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Original article

Efficient synthesis and identification of novel propane-1,3-diamino bridged CCR5 antagonists with variation on the basic center carrier

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ABSTRACT

By employing pharmacophore-based design and the privileged fragments reassembly, a series of piperidine-/tropane-/piperazine-bridged CCR5 antagonists were designed and synthesized via an efficient convergent synthesis strategy, with focus on the optimal choice of the basic center carrier structure. Significantly, the 4-amino-4-methylpiperidine bridged 1-acyl-1,3-propanediamine compounds were identified as a new class of nanomolar CCR5 antagonists, providing an efficient approach and novel scaffolds for further development of potent CCR5 inhibitors.

1. Introduction

Human immunodeficiency virus (HIV) infection with its clinical progression to AIDS has become one of the fatal diseases in the world. Though highly active antiretroviral therapy (HAART) has been successful in reducing HIV-1-associated mortality and morbidity, the emergence of multi-drug resistant viral strains and intolerance to available agents render a compelling need to discover new drugs or targets for effective therapeutic intervention. The C–C chemokine receptor 5 (CCR5), an essential co-receptor for HIV-1 recognition and entry into $CD4^+$ macrophages and T-cells [1] but not essential for human functions [2] is an attractive target for antiretroviral intervention [3]. Many pharmaceutical companies and academic institutions have been enthusiastically investigating novel antagonists against CCR5 as novel anti-HIV agents [4,5]. As a result, several small-molecule CCR5 antagonists (Sch-D [6], UK-427857 [7], GW-873140 [8], TAK 220 [9] as shown in Fig. 1) are now being evaluated in clinical trials, in which the UK-427857 (Maraviroc) has become the first FDA-approved CCR5 inhibitor as anti-HIV drug, further validating the CCR5 as an anti-HIV therapeutic target.

CCR5 belongs to the seven-transmembrane G protein-coupled receptor (GPCR) superfamily. The GPCRs are structural transmembrane polypeptides that typically contain seven loops and mediate various intracellular events when triggered by extracellular ligands. Based on the structural and molecular interactions of CCR5 inhibitors with CCR5 [10], the molecular modeling-guided mutagenesis study using homology-based approach suggested that the binding pocket of CCR5 is located within a predominantly lipophilic cavity near the extracellular surface formed by transmembrane helices 2, 3, 6, and 7. And the residue E283 within TM7, which is highly conserved in CC-chemokine receptors, was proved to be critically important for the interaction of the antagonists with CCR5 protein [11–13].

Correspondingly, the literature-reported CCR5 antagonists are generally characterized by two hydrophobic domains and a basic centre within the framework. As depicted in Fig. 2, we deduced a general pharmacophore model for CCR5 inhibition. The propane-1,3-diamine served as the bridge to link the two hydrophobic domains, which preferred for aryl group on one side and the heterocycle or polar group substituted aryl portion on the other side. The incorporation of heterocycle was recognized to improve the antiviral activity and pharmacokinetic properties in the context of CCR5 inhibitors [14]. The basic centre afforded electronic interactions with the key residue E283, usually in the form of aliphatic tertiary amine which is part of the 1,3-propanediamine core

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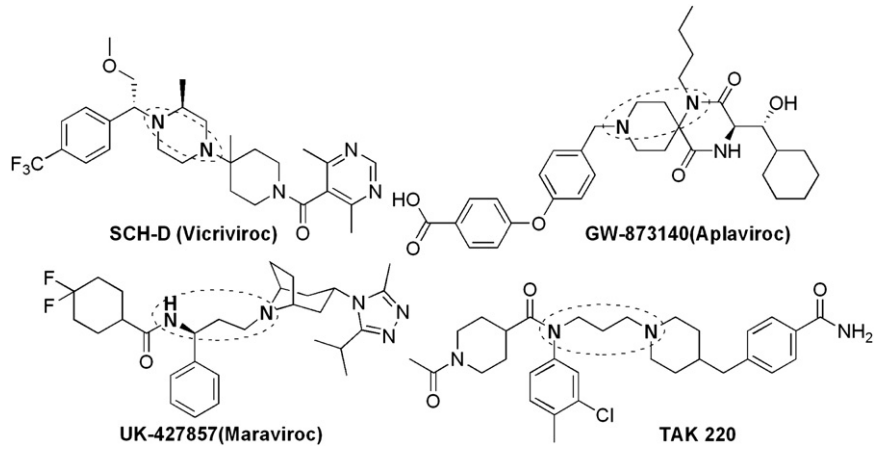


Fig. 1. Representative structures of small molecule CCR5 antagonists, sharing the common propane-1,3-diamino skeleton flanked by two hydrophobic domains.

structure and supplied by piperdine, tropane or piperizine. Since the basic center is critical for the CCR5 binding, and the conformationally constrained amine linker can orient the relative positioning of the two hydrophobic domains, the optimal basic center carrier was especially investigated in this study to search for new scaffold.

According to our proposed pharmacophore model for the CCR5 inhibition, we selected some privileged fragments as the modular structure to assemble new structure CCR5 inhibitors. Privileged structure-based drug discovery recently gained particular attention and has been widely applied to finding new drugs in a shorter time [15]. In this study, we employed phenyl ring, heteroaromatic ring and aliphatic ring as the hydrophobic group, and the conformationally constrained amine as the linker to fulfill the putative 3-domain pharmacophore model, providing novel and rational approach for the discovery of new structure CCR5 inhibitors.

2. Chemistry

Since CCR5 antagonist represents a promising new class of antiretroviral agents for the treatment of ART-experienced patients, furthermore, the emergence of viral strains resistant to clinically studied CCR5 inhibitors and the dynamic nature of the HIV-1 genome demand a continued effort toward the discovery of novel inhibitors, we were intrigued to design and discover new structure CCR5 antagonists by combining the pharmacophore-based approach and the privileged structures.

We applied lead deconstruction strategy to a range of literature-reported potent CCR5 antagonists, in combination with analyzing the structural features of the CCR5 binding pocket. Hence, we deduced a general 3-domain pharmacophore model for the CCR5 inhibition, and selected an amine and an aldehyde as the key building blocks to build focused library with structural diversity. As described in Scheme 1, a convergent synthesis strategy was employed to construct the propane-1,3-diamino bridged CCR5 antagonists from two building blocks of (*S*)-β-amino-β-arylpropanal (**6a**–**c**) and the piperidine-/tropane/piperazine-substituted heteroaromatics (**5-1** to **5-6**) via a reductive amination reaction [16]. Alkylation or acylation of the amino group in the intermediate **7** resulted in the desired products **1**–**4**(**a**–**i**) with structural variation on the basic center carrier and hydrophobic groups.

In this work, efficient synthesis was developed to prepare the two building blocks, namely the β-aryl substituted β-amino aldehyde and the piperidine-/tropane-substituted heteroaromatics. The synthesis of (*S*)-β-amino-β-arylpropanal (**6a**–**c**) was achieved by employing Davies protocol as the key step [17–20]. As depicted in Scheme 2, the aryl aldehyde was treated with Horner-Emmons reagent to generate aryl substituted (*E*)-α,β-unsaturated esters (**8a**–**c**) [21,22]. Subsequent asymmetric conjugate addition by the chiral reagent (*R*)-*N*-benzyl-1-phenylethanamine produced one predominant diastereoisomer (**9a**–**c**) [17–20]. The resulting (*S*)-3-aryl-3-(benzyl((*R*)-1-phenylethyl)amino)-propanoate was subjected to a one-pot *N*-protecting group exchange (*N*-Bn -> *N*-Boc) (**10a**–**c**), followed by DIBAL-H reduction [23] to yield the final chiral β-aryl substituted β-amino aldehyde (**6a**–**c**).

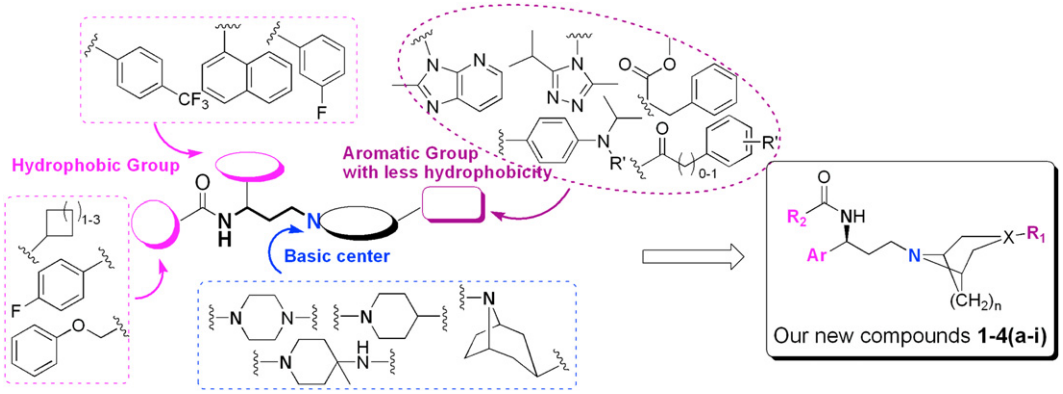
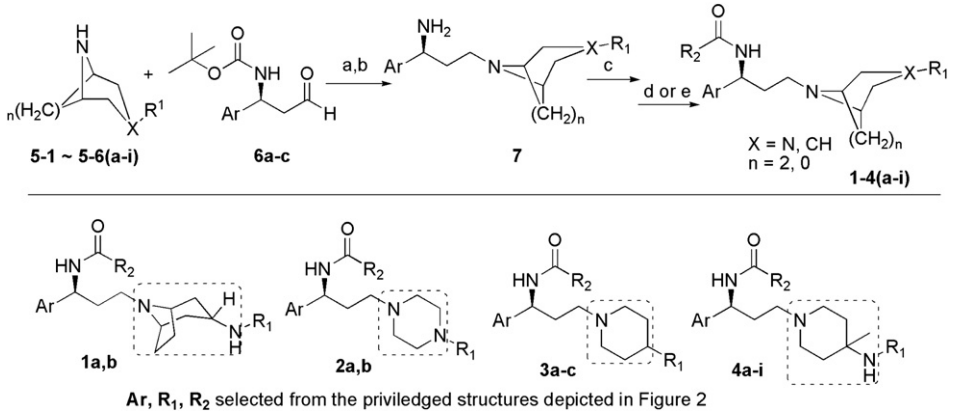


Fig. 2. Our deduced general pharmacophore model for effective CCR5 binding and the design of the propane-1,3-diamine bridged CCR5 antagonists by using the privileged fragments.



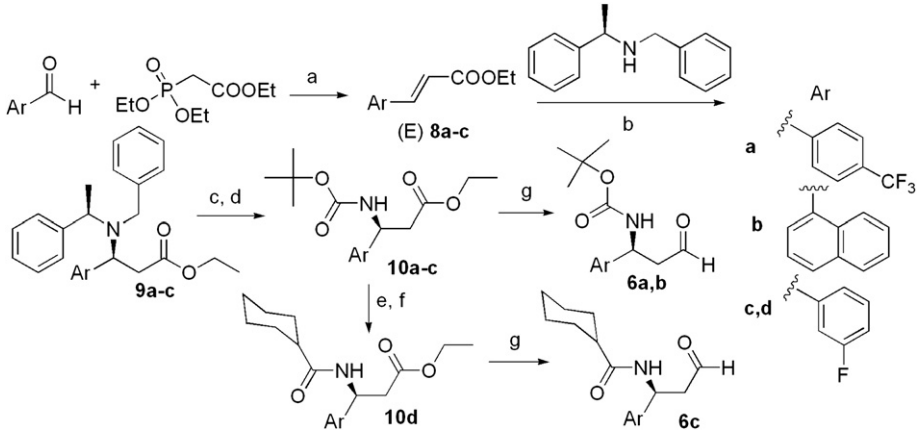
Scheme 1. The convergent synthesis strategy to construct the propane-1,3-diamine bridged CCR5 antagonists, categorized by the structure type of the basic centre carrier. Reagents and conditions: (a) $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (b) CF_3COOH/CH_2Cl_2; (c) R_2COOH, EDCI, HOAt, DIPEA, CH_2Cl_2; (d) $LiAlH_4$,THF, −78 °C (for the conversion of compounds **3a**–**3b**); (e) 10% Pd–C, then Ac_2O, 60 °C, 3–5 h (for the conversion of compounds **2a**–**2b**).

