Articles

Design of Noncompetitive Interleukin-8 Inhibitors Acting on CXCR1 and CXCR2

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Chemokines CXCL8 and CXCL1 play a key role in the recruitment of neutrophils at the site of inflammation. CXCL8 binds two membrane receptors, CXCR1 and CXCR2, whereas CXCL1 is a selective agonist for CXCR2. In the past decade, the physiopathological role of CXCL8 and CXCL1 has been investigated. A novel class of small molecular weight allosteric CXCR1 inhibitors was identified, and reparixin, the first drug candidate, is currently under clinical investigation in the prevention of ischemia/reperfusion injury in organ transplantation. Reparixin binding mode to CXCR1 has been studied and used for a computer-assisted design program of dual allosteric CXCR1 and CXCR2 inhibitors. In this paper, the results of modeling-driven SAR studies for the identification of potent dual inhibitors are discussed, and three new compounds (**56**, **67**, and **79**) sharing a common triflate moiety have been selected as potential leads with optimized pharmacokinetic characteristics.

Introduction

The chemokine family is a group of low molecular weight, multifunctional cytokines that play a primary role in the inflammatory response, finely regulating the leukocytes recruitment in the inflamed tissue.[1,2] These molecules exert additional functions in physiological and pathological conditions including wound healing and tumorigenesis.[3,4]

Disregulation of the chemokines network has been evoked as a crucial event in the insurgence and progression of severe chronic diseases including rheumatoid arthritis (RA[a]), chronic obstructive pulmonary disease (COPD), asthma, Alzheimer's disease, melanoma, ulcerative colitis (UC), multiple sclerosis, and psoriasis.[5−13] Hence, interference with chemokine function is generally considered a promising approach for the development of novel anti-inflammatory medications.

Among chemotactic factors, interleukin-8 (CXCL8) and related chemokines, including GRO-α (CXCL1), belong to the CXC chemokines family and play a major role in the activation and recruitment of neutrophils.[3] Two membrane receptors, the type A CXCL8 receptor (CXCR1) and type B CXCL8 receptor (CXCR2), have been shown to bind CXCL8 with high affinity.[14] CXCR1 and CXCR2 belong to the class A (rhodopsin-like) of the 7-transmembrane G-protein coupled receptors (7-TM-GPCRs) and share 78% amino acid identity.[15] CXCR1 is selective for CXCL8, whereas CXCR2 also interacts with the CXCR2-selective agonist CXCL1. CXCR1 and CXCR2 are mainly expressed on neutrophils but low expression is also evident on keratinocytes, fibroblasts, endothelial, and melanoma cells.[14]

The role of CXCL8 in acute and chronic inflammatory conditions characterized by a prominent polymorphonucleate (PMN) infiltrate as, for instance, UC and COPD, has been recently reviewed.[16]

Furthermore, recent data strongly support the hypothesis that expression of CXCL8 and its receptors CXCR1 and CXCR2 contributes to aggressive growth and metastasis in human malignant melanoma.

To date, a limited number of small molecular weight (SMW) CXCL8 inhibitors have been disclosed in the literature and the first drug candidates have only recently entered clinical studies aimed at the assessment of the therapeutic potential of this class.[17,18]

The most comprehensively described class of SMW CXCL8 inhibitors is a class of bisaryl urea derivatives discovered and characterized by GlaxoSmithKline (GSK) laboratories as selective CXCR2 antagonists.[19,20] The first lead compound in this series, *N*-(2-bromophenyl)-*N*′-(2-hydroxy-4-nitrophenyl)urea (SB225002, Figure 1), is >150-fold selective for CXCR2 over CXCR1 in a binding assay but, in vitro, it potently inhibited human and rabbit neutrophil chemotaxis induced by both CXCL8 and CXCL1. The in vivo efficacy of the compound was proved in some relevant animal models such as CXCL8-induced PMN margination in rabbits,[19] but protracted lead optimization studies delayed the selection of appropriate clinical candidates. To date, a novel candidate, *N*-(2-chloro-3-fluorophenyl)-*N*′-[4-chloro-2-hydroxy-3-(piperazin-1-ylsulfonyl) phenyl]-urea (SB656933, Figure 1) is in phase I clinical trials for the treatment of COPD.

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[a] Abbreviations: I/R, ischemia/reperfusion; RA, rheumatoid arthritis; COPD, chronic obstructive pulmonary disease; UC, ulcerative colitis; DGF, delayed graft function; PGD, primary graft dysfunction; PMN, polimorphonuclear neutrophil; LPS, lypopolysaccaride; 7-TM-GPCRs, 7-transmembrane G-protein coupled receptors; SMW, small molecular weight; SAR, structure−activity relationship; COX, cyclooxygenase.

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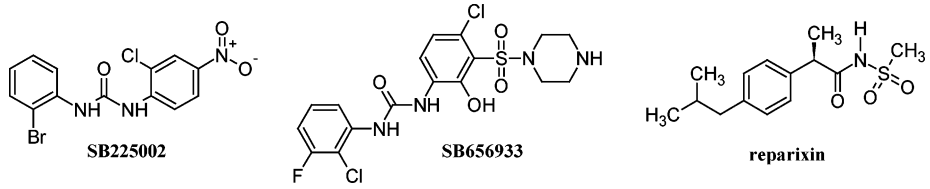


Figure 1. Chemical structures of SB225002, SB656933, and reparixin.

In recent years, a novel class of SMW noncompetitive allosteric CXCR1 inhibitors has been widely investigated in our laboratories.[21]

(2*R*)-2-[4-(2-methylpropyl)phenyl]-*N*-(methylsulfonyl)propanamide (reparixin, Figure 1), the compound selected from this class, is a potent and selective inhibitor of CXCL8-induced chemotaxis and has been proved efficacious in several ischemia/reperfusion (I/R) experimental models.[22−24] On the basis of its pharmacological characteristics, reparixin has been selected to enter clinical development for the prevention and treatment of the delayed graft function (DGF) in kidney transplant and primary graft dysfunction (PGD) in lung transplant. Phase II clinical trials are ongoing for both of these indications.

Reparixin is a potent functional inhibitor of CXCL8-induced biological activities on human PMNs with a marked selectivity (around 400-fold) for CXCR1, as shown in specific experiments on CXCR1/L1.2 and CXCR2/L1.2 transfected cells and on human PMNs.[22] Reparixin mechanism of action has been deeply investigated leading to the full characterization of a binding pocket in the transmembrane (TM) region of CXCR1. The binding of the inhibitor effectively blocks the agonist-induced receptor signaling in the intracellular compartment, while it does not directly affect the CXCL8 binding affinity or the number of expressed receptors.

There is conflicting information as to whether neutrophil chemotaxis, the best characterized biological effect of CXCL8, is mediated by one or both the CXCL8 receptors.[16]

As previously discussed, our data support a major role of CXCR1 signaling in the regulation of human neutrophil chemotaxis, which is the key pathophysiological event in post-ischemia reperfusion conditions.

Starting from the above considerations, we attempted to exploit the information on the reparixin binding mode to rationally design a novel class of potent and selective CXCL8 inhibitors with comparable potency on CXCR1 and CXCR2 and with appropriate pharmacokinetic (PK) profile for the treatment of chronic diseases.

In fact, accumulating evidence indicates a predominant, if not exclusive, role of the CXCR2 receptor subtype in complex pathologies such as psoriasis, COPD, and melanoma.[25−27]

Therefore, dual inhibitors of the CXCL8 activity, blocking both CXCR1 and CXCR2 receptors, could be an appropriate and a more complete therapeutic strategy in a number of inflammatory diseases where the CXCR2 pathway is involved specifically or in conjunction with the CXCR1 signaling.

Here we describe the results obtained by structure−activity relationship (SAR) studies in the class of 2-arylpropionic CXCL8 inhibitors that have led to the identification of novel, potent, and selective noncompetitive dual inhibitors of CXCR1 and CXCR2 receptors.

The demonstration of in vivo efficacy for CXCR1/CXCR2 dual inhibitors could represent a major advance in the treatment of severe pathological conditions ranging from COPD to aggressive melanoma.

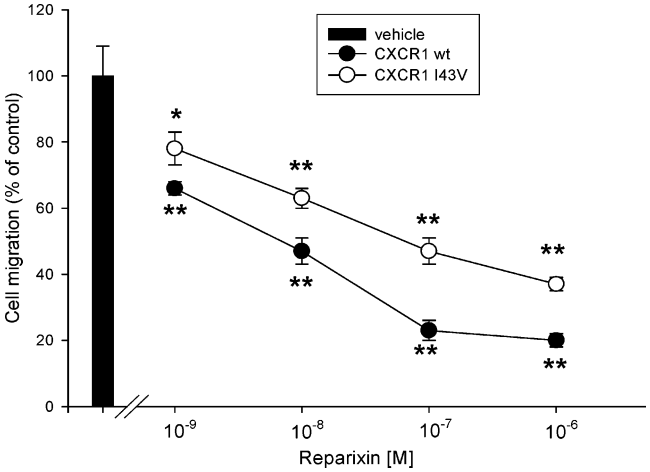


Figure 2. Migration of L1.2 transfectants expressing wild type CXCR1 (●) and Ile43Val CXCR1 (○) was induced by 10 nM CXCL8 in the presence or absence of increasing concentrations of reparixin as indicated. Results are expressed as percent of migration in the absence of reparixin (±SD) at least in three independent experiments: (**) $P < 0.01$ and (*) $P < 0.05$ vs cell migration in the absence of reparixin (Mann−Whitney U test). Spontaneous migration was 4000 ± 3000 cells/mL; CXCL8-induced cell migration was 420 000 ± 20 000 cells/mL.

Results and Discussion

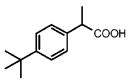
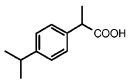
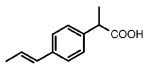
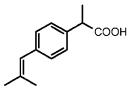
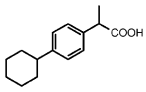
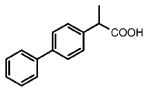
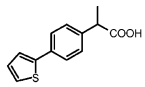
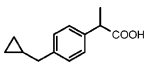
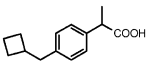
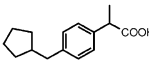
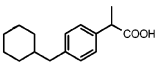
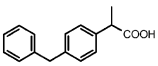
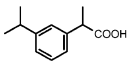
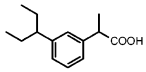
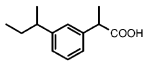
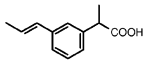
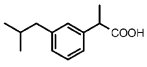
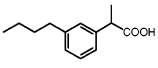
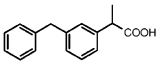
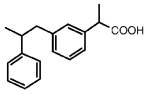
Ile43Val Replacement. Effect of Reparixin on hCXCR1 Ile43Val Mutant. The prediction of the above-described model was that the hCXCR1 Ile43Val mutant still supported CXCL8-induced chemotaxis, but with reduced sensitivity to reparixin inhibition. The valine-replacement mutant was expressed transiently in L1.2 cells and receptor expression was confirmed by flow cytometry analysis (data not shown). The CXCR1 mutant did not significantly differ from wild-type CXCR1 transfectant in terms of receptor expression levels, ligand binding properties, and chemotactic migration to CXCL8.

Reparixin was tested in a wide range of concentrations (1−1000 nM). As expected, wild-type CXCR1/L1.2 transfectants migration induced by CXCL8 (10 nM) was significantly inhibited by reparixin (Figure 2), the inhibition being concentration-dependent and reaching the maximum (80%) at 0.1 μM of reparixin. The efficacy of reparixin was significantly lower in cells expressing Ile43Val CXCR1 mutant (IC_{50} values of 5.6×10^{-9} M and 8.0×10^{-8} M for CXCR1 wt and CXCR1 Ile43Val, respectively).

Chemistry. The results described in this study are shown in Tables 1−3, and the related synthetic methods are outlined in Schemes 1−8.

The synthesis of 2-arylpropionic acids was performed following several strategies depending on the different substitution pattern of the aromatic ring. The choice of different methods was guided by the commercial availability of starting materials and reagents. Compounds **4** and **5** were obtained starting from intermediate **80**, prepared as described,[21] by direct coupling with 2-methyl-1-propenyltributyltin and cyclohexylzinc bromide,

Table 1. Effect of 3- and 4-Substituted 2-Arylpropionic Acids on CXCL8- and CXCL1-Induced Human PMN Chemotaxis[a]

N.	Structure	CXCL8*	CXCL1*
1		6±19	n.t.
2		15±9	n.t.
3		11±17	n.t.
4		14±7	n.t.
5		10±9	n.t.
6		0±8	n.t.
7		11±6	n.t.
8		24±1	30±1
9		55±12	59±3
10		10±11	40±5
11		2±8	39±4
12		1±1	35±7
13		62±5	55±8
14		58±15	67±6
15		50±8**	n.t.
16		-1±15	n.t.
17		-10±7	n.t.
18		3±8	n.t.
19		10±5	n.t.
20		0±2	n.t.

[a] (*) % of inhibition at 10^{-8}M. (**) % of inhibition at 10^{-7}M. n.t.: not tested.

respectively, and following methyl ester basic hydrolysis (Scheme 1). The direct alkylation of the commercial 2-[4-(bromomethyl)phenyl] propanoic acid with the appropriate organomagnesium reagents in Grignard reaction conditions afforded the 4-alkylderivatives **8**−**10** (Scheme 2). Compound **20** was obtained by Heck coupling from the intermediate **82**[21] and α-styrene, followed by Pd/C hydrogenation and hydrolysis (Scheme 3).

The commercial 3-(1-cyanoethyl)benzoic acid was reacted with thionyl chloride to give the corresponding acid chloride that, by treatment with the appropriate Grignard reagent and acidic hydrolysis, led to the compounds **23**−**26**. Similarly, the same intermediate was reacted with heteroaryl lithium to give, after hydrolysis, compounds **27**−**30**. Treatment of the above acid chloride with sodium azide under Curtius reaction conditions afforded the corresponding arylamine that was converted under Sandmeyer conditions to the intermediate **81** that, by reaction with benzenesulfinic acid sodium salt and hydrolysis, was converted to the sulfone **37** (Scheme 4).

Following a typical Wittig procedure and basic hydrolysis, the methyl ester of commercial ketoprofen was transformed into the compound **31**; parallely, the vinyl intermediate was hydrogenated and hydrolyzed to give **35**. The direct alkylation of ketoprofen by methyl magnesium bromide afforded compound **36** (Scheme 5).

Compounds **39** and **40** were prepared starting from the commercial 2-(4-hydroxyphenyl)propanoic acid and the appropriate acid chloride following a classical Schotten−Baumann procedure in aqueous solution. The methyl ester of the 2-(4-hydroxyphenyl)propanoic acid was converted into 4-arylsulfonates **51**−**54** by reaction with selected sulfonyl chlorides and following hydrolysis (Scheme 6).

The same procedure was used to obtain sulfonamides **44**−**50** from intermediate **83**. Treatment of **83** with benzoyl chloride and subsequent hydrolysis afforded compound **41**, while the condensation of **83** with 4-chlorobutyryl chloride, and following basic hydrolysis, allowed to obtain compound **43** (Scheme 7).

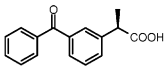
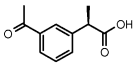
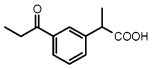
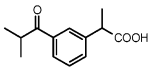
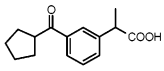
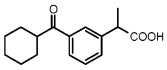
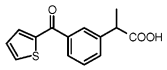
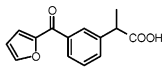
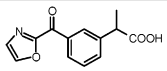
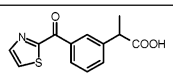
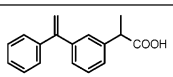
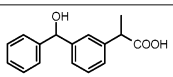
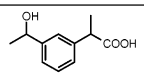
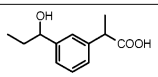
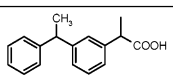
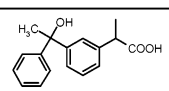
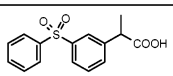
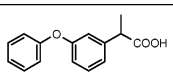
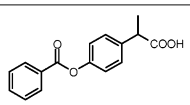
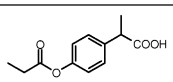
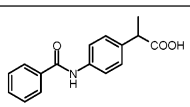
(2*R*)-2-{4-[(Trifluoromethyl)sulfonyl]phenyl}propanoic acid **56** was transformed into compounds **58**−**62** by reaction with the appropriate alkyl, aryl or heteroarylsulfonamide and into compounds **68**−**79** by classical coupling procedures with amines. For compound **79**, the not commercially available amine (2-amino-4-trifluoromethylthiazole) was prepared according to a published procedure.[28] Compound **56** was converted into the hydroxamic acid **63** and into N- and O-alkyl derivatives **64**−**66** by coupling with commercial N- or O-alkylhydroxylamines (Scheme 8).

