2-Arylpropionic CXC Chemokine Receptor 1 (CXCR1) Ligands as Novel Noncompetitive CXCL8 Inhibitors

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The CXC chemokine CXCL8/IL-8 plays a major role in the activation and recruitment of polymorphonuclear (PMN) cells at inflammatory sites. CXCL8 activates PMNs by binding the seven-transmembrane (7-TM) G-protein-coupled receptors CXC chemokine receptor 1 (CXCR1) and CXC chemokine receptor 2 (CXCR2). (*R*)-Ketoprofen (**1**) was previously reported to be a potent and specific noncompetitive inhibitor of CXCL8-induced human PMNs chemotaxis. We report here molecular modeling studies showing a putative interaction site of **1** in the TM region of CXCR1. The binding model was confirmed by alanine scanning mutagenesis and photoaffinity labeling experiments. The molecular model driven medicinal chemistry optimization of **1** led to a new class of potent and specific inhibitors of CXCL8 biological activity. Among these, repertaxin (**13**) was selected as a clinical candidate drug for prevention of post-ischemia reperfusion injury.

Introduction

Chemokines or "chemotactic cytokines" are a class of 8−14 kDa proteins that regulate the trafficking of leukocytes[1] and other biological processes including cell growth, angiogenesis, and hematopoiesis.[2−4] Chemokine receptors belong to the superfamily of seven-transmembrane G-protein-coupled receptors (7-TM GPCRs) and, specifically, to the class A (rhodopsin-like) GPCR family.[5] Disregulation of the chemokines network has been implicated in a variety of diseases including rheumatoid arthritis (RA), chronic obstructive pulmonary disease (COPD), asthma, Alzheimer's disease, melanoma, and psoriasis.[6−10]

CXCL8 belongs to the CXC chemokines family and plays a major role in the activation and recruitment of neutrophils.[11] CXCL8 activates the receptors CXCR1 and CXCR2 expressed on human neutrophil surface, whereas the closely related chemokine CXCL1 (GRO-α) is a selective agonist for CXCR2.[12] The role of CXCL8 in acute and chronic human diseases has been recently reviewed.[13] In particular, CXCL8 has been implicated in polymorphonuclear (PMN) recruitment and activation in post-ischaemia reperfusion in which neutralizing anti-CXCL8 antibodies and high molecular weight antagonists prevented PMN infiltration and the associated tissue injury.[14,15] To date, only a limited number of small molecular weight (SMW) CXCL8 inhibitors have been described.[16,17] The main class of SMW CXCL8 inhibitors so far reported in the literature is a class of bisarylurea derivatives.[18,19] *N*-(2-Bromophenyl)-*N*′-(2-hydroxy-4-nitrophenyl)urea (SB225002), the first lead compound in this class, is >150-fold selective for CXCR2 compared to CXCR1 in a binding assay. In vitro, SB225002 potently inhibits human and rabbit neutrophil chemotaxis induced by CXCL8 and CXCL1 and in vivo proved to be efficacious in inhibiting CXCL8-induced PMN margination in rabbits.[18] Although SB225002 is the most thoroughly described CXCL8 inhibitor in the literature, additional candidates with an improved pharmacokinetic and pharmacodynamic profile are currently under preclinical investigation.[19,20]

We previously reported that both enantiomers of ketoprofen, a widely used nonsteroidal antiinflammatory drug (NSAID), are potent and selective inhibitors of CXCL8-induced human PMN chemotaxis not affecting chemokine receptor binding. Interestingly, this unprecedented biological activity of ketoprofen was clearly not related to the inhibition of the cyclooxygenase (COX) pathway.[21] In this paper, we describe the identification of an allosteric interaction site between (*R*)-ketoprofen (**1**) and CXCR1. Moreover, medicinal chemistry driven by the molecular model of interaction between (*R*)-ketoprofen (**1**) and CXCR1 led to a novel class of potent and specific inhibitors of CXCL8 biological activity. Results are consistent with a mechanism of action whereby inhibitors act as noncompetitive allosteric blockers interacting with the TM region of CXCR1, locking this receptor in an inactive conformation unable to activate intracellular signal transduction.

Results

(*R*)-Ketoprofen (1) Inhibits CXCL8-Induced G-Protein Activation. We previously reported that (*R*)- and (*S*)-ketoprofen (**1** and **2**) are potent and specific

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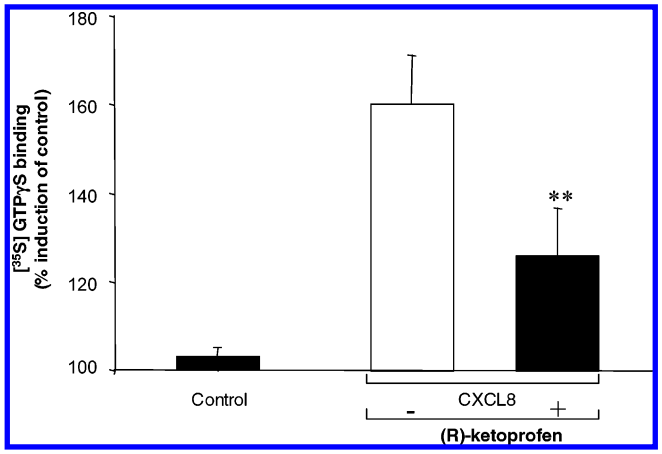
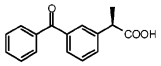
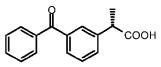
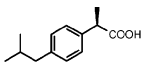
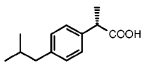
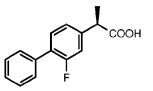
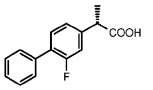
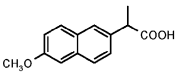
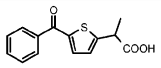
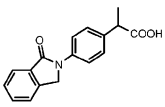
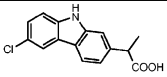


Figure 1. (R)-Ketoprofen **1** inhibits G-protein activation induced by CXCL8. The binding of [^{35}S]GTPγS to PMN membranes stimulated with CXCL8 (300 nM) in the presence or absence of **1** (1 μM) was measured. Results are shown as the percentage of induction of [^{35}S]GTPγS binding relative to unstimulated PMN membranes. Values are the mean ± SD of two independent experiments: (**) $P < 0.01$ vs GTP binding in the absence of **1** (Student's t test).

inhibitors of CXCL8-induced chemotaxis of human PMNs in a COX-independent fashion. We sought to elucidate the mechanism of action of ketoprofen enantiomers. Since **1** and **2** did not affect CXCL8 receptor binding,[21] we postulated that these molecules might affect intracellular signal trasduction activated by CXCL8 receptors. As shown in Figure 1, **1** significantly inhibited CXCL8-induced activation of the G-protein. Consistently, signal transduction events downstream to G-protein activation were also inhibited in cells activated with CXCL8 in the presence of **1** and **2**, including inhibition of intracellular calcium increase and extracellular signal regulated kinase (ERK)-1/2 activation.[21]

Molecular Modeling Studies. Having found that **1** significantly inhibits CXCL8-induced G-protein activation, we reasoned that **1** might interact with the CXCL8 receptor CXCR1, preventing signal transduction while leaving CXCL8 binding unaffected. The finding that, in addition to ketoprofen, additional 2-arylpropionic acid NSAIDs inhibit CXCL8 activity (Table 1) suggested that these molecules might interact with a homologous binding site in both COX and CXCR1. A binding model for **1** in COX-1 was built using as a template the known crystallized structure of the enzyme in complex with *S*-flurbiprofen (Figure 2a). *S*-Flurbiprofen, as other phenylpropionic NSAIDs, coordinate a network of polar interactions involving Arg120, Glu254, Tyr355, and Hys90 at the bottom of a hydrophobic channel of COX, thus blocking the active site of the enzyme.[22,23] PASS analysis of the TM region of CXCR1, followed by GRID mapping of the solvent accessible sites, allowed us to select potential ketoprofen binding sites and to compare their physicochemical properties with the COX channel.[24−26] In the description of the binding hypothesis, the Weinstein−Ballesteros numbering will be used to emphasize the relative positions of the CXCR1 TM residues in the helix bundle. A putative ketoprofen binding site was identified in a cavity between helices 1, 2, 3, 6, and 7 (Figure 2b). The overall pattern of interactions is well conserved in the binding models of **1** with both COX and CXCR1. In both cases, the inhibitor is well-anchored at the bottom of a

Table 1. Effect of 2-Arylpropionic Acids on CXCL8-Induced Human PMN Chemotaxis[a]

N.	Structure	CXCL8*	PGE_2**
1		64±4	> 99
2		52±4	> 99
3		30±6	37±2
4		34±10	> 99
5		20±8	48±10
6		22±6	> 99
7		35±17	> 99
8		7±5	> 99
9		56±5	> 99
10		5±19	> 99

[a] (*) % of inhibition at 10^{-8} M. (**) % of inhibition at 10^{-5} M.

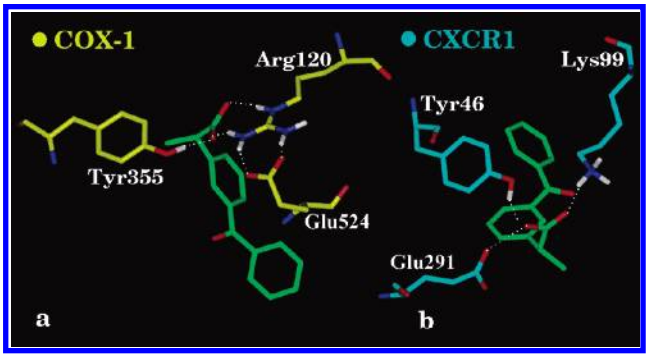


Figure 2. Comparison between the (*R*)-ketoprofen **1** binding mode in COX-1 and the putative CXCR1 allosteric site: key polar interactions engaged by the carboxylic acid. (a) Binding model of **1** (green) in the COX-1 (yellow) binding site is shown. The carboxylic group of the inhibitor is involved in a strong electrostatic interaction (dashed lines) with the positively charged guanidinium group of Arg120. The inhibitor bridges the side chains of Tyr355 and Glu524 in a well-organized polar network. (b) Orientation of **1** (green) in the putative CXCR1 (light-blue) binding site is shown. In the proposed model an electrostatic interaction occurs between the hydroxyl group of $Tyr46_{1.39}$ and the aromatic ring of the inhibitor. Two additional polar interactions (dashed lines) orientate the side chains of two polar residues from TM2 ($Lys99_{2.64}$) and TM7 ($Glu291_{7.35}$). The overall interactions pattern of **1** with CXCR1 shows high similarity with the COX-1 binding mode.

hydrophobic channel where the carboxylic moiety engages a strong ionic bond with a basic amino acid residue (Arg120 of COX-1 and $Lys99_{2.64}$ of CXCR1). This ionic bond is additionally strengthened by an additional

polar interaction involving the carbonyl group and a hydrogen bond donor residue (Tyr355 of COX-1 and $Glu291_{7.35}$ of CXCR1). Moreover, the benzoyl group is accommodated in a well-organized hydrophobic pocket in COX-1 and CXCR1. This hydrophobic pocket in CXCR1 involves at least the lipophilic side chains of $Ile43TM1_{1.36}$, $Val113TM3_{3.28}$, and $Ile283TM7_{7.31}$ and the aliphatic chain of $Lys99TM2_{2.64}$. According to the model, $Lys99TM2_{2.64}$ is proposed to establish both polar and hydrophobic interactions with the inhibitor. Finally, in the CXCR1 binding model, a specific electrostatic interaction apparently directs the phenolic group of $Tyr46_{1.39}$ of CXCR1 toward the phenyl ring of **1**. This kind of interaction, involving the π ring system as hydrogen bond acceptor and the hydroxyl group of $Tyr46_{1.39}$ as the hydrogen bond donor, belongs to the family of weak noncovalent interactions.[27] OH$-\pi$ interactions have been observed in high-resolution protein structures, and they are important for the stability of protein structures.[28] Molecular dynamics calculations led to the identification of this interaction as a key feature of the binding mode; nevertheless, the arrangement of the groups is also compatible with a CH$-\pi$ interaction that could be underestimated by the force field. Specific mutagenesis studies on the nature of this interaction are still running, but the alanine scanning mutagenesis studies confirm the relevance of the interaction between $Tyr46_{1.39}$ and the inhibitor.

Alanine Scanning Mutagenesis of the Interaction Site between (*R*)-Ketoprofen (1) and CXCR1. To test the above binding model of **1** with CXCR1, amino acids of CXCR1 supposed to be directly involved in the binding of **1** were selected for alanine-replacement mutagenesis experiments. The alanine-replacement mutants Lys99Ala and Glu291Ala were expressed in L1.2 cells. **1** was tested in a wide range of concentrations (0.1−100 nM) known to affect CXCL8-induced PMN chemotaxis.[21] Wild-type CXCR1/L1.2 transfectants migration induced by CXCL8 (10 nM) was significantly inhibited by **1** (Figure 3), as expected. The inhibition of wild-type CXCR1/L1.2 transfectant migration was concentration-dependent, reaching a maximal inhibition (74%) at 0.1 μM **1**. In contrast, cells expressing the Lys99Ala CXCR1 mutant completely resisted the action of **1** while the Glu291Ala CXCR1 mutant had partial resistance to **1**. Receptor expression levels, CXCL8 binding affinity, and chemotactic migration to CXCL8 of the Lys99Ala CXCR1 transfectant were similar to those of the wild-type CXCR1/L1.2 transfectant (data not shown). The finding that CXCL8 binding to mutated CXCR1 is similar to wild-type CXCR1 is in keeping with the concept that the interaction site between **1** and CXCR1 is not involved in CXCL8 binding.

Binding of (*R*)-Ketoprofen (1) to CXCR1 Is Abolished in Lys99Ala CXCR1 Mutant. To provide additional evidence that the interaction between **1** and the amino acid $Lys99_{2.64}$ is crucial for CXCR1 binding, we took advantage of the ability of **1** to be photoactivated[29] in order to generate a covalent complex with the target protein. To this aim, wild-type CXCR1/L1.2 and mutated Lys99Ala CXCR1 cell membranes were incubated with [^{14}C]-**1** and irradiated. The immunoprecipitated CXCR1 was examined by SDS−PAGE. Radiolabeled [^{14}C]-**1** binds to wild-type CXCR1/L1.2 membranes. In

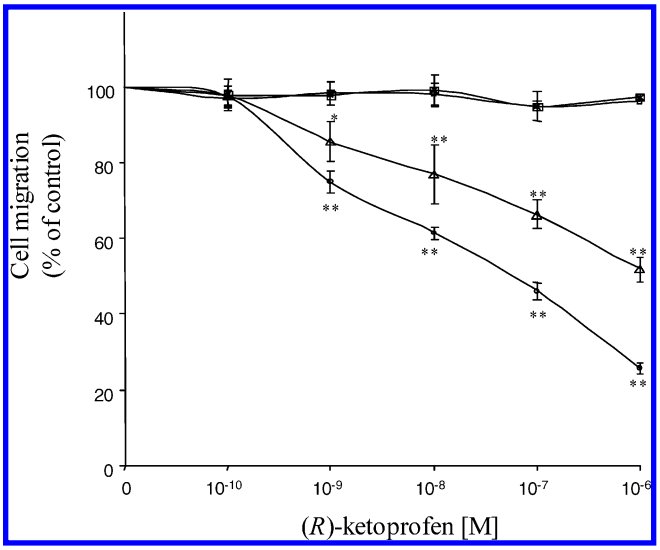


Figure 3. Effect of (*R*)-ketoprofen **1** on CXCL8-induced migration of L1.2 transfectants expressing wild-type CXCR1, mutated Lys99Ala CXCR1, and Glu291Ala. Cell migration was induced on L1.2 transfectants expressing wild-type CXCR1 (○), mutated Lys99Ala (□), and Glu291Ala (△) by CXCL8 (10 nM) in the presence or absence of increasing concentrations of **1**. Effect of **1** on L1.2 untransfected cell migration in response to CXCL12/SDF1 is also shown. Results are expressed as the percentage of migration in the absence of **1**. Values are the mean ± SD of three independent experiments: (∗) $P < 0.05$ vs cell migration in the absence of **1**; (∗∗) $P < 0.01$ vs cell migration in the absence of **1** (Mann−Whitney U test).

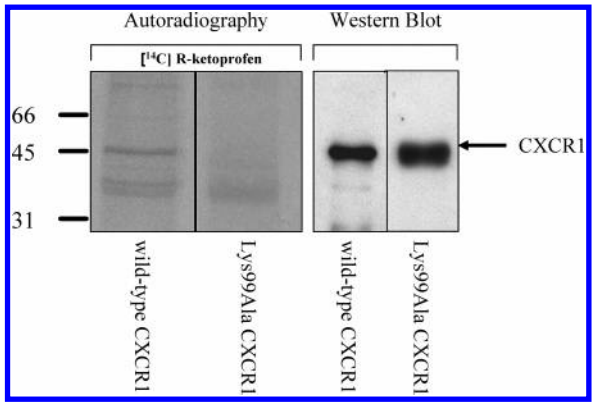


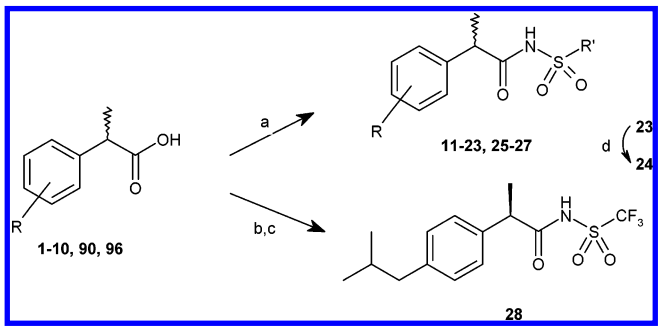
Figure 4. Binding of (*R*)-ketoprofen **1** on CXCR1 is abolished in the Lys99Ala CXCR1 mutant. Membrane preparations from L1.2 transfectants expressing wild-type CXCR1 or Lys99Ala CXCR1 mutant were incubated with [^{14}C]-**1**. After photochemical cross-linking, CXCR1 was immunoprecipitated and analyzed by SDS−PAGE and Western blot, as indicated. The arrow marks CXCR1. Data are from one experiment of two performed.

contrast, binding of **1** to Lys99Ala CXCR1 mutant membranes was completely abolished (Figure 4). These data further support the above-described model of interaction between **1** and CXCR1.

