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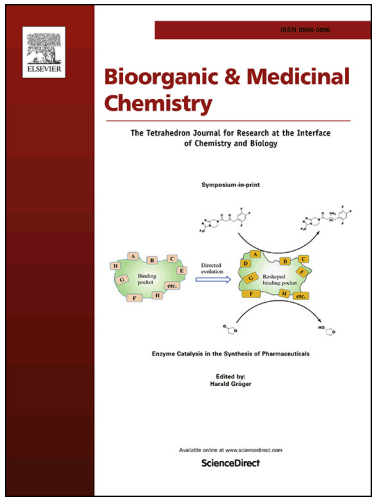

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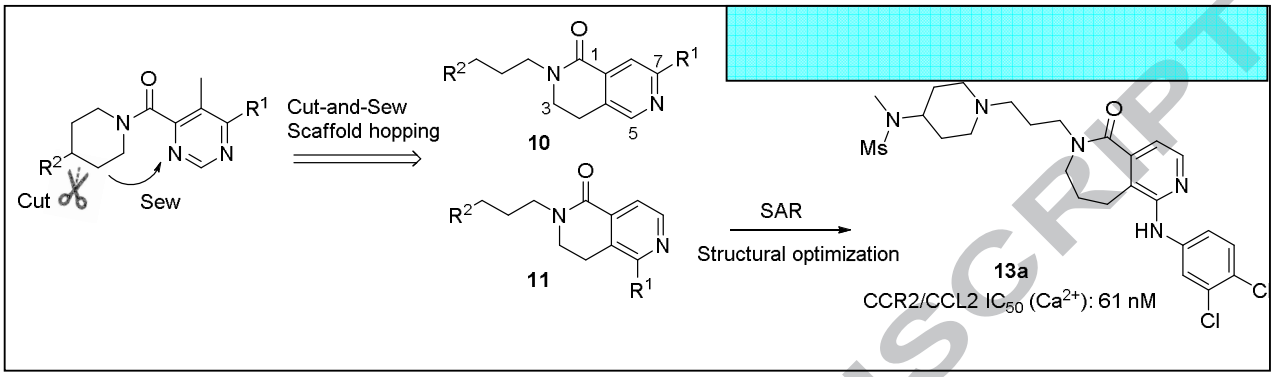
Graphical Abstract



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Discovery and synthesis of 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one-based novel chemotype CCR2 antagonists via scaffold hopping strategy

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CCR2 antagonist
Scaffold hopping
Structure-activity relationship
Selectivity of CCR2 over CCR5

ABSTRACT

The chemokine CC receptor subtype 2 (CCR2) has attracted intensive interest for drug development in diverse therapeutic areas, including chronic inflammatory diseases, diabetes, neuropathic pain, atherogenesis and cancer. By employing a cut-and-sew scaffold hopping strategy, we identified an active scaffold of 3,4-dihydro-2,6-naphthyridin-1(2*H*)-one as the central pharmacophore to derive novel CCR2 antagonists. Systematic structure-activity relationship study with respect to the ring size and the substitution on the naphthyridinone ring gave birth to 1-arylamino-6-alkylheterocycle-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-ones as a brand new chemotype of CCR2 antagonists with nanomolar inhibitory activity. The best antagonism activity in this series was exemplified by compound **13a**, which combined the optimal substitutions of 3,4-dichlorophenylamino at C-1 and 3-(4-(N-methylmethylsulfonamido)piperidin-1-yl)propyl at N-6 position, leading to an IC_{50} value of 61 nM and 10-fold selectivity for CCR2 over CCR5. Efficient and general synthesis was established to construct the innovative core structure and derivethe compound collections. This is the first report on our designed 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one as novel CCR2 antagonist scaffold and its synthesis.

1. Introduction

Chemokines are chemotactic cytokines that play an important role in the activation and migration of leukocytes.[1] Among them, the monocyte chemoattractant protein-1 (MCP-1), also known as CC chemokine ligand-2 (CCL2), primarily activated and migrated monocytes to areas of inflammation by interacting with its cognate cell-surface receptor, CC chemokine receptor 2 (CCR2).[2] The interaction of the CCL2 with CCR2 has been implicated in the pathogenesis of several disease processes,[3] such as rheumatoid arthritis,[4] diabetes,[5] multiple sclerosis,[6] neuropathic pain,[7] cancer,[8] and atherogenesis,[9] thus prompting continuing interest in the biology of this axis. Excessive recruitment of the monocytes to sites of inflammation is presumed to be one cause for these diseases. So, CCR2 antagonists would be an effective treatment for these inflammation related diseases. So far, both the academic and pharmaceutical communities have directed a tremendous amount of research efforts toward the discovery and development of different chemical classes of CCR2 antagonists[10] (**Fig. 1**). Several drug candidates have been advanced into clinical development. For example, CCR2 antagonist CCX-140 has completed Phase II clinical trials for treatment of diabetic nephropathy,[11] providing a clinical proof-of-concept for CCR2 as a valid therapeutic target.

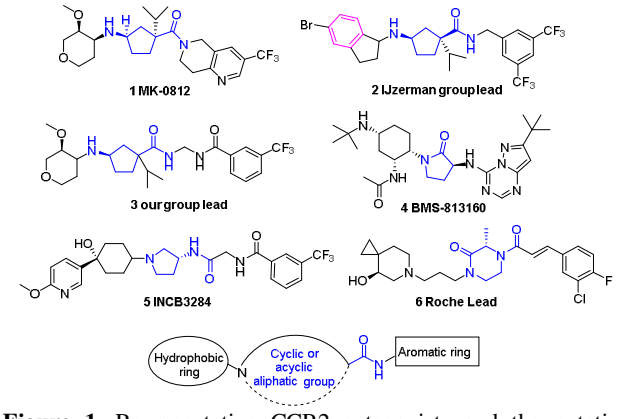

Figure 1. Representative CCR2 antagonists and the putative pharmacophore model

However, several CCR2 antagonists were terminated because of failing to show significant efficacy in clinical trials, such as MK-0812 (**1**) from Merck group for the treatment of rheumatoid arthritis.[12] Therefore, deep understanding of the pharmacobiology of CCR2/CCL2 axis and structurally diverse CCR2 angonists are needed to advance the CCR2-targting therapeutics development.

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Recently, IJzerman group reported that the drug-target residence time could be used as a predictor for drug efficacy and safety, and they developed several CCR2 antagonists with longer residence time by fusing an aromatic moiety with the cyclopentane in the left hand side, which may help to develop efficient drug candidates (**2**, **Fig. 1**).[13, 14] Obviously, there is still large chemical space and biological space to explore for CCR2 antagonists and thus achieve better drug-like properties.

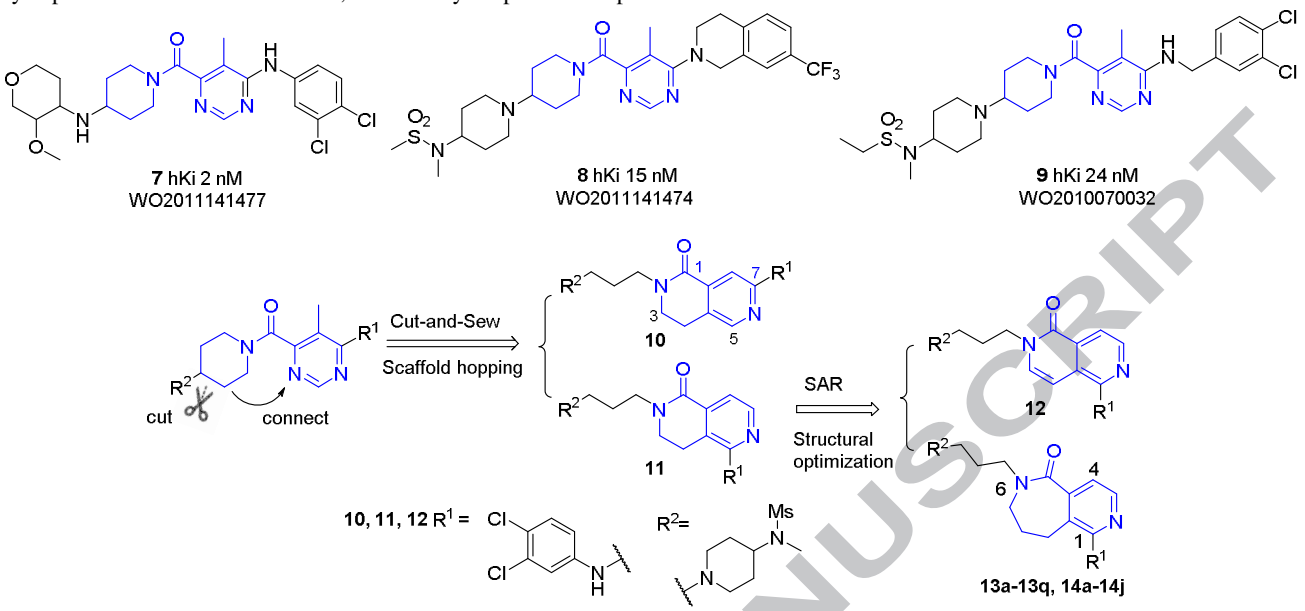


Figure 2. The (5-methylpyrimidin-4-yl)(piperidin-1-yl)methanone-based CCR2 antagonists and our design strategy for a fused aromatic scaffold of CCR2 antagonists

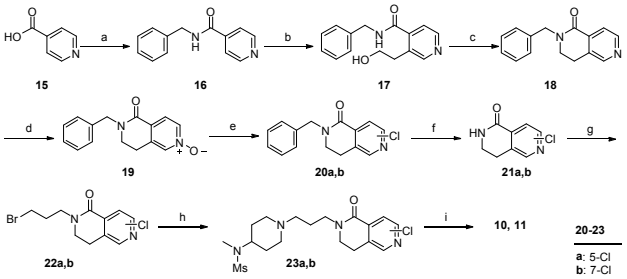
Previously, our group designed new structure CCR2 antagonists (**3**, **Fig. 1**) by incorporating polar moiety into the central core on the putative pharmacophore model concluded by analyzing those known CCR2 antagonists (**Fig. 1**),[15] which consists of a tertiary amine and an amide group in the central, two lipophilic moieties pending at both ends, respectively. In common, most of the potent CCR2 antagonists share aliphatic groups as the central rings, such as pyrrolidine, piperidine, azetidine, cyclopentylamine, cyclohexylamine or glycinamide, as exemplified by the representative compounds in **Fig. 1**. Inspired by IJzerman group's finding that the aromatic moiety is beneficial for the drug-target residence time,[13, 14] we were intrigued to explore the central pharmacophore with aromatic structure distinct from those aforementioned compounds, thus providing diverse structure CCR2 antagonists which might endow promising drug-likeness, at least more stable metabolic property than the aliphatic counterpart.

Interestingly, Boehringer-Ingelheim company licensed a new series of CCR2 antagonists featured with one more aromatic ring (i.e., pyrimidine) inserted between the right hand side aromatic ring and the aliphatic heterocycle core (**7-9**, **Fig. 2**), exhibiting potent CCR2 binding affinity. This unique (5-methylpyrimidin-4-yl)(piperidin-1-yl)methanone core drew our attention. Based on their lead compounds **7-9**, we tried a cut-and-sew scaffold hopping strategy to derive new chemotype CCR2 antagonists bearing a fused aromatic ring core. Fortunately, the resulting 3,4-dihydro-2,6-naphthyridin-1(2*H*)-one derivatives (**10-11, Fig. 2**) displayed effective CCR2 antagonistic activity with 2,5-disubstituted-3,4-dihydro-2,6-naphthyridin-1(2*H*)-one (**11**) being a superior regioisomer. Further SAR study and structural optimization on this active scaffold was undertaken with respect to the ring size and substitution, giving birth to a brand new chemotype of potent CCR2 antagonists bearing our created scaffold of 1-arylamino-6-alkylheterocycle-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one. We have established efficient and general synthetic methodology to build the novel molecular framework and derive structurally diverse library.

2. Chemistry

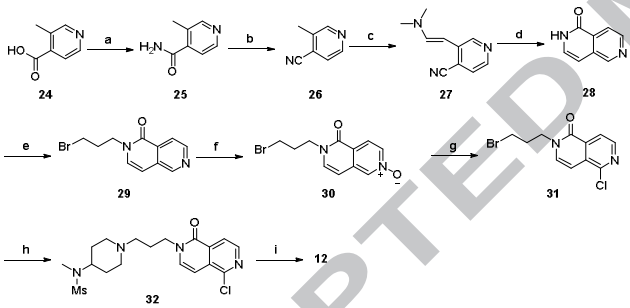
This is the first report on the design and synthesis of the fused aromatic rings, *i.e.*, chloro substituted 3,4-dihydro-2,6-naphthyridin-1(2*H*)-one and 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one as the core pharmacophores of the CCR2 antagonists. We established efficient synthetic methodology to construct the novel core structure-based library with various substituents on the rings.

