3H), 0.91 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.1, 169.9, 168.2, 167.5, 158.5, 141.7, 130.0, 120.1, 82.6, 75.9, 67.3, 66.1, 54.8, 54.0, 51.6, 47.0, 44.5, 33.5, 32.8, 28.4, 26.7, 25.3, 23.9, 23.4, 21.5, 9.1; LRMS (ES+): $(M+H)^+$ 589.

(1*R*)-1-[3-[2-[*N*-(*tert*-Butoxycarbonyl)ethanamine]phenoxy]-3-(3,4-dimethoxyphenyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (17). General procedure F was used for the coupling of alcohol **9** and acid **14**. The crude product was chromatographed (30% then 40% EtOAc/hexane) to afford product (447 mg, 64%) as an oil: TLC (EtOAc/hexane, 2/3) $R_f = 0.40$; IR (neat) 3380, 2970, 1700, 1645, 1515, 1455, 1260, 1160, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.29–7.24 (m, 2H), 6.94–6.77 (m, 3H), 6.70–6.67 (m, 2H), 5.80–5.75 (m, 1H), 5.32 (d, $J = 5.0$ Hz, 1H), 5.02 (br s, 1H), 4.03 (t, $J = 5.1$ Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.54–3.52 (m, 2H), 3.37 (d, $J = 13.3$ Hz, 1H), 3.16 (td, $J = 12.6$, 2.9 Hz, 1H), 2.64–2.51 (m, 2H), 2.37 (d, $J = 13.5$ Hz, 1H), 2.31–2.18 (m, 1H), 2.13–1.92 (m, 1H), 1.78–1.50 (m, 7H), 1.45 (s, 9H), 1.23 (s, 3H), 1.21 (s, 3H), 0.89 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.2, 170.1, 167.6, 159.2, 156.3, 149.3, 147.8, 141.9, 133.9, 130.1, 120.6, 119.6, 114.5, 113.4, 112.2, 111.8, 77.0, 67.6, 56.2, 51.7, 47.1, 44.6, 38.4, 32.9, 31.6, 28.8, 26.9, 25.4, 23.9, 23.5, 21.6, 9.1; LRMS (ES+): $(M+H)^+$ 669, $(M+NH_4)^+$ 686, $(M+H)^+$ 691.

(1*R*)-1-[3-*N*-(*tert*-Butoxycarbonyl)amino]phenyl]-3-(3,4-dimethoxyphenyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (19). General procedure F was used for the coupling of alcohol **11** and acid **14**. The crude product was chromatographed (30% then 50% EtOAc/hexane) to afford product (130 mg, 43%) as a white foam: TLC (EtOAc/hexane, 1/1) $R_f = 0.43$; IR (neat) 2937, 1740, 1702, 1643, 1516, 1146, 1260, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.37–7.20 (m, 4H), 6.78–6.65 (m, 3H), 5.81 (t, $J = 5.7$ Hz, 1H), 5.30 (d, $J = 4.4$ Hz, 1H), 3.83 (s, 6H), 3.34 (d, $J = 12.3$ Hz, 1H), 3.13 (t, $J = 10.5$ Hz, 1H), 2.60–2.52 (m, 2H), 2.35–2.22 (m, 2H), 2.10–2.05 (m, 1H), 1.78–1.55 (m, 7H), 1.41 (s, 9H), 1.23 (s, 3H), 1.20 (s, 3H), 0.89 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 207.7, 169.7, 167.3, 151.9, 149.1, 147.5, 140.7, 139.3, 133.5, 129.1, 127.9, 126.7, 126.1, 120.3, 112.0, 111.6, 83.4, 76.4, 56.0, 55.9, 51.3, 46.7, 44.3, 38.0, 32.5, 31.3, 28.0, 26.5, 25.0, 23.6, 23.2, 21.2, 8.8; HRMS (FAB): $(M+Na)^+$ calcd: 647.3308, recorded: 647.3308.

(1*R*)-1-[4-[2-(2-Trimethylsilylethoxy)-2-oxoethoxy]phenyl]-3-(3,4-dimethoxyphenyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (21). General procedure F was used for the coupling of alcohol **13** with acid **14**. The crude product was chromatographed (30% EtOAc/hexane) to afford product (760 mg, 83%) as a colorless oil: TLC (EtOAc/hexane, 3.7) $R_f = 0.44$; IR (neat) 2950, 1735, 1645, 1515, 1445, 1250, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.25–7.22 (m, 2H), 6.86–6.82 (m, 2H), 6.73 (d, $J = 8.6$ Hz, 1H), 6.64–6.61 (m, 2H), 5.73 (t, $J = 6.2$ Hz, 1H), 5.24 (d, $J = 4.8$ Hz, 1H), 4.55 (s, 2H), 4.26 (t, $J = 8.4$ Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.29 (d, $J = 13.2$ Hz, 1H), 3.04 (td, $J = 12.7$, 3.0 Hz, 1H), 2.57–2.46 (m, 2H), 2.32-2.17 (m, 1H), 2.06–1.99 (m, 1H), 1.71–1.25 (m, 7H), 1.18 (s, 3H), 1.16 (s, 3H), 0.99 (t, $J = 8.6$ Hz, 2H), 0.84 (t, $J = 7.4$ Hz, 3H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 209.3, 171.2, 170.4, 168.7, 159.4, 150.5, 148.9, 135.0, 134.4, 129.8, 121.7, 116.2, 112.9, 111.8, 78.0, 67.1, 65.3, 57.4, 52.8 48.2, 45.7, 39.3, 34.0, 32.8, 27.9, 26.5, 25.1, 24.6, 22.7, 18.9, 10.3, 0.0; LRMS (ES+): $(M+Na)^+$ 701.

(1*R*)-1-[3-(Carboxymethoxy)phenyl]-3-phenyl-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (2a). General procedure G was used for the acidolysis of **15a**. The crude product was chromatographed (10% $MeOH/CH_2Cl_2$) to afford product (177 mg, 99%) as a colorless gum: TLC ($MeOH/CHCl_3$, 15/85) $R_f = 0.35$; IR (neat) 2940, 1740, 1700, 1640, 1445, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.30–6.80 (m,

9H), 5.75 (m, 1H), 5.30 (d, $J=4.8$ Hz, 1H), 4.66 (s, 2H), 3.35 (d, $J=9.27$ Hz, 1H), 3.19 (td, $J=12.4$, 2.9 Hz, 1H), 2.69 (m, 2H), 2.39 (d, $J=16.2$ Hz, 1H), 2.30 (m, 1H), 2.10 (m, 1H), 1.90–1.60 (m, 6H), 1.50 (m, 1H), 1.19 (s, 3H), 1.17 (s, 3H), 0.85 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.0, 172.3, 169.8, 167.9, 158.2, 142.2, 141.1, 130.2, 128.9, 128.7, 126.5, 120.3, 115.5, 111.8, 65.5, 57.2, 52.0, 47.2, 44.6, 38.3, 33.0, 32.9, 32.1, 27.0, 25.3, 25.2, 23.9, 23.4, 21.5, 9.1; HRMS (FAB): $(M+Na)^+$ calcd: 546.2468, recorded: 546.2461.

(1*R*)-1-[3-(Carboxymethoxy)phenyl]-3-(3,4,5-trimethoxyphenyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (2b). General procedure G was used for the acidolysis of **15b**. The crude product was chromatographed (10% $MeOH/CH_2Cl_2$) to afford product (358 mg, 98%) as a white foam: TLC ($MeOH/CHCl_3$, 15/85) $R_f=0.40$; IR (neat) 3445, 2940, 1735, 1700, 1635, 1460, 1210, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.30–6.80 (m, 4H), 6.39 (s, 2H), 5.82 (m, 1H), 5.33 (d, $J=4.6$ Hz, 1H), 4.70 (m, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 3.38 (d, $J=12.6$ Hz, 1H), 3.22 (td, $J=12.8$, 3.1 Hz, 1H), 2.60 (m, 2H), 2.45–2.05 (m, 3H), 1.70 (m, 6H), 1.45 (m, 2H), 1.23 (s, 3H), 1.21 (s, 3H), 0.89 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.0, 175.0, 171.7, 169.8, 167.8, 158.2, 153.6, 142.1, 136.9, 130.2, 129.4, 128.6, 125.7, 120.3, 115.5, 111.8, 107.9, 105.8, 65.6, 61.2, 56.5, 52.0, 47.2, 44.6, 38.3, 32.9, 32.5, 27.0, 25.3, 23.8, 23.4, 21.5, 9.1; HRMS (FAB): $(M+Na)^+$ calcd: 636.2785, recorded: 636.2756.

(1*R*)-1-[3-(Carboxymethoxy)phenyl]-3-(1,3-benzodioxol-5-yl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (2c). General procedure G was used for the acidolysis of **15c**. The crude product was chromatographed (10% $MeOH/CH_2Cl_2$) to afford product (483 mg, 85%) as a colorless oil: TLC ($MeOH/CHCl_3$, 15/85) $R_f=0.40$; IR (neat) 3420, 2940, 1735, 1700, 1640, 1490, 1440, 1245, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.12 (t, $J=6.7$ Hz, 1H), 6.92–6.81 (m, 3H), 6.68–6.52 (m, 3H), 5.86 (s, 2H), 5.73 (t, $J=7.2$ Hz, 1H), 5.33 (s, 1H), 4.40 (s, 2H), 3.34 (d, $J=12.2$ Hz, 1H), 3.19 (t, $J=12.0$ Hz, 1H), 2.54–2.46 (m, 2H), 2.34 (d, $J=12.6$ Hz, 1H), 2.24–2.00 (m, 2H), 1.73–1.32 (m, 7H), 1.18 (s, 3H), 1.16 (s, 3H), 0.84 (t, $J=7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.0, 169.9, 167.79, 158.3, 148.0, 146.2, 141.9, 135.0, 130.1, 121.5, 109.1, 108.6, 107.2, 101.2, 77.0, 51.9, 47.0, 44.6, 38.6, 32.9, 31.8, 26.9, 25.3, 23.9, 23.3, 21.6, 9.1. HRMS (FAB): $(M-H)^-$ calcd: 566.2390, recorded: 566.2365.

