Introduction

Metabolic syndrome is a cluster of factors associated with an increased risk of atherosclerotic cardiovascular disease and diabetes. The characteristics of metabolic syndrome include central obesity, insulin resistance, atherogenic dyslipidemia, and hypertension[1]. Recent investigations have indicated that glucocorticoid excess in tissues such as liver and adipose might contribute to the development of metabolic syndrome [2, 3]. Glucocorticoid hormones are important metabolic regulators. The major glucocorticoid in humans is cortisol. Cortisol concentration in target tissues is modulated by two tissue-specific enzymes: 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and type 2 (11β-HSD2). 11β-HSD1 converts inactive cortisone into receptor-active glucocorticoid cortisol, which is highly expressed in the liver, adipose tissue, and the central nervous system, whereas 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) converts cortisol into cortisone and is primarily expressed in the kidney, the colon, and other tissues (Figure 1)[4, 5]. Inhibition of 11β-HSD2 can lead to sodium retention, hypokalemia, and hypertension[4]; therefore, inhibitors should be selective for 11β-HSD1 over 11β-HSD2.

A potential role for 11β-HSD1 inhibitors in metabolic disease in vivo has been demonstrated using a transgenic mouse approach. Mice overexpressing 11β-HSD1 in adipose tissue showed metabolic syndrome-like phenotypes such as central obesity, glucose intolerance, and insulin resistance[6, 7]. In contrast, 11β-HSD1 deficient mice were resistant to the development of high-fat diet-induced obesity and exhibited improved insulin sensitivity and lipid profiles[6, 7]. These data suggest that 11β-HSD1 could be a drug target for the treatment of metabolic syndromes, such as type 2 diabetes.

In the past few years, a number of small molecule inhibitors of 11β-HSD1 have been discovered (Figure 2), and Incyte’s small molecule inhibitor INCB-13739 is currently in phase II clinical trials[10]. Work from our laboratories has demonstrated that 4-(phenylsulfonamido-methyl)nicotine and (phenylsulfonamido-methyl)thiazole as novel 11β-hydroxysteroid dehydrogenase type 1 inhibitors: synthesis and biological activities in vitro

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Aim: To design and synthesize a novel class of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors, featuring the (phenylsulfonamido-methyl)pyridine and (phenylsulfonamido-methyl)thiazole framework.

Methods: Our initial lead 4-(phenylsulfonamido-methyl)benzamides were modified. Inhibition of human and mouse 11β-HSD1 enzymatic activities by the new compounds was determined by a scintillation proximity assay (SPA) using microsomes containing 11β-HSD1.

Results: Sixteen new compounds (6a–6h, 7a–7h) were designed, synthesized and bioassayed. In dose-response studies, several compounds showed strong inhibitory activities with IC50 values at nanomolar or low nanomolar concentrations. Structure-activity relationships are also discussed with respect to molecular docking results.

Conclusion: This study provides two promising new templates for 11β-HSD1 inhibitors.

Keywords: 11β-hydroxysteroid dehydrogenase type 1; inhibitors; molecular modeling

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nylsulfonamidomethyl)benzamides (Figure 3) are inhibitors of 11β-HSD1 [unpublished data]. In particular, highly potent compounds are obtained when R1 is 3-Cl in combination with various secondary amines at the R2 position. As an extension of this work, the analogues (phenylsulfonamido-methyl)pyridine and (phenylsulfonamido-methyl)thiazole (Figure 3) were investigated.

**Materials and methods**

**Synthetic procedures**

(Phenylsulfonamido-methyl)pyridines and (phenylsulfonamido-methyl)thiazoles were prepared via the route shown in Scheme 1–3. Hydrogenation of the 6-cyanonicotinic acid (1) catalyzed by 10% Pd/C afforded 2 in excellent yields. Protection of the acid 2 using methyl ester by Fischer esterification with acidic methanol gave the key intermediate 3a, whereas 3b was prepared according to the four-step process described in the literature [11]. Sulfonation of the amino ester 3a or 3b using 3-chlorobenzenesulfonyl chloride in the presence of triethylamine afforded intermediate 4. Hydrolysis of ester 4 in methanol using potassium hydroxide gave carboxylic acid 5 in high yields. Final products 6 and 7 were obtained by treatment of intermediate acid 5 with various amines using 1-hydroxybenzotriazole and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride as amide-coupling reagents. The non-commercially available variants of N-substituted cycloheptanamine 8 were prepared according to methodologies described in the literature [12].