Chemistry. The compounds described in this study are shown in Tables 1−7, and their synthetic methods are outlined in Schemes 1−6.

The synthesis of acylsulfonamides (**11**−**27**) was carried out according to a disclosed procedure[30] starting from chiral or racemic 2-phenylpropionic acids **1**−**10**. Following this method the carboxylic acid was coupled to the selected alkyl or arylsulfonamide using 1,1′-carbonyldiimidazole in the presence of a base at room temperature. The trifluoromethanesulfonamide **28** was

Scheme 1[a]



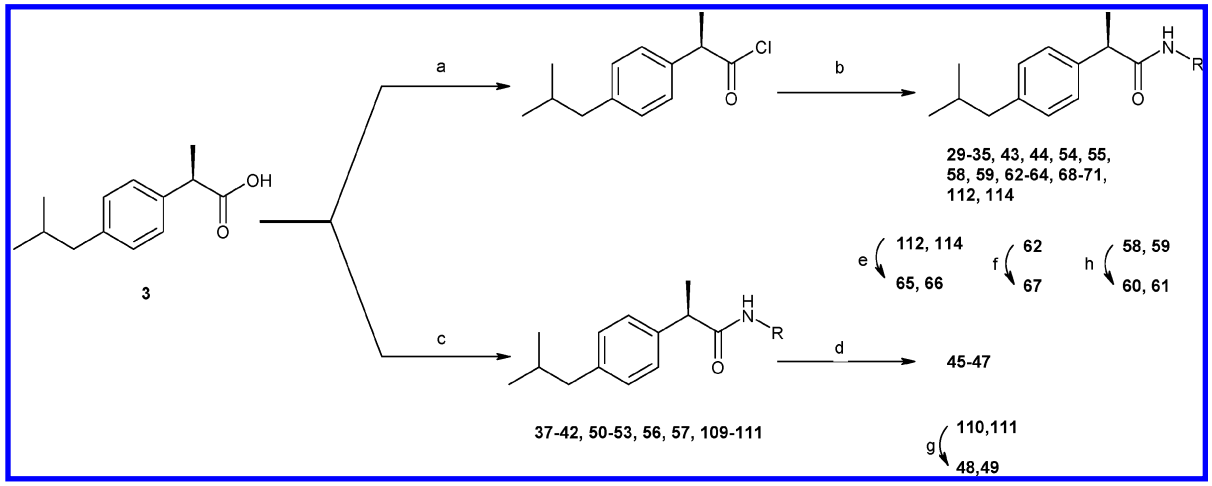
[a] Conditions: (a) CDI, DBU, CH_2Cl_2, $R'SO_2NH_2$; (b) $SOCl_2$, reflux; (c) $CF_3SO_2NH_2$, TEA, room temp; (d) NH_2NH_2, EtOH, reflux.

prepared by direct coupling of the corresponding acid chloride to commercial trifluoromethanesulfonamide in the presence of triethylamine (Scheme 1).

The synthesis of (*R*)-2-(4-isobutylphenyl)propionyl amides **29**−**35** and **37**−**71** was performed as described in Scheme 2. Most amines were commercially available; the others were prepared according to known procedures, as described in the Experimental Section. (*R*)-2-(4-Isobutylphenyl)propionic acid ((*R*)-ibuprofen) **3** was coupled to the corresponding amines by two different strategies. According to the first route, **3** was treated with thionyl chloride at reflux to give the acid chloride, which was reacted with the desired amine in the presence of triethylamine at room temperature to give the final compounds **29**−**35**, **43**, **44**, **54**, **55**, **58**, **59**, **62**−**64**, **68**−**71** and the intermediates **112** and **114**. The acidic hydrolysis of **112** and **114** by 3 M HCl afforded compounds **65** and **66** in high yield. Treatment of compound **62** with iodomethane yielded the corresponding quaternary ammonium salt **67**. Treatment of compounds **58** and **59** with diazomethane yielded the corresponding ethers **60** and **61**. Alternatively, the direct coupling between the acid **3** and amines with 1,3-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole was performed. Following this procedure, the final compounds **37**−**42**, **50**−**53**, **56**, **57** and the intermediates **109**−**111** were obtained in good to high yield. The basic hydrolysis in nonracemizing conditions (1 equiv of 1 N NaOH in 1,4-dioxane) of **50**, **51**, and **109** afforded compounds **45**−**47**, whereas treatment of **110** and **111** with BBr_3 afforded compounds **48** and **49**.

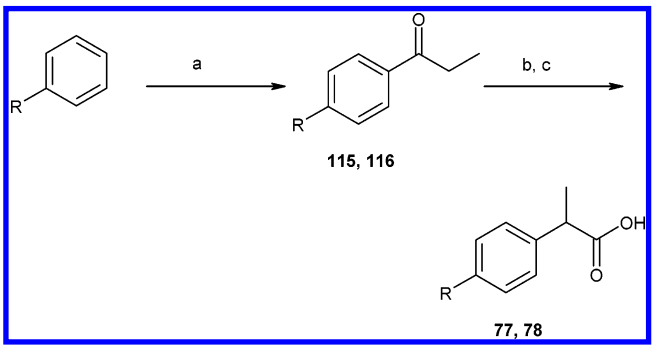
The synthesis of 2-arylpropionic acids was performed following several methods depending on the different substitution pattern of the aromatic ring. The choice of different methods was guided by the commercial availability of the reagents to derivatize trifluoromethanesulfonate intermediates. Simple 4-alkyl derivatives **77** and **78** were prepared by Friedel−Crafts acylation of the corresponding alkylbenzene. The following Willgerodt rearrangement[31] of the intermediate ketone and ester hydrolysis afforded the desired compounds (Scheme 3). Treatment of the methyl ester of the commercial 2-(4-hydroxyphenyl)propionic acid (**84**) with trifluoromethanesulfonic anhydride allowed us to obtain intermediate **117**, which was transformed into the compounds **80**, **81**, **85**, and **86** by reaction with the appropriate alkylzinc or arylzinc bromide and following methyl ester basic hydrolysis. Stille coupling of **117** with the appropriate organotin reagent afforded compound **79**. Alkylation of the potassium salt of the above methyl ester by alkyl iodide and hydrolysis afforded 4-alkoxy derivatives **82** and **83** (Scheme 4). Starting from the 3-hydroxyphenylacetic acid, intermediate **119** was prepared (Scheme 5) as described for **117**. Compound **95** was obtained from **119** as described above for **81**. When the same intermediate and the appropriate alkyltin reagents were used, compounds **88** and **89** were obtained after basic hydrolysis, while the reaction with triisopropyl aluminum gave compound **91**. The classical Stille procedure for the coupling of trifluoromethanesulfonates with alkenyltributyltin reagents[32] was followed for the synthesis of unsaturated intermediates **120**−**124** that, after hydrogenation on Pd/C and hydrolysis, afforded the final compounds **90**, **92**, **93**, and **96**. By hydration of the double bond of intermediate **123** and hydrolysis, compound **97** was obtained. Direct hydrolysis of intermediate **123** afforded compound **94**. Finally, Scheme 6 outlines the preparation of compounds **98**−**100**. The direct acidic hydrolysis of the commercial 2-(3-carboxyphenyl)propionic acid afforded compound **100**. The treatment of 2-(3-carboxyphenyl)propionic acid with Meldrum's acid sodium salt allowed us to isolate the intermediate **125**, which after acidic hydrolysis yielded

Scheme 2[a]



[a] Conditions: (a) $SOCl_2$, reflux; (b) RNH_2, TEA, room temp; (c) DCC, HOBT, TEA, DMF, room temp; (d) 1 N NaOH, 1,4-dioxane, room temp; (e) 3 M HCl, room temp; (f) CH_3I, THF, room temp; (g) BBr_3, CH_2Cl_2, −10 °C; (h) CH_2N_2, Et_2O, room temp.

Scheme 3[a]



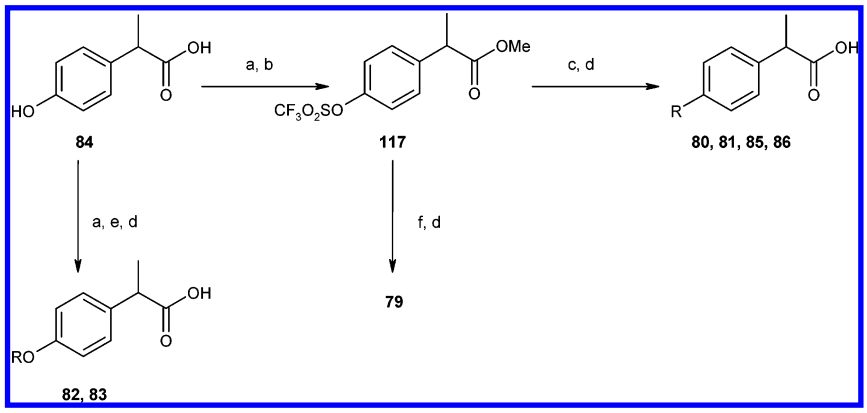
[a] Conditions: (a) $AlCl_3$, $ClCOCH_2CH_3$, CH_2Cl_2, reflux; (b) $AgNO_3$, I_2, $CH(OCH_3)_3$, MeOH, room temp; (c) NaOH, MeOH, reflux.

compound **99**. The reduction with $NaBH_4$ to intermediate **126** and the following hydrolysis afforded compound **98**. Starting from the commercial acid **87** and following the same procedure described above, compound **101** was also prepared in good yield. Starting from selected arylpropionic acids, compounds **102**−**108** were synthesized following the above-described procedures.

Structure−**Activity Relationship Studies.** (*R*)-2-Phenylpropionic acids **1** and **3** were found to be potent CXCL8 inhibitors with a marked selectivity (2 logs) versus the classical COX inhibition. On the other hand, (*R*)-enantiomers of 2-phenylpropionic acids have been reported to undergo chiral inversion in vivo in several animal species.[33] Although the interconversion of **1** to **2** was not observed in humans, significant interconversion to **2** was detected when **1** was administered to rats and dogs.[34] Since in vivo generated (*S*)-2-phenylpropionic acids do have COX-related antiinflammatory activity, it was important to design novel selective phenylpropionic derived CXCL8 inhibitors.

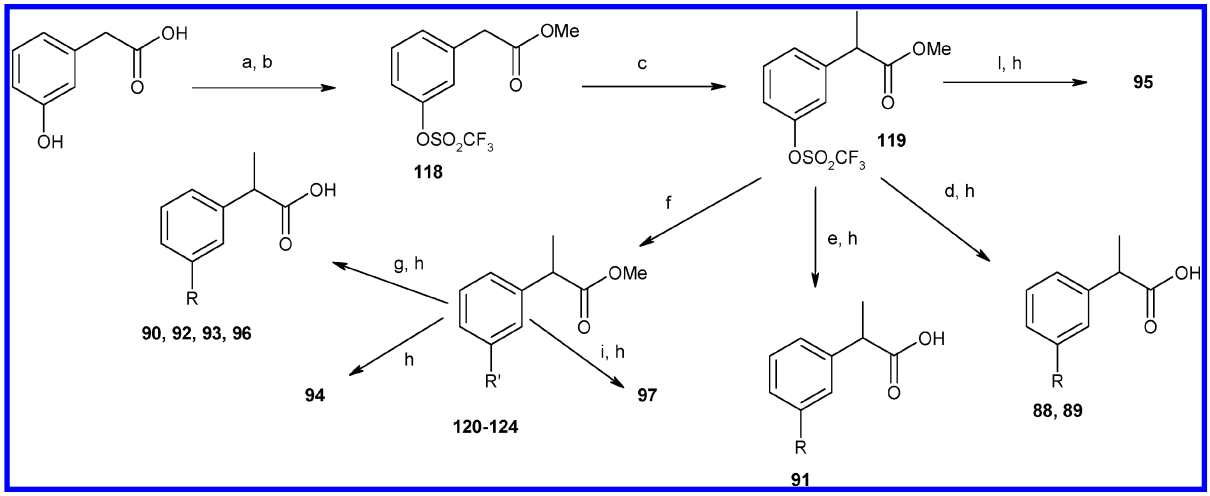
To this aim, on the basis of the above-discussed binding model, acylmethanesulfonamides, because of their fairly high acidity, were evaluated as potential bioisosteres of the carboxylic acid resistant to in vivo interconversion. The chiral inversion is an enzymatic process that mainly occurs in the liver and involves the formation of a coenzyme A thioester intermediate.[35] Thus, we hypothesized that the enzymatic inversion of metabolically stable carboxylic derivatives should be disallowed. The CXCL8 inhibitory activity was well-conserved when phenylpropionic acids of Table 1 were converted to (*R*)-2-arylpropionylmethanesulfonamides (Table 2). By contrast, the same methanesulfonamides were found to be considerably less potent than the corresponding carboxylic acids as COX inhibitors. In

Scheme 4[a]



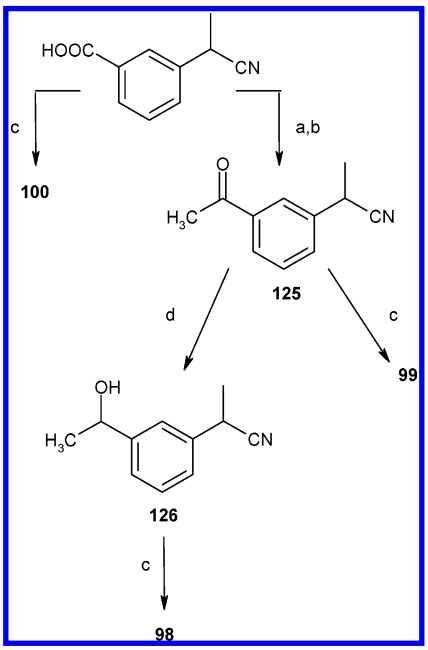
[a] Conditions: (a) concentrated H_2SO_4, MeOH, room temp; (b) $^iPr_2EtN$, $(CF_3SO_2)_2O$, CH_2Cl_2, −15 °C; (c) RZnBr, $Pd(PPh_3)_4$, LiCl, THF; (d) KOH, MeOH, room temp; (e) RI, K_2CO_3, acetone, room temp; (f) Bu_3SnR', Pd_2dba_3, $AsPh_3$, LiCl, CuI, NMP, 90 °C.

Scheme 5[a]



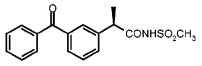
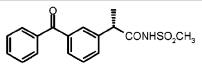
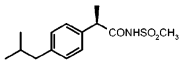
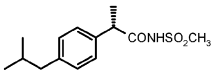
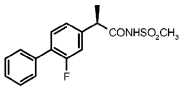
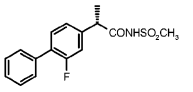
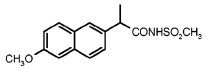
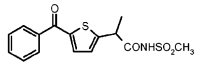
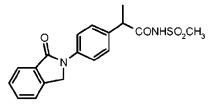
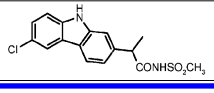
[a] Conditions: (a) concentrated H_2SO_4, MeOH, room temp; (b) $^iPr_2EtN$, $(CF_3SO_2)_2O$, CH_2Cl_2, −15 °C; (c) 60% NaH, CH_3I, THF, −25 °C; (d) SnR_4, Pd_2dba_3, $AsPh_3$, LiCl, CuI, NMP, 90 °C; (e) AlR_3, $Pd(PPh_3)_4$, THF, reflux; (f) Bu_3SnR', Pd_2dba_3, $AsPh_3$, LiCl, CuI, NMP, 90 °C; (g) H_2, 10% Pd/C, EtOH; (h) KOH, MeOH, room temp; (i) (1) BH_3, THF, 0 °C; (2) H_2O_2, NaOH; (l) RZnBr, LiCl, $Pd(PPh_3)_4$, THF, reflux.

Scheme 6[a]



[a] Conditions: (a) $SOCl_2$, reflux; (b) (1) Meldrum's acid sodium salt, pyridine, CH_2Cl_2, 0−5 °C; (2) AcOH/H_2O, reflux; (c) concentrated HCl, 1,4-dioxane, reflux; (d) $NaBH_4$, THF/H_2O, room temp.

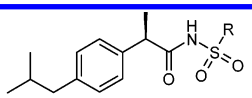
Table 2. Effect of 2-Arylpropionylmethanesulfonamides on CXCL8-Induced Human PMN Chemotaxis[a]

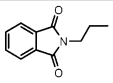
N.	Structure	CXCL8*	PGE_2**
11		40±6	52±2
12		42±3	72±7
13		65±5	8±4
14		30±4	17±4
15		11±7 30±5 (10^{-7}M)	21±7
16		4±8 19±5 (10^{-7}M)	11±1
17		43±7	70±10
18		71±2	62±10
19		71±2	85±4
20		n.a.	n.t.