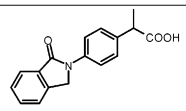
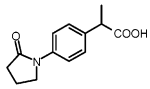
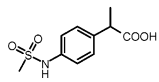
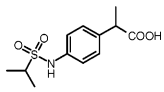
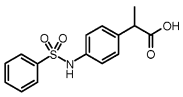
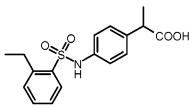
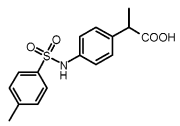
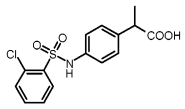
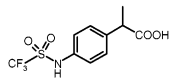
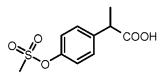
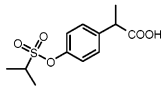
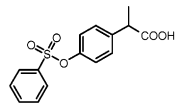
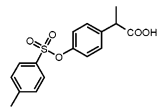
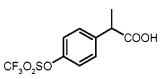
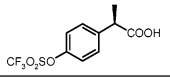
The synthetic methods for the preparation of compounds **1**−**3**, **6**, **7**, **11**−**19**, **21**, **22**, **32**−**34** and intermediates **80** and **82**[21] and of compounds **55**, **56**, **57**, and **67**[29] have been described before.

Structure−Activity Relationship (SAR) Studies. Reparixin, a 2-phenylpropionic acid derivative, was previously demonstrated to act as a noncompetitive allosteric blocker of CXCL8 receptors with a marked selectivity for CXCR1.[22]

Alanine scanning mutagenesis studies, supported by molecular modeling techniques, allowed us to define the overall pattern of interactions engaged by reparixin in a pocket located in the TM region of hCXCR1. For a better comprehension of amino acid residues position in the TM region of the receptor, the Weinstein−Ballesteros numbering will be used[30] in the following section and throughout the rest of the paper.

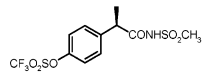
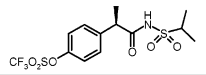
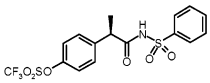
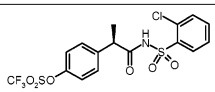
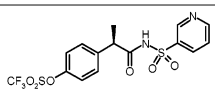
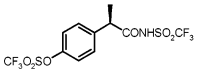
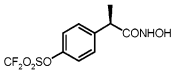
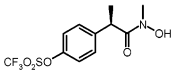
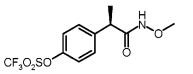
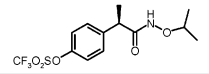
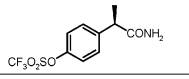
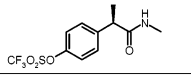
Table 2. Effect of 3- and 4-substitued 2-Arylpropionic Acids on CXCL8- and CXCL1-Induced Human PMN Chemotaxis[a]

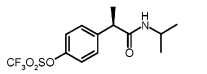
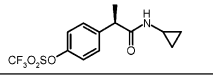
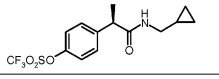
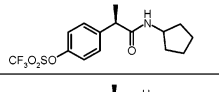
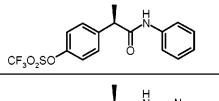
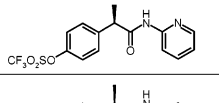
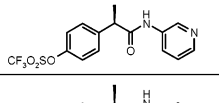
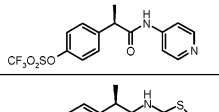
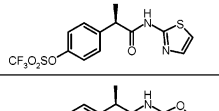
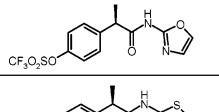
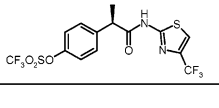
N.	Structure	CXCL8*	CXCL1*
21		64±8	61±7
22		5±1	n.t.
23		1±4	n.t.
24		20±3	n.t.
25		-5±21	2±4
26		5±11	4±12
27		51±7	50±7
28		-3±11	n.t.
29		26±1	n.t.
30		63±2	48±7
31		47±4	2±1
32		31±8	40±6
33		43±8	40±8
34		57±6	40±3
35		55±2	45±7
36		0±6	n.t.
37		9±11	n.t.
38		-17±21	n.t.
39		32±3	n.t.
40		-6±15	n.t.
41		8±12	n.t.

N.	Structure	CXCL8*	CXCL1*
42		50±3	40±8**
43		10±3	n.t.
44		-8±10	n.t.
45		44±3	n.t.
46		45±10	14±9
47		47±10	80±10
48		69±13	0±12
49		-2±15	66±10
50		10±11	n.t.
51		5±10	n.t.
52		49±8	46±6
53		55±10	54±10
54		49±7	65±5
55		57±7	57±5
56		68±7	65±5

[a] (*) % of inhibition at 10^{-8}M. (**) % of inhibition at 10^{-7}M. n.t.: not tested.

Table 3. Effect of (*R*)-2-Arylpropionic Derivatives on CXCL8- and CXCL1-Induced Human PMN Chemotaxis[a]

N.	Structure	CXCL8*	CXCL1*
57		60±9	61±6
58		60±6	15±17
59		43±12	8±6
60		18±10	n.t.
61		11±4	n.t.
62		-4±7	n.t.
63		48±5	50±3
64		48±7	47±6
65		60±5	40±8
66		50±18	40±5
67		60±1	58±2
68		22±4	n.t.

N.	Structure	CXCL8*	CXCL1*
69		50±4**	72±12
70		-11±4	n.t.
71		12±5	n.t.
72		0±1	n.t.
73		10±13	n.t.
74		48±1	50±3
75		5±4	n.t.
76		11±7	n.t.
77		57±4	56±9
78		50±4	48±3
79		64±10	60±7

[a] (*) % of inhibition at 10^{-8}M. (**) % of inhibition at 10^{-9}M. n.t.: not tested.

According to the proposed binding mode, the acylmethanesulfonamide moiety engages strong polar interactions with five residues in the TM domain ($Tyr46_{1.39}$, $Lys99_{2.64}$, $Asn120_{3.35}$, $Tyr258_{6.51}$, and $Glu291_{7.39}$), whereas three aliphatic amino acids ($Val42_{1.35}$, $Val113_{3.28}$, and $Ile43_{1.36}$) are putatively involved in the recognition of the isobutyl residue of reparixin in a hydrophobic cavity in the TM region of CXCR1.

The chemotaxis experiments on this set of mutants clearly showed that hydrophobic interactions strongly contribute to tune the overall affinity of the inhibitor, since single replacement of the three hydrophobic residues for Ala amino acid considerably reduced the potency of reparixin.

Reparixin binding site in CXCR2 was also studied by molecular mechanics, molecular dynamics calculations (MM/MD) and GRID analysis. In the model, as expected on the basis of the high CXCR1 and CXCR2 homology in the TM region, the pattern of polar interactions engaged by reparixin appeared strictly conserved (Figure 3, panels A and B). In contrast, some nonconserved residues in the helix bundle apparently account for the larger dimensions of the hydrophobic cavity in the TM of CXCR2. In particular, the replacement of Ile43 (CXCR1) by Val52 (CXCR2) could, to some extent, explain the lower affinity of the inhibitor.

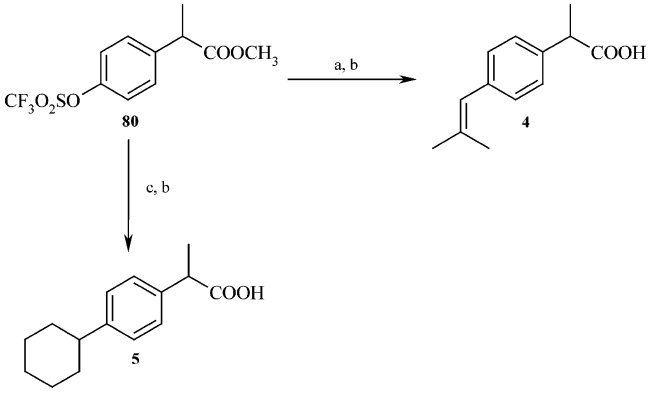
This hypothesis was in further agreement with the previous observation that Ile43Ala mutation in CXCR1 caused a 100-fold reduction of the inhibitor potency. The significant decrease of reparixin potency on CXCR1 Ile43Val mutant indirectly suggests that the loss of hydrophobic interactions could account for reparixin lower affinity toward CXCR2.

Supported by these results, we decided to follow a molecular modeling aided strategy to design dual CXCR1/CXCR2 allosteric inhibitors.

In our previous work, SAR in the class of 2-arylpropionic CXCR1 ligands were extensively investigated by using the CXCL8-induced human PMN chemotaxis assay as primary functional screening. Due to the specific objectives of the study, the CXCR2 selectivity of the test compounds was not extensively analyzed, and the CXCL1-induced chemotaxis assay was performed on a limited number of molecules selected for the lead optimization phase.

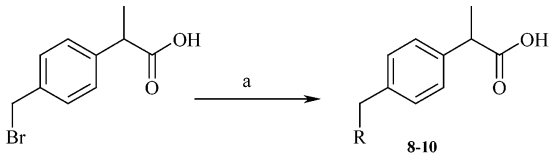
With the objective to select novel scaffolds for the design of equipotent CXCR1/2 inhibitors, and in strict analogy with the approach followed in our previous paper,[21] we first investigated the selectivity profile of a representative set of racemic 2-phenylpropionic acids in CXCL1-induced human PMN chemo-

Scheme 1[a]



[a] Reagents and conditions: (a) Pd_2dba_3, $AsPh_3$, LiCl, CuI, 2-methyl-1-propenyltributyltin, NMP, 90 °C; (b) KOH, MeOH, rt; (c) cyclohexylzinc bromide, $Pd(PPh_3)_4$, LiCl, THF, reflux.

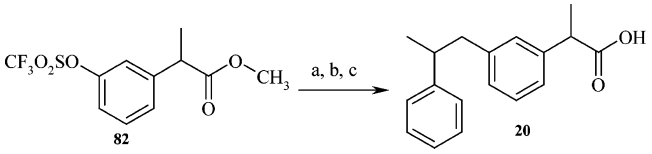
Scheme 2[a]



R	Product
	8
	9
	10

[a] Reagents and conditions: (a) RMgBr, CuI, THF, 0 °C→ rt.

Scheme 3[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, TEA, α-methylstyrene, DMF, 90 °C; (b) 10% Pd/C, EtOH, rt; (c) KOH, MeOH, rt.

taxis. Only potent CXCL8 inhibitors (>50% at $c = 10^{-8}$M) were selected for CXCL1 chemotaxis assay.

Starting from the above binding mode hypothesis, we expected that, in the series of 4-substituted-phenylpropionic acids, the introduction of larger hydrophobic substituents could favorably influence the affinity to CXCR2.

In agreement with previous SAR studies, the replacement of the 4-isobutyl residue with more rigid alkyl chains (**1**−**4**) or cyclic aliphatic (**5**) substituents led to a dramatic loss of biological activity and, similarly, the introduction of 4-aryl substituents (**6**, **7**) was not tolerated in CXCR1 binding pocket.

Flexibility is required for a correct accommodation in the cavity, and the size of the hydrophobic group was confirmed as a key factor for the modulation of the affinity at CXCR2. Nevertheless, as emerged in the series of 4-cycloalkylmethyl substituted acids (**8**−**12**), a limited size increase was tolerated and the cyclobutylmethyl residue was found as the best compromise for high affinity to both receptors. Thus, in this series, **9** was selected as the first potent dual inhibitor of CXCL8- and CXCL1-induced chemotaxis.

Before proceeding with the lead optimization, we considered a key factor for the success of the program the selection of several compounds with different structural and physicochemical properties. Two 3-substituted-2-phenylpropionic acids, previously selected by SAR studies as potent CXCL8 inhibitors, 3-isopropyl (**13**) and 3-benzoyl (**21**) phenylpropionic acids were tested for CXCL1 biological activity.

Compound **13** showed a comparable potency in inhibiting CXCL8- and CXCL1-induced chemotaxis. Binding of **13** in the TM region of CXCR1 and CXCR2 was investigated by MM/MD and GRID analysis. Interestingly, both polar and hydrophobic interactions engaged by the ligand are well conserved in the two binding models. According to the model, the forced perpendicular orientation of the isopropyl group significantly modifies, if compared to the 4-isobutyl derivatives, the hydrophobic pattern of recognition that, in this case, involves conserved residues in the two receptor subtypes (data not shown).

The importance of the orientation of the hydrophobic chain/group was confirmed by the observed SAR. In the series of 3-alkyl-substituted phenylpropionic acids (**13**−**20**), **14** showed a good potency and, like **13**, dual activity. Also the 3-*sec*-butyl analogue **15** maintained a moderate activity, while the introduction of planar unsaturated groups (**16**) as well as flexible, linear, or branched alkyl chains (**17**−**20**) invariably afforded a dramatic loss of affinity.

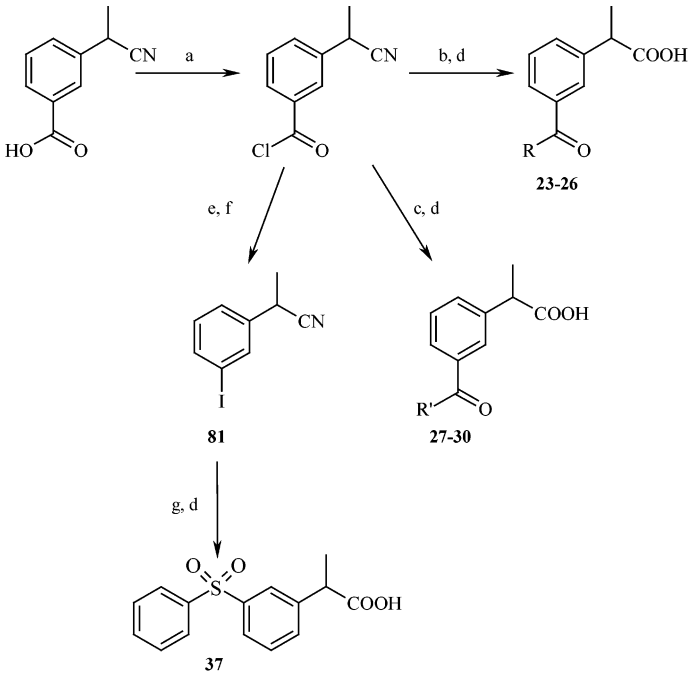
The last phenylpropionic scaffold analyzed for the CXCR2 selectivity was *R*-ketoprofen (**21**), the first CXCL8 inhibitor ever discovered in our laboratories. The polar interactions engaged by **21** in the TM region of CXCR1 were previously discussed in deep.[21] To allow a direct comparison of the binding pocket in the receptor subtypes, a binding model of **21** in CXCR2 was obtained by molecular modeling techniques. We found the carboxylic group engaging a double ionic bond with $Lys108_{2.64}$ and $Glu300_{7.39}$ in CXCR2, and in general, the hydrophilic interactions pattern appeared strictly conserved in the two receptor subtypes. Furthermore, the analysis shows that the benzoyl moiety well accommodates (Figure 3, panels C and D) in a conserved hydrophobic cavity spanned by $Val122_{3.28}$ ($Val113_{3.28}$ in CXCR1), $Ile292_{7.31}$ ($Ile283_{7.31}$), and the aliphatic side chain of $Lys126_{3.32}$ ($Lys117_{3.32}$). In both receptors, the complex seems further stabilized by an electrostatic interaction between the phenol group of $Tyr55_{1.39}$ ($Tyr46_{1.39}$ in CXCR1) and the phenyl group of the ligand.

In agreement with the conserved binding mode, **21** potently inhibited CXCL1-induced PMN chemotaxis (Table 2).

A set of 2-(3-acylphenyl)propionic acids (**22**−**30**), ketoprofen analogues, was designed and tested for activity toward CXCL8 and CXCL1.

In the proposed binding model, the carbonyl group seems not involved in direct interactions with polar residues in the TM region even if, from a geometrical point of view, the amino acid residue $Lys117_{3.32}$ in CXCR1 ($Lys126_{3.32}$ in CXCR2) could be accessible for hydrogen-bond interaction. As a matter of fact, a benzophenone carbonyl, due to the electron-withdrawing effect of the two phenyl groups, is a weak hydrogen-bond acceptor. Thus, we attempted to reinforce the acceptor characteristics of the carbonyl group, introducing hydrophobic substituents with electron-donor properties. Data reported in Table 2 show that the replacement of the phenyl moiety with small and rigid alkyl chains (**22**−**24**) was detrimental for the affinity of the ligands and also that the inclusion of cycloalkyl residues (**25**, **26**) did not afford significant improvement of the receptor affinity.

