

Article

Structure–Activity Relationship Study on Soticlestat Derivatives for the Discovery of CYP46A1 (CH24H) Inhibitors

Xinwei Hu ^{1,2,†}, Wenqian Huang ^{2,3,4,†}, Xiaotong Lin ², Hao Zhang ^{2,3,4}, Yishu Huang ^{2,3,4}, Jiang Wu ^{5,*} and Guilong Zhao ^{1,2,3,4,*} 

¹ Guangzhou University of Chinese Medicine, Guangzhou 510006, China; 19966405675@163.com

² Zhongshan Institute for Drug Discovery, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Zhongshan 528400, China; 18379981865@163.com (W.H.); linxiaotong@zidd.ac.cn (X.L.); 19003708@mail.ecust.edu.cn (H.Z.); huangyishu@simm.ac.cn (Y.H.)

³ Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

⁴ University of Chinese Academy of Sciences, Beijing 100049, China

⁵ College of Pharmacy, Shenzhen Technology University, Shenzhen 518118, China

* Correspondence: wujiang@sztu.edu.cn (J.W.); zhao_guilong@126.com (G.Z.)

† These authors contributed equally to this work.

Abstract

Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) are rare, severe developmental and epileptic encephalopathies with poor prognosis, and novel drugs are urgently needed to meet clinical needs. CYP46A1 (cholesterol 24-hydroxylase, CH24H) is mainly responsible for the metabolism of cholesterol to 24(S)-hydroxycholesterol in the brain and is implicated in many brain disorders through the mediation of excitatory amino acid transporter 2 (EAAT2) and N-methyl-D-aspartate (NMDA) receptors. Inhibition of CYP46A1 is supposed to provide a novel treatment for disorders associated with neural hyperexcitation, such as epilepsy and epileptic syndromes. Soticlestat, a potent CYP46A1 inhibitor being developed by Takeda, is indicated for LGS and DS but suffers from unsatisfactory *in vivo* potency in animal models and clinical trials. We designed three series of soticlestat derivatives to explore the structure–activity relationship (SAR) with the aim of finding more potent CYP46A1 inhibitors and understanding the SAR of CYP46A1 inhibitors represented by soticlestat. Eventually, three compounds with a benzenesulfonamide moiety (in subseries C-4) that serves as an isostere of OH in soticlestat were discovered with very potent CYP46A1 inhibitory activities comparable to soticlestat, and an interesting flat SAR profile was observed in some subseries. The findings in the present study provide insight into the SAR of CYP46A1 inhibitors and should be valuable for the future design of novel CYP46A1 inhibitors.

Keywords: CH24H; CYP46A1; soticlestat; structure-activity relationship; Dravet syndrome; Lennox-Gastaut syndrome



Academic Editor: M^a Ángeles Castro

Received: 13 January 2026

Revised: 23 January 2026

Accepted: 24 January 2026

Published: 28 January 2026

Copyright: © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

1. Introduction

Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) belong to rare, severe developmental and epileptic encephalopathies (DEEs), which are characterized by early-onset treatment-resistant seizures, cognitive and behavioral impairment, poor prognosis, and high mortality rates [1–3]. Advances have been made over the past few decades in the development of pharmacological and non-pharmacological therapies for DS and LGS, such as clobazam, fenfluramine, stiripentol, cannabidiol, the ketogenic diet, and emerging

therapies targeting DNA and RNA regulation; however, there are still urgent clinical needs for novel drugs due to low response rates and severe adverse effects associated with current therapies [4–6].

Cholesterol is an important structural and functional component in the brain. After de novo synthesis in the brain, cholesterol is metabolized to 24(S)-hydroxycholesterol, which then crosses the blood–brain barrier (BBB) to enter the circulation and is delivered to the liver for further degradation [7]. The main enzyme responsible for the metabolism of cholesterol is cholesterol 24-hydroxylase (CH24H), also known as cholesterol 24S-hydroxylase or CYP46A1. CYP46A1 is predominantly expressed in the brain and is a crucial enzyme in brain cholesterol homeostasis. It is implicated in many neurological functions by regulating the level of 24(S)-hydroxycholesterol in the brain and is thus emerging as a novel promising therapeutic target for the treatment of a lot of brain disorders, such as Alzheimer’s disease (AD), Parkinson’s disease (PD), and Huntington’s disease (HTD) [8–10]. Under certain pathological conditions, CYP46A1 is upregulated and disrupts the glutamate transporter excitatory amino acid transporter 2 (EAAT2) [11], thereby impairing glutamate uptake function; in addition, 24(S)-hydroxycholesterol is a positive allosteric modulator of N-methyl-D-aspartate (NMDA) receptors, an important class of excitatory receptors in the brain [12]. Increased levels of extracellular glutamate arising from EAAT2 disruption and NMDA receptor activation by 24(S)-hydroxycholesterol can cause glutamate-evoked neuronal excitotoxicity. Therefore, CYP46A1 inhibitors are supposed to suppress neuronal excitotoxicity present in CYP46A1 pathological conditions and provide a novel treatment for disorders associated with neural hyperexcitation, such as epilepsy and epileptic syndromes.

Takeda Pharmaceuticals Company has been developing soticlestat (TAK-935, OV-935), a potent CYP46A1 inhibitor, for the treatment of LGS and DS (Figure 1) [13,14]. However, it suffers from unsatisfactory in vivo potency in animals and clinical trials. In a preclinical study, soticlestat reduced seizures by only 42% and lowered brain 24(S)-hydroxycholesterol levels by only 55% at 30 mg/kg (po), a dose associated with near-maximal efficacy [15]. In major clinical trials, soticlestat, at doses of up to 600 mg/day, did not show significantly higher efficacy in reducing convulsive seizures in patients with LGS, although such significance was observed in patients with DS [14]. Encouraged by these aforementioned shortcomings, we initiated a program aiming to find more potent CYP46A1 inhibitors based on soticlestat as a chemical template. A total of three series with 85 derivatives were designed through the modification of the distal pyridine ring in soticlestat (Series A), modification of the linker connecting the bipyridine and piperidine ring in soticlestat (Series B), and replacement of the hydroxyl group in soticlestat using a bioisosterism strategy (Series C, further categorized into four subseries, C-1, C-2, C-3, and C-4). These compounds were evaluated for in vitro CYP46A1 inhibitory activity, and some CYP46A1 inhibitors with potent inhibitory activities (IC_{50}) comparable to that of soticlestat were discovered (Figure 1). These findings should be valuable for the future design of novel CYP46A1 inhibitors.

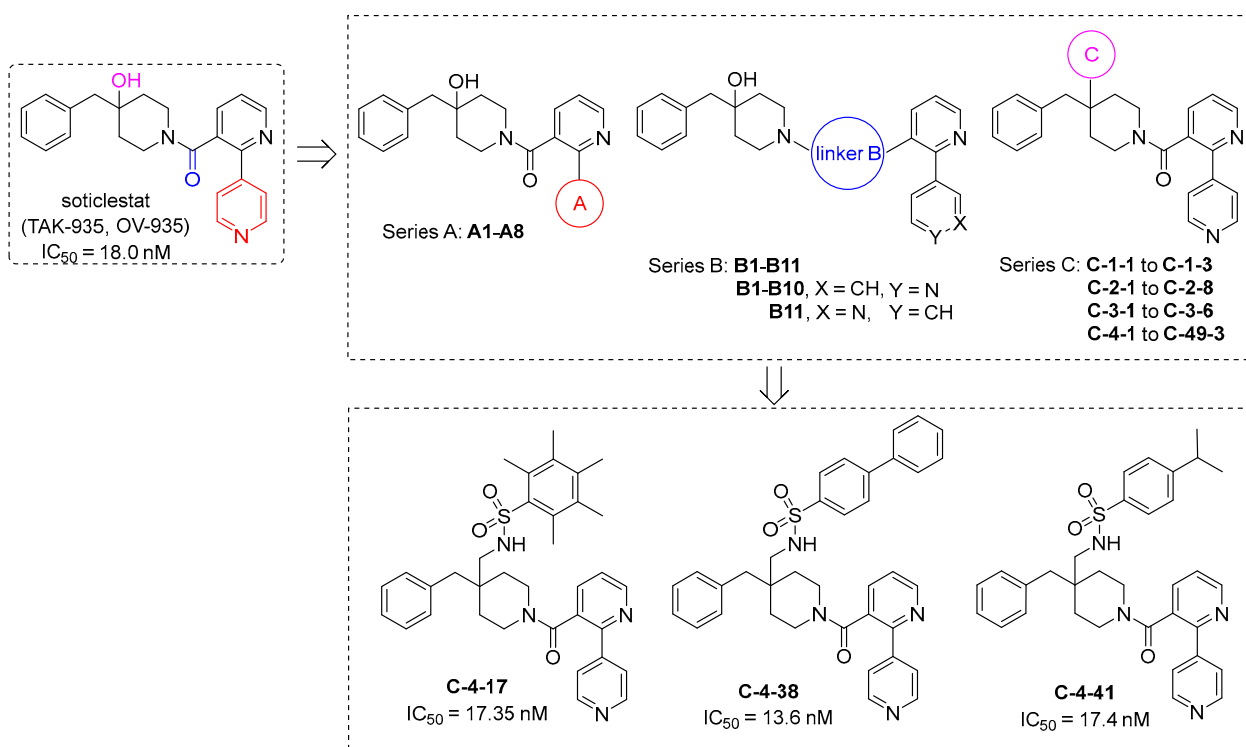
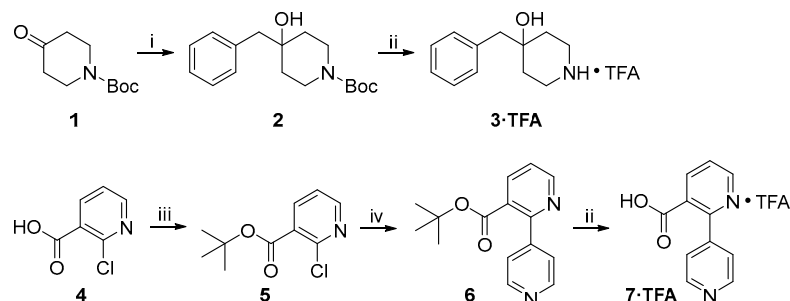


Figure 1. Chemical modifications based on soticlestat in the present study.

2. Results and Discussion

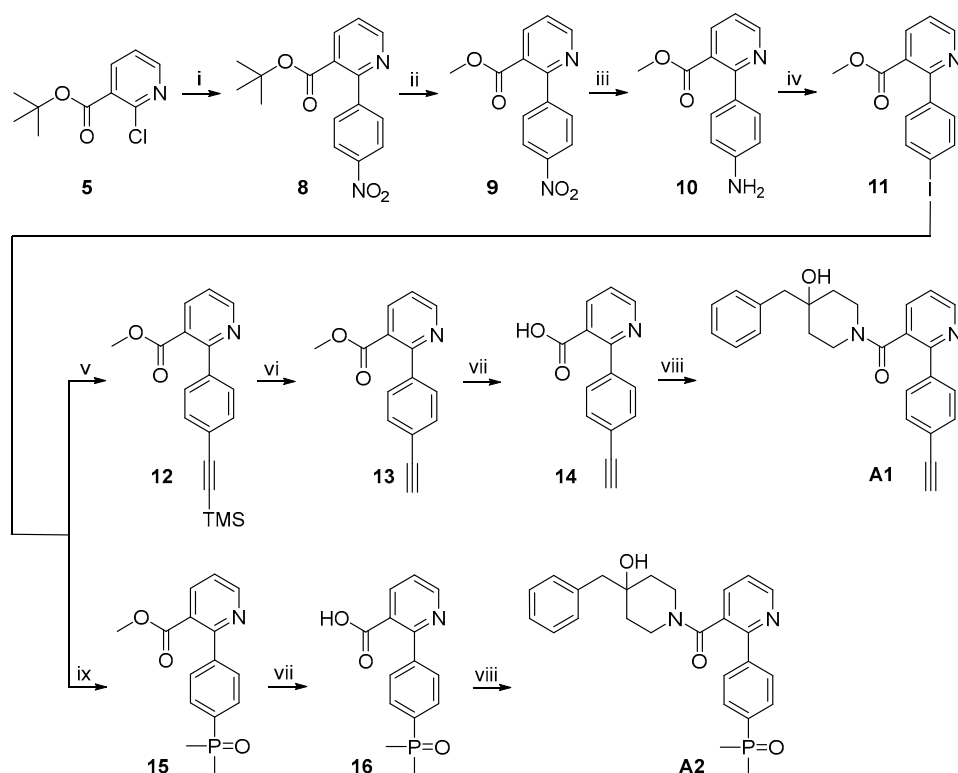
2.1. Chemistry

The synthetic routes to two key intermediates **3** and **7** (both as trifluoroacetic acid (TFA) salts) are shown in Scheme 1. Commercially available ketone **1** was treated with BnMgCl to give tertiary alcohol **2**, and the Boc protecting group in the latter was then cleaved by TFA to give **3** as a TFA salt. On the other hand, treatment of commercially available carboxylic acid **4** with $(\text{COCl})_2$ in the presence of a catalytic amount of N,N -dimethylformamide (DMF) afforded the corresponding carbonyl chloride, which was subsequently treated with $t\text{-BuOK}$ to give the corresponding *tert*-butyl ester. Suzuki coupling of **5** and pyridine-4-boronic acid in the presence of $\text{Pd}(\text{PPh}_3)_4$ as a catalyst and Na_2CO_3 as a base in refluxing DME (1,2-dimethoxyethane)/ H_2O produced bipyridine **6**. Cleavage of the *tert*-butyl ester moiety with TFA gave the corresponding carboxylic acid **7** as a TFA salt.



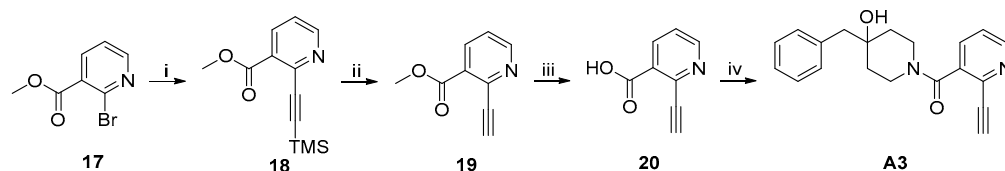
Scheme 1. Synthetic routes to intermediates **3·TFA** and **7·TFA**. Reagents and conditions: (i) BnMgCl , dried THF, 0°C –rt, N_2 , 48%; (ii) TFA, CH_2Cl_2 , 0°C –rt; (iii) (a) $(\text{COCl})_2$, DMF (cat.), dried CH_2Cl_2 , 0°C –rt, N_2 ; (b) $t\text{-BuOK}$, dried THF, -10°C –rt, N_2 , 60% (over two steps); (iv) pyridine-4-boronic acid, $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , DME/ H_2O , reflux, N_2 , 50%.

The synthetic routes to target compounds **A1** and **A2** are shown in Scheme 2. Suzuki coupling of **5** and 4-nitrophenylboronic acid under the same conditions used above produced **8**. The *tert*-butyl ester functionality in **8** was converted to the corresponding methyl ester functionality in **9** by cleavage with TFA followed by acid-catalyzed esterification of the carboxylic acid intermediate in refluxing MeOH. Pd-catalyzed hydrogenolysis of NO₂ in **9** at atmospheric pressure and room temperature smoothly afforded aniline **10**, which was subjected to a Sandmeyer reaction to give iodobenzene **11**. CuI/PdCl₂(PPh₃)₂-mediated Sonogashira coupling of **11** and trimethylsilylacetylene furnished **12**, which was treated with tetra-*n*-butylammonium fluoride (TBAF) to remove the trimethylsilyl (TMS) protecting group to give **13**. NaOH-mediated saponification of methyl ester **13** followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI)/1-hydroxybenzotriazole (HOBT)-mediated amide formation with 3-**TFA** produced target compound **A1** [16,17]. Pd-mediated cross-coupling of **11** with dimethylphosphine oxide in the presence of Pd₂(dba)₃/Xantphos afforded **15** [18], which was converted to target compound **A1** by a procedure identical to that used for the synthesis of **A1** from **13**.



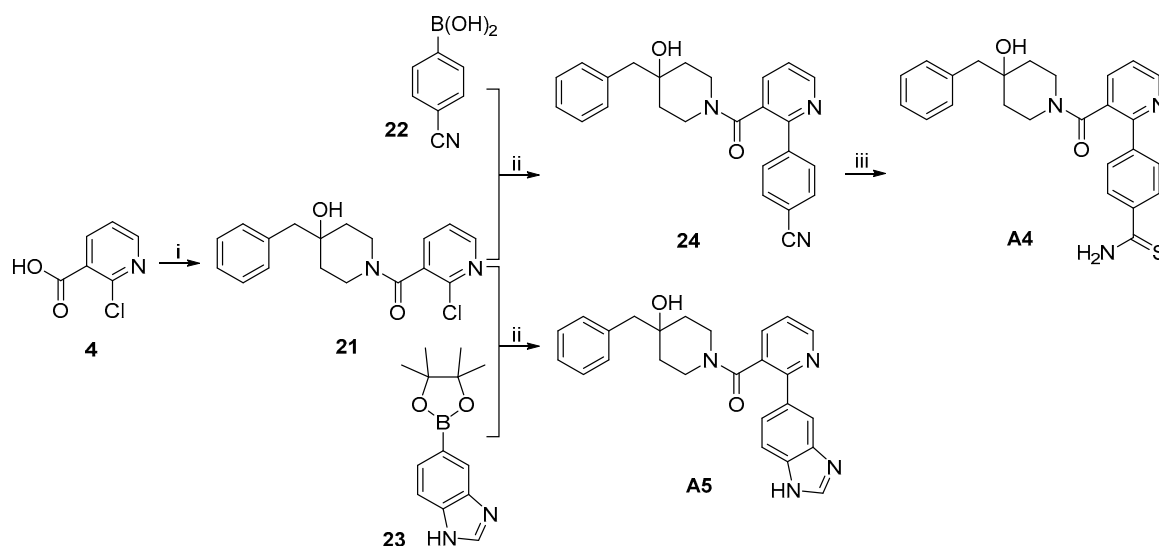
Scheme 2. Synthetic routes to target compounds **A1** and **A2**. Reagents and conditions: (i) 4-nitrophenylboronic acid, Pd(PPh₃)₄, Na₂CO₃, DME/H₂O, reflux, N₂, 86%; (ii) (a) TFA, CH₂Cl₂, 0 °C–rt; (b) SOCl₂/MeOH, reflux, N₂, 76% (over two steps); (iii) H₂, 10%Pd/C, MeOH, rt, 75%; (iv) (a) NaNO₂, HCl/H₂O, 0 °C; (b) KI, 0 °C–rt, 44%; (v) trimethylsilylacetylene, CuI/PdCl₂(PPh₃)₂, Et₃N, dried THF, rt, N₂, 73%; (vi) TBAF, dried THF, 0 °C–rt, N₂, 65%; (vii) aqNaOH, MeOH, rt; (viii) 3-**TFA**, EDCI/HOBT, DIPEA, dried THF, 0 °C–rt, N₂, 44% (overall for **13** to **A1**), 18% (overall for **15** to **A2**); (ix) HP(=O)Me₂, Xantphos, Pd₂(dba)₃, Et₃N, dioxane, rt, N₂, 59%.

The synthetic route to **A3** is shown in Scheme 3. Sonogashira coupling of commercially available **17** and trimethylsilylacetylene under the same conditions described above gave **18**, which was converted to target compound **A3** following the same procedure used for the synthesis of **A1** from **12**.



Scheme 3. Synthetic route to target compound **A3**. Reagents and conditions: (i) trimethylsilylacetylene, CuI/PdCl₂(PPh₃)₂, Et₃N, dried THF, rt, N₂, 74%; (ii) TBAF, dried THF, 0 °C–rt, N₂, 66%; (iii) aqNaOH, MeOH, rt; (iv) **3-TFA**, EDCI/HOBT, DIPEA, dried THF, 0 °C–rt, N₂, 38% (overall for **19** to **A3**).

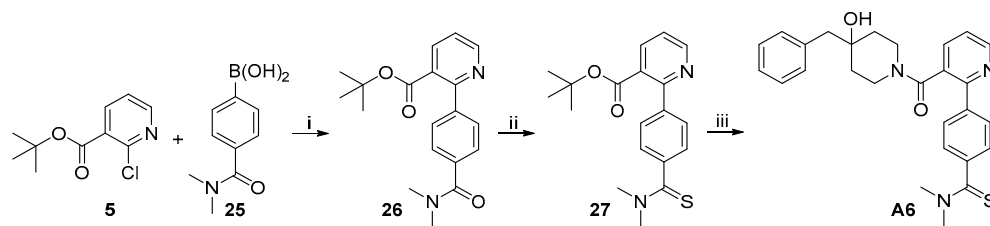
The synthetic routes to target compounds **A4** and **A5** are shown in Scheme 4. Treatment of **4** with (COCl)₂ in the presence of a catalytic amount of DMF afforded the corresponding carbonyl chloride, which was reacted with **3-TFA** in the presence of Et₃N to give amide **21**. Suzuki coupling of **21** and boronic acid **22** under the same conditions used above produced **24**, which was heated with (NH₄)₂S in the presence of Et₃N in pyridine at 50 °C to give target compound **A4** [19]. Suzuki coupling of **21** and boronic acid **23** under the same conditions above produced target compound **A5**.



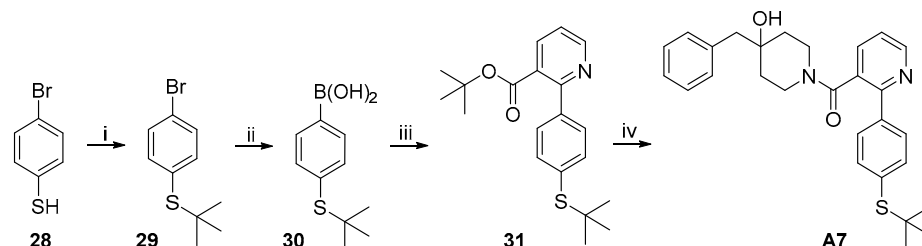
Scheme 4. Synthetic routes to target compounds **A4** and **A5**. Reagents and conditions: (i) (a) (COCl)₂, DMF (cat.), dried CH₂Cl₂, 0 °C–rt, N₂; (b) **3-TFA**, Et₃N, dried THF, 0 °C–rt, N₂, 31% (over two steps); (ii) Pd(PPh₃)₄, Na₂CO₃, DME/H₂O, reflux, N₂, 61% for **24**, 10% for **A5**; (iii) (NH₄)₂S, Et₃N, pyridine, 50 °C, N₂, 87%.

The synthetic route to target compound **A6** is depicted in Scheme 5. Suzuki coupling of **5** and boronic acid **25** under the same conditions used above produced **26**. The amide moiety in **26** was transformed into the corresponding thioamide with Lawesson reagent in refluxing toluene to give **27** [20], which was further converted to target compound **A6** by the same procedure used for the synthesis of **A1** from **14**.

The synthetic route to target compound **A7** is shown in Scheme 6. Treatment of commercially available thiophenol **28** with *t*-BuCl in the presence of anhydrous AlCl₃ produced thioether **29** [21]. Lithiation of phenyl bromide **29** by treatment with *n*-BuLi at −78 °C followed by trapping of the phenyl carbanion with B(OMe)₃ afforded phenyl boronic acid **30**. Suzuki coupling of **30** and **5** under the same conditions described above gave **31**, which was converted to target compound **A7** by the same procedure used for the synthesis of **A6** from **27**.

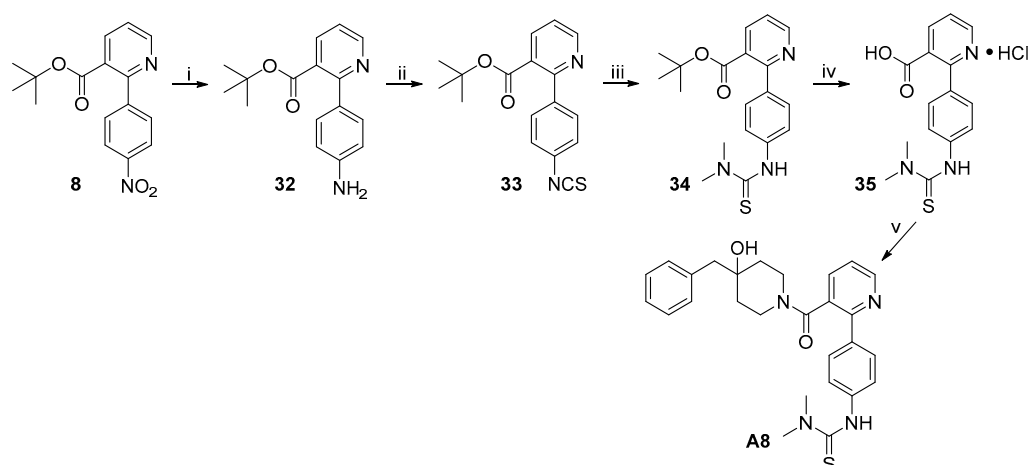


Scheme 5. Synthetic route to target compound **A6**. Reagents and conditions: (i) $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , $\text{DME}/\text{H}_2\text{O}$, reflux, N_2 , 76%; (ii) Lawesson reagent, PhCH_3 , reflux, N_2 , 57%; (iii) (a) TFA, CH_2Cl_2 , 0°C -rt; (b) **3**·TFA, EDCI/HOBT, DIPEA, dried THF, 0°C -rt, N_2 , 45% (over two steps).



Scheme 6. Synthetic route to target compound **A7**. Reagents and conditions: (i) *t*-BuCl, anhydrous AlCl_3 , MeCN, rt, N_2 , 80%; (ii) (a) *n*-BuLi, dried THF, -78°C , N_2 ; (b) $\text{B}(\text{OCH}_3)_3$, -78°C -rt, N_2 , 72%; (iii) **5**, $\text{Pd}(\text{PPh}_3)_4$, K_2CO_3 , dioxane/ H_2O , reflux, N_2 , 80%; (iv) (a) TFA, CH_2Cl_2 , 0°C -rt; (b) **3**·TFA, EDCI/HOBT, DIPEA, dried THF, 0°C -rt, N_2 , 58% (over two steps).

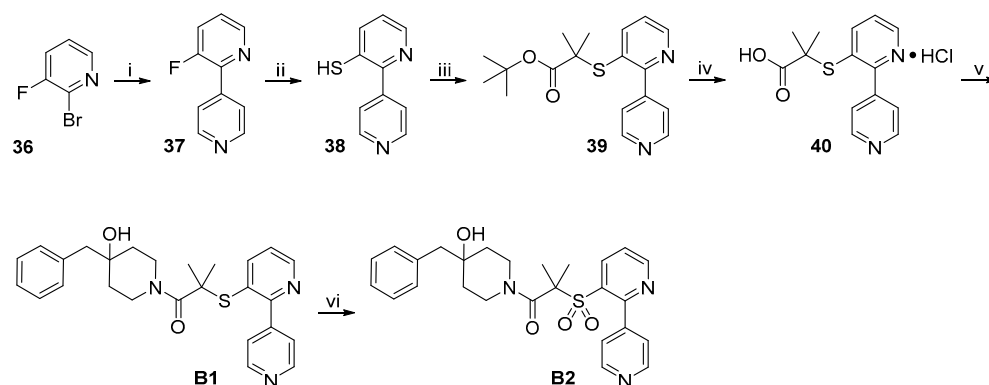
The synthetic route to target compound **A8** is outlined in Scheme 7. Hydrogenolysis of nitrobenzene **8** to aniline **32** was achieved under the same conditions described above, and the latter was transformed into thiourea **34** by initial treatment with CSCl_2 to give isothiocyanate **33** and subsequent treatment with dimethylamine. Cleavage of the *tert*-butyl ester moiety with TFA followed by treatment with HCl in MeOH generated in situ by SOCl_2 in MeOH gave **35** as an HCl salt. EDCI/HOBT-mediated amide formation of **35** and **3**·TFA under the same conditions described above produced target compound **A8**.



Scheme 7. Synthetic route to target compound **A8**. Reagents and conditions: (i) H_2 , 10%Pd/C, MeOH, 71%; (ii) CSCl_2 , Et_3N , dried CH_2Cl_2 , 0°C -rt, N_2 , 78%; (iii) $\text{NH}(\text{CH}_3)_2\cdot\text{HCl}$, Et_3N , dried THF, 0°C -rt, N_2 , 82%; (iv) (a) TFA, CH_2Cl_2 ; (b) SOCl_2 /MeOH, 0°C -rt; (v) **3**·TFA, EDCI/HOBT, DIPEA, dried THF, 0°C -rt, N_2 , 62% (overall for **34** to **A8**).

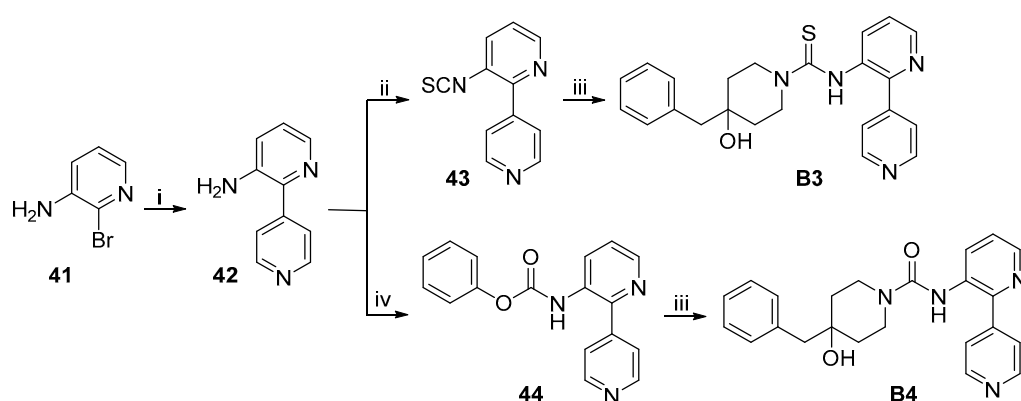
The synthetic route to target compounds **B1** and **B2** is shown in Scheme 8. Suzuki coupling of commercially available **36** and pyridine-4-boronic acid afforded **37** under the

same conditions used above. Treatment of fluoropyridine **37** with Na₂S in the presence of K₂CO₃ in DMF at 120 °C led to the formation of thiophenol **38** via aromatic nucleophilic substitution. Substitution reaction of **38** with *tert*-butyl 2-bromo-2-methylpropanoate in the presence of K₂CO₃ in DMF at 45 °C gave **39**, which was converted to target compound **B1** by the same procedure described above. Oxidation of thioether **B1** to the corresponding sulfone **B2** was achieved by treatment with *m*-chloroperoxybenzoic acid (*m*CPBA) in CH₂Cl₂ at room temperature.



Scheme 8. Synthetic route to target compounds **B1** and **B2**. Reagents and conditions: (i) pyridine-4-boronic acid, Pd(PPh₃)₄, K₂CO₃, dioxane/H₂O, reflux, N₂, 79%; (ii) Na₂S, K₂CO₃, DMF, 120 °C, N₂, 21%; (iii) BrC(CH₃)₂CO₂Bu^t, K₂CO₃, DMF, 45 °C, N₂, 36%; (iv) (a) TFA, CH₂Cl₂, 0 °C-rt; (b) SOCl₂/MeOH, 0 °C-rt; (v) **3**·TFA, EDCI/HOBT, DIPEA, dried THF, 0 °C-rt, N₂, 41% (overall for **39** to **B1**); (vi) *m*CPBA, CH₂Cl₂, 0 °C-rt, N₂, 82%.

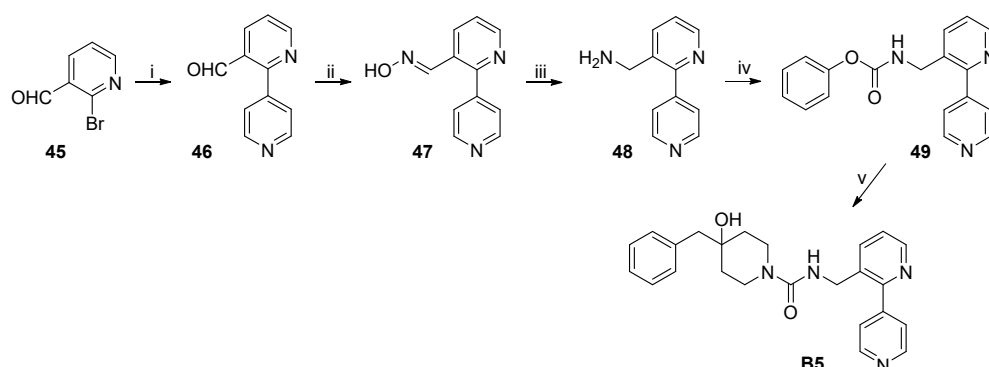
The synthetic routes to target compounds **B3** and **B4** are shown in Scheme 9. Suzuki coupling of commercially available **41** and pyridine-4-boronic acid afforded **42** under the same conditions used above. The amine **42** was converted to isothiocyanate **43** by treatment with CSCl₂ as described above. Treatment of **43** with **3**·TFA in the presence of Et₃N afforded target compound **B3**. Treatment of amine **42** with phenyl chloroformate in the presence of pyridine gave benzyl carbamate **44**, which was subsequently treated with **3**·TFA in the presence of Et₃N to produce target compound **B4**.



Scheme 9. Synthetic routes to target compounds **B3** and **B4**. Reagents and conditions: (i) pyridine-4-boronic acid, Pd(PPh₃)₄, K₂CO₃, dioxane/H₂O, reflux, N₂, 37%; (ii) CSCl₂, Et₃N, dried CH₂Cl₂, 0 °C-rt, N₂; (iii) **3**·TFA, Et₃N, dried THF, 0 °C-rt, N₂, 65% for **B3**, 78% for **B4**; (iv) PhOCOCl, pyridine, MeCN, 0 °C-rt, N₂, 84%.

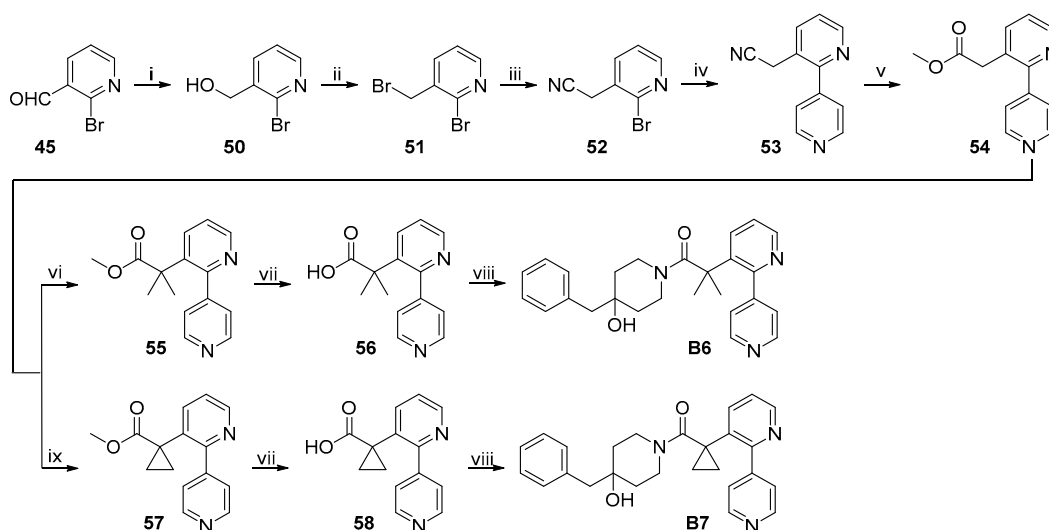
The synthetic route to target compound **B5** is shown in Scheme 10. Suzuki coupling of commercially available **45** and pyridine-4-boronic acid, as described above, afforded **46**. Aldehyde **46** was treated with hydroxylamine to give oxime **47**, which was then reduced to

primary amine **48** with zinc powder in the presence of AcONH₄ and aqueous ammonia in refluxing MeCN. Treatment of **48** with phenyl chloroformate followed by reaction with **3**·TFA produced **B5** by the same procedure described above.



Scheme 10. Synthetic route to target compound **B5**. Reagents and conditions: (i) pyridine-4-boric acid, Pd(PPh₃)₄, K₂CO₃, dioxane/H₂O, reflux, N₂, 57%; (ii) NH₂OH·HCl, NaOH, EtOH/H₂O, reflux, N₂, 55%; (iii) Zn, AcONH₄, NH₃·H₂O, MeCN, reflux, N₂; (iv) PhOCOCl, pyridine, MeCN, 0 °C-rt, N₂; (v) **3**·TFA, Et₃N, dried THF, 0 °C-rt, N₂, 76% (overall for **47** to **B5**).

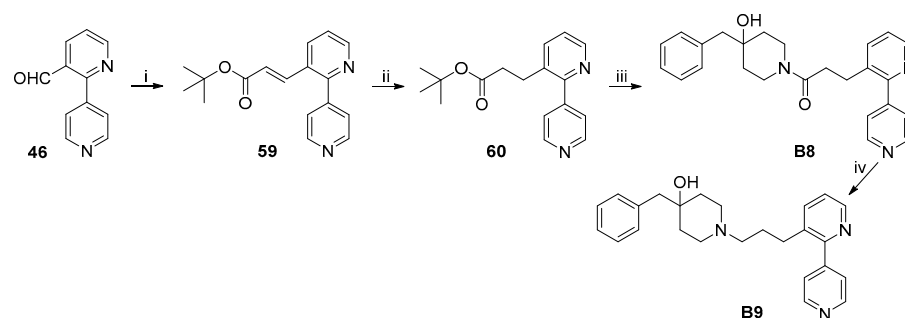
The synthetic routes to target compounds **B6** and **B7** are shown in Scheme 11. Aldehyde **45** was reduced by NaBH₄ to the corresponding primary alcohol **50**, and the latter was subsequently converted to the corresponding bromide **51** by treatment with PBr₃ in refluxing CH₂Cl₂. TBAF-mediated substitution of **51** with TMSCN afforded nitrile **52**. Suzuki coupling of **52** and pyridine-4-boronic acid under the same conditions described above gave **53**. Acidic hydrolysis of nitrile **53** with H₂SO₄ in refluxing aqueous acetic acid gave corresponding carboxylic acid, which was then esterified to the corresponding methyl ester **54** in refluxing HCl/MeOH. Deprotonation of **54** with excess lithium bis(trimethylsilyl)amide (LiHMDS) followed by *gem*-dimethylation with excess MeI produced *gem*-dimethylated ester **55** [22]. Saponification of **55** with NaOH led to the corresponding acid **56**, which was converted to target compound **B6** by a procedure identical to that used for the synthesis of **21** from **4**. Deprotonation of **54** with excess LiHMDS followed by treatment with 1,3,2-dioxathiolane 2,2-dioxide produced a cyclopropane counterpart **57** [23], which was converted to target compound **B7** following the same procedure used for **B6**.



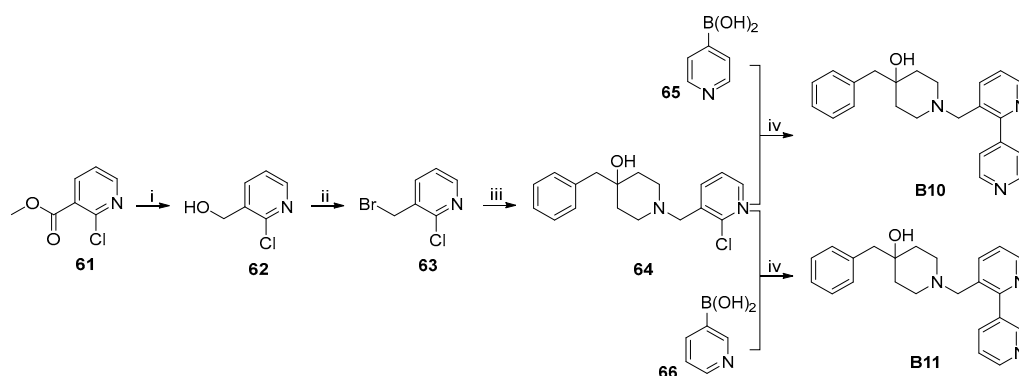
Scheme 11. Synthetic routes to target compounds **B6** and **B7**. Reagents and conditions: (i) NaBH₄, MeOH, 0 °C-rt, N₂, 96%; (ii) PBr₃, dried CH₂Cl₂, 0 °C-reflux, N₂, 51%; (iii) TMSCN, TBAF, MeCN,

0 °C-rt, N₂, 85%; (iv) pyridine-4-boronic acid, Pd(PPh₃)₄, Na₂CO₃, DME/H₂O, reflux, N₂, 56%; (v) (a) H₂SO₄/H₂O/AcOH (1/1/10 by *v/v/v*), reflux, N₂; (b) SOCl₂, MeOH, 0 °C-reflux, N₂, 47% (over two steps); (vi) (a) LiHMDS, dried THF, −78 °C, N₂; (b) CH₃I, dried THF, −78 °C-rt, N₂, 84%; (vii) aqNaOH, MeOH, 45 °C, 34% for **56**, 76% for **58**; (viii) (a) (COCl)₂, DMF (cat.), dried CH₂Cl₂, 0 °C-rt, N₂; (b) **3**·TFA, Et₃N, dried THF, 0 °C-rt, N₂, 19% for **B6** (over two steps), 38% for **B7** (over two steps); (ix) (a) LiHMDS, dried THF, −78 °C, N₂; (b) 1,3,2-dioxathiolane 2,2-dioxide, dried THF, −78 °C-rt, N₂, 60%.

The synthetic routes to target compounds **B8–B11** are shown in Schemes 12 and 13. The experimental details have been published in our earlier work [24].

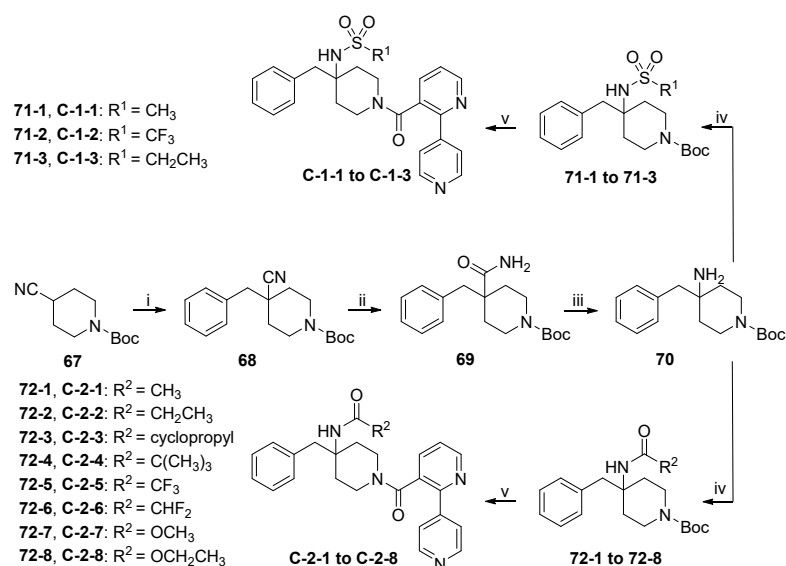


Scheme 12. Synthetic route to target compounds **B8** and **B9**. Reagents and conditions: (i) Ph₃P=CHCOOBu^t, DBU, dried THF, 0 °C-rt, N₂, 50%; (ii) H₂, 10%Pd/C, MeOH, 83%; (iii) (a) TFA, CH₂Cl₂, 0 °C-rt; (b) **3**·TFA, EDCI/HOBT, DIPEA, dried THF, 0 °C-rt, N₂, 41% (over two steps); (iv) LiAlH₄, dried THF, 0–50 °C, N₂, 50%.



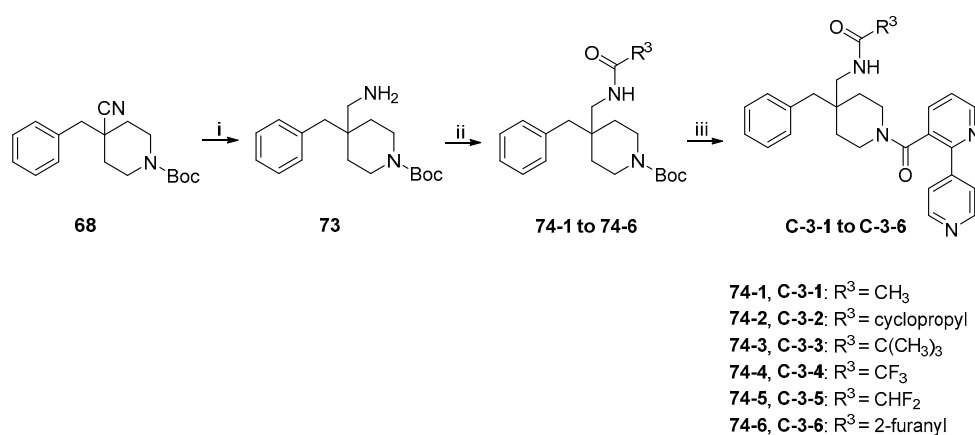
Scheme 13. Synthetic routes to target compounds **B10** and **B11**. Reagents and conditions: (i) LiAlH₄, dried THF, 0 °C-rt, N₂, 27%; (ii) PBr₃, dried CH₂Cl₂, 0 °C-rt, N₂, 47%; (iii) **3**·TFA, aqNaOH, dioxane, 0 °C-rt, 60%; (iv) Pd(PPh₃)₄, K₂CO₃, dioxane/H₂O, reflux, N₂, 46% for **B10**, 54% for **B11**.

The synthetic routes to target compounds **C-1-1** to **C-1-3** and **C-2-1** to **C-2-8** are shown in Scheme 14. Deprotonation of commercially available **67** with lithium diisopropylamide (LDA) at −78 °C followed by benzylation with BnBr afforded **68**, which then gave rise to amide **69** upon treatment with H₂O₂/K₂CO₃ in DMSO [25]. Phenyliodine (III) bis(trifluoroacetate) (PIFA)-mediated Hofmann rearrangement of amide **69** in MeCN/H₂O at room temperature smoothly led to the formation of tertiary amine **70** [26]. Reactions of amine **70** with sulfonyl chlorides or anhydrides produced sulfonamides **71-1** to **71-3**, while reactions with carbonyl chlorides or anhydrides produced amides **72-1** to **72-8**. Cleavage of Boc in **71-1** to **71-3** and **72-1** to **72-8** followed by EDCI/HOBT-mediated amide formation with **7**·TFA, as described above, gave target compounds **C-1-1** to **C-1-3** and **C-2-1** to **C-2-8**, respectively.



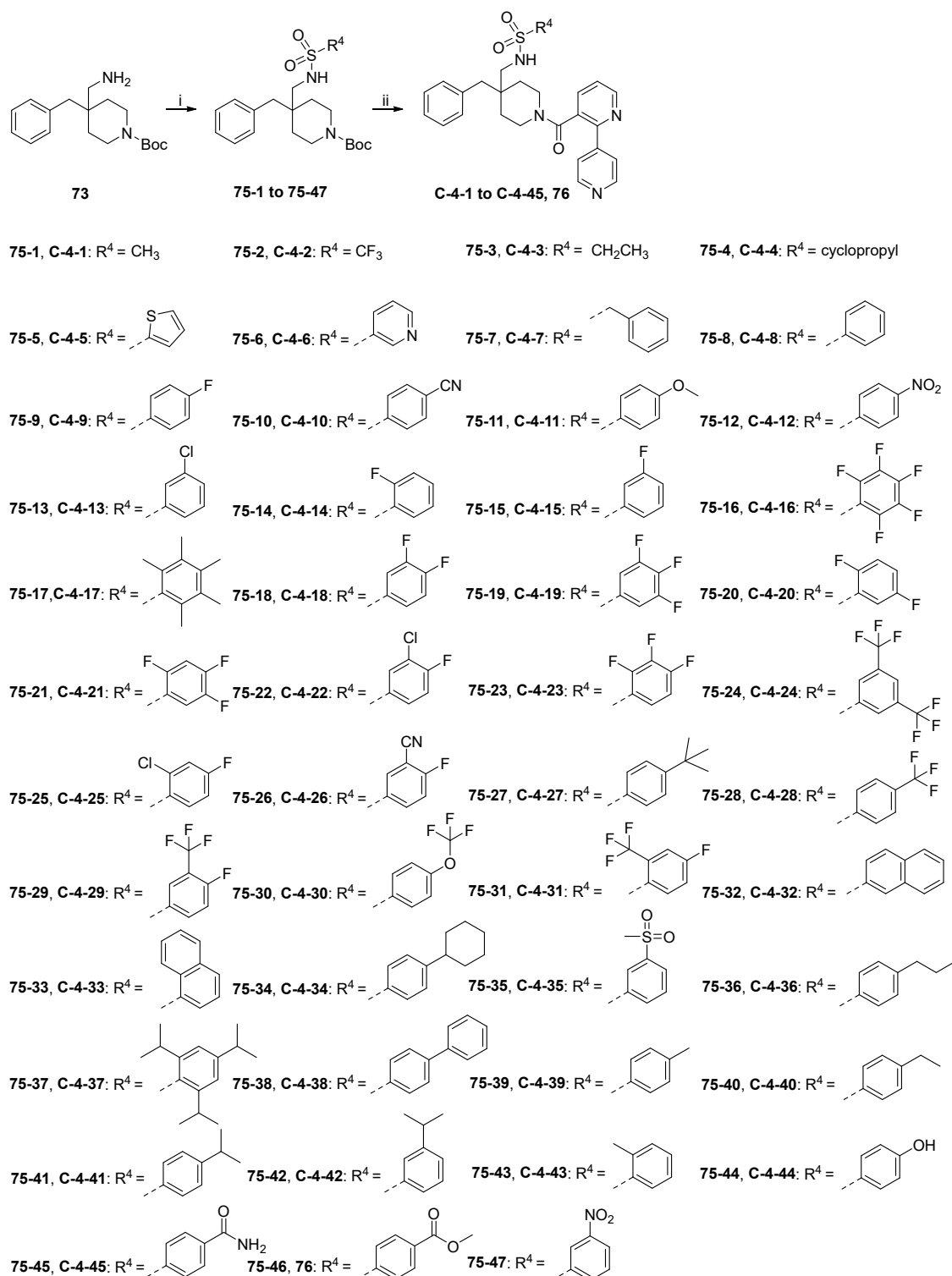
Scheme 14. Synthetic routes to target compounds C-1-1 to C-1-3 and C-2-1 to C-2-8. Reagents and conditions: (i) (a) LDA, dried THF, -78°C , N_2 ; (b) BnBr, dried THF, -78°C -rt, N_2 , 82%; (ii) K_2CO_3 , H_2O_2 , DMSO, 0°C -rt, 94%; (iii) PIFA, MeCN/ H_2O , rt, 55%; (iv) for 71-3, 72-1, 72-3, and 72-4: carbonyl or sulfonyl chlorides, Et_3N , dried CH_2Cl_2 , 0°C -rt, N_2 , 6% for 71-3, 52% for 72-1, 35% for 72-3, 78% for 72-4; for the others: carbonyl or sulfonyl anhydrides, DMAP, Et_3N , dried CH_2Cl_2 , 0°C -rt, N_2 , 47% for 71-1, 50% for 71-2, 72% for 72-2, 60% for 72-5, 80% for 72-6; 77% for 72-7, 72% for 72-8; (v) (a) TFA, CH_2Cl_2 , 0°C -rt; (b) 7-TFA, EDCI/HOBT, DIPEA, dried THF, 0°C -rt, N_2 , 50% for C-1-1, 49% for C-1-2, 45% for C-1-3, 45% for C-2-1, 47% for C-2-2, 61% for C-2-3, 16% for C-2-4, 60% for C-2-5, 17% for C-2-6, 24% for C-2-7, 55% for C-2-8, all yields were for two steps.