[a] (∗) % of inhibition at 10^{-8} M. (∗∗) % of inhibition at 10^{-5} M. n.a.: compound not active at 10^{-6}M. n.t.: not tested.

particular, **13** inhibited CXCL8-induced chemotaxis with $IC_{50} = 1$ nM while it did not affect lipopolysaccharide (LPS) induced prostaglandin E (PGE) production

Table 3. (*R*)-2-(4-Isobutylphenyl)propionylsulfonamides[a]



N.	R	CXCL8*
13	CH_3	65±5
21		4±13 (40±7 c= 10^{-7}M)
22		-9±2 (30±7 c= 10^{-7}M)
23		n.a.
24		n.a.
25		n.a.
26		n.a.
27		n.a.
28	CF_3	n.a.

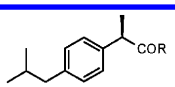
[a] (∗) % inhibition at 10^{-8} M. n.a.: compound not active at 10^{-6} M.

at 10^{-5} M. On the basis of the bioisosterism hypothesis, derivatization of inactive phenylpropionic/acetic acids of Table 1 to acylmethanesulfonamides was expected to afford inactive compounds. Thus, it was surprising to find that acylmethanesulfonamide **18** was much more potent than the parent tiaprofenic acid **8**. Compound **8** shows a close structural similarity with ketoprofen but, interestingly, is significantly more acidic than the other phenylpropionic acids of Table 1.[36] The high potency of the corresponding methanesulfonamide **18** suggests that the pK_a decrease disfavors the interaction with CXCR1. Under the assumption that the carboxylic group engages in an ionic interaction with $Lys99_{2.64}$ and hydrogen bonding with $Glu291_{7.35}$, it is conceivable that the protonation of the ϵ-amino group of $Lys99_{2.64}$ occurs in the TM pocket of CXCR1.

To gain further insight on the SAR, we decided to change the nature of the polar group (Table 3). (*R*)-Ibuprofen **3** was chosen as a scaffold because of its intrinsic low potency in the PGE production assay. First, we changed the nature of the sulfonamide residue to yield a set of analogues of **13**. The size of the alkyl substituent of the sulfonamide strongly affects the potency of the inhibitors (**21**, **22**), and the introduction of phenyl or alkylamino groups resulted in complete activity loss (**24**−**27**). Replacement of the methyl by a trifluoromethyl group has only minimal effect on the steric hindrance while strongly enhancing the acidic properties of the molecule. The lack of activity of trifluoromethanesulfonamide **28** supports the proposed model in which the inhibitor binds CXCR1 in the protonated form.

On the basis of these SAR data, we decided to move from acidic to neutral amide compounds designed to engage a double hydrogen bond with the $Lys99_{2.64}$/$Glu291_{7.35}$ couple. This modification was supposed to increase the CXCL8/COX selectivity. Results are summarized in Table 4. The acidic hydroxamic analogue **29**

Table 4. Effect of (*R*)-2-(4-Isobutylphenyl)propionylamides on CXCL8-Induced Human PMN Chemotaxis[a]



N.	R	CXCL8*	PGE_2**	N.	R	CXCL8*	PGE_2**
29	NHOH	52±11	39±9	**51**		n.a.	n.t.
30	$NHOCH_3$	42±2	19±3	**52**		n.a.	n.t.
31	NH_2	67±8	12±16	**53**		n.a.	n.t.
32	$NHCH_3$	25±9 (40±7 c= 10^{-7}M)	3±3	**54**		12±8	39±9
33	$NHCH_2CH_3$	4±5 (26±7 c= 10^{-7}M)	8±3	**55**		60±8	30±5
34	$N(CH_3)_2$	n.a.	n.t.	**56**		54±5	23±2
35		n.a.	n.t.	**57**		n.a.	n.t.
36	OCH_3	n.a.	n.t.	**58**		16±6	n.t.
37		9±10 (30±9 c= 10^{-7}M)	63±10	**59**		14±12	n.t.
38		36±6	40±5	**60**		57±10	n.t.
39		22±5	46±11	**61**		25±10	n.t.
40		18±10	n.t.	**62**		66±10	15±3
41		50±12	63±7	**63**		56±13	12±2
42		47±20	76±6	**64**		34±6	55±8
43		55±10	n.t.	**65**		n.a.	n.t.
44		60±5	n.t.	**66**		19±6	n.t.
45		67±4	10±2	**67**		n.a.	n.t.
46		n.a.	n.t.	**68**		4±9	n.t.
47		42±5	6±2	**69**		n.a.	n.t.
48		12±4	n.t.	**70**		n.a.	n.t.
49		n.a.	n.t.	**71**		n.a.	n.t.
50		n.a.	n.t.	**72**	CH_3	54±5	5±4

[a] (*) % of inhibition at 10^{-8} M. (**) % of inhibition at 10^{-5} M. n.a.: compound not active at 10^{-6} M. n.t.: not tested.

is approximately as potent as the methanesulfonamide **13** but, as expected, retains significant COX inhibitory activity. Interestingly, several neutral propionamides potently inhibited CXCL8, and the primary amide **31** was one of the most potent CXCL8 inhibitors in this class. Furthermore, the lack of effect of **31** at 10^{-5} M on PGE production confirmed the hypothesis on selectivity. A considerable loss in affinity was generally observed with *N*-alkyl-substituted secondary amides (**32**, **33**).

The lack of activity of *N*,*N*-dialkylamides **34** and **35** and of the methyl ester **36** is in agreement with a binding mode in which both CO and NH groups replace the carboxylic moiety in the interaction with $Lys99_{2.64}$ and $Glu291_{7.35}$.

A model for the binding of **31** in CXCR1 was built using the same procedure as described for **1**. The polar interactions engaged by **31** in the TM pocket are represented in Figure 5a. The effect of **31** on the CXCL8-induced chemotaxis of CXCR1/L1.2 transfectant and Lys99Ala and Glu291Ala mutants confirms that the neutral amide **31** binds CXCR1 in the same region of the carboxylic acid **1** (Figure 5b). Interestingly, whereas the Lys99Ala mutant was found to be completely resistant to the action of **1**, both Lys99Ala and Glu291Ala mutants similarly showed partial resistance to the action of **31.** This result is in keeping with a shift from an ionic bond to a double hydrogen bond interaction between the amide moiety of **31** and the side chains of $Lys99_{2.64}$ and $Glu291_{7.35}$ in the receptor site.

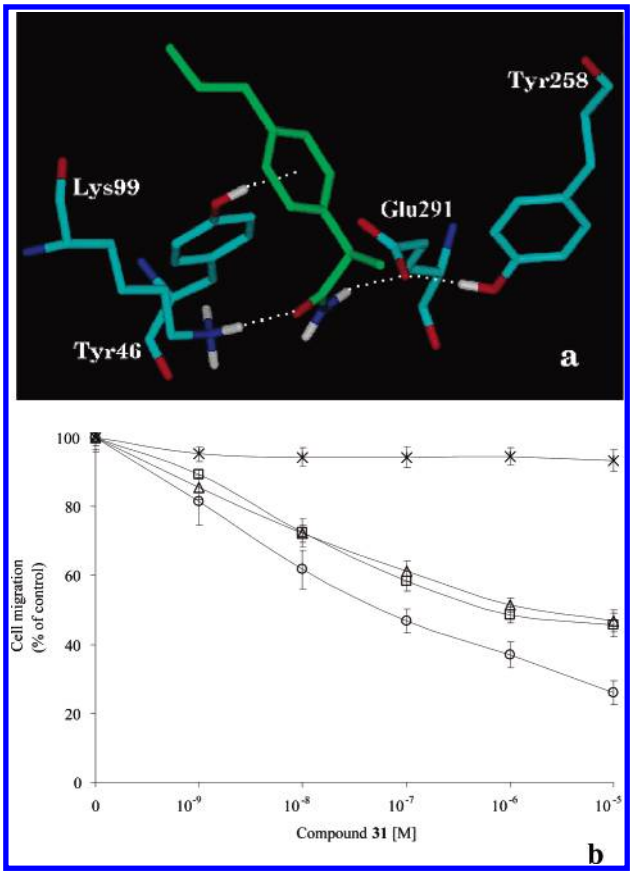


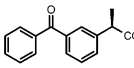
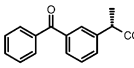
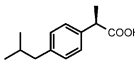
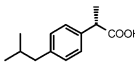
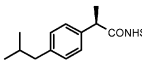
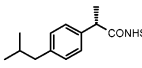
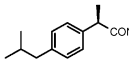
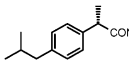
Figure 5. Binding of compound **31** in the TM region of CXCR1. (a) Details of the polar interactions of **31** (green) in the putative CXCR1 (light blue) binding site are shown. In the proposed model an electrostatic interaction occurs between the hydroxyl group of $Tyr46_{1.39}$ and the aromatic ring of the inhibitor. The amide group engages two hydrogen bond interactions (dashed lines) with the side chains of $Lys99_{2.64}$ and $Glu291_{7.35}$. An additional electrostatic interaction orientates the phenol group of $Tyr258_{6.51}$ toward $Glu291_{7.35}$. (b) Effect of **31** on CXCL8-induced migration of L1.2 transfectants expressing wild-type CXCR1, mutated Lys99Ala CXCR1, and Glu291Ala. Cell migration was induced on L1.2 transfectants expressing wild-type CXCR1 (○), mutated Lys99Ala (□), and Glu291Ala (△) by CXCL8 (10 nM) in the presence or absence of increasing concentrations of **31**. Effect of **31** on L1.2 untransfected cell migration in response to CXCL12/SDF1 (∗) is also shown. Results are expressed as the percent of migration in the absence of **31**. Values are the mean ± SD of three independent experiments: (∗) $P < 0.05$ vs cell migration in the absence of **31**; (∗∗) $P < 0.01$ vs cell migration in the absence of **31** (Mann−Whitney *U* test).

The proposed binding mode anticipates that amide derivatives with putative trans geometries should be strongly favored in setting the double polar interaction with the two residues from TM2 and TM7. Additionally, the good potency of **13** and **29** supports a model in which a trans amide bond is in the correct orientation for the receptor binding. Hence, in principle, the cis/trans amide isomer ratio could strongly influence the SAR in this series. Several external and internal parameters influence the magnitude of the rotational barrier separating cis and trans isomers, and the most stable isomer in solution is not easily predictable. Nevertheless, on the basis of literature data,[37,38] it is conceivable to assume for SAR purposes that trans isomers are the most abundant at least for *N*-arylamides **37**−**44** and α-aminoacylamides **45**−**51**.

N-Phenylamide, like the *N*-alkyl analogues, showed only moderate affinity for the receptor. Conversely, the insertion of a heteroatom in the 2-position (with respect to the carbon bearing the amino group) of the aromatic ring dramatically increased the inhibitory potency. A plausible explanation for SAR in the series of *N*-arylamides is that an increase in the π-bond character of the C−N bond results in a significant potency enhancement. Indeed, the presence of a heteroatom with basic or hydrogen bond acceptor characteristics could determine, in the most active compounds (**38**, **41**−**44**), a significant dextral shift of the amido/imido equilibrium, thus tuning the binding ability of the amido group. Unfortunately compounds **38**, **41**, and **42** retained a remarkable inhibitory effect on COX activity and thus were not selected for further in vivo characterization. An additional objective of our work was the selection of candidates with high water solubility suitable for parenteral administration. To this aim, we introduced several functional groups with hydrophilic characteristics on the nitrogen atom of **31**. The results reported in Table 4 show that, although simple alkylamides are only modest CXCL8 inhibitors, a variety of hydrophilic side chains can be accommodated in the receptor binding pocket to improve the water solubility of the inhibitors.

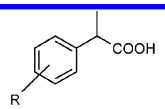
Amides of **3** with α-amino acids **45**−**51** are potent and specific CXCL8 inhibitors. In this series, the stereochemistry of both chiral centers strongly influences the receptor affinity. The four diastereomeric alanylamides were synthesized and tested in the chemotaxis assay; only the diastereoisomer **45** was efficacious in inhibiting CXCL8 activity. In addition, **45** was not efficacious as a COX inhibitor. The replacement of the alanine methyl group with functionalized groups (**48** and **49**) invariably resulted in a high activity loss. The esterification of the potent inhibitors **45** and **47** (**50** and **51**) dramatically reduced the potency, suggesting a key role of the acidic carboxylic moiety. Also, the position of the acidic function is crucial for biological activity (**52** and **53**). In fact, the elongation of the spacer between the amidic and carboxylic moieties led to a substantial activity loss. A hydroxyl group on the alkyl chain appears to be poorly tolerated (**54**, **58**, and **59**), whereas its transformation into methyl ether generated active compounds **55**, **60**, and **61**. Interestingly, as shown by the direct comparison between compounds **56** and **57**, the introduction of an ethereal oxygen along the chain restored the activity of the long-chain amido alcohol. These results suggest that hydrogen bond acceptor groups along the *N*-alkyl chain strongly reinforce the affinity for the receptor. This hypothesis was further confirmed by the activity data of a series of aminoalkylamides. *N*,*N*-Dimethylaminoalkylamides **62**−**64** exhibited a potency comparable to that of the most potent compounds in the series. It was initially surprising to find out that basic, positively charged groups were well-tolerated in the receptor pocket. Data shown in Table 4 suggest that the tertiary alkylamino group behaves as a hydrogen bond acceptor rather than as a basic or positively charged group. Secondary and primary amines (**65** and **66**) with dual hydrogen bond acceptor and donor characteristics showed negligible inhibitory potency in strict analogy with amido alcohols **54**, **58**, and **59**. Furthermore, the positively charged related quaternary ammonium salt de-

Table 5. IC_{50} Values for (*R*)- and (*S*)-Enantiomers of Representative CXCL8 Inhibitors

N.	Structure	IC_{50} ± SE (nM)
1		34±18
2		50±27
3		110±20
4		100±26
13		5.3±1.2
14		80±13
30		1.8±0.6
73		n.a.

rivative **67** completely lost the inhibitory activity. In conclusion, the similar trend observed in the series of amido alcohols and ethers and aminoalkylamides supports the hypothesis of a common binding mode for the different chemical classes herein described in which the ether oxygen and the amino nitrogen are involved in a supplementary hydrogen bond interaction. In contrast, hydrogen bond donors, such as alcoholic and primary/secondary amino groups, are not tolerated in the CXCR1 receptor pocket. It is also noteworthy that the inclusion of the hydrogen bond acceptor moiety in five- or six-membered cycles with reduced structure flexibility led to inactive compounds (**68**−**71**). From the receptor binding point of view, it is likely that the acceptor moiety engages favorable interactions with other amino acids in the TM region. Nevertheless, all the most potent compounds along the three classes share a heteroatom in such a position that the formation of an intramolecular hydrogen bond interaction with the amide group is allowed. Thus, it is possible to speculate that the hydrogen bond acceptor group cooperates in reinforcing the binding of the amide group with $Lys99_{2.64}$ and $Glu291_{7.35}$ rather than establishing additional interactions. The simple methyl ketone **72** is a highly potent and selective CXCL8 inhibitor (IC_{50} = 7 nM), but a dramatic loss of activity was observed when a set of analogues was designed on the basis of the SAR criteria previously learned. Considering the marked reactivity of the carbonyl group, it is likely that a covalent interaction with the $Lys99_{2.64}$ ϵ-amino group can replace the double polar interaction in the binding pocket. Further information on the inhibitor's binding mode with CXCR1 arise from a comparison of the IC_{50} values of different pairs of enantiomeric phenylpropionic derivatives (Table 5). (*R*)-Ibuprofen **3** and (*S*)-ibuprofen **4** exhibited, as previously described for ketoprofen enantiomers,[21] a similar potency as CXCL8 inhibitors. By contrast, a progressive increase of the eudismic ratio was observed when the enantiomers of 2-(4-isobutylphenyl)propionylmethanesulfonamide (**13** and **14**) and 2-(4-isobutylphenyl)propionamide (**30** and **73**) were compared in the CXCL8-induced chemotaxis assay. Noticeably, the primary amide **73** was also found to be inactive at high concentration (10^{-5} M), and a similar trend has also been described above for compounds **45** and **46**. Taking into account our binding mode hypothesis, a plausible explanation is that the shift from partially ionic to polar hydrogen bond interactions could result in a subtle rearrangement of the amino acids in the binding pocket.

Table 6. Effect of Ring Substituents of Racemic 2-Arylpropionic Acids on CXCL8-Induced Human PMN Chemotaxis[a]

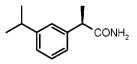
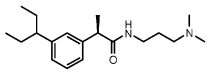
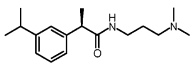
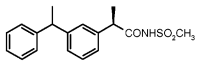
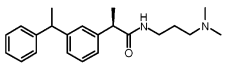
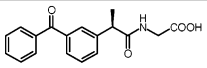
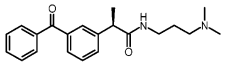


N.	R	CXCL8*	N.	R	CXCL8*
Substituents on position 4			Substituents on position 3		
74		44±6	**87**		64±4
75	H	17±9	**88**		47±11
76	CH_3	29±2	**89**		n.a.
77		15±9 (32±9 c= 10^{-7}M)	**90**		62±5
78		n.a.	**91**		n.a.
79		11±17	**92**		16±25 (50±8 c= 10^{-7}M)
80		n.a.	**93**		58±15
81		n.a.	**94****		n.a.
82		13±4 (38±6 c= 10^{-7}M)	**95**		10±5 (30±8 c= 10^{-7}M)
83	CH_3O	34±2	**96**		55±2
84	OH	n.a.	**97**		57±6
85		n.a.	**98**		43±8
86		n.a.	**99**		n.a.
			100	COOH	n.a.
			101		41±8

[a] (∗) % of inhibition at 10^{-8} M. (∗∗) 3:1 *E*/*Z* mixture. n.a.: compound not active at 10^{-6} M.