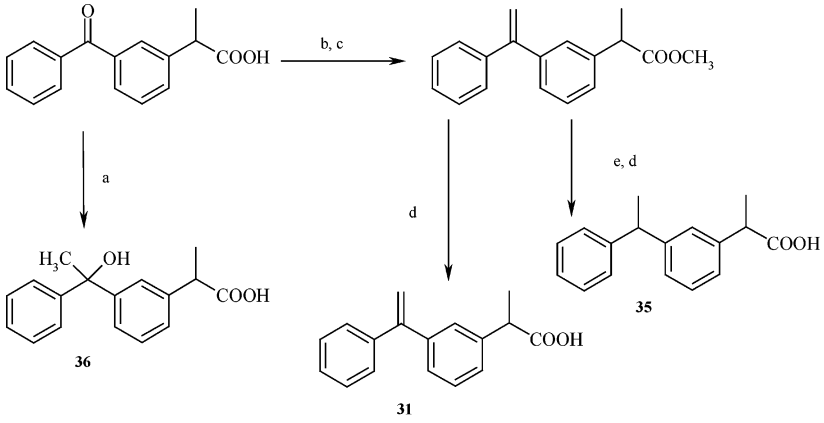
Scheme 4[a]



R	Product	R'	Product
CH_3CH_2	**23**		**27**
$(CH_3)_2CH$	**24**		**28**
	**25**		**29**
	**26**		**30**

[a] Reagents and conditions: (a) $SOCl_2$, reflux; (b) RMgCl, $ZnCl_2$, (dppf)$PdCl_2$, 0 °C → rt; (c) R′H (heterocycle), BuLi, THF, $ZnCl_2$, CuI, −78°→ 0 °C; (d) 37% HCl, 1,4-dioxane, 70 °C; (e) (1) NaN_3, CH_2Cl_2/H_2O, 0 °C; (2) TFA, reflux; (3) K_2CO_3, H_2O/MeOH, 60 °C; (f) concd HCl, $NaNO_2$, KI, 0°−5 °C; (g) $PhSO_2Na$, CuI, L-proline sodium salt, DMSO, 80 °C.

Scheme 5[a]



[a] Reagents and conditions: (a) CH_3MgBr (2 equiv), Et_2O, reflux; (b) concd H_2SO_4, MeOH, rt; (c) $Ph_3CH_3P^+Br^-$, BuLi, THF, rt; (d) 1 N NaOH, MeOH, rt; (e) 10% Pd/C, EtOH, rt.

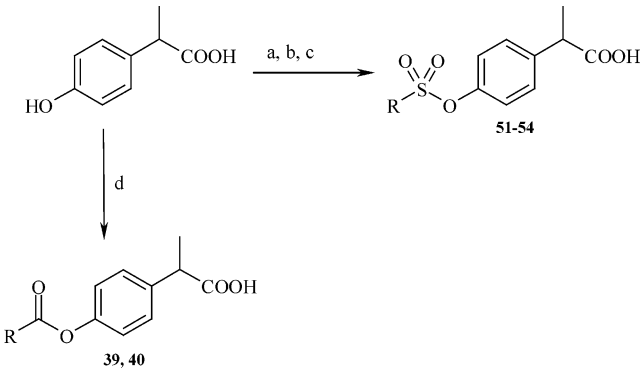
The key role of aromatic hydrophobic interactions, anticipated by the above observations, was further confirmed by the SAR studies in a limited set of heteroaromatic analogues (**27**−**30**).

The thiophene derivative **27**, a classical benzene bioisoster, was a very potent dual inhibitor, while the introduction of the more polar furan ring (**28**) was not well-tolerated. Analogous SAR were found in the CXCL8-induced chemotaxis assay by comparing the 2-oxazolyl (**29**) with the 2-thiazolyl (**30**) analogue. Compound **30**, as reported in Table 2, was also confirmed as a potent CXCR2 inhibitor.

On the basis of these results, we argued that, in accordance with the models, the second aromatic moiety is essential in this series of derivatives and that the carbonyl group behaves as a spacer for the correct orientation of the two aromatic rings.

To further support the above assumption, we synthesized the phenylvinyl derivative (**31**) that, while loosing hydrogen-bond

Scheme 6[a]



R	Product
	**39**
CH_3CH_2	**40**
CH_3	**51**
$(CH_3)_2CH$	**52**
	**53**
	**54**

[a] Reagents and conditions: (a) conc. H_2SO_4, MeOH, rt; (b) RSO_2Cl, Py, reflux; (c) 37% HCl, glacial AcOH, reflux; (d) 1 N NaOH, RCOCl, rt.

acceptor properties, retains a benzophenone-like spatial disposition. The obtained results (Table 2) confirmed the scarce importance of the carbonyl oxygen but the good selectivity of **31** for CXCR1 suggests that the hydrophobic pattern of interactions is not fully conserved in the TM cavities of CXCR1/2.

In apparent contradiction with the above considerations, the hydroxyl derivatives **32**−**34**, obtained by partial reduction of **21**−**23**, retained good potency, despite the substantial change in hybridization and geometry of the molecule.

Compound **32** was a good dual inhibitor, but interestingly, in this series, the replacement of the aromatic moiety (**32**) for smaller alkyl chains (**33** and **34**) did not compromise the activity of the inhibitors.

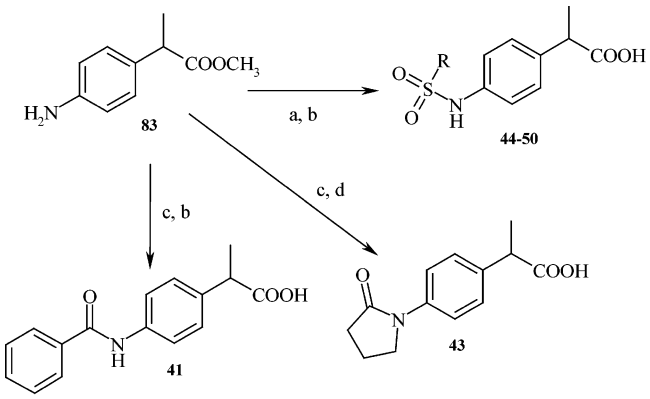
Compounds **35** and **36** were synthesized with the aim to gain further information on the unexpected biological activity of **32**−**34**. The hydroxyl group seems not directly involved in the receptor binding, since the substitution of hydroxyl for methyl (**35**), but not the methylation of the hydroxyl-bearing carbon (**36**), did not compromise the biological activity.

The above-reported results are reminiscent of SAR in the series of the analogues of the 3-isopropyl derivative **13**, thus suggesting that the two classes of derivatives could share a similar binding mode in which the hydroxyl moiety is not directly involved in interactions with the receptor.

On the basis of these considerations, the lack of activity of the phenylsulfonyl (**37**) and phenoxyphenyl (**38**) derivatives is most likely due to the different orientation and mutual distances of the aromatic moieties than to electronic effects.

As a further step of the project, the relatively rigid structure of the ketoprofen scaffold was chosen as template for design and synthesis of novel 4-substituted phenylpropionic acids with dual CXCR1/2 activity. With the aim of directing a second aromatic group in the hydrophobic pocket occupied by the benzoyl group, several spacers (ester, amide, sulfonate, and sulfonamide) were evaluated in parallel.

Scheme 7[a]



R	Product
CH_3	**44**
$(CH_3)_2CH$	**45**
	**46**
	**47**
	**48**
	**49**
CF_3	**50**

[a] Reagents and conditions: (a) RSO_2Cl, Py, acetone, rt; (b) 2 N NaOH, EtOH, rt; (c) RCOCl, Py, acetone, rt; (d) 6% NaOH, *i*-PrOH, rt.

The benzoic ester (**39**) showed a moderate activity, as CXCL8 inhibitor, that was completely lost in the corresponding propionic ester (**40**). These preliminary results partially supported the validity of the approach, but the in vivo liability of the ester group prompted us to shift to alternative scaffolds for the prosecution of the SAR studies.

The corresponding benzoyl amide (**41**) was found completely inactive, whereas the tertiary cyclic amide (**42**) in which the aromatic residue is part of a rigid bicyclic structure was a good and selective CXCL8 inhibitor. The marked rigidity of the structure could explain the weak inhibitory potency of **42** as CXCL1 inhibitor, but also in this case, the crucial relevance of the second aromatic ring was confirmed by the complete activity loss of the corresponding oxopyrrolidinyl derivative (**43**).

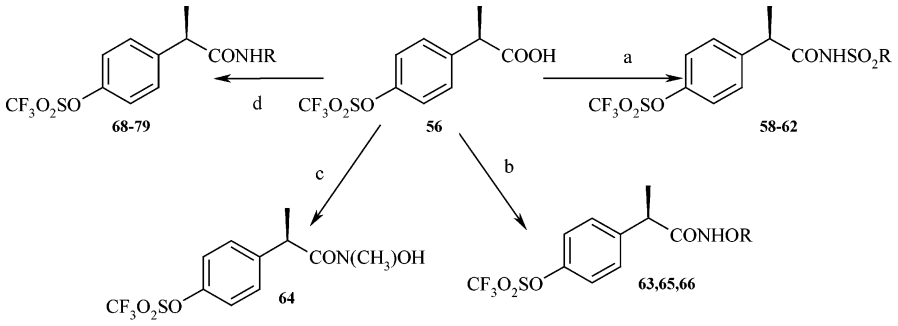
With the aim of refining the geometry and the physicochemical properties of the spacer, the activity of 4-aryl and 4-alkylsulfonylamino derivatives was investigated.

The simple 4-methanesulfonamide (**44**) was completely devoid of biological activity, but the replacement of the methyl group with the isopropyl (**45**) led to a significant potency increase on CXCL8. As expected, the introduction of a phenyl group (**46**) strongly enhanced the affinity at CXCR1 but not yet at CXCR2.

By varying the nature and the position of the substituents of the phenylsulfonyl moiety (**47**−**49**), a clear modulation of the affinity for both the receptors resulted and the 2-ethyl derivative (**47**) was identified as a dual and potent inhibitor.

Because the direct comparison between the benzoate (**39**) derivative and the corresponding benzamide (**41**) suggested a

Scheme 8[a]



R	Product	R	Product
$(CH_3)_2CH$	**58**		**70**
	**59**		**71**
	**60**		**72**
	**61**		**73**
CF_3	**62**		**74**
H	**63**		**75**
CH_3	**65**		**76**
$(CH_3)_2CH$	**66**		**77**
CH_3	**68**		**78**
$(CH_3)_2CH$	**69**		**79**

[a] Reagents and conditions: (a) RSO_2NH_2, CDI, DBU, CH_2Cl_2, rt; (b) $SOCl_2$, $RONH_2$, $NaHCO_3$, CH_2Cl_2, rt; (c) oxalyl chloride, DMF, $(CH_3)NHOH$, CH_2Cl_2, rt; (d) $SOCl_2$, RNH_2, CH_2Cl_2, rt.

detrimental effect of the amide hydrogen on the activity, a series of alkyl and aryl sulfonates was synthesized and tested.

As expected on the basis of the pharmacophore hypothesis, the simple mesylate (**51**) showed no activity, although this result has to be prudently considered due to the intrinsic reactivity of the mesylate group that could compromise the SAR interpretation. The gradual size increase of the hydrophobic group was paralleled by a potency increase in the series of sulfonate compounds (**52**−**54**) and, consistent with the premises, the phenylsulfonate ester (**53**) exhibited higher potency than the corresponding phenylsulfonamide (**46**).

Compounds **52**−**54** were all three potent and dual CXCR1/2 inhibitors and the sulfonate spacer was confirmed as optimal from a spatial point of view for the correct orientation in the hydrophobic pocket. Nevertheless, sulfonic esters, still more clearly than carboxylic esters, suffer the problem of liability due to their inherent sensitivity to hydrolytic conditions and high reactivity toward nucleophilic groups.

To overcome this issue, we focused on the trifluoromethanesulfonyl (triflate) group, because this moiety, even if scarcely used in medicinal chemistry programs, is considerably more stable than aliphatic and aromatic sulfonates versus hydrolysis and nucleophilic attack. Furthermore, due to the marked electron-withdrawing effect of the substituent, aryltriflates are expected to show a good resistance to in vivo metabolic oxidation of the aromatic ring.[31−33]

Starting from these considerations, particular attention was paid to the results obtained with 2-(4-trifluoromethanesulfonyloxy)phenylpropionic acid (**55**) and the related 2*R*-enantiomer (**56**), which is to date the most potent dual inhibitor in the series of 2-phenylpropionic acid derivatives. Nevertheless, the pronounced receptor affinity of **56** does not obviously fit with the above-described SAR that, along this series of compounds, repeatedly confirmed the importance of strong hydrophobic interactions for a favorable ligand binding.

The paucity of medicinal chemistry studies related to triflate derivatives, hardly limited so far the comprehension of specific properties, and the potential usefulness of this group for bioisosteric replacement purposes remains unexplored.

The marked potency increase, observed substituting methyl (**51**) for trifluoromethyl (**55**) group in the sulfonate esters series, suggests a key role of this residue, but an adequate contribution to the establishment of a network of hydrophobic interactions seems hardly plausible due to the high polarity and relatively small size of the group. In fact, logP/logD value calculations (ACD Labs/logD Suite release 9.0; data not shown) do not evidence a strong influence of the trifluoromethyl group on the overall lipophilicity of the molecule. By contrast, the hydrogen-bonding capability of the trifluoromethyl group is well-documented in the literature, and several structural studies highlight the evident hydrogen-bond acceptor capability in protein−ligand complexes, as assessed by PDB analysis.[34]

To gain insight into this topic, the binding mode of **56** in CXCR1 and CXCR2 was studied by means of exhaustive MM/MD and GRID analysis.

Like the other CXCL8 inhibitors, the acid carboxylic group of **56** was found to directly engage strong polar interactions with the common binding motif of the class (the couple $Lys99_{2.64}$

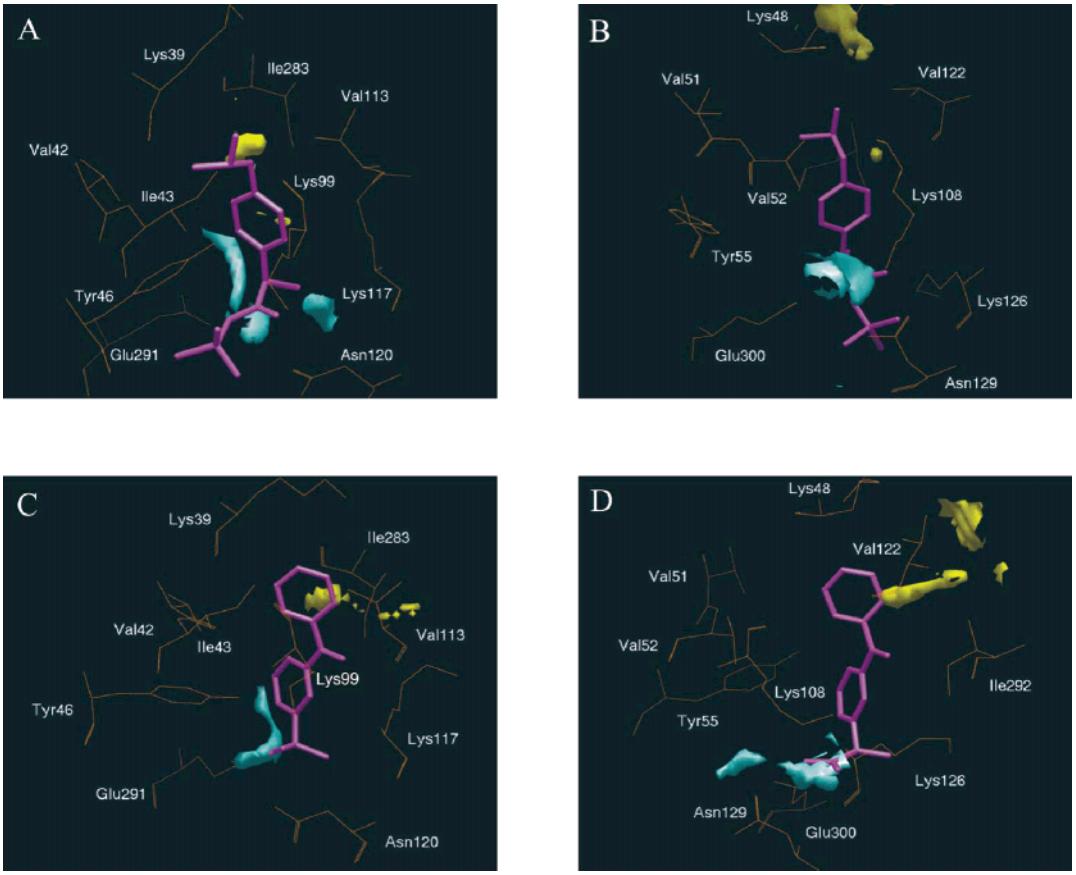


Figure 3. (Panels A and B) Comparison of the 3D MIFs calculated on the allosteric site of reparixin in CXCR1 and CXCR2 by using the DRY (contoured in yellow at −0.4 kcal/mol) and OH2 (contoured in cyan at −8.0 kcal/mol) probes. From a visual inspection it can be seen that CXCR2 does not have an extended favorable hydrophobic region as in CXCR1 cavity and this leads to a partial loss of reparixin activity in CXCR2. (Panels C and D) GRID maps determined on the allosteric site of **21** in CXCR1 and CXCR2 by using the DRY and OH2 (cyan) probes. The hydrophobic regions (contoured in yellow at −0.4 kcal/mol), generated from the residues of a conserved pocket of CXCR1 and CXCR2, closely map the benzoyl moiety; furthermore, the hydrophilic (contoured in cyan at −8.0 kcal/mol) contours superimpose the carboxylic group of **21**. For clarity, only a part of the entire GRID maps is shown.

and Glu291$_{7.39}$) in both the receptors. However, in both the derived binding models, the trifluoromethyl residue does not seem to be directly involved in polar interactions but, as assumed for the other phenylpropionic acids, it appears comfortably accommodated in the hydrophobic cavity spanned by the helices 1, 3, and 7 (Figure 4, panels A and B). Molecular interaction fields (MIFs) show that, in CXCR1 and CXCR2, the triflate group well occupies the hydrophobic region generated by the same residues previously described.