The 3,4-dihydro-2,6-naphthyridin-1(2*H*)-one-based derivatives were synthesized via an intramolecular mitsunobu reaction and chlorination on the 5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine 2-oxide ring as the key steps, as depicted in **Scheme 1**. Commenced with isonicotinic acid, the conversion to the acid chloride using $SOCl_2$ followed by coupling with benzylamine yielded the amide **16**. Then, treatment with *n*-butyl-lithium in tetrahydrofuran and addition of ethylene oxide gave the key intermediate **17**, which underwent intramolecular mitsunobu reaction to form the core of 3,4-dihydro-2,6-naphthyridin-1(2*H*)-one **18.** Oxidation of **18** with *m*-CPBA followed by chlorination with phosphorus oxychloride generated regioisomeric 5- or 7-chloro substituted derivatives **20a** and **20b**. The separation of the two regioisomers was carefully performed by silica gel column chromatography to afford the isomers separately. Benzyl removal by TFA and trifluoromethanesulfonic acid followed by nucleophilic substitution on 1,3-dibromopropane using NaH in DMF provided 2-*N*-(3-bromopropyl)-3,4-dihydro-2,6-naphthyridin-1(2*H*)-ones **22a** and **22b**. Further nucleophilic substitution reaction with *N*-methyl-*N*-(piperidin-4-yl)methanesulfonamide afforded the precursor **23a** and **23b**. The target products **10-11** were furnished by cross coupling with substituted aniline under optimized catalyst and base.



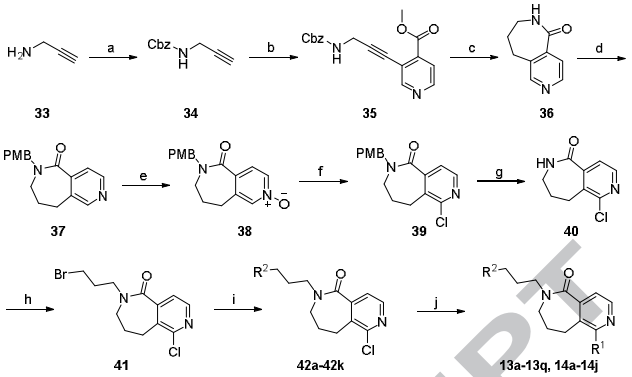
Scheme 1. Reagent and conditions: a) $SOCl_2$, Benzylamine, TEA, THF, 81%; b) *n*-BuLi, ethylene oxide, THF, -78℃, 39%; c) DEAD, PPh_3, THF, rt, 37%; d) *m*-CPBA, DCM, rt, 74%; e) $POCl_3$, toluene, 90℃, 25%-40%; f) CF_3SO_3H, CF_3COOH, 70℃, 50%-53%; g) NaH, 1,3-dibromopropane, DMF, 0℃, 42%-67%; h) K_2CO_3, DMF, 60-74%; i) 3,4-dichloroaniline, $Pd(OAc)_2$, BINAP, ^{t}BuONa, 1,4-dioxane, 42%-57%.

The synthesis of 2,6-naphthyridin-1(2*H*)-one derivative **12** was demonstrated in **Scheme 2**. Treatment of 3-methyl-4-pyridinecarboxylic acid with thionyl chloride gave acyl chloride, which was added in small portions to a cold concentrated ammonium hydroxide solution to produce amide **25**. Dehydration of **25** in phosphorus oxychloride produced 3-methylisonicotinonitrile **26**. Following treatment with 1,1-dimethoxy-*N*,*N*-dimethylmethanamine in DMF introduced the (*E*)-3-(2-(dimethylamino)vinyl substituent (**27**). Then, **27** was refluxed for 16 h in the presence of HBr in ethanol to form the core 2,6-naphthyridin-1(2*H*)-one **28**. The subsequent nucleophilic substitution and coupling reactions afforded the target compound **12**, by applying the same procedure as the preparation of **10** and **11** indicated in **Scheme 1**.



Scheme 2. Reagent and conditions: a) $SOCl_2$, $NH_3.H_2O$, 63%; b) $POCl_3$, reflux, 65%; c) DMF-DMA, DMF, 150℃, 20%; d) HBr (48% in H_2O), EtOH, reflux, 60%; e) NaH, DMF, 74%; f) *m*-CPBA, DCM, 92%; g) $POCl_3$, 79%; h) K_2CO_3, DMF, 58%; i) 3,4-dichloroaniline, $Pd(OAc)_2$, BINAP, ^{t}BuONa, 1,4-dioxane, 51%.

A general synthetic route toward novel 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one derivatives (**13a**-**13q**, **14a**-**14j**) was developed, as depicted in **Scheme 3**. The construction of previously unreported 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (**36**) was commenced with the commercially available propargylamine, via sequent *N*-protecting with benzyl chloroformate and sonogoshira coupling with 3-bromoisonicotinic acid methyl ester to generat the precursor **35**. Reduction of the triple bond and deprotection of Cbz group provided the free amine, which was readily converted to the core **36** via lactamization. Subsequent *N*-benzylation gave *N*-benzyl derivative **37**, followed by a similar strategy as described in **Scheme 1** to afford the final products with various substituents at 1,6-positions.



Scheme 3. Reagent and conditions: a) Cbz-Cl, TEA, ethyl acetate, rt, 90%; b) CuI, $Pd(PPh_3)_2Cl_2$, Et_3N, THF, reflux, 80%; c) 10% Pd/C, MeOH, reflux, 64%; d) NaH, DMF, 67%; e) *m*-CPBA, DCM, 80%; f) $POCl_3$, toluene, 33%; g) CF_3SO_3H, CF_3COOH, 80%; h) NaH, DMF, 68%; i) K_2CO_3, DMF, 63%-81%; j) amine or alcohol, $Pd(OAc)_2$, BINAP, ^{t}BuONa, 1,4-dioxane, 39%-65%.

3. Results and discussion

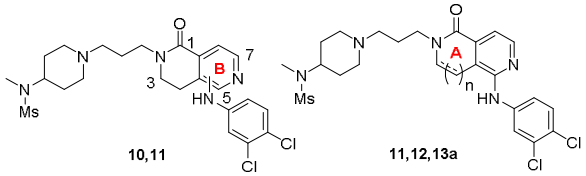
All these 3,4-dihydro-2,6-naphthyridin-1(2*H*)-one and 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one derivatives were tested in functional assays for antagonism of CCR2, and select inhibitor for antagonism of CCR5 as well (Tables 1- 3).

3.1 Identification of 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one being a superior fused aromatic core for CCR2 antagonism.

Initially, the cut-and-sew manipulation on the (5-methylpyrimidin-4-yl)(piperidin-1-yl)methanone core produced regioisomeric 2,7- and 2,5-disubstituted 3,4-dihydro-2,6-naphthyridin-1(2*H*)-ones (**Table 1**, compound **10**, **11**). The functional calcium flux assay indicated that the C5 substituted analog **11** had superior inhibitory activity by almost 4-fold to the C7 substituted isomer **10**.

Fixing the optimal 2,5-disubstitution pattern, further structural exploration on the central ring (A ring) of hit compound **11** was focused on the rigidity of ring, including the unsaturation degree and size. As shown in **Table 1**, the aromatic bicycle **12** displayed reduced activity relative to the parent compound **11** by confining the flexible central ring into relatively rigid 2,6-naphthyridin-1(2*H*)-one. On the contrary, expanding central ring from 6 to 7 members resulted in **13a** with substantially increased activity by 10.5-fold, probably due to allowing the pended aliphatic chain to adopt a favorable conformation and proper spacial positioning. Consequently, the newly created structure of 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one served as the optimal scaffold for further SAR and structural optimization study.

Table 1. Effect of central ring of compound **11** derivatives on inhibition of CCR2 from functional calcium flux assay.



Cpd	B ring substitution	IC_{50} (nM)[a]	Cpd	A ring	IC_{50} (nM)
10	7-(3,4-dichlorophenylamino)	2502	**11**		638

11	5-(3,4-dichlorophenylamino)	638	**12**		3864
[b]TAK-779[16, 17]	/	12	**13a**		61

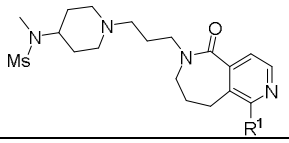
[a] CCL2 was added in 10 nM concentration. [b] TAK-779 is a dual CCR2/CCR5 inhibitor developed by Takeda company, [16, 17] serving as a reference compound for the assay.

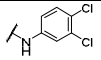
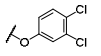
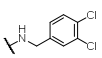
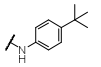
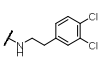
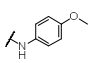
3.2 3,4-Dichlorophenylamino group being an optimal C1-substituent on the 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one core for CCR2 antagonism.

We then explored the SAR of the right side R^1 group on lead compound **13a** (**Table 2**). Compared to the original 3,4-dichlorophenylamino substituent, extending the spacer length between the phenyl ring and amino nitrogen with one or two methylene moiety abrogated the activity (**13b, 13c** vs **13a**). Meanwhile, replacing the phenyl group with aliphatic rings, such as cyclohexyl or cyclopropyl group, all abolished CCR2 activity (**13d**, **13e**). However, heteroaryl ring such as pyridine was tolerated with a slight loss in CCR2 activity (**13f**, IC_{50} = 550 nM), indicating that aromatic ring in C1-position was essential for effective antagonism. Furthermore, the secondary amino functionality bridging the aromatic rings was also critical for the CCR2 antagonism activity. Converting the secondary amine to a tertiary amine by *N*-methylation (**13g**), removing the nitrogen atom (**13h**) or switching nitrogen to amide (**13i**), oxygen (**13j**), all impaired the activity, only compound **13j** retaining weak activity (IC_{50} = 2.466 μM).

Next, we examined the substitution effect on the phenyl ring. Replacing 3,4-dichloro substituent with tertbutyl, methoxy, trifluromethyl, or other halo atoms (**13k-q**) significantly decreased CCR2 antagonism activity except for 4-chloro mono substituted compound **13o** which showed similar potency to compound **13a**. Comparison of the activity of compound **13k** or **13l** with **13o** implied that electron-donating group especially 4-methoxy (**13l**) was disfavored on this position. Among the electron-withdrawing groups such as 3-F (**13m**), 3-CF_3 (**13n**) and 4-Cl (**13o**), only 4-Cl substituted **13o** showed similar IC_{50} value to the parent compound **13a**. Further investigation on disubstitution pattern revealed that 3,4-disubstitution was preferred for good activity over 3,5-disubstitution (**13q** vs **13a**), and replacing 3,4-dichoro substituent with 3-fluoro-4-chloro substituent (**13p**) displayed a deleterious effect on CCR2 activity.

Table 2. Effect of R^1 group in 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one derivatives on inhibition of CCR2 from functional calcium flux assay.



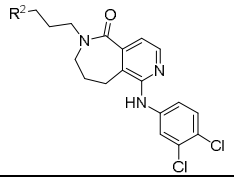
Cpd	R^1	IC_{50} (nM)[a]	Cpd	R^1	IC_{50} (nM)
13a		61	**13j**		2466
13b		NA[b]	**13k**		5053
13c		7833	**13l**		NA
13d		NA	**13m**		4936
13e		NA	**13n**		1821
13f		550	**13o**		74
13g		NA	**13p**		1731
13h		NA	**13q**		2971
13i		NA	TAK-779[c]	/	12

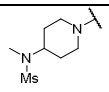
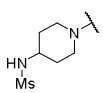
[a]CCL2 was added in 10 nM concentration; [b]NA = no activity; [c]TAK-779 is a dual CCR2/CCR5 inhibitor developed by Takeda company, used in the assay as a reference compound.

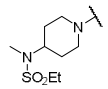
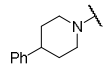
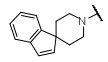
3.3 3-(4-(*N*-Methylmethylsulfonamido)piperidin-1-yl)propyl group being favorable for N6-substituent on the 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one core for CCR2 antagonism.

Finally, we turned to explore the SAR of 4-(*N*-methylmethylsulfonamido)piperidin-1-yl as R^2 group on the left hand side (**Table 3**). Comparison of compound **14a** or **14b** with compound **13a**, it was found that removing the methyl group from sulfonamide or replacing methanesulfonyl with ethanesulfonyl group decreased the activity by 5-fold. Then, completely deleting the *N*-methylmethanesulfonamido group, the resulting piperidine and substituted piperidine analogs (**14c**-**14g**) were synthesized to assess the substitution effect. Though 4-phenylpiperidine analog (**14d**, IC_{50} = 195 nM) exhibited much higher potency than unsubstituted piperidine counterpart (**14c**, IC_{50} = 1261 nM), the bulky conformationally constricted bicyclic substituent (**14e-f**) impaired inhibitory activity for CCR2 receptor, among which the conformationally locked spiroindenylpiperidine analogue **14e** was 2-fold more potent than closely related 3*H*-spiro[benzo[*c*]thiophene-1,4'-piperidine] **14f**. Comparison of **14c** with **14g** indicated that 4-methoxyl group substituted on the piperidine reduced activity slightly. Replacing the piperidine with other heterocycles such as morpholine and piperazine all damaged activity remarkably (**14h**-**14j**).