**Scintillation proximity assay (SPA)**

Inhibition of mouse or human 11β-HSD1 enzymatic activities was determined by the scintillation proximity assay (SPA) using microsomes containing 11β-HSD1 according to previous studies [13, 14]. Briefly, the full-length cDNAs of human and murine 11β-HSD1 were isolated from cDNA libraries provided by the NIH Mammalian Gene Collection and cloned into the pcDNA3 expression vector (Invitrogen, Carlsbad, Ca, USA) by PCR. HEK293 cells were transfected with the pcDNA3-derived expression plasmids and selected by cultivation in the presence of 700 µg/mL G418. Microsomal fractions overexpressing 11β-HSD1 were prepared from HEK293 cells stably transfected with 11β-HSD1 and used as the enzyme source for SPA. The assay was performed in a 96-well microtiter plate. Different concentrations of compound were added, followed by the addition of 80 µL of 50 mmol/L HEPES buffer, pH 7.4, containing 25 nmol/L [1,2-(n)3H]cortisone (Amersham, Buckinghamshire, UK) and 1.25 mmol/L NADPH. Reactions were initiated by the addition of the 11β-HSD1 enzyme preparation as microsomal fractions from HEK293 cells stably transfected with 11β-HSD1 and used as the enzyme source for SPA. The assay was performed in a 96-well microtiter plate. Different concentrations of compound were added, followed by the addition of 80 µL of 50 mmol/L HEPES buffer, pH 7.4, containing 25 nmol/L [1,2-(n)3H]cortisone (Amersham, Buckinghamshire, UK) and 1.25 mmol/L NADPH. Reactions were initiated by the addition of the 11β-HSD1 enzyme preparation as microsomal fractions from HEK293 cells in a final concentration of 80 µg/mL of 11β-HSD1. After incubation for 60 min at 37 °C, the reaction was stopped by the addition of 35 µL of 10 mg/mL protein A-coated SPA beads (GE, Piscataway, NJ, USA) suspended in Superblock® Blocking Buffer (Pierce, Rockford, IL) with 3 μg/mL of murine monoclonal cortisol antibody (East Coast Biologics, North Berwick, Maine, USA) and 314 µmol/L glycyrrhetinic acid (Sigma-Aldrich, St Louis, MO). The plates were incubated under plastic film on an orbital shaker for 120 min at room temperature. The [3H]cor-
tisol generated in the enzymatic reaction was captured by the beads and measured in a liquid scintillation counter equipped to read microplates. Percentage inhibition was calculated relative to an uninhibited control. Data were obtained from at least three independent experiments. IC₅₀ values were calculated using Prism Version 4 (GraphPad Software, San Diego, CA).

Molecular docking
Crystal structures of several human 11β-HSD1 complexes and one murine 11β-HSD1 complex were acquired from the Protein Data Bank. A structural alignment protocol within Discovery Studio³ was used to compare these structures. Finally, PDB entries 3CZR, 2IRW (human) and 1Y5R (murine) were chosen for the following docking study employing Schrödinger Glide⁴.

The NADPH cofactor observed in the PDB structure was retained to mimic the real inhibition process, forming a complex receptor with 11β-HSD1. Protein Preparation and Grid Preparation tools in Schrödinger Maestro were used for receptor preparation. A neutralization zone was defined around the ligand during the refinement process. The original location of small molecules in the published PDB structure was set as the binding site for Receptor Grid Generation. All compounds were docked in extra precision (XP) mode and output files were compiled from 50 poses with the highest G-score per ligand to ensure that a variety of binding modes were explored with high accuracy. Pose with RMSD values less than 0.5 Å were discarded as duplicates to simplify subsequent analysis.

Scheme 1. Reagents and conditions: (a) H₂, Pd/C, MeOH; (b) SOCl₂, MeOH, reflux; (c) 3-chlorobenzensulfonyl chloride, Et₃N, CH₂Cl₂; (d) 1 mol/L KOH, MeOH, reflux; (e) HOBt, EDCI, CH₂Cl₂.

Scheme 2. Reagents and conditions: (a) 3-chlorobenzensulfonyl chloride, Et₃N, CH₂Cl₂; (b) 1 mol/L KOH, MeOH, reflux; (c) HOBt, EDCI, CH₂Cl₂.