The synthetic route to target compounds C-3-1 to C-3-6 is shown in Scheme 15. Nitrile 68 was reduced with NaBH_4 mediated by $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ in MeOH to give primary amine 73, which was converted to amides 74-1 to 74-6 by the same procedure described above for 72-1 to 72-8. Cleavage of Boc in 74-1 to 74-6 followed by EDCI/HOBT-mediated amide formation with 7-TFA, using the same procedure as above, led to the formation of target compounds C-3-1 to C-3-6.



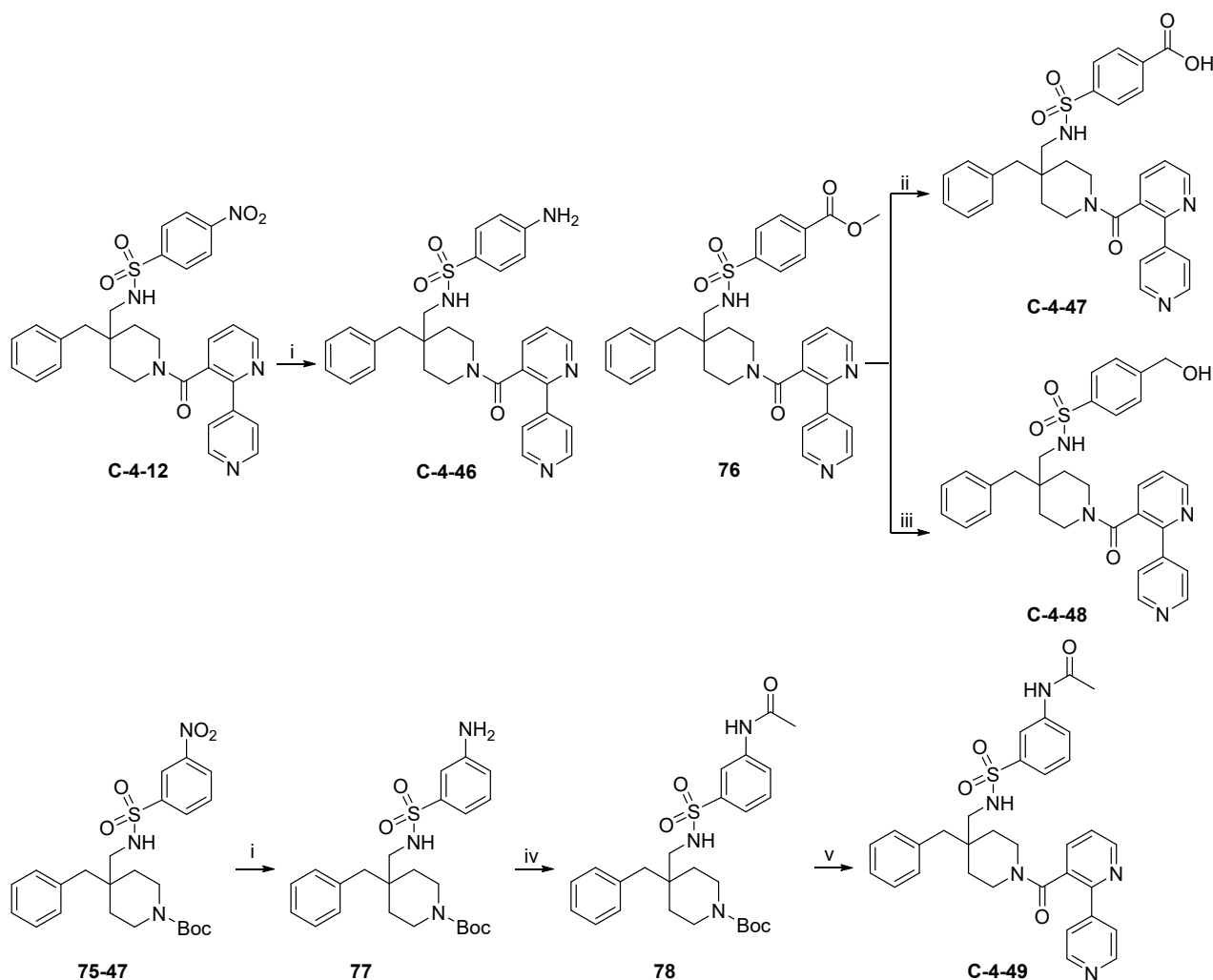
Scheme 15. Synthetic route to target compounds C-3-1 to C-3-6. Reagents and conditions: (i) NaBH_4 , $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, MeOH, 0°C -rt, N_2 , 88%; (ii) for 74-4 and 74-5: carbonyl anhydrides, DMAP, Et_3N , dried CH_2Cl_2 , 0°C -rt, N_2 , 73% for 74-4, 70% for 74-5; for the others: carbonyl chlorides, Et_3N , dried CH_2Cl_2 , 0°C -rt, N_2 , 95% for 74-1, 71% for 74-2, 90% for 74-3, 88% for 74-6; (iii) (a) TFA, CH_2Cl_2 , 0°C -rt; (b) 7-TFA, EDCI/HOBT, DIPEA, dried THF, 0°C -rt, N_2 , 14% for C-3-1, 55% for C-3-2, 62% for C-3-3, 55% for C-3-4, 48% for C-3-5, 41% for C-3-6, all yields were for two steps.

The synthetic route to target compounds **C-4-1** to **C-4-45** is shown in Scheme 16. Primary amine **73** was converted to **C-4-1** to **C-4-45** by a procedure identical to that used for **C-3-1** to **C-3-6**, as discussed above.



Scheme 16. Synthetic route to target compounds **C-4-1** to **C-4-45** and **76**. Reagents and conditions: (i) for **75-1**: Ms_2O , DMAP, Et_3N , dried CH_2Cl_2 , 0°C -rt, N_2 , 35%; for the others: acid chlorides, Et_3N , dried CH_2Cl_2 , 0°C -rt, N_2 , for isolated yields, see experimental section. (ii) (a) TFA, CH_2Cl_2 , 0°C -rt; (b) **7**·TFA, EDCI/HOBT, DIPEA, dried THF, 0°C -rt, N_2 , for isolated yields, see experimental section.

The synthetic routes to target compounds **C-4-46** to **C-4-49** are shown in Scheme 17. **C-4-12** was reduced to **C-4-46** by Pd-catalyzed hydrogenolysis under the same condition used above. Saponification of the ester moiety in **76** with aqueous NaOH in MeOH led to the formation of **C-4-47**, while reduction of **76** with LiAlH₄ produced **C-4-48**. Reduction of **75-47** by Pd-catalyzed hydrogenolysis gave aniline **77**, which was acylated with AcCl in the presence of Et₃N to afford **78**. Compound **78** was converted to target compound **C-4-49** by the identical procedure used above.



Scheme 17. Synthetic routes to target compounds **C-4-46** to **C-4-49**. Reagents and conditions: (i) H₂, 10%Pd/C, MeOH, rt, 40% for **C-4-46**, 87% for **77**; (ii) aqNaOH, MeOH, rt, 41%; (iii) LiAlH₄, dried THF, 0 °C-rt, N₂, 12%; (iv) AcCl, Et₃N, dried CH₂Cl₂, 0 °C-rt, N₂, 12%; (v) (a) TFA, CH₂Cl₂, 0 °C-rt; (b) 7-TFA, EDCI/HOBT, DIPEA, dried THF, 0 °C-rt, N₂, 82%.

It should be noted that all target compounds in Series A and Series C in the present study exhibited unusual NMR characteristics because there are four stable conformations at room temperature, which exist as two diastereomers, each as a pair of enantiomers, due to restricted bond rotations around two axes, i.e., the amide CO-N and CO-pyridine. This phenomenon has been intensively investigated by variable-temperature ¹³C NMR, molecular mechanics, and quantum mechanics in our earlier study [24], and will not be further discussed here.

2.2. In Vitro CYP46A1 Inhibition

The in vitro CYP46A1 inhibitory activity of the target compounds was determined by the inhibition of CYP46A1-mediated metabolism of testosterone to 16 β -hydroxyltestosterone by the compounds tested and expressed as the half-maximal inhibitory concentration (IC₅₀) using soticlestat as a positive control [27]. The results are summarized in Table 1.

Table 1. In vitro CYP46A1 inhibitory activity (IC₅₀) of target compounds A1–A8, B1–B11, C-1-1 to C-1-3, C-2-1 to C-2-8, C-3-1 to C-3-6, and C-4-1 to C-4-49.

Compound	IC ₅₀ (nM)	Compd	IC ₅₀ (nM)	Compd	IC ₅₀ (nM)	Compd	IC ₅₀ (nM)
Soticlestat	18.0	C-1-3	296.3	C-4-8	41.8	C-4-30	36.47
A1	>10,000	C-2-1	3562	C-4-9	36.2	C-4-31	56.13
A2	>10,000	C-2-2	>10,000	C-4-10	79.4	C-4-32	25.7
A3	>10,000	C-2-3	>10,000	C-4-11	113.2	C-4-33	82.3
A4	>10,000	C-2-4	>10,000	C-4-12	168.6	C-4-34	32.5
A5	>10,000	C-2-5	5900	C-4-13	63.76	C-4-35	371.4
A6	>10,000	C-2-6	4346	C-4-14	117.3	C-4-36	51.2
A7	>10,000	C-2-7	111.8	C-4-15	63.02	C-4-37	24.2
A8	>10,000	C-2-8	>10,000	C-4-16	54.49	C-4-38	13.6
B1	3375	C-3-1	>10,000	C-4-17	17.35	C-4-39	117.7
B2	>10,000	C-3-2	2193	C-4-18	56.15	C-4-40	63.0
B3	1023	C-3-3	226.7	C-4-19	65.67	C-4-41	17.4
B4	>10,000	C-3-4	156.1	C-4-20	50.92	C-4-42	48.6
B5	>10,000	C-3-5	1634	C-4-21	41.7	C-4-43	127.5
B6	>10,000	C-3-6	372.6	C-4-22	43.99	C-4-44	150.6
B7	>10,000	C-4-1	526.9	C-4-23	62.05	C-4-45	317.9
B8	>10,000	C-4-2	151.5	C-4-24	56.38	C-4-46	147.4
B9	>10,000	C-4-3	1849	C-4-25	52.68	C-4-47	3240
B10	140.9	C-4-4	982.6	C-4-26	74.22	C-4-48	379.5
B11	>10,000	C-4-5	133	C-4-27	27.5	C-4-49	166.1
C-1-1	102	C-4-6	126.1	C-4-28	41.23		
C-1-2	5583	C-4-7	526.3	C-4-29	33.31		

As shown in Figure 1, Series A focuses on the modification of the distal pyridine ring in soticlestat with the aim of finding a moiety that can bind to the heme iron in CYP46A1 with higher affinity, because the N in the distal pyridine ring in soticlestat was believed to be a critical moiety for ligation to the CYP46A1 heme iron [13]. Unfortunately, among all the moieties screened in A1–A8, none were superior to the distal pyridine N atom in soticlestat; in fact, all modifications led to complete loss of CYP46A1 inhibition (IC₅₀ values > 10,000 nM).

Series B focuses on modification of the linker connecting the bipyridine and piperidine rings, which is C=O in soticlestat. Thus, all linkers in B1–B11 were associated with weaker CYP46A1 inhibitory activity than soticlestat, and the most potent one was B10 (IC₅₀ = 140.9 nM), with a CH₂ linker compared to the C=O linker in soticlestat (IC₅₀ = 18.0 nM). It should be noted that the orientation of the distal pyridine N is very important, as indicated by the dramatic difference in CYP46A1 inhibitory activity between B10 (IC₅₀ = 140.9 nM) and B11 (IC₅₀ > 10,000 nM).

Series C focuses on modification of the hydroxyl group in soticlestat using a bioisosterism strategy and is further categorized into four subseries, i.e., C-1, C-2, C-3, and C-4. Series C-1 included three compounds designed by replacement of the OH group in soticlestat with RSO₂NH; however, none of them showed stronger CYP46A1 inhibitory activity than parent soticlestat, with the most potent one being C-1-1, with an IC₅₀ of 102 nM. In Series

C-2, the OH in soticlestat was replaced by RCONH and eight compounds were designed; like Series C-1, none of them were stronger than soticlestat, and the most potent one was **C-2-7**, with an IC_{50} of 111.8 nM. The same result was obtained in Series C-3, where the OH in soticlestat was replaced by RCONHCH₂ and six compounds were designed, with the most potent one being **C-3-4**, with an IC_{50} of 156.1 nM. In Series C-4, we introduced RSO₂NHCH₂ to replace the OH in soticlestat. Four small alkyl substituents (the “R” in RSO₂NHCH₂) were initially introduced in RSO₂NHCH₂ to explore the space (**C-4-1** to **C-4-4**), but all of them were associated with a dramatic decrease in activity. Four different types of aromatic substituents were then introduced (**C-4-5** to **C-4-8**), and fortunately, when R = benzene ring, the CYP46A1 inhibitory activity was only slightly less potent than that of soticlestat (IC_{50} = 41.8 nM for **C-4-8** vs. 18.0 for soticlestat). Inspired by this encouraging observation, some electron-withdrawing and electron-donating groups were then explored by attaching them to the benzene ring (**C-4-9** to **C-4-13**), and it turned out that F, CN, and Cl were associated with potent activity, whereas MeO and NO₂ had opposite effects. Based on this, a large number of derivatives with PhSO₂NHCH₂, where the Ph ring was substituted with F, Cl, CN, CF₃, OCF₃, and their various combinations, were further designed (**C-4-14** to **C-4-31**), which also included two derivatives in which the benzene ring was substituted with bulky alkyl groups, i.e., pentamethyl (**C-4-17**) and 4-*tert*-butyl (**C-4-27**), and the results showed that the SAR exhibited a flat profile, as indicated by the observation that CYP46A1 inhibitory activity did not change significantly with structural modification in these compounds, and most of them exhibited very potent CYP46A1 inhibitory activity with IC_{50} < 100 nM. However, among them, the two most potent compounds had the Ph ring substituted with pentamethyl (**C-4-17**, IC_{50} = 17.35 nM) and 4-*tert*-butyl (**C-4-27**, IC_{50} = 27.5 nM), although many other counterparts substituted with multiple halogens also exhibited IC_{50} values of < 50 nM. Inspired by this surprising result, we turned to further design many compounds with PhSO₂NHCH₂ where the Ph ring was substituted with a variety of alkyl groups (**C-4-32** to **C-4-34** and **C-4-36** to **C-4-43**). The assay results showed that a similar flat SAR was observed, with all alkyl-substituted compounds being very potent (IC_{50} < 100 nM), and two compounds exhibited CYP46A1 inhibitory activity slightly more potent than soticlestat (IC_{50} = 13.6 nM for **C-4-38** and 17.4 nM for **C-4-41** vs. 18.0 nM for soticlestat). Notably, in subseries C-4, the introduction of hydrophilic substituents to the benzene ring led to a dramatic decrease in activity (**C-4-35** and **C-4-44** to **C-4-49**).

2.3. In Vitro Inhibitory Activities of Target Compounds Against CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4

In order to evaluate the off-target inhibition of compounds in the present study against other CYP enzymes, four potent compounds, **C-4-9**, **C-4-32**, **C-4-38**, and **C-4-41**, were selected to test their inhibition against five main CYP enzymes, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. As shown in Table 2, all four selected compounds displayed weak inhibitory activities against CYP1A2, with IC_{50} values > 50 μ M and high selectivities > 1000, and moderate inhibitory activities against CYP2C9, 2C19, and 2D6, with IC_{50} values of 1.54–14.7 μ M and moderate selectivities of 80–406. However, these four compounds showed strong CYP3A4/5 inhibitory activities (IC_{50} values = 0.0402 to 0.403 μ M), which led to low selectivities ranging from 3.0 to 11. The exact reason or chemical moieties responsible for the strong inhibition against CYP3A4/5 are unknown, since CYP3A4/5 enzymes are known to be associated with broad substrate specificity encompassing a wide range of chemical structures. However, this poor selectivity will be optimized in future work to minimize the potential for drug–drug interactions, since CYP3A4/5 is a predominant drug-metabolizing enzyme for both antiepileptic drugs and many other drugs.

Table 2. Inhibitory activities of selected compounds **C-4-9**, **C-4-32**, **C-4-38**, and **C-4-41** against off-target CYP enzymes (1A2, 2C9, 2C19, 2D6, and 3A4/5).

Compd	1A2		2C9		2C19		2D6		3A4/5	
	IC ₅₀ (μM)	SR ^a	IC ₅₀ (μM)	SR ^a	IC ₅₀ (μM)	SR ^a	IC ₅₀ (μM)	SR ^a	IC ₅₀ (μM)	SR ^a
C-4-9	>50	>1381	6.29	173	14.7	406	2.90	80	0.403	11
C-4-32	>50	>1946	4.27	166	3.34	130	5.81	226	0.0948	3.7
C-4-38	>50	>3676	1.85	136	1.54	113	4.04	297	0.0402	3.0
C-4-41	>50	>2874	5.20	299	4.59	264	2.95	170	0.0898	5.2

^a SR = selectivity ratio = IC₅₀ (off-target CYP)/IC₅₀ (CYP4A1).

3. Materials and Methods

3.1. Chemistry

Unless stated otherwise, all chemical reagents were obtained commercially and used without further purification. All dried solvents were prepared by standard methods. Reaction progress was monitored by thin-layer chromatography (TLC) on commercially available precoated TLC silica gel plates or by liquid chromatography–mass spectrometry (LC-MS), and separation and purification by flash column chromatography were performed on silica gel columns (200–300 mesh) eluting with EtOAc/petroleum ether (PE) or MeOH/CH₂Cl₂ (as *v/v*). Melting points were measured in open capillaries with an SGW X-4A microscopic melting point apparatus (Shanghai INESA Physico-Optical Instrument Co., Ltd., Shanghai, China) and are uncorrected. NMR spectra were recorded on Bruker Ascend 500, 600, or 800 NMR spectrometers (Bruker Switzerland AG, Fällanden, Switzerland) using CDCl₃, DMSO-*d*₆, or CD₃OD as solvent and TMS (for ¹H NMR) or the known carbon chemical shifts in deuterated solvents (for ¹³C NMR) as internal standards. High-resolution mass spectra (HR-MS) were determined with a Thermo Scientific Exactive Plus mass spectrometer (Thermo Fisher Scientific, Bremen, Germany) using electrospray ionization (ESI) and Orbitrap techniques. Unless stated otherwise, evaporation on a rotary evaporator was conducted at temperatures below 40 °C.

The copies of ¹H NMR, ¹³C NMR, ¹⁹F NMR, ³¹P NMR and HR-MS spectra of the synthesized intermediates and target compounds can be seen in Supplementary Materials.

Synthesis of *tert*-butyl 4-benzyl-4-hydroxypiperidine-1-carboxylate (**2**). To a stirred solution of **1** (3.00 g, 15.1 mmol) in dried THF (30 mL), cooled at 0 °C under N₂, a solution of BnMgCl in THF (11.3 mL, 18.1 mmol, 1.6 M in THF) was added dropwise. After addition, the reaction mixture was stirred at room temperature overnight. TLC analysis indicated completion of the reaction, after which the mixture was poured into ice–water (50 mL). The resulting mixture was extracted with EtOAc (100 mL × 3), and the combined extracts were washed successively with 0.1 M HCl (100 mL) and brine (100 mL), dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/3, by *v/v*) to give **2** as a pale yellow oil, 2.10 g (48%). ¹H NMR (500 MHz, CDCl₃) δ 7.34–7.31 (m, 2H), 7.28–7.25 (m, 1H), 7.20–7.18 (m, 2H), 3.87–3.83 (m, 2H), 3.12–3.07 (m, 2H), 2.76 (s, 2H), 1.63–1.57 (m, 2H), 1.51–1.49 (m, 2H), 1.46 (s, 9H). The ¹H NMR data were consistent with those reported in the literature [28].

Synthesis of 4-benzylpiperidin-4-ol trifluoroacetic acid salt (**3**·TFA). To a stirred solution of **2** (6.30 g, 21.6 mmol) in CH₂Cl₂ (63 mL), cooled to 0 °C, TFA was added (31.5 mL). After addition, the reaction mixture was stirred at room temperature overnight. TLC analysis indicated completion of the reaction, and the mixture was evaporated on a rotary evaporator to dryness to give crude **3** as the trifluoroacetic acid salt. The crude **3** was used directly in the next step without further purification or characterization.

Synthesis of *tert*-butyl 2-chloronicotinate (**5**). To a stirred solution of **4** (10.00 g, 63.5 mmol) in dried CH₂Cl₂ (100 mL) in a 250 mL round-bottomed flask equipped with a drying tube fitted with anhydrous CaCl₂ and cooled at 0 °C, (COCl)₂ (16.1 g, 127 mmol) was added dropwise, followed by addition of DMF (three drops). The reaction mixture was thus stirred at room temperature until completion, as indicated by TLC analysis (typically within 2–3 h). The reaction mixture was evaporated on a rotary evaporator to remove all volatiles, and the residue thus obtained was dissolved in dried THF (100 mL). The resulting solution was cooled to –10 °C, and a solution of *t*-BuOK in THF (152.4 mL, 152.4 mmol, 1.0 M in THF) was added dropwise. After addition, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction. Saturated aqueous NaHCO₃ was added dropwise to the reaction mixture (100 mL), and the resulting mixture was extracted with CH₂Cl₂ (150 mL × 3). The combined extracts were washed with brine (100 mL), dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/5, by *v/v*) to give **5** as a pale yellow oil, 8.20 g (60%). ¹H NMR (500 MHz, CDCl₃) δ 8.48 (dd, *J* = 2.3 Hz and 4.8 Hz, 1H), 8.07 (dd, *J* = 2.0 Hz and 7.5 Hz, 1H), 7.34–7.31 (m, 1H), 1.62 (s, 9H). The ¹H NMR data were consistent with those reported in the literature [29].

Synthesis of *tert*-butyl [2,4'-bipyridine]-3-carboxylate (**6**). A mixture of **5** (15.00 g, 70.2 mmol), pyridine-4-boronic acid (10.34 g, 84.2 mmol), Pd(PPh₃)₄ (2.43 g, 2.10 mmol), and Na₂CO₃ (23.2 g, 210.6 mmol) in a mixed solvent of DME (100 mL) and water (100 mL) was refluxed under N₂ overnight until TLC analysis indicated completion of the reaction. After cooling to room temperature, the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (150 mL × 3). The combined extracts were washed with brine (100 mL), dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/1, by *v/v*) to give **6** as a pale yellow solid, 9.00 g (50%). m.p. 78.1–79.9 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.77 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 8.72 (dd, *J* = 1.8 Hz and 4.3 Hz, 2H), 8.17 (dd, *J* = 1.5 Hz and 8.0 Hz, 1H), 7.44 (dd, *J* = 1.5 Hz and 8.0 Hz, 2H), 7.42 (t, *J* = 4.0 Hz, 1H), 1.32 (s, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 165.78, 156.09, 150.90, 149.26, 148.10, 137.96, 128.49, 123.16, 122.54, 82.47, 27.28; ESI-HR-MS: (*m/z*) calcd. for C₁₅H₁₇N₂O₂ ([M+H]⁺) 257.1285, found 257.1289.

Synthesis of [2,4'-bipyridine]-3-carboxylic acid trifluoroacetic acid salt (**7·TFA**). Following the procedure for the synthesis of **3·TFA** from **2**, **7·TFA** was synthesized from **6** (5.00 g, 19.5 mmol) in CH₂Cl₂ (15 mL) and TFA (25 mL) at room temperature. After evaporation of all volatiles on a rotary evaporator, the residue was triturated with THF (30 mL) to afford **7·TFA** (4.92 g). The sample was used directly in the next step without characterization.

Synthesis of *tert*-butyl 2-(4-nitrophenyl)nicotinate (**8**). Following the procedure for the synthesis of **6** from **5** and pyridine-4-boronic acid, **8** was prepared from **5** (2.00 g, 9.36 mmol) and 4-nitrophenylboronic acid (1.87 g, 11.2 mmol) in the presence of Pd(PPh₃)₄ (0.33 g, 0.281 mmol) and Na₂CO₃ (2.98 g, 28.1 mmol) in a refluxing mixture of DME/H₂O (20 mL/20 mL) under N₂. Product **8** was isolated and purified by column chromatography (EtOAc/PE = 1/5, by *v/v*). Pale yellow solid, 2.42 g (86%). m.p. 112.9–113.8 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.78 (dd, *J* = 1.5 Hz and 5.0 Hz, 1H), 8.32 (d, *J* = 8.5 Hz, 1H), 8.19 (dd, *J* = 1.8 Hz and 7.8 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.44 (dd, *J* = 4.8 Hz and 7.8 Hz, 1H), 1.34 (s, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 166.16, 156.76, 151.27, 147.86, 147.16, 138.43, 129.91, 128.91, 123.35, 122.88, 83.00, 27.77; ESI-HR-MS: (*m/z*) calcd. for C₁₆H₁₇N₂O₄ ([M+H]⁺) 301.1183, found 301.1182.

Synthesis of methyl 2-(4-nitrophenyl)nicotinate (**9**). To a stirred solution of **8** (1.00 g, 3.33 mmol) in CH₂Cl₂ (3 mL), cooled to 0 °C, TFA was added dropwise (5 mL). After addition, the reaction mixture was stirred at room temperature overnight. TLC analysis indicated completion of the reaction, and the mixture was subsequently evaporated to

dryness on a rotary evaporator. The residue was dissolved in MeOH (10 mL) and the resulting mixture was cooled to 0 °C, followed by dropwise addition of SOCl₂ (1.3 mL). The reaction mixture was refluxed under N₂ until completion, as indicated by TLC analysis (typically within 4 h). After cooling to room temperature, the reaction mixture was poured into saturated aqueous NaHCO₃ (50 mL) and extracted with EtOAc (50 mL × 3). The combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a solid, which was triturated with *n*-hexane to give **9**. White solid, 0.65 g (76%). m.p. 113.3–113.9 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.87 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 8.32–8.30 (m, 2H), 8.27 (dd, *J* = 1.8 Hz and 7.8 Hz, 1H), 7.78–7.76 (m, 2H), 7.63 (dd, *J* = 4.8 Hz and 7.8 Hz, 1H), 3.67 (s, 3H). The ¹H NMR data were consistent with those reported in the literature [30].

Synthesis of methyl 2-(4-aminophenyl)nicotinate (**10**). A suspension of **9** (0.30 g, 1.16 mmol) and 10% Pd/C (30 mg) in MeOH (3 mL) was subjected to standard procedure of hydrogenation at atmospheric pressure (balloon) and room temperature overnight until TLC analysis indicated completion of the reaction. The reaction mixture was filtered through Celite and the filtrate was poured into water (20 mL). The resulting mixture was extracted with EtOAc (30 mL × 3), and the combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/3, by *v/v*) to give **10**. Pale yellow solid, 0.20 g (75%). m.p. 107.8–108.6 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.67 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 7.95 (dd, *J* = 1.8 Hz and 7.8 Hz, 1H), 7.31 (dd, *J* = 4.8 Hz and 7.8 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 2H), 3.70 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 169.36, 158.25, 151.03, 147.47, 137.67, 129.85, 129.65, 126.26, 120.47, 114.58, 52.31; ESI-HR-MS: (*m/z*) calcd. for C₁₃H₁₃N₂O₂ ([M+H]⁺) 229.0972, found 229.0971.

Synthesis of methyl 2-(4-iodophenyl)nicotinate (**11**). To stirred concentrated HCl (2.5 mL) at 0 °C, **10** was added (1.00 g, 4.38 mmol) in portions, followed by the addition of water (2.5 mL). A solution of NaNO₂ (0.36 g, 5.26 mmol) in a minimum amount of water was added dropwise. After that, stirring was continued for 15 min at this temperature, followed by dropwise addition of a solution of KI (1.45 g, 8.76 mmol) in a minimum amount of water. After addition, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction, then poured into water (30 mL). The resulting mixture was brought to pH = 8–9 and extracted with EtOAc (50 mL × 3). The combined extracts were washed successively with 10% Na₂S₂O₃ (50 mL) and brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/3, by *v/v*) to give **11**. Pale yellow oil, 0.65 g (44%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.80 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 8.15 (dd, *J* = 1.8 Hz and 7.8 Hz, 1H), 7.84–7.81 (m, 2H), 7.53 (dd, *J* = 4.8 Hz and 7.8 Hz, 1H), 7.32–7.29 (m, 2H), 3.69 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 168.04, 157.78, 151.47, 139.50, 138.11, 137.23, 130.38, 126.63, 121.88, 95.16, 52.49; ESI-HR-MS: (*m/z*) calcd. for C₁₃H₁₁INO₂ ([M+H]⁺) 339.9829, found 339.9833.

Synthesis of methyl 2-(4-((trimethylsilyl)ethynyl)phenyl)nicotinate (**12**). A mixture of **11** (1.50 g, 4.42 mmol), trimethylsilylacetylene (1.41 g, 14.4 mmol), CuI (42.0 mg, 0.719 mmol), PdCl₂(PPh₃)₂ (0.47 g, 0.663 mmol), and Et₃N (6 mL, 43.5 mmol) in dried THF (15 mL) was stirred at room temperature under N₂ until TLC analysis indicated the completion of reaction. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (50 mL × 3). The combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/3, by *v/v*) to give **12**. Black oil, 1.00 g (73%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.81 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 8.16 (dd, *J* = 1.8 Hz and 7.8 Hz, 1H), 7.55 (s, 1H), 7.54–7.52 (m, 2H), 7.51–7.49 (m, 2H), 3.67 (s, 3H), 0.25 (s,

9H); ^{13}C NMR (151 MHz, CDCl_3) δ 168.39, 157.91, 151.37, 139.99, 138.04, 131.78, 128.49, 127.01, 123.58, 121.85, 104.87, 95.51, 52.43, 0.01; ESI-HR-MS: (m/z) calcd. for $\text{C}_{18}\text{H}_{20}\text{NO}_2\text{Si}$ ($[\text{M}+\text{H}]^+$) 310.1258, found 310.1263.

Synthesis of methyl 2-(4-ethynylphenyl)nicotinate (**13**). To a stirred solution of **12** (1.00 g, 3.23 mmol) in dried THF (10 mL), cooled to 0 °C under N_2 , a solution of TBAF in THF (3.23 mL, 3.23 mmol, 1.0 M in THF) was added dropwise. After addition, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction, after which the mixture was poured into water (30 mL). The resulting mixture was extracted with EtOAc (50 mL $\times$ 3), and the combined extracts were washed with brine, dried (MgSO_4), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/3, by v/v) to give **13**. Dark brown oil, 0.50 g (65%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.81 (dd, J = 1.8 Hz and 4.8 Hz, 1H), 8.17 (dd, J = 1.8 Hz and 7.8 Hz, 1H), 7.57 (s, 1H), 7.56–7.54 (m, 2H), 7.53–7.51 (m, 2H), 4.30 (s, 1H), 3.68 (s, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 168.35, 158.06, 151.54, 140.49, 138.19, 132.05, 128.66, 127.01, 122.62, 122.00, 83.53, 78.38, 52.56; ESI-HR-MS: (m/z) calcd. for $\text{C}_{15}\text{H}_{12}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) 238.0863, found 238.0867.

Synthesis of 2-(4-ethynylphenyl)nicotinic acid (**14**). To a stirred solution of **13** (0.40 g, 1.69 mmol) in MeOH (4 mL) a solution of NaOH (0.135 g, 3.38 mmol) in water (0.3 mL) was added. After addition, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction. The reaction mixture was cooled to 0 °C and concentrated HCl (0.28 mL) was added. A stirred white slurry was obtained, and the precipitate was collected via suction filtration and dried in vacuo at room temperature to give crude **14**. White solid, 0.55 g. The crude product **14** was used directly in the next step without further purification or characterization.

Synthesis of (4-benzyl-4-hydroxypiperidin-1-yl)(2-(4-ethynylphenyl)pyridin-3-yl) methanone (**A1**). To a stirred solution of **14** (0.55 g, 2.36 mmol) in dried THF (5.5 mL), cooled to 0 °C, under N_2 , EDCI (1.13 g, 5.90 mmol), HOBT (24 mg, 0.177 mmol), and DIPEA (1.83 g, 14.2 mmol) were added successively. After addition, a solution of **3**·TFA (0.82 g, 2.83 mmol) in dried THF (2 mL) was added dropwise. After that, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction, after which the mixture was poured into water (15 mL). The resulting mixture was extracted with EtOAc (20 mL $\times$ 3), and the combined extracts were washed with brine, dried (MgSO_4), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc) to give **A1**. White solid, 295 mg (overall 44% from **13** to **A1**). m.p. 155.5–156.9 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ : 8.73 (dd, J = 1.8 Hz and 4.8 Hz, 1H), 7.81–7.76 (m, 1H), 7.71–7.69 (m, 1H), 7.64–7.55 (m, 3H), 7.48–7.46 (m, 1H), 7.25–7.21 (m, 2H), 7.19–7.15 (m, 2H), 7.08–7.06 (m, 1H), 4.36–4.29 (m, 3H), 4.20–4.17 (m, 0.41H), 3.02–2.96 (m, 0.71H), 2.93–2.87 (m, 1H), 2.81–2.76 (m, 1H), 2.67–2.61 (m, 1H), 2.42–2.39 (m, 0.57H), 2.27–2.24 (m, 0.56H), 1.48–1.28 (m, 2H), 1.19–1.06 (m, 1H), 0.80–0.77 (m, 0.58H), -0.08 – -0.15 (m, 0.56H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.88, 167.63, 153.91, 153.27, 150.18, 150.12, 139.39, 139.14, 136.26, 136.11, 135.75, 135.71, 132.22, 132.19, 131.45, 130.98, 130.40, 130.31, 129.37, 128.46, 128.36, 128.34, 126.86, 126.79, 123.16, 122.86, 122.62, 122.48, 83.28, 82.88, 79.21, 78.81, 69.06, 68.87, 49.13, 49.06, 42.92, 42.38, 37.63, 37.53, 36.55, 36.13, 35.62, 35.43; ESI-HR-MS: (m/z) calcd. for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_2$ ($[\text{M}+\text{H}]^+$) 397.1911, found 397.1919.

Synthesis of methyl 2-(4-(dimethylphosphoryl)phenyl)nicotinate (**15**). Flask 1 was charged with **11** (1.00 g, 2.95 mmol), $\text{HP}(=\text{O})\text{Me}_2$ (0.23 g, 2.95 mmol), and dioxane (5 mL), and the mixture thus obtained was stirred under N_2 at room temperature. Flask 2 was charged with $\text{Pd}_2(\text{dba})_3$ (0.14 g, 0.148 mmol), XantPhos (0.17 g, 0.295 mmol), and dioxane (5 mL), and the mixture was stirred under N_2 at room temperature for 10 min and subse-

quently added to Flask 1. The mixture thus obtained was stirred, followed by addition of Et₃N (0.36 g, 3.54 mmol). Stirring was continued at room temperature overnight until TLC analysis indicated completion of the reaction. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (50 mL × 3). The combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc) to give **15**. White solid, 295 mg (44%). Pale yellow oil, 0.50 g (59%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.83 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 8.20 (dd, *J* = 1.5 Hz and 8.0 Hz, 1H), 7.85 (dd, *J* = 8.3 Hz and 11.3 Hz, 2H), 7.63 (dd, *J* = 2.3 Hz and 8.3 Hz, 2H), 7.56 (dd, *J* = 4.5 Hz and 8.0 Hz, 1H), 3.70 (s, 3H), 1.71 (s, 3H), 1.68 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 167.84, 157.89, 151.63, 143.49 (d, *J* = 3.0 Hz), 138.30, 134.76 (d, *J* = 98.6 Hz), 129.53 (d, *J* = 10.0 Hz), 128.96 (d, *J* = 11.9 Hz), 126.88, 122.30, 52.58, 18.11 (d, *J* = 71.6 Hz); ³¹P NMR (202 MHz, DMSO-*d*₆) δ 32.40; ESI-HR-MS: (*m/z*) calcd. for C₁₅H₁₇NO₃P ([M+H]⁺) 290.0941, found 290.0938.

Synthesis of 2-(4-(dimethylphosphoryl)phenyl)nicotinic acid (**16**). Following the procedure for the synthesis of **14** from **13**, **16** was prepared from **15** (0.44 g, 1.52 mmol) and NaOH (0.12 g, 3.04 mmol) in MeOH (4.4 mL) and water (0.3 mL). Neutralization with concentrated HCl (0.25 mL) afforded crude **16** (471 mg). The crude **16** sample was used directly in the next step without further purification or characterization.

Synthesis of (4-benzyl-4-hydroxypiperidin-1-yl)(2-(4-(dimethylphosphoryl)phenyl)pyridin-3-yl)methanone (**A2**). Following the procedure for the synthesis of **A1** from **14** and **3-TFA**, **A2** was prepared from **16** (0.40 g, 1.45 mmol) and **3-TFA** (0.63 g, 2.18 mmol) using EDCI (0.70 g, 3.63 mmol), HOBT (15 mg, 0.109 mmol), and DIPEA (1.13 g, 8.72 mmol) in dried THF (4 mL). White foam, 0.12 g (overall 18% from **15** to **A2**). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.76–8.74 (m, 1H), 7.95–7.91 (m, 1H), 7.86–7.79 (m, 3H), 7.71–7.70 (m, 1H), 7.51–7.48 (m, 1H), 7.24–7.21 (m, 2H), 7.18–7.15 (m, 2H), 7.05–7.04 (m, 1H), 4.38–4.32 (m, 1H), 4.30–4.08 (m, 1H), 3.06–2.98 (m, 1H), 2.93–2.83 (m, 1.67H), 2.76–2.64 (m, 1H), 2.32–2.24 (m, 1H), 1.73–1.66 (m, 6H), 1.49–1.43 (m, 0.36H), 1.37–1.31 (m, 1H), 1.10–0.99 (m, 1H), 0.91–0.89 (m, 0.61H), 0.06–0.01 (m, 0.53H); ¹³C NMR (151 MHz, CDCl₃) δ 167.79, 167.65, 153.66, 153.18, 150.30, 150.24, 142.51, 142.49, 142.26, 142.24, 136.15, 136.11, 135.94, 135.91, 135.44, 135.26, 134.80, 131.60, 131.36, 130.46, 130.40, 129.89, 129.86, 129.82, 129.79, 129.58, 129.50, 128.96, 128.88, 128.46, 128.37, 126.92, 126.84, 122.92, 122.88, 69.05, 68.66, 49.09, 48.66, 43.14, 42.70, 37.77, 37.66, 36.51, 36.15, 36.07, 35.71, 18.51, 18.47, 18.16, 18.15, 18.03, 18.00, 17.69, 17.67; ³¹P NMR (203 MHz, DMSO-*d*₆) δ 32.39, 32.10; ESI-HR-MS: (*m/z*) calcd. for C₂₆H₃₀N₂O₃P ([M+H]⁺) 449.1989, found 449.1989.

Synthesis of methyl 2-((trimethylsilyl)ethynyl)nicotinate (**18**). Following the procedure for the synthesis of **12** from **11**, **18** was prepared from **17** (3.00 g, 13.9 mmol) and trimethylsilylacetylene (4.43 g, 45.1 mmol) using PdCl₂(PPh₃)₂ (1.47 g, 2.09 mmol), CuI (0.13 g, 0.695 mmol), and Et₃N (12 mL, 87 mmol) in dried THF (30 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **18**. Black oil, 2.40 g (74%). ¹H NMR (500 MHz, CDCl₃) δ 8.71–8.70 (m, 1H), 8.22–8.20 (m, 1H), 7.34–7.31 (m, 1H), 3.96 (s, 3H), 0.30 (s, 9H). The ¹H NMR data were consistent with those reported in the literature [31].

Synthesis of methyl 2-ethynylnicotinate (**19**). Following the procedure for the synthesis of **13** from **12**, **19** was prepared from **18** (2.40 g, 10.3 mmol) using TBAF (10.3 mL, 10.3 mmol, 1.0 M in THF) in dried THF (24 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **19**. Brown oil, 1.10 g (66%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.74 (dd, *J* = 1.5 Hz and 5.0 Hz, 1H), 8.21 (dd, *J* = 1.5 Hz and 8.0 Hz, 1H), 7.55 (dd, *J* = 5.0 Hz and 8.0 Hz, 1H), 4.55 (s, 1H), 3.87 (s, 3H). The ¹H NMR data were consistent with those reported in the literature [31].

Synthesis of 2-ethynylnicotinic acid (**20**). Following the procedure for the synthesis of **14** from **13**, **20** was prepared from **19** (0.80 g, 4.96 mmol) using NaOH (0.40 g, 9.92 mmol) in

MeOH (8 mL). Yellow solid, 0.72 g. This sample was used directly in the next step without further purification or characterization.

Synthesis of (4-benzyl-4-hydroxypiperidin-1-yl)(2-ethynylpyridin-3-yl)methanone (**A3**). Following the procedure for the synthesis of **A1** from **14** and **3-TFA**, **A3** was prepared from **20** (0.30 g, 2.04 mmol) and **3-TFA** (0.71 g, 2.45 mmol) using EDCI (0.98 g, 5.10 mmol), HOBT (21 mg, 0.109 mmol), and DIPEA (1.58 g, 12.2 mmol) in dried THF (3 mL). White solid, 0.20 g (overall 38% from **19** to **A3**). m.p. 138.2–139.8 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.58 (d, *J* = 4.5 Hz, 1H), 7.74 (s, 1H), 7.49–7.46 (m, 1H), 7.28–7.19 (m, 5H), 4.52–4.00 (m, 3H), 3.28–3.22 (m, 0.72H), 3.10–3.01 (m, 2H), 2.69 (s, 2H), 1.66–1.39 (m, 3.47H), 1.32–1.29 (m, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 166.01, 149.97, 138.15, 136.38, 136.14, 135.91, 134.41, 133.98, 130.58, 128.29, 126.63, 123.52, 81.16, 80.34, 69.67, 69.31, 49.92, 49.29, 43.58, 42.99, 37.77, 36.86, 36.32, 36.09, 35.43; ESI-HR-MS: (*m/z*) calcd. for C₂₀H₂₁N₂O₂ ([M+H]⁺) 321.1598, found 321.1605.

Synthesis of (4-benzyl-4-hydroxypiperidin-1-yl)(2-chloropyridin-3-yl)methanone (**21**). The corresponding carboxylic acid chloride of **4** was prepared from **4** (3.0 g, 19.0 mmol) following the procedure described above using (COCl)₂ (4.82 g, 38.0 mmol) and DMF (2 drops) in dried CH₂Cl₂ (30 mL). The crude carboxylic acid chloride of **4** was dissolved in dried THF (30 mL), and the resulting mixture was cooled at 0 °C and stirred under N₂, followed by addition of **3-TFA** (6.05 g, 20.9 mmol) in one portion and Et₃N (10.6 mL, 76.0 mmol) in a dropwise manner. After addition, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction, after which the mixture was poured into saturated aqueous NaHCO₃ (100 mL). The mixture thus obtained was extracted with EtOAc (50 mL × 3), and the combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/1, by *v/v*) to give **21**. White solid, 1.98 g (31%). m.p. 138.4–138.9 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.47–8.43 (m, 1H), 7.88–7.81 (m, 1H), 7.52–7.47 (m, 1H), 7.27–7.24 (m, 2H), 7.21–7.17 (m, 3H), 4.54 (d, *J* = 5.5 Hz, 1H), 4.26–4.22 (m, 1H), 3.30–3.21 (m, 1H), 3.13–3.02 (m, 2H), 2.71–2.70 (m, 2H), 1.58–1.40 (m, 3H), 1.36–1.29 (m, 1H). The ¹H NMR data were consistent with those reported in the literature [13].

Synthesis of 4-(3-(4-benzyl-4-hydroxypiperidine-1-carbonyl)pyridin-2-yl)benzonitrile (**24**). Following the procedure for the synthesis of **6** from **5** and pyridine-4-boronic acid, **24** was prepared from **21** (1.00 g, 9.36 mmol) and **22** (0.53 g, 3.63 mmol) using Pd(PPh₃)₄ (0.11 g, 0.093 mmol) and Na₂CO₃ (0.96 g, 9.06 mmol) in DME/H₂O (10 mL/10 mL). Purification by column chromatography (EtOAc/PE = 1/1, by *v/v*) gave **24**. White solid, 0.72 g (61%). m.p. 188.8–190.4 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.77–8.75 (m, 1H), 7.97–7.93 (m, 2H), 7.86–7.75 (m, 3H), 7.54–7.51 (m, 1H), 7.25–7.15 (m, 4H), 7.06–7.05 (m, 1H), 4.41–4.39 (m, 1H), 4.29–4.15 (m, 1H), 3.09–3.03 (m, 0.73H), 2.96–2.91 (m, 1H), 2.85–2.83 (m, 1H), 2.72–2.64 (m, 1.43H), 2.44–2.32 (m, 1H), 1.51–1.31 (m, 2H), 1.13–1.05 (m, 1H), 0.93–0.90 (m, 0.58H), 0.06–0.03 (m, 0.54H); ¹³C NMR (151 MHz, CDCl₃) δ 167.38, 167.26, 152.68, 152.13, 150.28, 150.18, 143.25, 143.08, 136.03, 135.98, 135.56, 135.43, 132.14, 132.03, 131.58, 131.25, 130.41, 130.39, 130.31, 130.19, 129.77, 129.14, 128.31, 126.91, 126.82, 123.19, 123.15, 118.42, 118.26, 112.58, 68.95, 68.74, 49.26, 49.03, 42.94, 42.43, 37.53, 37.50, 36.46, 36.01, 35.74, 35.44; ESI-HR-MS: (*m/z*) calcd. for C₂₅H₂₄N₃O₂ ([M+H]⁺) 398.1863, found 398.1863.

Synthesis of 4-(3-(4-benzyl-4-hydroxypiperidine-1-carbonyl)pyridin-2-yl)benzothioamide (**A4**). A mixture of **24** (0.50 g, 1.26 mmol), (NH₄)₂S (95 mg, 1.39 mmol), and Et₃N (0.14 g, 1.39 mmol) in pyridine (5 mL) was stirred at 50 °C under N₂ overnight until TLC analysis indicated completion of the reaction. After cooling to room temperature, the reaction mixture was poured into water (15 mL) and extracted with EtOAc (20 mL × 3). The combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to

afford a residue, which was purified by column chromatography (EtOAc/PE = 1/1, by *v/v*) to give **A4**. Yellow solid, 0.47 g (87%). m.p. 136.2–137.5 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.99–9.93 (m, 1H), 9.65–9.56 (m, 1H), 8.74–8.73 (m, 1H), 8.07–7.95 (m, 2H), 7.81–7.77 (m, 1H), 7.71–7.60 (m, 2H), 7.49–7.47 (m, 1H), 7.23–7.04 (m, 5H), 4.37–4.18 (m, 2H), 3.02–2.96 (m, 1H), 2.91–2.85 (m, 0.67H), 2.82–2.77 (m, 1H), 2.64 (m, 0.63H), 2.36–2.26 (m, 1H), 1.47–1.27 (m, 2H), 1.26–1.22 (m, 0.66H), 1.17–1.10 (m, 1H), 0.87–0.84 (m, 0.60H), 0.79–0.76 (m, 0.64H), –0.08–0.14 (m, 0.67H); ¹³C NMR (151 MHz, CDCl₃) δ 201.86, 201.73, 167.98, 167.71, 153.60, 153.15, 150.33, 150.24, 141.82, 141.74, 140.30, 139.71, 136.42, 136.24, 135.83, 135.73, 131.61, 131.16, 130.59, 130.57, 129.20, 128.54, 128.45, 127.47, 127.36, 126.96, 126.88, 123.05, 122.94, 69.47, 68.97, 48.89, 48.74, 43.12, 42.74, 37.89, 37.76, 36.50, 36.08, 35.74, 35.50, 31.66, 22.73, 14.21; ESI-HR-MS: (*m/z*) calcd for C₂₅H₂₆N₃O₂S ([M+H]⁺) 432.1740, found 432.1741.