Prior to the synthesis of another building block of piperidine-/tropane-substituted heteroaromatics (**5-1** to **5-6**), the precursors *N*-protected piperidine and *endo*-tropanamine were prepared. As shown in Scheme 3, tropinone was conveniently converted into *endo*-tropanamine by sequential *N*-demethylation with ethyl chloroformate [24] and reductive amination with ammonium formate in the presence of 10% Pd–C catalyst [25,26]. The resulting *endo*-tropanamine (**12**) was coupled with isobutyric acid to afford the *N*-(8-ethylcarbamate-8-aza-bicyclo[3.2.1]octan-3-yl) isobutyramide (**13**) which served as the starting material for the synthesis of *endo*-tropane-substituted 1,2,4-triazole.

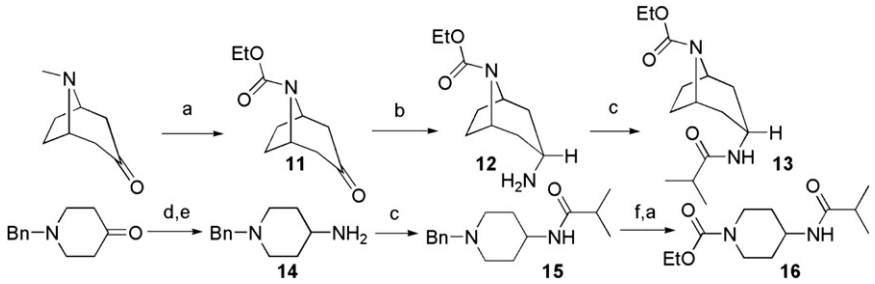
For the synthesis of piperidine-substituted 1,2,4-triazole, similar strategy was employed, as shown in Scheme **3**. Starting from the commercially available 1-benzylpiperidin-4-one, the reductive amination with hydroxylamine hydrochloride and sodium in *n*-propanol afforded the 1-benzylpiperidin-4-amine **14** in high yield. Introduction of the isobutyroyl group on the 4-amino of the piperidine ring (**15**) provided the handle to generate 1,2,4-triazole. The subsequent *N*-protecting group exchange yielded the precursor **16**, in which the ethyl carbamate served as the optimal protective group for the following conversion reaction into triazole.

With the *N*-protected-piperidine/-tropanamine in hand, *endo*-tropane-substituted 3H-imidazo[4,5-b]pyridine (**5-1**) or piperidine-/*endo*-tropane-substituted 1,2,4-triazole (**5-2** and **5-3**) were synthesized by using our modified methodology, as indicated in Scheme 4. It is worthwhile to note that the choice of *N*-ethoxycarbonyl protecting group is of significance for the production of the heterocycle-substituted 1,2,4-triazole derivatives. On one hand, the tropinone was demethylated by treatment with ethyl chloroformate; on the other hand, the resulting ethyl carbamate functioned as the *N*-protecting group. Furthermore, the presence of the ethoxycarbonyl group was beneficial for the formation of the tropane-substituted 1,2,4-triazole. As shown in Scheme 4, the 1,2,3-triazole (**19**, **20**) was synthesized under acidic conditions [27], so the basic nature of the tropane might interfere with this reaction. Then, the ethoxycarbonyl group dispersed the electron density of the nitrogen bridge by conjugation effect, resulting in neutralized basicity of the tropane alkaloid thus securing the formation of the 1,2,4-triazole functionality. As a comparison, the *N*-benzyl protected analog failed to produce the *endo*-tropane-substituted 1,2,4-triazole under the same conditions.

Meanwhile, the synthesis of N^1-Boc-4-amino-4-methyl-piperidine was conveniently achieved by employing isonipecotate as a starting material and Curtius rearrangement as a key step, which was previously reported by our laboratory [28]. Thus the piperidine-/4-amino-4-mthyl-piperidine-/piperazine-substituted aromatics (**5-4, 5-5** and **5-6a**–**e**) were readily prepared by employing reductive amination [28], alkylation or acylation as the key reactions, as depicted in Scheme 5.



Scheme 2. The synthesis of the (*S*)-β-amino-β-arylpropanal by employing the Davies protocol as the key step. Reagents and conditions: 9a) *t*-BuOK/THF, 0 °C -rt, 4 h, 81–84%; (b) *n*-BuLi/THF, −78 °C, 70–89%; (c) 20% $Pd(OH)_2$–C/H_2/EtOH; (d) $(Boc)_2O$, two steps overall yield 83–87%; (e) TFA/CH_2Cl_2, rt, 66%; (f) cyclohexanecarboxylic acid, EDCI/HOBt/NMM/CH_2Cl_2, rt, two steps overall yield 66%; (g) DIBAL-H/CH_2Cl_2, −78 °C, 60–76%.



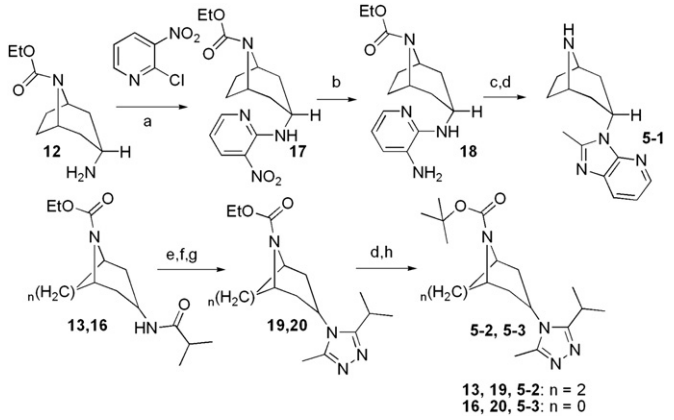
Scheme 3. The synthesis of the *N*-protected piperidine and endo-tropanamine which served as the starting materials to prepare piperidine-/tropane-substituted heteroaromatics. Reagents and conditions: (a) $ClCOOEt/K_2CO_3$, $CHCl_3$, reflux, 88–90%; (b) $HCOONH_4$/10%Pd–C, CH_3OH-H_2O, rt, 84%; (c) isobutyric acid, DCC/THF, rt, 60–85%; (d) $HONH_2$.HCl/EtOH/Py, reflux, 99%; (e) Na/*n*-PrOH, reflux, 95%; (f) 10% Pd–C, H_2, EtOH, 90%.

After the successful preparation of the building block sets, convergent synthesis proceeded smoothly between the (*S*)-β-amino-β-arylpropanal (**6a,b**) and the piperidine/tropane/piperazine-substituted heteroaromatics (**5-1** to **5-5**), followed by coupling reaction with carboxylic acid or acyl chloride, affording the propane-1,3-diamino bridged CCR5 antagonists **1**–**3**(**a**–**c**), as indicated in Scheme 1. For the synthesis of 4-amino-4-methylpiperidine-linked CCR5 inhibitors, the acidic removal of N^1-Boc of **5**–**6** **(a**–**i)** followed by the reductive amination with (*S*)-β-amino-β-arylpropanal **6c** furnished the desired products **4a**–**i**.

3. Biological assay

These pharmacophore-based compounds were evaluated for their inhibitory effects on RANTES-stimulated [^{35}S]-GTPγS binding to CCR5-expressing CHO cell membranes. The results are summarized in Table 1 as IC_{50} values or inhibition rates at the concentrations of 300 nM and 30 nM.

SPA-WGA based [^{35}S] guanosine 5′-[γ-thio] triphosphate (GTPγS)-binding assay. Exchange of [^{35}S]GTPγS (>1000 Ci/mmol) was measured using a scintillation proximity assay (SPA) in 100 μl reaction volume. 10 μg of CHO/CCR5 cell membranes, 0.1 mg of WGA-coated SPA beads, 10 μM GDP, 10 nM RANTES and 0.5 nM [^{35}S] GTPγS (Amersham Biosciences) in SPA binding buffer (50 mM HEPES, 10 mM $MgCl_2$, 1 mM EDTA, 100 mM NaCl, 0.1% BSA, pH 7.6) were incubated with compounds in 96-well plate for 30 min at 25 °C. The incubation was then continued at room temperature with 0.5 nM [^{35}S]GTPγS for another 30 min, membrane-bound [^{35}S] GTPγS was measured using a scintillation counter. Basal binding



Scheme 4. The synthesis of the piperidine-/tropane-substituted heteroaromatics. Reagents and conditions: 9a) K_2CO_3/CH_3CN, reflux, 24 h, 99%; (b) 10% Pd–C/H_2,THF, 22 h, 94%; c) Ac_2O/165 °C, 24 h,; (d) HCl, reflux, 70% in two steps; (e) PCl_5/CH_2Cl_2, 0–20 °C, 10 h; (f) $CH_3CONHNH_2/CH_2Cl_2$/*t*-amyl alcohol, 0 °C, 12 h; g) PhMe/TsOH, reflux, 20 h; (h) $(Boc)_2O$/NaOH (aq).

was determined in the absence of agonists, and nonspecific binding was obtained in the presence of 10 μM GTPγS (Sigma).

4. Results and discussion

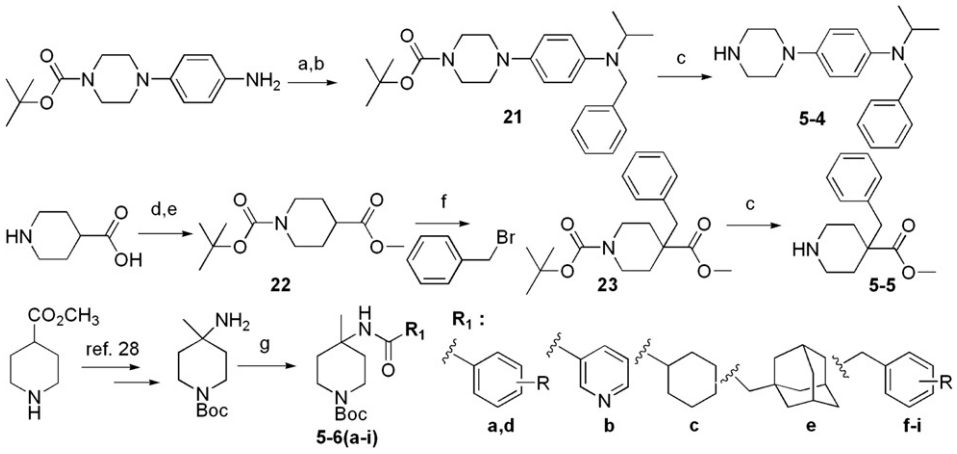
As we expected, the conformationally constrained amino linker played an important role in the interaction with CCR5 protein. Among the propane-1,3-diamino bridged CCR5 inhibitors, the *endo*-tropane-substituted heteroaromatics containing compounds, exemplified by **1a** ($IC_{50} = 0.253$ μM), were found to exhibit high affinity binding to CCR5, while the piperazine-containing analogs (**2a** and **2b**) turned out inactive. Piperidino-linked analogs displayed moderate or weak inhibition against CCR5 (**3a**, $IC_{50} = 10$ μM). However, the 4-amino-4-methyl-piperidino linker displayed a remarkable activity-enhancing effect, which constituted a new class of small molecule CCR5 inhibitors with an IC_{50} value varying in the range of 300 to 30 nM (**4b**, **4e**–**i**). In terms of the hydrophobic group at the left side of the 3-feature pharmacophore model, 4-trifluoromethylphenyl or 3-fluorophenyl was preferred over the bulky naphthalenyl moiety.

For this novel 4-amino-4-methyl-piperidino-bridged series, a preliminary SAR study was conducted with respect to the right side hydrophobic group. The 4'-substituted phenyl (**4a, 4d**), the pyridinyl (**4b**), the cyclohexyl (**4c**), the adamantylmethyl (**4e**), and the substituted benzyl (**4f-i**) rings were investigated. As the activity data indicated (Table 1), the aromatic ring was an optimal group for the right side hydrophobic domain (**4a, 4b** vs. **4c**, **4f-i** vs. **4e**) to achieve effective CCR5 inhibition. In addition, the electron-negativity and hydrphobicity of the aromatic group were favored for the interaction with CCR5 protein (**4a, 4b** and **4f-i**), while the electron-withdrawing group on the phenyl ring was detrimental to the binding (**4d**). Furthermore, one more methylene extention of the aromatic ring away from the basic center was beneficial for the potency (**4e**–**i**), thus the benzyl group was obviousely advantageous over the phenyl group acylated with the 4-amino-4-methylpiperidine linker in the context of CCR5 inhibition (**4e**–**i** vs. **4a**–**d**).

So, based on our proposed 3-feature pharmacophore model and the priviledged structure re-assembly, we discovered potent new structure CCR5 inhibitors (**1a** and **4f**–**i**), which in turn positively supported our hypothesis about the pharmacophore model for CCR5 inhibition. More significantly, the identification of 4-amino-4-methylpiperidine-bridged CCR5 antagonists via the pharmacophore-based design and the efficient synthesis provides promising new scaffold for further lead optimization and development of new structure CCR5 antagonists.