(1*R*)-1-[3-(Carboxymethoxy)phenyl]-3-(3,4-dimethoxyphenyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (2d). General procedure G was used for the acidolysis of **15d**. The crude product was chromatographed (10% $MeOH/CH_2Cl_2$) to afford product (315 mg, 86%) as a foam: TLC ($MeOH/CHCl_3$, 15/85) $R_f=0.35$; IR (neat) 2940, 1740, 1640, 1515, 1445, 1260, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.00 (br s, 1H), 7.35–6.70 (m, 7H), 5.82 (m, 1H), 5.33 (d, $J=4.5$ Hz, 1H), 4.71 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.38 (d, $J=12.6$ Hz, 1H), 3.24 (td, $J=12.3$, 2.7 Hz, 1H), 2.60 (m, 2H), 2.45–2.05 (m, 3H), 1.70 (m, 6H), 1.45 (m, 2H), 1.23 (s, 3H), 1.21 (s, 3H), 0.89 (t, $J=7.4$ Hz, 3H); ^{1}H NMR (CD_3OD, 300 MHz) 7.30 (t, $J=7.9$ Hz, 1H), 7.00–6.77 (m, 5H), 6.72 (dd, $J=8.1$, 1.8 Hz, 1H), 5.80–5.74 (m, 1H), 5.24 (d, $J=4.5$ Hz, 1H), 4.69 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.38 (dd, $J=13.3$, 8.5 Hz, 1H), 3.18 (td, $J=12.8$, 2.9 Hz, 1H), 2.69–2.54 (m, 2H), 2.37–2.15 (m, 2H), 2.13–2.01 (m, 1H), 1.79–1.61 (m, 5H), 1.53–1.30 (m, 2H), 1.25 (s, 3H), 1.23 (s, 3H), 0.90 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.0, 172.0, 169.8, 167.8, 158.2, 149.4, 147.8, 142.2, 133.7, 130.2, 129.4, 128.6, 125.7, 120.6, 120.3, 115.5, 112.2, 111.8, 111.7, 108.2, 65.5, 56.3, 51.9, 47.2, 44.6, 38.5, 32.9, 31.7, 28.4, 27.0, 25.3, 23.9, 23.4, 21.8, 21.5, 9.1; ^{13}C NMR (CD_3OD, 75 MHz) 207.9, 171.4, 169.8, 167.9, 158.5, 149.3, 147.7, 142.0, 134.1, 129.6, 120.5, 119.7, 114.4, 112.7, 112.4, 112.1, 76.8, 64.8, 55.4, 55.3, 51.6, 46.5, 44.6, 37.9, 32.4, 31.0, 26.1, 24.7, 22.7, 22.4, 20.9, 7.9; HRMS (FAB): $(M+Na)^+$ calcd: 606.2679, recorded: 606.2692.

(1*R*)-1-[3-(Carboxymethoxy)phenyl]-3-(4-methoxyphenyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (2e). General procedure G was used for the acidolysis of **15e**. The crude product was chromatographed (10% $MeOH/CH_2Cl_2$) to afford product (45 mg, 71%) as a foam: TLC ($MeOH/CHCl_3$, 15/85) $R_f=0.35$; IR (neat) 2940, 1735, 1700, 1635, 1455, 1210 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) 7.14–7.00 (m, 1H), 6.85 (d, $J=8.1$ Hz, 2H), 6.77–6.67 (m, 3H), 6.61 (d, $J=8.2$ Hz, 2H), 5.55–5.50 (m, 1H), 5.01 (d, $J=4.5$ Hz, 1H), 4.45 (s, 2H), 3.54 (s, 3H), 3.18 (d, $J=13.0$ Hz, 1H), 2.95 (t, $J=12.6$ Hz, 1H), 2.45–2.25 (m, 2H), 2.20–1.80 (m, 3H), 1.60–1.40 (m, 5H), 1.35–1.10 (m, 2H), 1.02 (s, 3H), 1.00 (s, 3H), 0.67 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (CD_3OD, 75 MHz) 210.0, 171.9, 170.1, 160.7, 160.5, 144.1, 135.3, 131.8, 131.4, 121.85, 116.6, 116.0, 116.0, 114.9, 79.1, 56.7, 53.8, 48.7, 46.7, 40.2, 34.6, 32.8, 28.3, 26.9, 24.9, 24.6, 23.1, 10.1; LRMS (ES+): $(M+Na)^+$ 576; (ES−): $(M-H)^-$ 552; HRMS (FAB): $(M-H)^-$ calcd: 552.2597, recorded: 552.2585.

(1*R*)-1-[3-(Carboxymethoxy)phenyl]-3-(3-pyridinyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (2f). General procedure G was used for the acidolysis of **15f**. The crude product was not chromatographed. Product (424 mg, 96%, as trifluoroacetic acid salt) was obtained as a foam: ^{1}H NMR ($CDCl_3$, 300 MHz) 8.75 (s, 1H), 8.67 (d, $J=10.4$ Hz, 1H), 8.23

(t, $J=5.6$ Hz, 1H), 7.79 (dd, $J=7.9$, 5.6 Hz, 1H), 7.35–6.75 (m, 4H), 5.80 (t, $J=6.1$ Hz, 1H), 5.25 (d, $J=5.0$ Hz, 1H), 4.75 (m, 2H), 3.35 (d, $J=13.2$ Hz, 1H), 3.14 (td, $J=12.6$, 3.0 Hz, 1H) 2.75 (m, 2H), 2.30 (m, 3H), 1.70 (m, 6H), 1.40 (m, 2H), 1.22 (s, 6H), 0.92 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3, 172.3, 169.9, 167.8, 158.6, 145.5, 142.5, 142.0, 139.8, 139.5, 130.6, 129.4, 128.6, 120.2, 117.1, 111.8, 65.2, 51.8, 47.1, 44.8, 36.7, 32.8, 28.4, 26.6, 25.2, 23.7, 21.4, 9.1. HRMS (FAB): $(M+Na)^+$ calcd: 547.2420, recorded: 547.2415.

(1*R*)-1-[3-(Carboxymethoxy)phenyl]-3-(4-morpholinyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (2g). General procedure H was used for the acidolysis of **16**. The crude product was not chromatographed. Product (297 mg, 95%, as hydrochloric acid salt) was obtained as a foam: IR (neat) 2970, 1740, 1700, 1635, 1445, 1200, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 11.80 (br s, 1H), 7.19–71.3 (m, 1H), 6.82–6.76 (m, 2H), 5.75 (br s, 1H), 5.11 (d, $J=4.9$ Hz, 1H), 4.52 (s, 2H), 4.02 (br s, 2H), 3.79 (d, $J=11.8$ Hz, 1H), 3.35–3.20 (m, 2H), 3.09–2.74 (m, 5H), 2.35–2.21 (m, 3H), 1.66–1.16 (m, 7H), 1.11 (s, 3H), 1.10 (s, 3H), 0.78 (t, $J=7.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 209.0, 170.7, 169.7, 168.0, 158.5, 139.7, 130.6, 119.6, 116.1, 112.4, 65.5, 64.0, 54.1, 52.8, 52.3, 51.9, 47.1, 45.0, 32.8, 30.0, 26.4, 25.1, 23.9, 23.4, 21.4, 9.1; LRMS (ES+): $(M+H)^+$ 533; (ES−): $(M-H)^-$ 531; HRMS (FAB): $(M-H)^-$ calcd: 531.2706, recorded: 531.2712.

(1*R*)-3-(3,4-Dimethoxyphenyl)-1-[3-[2-ethanamine]phenoxy]-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate hydrochloride (18). General procedure H was used for the acidolysis of **17**. The crude hydrochloride salt product was not chromatographed. Product was obtained as a foam: IR (neat) 2965, 1735, 1700, 1640, 1515, 1455, 1260, 1160, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.53 (br s, 2H), 7.30–7.10 (m, 1H), 7.00–6.68 (m, 6H), 5.80–5.70 (m, 1H), 5.35–5.30 (m, 1H), 4.30–4.15 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.40–3.20 (m, 3H), 3.15 (t, $J=12.0$ Hz, 1H), 2.32–2.15 (m, 1H), 2.13–2.00 (m, 1H), 1.80–1.30 (m, 8H), 1.20 (s, 3H), 1.18 (s, 3H), 0.86 (t, $J=7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3, 170.1, 167.7, 158.3, 149.3, 147.8, 142.1, 133.9, 130.2, 120.6, 112.0, 114.7, 113.7, 112.3, 111.8, 77.1, 64.0, 56.3, 51.8, 47.1, 44.6, 39.5, 38.7, 32.8, 31.7, 26.8, 25.3, 23.8, 23.5, 21.6, 9.1; LRMS (ES+): $(M+H)^+$ 569; HRMS (FAB): $(M+H)^+$ calcd: 569.3227, recorded: 569.3247.

(1*R*)-1-(3-Aminophenyl)-3-(3,4-dimethoxyphenyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (20). General procedure G was used for the acidolysis of **19**. The crude product was chromatographed (50% EtOAc/hexane with 1% AcOH) to afford product (313 mg, 77%) as a foam: TLC (EtOAc/hexane 1:1, with 1% AcOH) $R_f=0.43$; IR (neat) 3370, 2940, 1740, 1700, 1640, 1515, 1200, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.26–6.67 (m, 7H), 6.03 (br s, 2H), 5.76 (t, $J=5.7$ Hz, 1H), 5.31 (d, $J=4.8$ Hz, 1H), 3.84 (s, 6H), 3.83 (s, 3H), 3.35 (d, $J=12.6$ Hz, 1H), 3.14 (t, $J=10.1$ Hz, 1H), 2.63–2.49 (m, 2H), 2.38–2.10 (m, 2H), 22.08–2.00 (m, 1H), 1.77–1.60 (m, 5H), 1.56–1.37 (m, 2H), 1.21 (s, 3H), 1.19 (s, 3H), 0.86 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3, 170.0, 167.7, 149.3, 147.8, 141.6, 133.9, 130.1, 129.4, 128.6, 120.6, 118.2, 116.3, 112.2, 111.8, 76.9, 56.3, 56.2, 51.7, 47.1, 44.6, 38.4, 31.9, 31.6, 26.7, 25.3, 23.0, 21.5, 9.1; HRMS (FAB): $(M)^+$ calcd: 547.2784, recorded: 547.2790.