The experimental confirmation of the proposed binding model would suggest an unexpected ability of the small trifluoromethyl group in establishing a network of strong hydrophobic interactions.

At the end of this preliminary phase aimed at the SAR investigation and the assessment of the binding hypotheses, three phenylpropionic acids **9**, **13**, and **56** were selected as potential candidates for the following lead optimization phase.

As widely discussed, the lack of cyclooxygenases (COXs) inhibitory activity and the selectivity toward other chemokine/chemotactic factors were considered the main criteria for the selection of candidates for in vivo studies.[21]

The *R*- and *S*-enantiomers of **9**, **13**, and **56** were evaluated at the maximal concentration for inhibition of the LPS-induced PGE_2 production in human macrophages and for the effect on human PMN chemotaxis induced by fMLP, C5a, and MCP1 (data not shown). Among the tested compounds, only **56** was completely inactive in the PGE_2 production assay at the concentration of 10^{-5} M (% inhibition: 17 ± 8).

Starting from the binding mode of **56**, a set of phenylpropionamide derivatives, ranging from weakly acidic to neutral aliphatic or aromatic amides, was built up. We first evaluated a series of acylsulfonamides as potential bioisosteres of the carboxylic group. As shown in Table 3, along this class (**57**−**61**), the increase of the hydrophobic group size led to a significant potency loss toward CXCL8 and the substitution of trifluoromethyl for methyl (**62**) led to an absolutely inactive compound. This effect seemed still more pronounced in CXCL1 inhibition, and the methanesulfonamide **57** was the only potent and dual inhibitor of the series. The results obtained in CXCL8-induced chemotaxis assay are in fair agreement with the SAR reported for reparixin analogues, and this observation further supports the validity of the binding mode hypothesis. Following the same approach as reported for reparixin derivatives,[21] we investigated the possibility of replacing the ionic interaction between the inhibitor and the Lys99$_{2.64}$/Glu291$_{7.39}$ couple with a double hydrogen-bond interaction. A set of hydroxamate derivatives was evaluated as alternative bioisosteres of the carboxylic acid functionality. The hydroxamic acid (**63**) was, as expected, a dual and potent inhibitor, and both O- and N-alkylation (**64**−**66**) were compatible with binding to CXCR1 and CXCR2.

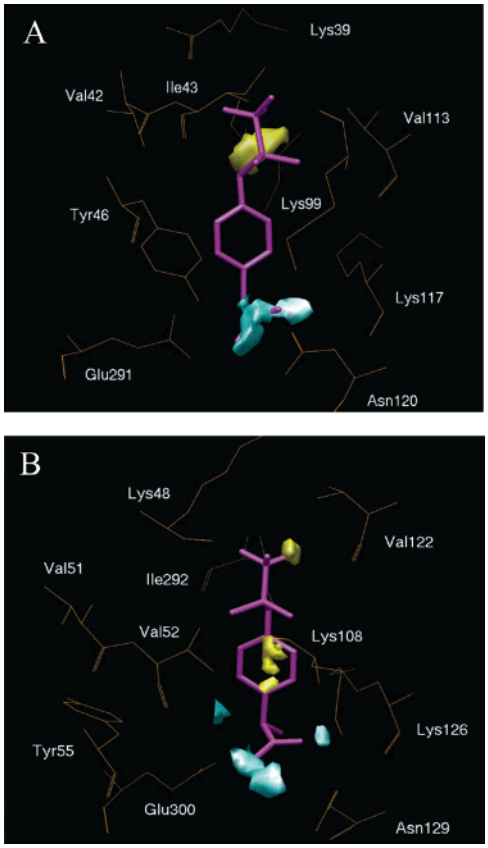


Figure 4. (Panels A and B) MIFs calculated on the allosteric site of **56** in CXCR1 and CXCR2 by using the DRY (contoured in yellow at −0.5 kcal/mol) and OH2 (contoured in cyan at −9.0 kcal/mol) probes. The figure shows a common and favorable hydrophobic cavity spanned by the elices 1, 3, and 7 of CXCR1 and CXCR2. The triflate group of **56** fits this hydrophobic pocket. For the sake of clarity, only a part of the entire GRID map is shown.

Finally, several alkyl and aryl amides derived from **56** were synthesized and tested. The primary amide (**67**) preserved a potent inhibitory effect toward CXCL8 and CXCL1, whereas, in strict analogy with reparixin derivatives, relatively small alkyl substituents on the amido nitrogen were poorly tolerated (**68**, **70**−**72**) in the receptor pocket. Nevertheless, the N-isopropyl derivative (**69**) was identified as a potent and dual inhibitor of CXCL8 and CXCL1 up to the concentration of 10^{-9} M.

Among the N-aryl derivatives (**73**−**79**), the N-phenyl amide **73** did not show any activity, but the insertion of a heteroatom in the 2-position of the aromatic ring favorably influenced the biological activity and, in fact, compounds **74**, **77**−**79** were all effective dual and potent inhibitors of CXCR1 and CXCR2, whereas the shift of the heteroatom in the 3- and 4-position led to inactive compounds (**75**, **76**). As previously discussed, the good activity of heteroaryl derivatives seems coherent with the formation of an intramolecular hydrogen bond involving the heteroatom as acceptor, able to determine a significant dextral shift of the amido/imido equilibrium, thus tuning the binding ability of the amido group.

The overall data obtained with derivatives of **56** are in excellent agreement with the SAR observed for reparixin analogues and, in general, the modification/functionalization of the carboxylic group parallely affects CXCL8 and CXCL1 inhibition.

This observation is a further confirmation that hydrophobic interactions are key determinants for CXCR1/CXCR2 selectivity and that the biologically validated reparixin/CXCR1 binding mode can be used as a reliable tool for the interpretation of SAR of this class of allosteric inhibitors.

Among the selected compounds, a set of dual inhibitors has been further filtered on the basis of the selectivity (related GPCRs and COX activity), PK profile, and oral biovailability in rodent species (data not shown). Interestingly, PK profile of **56**, **67**, and **79** confirmed the hypothesized in vitro and in vivo metabolic stability of triflate moiety, supporting further investigations on this group up to date not yet duly explored for medicinal chemistry purposes. Compounds **56**, **67**, and **79** are very stable in plasma and corresponding half-life time ranges from 3 to 24 h. In addition, the related metabolic pathways have been completely characterized and will be the subject of a specific publication.

Compounds **56**, **67**, and **79**, unlike reparixin, show a PK profile and oral bioavailability from suitable to optimal, amenable for long-term treatments. They are currently under preclinical investigation, not only for I/R prevention, but also for the treatment of several chronic diseases including UC and metastatic melanoma.

Conclusion

In the present work, we report a computer-assisted design approach for the identification of novel allosteric CXCL8 inhibitors acting with comparable potency at both CXCR1 and CXCR2. The reparixin binding model in the CXCR1 TM region, validated by extensive mutagenesis experiments, guided the analysis of the main determinants for CXCR1/CXCR2 selectivity. Molecular modeling studies on selected inhibitors provided useful information for the interpretation of the SAR results.

A series of 2-arylpropionic acids has been investigated for the comprehension of SAR and for the selection of ring substituents optimized in terms of dual CXCR1/CXCR2 activity. The 4-triflate derivatives have been selected because of their interesting pharmacophoric features, and a set of **56** analogues has been further investigated. Among the selected dual inhibitors, three potential novel lead compounds, **56**, **67**, and **79**, share the triflate moiety and exhibit optimized PK and disposition characteristics.

The obtained data suggest an unexpected ability of the small triflate group in establishing a network of strong hydrophobic interactions.

The proposed binding site and the allosteric mechanism of action have been confirmed by testing **57** on CXCR1/L1.2 transfected cells (paper in preparation), and specific point mutagenesis studies will allow in the near future to definitively clarify the peculiar pattern of interactions engaged by the triflate group in the binding pocket. If confirmed, these results, together with the in vivo PK and metabolic profile of the leads, could offer new insights into the peculiar characteristic of the triflate group and in its potential relevance in medicinal chemistry research programs.

Several studies[35−38] converge in indicating CXCL8 inhibition as a promising pharmacological target for the treatment of still unmet medical needs. Although CXCR1 activation has been reported to play a major role in CXCL8-induced human PMN chemotaxis, CXCR2 signaling seems directly and specifically involved in the pathogenesis of demanding chronic diseases such as psoriasis and COPD.

Furthermore, there is accumulating evidence that the pathophysiological role of CXCL8 in melanoma progression and metastases could be mediated by CXCR2 activation.

The availability of potent and selective dual inhibitors blocking both CXCR1 and CXCR2 subtypes could hence represent a powerful tool for the treatment of those pathologies characterized by an abnormal activation of the CXCL8/CXCL1 pathway.

Finally, the results herein reported confirm the valuable contribution of homology models to SAR program when MM/MD analysis is matched with information coming from point mutagenesis studies. Following the same approach, a novel class of CXCR2 selective inhibitors has been recently identified, and the pharmacological characterization of selected compounds is currently in progress.

Experimental Section

A. Biology. Reagents. Compounds were routinely dissolved at the indicated final concentrations in saline (Bieffe Medital, Sondrio, Italy). All chemokines were from PeproTech (London, United Kingdom). All chemicals, cell culture reagents, and protease inhibitors were from Sigma (St. Louis, Missouri). Ficol/Hipaque, Percoll, and dextran were from Pharmacia LKB. Diff-Quik was from Harleco. Boyden chambers and polycarbonate filter were from Neuroprobe, Inc. Transwell filters were from Costar (Cambridge, Massachusetts). Thioglycolate and LPS (from *E. coli* 055:B5) were from Difco (Detroit, MI). Pfx DNA polymerase and pcDNA3 were from Invitrogen (Carlbad, California). Human CXCR1 monoclonal antibody (clone 5A12) was from BD PharMingen, (San Diego, California).

Cells. Human mononuclear cells and PMNs were obtained from buffy coats of heparinized blood from normal volunteers through the courtesy of Centro Trasfusionale, Ospedale S. Salvatore, L'Aquila, Italy. Mononuclear cells were obtained by centrifugation on Ficoll/Hipaque. Monocytes were separated by Percoll gradient centrifugation.[39] Human PMNs were prepared to 95% purity by dextran sedimentation followed by hypotonic lysis of contaminating red blood cells.[40] Cellular viability was >95% in all experiments, as measured by trypan blue dye exclusion.

Migration Assay. Cell migration of human PMNs, human monocytes, was evaluated using a 48-well micro-chemotaxis chamber, as previously described.[41] Cell suspension ($1.5 - 3 \times 10^6$ cells/mL) was incubated at 37 °C for 15 min in the presence of vehicle or of indicated concentrations of compounds and next seeded in triplicates in the upper compartment of the chemotactic chamber. Different agonists were seeded in the lower compartment of the chamber at the following concentrations: 1nM CXCL8, 0.03 nM fMLP, 10 nM CXCL1, 2.5 nM CCL2, 30 nM C5a. The chemotactic chamber was incubated at 37 °C in air with 5% CO_2 for 45 min (human PMNs) or 2 h (monocytes). At the end of incubation, the filter was removed, fixed, and stained and five oil immersion fields at high magnification (100×) were counted for each migration well after sample coding. L1.2 migration was evaluated using 5 μm pore size Transwell filters, as previously described.[42] Briefly, cells were preincubated overnight in growth medium containing 5 mM sodium butyrate to maximize receptor expression, resuspended at 10^7 cells/mL in culture medium, and pretreated for 30 min at 37 °C with indicated concentrations of compound. After treatment, 100 μL of cell suspension were placed onto each Transwell filter, which was transferred into wells containing 600 μL of culture medium supplemented with 1 nM CXCL8 and compound (at the same concentration of the corresponding upper chamber). After 4 h of incubation at 37 °C, the upper chamber was removed and the number of migrated cells was evaluated in a Bürker chamber.

Macrophage Preparation and LPS-Induced PGE_2 Production. Peritoneal exudates cells were collected from peritoneal washing 5 days after i.p. inoculum of 3% thioglycolate in saline (1.5 mL for mouse), as previously described.[43] Cells were then plated at the density of 6×10^5/well in 96-well plates in RPMI 1640 medium, and nonadherent cells were removed by repeated washing 2 h later. Compounds were then added to the macrophages, and 30 min later, 1 μg/mL LPS was added. Control wells received saline at the appropriate dilution. Culture supernatants were harvested 12 h after LPS stimulation. PGE_2 production was measured with an EIA kit (Amersham; sensitivity 2.5 pg/well).

Mutation Analysis of CXCR1. The human CXCR1 open reading frame was PCR amplified from a CXCR1/pCEP4 plasmid (kindly provided by Dr. P. M. Murphy, NIH, Bethesda) using the high fidelity Pfx DNA polymerase. Point mutants were obtained by two-step PCR, as previously described.[44] Wild type and CXCR1 I43V were cloned in the mammalian expression vector pcDNA3. The nucleotide sequence of each construct was confirmed by double-stranded DNA sequencing. The mouse L1.2 lymphoma cell line was grown and transfected transiently by electroporation, as previously described.[45] After 48 h from transfection, expression of CXCR1 was assessed by flow cytometry using an antihuman CXCR1 monoclonal antibody and cells were used for chemotaxis experiments.

B. Molecular Modeling. All the calculations were performed using an IBM eServer 326 Cluster under the Red Hat Enterprise WS3 operating system. The conformational analysis of the ligands was performed with the systematic torsional sampling method implemented in Macromodel 8.6[46] software. Atomic charges and potentials were fixed using the standard OPLS2001 force-field, and the energy level was fixed at 50 kJ/mol.

The minimum-energy conformer of each ligand was manually docked in the putative binding cavity of CXCL8 receptor homology models. With the aim to relax nonbonding interactions in the system, the complexes were energy-refined using steepest descent and conjugate gradient algorithms, as implemented in the DISCOVER package, using the CVFF force field.[47] After, the complexes were submitted to molecular dynamics calculations by using a previously described protocol.[21]

The interaction energies were carried out by using GRID.[48] The grid spacing was fixed at 0.5 Å and the directive MOVE was set to 0. The water (OH2) and DRY probes were used to calculate the MIFs in the putative CXCR1 and CXCR2 allosteric sites of CXCL8 inhibitors. The water probe (OH2) simulates the solvation−desolvation process, whereas the hydrophobic probe (DRY) computes the hydrophobic energy.

All the figures were depicted by using the BODIL package.[49]

C. Chemistry. General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 241 polarimeter and the $[\alpha]_D^{25}$ 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 are reported only with symbols.

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 2-arylpropionic acids **38** (Fenoprofen) and **42** (Indoprofen) are commercially available (Sigma).