5. Conclusion

Based on the putative three-feature pharmacophore model, we designed and synthesized a new class of CCR5 inhibitors by



Scheme 5. The synthesis of the piperidine-/piperazine-substituted aromatics. Reagents and conditions: (a) $NaB(OAc)_3H$/HOAc, CH_3COCH_3, rt, 96%; (b) BnBr/K_2CO_3, CH_3CN. rt, 93%; (c) CF_3COOH/CH_2Cl_2, rt, 1 h, 99%; (d) $SOCl_2/CH_3OH$, rt; (e) $(Boc)_2O/CH_2Cl_2$/TEA, rt, 99%; (f) LDA/THF, −78 °C, 87%; (g) aryl-/alkyl-carboxylic acid, EDCI/HOBt/NMM/CH_2Cl_2, rt, 60–80%.

selecting privileged fragments for the three functional domains, focused on the basic center carrier structure which is critical for the CCR5 binding due to the electronic interaction with the key residue E283 and the orientation effect. Efficient synthesis was developed to build the target molecules and construct the building block sets in this work. Evaluation of these analogues in the RANTES-stimulated [^{35}S]-GTPγS binding assay resulted in the discovery of new structure nanomolar CCR5 inhibitors. Especially, the 4-amino-4-methylpiperidine containing compounds represent a new class of CCR5 antagonists identified via the pharmacophore-based design and the efficient synthesis strategy, affording novel scaffolds for further development of the potent CCR5 inhibitors.

6. Experimental protocols

6.1. General

Solvents were distilled and dried according to standard procedures. ^{1}H NMR spectra were recorded on a Varian 300-MHz or 400-MHz spectrometer. ^{13}C NMR spectra were recorded on a Varian Mercury VX 400-MHz spectrometer. Melting points (uncorrected) were determined on a Buchi-510 capillary apparatus. Specific rotations (uncorrected) were determined in a Perkin-Elmer 241 polarimeter. Low and high-resolution mass spectra were determined on Finnigan MAT-95 mass spectrometer. TLC was performed on 0.25 mm HSGF 254 silica gel plates. The key products were characterized by NMR, MS and high-resolution mass spectra.

6.2. (E)-Ethyl 3-(4-(trifluoromethyl)phenyl)acrylate (**8a**) [29]

To the solution of triethyl phosphonoacetate (3.3 mL, 16.5 mmol) in dry THF (50 mL) was added NaH (0.72 g, 30 mmol) at 0 °C. The reaction mixture was gently stirred for 45 min at 0 °C, then was added 4-(trifluoromethyl)benzaldehyde (2.61 g, 15 mmol) in dry THF (2 mL) dropwise. After 3 hours of stirring at 0 °C and 1 h at room temperature, the mixture was quenched with saturated aqueous solution of ammonium chloride, filtered and washed with EtOAc (2 × 50 mL). The combined organic phases were concentrated under vacuum, and the residue was purified by silica gel column chromatography with the eluent of petroleum ether/EtOAc = 40/1 to give compound **8a** (2.74 g, yield 84.1%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, 1H, J = 15.6 Hz), 7.63 (s, 4H), 6.50 (d, H, J = 16.2 Hz), 4.27 (q, 2H, J = 7.2 Hz), 1.34 (t, 3H, J = 7.2 Hz). TLC R_f = 0.55 (petroleum ether/EtOAc = 20:1).

6.3. (E)-Ethyl 3-(naphthalen-1-yl)acrylate (**8b**) [30]

8b was prepared in a similar fashion as described for **8a**, colorless oil, yield 81.6%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (d, 1H, J = 15.9 Hz), 8.19–8.20 (m, 1H), 7.86–7.90 (m, 2H), 7.74–7.77 (m, 1H), 7.48–7.56 (m, 3H), 6.52 (d, 1H, J = 16.2 Hz), 4.31 (q, 2H, J = 7.2 Hz), 1.38 (t, 3H, J = 7.2 Hz). TLC R_f = 0.7 (petroleum ether/EtOAc = 10/1).

6.4. (E)-Ethyl 3-(3-fluorophenyl)acrylate (**8c**)

8c was prepared in a similar fashion as described for **8a**, colorless oil, yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, 1H, J = 15.9 Hz), 7.19–7.39 (m, 3H), 7.04–7.10 (m, 1H), 6.42 (d, 1H, J = 15.9 Hz), 4.27 (q, 2H, J = 7.2 Hz), 1.34 (t, 3H, J = 7.2 Hz).

6.5. (S)-Ethyl 3-(N-benzyl-N-((R)-1-phenylethyl)amino)-3-(4-(trifluoromethyl)phenyl) propanoate (**9a**)

Under N_2 protection, *n*-butyllithiumm 1.6 M in hexane (10.5 mL, 16.8 mmol) was added dropwise to the solution of (*R*)-*N*-benzyl-1-phenylethyl ethanamine (2.88 g, 13.6 mmol) in dry THF (40 mL) at −15 °C. After stirring for 30 min, the mixture was allowed to warm to room temperature for 10 min, then cooled to −78 °C. The solution of compound **8a** (2.56 g, 10.5 mmol) in THF (10 mL) was introduced via syringe. After 3 hours of stirring at −78 °C, the reaction was quenched with saturated NH_4Cl aqueous solution (5 mL) and warmed to room temperature. The aqueous phase was separated and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by silica gel column chromatography with eluent of petroleum ether/EtOAc = 40/1 to afford the compound **9a** (3.337 g, yield 69.8%) as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58–7.67 (m, 4H), 7.23–7.48 (m, 10H), 4.56–4.60 (m, 1H), 3.96–4.06 (m, 3H), 3.75 (q, 2H, J = 5.7 Hz), 2.63–2.67 (m, 2H), 1.34 (d, 3H, J = 6.9 Hz), 1.10 (t, 3H, J = 6.9 Hz). TLC R_f = 0.35 (petroleum ether/EtOAc = 20/1).

6.6. (S)-Ethyl-3-(N-benzyl-N-((R)-1-phenylethyl)amino)-3-(naphthalen-1-yl) propanoate (**9b**)

9b was prepared in a similar fashion as described for **9a**, colorless oil, yield 80 %. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.29 (brs, 1H) 7.69–7.83 (m, 3H), 7.41–7.49 (m, 5H), 7.14–7.29 (m, 8H), 5.11–5.56

Table 1
CCR5 inhibition activity of 1,3-propanediamine bridged compounds with variation on the basic center carrier.

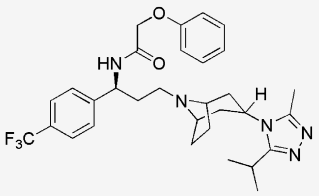
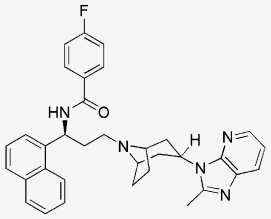
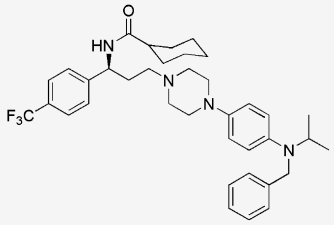
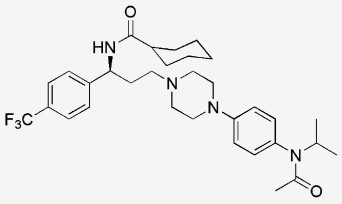
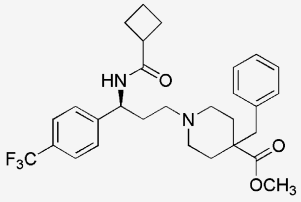
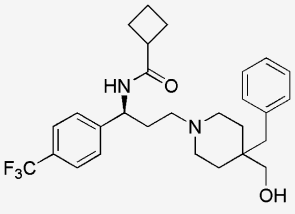
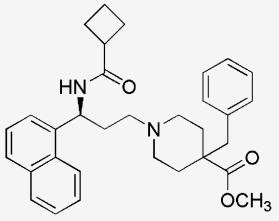
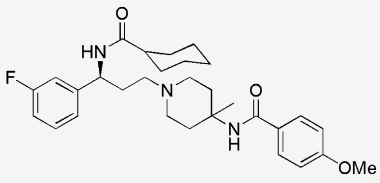
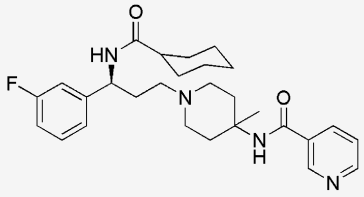
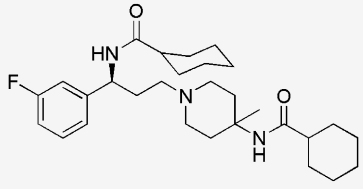
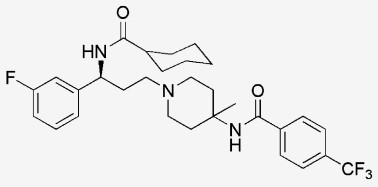
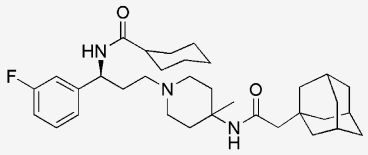
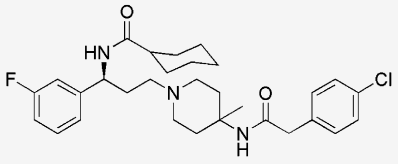
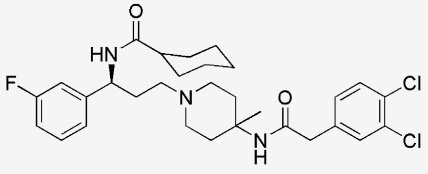
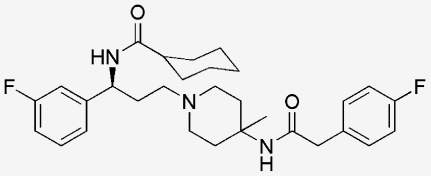
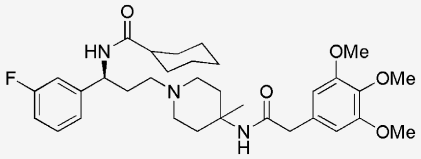
Entry	Compounds	Structures	IC_{50}, μM[a] or inhibition rate
1	**1a**		0.253
2	**1b**		~10
3	**2a**		>10
4	**2b**		>10
5	**3a**		~10
6	**3b**		>10
7	**3c**		>10

Table 1 (*continued*)

Entry	Compounds	Structures	IC_{50}, μM[a] or inhibition rate
8	**4a**		33% at 300 nM, 9% at 30 nM
9	**4b**		44% at 300 nM, 35% at 30 nM
10	**4c**		29% at 300 nM, 6% at 30 nM
11	**4d**		7% at 300 nM, 3% at 30 nM
12	**4e**		46% at 300 nM, 21% at 30 nM
13	**4f**		91% at 300 nM, 28% at 30 nM
14	**4g**		97% at 300 nM, 36% at 30 nM
15	**4h**		95% at 300 nM, 31% at 30 nM

(*continued on next page*)

Table 1 (*continued*)

Entry	Compounds	Structures	IC_{50}, μM[a] or inhibition rate
16	**4i**		98% at 300 nM, 22% at 30 nM

[a] Inhibition of RANTES-stimulated [^{35}S]-GTPγS binding to CCR5-expressing CHO cell membranes.

(m, 1H), 3.96–4.03 (m, 1H), 3.77–3.92 (m, 2H), 3.73 (q, 2H, $J = 7.2$ Hz), 2.92–2.74 (m, 2H), 1.22 (d, 3H, $J = 6.9$ Hz), 0.80 (t, 3H, $J = 7.2$ Hz). $[\alpha]_D^{20} = +45.8°$ ($c = 1.02$, $CHCl_3$). TLC $R_f = 0.4$ (petroleum ether/EtOAc = 20/1).

6.7. *tert*-Butyl-(*S*)-2-(ethoxycarbonyl)-1-(4-(trifluoromethyl) phenyl)ethylcarbamate (**10a**)

The suspension of compound **9a** (3.337 g, 7.33 mmol), 20% Pd $(OH)_2$ on carbon (0.4 g) and di-*tert*-dicarbonate (3.21 g,1 4.7 mmol) in ethanol (40 mL) was hydrogenated at room temperature for 70 h until the reaction was completed. The slurry was filtered, rinsed with CH_3OH (50 mL), and concentrated to an oil. The crude product was purified by silica gel column chromatography with eluent of petroleum ether/EtOAc = 8/1 to give the compound **10a** (2.303 g, yield 86.9%) as white solid. M.p.75–78 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59 (d, 2H, $J = 8.1$ Hz), 7.41 (d, 2H, $J = 8.1$ Hz), 5.67 (brs, 1H), 4.06 (q, 2H, $J = 6.9$ Hz), 2.82–2.84 (m,2H), 1.42 (s, 9H), 1.16 (t, $J = 6.9$ Hz, 3H). EI-MS (*m*/*z*): 361 (M^+). $[\alpha]_D^{22} = -14.6°$ ($c = 0.64$, $CHCl_3$). TLC $R_f = 0.3$ (petroleum ether/EtOAc = 8/1).