Synthesis of (2-(1H-benzo[d]imidazol-5-yl)pyridin-3-yl)(4-benzyl-4-hydroxypiperidin-1-yl)methanone (**A5**). Following the procedure for the synthesis of **6** from **5** and pyridine-4-boronic acid, **A5** was prepared from **21** (0.56 g, 1.69 mmol) and **23** (0.50 g, 2.03 mmol) using Pd(PPh₃)₄ (98 mg, 0.085 mmol) and Na₂CO₃ (0.54 g, 5.07 mmol) in DME/H₂O (6 mL/6 mL). Purification by column chromatography (EtOAc) gave **A5**. White solid, 70 mg (10%). m.p. 137.8–138.9 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.71 (s, 1H), 8.72–8.70 (m, 1H), 8.40–8.26 (m, 1H), 7.93–7.62 (m, 4H), 7.43–7.40 (m, 1H), 7.23–7.10 (m, 4H), 6.74–6.72 (m, 1H), 4.35–4.16 (m, 2H), 2.95–2.70 (m, 3.40H), 2.64–2.54 (m, 1H), 1.93–1.90 (m, 0.60H), 1.59–1.57 (m, 0.68H), 1.44–1.19 (m, 1.68H), 1.04–0.95 (m, 1H), 0.47–0.45 (m, 0.64H), –0.72–0.78 (m, 0.69H); ¹³C NMR (151 MHz, CD₃OD + CDCl₃) δ 168.43, 168.21, 155.31, 154.49, 149.77, 142.57, 142.21, 136.57, 136.29, 136.09, 135.65, 133.35, 133.21, 131.41, 131.02, 130.35, 130.05, 127.99, 127.81, 126.46, 126.33, 124.01, 123.22, 122.19, 122.07, 116.34, 115.86, 115.56, 114.92, 68.81, 68.40, 48.79, 43.00, 42.54, 37.66, 37.52, 36.06, 35.59, 35.44, 34.66; ESI-HR-MS: (*m/z*) calcd. for C₂₅H₂₅N₄O₂ ([M+H]⁺) 413.1972, found 413.1981.

Synthesis of tert-butyl 2-(4-(dimethylcarbamoyl)phenyl)nicotinate (**26**). Following the procedure for the synthesis of **6** from **5** and pyridine-4-boronic acid, **26** was prepared from **5** (2.00 g, 9.36 mmol) and **25** (2.16 g, 11.2 mmol) using Pd(PPh₃)₄ (0.32 g, 0.281 mmol) and Na₂CO₃ (2.98 g, 28.1 mmol) in DME/H₂O (20 mL/20 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **A5**. White solid, 2.82 g (76%). m.p. 85.2–86.4 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.78 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 8.12 (dd, *J* = 1.8 Hz and 7.8 Hz, 1H), 7.54–7.49 (m, 5H), 3.01 (s, 3H), 2.96 (s, 3H), 1.28 (s, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 170.64, 166.42, 157.30, 150.43, 141.44, 137.49, 135.96, 128.52, 128.34, 126.56, 121.62, 81.94, 39.12, 34.95, 27.19; ESI-HR-MS: (*m/z*) calcd. for C₁₉H₂₃N₂O₃ ([M+H]⁺) 327.1703, found 327.1702.

Synthesis of tert-butyl 2-(4-(dimethylcarbamothioyl)phenyl)nicotinate (**27**). A mixture of **26** (2.00 g, 6.13 mmol) and Lawesson reagent (1.49 g, 11.2 mmol) in toluene (20 mL) was refluxed overnight under N₂ until TLC analysis indicated completion of the reaction. After cooling to room temperature, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (50 mL × 3). The combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc) to give **27**. Pale yellow solid, 1.20 g (57%). m.p. 96.8–97.9 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.77 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 8.11 (dd, *J* = 1.8 Hz and 7.8 Hz, 1H), 7.53–7.48 (m, 3H), 7.41–7.39 (m, 2H), 3.53 (s, 3H), 3.20 (s, 3H), 1.30 (s, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 200.32, 166.45, 157.19, 143.35, 139.92, 138.27, 128.91, 128.56, 125.55, 122.03, 82.53, 44.05, 43.08, 27.42; ESI-HR-MS: (*m/z*) calcd. for C₁₉H₂₃N₂O₂S ([M+H]⁺) 343.1475, found 343.1474.

Synthesis of 4-(3-(4-benzyl-4-hydroxypiperidine-1-carbonyl)pyridin-2-yl)-N,N-dimethylbenzothioamide (**A6**). To a stirred solution of **27** (2.00 g, 5.84 mmol) in CH₂Cl₂ (6 mL), cooled to 0 °C, TFA was added dropwise (10 mL). After addition, the reaction mix-

ture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction, after which the mixture was evaporated on a rotary evaporator to dryness. The residue thus obtained was dissolved in dried THF (20 mL), followed by addition of EDCI (2.80 g, 14.6 mmol), HOBT (59 mg, 0.438 mmol), and DIPEA (4.52 g, 35.0 mmol). The resulting mixture was stirred at 0 °C under N₂, and a solution of **3**·TFA (2.03 g, 7.10 mmol) in dried THF (3 mL) was added dropwise. After addition, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction, after which the mixture was poured into water (30 mL). The mixture thus obtained was extracted with EtOAc (50 mL × 3), and the combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc) to give **A6**. Yellow solid, 1.21 g (overall 45% from **27** to **A6**). m.p. 89.4–91.3 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.73–8.72 (m, 1H), 7.81–7.76 (m, 1H), 7.70–7.58 (m, 2H), 7.49–7.35 (m, 3H), 7.25–7.18 (m, 3H), 7.17–7.11 (m, 2H), 4.31–4.09 (m, 2H), 3.60–3.51 (m, 3H), 3.21–3.13 (m, 3H), 3.06–2.96 (m, 1.43H), 2.94–2.81 (m, 2H), 2.66–2.63 (m, 1H), 2.47–2.46 (m, 0.61H), 1.47–1.29 (m, 2H), 1.12–1.00 (m, 1H), 0.94–0.91 (m, 0.52H), 0.26–0.20 (m, 0.60H). ¹³C NMR (151 MHz, CDCl₃) δ 201.60, 201.44, 167.90, 167.64, 153.50, 153.05, 150.24, 150.14, 141.56, 141.45, 140.20, 139.67, 136.40, 136.21, 135.92, 135.82, 131.44, 131.03, 130.57, 130.54, 129.03, 128.40, 128.29, 127.48, 127.41, 126.79, 126.72, 123.02, 122.92, 69.43, 68.94, 48.80, 48.68, 43.06, 42.68, 37.85, 37.73, 36.29, 35.89, 35.54, 35.36, 31.58, 22.66, 14.15; ESI-HR-MS: (*m/z*) calcd. for C₂₇H₃₀N₃O₂S ([M+H]⁺) 460.2053, found 460.2055.

Synthesis of (4-bromophenyl)(*tert*-butyl)sulfane (**29**). To a stirred solution of **28** (5.00 g, 26.5 mmol) and *t*-BuCl (3.93 g, 56 mmol) in MeCN (50 mL) at room temperature under N₂, anhydrous AlCl₃ (0.18 g, 1.33 mmol) was added in portions. After addition, the reaction mixture was stirred at room temperature until completion, as indicated by TLC analysis (typically within 2 h). The reaction mixture was slowly poured into ice–water (150 mL) and extracted with *n*-hexane (100 mL × 3). The combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to give a residue, which was purified by column chromatography (PE) to give **27**. Pale yellow oil, 5.19 g (80%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.57 (dd, *J* = 1.5 Hz and 8.5 Hz, 1H), 7.41 (dd, *J* = 1.3 Hz and 8.3 Hz, 1H), 1.22 (s, 9H). The ¹H NMR data were consistent with those reported in the literature [32].

Synthesis of (4-(*tert*-butylthio)phenyl)boronic acid (**30**). To a stirred solution of **29** (6.48 g, 26.5 mmol) in dried THF (65 mL), cooled to −78 °C under N₂, a solution of *n*-BuLi in *n*-hexane (18.3 mL, 29.2 mmol, 1.6 M in *n*-hexane) was added dropwise. After addition, the reaction mixture was stirred at this temperature for an additional 1 h, followed by dropwise addition of B(OMe)₃ (5.51 g, 53.0 mmol). After addition, stirring was continued at this temperature for an additional 1 h and then at room temperature until TLC analysis indicated completion of the reaction. The reaction mixture was poured into ice–water (100 mL) and extracted with EtOAc (100 mL × 3). The combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/3, by *v/v*) to give **30**. White solid, 4.00 g (72%). m.p. 172.3–173.2 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.13 (s, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 1.24 (s, 9H). The ¹H NMR data were consistent with those reported in the literature [33].

Synthesis of *tert*-butyl 2-(4-(*tert*-butylthio)phenyl)nicotinate (**31**). Following the procedure for the synthesis of **6** from **5** and pyridine-4-boronic acid, **31** was prepared from **30** (0.20 g, 0.95 mmol) and **5** (0.24 g, 1.14 mmol) using Pd(PPh₃)₄ (55 mg, 0.048 mmol) and K₂CO₃ (0.39 g, 2.85 mmol) in refluxing dioxane/H₂O (2 mL/2 mL) under N₂. Purification by column chromatography (EtOAc) gave **31**. White solid, 0.26 g (80%). m.p. 72.3–74.2 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.76 (dd, *J* = 1.5 Hz and 5.0 Hz, 1H), 8.10 (dd, *J* = 1.8 Hz

and 7.8 Hz, 1H), 7.59 (dd, $J = 2.0$ Hz and 6.5 Hz, 2H), 7.53–7.49 (m, 3H), 1.29 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.14, 158.03, 150.84, 141.08, 137.93, 137.13, 133.21, 129.05, 128.90, 121.89, 82.45, 46.22, 31.02, 27.63; ESI-HR-MS: (m/z) calcd. for $\text{C}_{20}\text{H}_{26}\text{NO}_2\text{S}$ ($[\text{M}+\text{H}]^+$) 344.1679, found 344.1688.

Synthesis of (4-benzyl-4-hydroxypiperidin-1-yl)(2-(4-(tert-butylthio)phenyl)pyridin-3-yl)methanone (**A7**). Following the procedure for the synthesis of **A6** from **27**, **A7** was prepared from **31**. Thus, **31** (2.00 g, 5.82 mmol) was first treated with TFA (10 mL) in CH_2Cl_2 (6 mL) at room temperature to give the corresponding carboxylic acid, which was then reacted with **3**·TFA (2.02 g, 6.98 mmol) using EDCI (2.80 g, 14.6 mmol), HOBT (59 mg, 0.437 mmol), and DIPEA (4.51 g, 34.9 mmol) in dried THF (20 mL). Purification by column chromatography (EtOAc) gave **A7**. White solid, 1.55 g (overall 58% from **31** to **A7**). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.73–8.72 (m, 1H), 7.81–7.76 (m, 1H), 7.72–7.70 (m, 1H), 7.64–7.55 (m, 3H), 7.49–7.46 (m, 1H), 7.24–7.21 (m, 2H), 7.18–7.13 (m, 2H), 7.03–7.02 (m, 1H), 4.33–4.16 (m, 2H), 3.05–2.99 (m, 0.65H), 2.95–2.87 (m, 1H), 2.81–2.71 (m, 1H), 2.62–2.55 (m, 1H), 2.37–2.23 (m, 1H), 1.46–1.36 (m, 1H), 1.33–1.26 (m, 10H), 1.23–1.16 (m, 0.41H), 1.12–1.06 (m, 1H), 0.91–0.87 (m, 0.59H), 0.11–0.05 (m, 0.60H); ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$) δ 166.80, 166.73, 153.07, 152.53, 149.89, 149.84, 139.27, 139.23, 137.31, 136.94, 136.64, 135.98, 135.82, 133.30, 132.97, 131.36, 131.12, 130.51, 130.33, 129.00, 128.42, 127.54, 127.52, 125.89, 125.84, 122.71, 68.13, 67.76, 48.43, 48.31, 46.07, 45.97, 42.52, 42.10, 40.06, 37.00, 36.93, 35.89, 35.38, 35.31, 30.73; ESI-HR-MS: (m/z) calcd. for $\text{C}_{28}\text{H}_{33}\text{N}_2\text{O}_2\text{S}$ ($[\text{M}+\text{H}]^+$) 461.2257, found 461.2267.

Synthesis of tert-butyl 2-(4-aminophenyl)nicotinate (**32**). Following the procedure for the synthesis of **10** from **9**, **32** was prepared from **8** (6.30 g, 21.0 mmol) under standard hydrogenolysis condition using 10% Pd/C (0.63 g) in MeOH (63 mL) at atmospheric pressure and room temperature. Purification by column chromatography (EtOAc/PE = 2/1, by v/v) gave **32**. White solid, 4.00 g (71%). m.p. 129.4–130.7 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.64 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 7.90 (dd, $J = 1.8$ Hz and 7.8 Hz, 1H), 7.30 (dd, $J = 4.8$ Hz and 7.8 Hz, 1H), 7.24 (dd, $J = 2.0$ Hz and 6.5 Hz, 2H), 6.61 (dd, $J = 2.0$ Hz and 6.5 Hz, 2H), 5.39 (s, 2H), 1.37 (s, 9H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.77, 158.12, 150.24, 147.31, 137.31, 129.89, 129.84, 128.16, 120.38, 114.23, 81.83, 27.49; ESI-HR-MS: (m/z) calcd. for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_2$ ($[\text{M}+\text{H}]^+$) 271.1441, found 271.1446.

Synthesis of tert-butyl 2-(4-isothiocyanatophenyl)nicotinate (**33**). To a stirred solution of **32** (1.00 g, 3.70 mmol) and Et_3N (0.75 g, 7.41 mmol) in CH_2Cl_2 (10 mL), cooled to 0 °C under N_2 , CSCl_2 (0.85 g, 7.41 mmol) was added in a dropwise manner. After addition, the reaction mixture was stirred at room temperature until completion, as indicated by TLC analysis (typically within 1 h), and then poured into ice–water (15 mL). The resulting mixture was brought to pH = 7–8 with saturated aqueous NaHCO_3 and extracted with EtOAc (50 mL $\times$ 3). The combined extracts were washed with brine, dried (MgSO_4), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/4, by v/v) to give **33**. Pale yellow solid, 0.90 g (78%). m.p. 67.4–69.8 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 8.12 (dd, $J = 1.8$ Hz and 7.8 Hz, 1H), 7.56–7.51 (m, 5H), 1.31 (s, 9H); ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$) δ 166.24, 155.99, 151.03, 139.46, 137.70, 134.18, 130.14, 130.11, 128.26, 125.57, 122.50, 81.96, 27.21; ESI-HR-MS: (m/z) calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_2\text{S}$ ($[\text{M}+\text{H}]^+$) 313.1005, found 313.1011.

Synthesis of tert-butyl 2-(4-(3,3-dimethylthioureido)phenyl)nicotinate (**34**). To a stirred solution of **33** (1.16 g, 3.71 mmol) and Et_3N (1.12 g, 11.1 mmol) in dried THF, cooled to 0 °C under N_2 , $\text{Me}_2\text{NH}\cdot\text{HCl}$ was added in portions. After addition, the reaction mixture was stirred at room temperature until completion, as indicated by TLC analysis (typically within 1 h), and then poured into ice–water (50 mL). The resulting mixture was extracted with EtOAc (50 mL $\times$ 3). The combined extracts were washed with brine, dried (MgSO_4),

and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 2/1, by *v/v*) to give **34**. White solid, 1.08 g (82%). ^1H NMR (500 MHz, DMSO- d_6) δ 9.13 (s, 1H), 8.74 (d, J = 5.0 Hz, 1H), 8.04 (d, J = 7.5 Hz), 7.46–7.42 (m, 5H), 3.30 (s, 6H), 1.34 (s, 9H); ^{13}C NMR (151 MHz, DMSO- d_6) δ 181.22, 167.02, 156.74, 150.71, 141.59, 137.26, 135.46, 128.43, 128.16, 124.59, 121.73, 81.90, 40.97, 27.27; ESI-HR-MS: (m/z) calcd. for $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_2\text{S}$ ($[\text{M}+\text{H}]^+$) 358.1584, found 358.1591.

Synthesis of 2-(4-(3,3-dimethylthioureido)phenyl)nicotinic acid hydrochloric acid salt (**35**). To a stirred solution of **34** (1.46 g, 4.08 mmol) in CH_2Cl_2 (4.5 mL), cooled to 0 °C, TFA (7.5 mL) was added in a dropwise manner. After addition, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction, after which the mixture was evaporated on a rotary evaporator to give a residue. Another flask, cooled to 0 °C, was charged with MeOH (10 mL), to which SOCl_2 (2 mL) was added dropwise. The mixture thus obtained was stirred at this temperature for another 30 min, followed by the slow addition of the residue prepared above. The resulting mixture was stirred at room temperature for another 2 h and subsequently evaporated on a rotary evaporator to give **35** as a hydrochloric acid salt. The product was obtained as a pale yellow solid. This sample was used directly in the next step without further purification or characterization.

Synthesis of 3-(4-(3-(4-benzyl-4-hydroxypiperidine-1-carbonyl)pyridin-2-yl)phenyl)-1,1-dimethylthiourea (**A8**). Following the procedure for the synthesis of **A1** from **14** and **3-TFA**, **A8** was prepared from **35** (1.60 g, 4.74 mmol) and **3-TFA** (1.09 g, 5.69 mmol) using EDCI (2.28 g, 11.9 mmol), HOBT (48 mg, 0.356 mmol), and DIPEA (3.67 g, 28.4 mmol) in dried THF (16 mL). Purification by column chromatography (EtOAc) gave **A8**. White solid, 1.40 g (62%). m.p. 119.6–122.3 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 9.19–9.13 (m, 2H), 8.70–8.68 (m, 1H), 7.76–7.72 (m, 1H), 7.63–7.61 (m, 1H), 7.54–7.51 (m, 2H), 7.42–7.40 (m, 1H), 7.23–7.07 (m, 5H), 4.29–4.27 (m, 1H), 4.22–4.17 (m, 1H), 3.30–3.29 (m, 6H), 3.02–2.73 (m, 3H), 2.45–2.44 (m, 1H), 1.49–1.06 (m, 4H), 0.87–0.82 (m, 1.41H), 0.28–0.22 (m, 0.61H); ^{13}C NMR (126 MHz, DMSO- d_6) δ 181.10, 181.02, 167.12, 167.07, 153.42, 153.12, 149.72, 149.66, 142.18, 141.74, 137.41, 137.34, 135.90, 135.61, 134.51, 134.18, 131.04, 130.71, 130.59, 130.55, 128.22, 127.80, 127.58, 127.37, 125.88, 125.67, 124.56, 124.08, 122.07, 122.03, 68.36, 67.95, 48.22, 48.11, 42.51, 42.22, 41.00, 37.03, 36.90, 35.97, 35.53, 35.27, 35.23, 30.96, 22.07, 13.97; ESI-HR-MS: (m/z) calcd. for $\text{C}_{27}\text{H}_{31}\text{N}_4\text{O}_2\text{S}$ ($[\text{M}+\text{H}]^+$) 475.2162, found 475.2174.

Synthesis of 3-fluoro-2,4'-bipyridine (**37**). Following the procedure for the synthesis of **6** from **5** and pyridine-4-boronic acid, **37** was prepared from **36** (2.00 g, 11.4 mmol) and pyridine-4-boronic acid (1.54 g, 12.5 mmol) using $\text{Pd}(\text{PPh}_3)_4$ (0.66 g, 0.57 mmol) and K_2CO_3 (4.73 g, 34.2 mmol) in dioxane/ H_2O (66 mL/33 mL). Purification by column chromatography (EtOAc/PE = 1/2, by *v/v*) gave **37**. White solid, 1.56 g (79%). m.p. 73.3–75.2 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 8.74–8.73 (m, 2H), 8.62–8.61 (m, 1H), 7.94–7.88 (m, 3H), 7.62–7.58 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.31 (d, J = 263.3 Hz), 150.27, 145.90 (d, J = 5.3 Hz), 143.27 (d, J = 10.0 Hz), 142.66 (d, J = 5.4 Hz), 125.28 (d, J = 4.3 Hz), 124.70 (d, J = 20.5 Hz), 122.91 (d, J = 6.6 Hz); ^{19}F NMR (471 MHz, CDCl_3) δ –121.62; ESI-HR-MS: (m/z) calcd. for $\text{C}_{10}\text{H}_8\text{N}_2\text{F}$ ($[\text{M}+\text{H}]^+$) 175.0667, found 175.0671.

Synthesis of [2,4'-bipyridine]-3-thiol (**38**). A mixture of **37** (2.00 g, 11.5 mmol), Na_2S (1.35 g, 12.76 mmol), and K_2CO_3 (3.18 g, 23.0 mmol) in DMF (50 mL) was stirred overnight at 120 °C under N_2 until TLC analysis indicated completion of the reaction. After cooling to room temperature, the reaction mixture was evaporated on a rotary evaporator to remove most of the solvent under highly reduced pressure and the residue thus obtained was diluted with water (50 mL). The resulting mixture thus obtained was extracted with EtOAc (100 mL $\times$ 3), and the combined extracts were washed with brine, dried (MgSO_4) and evaporated on a rotary evaporator to afford a residue, which was purified by column

chromatography (MeOH/CH₂Cl₂ = 1/10, by *v/v*) to give **38**. Pale yellow solid, 0.42 g (21%). m.p. 149.0–151.0 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.59–8.57 (m, 3H), 7.67 (dd, *J* = 1.5 Hz and 8.0 Hz, 1H), 7.40–7.37 (m, 3H); ¹³C NMR (126 Hz, DMSO-*d*₆) δ 156.33, 149.38, 148.64, 146.14, 140.94, 129.81, 124.34, 123.35; ESI-HR-MS: (*m/z*) calcd. for C₁₀H₉N₂S ([M+H]⁺) 189.0481, found: 189.0486.

Synthesis of tert-butyl 2-([2,4'-bipyridin]-3-ylthio)-2-methylpropanoate (**39**). A mixture of **38** (2.70 g, 14.3 mmol), tert-butyl 2-bromo-2-methylpropanoate (4.80 g, 21.5 mmol) and K₂CO₃ (5.93 g, 12.9 mmol) in DMF (135 mL) was stirred overnight at 45 °C under N₂, when TLC analysis indicated the completion of reaction. On cooling to room temperature, the reaction mixture was evaporated on a rotary evaporator to give a residue, which was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (100 mL × 3), and the combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/1, by *v/v*) to give **39**. Pale yellow oil, 1.71 g (36%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.73 (dd, *J* = 1.8 Hz and 4.3 Hz, 2H), 8.57 (dd, *J* = 1.5 Hz and 5.0 Hz, 1H), 8.32 (dd, *J* = 1.5 Hz and 8.0 Hz, 1H), 7.59 (dd, *J* = 1.5 Hz and 4.4 Hz, 2H), 7.56 (dd, *J* = 4.5 Hz and 8.0 Hz, 1H), 1.33 (s, 6H), 1.20 (s, 9H); ¹³C NMR (126 Hz, DMSO-*d*₆) δ 172.64, 160.26, 149.36, 149.29, 147.58, 144.97, 128.54, 125.07, 123.02, 81.63, 53.02, 27.85, 27.83, 26.17; ESI-HR-MS: (*m/z*) calcd. for C₁₈H₂₃N₂O₂ ([M+H]⁺) 331.1475, found 331.1482.

Synthesis of 2-([2,4'-bipyridin]-3-ylthio)-2-methylpropanoic acid hydrochloric acid salt (**40**). Following the procedure for the synthesis of **35** from **34**, **39** (2.00 g, 6.05 mmol) was first cleaved with TFA (10 mL) in CH₂Cl₂ (10 mL), and then the corresponding carboxylic acid was converted to the hydrochloric acid salt **40** with HCl/MeOH generated by SOCl₂ (2 mL) in MeOH (10 mL). The sample was used directly in the next step without further purification or characterization.

Synthesis of 2-([2,4'-bipyridin]-3-ylthio)-1-(4-benzyl-4-hydroxypiperidin-1-yl)-2-methylpropan-1-one (**B1**). Following the procedure for the synthesis of **6** from **5** and **3·TFA**, **B1** was prepared from **40** (1.50 g, 4.83 mmol) and **3·TFA** (2.79 g, 9.66 mmol) using EDCI (2.42 g, 12.6 mmol), HOBT (49 mg, 0.362 mmol), and DIPEA (2.18 g, 16.9 mmol) in dried THF (75 mL). Purification by column chromatography (EtOAc) gave **B1**. White solid, 1.12 g (overall 41% for **39** to **B1**). m.p. 71.0–73.0 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.67 (dd, *J* = 1.8 Hz and 4.3 Hz, 2H), 8.61 (dd, *J* = 1.5 Hz and 4.5 Hz, 1H), 7.75 (dd, *J* = 1.5 Hz and 3.0 Hz, 1H), 7.51 (dd, *J* = 1.8 Hz and 4.3 Hz, 2H), 7.40 (dd, *J* = 4.5 Hz and 8.0 Hz, 1H), 7.25–7.22 (m, 2H), 7.19–7.16 (m, 3H), 4.46 (s, 1H), 4.07–4.04 (m, 2H), 3.07–2.82 (m, 2H), 2.64 (m, 2H), 1.35–1.34 (m, 4H), 1.27 (s, 6H); ¹³C NMR (151 MHz, CDCl₃) δ 170.80, 158.63, 149.30, 148.50, 147.76, 141.66, 135.84, 130.57, 129.31, 128.64, 127.13, 124.81, 123.51, 69.45, 51.59, 49.36, 37.16, 28.24; ESI-HR-MS: (*m/z*) calcd. for C₂₆H₃₀N₃O₂S ([M+H]⁺) 448.2053, found 448.2065.

Synthesis of 2-([2,4'-bipyridin]-3-ylsulfonyl)-1-(4-benzyl-4-hydroxypiperidin-1-yl)-2-methylpropan-1-one (**B2**). To a stirred solution of **B1** (1.00 g, 2.23 mmol) in CH₂Cl₂ (10 mL), cooled to 0 °C, *m*CPBA was added portionwise (1.16 g, 6.70 mmol). After addition, the reaction temperature was slowly raised to room temperature until TLC analysis indicated completion of the reaction. The reaction mixture was poured into aqueous 10% Na₂S₂O₃ (30 mL) with ice, and the resulting mixture was extracted with EtOAc (50 mL × 3). The combined extracts were washed successively with saturated aqueous NaHCO₃ (50 mL) and brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc) to give **B2**. White solid, 0.88 g (82%). m.p. 139.0–141.0 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.93 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 8.31 (dd, *J* = 1.8 Hz and 8.3 Hz, 1H), 8.26–8.24 (m, 2H), 7.68 (dd, *J* = 4.5 Hz and 8.0 Hz, 2H), 7.49–7.47 (m, 2H), 7.28–7.17 (m, 5H), 4.45 (s, 1H), 3.93–3.91 (m, 2H), 3.00 (s, 2H), 2.67 (s, 2H), 1.40 (s, 6H), 1.36–1.34 (m, 4H); ¹³C NMR (151 MHz, CDCl₃) δ 165.74, 156.15, 153.49, 141.55,

137.74, 136.96, 136.26, 131.58, 130.63, 128.66, 128.36, 126.77, 122.94, 71.57, 69.06, 49.34, 42.24, 36.76, 23.59; ESI-HR-MS: (m/z) calcd. for $C_{26}H_{30}N_3O_4S$ ($[M+H]^+$) 480.1952, found 480.1960.

Synthesis of [2,4'-bipyridin]-3-amine (**42**). Following the procedure for the synthesis of **6** from **5** and pyridine-4-boronic acid, **42** was prepared from **41** (1.00 g, 5.78 mmol) and pyridine-4-boronic acid (0.71 g, 5.78 mmol) using $Pd(PPh_3)_4$ (0.33 g, 0.289 mmol) and K_2CO_3 (1.20 g, 8.67 mmol) in dioxane/ H_2O (32 mL/16 mL). Purification by column chromatography (EtOAc) gave **42**. White solid, 0.39 g (37%). m.p. 134–141 °C. 1H NMR (500 MHz, $DMSO-d_6$) δ 8.93 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 8.31 (dd, $J = 1.8$ Hz and 8.3 Hz, 1H), 8.26–8.24 (m, 2H), 7.68 (dd, $J = 4.5$ Hz and 8.0 Hz, 2H), 7.49–7.47 (m, 2H), 7.28–7.17 (m, 5H), 4.45 (s, 1H), 3.93–3.91 (m, 2H), 3.00 (s, 2H), 2.67 (s, 2H), 1.40 (s, 6H), 1.36–1.34 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.74, 156.15, 153.49, 141.55, 137.74, 136.96, 136.26, 131.58, 130.63, 128.66, 128.36, 126.77, 122.94, 71.57, 69.06, 49.34, 42.24, 36.76, 23.59; ESI-HR-MS: (m/z) calcd. for $C_{10}H_{10}N_3$ ($[M+H]^+$) 172.0869, found 172.0873.

Synthesis of 3-isothiocyanato-2,4'-bipyridine (**43**). Following the procedure for the synthesis of **33** from **32**, **43** was prepared from **42** (2.37 g, 13.8 mmol) using $CSCl_2$ (3.17 g, 27.6 mmol) and Et_3N (2.79 g, 27.6 mmol) in dried CH_2Cl_2 (48 mL). Crude **43**, a brown solid (1.83 g), was used directly in the next step without further purification or characterization.

Synthesis of N-([2,4'-bipyridin]-3-yl)-4-benzyl-4-hydroxypiperidine-1-carbothioamide (**B3**). Following the procedure for the synthesis of **34** from **33** and $Me_2NH \cdot HCl$, **B3** was prepared from **43** (1.50 g, 7.03 mmol) and **3-TFA** (2.44 g, 8.44 mmol) using Et_3N (2.14 g, 21.1 mmol) in dried THF (48 mL). Purification by column chromatography (EtOAc) gave **B3**. White solid, 1.85 g (65%). m.p. 190.0–192.0 °C. 1H NMR (500 MHz, $DMSO-d_6$) δ 9.22 (s, 1H), 8.58–8.56 (m, 3H), 7.67 (dd, $J = 1.5$ Hz and 8.0 Hz, 1H), 7.60 (dd, $J = 1.8$ Hz and 4.3 Hz, 2H), 7.46 (dd, $J = 4.5$ Hz and 8.0 Hz, 1H), 7.30–7.27 (m, 2H), 7.24–7.22 (m, 3H), 4.55 (s, 1H), 4.40 (s, 2H), 3.37–3.30 (m, 2H), 2.71 (s, 2H), 1.41–1.38 (m, 4H); ^{13}C NMR (126 MHz, $DMSO-d_6$) δ 180.57, 152.85, 149.37, 147.53, 146.20, 139.33, 137.44, 135.88, 130.59, 127.71, 126.02, 123.69, 123.13, 68.44, 48.57, 44.39, 36.48; ESI-HR-MS: (m/z) calcd. for $C_{23}H_{25}N_4OS$ ($[M+H]^+$) 405.1744, found 405.1754.

Synthesis of phenyl [2,4'-bipyridin]-3-ylcarbamate (**44**). To a stirred solution of $PhO-COCl$ (1.50 g, 8.76 mmol) in MeCN, cooled to 0 °C under N_2 , pyridine (1.23 g, 17.5 mmol) and a solution of **42** (1.00 g, 5.84 mmol) in MeCN (3 mL) were added dropwise in sequence. After addition, the reaction mixture was stirred at room temperature until TLC indicated analysis completion of the reaction (typically within 1 h) and then poured into ice–water (50 mL). The resulting mixture was extracted with EtOAc (50 mL $\times$ 3), and the combined extracts were washed with brine, dried ($MgSO_4$), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 2/1, by v/v) to give **44**. White solid, 1.43 g (84%). m.p. 133.0–134.0 °C. 1H NMR (500 MHz, $DMSO-d_6$) δ 8.86–8.80 (m, 2H), 8.50–8.47 (m, 0.69H), 7.73–7.70 (m, 0.70H), 7.67–7.64 (m, 1.49H), 7.42–7.39 (m, 3H), 7.30–7.27 (m, 1.46H), 7.00–6.97 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.52, 150.54, 150.45, 150.37, 150.16, 145.38, 137.36, 132.94, 129.74, 126.73, 124.50, 123.05, 120.97; ESI-HR-MS: (m/z) calcd. for $C_{17}H_{14}N_3O_2$ ($[M+H]^+$) 292.1081, found 292.1084.

Synthesis of N-([2,4'-bipyridin]-3-yl)-4-benzyl-4-hydroxypiperidine-1-carboxamide (**B4**). Following the procedure for the synthesis of **B3** from **43** and **3-TFA**, **B4** was prepared from **44** (0.60 g, 2.06 mmol) and **3-TFA** (0.79 g, 4.12 mmol) using Et_3N (0.63 g, 6.18 mmol) in dried THF (10 mL). Purification by column chromatography (EtOAc) gave **B4**. White solid, 0.62 g (78%). m.p. 99.0–101.1 °C. 1H NMR (500 MHz, $DMSO-d_6$) δ 8.56 (dd, $J = 1.5$ Hz and 4.5 Hz, 2H), 8.47 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 8.40 (s, 1H), 7.70 (dd, $J = 1.5$ Hz and 8.0 Hz, 1H), 7.57 (dd, $J = 1.5$ Hz and 4.5 Hz, 2H), 7.41 (dd, $J = 4.5$ Hz and 8.0 Hz, 1H), 7.30–7.27 (m, 2H), 7.23–7.19 (m, 3H), 4.40 (s, 1H), 3.70–3.66 (m, 2H), 3.07–3.01 (m, 2H), 2.68 (m, 2H), 1.33–1.30 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.35, 150.52, 146.64, 146.02,

144.76, 135.74, 133.60, 130.57, 130.54, 128.63, 127.10, 124.12, 123.49, 69.23, 49.39, 40.47, 36.60; ESI-HR-MS: (m/z) calcd. for $C_{23}H_{25}N_4O_2$ ($[M+H]^+$) 389.1973, found 389.1980.

Synthesis of [2,4'-bipyridine]-3-carbaldehyde (**46**). Following the procedure for the synthesis of **6** from **5** and pyridine-4-boronic acid, **46** was prepared from **45** (10.00 g, 54.3 mmol) and pyridine-4-boronic acid (7.35 g, 59.8 mmol) using $Pd(PPh_3)_4$ (3.14 g, 2.72 mmol) and K_2CO_3 (22.51 g, 16.3 mmol) in dioxane/ H_2O (200 mL/100 mL). Purification by column chromatography (EtOAc) gave **46**. White solid, 5.20 g (57%). m.p. 108.0–110.0 °C. 1H NMR (500 MHz, $DMSO-d_6$) δ 10.00 (s, 1H), 8.95 (dd, J = 2.0 and 5.0 Hz, 1H), 8.75–8.74 (m, 2H), 8.34 (dd, J = 1.75 and 7.8 Hz, 1H), 7.70 (dd, J = 5.0 and 8.0 Hz, 1H), 7.66–7.65 (m, 2H). The 1H NMR data were consistent with those reported in the literature [24].

Synthesis of (E)-[2,4'-bipyridine]-3-carbaldehyde oxime (**47**). To a stirred solution of **46** (5.00 g, 27.1 mmol) in EtOH/ H_2O (25 mL/25 mL) at room temperature, $NH_2OH \cdot HCl$ (2.07 g, 29.8 mmol) and NaOH (1.08 g, 27.1 mmol) were added successively in a portionwise manner. After addition, the reaction mixture was stirred at reflux overnight until TLC analysis indicated completion of the reaction. After cooling to room temperature, the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (50 mL $\times$ 3). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc) to give **47**. White solid, 3.00 g (55%). m.p. 156.0–157.2 °C. 1H NMR (500 MHz, $DMSO-d_6$) δ 11.73 (s, 1H), 8.72–8.71 (m, 3H), 8.24 (dd, J = 2.0 Hz and 8.0 Hz, 1H), 8.01 (s, 1H), 7.54–7.52 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.05, 150.45, 149.64, 146.83, 146.34, 135.16, 127.19, 124.63, 123.75; ESI-HR-MS: (m/z) calcd. for $C_{11}H_{10}N_3O$ ($[M+H]^+$) 200.0809, found 200.0823.

Synthesis of [2,4'-bipyridin]-3-ylmethanamine (**48**). To a stirred solution of **47** (0.50 g, 2.51 mmol) in EtOH/ H_2O (5 mL/5 mL), cooled to 0 °C under N_2 , $AcONH_4$ (0.48 g, 6.27 mmol) and concentrated aqueous ammonia (7.5 mL) were added successively, followed by addition of zinc powder (0.82 g, 12.6 mmol). After addition, the reaction mixture was refluxed overnight until TLC analysis indicated completion of the reaction. After cooling to room temperature, the reaction mixture was evaporated on a rotary evaporator to remove EtOH and then diluted with saturated brine (50 mL). The resulting mixture was extracted with EtOAc (50 mL $\times$ 3), and the combined extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography ($MeOH/CH_2Cl_2$ = 1/15, by v/v) to give **48**. Pale yellow oil (0.24 g). This sample was directly used in the next step without further purification or characterization.

Synthesis of phenyl ([2,4'-bipyridin]-3-ylmethyl)carbamate (**49**). Following the procedure for the synthesis of **44** from **42**, **49** was prepared from **48** (0.24 g, 1.32 mmol) and $PhOCOCl$ (0.31 g, 1.98 mmol) using pyridine (0.52 g, 6.64 mmol) in MeCN (5 mL). Purification by column chromatography (EtOAc) gave **49**. Colorless oil, 0.05 g. This sample was directly used in the next step without characterization.

Synthesis of N-([2,4'-bipyridin]-3-ylmethyl)-4-benzyl-4-hydroxypiperidine-1-carboxamide (**B5**). Following the procedure for the synthesis of **B3** from **43** and **3-TFA**, **B5** was prepared from **49** (0.10 g, 0.328 mmol) and **3-TFA** (0.19 g, 0.656 mmol) using Et_3N (0.10 g, 0.984 mmol) in dried THF (10 mL). Purification by column chromatography (EtOAc) gave **B5**. White solid, 50 mg (overall 76% for **47** to **B5**). m.p. 181.3–183.4 °C. 1H NMR (500 MHz, $DMSO-d_6$) δ 8.67 (d, J = 5.0 Hz, 2H), 8.55 (d, J = 4.5 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 5.0 Hz, 2H), 7.43 (dd, J = 4.5 Hz and 8.0 Hz, 1H), 7.27–7.24 (m, 2H), 7.21–7.18 (m, 3H), 7.01 (t, J = 5.5 Hz, 1H), 4.35 (s, 1H), 4.24–4.23 (m, 2H), 3.63–3.59 (m, 2H), 3.03–2.97 (m, 2H), 2.67 (s, 2H), 1.36–1.28 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.31, 155.39, 150.01, 148.48, 147.68, 137.15, 135.91, 133.35, 130.61, 128.59, 127.03, 123.77, 123.60, 69.35, 49.40, 41.95, 40.22, 36.55; ESI-HR-MS: (m/z) calcd. for $C_{24}H_{27}N_4O_2$ ($[M+H]^+$) 403.2199, found 403.2139.

Synthesis of (2-bromopyridin-3-yl)methanol (**50**). To a stirred solution of **45** (3.00 g, 16.1 mmol) in MeOH (30 mL), cooled to 0 °C under N₂, NaBH₄ (0.73 g, 19.3 mmol) was added portionwise. After addition, the reaction temperature was slowly raised to room temperature until TLC analysis indicated completion of the reaction. The reaction mixture was poured into saturated aqueous NH₄Cl (100 mL), and the resulting mixture was extracted with EtOAc (100 mL × 3). The combined extracts were washed with saturated brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/3, by *v/v*) to give **50**. White solid, 2.90 g (96%). m.p. 66.0–69.0 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.28–8.26 (m, 1H), 7.90–7.88 (m, 1H), 7.49–7.46 (m, 1H), 5.60 (s, 1H), 4.49 (s, 2H). The ¹H NMR data were consistent with those reported in the literature [34].

Synthesis of 2-bromo-3-(bromomethyl)pyridine (**51**). To a stirred solution of **50** (2.82 g, 15.0 mmol) in dried CH₂Cl₂ (30 mL), cooled to 0 °C under N₂, PBr₃ (8.12 g, 30.0 mmol) was added in a dropwise manner. After addition, the reaction mixture was stirred at reflux until completion, as indicated by TLC analysis (typically within 3 h). After cooling to room temperature, the reaction mixture was slowly poured into saturated aqueous NaHCO₃ (100 mL), and the resulting mixture was extracted with EtOAc (100 mL × 3). The combined extracts were washed with saturated brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/5, by *v/v*) to give **51**. Pale yellow oil, 1.90 g (51%). ¹H NMR (500 MHz, CD₃OD) δ 8.28 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 7.95 (dd, *J* = 1.8 Hz and 7.8 Hz, 1H), 7.41 (dd, *J* = 5.0 Hz and 7.5 Hz, 1H), 4.65 (s, 2H). The ¹H NMR data were consistent with those reported in the literature [35].

Synthesis of 2-(2-bromopyridin-3-yl)acetonitrile (**52**). To a stirred solution of **51** (3.40 g, 13.6 mmol) in MeCN (34 mL), cooled to 0 °C under N₂, TMSCN (4.05 g, 40.8 mmol) was added slowly, followed by dropwise addition of a solution of TBAF in THF (17.7 mL, 17.7 mmol, 1.0 M in THF). After addition, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction and was then poured into ice–water (100 mL). The resulting mixture was extracted with EtOAc (100 mL × 3), and the combined extracts were washed with saturated brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/4, by *v/v*) to give **52**. White solid, 2.30 g (85%). m.p. 80.0–82.0 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.39 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 7.96 (dd, *J* = 1.8 Hz and 7.8 Hz, 1H), 7.53 (dd, *J* = 4.5 Hz and 7.5 Hz, 1H), 4.11 (s, 2H). The ¹H NMR data were consistent with those reported in the literature [36].

Synthesis of 2-([2,4'-bipyridin]-3-yl)acetonitrile (**53**). Following the procedure for the synthesis of **6** from **5** and pyridine-4-boronic acid, **53** was prepared from **52** (1.85 g, 9.39 mmol) and pyridine-4-boronic acid (1.39 g, 11.3 mmol) using Pd (PPh₃)₄ (0.34 g, 0.282 mmol) and Na₂CO₃ (2.99 g, 28.2 mmol) in DME/H₂O (20 mL/20 mL). White solid, 1.02 g (56%). m.p. 150.0–152.1 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.72 (dd, *J* = 3.5 Hz and 4.3 Hz, 2H), 8.69 (dd, *J* = 1.5 Hz and 5.0 Hz, 1H), 8.01 (dd, *J* = 1.5 Hz and 8.0 Hz, 1H), 7.57–7.54 (m, 3H), 4.14 (s, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 155.93, 150.44, 149.75, 146.36, 137.73, 124.21, 123.96, 123.39, 116.94, 21.77; ESI-HR-MS: (*m/z*) calcd. for C₁₂H₁₀N₃ ([M+H]⁺) 196.0870, found 196.0870.

Synthesis of methyl 2-([2,4'-bipyridin]-3-yl)acetate (**54**). To a stirred solution of **53** (1.00 g, 5.12 mmol) in AcOH (20 mL)/H₂O (2 mL), cooled to 0 °C under N₂, concentrated H₂SO₄ (2 mL) was added dropwise. After addition, the reaction mixture was refluxed overnight until TLC analysis indicated completion of the reaction. Upon cooling to room temperature, the reaction mixture was evaporated on a rotary evaporator to afford a residue, which was diluted with a mixed solvent of MeOH (4 mL) and CH₂Cl₂ (40 mL). The mixture

thus obtained was dried (MgSO_4) and evaporated on a rotary evaporator to afford a residue, which was dissolved in MeOH (10 mL). The resulting solution was cooled at 0 °C, followed by dropwise addition of SOCl_2 (2 mL), and the reaction mixture was then refluxed under N_2 overnight, until TLC analysis indicated completion of the reaction. Upon cooling to room temperature, saturated aqueous NaHCO_3 was slowly added to the reaction mixture until pH > 8. The mixture thus obtained was extracted with EtOAc (50 mL $\times$ 3), and the combined extracts were washed with saturated brine, dried (MgSO_4), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/1, by *v/v*) to give **54**. Pale yellow oil, 0.55 g (47%). ^1H NMR (500 MHz, CDCl_3) δ 8.73–8.72 (m, 2H), 8.64 (dd, J = 1.8 Hz and 4.8 Hz, 1H), 7.76 (dd, J = 1.8 Hz and 7.8 Hz, 1H), 7.44 (d, J = 6.0 Hz, 2H), 7.35 (dd, J = 4.8 Hz and 7.8 Hz, 1H), 3.68 (s, 3H), 3.70 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 171.20, 156.53, 149.91, 148.70, 147.53, 139.13, 127.78, 123.79, 123.40, 52.39, 37.90; ESI-HR-MS: (m/z) calcd. for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2$ ($[\text{M}+\text{H}]^+$) 229.0972, found 229.0971.

Synthesis of methyl 2-([2,4'-bipyridin]-3-yl)-2-methylpropanoate (**55**). To a stirred solution of **54** (0.50 g, 2.19 mmol) in dried THF (5 mL), cooled to −78 °C under N_2 , a solution of LiHMDS in THF (6.6 mL, 6.6 mmol, 1.0 M in THF) was added dropwise. After addition, the resulting mixture was stirred at this temperature for another 1 h, followed by dropwise addition of a solution of MeI (0.93 g, 6.57 mmol) in dried THF (5 mL). After addition, the reaction mixture was stirred at this temperature for 1 h and then at room temperature overnight until LC-MS analysis indicated completion of the reaction and was then poured into ice–water (20 mL). The mixture thus obtained was extracted with EtOAc (30 mL $\times$ 3), and the combined extracts were washed with brine, dried (MgSO_4), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/1, by *v/v*) to give **55**. White solid, 0.47 g (84%). m.p. 103.1–105.3 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.68 (d, J = 5.0 Hz, 2H), 8.57 (dd, J = 1.3 Hz and 4.8 Hz, 1H), 7.88 (dd, J = 1.5 Hz and 8.0 Hz, 1H), 7.38 (dd, J = 4.8 Hz and 8.3 Hz, 1H), 7.27–7.26 (m, 2H), 3.37 (s, 3H), 1.53 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 176.49, 156.26, 149.42, 149.30, 147.32, 138.62, 134.84, 124.17, 123.18, 52.13, 45.84, 28.28; ESI-HR-MS: (m/z) calcd. for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_2$ ($[\text{M}+\text{H}]^+$) 257.1285, found 257.1285.

Synthesis of 2-([2,4'-bipyridin]-3-yl)-2-methylpropanoic acid (**56**). To a stirred solution of **55** (0.43 g, 1.68 mmol) in MeOH (5 mL) a solution of NaOH (0.13 g, 3.36 mmol) in H_2O (1 mL) was added. After addition, the reaction mixture was stirred at 45 °C overnight until TLC analysis indicated completion of the reaction. Upon cooling to room temperature, the reaction mixture was cooled in an ice–water bath, followed by dropwise addition of concentrated HCl (0.28 mL, 3.36 mmol). After that, the mixture became a white slurry, and stirring was continued for another 1 h. The precipitate was collected via suction filtration and dried in vacuo at room temperature to give **56**. White solid, 0.12 g (34%). m.p. 135.4–137.1 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 12.44 (s, 1H), 8.59–8.58 (m, 2H), 8.51–8.49 (m, 1H), 7.99–7.97 (m, 1H), 7.47 (dd, J = 4.8 Hz and 8.3 Hz, 1H), 7.27–7.26 (m, 2H), 1.36 (s, 6H); ^{13}C NMR (151 MHz, CD_3OD) δ 179.88, 157.11, 151.31, 149.57, 147.52, 140.69, 137.16, 126.45, 125.01, 46.69, 28.17; ESI-HR-MS: (m/z) calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_2$ ($[\text{M}+\text{H}]^+$) 243.1129, found 243.1129.

Synthesis of 2-([2,4'-bipyridin]-3-yl)-1-(4-benzyl-4-hydroxypiperidin-1-yl)-2-methylpropan-1-one (**B6**). Following the procedure for the synthesis of **21** from **4** and **3·TFA**, **56** (0.60 g, 2.48 mmol) was first treated with $(\text{COCl})_2$ (0.94 g, 7.44 mmol) using DMF (one drop) as catalyst in dried CH_2Cl_2 (6 mL) to give the corresponding carboxylic acid chloride, which was subsequently treated with **3·TFA** (0.93 g, 3.22 mmol) using Et_3N (1.51 g, 14.9 mmol) in dried THF (8 mL) to give **B6** after column chromatography (EtOAc/PE = 1/1, by *v/v*). White solid, 0.13 g (16%). m.p. 150.3–152.4 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.53–8.51

(m, 3H), 7.91 (dd, $J = 1.8$ Hz and 8.3 Hz, 1H), 7.45 (dd, $J = 4.8$ Hz and 8.3 Hz, 1H), 7.25–7.13 (m, 7H), 4.34 (s, 1H), 3.61–3.58 (m, 1H), 2.90–2.87 (m, 1H), 2.73–2.69 (m, 1H), 2.60 (s, 2H), 2.48–2.36 (m, 1H), 1.41 (s, 3H), 1.37 (s, 3H), 1.27–1.12 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.37, 154.92, 148.95, 148.81, 147.36, 139.92, 135.90, 134.56, 130.53, 128.54, 126.97, 123.78, 123.64, 69.23, 49.43, 45.98, 42.27, 37.99, 36.71, 36.25, 31.52, 28.52; ESI-HR-MS: (m/z) calcd. for $\text{C}_{26}\text{H}_{30}\text{N}_3\text{O}_2$ ($[\text{M}+\text{H}]^+$) 416.2333, found: 416.2332.