Synthesis of Racemic 2-Arylpropanoic Acids (Schemes 1−7). 2-{4[(2-Methylprop-1-enyl]phenyl}propanoic Acid (4). To a solution of intermediate **80** (0.35 g, 1.12 mmol) in anhydrous 1-methyl-2-pyrrolidinone (3 mL) under nitrogen and vigorous stirring, LiCl (0.142 g, 3.37 mmol), CuI (11 mg, 0.056 mmol), $AsPh_3$ (27 mg, 0.09 mmol), and Pd_2dba_3 (21 mg, 0.02 mmol) were added. After stirring 10 min, 2-methyl-1-propenyltributyltin (prepared as described;[50] 0.46 g, 1.34 mmol) was added, and the reaction mixture was left stirring 5 h at 90 °C. After cooling at room temperature, a saturated solution of KF (10 mL) was added and, after stirring 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 back 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[(2-methylprop-1-enyl)phenyl]-

propanoate as a yellow oil (0.18 g, 74% yield). The methyl ester was dissolved in 95% EtOH (3 mL), a 20% alcoholic solution of KOH (3 mL) was added, and the resulting mixture was left stirring 4 h at room temperature. After solvent evaporation, the residue was diluted with water (5 mL) and washed with Et_2O (3 × 5 mL); the aqueous phase was acidified with 1 N HCl (2 × 5 mL) to pH 1 and extracted with EtOAc (2 × 5 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 (petroleum ether/EtOAc 1:1), afforded pure **4** as an off-white wax (0.143 g, 85% yield). ^{1}H NMR ($CDCl_3$): δ 7.47 (d, 2H, J = 7 Hz), 7.18 (d, 2H, J = 7 Hz), 6.24 (m, 1H), 3.74 (q, 1H, J = 7 Hz), 1.88 (d, 6H, J = 8 Hz), 1.53 (d, 3H, J = 7 Hz). Anal. ($C_{13}H_{16}O_2$) C, H.

2-[4-(Cyclohexylphenyl)propanoic Acid (5). To a solution of **80** (5 g, 16.01 mmol) in dry THF (20 mL) under nitrogen atmosphere, LiCl (2.035 g, 48.03 mmol) and $Pd(PPh_3)_4$ (0.74 g, 0.64 mmol) were added. After stirring 10 min at room temperature, cyclohexylzinc bromide (0.5 M in THF; 5.82 g, 24.02 mmol) was added, and the resulting mixture was refluxed overnight. After cooling at room temperature, the solvent was evaporated and the residue was diluted with EtOAc (15 mL), washed with water (2 × 15 mL), dried over Na_2SO_4, and evaporated to give an oily crude that was purified by flash chromatography (*n*-hexane/EtOAc 8:2) to give methyl 2-[4-(cyclohexyl)phenyl]propanoate (3.04 g, 77% yield) as a colorless oil. The methyl ester hydrolysis was performed as described for **4**. Pure **5** was isolated as a white powder (2.64 g, 92% yield), mp 72−74 °C. ^{1}H NMR ($CDCl_3$): δ 10.20 (bs, 1H), 7.18 (d, 2H, J = 7 Hz), 7.10 (d, 2H, J = 7 Hz), 3.75 (q, 1H, J = 7 Hz), 2.50 (m, 1H), 1.90−1.70 (m, 6H), 1.52 (d, 3H, J = 7 Hz), 1.45−1.28 (m, 4H). Anal. ($C_{15}H_{20}O_2$) C, H.

2-[4-(Cyclopropylmethyl)phenyl]propanoic Acid (8). A catalytic amount of CuI was added to commercial cyclopropylmagnesium bromide (0.5 M in THF) (0.61 g, 4.21 mmol) under a nitrogen atmosphere at 0−5 °C, and after stirring 30 min at the same temperature, a solution of commercial 2-[4-(bromomethyl)phenyl]-propanoic acid (0.5 g, 2.05 mmol) in dry THF (5 mL) was added by dripping. After stirring overnight at room temperature, the resulting dark green solution was quenched by adding a KH_2PO_4 buffer solution (pH 2.5, 20 mL). CH_2Cl_2 (20 mL) was added and the two phases were separated. The organic phase was extracted with a saturated solution of $NaHCO_3$ (3 × 5 mL); the collected aqueous extracts were acidified with 2 N HCl to pH 2 and extracted back with CH_2Cl_2 (3 × 10 mL); the collected organic extracts were dried over Na_2SO_4 and, after solvent removal under reduced pressure, afforded the pure compound **8** (0.31 g, yield 75%) as pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.25 (s, 4H), 3.75 (q, 1H, J = 7 Hz), 2.55 (d, 2H, J = 7 Hz), 1.55 (d, 3H, J = 7 Hz), 1.05 (m, 1H), 0.60−0.48 (m, 2H), 0.15 (m, 2H). Anal. ($C_{13}H_{16}O_2$) C, H.

2-[4-(Cyclobutylmethyl)phenyl]propanoic Acid (9). Following the same procedure described for the preparation of **8** and starting from 2-[4-(bromomethyl)phenyl]propanoic acid (0.5 g, 2.05 mmol) and cyclobutylmagnesium bromide (prepared by treatment of cyclobutyl bromide with magnesium turnings;[51] 0.57 g, 4.21 mmol), after workup, **9** was isolated as a colorless oil (0.35 g, yield 79%). ^{1}H NMR ($CDCl_3$): δ 7.24 (d, 2H, J = 7 Hz), 7.10 (d, 2H, J = 7 Hz), 3.75 (q, 1H, J = 7 Hz), 2.75 (d, 2H, J = 7 Hz), 2.55 (m, 1H), 2.11−2.01 (m, 2H), 1.91−1.80 (m, 2H), 1.77−1.68 (m, 2H), 1.52 (d, 3H, J = 7 Hz). Anal. ($C_{14}H_{18}O_2$) C, H.

2-[4-(Cyclopentylmethyl)phenyl]propanoic Acid (10). Following the same procedure described for the preparation of **8** and starting from 2-[4-(bromomethyl)phenyl]propanoic acid (0.5 g, 2.05 mmol) and cyclopentylmagnesium bromide (0.63 g, 4.21 mmol), after workup, **10** was isolated as a colorless oil (0.35 g, yield 73%). ^{1}H NMR ($CDCl_3$): δ 7.25 (d, 2H, J = 7 Hz), 7.10 (d, 2H, J = 7 Hz), 3.72 (q, 1H, J = 7 Hz), 2.60 (d, 2H, J = 7 Hz), 2.05 (m, 1H), 1.81−1.60 (m, 6H), 1.55 (d, 3H, J = 7 Hz), 1.32−1.12 (m, 2H). Anal. ($C_{15}H_{20}O_2$) C, H.

2-[3-(2-Phenylpropyl)phenyl]propanoic Acid (20). To a suspension of intermediate **82** (0.63 g, 2 mmol) in dry DMF (5 mL) under nitrogen and vigorous stirring, bis(triphenylphosphine) palladium(II) chloride (0.14 g, 0.2 mmol) and triethylamine (0.28 mL, 2 mmol) were added. After stirring for 10 min, α-methylstyrene (0.29 mL, 2.2 mmol) was added and the reaction was left stirring for 24 h at 90 °C. After cooling at room temperature, the reaction mixture was diluted with toluene (10 mL) and washed with water (10 mL) and 6 N HCl. The aqueous layers were extracted back with toluene (2 × 10 mL), and the collected organic extracts were washed with water (10 mL) and brine (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 95:5), afforded methyl 2-{3-[2-phenylprop-1-en-1-yl]phenyl}-propanoate as yellow oil (0.42 g, 75% yield). To palladium on charcoal (10% Pd, 50 mg), a solution of the methyl ester (0.4 g, 1.42 mmol) in EtOH (10 mL) was added, and the mixture was stirred under hydrogen until complete disappearance (6 h) of the starting material (TLC). After filtration on a Celite pad, concentration of the mother liquors gave pure methyl 2-[3-(2-phenylpropyl)-phenyl]propanoate (0.39 g, 96% yield). Hydrolysis of the methyl ester was performed as described for **4**. Pure **20** was isolated by flash chromatography (*n*-hexane/EtOAc 9:1) as a pale yellow oil (0.31 g, 85% yield). ^{1}H NMR ($CDCl_3$): δ 7.65 (s, 1H), 7.45−7.12 (m, 7H), 7.05 (t, 1H, J = 3 Hz), 3.60 (q, 1H, J = 7 Hz), 3.35 (q, 1H, J = 7 Hz), 2.85 (dd, 2H, J_1 = 7 Hz, J_2 = 3 Hz), 1.55 (d, 3H, J = 7 Hz), 1.25 (d, 3H, J = 7 Hz). Anal. ($C_{18}H_{20}O_2$) C, H.

2-(3-Propionylphenyl)propanoic Acid (23). Compound **23** was prepared following a described procedure[52] with minor modifications. To a suspension of $ZnCl_2$ (0.390 g, 2.85 mmol) in dry THF (5 mL) at 0 °C under a nitrogen atmosphere commercial ethylmagnesium chloride (2M in Et_2O, 2.85 mL, 5.70 mmol) was added. After stirring for 20 min, dichloro[1,1′-bis(diphenylphosphino)-ferrocene] palladium(II) dichloromethane adduct ($PdCl_2$(dppf); 1 mol %, 46 mg, 0.057 mmol) was added and then a solution of 3-(1-cyanoethyl)benzoyl chloride (1.11 g, 5.72 mmol) in dry THF (5 mL) was dripped. The mixture was stirred for 1 h at 0 °C and for 3 h at room temperature. After cooling to 0 °C, 3 N HCl (10 mL) and Et_2O (30 mL) were added. The two phases were separated and the organic one was washed sequentially with a saturated solution of $NaHCO_3$ (2 × 30 mL) and brine (30 mL), dried over Na_2SO_4, and evaporated under vacuum to a crude oil. The crude was purified by flash chromatography (*n*-hexane/EtOAc 95:5) to afford the intermediate 2-(3-propionylphenyl) propionitrile as pale yellow oil (0.87 g, 81% yield). ^{1}H NMR ($CDCl_3$): δ 7.86 (s, 1H), 7.76 (d, 1H, J = 7 Hz), 7.45−7.35 (m, 2H), 3.84 (q, 1H, J = 7 Hz), 3.45 (m, 1H), 1.68 (d, 3H, J = 7 Hz), 1.1 (d, 6H, J = 7 Hz).

To a solution of 2-(3-propionylphenyl)propionitrile (0.85 g, 4.54 mmol) in dioxane (10 mL), 37% HCl (10 mL) was added. The resulting mixture was left stirring at 70 °C for 4 h. After cooling at room temperature, the solvent was evaporated and the residue was diluted with cold water (10 mL) and extracted with EtOAc (2× 8 mL). The organic layer was extracted back with 1 N NaOH (2 × 5 mL), and the basic aqueous phase was acidified with 1 N HCl to pH 1 and extracted with EtOAc (2 × 5 mL). The collected organic extracts were dried over Na_2SO_4 and evaporated to give pure **23** as a pale yellow oil (0.81 g, 85% yield). ^{1}H NMR ($CDCl_3$): δ 10.50 (bs, 1H), 8.05 (s, 1H), 7.92 (d, 1H, J = 7 Hz), 7.65−7.48 (m, 2H), 3.95 (q, 1H, J = 7 Hz), 3.10 (q, 2H, J = 7 Hz), 1.70 (d, 3H, J = 7 Hz), 1.35 (t, 3H, J = 7 Hz). Anal. ($C_{14}H_{14}O_3$) C, H.

2-(3-Isobutyrylphenyl)propanoic Acid (24). Following the same procedure described for **23** and starting from 3-(1-cyanoethyl)-benzoyl chloride (1.10 g, 5.70 mmol) and commercial isopropylmagnesium chloride (2 M in Et_2O; 0.58 g, 5.70 mmol), after workup and following hydrolysis of the nitrile intermediate, **24** was isolated as a colorless oil (0.86 g, 85% yield). ^{1}H NMR ($CDCl_3$): δ 10.60 (bs, 1H), 7.86 (s, 1H), 7.76 (d, 1H, J = 7 Hz), 7.45−7.35 (m, 2H), 3.79 (q, 1H, J = 7 Hz), 3.45 (m, 1H), 1.45 (d, 3H, J = 7 Hz), 1.15 (d, 6H, J = 7 Hz). Anal. ($C_{13}H_{16}O_3$) C, H.

2-[3-(Cyclopentylcarbonyl)phenyl]propanoic Acid (25). Following the same procedure described for **23** and starting from 3-(1-cyanoethyl)benzoyl chloride (1.10 g, 5.70 mmol) and commercial cyclopentylmagnesium chloride (2 M in Et_2O; 0.73 g, 5.70 mmol),

after workup and following hydrolysis of the nitrile intermediate, **25** was isolated as a pale yellow oil (1.04 g, 74% yield). ^{1}H NMR ($CDCl_3$): δ 7.86 (m, 1H), 7.79 (d, 1H, $J = 7$ Hz), 7.52 (d, 1H, $J = 7$ Hz), 7.37 (m, 1H), 3.82 (q, 1H, $J = 7$ Hz), 3.71 (m, 1H), 2.22 (s, 2H), 2.01 (m, 3H), 1.82 (m, 3H), 1.58 (d, 3H, $J = 7$ Hz). Anal. ($C_{15}H_{18}O_3$) C, H.

2-[3-(Cyclohexylcarbonyl)phenyl]propanoic Acid (26). Following the same procedure described for **23** and starting from 3-(1-cyanoethyl)benzoyl chloride (1.10 g, 5.70 mmol) and commercial cyclohexylmagnesium chloride (2 M in Et_2O; 0.81 g, 5.70 mmol), after workup and following hydrolysis of the nitrile intermediate, **26** was isolated as a pale yellow oil (1.19 g, 80% yield). ^{1}H NMR ($CDCl_3$): δ 7.86 (m, 1H), 7.79 (d, 1H, $J = 7$ Hz), 7.52 (d, 1H, $J = 7$ Hz), 7.37 (m, 1H), 3.80 (q, 1H, $J = 7$ Hz), 3.15 (m, 1H), 1.95−1.80 (m, 4H), 1.52 (d, 3H, $J = 7$ Hz), 1.42−1.18 (m, 6H). Anal. ($C_{16}H_{20}O_3$) C, H.

2-[3-(Thien-2-ylcarbonyl)phenyl]propanoic Acid (27). Compound **27** was prepared essentially following a described procedure[53] but with some modifications. To a solution of thiophene (0.61 mL, 7.60 mmol) in dry THF (50 mL) at −78 °C under nitrogen atmosphere n-BuLi (1.6 M in hexanes, 4.7 mL, 7.60 mmol) was added. After stirring for 20 min, $ZnCl_2$ (2.071 g, 15.20 mmol) was added and the mixture was warmed to 0 °C and stirred for 45 min. CuI (1.45 g, 7.60 mmol) was added, and after stirring for 20 min, a solution of 3-(1-cyanoethyl)benzoyl chloride (2.94 g, 15.2 mmol) in dry THF (10 mL) was added by dripping. After stirring for 2 h, the mixture was diluted with EtOAc (30 mL) and washed sequentially with a saturated solution of $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried over Na_2SO_4, and evaporated under vacuum to a crude oil. The crude was purified by flash chromatography (*n*-hexane/EtOAc 95:5) to afford the intermediate 2-[3-(thien-2-ylcarbonyl)phenyl)propanenitrile as pale yellow oil (1.36 g, 74% yield). ^{1}H NMR ($CDCl_3$): δ 7.85 (m, 2H), 7.70 (m, 1H), 7.60 (d, 1H, $J = 7$ Hz), 7.52 (m, 1H), 7.46 (t, 1H, $J = 7$ Hz), 7.09 (t, 1H, $J = 7$ Hz), 3.95 (q, 1H, $J = 7$ Hz), 1.65 (d, 3H, $J = 7$ Hz).

To a solution of 2-[3-(thien-2-ylcarbonyl)phenyl)propanenitrile (1.07 g, 4.43 mmol) in dioxane (10 mL), 37% HCl (10 mL) was added. The resulting mixture was left stirring at 70 °C for 4 h. After cooling at room temperature, the solvent was evaporated under vacuum and the residue was diluted with EtOAc (15 mL) and washed with cold water (10 mL). The organic layer was extracted back with 1 N NaOH (2 × 5 mL). The aqueous phase was acidified with 1 N HCl to pH 1 and extracted with EtOAc (2 × 10 mL). The organic collected extracts were dried over Na_2SO_4 and evaporated under vacuum to give pure **27** as a brown oil (0.83 g, 72% yield). ^{1}H NMR ($CDCl_3$): δ 7.85 (m, 2H), 7.70 (m, 1H), 7.60 (d, 1H, $J = 7$ Hz), 7.52 (m, 1H), 7.46 (t, 1H, $J = 7$ Hz), 7.15 (t, 1H, $J = 7$ Hz), 3.85 (q, 1H, $J = 7$ Hz), 1.60 (d, 3H, $J = 7$ Hz). Anal. ($C_{14}H_{12}O_3S$) C, H, S.