6.8. *tert*-Butyl-(*S*)-2-(ethoxycarbonyl)-1-(naphthalen-1-yl) ethylcarbamate (**10b**)

10b was prepared in a similar fashion as described for **10a**, white solid, yield 83%. M.p.88–90 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δδ 8.13 (d, 1H, $J = 8.1$ Hz), 7.77–7.98 (m, 2H), 7.41–7.59 (m, 4H), 5.96 (brs, 1H), 5.55 (brs, 1H), 4.05 (q, 2H, $J = 6.9$ Hz), 2.98–3.00 (m, 2H), 1.43 (s, 9H), 1.12 (t, 3H, $J = 6.9$ Hz). EI-MS (*m*/*z*): 343 (M^+). $[\alpha]_D^{20} = -13.6°$ ($c = 0.99$, $CHCl_3$). TLC $R_f = 0.4$ (petroleum ether/EtOAc = 8/1).

6.9. (*S*)-Ethyl 3-(*tert*-butoxycarbonylamino)-3-(3-fluorophenyl) propanoate (**10c**)

To a stirred solution of (*R*)-*N*-benzyl-1-phenylethanamine (9.8 g, 46.5 mmol) in 100 mL dry THF at −78 °C was added ^{n}BuLi (32 mL, 50.7 mmol). The resulting mixrture was allowed to rt over 10 min before re-cooling to −78 °C, then was added the solution of **8c** (8.195 g, 42.4 mmol) in 80 mL dry THF. The resulting mixture was stirred at −78 °C for 2 h then quenched by the addition of saturated aqueous NH_4Cl solution. After warming to rt, the organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (PE/EA = 30:1) to afford the product **9c** as colorless oil (11.68 g, 68% yield). $[\alpha]_D^{23} = +2.3°$ ($c = 1.0$, $CHCl_3$). To the stirred solution of **9c** (4.05 g, 10 mmol) in 100 mL EtOH was added Boc_2O (4.36 g, 20 mmol) and 10% $Pd(OH)_2$/C (400 mg). The mixture was hydrogenated at rt for 24 h then filtered, evaporated to remove the solvent. The crude product was purified by column chromatography (PE/EA = 5:1) to give **10c** as colorless oil (2.36 g, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25–7.31 (m, 1H), 6.91–7.08 (m, 3H),5.58 (br, 1H), 5.09 (br, 1H), 4.07 (q, 2H, $J = 7.1$ Hz), 2.79–2.80 (m, 2H), 1.42 (s, 9H), 1.17 (t, 3H, $J = 7.1$ Hz).

6.10. *tert*-Butyl-(*S*)-1-(4-(trifluoromethyl)phenyl)-2-formylethylcarbamate (**6a**) [31]

To the solution of the compound **10a** (0.723 g, 2 mmol) in dry CH_2Cl_2 (20 mL) was added DIBAl-H (1 M in toluene, 3 mL) at −78 °C under N_2 protection and the resulting solution was stirred at −78 °C for 3 h until the starting material disappeared. The reaction was quenched with saturated NH_4Cl aqueous solution (2 mL) and water (10 mL). After extraction with CH_2Cl_2 (4 × 20 mL), the combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound **6a** (0.38 g, yield 60.2%). TLC $R_f = 0.4$ (petroleum ether/EtOAc = 4/1). The crude product was not purified and used directly for the next step.

6.11. (*S*)-Ethyl 3-(cyclohexanecarboxamido)-3-(3-fluorophenyl) propanoate (**10d**)

To a stirred solution of **10c** (1.127 g, 3.6 mmol) in 20 mL DCM was added TFA (1.4 mL, 18 mmol), the mixture was stirred at rt for 12 h. Evaporated to remove the solvent and TFA, the residue was dissolved in 20 mL DCM. To the solution was added cyclohexanecarboxylic acid (0.52 mL, 4.3 mmol), EDCI (1.038 g, 5.4 mmol), HOBt (0.734 g, 5.4 mmol) and DIPEA (2.53 ml, 14.5 mmol). The mixture was stirred at rt for another 12 h. Usual work-up and purification by column chromatography (PE/EA = 3:1) gave **10d** as colorless oil (0.75 g, 66% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.33 (m, 1H), 7.05–7.08 (m, 1H), 6.92–7.01 (m, 2H), 6.75–6.78 (m, 1H), 5.39–5.45 (m, 1H), 4.09 (q, 2H, $J = 7.2$ Hz), 2.77–2.92 (m, 2H), 2.12–2.22 (m, 1H), 1.89–1.94 (m, 2H), 1.78–1.84 (m, 2H), 1.66–1.71 (m, 1H), 1.40–1.52 (m, 2H), 1.23–1.37 (m, 3H), 1.19 (t, 3H, $J = 7.2$ Hz).

6.12. (*S*)-*N*-(1-(3-Fluorophenyl)-3-oxopropyl) cyclohexanecarboxamide (**6c**)

Compound **6c** was prepared from **10d** in a similar fashion as described for **6a**, colorless oil in yield of 56%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (s, 1H), 7.27–7.30 (m, 1H), 7.05 (d, 1H, $J = 7.8$ Hz), 6.92–6.97 (m, 2H), 6.40–6.43 (m, 1H), 5.48 (dd, 1H, $J = 6.6$ Hz, 13.8 Hz), 2.87–3.06 (m, 2H), 2.04–2.13 (m, 2H), 1.75–1.84 (m, 4H), 1.38–1.42 (m, 2H), 1.19–1.24 (m, 3H).

6.13. Ethyl 8-carboxylate-8-aza-bicyclo[3.2.1]octan-3-one (**11**) [32]

A suspension of tropinone (27.84 g, 200 mmol), ethyl chloroformate (43.41 g, 38.2 mL, 400 mmol) and anhydrous K_2CO_3 (110 g, 800 mmol) in $CHCl_3$ (300 mL) was heated to reflux for 3 h. TLC monitored the reaction progress until the reaction was

completed. The slurry was filtered, rinsed with 100 mL of CH_2Cl_2. The organic layer was treated with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was washed with brine and concentrated in vacuum. The residue was purified by silica gel chromatography with eluent of $CH_2Cl_2/CH_3OH = 20/1$ to afford the compound **11** (34.7 g, yield 88.1%) as colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.51 (brs, 2H), 4.15 (q, 2H, $J = 6.9$ Hz), 2.62 (brs, 2H), 2.27–2.34 (m, 2H), 2.05–2.07 (m, 2H), 1.63–1.67 (m, 2H), 1.25 (t, 3H, $J = 6.9$ Hz). TLC $R_f = 0.8$ ($CH_2Cl_2/CH_3OH = 10/1$).

6.14. 8-(Ethoxycarbonyl)-8-aza-bicyclo[3.2.1]octan-3-amine (**12**) (endo-) [33]

The solution of **11** (1.97 g, 10 mmol) in MeOH (50 mL) was treated with ammonium formate (6.4 g, 100 mol) and water (6 mL) under vigorous stirring. After complete dissolution, 10% Pd/C (1 g) was added carefully and the reaction mixture was stirred overnight at room temperature. After TLC indicated a complete consumption of the starting material, the catalyst was filtered off on Celite and the solution was concentrated under reduced pressure. The oily residue was basified with saturated aqueous $NaHCO_3$ to pH 9–10 and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine and dried over Na_2SO_4, concentrated in vacuum. The crude product was purified by column chromatography with eluent of $CH_2Cl_2/MeOH = 50/1$ to 20/1 to afford the compound **12** (1.583 g, 80.1 yield) as colorless oil. After standing at room temperature, the oil turns into light yellow solid. M.p.64–68 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.22 (brs, 2H), 4.12 (q, 4H, $J = 7.2$ Hz), 3.324 (t, 1H, $J = 6.0$ Hz), 2.10–2.17 (m, 4H), 1.91–1.96 (m, 2H), 1.43 (d, 2H, $J = 13.2$ Hz), 1.24 (t, 3H, $J = 7.2$ Hz). TLC $R_f = 0.3$ ($CH_2Cl_2/MeOH = 10/1$).

6.15. N-(8-Ethoxycarbonyl-8-aza-bicyclo[3.2.1]octan-3-yl) isobutyramide (**13**)

To a stirred solution of isobutyric acid (1.76 g, 20 mmol) and DCC (4.76 g, 20 mmol) in dry THF (30 mL) at room temperature for 30 min was added the compound **12** (3.9 g, 20 mmol). The mixture was stirred for another 24 h until reaction was completed. The slurry was filtrated, rinsed with THF. The organic layer was concentrated and extracted with EtOAc (3 × 50 mL). The organic layer was washed with brine and concentrated. The crude product was purified by silica gel chromatography with eluent of PE: EtOAc = 2:1 to afford **13** (4.8 g, 90% yield) as white solid. M. p.99–100 °C.^1H NMR ($CDCl_3$, 300 MHz): δ 5.87 (brs, 1H), 5.28 (s, 1H), 4,28 (brs, 2H), 4.12 (q, 2H, $J = 7.2$ Hz), 2.30 (sep, 1H, $J = 6.9$ Hz), 2.18 (brs, 2H), 2.05–2.10 (m, 2H), 1.80–1.83 (m, 2H), 1.64–1.69 (m, 2H), 1.24 (t, 3H, $J = 7.2$ Hz), 1.13 (d, 6H, $J = 6.6$ Hz). EI-MS (m/z): 268 (M^+). TLC $R_f = 0.75$ ($CH_2Cl_2/CH_3OH = 10:1$).

6.16. 1-Benzylpiperidin-4-amine (**14**) [34]

To the solution of 1-benzylpiperidin-4-one (9.45 g, 50 mmol) in anhydrous EtOH (150 mL) was added $NH_2OH.HCl$ (7 g, 100 mmol) under ice bath, then added pyridine (17 mL) with vigorous stirring. The reaction mixture was heated to reflux for 5 h until the starting material disappeared. The reaction mixture was evaporated and the residue was dissoved in saturated NaCl aqueous solution and was adjusted by 1 N NaOH to pH 9–10, then extracted with ethyl acetate. Usual work-up gave yellow solid which was chromatographied with eluent of PE:EtOAc = 2:1 to afford 1-benzylpiperidin-4-one oxime as white solid (10.7 g, yield 99%). The intermediate (9.5 g, 46 mmol) was dissolved in *n*-PrOH (150 mL), and sodium piece (10.6 g, 460 mmol) was added to the solution under ice-bath. After stirring for 0.5 h, the reaction mixture was heated to reflux for 3 h until the reaction completed. The solvent was removed under vaccum and the residue was dissolved in saturated NaCl aq. under ice-bath. The solution was extracted with CH_2Cl_2 followded by usual work-up to give compound **14** as brown oil (8.43 g, yield 95.1%).

6.17. N-(1-Benzylpiperidin-4-yl)isobutyramide (**15**) [35]

To the solution of **14** (3.8 g, 20 mmol) in THF (20 mL) was added the solution of isobutyric acid (3.5 g, 40 mmol) and DCC (8.26 g, 40 mmol) in 30 mL of THF at room temperature. The reaction mixture was stirred for 10 h, then filtered to remove the white solid. The filtrate was concentrated under vaccum and extracted with CH_2Cl_2. The combined organic layers was washed with saturated NaCl aq. and dried over anhydrous Na_2SO_4. Evaporation afforded **15** as yellow solid (6.73 g, yield 83%). M.p.126–127 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.24–7.32 (m, 5H), 5.26–5.29 (brs, 1H), 3.77–3.82 (m, 1H), 3.50 (s, 2H), 2.79–2.83 (m, 2H), 2.24–2.33 (m, 1H), 2.08–2.17 (m, 2H), 1.37–1.47 (m, 2H), 1.25 (m, 2H), 1.09 (d, 6H, $J = 6.6$ Hz). EI-MS: m/z 260 (M^+).

6.17.1. Ethyl 4-(isobutyramido)piperidine-1-carboxylate (**16**)

Compound **16** was prepared in a similar fashion as described for **11** (yield 93.8%) as white solid. M.p.128–130 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 5.38 (s, 1H), 4.08–4.15 (m, 4H), 3.38–3.97 (m, 1H), 2.88 (t, 2H, $J = 12$ Hz), 2.29 (sep, 1H, $J = 6.6$ Hz,), 1.88–1.95 (m, 2H), 1.22–1.35 (m, 5H), 1.12 (d, 6H, $J = 6.6$ Hz). TLC $R_f = 0.5$ ($CH_2Cl_2/CH_3OH = 20/1$).