Table 3. Effect of R^2 group in 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one derivatives on inhibition of CCR2 from functional calcium flux assay.



Cpd	R^2	IC_{50} (nM)[a]	Cpd	R^2	IC_{50} (nM)
13a		61	**14f**		1614
14a		336	**14g**		1566

14b		390	**14h**		4450
14c		1261	**14i**		12330
14d		195	**14j**		19390
14e		720	TAK -779[b]	/	12

[a]CCL2 was added in 10 nM concentration; [b]TAK-779 is a dual CCR2/CCR5 inhibitor developed by Takeda company, used in the assay as a reference compound.

Taken together (Table **1**-**3**), compound **13a** exhibited the most potent CCR2 antagonistic activity with all optimal structural features. We chose lead compound **13a** for further selectivity evaluation for CCR2 over the most closely related CCR5. Gratifyingly, **13a** displayed an IC_{50} value of 660 nM in CCR5 Ca^{2+} assay, indicating a 10-fold selectivity for CCR2 over CCR5

4. Conclusions

Chemokine receptor CCR2 is an attractive target for developing new therapeutic interventions of the inflammation-related diseases such as rheumatoid arthritis, multiple sclerosis, atherosclerosis, diabetes and even cancer. However, so far only one CCR2 antagonist has completed Phase II clinical trials for treatment of diabetic nephropathy. More structurally diverse CCR2 antagonists are needed to achieve better drug-likeness and in vivo efficacy. By employing a cut-and-sew scaffold hopping strategy, based on a (5-methylpyrimidin-4-yl)(piperidin-1-yl)methanone template, we designed and discovered novel scaffold CCR2 antagonists bearing unique 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one core. Systematic SAR study has identified the 3,4-dichlorophenylamino and 3-(4-(*N*-methylmethylsulfonamido)piperidin-1-yl)propyl group as the optimal C1- and N6-substituent, respectively, conferring lead compound **13a** with an IC_{50} value of 61 nM against CCR2 and 10-fold selectivity for CCR2 over CCR5. Efficient and general synthesis was established to construct the newly designed 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one core structure and its derivatives with various substituents at the C1- and N6-positions. This innovative chemotype CCR2 antagonist expands the chemical space and pharmacological potential for the development of CCR2 antagonists into treatments for inflammation-related diseases.

5. Experimental

5.1 Chemistry

5.1.1 General

All commercial starting materials and reagent were used without further purification, unless otherwise stated. THF was freshly distilled from sodium/benzophenone. All reagents were weighed and handled in air at room temperature. Column chromatography was performed on silica gel (200-300 mesh). All new compounds were characterized by ^{1}H NMR, ^{13}C NMR and low/high resolution mass spectroscopy. NMR spectra were recorded on Brucker AVANCE 300 NMR spectrometer or Brucker AVANCE III 400 NMR spectrometer. Chemical shifts for proton magnetic resonance spectra (^{1}H NMR) were quoted in parts per million (ppm) referenced to the signals of residual chloroform (7.26 ppm), dimethyl sulfoxide (2.50 ppm). All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), dimethyl sulfoxide (39.52 ppm). The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multriplet, dd = doublet of doublet. Mass spectra were recorded using an ESI ion source unless stated otherwise. All melting points were measured using a BÜCHI 510 melting point apparatus. The yields in this paper refer to isolated yields，Purity of all compounds was determined by analytical Gilson high-performance liquid chromatography (HPLC) using an YMC ODS3 column (50 mm × 4.6 mm, 5 μM). Conditions were as follows: CH_3CN/H_2O eluent at 2.5 $mLmin^{-1}$ flow [containing 0.1% trifluoroacetic acid (TFA)] at 35 °C, 8 min, gradient 5% CH_3CN to 95% CH_3CN, monitored by UV absorption at 214 nm and 254 nm.

5.1.2 *N*-benzylisonicotinamide (16)

Thionyl chloride (15 mL) was added to a stirred isonicotinic acid (1 g, 8.1 mmol), and the mixture was heated to 50℃ for 5 h. Then the mixture was cooled to ambient, solvent was evaporated to dryness under reduced pressure. The residue was treated with dry THF (20 mL) at 0℃, added benzylamine (885 μL, 8.1 mmol) and triethyl amine (3.4 mL, 24.3 mmol) and stirred for another 2 h. After completion of the reaction, the mixture was quenched with NH_4Cl (aq). The aqueous phase was extracted with ethyl acetate (2×30 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (EtOAc/Petroleum ether 1:4) to yield the white solid (81%).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 5.6 Hz, 2H), 7.62 (d, *J* = 5.4 Hz, 2H), 7.43 – 7.28 (m, 5H), 4.66 (d, *J* = 5.6 Hz, 2H).

5.1.3 *N*-Benzyl-3-(2-hydroxyethyl)isonicotinamide (17)

n-Butyl lithium (2.5 mL of a 2.5 M solution in hexane, 6.2 mmol) was added dropwise to a stirred solution of *N*-benzylisonicotinamide (**16**, 625 mg, 2.9 mmol) in THF (15 mL) at -78℃ under N_2. The reaction mixture was stirred for 1 h. A solution of ethylene oxide (1.3 mL of a 2.5 M solution in THF, 3.2 mmol) was then added and the resulting mixture stirred at -78 ℃ for 3 h. After completion of the reaction, the mixture was warmed to room temperature and quenched with MeOH. The resulting mixture was poured into water and extracted with EtOAc (3×25 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$ 1:40) to yield the oil (39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (t, *J* = 5.5 Hz, 1H), 8.25 (s, 1H), 8.19 (d, *J* = 5.0 Hz, 1H), 7.33 – 7.20 (m, 6H), 4.52 (d, *J* = 5.7 Hz, 2H), 3.79 (t, *J* = 5.6 Hz, 2H), 2.85 (t, *J* = 5.6 Hz, 2H).

5.1.4 2-Benzyl-3,4-dihydro-2,6-naphthyridin-1(2*H*)-one (18)

Diethyl azodicarboxylate (197 μL, 1.2 mmol) was added dropwise to a stirred solution of *N*-benzyl-3-(2-hydroxyethyl)isonicotinamide (**17**, 290 mg, 1.1 mmol) and PPh_3 (325 mg, 1.2 mmol) in THF (10 mL) at room temperature under N_2, the reaction mixture was stirred overnight, then heated to 40 ℃ for another 8 h. After completion of the reaction, water was added. The mixture was extracted with DCM and then organic phases washed with brine. Dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, the resulting residue was purified by flash column chromatography on silica gel (EtOAc/Petroleum ether 1:2) to yield the oil (37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.9 Hz, 1H), 8.53 (s, 1H), 7.94

(d, *J* = 5.0 Hz, 1H), 7.38 – 7.27 (m, 5H), 4.79 (s, 2H), 3.54 (t, *J* = 6.6 Hz, 2H), 2.95 (t, *J* = 6.6 Hz, 2H).

5.1.5 6-Benzyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine 2-oxide (19)

To a solution of 2-Benzyl-3,4-dihydro-2,6-naphthyridin-1(2*H*)-one (**18**, 100 mg, 0.4 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (115 mg, 0.5 mmol). The reaction mixture was stirred for 1 h, then the organic layer was washed with saturated sodium bicarbonate. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum, the residue was purified by flash column chromatography on silica gel (DCM/MeOH 30:1) to yield the white solid (74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 6.6 Hz, 1H), 8.05 (s, 1H), 7.96 (d, *J* = 6.7 Hz, 1H), 7.40 – 7.28 (m, 5H), 4.76 (s, 2H), 3.53 (t, *J* = 6.6 Hz, 2H), 2.89 (t, *J* = 6.6 Hz, 2H).

5.1.6 2-Benzyl-7-chloro-3,4-dihydro-2,6-naphthyridin-1(2*H*)-one (20b)

Phosphorus oxychloride (2 mL) was added slowly to a stirred 6-benzyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine 2-oxide (**19**, 68 mg, 0.3 mmol). The mixture was heated to 90℃ for 4 hours. After cooling, the solvent was removed under reduced pressure, and the saturated aqueous sodium carbonate solution was slowly added under an ice bath until pH value reached to 7~8. Methylene chloride was then added, all organic layer was obtained after washing with brine. The solvent was removed under reduced pressure, and this mixture of regioisomers was carefully purified by silica gel column chromatography (EtOAc/Petroleum ether 1:6) to give **20b** as oil (25%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.98 (s, 1H), 7.39 – 7.28 (m, 5H), 4.78 (s, 2H), 3.52 (t, *J* = 6.6 Hz, 2H), 2.93 (t, *J* = 6.6 Hz, 2H). The polar isomer was **20a**, solid, 40%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.9 Hz, 1H), 7.94 (d, *J* = 4.9 Hz, 1H), 7.41 – 7.28 (m, 5H), 4.78 (s, 2H), 3.55 (t, *J* = 6.8 Hz, 2H), 3.05 (t, *J* = 6.8 Hz, 2H).

5.1.7 5-Chloro-3,4-dihydro-2,6-naphthyridin-1(2*H*)-one (21a)

Compound **20a** (50 mg, 0.3 mmol) was taken up in trifluoacetic acid (1 mL) and trifluoromethanesulfonic acid (1 mL), and then the mixture was stirred at 70℃ for 4 h. After completion of the reaction, the mixture was cooled to ice bath. Water and saturated aqueous sodium carbonate solution was slowly added until pH value reached to 7~8, and then aqueous phase was extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Resulting residue was purified by flash column chromatography on silica (EtOAc/Petroleum ether 1:1) to yield the white solid (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.9 Hz, 1H), 7.85 (d, *J* = 4.9 Hz, 1H), 6.54 (s, br, 1H), 3.64 (td, *J* = 6.8, 2.9 Hz, 2H), 3.13 (t, *J* = 6.7 Hz, 2H).

5.1.8 7-Chloro-3,4-dihydro-2,6-naphthyridin-1(2*H*)-one (21b)

Following the similar procedures as for compound **21a** gave compound **21b**, 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.90 (s, 1H), 6.74 (s, br, 1H), 3.62 (td, *J* = 6.8, 2.7 Hz, 2H), 3.00 (t, *J* = 6.5 Hz, 2H).

5.1.9 2-(3-Bromopropyl)-5-chloro-3,4-dihydro-2,6-naphthyridin-1(2*H*)-one (22a)

NaH (12 mg, 0.3 mmol, 60% in paraffin liquid) was added in portions to a solution of 5-chloro-3,4-dihydro-2,6-naphthyridin-1(2*H*)-one (**21a**, 27mg, 0.2mmol) in dry DMF (3 mL) at ice bath. The mixture was stirred for 30 min at the same temperature until evolution of hydrogen ceased, then 1,3-dibromopropane (80 μL, 0.8 mmol) was added. The resulting mixture was stirred for 3 h at room temperature. After cooling with ice bath, water was added slowly to destroy the excess of sodium hydride. The phases were separated and then the aqueous phase was extracted with ethyl acetate (2×10 mL). Combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica (EtOAc/Petroleum ether 1:5) to yield the oil (67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.9 Hz, 1H), 7.83 (d, *J* = 4.9 Hz, 1H), 3.73 – 3.63 (m, 4H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.11 (t, *J* = 6.7 Hz, 2H), 2.28 – 2.15 (m, 2H).

5.1.10 2-(3-Bromopropyl)-7-chloro-3,4-dihydro-2,6-naphthyridin-1(2*H*)-one (22b)

Following the similar procedures as for compound **22a** gave compound **22b**, 42%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.90 (s, 1H), 3.74 – 3.63 (m, 4H), 3.46 (t, *J* = 6.5 Hz, 2H), 3.01 (t, *J* = 6.6 Hz, 2H), 2.27 – 2.18 (m, 2H).

