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An improved synthesis of piperazino-piperidine based CCR5 antagonists with flexible variation on pharmacophore sites

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Abstract—An improved and efficient synthetic route towards piperidino-piperazine based CCR5 antagonists was developed. The new approach was flexible for introducing various substituents in the pharmacophore sites via Grignard reagent addition and reductive amination. L-Amino acids were used as a chiral pool to introduce and then induce the desired stereochemistries, meanwhile rendering the variable substitution. The efficient construction of the piperazino-piperidine nucleus was achieved in a highly convergent manner with a key building block of N^1-Boc-4-substituent-4-aminopiperidine, exhibiting significant advantages in terms of concise synthetic route and environmental-friendly reagents over the previously described stepwise synthesis, in which a modified Strecker reaction was involved with highly toxic reagents such as diethylaluminum cyanide.

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) is the etiological agent of acquired immunodeficiency syndrome (AIDS). Currently HIV-1 reverse transcriptase and protease inhibitors are available for the treatment of AIDS, and the highly active antiretroviral therapy has been very effective in bringing down the viral load; however, emergence of multi-drug resistant viral strains and intolerance to available agents can complicate the response to the treatment. Recently, CCR5, a co-receptor essential for HIV-1 recognition and entry into $CD4^+$ macrophages and T-cells[1] but not essential for human functions[2] has emerged as a highly validated target for antiviral therapy.[3] The blockade of viral entry with small molecules targeting the CCR5 co-receptor could represent a new class of anti HIV-1 agent.[3,4] A proof of concept for this approach has been provided by Sch-C and Sch-D, two CCR5 antagonists as HIV-1 entry inhibitors under clinical trials (Fig. 1).[5]

Among an impressive number of structurally diverse, small-molecule CCR5 inhibitors reported so far,[4–11] piperidine- and piperazine-based compounds disclosed by Schering–Plough Research Institute are an attractive and promising class of potent CCR5 antagonists, as exemplified by compounds in Figure 1. The SAR investigation in the two series has disclosed that the 1-*N*-substituents and 2(*S*)-substituents in the piperazine ring as well as the 4-substitution at the phenyl group are important pharmacophore elements determining the potency and selectivity.[6–8] The methyl group at the 4-position of the piperidine ring enhanced the binding potency by 3–7 fold relative to its des-methylation counterparts. However, the three important sites in the pharmacophore were inaccessible through previously reported synthetic methodology, and the introduction of the methyl group at the 4-position of the piperidine ring involved a highly toxic reagent of diethylaluminum cyanide.[6,7]

To enable further structural optimization and pharmacological study of the promising piperazine-core compounds, we sought a facile and practical synthesis of the structurally diverse piperazino-piperidine analogs. In this paper, we report a versatile synthetic approach which provides potential for the variation of the pharmacophore elements without using highly toxic and flammable reagent such as diethylaluminum cyanide employed by the Schering–Plough's modified Strecker reaction.

2. Results and discussion

As part of our program to further refine compounds in the piperazino-piperidine family for improved potency and higher selectivity, we developed a concise and convenient

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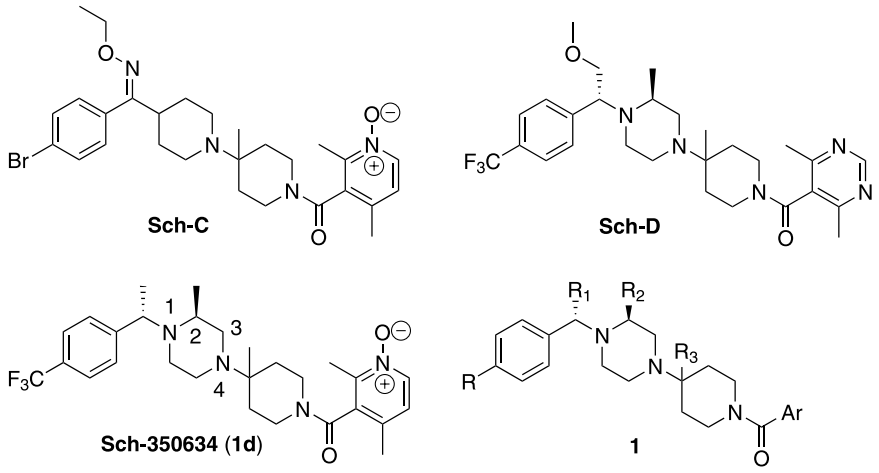
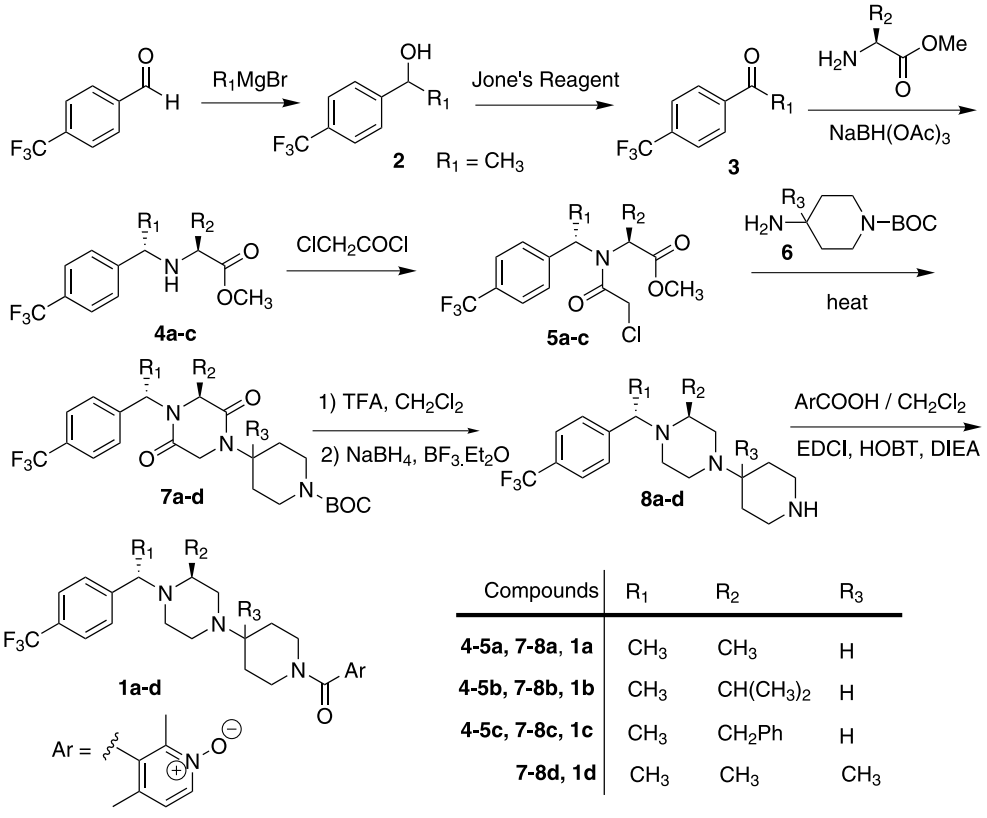