6.18. Ethyl 3-(3-nitropyridin-2-ylamino)-8-aza-bicyclo[3.2.1] octan-8-carboxylate (17) (endo-)

A suspension of compound **12** (1.28 g, 8.09 mmol), 2-chloro-3-nitropyridine (1.603 g, 8.09 mmol) and K_2CO_3 (4.5 g, 32.4 mmol) in 100 mL of dry CH_3CN was heated at refluxing for 10 h until the reaction was complete. The mixture was concentrated to driness and 50 mL of water was added. Extracted with EtOAc (2 × 30 mL), the combined organic phases were washed with saturated NaCl aqueous solution (40 mL). After drying over Na_2SO_4 and evaporation, the crude product was purified by silica gel chromatography with petroleum ether/EtOAc = 2/1 to afford **17** (2.134 g, yield 82.4%) as yellow solid. M.p.140–144 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.92 (brs, 1H), 8.07–8.11 (m, 1H), 6.33–6.36 (m, 1H), 6.03–6.05 (m, 1H), 4.28 (brs, 2H), 4.07–4.13 (m, 3H), 2.24 (brs, 2H), 1.91–2.05 (m, 4H), 1.76–1.80 (m, 2H), 1.21 (t, 3H, $J = 6.9$ Hz). TLC $R_f = 0.5$ (petroleum ether/EtOAc = 1/1).

6.19. Ethyl 3-(3-aminopyridin-2-ylamino)-8-aza-bicyclo[3.2.1] octan-8-carboxylate (18) (endo-)

The mixture of compound **17** (2.140 g, 6.7 mmol) and 10% palladium-C (0.03 g) in dry CH_3OH (50 mL) was stirred under hydrogen for 8 h at room temperature. After filtration and removal of the solvent under reduced pressure, the crude product was purified by silica gel chromatography with eluent $CH_2Cl_2/CH_3OH = 20/1$ to 10/1 to afford **18** (1.81 g, yield 93.7%) as brown solid. M.p.9–95 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.64–7.65 (m, 1H), 6.92–6.96 (m, 1H), 6.19–6.22 (m, 1H), 4.26 (brs, 2H), 4.11 (q, 1H, $J = 6.9$ Hz), 3.75 (brs, 1H), 3.03 (brs, 2H), 2.20 (brs, 2H), 1.99 (s, 4H), 1.72–1.78 (m, 2H), 1.23 (t, 3H, $J = 6.9$ Hz). TLC $R_f = 0.1$ ($CH_2Cl_2/CH_3OH = 50/1$).

6.20. endo-3-(8-Aza-bicyclo[3.2.1]octan-3-yl)-2-methyl-3H-imidazo[4,5-b]pyridine (**5-1**)

The compound **18** (1.45 g, 5 mmol) was heated with acetic anhydride (10 mL) at 165 °C for 24 hs until the reaction completed. The resultant solution was concentrated under reduced pressure and the residue was dissolved in Na_2CO_3 aqueous solution to adjust pH 9–10. Usual work-up afforded the intermediate of ethyl-3-(2-methyl-3H-imidazo[4,5-b]pyridin-3-yl)-8-aza-bicyclo[3.2.1]octan-8-carboxylate (*endo*-).

6.21. Ethyl-3-(2-Methyl-3H-imidazo[4,5-b]pyridin-3-yl)-8-aza-bicyclo[3.2.1]octan-8-carboxylate (endo-)

As light brown solid. M.p.91–93 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.22 (d, 1H, $J = 1.5$ Hz), 7.86 (d, 1H, $J = 1.5$ Hz), 7.09 (q, 1H, $J = 1.5$ Hz), 4.47 (brs, 2H), 4.16–4.32 (m, 3H), 2.52 (s, 3H), 2.41–2.55 (m, 2H), 2.42 (m, 2H), 2.04–2.08 (m, 4H), 1.28 (t, 3H, $J = 6.9$ Hz). TLC $R_f = 0.4$ (CH_2Cl_2/CH_3OH = 20/1).

The intermediate was dissolved in 6 N HCl (5 mL) and stirred at reflux for 12 h. After cooling, the mixture was extracted with CH_2Cl_2, basified, and the aqueous layer was treated with 10% aqueous NaOH solution and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine and concentrated. The residue was purified by silica gel column chromatography with eluent CH_2Cl_2/CH_3OH = 10/1 to 1/1 to afford compound **5-1** as light brown solid (0.848 g, yield 70.1% in two steps). M.p.170–174 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.22–8.24 (m, 1H), 7.83–7.86 (m,1H), 7.07–7.11 (m, 1H), 4.64–4.68 (m, 1H), 3.68–3.72 (m, 2H), 2.60 (s, 3H), 2.26–2.43 (m, 4H), 1.99–2.01 (m, 2H), 1.80–1.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 153.1, 148.5, 142.3, 135.1, 125.8, 117.4, 52.0, 46.4, 34.5, 33.7, 15.2. EI-MS (*m*/*z*): 242 (M^+). TLC $R_f = 0.5$ (CH_2Cl_2/CH_3OH = 1/1).

6.22. endo-tert-Butyl-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-aza-bicyclo[3.2.1] octan-8-carboxylate (**5-2**)

To a stirred solution of the compound **13** (0.96 g, 3.56 mmol) and *N*,*N*-dimethylbenzenamine (0.05 g, 0.4 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C was added PCl_5 (1.11 g, 5.35 mmol) in three portions. After 2 h stirring at 0 °C, acetic hydrazide (1.31 g, 17.8 mmol) in 10 mL of *t*-Amyl alcohol was added and the reaction mixture was stirred for another 12 h, then allowed to warm to room temperature. The solvent was removed in vacuo, and the residue was mixed with p-TsOH (0.06 g, 0.4 mmol) in toluene (10 mL). The resultant solution was heated to reflux for 6 h. After cooling, the solvent was removed. The crude product **19** was stirred with 6 N HCl (10 mL) at refluxing for 12 h, then the mixture was basified to pH 10–11 with 10% aqueous NaOH solution at room temperature. Boc_2O (1.1 g, 5.2 mmol) was added and the resulting solution was stirred for 24 h. Extracted with CH_2Cl_2 (5 × 20 mL), the combined organic layers were washed with brine and concentrated in vacuo. The residue was purified by silica gel column chromatography with eluent of CH_2Cl_2/CH_3OH = 20/1 to afford **5-2** (0.771 g, yield 64.7% in three steps) as white solid. M.p. 183–185 °C. ^{1}H NMR ($CDCl_3$,300 MHz): δ 4.36–4.44 (m, 2H), 3.96–4.03 (m, 1H), 2.89–2.95 (m, 1H), 2.47–2.57 (m, 2H), 2.50 (s, 3H), 2.16–2.19 (m, 2H), 1.69–1.77 (m, 4H), 1.50 (s, 9H), 1.37 (d, 6H, $J = 6.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 154.5, 150.7, 50.4, 49.7, 45.3, 35.6, 34.8, 32.1, 31.5, 28.2, 25.6, 21.3, 13.1; EI-MS: $C_{18}H_{30}N_4O_2$ *m*/*z* 334 (M^+). TLC $R_f = 0.35$ (CH_2Cl_2/CH_3OH = 10/1).

6.23. Ethyl 4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl) piperidine-1-carboxylate (**20**)

Compound **20** was prepared from the starting marterial **16** in a similar fashion as described for **19** as light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.34–4.38 (brs, 2H), 4.13 (q, 2H, $J = 7.2$ Hz), 3.98–4.0 (m, 1H), 2.94–3.01 (m, 1H), 2.82 (t, 2H, $J = 12$ Hz), 2.46 (s, 3H), 1.97–2.09 (m, 2H), 1.79–1.84 (m, 2H), 1.35 (d, 6H, $J = 6.6$ Hz), 1.25 (t, 3H, $J = 7.2$ Hz). TLC $R_f = 0.1$ (CH_2Cl_2/CH_3OH = 20/1).

6.24. tert-Butyl 4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl) piperidine-1-carboxylate (**5-3**)

Compound 5-3 was prepared in a similar fashion as described for **5-2** as white solid. M.p. 148–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.29–4.30 (brs, 2H), 3.97–4.01 (m,1H), 2.97 (sep, 1H, $J = 6.9$ Hz), 2.74–2.82 (m, 2H), 2.48 (s, 3H), 1.97–2.10 (m, 2H), 1.78–1.83 (m, 2H), 1.46 (s, 9H), 1.36 (d, 6H, $J = 6.6$ Hz). EI-MS: *m*/*z* 308 (M^+). TLC $R_f = 0.15$ (CH_2Cl_2/CH_3OH = 20/1).

6.25. tert-Butyl 4-(4-(N-benzyl-N-isopropylamino)phenyl) piperazine-1-carboxylate (**21**)

To a stirred solution of *tert*-butyl 4-(4-aminophenyl)piperazine-1-carboxylate (1.748 g, 6.16 mmol) and glacial acetic acid (1.19 g, 18.5 mmol) in dry acetone (30 mL) was added $NaB(OAc)_3H$ (3.90 g, 18.5 mmol) at room temperature, stirred for another 7 h at room temperature. The mixture was concentrated and the residue was dissolved in $NaHCO_3$ solution to pH 9–10 and extracted with CH_2Cl_2 (3 × 50 mL), The organic extracts were combined, the organic layer was washed with brine, dried over Na_2SO_4, concentrated to afford the intermediate of *tert*-butyl 4-(4-(isopropylamino)phenyl)piperazine-1-carboxylate (1.897 g, yield 96.5%) as light brown solid. M.p. 67–68 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.84 (brs, 2H), 6.58 (brs, 2H), 3.54–3.58 (m, 5H), 2.96 (s, 4H), 1.48 (s, 9H), 1.19 (d, 6H, $J = 6.0$ Hz).

At 0 °C, 1-(bromomethyl)benzene (0.96 g, 5.62 mmol) was added dropwise to the suspension of the intermediate (1.494 g, 4.68 mmol), K_2CO_3 (2.58 g, 18.72 mmol) in dry CH_3CN (30 mL) over 30 min, the mixture was stirred for another 5 h, TLC monitor reaction progress until the reaction was complete, filtered and concentrated, Extracted with EtOAc (3 × 50 mL), washed with brine and dried over Na_2SO_4, the crude was purified by column chromatography with elute DCM/CH_3OH = 50/1 to afford the compound **21** (1.773 g, yield 92.8%) as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29–7.37 (m, 5H), 6.80–6.83 (m, 2H), 6.67–6.69 (m, 2H), 4.34 (s, 2H), 4.09–4.15 (m, 1H), 3.52–3.55 (m, 4H), 2.94 (s, 4H), 1.47 (s, 9H), 1.18 (d, 6H, $J = 6.6$ Hz).

6.26. N-benzyl-N-isopropyl-4-(piperazin-1-yl)benzenamine (**5-4**)

At 0 °C, TFA 0.2 mL in dry CH_2Cl_2 (1 mL) was added dropwise to the solution of compound **21** (0.409 g, 10 mmol) in dry CH_2Cl_2 (4 mL). The resultant solution was stirred at room temperature for 1 h. Both the solvent and TFA were removed under vacuum. The residue of light brown solid was used directly into next step without further purification.

6.27. 1-tert-Butyl 4-methyl 4-benzylpiperidine-1,4-dicarboxylate (**23**) [28]

To a solution of diisopropylamine (2.1 mL) in anhydrous THF (10 mL) was added n-butyllithium in hexanes (1.6 M, 10 mL) via syringe at −15 °C under N_2 protection. After 30 min stirring at −15 °C, the mixture was added dropwise to the solution of compound **22** (2.43 g, 10 mmol) [36] in anhydrous THF (50 mL) via syringe over 30 min at −78 °C. The reaction mixture was then stirred at −78 °C for 1 more hour. The solution of 1-(bromomethyl) benzene (3.4 g, 20 mmol) in anhydrous THF (10 mL) was added dropwise via syringe over 30 min. The resultant mixture was

stirred for 2 h at −78 °C, then warmed to room temperature. The reaction was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and solvents removed in vacuo. The residue was purified by silica gel column chromatography with elute PE/EtOAc = 50/1 to 10/1 to afford **23** as colorless oil (3.03 g, yield 87.3%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21–7.28 (m, 3H), 7.01–7.03 (m, 2H), 3.88–3.96 (s, 2H), 3.63 (s, 3H), 2.81 (brs, 4H), 2.05–2.10 (m, 2H), 1.44(s, 9H), 1.40–1.46 (m, 2H). TLC R_f = 0.32 (petroleum ether/EtOAc = 10/1).

