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Design, synthesis, and structure–activity relationship of novel CCR2 antagonists ☆

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ABSTRACT

A series of novel 1-aminocyclopentyl-3-carboxyamides incorporating substituted tetrahydropyran moieties have been synthesized and subsequently evaluated for their antagonistic activity against the human CCR2 receptor. Among them analog **59** was found to posses potent antagonistic activity.

Monocyte Chemotactic Protein-1 (MCP-1) is a member of the chemokine family of pro-inflammatory proteins that are involved in chemo trafficking and activation of leucocytes by the activation of CCR2 receptors.[1] MCP-1, is expressed not only from monocytes but also in a host of other cells that includes T-cell, macrophages, etc. There is a strong body of evidence to suggest that MCP-1 is associated with inflammatory diseases such as rheumatoid arthritis[2] and atherosclerosis.[3] Studies with CCR2 $^{-/-}$[4] and MCP-1$^{-/-}$[5] mice as well as with peptide based MCP-1 antagonists[6] suggest that blocking the interaction of CCR2 and MCP-1 may provide useful therapy for the diseases indicated above.[7,8]

A host of CCR2 receptor antagonists have been identified, including those detailed in the literature from this laboratory.[9] Within the scope of the present investigation two such CCR2 antagonists warrant attention (Fig. 1). The nonselective quaternary salt **1** (TAK-779) from Takeda[10] was a potent CCR5 antagonist (IC_{50} = 1.4 nM) in addition to being an equally impressive CCR2 antagonist (IC_{50} = 28 nM). A second lead class is represented by the cyclopentane based structure **2** that was recently disclosed.[11] The cyclopentane lead **2** showed a good potency in a functional assay to match its excellent in vitro binding potency.

The present communication describes our preliminary efforts towards the identification of a newer class of CCR2 receptor antagonists that displays high binding and functional potency in the human CCR2 receptor. In accomplishing these objectives, we have incorporated features from structures such as **1** and **2** to generate hybrid analogs represented by generic structure **5**, shown below. Our primary focus was the synthesis, SAR, and biological evaluation for analogs of **5** (Fig. 2) that specifically altered the amino end of the molecule. A cross species pharmacokinetic profile for the best compound in this novel lead class is also discussed.

Analogs of **5** were synthesized by simply carrying out reductive aminations of amine (**4**) and the pyranoketone (**3**) as shown below (Fig. 3). The synthesis of substituted pyrans (**3**) and the chiral cyclopentylamine (**4**) are discussed next.

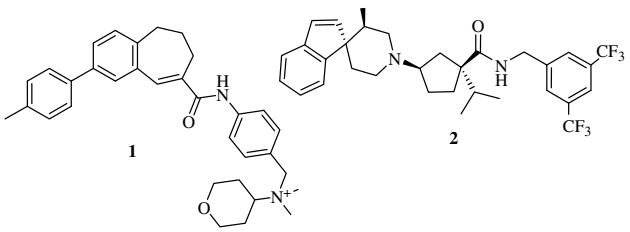

Figure 1. Takeda (1) and Merck (2) CCR2 antagonists.

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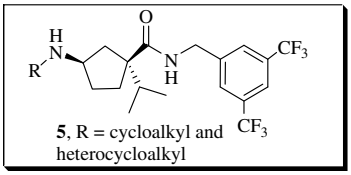


Figure 2. Proposed lead molecule.

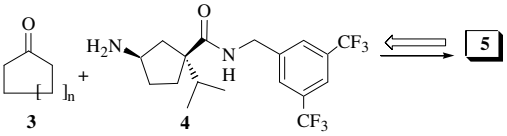
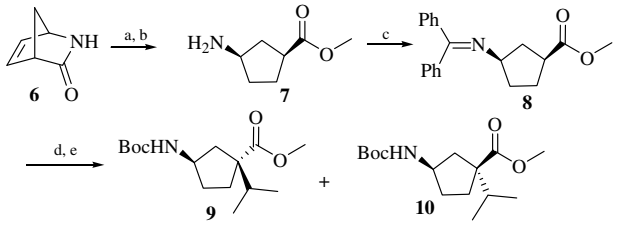