Scheme 3. Reagents and conditions: (a) i: Ti(OPr)i₄; ii: NaBCNH₃.
Results
Inhibitor design and synthesis
On the basis of the structure of 4-(phenylsulfonamidomethyl) benzamides, which were previously discovered in our laboratories to be 11β-HSD1 inhibitors, their analogues (phenylsulfonamido-methyl)nicotines and (phenylsulfonamido-methyl)thiazoles were designed and synthesized; their chemical structures are shown in Table 1. These compounds were synthesized according to the route outlined in Figure 4, and the details of the synthetic procedures are described in the Appendix.

Biological assay
The inhibitory properties of the synthesized molecules were evaluated in a scintillation proximity assay (SPA) with human and mouse 11β-HSD1 (from HEK293 cells transfected with a full-length pcDNA3-derived expression plasmid). For the primary assay, percentage inhibition of 11β-HSD1 was measured at a concentration of 1 μmol/L of each small molecule. The results are summarized in Table 1. To determine the exact potency of the compounds that exhibited significant inhibitory activities (percentage inhibition at 1 μmol/L >50%), eight compounds (6e–6h, 7e–7h) were further investigated in dose-response studies (Table 2).

Molecular modeling
In order to obtain insight into the possible binding mode, docking experiments were conducted using the Glide program. All compounds were docked into three X-ray crystal structures, 3CZR, 2IRW (human) and 1Y5R (murine). Several conformations were retained in a single docking output file. Almost all compounds showed a similar binding mode, which appeared in most poses with the highest G-score. The complex of 6f and 3CZR is shown as an example (Figure 4) to illustrate the general pose for the two series of 11β-HSD1 inhibitors. Two hydrogen bonds and a hydrophobic interaction were observed and are discussed in the following section.

Discussion
As shown in Table 1, the 11β-HSD1 inhibitory activities of (phenylsulfonamido-methyl)nicotines 6 and (phenylsulfonamido-methyl)thiazoles 7 followed a similar trend. When R2 was pyrrolidine, (2R,6S)-2,6-dimethylmorpholine, diethylam-
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Table 2. Determination of IC<sub>50</sub> of selected compounds.

| Compound          | Human IC<sub>50</sub> (nmol/L) | Mouse IC<sub>50</sub> (nmol/L) |
|-------------------|--------------------------------|--------------------------------|
| 6e                | -                              | 849±145                         |
| 7e                | 222±72                         | 1055±150                        |
| 6f                | 57±3                           | 45±6                            |
| 7f                | 6±1                            | 307±122                         |
| 6g                | 375±47                         | 80±29                           |
| 7g                | 78±16                          | 279±33                          |
| 6h                | 143±42                         | 24±6                            |
| 7h                | 84±10                          | 210±49                          |

In summary, two series of novel (phenylsulfonamido-methyl)nicotines and (phenylsulfonamido-methyl)thiazoles were synthesized. All of the compounds were evaluated in a scintillation proximity assay (SPA) against human and mouse 11β-HSD1. The hydrogen bond interactions between the amino position (f-h) may be attributed to an increase in electron density at the amide group, which may strengthen the hydrogen bond interaction. The hydrogen bond interaction with H-bond donor Tyr183 and the H-bond acceptor amide group. Increased activity exhibited by compounds with an alkyl group at the amino position (f-h) may be attributed to an increase in electron density at the amide group, which may strengthen the hydrogen bond interaction. In dose-response studies, several compounds showed prominent inhibitory activities with IC<sub>50</sub> values in the nanomolar or low nanomolar ranges. Molecular modeling studies for 6f were also performed to demonstrate the binding modes between the ligands and receptors; information gleaned from the models will aid in further lead optimization.

Appendix

Reagents were purchased from Lancaster, Acros and Shanghai Chemical Reagent Company and used without further purification. Analytical thin-layer chromatography (TLC) was performed with HSGF 254 (150-200 µm thickness, Yantai Huiyou Company, China). Yields were not optimized. 1H NMR spectral data were recorded in DMSO-d<sub>6</sub>, D<sub>2</sub>O or CDCl<sub>3</sub> on Varian Mercury 400 or 300 NMR spectrometer. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), or broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were obtained by electrospray and matrix-assisted laser desorption ionization (EI, ESI and MALDI) produced by Finnigan MAT-95, LCQ-DECA and IonSpec 4.7 Tesla spectrometers, respectively.