5.1.11 *N*-(1-(3-(5-chloro-1-oxo-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (23a)

A solution of 2-(3-bromopropyl)-5-chloro-3,4-dihydro-2,6-naphthyridin-1(2*H*)-one (**22a**, 40 mg, 0.13 mmol) and *N*-methyl-*N*-(piperidin-4-yl)methanesulfonamide (25 mg, 0.13 mmol) in 20 mL of DMF was treated with K_2CO_3 (28 mg, 0.2 mmol). The resulting mixture was heated at 50℃ for 2 h. After the reaction was completed, the reaction mixture was poured into ice water, aqueous phase was extracted with ethyl acetate (2×10 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica (DCM/MeOH 30:1) to yield the oil (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.9 Hz, 1H), 7.88 (d, *J* = 4.9 Hz, 1H), 3.81 – 3.72 (m, 1H), 3.68 – 3.59 (m, 4H), 3.13 (t, *J* = 6.7 Hz, 2H), 3.05 – 2.97 (m, 2H), 2.86 (s, 3H), 2.81 (s, 3H), 2.42 (t, *J* = 7.2 Hz, 2H), 2.06 (t, *J* = 11.9 Hz, 2H), 1.89 – 1.76 (m, 4H), 1.75 – 1.67 (m, 2H).

5.1.12 *N*-(1-(3-(7-chloro-1-oxo-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (23b)

Following the similar procedures as for compound **23a** gave compound **23b**, 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.90 (s, 1H), 3.73 (tt, *J* = 11.8, 4.3 Hz, 1H), 3.63 – 3.58 (m, 4H), 3.02 – 2.95 (m, 4H), 2.83 (s, 3H), 2.78 (s, 3H), 2.42 – 2.36 (m, 2H), 2.03 (td, *J* = 11.7, 2.5 Hz, 2H), 1.85 – 1.75 (m, 4H), 1.71 – 1.65 (m, 2H).

5.1.13 *N*-(1-(3-(7-((3,4-dichlorophenyl)amino)-1-oxo-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (10)

A solution of **23b** (50 mg, 0.12 mmol), 3,4-dichloroaniline (20 mg, 0.12 mmol), palladium(II) acetate (4 mg), sodium *tert*-butoxide (20 mg, 0.21 mmol) and (+/-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (56 mg, 0.09 mmol) in dioxane (6 mL) under argon atmosphere was heated to 90℃ and stirred for 3 h. After cooling to room temperature, the reaction mixture was poured into 10 mL water and extracted with EtOAc (2×10 mL). The combined organic layer was washed with brine, dried over sodium sulfate and concentrated in vacuo to give a brown oil. The residue was purified by flash column chromatography on silica gel (DCM/MeOH 30:1) to yield the white solid (57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.71 (d, *J* = 2.6 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.34 (s, 1H), 7.29 – 7.27 (m, 1H), 3.78 – 3.71 (m, 1H), 3.64 – 3.55 (m, 4H), 3.01 – 2.90 (m, 4H), 2.83 (s, 3H), 2.78 (s, 3H), 2.42 – 2.36 (m, 2H),

2.06 – 1.99 (m, 2H), 1.85 – 1.75 (m, 4H), 1.71 – 1.65 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.66, 154.81, 145.71, 140.45, 137.52, 132.08, 129.99, 123.80, 122.78, 119.98, 117.92, 108.13, 55.07, 54.60, 52.64, 46.47, 45.93, 38.18, 29.27, 28.18, 24.98, 24.09. HRMS (ESI): calcd for $C_{24}H_{32}Cl_2N_5O_3S$ $[M+H]^+$: 540.1597; found 540.1602. Retention time 2.71 min, > 95% pure.

5.1.14 *N*-(1-(3-(5-((3,4-dichlorophenyl)amino)-1-oxo-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (11)

Following the similar procedures as for compound **10** gave compound **11**, 42%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.1 Hz, 1H), 7.71 (d, *J* = 2.3 Hz, 1H), 7.47 (d, *J* = 5.1 Hz, 1H), 7.35 – 7.27 (m, 2H), 6.37 (s, 1H), 3.75 – 3.66 (m, 1H), 3.63 – 3.54 (m, 4H), 3.00 – 2.93 (m, 2H), 2.84 – 2.78 (m, 5H), 2.77 (s, 3H), 2.41 – 2.35 (m, 2H), 2.01 (td, *J* = 11.8, 2.1 Hz, 3H), 1.85 – 1.72 (m, 4H), 1.70 – 1.62 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.44, 151.40, 146.25, 139.90, 137.37, 132.25, 130.05, 124.77, 120.51, 118.43, 118.08, 113.97, 55.19, 54.68, 52.68, 45.70, 44.94, 38.23, 29.33, 28.31, 24.98, 22.14. HRMS (ESI): calcd for $C_{24}H_{32}Cl_2N_5O_3S$ $[M+H]^+$: 540.1597; found 540.1596. Retention time 2.62 min, > 99% pure.

5.1.15 3-Methylisonicotinamide (25)

A solution of 3-methyl-4-nicotinic acid (0.5 g, 3.6 mmol) in thionyl chloride (3 mL) was heated to reflux for 3 h. Then thionyl chloride was evaporated, the solid acid chloride was added in portions to an ammonium hydroxide solution (30 mL, 25% in water) under ice bath. Slowly warming the mixture to room temperature and stirred for 10 min, the solvent was concentrated, and the resulting residue was purified by flash column chromatography on silica gel (MeOH/CH_2Cl_2 1:40) to yield the white solid (63%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 – 8.48 (m, 1H), 8.46 – 8.44 (m, 1H), 7.42 (d, *J* = 5.0 Hz, 1H), 2.45 (s, 3H).

5.1.16 3-Methylisonicotinonitrile (26)

Phosphorus oxychloride (2 mL) was slowly added to a stirred 3-Methylisonicotinamide (**25**, 300 mg, 2.2 mmol). The resulting solution was heated to reflux for 24 h, then reaction mixture was cooled to room temperature, and the excess phosphorus oxychloride was removed under reduced pressure. Crushed ice was slowly added to the oily residue, and the solution was neutralized with saturated aqueous sodium carbonate solution. The crude product was extracted with EtOAc (3×25 mL), and combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Resulting residue was purified by flash column chromatography on silica gel (EtOAc/Petroleum ether 1:4) to yield the white solid (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.59 (d, *J* = 5.0 Hz, 1H), 7.46 (d, *J* = 5.0 Hz, 1H), 2.54 (s, 3H).

5.1.17 (*E*)-3-(2-(dimethylamino)vinyl)isonicotinonitrile (27)

To a solution of 3-methylisonicotinonitrile (**26**, 168 mg, 1.4 mmol) in DMF (3 mL) was added 1,1-dimethoxyl-*N*,*N*-dimethylmethanamine (400 μL, 2.8 mmol). The mixture was heated to reflux overnight. Then the mixture was cooled to RT and additional 200 μL of 1,1-dimethoxyl-*N*,*N*-dimethylmethanamine was added to the mixture. The mixture was heated to reflux overnight. Then repeated addition of 200 μL 1,1-dimethoxyl-*N*,*N*-dimethylmethanamine to the mixture. The mixture was heated to reflux overnight. After completion of the reaction, the mixture was cooled to RT and concentrated in vacuo to give a brown oil, the residue was purified by flash column chromatography on silica (EtOAc/Petroleum ether 1:2) to yield the yellow solid (20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.14 – 8.11 (m, 1H), 7.25 – 7.23 (m, 1H), 7.16 (d, *J* = 13.6 Hz, 1H), 5.21 (d, *J* = 13.6 Hz, 1H), 2.95 (s, 6H).

5.1.18 2,6-Naphthyridin-1(2*H*)-one (28)

To a suspension of (*E*)-3-(2-(dimethylamino)vinyl)isonicotinonitrile (**27**, 40 mg, 0.23 mmol) in ethanol (3 mL) was added 1 mL of HBr (48% in water). The mixture was heated to reflux overnight. After completion of the reaction, the organic solvents were removed, and the solution was neutralized with saturated aqueous sodium carbonate solution. The crude product was extracted with EtOAc (3×10 mL), combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (EtOAc/Petroleum ether 1:2) to yield the white solid (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.67 (d, *J* = 5.1 Hz, 1H), 8.14 (d, *J* = 5.0 Hz, 1H), 7.24 (d, *J* = 7.0 Hz, 1H), 6.63 (d, *J* = 6.9 Hz, 1H).

5.1.19 2-(3-Bromopropyl)-2,6-naphthyridin-1(2*H*)-one (29)

Following the similar procedures as for compound **22a** gave compound **29**, 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, *J* = 0.9 Hz, 1H), 8.68 (d, *J* = 5.4 Hz, 1H), 8.16 – 8.13 (m, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 6.61 – 6.57 (m, 1H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.44 (t, *J* = 6.2 Hz, 2H), 2.41 – 2.33 (m, 2H).

5.1.20 6-(3-Bromopropyl)-5-oxo-5,6-dihydro-2,6-naphthyridine 2-oxide (30)

Following the similar procedures as for compound **19** gave compound **30**, 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.45 (m, 1H), 8.20 – 8.18 (m, 2H), 7.31 (d, *J* = 7.4 Hz, 1H), 6.39 (d, *J* = 7.4 Hz, 1H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.48 – 3.44 (m, 2H), 2.42 – 2.34 (m, 2H).

5.1.21 2-(3-Bromopropyl)-5-chloro-2,6-naphthyridin-1(2*H*)-one (31)

Following the similar procedures as for compound **20b** gave compound **31**, 79%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.3 Hz, 1H), 8.12 (d, *J* = 5.3 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 4.19 (t, *J* = 6.6 Hz, 2H), 3.43 (t, *J* = 6.2 Hz, 2H), 2.44 – 2.32 (m, 2H).

5.1.22 *N*-(1-(3-(5-chloro-1-oxo-2,6-naphthyridin-2(1*H*)-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (32)

Following the similar procedures as for compound **23a** gave compound **32**, 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.3 Hz, 1H), 8.13 (dd, *J* = 5.3, 0.7 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 6.83 (dd, *J* = 7.6, 0.7 Hz, 1H), 4.08 (t, *J* = 6.9 Hz, 2H), 3.77 – 3.67 (m, 1H), 2.98 – 2.91 (m, 2H), 2.83 (s, 3H), 2.76 (s, 3H), 2.38 (t, *J* = 6.7 Hz, 2H), 2.05 – 1.92 (m, 4H), 1.78 – 1.64 (m, 4H).

5.1.23 *N*-(1-(3-(5-((3,4-dichlorophenyl)amino)-1-oxo-2,6-naphthyridin-2(1*H*)-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (12)

Following the similar procedures as for compound **10** gave compound **12**, white solid, 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 5.5 Hz, 1H), 7.86 (d, *J* = 2.4 Hz, 1H), 7.66 (d, *J* = 5.5 Hz, 1H), 7.46 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.23 (s, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 7.6 Hz, 1H), 4.02 (t, *J* = 6.9 Hz, 2H), 3.70 – 3.59 (m, 1H), 2.88 (d, *J* = 11.5 Hz, 2H), 2.80 (s, 3H), 2.71 (s, 3H), 2.31 (t, *J* = 6.7 Hz, 2H), 1.99 – 1.85 (m, 4H), 1.74 – 1.54 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.79, 150.70, 143.91, 139.95, 133.19, 132.37, 132.30, 130.25, 125.19, 121.25, 120.83, 119.20, 112.47, 98.72, 65.85, 55.06, 54.61, 52.69, 48.12, 38.55, 29.63, 28.62, 25.97, 15.28. Retention time 2.62 min, > 97% pure.

5.1.24 Benzyl prop-2-yn-1-ylcarbamate (34)

To a magnetically stirred solution of prop-2-yn-1-amine (1 g, 18 mmol) and triethylamine (2.5 mL, 18 mmol) in ethyl acetate (10 mL) under an atmosphere of nitrogen was added benzyl chloroformate (2.5 mL, 18 mmol) at 0℃. The resulting mixture was warmed to room temperature to stirred for 3 h and then quenched with NH_4Cl (aq), aqueous phase was extracted with ethyl acetate (2×50 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (EtOAc/Petroleum ether 1:5) to yield the white solid (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 5H), 5.13 (s, 2H), 3.99 (dd, *J* = 5.7, 2.6 Hz, 2H), 2.25 (t, *J* = 2.5 Hz, 1H).

5.1.25 Methyl 3-(3-(((benzyloxy)carbonyl)amino)prop-1-yn-1-yl)isonicotinate (35)

To a solution of benzyl prop-2-yn-1-ylcarbamate (**34**, 198 mg, 1.1 mmol) in THF (5 mL) and Et_3N (5 mL) were added CuI (9 mg), dichlorobis(triphenylphosphine)palladium(II) (16 mg), and methyl 3-bromopyridine-4-carboxylate (216 mg, 1 mmol). The mixture was stirred under Ar at 75℃ for 8 h. After cooling down, the mixture was filtered through a pad of celite and the solvent was removed in vacuo. Then, the residue was purified by flash column chromatography on silica gel (EtOAc/ Petroleum ether 1:2) to yield an oil (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.62 (d, *J* = 5.1 Hz, 1H), 7.72 (dd, *J* = 5.1, 0.6 Hz, 1H), 7.40 – 7.29 (m, 5H), 5.15 (s, 2H), 4.31 (d, *J* = 5.5 Hz, 2H), 3.92 (s, 3H).