Figure 3. Reductive amination synthesis of **5.**

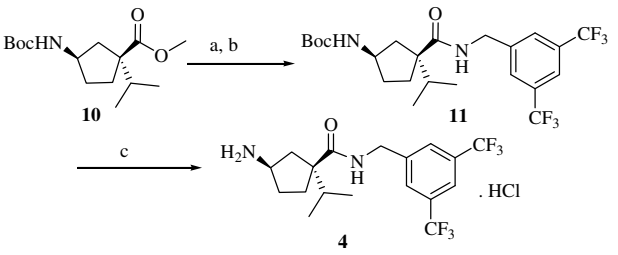
As shown in Scheme 1, commercially available (1*S*,4*R*)-(+)-2-azabicyclo-[2.2.1] hept-5-en-3-one (**6**) was transformed to the ester **7** in a two step sequence of reactions involving catalytic hydrogenation followed by the opening of the lactam ring. The amino group in **7** was protected under O'Donnell conditions[12] to give the imine **8** that was carried forward crude to the next step. The lithium enolate formed from the ester **8** using LDA was alkylated with 2-iodopropane to yield a mixture of diastereomers. To facilitate the isolation of the desired product, the crude reaction mixture was subjected to hydrolysis under acidic conditions (to unravel the benzophenone imine), after which the regenerated amine was subsequently protected as *N*-Boc. This produced a 1:1 mixture of **9** and the desired **10**, which was readily separated. Previous results from this laboratory had disclosed that the *cis*-placed amine/ester **10** led to the most potent analogs, while the compounds derived from **9** were comparatively less active or inactive.[13]

The *cis*-ester **10** was saponified and then transformed to the amide **11** under EDC conditions. Removal of the *N*-Boc protection in **11** under acidic conditions produced the amine **4** as the hydrochloride salt (Scheme 2).

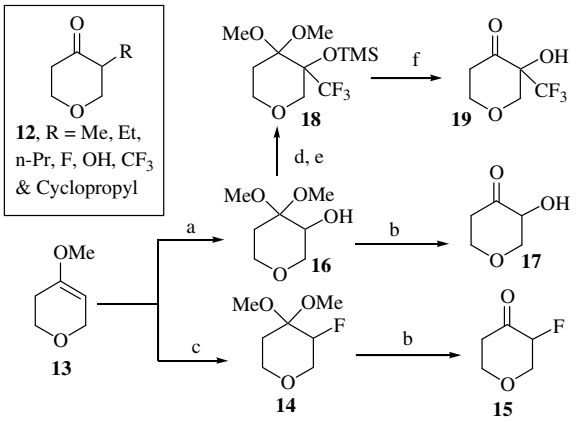
The syntheses of substituted pyran-4-ones (**3**) required a multitude of approaches, as shown below. The synthesis of mono alkylated pyranoketones (**12**, R = Me, Et, *n*-Pr) was straight forward and followed a literature procedure.[14] The α-fluoro and α-hydroxy analogs were synthesized as shown in Scheme 3. Thus, 4-methoxy-3, 6-dihydro-2H-pyran **13** undergoes electrophilic fluorination[15] with selectfluor™ in the presence of methanol to afford the acetal **14** that on treatment with acid gave **15**. In an analogous fashion, **13** underwent smooth epoxidation followed by nucleophilic ring opening of the epoxide with methanol to afford **16**. Simple acidic hydrolysis of **16** gave **17**. The ketol **16** was further utilized to afford **19** as shown below (Scheme 3). A two step sequence that involved TPAP oxidation[16] of **16** followed by nucleophilic addition of the trifluoromethyl anion[17] to the intermediate ketone gave the silyl ether **18**. The ketol and the silyl protection in **18** were removed under acidic conditions to give **19**.