Since 2-arylpropionic amides and sulfonamides were potent and selective inhibitors of CXCL8 activity, we decided to investigate the influence of the substituents on the phenyl ring. In this paper only a limited number of examples will be discussed. To this aim, racemic phenylpropionic acids were synthesized. As expected on the basis of the preliminary observations reported for NSAIDs, the size and nature of the substituents are crucial in determining the affinity for the receptor, and modifications of the phenyl ring substituents generated molecules ranging from highly potent inhibitors to completely inactive ones. In Table 6 inhibition at 10^{-8} M of some racemic 2-arylpropionic acids is reported in order to highlight the most potent compounds; however,

Table 7. Derivatives of (*R*)-2-Phenylpropionic Acids Selected as CXCL8 Inhibitors[a]

N.	Structure	CXCL8*
102		34±2
103		68±4
104		58±10
105		66±9
106		54±9
107		37±2
108		53±8

[a] (∗) % inhibition at 10^{-8} M.

several inactive compounds recovered inhibitory potency at higher concentrations (10^{-6} M). The replacement of the 4-isobutyl group (**74**) with smaller alkyl chains (**75**−**77**) in the same position led to a moderate potency decrease, whereas larger hydrophobic groups (**78**−**81**, **85**, and **86**) dramatically reduced receptor affinity, leading to completely inactive compounds. 2-(4-Alkoxyphenyl)propionic acid analogous **82** and **83** exhibited weak to moderate activity as CXCL8 inhibitors, whereas the 4-hydroxyphenyl analogue **84** was inactive at maximal concentration. Next, we examined the effect of hydrophobic groups on the 3-position (**87**−**101**). Interestingly, the compounds with flexible alkyl chains on the 3-position were only moderately active, whereas the introduction of a branch on the benzylic carbon invariably resulted in potent inhibitors. The 3-isopropyl derivative **90** was the most active compound in the series, but larger aliphatic (**93)** and aromatic substituents (**96**) were well-tolerated too. The forced perpendicular orientation of a branched substituent in the 3-position seems crucial for a correct arrangement of the inhibitor in the binding pocket. Replacing the methyl group by a hydroxyl group (**98**) on the branch surprisingly had only minimal effect on the potency, whereas the oxidized 3-acetyl (**99**) and 3-carboxy (**100**) analogues lack biological activity.

Finally, on the basis of the activity data of all the tested compounds, we synthesized several 2-arylpropionamides (**102**−**104**, **106**−**108**) and the 2-arylpropionylsulfonamide **105** starting from selected active phenylpropionic acids of Table 6. The results are reported in Table 7. The structure−activity trend observed in the series of ibuprofen derivatives was well-conserved when different phenylpropionic scaffolds were examined, and this observation strongly supports the hypothesis of a common binding mode for the whole class of CXCL8 inhibitors. Thus, the screening of racemic phenylpropionic acids is a reliable strategy to select novel scaffolds for the lead optimization phase, although the carboxylic acid pK_a value must be taken into account. As a consequence, in the screening phase, inactive carboxylic acids with a theorical pK_a less than 4.3 were not excluded from the derivatization program.

The compounds **13**, **45**, and **56** showed the desired characteristics of potency, selectivity, and water solubility and were selected as viable candidates for pharmacological in vivo studies. The comparison of their pharmacokinetic and pharmacodynamic profile led us to select **13**, *N*-[(*R*)-2-(4-isobutylphenyl)propionyl]-methanesulfonamide (repertaxin), for preclinical and clinical development. To date, repertaxin has been proved to be efficacious in several models of reperfusion injury (RI) and is currently undergoing phase II clinical trials.[39,40] In vivo studies confirmed the hypothesis that (*R*)-2-phenylpropionamides and (*R*)-2-phenylpropionylsulfonamides do not interconvert to the (*S*)-enantiomers. The metabolic profile of repertaxin has been widely characterized in several animal species, and the formation of the corresponding (*S*)-enantiomer is not observed in rats, mice, dogs, and humans (data not shown).

Discussion

The results reported here describe SAR studies of a novel class of noncompetitive allosteric inhibitors of the CXCL8 receptor CXCR1. Photoactivation and alanine scanning mutagenesis experiments show that the prototypic inhibitor **1** binds to the TM region of CXCR1 in a pocket defined by TM helices 1, 2, 3, 6, and 7. The identification of the molecular interactions that take place between ketoprofen and CXCR1 guided the site-directed design of a novel class of potent and specific blockers of CXCL8 activity. Among the CXCL8 blockers described here, **13** was selected as a clinical candidate that is now in phase II clinical studies for the prevention of reperfusion injury.

We previously described that **1** inhibits CXCL8-induced chemotaxis of human PMN. We describe here that **1** interacts with a pocket defined by TM helices 1, 2, 3, 6, and 7 of CXCR1. The carboxylic moiety of **1** establishes with Lys99TM$2_{2.64}$ of CXCR1 a strong ionic interaction reinforced by an additional hydrogen bond with the side chain of and Glu291TM$7_{7.35}$. Additional polar and hydrophobic interactions contribute to determine the affinity of **1** at the binding site of CXCR1. In the proposed model an electrostatic interaction occurs between the hydroxyl group of Tyr46TM$1_{1.39}$ and the phenylpropionic ring of the inhibitor; the benzoyl substituent engages hydrophobic interactions with the side chains of Ile43TM$1_{1.36}$, Val113TM$3_{3.28}$, and Ile283TM$7_{7.31}$ and with the aliphatic chain of Lys99TM$2_{2.64}$.

Agonist activation of GPCR induces conformational changes that are still poorly understood, but evidence is emerging that receptor proteins exist in multiple conformational states. Microdomains have been identified in several GPCRs that could function as activation switches, and in particular, the rearrangement of specific residues of TM2 and TM7 could fine-tune the active/inactive conformational equilibrium.[41] The finding that **1** inhibits the signal transduction induced by CXCL8 without affecting CXCL8 binding strongly suggests that the interaction between **1** and CXCR1 locks CXCR1 in an inactive conformation unable to activate downstream signaling events. All in all, the data in this

paper suggest that **1** is not a classical competitive inhibitor of CXCR1. This concept is further strengthened by the finding that mutation of residues in the binding site of **1** in CXCR1 does not alter CXCL8 binding in terms of affinity constant and biological response.

The identification of the molecular interactions between **1** and CXCR1 prompted an extensive medicinal chemistry study aimed at identifying potent and specific blockers of CXCL8 activity. Several derivatives belonging to different chemical classes were synthesized and tested in CXCL8-induced chemotaxis of human PMNs. The SAR data suggest that specific polar interhelical interactions engaged by the amide moiety are key requirements for the general inhibitory property of the class, whereas hydrophobic interactions established by the ring substituent play a crucial role in determining the potency. The replacement of the ionic interaction between the carboxylic moiety of phenylpropionic acids with a double hydrogen bond interaction between the novel inhibitors and the $Glu291TM7_{7.35}$/$Lys99TM2_{2.64}$ couple resulted in very potent inhibitors with negligible residual activity on COXs. This observation is consistent with the binding mode of phenylpropionic NSAIDs in COXs in which the acidic moiety engages a crucial ionic interaction with Arg120.

It has been proposed[42] that allosteric sites in the TM domain of GPCRs may represent a valuable target for rational drug design of potent, noncompetitive inhibitors that block agonist induced G-protein activation. Since chemokines are relatively large ligands, it is evident that SMW antagonists can hardly compete for receptor binding. Onuffer and Horuk[43] have recently discussed the theoretical possibility of identifying chemokine inhibitors able to disrupt receptor function without displacing chemokine binding, but to date, the general use of chemokine binding as the primary assay in most of the screening programs hardly limited the discovery of noncompetitive inhibitors. The results herein reported show that the use of a functional assay (e.g., chemotaxis) in the primary screening phase, even if onerous, gives the opportunity of selecting novel classes of noncompetitive inhibitors. Moreover, since it is generally assumed that structural motifs might be well-conserved along subfamilies of the rhodopsin-like GPCR family, it is conceivable that the identification of the above-described allosteric site in CXCR1 might represent a novel strategy of general interest for the rational design of novel classes of compounds targeting other members of the peptidergic receptors subfamily of GPCRs. Currently, homology-based structural analysis of the main pharmacologically relevant peptidergic and not peptidergic receptors is being carrying out. Preliminary results confirm that a subfamily of GPCRs share the allosteric motif, and on the basis of this structural approach, we have now successfully generated potent and specific inhibitors for other chemoattractant receptors.

Among the diverse CXCL8 inhibitors shown in this work, the clinical candidate repertaxin (**13**) was selected for further characterization. The binding site of **13** is highly homologous in the two CXCL8 receptor subtypes CXCR1 and CXCR2.[39] Accordingly, **13** is a noncompetitive allosteric blocker of both receptor subtypes, as assessed by experiments with CXCR1/L1.2 and CXCR2/L1.2 transfected cells.[39] The difference in the IC_{50} values of **13** on CXCR1 (1 nM) and CXCR2 (100 nM) transfected cells can be explained by the lack of specific hydrophobic residues in CXCR2 involved in the recognition of the isobutyl group.[39] There is conflicting information as to whether CXCL8-induced chemotaxis of PMN is mediated by one or both of the CXCL8 receptors.[18,44] The high potency of **13** as inhibitor of the human PMN-induced chemotaxis, together with data on transfected cells, supports a prominent role of CXCR1. **13** has been proven to be efficacious and well-tolerated in several ischemia/reperfusion in vivo animal models.[39,40] On the basis of the pharmacological results, **13** has been selected as a candidate drug for the prevention and treatment of delayed graft function (DGF) and is currently undergoing phase II clinical trials.

Experimental Section

A. Biology. Reagents. Chemokines were from Pepro Tech (London, U.K.). Chemicals and protease inhibitors were from Sigma (St. Louis, MO). The L1.2 lymphoma cell line was from ATCC (Rockville, MD). Diff-Quik was from Dade Behring (Switzerland). G418 was from Life Technologies (Grand Island, NY). Polycarbonate filters were from Neuroprobe Inc. (Pleasanton, CA). Transwell filters were from Costar (Costar, Cambrige, MA). Cellulose nitrate membrane filters were from Whatman International Ltd, (England). [^{35}S]GTPγS (1250 Ci/mmol) and [^{14}C]-(*R*)-ketoprofen (87 Ci/mmol) were from Amersham (Bucks, U.K.). Antihuman CXCR1 was from Biosource International Inc., Camarillo, CA). pcDNA3 was from Invitrogen.

Animals. Female CD1 mice were obtained from Charles River Laboratories (Calco, LC, Italy). Animals were housed and acclimatized for 1 week under controlled temperature (20 $\pm$ 2 °C), humidity (55 $\pm$ 10%), and lighting (7 a.m. to p.m.). Standard sterilized food and water were supplied ad libitum during acclimatization and experiments.

All the procedures were performed in the animal facilities according to ethical guidelines for the conduct of animal research (Authorization Italian Ministry of Health No. 47/2001-B; Italian Legislative Decree 116/92, Gazzetta Ufficiale della Repubblica Italiana No. 40, February 18, 1992, EEC Council Directive 86/609 OJ358, December 12, 1987; NIH Guide for the Care and Use of Laboratory Animals; NIH Publication No. 85-23, 1985).

Migration Assay. Cell migration of human PMN was evaluated using a 48-well microchemotaxis chamber.[40] CXCL8 (1 nM) was seeded in the lower compartment. Cell suspensions (1.5×10^6/mL), preincubated at 37 °C for 10 min in the presence or absence of compounds, were seeded in the upper compartment. The two compartments of the chemotactic chamber were separated by a 5 μm polycarbonate filter (PVP-free for PMN chemotaxis). The chamber was incubated at 37 °C in air with 5% CO_2 for 45 min. At the end of incubation, filters were removed, fixed, and stained with Diff-Quik, and five oil immersion fields at high magnification (100×) were counted after sample coding. Cell migration of L1.2 was evaluated in 5 μm pore size Transwell filters.[46] The Transwell filter was incubated at 37 °C in air with 5% CO_2 for 4 h, and the cells were counted in a Bürker chamber.

[^{35}S]GTPγS Assay. [^{35}S]GTPγS assays were performed as previously described[47] with the following modifications: a total of 20 μg of PMN plasma membranes was incubated in buffer (143 mM NaCl, 50 mM triethanolamine, pH 7.3, 1 mM EDTA, 5 mM $MgCl_2$, and 20 μM GDP) at 30 °C for 20 min in the presence or absence of **1**. CXCL8 (300 nM) was added and followed 10 min later by [^{35}S]GTPγS (0.8 nM). The total volume was 100 μL. The reaction was allowed to proceed at 30 °C for 15 min and terminated by filtration through 0.45 μM cellulose nitrate membrane filters. The filters were washed two times with 2 mL of washing buffer (50 mM Tris-HCl, pH 7.3, 5 mM $MgCl_2$, 1 mM EDTA) and transferred to scintillation vials containing 10 mL of scintillation fluid, and the bound

[^{35}S]GTPγS was determined by an L96500 multipurpose scintillation counter.

Mutagenesis of CXCR1 and Cell Transfection. The human CXCR1 open reading frame was PCR amplified from a CXCR1/pCEP4 plasmid (kindly provided by Dr. P. M. Murphy, NIH, Bethesda, MD). Receptor mutant was obtained by standard two-step PCR. Wild-type and mutated receptors were cloned in the mammalian expression vector pcDNA3. The nucleotide sequence of each construct was confirmed by double strand DNA sequencing. The mouse L1.2 lymphoma cell line was transfected by electroporation and selected with G418 (800 μg/mL).

Photochemical Cross-Linking of CXCR1. Membranes prepared from both wild-type L1.2 CXCR1 and mutated Lys99Ala CXCR1 cells were incubated with [^{14}C]-**1** (0.1 mM) at room temperature for 10 min. CXCL8 (80 nM) was added and followed 10 min later by irradiation (10 cm distance) with an hand-held UV illuminator at 0 °C for 30 min. After centrifugation (30000*g*) at 4 °C for 15 min, membrane suspensions were solubilized and homogenized in a glass−glass homogenizer. After centrifugation (10000*g*) at 4 °C for 10 min, the supernatants were subjected to immunoprecipitation with 10 μg of antihuman CXCR1. The immune complexes were resolved by SDS−PAGE (15% gel). After electrophoresis, the gel was stained with Comassie Blue, dried, and exposed to autoradiography at −80 °C for 1 month.

Macrophage Preparation and LPS-Induced PGE_2 Production Assay. Peritoneal exudate cells were collected from peritoneal washing 5 days after ip inoculum of 3% thioglycolate (Difco, Detroit, MI) in saline (1.5 mL for mouse). Cells were plated at a density of 6×10^5/well in 96-well plates in RPMI 1640 (Sigma, St. Louis, MO) medium, and nonadherent cells were removed by repeated washing 2 h later. Compounds were then added to the macrophages at 10 μM, and 30 min later LPS (from *E. coli* 0.55: B5, Difco; 1 μg/mL) was added. Control wells received saline or DMSO (Sigma) at the appropriate dilution. Culture supernatants were harvested 4 h after LPS stimulation for PGE_2 production measured with an EIA kit (Amersham; sensitivity of 2.5 pg/well).

B. Molecular Modeling. The starting rhodopsin-based CXCR1 molecular model has been extracted from the GPCRDB database, whereas (*S*)-flurbiprofen bound COX-1 from the Protein Data Bank (designation 1EQH). Conformational analysis of the ligands has been performed with molecular mechanics (MM) methods. Steepest descent (SD) and conjugate gradient (CG) algorithms are as implemented in the DISCOVER (Insight II package, release 2000, Accelrys Inc., San Diego, CA) package using the CVFF force field. After reiterated minimizations (SD + CG) of the ligand in the putative receptor binding cavity, the energy-refined model was used as input of NVT (305 K) molecular dynamics (MD) for 1000 ps starting from 5 to 305 K, by incrementing 50 K per 2 ps of simulation. A supplementary elastic potential term (50 kcal/Å^2) has been added on the α carbon of CXCR1 to preserve the secondary structure of the TM bundle during the simulation. Following gradual annealing (from 305 to 5 K, 50 K per 2 ps), the obtained structure has been minimized by MM (CG). To confirm the reproducibility of the model, starting from different conformations, the overall calculation has been repeated three times, and the three final structures were identical. The stability of the final structure was assessed through 50 ps of high-temperature MD calculations (from 5 to 1000 K, 50 K per 2 ps) with an increasing tethering potential (50 kcal/Å^2 up to 200 for higher temperature values) associated with the α carbon of CXCR1. After the annealing step (from 1000 to 5 K), a final MM (CG) calculation followed. All simulations have been performed on an SGI O2 R12000 (IRIX6.5) instrument.