Figure 1. Piperidine- and piperazine-based CCR5 antagonists.

synthetic approach (Scheme 1) to afford structurally diverse piperidino-piperazine containing compounds typified by the general structure of **1**, in which the 1-*N*-substituents and 2(*S*)-substituents in the piperazine ring as well as the group at the 4-position of the piperidine can be varied readily. Our improved methodology provides a general access to a variety of piperazino-piperidine amide analogs for further pharmacological study as HIV-1 entry inhibitors.

Following an early finding that the chirality of piperazine 2-substituent requires (*S*)-configuration for effective CCR5 binding,[7] we envisioned that this stereochemistry could be introduced using natural amino acids as a chiral pool, which also renders the structural variation of 2-substituent. Accordingly, the adjacent asymmetric center of the 1-*N*-substituent (*S*-configuration is preferred) could be installed via asymmetric induction by the reductive amination of the aryl methyl ketone with the L-amino acid. Our experiments showed that the asymmetric induction effect is dependent on the structure of the side chain of L-amino acid. Under our reaction conditions, the dr value [the diastereomeric ratio of (1*S*,2*S*) over (1*R*,2*S*)] varied in the range of 50–72% with the 2*S*-methyl group being the best one. The resulting diastereoisomers were easily separated by flash silica gel chromatography (for **4b**, its following chloroacetylated products were more easy to separate by column chromatography). The stereochemistry of the synthetic **4a** was determined by the comparison of ^{1}H NMR data with the



Compounds	R_1	R_2	R_3
4-5a, 7-8a, 1a	CH_3	CH_3	H
4-5b, 7-8b, 1b	CH_3	$CH(CH_3)_2$	H
4-5c, 7-8c, 1c	CH_3	CH_2Ph	H
7-8d, 1d	CH_3	CH_3	CH_3

Scheme 1. A general procedure to synthesize various piperazino-piperidine based CCR5 antagonists.

literature.[12] The less polar diastereomer was found to be (1*S*,2*S*)-configured, and the more polar counterpart was the (1*R*,2*S*)-configured. The configuration of the resulting diastereoisomers [(1*S*,2*S*)-**4** and (1*R*,2*S*)-**4**] was further confirmed in the case of compound **4c**, by synthesizing an authentic sample according to the literature method,[6] which was identified to correspond to the less polar fraction of the diastereomer pair generated by the reductive amination. Therefore, the established guideline could be applied to the determination of the absolute configuration of the 1*N*-substituent of the piperazine ring produced by the asymmetric induction of the adjacent L-amino acid.

The general synthetic method for the preparation of structurally diverse piperidino-piperazine amides is depicted in Scheme 1. Nucleophilic addition of alkylmagnesium reagent to commercially available 4-trifluoromethylbenzaldehyde followed by Jone's oxidation afforded ketone **3**, possessing the various R_1 substituents. Reductive amination of the ketone **3** with various L-amino acid produced diastereoisomers which were easily separated by flash silica gel chromatography to afford the desired (1*S*,2*S*)-amine **4**, introducing a variable group of R_2. The secondary amine was then reacted with 2-chloroacetyl chloride to yield the corresponding (2-chloroacetyl)-amino-acetic acid methyl ester **5**, which was converted to the desired aryl diketopiperazino-piperidine **7** by treatment with 4-substituent-4-amino-piperidine-1-*N*-Boc **6**, allowing the introduction of an alkyl or aryl group (R_3) at the 4-position of the piperidine. The key building blocks **6** were conveniently prepared according to our recently developed efficient methodology employing isonipecotate as a starting material and Curtius rearrangement as a key step.[13] Boc removal of **7** with trifluoroacetic acid followed by reduction with $NaBH_4$ in the presence of boron trifluoride etherate gave the aryl piperazino-piperidine analogs **8**. The coupling of the resulting free amine with the desired aromatic acids proceeded under standard conditions to furnish the desired products **1**.

Notably, our approach employed the 4-substituent-4-amino-piperidine-1-*N*-Boc **6** as a building block to construct the piperazino-piperidine scaffold in a highly convergent manner. The reactivity was affected by the substituent at the 4-position of the 4-amino-piperidine. When N^1-Boc-4-aminopiperidine **6a** is used, the cyclization was readily accomplished in one step with high yield (compounds **7a**–**c**), while the mono-substituted intermediate was isolated and continued the intramolecular lactamization in a different reaction condition (with refluxing toluene and catalytic 2-pyridinol)[14] when N^1-Boc-4-methyl-4-amino-piperidine **6b** is used (compound **7d**). In both cases, no racemization was observed. Our developed methodology is devoid of using highly toxic and flammable reagent such as diethylaluminum cyanide employed by the Schering–Plough's modified Strecker reaction, and provides potential for convenient introduction of various substituents at the important 4-position of the piperidine ring.

Using this improved methodology, we efficiently synthesized a series of piperazino-piperidine amide analogs **1a**–**d** with a variety of 2-substituents on the piperazine ring. The concise synthesis of compound **1d** (Sch-350634), a potent and orally active CCR5 antagonist as HIV-1 entry inhibitor developed by Schering–Plough Research Institute, was accomplished in excellent yield using ^1N-Boc-4-methyl-4-aminopiperidine as a smart building block. Compared to previously reported procedure, the newly developed methodology provides us with a facile and practical access to structurally diverse piperazino-piperidine compounds for the elaboration of effective inhibitors of HIV-1 cell entry.