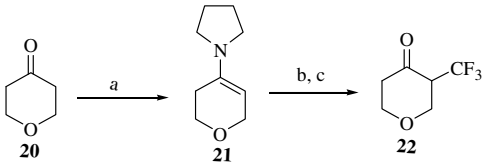
Scheme 1. Reagents and conditions: (a) Pd/C, EtOAc, H_2, RT; (b) MeOH, HCl; (c) benzophenone imine, CH_2Cl_2; (d) LDA, 2-iodo-propane, THF, −78 to 0 °C; (e) 1 M HCl and then $NaHCO_3/BOC_2O$, RT.



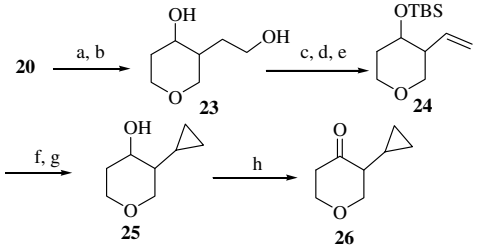
Scheme 2. Reagents and conditions: (a) NaOH, MeOH/H_2O, 60 °C; (b) EDC. HCl, 3,5-bis-trifluoromethylbenzylamine hydrochloride, CH_2Cl_2, Hunig base, RT; (c) EtOAc/HCl, 0 °C to RT.



Scheme 3. Reagents and conditions: (a) *m*-CPBA/MeOH, 0 °C to RT; (b) MeOH/HCl; (c) MeCN-MeOH/Slectfluor™; (d) TPAP oxidation; (e) CF_3TMS, TBAF, THF; (f) CF_3COOH, CH_2Cl_2.



Scheme 4. Reagents and conditions: (a) pyrrolidine, RT; (b) 5-(trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate, DMAP, DMF, RT; (c) HCl.



Scheme 5. Reagents and conditions: (a) LDA, THF/HMPA, allylbromide; (b) O_3/CH_2Cl_2, −78 °C and then $NaBH_4$: (c) O-NO_2PhSeCN/*n*-Bu_3P; (d) TBSCl, imidazole; (e) H_2O_2/THF; (f) CH_2N_2, $Pd(OAc)_2$, ether; (g) TBAF/THF; (h) Swern oxidation.

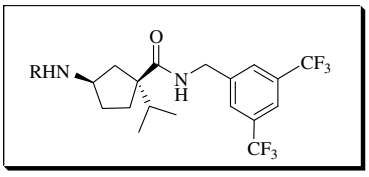
More challenging trifluoromethyl and the cyclopropyl pyran-4-ones (**22** and **26**), were obtained starting from **20** and are shown in Schemes 4 and 5. Transformation of **20** to enamine **21** was accomplished with pyrrolidine at RT. The enamine **21** underwent smooth trifluoromethylation[18] that was subsequently followed by acidic workup, as shown, to give **22**.

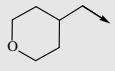
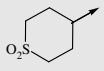
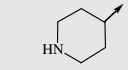
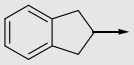
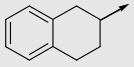
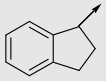
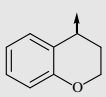
The preparation of cyclopropyl compound **26** began with the alkylation of **20** with allyl bromide to give the mono allylated compound that in a subsequent step was ozonized followed by reductive work up to give the diol **23**. The diol was then transformed to the olefin **24** in a three step sequence that involved conversion of the diol **23** to the selenide, hydroxyl protection, followed by selenoxide elimination[19] to give **24**. Cyclopropanation[20] of the olefin **24** followed by the removal of the TBS protecting group gave **25**. Oxidation of **25** to give **26** was accomplished under Swern oxidation conditions.[21]

The synthesized pyran 4-ones (Schemes 3–5) and the commercially available ketones were subjected to reductive aminations[22,27] with **4** to furnish the desired products that were transformed to their hydrochloride salts prior to being assayed. Mixtures of stereoisomer were initially submitted for the binding assay (Tables 1 and 2). If the initial results from the binding assay looked promising, the racemic/diastereomeric amines were further separated by chiral chromatography to yield individual diastereomers for further follow up studies (Table 3).