Synthesis of methyl 1-([2,4'-bipyridin]-3-yl)cyclopropane-1-carboxylate (**57**). To a stirred solution of **54** (3.00 g, 13.1 mmol) in dried THF (30 mL), cooled to -78°C under N_2 , a solution of LiHMDS in THF (15.7 mL, 15.7 mmol, 1.0 M in THF) was added dropwise. After addition, the resulting mixture was stirred at this temperature for another 1 h, followed by dropwise addition of a solution of 1,3,2-dioxathiolane 2,2-dioxide (1.95 g, 15.7 mmol) in dried THF (6 mL). After addition, the resulting mixture was stirred at -20°C for 1.5 h and then cooled to -78°C , followed by addition of a solution of LiHMDS in THF (15.7 mL, 15.7 mmol, 1.0 M in THF). After that, the reaction mixture was stirred at room temperature overnight until LC-MS analysis indicated completion of the reaction, and poured into ice–water (100 mL). The mixture thus obtained was extracted with EtOAc (50 mL $\times$ 3), and the combined extracts were washed with brine, dried (MgSO_4), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/1, by v/v). White solid, 2.00 g (60%). m.p. 89.1 – 91.5°C . ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.66 (dd, $J = 1.5$ Hz and 4.5 Hz, 2H), 8.61 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 7.91 (dd, $J = 1.5$ Hz and 8.0 Hz, 1H), 7.46 (dd, $J = 4.8$ Hz and 7.8 Hz, 1H), 7.40 (dd, $J = 1.8$ Hz and 4.3 Hz, 1H), 3.52 (s, 3H), 1.39 (d, $J = 3.5$ Hz, 2H), 1.08 (d, $J = 3.0$ Hz, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.23, 157.41, 152.88, 149.20, 147.94, 142.91, 136.27, 126.37, 125.46, 28.26, 19.41; ESI-HR-MS: (m/z) calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_2$ ($[\text{M}+\text{H}]^+$) 255.1129, found 255.1127.

Synthesis of 1-([2,4'-bipyridin]-3-yl)cyclopropane-1-carboxylic acid (**58**). Following the procedure for the synthesis of **56** from **55**, **58** was prepared from **57** (2.00 g, 7.87 mmol) first by treatment with NaOH (0.94 g, 23.6 mmol) in a mixture of MeOH (20 mL)/ H_2O (2 mL), and subsequent acidification with concentrated HCl (1.97 mL, 23.6 mmol). White solid, 1.43 g (76%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 12.69 (s, 1H), 8.77 (d, $J = 5.5$ Hz, 2H), 8.63 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 7.94 (dd, $J = 1.5$ Hz and 7.5 Hz, 1H), 7.65 (d, $J = 5.0$ Hz, 2H), 7.49 (dd, $J = 4.8$ Hz and 7.8 Hz, 1H), 1.39 (s, 2H), 0.97 (s, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.18, 157.42, 152.90, 149.21, 147.94, 142.89, 136.28, 126.38, 125.44, 28.26, 19.40; ESI-HR-MS: (m/z) calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_2$ ($[\text{M}+\text{H}]^+$) 241.0972, found 241.0971.

Synthesis of (1-([2,4'-bipyridin]-3-yl)cyclopropyl)(4-benzyl-4-hydroxypiperidin-1-yl)methanone (**B7**). Following the procedure for the synthesis of **B6** from **56**, **58** (0.50 g, 2.08 mmol) was first treated with $(\text{COCl})_2$ (0.53 g, 4.16 mmol) in the presence of DMF (one drop) in dried CH_2Cl_2 (5 mL) to form the corresponding carboxylic acid chloride, which was subsequently treated with **3**•TFA (0.78 g, 2.70 mmol) in the presence of Et_3N (1.26 g, 12.5 mmol) in dried THF (5 mL) to give **B7** after column chromatography (EtOAc). White solid, 0.33 g (38%). m.p. 122.5 – 124.1°C . ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.56 (dd, $J = 1.3$ Hz and 4.8 Hz, 1H), 8.46 (dd, $J = 1.5$ Hz and 4.5 Hz, 2H), 7.87 (dd, $J = 1.5$ Hz and 8.0 Hz, 1H), 7.43 (dd, $J = 4.5$ Hz and 8.0 Hz, 1H), 7.31–7.28 (m, 2H), 7.24–7.21 (m, 1H), 7.17–7.16 (m, 2H), 7.08–7.07 (m, 2H), 4.31 (s, 1H), 3.26–3.22 (m, 2H), 2.64–2.55 (m, 4H), 1.43–1.33 (m, 4H), 1.00–0.82 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 169.52, 157.14, 149.35, 147.81, 147.28, 135.98, 135.14, 134.17, 130.54, 128.55, 127.05, 124.12, 123.44, 69.49, 49.57, 35.76, 27.85, 16.19; ESI-HR-MS: (m/z) calcd. for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_2$ ($[\text{M}+\text{H}]^+$) 414.2177, found 414.2174.

Synthesis of *tert*-butyl 4-benzyl-4-cyanopiperidine-1-carboxylate (**68**). To a stirred solution of **67** (3.00 g, 14.3 mmol) in dried THF (30 mL), cooled to -78°C under N_2 , a solution of LDA in THF (9.3 mL, 18.6 mmol, 2.0 M in THF) was added dropwise. After addition, the mixture thus obtained was stirred at this temperature for 40 min, followed

by dropwise addition of BnBr (3.18 g, 18.6 mmol). After that, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction, and poured into ice-water (50 mL). The resulting mixture was extracted with EtOAc (50 mL $\times$ 3), and the combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/10, by *v/v*) to give **68**. White solid, 3.50 g (82%). m.p. 85.1–86.5 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.36–7.33 (m, 2H), 7.30–7.27 (m, 3H), 4.00–3.97 (m, 2H), 2.91–2.78 (m, 4H), 1.76–1.73 (m, 2H), 1.57–1.51 (m, 2H), 1.40 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 154.54, 134.42, 130.39, 128.62, 127.68, 121.95, 80.15, 45.95, 40.93, 39.24, 34.77, 28.50; ESI-HR-MS: (*m/z*) calcd. for C₁₈H₂₄N₂NaO₂ ([M+Na]⁺) 323.1730, found 323.1737.

Synthesis of *tert*-butyl 4-benzyl-4-carbamoylpiperidine-1-carboxylate (**69**). To a stirred solution of **68** (2.00 g, 6.66 mmol) in DMSO (20 mL), cooled to 0 °C, K₂CO₃ (1.82 g, 13.2 mmol) and H₂O₂ (1.13 g, 33.3 mmol) were added successively. After addition, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction, and poured into ice-water (60 mL). The resulting mixture was extracted with EtOAc (50 mL $\times$ 3), and the combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc/PE = 1/5, by *v/v*) to give **69**. White solid, 2.00 g (94%). m.p. 159.9–162.1 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.29–7.23 (m, 3H), 7.21–7.18 (m, 1H), 7.14–7.12 (m, 2H), 7.05 (br, 1H), 3.71–3.68 (m, 2H), 2.84–2.77 (m, 4H), 1.91–1.89 (m, 2H), 1.37 (s, 9H), 1.30–1.24 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 177.05, 154.96, 136.32, 130.30, 128.29, 126.98, 79.75, 46.79, 46.24, 41.46, 41.03, 40.70, 33.55, 28.53; ESI-HR-MS: (*m/z*) calcd. for C₁₈H₂₇N₂O₃ ([M+H]⁺) 319.2017, found 319.2017.

Synthesis of *tert*-butyl 4-amino-4-benzylpiperidine-1-carboxylate (**70**). To a stirred solution of **69** (1.93 g, 6.06 mmol) in MeCN/H₂O (10 mL/10 mL) at room temperature, PIFA (2.61 g, 6.06 mmol) was added. After addition, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction, and poured into ice-water (50 mL). The resulting mixture was extracted with EtOAc (50 mL $\times$ 3), and the combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography (EtOAc) to give **70**. White solid, 0.96 g (55%). m.p. 163.4–166.2 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.83 (br, 2H), 7.38–7.31 (m, 3H), 7.25–7.24 (m, 2H), 3.50–3.46 (m, 4H), 2.98–2.97 (m, 2H), 1.64–1.58 (m, 4H), 1.38 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 154.90, 137.50, 130.39, 128.02, 126.17, 79.30, 45.84, 40.98, 39.80, 39.12, 36.46, 31.99, 28.37; ESI-HR-MS: (*m/z*) calcd. for C₁₇H₂₇N₂O₂ ([M+H]⁺) 291.2067, found 291.2065.

General Procedure 1: Synthesis of **71-1**, **72-1**, **72-3**, and **72-4**. To a stirred solution of **70** (1.0 eq) in dried CH₂Cl₂ (10 *v/w*, based on **70**), cooled to 0 °C under N₂, Et₃N (2–3 eq) was added, followed by dropwise addition of carbonyl or sulfonyl chloride (1.2–1.5 eq). After that, the reaction mixture was stirred at room temperature until completion, as indicated by TLC analysis (typically within 2–3 h), and poured into ice-water. The resulting mixture thus obtained was extracted with CH₂Cl₂ in three portions, and the combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography to give the desired product.

General Procedure 2: Synthesis of **71-2**, **71-3**, **72-2**, and **72-5** to **72-8**. To a stirred solution of **70** (1.0 eq) and DMAP (0.2 eq) in dried CH₂Cl₂ (10 *v/w*, based on **70**), cooled to 0 °C under N₂, Et₃N (2–3 eq) was added, followed by dropwise addition of carbonyl or sulfonyl anhydride (1.2–1.5 eq). After that, the reaction mixture was stirred at room temperature until completion, as indicated by TLC analysis (typically within 2–3 h), and poured into ice-water. The resulting mixture thus obtained was extracted with CH₂Cl₂ in three portions,

and the combined extracts were washed with brine, dried (MgSO_4), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography to give the desired product.

tert-butyl 4-benzyl-4-(methylsulfonamido)piperidine-1-carboxylate (**71-1**). Compound **71-1** was prepared according to General Procedure 2 from **70** (2.00 g, 6.89 mmol) using Ms_2O (1.44 g, 8.27 mmol), DMAP (0.17 g, 1.38 mmol), and Et_3N (1.41 g, 13.8 mmol) in dried CH_2Cl_2 (20 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by *v/v*) gave **71-1**. White foam. 1.20 g (47%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.31–7.27 (m, 4H), 7.23–7.20 (m, 1H), 6.74 (s, 1H), 3.62 (d, $J = 13.5$ Hz, 2H), 3.12 (br, 2H), 3.01 (s, 5H), 1.81 (d, $J = 13.5$ Hz, 2H), 1.45–1.39 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.63, 135.80, 131.19, 128.17, 126.77, 79.78, 58.53, 45.66, 45.04, 39.91, 39.17, 34.40, 28.38; ESI-HR-MS: (m/z) calcd. for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 391.1662, found 391.1664.

tert-butyl 4-benzyl-4-((trifluoromethyl)sulfonamido)piperidine-1-carboxylate (**71-2**). Compound **71-2** was prepared according to General Procedure 2 from **70** (1.50 g, 5.17 mmol) using Tf_2O (1.75 g, 6.20 mmol), DMAP (0.13 g, 1.03 mmol), and Et_3N (1.04 g, 10.3 mmol) in dried CH_2Cl_2 (15 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by *v/v*) gave **71-2**. White foam, 1.10 g (50%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.37 (s, 1H), 7.31–7.22 (m, 5H), 3.66–3.62 (m, 2H), 2.98–2.92 (m, 4H), 1.90–1.87 (m, 1H), 1.68–1.65 (m, 1H), 1.60–1.54 (m, 1H), 1.48–1.42 (m, 1H), 1.34 (s, 9H); ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ −76.26; ^{13}C NMR (151 MHz, CDCl_3) δ 154.63, 134.38, 128.60, 127.31, 123.81 (q, $J = 332.6$ Hz), 79.96, 57.55, 49.67, 39.40, 38.59, 35.61, 33.93, 28.44; ESI-HR-MS: (m/z) calcd. for $\text{C}_{18}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_4\text{S}$ ($[\text{M}-\text{H}]^-$) 421.1414, found 421.1416.

tert-butyl 4-benzyl-4-(ethylsulfonamido)piperidine-1-carboxylate (**71-3**). Compound **71-3** was prepared according to General Procedure 1 from **70** (1.50 g, 5.17 mmol) using $\text{CH}_3\text{CH}_2\text{SO}_2\text{Cl}$ (0.80 g, 6.20 mmol) and Et_3N (1.04 g, 10.3 mmol) in dried CH_2Cl_2 (15 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by *v/v*) gave **71-3**. White foam, 0.11 g (6%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.32–7.27 (m, 4H), 7.23–7.20 (m, 1H), 6.67 (s, 1H), 3.62–3.58 (m, 2H), 3.08–3.00 (m, 2H), 1.82–1.79 (m, 2H), 1.45–1.39 (m, 2H), 1.36 (s, 9H), 1.22 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.60, 135.79, 131.22, 128.18, 126.78, 79.78, 58.43, 50.98, 45.70, 39.94, 30.24, 34.46, 28.38, 8.52; ESI-HR-MS: (m/z) calcd. for $\text{C}_{19}\text{H}_{30}\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 405.1818, found 405.1815.

tert-butyl 4-acetamido-4-benzylpiperidine-1-carboxylate (**72-1**). Compound **72-1** was prepared according to General Procedure 1 from **70** (0.30 g, 1.03 mmol) using AcCl (97 mg, 1.24 mmol) and Et_3N (0.21 g, 2.06 mmol) in dried CH_2Cl_2 (3 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by *v/v*) gave **72-1**. White foam, 0.18 g (52%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.30–7.27 (m, 2H), 7.22–7.19 (m, 1H), 7.17 (s, 1H), 7.09–7.07 (m, 2H), 3.69–3.66 (m, 2H), 2.96 (s, 2H), 2.85 (s, 2H), 2.00–1.96 (m, 2H), 1.83 (s, 3H), 1.38 (s, 9H), 1.36–1.32 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 170.68, 154.78, 136.82, 130.47, 127.98, 126.43, 79.58, 54.86, 43.18, 39.93, 38.96, 34.09, 28.39, 24.25; ESI-HR-MS: (m/z) calcd. for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{NaO}_3$ ($[\text{M}+\text{Na}]^+$) 355.1992, found 355.1990.

tert-butyl 4-benzyl-4-propionamidopiperidine-1-carboxylate (**72-2**). Compound **72-2** was prepared according to General Procedure 2 from **70** (1.50 g, 5.17 mmol) using $(\text{CH}_3\text{CH}_2\text{CO})_2\text{O}$ (0.81 g, 6.20 mmol), DMAP (0.13 g, 1.03 mmol), and Et_3N (1.04 g, 10.3 mmol) in dried CH_2Cl_2 (15 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by *v/v*) gave **72-2**. White foam, 1.28 g (72%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.29–7.26 (m, 2H), 7.22–7.18 (m, 1H), 7.08–7.06 (m, 2H), 3.70–3.67 (m, 2H), 2.96 (s, 2H), 2.84 (s, 2H), 2.10–2.06 (m, 2H), 2.02–1.99 (m, 2H), 1.38 (s, 9H), 1.02 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 174.18, 154.54, 136.63, 130.32, 127.71, 126.20, 79.29, 54.33, 43.13, 39.76, 38.77, 33.88, 30.22, 28.19, 9.95; ESI-HR-MS: (m/z) calcd. for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{NaO}_3$ ($[\text{M}+\text{Na}]^+$) 369.2149, found 369.2146.

tert-butyl 4-benzyl-4-(cyclopropanecarboxamido)piperidine-1-carboxylate (**72-3**). Compound **72-3** was prepared according to General Procedure 1 from **70** (0.30 g, 1.03 mmol) using cyclopropanecarbonyl chloride (0.65 g, 6.20 mmol) and Et₃N (1.04 g, 10.3 mmol) in dried CH₂Cl₂ (15 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **72-3**. White foam, 0.65 g (35%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.40 (s, 1H), 7.29–7.26 (m, 2H), 7.22–7.19 (m, 2H), 7.08–7.06 (m, 2H), 3.70–3.68 (m, 2H), 2.96 (s, 2H), 2.87 (s, 2H), 2.01–1.99 (m, 2H), 1.65–1.60 (m, 1H), 1.38 (s, 9H), 1.36–1.35 (m, 2H), 0.73–0.70 (m, 2H), 0.63–0.59 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 173.78, 154.91, 136.85, 130.68, 128.02, 126.49, 79.65, 54.87, 43.46, 39.94, 39.01, 34.41, 28.46, 15.38, 6.87; ESI-HR-MS: (*m/z*) calcd. for C₂₁H₃₁N₂O₃ ([M+H]⁺) 359.2329, found 1359.2325.

tert-butyl 4-benzyl-4-pivalamidopiperidine-1-carboxylate (**72-4**). Compound **72-4** was prepared according to General Procedure 1 from **70** (0.20 g, 0.689 mmol) using pivaloyl chloride (0.12 g, 1.03 mmol) and Et₃N (0.21 g, 2.07 mmol) in dried CH₂Cl₂ (2 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **72-4**. White solid, 0.20 g (78%). m.p. 91.3–93.1 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.27–7.24 (m, 2H), 7.21–7.17 (m, 1H), 7.07–7.05 (m, 2H), 6.22 (s, 1H), 3.71–3.68 (m, 2H), 2.95 (s, 2H), 2.79 (s, 2H), 2.14–2.11 (m, 1H), 1.38 (s, 9H), 1.35–1.29 (m, 2H), 1.09 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 178.37, 154.89, 136.78, 130.77, 127.99, 126.60, 79.81, 54.19, 43.50, 39.56, 34.34, 28.52, 27.87, 27.19; ESI-HR-MS: (*m/z*) calcd. for C₂₂H₃₅N₂O₃ ([M+H]⁺) 375.2643, found 375.2650.

tert-butyl 4-benzyl-4-(2,2,2-trifluoroacetamido)piperidine-1-carboxylate (**72-5**). Compound **72-5** was prepared according to General Procedure 2 from **70** (0.30 g, 1.03 mmol) using (CF₃CO)₂O (0.26 g, 1.24 mmol), DMAP (25 mg, 0.206 mmol), and Et₃N (0.21 g, 2.06 mmol) in dried CH₂Cl₂ (3 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **72-5**. White foam, 0.24 g (60%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.57 (s, 1H), 7.32–7.28 (m, 2H), 7.25–7.22 (m, 1H), 7.08–7.06 (m, 2H), 3.74–3.71 (m, 2H), 2.99 (s, 2H), 2.82 (s, 2H), 2.14–2.11 (m, 2H), 1.53–1.47 (m, 2H), 1.39 (s, 9H); ¹³C NMR (151 MHz, CDCl₃) δ 156.94 (q, *J* = 36.3 Hz), 154.69, 135.40, 130.43, 128.45, 127.13, 115.53 (q, *J* = 289.6 Hz), 80.02, 56.49, 42.96, 39.78, 38.90, 33.81, 28.44; ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ −73.69; ESI-HR-MS: (*m/z*) calcd. for C₁₉H₂₄F₃N₂O₃ ([M-H][−]) 385.1745, found 385.1743.

tert-butyl 4-benzyl-4-(2,2-difluoroacetamido)piperidine-1-carboxylate (**72-6**). Compound **72-6** was prepared according to General Procedure 2 from **70** (0.10 g, 0.344 mmol) using (CHF₂CO)₂O (90 mg, 0.516 mmol), DMAP (8 mg, 0.069 mmol), and Et₃N (0.10 g, 1.03 mmol) in dried CH₂Cl₂ (1 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **72-6**. White solid, 0.10 g (80%). m.p. 87.9–90.4 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.09 (s, 1H), 7.30–7.27 (m, 2H), 7.24–7.21 (m, 1H), 7.09–7.07 (m, 2H), 6.10 (t, *J* = 54.0 Hz, 1H), 3.73–3.70 (m, 2H), 2.99 (s, 2H), 2.83 (s, 2H), 2.05–2.02 (m, 2H), 1.51–1.43 (m, 2H), 1.38 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 162.57 (t, *J* = 24.1 Hz), 154.74, 135.73, 130.49, 128.31, 126.94, 108.52 (t, *J* = 254.1 Hz), 79.91, 55.70, 43.22, 39.70, 38.96, 33.88, 28.44; ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ −124.41; ESI-HR-MS: (*m/z*) calcd. for C₁₉H₂₆N₂F₂NaO₃ ([M+Na]⁺) 391.1804, found 391.1804.

tert-butyl 4-benzyl-4-((methoxycarbonyl)amino)piperidine-1-carboxylate (**72-7**). Compound **72-7** was prepared according to General Procedure 2 from **70** (0.50 g, 1.72 mmol) using (CH₃OCO)₂O (0.28 g, 2.06 mmol), DMAP (42 mg, 0.342 mmol), and Et₃N (0.35 g, 3.42 mmol) in dried CH₂Cl₂ (5 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **72-7**. White foam, 0.46 g (77%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.29–7.26 (m, 2H), 7.22–7.19 (m, 1H), 7.07 (d, *J* = 7.5 Hz, 2H), 6.77 (s, 1H), 3.67–3.65 (m, 2H), 3.56 (s, 3H), 2.91 (br, 4H), 1.94–1.91 (m, 2H), 1.38 (s, 9H), 1.36–1.30 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 155.62, 154.74, 136.55, 130.46, 128.02, 126.46, 79.46, 53.69, 51.70, 44.09, 39.77, 38.90, 34.23, 28.38; ESI-HR-MS: (*m/z*) calcd. for C₁₉H₂₈N₂NaO₄ ([M+Na]⁺) 371.1941, found 371.1939.

tert-butyl 4-benzyl-4-((ethoxycarbonyl)amino)piperidine-1-carboxylate (**72-8**). Compound **72-8** was prepared according to General Procedure 2 from **70** (0.50 g, 1.72 mmol) using (CH₃CH₂OCO)₂O (0.33 g, 2.06 mmol), DMAP (42 mg, 0.342 mmol), and Et₃N (0.35 g, 3.42 mmol) in dried CH₂Cl₂ (5 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **72-8**. White foam, 0.45 g (72%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.28–7.25 (m, 2H), 7.22–7.19 (m, 1H), 7.09–7.07 (m, 2H), 6.70 (s, 1H), 4.03–4.01 (m, 2H), 3.68–3.65 (m, 2H), 2.91 (br, 4H), 1.94 (br, 2H), 1.39–1.34 (s, 11H), 1.20 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 155.23, 154.76, 136.61, 130.49, 128.00, 126.45, 79.44, 60.28, 53.64, 44.10, 39.76, 38.88, 34.29, 28.40, 14.70; ESI-HR-MS: (*m/z*) calcd. for C₂₀H₃₀N₂NaO₄ ([M+Na]⁺) 385.2098, found 385.2096.

General Procedure 3: Synthesis of **C-1-1** to **C-1-3** and **C-2-1** to **C-2-8**. To a stirred solution of **72-1** to **72-3** or **72-2-1** to **72-2-8** (1.0 eq) in CH₂Cl₂, cooled to 0 °C, TFA (about 1.67 *v/v* based on CH₂Cl₂) was added dropwise. After addition, the reaction mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction, and then evaporated on a rotary evaporator to afford a residue. Another flask, charged with 7·TFA (1.2 eq), EDCI (2.5 eq), HOBT (0.075 eq), DIPEA (6 eq), and dried THF, was stirred at 0 °C, followed by dropwise addition of a solution of the residue obtained above in a small amount of dried THF. After addition, the resulting mixture was stirred at room temperature overnight until TLC analysis indicated completion of the reaction, and then poured into water. The mixture thus obtained was extracted with EtOAc in three portions, and the combined extracts were washed with brine, dried (MgSO₄), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography to afford the target products.

N-(1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methanesulfonamide (**C-1-1**). Following General Procedure 3, **71-1** (0.90 g, 2.44 mmol) was first treated with TFA (4.5 mL) in CH₂Cl₂ (2.7 mL), and the intermediate obtained was reacted with 7·TFA (0.87 g, 2.93 mmol) using EDCI (1.22 g, 6.34 mmol), HOBT (25 mg, 0.183 mmol), and DIPEA (1.89 g, 14.6 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-1-1**. White foam, 0.55 g (50%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.79–8.67 (m, 3H), 7.87–7.84 (m, 1H), 7.60–7.56 (m, 3H), 7.30–7.14 (m, 5H), 6.73–6.69 (m, 1H), 4.26–4.05 (m, 1H), 3.13–2.88 (m, 7H), 2.82–2.79 (m, 1H), 2.60–2.58 (m, 0.58H), 1.95–1.76 (m, 1H), 1.54–1.41 (m, 1.66H), 1.23–1.17 (m, 0.59H), 0.29–0.26 (m, 1H); ¹³C NMR (151 MHz, CDCl₃ + CD₃OD) δ 167.36, 167.19, 151.47, 151.37, 150.38, 150.30, 149.31, 146.48, 146.30, 136.10, 135.36, 135.12, 131.07, 130.93, 130.80, 130.73, 130.57, 127.97, 126.72, 126.65, 123.75, 123.66, 123.25, 123.12, 57.74, 57.64, 46.34, 45.49, 44.28, 42.78, 42.45, 37.42, 37.33, 33.86, 33.71, 33.46, 33.26; ESI-HR-MS: (*m/z*) calcd. for C₂₄H₂₇N₄O₃S ([M+H]⁺) 451.1798, found 451.1810.

N-(1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)-1,1,1-trifluoromethanesulfonamide (**C-1-2**). Following General Procedure 3, **71-2** (1.10 g, 2.60 mmol) was first treated with TFA (5.5 mL) in CH₂Cl₂ (3.3 mL), and the intermediate obtained was reacted with 7·TFA (0.93 g, 3.12 mmol) using EDCI (1.25 g, 6.50 mmol), HOBT (26 mg, 0.195 mmol), and DIPEA (2.02 g, 15.6 mmol) in dried THF (11 mL). Purification by column chromatography (EtOAc) gave **C-1-2**. White foam, 0.64 g (49%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.78 (s, 1H), 8.65–8.56 (m, 2H), 7.87–7.84 (m, 1H), 7.55–7.51 (m, 3H), 7.34–7.11 (m, 6H), 4.26–4.14 (m, 1H), 3.06–2.92 (m, 2H), 2.88–2.72 (m, 2H), 2.66–2.54 (m, 1H), 2.02–1.91 (m, 0.69H), 1.78–1.52 (m, 1.78H), 1.38–1.23 (m, 1.60H), 0.71–0.42 (m, 0.45H); ¹³C NMR (151 MHz, CDCl₃) δ 167.61, 167.34, 167.28, 152.16, 151.59, 151.51, 150.66, 150.63, 150.05, 150.03, 149.92, 146.30, 146.27, 146.08, 136.28, 136.19, 136.06, 133.89, 133.67, 133.59, 131.14, 131.08, 130.84, 128.57, 128.52, 127.39, 127.33, 123.63, 123.56, 123.44, 122.72, 122.68, 57.23, 57.10, 57.02, 56.93, 49.75, 49.67, 49.54, 42.23, 42.13, 41.61, 41.47, 36.90, 36.71, 35.39, 34.96, 34.80, 34.39, 33.69, 33.37, 33.01, 32.93; ¹⁹F

NMR (471 MHz, DMSO- d_6) δ −76.07, −76.15, −76.38, −76.42; ESI-HR-MS: (m/z) calcd. for $C_{24}H_{24}F_3N_4O_3S$ ($[M+H]^+$) 505.1516, found 505.1516.

N-(1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)ethanesulfonamide (**C-1-3**). Following General Procedure 3, **71-3** (0.60 g, 1.57 mmol) was first treated with TFA (3 mL) in CH_2Cl_2 (1.8 mL), and the intermediate obtained was reacted with **7-TFA** (0.56 g, 1.88 mmol) using EDCI (0.75 g, 3.93 mmol), HOBT (16 mg, 0.118 mmol), and DIPEA (1.22 g, 9.42 mmol) in dried THF (11 mL). Purification by column chromatography (EtOAc) gave **C-1-3**. White foam, 0.33 g (45%). 1H NMR (500 MHz, DMSO- d_6) δ 8.78–8.77 (m, 1H), 8.68–8.66 (m, 2H), 7.87–7.85 (m, 1H), 7.59–7.55 (m, 3H), 7.28–7.15 (m, 5H), 6.64–6.58 (m, 1H), 4.24–4.03 (m, 1H), 3.09–2.89 (m, 5H), 2.88–2.80 (m, 1.4H), 2.67–2.55 (m, 1H), 1.95–1.74 (m, 1H), 1.52–1.40 (m, 2H), 1.22–1.17 (m, 2H), 1.10–1.07 (m, 1H), 0.28–0.23 (m, 0.52H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.54, 167.37, 151.92, 151.81, 150.71, 150.65, 150.11, 150.04, 146.32, 146.19, 136.26, 136.22, 135.25, 135.01, 131.17, 131.12, 131.00, 128.36, 127.07, 123.67, 123.61, 123.35, 123.07, 58.12, 58.07, 51.04, 50.99, 46.28, 45.40, 42.90, 42.48, 37.64, 37.58, 34.37, 34.30, 33.91, 33.66, 8.51; ESI-HR-MS: (m/z) calcd. for $C_{25}H_{29}N_4O_3S$ ($[M+H]^+$) 465.1955, found 465.1954.

N-(1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)acetamide (**C-2-1**). Following General Procedure 3, **72-1** (0.63 g, 1.90 mmol) was first treated with TFA (9.5 mL) in CH_2Cl_2 (5.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.68 g, 2.28 mmol) using EDCI (0.91 g, 4.75 mmol), HOBT (19 mg, 0.143 mmol), and DIPEA (1.47 g, 11.4 mmol) in dried THF (6.3 mL). Purification by column chromatography (EtOAc) gave **C-2-1**. White foam, 0.35 g (45%). 1H NMR (500 MHz, DMSO- d_6) δ 8.79–8.65 (m, 3H), 7.93–7.83 (m, 1H), 7.67–7.54 (m, 3H), 7.29–7.14 (m, 4H), 7.04–6.90 (m, 2H), 4.32–4.21 (m, 1H), 3.34 (s, 1H), 3.05–2.64 (m, 4.66H), 2.46–2.17 (m, 1H), 2.04–2.01 (m, 0.43H), 1.79–1.76 (m, 3H), 1.50–1.41 (m, 1H), 1.10–1.05 (d, 0.51H), 0.07–0.00 (m, 0.52H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.88, 170.78, 167.37, 167.19, 151.79, 151.51, 150.52, 150.45, 149.85, 149.79, 146.33, 146.26, 136.25, 136.17, 135.98, 135.94, 131.34, 131.11, 130.32, 130.27, 128.06, 128.03, 126.60, 126.56, 123.58, 123.54, 123.48, 122.94, 54.68, 54.44, 43.23, 42.95, 42.82, 42.42, 37.38, 33.92, 33.89, 33.42, 33.11, 24.11; ESI-HR-MS: (m/z) calcd. for $C_{25}H_{27}N_4O_2$ ($[M+H]^+$) 415.2129, found 415.2138.

N-(1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)propionamide (**C-2-2**). Following General Procedure 3, **72-2** (1.23 g, 3.55 mmol) was first treated with TFA (6.2 mL) in CH_2Cl_2 (3.7 mL), and the intermediate obtained was reacted with **7-TFA** (1.27 g, 4.26 mmol) using EDCI (1.70 g, 8.88 mmol), HOBT (36 mg, 0.266 mmol), and DIPEA (2.75 g, 21.3 mmol) in dried THF (12.3 mL). Purification by column chromatography (EtOAc) gave **C-2-2**. White foam, 0.71 g (47%). 1H NMR (500 MHz, DMSO- d_6) δ 8.79–8.77 (m, 2H), 8.65–8.64 (m, 1H), 7.93–7.83 (m, 1H), 7.68–7.66 (m, 1H), 7.58–7.53 (m, 2H), 7.27–7.24 (m, 2H), 7.20–7.17 (m, 1H), 7.08–7.01 (m, 2H), 6.91–6.89 (m, 1H), 4.32–4.21 (m, 1H), 3.02–2.67 (m, 5H), 2.46–2.18 (m, 1H), 2.05–2.00 (m, 2H), 1.84–1.81 (m, 0.37H), 1.53–1.49 (m, 1H), 1.42–1.03 (m, 1H), 1.00–0.94 (m, 3H), 0.06–0.01 (m, 0.54H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.24, 167.12, 166.84, 151.47, 151.14, 150.27, 150.22, 149.51, 146.07, 136.06, 135.98, 135.69, 131.10, 130.87, 130.16, 130.10, 127.74, 126.33, 123.35, 123.29, 122.67, 54.13, 53.86, 43.11, 42.89, 42.58, 42.17, 37.19, 33.66, 33.62, 33.28, 32.76, 29.99, 9.74; ESI-HR-MS: (m/z) calcd. for $C_{26}H_{29}N_4O_2$ ($[M+H]^+$) 429.2285, found 429.2285.

N-(1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)cyclopropanecarboxamide (**C-2-3**). Following General Procedure 3, **72-3** (0.60 g, 1.67 mmol) was first treated with TFA (3 mL) in CH_2Cl_2 (1.8 mL), and the intermediate obtained was reacted with **7-TFA** (0.60 g, 2.00 mmol) using EDCI (0.80 g, 4.18 mmol), HOBT (17 mg, 0.125 mmol), and DIPEA (1.29 g, 10.0 mmol) in dried THF (6 mL). Purification by column chromatography (EtOAc) gave **C-2-3**. White foam, 0.45 g (61%). 1H NMR (500 MHz, DMSO- d_6) δ 8.79–8.65 (m, 3H), 7.94–7.84 (m, 1H), 7.67–7.54 (m, 3H), 7.41–7.37 (m, 1H), 7.28–7.18 (m, 3H), 7.04–6.90 (m, 2H), 4.32–4.22 (m, 1H), 3.07–2.67 (m, 4.40H), 2.46–1.80 (m, 2H), 1.59–1.44 (m, 2.42H), 1.12–1.07

(m, 0.52H), 0.72–0.58 (m, 4H), 0.12–0.06 (m, 0.53H); ^{13}C NMR (151 MHz, CDCl_3) δ 173.99, 173.88, 167.10, 166.88, 151.53, 151.15, 150.25, 150.21, 149.52, 146.10, 136.11, 136.02, 135.77, 135.64, 131.16, 130.93, 130.28, 130.19, 127.78, 126.33, 123.38, 123.32, 122.71, 54.44, 54.10, 43.26, 43.10, 42.62, 42.32, 37.25, 33.95, 33.86, 33.43, 32.92, 14.71, 14.64, 6.69, 6.59, 6.53; ESI-HR-MS: (m/z) calcd. for $\text{C}_{27}\text{H}_{29}\text{N}_4\text{O}_2$ ($[\text{M}+\text{H}]^+$) 441.2285, found 441.2284.

N-(1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)pivalamide (**C-2-4**). Following General Procedure 3, **72-4** (1.50 g, 4.00 mmol) was first treated with TFA (7.5 mL) in CH_2Cl_2 (4.5 mL), and the intermediate obtained was reacted with **7-TFA** (1.43 g, 4.80 mmol) using EDCI (1.92 g, 10.0 mmol), HOBT (41 mg, 0.300 mmol), and DIPEA (3.10 g, 24.0 mmol) in dried THF (15 mL). Purification by column chromatography (EtOAc) gave **C-2-4**. White foam, 0.30 g (16%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.79–8.77 (m, 2H), 8.63–8.62 (m, 1H), 7.93–7.84 (m, 1H), 7.68–7.67 (m, 1H), 7.59–7.51 (m, 2H), 7.26–7.17 (m, 3H), 7.00–6.88 (m, 2H), 6.23–6.14 (m, 1H), 4.33–4.22 (m, 1H), 2.95–2.55 (m, 4H), 2.47–2.10 (m, 2H), 1.93–1.65 (m, 1H), 1.46–1.24 (m, 1.47H), 1.06–1.00 (m, 9H), 0.04–0.01 (m, 0.53H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.50, 167.82, 152.04, 150.74, 150.10, 149.89, 146.57, 136.34, 136.16, 131.33, 130.63, 128.12, 126.84, 123.70, 123.22, 53.92, 43.44, 43.11, 42.44, 39.56, 37.60, 34.17, 33.80, 33.59, 31.70, 27.80, 22.77, 14.24; ESI-HR-MS: (m/z) calcd. for $\text{C}_{28}\text{H}_{33}\text{N}_4\text{O}_2$ ($[\text{M}+\text{H}]^+$) 457.2598, found 457.2601.

N-(1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)-2,2,2-trifluoroacetamide (**C-2-5**). Following General Procedure 3, **72-5** (0.90 g, 2.33 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.84 g, 2.80 mmol) using EDCI (1.12 g, 5.83 mmol), HOBT (24 mg, 0.175 mmol), and DIPEA (1.81 g, 14.0 mmol) in dried THF (15 mL). Purification by column chromatography (EtOAc) gave **C-2-5**. White foam, 0.66 g (60%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.80–8.52 (m, 4H), 7.96–7.85 (m, 1H), 7.67–7.53 (m, 3H), 7.30–7.22 (m, 3H), 7.03–6.91 (m, 2H), 4.33–4.24 (m, 1H), 3.35–3.34 (m, 0.53H), 3.11–2.54 (m, 5H), 2.30–2.15 (m, 1H), 1.90–1.71 (m, 1H), 1.66–1.56 (m, 0.75H), 1.25–0.22 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 171.27, 167.41, 167.20, 157.64 (q, $J = 35.8$ Hz), 151.75, 151.37, 150.61, 150.58, 149.68, 149.46, 146.28, 136.05, 135.91, 135.03, 134.92, 131.07, 130.82, 130.26, 130.20, 128.29, 127.01, 123.61, 123.50, 122.84, 115.37 (q, $J = 289.6$ Hz), 60.35, 56.13, 55.91, 43.02, 42.76, 42.63, 42.21, 37.26, 33.38, 33.25, 32.87, 32.59, 20.86, 14.05; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ –73.73, –73.76; ESI-HR-MS: (m/z) calcd. for $\text{C}_{25}\text{H}_{24}\text{F}_3\text{N}_4\text{O}_2$ ($[\text{M}+\text{H}]^+$) 469.1846, found 469.1856.

N-(1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)-2,2-difluoroacetamide (**C-2-6**). Following General Procedure 3, **72-6** (0.10 g, 0.271 mmol) was first treated with TFA (0.5 mL) in CH_2Cl_2 (0.3 mL), and the intermediate obtained was reacted with **7-TFA** (97 mg, 0.325 mmol) using EDCI (0.13 g, 0.676 mmol), HOBT (3 mg, 0.020 mmol), and DIPEA (0.21 g, 1.63 mmol) in dried THF (5 mL). Purification by column chromatography (EtOAc) gave **C-2-6**. White solid, 21 mg (17%). m.p. 97.9–99.4 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.80–8.78 (m, 2H), 8.65 (s, 1H), 8.10–8.06 (m, 1H), 7.95–7.84 (m, 1H), 7.67–7.54 (m, 3H), 7.29–7.20 (m, 3H), 7.04–6.91 (m, 2H), 6.17–5.92 (m, 1H), 4.34–4.24 (m, 1H), 3.11–3.08 (m, 0.44H), 2.97–2.94 (m, 2H), 2.84–2.63 (m, 2H), 2.22–2.07 (m, 1H), 1.83–1.53 (m, 2H), 1.27–1.15 (m, 2H), 0.87–0.84 (m, 1H), 0.16–0.12 (m, 0.53H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.56, 162.89, 162.70, 152.24, 151.85, 150.77, 150.28, 150.20, 146.38, 136.34, 136.23, 135.06, 131.37, 131.09, 130.44, 130.36, 128.51, 128.48, 127.22, 123.74, 123.65, 123.02, 110.58, 108.56, 108.38, 106.54, 55.56, 55.41, 43.50, 43.08, 42.82, 42.37, 37.43, 33.83, 33.33, 33.19, 29.81; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ –124.47; ESI-HR-MS: (m/z) calcd. for $\text{C}_{25}\text{H}_{25}\text{F}_2\text{N}_4\text{O}_2$ ($[\text{M}+\text{H}]^+$) 451.1940, found 451.1940.

methyl (1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)carbamate (**C-2-7**). Following General Procedure 3, **72-7** (0.44 g, 1.27 mmol) was first treated with TFA (2.2 mL) in CH_2Cl_2 (1.3 mL), and the intermediate obtained was reacted with **7-TFA** (0.45 g, 1.52 mmol) using EDCI (0.61 g, 3.18 mmol), HOBT (13 mg, 0.095 mmol), and DIPEA (0.98 g, 7.62 mmol)

in dried THF (4.4 mL). Purification by column chromatography (EtOAc) gave **C-2-7**. White foam, 0.13 g (24%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.79–8.65 (m, 3H), 7.92–7.83 (m, 1H), 7.67–7.54 (m, 3H), 7.28–7.18 (m, 3H), 7.03–6.89 (m, 2H), 6.76–6.74 (m, 1H), 4.31–4.20 (m, 1H), 3.53 (s, 3H), 3.03–2.69 (m, 4.50H), 2.40–2.38 (m, 0.50H), 2.13–1.95 (m, 1H), 1.74–1.40 (m, 2H), 1.13–0.04 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.20, 167.09, 155.66, 151.84, 151.47, 150.38, 150.32, 149.83, 149.77, 146.15, 136.00, 135.94, 135.89, 135.85, 131.37, 131.06, 130.25, 130.18, 128.02, 127.98, 126.56, 126.50, 123.45, 123.41, 122.75, 53.55, 53.25, 51.70, 44.06, 43.94, 42.64, 42.27, 37.26, 34.15, 33.96, 33.55, 33.12; ESI-HR-MS: (m/z) calcd. for $\text{C}_{25}\text{H}_{27}\text{N}_4\text{O}_3$ ($[\text{M}+\text{H}]^+$) 431.2078, found 431.2077.

ethyl (1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)carbamate (**C-2-8**). Following General Procedure 3, **72-8** (0.95 g, 2.64 mmol) was first treated with TFA (13.2 mL) in CH_2Cl_2 (7.9 mL), and the intermediate obtained was reacted with **7-TFA** (0.95 g, 3.17 mmol) using EDCI (1.27 g, 6.60 mmol), HOBT (27 mg, 0.198 mmol), and DIPEA (2.04 g, 15.8 mmol) in dried THF (9.5 mL). Purification by column chromatography (EtOAc) gave **C-2-8**. White foam, 0.64 g (55%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.79–8.65 (m, 3H), 7.92–7.82 (m, 1H), 7.67–7.54 (m, 3H), 7.27–7.18 (m, 3H), 7.05–6.90 (m, 2H), 6.70–6.67 (m, 1H), 4.31–4.20 (m, 1H), 4.03–3.95 (m, 2H), 3.03–2.69 (m, 4.5H), 2.41–2.37 (m, 0.54H), 2.15–1.98 (m, 1H), 1.77–1.39 (m, 2H), 1.18–1.15 (m, 3H), 1.10–1.07 (m, 0.58H), 0.09–0.02 (m, 0.51H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.01, 166.88, 155.16, 151.63, 151.24, 150.19, 150.14, 149.61, 149.54, 145.99, 135.89, 135.83, 135.81, 135.69, 131.23, 130.93, 130.12, 130.05, 127.81, 127.77, 126.35, 126.30, 123.31, 123.26, 122.58, 60.07, 53.36, 53.02, 43.88, 42.47, 42.15, 37.11, 34.03, 33.83, 33.42, 32.92, 14.44, 14.41; ESI-HR-MS: (m/z) calcd. for $\text{C}_{26}\text{H}_{29}\text{N}_4\text{O}_3$ ($[\text{M}+\text{H}]^+$) 445.2234, found 445.2234.

Synthesis of *tert*-butyl 4-(aminomethyl)-4-benzylpiperidine-1-carboxylate (**73**). To a stirred solution of **68** (10.00 g, 33.3 mmol) in MeOH (100 mL), cooled to 0 °C under N_2 , $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (15.8 g, 66.6 mmol) in one portion and NaBH_4 (12.6 g, 333 mmol) in portions were added successively. After addition, the reaction mixture was stirred at room temperature until completion, as indicated by TLC analysis (typically within 5 h), filtered through Celite, and poured into ice–water (100 mL). The resulting mixture was extracted with EtOAc (150 mL $\times$ 3), and the combined extracts were washed with brine, dried (MgSO_4), and evaporated on a rotary evaporator to afford a residue, which was purified by column chromatography ($\text{MeOH}/\text{CH}_2\text{Cl}_2$ = 1/10, by v/v) to give **73**. Colorless oil, 8.88 g (88%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.28–7.25 (m, 2H), 7.20–7.16 (m, 3H), 3.45–3.40 (m, 2H), 3.27–3.20 (m, 2H), 2.63 (s, 2H), 2.38 (s, 2H), 1.37 (s, 9H), 1.33–1.28 (m, 2H), 1.25–1.19 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.05, 137.68, 130.52, 128.16, 126.30, 79.45, 46.05, 41.13, 39.91, 39.24, 36.65, 32.16, 28.51; ESI-HR-MS: (m/z) calcd. for $\text{C}_{18}\text{H}_{29}\text{N}_2\text{O}_2$ ($[\text{M}+\text{H}]^+$) 305.2224 found 305.2221.

Synthesis of *tert*-butyl 4-(acetamidomethyl)-4-benzylpiperidine-1-carboxylate (**74-1**). Compound **74-1** was prepared according to General Procedure 1 described above from **73** (0.80 g, 2.63 mmol) using AcCl (0.25 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **74-1**. White solid, 0.85 g (95%). m.p. 48.2–50.5 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.26 (t, J = 6.0 Hz, 1H), 7.29–7.26 (m, 2H), 7.22–7.17 (m, 3H), 3.46–3.41 (m, 2H), 3.26 (s, 2H), 3.02 (d, J = 6.0 Hz, 2H), 2.61 (s, 2H), 1.89 (s, 3H), 1.35 (s, 9H), 1.26–1.17 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.23, 155.04, 137.49, 130.38, 128.58, 126.83, 79.57, 44.19, 44.00, 36.89, 32.59, 28.56, 23.47; ESI-HR-MS: (m/z) calcd. for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{NaO}_3$ ($[\text{M}+\text{Na}]^+$) 369.2149, found 369.2145.

Synthesis of *tert*-butyl 4-benzyl-4-(cyclopropanecarboxamidomethyl)piperidine-1-carboxylate (**74-2**). Compound **74-2** was prepared according to General Procedure 1 described above from **73** (0.80 g, 2.63 mmol) using cyclopropanecarbonyl chloride (0.33 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **74-2**. White solid, 0.85 g (95%). White

solid, 0.70 g (71%). m.p. 66.6–69.2 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.33–7.30 (m, 2H), 7.27–7.24 (m, 1H), 7.16–7.14 (m, 2H), 5.48 (t, J = 6.3 Hz, 1H), 3.59–3.56 (m, 2H), 3.39–3.17 (m, 4H), 2.65 (s, 2H), 1.44 (s, 9H), 1.43–1.41 (m, 3H), 1.21–1.16 (m, 1H), 0.91–0.88 (m, 2H), 0.71–0.67 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.79, 155.03, 137.52, 130.42, 128.52, 126.74, 79.48, 44.08, 43.96, 36.98, 32.51, 28.54, 14.84, 7.22; ESI-HR-MS: (m/z) calcd. for $\text{C}_{22}\text{H}_{32}\text{N}_2\text{NaO}_3$ ($[\text{M}+\text{Na}]^+$) 395.2305, found 395.2304.

Synthesis of *tert*-butyl 4-benzyl-4-(pivalamidomethyl)piperidine-1-carboxylate (**74-3**). Compound **74-3** was prepared according to General Procedure 1 described above from **73** (0.80 g, 2.63 mmol) using pivaloyl chloride (0.38 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **74-3**. White solid, 0.95 g (90%). m.p. 66–69 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.30–7.27 (m, 2H), 7.22–7.21 (m, 1H), 7.18–7.17 (m, 2H), 7.06 (t, J = 6.3 Hz, 1H), 3.36 (s, 4H), 3.08 (d, J = 6.0 Hz, 2H), 2.63 (s, 2H), 1.34 (s, 9H), 1.29–1.24 (m, 2H), 1.19–1.14 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (151 MHz, CDCl_3) δ 178.15, 154.74, 137.78, 130.02, 130.00, 128.66, 128.60, 126.73, 79.19, 45.50, 43.51, 43.49, 39.98, 38.94, 38.52, 37.17, 37.13, 32.78, 28.36, 28.33, 27.28, 27.25; ESI-HR-MS: (m/z) calcd. for $\text{C}_{23}\text{H}_{36}\text{N}_2\text{NaO}_3$ ($[\text{M}+\text{Na}]^+$) 411.2618, found 411.2618.