3. Conclusions

In summary, we developed an improved and efficient procedure to prepare various piperidino-piperazine based CCR5 antagonists. Starting from commercially available 4-substituted-benzaldehyde, the nucleophilic addition of the Grignard reagent followed by Jone's oxidation afforded the aryl alkyl ketone. Reductive amination of the aryl alkyl ketone with L-amino acid introduced the desired chirality and the substitution at the 2(*S*)-position of the piperazine ring. Subsequently the efficient and concise synthesis of the piperazino-piperidine nucleus was achieved in a highly convergent manner with a key building block of ^1N-Boc-4-substituted-4-amino-piperidine, devoid of using highly toxic reagents employed by previously described stepwise synthetic approach. The improved methodology was versatile and flexible for introducing various substituents in the key positions of the pharmacophore, thus potentially benefits the SAR studies of piperazino-piperidine compounds as HIV-1 entry inhibitors.

4. Experimental

4.1. General

All reactions were performed under nitrogen atmosphere with flame-dried glassware. 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. Elemental analysis were determined to be within $\pm 0.4\%$ of the theoretical values for elements C, H and N. IR spectra were recorded on a DTGS spectrometer in KBr pellets. 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. All final products were characterized by NMR, IR, MS and elemental analysis or high resolution mass spectra.

4.1.1. 1-(4-Trifluoromethyl-phenyl)-ethanol (2).[15] Magnesium turnings (0.631 g, 25.0 mmol) were placed into a dry three-neck flask, equipped with an addition funnel and condenser. Anhydrous ether (10 mL) was added to cover the turnings. To initiate the reaction, about 2 mL of a solution of CH_3I (1.6 mL, 25.0 mmol) and 16.0 mL of anhydrous ether were added. After formation of bubbles at the surface of the turnings, the remaining CH_3I–ether solution was added

dropwise (at a ratio to maintain a moderate reflux). After the addition, the mixture was stirred at room temperature for 45 min. To the above ethereal Grignard reagent (11.0 mL), α,α,α-trifluro-*p*-tolualdehyde (1.68 mL, 12.26 mmol) in 15.0 mL of anhydrous ether was added with constant agitation at 0 °C under N_2. The mixture was refluxed for 1.5 h, then poured into a cold aqueous ammonium chloride solution. The aqueous layer was extracted with Et_2O, the combined Et_2O extracts were washed with saturated aqueous $Na_2S_2O_3$ and brine, then dried over Na_2SO_4- and evaporated under vacuum. The residue was purified by chromatography using petroleum ether/ether = 10:1 to afford compound **2** (3.145 g, 100%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 2H, *J* = 8.2 Hz); 7.48 (d, 2H, *J* = 8.1 Hz); 4.96 (q, 1H, *J* = 6.4 Hz); 2.03 (s, 1H); 1.50 (d, 1H, *J* = 6.4 Hz).

4.1.2. 1-(4-Trifluoromethyl-phenyl)-ethanone (3).[16] A solution of CrO_3 (26.72 g, 267.2 mmol) in 23.0 mL of concentrated sulfuric acid was diluted with water to a volume of 100 mL to afford 2.672 N Jone's reagent. To a solution of compound **2** (3.314 g, 17.25 mmol) in 50 mL of acetone at 0 °C was added Jone's reagent (13.11 mL) dropwise with stirring. The resulting orange solution was stirred at 0 °C for 0.5 h. The cooling bath was removed and 2-propanol was added dropwise, whereupon a green precipitate formed immediately. The mixture was stirred at room temperature for 20 min and filtered through celite. The flask and the celite pad was washed with acetone and the solvent was removed, the yellow oil was purified by flash chromatography on silica gel eluted with petroleum ether/ether = 10:1 to obtain compound **3** (2.588 g, 82.2%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, 2H, *J* = 8.0 Hz); 7.60 (d, 2H, *J* = 8.0 Hz); 2.67 (s, 3H).

4.1.3. 2-[1-(4-Trifluoromethyl-phenyl)-ethylamino]-propionic acid methyl ester (4a). To the solution of L-alanine methyl ester hydrochloride (1.023 g, 6.41 mmol) in dry 1,2-dichloroethane (15 mL) was added Et_3N (1.117 mL, 6.41 mmol). After stirring at room temperature for 0.5 h, 4′-(trifluoromethyl)acetophenone (1.0 g, 5.34 mmol) was added, then the reaction mixture was treated with sodium triacetoxyborohydride (2.266 g, 10.69 mmol) and HOAc (0.61 mL, 10.69 mmol). The mixture was stirred at room temperature for 22 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O. The organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4. The solvent was removed under vacuum. The residue was purified by chromatography using petroleum ether/ether = 10:1 to give compound **4a** (0.788 g, yield 54.2%) as colorless oil. $[\alpha]_D^{20} = -113.6$ (*c* = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, *J* = 8.1 Hz); 7.45 (d, 2H, *J* = 8.1 Hz); 3.80 (q, 1H, *J* = 6.6 Hz); 3.72 (s, 3H); 3.06 (q, 1H, *J* = 7.0 Hz); 1.38 (d, 3H, *J* = 6.6 Hz); 1.25 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.42, 149.25, 129.64, 126.98 (×2), 125.19 (×2), 122.79, 56.25, 54.13, 51.42, 24.92, 19.43. IR (KBr) ν: 3334, 2975, 1737, 1619, 1452, 1419, 1324, 1203, 1164, 1124, 1066, 1016, 844 cm^{-1}. EI-MS (*m*/*z*, %): 274 ($M^+ - 1$, 1.0); 260 (7.0); 216 (100.0); 173 (99.0); 153 (37.0).

The (1*R*, 2*S*) isomer is colorless oil, yield 17.0%. $[\alpha]_D^{20} = +9.5$ (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, *J* = 8.1 Hz); 7.44 (d, 2H, *J* = 8.1 Hz); 3.87 (q, 1H, *J* = 6.6 Hz); 3.61 (s, 3H); 3.34 (q, 1H, *J* = 6.9 Hz); 1.93 (br, 1H); 1.36 (d, 3H, *J* = 6.6 Hz); 1.29 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.50, 148.97, 129.21, 126.95(×2), 125.23(×2), 125.19, 55.41, 53.81, 51.48, 22.95, 18.46. IR (KBr) ν: 3330, 2977, 1739, 1619, 1454, 1326, 1201, 1162, 1124, 1068, 1016, 844 cm^{-1}.