Results and discussion: The compounds listed in Table 1, illustrates the effect on binding of systematic variation of the amine end of the molecule. The binding assay[23] involved a recombinant version of the human CCR2 receptor expressed in CHO cells. Thus, going from 4 to 7 member ring compounds (**27**–**30**), we notice that the analog **29**, with cyclohexyl ring, was two to three folds more potent than the other analogs (**27**, **28**, and **30**). Significant enhancement in the potency for **29** was accomplished by the placement of heteroatom at the cyclohexane core. In particular, compound **34** with a distal oxygen atom on the tetrahydropyran ring registered a 14-fold gain in potency over the cyclohexane analog **29**. Interestingly, the analog **36**, with an additional methylene group in be-

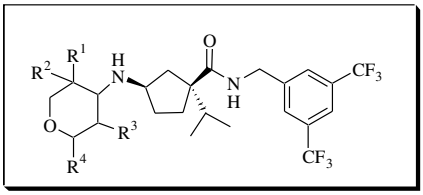
Table 1
Human binding affinities in the 3,5-bis-trifluoromethylbenzylamide series[a]



Entry	R	IC_{50} (nM)[b]	Entry	R	IC_{50} (nM)[b]
27		193	**36**		362
28		156	**37**		22
29		64	**38**		36
30		175	**39**		631
31[c]		469	**40**		21% 1 μM
32		85	**41**		187
33		56	**42**		239
34		4.6	**43**		77
35		30	**44**		419

[a] IC_{50} reported are averages of triplicate measurements whose standard errors were normally <15% in a given assay. Assay to assay variability was with in ± twofold based on the standard compound.
[b] Displacement of [^{125}I]-labeled of hMCP-1 from the CCR2 receptor expressed on CHO cells.
[c] The trifluoroaceate salt of the corresponding **31** was prepared.

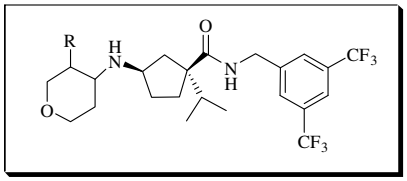
Table 2
Binding affinities and chemotaxis (CTX) in the 3,5-bis-trifluoromethylbenzylamide series[a,c]



Entry	R^1	R^2	R^3	R^4	Binding IC_{50}, nM *h*CCR2[b]	CTX (nM)
34	H	H	H	H	4.6	57
45	Me	H	H	H	1.5	0.2
46	Et	H	H	H	3.0	0.3
47	*n*-Pr	H	H	H	7.8	5.1
48	Cyclopropyl	H	H	H	123	ND
49	OH	H	H	H	51	ND
50	*F*	H	H	H	6.0	1.0
51	CF_3	H	H	H	5.5	1.0
53	CF_3	OH	H	H	765	ND
54	H	H	H	Me	28	ND
55	Me	Me	H	H	230	ND
56	Me	H	Me	H	7	ND

[a] IC_{50} reported are averages of triplicate measurements whose standard errors were normally <15% in a given assay. Assay to assay variability was with in ± twofold based on the standard compound.
[b] Displacement of [^{125}I]-labeled of hMCP-1 from the CCR2 receptor expressed on CHO cells.
[c] Analogs reported are mixtures of racemic/diastereomeric mixtures. ND, not determined.