6-(Aminomethyl)nicotinic acid (2)

6-Cyanonicotinic acid (3g, 20 mmol) was added to a suspension of 10% Pd/C (300 mg) in MeOH (100 mL) and pressurized with 1 bar of hydrogen gas. The mixture was stirred at room temperature for 4 h. The precipitate was redissolved by the addition of water and the resulting mixture was filtered. The filtrate was evaporated to dryness to give 2 as a pale solid. Yield: 59%. 1H NMR (D<sub>2</sub>O, 400 MHz): δ 4.27 (s, 2H), 7.31 (m, 1H), 8.11 (m, 1H), 8.83 (m, 1H).

Methyl 6-(aminomethyl)nicotinate hydrochloride (3a)

6-(Aminomethyl)nicotinic acid 2 (1.5 g, 9.9 mmol) in MeOH (200 mL) was treated with SOCl<sub>2</sub> (2 mL) and refluxed at 70 °C overnight. The mixture was stirred at room temperature for 6 h. The reaction mixture was washed successively with 1 mol/L HCl (2×20 mL) and saturated NaHCO<sub>3</sub> (2×20 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was subjected to silica gel chromatography to give 3a as a yellow solid. Yield: 94%. 1H NMR (DMSO, 300 MHz): δ 3.89 (s, 3H), 4.29 (s, 2H), 7.64 (m, 1H), 8.13 (m, 1H), 8.34 (m, 1H), 9.08 (m, 1H).

Methyl 6-(3-chlorobenzenesulfonylamido)methyl)nicotinate (4a)

3-Chlorobenzenesulfonyl chloride (211 mg, 0.1 mmol) and Et<sub>3</sub>N (1 mL) were added to a suspension of methyl 6-(aminomethyl)nicotinate hydrochloride (239 mg, 0.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The mixture was stirred at room temperature for 6 h. The reaction mixture was washed successively with 1 mol/L HCl (2×20 mL) and saturated NaHCO<sub>3</sub> (2×20 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was subjected to silica gel chromatography to give 4a as a yellow solid. Yield: 67%. 1H NMR (CDCl<sub>3</sub>, 300 MHz): δ 3.96 (s, 3H), 4.36 (d, J=5.4 Hz, 2H), 7.27 (m, 1H), 7.37 (m, 1H), 7.47 (m, 1H), 7.73 (m, 1H), 7.81 (m, 1H), 8.22 (m, 1H), 9.05 (m, 1H).

Ethyl 2-((3-chlorobenzenesulfonylamidomethyl)thiazole-4-carboxylate (4b)

The compound was prepared according to the procedure for 4a using ethyl 2-(aminomethyl)thiazole-4-carboxylate hydrobromide. Yield: 63%. 1H NMR (CDCl<sub>3</sub>, 400 MHz): δ 1.37 (t, J=6.8 Hz, 3H), 4.36 (q, J=6.8 Hz, 2H), 4.53 (d, J=6.4 Hz, 2H), 5.79 (t, J=5.4 Hz, 1H), 7.42 (m, 1H), 7.52 (m, 1H), 7.73 (m, 1H), 7.81 (m, 1H), 8.09 (m, 1H).

6-((3-Chlorobenzenesulfonylamido)methyl)nicotinic acid (5a)

Methyl 6-((3-chlorobenzenesulfonylamido)methyl)nicotinate (210 mg, 0.62 mmol) was treated with 1 mol/L KOH (3 mL) and stirred at 60 °C for 4 h. The MeOH was removed under reduced pressure. The residue was neutralized to pH 7 with 1 mol/L HCl to give a white precipitate that was filtered to afford 5a as a white solid. Yield: 84%. 1H NMR (DMSO, 300 MHz): δ 4.20 (s, 2H), 7.42 (m, 1H), 7.52 (m, 1H), 7.62 (m, 2H), 7.67 (m, 1H), 8.13 (m, 1H), 8.84 (m, 1H).
2-[(3-Chlorophenylsulfonamido)methyl]thiazole-4-carboxylic acid (5b)

The compound was prepared according to the procedure for 5a using ethyl 2-[(3-chlorophenylsulfonamido)methyl]thiazole-4-carboxylate. Yield: 81%. $^1$H NMR (DMSO, 300 MHz): δ 4.38 (s, 2H), 7.58 (m, 1H), 7.72 (m, 3H), 8.35 (s, 1H).