4.1.4. 3-Methyl-2-[1-(4-trifluoromethyl-phenyl)-ethylamino]-butyric acid methyl ester (4b). The solution of L-valine methyl ester hydrochloride (1.10 g, 6.57 mmol) in dry 1,2-dichloroethane (25.0 mL) was treated with sequential 4′-(trifluoromethyl)-acetophenone (1.12 g, 5.98 mmol) and sodium triacetoxyborohydride (1.77 g, 8.37 mmol) in a similar way to the preparation of **4a**. The residue was purified by chromatography using petroleum ether/EtOAc = 10:1 as eluent to give compound **4b** (0.91 g, yield 50.0%) as colorless oil (mixture of two diastereoisomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.42 (m, 9.44H); 3.75 (q, 1.36H, *J* = 6.5 Hz); 3.71 (s, 3H); 3.67 (q, 1H, *J* = 6.6 Hz); 3.57 (s, 4.08H); 3.06 (d, 1.36H, *J* = 6.2 Hz); 2.70 (d, 1H, *J* = 6.2 Hz); 1.92–1.79 (m, 4.72H); 1.32 (d, 1H, *J* = 6.5 Hz); 1.31 (d, 1.36H, *J* = 6.6 Hz); 0.94 (d, 4.08H, *J* = 6.7 Hz); 0.93 (d, 4.08H, *J* = 6.7 Hz); 0.91 (d, 3H, *J* = 6.7 Hz); 0.87 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.90, 175.20, 149.50, 149.10, 129.25, 127.32, 127.18, 125.29, 64.79, 56.74, 56.64, 51.2, 51.33, 31.65, 25.43, 22.61, 19.42, 19.03, 18.63, 18.38. IR (KBr) ν: 3446, 2996, 1735, 1619, 1469, 1419, 1324, 1199, 1162, 1126, 1066, 1018, 844, 781, 609 cm^{-1}. EI-MS (*m*/*z*, %): 302 ($M^+ - 1$); 260 (20.0); 228 (8.0); 173 (100.0); 153 (37.0).

4.1.5. 3-Phenyl-2-[1-(4-trifluoromethyl-phenyl)-ethylamino]-propionic acid methyl ester (4c). The solution of L-phenylalanine methyl ester hydrochloride (2.588 g, 12.0 mmol) in 30.0 mL of dry 1,2-dichloroethane was treated with 4′-(trifluoromethyl) -acetophenone (1.871 g, 10.0 mmol) and sodium triacetoxyborohydride (3.179 g, 15.0 mmol) in a similar way to the preparation of **4a**. The purification from chromatography using petroleum ether/EtOAc (12:1) gives compound **4c** (1.342 g, yield 37%) as glassy solid. $[\alpha]_D^{20} = -49.7$ (*c* = 1.6, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, 2H, *J* = 8.0 Hz); 7.31–7.26 (m, 3H); 7.17 (d, 2H, *J* = 8.0 Hz); 7.12–7.10 (m, 2H); 3.74 (q, 1H, *J* = 6.4 Hz); 3.68 (s, 3H); 3.19 (dd, 1H, *J* = 8.0, 6.0 Hz); 2.93 (dd, 1H, *J* = 13.2, 5.6 Hz); 2.81 (dd, 1H, *J* = 13.2, 8.0 Hz); 1.92 (br, 1H); 1.29 (d, 3H, *J* = 6.4 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.42, 149.03, 137.32, 129.33 (×3), 128.26 (×2), 127.03 (×2), 126.65 (×2), 125.26, 122.38, 60.49, 56.35, 51.69, 40.09, 25.22. EI-MS (*m*/*z*, %): 351 (M^+, 0.1); 332 (1.0); 292 (18.0); 260 (66.0); 173 (100.0). IR (KBr): 3346, 2928 (m), 1736, 1618, 1327, 1140, 1067, 702 cm^{-1}.

The (1*R*,2*S*) isomer, colorless oil in yield of 30%. $[\alpha]_D^{20} = +44.3$ (*c* = 0.7, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, 2H, *J* = 8.1 Hz); 7.40 (d, 2H, *J* = 8.1 Hz); 7.31–7.15 (m, 5H); 3.79 (q, 1H, *J* = 6.5 Hz); 3.52 (t, 1H, *J* = 6.7 Hz); 2.95 (d, 2H, *J* = 6.7 Hz); 1.90 (br, 1H); 1.28 (d, 2H, *J* = 6.6 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.20, 148.60, 137.00, 129.31, 129.17, 128.43, 128.27 (×2), 127.24 (×2), 127.05, 126.79, 125.38, 122.80, 60.59, 56.32, 51.62, 39.38,

23.00. EI-MS (*m/z*, %): 332 (M^+-19, 2.0); 292 (19.0); 260 (85.0); 173 (100.0); 153 (11.0); 91 (8.0).

4.1.6. 2-{(2-Chloro-acetyl)-[1-(4-trifluoromethyl-phenyl)-ethyl]-amino}-propionic acid methyl ester (5a). The secondary amine **4a** (0.479 g, 1.74 mmol) was dissolved in 1,2-dichloroethane (15.0 mL), chloroacetyl chloride (2.78 mL, 34.8 mmol) was added to the above solution at room temperature. The mixture was stirred under refluxing for 3 h. Both the solvent and chloroacetyl chloride was removed under vacuum. The remaining yellow syrup was purified by chromatography using petroleum ether/EtOAc (3.5:1) to give compound **5a** (0.589 g, yield 96.0%) as glassy solid. $[\alpha]_D^{20}=-105$ ($c=0.6$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.70–7.60 (m, 4H); 5.28 (q, 1H, $J=7.2$ Hz); 4.19 (q_{AB}, 2H, $J=12.4$ Hz); 3.57 (s, 3H); 3.49 (q, 1H, $J=7.2$ Hz); 1.77 (d, 3H, $J=7.2$ Hz); 1.56 (d, 3H, $J=7.2$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 170.30, 165.30, 142.24, 130.31, 128.23 (×2), 125.31 (×2), 122.53, 56.03, 52.60, 52.12, 41.45, 18.76, 15.93. EI-MS (*m/z*, %): 353 ($M^+ +2$, 0.3); 351 (M^+, 1.0); 274 (28.0); 266 (12.0); 264 (36.0); 173 (100.0); 153 (14.0). IR (KBr): 3467, 3037, 2958, 1741, 1633, 1437, 1329, 1240, 1121, 1068, 841, 613 cm^{-1}.