Table 3
Binding affinities and chemotaxis (CTX) of monosubstituted THP substituted analogs in the 3,5-bis-trifluoromethylbenzylamide series[a]



R	Entry	Binding IC_{50} (nM)[b]	CTX in nM
Me[c]	**57**	42	1
	58	4	0.2
	59	1.2	0.1
Et[c]	**60**	141	ND
	61	5.6	0.3
	62	3.0	0.3
F[d]	**63**	259	ND
	64	14.3	0.8
	65	8.6	3.3

[a] IC_{50} reported are averages of triplicate measurements whose standard errors were normally <15% in a given assay. Assay to assay variability was with in ± twofold based on the standard compound.
[b] Displacement of [^{125}I]-labeled of hMCP-1 from the CCR2 receptor expressed on CHO cells.
[c] Diastereomers separated by chiral OD column.
[d] Diastereomers separated by chiral AD column. ND, not determined.

tween the amine and the pyran core, led to a significant loss in binding compared to **34**. The isomeric pyran analog **33** lost a considerable potency in comparison to **34**. The dramatic effect of the oxygen atom in the ring that lead to the more potent analogs while going from **29** to **34** was found to be general, as illustrated by other compounds **31**, **32**, and **35** as shown, though all were significantly less potent than **34**. The effect was less profound when the 'O' atom in **34** was replaced by more lipophilic 'S' as in **37**. While the sulfone **39** lost significant activities compared to the parent (**37**) the more basic piperidine analog **40** had only 20% activity at 1 μM. The bicyclic compounds (**41**–**44**) were all significantly less potent than **34** and these systems were not pursued further. The most potent analog **34** (Table 1), was probed further to generate even more potent analogs as shown below in Table 2.

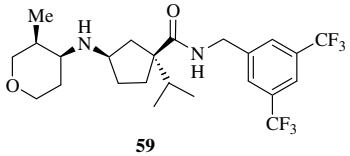
The preparation of more potent analogs derived from **34** was accomplished by the substitution of the pyran ring with alkyl, hydroxyl, and fluoro group at the either C-2 or C-3 position. The binding results for the newer analogs (Table 2) were compared with **34**. Additionally, the chemotaxis (CTX) data for the select compounds are also displayed. It should be noted that the assay results for the analogs displayed in Table 2 are for the racemic and diastereomeric mixtures.

Table 2 reveals that in comparison to **34**, the C-3 mono methyl compound **45** gained a threefold improvement in binding and a staggering 280-folds increase in the chemotaxis assay.[24] The binding and chemotaxis data for the ethyl analog **46** in many respects was similar to **45**. The homologous *n*-propyl analog **47** was slightly less potent in binding compared to either **45** or **46** and also had lost significant potency (relative) in the chemotaxis assay. Interestingly, all three compounds (**45**, **46**, and **47**) share a trend in that they all had a similar binding (compared to **34**) and also displayed better potency during the chemotaxis assay. Going forward, the bulkier cyclopropyl analog **48** lost considerable binding compared to **34**. This was also true for the aminol **49**. The C-3 monofluoro and trifluoromethyl analogs **50** and **51** displayed binding affinity similar to **34**, but again showed superior chemotactic properties. Analog **53** with geminal trifluoromethyl/hydroxyl at C-3, showed a substantial loss of potency. The isomeric methyl analog compound **54** was considerably less potent in binding and stands in contrast to either **45** or **46**. The presence of an additional methyl leading to the geminal dimethyl compound **55** resulted in significant loss of affinity compared to **34**. That the mono-substitution at C-3 of THP ring (analog **45**) led to an increase in potency and chemotaxis was further underscored by the preparation of analog **56**, with a methyl substituents flanked at either side (C-3/C-3′) of the pyran ring leading to significant improvement in the binding potency compared to **55**.

As the most potent analogs (**45**, **46**, and **50** from Table 2) were mixtures of diastereomers, an effort was undertaken to separate the individual diastereomer. It was our hope that even more potent analogs with better chemotactic properties were to be had from the isolation of the single diastereomer. Accordingly the analogs **45**, **46**, and **50** were successfully separated by chiral chromatography. Results from the biological assay for the separated diastereoisomers are discussed below in Table 3.