6.28. Methyl 4-benzylpiperidine-4-carboxylate (**5-5**)

Starting from compound **23**, acidic removal of the Boc group yielded **5-5,** in a similar fashion as described for **5-4.** Without further purification, the intermediate **5-5** was used directly for the next coupling reaction.

6.29. tert-Butyl 4-(4-methoxybenzamido)-4-methylpiperidine-1-carboxylate (**5**–**6a**)

Compound **5**–**6a** was prepared from *tert*-butyl 4-amino-4-methylpiperidine-1-carboxylate and 4-methoxybenzoic acid in a similar fashion as described for compound **10d**, colorless oil, yield 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, 2H, J = 9.0 Hz), 6.92 (d, 2H, J = 9.0 Hz), 5.75 (br, 1H), 3.86 (s, 3H), 3.71–3.76 (m, 2H), 3.16–3.25 (m, 2H), 2.18–2.22 (m, 2H), 1.62–1.72 (m, 2H), 1.53 (s, 3H), 1.47 (s, 9H).

6.30. tert-Butyl 4-methyl-4-(nicotinamido)piperidine-1-carboxylate (**5**–**6b**)

Compound **5**–**6b** was prepared from *tert*-butyl 4-amino-4-methylpiperidine-1-carboxylate and nicotinic acid according to the same procedure as **10d**. Colorless oil, yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.11 (s, 1H), 8.74 (d, 1H, J = 5.1 Hz), 8.21 (d, 1H, J = 7.8 Hz), 7.49 (dd, 1H, J = 5.1 Hz, 7.8 Hz), 6.15 (br, 1H), 3.71–3.75 (m, 2H), 3.21–3.31 (m, 2H), 2.21–2.26 (m, 2H), 1.67–1.76 (m, 2H), 1.56 (s, 3H), 1.48 (s, 9H).

6.31. tert-Butyl 4-(cyclohexanecarboxamido)-4-methylpiperidine-1-carboxylate (**5**–**6c**)

Compound **5**–**6c** was prepared from *tert*-butyl 4-amino-4-methylpiperidine-1-carboxylate and cyclohexanecarboxylic acid according to the same procedure as **10d,** colorless oil, yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 5.11 (br, 1H), 3.65–3.73 (m, 2H), 3.03–3.12 (m, 2H), 1.98–2.07 (m, 3H), 1.69–1.86 (m, 6H), 1.49–1.58 (m, 3H), 1.45 (s, 9H), 1.38 (s, 3H), 1.21–1.32 (m, 3H).

6.32. tert-Butyl 4-methyl-4-(4-(trifluoromethyl)benzamido) piperidine-1-carboxylate (**5**–**6d**)

Compounds **5**–**6d** were prepared from *tert*-butyl 4-amino-4-methylpiperidine-1-carboxylate and 4-(trifluoromethyl)benzoic acid according to the same procedure as **10d,** white foam, 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, 2H, J = 8.1 Hz), 7.70 (d, 2H, J = 8.1 Hz), 5.81 (br, 1H), 3.67–3.75 (m, 2H), 3.18–3.27 (m, 2H), 2.15–2.20 (m, 2H), 1.66–1.75 (m, 2H), 1.54 (s, 3H), 1.46 (s, 9H).

6.33. tert-Butyl 4-(2-(adamantylacetamido))-4-methylpiperidine-1-carboxylate (**5**–**6e**)

Compound **5**–**6e** was prepared from *tert*-butyl 4-amino-4-methylpiperidine-1-carboxylate and 2-adamantylacetic acid according to the same procedure as **10d,** colorless oil, 51% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.99 (br, 1H), 3.63–3.68 (m, 2H), 3.10–3.19 (m, 2H), 1.97–1.98 (m, 4H), 1.88 (s, 2H), 1.69–1.73 (m, 4H), 1.61–1.64 (m, 7H), 1.50–1.57 (m, 2H), 1.46 (s, 9H), 1.41 (s, 3H), 1.26–1.28 (m, 2H).

6.34. tert-Butyl 4-(2-(4-chlorophenyl)acetamido)-4-methylpiperidine-1-carboxylate (**5**–**6f**)

Compound **5**–**6f** was prepared from *tert*-butyl 4-amino-4-methylpiperidine-1-carboxylate and 2-(4-chlorophenyl)acetic acid according to the same procedure as **10d,** colorless oil, 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, 2H, J = 8.7 Hz), 7.19 (d, 2H, J = 8.7 Hz), 5.03 (br, 1H), 3.60–3.65 (m, 2H), 3.49 (s, 2H), 2.85–2.95 (m, 2H), 1.91–1.96 (m, 2H), 1.48–1.54 (m, 2H), 1.44 (s, 9H), 1.37 (s, 3H).

6.35. tert-Butyl 4-(2-(3,4-dichlorophenyl)acetamido)-4-methylpiperidine-1-carboxylate (**5**–**6g**)

Compound **5**–**6g** was prepared from *tert*-butyl 4-amino-4-methylpiperidine-1-carboxylate and 2-(3,4-dichlorophenyl)acetic acid according to the same procedure as **10d,** white foam, 67% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.42 (d, 1H, J = 8.1 Hz), 7.37 (d, 1H, J = 2.1 Hz), 7.11 (dd, 1H, J = 2.1 Hz, 8.1 Hz), 5.18 (br, 1H), 3.57–3.65 (m, 2H), 3.46 (s, 2H), 2.97–3.06 (m, 2H), 1.95–1.99 (m, 2H), 1.49–1.58 (m, 2H), 1.45 (s, 9H), 1.38 (s, 3H).

6.36. tert-Butyl 4-(2-(4-fluorophenyl)acetamido)-4-methylpiperidine-1-carboxylate (**5**–**6h**)

Compound **5**–**6h** was prepared from *tert*-butyl 4-amino-4-methylpiperidine-1-carboxylate and 2-(4-fluorophenyl)acetic acid according to the same procedure as **10d,** colorless oil, 63% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.22–7.26 (m, 2H), 7.07 (t, 2H, J = 8.7 Hz), 5.03 (br, 1H), 3.61–3.68 (m, 2H), 3.51 (s, 2H), 2.84–2.93 (m, 2H), 1.93–1.97 (m, 2H), 1.48–1.55 (m, 2H), 1.45 (s, 9H), 1.38 (s, 3H).

6.37. tert-Butyl 4-(2-(3,4,5-trimethoxyphenyl)acetamido)-4-methylpiperidine-1-carboxylate (**5**–**6i**)

Compound **5**–**6i** was prepared from *tert*-butyl 4-amino-4-methylpiperidine-1-carboxylate and 2-(3,4,5-trimethoxyphenyl) acetic acid according to the same procedure as **10d,** white foam, 46% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.47 (s, 2H), 5.15 (br, 1H), 3.86 (s, 9H), 3.64–3.68 (m, 2H), 3.48 (s, 2H), 2.85–2.95 (m, 2H), 1.96–2.00 (m, 2H), 1.49–1.55 (m, 2H), 1.45 (s, 9H), 1.39 (s, 3H).

6.38. endo-N-((S)-1-(4-(Trifluoromethyl)phenyl)-3-(3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-aza-bicyclo[3.2.1] octan-8-yl)propyl)-2-phenoxyacetamide (**1a**)

At 0 °C, TFA (0.2 mL) in dry CH_2Cl_2 (1 mL) was added dropwise to the solution of compound **5-2** (0.034 g, 0.1 mmol) in dry CH_2Cl_2 (1 mL). The resultant solution was stirred at room temperature for 1 h till the starting material disappeared. Then the solvent and TFA was removed under reduced pressure. The residue was dissolved in 5 mL of dry 1,2-dichloromethane and basified by adding Et_3N (1 mL). To the solution were added compound **6a** (0.032 g, 0.1 mmol), HOAc (0.012 g) and sodium triacetoxyborohydride (0.043 g, 0.2 mmol). The reaction mixture was stirred for 24 h at room temperature. Concentrated and the residue was dissolved in $NaHCO_3$ solution to adjust the pH 9–10 and extracted with CH_2Cl_2 (3 × 20 mL). Usual work-up gave the crude product of *tert*-butyl (*S*)-3-(3-(3-*iso*propyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-aza-bicyclo

[3.2.1]octan-8-yl)-1-(4-(trifluoromethyl)phenyl) propylcarbamate (0.038 g, yield 70.3%) as light brown solid.

The precursor (0.038 g, 0.07 mmol) was treated by TFA in dry CH_2Cl_2 (20% v/v) at room temperature for 1 h, then concentrated. The residue was dissolved in 10 mL of dry CH_2Cl_2 and basified by adding Et_3N (1 mL). To the solution were added 2-phenoxyacetic acid (0.012 g, 0.084 mmol), EDCI (0.016 g, 0.084 mmol), HOAt (0.011 g, 0.084 mmol) and DIPEA (0.1 mL). The mixture was stirred overnight at room temperature and was quenched by adding saturated aqueous $NaHCO_3$ (10 mL). Usual work-up followed by flash chromatography purification with eluent of CH_2Cl_2/CH_3OH = 10/1 produced **1a** as light brown solid (0.035 g, yield 88.0%). M.p.79.5–81 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56–7.59 (m, 2H), 7.25–7.39 (m, 7H), 6.11–6.14 (m, 1H), 5.19–5.26 (m, 1H), 4.48–4.54 (m, 1H), 3.59 (s, 2H), 3.26–3.28 (m, 2H), 2.96–3.05 (m, 1H), 2.46 (s, 3H), 2.38–2.42 (m, 2H), 2.11–2.16 (m, 2H), 2.03–2.06 (m, 2H), 1.83–1.88 (m, 2H), 1.54–1.58 (m, 4H), 1.36 (d, 6H, J = 6.9 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 169.7, 158.8, 150.2, 149.2, 136.6, 128.9, 128.2, 127.2, 126.4, 125.2, 57.2, 55.6, 50.0, 48.6, 44.9, 42.6, 36.8, 35.6, 29.7, 29.3, 24.8, 21.9, 21.6, 12.7. $[\alpha]_D^{22} = -2.1°$ (c = 0.45, $CHCl_3$). EI-MS (m/z) 568 $(M-1)^-$. TLC R_f = 0.45(CH_2Cl_2/CH_3OH = 10/1).

6.39. endo-4-Fluoro-N-((S)-3-(3-(2-methyl-3H-imidazo[4,5-b] pyridin-3-yl)-8-aza-bicyclo[3.2.1]octan-8-yl)-1-(naphthalen-1-yl) propyl)benzamide (**1b**)

Starting from the building blocks **5-1** and **6b**, compound **1b** was prepared in a similar fashion as described for **1a.** Grey solid, 61% yield in two steps. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.32–8.34 (m, 1H), 7.24–8.31 (m, 4H), 8.16–8.19 (m, 1H), 7.90–7.93 (m, 1H), 7.75–7.80 (m, 5H), 7.51–7.54 (m, 1H), 7.26–7.29 (m, 1H), 5.21 (brs, 1H), 4.08–4.13 (m, 1H), 3.37–3.42 (m, 2H), 2.82–2.85 (m, 2H), 2.63 (s, 3H), 2.35–2.46 (m, 2H), 1.83–1.87 (m, 2H), 1.68–1.74 (m, 2H), 1.28–1.37 (m, 4H). EI-MS (m/z) 547 (M^+). TLC R_f = 0.4–0.45(CH_2Cl_2/CH_3OH = 20/1).

The precursor of compound 1b: *endo-tert*-butyl *(S)*-3-(3-(2-methyl-3H-imidazo[4,5-b]pyridin-3-yl)-8-aza-bicyclo[3.2.1]octan-8-yl)-1-(naphthalen-1-yl)propylcarbamate. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.25 (d, 1H, J = 1.5 Hz), 7.87 (d, 1H, J = 1.5 Hz), 7.84 (d, 1H, J = 1.5 Hz), 7.46–7.53 (m, 4H), 7.10–7.14 (m, 1H), 6.08 (brs, 1H), 5.81 (brs, 1H), 4.86–4.94 (m, 1H), 3.39–3.46 (m, 2H), 2.70 (s, 3H), 2.49–2.57 (m, 4H), 2.11–2.12 (m, 4H), 1.89–1.93 (m, 4H), 1.43 (s, 9H). TLC R_f = 0.8 (CH_2Cl_2/CH_3OH = 10/1).