4.1.7. 2-{(2-Chloro-acetyl)-[1-(4-trifluoromethyl-phenyl)-ethyl]-amino}-3-methyl-butyric acid methyl ester (5b). Compound **5b** was prepared from **4b** according to the same procedure as **5a**. The residue was chromatographed using petroleum ether/EtOAc=7:1 to separate the diastereoisomers (0.797 g, total yield 84.0%, each isomer in yield of ~42%). The less polar isomer **5b** is colorless oil. $[\alpha]_D^{20}=-84.4$ ($c=2.4$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.56–7.39 (m, 4H); 5.31 (br, 1H); 4.29–3.81 (m, 3H); 3.39 (s, 3H); 2.55–2.38 (m, 1H); 1.76 (d, 3H, $J=6.6$ Hz); 1.02 (d, 6H, $J=6.3$ Hz). EI-MS (*m/z*, %): 381 ($M^+ +2$, 2.0); 379 (M^+, 6.0); 362 (3.0); 360 (9.0); 322 (1.3); 320 (3.9); 264 (20.0); 173 (100.0). IR (KBr): 3450 2989, 2974, 2881, 1734, 1714, 1651, 1452 (m), 1335, 1165, 1121, 1273, 1120, 849, 613 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{21}ClF_3NO_3$ 379.1162, found 379.1157.

The more polar isomer: $[\alpha]_D^{20}=-23.5$ ($c=1.1$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.66–7.57 (m, 4H); 5.33–5.31 (m, 1H); 4.34–4.13 (m, 2H); 3.80–3.72 (m, 3H); 3.40–3.37 (m, 1H); 2.42–2.25 (m, 1H); 1.71–1.63 (brd, 3H); 0.98–0.20 (m, 6H). EI-MS (*m/z*, %): 381 ($M^+ +2$, 3.0); 379 (M^+, 9.0); 362 (4.0); 360 (12.0); 322 (2.0); 320 (6.0); 264 (30.0); 173 (100.0).

4.1.8. 2-{(2-Chloro-acetyl)-[1-(4-trifluoromethyl-phenyl)-ethyl]-amino}-3-phenyl-propionic acid methyl ester (5c). Compound **5c** was prepared analogously to **5a**. The purification by chromatography using petroleum ether/EtOAc=6:1 afforded compound **5c** (0.553 g, yield 90.0%) as glassy solid. $[\alpha]_D^{20}=-72.6$ ($c=0.8$, $CDCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 2H, $J=8.2$ Hz); 7.45 (d, 2H, $J=8.1$ Hz); 7.36–7.21 (m, 5H); 5.10 (q, 1H, $J=7.0$ Hz); 4.28–4.13 (m, 2H); 3.70–3.67 (m, 1H); 3.58–3.53 (m, 1H); 3.51 (s, 3H); 1.12 (d, 3H, $J=7.0$ Hz). EI-MS (*m/z*, %): 429 ($M^+ +2$, 2.0); 427 (M^+, 6.0); 410 (1.0); 408 (3.0); 350 (12.0); 336 (6.0); 292 (14.0); 260 (39.0); 196 (16.0); 173 (40.0); 162 (100.0); 91 (20.0). IR (film): 2953 (m), 1740, 1653, 1456 (m), 1327, 1167, 1122, 1070, 847, 754, 704 cm^{-1}.

4.1.9. 4-{3-Methyl-2,5-dioxo-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester (7a). The compound **5a** (0.8 g, 2.28 mmol), N^1-Boc-4-aminopiperidine **6a** (0.5 g, 2.5 mmol) and Et_3N (0.35 mL) in CH_3OH (10 mL) were refluxed overnight and the solvent was removed under reduced pressure. The residue was purified by chromatography using petroleum ether/EtOAc=1:1 to give compound **7a** (0.644 g, yield 59%) as white solid. $[\alpha]_D^{20}=-42.0$ ($c=1.0$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 2H, $J=8.2$ Hz); 7.35 (d, 2H, $J=8.3$ Hz); 5.83 (q, 1H, $J=7.1$ Hz); 4.47–4.41 (m, 1H); 4.24–4.21 (m, 2H); 3.90 (s, 2H); 3.75 (q, 1H, $J=7.1$ Hz); 2.78–2.75 (m, 2H); 1.65 (d, 3H, $J=7.1$ Hz); 1.70–1.48 (m, 4H); 1.47 (d, 3H, $J=7.1$ Hz); 1.46 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.69, 164.82, 154.46, 143.40, 130.24, 127.21 (×2), 125.88, 125.20, 122.50, 79.95, 53.51, 51.57, 50.67, 45.04, 42.94 (×2), 28.59 (×2), 28.38 (×3), 19.45, 17.64. EI-MS (*m/z*, %): 484 ($M^+ +1$, 1.0); 483 (M^+, 7.0); 427 (24.0); 410 (20.0); 301 (13.0); 173 (12.0); 82 (100). IR (KBr): 3431, 2982, 1676, 1659, 1443, 1327, 1142 cm^{-1}.