C. Chemistry. General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 241 polarimeter, and the $[\alpha]^{25}_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra were recorded on a Bruker ARX 300 spectrometer. Melting points were determined using a Büchi capillary melting point apparatus and are uncorrected. Elemental analyses were within ±0.4% of the theoretical values calculated for C, H, and N and reported only with symbols. High-performance liquid chromatography (HPLC) was performed on a Waters 600E apparatus with a Waters 486 UV detector (monitoring at 254 nm) equipped with a Chiralcel OJ column and using a mixture consisting of 75:15:10 *n*-hexane/EtOH/^{i}PrOH and trifluoroacetic acid (TFA) (0.5%)

All reagents and solvents were purchased from Sigma-Aldrich or Lancaster and used without further purification. Reaction courses and product mixtures were monitored by thin-layer chromatography on silica gel (precoated F_{254} Macherey−Nagel plates); the spots were examined with UV light and visualized with I_2.

The following 2-arylpropionic acids are commercially available as racemic mixtures: ketoprofen (**87**), ibuprofen (**74**), flurbiprofen, naproxen (**7**), thiaprofenic acid (**8**), indoprofen (**9**), carprofen (**10**), 2-phenylpropionic acid (**75**), 2-(4-methyl)-phenylpropionic acid (**76**), and 2-(4-hydroxy)phenylpropionic acid (**84**).

General Procedure for the Optical Resolution of Racemic 2-Arylpropionic Acids. Compounds **1**−**6**, **90**, and **93** were obtained by optical resolution of the related racemic 2-arylpropionic acids as described[48] using the *R*-(+) or *S*-(−)-α-phenylethylamine as resolving agent.

(*R*)-2-(3-Benzoylphenyl)propionic Acid (1). Yield 38%. Anal. ($C_{16}H_{14}O_3$) C, H.

(*S*)-2-(3-Benzoylphenyl)propionic Acid (2). Yield 37%. Anal. ($C_{16}H_{14}O_3$) C, H.

(*R*)-2-(4-Isobutylphenyl)propionic Acid (3). Yield 35%. Anal. ($C_{13}H_{18}O_2$) C, H.

(*S*)-2-(4-Isobutylphenyl)propionic Acid (4). Yield 33%. Anal. ($C_{13}H_{18}O_2$) C, H.

(*R*)-2-(2-Fluorobiphenyl-4-yl)propionic Acid (5). Yield 30%. Anal. ($C_{15}H_{13}FO_2$) C, H.

(*S*)-2-(2-Fluorobiphenyl-4-yl)propionic Acid (6). Yield 35%. Anal. ($C_{15}H_{13}FO_2$) C, H.

Synthesis of Acylsulfonamides (Scheme 1). *N*-[(*R*)-2-(3-Benzoylphenyl)propionyl]methanesulfonamide (11). To a cooled mixture (0−5 °C) of **1** (2.0 g, 7.88 mmol) in CH_2Cl_2 (30 mL), 1,1′-carbonyldiimidazole (CDI) (1.72 g, 7.88 mmol) was added. After the mixture was stirred for 2 h at 0−5 °C, methanesulfonamide (0.79 g, 7.88 mmol) and diazobicyclo-[5.4.0]undec-7-ene (DBU) (1.22 mL, 7.88 mmol) were added. The mixture was left stirring for 4 h. Glacial AcOH (0.94 mL) was added, the reaction mixture was diluted with CH_2Cl_2 (10 mL), and the organic layer was washed with 10% buffer NaH_2PO_4 (pH 4) (4 × 15 mL) and water (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude residue that was purified by flash chromatography (CH_2Cl_2/CH_3OH 99:1) to afford **11** as a colorless oil (1.92 g, 74% yield). Anal. ($C_{17}H_{17}NSO_3$) C, H, S, N.

***N*-[(*S*)-2-(3-Benzoylphenyl)propionyl]methanesulfonamide (12).** Following the same procedure described for **11** and starting from **2** (2.0 g, 7.88 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 99:1), **12** was obtained as a transparent oil (1.84 g, 70.5% yield). Anal. ($C_{17}H_{17}NO_3S$) C, H, S, N.

***N*-[(*R*)-2-(4-Isobutylphenyl)propionyl]methanesulfonamide (13).** Following the same procedure described for **11** and starting from **3** (2.0 g, 9.7 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 95:5), **13** was obtained as a white powder (2.28 g, 83% yield). Anal. ($C_{14}H_{21}NO_3S$) C, H, S, N.

***N*-[(*S*)-2-(4-Isobutylphenyl)propionyl]methanesulfonamide (14).** Following the same procedure described for **11** and starting from **4** (2.0 g, 9.7 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 95:5), **14** was obtained as a white powder (2.20 g, 80% yield). Anal. ($C_{14}H_{21}NO_3S$) C, H, S, N.

***N*-[(*R*)-2-(2-Fluorobiphenyl-4-yl)propionyl]methanesulfonamide (15).** Following the same procedure described for **11** and starting from **5** (2.0 g, 8.18 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 95:

5), **15** was obtained as a white powder (1.79 g, 68% yield). Anal. ($C_{16}H_{16}FNO_3S$) C, H, S, N.

***N*-[(*S*)-2-(2-Fluorobiphenyl-4-yl)propionyl]methanesulfonamide (16).** Following the same procedure described for **11** and starting from **6** (2.0 g, 8.18 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 95:5), **16** was obtained as a slightly white powder (1.84 g, 70% yield). Anal. ($C_{16}H_{16}FNO_3S$) C, H, S, N.

***N*-[2-(6-Methoxynaphthalen-2-yl)propionyl]methanesulfonamide (17).** Following the same procedure described for **11** and starting from **7** (2.0 g, 8.68 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 99:1), **17** was obtained as a pale-yellow powder (1.56 g, 78% yield). Anal. ($C_{15}H_{17}NO_4S$) C, H, S, N.

***N*-[2-(5-Benzoylthiophen-2-yl)propionyl]methanesulfonamide (18).** Following the same procedure described for **11** and starting from **9** (2.0 g, 7.68 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 98:2), **18** was obtained as a white powder (1.68 g, 65% yield). Anal. ($C_{15}H_{15}NO_4S_2$) C, H, S, N.

***N*-{2-[4-(1,3-Dihydroisoindol-2-yl)phenyl]propionyl}methanesulfonamide (19).** Following the same procedure described for **11** and starting from **8** (2.0 g, 7.11 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 99:1), **19** was obtained as a white powder (1.68 g, 65% yield). Anal. ($C_{18}H_{18}N_2O_4S$) C, H, S, N.

***N*-[2-(6-Chloro-9*H*-carbazol-2-yl)propionyl]methanesulfonamide (20).** Following the same procedure described for **11** and starting from **10** (2.0 g, 7.31 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 99:1), **20** was obtained as a white powder (1.84 g, 72% yield). Anal. ($C_{16}H_{15}ClN_2O_3S$) C, H, S, N.

General Procedure for the Synthesis of Intermediates Alkyl- and Arylsulfonamides. The noncommercial alkyl- and arylsulfonamides were prepared according to the described procedure. A suitable alkyl- or arylsulfonyl chloride was dissolved in dry Et_2O (or 1,4-dioxane if insoluble), and gaseous ammonia was bubbled into the solution until the precipitation of ammonium chloride was complete. After filtration, the mother liquors were evaporated under reduced pressure and hot water was added to the crude. The resulting solution was left cooling at room temperature, and the pure alkyl- or aryl sulfonamide was isolated as a white solid by filtration and characterized by mp and ^{1}H NMR analysis.

***N*-[(*R*)-2-(4-Isobutylphenyl)propionyl]ethanesulfonamide (21).** Following the same procedure described for **11** and starting from **3** (2.0 g, 9.7 mmol) and ethanesulfonamide (1.06 g, 9.7 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 98:2), **21** was obtained as a pale-yellow solid (2.31 g, 80% yield). Anal. ($C_{15}H_{23}NO_3S$) C, H, S, N.

***N*-[(*R*)-2-(4-Isobutylphenyl)propionyl]isopropylsulfonamide (22).** Following the same procedure described for **11** and starting from **3** (2.0 g, 9.7 mmol) and propane-2-sulfonamide (1.19 g, 9.7 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 98:2), **22** was obtained as a waxy solid (1.67 g, 55% yield). Anal. ($C_{16}H_{25}NO_3S$) C, H, S, N.

2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)ethanesulfonic Acid [(*R*)-2-(4-Isobutylphenyl)propionyl]amide (23). Following the same procedure described for **11** and starting from **3** (2.0 g, 9.7 mmol) and 2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-ethanesulfonic acid amide (2.46 g, 9.7 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 95:5), **23** was obtained as a white powder (3.13 g, 73% yield). Anal. ($C_{23}H_{26}N_2O_5S$) C, H, S, N.

2-Aminoethanesulfonic Acid [(*R*)-2-(4-Isobutylphenyl)-propionyl]amide (24). 24 was obtained by treatment of **23** (2.0 g, 4.52 mmol) with hydrazine according a known procedure.[49] Pure **24** was isolated as a white powder (1.27 g, 90% yield). Anal. ($C_{15}H_{24}N_2O_3S$) C, H, S, N.

***N*-[(*R*)-2-(4-Isobutylphenyl)propionyl]benzenesulfonamide (25).** Following the same procedure described for **11** and starting from **3** (2.0 g, 9.7 mmol) and benzenesulfonamide (1.52 g, 9.7 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 98:2), **25** was obtained as a white powder (2.85 g, 85% yield). Anal. ($C_{19}H_{23}NO_3S$) C, H, S, N.

***N*-[(*R*)-2-(4-Isobutylphenyl)propionyl]pyrid-3-ylsulfonamide Hydrochloride (26).** Following the same procedure described for **11** and starting from **3** (2.0 g, 9.7 mmol) and pyrid-3-ylsulfonamide (1.53 g, 9.7 mmol), after workup gaseous HCl was bubbled into an ethereal solution of the crude. **26** was isolated by filtration in the form of a hydrochloride as a white powder (1.71 g, 46% yield). Anal. ($C_{18}H_{23}ClN_2O_3S$) C, H, S, N.

4-Chloro-*N*-[(*R*)-2-(4-isobutylphenyl)propionyl]benzenesulfonamide (27). Following the same procedure described for **11** and starting from **3** (2.0 g, 9.7 mmol) and 4-chlorobenzenesulfonamide (1.86 g, 9.7 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 99:1), **27** was obtained as a white powder (2.14 g, 58% yield). Anal. ($C_{19}H_{22}ClNO_3S$) C, H, S, N.

***N*-[(*R*)-2-(4-Isobutylphenyl)propionyl]trifluoromethanesulfonamide (28). 3** (0.56 g, 2.71 mmol) was dissolved in $SOCl_2$ (5 mL), and the resulting solution was left stirring at reflux for 3 h. After cooling at room temperature, the mixture was evaporated under reduced pressure. The crude acyl chloride was diluted with dry CH_2Cl_2 (10 mL), and triethylamine (0.83 mL, 5.96 mmol) was added. A solution of trifluoromethanesulfonamide (0.4 g, 2.71 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise, and the resulting mixture was left under stirring at room temperature for 4 h. The mixture was diluted with CH_2Cl_2 (10 mL), washed with water (2 × 10 mL), and extracted with a saturated solution of $NaHCO_3$ (2 × 10 mL). The basic aqueous phase was acidified with 37% HCl to pH 2 until the complete precipitation of the acid. The pure compound **28** was obtained by filtration as a slightly yellow powder (0.65 g, 70% yield). Anal. ($C_{14}H_{18}F_3NO_3S$) C, H, S, N.

Synthesis of Amides (Scheme 2). (*R*)-*N*-Hydroxy-2-(4-isobutylphenyl)propionamide (29). To a solution of (*R*)-2-(4-isobutylphenyl)propionyl chloride (prepared as described for compound **28**) (24.5 mmol) in CH_2Cl_2 (25 mL), a suspension of hydroxylamine hydrochloride (2.04 g, 29.4 mmol) and triethylamine (8.2 mL, 58.8 mmol) in CH_2Cl_2 (25 mL) was added by dripping. A 6 N HCl (15 mL) solution was added after stirring for 4 h. The two phases were separated, and the organic one was washed with water (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give a crude. When pulped in isopropyl ether (15 mL) overnight at room temperature, pure **29** was isolated by filtration as a white powder (4.5 g, 83% yield). Anal. ($C_{13}H_{19}NO_2$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-methoxypropionamide (30). Following the same procedure described for **29** and starting from **3** (2.47 g, 12 mmol) and methoxylamine hydrochloride (1.2 g, 14.4 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 98:2), **30** was obtained as a yellow oil (2.12 g, 75% yield). Anal. ($C_{14}H_{21}NO_2$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)propionamide (31). Following the same procedure described for **29** and starting from **3** (2.47 g, 12 mmol) and gaseous ammonia, after workup and purification by crystallization from EtOAc, **31** was obtained as a white powder (1.38 g, 56% yield). Anal. ($C_{13}H_{19}NO$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-methylpropionamide (32). Following the same procedure described for **29** and starting from **3** (2.47 g, 12 mmol) and methylamine (2.0 M in THF, 12 mmol), after workup and crystallization from acetone, **32** was obtained as a white powder (1.57 g, 60% yield). Anal. ($C_{14}H_{21}NO$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-ethylpropionamide (33). Following the same procedure described for **29** and starting from **3** (2.47 g, 12 mmol) and ethylamine (2.0 M in THF, 12 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 98:2), compound **33** was obtained as a colorless oil (1.79 g, 64% yield). Anal. ($C_{15}H_{23}NO$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*,*N*-dimethylpropionamide (34). Following the same procedure described for **29** and starting from **3** (2.47 g, 12 mmol) and *N*,*N*-dimethylamine (2.0

M in THF, 12 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 99:1), compound **34** was obtained as a colorless oil (1.34 g, 48% yield). Anal. ($C_{15}H_{23}NO$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-1-piperidin-1-ylpropan-1-one (35). Following the same procedure described for **29** and starting from **3** (1 g, 4.85 mmol) and piperidine (0.48 mL, 4.85 mmol), after workup and purification by flash chromatography (*n*-hexane/EtOAc 8:2), **35** was obtained as a colorless oil (0.88 g, 66% yield). Anal. ($C_{18}H_{27}NO$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)propionic Acid Methyl Ester (36). To a solution of **3** (1.03 g, 5 mmol) in CH_3OH (5 mL), a few drops of concentrated H_2SO_4 were added. The resulting solution was left stirring at room temperature overnight. The solvent was evaporated, and the residue, dissolved in CH_2Cl_2 (15 mL), was washed with a saturated solution of $NaHCO_3$ (2 × 10 mL) and with brine (2 × 10 mL), dried over Na_2SO_4, and evaporated to give pure **36** as a colorless oil (1.1 g, quantitative yield). Anal. ($C_{14}H_{20}O_2$) C, H.

(*R*)-2-(4-Isobutylphenyl)-*N*-phenylpropionamide (37). To a cooled (0−5 °C) solution of **3** (0.502 g, 2.4 mmol) in DMF (10 mL), 1-hydroxybenzotriazole hydrate (HOBT) (0.324 g, 2.4 mmol) and 1,3-dicyclohexylcarbodiimide (DCC) (0.495 g, 2.4 mmol) were added. After 1 h of stirring at the same temperature, aniline (0.22 mL, 2.4 mmol) was added, and the resulting mixture was left stirring overnight at room temperature. DMF was distilled off, and the crude residue was diluted with CH_3CN (15 mL). The precipitated 1,3-dicyclohexylurea (DCU) was filtered off, and this treatment was repeated twice to completely eliminate the residual DCU. The crude was diluted with CH_2Cl_2 (20 mL), washed with 1 N HCl (2 × 10 mL), with a saturated solution of $NaHCO_3$ (2 × 10 mL), and with brine, dried over Na_2SO_4, and evaporated to give a crude that was purified by flash chromatography (CH_2Cl_2/CH_3OH 98:2). The pure **37** was obtained as a colorless oil (0.51 g, 76% yield). Anal. ($C_{19}H_{23}N_2O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(pyrid-2-yl)propionamide (38). Following the same procedure described for **37** and starting from **3** (0.502 g, 2.4 mmol) and 2-aminopyridine (0.23 g, 2.42 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 98:2), **38** was obtained as a colorless oil (0.36 g, 54% yield). Anal. ($C_{18}H_{22}N_2O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(pyrid-4-yl)propionamide (39). Following the same procedure described for **37** and starting from **3** (0.502 g, 2.4 mmol) and 4-aminopyridine (0.23 g, 2.42 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 95:5), **39** was obtained as a colorless oil (0.48 g, 71% yield). Anal. ($C_{18}H_{22}N_2O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(pyrid-3-yl)propionamide (40). Following the same procedure described for **37** and starting from **3** (0.5 g, 2.4 mmol) and 3-aminopyridine (0.23 g, 2.42 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 98:2), **40** was obtained as a waxy solid (0.34 g, 50% yield). Anal. ($C_{18}H_{22}N_2O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(pyrimidin-4-yl)propionamide (41). Following the same procedure described for **37** and starting from **3** (0.88 g, 4.27 mmol) and 4-aminopyrimidine (0.41 g, 4.27 mmol), after workup and purification by pulping in *n*-hexane, **41** was obtained as a white powder (0.72 g, 60% yield). Anal. ($C_{17}H_{21}N_3O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(pyrazin-2-yl)propionamide (42). Following the same procedure described for **37** and starting from **3** (1.012 g, 5.10 mmol) and aminopyrazine (0.485 g, 5.10 mmol), after workup and purification by flash chromatography (CH_2Cl_2 to CH_2Cl_2/CH_3OH 95:5), **42** was obtained as a pale-yellow oil (0.75 g, 52% yield). Anal. ($C_{17}H_{21}N_3O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(thiazol-2-yl)propionamide (43). Following the same procedure described for **29** and starting from **3** (0.5 g, 2.42 mmol) and 2-aminothiazole (0.243 g, 2.42 mmol), after workup and purification by pulping in *n*-hexane, **43** was obtained as a white powder (0.48 g, 69% yield). Anal. ($C_{16}H_{20}N_2OS$) C, H, S, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(isoxazol-2-yl)propionamide (44). Following the same procedure described for **29** and starting from **3** (0.5 g, 2.42 mmol) and 2-aminoisoxazole (0.18 mL, 2.42 mmol), after workup and purification by pulping in *n*-hexane, **44** was obtained as a white powder (0.4 g, 60% yield). Anal. ($C_{16}H_{20}N_2O_2$) C, H, N.