(1*R*)-1-[4-(Carboxymethoxy)phenyl]-3-(3,4-dimethoxyphenyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (22). A solution of ester **21** (150 mg, 0.219 mmol) in DMF (2 mL) at 0 °C was treated with a solution of tetrabutylammonium fluoride in THF (1.0 N, 439 μL, 0.439 mmol). The reaction mixture was allowed to stir for 1 h then partitioned between EtOAc (10 mL) and a 0.5 N HCl solution (10 mL). The organic layer was washed with an additional portion of 0.5 N HCl solution followed by brine (2×10 mL), then dried over Na_2SO_4, filtered, evaporated, and chromatographed (5% then 10% $MeOH/CH_2Cl_2$) to afford product (110 mg, 86%) as a colorless foam: TLC ($MeOH/CHCl_3$, 15/85) $R_f=0.40$; IR (neat) 2940, 1735, 1640, 1515, 1445, 1235 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.32–7.26 (m, 2H), 6.92–6.89 (m, 2H), 6.78 (d, $J=8.7$ Hz, 1H), 6.69–6.66 (m, 2H), 5.78 (t, $J=6.2$ Hz, 1H), 5.29 (d, $J=4.8$ Hz, 1H), 4.67 (s, 2H), 3.85 (s, 6H), 3.34 (d, $J=13.4$ Hz, 1H), 3.09 (td, $J=12.6$, 3.0 Hz, 1H), 2.59–2.50 (m, 2H), 2.37–2.23 (m, 2H), 2.08–2.03 (m, 1H), 1.75–1.25 (m, 7H), 1.23 (s, 3H), 1.20 (s, 3H), 0.89 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208, 172.3, 170.1, 167, 157.7, 149.3, 147.8, 133.9, 133.8, 128.8, 120.6, 115.2, 112.2, 111.8, 77.0, 65.3, 56.3, 56.2, 51.7, 47.1, 44.6, 38.1, 32.9, 31.7, 26.8, 25.3, 23.9, 23.5, 21.6, 9.1; LRMS (ES+): $(M+NH_4)^+$ 601. HRMS (FAB): $(M)^+$ calcd: 583.2781, recorded: 583.2763; $(M+Na)^+$ calcd: 606.2679, recorded: 606.2680.

Dimer (1a). General procedure I was used for the dimerization of **2a**. The crude product was chromatographed (75% then 100% EtOAc/hexane) to afford product (470 mg, 82%) as a foam: TLC (EtOAc/hexane, 3/1) $R_f=0.45$; IR (neat) 3350, 2940, 1740, 1675, 1644, 1540, 1442, 1265, 1200, 1075, 990 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.27–7.12 (m, 6H), 6.99–6.83 (m, 3H), 5.82–5.80 (m, 1H), 5.32 (s, 1H), 4.43 (s, 2H), 3.54 (s, 2H), 3.37 (d, $J=12$ Hz, 1H), 3.18 (t, $J=12$ Hz, 1H), 2.66–2.53 (m, 2H), 2.39–2.11 (m, 3H), 1.87–1.63 (m, 5H), 1.53–1.35 (m, 2H), 1.22 (s, 6H), 0.88 (t, $J=7.4$ Hz,

3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.25, 170.0, 169.6, 167.7, 157.8, 142.2, 141.2, 130.4, 128.9, 128.7, 126.5, 120.5, 114.5, 113.8, 76.9, 67.6, 51.7, 47.1, 44.5, 39.8, 38.4, 32.9, 32.0, 25.3, 24.9, 23.9, 23.5, 21.6, 9.1; HRMS (FAB): $(M+Na)^+$ calcd: 1093.5514, recorded: 1093.5536.

Dimer (1b). General procedure I was used for the dimerization of **2b**. The crude product was chromatographed (50% then 75% EtOAc/hexane then EtOAc) to afford product (65 mg, 66%) as a colorless foam: TLC (EtOAc/hexane, 3/1) $R_f=0.15$; IR (neat) 3360, 2940, 1740, 1645, 1590, 1445, 1240, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.31–7.26 (m, 2H), 7.00–6.97 (m, 2H), 6.87–6.84 (m, 1H), 6.40–6.36 (m, 2H), 5.81–5.78 (m, 1H), 5.31 (d, $J=4.8$ Hz, 1H), 4.45 (s, 2H), 3.83 (s, 6H), 3.81 (s, 3H), 3.54, (s, 2H), 3.38 (d, $J=1.8$ Hz, 1H), 3.17 (td, $J=12.7$, 2.5 Hz, 1H), 2.62–2.53 (m, 2H), 2.36 (d, $J=13.6$ Hz, 1H), 2.29–2.22 (m, 1H), 2.12–2.02 (m, 1H), 1.74–1.62 (m, 7H), 1.22 (s, 3H), 1.21 (s, 3H), 0.88 (d, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 207.9, 169.7, 169.2, 167.3, 157.5, 153.2, 141.9, 136.6, 130.0, 120.1, 114.0, 113.5, 76.5, 67.3, 60.8, 56.1, 51.3, 46.7, 44.2, 39.5, 38.1, 32.6, 32.1, 26.4, 25.0, 23.3, 21.0, 8.8; HRMS (FAB): $(M+Na)^+$ calcd: 1273.6148, recorded: 1273.6193.

Dimer (1c). General procedure I was used for the dimerization of **2c**. The crude product was chromatographed (50% EtOAc/hexane) to afford product (38 mg, 27%) as a colorless foam: TLC (EtOAc/hexane, 3/1) $R_f=0.39$; IR (neat) 3355, 2940, 1740, 1675, 1645, 1540, 1490, 1440, 1245, 1190, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.36–7.25 (m, 2H), 7.00–6.91 (m, 2H), 6.84 (d, $J=8.1$ Hz, 1H), 6.72–6.56 (m, 3H), 5.90 (s, 2H), 5.77 (t, $J=5.7$ Hz, 1H), 5.29 (d, $J=4.8$ Hz, 1H), 4.44 (s, 2H), 3.55 (s, 2H), 3.37 (d, $J=12.5$ Hz, 1H), 3.16 (td, $J=12.6$, 2.6 Hz, 1H), 2.60–2.47 (m, 2H), 2.36 (d, $J=13.3$ Hz, 1H), 2.26–2.17 (m, 1H), 2.09–1.99 (m, 1H), 1.86–1.27 (m, 7H), 1.22 (s, 3H), 1.20 (s, 3H), 0.88 (d, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3, 170.0, 169.6, 167.7, 157.8, 148.1, 146.2, 142.2, 135.0, 130.4, 121.5, 120.5, 114.5, 113.8, 109.1, 108.6, 76.7, 67.6, 51.7, 47.1, 44.5, 39.9, 38.6, 32.9, 31.7, 26.8, 25.3, 23.9, 23.5, 21.6, 9.1; HRMS (FAB): $(M+Na)^+$ calcd: 1181.5311, recorded: 1181.5317.

Dimer (1d). General procedure J was used for the dimerization of **2d**. Ethylenediamine dihydrochloride was used as the coupling reagent. The crude product was chromatographed (75% then 100% EtOAc/hexane) to afford product (562 mg, 42%) as a colorless foam: TLC (EtOAc) $R_f=0.33$; IR (neat) 3360, 2940, 1740, 1680, 1645, 1515, 1445, 1260, 1160, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.30–7.25 (m, 2H), 6.98–6.93 (m, 1H), 6.85 (d, $J=8.0$ Hz, 1H), 6.78 (t, $J=6.3$ Hz, 1H), 6.76–6.68 (m, 2H), 5.80 (d, $J=5.6$ Hz, 1H), 5.31 (d, $J=4.7$ Hz, 1H), 4.45 (s, 2H), 3.85 (s, 6H), 3.54 (s, 2H), 3.38 (d, $J=12.4$ Hz, 1H), 3.18 (t, $J=10.4$, 1H), 2.72–2.52 (m, 2H), 2.37 (d, $J=13.1$ Hz, 1H), 2.30–2.21 (m, 1H), 2.11–2.02 (m, 1H), 1.74–1.62 (m, 5H), 1.51–1.33 (m, 2H), 1.22 (s, 6H), 0.88 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3, 170.0, 169.6, 167.7, 157.8, 149.3, 147.8, 142.3, 133.8, 130.3, 120.6, 114.5, 113.8, 112.2, 111.8, 76.8, 67.6, 56.2, 51.7, 47.1, 44.5, 39.8, 38.5, 32.9, 31.6, 26.8, 25.3, 23.9, 23.8, 21.5, 9.1; HRMS (FAB): $(M+Na)^+$ calcd: 1213.5937, recorded: 1213.5905.

Compound **1d** was also prepared from the DCC coupling of diol **28** with acid **14** via general procedure K. The crude product was chromatographed (75% EtOAc/hexane then EtOAc) to afford product (196 mg, 94%) identical in all respects to that obtained above.