2-[3-(Furan-2-carbonyl)phenyl]propanoic Acid (28). Following the same procedure described for **27** and starting from commercial furan (0.55 mL, 7.60 mmol) and 3-(1-cyanoethyl)-benzoyl chloride (2.94 g, 15.2 mmol), after workup and following hydrolysis of the nitrile intermediate, **28** was isolated as a pale yellow oil (1.48 g, 80% yield). ^{1}H NMR ($CDCl_3$): δ 7.95 (m, 1H), 7.85 (m, 1H), 7.72 (s, 1H); 7.60 (m, 1H), 7.48 (t, 1H, $J = 7$ Hz), 7.20 (d, 1H, $J = 3$ Hz), 6.60 (m, 1H), 3.85 (q, 1H, $J = 7$ Hz), 1.65 (d, 3H, $J = 7$ Hz). Anal. ($C_{14}H_{12}O_4$) C, H.

2-[3-(1,3-Oxazol-2-ylcarbonyl)phenyl]propanoic Acid (29). Following the same procedure described for **27** and starting from commercial oxazole (0.54 g, 7.60 mmol) and 3-(1-cyanoethyl)-benzoyl chloride (2.94 g, 15.2 mmol), after workup and following hydrolysis of the nitrile intermediate, **29** was isolated as a white solid (1.21 g, 65% yield): mp 121−122 °C. ^{1}H NMR ($CDCl_3$): δ 8.45 (m, 2H), 7.90 (s, 1H), 7.60 (d, 1H, $J = 7$ Hz), 7.45 (t, 1H, $J = 7$ Hz), 7.35 (s, 1H), 3.85 (q, 1H, $J = 7$ Hz), 1.60 (d, 3H, $J = 7$ Hz). Anal. ($C_{13}H_{11}NO_4$) C, H, N.

2-[3-(1,3-Thiazol-2-ylcarbonyl)phenyl]propanoic Acid (30). Following the same procedure described for **27** and starting from commercial thiazole (0.54 mL, 7.60 mmol) and 3-(1-cyanoethyl)-benzoyl chloride (2.94 g, 15.2 mmol), after workup and following hydrolysis of the nitrile intermediate, **30** was isolated as a white glassy solid (1.43 g, 72% yield). ^{1}H NMR ($CDCl_3$): δ 8.40 (m, 2H), 8.10 (s, 1H), 7.75 (s, 1H), 7.60 (d, 1H, $J = 7$ Hz), 7.50 (t, 1H, $J = 7$ Hz), 3.90 (q, 1H, $J = 7$ Hz), 1.60 (d, 3H, $J = 7$ Hz). Anal. ($C_{13}H_{11}NO_3S$) C, H, N, S.

2-[3-(1-Phenylvinyl)phenyl]propanoic Acid (31). To a solution of commercial 2-(3-benzoylphenyl)propanoic acid (ketoprofen; 1 g, 3.93 mmol) in methanol (100 mL), a few drops of concentrated H_2SO_4 were added, and the resulting mixture was left stirring at room temperature overnight. After solvent evaporation at reduced pressure, the crude was diluted with CH_2Cl_2 (25 mL), and the organic phase was washed with 1 N NaOH (2 × 20 mL), dried over Na_2SO_4, and evaporated under vacuum to give 2-(3-benzoylphenyl)propanoic acid methyl ester (0.95 g, 3.54 mmol) as a colorless oil.

To a solution of methyltriphenylphosphonium bromide (1.26 g, 3.54 mmol) in dry THF (10 mL) at room temperature under a nitrogen atmosphere, *n*-BuLi (1.6 M in hexanes, 2.23 mL, 3.54 mmol) was added. After stirring for 3 h, a solution of 2-(3-benzoylphenyl)propanoic acid methyl ester (0.95 g, 3.54 mmol) in dry THF (10 mL) was added by dripping, and the resulting mixture was left stirring overnight at room temperature. After solvent evaporation, the crude was diluted with EtOAc (20 mL) and washed with a 40% $Na_2S_2O_5$ solution (2 × 15 mL) and with water (2 × 15 mL), dried over Na_2SO_4, and evaporated under vacuum to give a crude residue. The crude was purified by flash chromatography (*n*-hexane/EtOAc 95:5) to give methyl 2-[3-(1-phenylvinyl)phenyl]-propanoate (0.56 g, 2.12 mmol) as a colorless oil. The ester (0.31 g, 1.16 mmol) was dissolved in methanol (8 mL) and 1 N NaOH (2 mL) was added. The solution was left stirring overnight at room temperature. After solvent evaporation under reduced pressure, the residue was diluted with CH_2Cl_2 (10 mL) and the organic phase was extracted with H_2O (2 × 5 mL); the collected aqueous extracts were acidified to pH 1 with 1 N HCl and extracted back with CH_2Cl_2 (2 × 10 mL). After drying over Na_2SO_4 and solvent evaporation under vacuum, pure **31** was obtained (0.29 g, quantitative yield) as colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.30−7.15 (m, 9H), 5.50 (m, 2H), 3.80 (q, 1H, $J = 7$ Hz), 1.55 (d, 3H, $J = 7$ Hz). Anal. ($C_{17}H_{16}O_2$) C, H.

2-[3-(1-Phenethylethyl)phenyl]propanoic Acid (35). The synthesis of **35** was performed following a described procedure,[21] using racemate methyl 2-(3-benzoylphenyl)propanoate as starting material. **35** was isolated pure as pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.35−7.12 (m, 9H), 4.15 (q, 1H, $J = 7$ Hz), 3.75 (q, 1H, $J = 7$ Hz), 1.70 (d, 3H, $J = 7$ Hz), 1.48 (d, 3H, $J = 7$ Hz). Anal. ($C_{17}H_{18}O_2$) C, H.

2-[3-(1-Hydroxy-1-phenethylethyl)phenyl]propanoic Acid (36). To a solution of 2-(3-benzoylphenyl)propanoic acid (0.33 g, 1.30 mmol) in dry Et_2O (10 mL) at room temperature under a nitrogen atmosphere, methylmagnesium bromide (3 M in Et_2O, 0.9 mL, 2.7 mmol) was added. The resulting mixture was refluxed for 3 h and, after cooling at room temperature, diluted with Et_2O (10 mL), washed with 2 N HCl (3 × 10 mL) and with water (2 × 10 mL), dried over Na_2SO_4, and evaporated under vacuum to give a crude. After purification by flash chromatography (eluent: $CHCl_3$/CH_3-OH 98:2), pure **36** was obtained as a white powder (0.26 g, 74% yield): mp 93−95 °C. ^{1}H NMR ($CDCl_3$): δ 7.45−7.38 (m, 4H), 7.30−7.15 (m, 5H), 3.65 (q, 1H, $J = 7$ Hz), 1.95 (s, 3H), 1.55 (d, 3H, $J = 7$ Hz). Anal. ($C_{17}H_{18}O_3$) C, H.

2-[3-(Phenylsulfonyl)phenyl]propanoic Acid (37). Compound **37** was prepared following a described procedure[54] starting from intermediate **81** (0.5 g, 1.94 mmol) and commercial benzenesulfinic acid sodium salt (0.38 g, 2.33 mmol). The following hydrolysis of the nitrile intermediate 2-[3-(phenylsulfonyl)phenyl]propanenitrile allowed to obtain pure **37** as a white powder (75% yield from **81**): mp 95−98 °C. ^{1}H NMR ($CDCl_3$): δ 8.00 (s, 1H), 7.95−7.90 (m, 3H), 7.50−7.42 (m, 3H), 7.30 (m, 2H), 3.90 (q, $J = 7$ Hz, 1H), 1.55 (d, 3H, $J = 7$ Hz). Anal. ($C_{15}H_{14}O_4S$) C, H, S.

2-[4-(Benzoyloxy)phenyl]propanoic Acid (39). 2-(4-hydroxyphenyl)propanoic acid (1 g, 6.01 mmol) was dissolved in 1 N NaOH (18 mL). Benzoyl chloride (1.74 mL, 15.02 mmol) was dripped into the solution and, at the same time, 2 N NaOH was

dripped in the flask to basic pH. At the end of the additions, the reaction mixture was left stirring at room temperature for 90 min, 3 N HCl was added to pH 2, and pure **39** was isolated by filtration as a white powder (1.35 g, 83% yield): mp 150−153 °C. ^{1}H NMR ($CDCl_3$): δ 8.25 (d, 2H, J = 7 Hz), 7.68 (t, 1H, J = 7 Hz), 7.55 (t, 2H, J = 7 Hz), 7.40 (d, 2H, J = 7 Hz), 7.21 (d, 2H, J = 7 Hz), 3.82 (q, 1H, J = 7 Hz), 1.55 (d, 3H, J = 7 Hz). Anal. ($C_{16}H_{14}O_4$) C, H.

2-[4-(Propionyloxy)phenyl]propanoic Acid (40). Following the same procedure described for **39** and starting from 2-(4-hydroxyphenyl)propanoic acid (1 g, 6.01 mmol) and propionyl chloride (1.3 mL, 15.02 mmol), after workup, **40** was obtained as a waxy solid (1.00 g, 75% yield). ^{1}H NMR ($CDCl_3$): δ 7.38 (d, 2H, J = 7 Hz), 7.15 (d, 2H, J = 7 Hz), 3.75 (q, 1H, J = 7 Hz), 2.62 (q, 2H, J = 7 Hz), 1.52 (d, 3H, J = 7 Hz), 1.27 (t, 3H, J = 7 Hz). Anal. ($C_{12}H_{14}O_4$) C, H.

2-[4-(Benzoylamino)phenyl]propanoic Acid (41). To a cooled (0−5 °C) solution of benzoyl chloride (0.38 mL, 3.3 mmol) in acetone (5 mL), pyridine (0.64 mL, 7.92 mmol) and methyl 2-(4-aminophenyl)propanoate **83** (0.71 g, 3.3 mmol) were added. The resulting solution was left stirring at room temperature overnight. The solvent was evaporated, and the oily crude was diluted with CH_2Cl_2 (15 mL) and washed with 1 N HCl (2 × 15 mL), water (2 × 10 mL), and brine (20 mL), dried over Na_2SO_4, and evaporated under vacuum to give methyl 2-[4-(benzoylamino)phenyl]propanoic acid (0.67 g, 72% yield) as a yellow solid. To a solution of the methyl ester (0.67 g, 2.36 mmol) in EtOH (10 mL), 2 N NaOH (1.18 mL, 3.54 mmol) was added, and the resulting solution was stirred overnight at room temperature. HCl (1 N) was added by dripping until the precipitation of **41** was complete. Compound **41** was isolated by filtration as a pale yellow powder (0.635 g, quantitative yield): mp > 200 °C. ^{1}H NMR (DMSO-d_6): δ 10.20 (bs, 1H), 8.05 (d, 2H, J = 7 Hz), 7.75 (d, 2H, J = 7 Hz), 7.60−7.50 (m, 3H), 7.32 (d, 2H, J = 7 Hz), 3.65 (q, 1H, J = 7 Hz), 1.52 (d, 3H, J = 7 Hz). Anal. ($C_{16}H_{15}NO_3$) C, H, N.

2-[4-(2-Oxopyrrolidin-1-yl)phenyl]propanoic Acid (43). To a solution of **83** (0.6 g, 3.84 mmol) in CH_2Cl_2 (8 mL), triethylamine (0.54 mL, 3.84 mmoL) was added, and after stirring for 5 min, 4-chlorobutyryl chloride (0.54 g, 3.84 mmol) was dripped into the solution. After stirring for 20 min at room temperature, the solution was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The collected organic extracts were washed with water, dried over Na_2SO_4, and evaporated under vacuum to give methyl 2-{4-[(4-chlorobutanoyl)amino]phenyl}propanoate pure enough to be used in the next step. The ester was dissolved in 2-propanol (6 mL), and 6% NaOH was added by dripping until the complete conversion to **43** (TLC). The mixture was diluted with water (10 mL) and washed with Et_2O (20 mL). The aqueous layer was acidified with 1 N HCl and extracted with EtOAc (2 × 10 mL). The organic extracts were dried over Na_2SO_4 and evaporated under vacuum to give pure **43** as a waxy solid (0.58 g, 65% yield). ^{1}H NMR ($CDCl_3$): δ 7.59 (d, 2H, J = 7 Hz), 7.34 (d, 2H, J = 7 Hz), 3.84 (t, 2H, J = 7 Hz), 3.74 (q, 1H, J = 7 Hz), 2.62 (t, 2H, J = 7 Hz), 2.14 (dd, 2H, J_1 = 7 Hz, J_2 = 4 Hz), 1.51 (d, 3H, J = 7 Hz). Anal. ($C_{13}H_{15}NO_3$) C, H, N.

2-{4-[(Methylsulfonyl)amino]phenyl}propanoic Acid (44). To a solution of **83** (1.85 g, 10.35 mmol) in acetone (20 mL), pyridine (1.24 mL, 15.48 mmol) and methanesulfonyl chloride (0.81 g, 10.4 mmol) were added. The resulting solution was left stirring at room temperature overnight. The solvent was evaporated and the oily crude was diluted with CH_2Cl_2 (50 mL) and washed with water (3 × 100 mL), dried over Na_2SO_4, and evaporated under vacuum to give methyl 2-{4-[(methylsulfonyl)amino]phenyl}propanoate as a slightly pink powder by pulping in diisopropyl ether (2.15 g, 81% yield). The methyl ester hydrolysis was performed as described for **41**. Pure **44** was isolated as a white powder (1.87 g, 92% yield): mp 102−105 °C. ^{1}H NMR ($CDCl_3$): δ 7.32 (d, 2H, J = 7 Hz), 7.24 (d, 2H, J = 7 Hz), 6.52 (bs, 1H), 3.75 (q, 1H, J = 7 Hz), 3.05 (s, 3H), 1.52 (d, 3H, J = 7 Hz). Anal. ($C_{10}H_{13}NO_4S$) C, H, N, S.

2-{4-[(Isopropylsulfonyl)amino]phenyl}propanoic Acid (45). Following the same procedure described for **44** and starting from **83** (1.94 g, 10.82 mmol) and isopropylsulfonyl chloride (1.88 mL, 13 mmol), after workup and purification, **45** was obtained as a pale brown powder (1.7 g, 87% yield): mp 168−172 °C. ^{1}H NMR ($CDCl_3$): δ 7.40 (bs, 1H), 7.28 (d, 2H, J = 7 Hz), 7.17 (d, 2H, J = 7 Hz), 3.70 (q, 1H, J = 7 Hz), 3.25 (m, 1H), 1.52 (d, 3H, J = 7 Hz), 1.35 (d, 6H, J = 7 Hz). Anal. ($C_{12}H_{17}NO_4S$) C, H, N, S.

2-{4-[(Phenylsulfonyl)amino]phenyl}propanoic Acid (46). Following the same procedure described for **44** and starting from **83** (1.94 g, 10.82 mmol) and benzenesulfonyl chloride (1.66 mL, 13 mmol), after workup and purification, **46** was obtained as a white powder (2.64 g, 80% yield), mp 161−164 °C. ^{1}H NMR ($CDCl_3$): δ 9.38 (bs, 1H), 7.73 (m, 2H), 7.40−7.25 (m, 3H), 7.05 (d, 2H, J = 7 Hz), 6.92 (d, 2H, J = 7 Hz), 3.45 (q, 1H, J = 7 Hz), 1.27 (d, 3H, J = 7 Hz). Anal. ($C_{15}H_{15}NO_4S$) C, H, N, S.

2-(4-{[(2-Ethylphenyl)sulfonyl]amino}phenyl)propanoic Acid (47). Following the same procedure described for **44** and starting from **83** (1.94 g, 10.82 mmol) and 2-ethyl benzenesulfonyl chloride (prepared by treatment of 2-ethylbenzene sulfonic acid with thionyl chloride; 2.66 g, 13 mmol), after workup and purification, **47** was obtained as a glassy solid (2.81 g, 65% yield). ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H, J = 7 Hz), 7.67 (m, 1H), 7.52 (d, 1H, J = 7 Hz), 7.40 (bs, 1H), 7.35 (d, 2H, J = 7 Hz), 7.10 (d, 2H, J = 7 Hz), 3.80 (q, 1H, J = 7 Hz), 3.18 (q, 2H, J = 7 Hz), 1.57 (d, 3H, J = 7 Hz), 1.40 (t, 3H, J = 7 Hz). Anal. ($C_{17}H_{19}NO_4S$) C, H, N, S.