5.1.26 6,7,8,9-Tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (36)

Pd on carbon (30 mg, 10 wt %) was added to a solution of methyl 3-(3-(((benzyloxy)carbonyl)amino)prop-1-yn-1-yl)isonicotinate (**35**, 260 mg, 0.8 mmol) in MeOH (10 mL), and the reaction mixture was stirred under H_2 atmosphere (1 atm.) at 40℃ for 18 h. The catalyst was then removed by filtration through a pad of celite and the resulting solution was heated to reflux for 4 h. After cooling down, the solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (EtOAc/ Petroleum ether 1:1) to yield the yellow solid (64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.9 Hz, 1H), 8.51 (s, 1H), 7.56 (dd, *J* = 4.9, 0.6 Hz, 1H), 3.17 – 3.10 (m, 2H), 2.88 (t, *J* = 7.2 Hz, 2H), 2.12 – 2.02 (m, 2H).

5.1.27 6-(4-Methoxybenzyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (37)

To a solution of 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (**36**, 0.865g, 5.3mmol) in DMF (15 mL) was added sodium hydride (318 mg, 8 mmol, 60% in paraffin liquid) portionwise at 0℃. And then 4-methoxylbenzyl bromide (868 μL, 6.4 mmol) was added. The mixture was warmed to room temperature and stirred for 1 h. After cooling with ice, water was added slowly to destroy the excess of sodium hydride. The phases were then separated and the aqueous phase was extracted with ethyl acetate (2×20 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. Resulting residue was purified by flash column chromatography on silica gel (EtOAc/ Petroleum ether 1:3) to yield an oil (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.9 Hz, 1H), 8.42 (s, 1H), 7.58 (d, *J* = 4.9 Hz, 1H), 7.33 – 7.28 (m, 2H), 6.91 – 6.86 (m, 2H), 4.71 (s, 2H), 3.81 (s, 3H), 3.16 (t, *J* = 6.4 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 1.82 – 1.75 (m, 2H).

5.1.28 6-(4-Methoxybenzyl)-5-oxo-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepine 2-oxide (38)

To a solution of 6-(4-methoxybenzyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (**37**, 400 mg, 1.6 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (469 mg, 1.9 mmol) in portions, and then the mixture was stirred for 1 h at room temperature. After that, the organic layer was washed with saturated sodium bicarbonate. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum, and the residue was purified by flash column chromatography on silica (DCM/MeOH 30:1) to yield the white solid (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 6.6, 1.7 Hz, 1H), 8.01 – 7.99 (m, 1H), 7.62 (d, *J* = 6.6 Hz, 1H), 7.31 – 7.27 (m, 2H), 6.90 – 6.86 (m, 2H), 4.69 (s, 2H), 3.81 (s, 3H), 3.23 (t, *J* = 6.4 Hz, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 1.83 – 1.74 (m, 2H).

5.1.29 1-Chloro-6-(4-methoxybenzyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (39)

Phosphorus oxychloride (600 μL, 6.5 mmol) was added slowly to a solution of 6-(4-methoxybenzyl)-5-oxo-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepine 2-oxide (**38**, 300 mg, 1 mmol) in dry toluene (5 mL). The mixture was heated to 90℃ for 4 hours. After cooling to rt, the solvent was removed under reduced pressure, and the saturated aqueous sodium carbonate solution was slowly added under an ice bath until pH value reached to 7~8. Methylene chloride was then added. All organic layer was obtained after washing with brine. The solvent was removed under reduced pressure. This mixture of regioisomers was carefully purified by silica gel column chromatography (EtOAc/ Petroleum ether 1:7). The polar isomer was the desired products, 33%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 4.9 Hz, 1H), 7.51 (d, *J* = 4.9 Hz, 1H), 7.32 – 7.28 (m, 2H), 6.91 – 6.86 (m, 2H), 4.70 (s, 2H), 3.82 (s, 3H), 3.15 (t, *J* = 6.4 Hz, 2H), 2.91 (t, *J* = 7.1 Hz, 2H), 1.83 – 1.74 (m, 2H).

5.1.30 1-Chloro-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (40)

1-Chloro-6-(4-methoxybenzyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (**39**, 80 mg, 0.25 mmol) was taken up in trifluoacetic acid (2 mL) and trifluoromethanesulfonic acid (2 mL), the mixture was stirred at 50℃ for 2 h and then cooled to room temperature. Water and the saturated aqueous sodium carbonate solution was added slowly until pH value reached to 7~8. The aqueous phase was extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, the resulting residue was purified by flash column chromatography on silica gel (EtOAc/Petroleum ether 1:1) to yield the solid (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.8 Hz, 1H), 7.47 (d, *J* = 4.9 Hz, 1H), 3.14 – 3.02 (m, 4H), 2.13 – 2.04 (m, 2H).

5.1.31 6-(3-Bromopropyl)-1-chloro-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (41)

NaH (24 mg, 0.6 mmol, 60% in paraffin liquid) was added in portions to a solution of 1-chloro-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (**40**, 60 mg, 0.3 mmol) in dry DMF (3 mL) at ice bath. The mixture was stirred for 30 min at the same temperature until evolution of hydrogen ceased, then 1,3-dibromopropane (150 μL, 1.5 mmol) was added. The resulting mixture was stirred for 3 h at room temperature. After cooling with ice, water was added slowly to destroy the excess of sodium hydride. The phases were then separated and the aqueous phase was extracted with ethyl acetate (2×10 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by

flash column chromatography on silica gel (EtOAc/Petroleum ether 1:5) to yield the while solid (68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.9 Hz, 1H), 7.44 (d, *J* = 4.9 Hz, 1H), 3.68 (t, *J* = 7.1 Hz, 2H), 3.46 (t, *J* = 6.5 Hz, 2H), 3.22 (t, *J* = 6.5 Hz, 2H), 2.99 (t, *J* = 7.1 Hz, 2H), 2.28 – 2.18 (m, 2H), 2.15 – 2.05 (m, 2H).

5.1.32 *N*-(1-(3-(1-chloro-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (42a)

A solution of 6-(3-bromopropyl)-1-chloro-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (**41**, 64 mg, 0.2 mmol) and *N*-methyl-*N*-(piperidin-4-yl)methanesulfonamide (46 mg, 0.2 mmol) in 20 mL of DMF was treated with K_2CO_3 (42 mg, 0.3 mmol). The resulting mixture was heated at 50℃ for 2 h. After the reaction was completed, the reaction mixture was poured into water. The phases were then separated and the aqueous phase was extracted with ethyl acetate (2×20 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (DCM/MeOH 30:1) to yield the white solid (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.9 Hz, 1H), 7.44 (d, *J* = 4.9 Hz, 1H), 3.73 (tt, *J* = 11.8, 4.2 Hz, 1H), 3.61 – 3.54 (m, 2H), 3.18 (t, *J* = 6.5 Hz, 2H), 3.02 – 2.95 (m, 4H), 2.82 (s, 3H), 2.79 (s, 3H), 2.43 – 2.36 (m, 2H), 2.12 – 1.99 (m, 4H), 1.86 – 1.77 (m, 4H), 1.73 – 1.64 (m, 2H).

5.1.33 *N*-(1-(3-(1-chloro-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)methanesulfonamide (42b)

Following the similar procedures as for compound **42a** gave compound **42b**, 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.9 Hz, 1H), 7.44 (d, *J* = 4.9 Hz, 1H), 4.53 (d, *J* = 7.4 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.38 – 3.27 (m, 1H), 3.18 (t, *J* = 6.4 Hz, 2H), 3.02 – 2.94 (m, 5H), 2.88 – 2.80 (m, 2H), 2.43 – 2.35 (m, 2H), 2.14 – 1.94 (m, 7H), 1.86 – 1.76 (m, 2H), 1.63 – 1.50 (m, 2H).

5.1.34 *N*-(1-(3-(1-chloro-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylethanesulfonamide (42c)

Following the similar procedures as for compound **42a** gave compound **42c**, 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.9 Hz, 1H), 7.44 (d, *J* = 4.9 Hz, 1H), 3.67 (tt, *J* = 11.8, 4.2 Hz, 1H), 3.61 – 3.53 (m, 2H), 3.18 (t, *J* = 6.5 Hz, 2H), 3.03 – 2.91 (m, 6H), 2.79 (s, 3H), 2.42 – 2.35 (m, 2H), 2.12 – 1.99 (m, 4H), 1.86 – 1.76 (m, 4H), 1.72 – 1.64 (m, 2H), 1.32 (t, *J* = 7.4 Hz, 3H).

5.1.35 1-Chloro-6-(3-(piperidin-1-yl)propyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (42d)

Following the similar procedures as for compound **42a** gave compound **42d**, 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.9 Hz, 1H), 7.45 (d, *J* = 4.9 Hz, 1H), 3.61 – 3.54 (m, 2H), 3.20 (dd, *J* = 13.5, 6.9 Hz, 2H), 2.99 (t, *J* = 7.1 Hz, 2H), 2.43 – 2.31 (m, 4H), 2.13 – 2.03 (m, 2H), 1.92 – 1.88 (m, 2H), 1.87 – 1.80 (m, 2H), 1.61 – 1.51 (m, 4H), 1.48 – 1.37 (m, 2H).

5.1.36 1-Chloro-6-(3-(4-phenylpiperidin-1-yl)propyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (42e)

Following the similar procedures as for compound **42a** gave compound **42e**, 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 4.9 Hz, 1H), 7.46 (d, *J* = 4.9 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 3.65 – 3.57 (m, 2H), 3.26 – 3.18 (m, 2H), 3.09 – 2.97 (m, 4H), 2.54 – 2.41 (m, 3H), 2.15 – 2.01 (m, 4H), 1.95 – 1.71 (m, 6H).

5.1.37 1-Chloro-6-(3-(spiro[indene-1,4'-piperidin]-1'-yl)propyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (42f)

Following the similar procedures as for compound **42a** gave compound **42f**, 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 4.9 Hz, 1H), 7.48 – 7.44 (m, 1H), 7.38 – 7.28 (m, 2H), 7.25 – 7.15 (m, 2H), 6.83 (d, *J* = 5.7 Hz, 1H), 6.74 (d, *J* = 5.7 Hz, 1H), 3.67 – 3.58 (m, 2H), 3.30 – 3.16 (m, 2H), 3.06 – 2.97 (m, 4H), 2.58 – 2.51 (m, 2H), 2.39 – 2.30 (m, 2H), 2.24 – 2.04 (m, 5H), 1.98 – 1.88 (m, 2H), 1.39 – 1.32 (m, 2H).

5.1.38 6-(3-(3*H*-spiro[benzo[*c*]thiophene-1,4'-piperidin]-1'-yl)propyl)-1-chloro-6,7,8,9-Tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (42g)

Following the similar procedures as for compound **42a** gave compound **42g**, 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 4.9 Hz, 1H), 7.46 (d, *J* = 4.9 Hz, 1H), 7.25 – 7.19 (m, 4H), 4.16 (s, 2H), 3.65 – 3.58 (m, 2H), 3.26 – 3.18 (m, 2H), 3.04 – 2.97 (m, 4H), 2.52 – 2.45 (m, 2H), 2.33 – 2.18 (m, 4H), 2.14 – 2.06 (m, 2H), 1.96 – 1.85 (m, 4H).

5.1.39 1-Chloro-6-(3-(4-methoxypiperidin-1-yl)propyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (42h)

Following the similar procedures as for compound **42a** gave compound **42h**, 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 4.9 Hz, 1H), 7.40 (d, *J* = 4.9 Hz, 1H), 3.56 – 3.50 (m, 2H), 3.28 (s, 3H), 3.20 – 3.13 (m, 3H), 2.95 (t, *J* = 7.1 Hz, 2H), 2.75 – 2.65 (m, 2H), 2.38 – 2.31 (m, 2H), 2.13 – 2.00 (m, 4H), 1.90 – 1.75 (m, 4H), 1.59 – 1.48 (m, 2H).

5.1.40 1-Chloro-6-(3-morpholinopropyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (42i)

Following the similar procedures as for compound **42a** gave compound **42i**, 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 4.9 Hz, 1H), 7.43 (d, *J* = 4.9 Hz, 1H), 3.72 – 3.66 (m, 4H), 3.61 – 3.54 (m, 2H), 3.22 – 3.14 (m, 2H), 2.98 (t, *J* = 7.1 Hz, 2H), 2.48 – 2.36 (m, 6H), 2.12 – 2.02 (m, 2H), 1.87 – 1.77 (m, 2H).