Dimer (1e). General procedure I was used for the dimerization of **2e**. The crude product was chromatographed (75% then 100% EtOAc/hexane) to afford product (33 mg, 37%) as a colorless foam: TLC (EtOAc) $R_f=0.33$; IR (neat) 3360, 2940, 1740, 1680, 1645, 1515, 1445, 1260, 1160, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.30–7.25 (m, 2H), 7.05 (d, $J=8.5$ Hz, 2H), 6.98–6.94 (m, 1H), 6.83–6.79 (m, 3H), 5.77 (dd, $J=7.3$, 5.8 Hz, 1H), 5.30 (d, $J=4.9$ Hz, 1H), 4.44 (s, 2H), 3.77 (s, 3H), 3.54 (s, 2H), 3.37 (d, $J=13.4$ Hz, 1H), 3.17 (td, $J=12.6$, 2.5, 1H), 2.63–2.49 (m, 2H), 2.36 (d, $J=13.6$ Hz, 1H), 2.28–2.15 (m, 1H), 2.08–2.01 (m, 1H), 1.79–1.60 (m, 5H), 1.51–1.30 (m, 2H), 1.22 (s, 3H), 1.20 (s, 3H), 0.88 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 207.13, 168.8, 168.4, 168.3, 166.5, 157.24, 156.7, 141.1, 132.1, 129.2, 128.5, 119.3, 113.2, 112.6, 76.7, 66.5, 54.5, 50.5, 46.0, 43.4, 38.7, 37.5, 31.7, 30.0, 25.7, 24.2, 22.7, 22.4, 20.42, 8.0; LRMS (ES+): $(M+H)^+$ 1131, $(M+Na)^+$ 1153; HRMS (FAB): $(M+Na)^+$ calcd: 1153.5725, recorded: 1153.2757.

Dimer (1f). General procedure J was used for the dimerization of **2f**. Ethylenediamine dihydrochloride was used as the coupling reagent. The crude product was chromatographed (10% MeOH/CH_2Cl_2) to afford product (79 mg, 42% from succinimidyl ester) as a colorless foam: TLC (MeOH/$CHCl_3$, 1/9) $R_f=0.29$; IR (neat) 3335, 2940, 1735, 1670, 1640, 1540, 1440, 1265, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.45–8.41 (m, 2H), 7.50 (d, $J=7.8$ Hz, 1H), 7.35–7.20 (m, 3H), 7.00–6.92 (m, 1H), 6.85 (dd, $J=8.0$, 2.1 Hz, 1H), 5.82–5.77 (m, 1H), 5.31 (d, $J=4.9$ Hz, 1H), 4.45 (s, 2H), 3.56 (br s, 2H), 3.37 (d, $J=12.6$ Hz, 1H), 3.16 (td, $J=12.6$, 2.8 Hz, 1H), 2.66–2.56 (m, 3H), 2.36 (d, $J=5.5$ Hz, 1H), 2.28–2.22 (m, 1H), 2.15–2.05 (m, 1H), 1.80–1.36 (m, 7H), 1.22 (s, 3H), 1.21 (s, 3H), 0.88 (d, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3, 170.0, 169.6, 167.7, 157.9, 149.8, 147.7 141.8, 136.6, 130.5, 123.9,

121.7, 120.3, 114.5, 113.8, 76.5, 67.6, 51.7, 47.1, 44.6, 39.9, 37.9, 32.9, 39.1, 26.7, 25.3, 23.8, 23.6, 21.5, 9.1; HRMS (FAB): $(M+Na)^+$ calcd: 1095.5419, recorded: 1095.5450.

Dimer (1g). General procedure I was used for the dimerization of **2g**. The crude product was chromatographed (10% $MeOH/CH_2Cl_2$) to afford product (220 mg, 77%) as a colorless foam: TLC (MeOH/$CHCl_3$, 1/9) $R_f=0.38$; IR (neat) 3330, 2940, 1740, 1670, 1640, 1540, 1445, 1265, 1205, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.34–7.26 (m, 2H), 7.00–6.94 (m, 2H), 6.88–6.85 (m, 1H), 5.88 (t, $J=6.3$ Hz, 1H), 5.28 (d, $J=4.7$ Hz, 1H), 4.46 (s, 2H), 3.71 (br s, 4H), 3.55 (s, 2H), 3.36 (d, $J=12.9$ Hz, 1H), 3.15 (td, $J=12.7$, 2.7 Hz, 1H), 2.43–2.33 (m, 7H), 2.21–2.15 (m, 1H), 1.99–1.91 (m, 1H), 1.73–1.27 (m, 7H), 1.22 (s, 3H), 1.20 (s, 3H), 0.88 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.0, 169.5, 169.2, 167.2, 157.4, 141.7, 130.0, 120.0, 114.0, 113.3, 75.2, 67.1, 66.8, 54.4, 53.6, 51.2, 46.7, 44.1, 39.4, 34.0, 32.5, 26.3, 24.9, 23.4, 23.2, 21.1, 8.8; HRMS (FAB): $(M+H)^+$ calcd: 1089.6124, recorded: 1089.6123.

Dimer (1i). General procedure I was used for the dimerization of **2d**. The diamine 1,3-diaminopropane replaces ethylenediamine as the coupling reagent. The crude product was chromatographed (75% then 100% EtOAc/hexane) to afford product (161 mg, 31%) as a colorless foam: TLC (EtOAc/hexane, 3/1) $R_f=0.33$; IR (neat) 3370, 2940, 1740, 1675, 1645, 1520, 1440, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.20–7.15 (m, 2H), 6.88–6.82 (m, 1H), 6.75 (dd, $J=7.6$, 2.1 Hz, 1H), 6.67–6.63 (m, 1H), 6.58–6.54 (m, 2H), 5.69–5.64 (m, 1H), 5.19 (d, $J=6.3$ Hz, 1H), 4.38 (s, 2H), 3.73 (s, 6H), 3.25–3.23 (m, 3H), 3.04 (t, $J=12.8$, 1H), 2.54–2.36 (m, 2H), 2.24 (d, $J=12.9$ Hz, 1H), 2.18–2.06 (m, 1H), 1.99–1.89 (m, 1H), 1.62–1.49 (m, 6H), 1.42–1.12 (m, 2H), 1.10 (s, 6H), 0.76 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3, 170.0, 169.0, 167.6, 157.8, 149.4, 147.8, 142.3, 133.8, 130.4, 120.6, 114.3, 114.0, 112.2, 111.8, 76.9, 67.6, 56.3, 51.7, 47.1, 44.5, 38.5, 35.9, 32.9, 31.6, 30.2, 26.8, 25.3, 23.9, 23.8, 21.5, 9.1; HRMS (FAB): $(M+Na)^+$ calcd: 1227.6093, recorded: 1227.6102.

Dimer (1j). General procedure J was used for the dimerization of **2d**. The diamine 2,2′-oxybis(ethylamine) dihydrochloride replaces ethylenediamine dihydrochloride as the coupling reagent. The crude product was chromatographed (EtOAc) to afford product (1.86 g, 55%) as a colorless foam: TLC (EtOAc) $R_f=0.26$; IR (neat) 3375, 2940, 1740, 1680, 1640, 1515, 1440, 1260, 1160, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.30–7.25 (m, 1H), 7.00–6.90 (m, 3H), 6.83 (dd, $J=8.2$, 2.2 Hz, 1H), 6.78 (d, $J=6.0$ Hz, 1H), 6.76–6.66 (m, 2H), 5.79–5.75 (m, 1H), 5.30 (d, $J=5.3$ Hz, 1H), 4.49 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.54 (s, 4H), 3.37 (d, $J=13.3$ Hz, 1H), 3.19 (td, $J=12.7$, 2.7, 1H), 2.64–2.52 (m, 2H), 2.36 (d, $J=13.4$ Hz, 1H), 2.270–2.20 (m, 1H), 2.10–2.00 (m, 1H), 1.79–1.32 (m, 7H), 1.22 (s, 3H), 1.20 (s, 3H), 0.88 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 207.8, 169.7, 168.2, 167.3, 157.4, 149.0, 147.5, 142.0, 133.4, 130.3, 120.2, 114.2, 113.3, 111.8, 111.4, 76.5, 69.6, 67.4, 55.9, 51.2, 46.7, 44.2, 38.8, 38.2, 32.5, 31.3, 26.4, 25.0, 23.6, 23.5, 21.2, 8.8; HRMS (FAB): $(M+Na)^+$ calcd: 1257.6199, recorded: 1257.6193.

Dimer (1k). General procedure J was used for the dimerization of **2d**. The diamine 2,2′-(ethylenedioxy)-bis(ethylamine) replaces ethylenediamine as the coupling reagent. The crude product was chromatographed (5% MeOH/EtOAc) to afford product (54 mg, 49%) as a colorless foam: TLC (EtOAc) $R_f=0.15$; IR (neat) 3365, 2940, 1735, 1680, 1645, 1515, 1445, 1260, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.33–7.27 (m, 1H), 7.06–6.67 (m, 7H), 5.79–5.75 (m, 1H), 5.31 (d, $J=6.5$ Hz, 1H), 4.49 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.58–3.54 (m, 6H), 3.38 (d, $J=12.4$ Hz, 1H), 3.17 (td, $J=12.6$, 2.7, 1H), 2.64–2.50 (m, 2H), 2.37 (d, $J=13.5$ Hz, 1H), 2.30–2.18 (m, 1H), 2.10–2.00 (m, 1H), 1.79–1.36 (m, 7H), 1.22 (s, 3H), 1.21 (s, 3H), 0.88 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 207.9, 169.7, 168.1, 167.3, 157.4, 148.9, 147.4, 141.9, 133.3, 130.0, 120.1, 114.3, 113.2, 111.7, 111.3, 76.6, 70.3, 69.7, 67.4, 55.9, 51.3, 46.7, 44.2, 38.8, 38.2, 32.5, 31.3, 26.4, 24.9, 23.5, 23.1, 21.2, 8.8; LRMS (ES+) $(M+NH_4)^+$ 1296, $(M+Na)^+$ 1301; HRMS (FAB): $(M+Na)^+$ calcd: 1301.6461, recorded: 1301.6510.