Synthesis of *tert*-butyl 4-benzyl-4-((2,2,2-trifluoroacetamido)methyl)piperidine-1-carboxylate (**74-4**). Compound **74-4** was prepared according to General Procedure 2 from **73** (0.80 g, 2.63 mmol) using $(\text{CF}_3\text{CO})_2\text{O}$ (0.66 g, 3.16 mmol), DMAP (65 mg, 0.53 mmol), and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **74-4**. White solid, 0.80 g (73%). m.p. 66–69 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.29 (t, J = 6.3 Hz, 1H), 7.30–7.27 (m, 2H), 7.23–7.17 (m, 3H), 3.41–3.37 (m, 4H), 3.20 (d, J = 6.0 Hz, 2H), 2.67 (s, 2H), 1.34 (s, 9H), 1.31–1.26 (m, 2H), 1.23–1.18 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 157.53 (q, J = 36.8 Hz), 154.87, 136.91, 130.07, 128.81, 127.14, 115.83 (q, J = 288.2 Hz), 79.69, 44.85, 43.93, 39.90, 38.95, 37.06, 32.41, 28.42; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ –73.79; ESI-HR-MS: (m/z) calcd. for $\text{C}_{20}\text{H}_{27}\text{F}_3\text{N}_2\text{NaO}_3$ ($[\text{M}+\text{Na}]^+$) 423.1866, found 423.1866.

Synthesis of *tert*-butyl 4-benzyl-4-((2,2-difluoroacetamido)methyl)piperidine-1-carboxylate (**74-5**). Compound **74-5** was prepared according to General Procedure 2 from **73** (0.80 g, 2.63 mmol) using $(\text{CHF}_2\text{CO})_2\text{O}$ (0.55 g, 3.16 mmol), DMAP (65 mg, 0.53 mmol), and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **74-5**. White solid, 0.70 g (70%). m.p. 66–69 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.67 (t, J = 6.3 Hz, 1H), 7.30–7.27 (m, 2H), 7.23–7.17 (m, 3H), 6.27 (t, J = 53.8 Hz, 1H), 3.44–3.40 (m, 2H), 3.33 (s, 2H), 3.14 (d, J = 6.0 Hz, 2H), 2.65 (s, 2H), 1.35 (s, 9H), 1.31–1.26 (m, 2H), 1.24–1.19 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 146.35 (t, J = 24.5 Hz), 154.88, 136.91, 130.13, 128.70, 127.00, 108.44 (t, J = 168.4 Hz), 79.60, 43.88, 43.81, 39.92, 38.97, 36.94, 32.43, 28.44; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ –125.00; ESI-HR-MS: (m/z) calcd. for $\text{C}_{20}\text{H}_{28}\text{F}_2\text{N}_2\text{NaO}_3$ ($[\text{M}+\text{Na}]^+$) 405.1960, found 405.1962.

Synthesis of *tert*-butyl 4-benzyl-4-((furan-2-carboxamido)methyl)piperidine-1-carboxylate (**74-6**). Compound **74-6** was prepared according to General Procedure 1 described above from **73** (0.80 g, 2.63 mmol) using furan-2-carbonyl chloride (0.41 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **74-6**. Pale yellow foam, 0.92 g (88%). m.p. 66–69 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.12 (t, J = 6.3 Hz, 1H), 7.83–7.82 (m, 1H), 7.30–7.27 (m, 2H), 7.22–7.19 (m, 3H), 7.14 (d, J = 3.5 Hz, 1H), 6.62–6.61 (m, 1H), 3.44–3.46 (m, 4H), 3.26 (d, J = 6.5 Hz, 2H), 2.68 (s, 2H), 1.34–1.33 (m, 2H), 1.32 (s, 9H), 1.25–1.19 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 158.44, 154.83, 147.66, 143.80, 137.15, 130.20, 128.43, 126.56, 114.08, 112.06, 79.30, 43.89, 43.14, 39.95, 38.98, 37.05, 32.37, 28.34; ESI-HR-MS: (m/z) calcd. for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{NaO}_4$ ($[\text{M}+\text{Na}]^+$) 421.2098, found 421.2100.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)acetamide (**C-3-1**). Following General Procedure 3, **74-1** (0.85 g, 2.45 mmol) was first treated with TFA (4.3 mL) in CH₂Cl₂ (2.6 mL), and the intermediate obtained was reacted with **7-TFA** (0.88 g, 2.94 mmol) using EDCI (1.18 g, 6.13 mmol), HOBT (25 mg, 0.184 mmol), and DIPEA (1.90 g, 14.7 mmol) in dried THF (8.5 mL). Purification by column chromatography (EtOAc) gave **C-3-1**. White solid, 0.15 g (14%). m.p. 146.3–148.5 °C. ¹H NMR (500 MHz, CD₃OD) δ 8.77 (dd, *J* = 1.5 Hz and 5.0 Hz, 1H), 8.67–8.58 (m, 2H), 7.87–7.80 (m, 1H), 7.70–7.67 (m, 2H), 7.57 (dd, *J* = 4.8 Hz and 7.8 Hz, 1H), 7.30–7.20 (m, 3H), 7.14–7.05 (m, 2H), 4.09–3.85 (m, 1H), 3.58–3.42 (m, 1H), 3.26–3.16 (m, 2H), 3.06–2.98 (m, 2H), 2.65 (s, 2H), 2.50–2.40 (m, 1H), 1.99 (s, 3H), 1.46–1.44 (m, 1H), 1.31–1.11 (m, 2H), 0.81–0.63 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 170.53, 170.22, 167.55, 167.39, 152.14, 151.88, 150.52, 150.46, 150.25, 150.19, 146.45, 146.30, 136.88, 136.78, 136.30, 136.13, 131.78, 131.62, 130.32, 130.00, 128.69, 128.56, 127.05, 126.92, 123.63, 123.58, 123.51, 123.32, 45.84, 44.30, 43.17, 42.96, 42.07, 37.65, 36.98, 36.90, 32.33, 32.29, 31.73, 31.45, 23.36, 23.30; ESI-HR-MS: (*m/z*) calcd. for C₂₆H₂₉N₄O₂ ([M+H]⁺) 429.2286, found 429.2283.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)cyclopropanecarboxamide (**C-3-2**). Following General Procedure 3, **74-2** (0.70 g, 1.88 mmol) was first treated with TFA (3.5 mL) in CH₂Cl₂ (2.1 mL), and the intermediate obtained was reacted with **7-TFA** (0.67 g, 2.26 mmol) using EDCI (0.90 g, 4.70 mmol), HOBT (19 mg, 0.141 mmol), and DIPEA (1.46 g, 11.3 mmol) in dried THF (7 mL). Purification by column chromatography (EtOAc) gave **C-3-2**. White solid, 0.47 g (55%). m.p. 161.5–162.3 °C. ¹H NMR (500 MHz, CD₃OD) δ 8.77 (dd, *J* = 1.5 Hz and 5.0 Hz, 1H), 8.67–8.58 (m, 2H), 7.86–7.80 (m, 1H), 7.70–7.67 (m, 2H), 7.56 (dd, *J* = 5.0 Hz and 7.5 Hz, 1H), 7.30–7.20 (m, 3H), 7.15–7.06 (m, 2H), 4.08–3.84 (m, 1H), 3.62–3.35 (m, 1.53H), 3.26–3.22 (m, 2H), 3.05–2.99 (m, 2H), 2.68–2.43 (m, 2H), 1.72–1.67 (m, 1H), 1.46–1.44 (m, 1H), 1.34–1.12 (m, 2H), 0.85–0.75 (m, 4H), 0.69–0.64 (m, 0.56H); ¹³C NMR (126 MHz, CDCl₃) δ 174.22, 173.87, 167.45, 167.39, 152.03, 151.86, 150.52, 150.43, 150.29, 150.17, 146.43, 146.35, 136.94, 136.82, 136.30, 136.23, 131.78, 131.67, 130.36, 130.05, 128.67, 128.52, 127.00, 126.85, 123.61, 123.49, 123.42, 45.81, 44.71, 43.22, 43.01, 42.41, 42.08, 37.65, 37.10, 36.96, 32.37, 32.18, 31.32, 31.17, 14.70, 14.64, 7.51, 7.43, 7.28; ESI-HR-MS: (*m/z*) calcd. for C₂₈H₃₁N₄O₂ ([M+H]⁺) 455.2442, found 455.2448.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)pivalamide (**C-3-3**). Following General Procedure 3, **74-3** (0.83 g, 2.14 mmol) was first treated with TFA (4.2 mL) in CH₂Cl₂ (2.4 mL), and the intermediate obtained was reacted with **7-TFA** (0.77 g, 2.57 mmol) using EDCI (1.03 g, 5.35 mmol), HOBT (22 mg, 0.161 mmol), and DIPEA (1.65 g, 12.8 mmol) in dried THF (8.3 mL). Purification by column chromatography (EtOAc) gave **C-3-3**. White foam, 0.62 g (62%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.77–8.76 (m, 1H), 8.66–8.58 (m, 2H), 7.79–7.73 (m, 1H), 7.59–7.53 (m, 3H), 7.30–7.16 (m, 4H), 7.10–6.94 (m, 2H), 3.86–3.75 (m, 1H), 3.48–3.40 (m, 1H), 3.21–2.94 (m, 4H), 2.63–2.56 (m, 0.85H), 2.47–2.40 (m, 1.21H), 1.37–1.12 (m, 3H), 1.07 (s, 9H), 0.86–0.61 (m, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 178.19, 167.12, 166.97, 151.90, 151.37, 150.09, 149.82, 149.77, 146.14, 145.91, 137.11, 137.06, 135.98, 135.55, 131.47, 131.24, 129.78, 129.56, 128.60, 128.53, 126.82, 126.76, 123.35, 123.25, 123.14, 122.69, 47.00, 45.31, 42.93, 42.87, 42.69, 41.75, 38.38, 38.30, 37.52, 37.34, 37.17, 37.04, 32.83, 32.48, 32.05, 31.87, 27.12, 27.02; ESI-HR-MS: (*m/z*) calcd. for C₂₉H₃₅N₄O₂ ([M+H]⁺) 471.2755, found 471.2761.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-2,2,2-trifluoroacetamide (**C-3-4**). Following General Procedure 3, **74-4** (0.72 g, 1.80 mmol) was first treated with TFA (3.6 mL) in CH₂Cl₂ (2.2 mL), and the intermediate obtained was reacted with **7-TFA** (0.64 g, 2.16 mmol) using EDCI (0.86 g, 4.50 mmol), HOBT (18 mg, 0.135 mmol), and DIPEA (1.40 g, 10.8 mmol) in dried THF (7.2 mL). Purification by column chromatography (EtOAc) gave **C-3-4**. White solid, 0.48 g (55%). ¹H NMR (500 MHz,

DMSO- d_6) δ 9.30–9.22 (m, 1H), 8.78–8.76 (m, 1H), 8.65–8.56 (m, 2H), 7.82–7.74 (m, 1H), 7.58–7.52 (m, 3H), 7.30–7.09 (m, 5H), 3.82–3.68 (m, 1H), 3.60–3.46 (m, 1H), 3.39–3.37 (m, 2H), 3.22–3.16 (m, 2H), 3.06–2.97 (m, 1.60H), 2.69–2.53 (m, 1H), 2.49–2.46 (m, 0.46H), 1.40–1.12 (m, 3H), 0.84–0.73 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.31, 167.19, 157.98, 157.73, 157.49, 157.24, 151.50, 150.29, 149.70, 146.16, 146.10, 136.07, 135.98, 135.85, 135.68, 131.14, 131.08, 129.97, 129.77, 128.52, 128.45, 126.99, 126.89, 123.41, 123.35, 123.12, 122.90, 118.48, 116.61, 116.57, 114.70, 114.66, 44.46, 44.32, 43.25, 42.76, 42.68, 42.48, 37.32, 37.27, 36.88, 36.80, 31.66, 31.62, 31.54, 31.20; ^{19}F NMR (471 MHz, DMSO- d_6) δ –73.66, –73.71; ESI-HR-MS: (m/z) calcd. for $\text{C}_{26}\text{H}_{26}\text{F}_3\text{N}_4\text{O}_2$ ($[\text{M}+\text{H}]^+$) 483.2002, found 483.2007.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-2,2-difluoroacetamide (**C-3-5**). Following general procedure 3, **74-5** (0.57 g, 1.49 mmol) was first treated with TFA (2.9 mL) in CH_2Cl_2 (1.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.53 g, 1.79 mmol) using EDCI (0.72 g, 3.73 mmol), HOBT (15 mg, 0.112 mmol), and DIPEA (1.16 g, 8.94 mmol) in dried THF (5.7 mL). Purification by column chromatography (EtOAc) gave **C-3-5**. White foam, 0.33 g (48%). ^1H NMR (500 MHz, CD_3OD) δ 8.77 (dd, J = 1.8 Hz and 4.8 Hz, 1H), 8.66–8.65 (m, 1H), 8.56–8.55 (m, 1H), 7.86–7.79 (m, 1H), 7.69–7.64 (m, 2H), 7.56 (dd, J = 4.8 Hz and 7.8 Hz, 1H), 7.31–7.22 (m, 3H), 7.15–7.06 (m, 2H), 6.21–5.97 (m, 1H), 4.03–3.81 (m, 1H), 3.65–3.45 (m, 1H), 3.35–3.32 (m, 1H), 3.28–3.20 (m, 1H), 3.12–3.00 (m, 2H), 2.68 (s, 1H), 2.55–2.47 (m, 1H), 1.50–1.47 (m, 1H), 1.34–1.17 (m, 2H), 0.81–0.75 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.30, 167.13, 163.22, 163.11, 163.06, 162.94, 162.89, 162.78, 151.66, 151.47, 150.22, 149.71, 146.11, 146.01, 136.08, 135.99, 135.86, 135.76, 131.19, 131.12, 129.98, 129.76, 128.42, 128.33, 126.85, 126.73, 123.37, 123.11, 122.92, 109.95, 109.79, 108.28, 108.13, 106.62, 106.46, 44.29, 43.91, 42.69, 42.47, 42.17, 37.28, 36.72, 36.65, 31.69, 31.54, 31.45, 30.97; ^{19}F NMR (471 MHz, CD_3OD) δ –127.59; ESI-HR-MS: (m/z) calcd. for $\text{C}_{26}\text{H}_{27}\text{F}_2\text{N}_4\text{O}_2$ ($[\text{M}+\text{H}]^+$) 465.2097, found 465.2104.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)furan-2-carboxamide (**C-3-6**). Following General Procedure 3, **74-6** (0.78 g, 1.96 mmol) was first treated with TFA (9.8 mL) in CH_2Cl_2 (5.9 mL), and the intermediate obtained was reacted with **7-TFA** (0.70 g, 2.35 mmol) using EDCI (0.94 g, 4.90 mmol), HOBT (20 mg, 0.147 mmol), and DIPEA (1.53 g, 11.8 mmol) in dried THF (7.8 mL). Purification by column chromatography (EtOAc) gave **C-3-6**. White solid, 0.39 g (41%). ^1H NMR (500 MHz, CD_3OD) δ 8.76 (dd, J = 1.8 Hz and 4.8 Hz, 1H), 8.56–8.53 (m, 2H), 7.86–7.77 (m, 1H), 7.67–7.63 (m, 3H), 7.55 (dd, J = 5.0 Hz and 8.0 Hz, 1H), 7.31–7.23 (m, 3H), 7.19–7.09 (m, 3H), 6.59–6.58 (m, 1H), 4.06–3.88 (m, 1H), 3.62–3.50 (m, 1H), 3.44–3.41 (m, 1H), 3.35–3.33 (m, 1H), 3.27 (s, 1.44H), 3.11–3.08 (m, 1H), 2.74 (s, 0.56H), 2.60–2.52 (m, 1H), 1.56–1.24 (m, 3H), 1.08–0.79 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.00, 166.86, 158.26, 158.19, 151.64, 151.32, 149.92, 149.60, 147.15, 147.04, 145.93, 145.77, 143.72, 136.33, 136.28, 135.74, 135.41, 131.24, 131.08, 129.89, 129.66, 128.22, 128.13, 126.44, 126.37, 123.15, 123.03, 122.97, 122.60, 113.87, 111.75, 44.94, 43.11, 42.77, 42.72, 42.53, 41.27, 37.30, 37.19, 36.93, 36.82, 31.84, 31.66, 31.35; ESI-HR-MS: (m/z) calcd. for $\text{C}_{29}\text{H}_{29}\text{N}_4\text{O}_3$ ($[\text{M}+\text{H}]^+$) 481.2234, found 481.2239.

Synthesis of *tert*-butyl 4-benzyl-4-(methylsulfonamidomethyl)piperidine-1-carboxylate (**75-1**). Compound **75-1** was prepared according to General Procedure 2 from **73** (0.80 g, 2.63 mmol) using Ms_2O (0.55 g, 3.16 mmol), DMAP (65 mg, 0.53 mmol), and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/2, by v/v) gave **75-1**. White solid, 0.35 g (35%). m.p 160.2–162.0 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 7.29–7.26 (m, 2H), 7.22–7.18 (m, 3H), 6.99 (t, J = 6.8 Hz, 1H), 3.46–3.41 (m, 2H), 3.26 (s, 2H), 2.91 (s, 3H), 2.86 (d, J = 7.0 Hz, 2H), 2.63 (s, 2H), 1.36 (s, 9H), 1.35–1.33 (m, 2H), 1.24–1.19 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 154.98, 136.73, 130.44, 128.52, 126.87, 79.68, 47.75, 42.22, 39.93, 36.32, 32.21, 28.52; ESI-HR-MS: (m/z) calcd. for $\text{C}_{19}\text{H}_{30}\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 405.1818, found 405.1815.

Synthesis of *tert*-butyl 4-benzyl-4-(((trifluoromethyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-2**). Compound **75-2** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using TiCl_4 (0.53 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by *v/v*) gave **75-2**. White solid, 0.65 g (57%). m.p. 161.3–162.1 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.33 (t, $J = 6.0$ Hz, 1H), 7.31–7.28 (m, 2H), 7.24–7.20 (m, 1H), 7.18–7.16 (m, 2H), 3.43–3.38 (m, 2H), 3.33–3.30 (m, 2H), 3.05 (d, $J = 6.0$ Hz, 2H), 2.70 (s, 2H), 1.40–1.38 (m, 2H), 1.36 (s, 9H), 1.27–1.22 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 154.99, 136.34, 130.29, 128.85, 127.27, 121.15, 118.59, 80.08, 49.76, 42.39, 36.47, 31.86, 28.50; ESI-HR-MS: (m/z) calcd. for $\text{C}_{19}\text{H}_{27}\text{F}_3\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 459.1536, found 459.1530.

Synthesis of *tert*-butyl 4-benzyl-4-(ethylsulfonamidomethyl)piperidine-1-carboxylate (**75-3**). Compound **75-3** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using $\text{CH}_3\text{CH}_2\text{SO}_2\text{Cl}$ (0.41 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by *v/v*) gave **75-3**. White solid, 0.75 g (72%). m.p. 124.6–126.1 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.29–7.26 (m, 2H), 7.21–7.19 (m, 3H), 7.04 (t, $J = 6.8$ Hz, 1H), 3.45–3.34 (m, 2H), 3.25 (s, 2H), 3.04–3.00 (m, 2H), 2.84 (d, $J = 6.5$ Hz, 2H), 2.64 (s, 2H), 1.38–1.36 (m, 2H), 1.35 (s, 9H), 1.23–1.19 (m, 5H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.02, 136.82, 130.36, 128.67, 127.02, 79.74, 47.73, 46.72, 42.76, 36.54, 32.39, 28.57, 8.45; ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 397.2156, found 397.2158.

Synthesis of *tert*-butyl 4-benzyl-4-(cyclopropanesulfonamidomethyl)piperidine-1-carboxylate (**75-4**). Compound **75-4** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using cyclopropanesulfonyl chloride (0.44 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by *v/v*) gave **75-4**. White solid, 0.55 g (51%). m.p. 66.3–69.7 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.32–7.29 (m, 2H), 7.27–7.23 (m, 1H), 7.17–7.15 (m, 2H), 4.48 (t, $J = 6.8$ Hz, 1H), 3.60–3.55 (m, 2H), 3.39–3.34 (m, 2H), 3.04–3.02 (m, 2H), 2.68 (s, 2H), 2.41–2.36 (m, 1H), 1.50–1.48 (m, 4H), 1.45 (s, 9H), 1.17–1.13 (m, 2H), 1.00–0.96 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 154.99, 136.83, 130.46, 128.53, 126.87, 79.67, 47.72, 42.38, 36.35, 32.31, 29.75, 28.54, 5.39; ESI-HR-MS: (m/z) calcd. for $\text{C}_{21}\text{H}_{32}\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 431.1975, found 431.1971.

Synthesis of *tert*-butyl 4-benzyl-4-((thiophene-2-sulfonamido)methyl)piperidine-1-carboxylate (**75-5**). Compound **75-5** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using thiophene-2-sulfonyl chloride (0.58 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by *v/v*) gave **75-5**. White solid, 1.02 g (86%). m.p. 131.2–131.7 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.94 (dd, $J = 1.0$ Hz and 5.0 Hz, 1H), 7.85 (t, $J = 6.5$ Hz, 1H), 7.60 (dd, $J = 1.3$ Hz and 3.8 Hz, 1H), 7.23–7.16 (m, 4H), 7.11–7.09 (m, 2H), 3.43–3.33 (m, 2H), 3.18 (s, 2H), 2.71 (d, $J = 6.5$ Hz, 2H), 2.64 (s, 2H), 1.35 (s, 9H), 1.33–1.31 (m, 2H), 1.24–1.19 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.92, 140.51, 136.58, 132.28, 132.05, 130.41, 128.40, 127.57, 126.73, 79.63, 47.63, 42.39, 39.79, 38.88, 36.10, 32.32, 28.50; ESI-HR-MS: (m/z) calcd. for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{NaO}_4\text{S}_2$ ($[\text{M}+\text{Na}]^+$) 473.1539, found 473.1540.

Synthesis of *tert*-butyl 4-benzyl-4-((pyridine-3-sulfonamido)methyl)piperidine-1-carboxylate (**75-6**). Compound **75-6** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using pyridine-3-sulfonyl chloride (0.56 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by *v/v*) gave **75-6**. White solid, 1.02 g (87%). m.p. 160.5–161.3 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.97 (d, $J = 2.5$ Hz, 1H), 8.83 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 8.21–8.19 (m, 1H), 7.87 (t, $J = 6.0$ Hz, 1H), 7.66 (dd, $J = 5.0$ Hz and 8.0 Hz, 1H), 7.22–7.15 (m, 3H), 7.10–7.08 (m, 2H), 3.44–3.39 (m, 2H), 3.18 (s, 2H), 2.68 (d, $J = 5.5$ Hz, 2H), 2.63 (s, 2H), 1.35 (s, 9H), 1.32–1.30

(m, 2H), 1.23–1.18 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.83, 153.17, 147.83, 136.52, 136.40, 134.71, 130.29, 128.29, 126.67, 123.86, 79.61, 47.68, 41.96, 39.70, 38.80, 36.10, 31.95, 28.38; ESI-HR-MS: (m/z) calcd. for $\text{C}_{23}\text{H}_{31}\text{N}_3\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 468.1927, found 468.1931.

Synthesis of *tert*-butyl 4-benzyl-4-(((phenylmethyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-7**). Compound **75-7** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using phenylmethanesulfonyl chloride (0.60 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by v/v) gave **75-7**. White solid, 0.72 g (60%). m.p. 150.5–151.9 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.41–7.35 (m, 5H), 7.29–7.26 (m, 2H), 7.22–7.19 (m, 1H), 7.16–7.11 (m, 3H), 4.36 (s, 2H), 3.43–3.38 (m, 2H), 3.23 (s, 2H), 2.72 (d, $J = 7.0$ Hz, 2H), 2.57 (s, 2H), 1.36 (s, 9H), 1.33–1.28 (m, 2H), 1.19–1.13 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.93, 136.68, 130.60, 130.32, 129.33, 129.03, 128.94, 128.43, 126.73, 79.56, 58.74, 47.79, 42.47, 39.78, 38.88, 36.49, 36.48, 32.10, 32.07, 28.51; ESI-HR-MS: (m/z) calcd. for $\text{C}_{25}\text{H}_{34}\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 481.2131, found 481.2130.

Synthesis of *tert*-butyl 4-benzyl-4-(phenylsulfonamidomethyl)piperidine-1-carboxylate (**75-8**). Compound **75-8** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using benzenesulfonyl chloride (0.56 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by v/v) gave **75-8**. White solid, 0.72 g (62%). m.p. 76.5–77.3 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.83–7.81 (m, 2H), 7.67–7.59 (m, 4H), 7.21–7.14 (m, 3H), 7.09–7.07 (m, 2H), 3.43–3.32 (m, 2H), 3.15 (s, 2H), 2.62–2.61 (m, 4H), 1.35 (s, 9H), 1.31–1.29 (m, 2H), 1.22–1.17 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 154.97, 139.62, 136.67, 132.95, 130.37, 129.36, 128.51, 127.14, 126.85, 79.70, 47.50, 42.68, 36.25, 32.46, 28.55; ESI-HR-MS: (m/z) calcd. for $\text{C}_{24}\text{H}_{33}\text{N}_2\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 445.2156, found 445.2151.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-fluorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-9**). Compound **75-9** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-fluorobenzenesulfonyl chloride (0.61 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by v/v) gave **75-9**. White solid, 1.10 g (90%). m.p. 176.4–177.8 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.89–7.87 (m, 2H), 7.67 (t, $J = 6.5$ Hz, 1H), 7.45 (t, $J = 8.8$ Hz, 2H), 7.22–7.15 (m, 3H), 7.09–7.08 (m, 2H), 3.43–3.39 (m, 2H), 3.17–3.15 (m, 2H), 2.62–2.61 (m, 4H), 1.35 (s, 9H), 1.33–1.28 (m, 2H), 1.23–1.17 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 166.03, 164.34, 154.93, 136.59, 135.73 (d, $J = 3.2$ Hz), 130.36, 129.84 (d, $J = 9.4$ Hz), 128.43, 126.81, 116.54 (d, $J = 22.5$ Hz), 79.68, 47.52, 42.36, 36.18, 32.33, 28.50; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ −107.10; ESI-HR-MS: (m/z) calcd. for $\text{C}_{24}\text{H}_{31}\text{FN}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 485.1881, found 485.1880.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-cyanophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-10**). Compound **75-10** was prepared according to General Procedure 1 from **73** (1.00 g, 3.28 mmol) using 4-cyanobenzenesulfonyl chloride (0.79 g, 3.94 mmol) and Et_3N (1.00 g, 9.84 mmol) in dried CH_2Cl_2 (10 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by v/v) gave **75-10**. White foam, 1.10 g (73%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.12–8.10 (m, 2H), 7.99–7.97 (m, 2H), 7.92 (t, $J = 6.3$ Hz, 1H), 7.22–7.15 (m, 3H), 7.10–7.08 (m, 2H), 3.43–3.39 (m, 2H), 3.17–3.15 (m, 2H), 2.67–2.62 (m, 4H), 1.35 (s, 9H), 1.32–1.29 (m, 2H), 1.23–1.17 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.94, 144.08, 136.50, 133.13, 130.29, 128.57, 127.73, 127.01, 117.35, 116.57, 79.84, 48.03, 42.37, 39.75, 38.94, 36.33, 32.26, 28.51; ESI-HR-MS: (m/z) calcd. for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 492.1927, found 492.1926.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-methoxyphenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-11**). Compound **75-11** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-methoxybenzenesulfonyl chloride (0.65 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatogra-

phy (EtOAc/PE = 1/5, by *v/v*) gave **75-11**. White solid, 0.99 g (79%). m.p. 113.1–114.2 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.75 (d, *J* = 10.0 Hz, 2H), 7.47 (t, *J* = 6.5 Hz, 1H), 7.21–7.16 (m, 3H), 7.13–7.07 (m, 4H), 3.84 (s, 3H), 3.43–3.33 (m, 2H), 3.14 (s, 2H), 2.62–2.57 (m, 4H), 1.35 (s, 9H), 1.30–1.28 (m, 2H), 1.22–1.17 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 163.01, 154.90, 136.69, 131.15, 130.44, 129.25, 128.30, 126.62, 114.42, 79.54, 55.70, 47.20, 42.32, 39.74, 38.92, 36.08, 32.33, 28.48; ESI-HR-MS: (*m/z*) calcd. for C₂₅H₃₄N₂NaO₅S ([M+Na]⁺) 497.2081, found 497.2078.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-nitrophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-12**). Compound **75-12** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-nitrobenzenesulfonyl chloride (0.70 g, 3.16 mmol) and Et₃N (0.80 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **75-12**. White solid, 1.10 g (85%). m.p. 164.1–164.9 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.45–8.42 (m, 2H), 8.09–7.99 (m, 2H), 7.71 (t, *J* = 6.5 Hz, 1H), 7.22–7.15 (m, 3H), 7.11–7.09 (m, 2H), 3.44–3.39 (m, 2H), 3.20–3.15 (m, 2H), 2.69 (d, *J* = 6.5 Hz, 2H), 2.63 (s, 2H), 1.34 (s, 9H), 1.32–1.30 (m, 2H), 1.24–1.18 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 154.95, 150.19, 145.64, 136.50, 130.29, 128.58, 128.36, 127.02, 124.56, 79.86, 48.17, 42.34, 39.76, 38.95, 36.35, 32.23, 28.51; ESI-HR-MS: (*m/z*) calcd. for C₂₄H₃₁N₃NaO₆S ([M+Na]⁺) 512.1826, found 512.1830.

Synthesis of *tert*-butyl 4-benzyl-4-(((3-chlorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-13**). Compound **75-13** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 3-chlorobenzenesulfonyl chloride (0.67 g, 3.16 mmol) and Et₃N (0.80 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **75-13**. White solid, 1.10 g (87%). m.p. 185.2–185.8 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.84 (t, *J* = 1.8 Hz, 1H), 7.79–7.74 (m, 3H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.22–7.15 (m, 3H), 7.10–7.08 (m, 2H), 3.44–3.39 (m, 2H), 3.17–3.15 (m, 2H), 2.65–2.63 (m, 4H), 1.35 (s, 9H), 1.32–1.30 (m, 2H), 1.23–1.17 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 154.94, 141.43, 136.58, 135.54, 133.01, 130.63, 130.35, 128.51, 127.20, 126.89, 125.19, 79.71, 47.67, 42.52, 39.81, 38.94, 36.25, 32.37, 28.53; ESI-HR-MS: (*m/z*) calcd. for C₂₄H₃₁ClN₂NaO₄S ([M+Na]⁺) 501.1585, found 501.1586.

Synthesis of *tert*-butyl 4-benzyl-4-(((2-fluorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-14**). Compound **75-14** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 2-fluorobenzenesulfonyl chloride (0.61 g, 3.16 mmol) and Et₃N (0.80 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **75-14**. White solid, 1.06 g (87%). m.p. 161.3–162.6 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.97 (s, 1H), 7.81–7.78 (m, 1H), 7.73–7.69 (m, 1H), 7.48–7.44 (m, 1H), 7.40–7.37 (m, 1H), 7.24–7.21 (m, 2H), 7.19–7.16 (m, 1H), 7.12–1.10 (m, 2H), 3.42–3.38 (m, 2H), 3.16 (s, 2H), 2.76 (s, 2H), 2.65 (s, 2H), 1.35 (s, 9H), 1.33–1.30 (m, 2H), 1.23–1.17 (m, 2H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.14, 157.13, 153.93, 137.09, 135.24 (d, *J* = 8.4 Hz), 130.63, 129.78, 128.31 (d, *J* = 14.2 Hz), 127.79, 126.09, 124.91 (d, *J* = 3.7 Hz), 117.26 (d, *J* = 21.3 Hz), 78.49, 47.07, 40.67, 35.53, 30.92, 28.05; ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ −110.11; ESI-HR-MS: (*m/z*) calcd. for C₂₄H₃₁FN₂NaO₄S ([M+Na]⁺) 485.1881, found 485.1881.

Synthesis of *tert*-butyl 4-benzyl-4-(((3-fluorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-15**). Compound **75-15** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 3-fluorobenzenesulfonyl chloride (0.61 g, 3.16 mmol) and Et₃N (0.80 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/5, by *v/v*) gave **75-15**. White solid, 1.04 g (86%). m.p. 151.0–152.2 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.76 (s, 1H), 7.70–7.66 (m, 2H), 7.63–7.61 (m, 1H), 7.55–7.51 (m, 1H), 7.22–7.15 (m, 3H), 7.10–7.08 (m, 2H), 3.44–3.40 (m, 2H), 3.17 (s, 2H), 2.65–2.62 (m, 4H), 1.35 (s, 9H), 1.32–1.29 (m, 2H), 1.23–1.18 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 163.41, 161.74, 154.94, 141.75 (d, *J* = 6.5 Hz), 136.57, 131.16 (d, *J* = 7.7 Hz), 130.36, 128.45, 126.84,

122.85, 122.83, 120.09 (d, $J = 21.3$ Hz), 114.50 (d, $J = 24.3$ Hz), 79.70, 47.64, 42.40, 39.79, 38.91, 36.22, 32.32, 28.51; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ −110.62; ESI-HR-MS: (m/z) calcd. for $\text{C}_{24}\text{H}_{31}\text{FN}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 485.1881, found 485.1881.

Synthesis of *tert*-butyl 4-benzyl-4-(((perfluorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-16**). Compound **75-16** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using perfluorobenzenesulfonyl chloride (0.84 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by v/v) gave **75-16**. White solid, 1.04 g (74%). m.p. 170.1–170.8 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.72 (s, 1H), 7.28–7.24 (m, 2H), 7.22–7.16 (m, 3H), 3.44–3.39 (m, 2H), 3.24 (s, 2H), 2.89 (s, 2H), 2.68 (s, 2H), 1.37–1.35 (m, 11H), 1.26–1.21 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.95, 145.12 (t, $J = 35.0$ Hz), 143.40 (t, $J = 37.4$ Hz), 138.85 (d, $J = 12.5$ Hz), 137.19 (t, $J = 17.8$ Hz), 136.52, 130.20, 128.80, 127.24, 116.14 (t, $J = 15.3$ Hz), 79.86, 48.14, 46.01, 42.97, 39.74, 38.90, 36.54, 32.50, 28.55; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ −137.97–−138.07 (m), −148.02 (tt, $J = 5.7$ and 22.6 Hz), −159.92–−160.05 (m); ESI-HR-MS: (m/z) calcd. for $\text{C}_{24}\text{H}_{27}\text{F}_5\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 557.1504, found 557.1505.

Synthesis of *tert*-butyl 4-benzyl-4-(((2,3,4,5,6-pentamethylphenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-17**). Compound **75-17** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 2,3,4,5,6-pentamethylbenzenesulfonyl chloride (0.78 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by v/v) gave **75-17**. White solid, 1.01 g (75%). m.p. 177.5–178.0 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.39 (t, $J = 6.5$ Hz, 1H), 7.22–7.15 (m, 3H), 7.07–7.06 (m, 2H), 3.37–3.36 (m, 2H), 3.13–3.08 (m, 2H), 2.61–2.59 (m, 4H), 2.48 (s, 6H), 2.23 (s, 3H), 2.18 (s, 6H), 1.34 (s, 9H), 1.32–1.27 (m, 2H), 1.17–1.12 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.93, 139.73, 136.95, 135.72, 134.99, 134.11, 130.41, 128.46, 126.78, 79.61, 46.93, 42.70, 39.82, 38.97, 36.31, 32.55, 28.54, 19.01, 17.89, 17.17; ESI-HR-MS: (m/z) calcd. for $\text{C}_{29}\text{H}_{42}\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 537.2757, found 537.2759.

Synthesis of *tert*-butyl 4-benzyl-4-(((3,4-difluorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-18**). Compound **75-18** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 3,4-difluorobenzenesulfonyl chloride (0.67 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/5$, by v/v) gave **75-18**. White solid, 1.09 g (86%). m.p. 185.9–186.3 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.89–7.86 (m, 1H), 7.77 (s, 1H), 7.72–7.69 (m, 2H), 7.23–7.16 (m, 3H), 7.11–7.09 (m, 2H), 3.43–3.39 (m, 2H), 3.18 (s, 2H), 2.66–2.62 (m, 4H), 1.35 (s, 9H), 1.32–1.29 (m, 2H), 1.23–1.17 (m, 2H); ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$) δ 153.95, 152.68 (d, $J = 12.4$ Hz), 151.00 (d, $J = 12.4$ Hz), 150.06 (d, $J = 13.4$ Hz), 148.40 (d, $J = 13.3$ Hz), 137.34 (t, $J = 4.2$ Hz), 130.64, 127.72, 126.09, 124.40 (q, $J = 3.9$ Hz), 118.63 (d, $J = 18.3$ Hz), 116.44 (d, $J = 19.6$ Hz), 78.43, 67.00, 46.97, 40.83, 35.51, 28.01; ESI-HR-MS: (m/z) calcd. for $\text{C}_{24}\text{H}_{30}\text{F}_2\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 503.1787, found 503.1787.

Synthesis of *tert*-butyl 4-benzyl-4-(((3,4,5-trifluorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-19**). Compound **75-19** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 3,4,5-trifluorobenzenesulfonyl chloride (0.73 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/3$, by v/v) gave **75-19**. White solid, 1.03 g (79%). m.p. 197.9–198.5 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.86 (s, 1H), 7.77 (t, $J = 6.5$ Hz, 2H), 7.24–7.12 (m, 3H), 7.14–7.12 (m, 2H), 3.45–3.40 (m, 2H), 3.19 (s, 2H), 2.70 (s, 2H), 2.62 (s, 2H), 1.35 (s, 9H), 1.33–1.30 (m, 2H), 1.24–1.18 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.98, 151.27 (ddd, $J = 3.2$, 10.6 and 257.2 Hz), 142.789 (dt, $J = 15.0$ and 185.4 Hz), 136.57, 135.96 (q, $J = 5.6$ Hz), 130.28, 128.69, 127.16, 112.31 (dd, $J = 5.6$ and 18.3 Hz), 79.91, 48.29, 42.61, 39.80, 38.99, 36.39, 32.41, 28.54; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ −131.39 (d, $J = 21.2$ Hz), −154.40 (d, $J = 21.2$ Hz); ESI-HR-MS: (m/z) calcd. for $\text{C}_{24}\text{H}_{29}\text{F}_3\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 521.1692, found 521.1694.

Synthesis of *tert*-butyl 4-benzyl-4-(((2,5-difluorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-20**). Compound **75-20** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 2,5-difluorobenzenesulfonyl chloride (0.67 g, 3.16 mmol) and Et₃N (0.80 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by *v/v*) gave **75-20**. White solid, 1.07 g (85%). m.p. 155.5–156.3 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.12 (t, *J* = 6.0 Hz, 1H), 7.62–7.53 (m, 3H), 7.24–7.21 (m, 2H), 7.19–7.16 (m, 1H), 7.13–7.11 (m, 2H), 3.43–3.38 (m, 2H), 3.19 (s, 2H), 2.79 (d, *J* = 5.5 Hz, 2H), 1.35 (s, 9H), 1.33–1.31 (m, 2H), 1.24–1.18 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 157.96 (dd, *J* = 2.5 and 248.5 Hz), 154.88, 136.55, 130.32, 128.99 (dd, *J* = 6.7 and 16.2 Hz), 128.48, 126.84, 121.66 (dd, *J* = 8.5 and 24.1 Hz), 118.45 (dd, *J* = 7.9 and 24.3 Hz), 117.37, 117.19, 79.64, 47.52, 42.48, 39.73, 38.85, 36.24, 32.25, 28.48; ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ −115.64 (d, *J* = 18.8 Hz), −116.31 (d, *J* = 18.8 Hz); ESI-HR-MS: (*m/z*) calcd. for C₂₄H₃₀F₂N₂NaO₄S ([M+Na]⁺) 503.1787, found 503.1786.

Synthesis of *tert*-butyl 4-benzyl-4-(((2,4,5-trifluorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-21**). Compound **75-21** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 2,4,5-trifluorobenzenesulfonyl chloride (0.73 g, 3.16 mmol) and Et₃N (0.80 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by *v/v*) gave **75-21**. White solid, 1.13 g (86%). m.p. 134.9–135.6 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.15 (t, *J* = 5.8 Hz, 1H), 7.91–7.82 (m, 2H), 7.25–7.11 (m, 5H), 3.43–3.39 (m, 2H), 3.21–3.17 (m, 2H), 2.78 (d, *J* = 5.5 Hz, 2H), 2.65 (s, 2H), 1.35 (s, 9H), 1.32–1.30 (m, 2H), 1.24–1.19 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 155.23 (dd, *J* = 2.9 Hz and 10.1 Hz), 154.49, 154.15 (dd, *J* = 2.9 Hz and 10.2 Hz), 153.55 (dd, *J* = 2.9 Hz and 10.2 Hz), 136.53, 130.30, 128.54, 126.93, 124.37 (dt, *J* = 4.2 Hz and 16.2 Hz), 119.04 (dt, *J* = 1.6 Hz and 20.9 Hz), 107.47 (dd, *J* = 21.7 Hz and 27.3 Hz), 79.72, 47.67, 42.47, 39.71, 38.88, 36.28, 32.27, 28.49; ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ −110.11 (dd, *J* = 8.0 and 16.5 Hz), −126.54 (dd, *J* = 8.2 and 22.4 Hz), −140.55 (dd, *J* = 15.8 and 22.4 Hz); ESI-HR-MS: (*m/z*) calcd. for C₂₄H₂₉F₃N₂NaO₄S ([M+Na]⁺) 521.1692, found 521.1697.

Synthesis of *tert*-butyl 4-benzyl-4-(((3-chloro-4-fluorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-22**). Compound **75-22** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 3-chloro-4-fluorobenzenesulfonyl chloride (0.72 g, 3.16 mmol) and Et₃N (0.80 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by *v/v*) gave **75-22**. White solid, 1.13 g (87%). m.p. 178.5–179.2 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.01 (dd, *J* = 2.3 Hz and 6.8 Hz, 1H), 7.85–7.82 (m, 1H), 7.77 (t, *J* = 6.5 Hz, 1H), 7.77 (t, *J* = 6.5 Hz, 1H), 7.23–7.15 (m, 3H), 7.11–7.09 (m, 2H), 3.44–3.39 (m, 2H), 3.19–3.16 (m, 2H), 2.66–2.62 (m, 4H), 1.35 (s, 9H), 1.31–1.29 (m, 2H), 1.23–1.18 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 161.54, 159.84, 154.96, 136.85 (d, *J* = 3.8 Hz), 136.59, 130.33, 130.06, 128.56, 127.59 (d, *J* = 8.5 Hz), 126.99, 122.65 (d, *J* = 18.7 Hz), 117.58 (d, *J* = 22.2 Hz), 79.79, 47.87, 42.54, 39.80, 38.95, 36.29, 32.39, 28.54; ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ −109.99; ESI-HR-MS: (*m/z*) calcd. for C₂₄H₃₀ClFN₂NaO₄S ([M+Na]⁺) 519.1491, found 519.1495.

Synthesis of *tert*-butyl 4-benzyl-4-(((2,3,4-trifluorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-23**). Compound **75-23** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 2,3,4-trifluorobenzenesulfonyl chloride (0.73 g, 3.16 mmol) and Et₃N (0.80 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by *v/v*) gave **75-23**. White solid, 1.12 g (85%). m.p. 151.7–152.6 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.19 (t, *J* = 6.3 Hz, 1H), 7.68–7.64 (m, 1H), 7.55–7.50 (m, 1H), 7.25–7.22 (m, 2H), 7.20–7.17 (m, 1H), 7.14–7.13 (m, 2H), 3.43–3.38 (m, 2H), 3.22–3.17 (m, 2H), 2.78 (d, *J* = 6.0 Hz, 2H), 2.66 (s, 2H), 1.35 (s, 9H), 1.34–1.31 (m, 2H), 1.24–1.19 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 154.93, 154.48 (ddd, *J* = 3.0, 10.2 and 259.3 Hz), 148.45 (ddd, *J* = 3.8, 11.5 and 258.0 Hz), 140.41 (dt, *J* = 15.3 and 257.4 Hz), 136.55, 130.25, 128.64, 127.05,

125.62 (d, $J = 9.8$ Hz), 124.60 (q, $J = 3.2$ Hz), 112.71 (dd, $J = 3.6$ and 18.1 Hz), 79.76, 47.70, 42.73, 39.76, 38.89, 36.37, 32.39, 28.53; ^{19}F NMR (471 MHz, CDCl_3) δ −124.18 (dd, $J = 13.0$ and 20.0 Hz), −131.04 (dd, $J = 13.0$ and 21.4 Hz), −156.25 (t, $J = 21.0$ Hz); ESI-HR-MS: (m/z) calcd. for $\text{C}_{24}\text{H}_{29}\text{F}_3\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 521.1692, found 521.1700.

Synthesis of *tert*-butyl 4-benzyl-4-(((3,5-bis(trifluoromethyl)phenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-24**). Compound **75-24** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 3,5-bis(trifluoromethyl)benzenesulfonyl chloride (0.99 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/3$, by v/v) gave **75-24**. White solid, 1.31 g (86%). m.p. 178.6–179.7 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.50 (s, 1H), 8.42–8.41 (m, 2H), 8.02 (t, $J = 6.0$ Hz, 1H), 7.20–7.15 (m, 3H), 7.10–7.08 (m, 2H), 3.43–3.38 (m, 2H), 3.23–3.17 (m, 2H), 2.71 (d, $J = 6.0$ Hz, 2H), 2.64 (s, 2H), 1.35 (s, 9H), 1.32–1.30 (m, 2H), 1.24–1.18 (m, 2H); ^{13}C NMR (151 MHz, CD_3OD) δ 156.60, 145.17, 138.11, 133.92 (q, $J = 34.2$ Hz), 131.73, 129.03, 128.56, 128.54, 127.50, 127.22 (t, $J = 3.7$ Hz), 124.17 (q, $J = 272.7$ Hz), 81.03, 42.36, 41.05, 40.12, 37.17, 32.54, 28.65; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ −61.49; ESI-HR-MS: (m/z) calcd. for $\text{C}_{26}\text{H}_{30}\text{F}_6\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 603.1723, found 603.1724.

Synthesis of *tert*-butyl 4-benzyl-4-(((2-chloro-4-fluorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-25**). Compound **75-25** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 2-chloro-4-fluorobenzenesulfonyl chloride (0.72 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/3$, by v/v) gave **75-25**. White solid, 1.18 g (90%). m.p. 204.4–206.3 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.01 (dd, $J = 6.0$ Hz and 9.0 Hz, 1H), 7.97 (t, $J = 6.3$ Hz, 1H), 7.71 (dd, $J = 2.5$ Hz and 8.5 Hz, 1H), 7.43–7.39 (m, 1H), 7.25–7.22 (m, 2H), 7.19–7.18 (m, 1H), 7.14–7.12 (m, 2H), 3.43–3.38 (m, 2H), 3.18–3.12 (m, 2H), 2.76 (d, $J = 6.5$ Hz, 2H), 2.65 (s, 2H), 1.34 (s, 9H), 1.32–1.30 (m, 2H), 1.23–1.17 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 165.69 (d, $J = 258.7$ Hz), 154.87, 136.63, 133.51 (d, $J = 9.7$ Hz), 133.28 (d, $J = 3.62$ Hz), 132.99 (d, $J = 11.0$ Hz), 130.37, 128.53, 126.87, 119.29 (d, $J = 25.5$ Hz), 114.74 (d, $J = 21.4$ Hz), 79.65, 47.43, 42.56, 39.71, 38.87, 36.32, 32.41, 28.50; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ −105.21; ESI-HR-MS: (m/z) calcd. for $\text{C}_{24}\text{H}_{30}\text{ClF}_2\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 519.1491, found 519.1499.