(*S*)-2-[(*R*)-2-(4-Isobutylphenyl)propionylamino]propionic Acid (45). 51 (2 g, 6.87 mmol) was dissolved in 1,4-dioxane (9 mL), and 1 N NaOH (9 mL) was added. The resulting mixture was left stirring at room temperature overnight. Water and concentrated H_2SO_4 were added until pH 2 was attained, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The collected organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give a solid residue that, after pulping in Et_2O, afforded **45** as a white powder (1.81 g, 95% yield). Anal. ($C_{16}H_{23}NO_3$) C, H, N.

(*R*)-2-[(*R*)-2-(4-Isobutylphenyl)propionylamino]propionic Acid (46). Following the same procedure described for **45** and starting from **109** (2 g, 6.86 mmol), after workup and purification by pulping in Et_2O, pure **46** was obtained as a colorless oil (1.83 g, 96% yield). Anal. ($C_{16}H_{23}NO_3$) C, H, N.

[(*R*)-2-(4-Isobutylphenyl)propionylamino]acetic Acid (47). Following the same procedure described for **45** and starting from **50** (1 g, 3.60 mmol), after workup and purification by pulping in *n*-hexane, **47** was obtained as a pale-yellow powder (0.85 g, 90% yield). Anal. ($C_{15}H_{21}NO_3$) C, H, N.

(*S*)-3-Hydroxy-2-[(*R*)-2-(4-isobutylphenyl)propionylamino]propionic Acid (48). To a cooled (−10 °C) solution of **110** (0.29 g, 0.94 mmol) in CH_2Cl_2 (15 mL), BBr_3 (1 M in CH_2Cl_2) (4.6 mL) was added by dripping. The resulting solution was left at −10 °C for 1 h and at room temperature for 2.5 h. The reaction was quenched adding, by dripping, water (23 mL). The two phases were separated and the organic one was extracted with a saturated solution of $NaHCO_3$ (2 × 10 mL). The collected aqueous extracts were acidified with 37% HCl to pH 2 and extracted back with CH_2Cl_2 (2 × 10 mL). The collected organic extracts were dried over Na_2SO_4 and evaporated to give pure **48** as a pale-yellow oil (0.20 g, 74% yield). Anal. ($C_{16}H_{23}NO_4$) C, H, N.

(*R*)-2-[(*R*)-2-(4-Isobutylphenyl)propionylamino]-3-mercaptopropionic Acid (49). Following the same procedure described for **48** and starting from **111** (1 g, 3.09 mmol), after workup and purification, pure **49** was obtained as a slightly white powder (0.82 g, 86% yield). Anal. ($C_{16}H_{23}NO_3S$) C, H, S, N.

[(*R*)-2-(4-Isobutylphenyl)propionylamino]acetic Acid Methyl Ester (50). 50 was prepared as described for **37** starting from **3** (5 g, 24.27 mmol) and from a mixture of glycine methyl ester hydrochloride (3.05 g, 24.27 mmol) and triethylamine (3.38 mL, 24.27 mmol) in DMF (15 mL). After workup and purification, **50** was obtained as a colorless oil (5.38 g, 80% yield). Anal. ($C_{16}H_{23}NO_3$) C, H, N.

(*S*)-2-[(*R*)-2-(4-Isobutylphenyl)propionylamino]propionic Acid Methyl Ester (51). 51 was prepared as described for **37** starting from **3** (5 g, 24.27 mmol) and from a mixture of L-alanine methyl ester hydrochloride (3.39 g, 24.27 mmol) and triethylamine (3.38 mL, 24.27 mmol) in DMF (25 mL). After workup and purification by pulping in *n*-hexane, **51** was obtained as a white powder (4.90 g, 69% yield). Anal. ($C_{17}H_{25}NO_3$) C, H, N.

3-[(*R*)-2-(4-Isobutylphenyl)propionylamino]propionic Acid (52). 52 was prepared by direct coupling of **3** (1 g, 4.85 mmol) with β-alanine (0.45 g, 4.85 mmol) as described for the preparation of **37**. After workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 98:2), **52** was obtained as a white powder (0.40 g, 30% yield). Anal. ($C_{16}H_{23}NO_3$) C, H, N.

3-[(*R*)-2-(4-Isobutylphenyl)propionylamino]butyric Acid (53). 53 was prepared by direct coupling of **3** (1 g, 4.85 mmol) with 4-aminobutyric acid (0.50 g, 4.85 mmol) as described for the preparation of **37**. After workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 99:1), **53** was obtained as a white powder (0.39 g, 28% yield). Anal. ($C_{17}H_{25}NO_3$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(2-hydroxyethyl)propionamide (54). Following the same procedure described for **29** and starting from **3** (2 g, 9.6 mmol) and ethanolamine (0.58 mL, 9.6 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 98:2), **54** was obtained as a colorless oil (2.16 g, 90% yield). Anal. ($C_{15}H_{23}NO_2$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(2-methoxyethyl)propionamide (55). Following the same procedure described for **29** and starting from **3** (2 g, 9.6 mmol) and 2-methoxyethylamine (0.83 mL, 9.6 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 99:1), **55** was obtained as a colorless oil (2.07 g, 82% yield). Anal. ($C_{16}H_{25}NO_2$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-[2-(2-hydroxyethoxy)ethyl]-propionamide (56). Compound **56** was prepared by direct coupling of **3** (1 g, 4.85 mmol) with 2-(2-aminoethoxy)ethanol (0.48 mL, 4.85 mmol) as described for the preparation of **37**. After workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 95:5), **56** was obtained as a colorless oil (0.91 g, 64% yield). Anal. ($C_{17}H_{27}NO_3$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-[2-(5-hydroxypentyl)]propionamide (57). 57 was prepared by direct coupling of **3** (1 g, 4.85 mmol) with 5-amino-1-pentanol (0.50 g, 4.85 mmol) as described for the preparation of **37**. After workup and purification by flash chromatography (*n*-hexane/EtOAc 9:1), **57** was obtained as a colorless oil (0.78 g, 55% yield). Anal. ($C_{18}H_{29}NO_2$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-((*R*)-2-hydroxy-1-methylethyl)propionamide (58). Following the same procedure described for **29** and starting from **3** (0.5 g, 2.42 mmol) and (*R*)-1-amino-2-propanol (0.19 mL, 2.42 mmol), after workup and purification by trituration from *n*-hexane, **58** was obtained as a white powder (0.25 g, 40% yield). Anal. ($C_{16}H_{25}NO_2$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-((*S*)-2-hydroxy-1-methylethyl)propionamide (59). Following the same procedure described for **29** and starting from **3** (0.5 g, 2.42 mmol) and (*S*)-1-amino-2-propanol (0.19 mL, 2.42 mmol), after workup and purification by pulping in *n*-hexane, **59** was obtained as a white powder (0.46 g, 72% yield). Anal. ($C_{16}H_{25}NO_2$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-((*S*)-2-methoxy-1-methylethyl)propionamide (60). To a cooled (0−5 °C) solution of **58** (0.4 g, 1.5 mmol) in Et_2O (15 mL), silica gel (0.2 g) was added. A solution of diazomethane was carefully added by dripping until a persistent yellow solution was obtained. The reaction mixture was left stirring until complete disappearance of starting material (TLC). The reaction was quenched by adding excess glacial AcOH. All the solvents were evaporated under reduced pressure, and the residue was diluted with CH_2Cl_2. The organic phase was filtered to eliminate silica gel, washed with water, dried over Na_2SO_4, and evaporated under reduced pressure to give a solid residue that, after purification by flash chromatography (*n*-hexane/EtOAc 1:1), afforded pure **60** as a waxy solid (0.33 g, 80% yield). Anal. ($C_{17}H_{27}NO_2$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-((*R*)-2-methoxy-1-methylethyl)propionamide (61). Following the same procedure described for **60** and starting from **59** (0.4 g, 1.5 mmol), after workup and purification by flash chromatography (*n*-hexane/EtOAc 1:1), **61** was obtained as a waxy solid (0.31 g, 75% yield). Anal. ($C_{17}H_{27}NO_2$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(3-dimethylaminopropyl)-propionamide Hydrochloride (62). Following the same procedure described for **29** and starting from **3** (2 g, 9.6 mmol) and 3-(dimethylamino)propylamine (1.22 mL, 9.6 mmol), after workup gaseous HCl was bubbled into an ethereal solution of the crude. **62** was isolated by filtration in the form of a hydrochloride as a white powder (2.45 g, 78% yield). Anal. ($C_{18}H_{31}ClN_2O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(3-dimethylaminoethyl)-propionamide (63). Following the same procedure described for **29** and starting from **3** (2 g, 9.6 mmol) and 2-(dimethylamino)ethylamine (1.12 mL, 9.6 mmol), after workup **63** was obtained as a pale-yellow oil (1.15 g, 44% yield). Anal. ($C_{17}H_{28}N_2O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(3-dimethylaminobutyl)-propionamide Hydrochloride (64). 4-(Dimethylamino)-butylamine was prepared starting from commercial *N*-(4-bromobutyl)phthalimide and dimethylamine hydrochloride according to the classical procedure for the Gabriel synthesis of amines.[39] Following the same procedure described for **29** and starting from **3** (0.62 g, 3 mmol) and 4-(dimethylamino)-butylamine (0.35 g, 3 mmol), after workup gaseous HCl was bubbled into an ethereal solution of the crude. **64** was isolated by filtration in the form of a hydrochloride as a pale-pink powder (0.43 g, 42% yield). Anal. ($C_{19}H_{33}ClN_2O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(3-aminopropyl)propionamide Hydrochloride (65). To a solution of **112** (1.4 g, 3.9 mmol) in CH_2Cl_2 (30 mL), 3 M HCl (4 mL) was added. The resulting solution was left stirring for 24 h at room temperature. The organic layer was washed with water (2 × 10 mL) and brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a residue that, after pulping in Et_2O, afforded pure **65** in the form of a hydrochloride as a white powder (0.775 g, 66% yield). Anal. ($C_{16}H_{26}N_2O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(3-methylaminopropyl)propionamide Hydrochloride (66). Starting from **114** and following the procedure described above for **65**, **66** was obtained, after pulping in Et_2O, in the form of a hydrochloride as a white powder (0.775 g, 66% yield). Anal. ($C_{17}H_{28}N_2O$) C, H, N.

{3-[(*R*)-2-(4-Isobutylphenyl)propionylamino]propyl}-trimethylammonium Iodide (67). To a solution of **62** free base (0.23 g, 0.67 mmol) in THF (10 mL), iodomethane (0.15 mL, 2.42 mmol) was added, and the resulting solution was left stirring at room temperature overnight. The solvent was evaporated, and the residue was suspended in isopropyl alcohol (5 mL) and left stirring for 4 h. Pure **67** was isolated by filtration as a white powder (0.203 g, 70% yield). Anal. ($C_{19}H_{33}IN_2O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-[(1-methyl)piperidin-4-yl]-propionamide Hydrochloride (68). Following the same procedure described for **29** and starting from **3** (1.03 g, 5 mmol) and 4-(aminomethyl)piperidine (0.57 g, 5 mmol), after workup gaseous HCl was bubbled into an ethereal solution of the crude. **68** was isolated after solvent removal in the form of a hydrochloride as a glassy solid (1.14 g, 67% yield). Anal. ($C_{19}H_{31}ClN_2O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(tetrahydropyran-4-yl)propionamide (69). Tetrahydropyran-4-ylamine was prepared starting from commercial 4-chlorotetrahydropyran by treatment with phthalimide[50] and, in the next step, with hydrazine[51] (80% yield). ^1H NMR ($CDCl_3$) δ 3.95 (m, 2H), 3.40 (m, 2H), 3.11 (m, 1H), 1.90 (m, 2H), 1.55 (m, 2H), 1.40 (bs, 2H, NH_2). Following the same procedure described for **29** and starting from **3** (1.03 g, 5 mmol) and tetrahydropyran-4-ylamine (0.505 g, 5 mmol), after workup and purification by pulping in *n*-hexane, **69** was obtained as a glassy solid (0.79 g, 55% yield). Anal. ($C_{18}H_{27}NO_2$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(1-methylpirrolidin-3-yl)-propionamide (70). 1-Methylpyrrolidin-3-ylamine was prepared starting from commercial 1-methyl-3-pyrrolidinol transformed into the corresponding bromide according a described procedure[52] and then treated with phthalimide[50] and, in the next step, with hydrazine[51] to afford the pure amine as a colorless oil (75% yield). ^1H NMR ($CDCl_3$) δ 3.11 (m, 1H), 2.55 (m, 4H), 2.35 (s, 3H), 1.90 (m, 2H), 1.45 (bs, 2H, NH_2). Following the same procedure described for **29** and starting from **3** (1.03 g, 5 mmol) and 1-methylpyrrolidin-3-ylamine (0.50 g, 5 mmol), after workup and purification by pulping in isopropyl ether, **70** was obtained as a waxy solid (0.72 g, 50% yield). Anal. ($C_{18}H_{28}N_2O$) C, H, N.

(*R*)-2-(4-Isobutylphenyl)-*N*-(tetrahydrofuran-3-yl)propionamide (71). Tetrahydrofuran-3-ylamine was prepared starting from commercial 3-hydroxytetrahydrofuran. After its transformation into the bromide derivative according a described procedure,[52] the following treatments with phthal-

imide[50] and, in the next step, with hydrazine[51] afforded the pure amine as a colorless oil (70% yield). ^{1}H NMR ($CDCl_3$) δ 3.85 (m, 2H), 3.40 (m, 2H), 3.12 (m, 1H), 2.10 (m, 1H), 1.85 (m, 1H), 1.45 (bs, 2H, NH_2). Following the same procedure described for **29** and starting from **3** (1.03 g, 5 mmol) and tetrahydrofuran-3-ylamine (0.43 g, 5 mmol), after workup and purification by pulping in *n*-hexane, **71** was obtained as a waxy solid (0.8 g, 58% yield). Anal. ($C_{17}H_{25}NO_2$) C, H, N.

(*R*)-3-(4-Isobutylphenyl)butan-2-one (72). 72 was prepared according to a described procedure[53] starting from **3** (4.8 g, 23.2 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (3.34 g, 23.2 mmol). **72** was isolated as a yellow oil (3.5 g, 74%). Anal. ($C_{14}H_{20}O$) C, H.

(*S*)-2-(4-Isobutylphenyl)propionamide (73). Following the same procedure described for **29** and starting from **4** (2.47 g, 12 mmol) and gaseous ammonia, after workup and purification by crystallization from EtOAc, **73** was obtained as a white powder (1.23 g, 50% yield). Anal. ($C_{13}H_{19}NO$) C, H, N.

Synthesis of 2-Arylpropionic Acids (Schemes 3−6). 2-(4-Isopropylphenyl)propanoic Acid (77). 115 (5 g, 28.41 mmol) was transformed into the methyl 2-(4-isopropylphenyl)-propanoate with I_2 and $AgNO_3$ following a described procedure[31] and obtained pure enough for the following step of hydrolysis. The methyl ester was dissolved in MeOH (20 mL) and treated with 32% NaOH (1 equiv) at reflux. After 4 h, the solvent was evaporated and the residue was diluted with CH_2Cl_2 and extracted with 1 N NaOH. A 37% HCl solution was added to the basic aqueous phase until the complete precipitation of **77** as a pale-yellow powder (2.18 g, 40% yield). Anal. ($C_{12}H_{16}O_2$) C, H.

2-(4-*tert*-Butylphenyl)propanoic Acid (78). Following the same procedure described for **77**, **116** (5 g, 26.28 mmol) was transformed into **78** and isolated pure as a white powder (2.06 g, 38% yield). Anal. ($C_{13}H_{18}O_2$) C, H.