Dimer (1l). A solution of amine **18** (75 mg, 0.124 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was treated with triethylamine (35 μL, 0.248 mmol) followed by a solution of CH_2Cl_2 (100 μL) containing oxalyl chloride (4.9 μL, 0.1239 mmol). The reaction mixture was stirred for 2 h, allowed to warm to room temperature, concentrated, and chromatographed (75% then 100% EtOAc/hexane) to afford product (21 mg, 32%) as a foam: TLC (EtOAc) $R_f=0.81$; IR (neat) 3320, 2940, 140, 1680, 1645, 1515, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.83 (t, $J=5.5$ Hz, 1H), 7.29–7.24 (m, 1H), 6.95–6.76 (m, 4H), 6.70–6.67 (m, 2H), 5.79–5.75 (m, 1H), 5.31 (d, $J=4.8$ Hz, 1H), 4.11–4.08 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.76–3.71 (m, 2H), 3.37 (d, $J=13.1$ Hz, 1H), 3.17 (dd, $J=12.7$, 2.7 Hz, 1H), 2.65–2.47 (m, 2H), 2.37 (d, $J=13.9$ Hz, 1H), 2.30–2.18 (m, 1H), 2.11–2.01 (m, 1H), 1.78–1.57 (m, 7H), 1.22 (s, 3H), 1.20 (s, 3H), 0.88 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.0, 170.1, 167.6, 160.2, 158.9, 149.3, 147.8, 141.9, 133.9, 130.2, 120.6, 119.9, 114.6, 113.3, 112.2, 111.8, 77.0, 66.5, 56.2, 51.7, 47.1, 44.6, 39.6, 38.4, 32.9, 31.6, 26.8, 25.4, 23.9, 23.5, 21.6, 9.1; LRMS (ES+): $(M+NH_4)^+$ 1208, $(M+Na)^+$ 1213; HRMS (FAB): $(M+Na)^+$ calcd: 1213.5937, recorded: 1213.5903.

Dimer (1m). A solution of **18** (100 mg, 0.165 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C was treated with triethylamine (46 μL, 0.331 mmol) followed by carbonyldiimidazole (12 mg, 0.074 mmol), and allowed to warm to room temperature and stir for 16 h. The organic layer was then dried over Na_2SO_4, filtered, concentrated, and chromatographed (75% then 100% EtOAc/hexane) to afford product (54 mg, 62%) as an oil: TLC (EtOAc) R_f = 0.55; IR (neat) 3380, 2940, 1740, 1645, 1515 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.27–7.21 (m, 1H), 6.92–6.76 (m, 4H), 6.68–6.66 (m, 2H), 5.78–5.73 (m, 1H), 5.29 (d, J = 4.8 Hz, 1H), 4.04 (br s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.58 (br s, 2H), 3.36 (d, J = 13.0 Hz, 1H), 3.18 (td, J = 13.2, 3.1 Hz, 1H), 2.61–2.48 (m, 2H), 2.35 (d, J = 13.4 Hz, 1H), 2.30–2.17 (m, 1H), 2.11–2.02 (m, 1H), 1.78–1.64 (m, 5H), 1.61–1.41 (m, 2H), 1.21 (s, 3H), 1.91 (s, 3H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3, 170.1, 167.8, 159.2, 149.3, 147.8, 141.9, 133.9, 130.1, 120.6, 119.5, 114.5, 113.4, 112.2, 111.8, 77.0, 68.0, 56.3, 51.7, 47.1, 44.5, 40.3, 38.4, 32.8, 31.7, 26.8, 25.3, 23.9, 23.5, 21.5, 9.2; LRMS (ES+): $(M+H)^+$ 1163, $(M+NH_4)^+$ 1180; HRMS (FAB): $(M+Na)^+$ calcd: 1185.5987, recorded: 1185.5973.

Dimer (1n). A solution of aniline **20** (65 mg, 0.12 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was treated with malonic acid (6.5 mg, 0.06 mmol) and DIEA (108 μL, 0.62 mmol) followed by BOP (82 mg, 0.19 mmol). The reaction mixture was stirred at room temperature for 16 h after which time the reaction was diluted with EtOAc (20 mL), washed consecutively with a 1 N HCl solution (2×10 mL), a saturated aqueous $NaHCO_3$ solution (2×10 mL), and brine (10 mL). The organic layer was then dried over Na_2SO_4, filtered, concentrated, and chromatographed (50% then 70% EtOAc/hexane) to afford product (51 mg, 74%) as a white foam: TLC (EtOAc/hexane 2/1) R_f = 0.34; IR (neat) 3329, 2938, 1737, 1698, 1641, 1515, 1443, 1262, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 9.39 (s, 2H), 7.66 (d, J = 7.9 Hz, 2H), 7.54 (s, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.07 (d, J = 7.4 Hz, 2H), 6.79–6.67 (m, 6H), 5.82 (t, J = 5.6 Hz, 2H), 5.34 (d, J = 4.4 Hz, 2H), 3.85 (s, 6H), 3.84 (s, 6H), 3.55 (s, 2H), 3.36 (d, J = 12.8 Hz, 2H), 3.12 (t, J = 12.2, 2H), 2.61–2.52 (m, 4H), 2.36 (d, J = 13.0 Hz, 2H), 2.27–2.04 (m, 6H), 1.76–1.62 (m, 10H), 1.48–1.41 (m, 4H), 1.24 (s, 6H), 1.23 (s, 6H), 0.90 (t, J = 7.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 209.0, 169.9, 167.4, 165.8, 149.3, 147.8, 141.4, 138.4, 133.9, 129.7, 122.9, 120.6, 120.1, 118.2, 112.2, 111.8, 76.8, 56.3, 56.2, 51.6, 47.2, 44.6, 38.6, 32.9, 31.5, 26.6, 25.4, 23.8, 21.4, 9.1; HRMS (FAB): M^+ calcd: 1139.5569, recorded: 1139.5520.

Dimer (1s). General procedure J was used for the dimerization of **22**. Ethylenediamine was used as the coupling reagent. The crude product was chromatographed (EtOAc) to afford product (94 mg, 75% from succinimidyl ester) as a foam: TLC (EtOAc) R_f = 0.30; IR (neat) 3360, 2940, 1730, 1645, 1515, 1445, 1240, 1030, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.32–7.29 (m, 2H), 7.18 (br s, 1H), 6.94–6.91 (m, 2H), 6.80 (d, J = 7.5 Hz, 1H), 6.76–6.65 (m, 2H), 5.77 (t, J = 6.2 Hz, 1H), 5.28 (d, J = 4.8 Hz, 1H), 4.48 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.55 (s, 2H), 3.35 (d, J = 13.1 Hz, 1H), 3.11 (td, J = 12.7, 2.8 Hz, 1H), 2.59–2.50 (m, 2H), 2.36–2.22 (m, 2H), 2.10–2.00 (m, 1H), 1.77–1.27 (m, 7H), 1.22 (s, 3H), 1.21 (s, 3H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.2, 170.1, 169.5, 167.6, 157.4, 149.4, 147.8, 133.9, 133.8, 128.8, 122.1, 120.6, 115.2, 112.2, 111.8, 76.6, 67.6, 56.3, 56.3, 51.7, 47.1, 44.5, 39.8, 38.3, 32.9, 31.7, 26.8, 25.3, 23.9, 23.5, 21.6, 9.1; HRMS (FAB): $(M+Na)^+$ calcd: 1213.5937, recorded: 1213.5914.

(*R*,*R*)-[2-[3-[3-(3,4-Dimethoxyphenyl)-1-hydroxypropyl]-phenoxy]-1-[3-[3-(3,4-dimethoxyphenyl)-1-hydroxypropyl]-phenoxymethyl]ethoxy]-dimethyl-(1,1-dimethylethyl)silane (23). A solution of potassium *tert*-butoxide (216 mg, 1.92 mmol) in DMF (2.0 mL) was treated with phenol **4d** (500 mg, 1.75 mmol) followed by epibromohydrin (60 μL, 0.70 mmol) and heated at 100 °C for 16 h. The reaction mixture was then cooled and treated with 0.05 M pH 7 phosphate buffer (10 mL) and EtOAc (10 mL). The organic layer was washed with brine (3×10 mL), dried over Na_2SO_4, filtered, and concentrated to afford a residue which was purified by flash chromatography (50% then 75% EtOAc/hexane) to afford alcohol product (210 mg, 48%; 56% based on recovery of **4d**) as a solid: TLC (EtOAc/hexane, 1/1) R_f = 0.24; IR (neat) 3490, 2935, 1680, 1590, 1515, 1440, 1260, 1555, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.41–7.36 (m, 2H), 7.20 (t, J = 8.0 Hz, 1H), 6.98 (dd, J = 8.1, 2.3 Hz, 1H), 6.63–6.62 (m, 3H), 4.28–4.23 (m, 0.5 H), 4.09–4.02 (m, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.10 (t, J = 7.2 Hz, 2H), 2.85 (t, J = 7.3 Hz, 2H), 2.66 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 198.3, 157.9, 148.2, 146.7, 137.6, 133.1, 129.0, 120.5, 119.5, 119.1, 112.4, 111.2, 110.7, 68.2, 67.9, 55.2, 55.1, 40.0, 29.1; LRMS (ES+): $(M+H)^+$ 629, $(M+NH_4)^+$ 649, $(M+Na)^+$ 651; (ES−): $(M-H)^-$ 627.

A solution of the above alcohol (900 mg, 1.43 mmol) in DMF (8.0 mL) was treated with *tert*-butyldimethylsilyl chloride (324 mg, 2.15 mmol) followed by imidazole (146 mg, 2.15 mmol). The reaction mixture was stirred for 6 h then treated with EtOAc (20 mL) and water (20 mL). The organic layer was washed with brine (4×50 mL) then dried over Na_2SO_4, filtered, concentrated, and flash chromatographed (30% then 50% EtOAc/hexane) to afford protected product (955 mg, 90%) as an oil: TLC (EtOAc/hexane, 2/3) R_f = 0.38; IR (neat) 2930, 1690, 1590, 1515, 1440, 1260, 1140,

1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.40–7.35 (m, 2H), 7.20 (t, $J=8.1$ Hz, 1H), 6.97 (dd, $J=8.2$, 2.0 Hz, 1H), 6.63 (s, 3H), 4.45–4.25 (m, 0.5H), 4.03–3.98 (m, 1H), 3.94–3.88 (m, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.11 (t, $J=7.4$ Hz, 2H), 2.85 (t, $J=7.3$ Hz, 2H), 0.76 (s, 4.5 H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.4, 159.4, 149.4, 147.9, 138.8, 134.3, 130.1, 121.3, 120.6, 120.4, 113.3, 112.4, 111.9, 70.3, 70.3, 56.3, 56.3, 41.2, 30.3, 26.2, −4.2; LRMS (ES+): $(M+H)^+$ 743, $(M+NH_4)^+$ 760, $(M+Na)^+$ 765; (ES−): $(M-H)^-$ 741.