6.40. N-((S)-3-(4-(4-(N-benzyl-N-isopropylamino)phenyl) piperazin-1-yl)-1-(4-(trifluoromethyl)phenyl)propyl) cyclohexanecarboxamide (**2a**)

To the solution of compound **5-4** (0.9 mmol) in 5 mL of dry 1,2-dichloromethane and Et_3N (1 mL) were added compound **6a** (0.095 g, 0.3 mmol), HOAc (0.054 g, 0.9 mmol) and sodium triacetoxyborohydride (0.19 g, 0.9 mmol). The resultant solution was stirred for 22 h at room temperature, then concentrated under reduced pressure. The residue was dissolved in $NaHCO_3$ solution to adjust pH to 9–10 and extracted with CH_2Cl_2 (3 × 50 mL). The usual-workup afforded 0.173 g solid which was dissolved in dry CH_2Cl_2 and treated with TFA (20% v/v) for 1 h at room temperature. Removal of the solvent in vacuo produced the residue. Purification by column chromatography with eluent of DCM/CH_3OH = 10/1 gave the intermediate of (*S*)-4-(4-(3-amino-3-(4-(trifluoromethyl) phenyl)propyl)piperazin-1-yl)-*N*-benzyl-*N*- *iso*propylbenzenamine as light brown colloidal solid (0.121 g, yield 79% in two step). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.57–7.60 (m, 2H), 7.45–7.48 (m, 2H), 7.15–7.31 (m, 5H), 6.79–6.82 (m, 2H), 6.66–6.69 (m, 2H), 4.33 (s, 2H), 4.05–4.16 (m, 1H), 3.03–3.06 (m, 4H), 2.54–2.65 (m, 4H), 2.35–2.39 (m, 4H), 1.85–1.98 (m, 2H), 1.17 (d, 6H, J = 6.9 Hz). TLC R_f = 0.4–0.5(CH_2Cl_2/CH_3OH = 10:1).

The intermediate (0.12 g, 0.25 mmol) was mixed with DCC (0.062 g, 0.3 mmol) and cyclohexanecarboxylic acid (0.038 g, 0.3 mmol) in dry THF (10 mL) at 0 °C. The mixture was stirred for 24 h until the reaction was complete. Filtrated and concentrated, basified with saturated $NaHCO_3$ aqueous solution to pH 8–9, extracted with CH_2Cl_2 (3 × 30 mL). Usual work-up followed by the column chromatography purification with eluent CH_2Cl_2/CH_3OH = 20/1 afforded compound **2a** (0.123 g, yield 79.4%) as light brown colloidal solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.18 (brs, 1H), 7.26–7.37 (m, 2H), 7.34–7.36 (m, 2H), 7.15–7.31 (m, 5H), 6.81–6.84 (m, 2H), 6.67–6.70 (m, 2H), 5.08–5.14 (m, 1H), 4.35 (s, 2H), 4.10–4.19 (m, 1H), 3.12 (s, 4H), 2.66–2.73 (m, 4H), 2.46 (s, 2H), 1.39–2.22 (m, 14H), 1.18 (d, 6H, J = 6.9 Hz). TLC R_f = 0.75 (CH_2Cl_2/CH_3OH = 20:1).

6.41. N-((S)-1-(4-(trifluoromethyl)phenyl)-3-(4-(4-(isopropylamino)phenyl)piperazin-1-yl)propyl) cyclohexanecarboxamide (**2b**)

The mixture of compound **2a** (0.14 g, 0.173 mmol) and palladium (10% on carbon, 0.05 g) in dry EtOH (20 mL) was stirred under hydrogen for 10 h at room temperature until the reaction was complete. After filtration and removal of the solvent under reduced pressure, the crude product was purified by silica gel chromatography with eluent of CH_2Cl_2/CH_3OH = 20/1 to give the precursor, namely (*S*)-*N*-(3-(4-(4-(*iso*propylamino)phenyl) piperazin-1-yl)-1-(4-(trifluoromethyl)phenyl)propyl)cyclohexanecarboxamide as light brown colloidal solid (0.083 g, yield 90.2%). ^1H NMR($CDCl_3$, 300 MHz): δ 8.27–8.29 (m, 1H), 7.56–7.59 (m, 2H), 7.34–7.36 (m, 2H), 6.84–6.86 (m, 2H), 6.56–6.60 (m, 2H), 5.11–5.17 (m, 1H), 3.54–3.60 (m, 1H), 3.10 (s, 4H), 2.57–2.71 (m, 4H), 2.35–2.42 (m, 2H), 2.07–2.16 (m, 2H), 1.39–1.92 (m, 12H), 1.19 (d, 6H, J = 6.9 Hz). TLC R_f = 0.3 (CH_2Cl_2/CH_3OH = 20:1).

To the stirred solution of the precursor (0.061 g, 0.11 mmol) in toluene (10 mL) was added Ac_2O (0.102 g, 1.1 mmol). The resultant solution was refluxed for 3 h, then concentrated and basified with saturated aqueous $NaHCO_3$ to pH 8–9, extracted with EtOAc (3 × 30 mL). Usual work-up followed by flash chromatography purification with DCM/CH_3OH = 50/1 to 20/1 gave **2b** as light brown solid (0.059 g, yield 93.6%). M.p.73–75 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.74–7.76 (m, 1H), 7.56–7.59 (m, 2H), 7.34–7.36 (m, 2H), 6.97–6.99 (m, 2H), 6.87–6.91 (m, 2H), 4.96–5.04 (m, 1H), 3.18–3.28 (m, 3H), 2.58–2.69 (m, 2H), 2.32–2.43 (m, 2H), 2.01–2.18 (m, 2H), 1.87–1.91 (m, 2H), 1.74 (s, 3H), 1.61–1.73 (m, 8H), 1.39–1.51 (m, 2H), 1.02 (d, 6H, J = 6.9 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.8, 169.1, 150.2, 148.9, 130.6, 129.5, 127.2, 125.8, 125.2, 115.2, 54.6, 52.7, 50.6, 47.7, 44.7, 44.0, 33.0, 29.3, 29.2, 26.1, 25.5, 25.3, 23.2, 20.8. EI-MS (m/z) 572 (M^+) . TLC R_f = 0.6 (CH_2Cl_2/CH_3OH = 10/1).

6.42. Methyl-4-benzyl-1-((S)-3-(cyclobutanecarboxamido)-3-(4-(trifluoromethyl)phenyl)propyl)piperidine-4-carboxylate (**3a**)

Starting from the building blocks of **5-5** and **6a,** compound **3a** was prepared in a similar fashion as described for **1a** as colorless oil (yield 85.6%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.92–7.95 (brs, 1H), 7.54–7.57 (m, 2H), 7.24–7.34 (m, 5H), 7.02–7.05 (m, 2H), 4.97–5.03 (m, 1H), 3.65 (s, 3H), 2.98–3.17 (m, 6H), 2.85 (s, 2H), 2.43–2.51 (m, 2H), 1.64–2.15 (m, 11H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.9, 173.5, 148.8, 136.6, 129.7, 128.0, 127.5, 127.2, 126.6, 125.8, 125.2, 123.1, 54.7, 51.4, 50.9, 50.5, 37.5, 32.8, 24.8, 24.7, 24.6, 17.9, 17.8. EI-MS (m/z) 516 (M^+). $[\alpha]_D^{20} = -26.4°$ (c = 0.36, $CHCl_3$). TLC R_f = 0.3 (CH_2Cl_2/CH_3OH = 20:1).

*6.43. N-((S)-3-(4-benzyl-4-(hydroxymethyl)piperidin-1-yl)-1-(4-(trifluoromethyl)phenyl)propyl)cyclobutanecarboxamide (**3b**)*

To the cold solution of $LiAlH_4$ (0.005 g, 0.13 mmol) in dry THF (1 mL) was added compound **3a** (0.052 g, 0.1 mmol) in dry THF (1 mL) via syringe under N_2 protection at −15 °C. The mixture was stirred for an hour at −15 °C until TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) followed by the usual work-up. The crude product was purified by column chromatography with eluent of $CH_2Cl_2/CH_3OH = 10/1$ to give compound **3b** as colorless colloidal solid (0.041 g, yield 83.6%). M.p.71–73 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.12–8.14 (m, 1H), 7.56–7.59 (m, 2H), 7.24–7.34 (m, 5H), 7.16–7.19 (m, 2H), 5.05–5.11 (m, 1H), 3.45 (s, 3H), 2.99–3.04 (m, 1H), 2.73 (s, 2H), 1.88–2.00 (m, 6H), 1.60–1.74 (m, 12H). EI-MS (*m*/*z*): 488 (M^+). $[\alpha]_D^{22} = -29°$ (*c* = 0.16, $CHCl_3$). TLC $R_f = 0.15$ ($CH_2Cl_2/CH_3OH = 20/1$).

*6.44. Methyl-4-benzyl-1-((S)-3-(cyclobutanecarboxamido)-3-(naphthalen-4-yl)propyl)piperidine-4-carboxylate (**3c**)*

Starting from the building blocks of **5-5** and **6b**, compound **3c** was prepared in a similar fashion as described for **1a** as colorless solid in yield of 90% for two steps. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.04–8.06 (m, 1H), 7.84–7.86 (m, 1H), 7.52–7.83 (m, 1H), 7.42–7.51 (m, 4H), 7.24–7.28 (m, 3H), 7.02–7.05 (m, 2H), 5.81–5.83 (m, 1H), 3.64 (s, 3H), 2.99–3.17 (m, 4H), 2.86 (s, 2H), 2.57–2.60 (m, 2H), 2.10–2.36 (m, 11H), 1.82–1.99 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 173.6, 148.4, 138.0, 130.6, 127.8, 127.6, 127.2, 125.9, 125.7, 125.2, 123.0, 54.4, 50.8, 48.7, 38.7, 36.1, 30.4, 24.6, 17.9. EI-MS (*m*/*z*): 498 (M^+). $[\alpha]_D^{20} = -18°$ (*c* = 0.074, $CHCl_3$). TLC $R_f = 0.3$ ($CH_2Cl_2/CH_3OH = 20/1$).

*6.45. (S)-N-(1-(3-(cyclohexanecarboxamido)-3-(3-fluorophenyl)propyl)-4-methylpiperidin-4-yl)-4-methoxybenzamide (**4a**)*

To a stirred solution of **5-6a** (191 mg, 0.55 mmol) in 5 mL DCM was added TFA (0.42 mL, 5.5 mmol). The mixture was stirred at rt for 8 h, then evaporated to remove the solvent and TFA. The residue was treated with 20 mL DCE, $NaBH(OAc)_3$ (171 mg, 0.81 mmol) and **6c** (112 mg, 0.4 mmol). The resultant mixture was stirred at rt for 22 h, then evaporated to remove the solvent. The crude product was purified by column chromatography (DCM/MeOH = 20:1) to give **4a** as white solid (140 mg, 69% yield). Mp: 67–69 °C; $[\alpha]_D^{21} = -15.1°$(*c* = 0.95, $CHCl_3$); EI-MS (*m*/*z*): 509 (M^+); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.95 (d, 1H, *J* = 7.5 Hz), 7.69 (d, 2H, *J* = 8.7 Hz), 7.23–7.30 (m, 1H), 7.01 (d, 1H, *J* = 7.5 Hz), 6.89–6.94 (m, 3H), 5.91 (br, 1H), 4.95–5.01 (m, 1H), 3.84 (s, 3H), 2.86–2.90 (m, 1H), 2.76–2.80 (m, 1H), 2.50–2.54 (m, 3H), 2.36–2.46 (m, 3H), 2.07–2.22 (m, 2H), 1.77–1.90 (m, 7H), 1.66–1.69 (m, 1H), 1.52 (s, 3H), 1.41–1.48 (m, 2H), 1.17–1.30 (m, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ: 179.4, 171.0, 164.8 (d, $^1J_{CF} = 243.6$ Hz), 164.3, 146.6 (d, $^3J_{CF} = 6.4$ Hz), 132.0 (d, $^3J_{CF} = 8.2$ Hz), 130.8, 129.2, 124.0, 115.7 (d, $^2J_{CF} = 21.4$ Hz), 115.1, 114.9 (d, $^2J_{CF} = 22.4$ Hz), 56.4, 56.1, 52.5, 52.4, 51.1, 50.9, 46.7, 35.2, 32.6, 31.2, 31.1, 27.3, 27.2, 27.1.