4.1.10. 4-{3-Isopropyl-2,5-dioxo-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester (7b). The compound **5b** (0.527 g, 1.39 mmol), N^1-Boc-4-aminopiperidine **6a** (0.2 g, 1.67 mmol) and DIPEA (0.44 mL, 2.51 mmol) in CH_3CN (10 mL) were refluxed overnight and the solvent was removed under reduced pressure. The residue was purified by chromatography using petroleum ether/EtOAc=1:1 to give the compound **7b** as white solid in yield of 42.3%. $[\alpha]_D^{20}=-16.8$ ($c=1.0$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 2H, $J=8.0$ Hz); 7.37 (d, 2H, $J=8.0$ Hz); 5.57–5.51 (m, 1H); 4.53–4.45 (m, 1H); 4.18 (brs, 2H); 3.95 (d, 1H, $J=17.6$ Hz); 3.82 (d, 1H, $J=17.6$ Hz); 3.56 (d, 1H, $J=7.2$ Hz); 2.21–2.12 (m, 1H); 1.85–1.71 (m, 2H); 1.65 (d, 3H, $J=7.2$ Hz); 1.59–1.48 (m, 4H); 1.46 (s, 9H); 1.04 (d, 3H, $J=6.8$ Hz); 0.96 (d, 3H, $J=6.8$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 165.01, 164.44, 154.46, 143.51, 130.12, 127.46 (×2), 125.81, 125.77, 122.57, 79.90, 64.01, 54.28, 50.72, 45.68, 33.99, 28.81 (×2), 28.34 (×3), 28.08 (×2), 20.42, 18.14, 16.86. EI-MS *m/z*: 511 (M^+).

The more polar isomer (1*R*,2*S*)-**5b** was analogously converted to the corresponding (1*R*,2*S*)-**7b** as white solid in yield of 48%. $[\alpha]_D^{20}=+55.1$ ($c=5.1$, EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, 2H, $J=8.4$ Hz); 7.49 (d, 2H, $J=8.4$ Hz); 5.35 (br, 1H); 4.56–4.44 (m, 1H); 4.18 (brs, 1H); 3.91 (d, 1H, $J=17.2$ Hz); 3.89 (d, 1H, $J=4.0$ Hz); 3.74 (d, 1H, $J=17.2$ Hz); 2.74 (br, 2H); 1.70 (d, 3H, $J=7.2$ Hz); 1.53 (br, 4H); 1.49 (s, 9H); 0.87 (d, 3H, $J=6.8$ Hz); 0.79 (d, 3H, $J=6.8$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.91, 164.35, 154.37, 143.43, 130.04, 127.65, 127.39, 125.73, 125.12, 122.41, 79.81, 63.93, 54.20, 50.64, 45.60, 33.92, 28.75 (×2), 28.26 (×3), 28.01 (×2), 20.34, 18.07, 16.88. IR (KBr): 3315, 2974, 2247, 1662, 1126, 1072, 1016, 922, 733 cm^{-1}. EI-MS (*m/z*, %): 511 (M^+), 455 (26.0); 438 (18.0); 369 (8.0); 173 (25.0); 82 (100); 57 (50.00). HREI-MS calcd for $C_{26}H_{36}F_3N_3O_4$ 511.2658, found 511.2668.

4.1.11. 4-{3-Benzyl-2,5-dioxo-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester (7c). The compound **7c** was prepared from **5c** and **6a** according to the same procedure as **7b**. The residue was purified by chromatography using petroleum ether/EtOAc = 1:1 to give compound **7c** (0.436 g, yield 83%) as white foam. $[\alpha]_D^{20} = -42.0$ ($c = 1.0$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, 2H, $J = 8.3$ Hz); 7.40 (d, 2H, $J = 8.0$ Hz); 7.33–7.29 (m, 3H); 7.15 (d, 2H, $J = 6.8$ Hz); 5.92 (q, 1H, $J = 7.4$ Hz); 4.45–4.38 (m, 1H); 4.15–4.09 (m, 2H); 4.03 (t, 1H, $J = 4.2$ Hz); 3.32 (d, 1H, $J = 17.1$ Hz); 3.27 (dd, 1H, $J = 13.9$, 3.6 Hz); 3.12 (dd, 1H, $J = 14.0$, 4.7 Hz); 2.74–2.67 (m, 2H); 2.12 (d, 1H, $J = 16.8$ Hz); 1.85 (d, 1H, $J = 7.2$ Hz); 1.46–1.37 (m, 3H); 1.43 (s, 9H); 1.10–1.06 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 165.85, 165.66, 154.31, 143.41, 134.56, 130.45, 130.12 (×2), 128.77 (×2), 127.88, 127.45 (×2), 125.88, 125.09, 122.39, 79.8, 58.82, 52.59, 50.52, 44.37, 42.78, 39.87 (×2), 28.26 (×3), 27.96 (×2), 18.26. EI-MS (*m*/*z*, %): 559 (M^+, 2.0), 503 (9.0), 486 (5.0), 459 (10.0), 368 (6.0), 285 (4.0), 173 (58.0), 91 (20.0), 82 (100.0). IR (KBr): 3442, 2978, 2933, 1691, 1662, 1427, 1327, 1167, 1124, 1072 cm^{-1}. HREI-MS calcd for $C_{30}H_{36}F_3N_3O_4$ 559.2658, found 559.2671.

4.1.12. 4-Methyl-4-{3-methyl-2,5-dioxo-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester (7d). Compound **5c** (0.221 g, 0.63 mmol), N^1-Boc-4-amino-4-methyl-piperidine **6b** (0.148 g, 0.69 mmol) in CH_3CN (5.0 mL) was refluxed overnight and the solvent was removed under reduced pressure. The residue was purified by chromatography using petroleum ether/EtOAc 1:1 as eluent to give the mono-substituted intermediate (0.265 g, yield 80.0%) as colorless oil. $[\alpha]_D^{20} = +80$ ($c = 1.65$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (AB, 2H, $J_{AB} = 8.3$ Hz); 7.60 (AB, 2H, $J_{AB} = 8.3$ Hz); 5.19 (q, 1H, $J = 6.9$ Hz); 3.56 (s, 3H); 3.52–3.40 (m, 7H); 1.97 (br, 1H, D_2O exchangeable); 1.71 (d, 3H, $J = 6.9$ Hz); 1.55 (d, 3H, $J = 6.9$ Hz); 1.49–1.47 (m, 2H); 1.44 (s, 9H); 1.08 (s, 3H). EI-MS (*m*/*z*, %): 529 (M^+, 3.0); 428 (6.0); 301 (23.0); 256 (21.0); 188 (56.0); 171 (100.0); 127 (62.0).