3-Chloro-N-[(5-pyrrolidine-1-carbonyl)pyridin-2-yl]methyl benzenesulfonamide (6a)

To a suspension of 6-[(3-chlorophenylsulfonamido)methyl]nicotinic acid (30 mg, 0.09 mmol) in CH$_2$Cl$_2$ (10 mL) was added HOBt (14 mg, 0.1 mmol) and EDCI (31 mg, 0.16 mmol). After being stirred for 1 h, pyrrolidine (7.1 mg, 0.1 mmol) was added and the resulting mixture was stirred for an additional 12 h. The mixture was then washed with water (3×10 mL). The organic layers were dried with Na$_2$SO$_4$ and concentrated in vacuo. The residue was subjected to silica gel chromatography to give 6a as a white solid. Yield: 70%. $^1$H NMR (CDCl$_3$, 300 MHz): δ 1.11 (m, 3H), 1.21 (m, 3H), 3.19 (m, 2H), 3.52 (m, 2H), 4.38 (s, 1H), 7.40 (m, 2H), 7.51 (m, 1H), 7.75 (2H), 8.41 (m, 1H). LR MS (EI) m/z 379 (M$^+$), 315 (100%); HR MS (EI) m/z calc'd for C$_{10}$H$_8$SClNO$_3$ (M$^+$) 379.0757, found 379.0741.

3-Chloro-N-[(5-(2R,6S)-2,6-dimethylmorpholine-4-carbonyl)pyridin-2-yl]methyl benzenesulfonamide (6b)

Using the procedure described earlier for 6a using (2R,6S)-2,6-dimethylmorpholine, the title compound was obtained in 84% yield. $^1$H NMR (CDCl$_3$, 300 MHz): δ 1.12 (m, 3H), 1.24 (m, 3H), 2.56 (m, 1H), 2.81 (m, 1H), 3.38 (m, 1H), 3.59 (m, 2H), 4.67 (d, J=5.4 Hz, 2H), 6.07 (t, J=5.4 Hz, 2H), 7.23 (m, 1H), 7.38 (m, 1H), 7.47 (m, 1H), 7.74 (m, 1H), 7.76 (m, 1H), 7.85 (m, 1H), 8.61 (m, 1H). LR MS (EI) m/z 379 (M$^+$), 315 (100%); HR MS (EI) m/z calc'd for C$_{10}$H$_8$SClNO$_3$ (M$^+$) 379.0757, found 379.0741.

6-[(3-Chlorophenylsulfonamido)methyl]-N-cycloheptyl-N-methylthiazole-4-carboxamide (6c)

Using the procedure described earlier for 6a using cycloheptanamine, the title compound was obtained in 32% yield. $^1$H NMR (CDCl$_3$, 300 MHz): δ 0.69–1.94 (m, 17H), 3.05/3.25/3.45 (3×m, 3H), 4.36 (m, 2H), 6.38 (m, 1H), 7.36 (m, 1H), 7.43 (m, 1H), 7.51 (m, 1H), 7.72 (m, 2H), 7.88 (m, 1H), 8.45 (m, 1H). LR MS (EI) m/z 463 (M$^+$), 368 (100%); HR MS (EI) m/z calc'd for C$_{19}$H$_{18}$SClNO$_3$ (M$^+$) 463.1696, found 463.1694.

N-butyl-6-[(3-chlorophenylsulfonamido)methyl]-N-cycloheptyl-N-propionamidic acid (6d)

Using the procedure described earlier for 6a using N-butylcycloheptanamine, the title compound was obtained in 33% yield. $^1$H NMR (CDCl$_3$, 300 MHz): δ 0.74–2.05 (m, 19H), 3.07/3.32/3.45 (3×m, 3H), 4.39 (m, 2H), 6.40 (m, 1H), 7.40 (m, 1H), 7.51 (m, 1H), 7.75 (2H), 7.88 (m, 1H), 8.47 (m, 1H). LR MS (EI) m/z 477 (M$^+$), 134 (100%); HR MS (EI) m/z calc'd for C$_{19}$H$_{18}$SClNO$_3$ (M$^+$) 477.1853, found 477.1840.

3-Chloro-N-[(4-(pyrrolidine-1-carbonyl)thiazol-2-yl)methyl]benzenesulfonamide (7a)

Using the procedure described earlier for 6a using 5b and pyrrolidine, the title compound was obtained in 60% yield. $^1$H NMR (CDCl$_3$, 300 MHz): δ 1.87 (m, 4H), 3.58 (t, J=6.3 Hz, 2H), 3.72 (t, J=6.3 Hz, 2H), 4.48 (m, 2H), 6.34 (m, 1H), 7.40 (m, 1H), 7.52 (m, 1H), 7.74 (m, 1H), 7.88 (m, 1H), 8.79 (m, 1H). LR MS (EI) m/z 385 (M$^+$), 70 (100%); HR MS (EI) m/z calc'd for C$_{20}$H$_{18}$SClNO$_3$ (M$^+$) 385.0322, found 385.0326.