The chiral separation of **45**, **46**, and **50** resulted in three sets of diastereomers in an order of elution that are shown in Table 3. In the C-3 methyl series, the analog **57** (first off the column) was the least potent in both binding and in chemotaxis assay. The second and third eluted analogs **58** and **59** were comparatively more potent in both assays. The chemotaxis assay for **59** was the best we have seen in this lead class. The C-3 ethyl analogs (**60**, **61**, and **62**) displayed a similar trend except that the most potent compound **62** had a profile similar to **46** (Table 2). The fluoro analogs (**63**, **64**, and **65**) after chiral separation behaved identically. Overall the C-3 fluoro analogs showed considerable loss of potency in both binding and in chemotaxis compared to the C-3 methyl/ethyl analogs. It is noteworthy that the most active analog (**59** vs **57**) in the binding assays were also the most potent in the chemotaxis assays as shown in Table 3.

While the contrasting potency between the monofluoro and mono methyl/ethyl analogs could be easily explained by the differences in the basicity of nitrogen on the pyran core, the differences in the potency between the stereoisomers **57** and **59** was hard to elucidate. Corroborative work done for the analogs[25,26] of **59** and congeners suggest that the most potent analog **59** had a *cis*-disposed substituents (β-oriented) on the pyran core.



59

The pharmacokinetic profile (po dosing) for the most potent analog (**59**) was measured in rat (Sprague–Dawley), dog (Beagle), and rhesus and is shown below.

Species	Dose (mg/kg)	AUC (μM h)	T_{max} (h)	C_{max} (μM)	*F*%
Rat	3	0.76	0.25	0.735	42
Dog	2	0.62	0.75	0.422	28
Rhesus	2	0.01	1.00	0.004	2

An oral dose of 3 mg/kg in rat gave a C_{max} of 735 ng/ml with a T_{max} of 0.25 h and the bio-availability was 42%. The oral bio-availability (at 2 mg/kg) for **59** in dogs was 28% and a dismal 2% in rhesus monkeys.

In summary, we have successfully synthesized a new class of CCR2 antagonists. The analog **59** displayed superb potency in both the binding and chemotaxis assays. It also displayed reasonably good PK in rats/dog, but poor oral absorption in rhesus. Efforts to improve the deficiencies of **59** by modification of the cyclopentane core and also at the amide end will be the subject of future communications from these laboratories.

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27. **General procedures**

*Preparation of (**7**):* A mixture of (1*S*,4*R*)-(+)-2-azabicyclo[2.2.1]-hept-5-en-3-one (10.3 g, 94.4 mmol) in EtOAc (200 ml) and 10% Pd/C (0.5 g), was hydrogenated at RT. After 24 h the reaction mixture was filtered and evaporated leaving behind 10. Four grams (100%) of the product that was taken up in 250 ml methanol and HCl (12 M, 6 ml). The resultant mixture was stirred at RT, until the reaction was complete (72 h). Evaporation of methanol followed by drying under high vacuo, yielded title compound as an off white solid (16.0 g, 96%). ^{1}H NMR (D_2O, 500 MHz): δ 3.70 (s, 3 H), 3.01 (m, 1H), 2.38 (m, 1H), 2.16–1.73 (m, 6H).

*Preparation of (**8**):* To a suspension of **7** (10.2 g, 56.8 mmol) in dry dichloromethane (200 ml) was added benzophenone imine (10.2 g, 56.8 mmol) at RT and the resultant mixture was stirred for 24 h. The reaction mixture was filtered and the filtrate was evaporated, to leave behind an yellow oil that was triturated with ether (100 ml), filtered and evaporated. This operation was repeated twice to ensure that the product was free of ammonium chloride impurities. The resultant oil was thoroughly dried under vacuo to yield the title compound (18.03 g, ~100%) and required no further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.5–7.18 (m, 10H), 3.75 (m, 1H), 3.7 (s, 3H), 2.78 (m, 1H), 2.26–1.7 (m, 6H).