2-(4-{[(4-Methylphenyl)sulfonyl]amino}phenyl)propanoic Acid (48). Following the same procedure described for **44** and starting from **83** (1.94 g, 10.82 mmol) and *p*-toluenesulfonyl chloride (2.47 g, 13 mmol), after workup and purification, **48** was obtained as a white powder (2.56 g, 74% yield): mp 150−152 °C. ^{1}H NMR (DMSO-d_6): δ 12.23 (bs, 1H), 10.19 (bs, 1H), 7.65 (d, 2H, J = 8 Hz), 7.34 (d, 2H, J = 8 Hz), 7.12 (d, 2H, J = 7 Hz), 7.02 (d, 2H, J = 7 Hz), 3.54 (q, 1H, J = 7 Hz), 2.33 (s, 3H), 1.27 (d, 3H, J = 7 Hz). Anal. ($C_{16}H_{17}NO_4S$) C, H, N, S.

2-(4-{[(2-Chlorophenyl)sulfonyl]amino}phenyl)propanoic Acid (49). Following the same procedure described for **44** and starting from **83** (1.94 g, 10.82 mmol) and 2-chlorobenzenesulfonyl chloride (prepared by treatment of 2-chlorobenzene sulfonic acid with thionyl chloride; 2.74 g, 13 mmol), after workup and purification, **49** was obtained as a wax (2.28 g, 62% yield). ^{1}H NMR ($CDCl_3$): δ 8.05 (d, 1H, J = 7 Hz), 7.40 (q, 2H, J = 3 Hz), 7.25 (m, 1H), 7.10 (d, 2H, J = 7 Hz), 6.95 (d, 2H, J = 7 Hz), 3.58 (q, 1H, J = 7 Hz), 1.45 (d, 3H, J = 7 Hz). Anal. ($C_{15}H_{14}ClNO_4S$) C, H, Cl, N, S.

2-(4-{[(Trifluoromethyl)sulfonyl]amino}phenyl)propanoic Acid (50). Following the same procedure described for **44** and starting from **83** (1.94 g, 10.82 mmol) and trifluoromethanesulfonyl chloride (1.38 mL, 13 mmol), after workup and purification, **50** was obtained as a white solid (1.41 g, 44% yield): mp 132−135 °C. ^{1}H NMR ($CDCl_3$): δ 7.25 (d, 2H, J = 7 Hz), 7.12 (d, 2H, J = 7 Hz), 3.60 (q, 1H, J = 7 Hz), 1.45 (d, 3H, J = 7 Hz). Anal. ($C_{10}H_{10}F_3NO_4S$) C, H, F, N, S.

2-{4-[(Methylsulfonyl)oxy]phenyl}propanoic Acid (51). To a solution of commercial 2-(4-hydroxy)phenylpropanoic acid (50 g, 0.29 mol) in CH_3OH (50 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)phenylpropanoate (51.6 g, 0.28 mol). To a solution of the methyl ester (3.4 g, 18.9 mmol) in pyridine (25 mL), methanesulfonyl chloride (1.46 mL, 18.9 mmol) was added by dripping. The reaction mixture was refluxed for 24 h. After cooling at room temperature, the solvent was evaporated, and the oily crude was diluted with CH_2Cl_2 (50 mL), washed with 1 N HCl (2 × 50 mL), 1 N NaOH (2 × 35 mL), and water (2 × 100 mL), dried over Na_2SO_4, and evaporated under vacuum to give methyl 2-{4-[(methylsulfonyl)oxy]phenyl}propanoate (3.48 g, 71% yield) as an oil. The methyl ester was dissolved in glacial AcOH

(15 mL), 37% HCl (2.7 mL) was added, and the resulting solution was refluxed overnight. After cooling at room temperature, the residue was dissolved in CH_2Cl_2 (30 mL) and washed with water (2 × 50 mL), dried over Na_2SO_4, and evaporated under vacuum to give **51** (3.11 g, 95% yield) as a pale yellow powder, mp 80−82 °C. ^{1}H NMR ($CDCl_3$): δ 7.45 (d, 2H, J = 7 Hz), 7.25 (d, 2H, J = 7 Hz), 3.82 (q, 1H, J = 7 Hz), 3.15 (s, 3H), 1.55 (d, 3H, J = 7 Hz). Anal. ($C_{10}H_{12}O_5S$) C, H, S.

2-{4-[(Isopropylsulfonyl)oxy]phenyl}propanoic Acid (52). Following the same procedure described for **51** and starting from methyl 2-(4-hydroxy)phenyl propanoate (3.4 g, 18.9 mmol) and 2-propanesulfonyl chloride (2.12 mL, 18.9 mmol), after workup and following hydrolysis of the methyl ester intermediate, **52** was obtained as a pale yellow powder (3.76 g, 73% yield): mp 62−64 °C. ^{1}H NMR ($CDCl_3$): δ 7.37 (d, 2H, J = 7 Hz), 7.25 (d, 2H, J = 7 Hz), 3.71 (q, 1H, J = 7 Hz), 3.45 (m, 1H), 1.55 (d, 3H, J = 7 Hz). Anal. ($C_{12}H_{16}O_5S$) C, H, S.

2-{4-[(Phenylsulfonyl)oxy]phenyl}propanoic Acid (53). Following the same procedure described for **51** and starting from methyl 2-(4-hydroxy)phenyl propanoate (3.4 g, 18.9 mmol) and benzenesulfonyl chloride (2.41 mL, 18.9 mmol), after workup and following hydrolysis of the methyl ester intermediate, **53** was obtained as a pale brown powder (4.74 g, 82% yield): mp 68−70 °C. ^{1}H NMR ($CDCl_3$): δ 7.86 (d, 2H, J = 7 Hz), 7.68 (t, 1H, J = 7 Hz), 7.54 (t, 2H, J = 7 Hz), 7.24 (d, 2H, J = 7 Hz), 6.96 (d, 2H, J = 7 Hz), 3.71 (q, 1H, J = 7 Hz), 1.43 (d, 3H, J = 7 Hz). Anal. ($C_{15}H_{14}O_5S$) C, H, S.

2-(4-{[(4-Methylphenyl)sulfonyl]oxy}phenyl)propanoic Acid (54). Following the same procedure described for **51** and starting from methyl 2-(4-hydroxy)phenyl propanoate (3.4 g, 18.9 mmol) and *p*-toluenesulfonyl chloride (3.6 g, 18.9 mmol), after workup and following hydrolysis of the methyl ester intermediate, **54** was obtained as a pale yellow oil (4.72 g, 78% yield). ^{1}H NMR ($CDCl_3$): δ 7.73 (d, 2H, J = 7 Hz), 7.33 (d, 2H, J = 7 Hz), 7.25 (d, 2H, J = 7 Hz), 6.96 (d, 2H, J = 7 Hz), 3.71 (q, 1H, J = 7 Hz), 2.47 (s, 3H), 1.43 (d, 3H, J = 7 Hz). Anal. ($C_{16}H_{16}O_5S$) C, H, S.

Synthesis of Acylsulfonamides (Scheme 8). 4-{(1*R*)-2-[(Isopropylsulfonyl)amino]-1-methyl-2-oxoethyl}phenyl trifluoromethanesulfonate (58). To a cooled mixture (0−5 °C) of **56** (0.5 g, 1.68 mmol) in CH_2Cl_2 (3 mL), 1,1′-carbonyldiimidazole (CDI) (0.27 g, 1.70 mmol) was added. After stirring 2 h at 0−5 °C, isopropylsulfonamide (0.21 g, 1.68 mmol) and diazobicyclo-[5.4.0]undec-7-ene (DBU; 0.26 mL, 1.68 mmol) were added, and the mixture was left stirring for 4 h. Glacial AcOH (0.2 mL, 3.5 mmol) 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 × 10 mL) and water (3 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a crude residue that was purified by flash chromatography (CH_2Cl_2/CH_3OH 95:5) to afford **58** as a pale yellow oil (1.24 g, 74% yield). $[\alpha]_D^{25}$ −20° (*c* 0.72, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 7.85 (bs, 1H), 7.52 (d, 2H, J = 7 Hz), 7.32 (d, 2H, J = 7 Hz), 3.75 (m, 2H), 1.57 (d, 3H, J = 7 Hz), 1.40 (d, 3H, J = 7 Hz), 1.25 (d, 3H, J = 7 Hz). Anal. ($C_{13}H_{16}F_3NO_6S_2$) C, H, S, N.

4-{(1*R*)-1-Methyl-2-oxo-2-[(phenylsulfonyl)amino]ethyl}phenyl trifluoromethanesulfonate (59). Following the same procedure described for **58** and starting from **56** (0.5 g, 1.68 mmol) and benzenesulfonamide (0.26 g, 1.68 mmol), after workup and purification by flash chromatography ($CHCl_3$/CH_3OH 95:5), **59** was obtained as a pale yellow oil (0.602 g, 82% yield). $[\alpha]_D^{25}$ −60° (*c* 0.62, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 8.05 (bs, 1H), 7.92 (d, 2H, J = 7 Hz), 7.65 (t, 1H, J = 7 Hz), 7.52 (t, 2H, J = 7 Hz), 7.18 (s, 4H), 3.60 (q, 1H, J = 7 Hz), 1.45 (d, 3H, J = 7 Hz). Anal. ($C_{16}H_{14}F_3NO_6S_2$) C, H, S, N.

4-[(1*R*)-2-{[(2-Chlorophenyl)sulfonyl]amino}-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (60). Following the same procedure described for **58** and starting from **56** (0.5 g, 1.68 mmol) and 2-chlorobenzenesulfonamide (0.32 g, 1.68 mmol), after workup and purification by flash chromatography ($CHCl_3$/CH_3OH 95:5), **60** was obtained as a white powder (0.602 g, 76% yield): mp 120−125 °C. $[\alpha]_D^{25}$ −62° (*c* 0.4, CH_3OH). ^{1}H NMR (DMSO-d_6): δ 8.10 (d, 1H, J = 7 Hz), 7.68−7.62 (m, 1H), 7.58−7.43 (m, 3H), 7.45 (d, 2H, J = 7 Hz), 7.38 (d, 2H, J = 7 Hz), 3.85 (q, 1H, J = 7 Hz), 1.30 (d, 3H, J = 7 Hz). Anal. ($C_{16}H_{13}ClF_3NO_6S_2$) C, H, S, N.

4-{(1*R*)-1-Methyl-2-oxo-2-[(pyridin-3-ylsulfonyl)amino]ethyl}phenyl trifluoromethanesulfonate (61). Following the same procedure described for **58** and starting from **56** (0.2 g, 0.67 mmol) and pyridine-2-sulfonamide (0.1 g, 0.67 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 9:1), **61** was obtained as a white powder (0.194 g, 66% yield): mp 157−160 °C. $[\alpha]_D^{25}$ −82° (*c* 0.5, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 9.20 (m, 1H), 8.92 (m, 1H), 8.40 (m, 1H), 7.55 (m, 1H), 7.25 (s, 4H), 3.65 (q, 1H, J = 7 Hz), 1.48 (d, 3H, J = 7 Hz). Anal. ($C_{15}H_{13}ClF_3N_2O_6S_2$) C, H, S, N.

4-[(1*R*)-1-Methyl-2-oxo-2-{[(trifluoromethyl)sulfonyl]amino}ethyl]phenyl trifluoromethanesulfonate (62). Following the same procedure described for **58** and starting from **56** (0.2 g, 0.67 mmol) and trifluoromethanesulfonamide (0.1 g, 0.67 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 9:1), **62** was obtained as a white powder (0.155 g, 54% yield), mp 102−104 °C. $[\alpha]_D^{25}$ −11° (*c* 0.5, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 7.85 (bs, 1H), 7.45 (d, 2H, J = 7 Hz), 7.38 (d, 2H, J = 7 Hz), 3.85 (q, 1H, J = 7 Hz), 1.60 (d, 3H, J = 7 Hz). Anal. ($C_{11}H_9F_6NO_6S_2$) C, H, S, N.

Synthesis of N- and O-Alkyl Derivatives (Scheme 8). 4-[(1*R*)-2-(Hydroxyamino)-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (63). Compound **56** (1.00 g, 3.3 mmol) was dissolved in toluene (10 mL), and $SOCl_2$ (3 mL) was added. 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 added by dripping to a suspension of hydroxylamine hydrochloride (0.23 g, 3.3 mmol) and $NaHCO_3$ (0.28 g, 3.3 mmol) in dry CH_2Cl_2 (5 mL). The resulting mixture was left under stirring at room temperature overnight. The mixture was diluted with CH_2Cl_2 (10 mL), and the organic layer was washed with 1 N HCl (2 × 10 mL) and brine (3 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a crude residue that was purified by pulping in *n*-hexane to give, after filtration, pure **63** as a pale brown powder (0.9 g, 87% yield): mp 82−84 °C. $[\alpha]_D^{25}$ −25° (*c* 0.7, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 8.20 (bs, 2H), 7.35 (d, 2H, J = 7 Hz), 7.15 (d, 2H, J = 7 Hz), 3.48 (q, 1H, J = 7 Hz), 1.47 (d, 3H, J = 7 Hz). Anal. ($C_{10}H_{10}F_3NO_5S$) C, H, S, N.

4-{(1*R*)-2-[Hydroxy(methyl)amino]-1-methyl-2-oxoethyl}phenyl trifluoromethanesulfonate (64). To a cooled (−20 °C) solution of DMF (0.42 mL, 5.42 mmol) in CH_2Cl_2 (2 mL), a solution of oxalyl chloride (0.16 mL, 1.83 mmol) in CH_2Cl_2 (5 mL) was added by dripping. The temperature was raised up to 0 °C, and after stirring for 30 min, **56** (0.5 g, 1.67 mmol) and 4-methylmorpholine (0.185 mL, 1.67 mmol) were added. After stirring for an additional 30 min, *N*-methylhydroxylamine hydrochloride (0.27 g, 3.3 mmol) and 4-methylmorpholine (0.73 mL, 6.6 mmol) were added. The resulting mixture was left stirring overnight at room temperature. After filtration of the formed precipitate, the mother liquors were evaporated, the crude was dissolved in CH_2Cl_2 (10 mL), and the organic layer was washed with 1 N HCl (2 × 10 mL), a saturated solution of $NaHCO_3$ (2 × 10 mL), and water (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude oily residue that, after flash chromatography (CH_2Cl_2/CH_3OH 95:5), afforded pure **64** as a colorless oil (0.27 g, 50% yield). $[\alpha]_D^{25}$ −23° (*c* 1, CH_3OH). ^{1}H NMR (DMSO-d_6): δ 9.95 (bs, 1H), 7.45 (m, 4H), 4.35 (q, 1H, J = 7 Hz), 3.10 (s, 3H), 1.32 (d, 3H, J = 7 Hz). Anal. ($C_{11}H_{12}F_3NO_5S$) C, H, S, N.

4-[(1*R*)-2-(Methoxyamino)-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (65). Following the same procedure described for **63** and starting from **56** (0.5 g, 1.67 mmol) and methoxyamine hydrochloride (0.14 g, 1.67 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 98:2), pure **65** was obtained as a colorless oil (0.37 g, 63% yield). $[\alpha]_D^{25}$ −18° (*c* 0.5, CH_3OH). ^{1}H NMR (DMSO-d_6): δ 10.95 (bs, 1H),

7.50−7.30 (m, 4H), 3.85 (m, 1H), 3.45 (q, 1H, $J = 7$ Hz), 1.30 (d, 3H, $J = 7$ Hz), 1.05 (d, 6H, $J = 7$ Hz). Anal. ($C_{13}H_{16}F_3NO_5S$) C, H, S, N.

4-[(1*R*)-2-(Isopropoxyamino)-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (66). Following the same procedure described for **63** and starting from **56** (0.5 g, 1.67 mmol) and *O*-isopropylhydroxylamine hydrochloride (0.19 g, 1.67 mmol), after workup and purification by pulping in *n*-hexane, pure **66** was obtained as a waxy solid (0.44 g, 81% yield). $[\alpha]_D^{25}$ −24° (*c* 0.5, CH_3OH). ^1H NMR ($CDCl_3$): δ 8.20 (bs, 1H), 7.48 (d, 2H, $J = 7$ Hz), 7.22 (d, 2H, $J = 7$ Hz), 3.72 (s, 3H), 3.45 (q, 1H, $J = 7$ Hz), 1.55 (d, 3H, $J = 7$ Hz). Anal. ($C_{11}H_{12}F_3NO_5S$) C, H, S, N.