5.1.41 6-(3-(4-Acetylpiperazin-1-yl)propyl)-1-chloro-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (42j)

Following the similar procedures as for compound **40a** gave compound **40j**, 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 4.9 Hz, 1H), 7.45 (d, *J* = 4.9 Hz, 1H), 3.65 – 3.57 (m, 4H), 3.49 – 3.44 (m, 2H), 3.25 – 3.17 (m, 2H), 3.00 (t, *J* = 7.0 Hz, 2H), 2.49 – 2.38 (m, 6H), 2.13 – 2.06 (m, 5H), 1.88 – 1.81 (m, 2H).

5.1.42 1-Chloro-6-(3-(4-methylpiperazin-1-yl)propyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (42k)

Following the similar procedures as for compound **42a** gave compound **42k**, 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 4.9 Hz, 1H), 7.43 (d, *J* = 4.9 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.23 – 3.15 (m, 2H), 2.98 (t, *J* = 7.1 Hz, 2H), 2.59 – 2.32 (m, 10H), 2.27 (s, 3H), 2.10 – 2.02 (m, 2H), 1.87 – 1.78 (m, 2H).

5.1.43 *N*-(1-(3-(1-((3,4-dichlorophenyl)amino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13a)

A solution of 3,4-dichloroaniline (34 mg, 0.21 mmol), **42a** (60 mg, 0.1 mmol), palladium(II) acetate (4 mg), sodium *tert*-butoxide (20 mg, 0.21 mmol) and (+/-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (56 mg, 0.09 mmol) in dioxane (5 mL) under argon atmosphere was heated to 90℃ and stirred for 3 h. After cooling to room temperature, the reaction

mixture was poured into 20 mL water and extracted with EtOAc (2×10 mL). The combined organic layer were washed with brine, dried over sodium sulfate and concentrated, the residue was purified by flash column chromatography on silica gel (DCM/MeOH 30:1) to yield the white solid (45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 5.0 Hz, 1H), 7.67 (d, *J* = 2.5 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.09 (d, *J* = 5.0 Hz, 1H), 6.47 (s, 1H), 3.79 – 3.73 (m, 1H), 3.62 – 3.55 (m, 2H), 3.23 (t, *J* = 6.3 Hz, 2H), 3.05 – 2.97 (m, 2H), 2.83 (s, 3H), 2.80 (s, 3H), 2.70 (t, *J* = 7.0 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 2.10 – 2.01 (m, 4H), 1.88 – 1.78 (m, 4H), 1.73 – 1.65 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.90, 151.64, 146.58, 145.60, 140.77, 132.53 , 130.33, 124.79, 120.63, 118.60, 117.38, 115.54, 55.55, 54.92, 53.01, 46.18, 45.82, 38.54, 29.65, 28.77, 28.58, 26.55, 22.95. HRMS (ESI): calcd for $C_{25}H_{34}Cl_2N_5O_3S$ $[M+H]^+$: 554.1754; found 554.1765. Retention time 2.59 min, > 99% pure.

5.1.44 *N*-(1-(3-(1-((3,4-dichlorobenzyl)amino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13b)

Following the similar procedures as for compound **13a** gave compound **13b**, white solid, 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 5.1 Hz, 1H), 7.43 (d, *J* = 1.8 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.21 – 7.15 (m, 1H), 6.84 (d, *J* = 5.1 Hz, 1H), 4.79 (t, *J* = 5.6 Hz, 1H), 4.65 – 4.59 (m, 2H), 3.78 – 3.68 (m, 1H), 3.62 – 3.53 (m, 2H), 3.21 (t, *J* = 6.3 Hz, 2H), 3.05 – 2.95 (m, 2H), 2.82 (s, 3H), 2.78 (s, 3H), 2.58 (t, *J* = 6.9 Hz, 2H), 2.43 – 2.33 (m, 2H), 2.08 – 1.98 (m, 4H), 1.87 – 1.76 (m, 4H), 1.72 – 1.61 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.41, 154.57, 146.52, 144.37, 140.39, 132.47, 130.98, 130.44, 129.56, 127.05, 114.53, 112.28, 55.59, 54.97, 53.01, 46.27, 45.72, 44.85, 38.50, 29.69, 28.71, 28.56, 26.62, 22.37. HRMS (ESI): calcd for $C_{26}H_{36}Cl_2N_5O_3S$ $[M+H]^+$: 568.1910; found 568.1898. Retention time 2.35 min, > 97% pure.

5.1.45 *N*-(1-(3-(1-((3,4-dichlorophenethyl)amino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13c)

Following the similar procedures as for compound **13a** gave compound **13c**, white solid, 45%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 5.1 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.24 (s, 1H), 7.03 – 6.98 (m, 1H), 6.82 (d, *J* = 5.1 Hz, 1H), 4.44 (t, *J* = 5.6 Hz, 1H), 3.79 – 3.64 (m, 3H), 3.55 (t, *J* = 7.3 Hz, 2H), 3.19 (t, *J* = 6.2 Hz, 2H), 3.04 – 2.95 (m, 2H), 2.89 (t, *J* = 6.6 Hz, 2H), 2.83 (s, 3H), 2.79 (s, 3H), 2.45 (t, *J* = 6.8 Hz, 2H), 2.39 (t, *J* = 7.3 Hz, 2H), 2.03 (t, *J* = 11.2 Hz, 2H), 1.98 – 1.88 (m, 2H), 1.87 – 1.74 (m, 4H), 1.71 – 1.64 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.51, 154.75, 146.59, 144.20, 140.17, 132.30, 130.88, 130.39, 130.28, 128.41, 114.58, 111.75, 55.59, 54.97, 53.01, 46.32, 45.71, 42.70, 38.51, 34.62, 29.68, 28.59, 28.56, 26.61, 22.27. HRMS (ESI): calcd for $C_{27}H_{37}Cl_2N_5O_3S$ $[M+H]^+$: 582.2067; found 582.2052. Retention time 2.42 min, > 98% pure.

5.1.46 *N*-(1-(3-(1-(cyclohexylamino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13d)

Following the similar procedures as for compound **13a** gave compound **13d**, white solid, 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 5.1 Hz, 1H), 6.73 (d, *J* = 5.1 Hz, 1H), 4.25 (d, *J* = 7.6 Hz, 1H), 3.99 – 3.89 (m, 1H), 3.79 – 3.69 (m, 1H), 3.58 – 3.51 (m, 2H), 3.19 (t, *J* = 6.3 Hz, 2H), 3.03 – 2.96 (m, 2H), 2.82 (s, 3H), 2.79 (s, 3H), 2.52 (t, *J* = 6.9 Hz, 2H), 2.42 – 2.36 (m, 2H), 2.09 – 2.02 (m, 3H), 2.01 – 1.96 (m, 2H), 1.90 – 1.62 (m, 10H), 1.49 – 1.37 (m, 2H), 1.23 – 1.09 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.74, 154.75, 146.54, 143.99, 114.11, 110.90, 55.62, 54.97, 53.02, 49.76, 46.30, 45.66, 38.50, 33.68, 29.67, 28.66, 28.56, 26.62, 25.95, 25.06, 22.39. HRMS (ESI): calcd for $C_{25}H_{42}N_5O_3S$ $[M+H]^+$: 492.3003; found 492.3002. Retention time 2.08 min, > 94% pure.

5.1.47 *N*-(1-(3-(1-(cyclopropylamino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13e)

Following the similar procedures as for compound **13a** gave compound **13e**, white solid, 41%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 5.2 Hz, 1H), 6.85 (d, *J* = 5.1 Hz, 1H), 4.75 (s, 1H), 3.80 – 3.70 (m, 1H), 3.61 – 3.52 (m, 2H), 3.20 (t, *J* = 6.3 Hz, 2H), 3.06 – 2.95 (m, 2H), 2.83 (s, 3H), 2.80 (s, 3H), 2.52 (t, *J* = 6.9 Hz, 2H), 2.44 – 2.36 (m, 2H), 2.06 – 1.94 (m, 4H), 1.85 – 1.76 (m, 4H), 1.73 – 1.69 (m, 2H), 0.86 – 0.81 (m, 2H), 0.52 – 0.46 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.38, 155.75, 146.46, 143.55, 114.35, 111.73, 55.22, 54.22, 52.62, 46.02, 45.24, 38.25, 28.89, 28.32, 28.27, 25.95, 24.48, 22.11, 7.14. HRMS (ESI): calcd for $C_{22}H_{36}N_5O_3S$ $[M+H]^+$: 450.2533; found 450.2542. Retention time 1.75 min, > 99% pure.

5.1.48 *N*-methyl-*N*-(1-(3-(5-oxo-1-(pyridin-2-ylamino)-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)methanesulfonamide (13f)

Following the similar procedures as for compound **13a** gave compound **13f**, white solid, 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.0 Hz, 1H), 8.22 – 8.15 (m, 2H), 7.67 – 7.61 (m, 1H), 7.34 (s, 1H), 7.10 (d, *J* = 5.0 Hz, 1H), 6.90 – 6.85 (m, 1H), 3.73 (tt, *J* = 11.9, 4.2 Hz, 1H), 3.61 – 3.54 (m, 2H), 3.22 (t, *J* = 6.4 Hz, 2H), 3.03 – 2.96 (m, 2H), 2.82 (s, 3H), 2.80 – 2.74 (m, 5H), 2.43 – 2.36 (m, 2H), 2.11 – 1.99 (m, 5H), 1.88 – 1.78 (m, 4H), 1.72 – 1.65 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.46, 153.38, 150.51, 147.25, 145.81, 144.94, 137.49, 117.29, 116.69, 115.01, 111.66, 55.06, 54.45, 52.52, 45.78, 45.36, 38.01, 29.17, 28.35, 28.07, 26.09, 22.55. HRMS (ESI): calcd for $C_{24}H_{35}N_6O_3S$ $[M+H]^+$: 487.2486; found 487.2493. Retention time 1.92 min, > 99% pure.

5.1.49 *N*-(1-(3-(1-((3,4-dichlorophenyl)(methyl)amino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13g)

To a solution of **13a** (105 mg, 0.2 mmol) in anhydrous DMF (5 mL) was added NaH (16 mg, 0.4 mmol, 60% in paraffin liquid) and stirred for 0.5 h, then the mixture was added iodomethane (12 μL, 0.2 mmol), and the resulting mixture was stirred at room temperature. After 1 h, the reaction was quenched and excess sodium hydride was destroyed by careful addition of water. The aqueous phase was extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, the resulting residue was purified by flash column chromatography on silica gel (DCM/MeOH 30:1) to yield the white solid (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 4.9 Hz, 1H), 7.41 (d, *J* = 4.9 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 2.8 Hz, 1H), 6.47 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.73 (tt, *J* = 11.9, 4.2 Hz, 1H), 3.60 – 3.54 (m, 2H), 3.31 (s, 3H), 3.20 (t, *J* = 6.4 Hz, 2H), 3.02 – 2.96 (m, 2H), 2.82 (s, 3H), 2.78 (s, 3H), 2.64 (t, *J* = 7.1 Hz, 2H), 2.43 – 2.36 (m, 2H), 2.08 – 1.95 (m, 4H), 1.86 – 1.75 (m, 4H), 1.71 – 1.64 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.10, 156.77, 148.78, 148.21, 146.88, 132.55, 130.28, 127.02, 122.58, 120.10, 117.57, 115.68, 55.17, 54.58, 52.67, 46.07, 45.57, 39.33, 38.21, 29.29, 28.34, 28.24, 26.14, 23.68. HRMS (ESI): calcd for $C_{26}H_{36}Cl_2N_5O_3S$ $[M+H]^+$: 568.1910; found 568.1917. Retention time 2.85 min, > 96% pure.

5.1.50 *N*-(1-(3-(1-(3,4-dichlorophenyl)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13h)

Following the similar procedures as for compound **13a** gave compound **13h**, white solid, 39%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.9 Hz, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.56 – 7.52 (m, 2H), 7.30 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.75 (tt, *J* = 11.7, 4.0 Hz, 1H), 3.65 – 3.58 (m, 2H), 3.30 (t, *J* = 6.4 Hz, 2H), 3.05 – 2.97 (m, 2H), 2.84 (s, 3H), 2.81 – 2.76 (m, 5H), 2.46 – 2.39 (m, 2H), 2.11 – 2.00 (m, 4H), 1.89 – 1.76 (m, 4H), 1.73 – 1.67 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.56, 156.05, 148.39, 145.61, 139.69, 132.76, 132.64, 131.06, 130.34, 128.92, 128.30, 121.83, 55.54, 54.92, 53.03, 46.17, 45.91, 38.51, 30.05, 29.66, 28.58, 26.56, 25.70. HRMS (ESI): calcd for $C_{25}H_{33}Cl_2N_4O_3S$ $[M+H]^+$: 539.1645; found 539.1647. Retention time 2.61 min, > 96% pure.