General procedure L was used for the reduction of the above bis-ketone. The crude product was chromatographed (30% then 50% EtOAc/hexane) to afford product (618 mg, 73%) as an oil (>97% de by comparative integration of ^{19}F NMR resonances of the (+)MPTA ester of chiral and racemic material): TLC (EtOAc/hexane, 1/1) $R_f=0.35$; IR (neat) 3490, 2930, 1590, 1515, 1445, 1260, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.11–7.07 (m, 1H), 6.77–6.72 (m, 2H), 6.69–6.55 (m, 4H), 4.48 (dd, $J=7.2$, 5.5 Hz, 1H), 4.26–4.21 (m, 0.5H), 3.98–3.93 (m, 1H), 3.88–3.83 (m, 1H), 3.68 (s, 6H), 2.59–2.41 (m, 2H), 1.99–1.77 (m, 2H), 0.76 (s, 4.5H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 158.0, 147.9, 146.3, 145.5, 133.5, 128.6, 119.3, 117.5, 112.7, 111.1, 110.9, 110.4, 72.8, 69.0, 68.8, 55.0, 54.9, 39.6, 30.7, 24.9, −4.2; LRMS (ES+): $(M+Na)^+$ 769; (ES−): $(M-H)^-$ 745.

(*R*,*R*)-1,5-Bis[3-[3-(3,4-Dimethoxyphenyl)-1-hydroxypropyl]phenoxy]-3-oxapentane (24). General procedure M was used for the alkylation of **4d**. The halide bis(2-iodoethyl) ether was used as the coupling reagent. The crude product was chromatographed (40% then 50% then 80% EtOAc/hexane) to afford product (6.76 g, 63%) as an oil: TLC (EtOAc/hexane, 1/1) $R_f=0.28$; IR (neat) 2935, 1685, 1515, 1460, 1260, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.54–7.36 (m, 2H), 7.33 (t, $J=7.9$ Hz, 1H), 7.11 (d, $J=8.1$ Hz, 1H), 6.81–6.77 (m, 3H), 4.19 (t, $J=4.1$ Hz, 2H), 3.94 (t, $J=4.4$ Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.45 (t, $J=7.3$ Hz, 2H), 3.00 (t, $J=7.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.6, 159.6, 149.5, 148.0, 138.8, 134.5, 130.1, 121.4, 120.8, 120.6, 113.8, 112.5, 112.0, 70.4, 68.3, 56.5, 56.4, 41.3, 30.4; LRMS (ES+): $(M+H)^+$ 643, $(M+Na)^+$ 665.

General procedure L was used for the reduction of the above bis-ketone. The crude product was chromatographed (50% then 80% EtOAc/hexane then EtOAc) to afford product (1.25 g, 46%) as a waxy solid (>95% de by comparative integration of ^{19}F NMR resonances of the (+)MPTA ester of chiral and racemic material): mp 96–99 °C; TLC (EtOAc/hexane, 3/1) $R_f=0.22$; IR (neat) 3505, 2935, 1590, 1515, 1451, 1260, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.26–7.20 (m, 1H), 6.92–6.70 (m, 6H), 4.64–4.60 (m, 1H), 4.15 (t, $J=4.4$ Hz, 2H), 3.92 (t, $J=5.0$ Hz, 2H), 3.84 (s, 6H), 2.73–2.54 (m, 2H), 2.13–1.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.4, 149.3, 147.6, 146.8, 134.8, 129.9, 120.6, 118.9, 114.0, 112.8, 112.3, 111.8, 74.1, 70.4, 67.9, 56.3, 56.2, 41.0, 32.0; LRMS (ES+): $(M+NH_4)^+$ 664, $(M+Na)^+$ 669.

(*R*,*R*)-1,8-Bis[3-[3-(3,4-Dimethoxyphenyl)-1-hydroxypropyl]-phenoxy]-3,6-dioxaoctane (25). General procedure M was used for the alkylation of **4d**. The halide 1,2-bis-(2-iodoethoxy)ethane was used as the coupling reagent. The crude product was chromatographed (50% then 75% EtOAc/hexane) to afford product (719 mg, 37%) as a waxy solid: mp 90–91 °C; TLC (EtOAc/hexane, 1/1) $R_f=0.16$; IR (neat) 2935, 1685, 1590, 1515, 1440, 1260, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.54–7.50 (m, 2H), 7.34 (t, $J=8.0$ Hz, 1H), 7.11 (dd, $J=7.6$, 2.0 Hz, 1H), 6.82–6.76 (m, 3H), 4.16 (t, $J=4.5$ Hz, 2H), 3.89–3.82 (m, 8H), 3.76 (s, 2H), 3.25 (t, $J=7.3$ Hz, 2H), 3.00 (t, $J=7.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.5, 159.4, 149.3, 147.8, 138.6, 134.3, 130.0, 121.2, 120.6, 120.4, 113.6, 112.3, 111.8, 71.3, 70.1, 68.0, 56.3, 56.2, 41.1, 30.2; LRMS(FAB): $(M+H)^+$ 686 $(M+Na)^+$ 709.

General procedure L was used for the reduction of the above bis-ketone. The crude product was chromatographed (75% EtOAc/hexane) to afford product (300 mg, 43%) as an oil (>95% de by comparative integration of ^{19}F NMR resonances of the (+)MPTA ester of chiral and racemic material): TLC (EtOAc/hexane, 3/1) $R_f=0.26$; IR (neat) 3445, 2935, 1590, 1515, 1450, 1260, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.09–7.02 (m, 1H), 6.75–6.71 (m, 2H), 6.65–6.54 (m, 4H), 4.41 (dd, $J=7.5$, 5.4 Hz, 1H), 3.93 (t, $J=4.4$ Hz, 2H), 3.68–3.66 (m, 8H), 3.56 (s, 2H), 2.55–2.36 (m, 2H), 1.93–1.75 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.4, 149.3, 147.6, 146.8, 134.8, 129.9, 120.6, 118.9, 114.0, 112.7, 112.2, 111.7, 74.1, 71.3, 70.2, 67.8, 56.3, 56.2, 41.0, 32.0; LRMS (FAB): $(M+H)^+$ 690 $(M+Na)^+$ 713.

(*R*,*R*)-1,11-Bis[3-[3-(3,4-Dimethoxyphenyl)-1-hydroxypropyl]phenoxy]-3,6,9-trioxaundecane (26). General procedure M was used for the alkylation of **4d**. The halide bis[2-(2-iodoethoxy)ethyl] ether was used as the coupling reagent. The crude product was chromatographed (70% then 80% EtOAc/hexane) to afford product (5.05 g, 83%) as an oil: TLC (EtOAc/hexane, 3/1) $R_f=0.38$; IR (neat) 2935, 1683, 1590, 1520, 1455, 1260, 1135, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.77–7.71 (m, 2H), 7.56 (t, $J=8.0$ Hz, 1H), 7.35 (dd $J=2.5$, 0.6 Hz, 1H), 7.14–6.99 (m, 3H), 4.39 (t, $J=4.6$ Hz, 2H), 4.10 (s, 3H), 4.08 (s, 3H) 3.98–3.90 (m, 4H), 3.48 (t, $J=7.2$ Hz, 2H), 3.23 (t, $J=7.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.5, 159.5, 149.3, 147.8, 138.6,

134.3, 130.0, 121.2, 120.6, 120.4, 113.6, 112.3, 111.8, 71.3, 71.1, 70.0, 68.0, 56.3, 41.2, 30.2; LRMS (ES+): $(M+H)^+$ 731, $(M+NH_4)^+$ 648, $(M+Na)^+$ 753.

General procedure L was used for the reduction of the above bis-ketone. The crude product was chromatographed (75% EtOAc/hexane then EtOAc) to afford product (1.35 g, 28%) as an oil (>95% de by comparative integration of ^{19}F NMR resonances of the (+)MPTA ester of chiral and racemic material): TLC (EtOAc) $R_f=0.39$; IR (neat) 3500, 2935, 1590, 1520, 1455, 1260, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.03 (t, $J=8.0$ Hz, 1H), 6.73–6.50 (m, 6H), 4.43 (dd $J=7.4$, 5.5 Hz, 1H), 3.91 (t, $J=4.6$ Hz, 2H), 3.64 (s, 6H), 3.50–3.48 (m, 4H), 2.48–2.39 (m, 2H), 1.89–1.76 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.4, 149.3, 147.6, 146.8, 134.8, 129.9, 120.6, 118.8, 114.1, 112.7, 112.2, 111.7, 74.1, 71.2, 71.1, 70.2, 67.8, 56.3, 56.2, 41.0, 32.0; LRMS (ES+): $(M+NH_4)^+$ 752, $(M+Na)^+$ 757.

(*R*)-[3-[3-(3,4-Dimethoxyphenyl)-1-hydroxypropyl]phenoxy]-acetic acid (27). A solution of **6d** (4.4 g, 1.09 mmol) in MeOH (20 mL) was treated with a solution of 6 N NaOH (18.2 mL, 109 mmol) and allowed to stir for 14 h. The reaction mixture was evaporated to half volume and partitioned between water (20 mL) and ether (25 mL). The aqueous portion was acidified to pH 4 with a 1 N HCl solution and extracted with EtOAc (2×25 mL). The combined organic extracts were washed brine (2×25 mL), dried over Na_2SO_4, filtered, and concentrated to afford product (3.5 g, 92%) as an colorless solid which may be recrystallized from EtOAc/hexane (97% ee, +99% ee for recrystallized material, by Chiralcel OJ HPLC, 40% *i*-PrOH/hexane with 0.2% TFA, retention time 14.0 min for the *R*-enantiomer and 11.5 min for the *S*-enantiomer): mp 124–125 °C; TLC ($AcOH/MeOH/CHCl_3$, 2/5/93) $R_f=0.22$; ^1H NMR (CD_3OD, 300 MHz) 7.02 (t, $J=8.1$ Hz, 1H), 6.74–6.71 (m, 2H), 6.63–6.48 (m, 4H), 4.42 (s, 2H), 4.35 (t, $J=6.0$ Hz, 1H), 3.57 (s, 3H), 3.56 (s, 3H), 2.46–2.28 (m, 2H), 1.85–1.67 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz) 171.6, 158.5, 149.3, 147.6, 147.2, 135.3, 129.3, 120.6, 119.2, 113.3, 112.5, 112.4, 112.2, 73.1, 64.8, 55.5, 55.3, 41.0, 31.5; LRMS (ES+): $(M+NH_4)^+$ 364, $(M+Na)^+$ 369; (ES−): M^- 345.