Synthesis of *tert*-butyl 4-benzyl-4-(((3-cyano-4-fluorophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-26**). Compound **75-26** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 3-cyano-4-fluorobenzenesulfonyl chloride (0.69 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/3$, by v/v) gave **75-26**. White solid, 0.74 g (58%). m.p. 207.8–209.5 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.36 (dd, $J = 2.5$ Hz and 6.0 Hz, 1H), 8.21–8.18 (m, 1H), 7.85–7.77 (m, 2H), 7.24–7.17 (m, 3H), 7.12–7.11 (m, 2H), 3.45–3.40 (m, 2H), 3.20–3.18 (m, 2H), 2.69 (d, $J = 6.5$ Hz, 2H), 2.62 (s, 2H), 1.35 (s, 9H), 1.31–1.29 (m, 2H), 1.23–1.18 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 165.13 (d, $J = 9.5$ Hz), 154.97, 137.60, 137.58, 136.58, 133.98, 133.91, 133.03, 130.23, 128.77, 127.26, 117.84 (d, $J = 20.7$ Hz), 112.35, 103.12 (d, $J = 16.6$ Hz), 79.93, 48.28, 42.77, 39.78, 38.97, 36.44, 32.51, 28.56; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ −102.49; ESI-HR-MS: (m/z) calcd. for $\text{C}_{25}\text{H}_{30}\text{FN}_3\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 510.1833, found 510.1839.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-*tert*-butyl)phenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-27**). Compound **75-27** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-*tert*-butylbenzenesulfonyl chloride (0.73 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($\text{EtOAc}/\text{PE} = 1/3$, by v/v) gave **75-27**. White solid, 1.10 g (84%) m.p. 190.0–190.9 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.76–7.73 (m, 2H), 7.63–7.60 (m, 2H), 7.57 (t, $J = 6.3$ Hz, 1H), 7.19–7.13 (m, 3H), 7.08–7.06 (m, 2H), 3.43–3.38 (m, 2H), 3.12–3.06 (m, 2H), 2.62–2.61 (m, 4H), 1.35 (s, 9H), 1.31 (s, 9H), 1.29–1.27 (m, 2H), 1.22–1.17 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ

156.66, 154.93, 136.70, 136.55, 130.44, 128.36, 127.03, 126.66, 126.29, 79.59, 47.22, 42.45, 39.76, 38.91, 36.18, 35.27, 32.38, 31.19, 28.52; ESI-HR-MS: (m/z) calcd. for $C_{28}H_{41}N_2O_4S$ ($[M+H]^+$) 501.2782, found 501.2790.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-(trifluoromethyl)phenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-28**). Compound **75-28** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-(trifluoromethyl)benzenesulfonyl chloride (0.77 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($EtOAc/PE = 1/3$, by v/v) gave **75-28**. White solid, 1.20 g (89%). m.p. 131.2–132.9 °C. 1H NMR (500 MHz, $DMSO-d_6$) δ 8.05–8.00 (m, 4H), 7.89 (t, $J = 5.5$ Hz, 1H), 7.20–7.14 (m, 3H), 7.08–7.06 (m, 2H), 3.44–3.39 (m, 2H), 3.18–3.13 (m, 2H), 2.67–2.63 (m, 4H), 1.35 (s, 9H), 1.32–1.30 (m, 2H), 1.24–1.18 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.95, 143.31, 136.54, 134.63 (q, $J = 33.1$ Hz), 130.30, 128.55, 127.65, 126.97, 126.51 (q, $J = 5.6$ Hz), 123.30 (q, $J = 273.1$ Hz), 79.79, 47.83, 42.48, 39.77, 38.96, 36.31, 32.38, 28.52; ^{19}F NMR (471 MHz, $DMSO-d_6$) δ −61.57; ESI-HR-MS: (m/z) calcd. for $C_{25}H_{31}F_3N_2NaO_4S$ ($[M+Na]^+$) 535.1849, found 535.1851.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-fluoro-3-(trifluoromethyl)phenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-29**). Compound **75-29** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-fluoro-3-(trifluoromethyl)benzenesulfonyl chloride (0.83 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($EtOAc/PE = 1/3$, by v/v) gave **75-29**. White solid, 0.96 g (69%). m.p. 196.2–197.1 °C. 1H NMR (500 MHz, $DMSO-d_6$) δ 8.21–8.16 (m, 2H), 7.86 (t, $J = 6.3$ Hz, 1H), 7.81–7.77 (m, 1H), 7.21–7.17 (m, 3H), 7.10–7.08 (m, 2H), 3.43–3.38 (m, 2H), 3.20–3.15 (m, 2H), 2.66–2.63 (m, 4H), 1.35 (s, 9H), 1.31–1.29 (m, 2H), 1.23–1.18 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.70 (d, $J = 264.1$ Hz), 155.15, 136.93 (d, $J = 3.9$ Hz), 136.44, 133.10 (d, $J = 9.8$ Hz), 130.33, 128.05, 126.62, 126.49, 122.00 (q, $J = 237.8$ Hz), 119.56–118.88 (m), 117.99 (d, $J = 27.4$ Hz), 77.94, 47.49, 41.49, 39.69, 38.73, 35.89, 31.57, 28.14; ^{19}F NMR (471 MHz, CD_3OD) δ −59.72 (d, $J = 11.8$ Hz), −108.93 (q, $J = 12.2$ Hz); ESI-HR-MS: (m/z) calcd. for $C_{25}H_{30}F_4N_2NaO_4S$ ($[M+Na]^+$) 553.1755, found 553.1755.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-(trifluoromethoxy)phenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-30**). Compound **75-30** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-(trifluoromethoxy)benzenesulfonyl chloride (0.82 g, 3.16 mmol) and Et_3N (0.80 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($EtOAc/PE = 1/3$, by v/v) gave **75-30**. White solid, 1.20 g (86%). m.p. 149.8–150.7 °C. 1H NMR (500 MHz, $DMSO-d_6$) δ 7.97–7.95 (m, 2H), 7.78 (t, $J = 6.0$ Hz, 1H), 7.61 (d, $J = 8.5$ Hz, 2H), 7.20–7.14 (m, 3H), 7.09–7.07 (m, 2H), 3.44–3.39 (m, 2H), 3.17–3.12 (m, 2H), 2.66–2.63 (m, 4H), 1.35 (s, 9H), 1.31–1.29 (m, 2H), 1.23–1.18 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.94, 152.26 (q, $J = 1.9$ Hz), 138.08, 136.55, 130.34, 129.28, 128.44, 126.84, 121.17, 120.33 (q, $J = 259.6$ Hz), 79.71, 47.62, 42.32, 39.77, 38.88, 36.23, 32.31, 28.49; ^{19}F NMR (471 MHz, $DMSO-d_6$) δ −56.77; ESI-HR-MS: (m/z) calcd. for $C_{25}H_{31}F_3N_2NaO_5S$ ($[M+Na]^+$) 551.1798, found 551.1804.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-fluoro-2-(trifluoromethyl)phenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-31**). Compound **75-31** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-fluoro-2-(trifluoromethyl)benzenesulfonyl chloride (0.82 g, 3.16 mmol) and Et_3N (0.83 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography ($EtOAc/PE = 1/3$, by v/v) gave **75-31**. White solid, 1.22 g (87%). m.p. 187.5–188.5 °C. 1H NMR (500 MHz, $DMSO-d_6$) δ 8.16–8.11 (m, 2H), 7.91 (dd, $J = 2.8$ Hz and 9.3 Hz, 1H), 7.82–7.78 (m, 1H), 7.27–7.24 (m, 2H), 7.21–7.17 (m, 1H), 7.15–7.13 (m, 2H), 3.43–3.39 (m, 2H), 3.21–2.18 (m, 2H), 2.81 (d, $J = 6.0$ Hz, 2H), 2.66 (s, 2H), 1.38–1.35 (m, 2H), 1.35 (s, 9H), 1.24–1.19 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.19, 163.48, 154.94, 136.59, 134.97 (d, $J = 8.8$ Hz), 134.59 (d, $J = 3.9$ Hz), 130.23, 128.63, 126.99, 122.22 (qd,

$J = 2.1$ and 274.3 Hz), 119.11 (d, $J = 20.8$ Hz), 116.94 (dq, $J = 6.4$ and 26.1 Hz), 79.76 , 47.87 , 42.45 , 39.75 , 38.90 , 36.47 , 32.45 , 28.54 ; ^{19}F NMR (471 MHz, DMSO- d_6) δ -56.52 , -105.12 ; ESI-HR-MS: (m/z) calcd. for $\text{C}_{25}\text{H}_{30}\text{F}_4\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 553.1755 , found 553.1754 .

Synthesis of *tert*-butyl 4-benzyl-4-((naphthalene-2-sulfonamido)methyl)piperidine-1-carboxylate (**75-32**). Compound **75-32** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using naphthalene-2-sulfonyl chloride (0.72 g, 3.16 mmol) and Et_3N (0.83 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **75-32**. White solid, 1.12 g (86%). m.p. 134.1 – 134.8 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 8.44 (s, 1H), 8.16 (d, $J = 8.5$ Hz, 2H), 8.06 (d, $J = 8.0$ Hz, 1H), 7.88 (dd, $J = 2.0$ Hz and 3.5 Hz, 1H), 7.74 – 7.66 (m, 3H), 7.11 – 7.05 (m, 5H), 3.42 – 3.37 (m, 2H), 3.17 – 3.12 (m, 2H), 2.51 – 2.79 (m, 4H), 1.33 (s, 9H), 1.31 – 1.29 (m, 2H), 1.22 – 1.17 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.92 , 136.64 , 136.39 , 134.94 , 132.24 , 130.39 , 129.77 , 129.34 , 129.02 , 128.59 , 128.35 , 128.04 , 127.78 , 126.70 , 122.24 , 79.60 , 47.43 , 42.44 , 39.79 , 38.90 , 36.18 , 32.36 , 28.50 ; ESI-HR-MS: (m/z) calcd. for $\text{C}_{28}\text{H}_{35}\text{N}_2\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 495.2312 , found 495.2308 .

Synthesis of *tert*-butyl 4-benzyl-4-((naphthalene-1-sulfonamido)methyl)piperidine-1-carboxylate (**75-33**). Compound **75-33** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using naphthalene-1-sulfonyl chloride (0.72 g, 3.16 mmol) and Et_3N (0.83 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **75-33**. White solid, 1.03 g (79%). m.p. 149.9 – 151.1 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 8.80 (d, $J = 8.5$ Hz, 1H), 8.23 (d, $J = 8.0$ Hz, 1H), 8.12 – 8.09 (m, 2H), 7.96 (t, $J = 6.3$ Hz, 1H), 7.78 – 7.74 (m, 1H), 7.72 – 7.68 (m, 1H), 7.65 – 7.62 (m, 1H), 7.11 – 7.04 (m, 3H), 6.97 – 6.95 (m, 2H), 3.36 – 3.31 (m, 2H), 3.00 (s, 2H), 2.63 (d, $J = 6.0$ Hz, 2H), 2.58 (s, 2H), 1.33 (s, 9H), 1.27 – 1.22 (m, 2H), 1.17 – 1.11 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.84 , 136.57 , 134.49 , 134.37 , 134.29 , 130.26 , 129.87 , 129.34 , 128.62 , 128.32 , 128.15 , 127.10 , 126.63 , 124.29 , 124.27 , 79.53 , 47.07 , 42.84 , 39.68 , 38.88 , 36.13 , 32.37 , 28.49 ; ESI-HR-MS: (m/z) calcd. for $\text{C}_{28}\text{H}_{35}\text{N}_2\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 495.2312 , found 495.2300 .

Synthesis of *tert*-butyl 4-benzyl-4-(((4-cyclohexylphenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-34**). Compound **75-34** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-cyclohexylbenzenesulfonyl chloride (0.82 g, 3.16 mmol) and Et_3N (0.83 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **75-34**. White solid, 1.16 g (84%). m.p. 169.4 – 170.5 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 7.72 (d, $J = 8.5$ Hz, 2H), 7.55 (t, $J = 6.5$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 2H), 7.20 – 7.13 (m, 3H), 7.08 – 7.06 (m, 2H), 3.43 – 3.38 (m, 2H), 3.12 – 3.06 (m, 2H), 2.61 – 2.58 (m, 5H), 1.81 – 1.78 (m, 4H), 1.73 – 1.70 (m, 1H), 1.47 – 1.37 (m, 4H), 1.35 (s, 9H), 1.32 – 1.28 (m, 2H), 1.23 – 1.17 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.93 , 153.54 , 136.84 , 136.70 , 130.43 , 128.40 , 127.78 , 127.26 , 126.70 , 79.60 , 47.26 , 44.66 , 42.54 , 39.77 , 38.93 , 36.20 , 34.22 , 32.41 , 28.53 , 26.76 , 26.06 ; ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{42}\text{N}_2\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 549.2763 , found 549.2758 .

Synthesis of *tert*-butyl 4-benzyl-4-(((3-(methylsulfonyl)phenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-35**). Compound **75-35** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 3-(methylsulfonyl)benzenesulfonyl chloride (0.80 g, 3.16 mmol) and Et_3N (0.83 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **75-35**. White solid, 1.04 g (76%). m.p. 155.3 – 156.1 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 8.33 – 8.32 (m, 1H), 8.24 – 8.22 (m, 1H), 8.16 – 8.14 (m, 1H), 7.93 – 7.88 (m, 2H), 7.22 – 7.16 (m, 3H), 7.09 – 7.08 (m, 2H), 3.43 – 3.38 (m, 2H), 3.32 (s, 3H), 3.18 (br, 2H), 2.68 – 2.63 (m, 4H), 1.35 (s, 9H), 1.32 – 1.30 (m, 2H), 1.23 – 1.18 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.94 , 142.19 , 141.85 , 136.55 , 132.04 , 131.33 , 130.67 , 130.37 , 128.54 , 126.93 , 126.28 , 79.75 , 47.89 , 44.46 , 42.41 , 39.76 , 38.91 , 36.29 , 32.22 , 28.52 ; ESI-HR-MS: (m/z) calcd. for $\text{C}_{25}\text{H}_{34}\text{N}_2\text{NaO}_6\text{S}_2$ ($[\text{M}+\text{Na}]^+$) 545.1750 , found 545.1750 .

Synthesis of *tert*-butyl 4-benzyl-4-(((4-propylphenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-36**). Compound **75-36** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-*n*-propylbenzenesulfonyl chloride (0.69 g, 3.16 mmol) and Et₃N (0.83 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by *v/v*) gave **75-36**. White solid, 1.13 g (88%). m.p. 161.5–162.7 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 6.5 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.20–7.14 (m, 3H), 7.09–7.07 (m, 2H), 3.43–3.38 (m, 2H), 3.14–3.09 (m, 2H), 2.66–2.60 (m, 6H), 1.66–1.58 (m, 2H), 1.35 (s, 9H), 1.32–1.28 (m, 2H), 1.21–1.16 (m, 2H), 0.893 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 154.94, 148.36, 136.82, 136.71, 130.42, 129.34, 128.41, 127.19, 126.73, 79.62, 47.32, 42.55, 39.79, 38.93, 37.96, 36.20, 32.41, 28.53, 24.29, 13.83; ESI-HR-MS: (*m/z*) calcd. for C₂₇H₃₈N₂NaO₄S ([M+Na]⁺) 509.2444, found 509.2444.

Synthesis of *tert*-butyl 4-benzyl-4-(((2,4,6-triisopropylphenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-37**). Compound **75-37** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 2,4,6-triisopropylbenzenesulfonyl chloride (0.96 g, 3.16 mmol) and Et₃N (0.83 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by *v/v*) gave **75-37**. White solid, 1.16 g (77%). m.p. 129.5–130.3 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.51 (t, *J* = 6.5 Hz, 1H), 7.22 (s, 2H), 7.20–7.14 (m, 3H), 7.08–7.06 (m, 2H), 4.18–4.13 (m, 2H), 3.37–3.33 (m, 2H), 3.14–3.09 (m, 2H), 2.94–2.88 (m, 1H), 2.70 (d, *J* = 6.0 Hz, 2H), 2.63 (s, 2H), 1.34 (s, 9H), 1.31–1.29 (m, 2H), 1.20–1.16 (m, 20H); ¹³C NMR (151 MHz, CDCl₃) δ 154.89, 152.99, 150.29, 136.77, 132.24, 130.36, 128.45, 126.71, 123.99, 79.62, 46.99, 42.29, 39.81, 38.96, 36.30, 34.22, 32.34, 29.87, 28.50, 25.09, 23.65; ESI-HR-MS: (*m/z*) calcd. for C₃₃H₅₀N₂NaO₄S ([M+Na]⁺) 593.3383, found 593.3381.

Synthesis of *tert*-butyl 4-([1,1'-biphenyl]-4-sulfonamido)methyl-4-benzylpiperidine-1-carboxylate (**75-38**). Compound **75-38** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using [1,1'-biphenyl]-4-sulfonyl chloride (0.80 g, 3.16 mmol) and Et₃N (0.83 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by *v/v*) gave **75-38**. White solid, 1.23 g (90%). m.p. 146.3–147.9 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.92–7.88 (m, 4H), 7.76–7.75 (m, 2H), 7.69 (t, *J* = 6.5 Hz, 1H), 7.54–7.51 (m, 2H), 7.47–7.43 (m, 1H), 7.20–7.13 (m, 3H), 7.10–7.08 (m, 2H), 3.44–3.39 (m, 2H), 3.18–3.14 (m, 2H), 2.67–2.64 (m, 4H), 1.34 (s, 9H), 1.32–1.31 (m, 2H), 1.24–1.19 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 154.93, 145.82, 139.28, 138.16, 136.66, 130.42, 129.18, 128.64, 128.39, 127.92, 127.66, 127.41, 126.72, 79.61, 47.41, 42.40, 39.79, 38.95, 36.21, 32.38, 28.51; ESI-HR-MS: (*m/z*) calcd. for C₃₀H₃₆N₂NaO₄S₂ ([M+Na]⁺) 543.2288, found 543.2289.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-methylphenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-39**). Compound **75-39** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-toluenesulfonyl chloride (0.60 g, 3.16 mmol) and Et₃N (0.83 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by *v/v*) gave **75-39**. White solid, 1.04 g (86%). m.p. 172.5–173.7 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.54 (t, *J* = 6.3 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.21–7.15 (m, 3H), 7.09–7.07 (m, 2H), 3.43–3.38 (m, 2H), 3.14 (s, 2H), 2.62–2.58 (m, 4H), 2.39 (s, 3H), 1.35 (s, 9H), 1.32–1.28 (m, 2H), 1.22–1.17 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 154.92, 143.66, 136.69, 136.62, 130.44, 129.90, 128.33, 127.15, 126.65, 79.56, 47.26, 42.39, 39.77, 38.89, 36.12, 32.34, 28.50, 21.62; ESI-HR-MS: (*m/z*) calcd. for C₂₅H₃₄N₂NaO₄S ([M+Na]⁺) 481.2131, found 481.2128.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-ethylphenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-40**). Compound **75-40** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-ethylbenzenesulfonyl chloride (0.65 g, 3.16 mmol) and Et₃N (0.83 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by *v/v*) gave **75-40**. White solid, 1.07 g (86%). m.p. 166.2–167.2 °C.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.73 (d, J = 8.0 Hz, 2H), 7.55 (t, J = 6.5 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.20–7.14 (m, 3H), 7.09–7.07 (m, 2H), 3.43–3.38 (m, 2H), 3.15–3.10 (m, 2H), 2.72–2.67 (m, 2H), 2.62–2.60 (m, 4H), 1.35 (s, 9H), 1.33–1.28 (m, 2H), 1.22–1.17 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.94, 149.80, 136.79, 136.69, 130.43, 128.76, 128.35, 127.26, 126.67, 79.61, 47.26, 42.42, 39.78, 38.90, 36.15, 32.36, 28.90, 28.51, 15.23; ESI-HR-MS: (m/z) calcd. for $\text{C}_{26}\text{H}_{36}\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 495.2288, found 495.2284.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-isopropylphenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-41**). Compound **75-41** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-isopropylbenzenesulfonyl chloride (0.69 g, 3.16 mmol) and Et_3N (0.83 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **75-41**. White solid, 1.04 g (81%). m.p. 186.0–186.5 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.75–7.72 (m, 2H), 7.56 (t, J = 6.3 Hz, 1H), 7.48–7.46 (m, 2H), 7.20–7.13 (m, 3H), 7.08–7.06 (m, 2H), 3.43–3.38 (m, 2H), 3.13–3.08 (m, 2H), 3.01–2.96 (m, 1H), 2.62–2.60 (m, 4H), 1.35 (s, 9H), 1.32–1.28 (m, 2H), 1.23 (d, J = 7.0 Hz, 6H), 1.20–1.17 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.91, 154.36, 136.90, 136.69, 130.44, 128.33, 127.38, 127.30, 126.64, 79.56, 47.20, 42.40, 39.77, 38.89, 36.16, 34.26, 32.36, 28.51, 23.75; ESI-HR-MS: (m/z) calcd. for $\text{C}_{27}\text{H}_{38}\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 509.2444, found 509.2442.

Synthesis of *tert*-butyl 4-benzyl-4-(((3-isopropylphenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-42**). Compound **75-42** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 3-isopropylbenzenesulfonyl chloride (0.69 g, 3.16 mmol) and Et_3N (0.83 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **75-42**. White solid, 1.01 g (79%). m.p. 158.2–160.2 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.69 (s, 1H), 7.63–7.61 (m, 1H), 7.58 (t, J = 6.3 Hz, 1H), 7.55–7.51 (m, 2H), 7.20–7.16 (m, 3H), 7.08–7.06 (m, 2H), 3.41–3.36 (m, 2H), 3.14–3.10 (m, 2H), 3.03–2.97 (m, 1H), 2.62–2.60 (m, 4H), 1.35 (s, 9H), 1.32–1.28 (m, 2H), 1.23 (d, J = 7.0 Hz, 6H), 1.20–1.16 (m, 2H); ^{13}C NMR (201 MHz, CDCl_3) δ 154.91, 150.50, 139.50, 136.64, 131.14, 130.40, 129.30, 128.35, 126.67, 124.99, 124.58, 79.58, 47.20, 42.42, 39.83, 38.87, 36.13, 34.19, 32.35, 28.50, 23.87; ESI-HR-MS: (m/z) calcd. for $\text{C}_{27}\text{H}_{38}\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 509.2444, found 509.2444.

Synthesis of *tert*-butyl 4-benzyl-4-(((2-methylphenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-43**). Compound **75-43** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 2-methylbenzenesulfonyl chloride (0.60 g, 3.16 mmol) and Et_3N (0.83 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **75-43**. White solid, 1.07 g (89%). m.p. 174.2–175.3 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.79–7.77 (m, 1H), 7.73–7.69 (m, 1H), 7.53–7.50 (m, 1H), 7.42–7.36 (m, 2H), 7.24–7.15 (m, 3H), 7.10–7.07 (m, 2H), 3.40–3.32 (m, 2H), 3.14 (s, 2H), 2.69–2.68 (m, 1H), 2.63–2.58 (m, 5H), 2.39 (s, 1H), 1.34 (s, 9H), 1.30–1.28 (m, 2H), 1.20–1.15 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.93, 137.66, 136.90, 136.82, 133.02, 132.76, 130.31, 129.59, 128.58, 126.89, 126.43, 79.68, 47.36, 42.91, 39.79, 38.91, 36.36, 32.48, 28.54, 20.44; ESI-HR-MS: (m/z) calcd. for $\text{C}_{25}\text{H}_{34}\text{N}_2\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 481.2131, found 481.2128.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-hydroxyphenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-44**). Compound **75-44** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-hydroxybenzenesulfonyl chloride (0.61 g, 3.16 mmol) and Et_3N (0.83 g, 7.89 mmol) in dried CH_2Cl_2 (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by v/v) gave **75-44**. White solid, 1.06 g (88%). m.p. 200.0–203.1 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.36 (s, 1H), 7.64–7.62 (m, 2H), 7.36 (t, J = 6.5 Hz, 1H), 7.21–7.14 (m, 3H), 7.08–7.06 (m, 2H), 6.92–6.90 (m, 2H), 3.43–3.38 (m, 2H), 3.17–3.13 (m, 2H), 2.61–2.56 (m, 4H), 1.35 (s, 9H), 1.32–1.28 (m, 2H), 1.21–1.16 (m, 2H); ^{13}C NMR (151 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 161.04, 155.06, 136.46, 130.22, 129.60, 128.88, 127.79, 126.12, 115.43, 79.73, 46.84, 41.62, 39.59, 38.61, 35.59, 31.53, 27.88; ESI-HR-MS: (m/z) calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{NaO}_5\text{S}$ ($[\text{M}+\text{Na}]^+$) 483.1924, found 483.1920.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-carbamoylphenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-45**). Compound **75-45** was prepared according to General Procedure 1 from **73** (0.80 g, 2.63 mmol) using 4-carbamoylbenzenesulfonyl chloride (0.69 g, 3.16 mmol) and Et₃N (0.83 g, 7.89 mmol) in dried CH₂Cl₂ (8 mL). Purification by column chromatography (EtOAc/PE = 1/3, by *v/v*) gave **75-45**. White solid, 1.06 g (83%). m.p. 157.5–158.6 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.17 (s, 1H), 8.06–8.04 (m, 2H), 7.89–7.87 (m, 2H), 7.74 (t, *J* = 6.5 Hz, 1H), 7.61 (s, 1H), 7.21–7.14 (m, 3H), 7.09–7.07 (m, 2H), 3.43–3.39 (m, 2H), 3.19–3.15 (m, 2H), 2.65–2.62 (m, 4H), 1.35 (s, 9H), 1.32–1.29 (m, 2H), 1.23–1.17 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 168.39, 155.03, 142.89, 137.43, 136.64, 130.47, 128.54, 128.42, 127.28, 126.81, 79.82, 47.72, 42.22, 39.83, 38.94, 36.22, 32.13, 28.53; ESI-HR-MS: (*m/z*) calcd. for C₂₅H₃₃N₃NaO₅S ([M+Na]⁺) 510.2033, found 510.2032.

Synthesis of *tert*-butyl 4-benzyl-4-(((4-(methoxycarbonyl)phenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-46**). Compound **75-46** was prepared according to General Procedure 1 from **73** (1.50 g, 4.93 mmol) using methyl 4-(chlorosulfonyl)benzoate (1.39 g, 5.92 mmol) and Et₃N (1.50 g, 14.8 mmol) in dried CH₂Cl₂ (15 mL). Purification by column chromatography (EtOAc/PE = 1/3, by *v/v*) gave **75-46**. White solid, 2.06 g (83%). m.p. 174.0–175.2 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.17–8.14 (m, 2H), 7.97–7.95 (m, 2H), 7.84 (t, *J* = 6.5 Hz, 1H), 7.21–7.14 (m, 3H), 7.10–7.08 (m, 2H), 3.90 (s, 3H), 3.42–3.38 (m, 2H), 3.18–3.13 (m, 2H), 2.67–2.62 (m, 4H), 1.34 (s, 9H), 1.31–1.28 (m, 2H), 1.22–1.17 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 165.67, 154.92, 143.63, 136.57, 134.06, 130.52, 130.33, 128.51, 127.12, 126.90, 79.71, 52.80, 47.73, 42.53, 39.77, 38.92, 36.27, 32.34, 28.51; ESI-HR-MS: (*m/z*) calcd. for C₂₆H₃₄N₂NaO₆S ([M+Na]⁺) 525.2030, found 525.2027.

Synthesis of *tert*-butyl 4-benzyl-4-(((3-nitrophenyl)sulfonamido)methyl)piperidine-1-carboxylate (**75-47**). Compound **75-47** was prepared according to General Procedure 1 from **73** (2.00 g, 6.57 mmol) using methyl 3-nitrobenzenesulfonyl chloride (1.75 g, 7.88 mmol) and Et₃N (2.00 g, 19.7 mmol) in dried CH₂Cl₂ (20 mL). Purification by column chromatography (EtOAc/PE = 1/3, by *v/v*) gave **75-47**. White solid, 2.67 g (83%). m.p. 20.1–208.4 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.57 (t, *J* = 2.0 Hz, 1H), 8.51–8.48 (m, 1H), 8.25–8.23 (m, 1H), 7.96–7.91 (m, 2H), 7.22–7.15 (m, 3H), 7.12–7.10 (m, 2H), 3.43–3.38 (m, 2H), 3.21–3.16 (m, 2H), 2.67–2.63 (m, 4H), 1.35 (s, 9H), 1.32–1.30 (m, 2H), 1.23–1.18 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 155.04, 148.12, 142.26, 136.30, 132.25, 130.40, 130.22, 127.79, 126.66, 126.21, 121.73, 79.77, 47.33, 41.25, 39.53, 38.58, 35.72, 31.28, 27.83; ESI-HR-MS: (*m/z*) calcd. for C₂₄H₃₁N₃NaO₆S ([M+Na]⁺) 512.1826, found 512.1827.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl) methanesulfonamide (**C-4-1**). Following General Procedure 3, **75-1** (0.30 g, 0.784 mmol) was first treated with TFA (1.5 mL) in CH₂Cl₂ (0.9 mL), and the intermediate obtained was reacted with **7-TFA** (0.28 g, 0.941 mmol) using EDCI (0.38 g, 1.96 mmol), HOBT (8 mg, 0.059 mmol), and DIPEA (0.61 g, 4.70 mmol) in dried THF (3 mL). Purification by column chromatography (EtOAc) gave **C-1-1**. White solid, 0.26 g (71%). m.p. 112.1–114.5 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.57 (t, *J* = 2.0 Hz, 1H), 8.51–8.48 (m, 1H), 8.25–8.23 (m, 1H), 7.96–7.91 (m, 2H), 7.22–7.15 (m, 3H), 7.12–7.10 (m, 2H), 3.43–3.38 (m, 2H), 3.21–3.16 (m, 2H), 2.67–2.63 (m, 4H), 1.35 (s, 9H), 1.32–1.30 (m, 2H), 1.23–1.18 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 155.04, 148.12, 142.26, 136.30, 132.25, 130.40, 130.22, 127.79, 126.66, 126.21, 121.73, 79.77, 47.33, 41.25, 39.53, 38.58, 35.72, 31.28, 27.83; ESI-HR-MS: (*m/z*) calcd. for C₂₅H₂₉N₄O₃S ([M+H]⁺) 465.1955 found 465.1953.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-1,1,1-trifluoromethanesulfonamide (**C-4-2**). Following General Procedure 3, **75-2** (0.65 g, 1.49 mmol) was first treated with TFA (3.3 mL) in CH₂Cl₂ (2 mL), and the intermediate obtained was reacted with **7-TFA** (0.53 g, 1.79 mmol) using EDCI (0.72 g, 3.73 mmol), HOBT (15 mg, 0.112 mmol), and DIPEA (1.16 g, 8.94 mmol) in dried THF (6.5 mL). Pu-

rification by column chromatography (EtOAc) gave **C-4-2**. White solid, 0.33 g (43%). m.p. 116.2–118.3 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.77–8.76 (m, 1H), 8.68–8.64 (m, 2H), 7.72–7.64 (m, 3H), 7.42–7.39 (m, 1H), 7.27–7.25 (m, 3H), 7.01–6.93 (m, 2H), 3.95–3.92 (m, 0.50H), 3.76–3.62 (m, 1H), 3.46–3.39 (m, 0.73H), 3.15–2.81 (m, 4H), 2.62 (s, 1H), 2.42–2.32 (m, 1H), 1.53–1.43 (m, 1H), 1.34–1.09 (m, 2H), 0.71–0.50 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.74, 167.62, 151.99, 151.80, 150.67, 149.96, 146.61, 146.56, 136.24, 136.10, 135.85, 135.63, 131.30, 130.33, 130.12, 128.72, 128.67, 127.27, 127.16, 123.73, 123.48, 123.38, 121.26, 118.69, 50.71, 49.72, 47.91, 43.00, 42.66, 41.06, 37.49, 36.29, 36.19, 31.65, 31.29, 30.98, 30.62; ESI-HR-MS: (m/z) calcd. for $\text{C}_{25}\text{H}_{26}\text{F}_3\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 519.1673, found 519.1667.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)ethanesulfonamide (**C-4-3**). Following General Procedure 3, **75-3** (0.75 g, 1.89 mmol) was first treated with TFA (3.8 mL) in CH_2Cl_2 (2.3 mL), and the intermediate obtained was reacted with **7-TFA** (0.68 g, 2.27 mmol) using EDCI (0.91 g, 4.73 mmol), HOBT (19 mg, 0.142 mmol), and DIPEA (1.46 g, 11.3 mmol) in dried THF (7.5 mL). Purification by column chromatography (EtOAc) gave **C-4-3**. White solid, 0.75 g (82%). m.p. 104.6–106.2 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.78 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 8.68–8.64 (m, 2H), 7.84–7.79 (m, 1H), 7.59–7.54 (m, 3H), 7.28–7.20 (m, 4H), 7.11–7.03 (m, 2H), 3.92–3.70 (m, 1H), 3.48–3.46 (m, 0.43H), 3.34–3.33 (m, 1H), 3.18–3.07 (m, 1H), 3.02–2.97 (m, 3H), 2.87–2.76 (m, 1H), 2.64 (s, 1.65H), 2.47–2.34 (m, 1H), 1.51–1.34 (m, 1.54H), 1.20 (t, $J = 7.3$ Hz, 3H), 1.16–1.10 (m, 1.41H), 0.88–0.51 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.62, 167.56, 152.08, 151.92, 150.57, 150.31, 150.21, 146.38, 136.27, 136.16, 136.10, 131.54, 130.30, 130.05, 128.68, 128.60, 127.15, 127.02, 123.64, 123.43, 123.31, 47.95, 46.78, 46.60, 46.10, 43.81, 42.76, 42.69, 41.25, 37.57, 37.47, 36.39, 31.94, 31.75, 31.59, 31.30; ESI-HR-MS: (m/z) calcd. for $\text{C}_{26}\text{H}_{31}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 479.2112, found 479.2109.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)cyclopropanesulfonamide (**C-4-4**). Following General Procedure 3, **75-4** (0.55 g, 1.35 mmol) was first treated with TFA (2.76 mL) in CH_2Cl_2 (1.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.48 g, 1.62 mmol) using EDCI (0.65 g, 3.38 mmol), HOBT (14 mg, 0.101 mmol), and DIPEA (1.05 g, 8.10 mmol) in dried THF (5.5 mL). Purification by column chromatography (EtOAc) gave **C-4-4**. White solid, 0.45 g (68%). m.p. 134.5–137.1 °C. ^1H NMR (500 MHz, CD_3OD) δ 8.78–8.77 (m, 1H), 8.68–8.60 (m, 2H), 7.88–7.84 (m, 1H), 7.69–7.68 (m, 2H), 7.59–7.56 (m, 1H), 7.30–7.08 (m, 5H), 4.59 (m, 0.51H), 4.01–3.80 (m, 1H), 3.60–3.41 (m, 1H), 3.22–3.17 (m, 1H), 3.07–2.98 (m, 2H), 2.86–2.79 (m, 1H), 2.69 (s, 1H), 2.55–2.44 (m, 2H), 1.60–1.23 (m, 3H), 1.04–0.97 (m, 4H), 0.70 (m, 0.55H); ^{13}C NMR (126 MHz, CD_3OD) δ 169.08, 151.65, 150.57, 148.32, 137.95, 137.66, 132.94, 131.82, 129.18, 127.65, 125.28, 124.88, 47.43, 44.23, 43.52, 41.61, 38.82, 37.20, 32.65, 31.94, 30.31, 5.51, 5.47; ESI-HR-MS: (m/z) calcd. for $\text{C}_{27}\text{H}_{31}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 491.2112, found 491.2110.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)thiophene-2-sulfonamide (**C-4-5**). Following General Procedure 3, **75-5** (0.82 g, 1.82 mmol) was first treated with TFA (4.1 mL) in CH_2Cl_2 (2.5 mL), and the intermediate obtained was reacted with **7-TFA** (0.65 g, 2.18 mmol) using EDCI (0.87 g, 4.55 mmol), HOBT (19 mg, 0.137 mmol), and DIPEA (1.41 g, 10.9 mmol) in dried THF (8.2 mL). Purification by column chromatography (EtOAc) gave **C-4-5**. White foam, 0.51 g (53%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 1.5$ Hz and 4.5 Hz, 1H), 8.67–8.64 (m, 2H), 7.95–7.93 (m, 1H), 7.86–7.81 (m, 2H), 7.60–7.54 (m, 4H), 7.22–7.16 (m, 4H), 7.08–6.98 (m, 2H), 4.12–4.09 (m, 0.25H), 3.86–3.69 (m, 1H), 3.38–3.35 (m, 0.42H), 3.30–3.25 (m, 0.76H), 3.18–3.13 (m, 1H), 3.04–2.99 (m, 1H), 2.81–2.72 (m, 1H), 2.66–2.53 (m, 2H), 2.37–2.35 (m, 0.60H), 1.49–1.46 (m, 0.60H), 1.32–1.22 (m, 1H), 1.14–1.07 (m, 1.65H), 0.84–0.55 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.47, 167.37, 151.90, 151.70, 150.40, 149.97, 149.93, 146.26, 146.23, 140.60, 140.46, 136.12, 136.01, 135.99, 135.79, 132.18, 131.98, 131.91, 131.85, 131.33, 130.26, 130.08, 128.28, 127.52, 127.46,

126.74, 126.69, 123.51, 123.28, 123.08, 47.46, 46.27, 42.90, 42.66, 42.51, 41.51, 37.45, 37.39, 35.98, 35.84, 31.83, 31.54, 31.42, 31.19; ESI-HR-MS: (m/z) calcd. for $C_{28}H_{29}N_4O_3S_2$ ($[M+H]^+$) 533.1676, found 533.1679.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)pyridine-3-sulfonamide (**C-4-6**). Following General Procedure 3, **75-6** (0.86 g, 1.93 mmol) was first treated with TFA (4.3 mL) in CH_2Cl_2 (2.6 mL), and the intermediate obtained was reacted with **7-TFA** (0.69 g, 2.32 mmol) using EDCI (0.93 g, 4.83 mmol), HOBT (20 mg, 0.145 mmol), and DIPEA (1.50 g, 11.6 mmol) in dried THF (8.6 mL). Purification by column chromatography (EtOAc) gave **C-4-6**. White foam, 0.59 g (58%). 1H NMR (500 MHz, $DMSO-d_6$) δ 8.97–8.96 (m, 1H), 8.85–8.83 (m, 1H), 8.78–8.77 (m, 1H), 8.66–8.63 (m, 2H), 8.20–8.19 (m, 1H), 7.89–7.78 (m, 2H), 7.67–7.65 (m, 1H), 7.57–7.54 (m, 3H), 7.19–7.16 (m, 3H), 7.07–6.97 (m, 2H), 3.85–3.68 (m, 1H), 3.42–3.41 (m, 0.40H), 3.29–3.27 (m, 0.60H), 3.17–3.14 (m, 1H), 3.04–2.99 (m, 1H), 2.84–2.70 (m, 1H), 2.63–2.60 (m, 1.49H), 2.46–2.34 (m, 1.51H), 1.47–1.45 (m, 0.56H), 1.33–1.23 (m, 1H), 1.13–1.06 (m, 1.55H), 0.79–0.55 (m, 1H); ^{13}C NMR (201 MHz, $CDCl_3 + CD_3OD$) δ 167.45, 167.34, 162.43, 162.25, 152.45, 151.58, 151.40, 150.26, 149.39, 149.29, 147.16, 146.40, 137.01, 136.10, 136.01, 135.85, 135.62, 134.91, 134.83, 131.14, 130.13, 130.00, 128.00, 126.52, 126.47, 123.98, 123.67, 123.24, 123.13, 116.96, 115.51, 47.15, 46.13, 42.66, 42.54, 42.03, 40.96, 37.41, 37.34, 35.84, 35.70, 31.31, 30.97, 30.79, 30.64; ESI-HR-MS: (m/z) calcd. for $C_{29}H_{30}N_5O_3S$ ($[M+H]^+$) 528.2064, found 528.2067.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-1-phenylmethanesulfonamide (**C-4-7**). Following General Procedure 3, **75-7** (0.63 g, 1.37 mmol) was first treated with TFA (3.2 mL) in CH_2Cl_2 (1.9 mL), and the intermediate obtained was reacted with **7-TFA** (0.49 g, 1.64 mmol) using EDCI (0.66 g, 3.43 mmol), HOBT (14 mg, 0.103 mmol), and DIPEA (1.06 g, 8.22 mmol) in dried THF (6.3 mL). Purification by column chromatography (EtOAc) gave **C-4-7**. White foam, 0.49 g (66%). 1H NMR (500 MHz, $DMSO-d_6$) δ 8.78–8.77 (m, 1H), 8.71–8.65 (m, 2H), 7.84–7.79 (m, 1H), 7.60–7.54 (m, 3H), 7.40–7.36 (m, 5H), 7.29–7.10 (m, 5H), 7.03–7.01 (m, 1H), 4.35–4.34 (m, 2H), 4.13–3.87 (m, 1H), 3.73–3.38 (m, 1H), 3.31–3.25 (m, 0.61H), 3.18–3.14 (m, 1H), 3.05–3.01 (m, 0.60H), 2.96–2.89 (m, 1H), 2.79–2.68 (m, 1H), 2.58–2.55 (m, 1.58H), 2.43–2.27 (m, 1H), 1.45–1.42 (m, 0.51H), 1.30–1.29 (m, 0.69H), 1.10–1.03 (m, 1.57H), 0.91–0.45 (m, 1H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 167.29, 167.21, 151.76, 151.55, 150.29, 150.26, 149.83, 149.78, 146.16, 136.06, 136.03, 135.93, 135.81, 131.31, 131.26, 130.52, 130.45, 130.15, 129.96, 129.24, 129.13, 128.72, 128.68, 128.59, 128.19, 128.16, 126.64, 126.55, 123.44, 123.42, 123.20, 123.03, 58.57, 58.48, 47.77, 46.01, 43.03, 42.53, 42.43, 41.11, 37.31, 37.23, 36.17, 36.04, 31.41, 31.07, 30.87; ESI-HR-MS: (m/z) calcd. for $C_{31}H_{33}N_4O_3S$ ($[M+H]^+$) 541.2268, found 541.2268.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)benzenesulfonamide (**C-4-8**). Following General Procedure 3, **75-8** (0.70 g, 1.57 mmol) was first treated with TFA (3.5 mL) in CH_2Cl_2 (2.1 mL), and the intermediate obtained was reacted with **7-TFA** (0.56 g, 1.88 mmol) using EDCI (0.75 g, 3.93 mmol), HOBT (16 mg, 0.118 mmol), and DIPEA (1.22 g, 9.42 mmol) in dried THF (7 mL). Purification by column chromatography (EtOAc) gave **C-4-8**. White solid, 0.33 g (40%). m.p. 105–108 °C. 1H NMR (500 MHz, CD_3OD) δ 8.76 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 8.67–8.58 (m, 2H), 7.86–7.81 (m, 3H), 7.67–7.53 (m, 6H), 7.19–7.17 (m, 3H), 7.05–6.93 (m, 2H), 7.03–7.01 (m, 1H), 3.98–3.78 (m, 1H), 3.44–3.33 (m, 1H), 3.19–3.16 (m, 0.49H), 3.11–2.98 (m, 1H), 2.88–2.72 (m, 1.59H), 2.63–2.38 (m, 3H), 1.53–1.50 (m, 0.59H), 1.44–1.28 (m, 1H), 1.25–0.98 (m, 2H), 0.65–0.60 (m, 0.54H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.55, 152.19, 151.94, 150.58, 150.32, 150.22, 146.38, 146.29, 139.61, 136.27, 136.15, 135.96, 132.96, 131.54, 131.46, 130.27, 130.03, 129.37, 128.55, 127.04, 126.94, 123.64, 123.59, 123.43, 123.20, 47.37, 46.11, 43.67, 42.78, 42.62, 41.96, 37.53, 37.46, 36.27, 36.12, 32.08, 31.83, 31.48; ESI-HR-MS: (m/z) calcd. for $C_{30}H_{31}N_4O_3S$ ($[M+H]^+$) 527.2112, found 527.2109.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-4-fluorobenzenesulfonamide (**C-4-9**). Following General Procedure 3, **75-9** (0.90 g, 1.95 mmol) was first treated with TFA (4.5 mL) in CH₂Cl₂ (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.70 g, 2.34 mmol) using EDCI (0.94 g, 4.88 mmol), HOBT (20 mg, 0.146 mmol), and DIPEA (1.51 g, 11.7 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-9**. White foam, 0.93 g (88%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.77 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 8.65–8.64 (m, 2H), 7.89–7.79 (m, 3H), 7.70–7.64 (m, 1H), 7.58–7.54 (m, 3H), 7.49–7.43 (m, 2H), 7.19–7.16 (m, 3H), 7.07–7.05 (m, 1H), 6.98–6.96 (m, 1H), 3.87–3.69 (m, 1H), 3.38 (m, 0.34H), 3.27–3.22 (m, 0.63H), 3.17–3.12 (m, 1H), 3.00–2.94 (m, 1H), 2.79 (m, 0.42H), 2.67–2.54 (m, 2H), 2.39–2.33 (m, 1.44H), 1.47–1.45 (m, 0.58H), 1.35–1.23 (m, 1H), 1.13–1.04 (m, 1.68H), 0.80–0.50 (m, 1H); ¹³C NMR (201 MHz, CDCl₃) δ 167.49, 167.47, 167.39, 167.36, 165.51, 164.23, 151.80, 151.64, 150.41, 149.90, 146.23, 136.08, 135.98, 135.81, 135.74, 131.24, 130.20, 130.06, 129.62, 129.58, 129.51, 129.47, 128.24, 128.18, 126.68, 123.51, 123.25, 123.10, 116.42, 116.37, 116.30, 47.26, 45.98, 42.64, 42.48, 41.23, 37.43, 37.37, 36.00, 35.96, 35.85, 35.81, 31.73, 31.36, 31.08, 31.03; ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ −106.93, −107.00; ESI-HR-MS: (*m/z*) calcd. for C₃₀H₃₀FN₄O₃S ([M+H]⁺) 545.2017, found 545.2026.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-4-cyanobenzenesulfonamide (**C-4-10**). Following General Procedure 3, **75-10** (1.00 g, 2.13 mmol) was first treated with TFA (5 mL) in CH₂Cl₂ (3 mL), and the intermediate obtained was reacted with **7-TFA** (0.76 g, 2.56 mmol) using EDCI (1.02 g, 5.33 mmol), HOBT (22 mg, 0.160 mmol), and DIPEA (1.65 g, 12.8 mmol) in dried THF (10 mL). Purification by column chromatography (EtOAc) gave **C-4-10**. White foam, 0.77 g (66%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.78–8.77 (m, 1H), 8.65–8.63 (m, 2H), 8.14–8.10 (m, 2H), 7.98–7.95 (m, 3H), 7.83–7.78 (m, 1H), 7.57–7.55 (m, 3H), 7.19–7.17 (m, 3H), 7.06–6.97 (m, 2H), 3.86–3.68 (m, 1H), 3.40 (m, 0.60H), 3.28–3.12 (m, 1H), 2.99–2.98 (m, 1H), 2.80 (m, 0.49H), 2.70–2.58 (m, 2H), 2.42–2.34 (m, 1.59H), 1.47–1.44 (m, 0.58H), 1.39 (m, 0.81H), 1.32–1.23 (m, 1H), 1.17–1.13 (m, 1.55H), 0.76–0.55 (m, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 167.51, 167.43, 151.78, 151.65, 150.49, 149.92, 149.88, 146.31, 146.27, 144.13, 136.06, 136.03, 135.89, 135.64, 133.05, 132.98, 131.19, 130.15, 129.99, 128.31, 127.49, 127.38, 126.87, 126.81, 123.55, 123.27, 123.21, 117.34, 117.24, 116.14, 47.86, 46.30, 42.65, 42.61, 42.50, 40.94, 37.44, 37.38, 36.08, 35.94, 31.68, 31.29, 31.17, 30.91, 28.64; ESI-HR-MS: (*m/z*) calcd. for C₃₁H₃₀N₅O₃S ([M+H]⁺) 552.2064, found 552.2067.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-4-methoxybenzenesulfonamide (**C-4-11**). Following General Procedure 3, **75-11** (0.84 g, 1.85 mmol) was first treated with TFA (4.2 mL) in CH₂Cl₂ (2.5 mL), and the intermediate obtained was reacted with **7-TFA** (0.66 g, 2.22 mmol) using EDCI (0.89 g, 4.63 mmol), HOBT (19 mg, 0.139 mmol), and DIPEA (1.43 g, 11.1 mmol) in dried THF (8.4 mL). Purification by column chromatography (EtOAc) gave **C-4-11**. White foam, 0.84 g (81%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.77 (dd, *J* = 1.8 Hz and 4.8 Hz, 1H), 8.66–8.64 (m, 2H), 7.84–7.79 (m, 1H), 7.74–7.73 (m, 2H), 7.58–7.54 (m, 3H), 7.49–7.45 (m, 1H), 7.17–7.10 (m, 5H), 7.05–6.96 (m, 2H), 4.11–4.08 (m, 0.29H), 3.85–3.84 (m, 4H), 3.70 (m, 0.49H), 3.25–3.20 (m, 0.65H), 3.18–3.12 (m, 1H), 2.96 (s, 1H), 2.77–2.61 (m, 2H), 2.37–2.31 (m, 1.71H), 1.47–1.44 (m, 0.61H), 1.30–1.23 (m, 1H), 1.11–1.03 (m, 1.63H), 0.80–0.51 (m, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 167.43, 167.31, 162.78, 151.85, 151.66, 150.34, 149.91, 146.20, 146.17, 136.09, 136.06, 135.95, 135.85, 131.30, 131.14, 130.25, 130.09, 128.91, 128.19, 128.13, 126.57, 123.47, 123.22, 123.03, 114.36, 114.33, 114.27, 55.59, 46.94, 45.80, 42.64, 42.48, 41.46, 37.42, 37.35, 35.94, 35.78, 31.78, 31.53, 31.34, 31.15; ESI-HR-MS: (*m/z*) calcd. for C₃₁H₃₃N₄O₄S ([M+H]⁺) 557.2217, found 557.2217.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-4-nitrobenzenesulfonamide (**C-4-12**). Following General Procedure 3, **75-12** (1.00 g,