3-Chloro-N-[(4-((2R,6S)-2,6-dimethylmorpholine-4-carbonyl)thiazol-2-yl)methyl]benzenesulfonamide (7b)

Using the procedure described earlier for 6a using 5b and (2R,6S)-2,6-dimethylmorpholine, the title compound was obtained in 70% yield. $^1$H NMR (CDCl$_3$, 300 MHz): δ 1.15–1.82 (m, 6H), 3.30 (m, 2H), 3.71 (m, 2H), 4.31 (d, J=5.4 Hz, 2H), 6.10 (t, J=5.4 Hz, 1H), 7.23 (m, 1H), 7.37 (m, 1H), 7.43 (m, 1H), 7.65 (m, 1H), 7.73 (m, 1H), 8.47 (m, 1H). LR MS (EI) m/z 393 (M$^+$), 329 (100%); HR MS (EI) m/z calc'd for C$_{20}$H$_{18}$SClNO$_3$ (M$^+$) 393.0914, found 393.0895.

6-[(3-Chlorophenylsulfonamido)methyl]-N-cycloheptylthiazole-4-carboxamide (7c)

Using the procedure described earlier for 6a using 5b and diethylamine, the title compound was obtained in 69% yield. $^1$H NMR (CDCl$_3$, 300 MHz): δ 1.11 (m, 6H), 3.46 (m, 4H), 4.43 (m, 2H), 4.38 (m, 2H), 6.42 (m, 1H), 6.56 (m, 1H), 7.35 (m, 2H), 7.47 (m, 1H), 7.73 (m, 1H), 7.79 (m, 1H), 8.12 (m, 1H), 8.89 (m, 1H). LR MS (EI) m/z 421 (M$^+$), 357 (100%); HR MS (EI) m/z calc'd for C$_{16}$H$_{26}$SClNO$_3$ (M$^+$) 421.1224, found 421.1209.

6-[(3-Chlorophenylsulfonamido)methyl]-N-cycloheptyl-N-methylthiazole-4-carboxamide (7d)

Using the procedure described earlier for 6a using N-methylcycloheptanamine, the title compound was obtained in 32% yield. $^1$H NMR (CDCl$_3$, 300 MHz): δ 1.24–1.88 (m, 12H), 2.80/2.97 (2×s, 3H), 3.51/4.52 (2×m, 1H), 4.35 (m, 2H), 6.35/6.47 (2×m, 1H), 7.34 (m, 1H), 7.39 (m, 1H), 7.49 (m, 1H), 7.69 (m, 2H), 7.85 (m, 1H), 8.48 (m, 1H). LR MS (EI) m/z 435 (M$^+$), 340 (100%); HR MS (EI) m/z calc'd for C$_{18}$H$_{28}$SClNO$_3$ (M$^+$) 435.1383, found 435.1391.

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3-Chloro-N-[(4-{piperidine-1-carbonyl}thiazol-2-yl)methyl]benzenesulfonamide (7d)

Using the procedure described earlier for 6a using 5b and piperidine, the title compound was obtained in 62% yield. 

\[ \text{HR MS (EI) } m/z 441.0948, \text{ found } 441.0961. \]

3-Chloro-N-[(4-{piperidine-1-carbonyl}thiazol-2-yl)methyl]thiazole-4-carboxamide (7f)

Using the procedure described earlier for 6a using 5b and thiazole-4-carboxamide, the title compound was obtained in 26% yield. 

\[ \text{HR MS (EI) } m/z 427.0791, \text{ found } 427.0792. \]

2-{[3-chlorophenylsulfonamido]methyl}-N-cycloheptylthiazole-4-carboxamide (7g)

Using the procedure described earlier for 6a using 5b and cycloheptanamine, the title compound was obtained in 58% yield. 

\[ \text{HR MS (EI) } m/z 416.1052, \text{ found } 416.1051. \]

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Author contribution

Jian-hua SHEN and Ying LENG designed the research; Xu ZHANG, Yang ZHOU, Yu SHEN, and Li-DU performed the experiments; Xu ZHANG and Jun-hua CHEN analyzed data; Xu ZHANG and Yang ZHOU wrote the manuscript.

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