(*R,R*)-1,10-Bis[3-[3-(3,4-dimethoxyphenyl)-1-hydroxypropyl]phenoxy]-4,7-diaza-1,10-dioxa-3,8-dioxo-decane (28). A solution of **27** (5.0 g, 14.4 mmol) in CH_2Cl_2 (40 mL) at −10 °C was treated with PyBOP (7.51 g, 14.4 mmol) followed by a CH_2Cl_2 solution (10 mL) containing ethylendiamine (507 μL, 7.58 mmol) and triethylamine (4.05 mL, 28.9 mmol). The reaction mixture was warmed to room temperature and stirred for 16 h after which time the reaction was evaporated to half volume and diluted with EtOAc (50 mL). The organic extract was then washed consecutively with a 1 N HCl solution (2×50 mL), a saturated aqueous $NaHCO_3$ solution (3×50 mL), and brine (2×50 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (7.5% MeOH/EtOAc) to afford product (4.45 g, 91%) as a solid: mp 123–123.5 °C; TLC (MeOH/CHCl3, 1/9) $R_f=0.40$; IR (neat) 3355, 2935, 1670, 1590, 1515, 1440, 1260, 1155, 1030 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) 7.93 (br s, 1H), 7.00 (t, $J=7.8$ Hz, 1H), 6.74–6.61 (m, 2H), 6.59–6.44 (m, 4H), 4.35 (t, $J=5.76$ Hz, 1H), 4.20 (s, 2H), 3.54 (s, 3H), 3.53 (s, 3H), 3.19 (s, 2H), 2.49–2.26 (m, 2H), 1.78–1.68 (m, 2H); ^1H NMR ($CDCl_3$, 300 MHz) 7.23–7.14 (m, 2H), 6.94–6.92 (m, 2H), 6.77–6.69 (m, 4H), 4.62 (t, $J=5.4$ Hz, 1H), 4.33 (s, 2H), 3.82 (s, 6H), 3.45 (s, 2H), 3.04 (br s, 1H), 2.70–2.57 (m, 2H), 2.08–1.94 (m, 2H), ^{13}C NMR (CD_3OD, 75 MHz) 172.3, 159.6, 150.7, 149.0, 136.8, 131.0, 122.1, 121.0, 115.0, 114.0, 113.7, 74.6, 68.6, 57.0, 56.9, 42.6, 40.4, 33.0; ^{13}C NMR ($CDCl_3$, 75 MHz) 169.6, 157.4, 148.9, 147.2, 147.1, 134.4, 129.7, 120.2, 119.8, 113.5, 112.4, 111.9, 111.4, 73.4, 67.1, 55.9, 55.8, 40.7, 39.1, 31.6; LRMS (ES+): $(M+H)^+$ 717, $(M+Na)^+$ 739; HRMS (FAB): $(M+Na)^+$ calcd: 739.3207, recorded: 739.3218.

Dimer (1o). General procedure K was used for the coupling of diol **23** with acid **14**. The crude product was chromatographed (30% EtOAc/hexane) to afford product (125 mg, 44%) as an oil: TLC (EtOAc/hexane, 1/1) $R_f=0.65$; IR (neat) 2930, 1740, 1700, 1645, 1515, 1450, 1450, 1260, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.15–7.08 (m, 1H), 6.81–6.52 (m, 6H), 5.63 (t, $J=6.0$ Hz, 1H), 5.17 (d, $J=4.8$ Hz, 1H), 4.28–4.24 (m, 0.5H), 4.09–3.96 (m, 1H), 3.94–3.84 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.21 (d, $J=13.2$ Hz, 1H), 3.00 (dd, $J=13.2$, 3.0 Hz, 1H), 2.47–2.38 (m, 2H), 2.22 (d, $J=13.4$ Hz, 1H), 2.16–2.01 (m, 1H), 1.95–1.89 (m, 1H), 1.65–1.11 (m, 7H), 1.08 (s, 3H), 1.05 (s, 3H), 0.78–0.70 (m, 7.5 H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.1, 170.1, 167.6, 159.3, 149.3, 147.8, 141.9, 133.9, 130.1, 120.6, 119.5, 113.4, 112.2, 111.8, 70.4, 70.2, 56.3, 56.2, 51.7, 47.1, 44.6, 38.5, 32.9, 31.7, 26.2, 25.4, 23.9, 23.5, 21.6, 18.6, 9.1, −4.2; LRMS (ES+): $(M+NH_4)^+$ 1238.

A solution of the above silyl ether (55 mg, 0.450 mmol) in CH_3CN (2.0 mL) was treated with a CH_3CN solution (2.0 mL) containing 49% hydrofluoric acid (40 μL). The resulting solution was allowed to stir for 1 h then partitioned between EtOAc (20 mL) and saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was washed with an additional portion of aqueous $NaHCO_3$ solution (10 mL) followed by brine (2×10 mL), then dried over Na_2SO_4, filtered, concentrated, and flash chromatographed (50% EtOAc/hexane) to afford product

(30 mg, 60%) as a colorless foam: TLC (EtOAc/hexane, 1/1) $R_f = 0.35$; IR (neat) 2940, 1740, 1700, 1645, 1515, 1450, 1260, 1160, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.23–7.17 (m, 1H), 6.88–6.60 (m, 6H), 5.71 (t, $J = 6.2$ Hz, 1H), 5.25 (d, $J = 4.8$ Hz, 1H), 4.39–4.32 (m, 0.5 H), 4.17–4.09 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.28 (d, $J = 13.3$ Hz, 1H), 3.08 (t, $J = 12.6$ Hz, 1H), 2.87–2.80 (m, 1H), 2.58–2.45 (m, 2H), 2.29 (d, $J = 13.4$ Hz, 1H), 2.23–2.11 (m, 1H), 2.04–1.95 (m, 5H), 1.70–1.20 (m, 2H), 1.14 (s, 3H), 1.13 (s, 3H), 0.81 (t, $J = 7.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3, 170.1, 167.6, 159.1, 149.3, 147.8, 141.9, 133.9, 130.1, 120.6, 119.8, 114.6, 113.4, 112.2, 111.8, 77.0, 69.3, 69.1, 56.3, 56.3, 51.7, 47.1, 44.6, 38.5, 33.0, 31.6, 26.8, 25.4, 23.9, 23.6, 21.5, 9.1 LRMS (ES+): $(M + NH_4)^+$ 1125, $(M + Na)^+$ 1129; HRMS (FAB): $(M + Na)^+$ calcd: 1129.5613, recorded: 1129.5652.

Dimer (1p). General procedure K was used for the coupling of diol **24** with acid **14**. The crude product was chromatographed (40% then 60% EtOAc/hexane) to afford product (338 mg, 56%) as a colorless oil: TLC (EtOAc/hexane, 1/1) $R_f = 0.20$; IR (neat) 2940, 1735, 1700, 1650, 1520, 1455, 1260, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.22–7.18 (m, 1H), 6.90–6.62 (m, 6H), 5.73 (dd, $J = 7.6$, 5.9 Hz, 1H), 5.26 (d, $J = 4.8$ Hz, 1H), 4.19–4.11 (m, 2H), 3.97–3.88 (m, 2H), 3.81 (s, 6H), 3.14 (d, $J = 12.6$ Hz, 1H), 3.11 (td, $J = 12.5$, 2.8 Hz, 1H), 2.60–2.42 (m, 2H), 2.31 (d, $J = 13.5$ Hz, 1H), 2.26–2.16 (m, 1H), 2.14–1.97 (m, 1H), 1.73–1.26 (m, 7H), 1.07 (s, 3H), 1.06 (s, 3H), 0.84 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.2, 170.1, 167.6, 159.3, 149.3, 147.8, 141.7, 133.9, 130.1, 120.6, 119.5, 114.7, 113.5, 112.2, 111.8, 70.4, 67.9, 56.2, 51.7, 47.1, 44.5, 38.4, 32.9, 31.6, 26.8, 25.3, 23.9, 23.8, 21.6, 9.1; HRMS (FAB): $(M + Na)^+$ calcd: 1143.5769, recorded: 1143.5785.

Dimer (1q). General procedure K was used for the coupling of diol **25** with acid **14**. The crude product was chromatographed (50% then 70% EtOAc/hexane) to afford product (70 mg, 41%) as a colorless oil: TLC (EtOAc/hexane, 3/1) $R_f = 0.61$; IR (neat) 2940, 1735, 1700, 1645, 1515, 1445, 1260, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.08–7.04 (m, 1H), 6.75–6.65 (m, 3H) 6.60–6.48 (m, 3H), 5.59 (t, $J = 6.1$ Hz, 1H), 5.12 (d $J = 4.6$ Hz, 1H), 3.95 (s, 2H), 3.67–3.66 (m, 8H), 3.57 (s, 2H), 3.17 (d, $J = 13.1$ Hz, 1H), 2.97 (td, $J = 12.7$, 2.7 Hz, 1H), 2.51–2.28 (m, 2H), 2.20–2.02 (m, 2H), 1.92–1.83 (m, 1H), 1.59–1.41 (m, 4H), 1.36–1.12 (m, 2H), 1.04 (s, 3H), 1.02 (s, 3H), 0.70 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.2, 170.1, 167.6, 159.4, 149.3, 147.8, 141.7, 133.9, 130.0, 120.6, 119.5, 114.6, 113.6, 112.2, 111.8, 77.1, 71.3, 70.2, 67.8, 57.1, 56.3, 56.2, 51.7, 47.1, 44.5, 38.2, 32.9, 31.6, 26.8, 25.4, 23.8, 23.5, 21.6, 9.1; HRMS (FAB): $(M + Na)^+$ calcd: 1187.6033, recorded: 1187.6089.