*Preparation of (**10**):* To a solution of LDA (prepared from disopropylamine (7.7 g, 76.1 mmol) and *n*-BuLi (30.4 ml, 2.5 M solution in hexane, 76.1 mmol) in THF (120 ml) at −78 °C was slowly added intermediate **8** (18.0 g, 58.6 mmol). The resultant burgundy colored solution was stirred for 20 min after which it was quenched with 2-iodopropane (14.9 g, 88 mmol). The resultant solution was gradually warmed over 3 h to 0 °C and held there for an additional 3 h. Reaction mixture was quenched with water and extracted with EtOAc. The solvent layer was washed with water, brine, dried (anhydrous magnesium sulfate) and concentrated to yield an oil. The removal of Schiff base protection at the amine group was brought about by taking the crude oil (20.0 g) in THF (100 ml) and treating it with HCl (5.0 ml, 12 M) and was allowed to stir at RT for 3 h. After the removal of all volatiles, the hydrochloride salt was taken in dichloromethane (250 ml), saturated solution of sodium bicarbonate solution (250 ml) and BOC_2O (26.0 g, 1.4 equiv). The resultant mixture was vigorously stirred overnight at RT. The solvent layer was separated and washed with water, brine, dried (anhydrous magnesium sulfate) and concentrated to yield oil. Purification by flash column chromatography and elution with hexane: EtOAc (19:1) afforded the title compound (4.91 g, 30%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.79 (br, ^{1}H), 4.01 (m, 1H), 3.71 (s, 3H), 2.18–1.60 (m, 6H), 1.44 (s, 9H), 0.87 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H).

*Preparation of (**11**):* This was a two step preparation that involved saponification of ester **10** to afford the intermediate acid followed by amidation.

Step A: To ester **10** (4.91 g, 17.2 mmol) in MeOH (100 ml) was added a solution of LiOH (3.6 g, 85 mmol) dissolved in water (20 ml) and THF (10 ml). The resultant mixture was heated at 80 °C until the reaction was complete (18 h). MeOH was removed under vacuo and the crude was taken in Water/EtOAc (200 ml, 1:4) and cooled to 0 °C. The pH of the reaction mixture was carefully adjusted to 6 and the EtOAc layer was separated and washed with water, brine, dried (anhydrous magnesium sulfate) and concentrated to yield oil. Purification by flash column chromatography and elution with hexane: EtOAc (1:1) + 2% AcOH gave acid (3.9 g, 84%) that was carried further.

Step B: To acid (**10**) from Step A (2.09 g, 7.71 mmol), 3,5-bis-trifluoromethyl-benzylamine hydrochloride (2.26 g, 8.1 mmol) in DCM (50.0 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.96 g, 15.4 mmol) and followed by diisopropylethylamine (2.1 g, 16.2 mmol). The resultant mixture was stirred at RT for 18 h. The reaction mixture was diluted DCM and twice washed with 1 N HCl, once with aqueous sodium carbonate and once with brine, dried (anhydrous magnesium sulfate), concentrated, purified by flash column chromatography. Eluting with hexane/EtOAc (2:3) gave **11** (2.23 g, 64%).

*Preparation of (**4**):* To a solution of 2.23 g (**11**) was added a saturated HCl (4 N solution in dioxane, 25.0 ml) and the mixture stirred at RT. After 1.5 h at RT, the volatiles were removed under reduced pressure to leave behind an oil that was triturated with ether followed by filtration to afford hydrochloride salt of **4** (1.79 g, 100%) as a white solid. LC–MS for $C_{18}H_{22}F_6N_2O$ [M+H$^+$] calculated 396.4; found 397.2 (M+H).

*Typical reductive amination of (**4**) with ketones:* The reductive amination of (**4**) with ketones are similar to the Ref. 22. Thus to a stirred solution 4 (33 mg, 0.076 mmol) in 2 ml of DCM at RT was added 16 μL (0.095 mmol) of diisopropylethylamine and ketone (0.076 mmol). To the reaction mixture was added 4 beads of molecular sieves (4A) followed by 24 mg of $Na(OAc)_3BH$. After stirring overnight the reaction mixture was evaporated, the DCM layer was washed with brine, dried (anhydrous $MgSO_4$), and evaporated to give the crude product. Further purification to afford the pure product was effected by Gilson reverse phase separation. This procedure was employed to prepare the analogs **27**–**56**.