5.1.51 3,4-Dichloro-*N*-(6-(3-(4-(*N*-methylmethylsulfonamido)piperidin-1-yl)propyl)-5-oxo-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-1-yl)benzamide (13i)

Following the similar procedures as for compound **13a** gave compound **13i**, white solid, 40%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 4.6 Hz, 1H), 8.15 (d, *J* = 2.0 Hz, 1H), 7.86 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 5.0 Hz, 1H), 3.79 – 3.69 (m, 1H), 3.65 – 3.57 (m, 2H), 3.31 (t, *J* = 6.3 Hz, 2H), 3.05 – 2.97 (m, 2H), 2.83 (s, 3H), 2.79 (s, 3H), 2.66 – 2.60 (m, 2H), 2.45 – 2.36 (m, 2H), 2.28 – 2.19 (m, 2H), 2.09 – 2.00 (m, 3H), 1.89 – 1.75 (m, 4H), 1.72 – 1.65 (m, 2H). HRMS (ESI): calcd for $C_{26}H_{34}Cl_2N_5O_4S$ $[M+H]^+$: 582.1703; found 582.1710. Retention time 2.62 min, > 95% pure.

5.1.52 *N*-(1-(3-(1-(3,4-dichlorophenoxy)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13j)

Following the similar procedures as for compound **13a** gave compound **13j**, white solid, 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 5.0 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.27 (d, *J* = 5.0 Hz, 1H), 7.23 (d, *J* = 2.7 Hz, 1H), 6.97 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.79 – 3.69 (m, 1H), 3.64 – 3.57 (m, 2H), 3.26 (t, *J* = 6.4 Hz, 2H), 3.05 – 2.98 (m, 2H), 2.94 (t, *J* = 7.1 Hz, 2H), 2.83 (s, 3H), 2.79 (s, 3H), 2.46 – 2.39 (m, 2H), 2.14 – 2.02 (m, 4H), 1.89 – 1.77 (m, 4H), 1.73 – 1.66 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.74, 159.34, 152.66, 146.98, 145.47, 132.54, 130.33, 127.75, 122.71, 120.21, 119.64, 117.88, 55.06, 54.44, 52.53, 45.95, 45.46, 38.03, 29.16, 28.37, 28.07, 26.06, 20.96. HRMS (ESI): calcd for $C_{25}H_{33}Cl_2N_4O_4S$ $[M+H]^+$: 555.1594; found 555.1590. Retention time 3.06 min, > 98% pure.

5.1.53 *N*-(1-(3-(1-((4-(tert-butyl)phenyl)amino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13k)

Following the similar procedures as for compound **13a** gave compound **13k**, white solid, 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 5.0 Hz, 1H), 7.35 – 7.29 (m, 4H), 7.00 (d, *J* = 5.0 Hz, 1H), 6.31 (s, 1H), 3.79 – 3.70 (m, 1H), 3.62 – 3.55 (m, 2H), 3.24 (t, *J* = 6.3 Hz, 2H), 3.05 – 2.97 (m, 2H), 2.83 (s, 3H), 2.80 (s, 3H), 2.70 (t, *J* = 6.9 Hz, 2H), 2.44 – 2.37 (m, 2H), 2.10 – 1.98 (m, 4H), 1.88 – 1.78 (m, 4H), 1.73 – 1.64 (m, 2H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.76, 152.29, 146.13, 144.85, 144.69, 137.90, 125.34, 119.02, 116.31, 113.87, 55.08, 54.46, 52.52, 45.80, 45.28, 38.02, 33.75, 30.94, 29.16, 28.27, 28.07, 26.09, 22.50. HRMS (ESI): calcd for $C_{29}H_{44}N_5O_3S$ $[M+H]^+$: 542.3159; found 542.3151. Retention time 2.48 min, > 95% pure.

5.1.54 *N*-(1-(3-(1-((4-methoxyphenyl)amino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13l)

Following the similar procedures as for compound **13a** gave compound **13l**, white solid, 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 5.1 Hz, 1H), 7.32 – 7.26 (m, 2H), 6.95 (d, *J* = 5.1 Hz, 1H), 6.88 – 6.83 (m, 2H), 6.28 (s, 1H), 3.78 (s, 3H), 3.77 – 3.68 (m, 1H), 3.59 – 3.54 (m, 2H), 3.22 (t, *J* = 6.3 Hz, 2H), 3.03 – 2.96 (m, 2H), 2.82 (s, 3H), 2.78 (s, 3H), 2.67 (t, *J* = 7.0 Hz, 2H), 2.43 – 2.36 (m, 2H), 2.08 – 1.98 (m, 4H), 1.87 – 1.75 (m, 4H), 1.71 – 1.65 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.80, 155.14, 152.91, 146.08, 144.62, 133.67, 122.10, 115.78, 113.83, 113.45, 55.08, 55.06, 54.46, 52.51, 45.82, 45.27, 38.01, 29.16, 28.23, 28.07, 26.09, 22.43. HRMS (ESI): calcd for $C_{26}H_{38}N_5O_4S$ $[M+H]^+$:516.2639; found 516.2642. Retention time 2.01 min, > 99% pure

5.1.55 *N*-(1-(3-(1-((3-fluorophenyl)amino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13m)

Following the similar procedures as for compound **13a** gave compound **13m**, white solid, 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 5.0 Hz, 1H), 7.38 (dt, *J* = 11.5, 2.3 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.08 – 7.02 (m, 2H), 6.70 – 6.64 (m, 1H), 6.53 (s, 1H), 3.73 (tt, *J* = 11.9, 4.2 Hz, 1H), 3.61 – 3.54 (m, 2H), 3.23 (t, *J* = 6.4 Hz, 2H), 3.04 – 2.96 (m, 2H), 2.82 (s, 3H), 2.78 (s, 3H), 2.70 (t, *J* = 7.0 Hz, 2H), 2.43 – 2.36 (m, 2H), 2.08 – 1.98 (m, 4H), 1.86 – 1.78 (m, 4H), 1.72 – 1.64 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.51, 162.82 (d, *J* = 243.5 Hz), 151.43, 146.09, 145.01, 142.48 (d, *J* = 11.0 Hz), 129.43 (d, *J* = 9.7 Hz), 117.04, 114.84, 113.86 (d, *J* = 2.3 Hz), 108.05 (d, *J* = 21.5 Hz), 105.66 (d, *J* = 26.1 Hz), 55.06, 54.46, 52.51, 45.72, 45.32, 38.02, 29.15, 28.28, 28.07, 26.06, 22.48. HRMS (ESI): calcd for $C_{25}H_{35}FN_5O_3S$ $[M+H]^+$: 504.2439; found 504.2442. Retention time 2.06 min, > 98% pure.

5.1.56 *N*-methyl-*N*-(1-(3-(5-oxo-1-((3-(trifluoromethyl)phenyl)amino)-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)methanesulfonamide (13n)

Following the similar procedures as for compound **13a** gave compound **13n**, white solid, 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 5.0 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.09 (d, *J* = 5.0 Hz, 1H), 6.59 (s, 1H), 3.74 (tt, *J* = 11.9, 4.2 Hz, 1H), 3.61 – 3.55 (m, 2H), 3.24 (t, *J* = 6.3 Hz, 2H), 3.04 – 2.96 (m, 2H), 2.83 (s, 3H), 2.79 (s, 3H), 2.72 (t, *J* = 7.0 Hz, 2H), 2.43 – 2.37 (m, 2H), 2.11 – 1.99 (m, 4H), 1.87 – 1.75 (m, 4H), 1.72 – 1.65 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.45, 151.32, 146.12, 145.11, 141.25, 130.77 (q, *J* = 32.2 Hz), 123.62 (q, *J* = 272.4 Hz), 121.67, 118.09 – 117.75 (m, 1C), 117.02, 115.20 – 115.01 (m, 2C), 55.06, 54.45, 52.51, 45.71, 45.33, 38.02, 29.15, 28.26, 28.07, 26.06, 22.47. HRMS (ESI): calcd for $C_{26}H_{35}F_3N_5O_3S$ $[M+H]^+$: 554.2407; found 554.2411. Retention time 2.42 min, > 99% pure.

5.1.57 *N*-(1-(3-(1-((4-chlorophenyl)amino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13o)

Following the similar procedures as for compound **13a** gave compound **13o**, white solid, 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 5.0 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.25 – 7.21 (m, 2H), 7.03 (d, *J* = 5.0 Hz, 1H), 6.48 (s, 1H), 3.72 (tt, *J* = 11.9, 4.2 Hz, 1H), 3.61 – 3.53 (m, 2H), 3.22 (t, *J* = 6.4 Hz, 2H), 3.02 – 2.95 (m, 2H), 2.82 (s, 3H), 2.78 (s, 3H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.41 – 2.35 (m, 2H), 2.07 – 1.98 (m, 4H), 1.86 – 1.77 (m, 4H), 1.71 – 1.64 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.58, 151.71, 146.03, 144.91, 139.24, 128.39, 126.47, 120.25, 116.64, 114.49, 55.05, 54.40, 52.50, 45.74, 45.29, 38.03, 29.10, 28.26, 28.08, 26.03, 22.45. HRMS (ESI): calcd for $C_{25}H_{35}ClN_5O_3S$ $[M+H]^+$: 520.2144; found 520.2141. Retention time 2.19 min, > 99% pure.

5.1.58 *N*-(1-(3-(1-((4-chloro-3-fluorophenyl)amino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13p)

Following the similar procedures as for compound **13a** gave compound **13p**, white solid, 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 5.0 Hz, 1H), 7.58 (dd, *J* = 6.5, 2.7 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.08 – 7.03 (m, 2H), 6.43 (s, 1H), 3.73 (tt, *J* = 11.9, 4.2 Hz, 1H), 3.61 – 3.54 (m, 2H), 3.23 (t, *J* = 6.4 Hz, 2H), 3.03 – 2.96 (m, 2H), 2.83 (s, 3H), 2.79 (s, 3H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.43 – 2.37 (m, 2H), 2.08 – 1.99 (m, 4H), 1.86 – 1.81 (m, 4H), 1.72 – 1.65 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.50, 153.13 (d, *J* = 243.7 Hz), 151.59, 146.00, 144.98, 137.29 (d, *J* = 2.8 Hz), 121.11, 120.31 (d, *J* = 18.5 Hz), 118.87 (d, *J* = 6.5 Hz), 116.39, 115.97 (d, *J* = 21.9 Hz), 114.58, 55.06, 54.46, 52.51, 45.71, 45.32, 38.02, 29.16, 28.25, 28.08, 26.06, 22.37. HRMS (ESI): calcd for $C_{25}H_{34}ClFN_5O_3S$ $[M+H]^+$: 538.2049; found 538.2051. Retention time 2.29 min, > 98% pure.

5.1.59 *N*-(1-(3-(1-((3,5-dichlorophenyl)amino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylmethanesulfonamide (13q)

Following the similar procedures as for compound **13a** gave compound **13q**, white solid, 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.0 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 2H), 7.11 (d, *J* = 5.0 Hz, 1H), 6.95 (t, *J* = 1.8 Hz, 1H), 6.55 (s, 1H), 3.74 (tt, *J* = 11.8, 4.2 Hz, 1H), 3.61 – 3.54 (m, 2H), 3.23 (t, *J* = 6.4 Hz, 2H), 3.03 – 2.96 (m, 2H), 2.83 (s, 3H), 2.79 (s, 3H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.43 – 2.36 (m, 2H), 2.08 – 1.99 (m, 4H), 1.87 – 1.78 (m, 4H), 1.72 – 1.64 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.32, 150.84, 146.16, 145.23, 142.78, 134.58, 121.07, 117.41, 116.39, 115.50, 55.05, 54.46, 52.51, 45.67, 45.36, 38.03, 29.16, 28.26, 28.08, 26.06, 22.47. HRMS (ESI): calcd for $C_{25}H_{34}Cl_2N_5O_3S$ $[M+H]^+$: 554.1754; found 554.1763. Retention time 2.74 min, > 95% pure.

5.1.60 *N*-(1-(3-(1-((3,4-dichlorophenyl)amino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)methanesulfonamide (14a)

Following the similar procedures as for compound **13a** gave compound **14a**, white solid, 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 5.0 Hz, 1H), 7.68 (d, *J* = 2.5 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.07 (d, *J* = 5.0 Hz, 1H), 6.57 (s, 1H), 3.61 – 3.55 (m, 2H), 3.41 – 3.29 (m, 1H), 3.23 (t, *J* = 6.4 Hz, 2H), 2.98 (s, 3H), 2.95 – 2.88 (m, 2H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.49 – 2.42 (m, 2H), 2.22 – 2.13 (m, 2H), 2.10 – 1.95 (m, 4H), 1.91 – 1.81 (m,2H), 1.70 – 1.58 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.75, 151.40, 146.23, 145.20, 140.50, 132.18, 130.00, 124.42, 120.31, 118.30, 117.20, 115.14, 55.21, 51.73, 50.39, 45.97, 45.44, 41.83, 32.79, 28.46, 25.93, 22.64. HRMS (ESI): calcd for $C_{24}H_{32}Cl_2N_5O_3S$ $[M+H]^+$: 540.1597; found 540.1603. Retention time 2.47min, > 99% pure.