Dimer (1r). General procedure K was used for the coupling of diol **26** with acid **14**. The crude product was chromatographed (50% then 70% EtOAc/hexane) to afford product (300 mg, 50%) as a colorless oil: TLC (EtOAc/hexane, 3/1) $R_f = 0.61$; IR (neat) 2940, 1735, 1700, 1650, 1520, 1455, 1260, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.14 (t, $J = 4.2$ Hz, 1H), 6.82–6.55 (m, 7H), 5.66 (t, $J = 7.4$ Hz, 1H), 5.20 (d $J = 4.7$ Hz, 1H), 4.02 (t, $J = 4.3$ Hz, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.61–3.58 (m, 4H), 3.25 (d, $J = 12.8$ Hz, 1H), 3.04 (td, $J = 12.6$, 2.9 Hz, 1H), 2.53–2.38 (m, 2H), 2.27–2.03 (m, 2H), 2.00–1.85 (m, 1H), 1.66–1.19 (m, 7H), 1.11 (s, 3H), 1.09 (s, 3H), 0.77 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.2, 170.0, 167.3, 159.4, 149.3, 147.8, 141.7, 133.9, 130.0, 120.6, 119.5, 114.6, 113.6, 112.2, 111.8, 77.1, 71.2, 70.2, 67.9, 57.1, 56.2, 51.7, 47.1, 44.5, 38.4, 32.8, 31.6, 26.8, 25.3, 23.9, 23.5, 21.6, 9.1; HRMS (FAB): $(M + Na)^+$ calcd: 1231.6294, recorded: 1231.6339.

(2*S*)-1-(3,3,-Dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylic acid (29). Prepared from the methyl ester of L-proline in an analogous manner to acid **14**: mp 80.5–81.5 °C; TLC ($MeOH/CHCl_3$, 15/85) $R_f = 0.30$; IR (neat) 2970, 1700, 1640, 1455, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 11.36 (br s, 1H), 4.55 (dd, $J = 8.6$, 4.2 Hz, 1H), 3.56–3.49 (m, 2H), 2.31–1.92 (m, 4H), 1.84–1.65 (m, 2H), 1.25 (s, 3H), 1.22 (s, 3H), 0.87 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 206.7, 176.3, 165.6, 58.4, 47.4, 47.1, 32.2, 28.7, 24.8, 23.7, 23.2, 8.9; MS (ES+): $(M + Na)^+$ 264; HRMS (FAB): $(M - H)^-$ calcd: 240.1236, recorded: 240.1245.

(1*R*)-1-[3-(Carboxymethoxy)phenyl]-3-(3,4-dimethoxyphenyl)-1-propanyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate (2h). General procedure F was used for the coupling of **6d** with **29**. The crude product was chromatographed (25% EtOAc/hexane) to afford product (280 mg, 72%) as an oil: TLC (EtOAc/hexane, 3/7) $R_f = 0.30$; IR (neat) 2970, 1750, 1645, 1515, 1450, 1261, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.29–7.23 (m, 1H), 6.95–6.76 (m, 4H), 6.69–6.65 (m, 2H), 5.76 (dd, $J = 7.8$, 5.5 Hz, 1H), 4.59 (dd, $J = 8.3$, 3.6 Hz, 1H), 4.45 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.54 (dd, $J = 6.6$, 4.4 Hz, 2H), 2.61–2.48 (m, 2H), 2.30–2.15 (m, 2H), 2.09–1.89 (m, 4H), 1.80–1.62 (m, 2H), 1.48 (s, 9H), 1.23 (s, 3H), 1.21 (s, 3H), 0.85 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 207.0, 170.7, 168.0, 165.1, 158.1, 148.9, 147.3, 141.6, 133.7, 129.6, 120.2, 119.7, 114.2, 112.9, 111.9, 111.4, 82.3, 76.1, 65.8, 59.8, 58.7, 55.9, 47.2, 46.9, 38.0, 38.7, 31.1, 29.0, 28.1, 24.9, 23.6, 23.3, 8.9; LRMS (ES+): $(M + NH_4)^+$ 643, $(M + Na)^+$ 648.

General procedure G was used for the acidolysis of the above ester. The crude product was chromatographed

(10% MeOH/CH_2Cl_2) to afford product (120 mg, 47%) as a foam: TLC (MeOH/$CHCl_3$, 15/85) $R_f = 0.25$; IR (neat) 2940, 1735, 1700, 1635, 1455, 1210 cm^{-1}; ^1H NMR (CD_3OD, 30 MHz) 7.15 (t, $J = 8.0$ Hz, 1H), 6.83–6.56 (m, 6H), 5.62–5.56 (m, 1H), 4.57 (s, 1H), 4.44–4.39 (m, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.53–3.36 (m, 2H), 2.53–2.39 (m, 2H), 2.24–2.01 (m, 2H), 2.00–1.77 (m, 4H), 1.66–1.45 (m, 2H), 1.11 (s, 3H), 1.10 (s, 3H), 0.74 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (CD_3OD, 75 MHz) 206.8, 170.6, 165.3, 157.7, 148.9, 147.4, 141.9, 133.6, 129.8, 120.2, 119.8, 114.7, 111.9, 111.4, 76.6, 58.6, 56.0, 47.3, 46.9, 38.0, 32.2, 31.7, 29.1, 24.8, 23.7, 23.2, 8.9; LRMS (ES+): $(M+Na)^+$ 592; HRMS (FAB): $(M+Na)^+$ calcd: 592.2523, recorded: 592.2507.

Dimer (1h). General procedure K was used for the coupling of diol **28** with acid **29**. The crude product was chromatographed (75% then 100% EtOAc/hexane) to afford product (433 mg, 85%) as a foam: TLC (EtOAc) $R_f = 0.20$; IR (neat) 3360, 2965, 1740, 1675, 1640, 1515, 1440, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.29–7.26 (m, 1H), 6.95–6.90 (m, 2H), 6.84–6.76 (m, 2H), 6.69–6.66 (m, 2H), 5.77 (dd, $J = 7.6$, 5.2 Hz, 1H), 4.59 (dd, $J = 8.3$, 3.3 Hz, 1H), 4.44 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.49 (br s, 4H), 2.62–2.49 (m, 2H), 2.32–2.15 (m, 2H), 2.10–1.87 (m, 4H), 1.73–1.60 (m, 2H), 1.21 (s, 3H), 1.19 (s, 3H), 0.84 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 207.0, 170.7, 169.3, 165.2, 157.4, 148.9, 147.4, 142.0, 133.6, 129.9, 120.2, 119.9, 114.2, 112.9, 111.9, 111.4, 76.0, 67.3, 59.8, 58.6, 56.0, 47.2, 46.9, 39.3, 38.2, 32.2, 31.1, 29.0, 24.9, 23.6, 23.3, 8.9; LRMS (ES+): $(M+H)^+$ 1163; HRMS (FAB): $(M+Na)^+$ calcd: 1185.5624, recorded: 1185.5635.

Fluorescence polarization assay for FKBP12 binding. The affinities of synthetic ligands for FKBP12 were determined using a competitive assay based on fluorescence polarization (FP). Full details of the assay will be provided elsewhere (C.T. Rollins, E. Laborde, D. Holt and T. Clackson, in preparation). Briefly, a fluorescent probe was prepared by coupling 4′-(aminomethyl)-fluorescein (Molecular Probes) to the modified allyl group of FK506 in a manner similar to the preparation of FK1012.[1] Recombinant human FKBP12 was expressed and purified by standard methods.[33] In the wells of a Dynatech microfluor plate, subsaturating concentrations of FKBP12 (11.25 nM) were incubated with 2.5 nM probe and serial dilutions of competitive ligand in FP buffer (50 mM potassium phosphate pH 7.8/150 mM NaCl/100 μg/mL bovine gamma globulin/1% EtOH). After equilibration for 30 min in the dark, fluorescence polarization was read on a Jolley FPM-2 (Jolley Consulting and Research, Inc., Grayslake, IL). The increase in polarization of the probe upon binding protein was used as a direct readout of percent probe bound, compared to controls containing no competitor (100%) and no protein (0%), and the concentration of competitor resulting in 50% binding (IC_{50}) was determined by a non-linear least square fit to a four-parameter equation.

Assay for inducible Fas activation in cell lines. Inducible Fas activation was assayed as previously described[10] In brief, the human fibrosarcoma cell line HT1080 was retrovirally transduced to express a chimeric construct encoding a myristoylation sequence followed by two FKBP domains then amino acids 175 to 304 of human Fas. Cell line clones expressing this construct were plated at 10E4 cells/well in 96-well plates and treated the next day with serial dilutions of compound, with 1 μM usually the highest concentration tested. Wells were assayed for viability one day later with the viability indicator Alamar Blue (Accumed, Westlake, OH), which measures reducing equivalents released during cell metabolism. Untransfected HT1080 cells were testedalso and were unaffected by the concentrations of compounds used in these experiments.

Assay for inducible transcriptional activation. Transcription factor fusions were expressed from the tricistronic vector pCGNN-F3p65/Z1F3/Neo.[10] An HT1080 (ATCC CCL-121) cell line, HT1080L cells, which contain an integrated secreted alkaline phosphatase (SEAP) target gene under control of a minimal interleukin 2 gene promoter and 12 ZFHD1 binding sites was generated as described.[25] Dimerizers were tested for their ability to activate transcription of a target gene in (a) HT1080L cells transiently transfected with pCGNN-F3p65/Z1F3/Neo and (b) HT1080L cells in which the transcription factor fusion proteins were expressed from a stably integrated vector as described previously.[10] Following incubation with compound for 18–24 h, the cell supernatant was removed and assayed for SEAP activity.[25] Background SEAP activity, measured from mock-transfected HT1080 cells, was subtracted from each value.

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