2-{4[(1*E*/*Z*)-Prop-1-enyl]phenyl}propanoic Acid (79). To a solution of **117** (0.26 g, 1.12 mmol) in anhydrous 1-methyl-2-pyrrolidinone (3 mL) under nitrogen and vigorous stirring, LiCl (0.142 g, 3.366 mmol), CuI (10 mg, 0.056 mmol), $AsPh_3$ (27 mg, 0.09 mmol), and Pd_2dba_3 (21 mg, 0.02 mmol) were added. After the mixture was stirred for 10 min, 1-propenyltributyltin (prepared as previously described[54]) (0.45 g, 1.35 mmol) was added and the reaction mixture was left stirring for 5 h at 90 °C. After the mixture was cooled at room temperature, a saturated solution of KF (10 mL) was added. After stirring for 15 min′, water was added (5 mL). The aqueous solution was extracted with Et_2O (3 × 10 mL), and the collected organic extracts were washed with water (2 × 10 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give a crude residue that, after purification by flash chromatography (*n*-hexane/EtOAc 9:1), afforded methyl 2-[(4-prop-1-enyl)phenyl]propanoate as a yellow oil (0.17 g, 75% yield). The methyl ester was dissolved in MeOH (2 mL), a 20% alcoholic solution of KOH (1 mL) was added, and the resulting mixture was left stirring overnight at room temperature. After solvent evaporation the residue was diluted with water (5 mL) and washed with Et_2O (2 × 5 mL). The aqueous phase was acidified with 1 N HCl (2 × 5 mL) to pH 1 and extracted with EtOAc (2 × 10 mL). The organic collected extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give a crude residue that, after purification by flash chromatography (*n*-hexane/EtOAc 1:1), afforded pure **79** as a pale-yellow oil (0.14 g, 90% yield) as a 3:1 mixture of *E*/*Z* isomers. Anal. ($C_{12}H_{14}O_2$) C, H.

2-[4-(Cyclohexylmethyl)phenyl]propanoic Acid (80). To a solution of **117** (5 g, 27.1 mmol) in dry THF (20 mL) under nitrogen atmosphere, LiCl (3.45 g, 81.4 mmol) and $Pd(PPh_3)_4$ (1.25 g, 1.084 mmol) were added. After the mixture was stirred for 10 min′ at room temperature, (cyclohexylmethyl)zinc bromide (0.5 M in THF) (9.85 g, 40.65 mmol) was added, and the resulting mixture was refluxed overnight. After the mixture was cooled at room temperature, the solvent was evaporated and the residue was diluted with EtOAc (20 mL), washed with water (2 × 20 mL), dried over Na_2SO_4, and evaporated to give an oily crude that was purified by flash chromatography (*n*-hexane/EtOAc 9:1) to give methyl 2-[4-(cyclohexylmethyl)phenyl]propanoate (6 g, 85% yield) as a colorless oil. The methyl ester hydrolysis was performed as described for **79**. Pure **80** was isolated as a slightly white powder (5.1 g, 90% yield). Anal. ($C_{16}H_{22}O_2$) C, H.

2-(4-Benzylphenyl)propanoic Acid (81). Following the same procedure described for the **80** and starting from **117** (5 g, 27.1 mmol) and commercial benzylzinc bromide (0.5 M in THF) (9.61 g, 40.65 mmol), after workup and following hydrolysis of the methyl ester intermediate, **81** was isolated as a white powder (5.21 g, 80% yield). Anal. ($C_{16}H_{16}O_2$) C, H.

2-(4-Isopropoxyphenyl)propanoic Acid (82). To a solution of 2-(4-hydroxy)phenylpropionic acid (**84**) (50 g, 0.29 mol) in CH_3OH (250 mL), concentrated H_2SO_4 (0.4 mL) was added. The resulting solution was left stirring overnight at room temperature. After solvent evaporation the oily residue was diluted with CH_2Cl_2 and washed with a saturated solution of $NaHCO_3$ (2 × 100 mL) and water (3 × 150 mL), dried over Na_2SO_4, and evaporated to give methyl 2-(4-hydroxy)phenyl-propanoate (51.6 g, 0.28 mol). To a solution of the methyl ester (2.0 g, 10.85 mmol) in acetone (10 mL), K_2CO_3 (1.5 g, 10.85 mmol) was added. The mixture was left stirring for 1 h at room temperature. Then 2-iodopropane (1.08 mL, 10.85 mmol) was added by dripping, and the resulting mixture was left under stirring overnight at room temperature. The solid was filtered off, and acetone was evaporated under reduced pressure to give a crude that was dissolved in CH_2Cl_2 (15 mL). The organic layer was washed with 0.5 N NaOH (2 × 10 mL) and water (2 × 10 mL), dried over Na_2SO_4, and evaporated to give the intermediate methyl 2-(4-isopropoxyphenyl)propanoate as a colorless oil (1.97 g, 8.73 mmol). The methyl ester was dissolved in MeOH (10 mL), a 20% alcoholic solution of KOH (5 mL) was added, and the resulting mixture was left stirring for 4 h at room temperature. After solvent evaporation under reduced pressure, the residue was diluted with CH_2Cl_2 (10 mL). The organic layer was extracted with 1 N NaOH (2 × 5 mL), and 37% HCl was added to the collected aqueous extracts until precipitation occurred. **82** was isolated by filtration as a white powder (1.67 g, 92% yield). Anal. ($C_{12}H_{16}O_3$) C, H.

2-(4-Methoxyphenyl)propanoic Acid (83). Following the same procedure described for the **82** and starting from methyl 2-(4-hydroxy)phenylpropanoate (2.0 g, 10.85 mmol) and iodomethane (0.67 mL, 10.85 mmol), after workup and following hydrolysis of the methyl ester intermediate, **83** was isolated as a white powder (1.86 g, 95% yield). Anal. ($C_{10}H_{12}O_3$) C, H.

2-(1,1′-Biphenyl-4-yl)propanoic Acid (85). Following the same procedure described for **80** and starting from **117** (5 g, 27.1 mmol) and commercial phenylzinc bromide (0.5 M in THF) (9.04 g, 40.65 mmol), after workup and following hydrolysis of the methyl ester intermediate, **85** was isolated as a white powder (3.37 g, 55% yield). Anal. ($C_{15}H_{14}O_2$) C, H.

2-(4-Thien-2-ylphenyl)propanoic Acid (86). Following the same procedure described for **80** and starting from **117** (5 g, 27.1 mmol) and 2-thienylzinc bromide (0.5 M in THF) (9.28 g, 40.65 mmol), after workup and following hydrolysis of the methyl ester intermediate, **86** was isolated as a waxy solid (5.35 g, 85% yield). Anal. ($C_{13}H_{12}O_2S$) C, H, S.

2-(3-Ethylphenyl)propanoic Acid (88). Following the same procedure described for **79** and starting from **119** (0.35 g, 1.12 mmol) and tetraethyltin (0.27 mL, 1.35 mmol), after workup and following hydrolysis of the methyl ester intermediate, **88** was isolated as a colorless oil (0.11 g, 85% yield). Anal. ($C_{11}H_{14}O_2$) C, H.

2-(3-Butylphenyl)propanoic Acid (89). Following the same procedure described for **79** and starting from **119** (0.35 g, 1.12 mmol) and commercial tetrabutyltin (0.44 mL, 1.35 mmol), after workup and following hydrolysis of the methyl ester intermediate, **89** was isolated as a pale-yellow oil (0.15 g, 64% yield from **119**). Anal. ($C_{13}H_{18}O_2$) C, H.

2-(3-Isopropylphenyl)propanoic Acid (90). To palladium on charcoal (10% Pd, 25 mg) a solution of **120** (0.2 g, 1 mmol) in EtOH (5 mL) was added, and the mixture was stirred under hydrogen until complete disappearance (4 h) of the starting material (TLC). After filtration on a Celite pad, concentration

of the mother liquors gave pure methyl 2-(3-isopropylphenyl)-propanoate (0.19 g, 95% yield). Hydrolysis of the methyl ester was performed as described for **79**. Pure **90** was isolated by flash chromatography (*n*-hexane/EtOAc 1:1) as a colorless oil (0.16 g, 90% yield from **120**). Anal. ($C_{12}H_{16}O_2$) C, H.

2-(3-Isobutylphenyl)propanoic Acid (91). To a solution of **119** (0.35 g, 1.12 mmol) in dry THF (5 mL) under nitrogen atmosphere, $Pd(PPh_3)_4$ (52 mg, 0.045 mmol) was added. After the mixture was stirred for 10 min at room temperature, triisobutylaluminum (1.0 M in hexanes) (1.68 mL, 1.68 mmol) was added. The resulting mixture was refluxed for 24 h. After the mixture was cooled at room temperature, the solvent was evaporated and the residue was diluted with EtOAc (10 mL), washed with water (2 × 10 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give an oily crude that was purified by flash chromatography (*n*-hexane/EtOAc 95:5) to give methyl 2-(3-isobutylphenyl)propanoate (0.185 g, 75% yield) as a colorless oil. The following hydrolysis of the methyl ester was performed as described for **79**. Pure **91** was isolated by flash chromatography (*n*-hexane/EtOAc 1:1) as a colorless oil (0.16 g, 95% yield from **119**). Anal. ($C_{13}H_{18}O_2$) C, H.

2-(3-*sec*-Butylphenyl)propanoic Acid (92). Following the same procedure described for **90** and starting from **121** (0.2 g, 0.92 mmol), after workup and following hydrolysis of the methyl ester intermediate, **92** was isolated as a colorless oil (0.16 g, 85% yield from **121**). Anal. ($C_{13}H_{18}O_2$) C, H.

2-[3-(1-Ethylpropyl)phenyl]propanoic Acid (93). Following the same procedure described for the **90** and starting from **122** (0.13 g, 0.56 mmol), after workup and following hydrolysis of the methyl ester intermediate, **93** was isolated as a colorless oil (86 mg, 70% yield from **122**). Anal. ($C_{14}H_{20}O_2$) C, H.

2-{3-[(1*E/Z*)-Prop-1-enyl]phenyl}propanoic Acid (94). Intermediate **123** (0.15 g, 0.73 mmol) was treated with KOH as described for **79**, and after workup, **94** was isolated as a pale-yellow oil (0.13 g, 70% yield from **123**) as a 3:1 mixture of *E*/*Z* isomers. Anal. ($C_{12}H_{14}O_2$) C, H.

2-(3-Benzylphenyl)propanoic Acid (95). Following the same procedure described for **80** and starting from **119** (2.5 g, 13.55 mmol) and commercial benzylzinc bromide (0.5 M in THF) (4.8 g, 20.32 mmol), after workup and following hydrolysis of the methyl ester intermediate, compound **95** was isolated as a colorless oil (2.41 g, 74% yield from **119**). Anal. ($C_{16}H_{16}O_2$) C, H.

2-[3-(1-Phenylethyl)phenyl]propanoic Acid (96). Following the same procedure described for **90** and starting from **124** (0.15 g, 0.56 mmol), after workup and following hydrolysis of the methyl ester intermediate, compound **96** was isolated as a colorless oil (0.12 g, 84% yield from **124**). Anal. ($C_{17}H_{18}O_2$) C, H.

2-[3-(1-Hydroxypropyl)phenyl]propanoic Acid (97). To a cooled (0 °C) solution of **123** (0.1 g, 0.49 mmol) in dry THF (5 mL) under nitrogen, a borane/methyl sulfide complex (5.0 M in Et_2O) (0.11 mL) was added, and the solution was left stirring for 3 h at 0 °C. Water (0.5 mL) was added by dripping, and after the mixture was stirred for 20 min′, 38% H_2O_2 (0.53 mL) and 1 N NaOH (1.78 mL) were added. After the mixture was stirred for 30 min at room temperature, the solution was diluted with water (2 mL) and 1 N HCl was added to obtain pH 1. The aqueous phase was extracted with EtOAc (2 × 5 mL), and the collected organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give an oily crude that was purified by flash chromatography (*n*-hexane/EtOAc 8:2) to give methyl 2-[3-(1-hydroxypropyl)phenyl]propanoate (0.087 g, 80% yield) as a colorless oil. The following methyl ester hydrolysis was performed as described for **79**. Pure **97** was isolated by flash chromatography (*n*-hexane/EtOAc 1:1) as a colorless oil (0.077 g, 95% yield from **123**). Anal. ($C_{12}H_{16}O_3$) C, H.

2-[3-(1-Hydroxyethyl)phenyl]propanoic Acid (98). To a solution of **126** (0.4 g, 2.3 mmol) in 1.4-dioxane (3 mL), 37% HCl (2.1 mL) was added, and the resulting solution was refluxed for 5 h. After the mixture was cooled at room temperature, the crude was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The collected organic extracts were washed with water (2 × 5 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give **98** as a pale-yellow oil (0.41 g, 94% yield). Anal. ($C_{11}H_{14}O_3$) C, H.

2-(3-Acetylphenyl)propanoic Acid (99). Following the same procedure described for **98** and starting from **125** (1 g, 5.8 mmol), after workup, **99** was isolated as a pale-yellow solid (1.05 g, 94% yield). Anal. ($C_{11}H_{12}O_3$) C, H.

3-(1-Carboxyethyl)benzoic Acid (100). Following the same procedure described for **98** and starting from commercial 2-(3-carboxyphenyl)propanenitrile (2.5 g, 14 mmol), after workup, **100** was isolated as a white powder (2.5 g, 92% yield). Anal. ($C_{10}H_{10}O_4$) C, H.

2-{3-[Hydroxyl(phenyl)methyl]phenyl}propanoic Acid (101). Methyl 2-(3-benzoyl)phenylpropanoate (0.99 g, 3.7 mmol), prepared as described for **82** starting from acid **87**, was hydrogenated following the procedure described for **90**. For our purposes triethylamine (1:1 with Pd w/w) was added. After workup and following basic hydrolysis of the intermediate ester, **101** was isolated by flash chromatography ((*n*-hexane/EtOAc 95:5) as a white powder (0.78 g, 78%). Anal. ($C_{16}H_{16}O_2$) C, H.

(*R*)-2-(3-Isopropylphenyl)propionamide (102). Following the same procedure described for **31** and starting from the (*R*)-enantiomer of **90** (30% yield, $[\alpha]^{25}_D$ −56° (*c* 0.2, absolute EtOH)) (35 mg, 0.18 mmol) and gaseous ammonia, after workup, **102** was obtained as a colorless oil (20 mg, 58% yield). Anal. ($C_{12}H_{17}NO$) C, H, N.

(*R*)-2-[3-(1-Ethylpropyl)phenyl]-*N*-(3-dimethylaminopropyl)propionamide Hydrochloride (103). Following the same procedure described for **62** and starting from the (*R*)-enantiomer of **93** (34% yield, $[\alpha]^{25}_D$ −28° (*c* 0.5, EtOH)) (80 mg, 0.36 mmol) and 3-(dimethylamino)propylamine (46 μL, 0.36 mmol), after workup and purification, **103** was obtained in the form of a hydrochloride as a colorless oil (84 mg, 68% yield). Anal. ($C_{19}H_{33}ClN_2O$) C, H, N.

(*R*)-2-[3-Isopropyl)phenyl]-*N*-(3-dimethylaminopropyl)propionamide (104). Following the same procedure described for **62** and starting from the (*R*)-enantiomer of **90** (80 mg, 0.41 mmol) and 3-(dimethylamino)propylamine (50 μL, 0.41 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 7:3), **104** was obtained as a colorless oil (65 mg, 57% yield). Anal. ($C_{17}H_{28}N_2O$) C, H, N.

***N*-[(*R*)-2-[3-(1-Phenylethyl)phenyl]propionylmethanesulfonamide (105).** Following the same procedure described for **11** and starting from **127** (89 mg, 0.35 mmol) and methanesulfonamide (33 mg, 0.35 mmol), after workup and purification by pulping in diisopropyl ether, **105** was obtained as a white powder (34 mg, 30% yield). Anal. ($C_{18}H_{21}NO_3S$) C, H, S, N.

(*R*)-2-[3-(1-Phenylethyl)phenyl]-*N*−(3-dimethylaminopropyl)propionamide (106). Following the same procedure described for **62** and starting from the **127** (56 mg, 0.22 mmol) and 3-(dimethylamino)propylamine (27 μL, 0.82 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 85:15), **106** was obtained as a colorless oil (46 mg, 62% yield). Anal. ($C_{22}H_{30}N_2O$) C, H, N.

[(*R*)-2-(3-Benzoylphenyl)propionylamino]acetic Acid (107). 107 was prepared according to the procedures described for the synthesis of **45** starting from **1** (0.55 g, 2.16 mmol). **107** was isolated as a glassy solid (0.31 g, 44% yield from **1**). Anal. ($C_{18}H_{17}NO_4$) C, H, N.

(*R*)-2-(3-Benzoylphenyl)-*N*-(3-dimethylaminopropyl)-propionamide (108). Following the same procedure described for **62** and starting from **1** (1 g, 3.93 mmol) and 3-(dimethylamino)propylamine (0.49 mL, 3.93 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 8:2), **108** was obtained as a colorless oil (0.55 g, 41% yield). Anal. ($C_{21}H_{26}N_2O_2$) C, H, N.

Synthesis of Intermediates. Methyl (2*R*)-2-{[(2*R*)-2-(4-Isobutylphenyl)propanoyl]amino]propanoate (109). 109 was prepared as described for **37** starting from **3** (2.5 g, 12.13 mmol) and from a mixture of D-alanine methyl ester hydrochloride (1.69 g, 12.13 mmol) and triethylamine (1.69 mL, 12.13 mmol) in DMF (15 mL). After workup and purification

by pulping in *n*-hexane, **109** was obtained as a white powder (4.97 g, 70% yield), mp 100−102 °C. ^{1}H NMR ($CDCl_3$) δ 7.20 (d, 2H, J = 7 Hz), 7.05 (d, 2H, J = 7 Hz), 5.90 (bs, 1H, CON*H*), 4.60 (m, 1H), 3.75 (s, 3H), 3.58 (q, 1H, J = 7 Hz), 2.48 (d, 2H, J = 7 Hz), 1.90 (m, 1H), 1.55 (d, 3H, J = 7 Hz), 1.30 (d, 3H, J = 7 Hz), 0.95 (d, 6H, J = 7 Hz).