*6.46. (S)-N-(1-(3-(cyclohexanecarboxamido)-3-(3-fluorophenyl)propyl)-4-methylpiperidin-4-yl)nicotinamide (**4b**)*

Compound **4b** was prepared from **5**–**6b** and **6c** according to the same procedure as **4a**. White solid, 70% yield. Mp: 58–60 °C; $[\alpha]_D^{22} = -34.4°$(*c* = 0.45, $CHCl_3$); EI-MS (*m*/*z*): 480 (M^+); ^1H NMR (300 MHz, $CDCl_3$): δ 9.28 (br, 1H), 8.70–8.72 (m, 1H), 8.41 (br, 2H), 8.26 (d, 1H, *J* = 7.5 Hz), 7.09–7.13 (m, 3H), 6.77–6.81 (m, 1H), 5.18–5.21 (m, 2H), 3.12–3.19 (m, 2H), 2.26–2.31 (m, 8H), 2.07–2.12 (m, 2H), 1.88–1.96 (m, 2H), 1.68–1.78 (m, 6H), 1.63 (s, 3H), 1.39–1.44 (m, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ : 175.1, 166.4, 162.2 (d, $^1J_{CF} = 241.8$ Hz), 151.7, 148.8, 146.1, 135.7, 130.9, 130.4, 123.3, 122.4, 113.9 (d, $^2J_{CF} = 14.2$ Hz), 113.1 (d, $^2J_{CF} = 14.6$ Hz), 50.1, 49.5, 48.5, 43.8, 33.2, 30.5, 30.1, 29.1, 29.0, 28.7, 25.7, 25.4, 25.2, 22.1.

*6.46.1. (S)-N-(1-(3-(cyclohexanecarboxamido)-3-(3-fluorophenyl)propyl)-4-methylpiperidin-4-yl)cyclohexanecarboxamide (**4c**)*

Compound **4c** was prepared from **5**–**6c** and **6c** according to the same procedure as **4a**. **4c** was a white solid. Mp: 83–85 °C; $[\alpha]_D^{21} = -25.2°$ (*c* = 0.75, $CHCl_3$); EI-MS (*m*/*z*): 485(M^+); ^1H NMR (300 MHz, $CDCl_3$): δ 8.09–8.11 (m, 1H), 7.02–7.04 (m, 1H), 6.92–6.95 (m, 2H), 5.09 (br, 2H), 2.76–2.81 (m, 1H), 2.61–2.65 (m, 1H), 2.35–2.43 (m, 3H), 2.12–2.27 (m, 7H), 1.78–1.89 (m, 17H), 1.68–1.72 (m, 5H), 1.42 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ : 175.3, 174.6, 162.2 (d, $^1J_{CF} = 241.8$ Hz), 147.0, 130.1 (d, $^3J_{CF} = 8.9$ Hz), 122.4, 113.4 (d, $^2J_{CF} = 20.1$ Hz), 112.9 (d, $^2J_{CF} = 21.6$ Hz), 54.4, 50.3, 49.6, 49.0, 44.4, 44.0, 34.6, 32.6, 29.4, 29.3, 29.2, 25.5, 25.3.

*6.47. (S)-N-(1-(3-(cyclohexanecarboxamido)-3-(3-fluorophenyl)propyl)-4-methylpiperidin-4-yl)-4-(trifluoromethyl)benzamide (**4d**)*

Compound **4d** was prepared from **5**–**6d** and **6c** according to the same procedure as **4a**, white solid, yield 68%. Mp: 93–95 °C; $[\alpha]_D^{21} = -19.0°$ (*c* = 1.05, $CHCl_3$); EI-MS (*m*/*z*): 547 (M^+); ^1H NMR (300 MHz, $CDCl_3$): δ 7.92–7.95 (m, 1H), 7.84 (d, 2H, *J* = 7.5 Hz), 7.70 (d, 2H, *J* = 7.5 Hz), 6.92–7.03 (m, 3H), 5.99 (br, 1H), 5.03–6.08 (m, 1H), 2.83–2.86 (m, 1H), 2.70–2.72 (m, 1H), 2.36–2.44 (m, 7H), 2.12–2.26 (m, 2H), 1.80–1.93 (m, 8H), 1.68–1.71 (m, 1H), 1.55 (s, 3H), 1.42–1.49 (m, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 174.7, 165.7, 162.2 (d, $^1J_{CF} = 241.8$ Hz), 139.6, 130.8 (d, $^2J_{CF} = 32.0$ Hz), 130.1 (d, $^3J_{CF} = 8.2$ Hz), 128.4, 125.1 (d, $^3J_{CF} = 2.9$ Hz), 124.0 (d, $^1J_{CF} = 270.8$ Hz), 122.4, 113.4 (d, $^2J_{CF} = 21.6$ Hz), 113.0 (d, $^2J_{CF} = 21.5$ Hz), 51.2, 50.2, 49.0, 43.9, 29.2, 29.1, 25.4, 25.3.

*6.48. (S)-N-(3-(4-(2-adamantylacetamido)-4-methylpiperidin-1-yl)-1-(3-fluorophenyl)propyl)cyclohexanecarboxamide (**4e**)*

Compound **4e** was prepared from **5**–**6e** and **6c** according to the same procedure as **4a**, white solid, 23% yield. Mp: 108–110 °C; $[\alpha]_D^{21} = -23.2°$(*c* = 0.25, $CHCl_3$); EI-MS (*m*/*z*): 552($M+1$)$^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.04–8.07 (m, 1H), 7.01 (d, 1H, *J* = 7.2 Hz), 6.90–6.93 (m, 2H), 5.05–5.07 (m, 1H), 5.01 (br, 1H), 2.74–2.76 (m, 1H), 2.59–2.62 (m, 1H), 2.34–2.40 (m, 4H), 2.10–2.26 (m, 7H), 1.87 (s, 2H), 1.62–1.82 (m, 23H), 1.42 (s, 3H), 1.23–1.31 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 176.8, 174.7, 162.2 (d, $^1J_{CF} = 241.8$ Hz), 146.2, 130.1, 122.3, 113.3, 112.9 (d, $^2J_{CF} = 14.2$ Hz), 50.6, 50.0, 48.6, 43.9, 42.2, 36.5, 32.3, 29.2, 29.1, 28.0, 25.4, 25.2.

*6.49. (S)-N-(3-(4-(2-(4-chlorophenyl)acetamido)-4-methylpiperidin-1-yl)-1-(3-fluorophenyl)propyl)cyclohexanecarboxamide (**4f**)*

Compound **4f** was prepared from **5-6f** and **6c** according to the same procedure as **4a**, white solid, 75% yield. Mp: 66–68 °C; $[\alpha]_D^{21} = -18.8°$ (*c* = 0.8, $CHCl_3$); EI-MS (*m*/*z*): 527(M^+); ^1H NMR (300 MHz, $CDCl_3$) : δ 7.92 (d, 1H, *J* = 6.9 Hz), 7.18–7.34 (m, 4H), 7.00 (d, 1H, *J* = 8.4 Hz), 6.92 (d, 2H, *J* = 9.0 Hz), 5.41 (br, 1H), 4.96–5.02 (m, 1H), 3.47 (s, 2H), 2.72–2.77 (m, 1H), 2.61–2.65 (m, 1H), 2.40–2.42 (m, 2H), 2.11–2.19 (m, 6H), 1.85–1.90 (m, 3H), 1.77–1.81 (m, 3H), 1.68–1.71 (m, 3H), 1.43–1.47 (m, 2H), 1.38 (s, 3H), 1.21–1.29 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ : 179.4, 174.2, 164.7 (d, $^1J_{CF} = 243.7$ Hz), 146.5 (d, $^3J_{CF} = 6.8$ Hz), 136.6, 134.2, 132.2, 132.1 (d, $^3J_{CF} = 8.2$ Hz), 130.0, 124.0, 115.8 (d, $^2J_{CF} = 21.4$ Hz), 114.9 (d,

$^2J_{CF}$ = 21.8 Hz), 52.4, 51.9, 50.8, 50.6, 50.4, 46.7, 44.3, 34.9, 32.4, 31.2, 31.1, 27.3, 27.2.

6.50. (S)-N-(3-(4-(2-(3,4-dichlorophenyl)acetamido)-4-methylpiperidin-1-yl)-1-(3-fluorophenyl)propyl) cyclohexanecarboxamide (**4g**)

Compound **4g** was prepared from **5**–**6g** and **6c** according to the same procedure as **4a**, white solid, 31% yield. Mp: 86–88 °C; $[\alpha]_D^{21} = -22.5°$ (c = 0.75, $CHCl_3$); EI-MS (m/z): 561 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.06–8.08 (m, 1H), 7.38–7.43 (m, 2H), 7.12 (d, 1H, J = 8.4 Hz), 7.00 (d, 1H, J = 7.8 Hz), 6.89–6.93 (m, 2H), 5.31 (br, 1H), 5.03–5.07 (m, 1H), 3.45 (s, 2H), 2.68–2.71 (m, 1H), 2.51–2.54 (m, 1H), 2.28–2.37 (m, 2H), 2.08–2.17 (m, 7H), 1.89–1.93 (m, 2H), 1.79–1.82 (m, 3H), 1.65–1.72 (m, 3H), 1.44–1.48 (m, 1H), 1.40 (s, 3H), 1.23–1.29 (m, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ : 174.6, 169.1, 162.2 (d, $^1J_{CF}$ = 241.9 Hz), 147.0, 138.1, 131.0, 130.6, 130.2, 130.1, 129.4, 128.9, 122.4, 113.3 (d, $^2J_{CF}$ = 21.6 Hz), 112.9 (d, $^2J_{CF}$ = 21.6 Hz), 54.5, 50.3, 48.9, 44.0, 42.0, 29.3, 29.2, 26.1, 25.5, 25.3.

6.51. (S)-N-(3-(4-(2-(4-fluorophenyl)acetamido)-4-methylpiperidin-1-yl)-1-(3-fluorophenyl)propyl) cyclohexanecarboxamide (**4h**)

Compound **4h** was prepared from **5**–**6h** and **6c** according to the same procedure as **4a**, white solid, 64% yield. Mp: 65–67 °C; $[\alpha]_D^{21} = -22.6°$ (c = 1.05, $CHCl_3$); EI-MS (m/z): 511 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.88 (d, 1H, J = 7.2 Hz), 7.22 (dd, 2H, J = 5.4 Hz, 8.7 Hz), 7.00–7.06 (m, 3H), 6.93 (d, 2H, J = 9.0 Hz), 5.45 (br, 1H), 4.95–5.01 (m, 1H), 3.47 (s, 2H), 2.74–2.80 (m, 1H), 2.65–2.71 (m, 1H), 2.46 (t, 2H, J = 6.3 Hz), 2.07–2.24 (m, 6H), 1.91–1.98 (m, 1H), 1.66–1.88 (m, 8H), 1.43–1.47 (m, 1H), 1.38 (s, 3H), 1.21–1.29 (m, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 174.7, 170.0, 162.2 (d, $^1J_{CF}$ = 241.8 Hz), 160.9 (d, $^1J_{CF}$ = 240.3 Hz), 146.8, 133.1, 130.7 (d, $^3J_{CF}$ = 8.2 Hz), 130.1 (d, $^3J_{CF}$ = 8.2 Hz), 122.4, 114.8 (d, $^2J_{CF}$ = 20.8 Hz), 113.4 (d, $^2J_{CF}$ = 20.9 Hz), 113.0 (d, $^2J_{CF}$ = 21.6 Hz), 54.2, 50.2, 48.5, 43.9, 42.2, 29.2, 29.1, 25.5, 25.3.

6.52. (S)-N-(3-(4-(2-(3,4,5-trimethoxyphenyl)acetamido)-4-methylpiperidin-1-yl)-1-(3-fluorophenyl)propyl) cyclohexanecarboxamide (**4i**)

Compound **4i** was prepared from **5**–**6i** and **6c** according to the same procedure as **4a**, white solid, 35% yield. Mp: 68–70 °C; $[\alpha]_D^{22} = -6.3°$ (c = 0.3, $CHCl_3$); EI-MS (m/z): 583 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.35 (m, 1H), 7.04 (d, 1H, J = 6.9 Hz), 6.95 (d, 2H, J = 6.9 Hz), 6.48 (s, 2H), 5.32 (s, 1H), 5.01 (br, 1H), 3.87(s, 6H), 3.85 (s, 3H), 3.48 (s, 2H), 2.77–2.82 (m, 1H), 2.59–2.66 (m, 1H), 2.12–2.23 (m, 4H), 1.78–1.91 (m, 6H), 1.65–1.71 (m, 4H), 1.46–1.56 (m, 4H), 1.42 (s, 3H), 1.30–1.37 (m, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ : 179.3, 174.6, 163.7 (d, $^1J_{CF}$ = 243.6 Hz), 154.9, 147.0, 138.4, 134.0, 132.0 (d, $^3J_{CF}$ = 6.4 Hz), 124.0, 115.6 (d, $^2J_{CF}$ = 20.9 Hz), 114.9 (d, $^2J_{CF}$ = 22.3 Hz), 107.9, 61.6, 57.2, 56.3, 52.7, 52.1, 50.8, 50.7, 46.8, 45.4, 35.3, 32.8, 31.2, 31.1, 27.4, 27.3, 27.2.

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