2.04 mmol) was first treated with TFA (5 mL) in CH_2Cl_2 (3 mL), and the intermediate obtained was reacted with **7-TFA** (0.73 g, 2.45 mmol) using EDCI (0.98 g, 5.10 mmol), HOBT (21 mg, 0.153 mmol), and DIPEA (1.58 g, 12.2 mmol) in dried THF (10 mL). Purification by column chromatography (EtOAc) gave **C-4-12**. Pale yellow foam, 0.92 g (79%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 8.64–8.63 (m, 2H), 8.47–8.42 (m, 2H), 8.07–7.96 (m, 3H), 7.83–7.78 (m, 1H), 7.57–7.53 (m, 3H), 7.19–7.17 (m, 3H), 7.09–6.98 (m, 2H), 3.86–3.68 (m, 1H), 3.42 (m, 0.49H), 3.31–3.25 (m, 0.66H), 3.17–3.13 (m, 1.57H), 3.03–2.96 (m, 1H), 2.80–2.71 (m, 1H), 2.64–2.63 (m, 1H), 2.44–2.35 (m, 1.51H), 1.48–1.45 (m, 0.59H), 1.34–1.23 (m, 1H), 1.13–1.06 (m, 1.66H), 0.76–0.53 (m, 1H); ^{13}C NMR (201 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 167.40, 167.28, 151.47, 151.33, 150.17, 149.66, 149.30, 149.15, 146.34, 145.82, 135.99, 135.80, 135.55, 131.07, 130.07, 129.95, 127.86, 127.82, 126.41, 126.34, 124.10, 124.07, 123.63, 123.16, 123.07, 47.13, 46.16, 42.58, 42.44, 41.90, 40.76, 37.32, 37.24, 35.76, 35.62, 31.16, 30.83, 30.61, 30.52; ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{30}\text{N}_5\text{O}_5\text{S}$ ($[\text{M}+\text{H}]^+$) 572.1962, found 572.1965.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-3-chlorobenzenesulfonamide (**C-4-13**). Following General Procedure 3, **75-13** (0.80 g, 1.67 mmol) was first treated with TFA (4 mL) in CH_2Cl_2 (2.4 mL), and the intermediate obtained was reacted with **7-TFA** (0.60 g, 2.00 mmol) using EDCI (0.80 g, 4.18 mmol), HOBT (17 mg, 0.125 mmol), and DIPEA (1.29 g, 10.0 mmol) in dried THF (8 mL). Purification by column chromatography (EtOAc) gave **C-4-13**. White foam, 0.79 g (84%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.78–8.77 (m, 1H), 8.66–8.63 (m, 2H), 7.85–7.73 (m, 5H), 7.68–7.63 (m, 1H), 7.58–7.54 (m, 3H), 7.19–7.17 (m, 3H), 7.07–6.97 (m, 2H), 3.87–3.69 (m, 1H), 3.39 (m, 0.48H), 3.29–3.25 (m, 0.58H), 3.18–3.12 (m, 1H), 3.03–2.95 (m, 1H), 2.82 (m, 0.47H), 2.70–2.56 (m, 2H), 2.43–2.34 (m, 1.44H), 1.48–1.46 (m, 0.58H), 1.34–1.22 (m, 1H), 1.15–1.06 (m, 1.51H), 0.82–0.51 (m, 1H); ^{13}C NMR (201 MHz, CDCl_3) δ 167.46, 167.34, 151.80, 151.58, 150.37, 149.90, 149.82, 146.19, 146.14, 141.46, 136.05, 135.92, 135.86, 135.63, 135.14, 132.69, 131.18, 131.15, 130.50, 130.46, 130.14, 129.99, 128.19, 126.77, 126.70, 126.65, 124.98, 124.81, 123.47, 123.44, 123.21, 123.03, 47.32, 46.01, 42.66, 42.59, 42.48, 41.24, 37.43, 37.33, 35.96, 35.80, 31.68, 31.33, 31.26, 31.01; ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{30}\text{ClN}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 561.1722, found 561.1724.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-2-fluorobenzenesulfonamide (**C-4-14**). Following General Procedure 3, **75-14** (0.85 g, 1.84 mmol) was first treated with TFA (4.3 mL) in CH_2Cl_2 (2.6 mL), and the intermediate obtained was reacted with **7-TFA** (0.66 g, 2.21 mmol) using EDCI (0.88 g, 4.60 mmol), HOBT (19 mg, 0.138 mmol), and DIPEA (1.42 g, 11.0 mmol) in dried THF (8.5 mL). Purification by column chromatography (EtOAc) gave **C-4-14**. White foam, 0.83 g (83%). ^1H NMR (500 MHz, CD_3OD) δ 8.76 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 8.67–8.58 (m, 2H), 7.85–7.83 (m, 2H), 7.67–7.65 (m, 3H), 7.56–7.54 (m, 1H), 7.37–7.30 (m, 2H), 7.22–7.17 (m, 3H), 7.09–6.98 (m, 2H), 4.59 (m, 0.24H), 3.98–3.80 (m, 1H), 3.43–3.32 (m, 1H), 3.18–3.08 (m, 1H), 3.04–3.00 (m, 0.53H), 2.90–2.83 (m, 1.49H), 2.68–2.64 (m, 1.78H), 2.52–2.41 (m, 1H), 1.55–1.52 (m, 0.56H), 1.43–1.40 (m, 1H), 1.26–1.20 (m, 1.51H), 1.04–0.62 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.41, 167.27, 159.48, 157.46, 151.85, 151.65, 150.32, 149.88, 146.20, 146.13, 136.05, 136.01, 135.92, 135.82, 135.09, 135.02, 131.33, 131.24, 130.40, 130.14, 129.96, 128.26, 127.64, 127.53, 127.44, 127.34, 126.70, 124.64, 124.54, 123.44, 123.23, 122.96, 116.95, 116.78, 46.86, 45.77, 43.11, 42.58, 42.37, 41.75, 37.33, 37.27, 36.01, 35.90, 31.71, 31.54, 31.35, 31.15; ^{19}F NMR (471 MHz, CD_3OD) δ −111.64, −111.70; ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{30}\text{FN}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 545.2017, found 545.2019.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-3-fluorobenzenesulfonamide (**C-4-15**). Following General Procedure 3, **75-15** (0.90 g, 1.95 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.70 g, 2.34 mmol) using EDCI (0.94 g, 4.88 mmol), HOBT

(20 mg, 0.146 mmol), and DIPEA (1.51 g, 11.7 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-15**. White foam, 0.91 g (86%). ^1H NMR (500 MHz, CD_3OD) δ 8.76 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 8.66–8.58 (m, 2H), 7.84–7.81 (m, 1H), 7.68–7.53 (m, 6H), 7.39–7.38 (m, 1H), 7.20–7.15 (m, 3H), 7.05–6.93 (m, 2H), 3.98–3.75 (m, 1H), 3.50–3.34 (m, 1H), 3.21–3.08 (m, 1H), 3.03–2.87 (m, 1H), 2.81–2.74 (m, 1H), 2.63–2.52 (m, 2H), 2.49–2.38 (m, 1H), 1.54–1.50 (m, 0.53H), 1.44–1.31 (m, 1H), 1.26–1.18 (m, 1.56H), 0.99–0.61 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.54, 167.44, 163.25, 163.22, 161.59, 161.55, 151.92, 151.72, 150.46, 150.01, 149.95, 146.27, 141.82, 141.78, 136.13, 136.00, 135.97, 135.74, 131.30, 131.28, 131.12, 131.08, 131.04, 130.20, 130.03, 128.31, 126.83, 126.77, 123.53, 123.29, 123.12, 122.70, 122.55, 119.99, 119.85, 114.26, 114.10, 47.47, 46.14, 42.93, 42.67, 42.54, 41.40, 37.47, 37.39, 36.07, 35.92, 31.81, 31.47, 31.43, 31.14; ^{19}F NMR (471 MHz, CD_3OD) δ –111.98, –111.99; ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{30}\text{FN}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 545.2017, found 545.2021.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-2,3,4,5,6-pentafluorobenzenesulfonamide (**C-4-16**). Following General Procedure 3, **75-16** (0.80 g, 1.50 mmol) was first treated with TFA (4 mL) in CH_2Cl_2 (2.4 mL), and the intermediate obtained was reacted with **7-TFA** (0.54 g, 1.80 mmol) using EDCI (0.72 g, 3.75 mmol), HOBT (15 mg, 0.113 mmol), and DIPEA (1.16 g, 9.00 mmol) in dried THF (8 mL). Purification by column chromatography (EtOAc) gave **C-4-16**. White foam, 0.78 g (85%). ^1H NMR (500 MHz, CD_3OD) δ 8.76 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 8.64–8.58 (m, 2H), 7.86–7.82 (m, 1H), 7.70–7.66 (m, 2H), 7.57–7.54 (m, 1H), 7.26–7.03 (m, 5H), 4.59 (m, 0.27H), 3.40–3.79 (m, 1H), 3.59–3.37 (m, 1H), 3.23–3.14 (m, 1H), 3.06–2.97 (m, 2H), 2.83–2.69 (m, 1.72H), 2.55–2.45 (m, 1H), 1.59–1.46 (m, 1H), 1.40–1.25 (m, 2H), 1.00–0.69 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.59, 167.50, 152.02, 151.73, 150.57, 150.03, 149.98, 146.47, 146.33, 145.27, 144.84, 143.23, 142.76, 138.93, 136.89, 136.25, 136.06, 135.95, 135.75, 131.35, 131.31, 130.23, 129.93, 128.56, 127.14, 127.04, 123.66, 123.57, 123.46, 123.24, 116.38, 116.25, 116.13, 48.26, 46.34, 43.44, 42.65, 41.12, 37.49, 37.39, 36.28, 36.20, 31.88, 31.60, 31.47, 31.20; ^{19}F NMR (471 MHz, CD_3OD) δ –139.47––139.53 (m), –150.30––150.39 (m), –162.19––162.34 (m); ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{26}\text{F}_5\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 617.1640, found 617.1643.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-2,3,4,5,6-pentamethylbenzenesulfonamide (**C-4-17**). Following General Procedure 3, **75-17** (0.87 g, 1.69 mmol) was first treated with TFA (4.4 mL) in CH_2Cl_2 (2.6 mL), and the intermediate obtained was reacted with **7-TFA** (0.61 g, 2.03 mmol) using EDCI (0.81 g, 4.23 mmol), HOBT (17 mg, 0.128 mmol), and DIPEA (1.31 g, 10.1 mmol) in dried THF (8.7 mL). Purification by column chromatography (EtOAc) gave **C-4-17**. White solid, 0.85 g (84%). m.p. 212.3–214.1 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 8.64–8.60 (m, 2H), 7.82–7.78 (m, 1H), 7.57–7.53 (m, 3H), 7.41–7.36 (m, 1H), 7.19–7.17 (m, 3H), 7.06–6.94 (m, 2H), 3.79–3.65 (m, 1H), 3.26–3.23 (m, 1H), 3.08–3.06 (m, 0.50H), 2.92–2.90 (m, 1H), 2.70–2.61 (m, 2H), 2.55–2.54 (m, 0.67H), 2.48 (m, 6.64H), 2.36–2.33 (m, 1.67H), 2.22–2.17 (m, 10H), 1.46–1.23 (m, 0.62H), 1.30–1.23 (m, 1H), 0.75–0.47 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.50, 167.40, 152.18, 151.88, 150.45, 150.15, 146.31, 146.12, 139.68, 136.41, 136.27, 136.20, 136.03, 135.87, 135.65, 134.98, 134.92, 133.89, 133.82, 131.53, 131.38, 130.22, 130.03, 128.46, 126.91, 123.53, 123.48, 123.38, 123.00, 46.35, 45.36, 43.89, 42.76, 42.60, 42.44, 37.44, 36.34, 36.19, 32.11, 32.05, 31.95, 31.72, 18.91, 17.84, 17.81, 17.12, 17.08; ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{26}\text{F}_5\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 597.2894, found 597.2899.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-3,4-difluorobenzenesulfonamide (**C-4-18**). Following General Procedure 3, **75-18** (0.88 g, 1.83 mmol) was first treated with TFA (4.4 mL) in CH_2Cl_2 (2.6 mL), and the intermediate obtained was reacted with **7-TFA** (0.66 g, 2.20 mmol) using EDCI (0.87 g, 4.56 mmol), HOBT (19 mg, 0.137 mmol), and DIPEA (1.42 g, 11.0 mmol) in dried THF

(8.8 mL). Purification by column chromatography (EtOAc) gave **C-4-18**. White foam, 0.79 g (77%). ^1H NMR (500 MHz, CD_3OD) δ 8.77 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 8.67–8.59 (m, 2H), 7.86–7.77 (m, 2H), 7.70–7.65 (m, 3H), 7.58–7.48 (m, 2H), 7.22–7.19 (m, 3H), 7.06–6.95 (m, 2H), 4.59–3.94 (m, 1H), 3.78–3.53 (m, 1H), 3.38–3.34 (m, 0.60H), 3.20–3.11 (m, 1H), 3.05–2.91 (m, 1H), 2.81–2.74 (m, 1H), 2.65 (m, 0.74H), 2.55–2.40 (m, 2H), 1.56–1.52 (m, 0.51H), 1.43–1.34 (m, 1H), 1.28–1.19 (m, 1.62H), 0.96–0.64 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.65, 167.59, 154.16, 154.06, 152.12, 152.01, 151.84, 151.25, 150.61, 150.11, 149.23, 146.38, 136.65, 136.22, 136.03, 135.80, 131.36, 130.21, 130.02, 128.51, 127.09, 127.00, 124.21, 124.00, 123.63, 123.39, 123.30, 118.47, 118.32, 116.95, 116.79, 47.95, 46.37, 43.26, 42.72, 42.62, 41.32, 37.54, 37.47, 36.20, 36.07, 31.95, 31.65, 31.48, 31.19; ^{19}F NMR (471 MHz, CD_3OD) δ –133.31––133.43 (m), –136.87––136.96 (m); ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{29}\text{F}_2\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 563.1923, found 563.1928.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-3,4,5-trifluorobenzenesulfonamide (**C-4-19**). Following General Procedure 3, **75-19** (0.80 g, 1.60 mmol) was first treated with TFA (4 mL) in CH_2Cl_2 (2.4 mL), and the intermediate obtained was reacted with **7-TFA** (0.57 g, 1.92 mmol) using EDCI (0.77 g, 4.00 mmol), HOBT (16 mg, 0.120 mmol), and DIPEA (1.24 g, 9.60 mmol) in dried THF (8 mL). Purification by column chromatography (EtOAc) gave **C-4-19**. White foam, 0.67 g (72%). ^1H NMR (500 MHz, CD_3OD) δ 8.77 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 8.67–8.58 (m, 2H), 7.86–7.82 (m, 1H), 7.68–7.63 (m, 4H), 7.58–7.55 (m, 1H), 7.23–7.20 (m, 3H), 7.08–7.00 (m, 2H), 4.59 (s, 1H), 4.00–3.95 (m, 0.53H), 3.77–3.57 (m, 1H), 3.40–3.35 (m, 1H), 3.22–3.02 (m, 1.52H), 2.93–2.76 (m, 1.62H), 2.66 (m, 0.69H), 2.59–2.41 (m, 2H), 1.55–1.21 (m, 3H), 0.91–0.66 (m, 1H); ^{13}C NMR (151 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 167.46, 167.36, 151.69, 151.61, 151.40, 150.23, 149.96, 149.35, 149.22, 146.40, 143.04, 141.31, 136.33, 136.03, 135.83, 135.60, 131.14, 130.12, 130.02, 127.93, 126.49, 123.67, 123.23, 123.12, 111.85, 111.73, 47.26, 46.24, 42.63, 41.95, 40.83, 37.34, 35.79, 35.68, 31.24, 30.94, 30.71, 30.62; ^{19}F NMR (471 MHz, CD_3OD) δ –132.96––132.02 (m), –156.32––156.48 (m); ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{28}\text{F}_3\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 581.1829, found 581.1835.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-2,5-difluorobenzenesulfonamide (**C-4-20**). Following General Procedure 3, **75-20** (0.80 g, 1.66 mmol) was first treated with TFA (4 mL) in CH_2Cl_2 (2.4 mL), and the intermediate obtained was reacted with **7-TFA** (0.59 g, 1.99 mmol) using EDCI (0.80 g, 4.15 mmol), HOBT (17 mg, 0.125 mmol), and DIPEA (1.29 g, 9.96 mmol) in dried THF (8 mL). Purification by column chromatography (EtOAc) gave **C-4-20**. White foam, 0.71 g (76%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 8.64–8.63 (m, 2H), 8.16–8.10 (m, 1H), 7.83–7.78 (m, 1H), 7.59–7.53 (m, 6H), 7.23–7.17 (m, 3H), 7.11–7.01 (m, 2H), 3.85–3.69 (m, 1H), 3.33–3.27 (m, 1H), 3.18–3.14 (m, 0.76H), 3.04–2.97 (m, 1H), 2.84–2.80 (m, 1H), 2.74–2.66 (m, 1.53H), 2.56–2.53 (m, 1.46H), 2.40–2.37 (m, 0.61H), 1.51–1.47 (m, 0.60H), 1.35–1.28 (m, 1H), 1.16–1.09 (m, 1.60H), 0.84–0.55 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.57, 167.44, 158.84, 156.86, 155.54, 153.56, 152.02, 151.78, 150.49, 150.10, 150.03, 146.33, 146.22, 136.18, 136.03, 135.84, 131.41, 131.33, 130.20, 129.97, 129.04, 126.96, 126.91, 123.57, 123.52, 123.36, 123.09, 121.76, 121.70, 121.57, 121.50, 118.57, 118.51, 118.38, 118.31, 117.36, 117.16, 116.95, 47.40, 46.05, 43.40, 42.66, 42.50, 41.68, 37.43, 37.36, 36.18, 36.08, 31.87, 31.66, 31.56, 31.27; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ –115.57––115.67 (m), –116.19––116.23 (m); ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{29}\text{F}_2\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 563.1923, found 563.1931.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-2,4,5-trifluorobenzenesulfonamide (**C-4-21**). Following General Procedure 3, **75-21** (0.91 g, 1.83 mmol) was first treated with TFA (4.6 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.66 g, 2.20 mmol) using EDCI (0.87 g, 4.56 mmol), HOBT (19 mg, 0.137 mmol), and DIPEA (1.42 g, 11.0 mmol) in

dried THF (9.1 mL). Purification by column chromatography (EtOAc) gave **C-4-21**. White foam, 0.84 g (79%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 8.63 (dd, $J = 2.0$ Hz and 4.5 Hz, 2H), 8.19–8.12 (m, 1H), 7.90–7.78 (m, 3H), 7.57–7.53 (m, 3H), 7.24–7.18 (m, 3H), 7.12–7.01 (m, 2H), 3.85–3.44 (m, 2H), 3.31–3.27 (m, 0.59H), 3.17–3.14 (m, 0.65H), 3.04–2.99 (m, 1H), 2.82–2.78 (m, 1H), 2.73–2.65 (m, 1.49H), 2.55–2.52 (m, 1H), 2.40–2.37 (m, 0.60H), 1.49–1.46 (m, 0.60H), 1.35–1.24 (m, 1H), 1.16–1.08 (m, 1.61H), 0.77–0.58 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.61, 167.49, 155.33, 155.25, 154.24, 153.31, 153.24, 152.16, 151.98, 151.80, 150.55, 150.04, 147.36, 146.39, 145.36, 136.20, 136.11, 136.02, 135.83, 131.40, 130.19, 129.95, 128.55, 128.52, 127.07, 126.99, 124.47, 124.33, 123.60, 123.40, 123.20, 119.13, 118.91, 117.73, 107.65, 107.48, 107.44, 107.26, 47.66, 46.19, 43.42, 42.66, 42.51, 41.51, 37.46, 37.38, 36.20, 36.13, 31.91, 31.61, 31.25; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ –110.07––110.16 (m), –126.25––126.39 (m), –140.39––140.47 (m); ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{28}\text{F}_3\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 581.1829, found 581.1837.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-3-chloro-4-fluorobenzenesulfonamide (**C-4-22**). Following General Procedure 3, **75-22** (0.90 g, 1.81 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.65 g, 2.17 mmol) using EDCI (0.87 g, 4.53 mmol), HOBT (18 mg, 0.136 mmol), and DIPEA (1.41 g, 10.9 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-22**. White foam, 0.54 g (51%). ^1H NMR (500 MHz, CD_3OD) δ 8.76 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 8.67–8.59 (m, 2H), 7.99–7.96 (m, 1H), 7.85–7.78 (m, 2H), 7.67–7.66 (m, 2H), 7.56–7.54 (m, 1H), 7.48–7.42 (m, 1H), 7.21–7.18 (m, 3H), 7.05–6.94 (m, 2H), 3.98–3.76 (m, 1H), 3.55–3.33 (m, 1H), 3.22–3.10 (m, 1H), 3.04–2.89 (m, 1H), 2.80–2.73 (m, 1H), 2.64–2.63 (m, 1H), 2.57–2.39 (m, 2H), 1.54–1.51 (m, 0.52H), 1.43–1.34 (m, 1H), 1.26–1.19 (m, 1.52H), 0.96–0.62 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.63, 161.64, 159.59, 151.86, 150.63, 150.11, 146.44, 136.90, 136.23, 136.05, 135.83, 131.40, 130.21, 130.01, 129.87, 128.57, 127.60, 127.39, 127.11, 123.67, 123.42, 122.66, 122.52, 117.68, 117.51, 48.05, 46.39, 43.42, 42.71, 41.37, 37.50, 36.24, 36.11, 32.00, 31.74, 31.48, 31.21; ^{19}F NMR (471 MHz, CD_3OD) δ –110.77, –110.81; ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{29}\text{ClF}_3\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 579.1627, found 579.1637.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-2,3,4-trifluorobenzenesulfonamide (**C-4-23**). Following General Procedure 3, **75-23** (0.85 g, 1.70 mmol) was first treated with TFA (4.3 mL) in CH_2Cl_2 (2.6 mL), and the intermediate obtained was reacted with **7-TFA** (0.61 g, 2.04 mmol) using EDCI (0.81 g, 4.25 mmol), HOBT (17 mg, 0.128 mmol), and DIPEA (1.32 g, 10.2 mmol) in dried THF (8.5 mL). Purification by column chromatography (EtOAc) gave **C-4-23**. White foam, 0.85 g (86%). ^1H NMR (500 MHz, CD_3OD) δ 8.78–8.76 (m, 1H), 8.68–8.58 (m, 2H), 7.87–7.84 (m, 1H), 7.68–7.66 (m, 3H), 7.58–7.54 (m, 1H), 7.32–7.19 (m, 4H), 7.10–7.01 (m, 2H), 3.98–3.80 (m, 1H), 3.50–3.35 (m, 1.44H), 3.20–3.05 (m, 1.59H), 2.92–2.85 (m, 1.51H), 2.68–2.65 (m, 1.60H), 2.54–2.44 (m, 1H), 1.55–1.44 (m, 1H), 1.37–1.34 (m, 0.51H), 1.30–1.24 (m, 1.61H), 0.99–0.69 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.71, 167.61, 155.21, 153.50, 152.06, 151.93, 150.66, 150.16, 149.25, 147.53, 146.49, 141.25, 139.55, 136.28, 136.07, 135.89, 131.49, 130.14, 129.91, 128.75, 127.30, 127.20, 125.63, 125.39, 124.83, 124.40, 123.70, 123.51, 123.36, 112.82, 47.73, 46.31, 43.95, 42.72, 42.54, 41.87, 37.47, 36.36, 36.29, 32.04, 31.89, 31.73, 31.42, 29.81; ^{19}F NMR (471 MHz, CD_3OD) δ –128.46––128.60 (m), –132.66––160.75 (m), –160.30––160.47 (m); ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{28}\text{F}_3\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 581.1829, found 581.1837.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-3,5-bis(trifluoromethyl)benzenesulfonamide (**C-4-24**). Following General Procedure 3, **75-24** (0.90 g, 1.55 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.55 g, 1.86 mmol)

using EDCI (0.74 g, 3.88 mmol), HOBT (16 mg, 0.116 mmol), and DIPEA (1.20 g, 9.30 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-24**. White foam, 0.78 g (76%). ^1H NMR (500 MHz, CD_3OD) δ 8.77 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 8.66–8.59 (m, 2H), 8.39–8.38 (m, 2H), 8.30 (s, 1H), 7.86–7.83 (m, 1H), 7.68–7.67 (m, 2H), 7.57–7.55 (m, 1H), 7.19–7.16 (m, 3H), 7.04–6.93 (m, 2H), 3.95–3.92 (m, 0.52H), 3.76–3.64 (m, 1H), 3.45–3.40 (m, 1H), 3.28–3.12 (m, 1H), 3.05–2.98 (m, 1H), 2.85–2.78 (m, 1H), 2.67–2.58 (m, 1.66H), 2.52–2.41 (m, 1H), 1.56–1.53 (m, 0.54H), 1.44–1.37 (m, 1H), 1.30–1.20 (m, 1.58H), 0.97–0.66 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.72, 152.02, 151.78, 150.66, 150.09, 150.04, 146.39, 143.05, 136.25, 136.14, 135.88, 135.63, 133.34, 133.11, 133.08, 132.88, 132.85, 132.65, 131.25, 131.21, 130.16, 129.97, 128.50, 127.32, 127.15, 127.07, 126.22, 125.19, 123.66, 123.59, 123.45, 123.40, 123.31, 121.64, 121.56, 119.75, 48.47, 46.65, 42.94, 42.72, 40.95, 37.60, 37.49, 36.19, 36.09, 31.82, 31.49, 31.23, 31.00; ^{19}F NMR (471 MHz, CD_3OD) δ –64.29, –64.33; ESI-HR-MS: (m/z) calcd. for $\text{C}_{32}\text{H}_{29}\text{F}_6\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 663.1859, found 663.1865.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-2-chloro-4-fluorobenzenesulfonamide (**C-4-25**). Following General Procedure 3, **75-25** (0.90 g, 1.81 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.65 g, 2.17 mmol) using EDCI (0.87 g, 4.53 mmol), HOBT (18 mg, 0.136 mmol), and DIPEA (1.41 g, 10.9 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-25**. White foam, 0.81 g (77%). ^1H NMR (500 MHz, CD_3OD) δ 8.77–8.75 (m, 1H), 8.67–8.59 (m, 2H), 8.07–8.05 (m, 1H), 7.85–7.83 (m, 1H), 7.67–7.66 (m, 2H), 7.57–7.54 (m, 1H), 7.49–7.46 (m, 1H), 7.23–7.19 (m, 4H), 7.10–6.99 (m, 2H), 3.96–3.80 (m, 1H), 3.38–3.32 (m, 1H), 3.17–3.14 (m, 0.49H), 3.10–2.98 (m, 1H), 2.84–2.77 (m, 1.54H), 2.65 (s, 1H), 2.55–2.40 (m, 2H), 1.54–1.51 (m, 0.54H), 1.43–1.33 (m, 1H), 1.25–1.20 (m, 1.59H), 0.98–0.62 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.66, 167.50, 165.71, 163.73, 163.65, 152.04, 151.89, 150.58, 150.16, 146.37, 136.23, 136.16, 135.96, 133.86, 133.78, 133.36, 133.28, 132.93, 132.81, 131.48, 131.40, 130.17, 130.01, 128.65, 127.10, 127.05, 123.61, 123.44, 123.19, 119.41, 119.21, 115.08, 114.91, 114.83, 114.66, 47.04, 46.00, 43.82, 42.68, 42.43, 42.14, 37.39, 36.32, 36.27, 32.04, 31.97, 31.87, 31.60; ^{19}F NMR (471 MHz, CD_3OD) δ –106.24, –106.34; ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{29}\text{ClF}_2\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 579.1627, found 579.1633.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-3-cyano-4-fluorobenzenesulfonamide (**C-4-26**). Following General Procedure 3, **75-26** (0.64 g, 1.31 mmol) was first treated with TFA (3.2 mL) in CH_2Cl_2 (1.9 mL), and the intermediate obtained was reacted with **7-TFA** (0.47 g, 1.57 mmol) using EDCI (0.63 g, 3.28 mmol), HOBT (13 mg, 0.098 mmol), and DIPEA (1.02 g, 7.86 mmol) in dried THF (6.4 mL). Purification by column chromatography (EtOAc) gave **C-4-26**. White foam, 0.55 g (74%). ^1H NMR (500 MHz, CD_3OD) δ 8.77–8.76 (m, 1H), 8.67–8.58 (m, 2H), 8.26–8.24 (m, 1H), 8.18–8.14 (m, 1H), 7.86–7.82 (m, 1H), 7.68–7.66 (m, 2H), 7.62–7.55 (m, 2H), 7.22–7.19 (m, 3H), 7.07–6.96 (m, 2H), 3.98–3.74 (m, 1H), 3.58–3.35 (m, 1H), 3.23–3.12 (m, 1H), 3.06–2.92 (m, 1H), 2.83–2.76 (m, 1H), 2.65 (s, 1H), 2.58–2.40 (m, 2H), 1.54–1.52 (m, 0.53H), 1.46–1.45 (m, 1H), 1.34–1.18 (m, 1.60H), 0.92–0.65 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.66, 166.03, 163.92, 151.88, 151.86, 150.66, 150.12, 146.51, 146.35, 137.67, 136.20, 136.00, 135.76, 134.11, 134.04, 133.85, 133.77, 133.02, 132.89, 131.35, 131.28, 130.23, 130.04, 128.55, 128.47, 127.17, 127.06, 123.67, 123.38, 123.34, 117.88, 117.71, 112.53, 112.42, 102.93, 102.81, 52.44, 48.44, 46.65, 43.06, 42.71, 42.65, 40.86, 37.59, 37.50, 36.23, 36.14, 31.88, 31.58, 31.28, 31.05, 28.82; ^{19}F NMR (471 MHz, CDCl_3) δ –99.05, –99.22, –107.07; ESI-HR-MS: (m/z) calcd. for $\text{C}_{31}\text{H}_{29}\text{FN}_5\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 570.1970, found 570.1976.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-4-(*tert*-butyl)benzenesulfonamide (**C-4-27**). Following General Procedure 3, **75-27** (0.90 g, 1.80 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL),

and the intermediate obtained was reacted with **7·TFA** (0.64 g, 2.16 mmol) using EDCI (0.86 g, 4.50 mmol), HOBT (18 mg, 0.135 mmol), and DIPEA (1.40 g, 10.8 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-27**. White foam, 0.75 g (72%). ^1H NMR (500 MHz, CD_3OD) δ 8.76 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 8.67–8.59 (m, 2H), 7.84–7.81 (m, 1H), 7.78–7.74 (m, 2H), 7.67–7.66 (m, 2H), 7.63–7.59 (m, 2H), 7.56–7.53 (m, 1H), 7.18–7.16 (m, 3H), 7.04–6.93 (m, 2H), 3.99–3.78 (m, 1H), 3.43–3.35 (m, 0.67H), 3.28–3.26 (m, 0.46H), 3.20–3.05 (m, 1H), 3.02–2.87 (m, 1H), 2.78–2.71 (m, 1H), 2.63 (s, 1H), 2.58–2.51 (m, 1H), 2.48–2.37 (m, 1H), 1.52–1.41 (m, 1.55H), 1.36–1.34 (m, 9H), 1.24–1.18 (m, 1.62H), 1.01–0.58 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.53, 167.42, 156.60, 152.08, 151.83, 150.45, 150.11, 150.05, 146.30, 136.56, 136.17, 136.02, 135.91, 131.46, 130.29, 130.10, 128.32, 126.82, 126.76, 126.28, 126.22, 123.53, 123.33, 123.12, 47.11, 45.85, 43.19, 42.72, 42.61, 41.72, 37.51, 37.41, 36.17, 35.98, 35.18, 31.93, 31.69, 31.60, 31.31, 31.10; ESI-HR-MS: (m/z) calcd. for $\text{C}_{34}\text{H}_{39}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 583.2737, found 583.2740.

Synthesis of N-((1-([2,4′-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-4-(trifluoromethyl)benzenesulfonamide (**C-4-28**). Following General Procedure 3, **75-28** (0.80 g, 1.56 mmol) was first treated with TFA (4 mL) in CH_2Cl_2 (2.4 mL), and the intermediate obtained was reacted with **7·TFA** (0.56 g, 1.87 mmol) using EDCI (0.75 g, 3.90 mmol), HOBT (16 mg, 0.117 mmol), and DIPEA (1.21 g, 9.36 mmol) in dried THF (8 mL). Purification by column chromatography (EtOAc) gave **C-4-28**. White foam, 0.67 g (72%). ^1H NMR (500 MHz, CD_3OD) δ 8.77–8.75 (m, 1H), 8.67–8.58 (m, 2H), 8.04–8.00 (m, 2H), 7.92–7.82 (m, 3H), 7.68–7.66 (m, 2H), 7.56–7.54 (m, 1H), 7.19–7.16 (m, 3H), 7.04–6.93 (m, 2H), 3.98–3.77 (m, 1H), 3.50–3.35 (m, 1H), 3.22–3.09 (m, 1H), 3.04–2.91 (m, 1H), 2.93–2.76 (m, 1H), 2.64–2.61 (m, 1H), 2.58–2.53 (m, 1H), 2.50–2.39 (m, 1H), 1.54–1.51 (m, 0.53H), 1.45–1.32 (m, 1H), 1.28–1.19 (m, 1.67H), 0.99–0.62 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.63, 167.54, 151.99, 151.80, 150.57, 150.06, 146.37, 143.39, 136.18, 136.11, 135.99, 135.74, 134.81, 134.55, 134.28, 131.34, 130.18, 130.00, 128.44, 127.50, 127.39, 127.00, 126.92, 126.43, 124.27, 123.60, 123.37, 123.28, 122.10, 47.81, 46.26, 43.12, 42.69, 42.59, 41.34, 37.52, 37.45, 36.20, 36.04, 31.89, 31.58, 31.42, 31.13; ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ −65.23, −65.26; ESI-HR-MS: (m/z) calcd. for $\text{C}_{31}\text{H}_{30}\text{F}_3\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 595.1985, found 595.1986.

Synthesis of N-((1-([2,4′-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-4-fluoro-3-(trifluoromethyl)benzenesulfonamide (**C-4-29**). Following General Procedure 3, **75-29** (0.80 g, 1.51 mmol) was first treated with TFA (4 mL) in CH_2Cl_2 (2.4 mL), and the intermediate obtained was reacted with **7·TFA** (0.54 g, 1.81 mmol) using EDCI (0.72 g, 3.78 mmol), HOBT (15 mg, 0.113 mmol), and DIPEA (1.17 g, 9.06 mmol) in dried THF (8 mL). Purification by column chromatography (EtOAc) gave **C-4-29**. White foam, 0.76 g (82%). ^1H NMR (500 MHz, CD_3OD) δ 8.78–8.76 (m, 1H), 8.67–8.59 (m, 2H), 8.17–8.14 (m, 2H), 7.86–7.83 (m, 1H), 7.68–7.67 (m, 2H), 7.59–7.55 (m, 2H), 7.20–7.18 (m, 3H), 7.05–6.94 (m, 2H), 3.97–3.77 (m, 1H), 3.58–3.35 (m, 1H), 3.22–3.11 (m, 1H), 3.05–2.92 (m, 1H), 2.81–2.74 (m, 1H), 2.66 (s, 1H), 2.59–2.54 (m, 1H), 2.51–2.41 (m, 1H), 1.55–1.52 (m, 0.53H), 1.46–1.33 (m, 1H), 1.28–1.21 (m, 1.56H), 0.96–0.65 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.65, 163.01, 160.91, 151.99, 151.84, 150.64, 150.12, 146.48, 146.39, 136.72, 136.69, 136.23, 136.17, 135.98, 135.76, 133.41, 133.34, 133.10, 133.02, 131.34, 130.18, 129.97, 128.54, 127.16, 127.06, 126.74, 123.65, 123.40, 122.76, 120.59, 119.82, 119.72, 119.55, 119.44, 118.40, 118.21, 48.17, 46.47, 43.25, 42.70, 41.20, 37.56, 37.47, 36.22, 36.10, 31.95, 31.66, 31.41, 31.13; ^{19}F NMR (471 MHz, CD_3OD) δ −63.08–−63.15 (m), −110.16–−110.26; ESI-HR-MS: (m/z) calcd. for $\text{C}_{31}\text{H}_{29}\text{F}_4\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 613.1891, found 613.1885.

Synthesis of N-((1-([2,4′-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-4-(trifluoromethoxy)benzenesulfonamide (**C-4-30**). Following General Procedure 3, **75-30** (0.90 g, 1.70 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7·TFA** (0.61 g, 2.04 mmol) using

EDCI (0.81 g, 4.25 mmol), HOBT (17 mg, 0.128 mmol), and DIPEA (1.32 g, 10.2 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-30**. White foam, 0.73 g (70%). ^1H NMR (500 MHz, CD_3OD) δ 8.77–8.76 (m, 1H), 8.68–8.59 (m, 2H), 7.97–7.92 (m, 2H), 7.86–7.82 (m, 1H), 7.68–7.67 (m, 2H), 7.57–7.54 (m, 1H), 7.51–7.47 (m, 2H), 7.20–7.17 (m, 3H), 7.05–6.94 (m, 2H), 3.99–3.78 (m, 1H), 3.49–3.34 (m, 1H), 3.22–3.09 (m, 1H), 3.03–2.88 (m, 1H), 2.81–2.75 (m, 1H), 2.64 (s, 1H), 2.60–2.52 (m, 1H), 2.50–2.40 (m, 1H), 1.54–1.42 (m, 1H), 1.36–1.33 (m, 0.52H), 1.27–1.20 (m, 1.49H), 1.00–0.62 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.53, 152.15, 152.14, 152.02, 151.84, 150.56, 150.10, 146.37, 138.13, 136.19, 136.11, 136.04, 135.79, 131.38, 130.21, 130.01, 129.16, 129.04, 128.43, 126.98, 126.90, 123.58, 123.37, 123.26, 121.27, 121.18, 121.11, 47.68, 46.18, 43.19, 42.70, 42.59, 41.43, 37.52, 37.44, 36.19, 36.04, 31.94, 31.62, 31.52, 31.19; ^{19}F NMR (471 MHz, CD_3OD) δ –59.27, –59.30; ESI-HR-MS: (m/z) calcd. for $\text{C}_{31}\text{H}_{30}\text{F}_3\text{N}_4\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 611.1934, found 611.1926.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-4-fluoro-2-(trifluoromethyl)benzenesulfonamide (**C-4-31**). Following General Procedure 3, **75-31** (0.90 g, 1.70 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.61 g, 2.04 mmol) using EDCI (0.81 g, 4.25 mmol), HOBT (17 mg, 0.128 mmol), and DIPEA (1.32 g, 10.2 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-31**. White solid, 0.71 g (68%), m.p. 102.4–103.8 °C. ^1H NMR (500 MHz, CD_3OD) δ 8.77 (dd, $J = 1.8$ Hz and 4.8 Hz, 1H), 8.67–8.58 (m, 2H), 8.18–8.11 (m, 1H), 7.85–7.82 (m, 1H), 7.75–7.73 (m, 1H), 7.67–7.66 (m, 2H), 7.62–7.55 (m, 2H), 7.24–7.18 (m, 3H), 7.09–6.99 (m, 2H), 3.96–3.78 (m, 1H), 3.49–3.35 (m, 1H), 3.20–3.11 (m, 1H), 3.05–2.86 (m, 2H), 2.67–2.65 (m, 2H), 2.54–2.44 (m, 1H), 1.57–1.54 (m, 0.56H), 1.45–1.34 (m, 1H), 1.30–1.25 (m, 1.63H), 0.99–0.67 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.62, 167.51, 165.30, 165.22, 163.26, 163.17, 151.95, 151.87, 150.56, 150.14, 146.34, 136.20, 136.16, 136.09, 135.86, 135.22, 135.15, 134.63, 134.52, 134.46, 134.22, 131.40, 130.00, 129.84, 128.61, 127.08, 127.01, 123.60, 123.38, 123.27, 119.43, 119.27, 119.15, 118.98, 116.98, 116.93, 116.78, 116.72, 47.61, 46.39, 43.55, 42.67, 42.46, 41.51, 37.43, 37.38, 36.36, 36.30, 31.91, 31.86, 31.80, 31.42; ^{19}F NMR (471 MHz, CD_3OD) δ –59.22, –106.31, –106.37; ESI-HR-MS: (m/z) calcd. for $\text{C}_{31}\text{H}_{29}\text{F}_4\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 613.1891, found 613.1882.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)naphthalene-2-sulfonamide (**C-4-32**). Following General Procedure 3, **75-32** (0.90 g, 1.82 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.65 g, 2.18 mmol) using EDCI (0.87 g, 4.55 mmol), HOBT (19 mg, 0.137 mmol), and DIPEA (1.41 g, 10.9 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-32**. White foam, 0.66 g (63%). ^1H NMR (500 MHz, CD_3OD) δ 8.74–8.73 (m, 1H), 8.63–8.56 (m, 2H), 8.40–8.39 (m, 1H), 8.05–7.95 (m, 3H), 7.87–7.76 (m, 2H), 7.66–7.61 (m, 4H), 7.54–7.49 (m, 1H), 7.11–7.05 (m, 3H), 6.99–6.87 (m, 2H), 3.96–3.75 (m, 1H), 3.45–3.35 (m, 0.68H), 3.29–3.27 (m, 0.44H), 3.17–3.00 (m, 1H), 2.95–2.86 (m, 1H), 2.81–2.75 (m, 1H), 2.62–2.54 (m, 2H), 2.47–2.36 (m, 1H), 1.51–1.49 (m, 0.62H), 1.40–1.33 (m, 1H), 1.22–1.15 (m, 1.75H), 1.00–0.55 (m, 1H); ^{13}C NMR (201 MHz, CDCl_3) δ 167.45, 167.29, 151.90, 151.64, 150.31, 149.99, 149.87, 146.17, 146.13, 136.36, 136.03, 135.98, 135.93, 135.73, 134.64, 132.07, 131.96, 131.27, 130.17, 130.02, 129.58, 129.22, 129.06, 128.85, 128.31, 128.12, 127.83, 127.62, 126.61, 126.55, 123.43, 123.20, 123.01, 121.90, 47.10, 45.91, 42.80, 42.60, 42.47, 41.48, 37.42, 37.33, 36.00, 35.82, 31.74, 31.43, 31.35, 31.09; ESI-HR-MS: (m/z) calcd. for $\text{C}_{34}\text{H}_{33}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 577.2268, found 577.2266.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)naphthalene-1-sulfonamide (**C-4-33**). Following General Procedure 3, **75-33** (0.82 g, 1.66 mmol) was first treated with TFA (4.1 mL) in CH_2Cl_2 (2.5 mL), and the intermediate obtained was reacted with **7-TFA** (0.59 g, 1.99 mmol) using EDCI (0.80 g, 4.15 mmol), HOBT (17 mg, 0.127 mmol), and DIPEA (1.29 g, 9.96 mmol) in dried THF

(8.2 mL). Purification by column chromatography (EtOAc) gave **C-4-33**. White solid, 0.69 g (72%). m.p. 121.2–122.8 °C. ^1H NMR (500 MHz, CD_3OD) δ 8.80–8.77 (m, 1H), 8.74 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 8.65–8.56 (m, 2H), 8.16–8.11 (m, 2H), 8.02–8.00 (m, 1H), 7.79–7.74 (m, 1H), 7.72–7.69 (m, 1H), 7.65–7.61 (m, 3H), 7.58–7.51 (m, 2H), 7.10–7.06 (m, 1H), 7.05–7.02 (m, 2H), 6.90–6.77 (m, 2H), 3.88–3.72 (m, 1H), 3.12–3.02 (m, 1.49H), 2.86–2.85 (m, 1H), 2.73–2.63 (m, 1.58H), 2.55 (s, 1H), 2.46–2.27 (m, 2H), 1.41–1.39 (m, 0.57H), 1.34–1.24 (m, 1H), 1.15–1.02 (m, 1.53H), 0.93–0.42 (m, 1H); ^{13}C NMR (201 MHz, CDCl_3) δ 167.40, 167.27, 151.94, 151.68, 150.36, 150.05, 149.95, 146.23, 146.12, 136.07, 135.94, 135.73, 134.35, 134.30, 134.20, 134.11, 131.36, 131.26, 130.08, 129.91, 129.73, 129.40, 129.22, 128.41, 128.35, 128.20, 127.90, 127.01, 126.94, 126.63, 124.34, 124.14, 124.11, 123.47, 123.44, 123.29, 122.99, 46.70, 45.66, 43.35, 42.58, 42.38, 42.06, 37.29, 37.24, 35.99, 35.85, 31.84, 31.78, 31.48, 31.28; ESI-HR-MS: (m/z) calcd. for $\text{C}_{34}\text{H}_{33}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 577.2268, found 577.2267.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl) piperidin-4-yl)methyl)-4-cyclohexylbenzenesulfonamide (**C-4-34**). Following General Procedure 3, **75-34** (0.90 g, 1.71 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.61 g, 2.05 mmol) using EDCI (0.82 g, 4.28 mmol), HOBT (17 mg, 0.128 mmol), and DIPEA (1.33 g, 10.3 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-34**. White foam, 0.88 g (85%). ^1H NMR (500 MHz, CD_3OD) δ 8.76–8.75 (m, 1H), 8.67–8.58 (m, 2H), 7.84–7.80 (m, 1H), 7.76–7.72 (m, 2H), 7.67–7.65 (m, 2H), 7.56–7.53 (m, 1H), 7.43–7.39 (m, 2H), 7.18–7.16 (m, 3H), 7.04–6.92 (m, 2H), 3.99–3.78 (m, 1H), 3.39–3.35 (m, 0.74H), 3.27–3.15 (m, 1H), 3.09–2.97 (m, 1H), 2.88–2.85 (m, 0.48H), 2.77–2.70 (m, 1H), 2.62–2.60 (m, 2H), 2.57–2.53 (m, 1H), 2.47–2.37 (m, 1H), 1.87–1.83 (m, 4H), 1.78–1.75 (m, 1H), 1.51–1.43 (m, 5H), 1.34–1.17 (m, 3H), 1.00–0.56 (m, 1H); ^{13}C NMR (201 MHz, CDCl_3) δ 167.44, 167.31, 153.31, 151.96, 151.70, 150.34, 150.02, 149.92, 146.20, 146.14, 136.82, 136.09, 135.94, 135.83, 131.36, 131.30, 130.23, 130.06, 128.18, 127.65, 127.59, 126.96, 126.89, 126.62, 126.56, 123.45, 123.42, 123.24, 123.02, 46.98, 45.74, 44.40, 42.92, 42.64, 42.51, 41.54, 37.44, 37.34, 36.03, 35.84, 34.02, 33.99, 31.80, 31.55, 31.41, 31.17, 26.55, 25.85; ESI-HR-MS: (m/z) calcd. for $\text{C}_{36}\text{H}_{41}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 609.2894, found 609.2893.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl) piperidin-4-yl)methyl)-3-(methylsulfonyl)benzenesulfonamide (**C-4-35**). Following General Procedure 3, **75-35** (0.90 g, 1.72 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.61 g, 2.06 mmol) using EDCI (0.82 g, 4.30 mmol), HOBT (17 mg, 0.129 mmol), and DIPEA (1.33 g, 10.3 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-35**. White foam, 0.60 g (58%). ^1H NMR (500 MHz, CD_3OD) δ 8.76–8.75 (m, 1H), 8.67–8.58 (m, 2H), 8.40 (s, 1H), 8.23–8.13 (m, 2H), 7.85–7.82 (m, 2H), 7.67–7.65 (m, 2H), 7.56–7.54 (m, 1H), 7.19–7.17 (m, 3H), 7.04–6.93 (m, 2H), 3.95–3.74 (m, 1H), 3.55–3.37 (m, 1H), 3.21–3.17 (m, 3.52H), 3.13–3.08 (m, 0.60H), 3.02–2.91 (m, 1H), 2.83–2.76 (m, 1H), 2.64–2.53 (m, 2H), 2.49–2.39 (m, 1H), 1.53–1.50 (m, 0.57H), 1.42–1.33 (m, 1H), 1.26–1.19 (m, 1.62H), 0.96–0.66 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.57, 167.49, 151.90, 151.76, 150.49, 150.06, 149.98, 146.30, 141.99, 141.85, 136.19, 136.12, 136.02, 135.76, 131.94, 131.78, 131.31, 131.15, 131.12, 130.67, 130.63, 130.27, 130.11, 128.37, 126.88, 126.81, 126.01, 123.59, 123.28, 123.24, 47.97, 46.42, 44.26, 44.20, 42.67, 42.57, 40.89, 37.52, 37.42, 36.12, 35.99, 31.75, 31.34, 31.25, 30.99; ESI-HR-MS: (m/z) calcd. for $\text{C}_{31}\text{H}_{33}\text{N}_4\text{O}_5\text{S}_2$ ($[\text{M}+\text{H}]^+$) 605.1887, found 605.1887.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl) piperidin-4-yl)methyl)-4-n-propylbenzenesulfonamide (**C-4-36**). Following General Procedure 3, **75-36** (0.90 g, 1.85 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.66 g, 2.22 mmol) using EDCI (0.89 g, 4.63 mmol), HOBT (19 mg, 0.139 mmol), and DIPEA (1.43 g, 11.1 mmol) in dried

THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-36**. White foam, 0.81 g (77%). ^1H NMR (500 MHz, CD_3OD) δ 8.75–8.74 (m, 1H), 8.66–8.58 (m, 2H), 7.83–7.80 (m, 1H), 7.76–7.71 (m, 2H), 7.66–7.65 (m, 2H), 7.55–7.52 (m, 1H), 7.39–7.35 (m, 2H), 7.18–7.16 (m, 3H), 7.04–6.92 (m, 2H), 3.97–3.76 (m, 1H), 3.43–3.35 (m, 0.59H), 3.29–3.26 (m, 0.43H), 3.19–3.15 (m, 0.50H), 3.09–2.96 (m, 1H), 2.90–2.86 (m, 0.51H), 2.77–2.73 (m, 1H), 2.69–2.62 (m, 3H), 2.57–2.50 (m, 1H), 2.47–2.37 (m, 1H), 1.69–1.63 (m, 2H), 1.52–1.49 (m, 0.62H), 1.40–1.33 (m, 1H), 1.24–1.17 (m, 1.65H), 1.01–0.92 (m, 3.59H), 0.62–0.58 (m, 0.58H); ^{13}C NMR (151 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 168.74, 168.58, 152.88, 152.61, 151.35, 150.44, 150.32, 148.98, 147.84, 138.62, 137.57, 137.32, 137.23, 132.55, 132.50, 131.45, 131.40, 130.08, 128.90, 127.81, 127.35, 127.30, 124.92, 124.56, 124.40, 48.23, 47.07, 43.90, 43.83, 43.37, 41.88, 38.53, 38.47, 36.90, 36.76, 32.48, 32.35, 31.82, 25.12, 14.07; ESI-HR-MS: (m/z) calcd. for $\text{C}_{33}\text{H}_{37}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 569.2581, found 569.2582.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-2,4,6-triisopropylbenzenesulfonamide (**C-4-37**). Following General Procedure 3, **75-37** (0.90 g, 1.58 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.57 g, 1.90 mmol) using EDCI (0.76 g, 3.95 mmol), HOBT (16 mg, 0.119 mmol), and DIPEA (1.23 g, 9.48 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-37**. White foam. 0.88 g (85%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 8.66–8.60 (m, 2H), 7.82–7.81 (m, 1H), 7.59–7.48 (m, 4H), 7.22 (s, 2H), 7.05–6.92 (m, 3H), 4.16–4.10 (m, 2H), 3.79–3.74 (m, 1H), 3.28–3.09 (m, 1.47H), 2.94–2.89 (m, 2H), 2.73–2.69 (m, 1H), 2.64–2.62 (m, 1.48H), 2.53–2.52 (m, 0.43H), 2.36–2.33 (m, 0.58H), 1.51–1.49 (m, 0.55H), 1.35–1.28 (m, 1H), 1.20–1.18 (m, 6.60H), 1.17–1.07 (m, 14H), 0.86–0.49 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.39, 152.96, 152.14, 151.80, 150.42, 150.05, 146.30, 146.09, 136.17, 136.01, 135.94, 132.20, 131.43, 131.29, 130.14, 129.98, 128.41, 126.78, 123.93, 123.54, 123.43, 123.34, 122.94, 46.03, 45.38, 43.28, 42.74, 42.65, 42.50, 37.43, 36.37, 36.12, 34.10, 32.16, 31.91, 31.70, 31.63, 29.69, 25.00, 24.98, 23.56, 23.55; ESI-HR-MS: (m/z) calcd. for $\text{C}_{39}\text{H}_{49}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 653.3520, found 653.3521.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonamide (**C-4-38**). Following General Procedure 3, **75-38** (0.90 g, 1.73 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.62 g, 2.08 mmol) using EDCI (0.83 g, 4.33 mmol), HOBT (18 mg, 0.130 mmol), and DIPEA (1.34 g, 10.4 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-38**. White solid, 0.63 g (60%). m.p. 215.5–216.4 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77–8.76 (m, 1H), 8.65–8.64 (m, 2H), 7.93–7.87 (m, 4H), 7.83–7.67 (m, 4H), 7.57–7.51 (m, 5H), 7.46–7.43 (m, 1H), 7.17–7.14 (m, 3H), 7.07–6.97 (m, 2H), 3.88–3.71 (m, 1H), 3.39–3.37 (m, 0.44H), 3.28–3.24 (m, 0.60H), 3.18–3.13 (m, 0.51H), 3.00–2.98 (m, 1H), 2.81–2.68 (m, 1H), 2.64–2.60 (m, 2H), 2.45–2.44 (m, 1H), 2.38–2.35 (m, 0.53H), 1.50–1.47 (m, 0.57H), 1.33–1.29 (m, 1H), 1.15–1.06 (m, 1.62H), 0.82–0.51 (m, 1H); ^{13}C NMR (201 MHz, CDCl_3) δ 167.61, 167.51, 152.14, 151.88, 150.52, 150.24, 150.13, 146.33, 146.27, 145.80, 145.75, 139.21, 139.10, 138.14, 136.21, 136.16, 136.10, 135.92, 131.47, 131.42, 130.28, 130.08, 129.19, 128.71, 128.64, 128.46, 128.44, 127.95, 127.87, 127.55, 127.47, 127.38, 127.33, 126.93, 126.85, 123.59, 123.55, 123.38, 123.18, 47.39, 46.08, 43.40, 42.75, 42.62, 41.77, 37.55, 37.46, 36.25, 36.07, 32.01, 31.73, 31.37; ESI-HR-MS: (m/z) calcd. for $\text{C}_{36}\text{H}_{35}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 603.2424, found 603.2425.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-4-methylbenzenesulfonamide (**C-4-39**). Following General Procedure 3, **75-39** (1.00 g, 2.18 mmol) was first treated with TFA (5 mL) in CH_2Cl_2 (3 mL), and the intermediate obtained was reacted with **7-TFA** (0.78 g, 2.62 mmol) using EDCI (1.04 g, 5.45 mmol), HOBT (22 mg, 0.164 mmol), and DIPEA (1.69 g, 13.1 mmol) in dried

THF (10 mL). Purification by column chromatography (EtOAc) gave **C-4-39**. White foam, 0.95 g (81%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (d, $J = 5.0$ Hz, 1H), 8.66–8.64 (m, 2H), 7.84–7.79 (m, 1H), 7.70–7.67 (m, 2H), 7.57–7.52 (m, 4H), 7.42–7.39 (m, 2H), 7.18–7.16 (m, 3H), 7.06–6.96 (m, 2H), 3.86–3.70 (m, 1H), 3.25–3.11 (m, 1H), 2.96–2.77 (m, 1.71H), 2.64–2.54 (m, 2H), 2.40–2.32 (m, 5.46H), 1.47–1.44 (m, 0.61H), 1.31–1.27 (m, 1H), 1.11–1.04 (m, 1.66H), 0.81–0.51 (m, 1H); ^{13}C NMR (201 MHz, CDCl_3) δ 167.38, 167.25, 151.82, 151.60, 150.28, 149.89, 149.82, 146.15, 146.10, 143.40, 136.56, 136.55, 136.01, 135.88, 135.77, 131.27, 131.21, 130.19, 130.02, 129.72, 129.67, 128.09, 126.80, 126.73, 126.55, 126.49, 123.41, 123.17, 122.96, 46.89, 45.75, 42.74, 42.58, 42.43, 41.44, 37.36, 37.28, 35.92, 35.75, 31.70, 31.45, 31.28, 31.08, 21.40, 21.39; ESI-HR-MS: (m/z) calcd. for $\text{C}_{31}\text{H}_{33}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 541.2268, found 541.2265.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-4-ethylbenzenesulfonamide (**C-4-40**). Following General Procedure 3, **75-40** (0.90 g, 1.90 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.68 g, 2.28 mmol) using EDCI (0.91 g, 4.75 mmol), HOBT (19 mg, 0.143 mmol), and DIPEA (1.47 g, 11.4 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-40**. White foam, 0.73 g (69%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 1.5$ Hz and 4.5 Hz, 1H), 8.66–8.64 (m, 2H), 7.84–7.79 (m, 1H), 7.72–7.69 (m, 2H), 7.58–7.54 (m, 4H), 7.46–7.42 (m, 2H), 7.17–7.15 (m, 3H), 7.05–6.95 (m, 2H), 3.87–3.70 (m, 1H), 3.24–3.11 (m, 1H), 2.96–2.75 (m, 1.72H), 2.71–2.66 (m, 2H), 2.64–2.61 (m, 1.56H), 2.55–2.52 (m, 0.62H), 2.39–2.32 (m, 1.69H), 1.47–1.44 (m, 0.64H), 1.31–1.26 (m, 1H), 1.22–1.18 (m, 3.49H), 1.11–1.04 (m, 2H), 0.80–0.50 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.43, 167.31, 151.92, 151.68, 150.33, 149.97, 149.89, 149.57, 146.20, 146.15, 136.78, 136.06, 135.93, 135.82, 131.33, 131.28, 130.22, 130.05, 128.63, 128.58, 128.16, 126.96, 126.89, 126.60, 126.55, 123.45, 123.22, 123.01, 46.97, 45.79, 42.86, 42.63, 42.49, 41.54, 37.42, 37.33, 35.99, 35.82, 31.79, 31.54, 31.38, 31.16, 28.68, 15.06; ESI-HR-MS: (m/z) calcd. for $\text{C}_{32}\text{H}_{35}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 555.2424, found 555.2421.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-4-isopropylbenzenesulfonamide (**C-4-41**). Following General Procedure 3, **75-41** (1.00 g, 2.05 mmol) was first treated with TFA (5 mL) in CH_2Cl_2 (3 mL), and the intermediate obtained was reacted with **7-TFA** (0.73 g, 2.46 mmol) using EDCI (0.98 g, 5.13 mmol), HOBT (21 mg, 0.154 mmol), and DIPEA (1.59 g, 12.3 mmol) in dried THF (10 mL). Purification by column chromatography (EtOAc) gave **C-4-41**. White foam, 0.62 g (53%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 8.66–8.64 (m, 2H), 7.84–7.79 (m, 1H), 7.73–7.71 (m, 2H), 7.58–7.53 (m, 4H), 7.49–7.45 (m, 2H), 7.16–7.14 (m, 3H), 7.06–6.95 (m, 2H), 3.89–3.70 (m, 1H), 3.23–3.10 (m, 1H), 3.00–2.95 (m, 2H), 2.78–2.75 (m, 0.48H), 2.66–2.53 (m, 2H), 2.47–2.32 (m, 2H), 1.47–1.44 (m, 0.58H), 1.31–1.21 (m, 7.51H), 1.14–1.04 (m, 1.66H), 0.82–0.47 (m, 1H); ^{13}C NMR (201 MHz, CDCl_3) δ 167.49, 167.36, 154.20, 152.00, 151.75, 150.39, 150.07, 149.99, 146.25, 146.19, 136.94, 136.13, 135.98, 135.87, 131.40, 131.34, 130.27, 130.10, 128.21, 127.33, 127.27, 127.06, 126.99, 126.64, 123.51, 123.46, 123.28, 123.06, 47.00, 45.79, 42.96, 42.69, 42.56, 41.61, 37.48, 37.38, 36.07, 35.89, 34.10, 31.85, 31.61, 31.46, 31.23, 23.64, 23.62; ESI-HR-MS: (m/z) calcd. for $\text{C}_{33}\text{H}_{37}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 569.2581, found 569.2581.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-3-isopropylbenzenesulfonamide (**C-4-42**). Following General Procedure 3, **75-42** (0.90 g, 1.85 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.66 g, 2.22 mmol) using EDCI (0.89 g, 4.63 mmol), HOBT (19 mg, 0.139 mmol), and DIPEA (1.43 g, 11.1 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-42**. White foam, 0.80 g (76%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 1.5$ Hz and 1.8 Hz, 1H), 8.65 (dd, $J = 2.0$ Hz and 4.5 Hz, 2H), 7.83–7.79 (m, 1H), 7.68–7.67 (m, 1H), 7.62–7.60 (m, 2H),

7.57–7.53 (m, 5H), 7.17–7.15 (m, 3H), 7.05–6.95 (m, 2H), 3.84–3.68 (m, 1H), 3.23–3.12 (m, 1H), 3.02–2.93 (m, 2H), 2.77–2.75 (m, 0.47H), 2.64–2.59 (m, 1.54H), 2.56–2.53 (m, 0.65H), 2.48–2.41 (m, 1.43H), 2.34–2.32 (m, 0.59H), 1.47–1.44 (m, 0.58H), 1.31–1.28 (m, 1H), 1.22–1.21 (m, 6.51H), 1.13–1.03 (m, 1.63H), 0.85–0.47 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.55, 167.45, 152.10, 151.83, 150.47, 150.16, 150.08, 146.31, 146.20, 139.53, 136.19, 136.11, 136.02, 135.88, 131.46, 131.38, 131.10, 130.25, 130.06, 129.27, 129.25, 128.36, 126.83, 126.77, 124.81, 124.74, 124.45, 124.32, 123.56, 123.49, 123.35, 123.09, 47.12, 45.91, 43.24, 42.70, 42.60, 41.81, 37.50, 37.40, 36.15, 35.97, 34.08, 31.97, 31.74, 31.60, 31.38, 23.80, 23.77; ESI-HR-MS: (m/z) calcd. for $\text{C}_{33}\text{H}_{37}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 569.2581, found 569.2582.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-2-methylbenzenesulfonamide (**C-4-43**). Following General Procedure 3, **75-43** (0.90 g, 1.96 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.70 g, 2.35 mmol) using EDCI (0.94 g, 4.90 mmol), HOBT (20 mg, 0.147 mmol), and DIPEA (1.53 g, 11.8 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-43**. White foam, 0.50 g (47%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 8.66–8.62 (m, 2H), 7.82–7.69 (m, 3H), 7.57–7.51 (m, 4H), 7.42–7.37 (m, 2H), 7.21–7.17 (m, 3H), 7.08–6.98 (m, 2H), 3.83–3.69 (m, 1H), 3.25–3.20 (m, 1H), 3.10–3.07 (m, 0.44H), 2.96 (s, 1H), 2.74–2.70 (m, 1H), 2.62–2.53 (m, 4.65H), 2.47–2.35 (m, 2H), 1.48–1.45 (m, 0.59H), 1.33–1.23 (m, 1H), 1.13–1.05 (m, 1.63H), 0.83–0.52 (m, 1H); ^{13}C NMR (201 MHz, CDCl_3) δ 167.46, 167.34, 151.97, 151.74, 150.41, 150.06, 149.99, 146.26, 146.15, 143.55, 137.75, 137.56, 136.74, 136.69, 136.17, 136.12, 136.00, 132.86, 132.83, 132.67, 132.64, 131.39, 131.27, 130.25, 130.16, 130.06, 129.97, 129.83, 129.78, 129.22, 128.96, 128.41, 128.37, 128.26, 126.92, 126.84, 126.78, 126.40, 126.25, 123.51, 123.48, 123.31, 123.28, 123.02, 46.84, 45.83, 43.45, 42.66, 42.45, 42.12, 37.34, 36.18, 36.06, 31.86, 31.77, 31.58, 31.50, 31.35, 20.23; ESI-HR-MS: (m/z) calcd. for $\text{C}_{31}\text{H}_{33}\text{N}_4\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 541.2268, found 541.2282.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)-4-hydroxybenzenesulfonamide (**C-4-44**). Following General Procedure 3, **75-44** (0.90 g, 1.95 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.70 g, 2.34 mmol) using EDCI (0.94 g, 4.88 mmol), HOBT (20 mg, 0.146 mmol), and DIPEA (1.51 g, 11.7 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-44**. White foam, 0.11 g (10%). ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 10.38 (s, 1H), 8.78–8.77 (m, 1H), 8.65–8.64 (m, 2H), 7.84–7.79 (m, 1H), 7.62–7.55 (m, 5H), 7.37–7.35 (m, 1H), 7.17–7.16 (m, 3H), 7.05–7.04 (m, 1H), 6.96–6.89 (m, 3H), 3.86–3.70 (m, 1H), 3.23–3.17 (m, 1H), 3.12–3.10 (m, 0.45H), 2.96 (s, 1H), 2.78–2.58 (m, 2H), 2.48–2.31 (m, 2.46H), 1.46–1.43 (m, 0.54H), 1.30–1.23 (m, 1H), 1.10–1.02 (m, 1.52H), 0.81–0.49 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 167.60, 161.61, 151.69, 150.65, 149.51, 149.24, 147.20, 146.91, 136.29, 136.11, 135.97, 131.40, 130.41, 130.28, 129.77, 129.32, 128.45, 126.90, 123.97, 123.88, 123.72, 116.38, 116.22, 46.73, 46.12, 43.20, 42.99, 42.69, 42.38, 37.68, 36.09, 36.02, 31.98, 31.49, 29.89, 29.81, 29.72, 29.63, 29.43; ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{31}\text{N}_4\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 543.2061, found 543.2061.

Synthesis of 4-(N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-ylmethyl)piperidin-4-yl)methyl)sulfamoyl)benzamide (**C-4-45**). Following General Procedure 3, **75-45** (0.90 g, 1.85 mmol) was first treated with TFA (4.5 mL) in CH_2Cl_2 (2.7 mL), and the intermediate obtained was reacted with **7-TFA** (0.66 g, 2.22 mmol) using EDCI (0.89 g, 4.63 mmol), HOBT (19 mg, 0.139 mmol), and DIPEA (1.43 g, 11.1 mmol) in dried THF (9 mL). Purification by column chromatography (EtOAc) gave **C-4-45**. White foam, 0.77 g (73%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (d, $J = 4.5$ Hz, 1H), 8.66–8.63 (m, 2H), 8.22–8.19 (m, 1H), 8.09–8.05 (m, 2H), 7.89–7.86 (m, 2H), 7.83–7.74 (m, 2H), 7.63 (s, 1H), 7.57–7.53 (m, 3H), 7.18–7.15 (m, 3H), 7.05–6.96 (m, 2H), 3.88–3.68 (m, 1H), 3.27–3.11 (m, 1H), 3.02–2.80 (m,

2H), 2.70–2.56 (m, 2.42H), 2.43–2.34 (m, 1.51H), 1.48–1.45 (m, 0.59H), 1.22–1.19 (m, 1H), 1.16–1.05 (m, 1.58H), 0.82–0.51 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 169.04, 168.77, 167.51, 167.41, 151.51, 150.37, 149.40, 146.61, 146.44, 142.77, 142.49, 137.16, 136.17, 135.98, 135.78, 131.22, 130.28, 130.11, 128.44, 128.10, 126.80, 126.58, 123.80, 123.30, 54.08, 47.11, 46.25, 42.75, 42.48, 42.26, 41.16, 37.45, 35.83, 31.45, 31.09, 30.94, 30.76, 17.55; ESI-HR-MS: (m/z) calcd. for $\text{C}_{31}\text{H}_{32}\text{N}_5\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 570.2170, found 570.2171.

Synthesis of methyl 4-(N-((1-([2,4'-bipyridine]-3-carbonyl)-4-(cyclohexa-1,5-dien-1-yl)methyl)piperidin-4-yl)methyl)sulfamoyl)benzoate (**76**). Following General Procedure 3, **75-46** (1.90 g, 3.78 mmol) was first treated with TFA (9.5 mL) in CH_2Cl_2 (5.7 mL), and the intermediate obtained was reacted with **7-TFA** (1.35 g, 4.54 mmol) using EDCI (1.81 g, 9.45 mmol), HOBT (38 mg, 0.284 mmol), and DIPEA (2.93 g, 22.7 mmol) in dried THF (19 mL). Purification by column chromatography (EtOAc) gave **76**. White foam, 1.91 g (86%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 1.5$ Hz and 5.0 Hz, 1H), 8.64–8.63 (m, 2H), 8.19–8.14 (m, 2H), 7.95–7.92 (m, 2H), 7.86–7.78 (m, 2H), 7.57–7.53 (m, 3H), 7.18–7.17 (m, 3H), 7.11–6.97 (m, 2H), 3.91 (s, 3H), 3.86–3.68 (m, 1H), 3.26–2.98 (m, 2.58H), 2.79–2.67 (m, 1H), 2.64–2.59 (m, 2H), 2.44–2.34 (m, 1.50H), 1.45–1.30 (m, 1H), 1.12–1.05 (m, 1.67H), 0.80–0.54 (m, 1H); ^{13}C NMR (201 MHz, CDCl_3) δ 167.48, 167.36, 165.56, 165.47, 151.85, 151.63, 150.40, 149.95, 149.87, 146.21, 146.19, 143.68, 136.07, 135.96, 135.92, 135.67, 133.72, 131.22, 130.33, 130.29, 130.15, 129.99, 128.23, 126.84, 126.75, 126.68, 123.48, 123.24, 123.07, 60.37, 52.64, 47.46, 46.09, 42.77, 42.60, 42.48, 41.25, 37.41, 37.33, 36.02, 35.86, 31.70, 31.45, 31.30, 30.99, 22.53, 20.98, 14.10, 14.05; ESI-HR-MS: (m/z) calcd. for $\text{C}_{32}\text{H}_{33}\text{N}_4\text{O}_5\text{S}$ ($[\text{M}+\text{H}]^+$) 585.2166, found 585.2164.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-4-aminobenzenesulfonamide (**C-4-46**). Following the procedure for the synthesis of **10** from **9**, **C-4-46** was prepared from **C-4-12** (0.40 g, 0.700 mmol) using 10% Pd/C (40 mg) in MeOH (4 mL). Purification by column chromatography (EtOAc) gave **C-4-46**. Pale yellow solid, 0.15 g (40%). m.p. 125.4–127.6 °C. ^1H NMR (500 MHz, CD_3OD) δ 8.77–8.76 (m, 1H), 8.68–8.60 (m, 2H), 7.85–7.83 (m, 1H), 7.67–7.66 (m, 2H), 7.58–7.55 (m, 1H), 7.52–7.47 (m, 2H), 7.21–7.19 (m, 3H), 7.06–6.93 (m, 2H), 6.72–6.68 (m, 2H), 3.99–3.96 (m, 1H), 3.26–3.17 (m, 1H), 3.05–2.99 (m, 1H), 2.86–2.83 (m, 0.58H), 2.73–2.63 (m, 2H), 2.50–2.37 (m, 2H), 1.53–1.50 (m, 0.67H), 1.42–1.34 (m, 1H), 1.23–1.20 (m, 1.61H), 1.03–0.86 (m, 1H), 0.62–0.60 (m, 0.58H); ^{13}C NMR (151 MHz, CD_3OD) δ 169.06, 168.94, 154.09, 153.23, 152.90, 151.60, 151.58, 150.62, 150.54, 148.25, 138.00, 137.77, 137.61, 137.51, 132.90, 132.83, 131.69, 129.96, 129.08, 127.50, 127.22, 125.22, 124.88, 124.69, 114.50, 48.20, 47.12, 44.17, 43.61, 42.14, 38.74, 37.03, 36.90, 32.84, 32.75, 32.11; ESI-HR-MS: (m/z) calcd. for $\text{C}_{30}\text{H}_{32}\text{N}_5\text{O}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 542.2220, found 542.2219.

Synthesis of 4-(N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)sulfamoyl)benzoic acid (**C-4-47**). Following the procedure for the synthesis of **14** from **13**, **C-4-47** was prepared from **76** (0.50 g, 0.855 mmol) using NaOH (68 mg, 1.71 mmol) dissolved in H_2O (0.12 mL) in MeOH (4 mL), followed by acidification by concentrated HCl (0.14 mL). White solid, 0.20 g (41%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.94–8.85 (m, 3H), 8.14–8.08 (m, 4H), 7.94–7.92 (m, 4H), 7.69–7.66 (m, 1H), 7.18–7.16 (m, 3H), 7.02 (s, 2H), 3.77–3.40 (m, 2H), 3.12–3.02 (m, 2H), 2.59 (s, 4H), 1.40–1.12 (m, 4H); ^{13}C NMR (151 MHz, CD_3OD) δ 168.16, 168.00, 156.42, 152.14, 149.96, 145.45, 143.41, 137.84, 137.64, 135.57, 133.62, 131.76, 131.47, 129.09, 128.04, 127.54, 127.48, 126.69, 44.38, 41.89, 38.84, 37.31, 32.34, 31.40; ESI-HR-MS: (m/z) calcd. for $\text{C}_{31}\text{H}_{31}\text{N}_4\text{O}_5\text{S}$ ($[\text{M}+\text{H}]^+$) 571.2010, found 571.2008.

Synthesis of N-((1-([2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)-4-(hydroxymethyl)benzenesulfonamide (**C-4-48**). Following the procedure for the synthesis of **B9** from **B8**, **C-4-48** was prepared from **76** (0.50 g, 0.855 mmol) using LiAlH_4 (39 mg, 1.03 mmol) in dried THF (5 mL) at room temperature. Purification by column chromatography (EtOAc) gave **C-4-48**. White solid, 55 mg (12%). m.p. 125.4–126.7 °C. ^1H NMR (500

MHz, DMSO- d_6) δ 8.77 (d, J = 4.5 Hz, 1H), 8.66–8.64 (m, 2H), 7.84–7.75 (m, 3H), 7.57–7.51 (m, 7H), 7.18–7.16 (m, 3H), 7.06–6.96 (m, 2H), 5.45–5.41 (m, 1H), 4.61–4.58 (m, 2H), 3.86–3.70 (m, 1H), 3.26–3.12 (m, 1.69H), 2.97 (s, 1H), 2.79–2.62 (m, 2H), 2.39–2.32 (m, 2H), 1.45–1.23 (m, 2H), 1.12–1.04 (m, 1.62H), 0.81–0.52 (m, 1H); ^{13}C NMR (151 MHz, DMSO- d_6) δ 166.49, 166.32, 151.41, 151.27, 150.17, 149.87, 147.41, 145.89, 138.54, 136.84, 136.60, 135.88, 135.78, 131.55, 131.44, 130.53, 130.47, 127.82, 126.74, 126.45, 126.16, 123.67, 122.88, 122.71, 62.24, 46.78, 45.67, 42.32, 42.18, 41.42, 36.83, 36.75, 35.55, 35.50, 31.32, 30.79; ESI-HR-MS: (m/z) calcd. for $\text{C}_{31}\text{H}_{33}\text{N}_4\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 557.2217, found 557.2222.

Synthesis of *tert*-butyl 4-(((3-aminophenyl)sulfonamido)methyl)-4-benzylpiperidine-1-carboxylate (**77**). Following the procedure for the synthesis of **10** from **9**, **77** was prepared from **75** to **47** (2.50 g, 5.11 mmol) using 10% Pd/C (0.25 g) in MeOH (25 mL). Column chromatography (EtOAc/PE = 1/2 by v/v) gave **77**. White solid, 2.04 g (87%). m.p. 159.1–160.3 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 7.44 (t, J = 6.3 Hz, 1H), 7.23–7.15 (m, 4H), 7.10–7.08 (m, 2H), 6.99 (t, J = 2.0 Hz, 1H), 6.92–6.89 (m, 1H), 6.76–6.74 (m, 1H), 5.56 (s, 2H), 3.44–3.39 (m, 2H), 3.16–3.14 (m, 2H), 2.62–2.61 (m, 4H), 1.35 (s, 9H), 1.33–1.30 (m, 2H), 1.22–1.17 (m, 2H); ^{13}C NMR (201 MHz, CDCl_3) δ 154.92, 147.56, 140.21, 136.68, 130.47, 130.13, 128.28, 126.58, 118.93, 116.32, 112.66, 79.54, 47.30, 42.27, 39.81, 38.84, 36.06, 32.18, 28.48; ESI-HR-MS: (m/z) calcd. for $\text{C}_{24}\text{H}_{33}\text{N}_3\text{NaO}_4\text{S}$ ($[\text{M}+\text{Na}]^+$) 482.2084, found 482.2084.

Synthesis of *tert*-butyl 4-(((3-acetamidophenyl)sulfonamido)methyl)-4-benzylpiperidine-1-carboxylate (**78**). Compound **78** was prepared according to General Procedure 1 from **77** (1.50 g, 5.11 mmol) using AcCl (0.31 g, 3.91 mmol) and Et_3N (0.99 g, 9.78 mmol) in dried CH_2Cl_2 (15 mL). Purification by column chromatography (EtOAc/PE = 1/1, by v/v) gave **78**. White foam, 1.27 g (78%). ^1H NMR (500 MHz, DMSO- d_6) δ 10.25 (s, 1H), 8.15 (s, 1H), 7.76–7.74 (m, 1H), 7.66 (t, J = 6.5 Hz, 1H), 7.54–7.50 (m, 1H), 7.48–7.46 (m, 1H), 7.21–7.16 (m, 3H), 7.10–7.08 (m, 2H), 3.43–3.38 (m, 2H), 3.15 (s, 2H), 2.64–2.62 (m, 4H), 2.07 (s, 3H), 1.35 (s, 9H), 1.33–1.30 (m, 2H), 1.22–1.17 (m, 2H); ^{13}C NMR (201 MHz, CDCl_3) δ 169.50, 155.09, 139.99, 139.51, 136.64, 130.51, 129.88, 128.37, 126.71, 124.11, 122.31, 117.88, 79.80, 47.57, 42.28, 39.88, 38.93, 36.14, 32.13, 28.53, 24.55; ESI-HR-MS: (m/z) calcd. for $\text{C}_{26}\text{H}_{35}\text{N}_3\text{NaO}_5\text{S}$ ($[\text{M}+\text{Na}]^+$) 524.2190, found 524.2190.

Synthesis of N-(3-(N-((1-[2,4'-bipyridine]-3-carbonyl)-4-benzylpiperidin-4-yl)methyl)sulfamoyl)phenyl)acetamide (**C-4-49**). Following General Procedure 3, **78** (1.10 g, 2.19 mmol) was first treated with TFA (5.5 mL) in CH_2Cl_2 (3.3 mL), and the intermediate obtained was reacted with **7-TFA** (0.78 g, 2.63 mmol) using EDCI (1.05 g, 5.48 mmol), HOBT (22 mg, 0.164 mmol), and DIPEA (1.69 g, 13.1 mmol) in dried THF (11 mL). Purification by column chromatography (EtOAc) gave **C-4-49**. Pale yellow foam, 1.05 g (82%). ^1H NMR (500 MHz, DMSO- d_6) δ 10.27–10.24 (m, 1H), 8.77 (dd, J = 1.8 Hz and 4.8 Hz, 1H), 8.65–8.64 (m, 2H), 8.16 (s, 1H), 7.84–7.65 (m, 3H), 7.58–7.50 (m, 4H), 7.47–7.45 (m, 1H), 7.18–7.17 (m, 3H), 7.06–6.97 (m, 2H), 3.83–3.69 (m, 1H), 3.26–3.14 (m, 1H), 2.97 (s, 1H), 2.82–2.63 (m, 2H), 2.57–2.56 (m, 1H), 2.44–2.33 (m, 1.46H), 2.07 (s, 3H), 1.45–1.23 (m, 2H), 1.14–1.05 (m, 1.58H), 0.85–0.53 (m, 1H); ^{13}C NMR (201 MHz, CDCl_3) δ 169.89, 169.43, 167.56, 167.51, 151.85, 151.32, 150.71, 150.48, 149.96, 149.39, 147.43, 146.39, 140.15, 139.85, 139.55, 139.50, 136.54, 136.22, 135.95, 131.59, 131.42, 130.53, 130.48, 130.42, 130.26, 129.75, 128.37, 128.35, 126.73, 124.27, 124.12, 124.01, 123.92, 123.61, 123.34, 121.96, 121.22, 117.79, 47.75, 46.28, 42.85, 42.81, 42.38, 40.63, 37.59, 37.52, 36.18, 35.99, 31.24, 30.95, 24.36, 24.26; ESI-HR-MS: (m/z) calcd. for $\text{C}_{32}\text{H}_{34}\text{N}_5\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 584.2326, found 584.2328.

3.2. In Vitro CYP46A1 Inhibition

Chemical Materials: The chemicals used in this assay were obtained commercially: terfenadine (Sigma-Aldrich, T9652, Shanghai, China), tolbutamide (Sigma-Aldrich, T0891, Shanghai, China), buspirone (MedChemExpress, HY-B1115A, Shanghai, China), KH_2PO_4

(Shanghai Titanchem, 7778-77-0, Shanghai, China), NADPH (ACROS, 328742500, Shanghai, China), and testosterone (Adamas Reagent, 171265, Shanghai, China).

Study Procedure: Recombinant human CYP46A1R bacosomes (Cypex, 1000 nM) were incubated with testosterone (15 μ M as substrate) and a series of test compounds across a seven-point concentration range (0, 0.31, 2.44, 19.5, 156, 1250, 10,000 nM) in 50 mM KH_2PO_4 buffer (pH 7.4) in a 96-deep well plate. The reaction mixture was incubated at 38 °C for 10 min after initiation with 5 mM NADPH and was then terminated with an MeCN quenching solution containing terfenadine, buspirone, and tolbutamide as internal standards. Following centrifugation, the supernatants were collected for LC-MS/MS analysis.

LC-MS/MS Conditions: The LC-MS/MS analysis was performed on an API 5500 mass spectrometer in positive ESI mode with unit resolution for both Q1 and Q3. Chromatographic separation used a Kinetex Polar C_{18} column (2.6 μ m, 2.1 $\times$ 50 mm) with a 3 min gradient at a flow rate of 0.7 mL/min, where mobile phase A was 0.1% formic acid in water and mobile phase B was 0.1% formic acid in acetonitrile. Key monitored multiple reaction monitoring (MRM) transitions included terfenadine (472.4/436.4), tolbutamide (271.025/91), 16 β -hydroxytestosterone (305.203/97.1 and 305.203/109.2), and buspirone (386.2/122).

Calculation: The enzyme activity for each concentration was calculated as the percentage of the substrate metabolite peak area ratio at a given concentration (0, 0.31, 2.44, 19.5, 156, 1250, 10,000 nM) relative to the peak area ratio at the zero-concentration control (0 nM). Correspondingly, the inhibition percentage was derived as follows: Inhibition (%) = 100% – Enzyme Activity (%). The half-maximal inhibitory concentration (IC_{50}) values were subsequently determined by analyzing the concentration–response curve using nonlinear regression in GraphPad Prism software (version 5.03, GraphPad Software, Inc., Boston, MA, USA).

3.3. *In Vitro* Inhibitory Activities of Target Compounds Against CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4

Chemical Materials: The study utilized pooled mixed-gender human liver microsomes (Corning, 452117, Suzhou, China). A panel of chemical inhibitors and substrates for specific CYP isoforms was obtained commercially from various vendors: terfenadine (Sigma-Aldrich, T9652, Shanghai, China), tolbutamide (Sigma-Aldrich, T0891, Shanghai, China), buspirone (MedChemExpress, HY-B1115A, Shanghai, China), phenacetin (Sigma-Aldrich, 101690303, Shanghai, China), diclofenac (MCE, HY-15036, Shanghai, China), mephentyoin (Glpbio, GC14486, Shanghai, China), dextromethorphan (Sigma-Aldrich, D9684-5G, Shanghai, China), midazolam (Shanghai yuanye Bio-Technology, PVJT-0H9Z, Shanghai, China), K_2HPO_4 (SCR, 20032117, Shanghai, China), and NADPH (ABCONE, N99640-100MG, Shanghai, China).

Study Procedure: The incubation was automated on a TECAN Fluent 780 workstation. A liver microsome working solution containing a 5-in-1 substrate cocktail (phenacetin, diclofenac, mephentyoin, dextromethorphan, and midazolam) was pre-incubated at 38 °C for 7 min. Test compounds were then added at six non-zero concentrations (0, 0.049, 0.20, 0.78, 3.1, 12.5, 50 μ M). The reaction was initiated with 5 mM NADPH and incubated at 38 °C for 10 min before termination with an MeCN quenching solution containing terfenadine, tolbutamide, and buspirone as internal standards. Following centrifugation, the supernatants were collected for LC-MS/MS analysis.

LC-MS/MS Conditions: Analysis was performed on an AB Sciex API 5500 mass spectrometer (AB SCIEX, Singapore) in positive ESI mode. Chromatographic separation used a Kinetex Polar C_{18} column (2.6 μ m, 2.1 $\times$ 50 mm, Phenomenex, Torrance, CA, USA) with a 2.5 min gradient of 0.1% formic acid in water (mobile phase A) and 0.1% formic acid in acetonitrile (mobile phase B) at a flow rate of 0.7 mL/min. Analytes were monitored via specific MRM transitions: acetaminophen (metabolite of phenacetin; 152.1/110.0),

4'-hydroxydiclofenac (metabolite of diclofenac; 312.1/230.0), 4'-hydroxymephenytoin (metabolite of mephenytoin; 235.0/150.0), dextrorphan (metabolite of dextromethorphan; 258.2/199.1), and 1'-hydroxymidazolam (metabolite of midazolam; 342.1/203.0).

Calculation: The enzyme activity for each compound concentration was calculated as the percentage of the substrate metabolite peak area ratio at a given concentration (0, 0.049, 0.20, 0.78, 3.1, 12.5, 50 μ M) relative to the peak area ratio at the zero-concentration control (0 nM). Correspondingly, the inhibition percentage was derived as follows: Inhibition (%) = 100% – Enzyme Activity (%). The half-maximal inhibitory concentration (IC₅₀) values were subsequently determined by analyzing the concentration–response curve using nonlinear regression in GraphPad Prism software (version 5.03, GraphPad Software, Inc., Boston, MA, USA).

4. Conclusions

In conclusion, three series of soticlestat derivatives were designed and evaluated for their in vitro CYP46A1 inhibitory activity. Among the designed series, Series A, B, and subseries C-1 to C-3 were associated with significantly decreased CYP46A1 inhibitory activity, while a lot of compounds with benzenesulfonamide moiety (subseries C-4) as an isostere of OH in soticlestat were discovered to possess CYP46A1 inhibitory activities comparable to that of soticlestat. The most potent compound was **C-4-38**, with an IC₅₀ of 13.6 nM, compared with an IC₅₀ of 18.0 nM for soticlestat. An interesting flat SAR profile was also observed in some compounds in subseries C-4. Although four selected compounds displayed low selectivity toward CYP3A4/5 inhibition, which will be optimized in future work to minimize potential drug–drug interactions, the findings in the present study still remain very valuable for the design of potent CYP46A1 inhibitors.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules31030460/s1>, the copies of all the ¹H NMR, ¹³C NMR, ¹⁹F NMR, ³¹P NMR, and HR-MS spectra of synthesized intermediates and target compounds.

Author Contributions: Conceptualization, J.W. and G.Z.; methodology, X.H., W.H., J.W. and G.Z.; formal analysis, X.H., W.H., J.W. and G.Z.; investigation, X.H., W.H., X.L., H.Z., Y.H., J.W. and G.Z.; resources, G.Z.; data curation, X.H., W.H. and G.Z.; writing—original draft preparation, X.H., W.H. and G.Z.; writing—review and editing, J.W. and G.Z.; supervision, J.W. and G.Z.; project administration, G.Z.; funding acquisition, G.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Special Funds of National Natural Science Foundation of China, grant number 82441046, the Zhongshan Municipal Natural Science Foundation, grant number 2023B2019, and the Creative Research Group of Zhongshan City (Lingnan Pharmaceutical Research and Innovation team), grant number CXTD2022011.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding authors.

Acknowledgments: The authors are grateful to the assistance from Yanlan Qin for the collection of ESI-HR-MS data.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AD	Alzheimer’s disease
BBB	blood–brain barrier
CH24H	cholesterol 24-hydroxylase
dba	dibenzylideneacetone
DEE	developmental and epileptic encephalopathy
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DS	Dravet syndrome
EAAT2	excitatory amino acid transporter 2
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ESI	electrospray ionization
HOBT	1-hydroxybenzotriazole
HR-MS	high-resolution mass spectrometry
HTD	Huntington’s disease
IC ₅₀	Half-maximal inhibitory concentration
LDA	lithium diisopropylamide
LGS	Lennox–Gastaut syndrome
LiHMDS	lithium bis(trimethylsilyl)amide
<i>m</i> CPBA	<i>m</i> -chloroperoxybenzoic acid
NMDA	N-methyl-D-aspartate
PD	Parkinson’s disease
PE	petroleum ether
PIFA	phenyliodine (III) bis(trifluoroacetate)
TBAF	tetra- <i>n</i> -butylammonium fluoride
TFA	trifluoroacetic acid
TLC	thin-layer chromatography
TMS	trimethylsilyl
Xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

References

- Asadi-Pooya, A.A. Lennox-Gastaut syndrome: A comprehensive review. *Neurol. Sci.* **2018**, *39*, 403–414. [[CrossRef](#)]
- Sullivan, J.; Benítez, A.; Roth, J.; Andrews, J.S.; Shah, D.; Butcher, E.; Jones, A.; Cross, J.H. A systematic literature review on the global epidemiology of Dravet syndrome and Lennox-Gastaut syndrome: Prevalence, incidence, diagnosis, and mortality. *Epilepsia* **2024**, *65*, 1240–1263. [[CrossRef](#)]
- Vasquez, A.; Wirrell, E.C. Prevalence, healthcare resource utilization and mortality of Lennox-Gastaut syndrome: Retrospective linkage cohort study. *Seizure-Eur. J. Epilep.* **2021**, *91*, 159–166. [[CrossRef](#)]
- Vasquez, A.; Wirrell, E.C. State-of-the-art management of Dravet syndrome. *Dev. Med. Child. Neurol.* **2025**, *67*, 1527–1535. [[CrossRef](#)] [[PubMed](#)]
- Zhu, Z.; Zhang, Z.; Xiao, W.; Wang, C.; Liang, R. Efficacy and safety of pharmacological and non-pharmacological therapies in Lennox-Gastaut syndrome: A systematic review and network meta-analysis. *Front. Pharmacol.* **2025**, *16*, 1522543. [[CrossRef](#)] [[PubMed](#)]
- Samanta, D.; Nath, M. Current and emerging pharmacotherapies in Lennox-Gastaut syndrome. *Expert Opin. Pharmacother.* **2025**, *26*, 1133–1147. [[CrossRef](#)]
- Moutinho, M.; Nunes, M.J.; Rodrigues, E. Cholesterol 24-hydroxylase: Brain cholesterol metabolism and beyond. *Biochim. Biophys. Acta* **2016**, *1861*, 1911–1920. [[CrossRef](#)] [[PubMed](#)]
- Alavi, M.S.; Karimi, G.; Ghanimi, H.A.; Roohbakhsh, A. The potential of CYP46A1 as a novel therapeutic target for neurological disorders: An updated review of mechanisms. *Eur. J. Pharmacol.* **2023**, *949*, 175726. [[CrossRef](#)]
- Pikuleva, I.A.; Cartier, N. Cholesterol hydroxylating cytochrome P450 46A1: From mechanisms of action to clinical applications. *Front. Aging Neurosci.* **2021**, *13*, 696778. [[CrossRef](#)]
- Petrov, A.M.; Pikuleva, I.A. Cholesterol 24-hydroxylation by CYP46A1: Benefits of modulation for brain diseases. *Neurotherapeutics* **2019**, *16*, 635–648. [[CrossRef](#)]

11. Tian, G.; Kong, Q.; Lai, L.; Ray-Chaudhury, A.; Lin, C.-L.G. Increased expression of cholesterol 24S-hydroxylase results in disruption of glial glutamate transporter EAAT2 association with lipid rafts: A potential role in Alzheimer's disease. *J. Neurochem.* **2010**, *113*, 978–989. [\[CrossRef\]](#)
12. Paul, S.M.; Doherty, J.J.; Robichaud, A.J.; Belfort, G.M.; Chow, B.Y.; Hammond, R.S.; Crawford, D.C.; Linsenbardt, A.J.; Shu, H.J.; Izumi, Y.; et al. The major brain cholesterol metabolite 24(S)-hydroxycholesterol is a potent allosteric modulator of N-methyl-D-aspartate receptors. *J. Neurosci.* **2013**, *33*, 17290–17300. [\[CrossRef\]](#)
13. Koike, T.; Yoshikawa, M.; Ando, H.K.; Farnaby, W.; Nishi, T.; Watanabe, E.; Yano, J.; Miyamoto, M.; Kondo, S.; Ishii, T.; et al. Discovery of soticlestat, a potent and selective inhibitor for cholesterol 24-hydroxylase (CH24H). *J. Med. Chem.* **2021**, *64*, 12228–12244. [\[CrossRef\]](#)
14. Zhang, L.; Jiang, N.; Wang, C. Efficacy, safety, and tolerability of soticlestat (TAK-935) as adjunctive therapy in pediatric patients with dravet syndrome and Lennox-Gastaut syndrome: A meta-analysis of 3 randomized controlled trials. *Front. Pharmacol.* **2025**, *16*, 1586098. [\[CrossRef\]](#)
15. Nishi, T.; Metcalf, C.S.; Fujimoto, S.; Hasegawa, S.; Miyamoto, M.; Sunahara, E.; Watanabe, S.; Kondo, S.; White, H.S. Anticonvulsive properties of soticlestat, a novel cholesterol 24-hydroxylase inhibitor. *Epilepsia* **2022**, *63*, 1580–1590. [\[CrossRef\]](#)
16. Jiang, S.; Yuan, J.; Qin, Y.; Luo, Y.; Jin, Z.; Zhao, G.; Ti, H. A concise, practical chiral resolution approach of racemic (E)-4,4-dimethyl-1-(4-nitrophenyl)pent-1-en-3-ol to its both enantiomers via strategy of diastereomeric ester formation and crystallization using both N-Boc-D- and N-Boc-L-phenylglycines as chiral auxiliaries. *Chem. Res. Chin. Univ.* **2024**, *40*, 1096–1105. [\[CrossRef\]](#)
17. Wu, Y.; Jin, Z.; Liu, Y.; Huang, W.; Zhao, G. Design, synthesis and bioactivity of NYX-2925 L-proline derivatives as N-methyl-D-aspartate (NMDA) receptor partial agonists. *Chin. J. Org. Chem.* **2024**, *44*, 1247–1263. [\[CrossRef\]](#)
18. Bloomfield, A.J.; Herzon, S.B. Room temperature, Palladium-mediated P-arylation of secondary phosphine oxides. *Org. Lett.* **2012**, *14*, 4370–4373. [\[CrossRef\]](#)
19. Louvel, J.; Guo, D.; Agliardi, M.; Mocking, T.A.M.; Kars, R.; Pham, T.P.; Xia, L.; de Vries, H.; Brussee, J.; Heitman, L.H.; et al. Agonists for the adenosine A1 receptor with tunable residence time. A case for nonribose 4-amino-6-aryl-5-cyano-2-thiopyrimidines. *J. Med. Chem.* **2014**, *57*, 3213–3222. [\[CrossRef\]](#) [\[PubMed\]](#)
20. Khatoon, H.; Abdulmalek, E. A focused review of synthetic applications of Lawesson's reagent in organic synthesis. *Molecules* **2021**, *26*, 6937. [\[CrossRef\]](#) [\[PubMed\]](#)
21. Reznikova, K.; Hsu, C.; Schosser, W.M.; Gallego, A.; Beltako, K.; Pauly, F.; van der Zant, H.S.J.; Mayor, M. Substitution pattern controlled quantum interference in [2.2]paracyclophane-based single-molecule junctions. *J. Am. Chem. Soc.* **2021**, *143*, 13944–13951. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Yang, G.; Wu, H.; Gallarati, S.; Corminboeuf, C.; Wang, Q.; Zhu, J. Migrative carbofluorination of saturated amides enabled by Pd-based dyotropic rearrangement. *J. Am. Chem. Soc.* **2022**, *144*, 14047–14052. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Casimiro-Garcia, A.; Allais, C.; Brennan, A.; Choi, C.; Dower, G.; Farley, K.A.; Fleming, M.; Flick, A.; Frisbie, R.K.; Hall, J.; et al. Discovery of a series of pyrimidine carboxamides as inhibitors of Vanin-1. *J. Med. Chem.* **2022**, *65*, 757–784. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Huang, W.; Hu, X.; Lin, X.; Khan, M.; Qian, C.; Wu, J.; Meng, F.; Zhao, G. Conformational analysis of soticlestat, an inhibitor of CYP46A1 (CH24H), and its derivatives by variable-temperature nmr and computational methods. *Struct. Chem.* **2025**, *mboxemph36*, 1305–1329. [\[CrossRef\]](#)
25. Weltrowska, G.; Lemieux, C.; Chung, N.N.; Guo, J.J.; Wilkes, B.C.; Schiller, P.W. 'Carba'-carfentanil (trans isomer): A μ opioid receptor (MOR) partial agonist with a distinct binding mode. *Bioorg. Med. Chem.* **2014**, *22*, 4581–4586. [\[CrossRef\]](#)
26. Xing, X.; Zhao, K.; Li, Z.; Ye, N.; Zhao, N.; Guo, F.; Qiao, C.; Xu, G.; Parmentier, M.; Gallou, F.; et al. Micelle-enabled Hofmann rearrangement in water. *Org. Process Res. Dev.* **2024**, *28*, 2945–2950. [\[CrossRef\]](#)
27. Mast, N.; Norcross, R.; Andersson, U.; Shou, M.; Nakayama, K.; Bjorkhem, I.; Pikuleva, I.A. Broad substrate specificity of human cytochrome P450 46A1 which initiates cholesterol degradation in the brain. *Biochemistry* **2003**, *42*, 14284–14292. [\[CrossRef\]](#)
28. Damalanka, V.C.; Wildman, S.A.; Janetka, J.W. Piperidine carbamate peptidomimetic inhibitors of the serine proteases HGFA, matriptase and hepsin. *MedChemComm* **2019**, *10*, 1646–1655. [\[CrossRef\]](#)
29. Romito, D.; Kählig, H.; Tecilla, P.; Sossio, G.C.; Bonifazi, D. Double chalcogen bonding recognition arrays in solution. *Chem. Eur. J.* **2024**, *30*, e202401346. [\[CrossRef\]](#)
30. Bena, A.R.; Bakalbassis, E.G.; Sigalas, M.M.; Lykakis, I.N. One-pot synthetic approach to 3-carboxyl- and 3-ketopyridines in aqueous media. *J. Org. Chem.* **2023**, *88*, 8055–8068. [\[CrossRef\]](#)
31. Galli, U.; Mesenzani, O.; Coppo, C.; Sorba, G.; Canonico, P.L.; Tron, G.C.; Genazzani, A.A. Identification of a sirtuin 3 inhibitor that displays selectivity over sirtuin 1 and 2. *Eur. J. Med. Chem.* **2012**, *55*, 58–66. [\[CrossRef\]](#)
32. Stühr-Hansen, N. The tert-butyl moiety-A base resistant thiol protecting group smoothly replaced by the labile acetyl moiety. *Synth. Commun.* **2003**, *33*, 641–646. [\[CrossRef\]](#)
33. Zeng, X.; Wang, C.; Batsanov, A.S.; Bryce, M.R.; Gigon, J.; Urasinska-Wojcik, B.; Ashwell, G.J. Synthesis and properties of functionalized oligo(arylene) molecular wires with thiolated termini: Competing thiol-Au and nitro-Au assembly. *J. Org. Chem.* **2010**, *75*, 130–136. [\[CrossRef\]](#)

34. Spivey, A.C.; Shukla, L.; Hayler, J.F. Conjugate addition of 2- and 4-pyridylcuprates: An expeditious asymmetric synthesis of natural (-)-evoninic acid. *Org. Lett.* **2007**, *9*, 891–894. [[CrossRef](#)] [[PubMed](#)]
35. Cui, X.; Lai, W.; Wei, C.; Xu, K.; Li, J.; Li, B. Modular synthesis of [1]benzothieno [3,2-b][1] benzothiophenes via formation of C–S and C=C bonds. *Org. Lett.* **2025**, *27*, 9878–9883. [[CrossRef](#)] [[PubMed](#)]
36. Balieu, S.; Toutah, K.; Carro, L.; Chamoreau, L.-M.; Rousselière, H.; Courillon, C. Radical cyclization of ynamides into six- or eight-membered rings. Application to the synthesis of a protoberberine analog. *Tetrahedron Lett.* **2011**, *52*, 2876–2880. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.