Methyl 3-Hydroxy-2-{[(2*R*)-2-(4-isobutylphenyl)propanoyl]amino}propanoate (110). 110 was prepared as described for **37** starting from **3** (1.5 g, 7.30 mmol) and from a mixture of L-serine methyl ester hydrochloride (1.13 g, 7.30 mmol) and triethylamine (1.02 mL, 7.30 mmol). After workup and purification by pulping in Et_2O, **110** was obtained as a colorless oil (1.63 g, 73% yield). ^{1}H NMR ($CDCl_3$) δ 7.20 (d, 2H, J = 7 Hz), 7.10 (d, 2H, J = 7 Hz), 6.45 (bs, 1H, CON*H*), 4.55 (m, 1H), 4.05 (m, 1H), 3.75 (s, 3H), 3.60 (m, 2H), 2.48 (d, 2H, J = 7 Hz), 2.30 (bs, 1H, O*H*), 1.85 (m, 1H), 1.48 (d, 3H, J = 7 Hz), 0.95 (d, 6H, J = 7 Hz).

Methyl 2-{[(2*R*)-2-(4-Isobutylphenyl)propanoyl]amino}-3-mercaptopropanoate (111). 111 was prepared as described for **37** starting from **3** (1.5 g, 7.30 mmol) and from a mixture of l-cysteine methyl ester hydrochloride (1.36 g, 7.30 mmol) and triethylamine (1.02 mL, 7.30 mmol). After workup and purification by pulping in *n*-hexane, **111** was obtained as a colorless oil (1.36 g, 60% yield). ^{1}H NMR ($CDCl_3$) δ 7.20 (d, 2H, J = 7 Hz), 7.05 (d, 2H, J = 7 Hz), 6.45 (bs, 1H, CON*H*), 4.90 (m, 1H), 4.25 (s, 3H), 3.75 (q, 1H, J = 7 Hz), 3.15 (dd, 2H, J_1 = 10 Hz, J_2 = 6 Hz), 2.60 (d, 2H, J = 7 Hz), 2.05 (bs, 1H, S*H*), 1.90 (m, 1H), 1.65 (d, 3H, J = 7 Hz), 1.05 (d, 6H, J = 7 Hz).

(*R*)-2-(4-Isobutylphenyl)-*N*-(3-*tert*-butoxycarbonylaminopropyl)propionamide (112). *N*-Boc-(3-aminopropyl)-amine was prepared as described[51] starting from 1,3-bromopropane. Pure *N*-Boc-(3-aminopropyl)amine was obtained as a pale-yellow oil (80% yield). ^{1}H NMR ($CDCl_3$) δ 4.90 (bs, 1H, CON*H*), 3.35 (m, 2H), 2.83 (t, 2H, J = 7 Hz), 1.68 (d, 2H, J = 7 Hz), 1.50 (s, 9H). Following the same procedure described for **29** and starting from **3** (3.6 g, 17.5 mmol) and *N*-Boc-(3-aminopropyl)amine (3.7 g, 17.5 mmol), after workup and purification by crystallization from MeOH, **112** was obtained as a white powder (4.8 g, 13.06 mmol). ^{1}H NMR ($CDCl_3$) δ 7.25 (d, 2H, J = 7 Hz), 7.12 (d, 2H, J = 7 Hz), 5.95 (bs, 1H, N*H*CO), 4.95 (bs, 1H, CON*H*), 3.55 (q, 1H, J = 7 Hz), 3.25 (t, 2H, J = 5 Hz), 3.08 (t, 2H, J = 5 Hz), 2.45 (d, 2H, J = 7 Hz), 1.88 (m, 1H), 1.52−1.47 (m, 5H), 1.42 (s, 9H), 0.90 (d, 6H, J = 7 Hz).

(3-Aminopropyl)methylcarbamic Acid *tert*-Butyl Ester (113). Starting from *N*-Boc-(3-aminopropyl)amine, the amino group was protected as described[50] to afford [3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propyl]carbamic acid *tert*-butyl ester. The compound was treated with NaH/CH_3I (1 equiv), and the resulting *N*-methyl derivative was treated with hydrazine[51] to give **113** as a colorless oil (80% yield). ^{1}H NMR ($CDCl_3$) δ 3.52 (t, 2H, J = 5 Hz), 3.25 (s, 3H), 2.72 (m, 2H), 2.25 (bs, 2H, NH_2), 1.70 (m, 2H), 1.50 (s, 9H).

{3-[(*R*)-2-(4-Isobutylphenyl)propionylamino]propyl}-methylcarbamic Acid *tert*-Butyl Ester (114). Following the same procedure described for **29** and starting from **3** (1.8 g, 8.75 mmol) and **113** (1.64 g, 8.75 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 98:2), **114** was obtained as a colorless oil (2.25 g, 6 mmol). ^{1}H NMR ($CDCl_3$) δ 7.50 (bs, 1H, CON*H*), 7.32 (d, 2H, J = 7 Hz), 6.83 (d, 2H, J = 7 Hz), 3.64 (q, 1H, J = 7 Hz), 3.41 (t, 2H, J = 5 Hz), 3.30 (t, 2H, J = 5 Hz), 3.25 (s, 3H), 2.43 (d, 2H, J = 7 Hz), 1.97 (m, 2H), 1.82 (m, 1H), 1.50 (s, 9H), 1.35 (d, 3H, J = 7 Hz), 0.90 (d, 6H, J = 7 Hz).

1-(4-Isopropylphenyl)propan-1-one (115). To a solution of cumene (5.18 mL, 37.25 mmol) in dry CH_2Cl_2 (50 mL), propionyl chloride (3.23 mL, 37.25 mmol) was added dropwise. The mixture was cooled to 0−5 °C, and $AlCl_3$ (4.97 g, 37.25 mmol) was added portionwise. The resulting mixture was refluxed for 3 h. After cooling at room temperature, the mixture was poured into a 1 N HCl/ice mixture and left stirring for 30 min′. The two phases were separated, and the aqueous one was extracted twice with CH_2Cl_2. The collected organic extracts were washed with water, dried over Na_2SO_4, and evaporated under reduced pressure to give **115** as a colorless oil (6.03 g, 33.64 mmol). ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2H, J = 7 Hz), 7.48 (d, 2H, J = 7 Hz), 3.00 (q, 2H, J = 7 Hz), 2.75 (m, 1H), 1.20 (d, 6H, J = 3 Hz), 1.15 (t, 3H, J = 7 Hz).

1-(4-*tert*-Butylphenyl)propan-1-one (116). Following the same procedure described for **115** but starting from *tert*-butylbenzene (5 g, 37.25 mmol), **116** was obtained as a colorless oil (5.90 g, 31 mmol). ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2H, J = 7 Hz), 7.48 (d, 2H, J = 7 Hz), 3.00 (q, 2H, J = 7 Hz), 1.35 (s, 9H), 1.15 (t, 3H, J = 7 Hz).

Methyl 2-{4-[(Trifluoromethanesulfonyloxy)phenyl}-propanoate (117). To a cooled solution (−15 °C) of methyl 2-(4-hydroxy)phenylpropanoate, prepared as described for **82** (48.5 g, 0.26 mol) in dry CH_2Cl_2 (500 mL), *N*,*N*-diisopropylethylamine (53.5 mL, 0.31 mol) was added by dripping for 10 min′. The resulting solution was left stirring for 30 min′ at −15 °C, and then trifluoromethanesulfonic anhydride (47.6 mL, 0.28 mol) was dropped and the mixture was left stirring for 1 h at −15 °C and overnight at room temperature. The mixture was transferred into a separatory funnel and washed with 1 N HCl (2 × 200 mL), 1 N NaOH (2 × 150 mL), and water (3 × 200 mL), dried over Na_2SO_4, and evaporated under vacuum to give **117** as dark, oily residue (80 g) pure enough to be used in the following step. An aliquot was purified by flash chromatography (CH_2Cl_2/CH_3OH 98:2) for analytical characterization. ^{1}H NMR ($CDCl_3$) δ 7.45 (d, 2H, J = 7 Hz), 7.25 (d, 2H, J = 7 Hz), 3.80 (q, 1H, J = 7 Hz), 3.65 (s, 3H), 1.50 (d, 3H, J = 7 Hz).

Methyl 2-{3-[(Trifluoromethanesulfonyloxy)phenyl}-acetate (118). Following the same procedure described for **117** but starting from commercial (3-hydroxyphenyl)acetic acid (50 g, 0.32 mol), **118** was obtained as a dark-red oil (84 g) pure enough to be used in the following step. An aliquot was purified by flash chromatography (CH_2Cl_2/CH_3OH 95:5) for analytical characterization. ^{1}H NMR ($CDCl_3$) δ 7.45−7.30 (m, 2H), 7.25 (s, 1H), 7.18 (m, 1H), 3.70 (s, 3H), 3.45 (s, 2H).

Methyl 2-{3-[(Trifluoromethanesulfonyloxy)phenyl}-propanoate (119). To a cooled (−25 °C) solution of crude **118** (82 g, 0.275 mol) in dry THF (500 mL), 60% NaH (11 g, 0.46 mol) was added portionwise. The resulting mixture was left stirring for 1 h at room temperature and then cooled again at −25 °C, and iodomethane (20.54 mL, 0.33 mol) was added by dripping. The mixture was left to warm to 0 °C in 3 h and was stirred overnight at 0 °C. Glacial AcOH (26.3 mL, 0.46 mol) was added to the mixture, and THF was evaporated. The oily crude was dissolved in CH_2Cl_2 (600 mL), washed with 1 N NaOH (2 × 250 mL) with a saturated solution of NH_4Cl (300 mL) and with a saturated solution of NaCl (300 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give a red crude oil (71.6 g). The oil was purified by flash chromatography (*n*-hexane, *n*-hexane/EtOAc 8:2). **119** was obtained as a yellow oil (42.2 g, 49% yield). ^{1}H NMR ($CDCl_3$) δ 7.45−7.30 (m, 2H), 7.25 (s, 1H), 7.18 (m, 1H), 3.85 (q, 1H, J = 7 Hz), 3.70 (s, 3H), 1.55 (d, 3H, J = 7 Hz).

Methyl 2-(3-Isopropenylphenyl)propanoate (120). 120 was prepared according to the same procedure described for the preparation of **79** starting from **119** (0.35 g, 1.12 mmol) and from isopropenyltributyltin (prepared as described[54]). It was isolated by flash chromatography as a colorless oil (0.2 g, 90% yield). ^{1}H NMR ($CDCl_3$) δ 7.40−7.28 (m, 2H), 7.20 (s, 1H), 7.15 (m, 1H), 5.30 (s, 1H), 5.02 (s, 1H), 3.75 (q, 1H, J = 7 Hz), 3.65 (s, 3H), 1.55 (d, 3H, J = 7 Hz), 1.45 (s, 3H).

Methyl 2-{3-[(1*E*/*Z*)-1-Methylprop-1-enyl]phenyl}propanoate (121). 121 was prepared according to the same procedure described for the preparation of **79** starting from **119** (0.35 g, 1.12 mmol) and from 1-methylprop-1-enyltributyltin (prepared as previously described[54]). It was isolated (as a mixture of *E*/*Z* isomers) by flash chromatography as a colorless oil (0.23 g, 95% yield). ^{1}H NMR ($CDCl_3$) δ 7.40−7.28 (m, 2H), 7.20 (s, 1H), 7.15 (m, 1H), 5.80 (d, 1H, J = 7 Hz, *Z* isomer), 5.36 (q, 1H, J = 7 Hz, *E* isomer), 3.70 (q, 1H, J = 7 Hz), 3.65 (s, 3H), 1.73 (dd, 3H, J = 7 Hz), 1.50 (d, 3H, J = 7 Hz), 1.45 (d, 3H, J = 7 Hz).

Methyl 2-[3-(1*E*/*Z*)-1-Ethylprop-1-enyl)phenyl]propanoate (122). 122 was prepared according to the same procedure described for the preparation of **79** starting from **119** (0.35 g, 1.12 mmol) and from pent-2-enyltributyltin. The organotin reagent was prepared as previously described[55] and obtained pure (as a mixture of *E*/*Z* isomers) by purification from the internal isomer. **122** was isolated by workup as a colorless oil (0.14 g, 55% yield). ^{1}H NMR ($CDCl_3$) δ 7.40−7.28 (m, 2H), 7.20 (s, 1H), 7.15 (m, 1H), 5.84 (q, 1H, J = 7 Hz, *Z* isomer), 5.36 (q, 1H, J = 7 Hz, *E* isomer), 3.70 (q, 1H, J = 7 Hz), 3.65 (s, 3H), 2.02 (m, 2H), 1.84 (d, 3H, J = 7 Hz), 1.50 (d, 3H, J = 7 Hz), 1.05 (t, 3H, J = 5 Hz).

Methyl 2-{3-[(1*E*/*Z*)-Prop-1-enyl]phenyl}propanoate (123). 123 was prepared according to the same procedure described for the preparation of **79** starting from **119** (0.7 g, 2.24 mmol) and from 1-propenyltributyltin (prepared as previously described[54]). **123** was isolated by flash chromatography (as a mixture of *E*/*Z* isomers) as a colorless oil (0.3 g, 66% yield). ^{1}H NMR ($CDCl_3$) δ 7.35−7.15 (m, 4H), 6.45 (q, 1H, J = 7 Hz), 5.85 (q, 1H, J = 7 Hz, *Z* isomer), 5.80 (q, 1H, J = 7 Hz, *E* isomer), 3.75 (q, 1H, J = 7 Hz), 3.68 (s, 3H), 1.80 (m, 3H), 1.55 (d, 3H, J = 7 Hz).

Methyl 2-[3-(1-Phenylethyl)phenyl]propanoate (124). 124 was prepared according to the same procedure described for the preparation of **79** starting from **119** (0.35 g, 1.12 mmol) and from α-styryltributyltin (prepared as previously described[54]). **124** was isolated by flash chromatography as a colorless oil (0.15 g, 51% yield). ^{1}H NMR ($CDCl_3$) δ 7.32−7.15 (m, 9H), 4.20 (q, 1H, J = 7 Hz), 3.74 (q, 1H, J = 7 Hz), 3.65 (s, 3H), 1.72 (d, 3H, J = 7 Hz), 1.55 (d, 3H, J = 7 Hz).

2-(3-Acetylphenyl)propanenitrile (125). The synthesis of **125** was performed according to a previously described procedure.[53] After purification by flash chromatography (*n*-hexane/EtOAc 8:2), **125** was obtained pure as a yellow oil (1.19 g, 60% yield). ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.65 (m, 1H), 7.50 (m, 1H), 4.05 (q, 1H, J = 7 Hz), 2.70 (s, 3H), 1.75 (d, 3H, J = 7 Hz).

2-[3-(1-Hydroxyethyl)phenyl]propanenitrile (126). To a solution of **125** (0.38 g, 2.19 mmol) in THF (4 mL) and water (1 mL), $NaBH_4$ (95 mg, 2.51 mmol) was added. The mixture was left stirring for 4 h at room temperature. AcOH (0.4 mL) and a saturated solution of NaCl (5 mL) were added to the mixture. The aqueous layer was extracted with Et_2O (2 × 10 mL). The collected organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give **126** as a colorless oil (0.29 g, 78% yield). ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 4H), 4.95 (q, 1H, J = 7 Hz), 4.10 (q, 1H, J = 7 Hz), 1.75 (d, 3H, J = 7 Hz), 1.55 (d, 3H, J = 7 Hz).

(2*R*)-2-[3-(1-Phenylethyl)phenyl]propanoic Acid (127). To a cooled (0−5 °C) solution of methyltriphenylphosphonium bromide (2.04 g, 5.59 mmol) in dry THF (5 mL), butyllithium (1.6 M in hexanes) (3.49 mL, 5.59 mmol) was added by dripping. The solution was left stirring at 0−5 °C for 3 h. Then the solution was dropped into a solution of methyl (2*R*)-2-(3-benzoylphenyl)propanoate (1.5 g, 5.59 mmol), prepared from **1** according to the procedure described for **82** in dry THF (5 mL). After the mixture was stirred overnight at room temperature, the solution was diluted with CH_2Cl_2 (10 mL). The organic layer was washed with 10% K_2HPO_4 buffer (3 × 15 mL) and water (2 × 20 mL), dried over Na_2SO_4, and evaporated to give an oily crude that was purified by flash chromatography (*n*-hexane/EtOAc 95:5) to give methyl (2*R*)-2-[3-(1-phenylvinyl)phenyl]propanoate (1.06 g, 71% yield) as a colorless oil. An aliquot of the methyl ester (0.35 g, 1.33 mmol) was hydrogenated for 18 h as described for **90**. Pure methyl (2*R*)-2-[3-(1-phenylethyl)phenyl]propanoate was isolated as a colorless oil (0.36, 98% yield). The following ester hydrolysis was performed as described for **79**, but to avoid any racemization, the solvent used was 1,4-dioxane. Pure **127** was obtained as a colorless oil (0.29 g, 87% yield). $[\alpha]^{25}_D$ −15° (*c* 1, MeOH); ^{1}H NMR (CDCl3) δ 7.32−7.15 (m, 9H), 4.10 (q, 1H, J = 7 Hz), 3.65 (q, 1H, J = 7 Hz), 1.55 (d, 3H, J = 7 Hz), 1.40 (d, 3H, J = 7 Hz).

Supporting Information Available: Spectroscopic data and results from elemental analysis of all the listed compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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