The mono-substituted intermediate (0.309 g, 0.58 mmol) and 2-hydroxy-pyridine (0.05 g, 0.43 mmol) were dissolved in dry toluene (1.5 mL) and stirred at 90 °C for 6 h. After removing the solvent, the residue was purified by chromatography using PE/EtOAc (1:1) as eluent to give compound **7d** as white solid (0.244 g, yield 84%). $[\alpha]_D^{20} = -16.3$ ($c = 1.2$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 2H, $J = 8.0$ Hz); 7.36 (d, 2H, $J = 8.0$ Hz); 5.82 (q, 1H, $J = 7.2$ Hz); 4.06 (d, 1H, $J = 12.8$ Hz); 3.91 (d, 1H, $J = 12.8$ Hz); 3.64 (q, 1H, $J = 7.2$ Hz); 3.59–3.48 (m, 2H); 3.26–3.11 (m, 2H); 2.44–2.39 (m, 1H); 2.26–2.21 (m, 1H); 1.79–1.68 (m, 2H); 1.66–1.62 (m, 3H); 1.48 (d, 3H, $J = 7.2$ Hz); 1.47 (s, 9H); 1.36 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.51, 164.75, 154.58, 143.47, 130.38, 128.16 (×2), 125.60, 125.15, 122.32, 79.69, 58.85, 54.83, 50.64, 46.48 (×2), 40.13, 35.43, 35.20, 28.32 (×3), 21.77, 18.06, 15.93. EI-MS (*m*/*z*, %): 497 (M^+); 441 (56.0); 424 (11.0); 301 (23.0); 173 (18.0); 96 (100); 57 (43.0). IR (KBr): 3400, 2980, 2862, 1684, 1653, 1414, 1327, 1140, 1173 cm^{-1}.

4.1.13. 2-Methyl-4-piperidin-4-yl-1-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazine (8a). The compound **7a** (0.242 g, 0.5 mmol) was dissolved in methylene chloride (2.5 mL) and trifluoroacetic acid (5 mL) was added. The mixture was stirred at room temperature for 2 h. After removing the solvent and trifluoroacetic acid under reduced pressure, 2 N NaOH was added and extractive work up with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. The solvent was removed under vacuum to give (*S*)-4-((*S*)-1-(4-trifluoromethyl)phenyl)- ethyl-3-methyl)-1-(piperidin-4-yl)piperazine-2,5-dione, which was used directly for next step without purification.

The crude diketopiperzaine (0.192 g, 0.5 mmol) prepared above was dissolved in dimethoxy ethane (5 mL) and sodium borohydride (0.189 g, 5.0 mmol), boron trifluoride etherate (0.38 mL, 3.0 mmol) were added to the solution. The mixture was stirred under reflux for 3 h and then cooled to 0 °C. Methanol (6 mL) and concentrated hydrogen chloride (3.6 mL) were added successively to the mixture and stirred for 15 min at room temperature, then refluxed for 45 min. The mixture was concentrated, and basified with 6 N sodium hydroxide, then extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum to give the compound **8a** as glassy solid. Used for next step without further purification.

4.1.14. 2-Isopropyl-4-piperidin-4-yl-1-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazine (8b). The preparation of **8b** is similar to that of **8a**.

4.1.15. 2-Benzyl-4-piperidin-4-yl-1-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazine (8c). The preparation of **8c** is also similar to that of **8a**.

4.1.16. 2-Methyl-4-(4-methyl-piperidin-4-yl)-1-[1-(4-trifluoromethyl-phenyl)-ethyl] -piperazine (8d). Prepared analogously to **8a**. Used directly for next step without further purification.

4.1.17. (2,4-Dimethyl-1-oxy-pyridin-3-yl)-(4-{3-methyl-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidin-1-yl)-methanone (1a).[17] The crude piperidine **8a** (0.178 g, 0.5 mmol) was dissolved in methylene chloride (2 mL) and treated with 2,4-dimethylnicotinic acid-*N*-oxide (0.1 g, 0.6 mmol), EDCI (0.144 g, 0.75 mmol), HOBT (0.101 g, 0.75 mmol) and DIPEA (0.175 mL). The mixture was stirred at room temperature overnight and the solvent was removed under reduced pressure. The residue was purified by chromatography using CH_2Cl_2/CH_3OH (30:1) to give the compound **1a** (0.1 g, 37.0% overall yield of three steps) as white foam. $[\alpha]_D^{20} = +12.1$ ($c = 1.0$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, 1H, $J = 6.3$ Hz); 7.58–7.51 (m, 4H); 7.00 (dd, 1H, $J = 6.3$, 3.6 Hz); 4.76 (brt, 1H); 4.11 (brs, 1H); 3.55 (brd, 1H); 3.04–2.75 (m, 4H); 2.58–2.56 (m, 1H); 2.44 (d, 3H, $J = 19.5$ Hz); 2.31–2.22 (m, 5H); 2.15 (d, 3H, $J = 19.5$ Hz); 2.04–2.00 (m, 1H); 1.80–1.76 (m, 2H); 1.54–1.48 (m, 1H); 1.29 (d, 3H, $J = 6.6$ Hz); 1.14 (dd, 3H, $J = 6.0$, 1.5 Hz). ESI-MS (*m*/*z*, %): 505 ($M^+ + 1$, 100). EI-MS (*m*/*z*, %): 504 (M^+, 0.85); 487 (40.0); 426 (51.0); 314 (41.0); 246 (44.0); 173 (31.0); 134 (100). HREI-MS calcd for $C_{27}H_{35}N_4O_2F_3$: 504.2712, found, 504.2719.