5.1.61 *N*-(1-(3-(1-((3,4-dichlorophenyl)amino)-5-oxo-5,7,8,9-tetrahydro-6*H*-pyrido[4,3-*c*]azepin-6-yl)propyl)piperidin-4-yl)-*N*-methylethanesulfonamide (14b)

Following the similar procedures as for compound **13a** gave compound **14b**, white solid, 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 5.0 Hz, 1H), 7.67 (d, *J* = 2.5 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.07 (d, *J* = 5.0 Hz, 1H), 6.55 (s, 1H), 3.72 – 3.63 (m, 1H), 3.61 – 3.53 (m, 2H), 3.22 (t, *J* = 6.3 Hz, 2H), 3.03 – 2.92 (m, 4H), 2.79 (s, 3H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.43 – 2.36 (m, 2H), 2.09 – 1.99 (m, 4H), 1.90 – 1.77 (m, 4H), 1.74 – 1.64 (m, 2H), 1.33 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.63, 151.37, 146.22, 145.26, 140.50, 132.16, 129.99, 124.40, 120.33, 118.32, 117.11, 115.16, 55.23, 54.50, 52.74, 45.97, 45.88, 45.50, 29.59, 28.49, 28.47, 26.20, 22.59, 7.93. HRMS (ESI): calcd for $C_{26}H_{36}Cl_2N_5O_3S$ $[M+H]^+$: 568.1910; found 568.1924. Retention time 2.59 min, > 99% pure.

5.1.62 1-((3,4-Dichlorophenyl)amino)-6-(3-(piperidin-1-yl)propyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (14c)

Following the similar procedures as for compound **13a** gave compound **14c**, white solid, 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 5.0 Hz, 1H), 7.67 (d, *J* = 2.5 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.28 – 7.24 (m, 1H), 7.07 (d, *J* = 5.0 Hz, 1H), 6.55 (s, 1H), 3.61 – 3.54 (m, 2H), 3.23 (t, *J* = 6.4 Hz, 2H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.48 – 2.35 (m, 6H), 2.10 – 1.99 (m, 2H), 1.91 – 1.81 (m, 2H), 1.64 – 1.56 (m, 4H), 1.48 – 1.40 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.43, 151.15, 146.00, 145.14, 140.33, 131.99, 129.79, 124.18, 120.11, 118.09, 116.99, 115.01, 55.97, 54.13, 45.67, 45.37, 28.27, 25.75, 25.29, 23.77, 22.45. HRMS (ESI): calcd for $C_{23}H_{29}Cl_2N_4O$ $[M+H]^+$: 447.1713; found 447.1725. Retention time 2.50 min, > 95% pure.

5.1.63 1-((3,4-dichlorophenyl)amino)-6-(3-(4-phenylpiperidin-1-yl)propyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (14d)

Following the similar procedures as for compound **13a** gave compound **14d**, white solid, 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 5.0 Hz, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.24 – 7.17 (m, 3H), 7.08 (d, *J* = 5.0 Hz, 1H), 6.63 (s, 1H), 3.65 – 3.56 (m, 2H), 3.24 (t, *J* = 6.3 Hz, 2H), 3.10 – 3.01 (m, 2H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.55 – 2.39 (m, 3H), 2.11 – 1.99 (m, 4H), 1.94 – 1.74 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.64, 151.37, 146.19, 145.93, 145.32, 140.54, 132.15, 129.97, 128.12, 126.53, 125.86, 124.34, 120.33, 118.33, 117.17, 115.17, 55.86, 54.19, 45.88, 45.63, 42.33, 33.15, 28.48, 26.23, 22.60. HRMS (ESI): calcd for $C_{29}H_{33}Cl_2N_4O$ $[M+H]^+$: 523.2026; found 523.2033. Retention time 2.92 min, > 99% pure.

5.1.64 1-((3,4-Dichlorophenyl)amino)-6-(3-(spiro[indene-1,4'-piperidin]-1'-yl)propyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (14e)

Following the similar procedures as for compound **13a** gave compound **14e**, white solid, 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 5.0 Hz, 1H), 7.68 (d, *J* = 2.5 Hz, 1H), 7.38 – 7.27 (m, 4H), 7.26 – 7.17 (m, 2H), 7.09 (d, *J* = 5.0 Hz, 1H), 6.84 (d, *J* = 5.7 Hz, 1H), 6.75 (d, *J* = 5.7 Hz, 1H), 6.60 (s, 1H), 3.68 – 3.59 (m, 2H), 3.26 (t, *J* = 6.3 Hz, 2H), 3.07 – 2.97 (m, 2H), 2.70 (t, *J* = 7.0 Hz, 2H), 2.57 – 2.50 (m, 2H), 2.40 – 2.28 (m, 2H), 2.24 – 2.17 (m, 2H), 2.11 – 2.02 (m, 3H), 1.97 – 1.88 (m, 2H), 1.40 – 1.33 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.66, 151.88, 151.37, 146.22, 145.32, 142.59, 141.11, 140.53, 132.17, 129.99, 129.29, 126.55, 124.89, 124.37, 121.39, 121.03, 120.33, 118.32, 117.16, 115.19, 56.03, 52.15, 51.73, 45.90, 45.65, 33.57, 28.50, 26.27, 22.61. HRMS (ESI): calcd for $C_{31}H_{33}Cl_2N_4O$ $[M+H]^+$: 547.2026; found 547.2032. Retention time 3.02 min, > 99% pure.

5.1.65 6-(3-(3*H*-spiro[benzo[*c*]thiophene-1,4'-piperidin]-1'-yl)propyl)-1-((3,4-dichlorophenyl)amino)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (14f)

Following the similar procedures as for compound **13a** gave compound **14f**, white solid, 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 5.0 Hz, 1H), 7.67 (d, *J* = 2.5 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.28 – 7.20 (m, 6H), 7.09 (d, *J* = 5.0 Hz, 1H), 6.51 (s, 1H), 4.17 (s, 2H), 3.65 – 3.59 (m, 2H), 3.26 (t, *J* = 6.4 Hz, 2H), 3.04 – 2.98 (m, 2H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.54 – 2.46 (m, 2H), 2.33 – 2.19 (m, 4H), 2.11 – 2.03 (m, 2H), 1.96 – 1.89 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.59, 151.31, 147.70, 146.26, 145.35, 140.48, 139.88, 132.22, 130.01, 127.07, 126.71, 124.84, 124.45, 122.80, 120.31, 118.27, 117.11, 115.29, 63.22, 55.69, 51.85, 45.86, 45.61, 40.59, 34.92, 28.49, 26.09, 22.66. HRMS

(ESI): calcd for $C_{30}H_{33}Cl_2N_4OS$ $[M+H]^+$: 567.1747; found 567.1752. Retention time 3.03 min, > 99% pure.

5.1.66 1-((3,4-Dichlorophenyl)amino)-6-(3-(4-methoxypiperidin-1-yl)propyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (14g)

Following the similar procedures as for compound **13a** gave compound **14g**, white solid, 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 5.0 Hz, 1H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.27 – 7.23 (m, 1H), 7.06 (d, *J* = 5.0 Hz, 1H), 6.55 (s, 1H), 3.59 – 3.54 (m, 2H), 3.33 (s, 3H), 3.25 – 3.18 (m, 3H), 2.78 – 2.71 (m, 2H), 2.68 (t, *J* = 7.0 Hz, 2H), 2.41 – 2.34 (m, 2H), 2.16 – 2.08 (m, 2H), 2.07 – 1.98 (m, 3H), 1.94 – 1.86 (m, 2H), 1.86 – 1.79 (m, 2H), 1.62 – 1.52 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.64, 151.36, 146.18, 145.30, 140.53, 132.15, 129.97, 124.34, 120.32, 118.31, 117.17, 115.15, 75.96, 55.38, 55.23, 50.86, 45.89, 45.59, 30.52, 28.43, 26.22, 22.58. HRMS (ESI): calcd for $C_{24}H_{31}Cl_2N_4O_2$ $[M+H]^+$: 477.1819; found 477.1833. Retention time 2.48 min, > 97% pure.

5.1.67 1-((3,4-Dichlorophenyl)amino)-6-(3-morpholinopropyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (14h)

Following the similar procedures as for compound **13a** gave compound **14h**, white solid, 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 5.0 Hz, 1H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.27 – 7.22 (m, 1H), 7.08 (d, *J* = 5.0 Hz, 1H), 6.48 (s, 1H), 3.75 – 3.68 (m, 4H), 3.63 – 3.57 (m, 2H), 3.24 (t, *J* = 6.4 Hz, 2H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.49 – 2.38 (m, 6H), 2.09 – 2.01 (m, 2H), 1.90 – 1.84 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.43, 151.14, 146.07, 145.11, 140.28, 132.02, 129.82, 124.27, 120.12, 118.09, 116.92, 115.04, 66.45, 55.68, 53.22, 45.74, 45.34, 28.23, 25.37, 22.43. HRMS (ESI): calcd for $C_{22}H_{27}Cl_2N_4O_2$ $[M+H]^+$: 449.1506; found 449.1506. Retention time 2.40 min, > 95% pure.

5.1.68 6-(3-(4-Acetylpiperazin-1-yl)propyl)-1-((3,4-dichlorophenyl)amino)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (14i)

Following the similar procedures as for compound **13a** gave compound **14i**, white solid, 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.0 Hz, 1H), 7.69 (d, *J* = 2.5 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.30 – 7.26 (m, 1H), 7.12 (d, *J* = 5.0 Hz, 1H), 6.47 (s, 1H), 3.70 – 3.60 (m, 4H), 3.54 – 3.48 (m, 2H), 3.28 (t, *J* = 6.3 Hz, 2H), 2.74 (t, *J* = 7.0 Hz, 2H), 2.55 – 2.43 (m, 6H), 2.12 – 2.05 (m, 5H), 1.94 – 1.85 (m, 2H). HRMS (ESI): calcd for $C_{24}H_{30}Cl_2N_5O_2$ $[M+H]^+$: 490.1771; found 490.1774. Retention time 2.39 min, > 96% pure.

5.1.69 1-((3,4-Dichlorophenyl)amino)-6-(3-(4-methylpiperazin-1-yl)propyl)-6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one (14j)

Following the similar procedures as for compound **13a** gave compound **14j**, white solid, 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 5.0 Hz, 1H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.27 – 7.23 (m, 3H), 7.09 (d, *J* = 5.0 Hz, 1H), 6.41 (s, 1H), 3.62 – 3.56 (m, 2H), 3.24 (t, *J* = 6.4 Hz, 2H), 2.70 (t, *J* = 7.1 Hz, 2H), 2.59 – 2.39 (m, 10H), 2.29 (s, 3H), 2.09 – 2.03 (m, 2H), 1.88 – 1.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.36, 151.09, 146.08, 145.17, 140.26, 132.06, 129.84, 124.32, 120.11, 118.05, 116.90, 115.13, 55.22, 54.59, 52.67, 45.70, 45.49, 45.38, 28.24, 25.71, 22.47. HRMS (ESI): calcd for $C_{23}H_{30}Cl_2N_5O$ $[M+H]^+$: 462.1822; found 462.1835. Retention time 2.32 min, > 96% pure.

5.2 Pharmacology

5.2.1 CCR2 calcium flux

Chinese hamster ovarian (CHO)-K1 cells stably expressing Ga16 and CCR2 were seeded onto 96-well plates and incubated for 24 h. Cells were loaded with 2 μM Fluo-4 AM in Hanks balanced salt solution (HBSS) at 37˚C for 45 min. After removal of excess dye, 50 μL HBSS containing antagonists was added. After incubation at room temperature for 10 min, 25 μL HBSS containing CCL2 was dispensed into the wells using a FlexStation III microplate reader (Molecular Devices), and intracellular calcium change was recorded at an excitation wavelength of 485 nm and an emission wavelength of 525 nm. IC_{50} values were analyzed using Graphpad Prism.

5.2.2 CCR5 calcium flux

Chinese hamster ovarian (CHO)-K1 cells stably expressing Ga16 and CCR5 were seeded onto 96-well plates and incubated for 24 h. Cells were loaded with 2 μM Fluo-4 AM in Hanks balanced salt solution (HBSS) at 37˚C for 45 min. After removal of excess dye, 50 μL HBSS containing antagonists was added. After incubation at room temperature for 10 min, 25 μL HBSS containing Rantes was dispensed into the wells using a FlexStation III microplate reader (Molecular Devices), and intracellular calcium change was recorded at an excitation wavelength of 485 nm and an emission wavelength of 525 nm. IC_{50} values were analyzed using Graphpad Prism. Maraviroc was used as reference compound, IC_{50} = 5 nM.

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