Synthesis of Amides (Scheme 8). 4-[(1*R*)-1-Methyl-2-(methylamino)-2-oxoethyl]phenyl trifluoromethanesulfonate (68). To a solution of 4-[(1*R*)-2-chloro-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (prepared as described for **63**; 0.54 g, 1.68 mmol) in CH_2Cl_2 (5 mL), methylamine (2.0 M in THF; 2.52 mL, 5.04 mmol) was added by dripping. After stirring for 4 h, solvents were evaporated, the crude was dissolved in CH_2Cl_2 (5 mL), and the organic layer was washed with 6 N HCl (2 × 10 mL), a saturated solution of $NaHCO_3$ (2 × 10 mL), and water (2 × 20 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give a crude residue. By flash chromatography (CH_2Cl_2/CH_3OH 98:2), pure **68** was isolated as a pale yellow oil (0.36 g, 69% yield). $[\alpha]_D^{25}$ −20° (*c* 1, MeOH). ^1H NMR ($CDCl_3$): δ 7.42 (d, 2H, $J = 7$ Hz), 7.25 (d, 2H, $J = 7$ Hz), 5.35 (bs, 1H), 3.56 (q, 1H, $J = 7$ Hz), 2.80 (s, 3H), 1.55 (d, 3H, $J = 7$ Hz). Anal. ($C_{11}H_{12}F_3NO_4S$) C, H, S, N.

4-[(1*R*)-2-(Isopropylamino)-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (69). Following the same procedure described for **68** and starting from 4-[(1*R*)-2-chloro-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (0.54 g, 1.68 mmol) and isopropylamine (0.29 g, 5.04 mmol), after workup and purification by pulping in *n*-hexane, pure **69** was obtained as a white powder (0.34 g, 60% yield): mp 78−80 °C. $[\alpha]_D^{25}$ −2° (*c* 0.5, CH_3OH). ^1H NMR ($CDCl_3$): δ 7.40 (d, 2H, $J = 7$ Hz), 7.25 (d, 2H, $J = 7$ Hz), 5.15 (bs, 1H), 4.08 (m, 1H), 3.50 (q, 1H, $J = 7$ Hz), 1.55 (d, 3H, $J = 7$ Hz), 1.15 (d, 3H, $J = 7$ Hz), 1.05 (d, 3H, $J = 7$ Hz). Anal. ($C_{13}H_{16}F_3NO_4S$) C, H, S, N.

4-[(1*R*)-2-(Cyclopropylamino)-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (70). Following the same procedure described for **68** and starting from 4-[(1*R*)-2-chloro-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (0.54 g, 1.68 mmol) and cyclopropylamine (0.35 mL, 5.04 mmol), after workup and purification by pulping in *n*-hexane, pure **70** was obtained as a white powder (0.41 g, 73% yield): mp 58−61 °C. $[\alpha]_D^{25}$ −5° (*c* 0.5, CH_3OH). ^1H NMR ($CDCl_3$): δ 7.40 (d, 2H, $J = 7$ Hz), 7.25 (d, 2H, $J = 7$ Hz), 5.45 (bs, 1H), 3.50 (q, 1H, $J = 7$ Hz), 2.80 (m, 1H), 1.52 (d, 3H, $J = 7$ Hz), 0.85−0.75 (m, 2H), 0.50−0.38 (m, 2H). Anal. ($C_{13}H_{14}F_3NO_4S$) C, H, S, N.

4-{(1*R*)-2-[(Cyclopropylmethyl)amino]-1-methyl-2-oxoethyl}phenyl trifluoromethanesulfonate (71). Following the same procedure described for **68** and starting from 4-[(1*R*)-2-chloro-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (0.54 g, 1.68 mmol) and (aminomethyl)cyclopropane (0.44 mL, 5.04 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 99:1), pure **71** was obtained as a pale yellow oil (0.41 g, 70% yield). $[\alpha]_D^{25}$ −15° (*c* 0.5, CH_3OH). ^1H NMR ($CDCl_3$): δ 7.45 (d, 2H, $J = 7$ Hz), 7.25 (d, 2H, $J = 7$ Hz), 5.50 (bs, 1H), 3.55 (q, 1H, $J = 7$ Hz), 3.10 (m, 2H), 1.52 (d, 3H, $J = 7$ Hz), 0.90 (m, 1H), 0.45 (d, 2H, $J = 7$ Hz), 0.15 (d, 2H, $J = 7$ Hz). Anal. ($C_{14}H_{16}F_3NO_4S$) C, H, S, N.

4-[(1*R*)-2-(Cyclopentylamino)-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (72). Following the same procedure described for **68** and starting from 4-[(1*R*)-2-chloro-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (0.54 g, 1.68 mmol) and cyclopropylamine (0.35 mL, 5.04 mmol), after workup and purification by pulping in isopropyl ether, pure **72** was obtained as a white powder (0.34 g, 56% yield): mp 107−110 °C. $[\alpha]_D^{25}$ −2° (*c* 0.5, CH_3OH). ^1H NMR ($CDCl_3$): δ 7.45 (d, 2H, $J = 7$ Hz), 7.25 (d, 2H, $J = 7$ Hz), 5.30 (bs, 1H), 4.20 (m, 1H), 3.55 (q, 1H, $J = 7$ Hz), 2.05−1.95 (m, 2H), 1.68−1.60 (m, 4H), 1.52 (d, 3H, $J = 7$ Hz), 1.35−1.20 (m, 2H). Anal. ($C_{15}H_{18}F_3NO_4S$) C, H, S, N.

4-[(1*R*)-2-Anilino-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (73). Following the same procedure described for **68** and starting from 4-[(1*R*)-2-chloro-1-methyl-2-oxoethyl]-phenyl trifluoromethanesulfonate (0.54 g, 1.68 mmol) and aniline (0.46 mL, 5.04 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 99:1), pure **73** was obtained as a colorless oil (0.31 g, 50% yield). $[\alpha]_D^{25}$ −30° (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$): δ 7.45 (d, 2H, $J = 7$ Hz), 7.32 (m, 2H), 7.25 (d, 2H, $J = 7$ Hz), 7.05 (t, 1H, $J = 7$ Hz), 6.95−6.80 (m, 2H), 5.30 (bs, 1H), 3.55 (q, 1H, $J = 7$ Hz), 1.52 (d, 3H, $J = 7$ Hz). Anal. ($C_{16}H_{14}F_3NO_4S$) C, H, S, N.

4-[(1*R*)-1-Methyl-2-oxo-2-(pyridin-2-ylamino)ethyl]phenyl trifluoromethanesulfonate (74). Following the same procedure described for **68** and starting from 4-[(1*R*)-2-chloro-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (0.54 g, 1.68 mmol), 2-aminopyridine (0.16 g, 1.68 mmol) and triethylamine (0.23 mL, 1.68 mmol), after workup and purification by pulping in isopropyl ether, pure **74** was obtained as a waxy solid (0.49 g, 78% yield). $[\alpha]_D^{25}$ −35° (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$): δ 8.28−8.20 (m, 2H), 8.10 (bs, 1H), 7.78−7.70 (m, 1H), 7.48 (d, 2H, $J = 7$ Hz), 7.30 (d, 2H, $J = 7$ Hz), 7.12−7.05 (m, 1H), 3.78 (q, 1H, $J = 7$ Hz), 1.65 (d, 3H, $J = 7$ Hz). Anal. ($C_{15}H_{13}F_3N_2O_4S$) C, H, S, N.

4-[(1*R*)-1-Methyl-2-oxo-2-(pyridin-3-ylamino)ethyl]phenyl trifluoromethanesulfonate (75). Following the same procedure described for **68** and starting from 4-[(1*R*)-2-chloro-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (0.54 g, 1.68 mmol), 3-aminopyridine (0.16 g, 1.68 mmol) and triethylamine (0.23 mL, 1.68 mmol), after workup and purification by pulping in isopropyl ether, pure **75** was obtained as a waxy solid (0.47 g, 75% yield). $[\alpha]_D^{25}$ −37° (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$): δ 8.20 (s, 1H), 8.15 (bs, 1H), 8.05 (m, 1H), 7.45 (d, 2H, $J = 7$ Hz), 7.30 (d, 2H, $J = 7$ Hz), 7.26−7.20 (m, 1H), 7.12−7.05 (m, 1H), 3.75 (q, 1H, $J = 7$ Hz), 1.60 (d, 3H, $J = 7$ Hz). Anal. ($C_{15}H_{13}F_3N_2O_4S$) C, H, S, N.

4-[(1*R*)-1-Methyl-2-oxo-2-(pyridin-4-ylamino)ethyl]phenyl trifluoromethanesulfonate (76). Following the same procedure described for **68** and starting from 4-[(1*R*)-2-chloro-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (0.54 g, 1.68 mmol), 4-aminopyridine (0.16 g, 1.68 mmol) and triethylamine (0.23 mL, 1.68 mmol), after workup and purification by flash chromatography (CH_2Cl_2/CH_3OH 95:5), pure **76** was obtained as a colorless oil (0.51 g, 82% yield). $[\alpha]_D^{25}$ −41° (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$): δ 8.15 (bs, 1H), 8.03 (d, 2H, $J = 5$ Hz), 7.45 (d, 2H, $J = 7$ Hz), 7.30 (d, 2H, $J = 7$ Hz), 6.90 (d, 2H, $J = 5$ Hz), 3.75 (q, 1H, $J = 7$ Hz), 1.60 (d, 3H, $J = 7$ Hz). Anal. ($C_{15}H_{13}F_3N_2O_4S$) C, H, S, N.

4-[(1*R*)-1-Methyl-2-oxo-2-(1,3-thiazol-2-ylamino)ethyl]phenyl trifluoromethanesulfonate (77). Following the same procedure described for **68** and starting from 4-[(1*R*)-2-chloro-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (0.54 g, 1.68 mmol) and 2-aminothiazole (0.5 g, 5.04 mmol), after workup and purification by pulping in isopropyl ether, pure **77** was obtained as a pale brown powder (0.47 g, 73% yield): mp 128−130 °C. $[\alpha]_D^{25}$ −55° (*c* 0.5, CH_3OH). ^1H NMR ($CDCl_3$): δ 10.65 (bs, 1H), 7.45 (m, 3H), 7.30 (d, 2H, $J = 7$ Hz), 7.05 (d, 1H, $J = 3$ Hz), 3.90 (q, 1H, $J = 7$ Hz), 1.75 (d, 3H, $J = 7$ Hz). Anal. ($C_{13}H_{11}F_3N_2O_4S_2$) C, H, S, N.

4-[(1*R*)-1-Methyl-2-(1,3-oxazol-2-ylamino)-2-oxoethyl]phenyl trifluoromethanesulfonate (78). Following the same procedure described for **68** and starting from 4-[(1*R*)-2-chloro-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (0.54 g, 1.68 mmol) and 2-aminooxazole (0.42 g, 5.04 mmol), after workup and purification by pulping in *n*-hexane, pure **78** was obtained as a white powder (0.24 g, 70% yield): mp 127−130 °C. $[\alpha]_D^{25}$ −8° (*c* 0.5, CH_3OH). ^1H NMR ($CDCl_3$): δ 8.50 (bs, 1H), 7.75 (s, 1H), 7.45 (s, 1H), 7.40 (d, 2H, $J = 7$ Hz), 7.27 (d, 2H, $J = 7$ Hz), 4.15 (q, 1H, $J = 7$ Hz), 1.60 (d, 3H, $J = 7$ Hz). Anal. ($C_{13}H_{11}F_3N_2O_5S_2$) C, H, S, N.

4-[(1*R*)-1-Methyl-2-oxo-2-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}ethyl]phenyl trifluoromethanesulfonate (79). Following the same procedure described for **68** and starting from 4-[(1*R*)-2-

chloro-1-methyl-2-oxoethyl]phenyl trifluoromethanesulfonate (0.54 g, 1.68 mmol) and 2-amino-4-trifluoromethylthiazole[28] (0.85 g, 5.04 mmol), after workup and purification by pulping in *n*-hexane, pure **79** was obtained as a white powder (0.68 g, 90% yield): mp 150−153 °C. $[\alpha]_D^{25}$ −21° (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$): δ 8.75 (bs, 1H), 7.50−7.40 (m, 3H), 7.28 (d, 2H, $J = 7$ Hz), 3.85 (q, 1H, $J = 7$ Hz), 1.55 (d, 3H, $J = 7$ Hz). Anal. ($C_{14}H_{10}F_6N_2O_4S_2$) C, H, S, N.

Synthesis of Intermediates. 2-(3-Iodophenyl)propanenitrile (81). Commercial 3-(1-cyanoethyl)benzoic acid (2.5 g, 14.25 mmol) was dissolved in $SOCl_2$ (5 mL), and the resulting solution was left stirring for 3 h at reflux. After cooling at room temperature, the mixture was evaporated under reduced pressure. The crude acyl chloride was diluted with CH_2Cl_2 (15 mL), tetrabutylammonium bromide (23 mg, 0.07 mmol) was added, and the mixture was cooled to 0−5 °C. Under vigorous stirring, a solution of NaN_3 (1.275 g, 19.5 mmol) in H_2O (5 mL) was added, and the resulting mixture was left stirring at 0−5 °C for 2 h. The formed precipitate was filtered off, and the organic phase was washed with H_2O (3 × 25 mL), dried over Na_2SO_4, treated with trifluoroacetic acid (TFA; 1.59 mL, 21.38 mmol), and refluxed for 48 h. After cooling at room temperature, TFA was evaporated under reduced pressure and the crude residue was diluted with CH_2Cl_2 (50 mL) and washed sequentially with a saturated solution of $NaHCO_3$ (2 × 25 mL) and H_2O (50 mL). After Na_2SO_4 drying and solvent evaporation under reduced pressure, 2-[(3-trifluoroacetylamino)phenyl]propanenitrile was obtained pure enough (TLC) to be used for the following step. A mixture of 2-[(3-trifluoroacetylamino) phenyl]-propanenitrile (2.5 g, 9.25 mmol) and K_2CO_3 (2.55 g, 17.6 mmol) in H_2O/CH_3OH (3:1; 50 mL) was heated at 60 °C for 16 h. After cooling at room temperature and solvent evaporation, the crude was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The collected organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give pure 2-(3-aminophenyl)-propanenitrile as a pale yellow oil (1.2 g, 90% yield). ^1H NMR ($CDCl_3$): δ 7.08 (m, 1H), 6.64 (m, 2H), 6.57 (m, 1H), 3.72 (q, 1H, $J = 7$ Hz), 3.65 (bs, 2H), 1.54 (d, 3H, $J = 7$ Hz).

To a stirred suspension of 2-(3-aminophenyl)propanenitrile (1.0 g, 6.75 mmol) in H_2O (12 mL), 37% HCl (1.6 mL, 20.2 mmol) was added dropwise. After stirring for 5 min, the mixture was cooled (0−4 °C), a solution of $NaNO_2$ (0.466 g, 6.75 mmol) in H_2O (5 mL) was added dropwise, and the resulting solution was left stirring for 20 min. Then a solution of KI (1.13 g, 6.76 mmol) in H_2O (5 mL) was added dropwise at 0−4 °C, and the resulting mixture was stirred for 3 h. The aqueous phase was extracted with EtOAc (2 × 15 mL), and the collected organic extracts were washed with H_2O (3 × 10 mL) and with a saturated solution of NaCl (3 × 10 mL). After drying over Na_2SO_4 and solvent evaporation under reduced pressure, pure **81** was obtained as a yellow oil (1.4 g, 80% yield). ^1H NMR ($CDCl_3$): δ 7.65 (d, 1H, $J = 7$ Hz), 7.30−7.02 (m, 3H), 3.80 (q, 1H, $J = 7$ Hz), 1.55 (d, 3H, $J = 7$ Hz).

Methyl 2-(4-Aminophenyl)propanoate (83). To a solution of 2-(4-nitrophenyl)propanoic acid (8 g, 41 mmol) in CH_3OH (10 mL), a few drops of conc. H_2SO_4 were added and the resulting solution was left stirring overnight at room temperature. After solvent evaporation, the crude oil was diluted with Et_2O (15 mL) and the organic layer was washed with a saturated solution of $NaHCO_3$ (3 × 20 mL). After drying over Na_2SO_4 and solvent evaporation under reduced pressure, methyl 2-(4-nitrophenyl) propanoate was obtained as a yellow oil (7.89 g, 92% yield). Palladium on charcoal (10% Pd, 0.95 g) was added to a solution of the methyl ester (7 g, 33.4 mmol) in CH_3OH (50 mL), and the mixture was hydrogenated until complete disappearance (overnight) of the starting material (TLC). After filtration on a Celite pad, the mother liquors were concentrated and the pure methyl 2-(4-aminophenyl)propanoate **83** (5.38 g, 90% yield) was isolated after flash chromatography (petroleum ether/EtOAc 9:1) as a white powder. ^1H NMR ($CDCl_3$): δ 7.58 (d, 2H, $J = 7$ Hz), 7.35 (d, 2H, $J = 7$ Hz), 4.45 (bs, 2H), 4.10 (s, 3H), 3.70 (q, 1H, $J = 7$ Hz), 1.50 (d, 3H, $J = 7$ Hz). Anal. ($C_{10}H_{13}NO_2$) C, H, N.

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Supporting Information Available: Results from elemental analysis of all the listed compounds and ^{13}C NMR spectra of some representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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