4.1.18. (2,4-Dimethyl-1-oxy-pyridin-3-yl)-(4-{3-isopropyl-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidin-1-yl)-methanone (1b). Prepared from the crude piperidine **8b** in a similar manner to **1a**. Chromatography purification using CH_2Cl_2/CH_3OH (30:1) afforded **1b** as white foam in an overall yield of 68.0%. $[\alpha]_D^{20}=-15.6$ ($c=0.70$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, 2H, $J=6.8$ Hz); 7.57 (m, 4H); 7.01 (dd, 1H, $J_1=4.0$ Hz, $J_2=6.8$ Hz); 4.78 (m, 1H); 4.34 (q, 1H, $J=6.8$ Hz); 3.39 (m, 1H); 3.02–2.82 (m, 3H); 2.72–2.53 (m, 2H); 2.44 (d, 3H, $J=25.2$ Hz); 2.38–2.33 (m, 1H) 2.15–2.05 (m, 3H); 2.25 (d, 3H, $J=25.2$ Hz); 2.10–1.99 (m, 2H); 1.57–1.45 (m, 1H); 1.30 (d, 3H, $J=6.8$ Hz); 1.26–1.24 (m, 2H); 0.97 (m, 6H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.63, 148.52, 145.08, 138.41, 134.70, 132.88, 132.67, 128.67, 127.85 (×2), 124.87 (×3), 61.77, 61.10, 52.83, 48.86, 45.60, 44.12, 40.69, 29.64, 29.00, 27.80, 26.14, 19.93, 18.34, 15.92, 15.39, 14.95. ESI-MS (*m/z*, %): 533 ($M^+ +1$, 100%).

Similarly the diastereoisomer (1*R*,2*S*)-**1b** was synthesized from (1*R*,2*S*)-**8b** in yield of 66.0% as white foam. $[\alpha]_D^{20}=+17.9$ ($c=0.7$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, 2H, $J=6.0$ Hz); 7.55 (d, 2H, $J=7.8$ Hz); 7.34 (d, 2H, $J=7.8$ Hz); 7.00 (d, 1H, $J=6.0$ Hz); 4.80–4.70 (m, 1H); 4.31 (q, 1H, $J=6.0$ Hz); 3.40–3.34 (m, 1H); 3.02–2.80 (m, 3H); 2.69–2.61 (m, 2H); 2.51–2.49 (m, 1H); 2.43 (d, 3H, $J=18.0$ Hz); 2.34–2.20 (m, 4H); 2.23 (d, 3H, $J=18.0$ Hz); 2.10–1.99 (m, 2H); 1.81–1.74 (m, 1H); 1.47–1.38 (m, 2H), 1.38 (d, 3H, $J=6.0$ Hz); 1.00–0.96 (m, 3H); 0.92 (d, 3H, $J=6.9$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.60, 145.90, 145.01, 138.36, 134.67, 132.74, 128.96, 128.13 (×2), 125.48, 124.93, 124.78, 122.78, 61.60, 60.29, 54.62, 47.54, 45.40, 44.55, 40.54, 29.60, 28.40, 27.20, 26.24, 19.80, 18.29, 17.14, 15.34, 14.90. IR (film): 3421, 2960, 2869, 1639, 1450, 1326, 1122 cm^{-1}. ESI-MS (*m/z*, %): 533 ($M^+ +1$, 100%). HR-ESIMS calcd for $C_{29}H_{39}O_2N_4F_3+H$: 533.3103, found: 533.3098.

4.1.19. (4-{3-Benzyl-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidin-1-yl)-(2,4-dimethyl-1-oxy-pyridin-3-yl)-methanone (1c). Prepared from the crude piperidine **8c** analogously to **1a**. The residue was purified by chromatography using CH_2Cl_2/CH_3OH (30:1) to give the compound **1c** (0.305 g, three steps in yield of 54.0%) as white foam. $[\alpha]_D^{20}=+6.1$ ($c=0.9$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, 1H, $J=6.4$ Hz); 7.57 (d, 2H, $J=8.0$ Hz); 7.52 (d, 2H, $J=8.4$ Hz); 7.34–7.29 (m, 2H); 7.25–7.17 (m, 3H); 7.18 (t, 2H, $J=7.6$ Hz); 4.77 (t, 1H, $J=13.6$ Hz); 3.98–3.96 (m, 1H); 3.36 (d, 1H, $J=9.6$ Hz); 3.26–3.24 (m,1H); 3.02–2.80 (m, 4H); 2.51–2.32 (m, 7H); 2.42 (d, 3H, $J=22.4$ Hz); 2.22 (d, 3H, $J=24.4$ Hz); 1.97–1.92 (m, 1H); 1.84 (s, 1H); 1.74–1.71 (m, 1H); 1.41 (d, 3H, $J=6.4$ Hz); 1.46–1.40 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.57, 149.97, 144.99, 140.11, 138.34, 134.69, 132.78, 129.08 (×2), 128.78, 128.41 (×2), 127.59 (×2), 125.96, 125.53, 125.17, 124.93, 124.77, 122.82, 61.27, 58.67, 56.68, 49.63, 45.57, 45.03, 40.74, 29.50, 28.44, 27.90, 18.27, 15.30, 14.88. IR (KBr): 3423, 2926 (m), 1637, 1450, 1325, 1283, 1161, 1121, 1067, 845, 744, 702 cm^{-1}. ESI-MS (*m/z*, %): 581 ($M^+ +1$, 100%). HREI-MS calcd for $C_{33}H_{39}N_4O_2F_3+H$: 581.3103, found 581.3110.

4.1.20. (2,4-Dimethyl-1-oxy-pyridin-3-yl)-(4-methyl-4-{3-methyl-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidin-1-yl)-methanone (1d).[6,7] Compound **1d** was synthesized from the crude piperidine **8d** analogously to **1a**. The residue was purified by chromatography ($CH_2Cl_2/CH_3OH=30:1$) to give compound **1d** (0.085 g, three steps in 64% yield) as white gum. $[\alpha]_D^{20}=+9.1$ ($c=0.9$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, 1H, $J=6.6$ Hz); 7.58–7.50 (m, 4H); 7.00 (d, 1H, $J=6.9$ Hz); 4.22 (brt, 1H); 3.98 (brs, 1H); 3.45–3.36 (m, 2H); 3.01–2.96 (m, 2H); 2.67–2.57 (m, 1H); 2.46 (d, 3H, $J=9.9$ Hz); 2.41–2.24 (m, 4H); 2.26 (d, 3H, $J=9.0$ Hz); 2.03–1.95 (brt, 1H); 1.76–1.70 (m, 2H); 1.46–1.34 (m, 3H); 1.29 (d, 3H, $J=6.9$ Hz); 1.14 (d, 3H, $J=6.3$ Hz); 0.93 (s, 3H). ESI-MS (*m/z*, %): 519 ($M^+ +H$, 100.0), 541 ($M^+ +Na$, 37.0).

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