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Synthesis of (*R*) and (*S*)-3-Chloro-5-(2,4-dimethylpiperazin-1-yl)-4*H*-1,2,6-thiadiazin-4-ones

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Abstract: The reaction of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one with (*R*) and (*S*)-1,3-dimethylpiperazines (1 equiv), in THF, at ca. 20 °C gives (*R*) and (*S*)-3-chloro-5-(2,4-dimethylpiperazin-1-yl)-4*H*-1,2,6-thiadiazin-4-ones in 70% and 68% yields, respectively. The new compounds were fully characterized.

Keywords: substitution; heterocycle; thiadiazine; piperazine; chirality

1. Introduction

Piperazines are important saturated nitrogen containing heterocycles and appear in a number of clinically used pharmaceuticals [1]. Among the nitrogen-containing heterocycles, piperazines rank as third in the most frequently used U.S. FDA-approved drugs [2], while other uses include the production of polyamide plastics and in the capture of CO_2 [3]. Examples of piperazine-containing drugs include the antibiotic ciprofloxacin, the erectile dysfunction drug sildenafil, and the anti-cancer BCR-ABL and src tyrosine kinase inhibitor bosutinib (SKI-606) [4] (Figure 1).

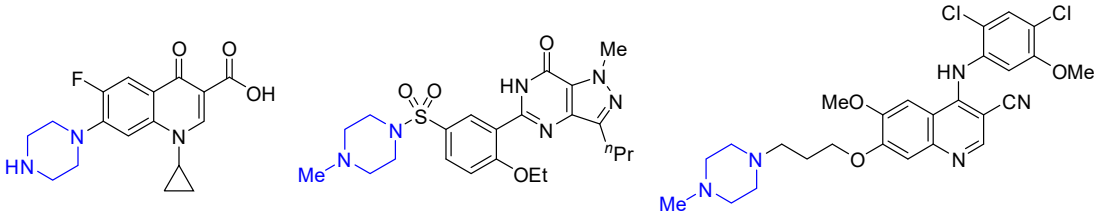


Figure 1. Piperazine-containing drugs.

The incorporation of an asymmetric 3-methyl substituent to the piperazine moiety can improve the biological activity of a compound and enhance its physicochemical characteristics. There are many examples in the literature of 3-methylpiperazines exhibiting anti-cancer activity [5], or acting as antiplatelet agents [6], among others.

The introduction of 3-methylpiperazine in the design of kinase inhibitors offers another route to enhance potency on target and selectivity. While the main purpose of the added methyl group is to act as a steric handle to increase the torsion between adjacent ring systems on the solvent front of the ATP-binding pocket, it can also be used to probe a pocket in the active site. The 3-methylpiperazine has

similar properties and uses to the 3-methylmorpholine substituent commonly used in kinase inhibitor design [7].

There are numerous examples of compounds where the 3-methylpiperazine substituent has had a pronounced effect on the overall profile of the compound (Figure 2) [5,8,9]. In the case of Talmapimod (SCIO-469), the incorporation of a 3-methylpiperazine into the structure helped reduce the metabolism of an adjacent benzyl group [8]. While in the case of a PAK4 inhibitor program that investigated compounds **1-3**, the methyl group on the 3-methylpiperazine helped improve the compounds' selectivity towards PAK4 over closely related PAK1 [5]. In a similar manner, the introduction of the *gem*-dimethylpiperazine moiety in a PI3K program (compound **4**) enabled selectivity over family members for the PI3Kδ isoform [9,10].

The methyl group of the 3-methylpiperazine can also be used to probe narrow-band activity profiles in any medicinal chemistry program. This methyl scanning method was applied by Berlex Biosciences to screen an ADP receptor ($P2Y_{12}$) antagonist hit [6]. The introduction of a methyl group is not always beneficial and the precise stereochemistry can be critical. While the steric effects can be achieved by other methods, the methyl group remains the most muted modification that provides substantial compound property improvements with a limited impact on ligand efficiency.

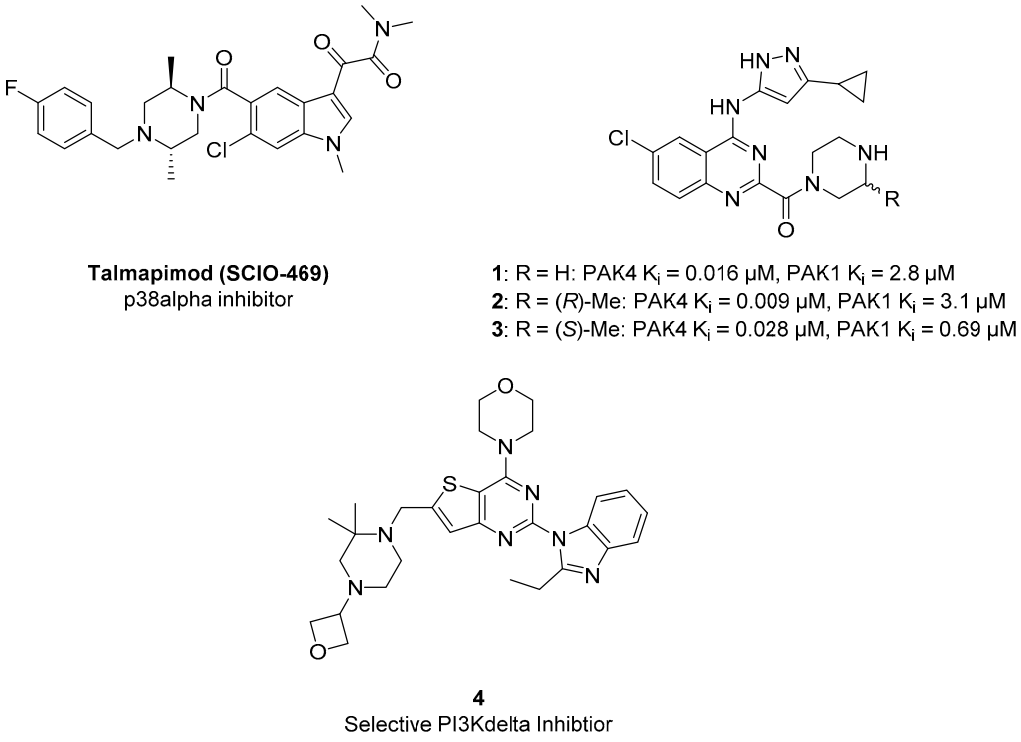
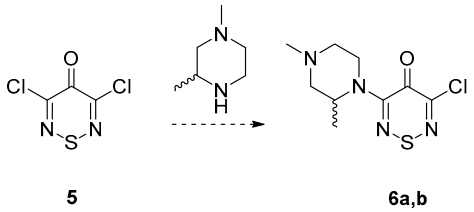


Figure 2. 3-Methylpiperazine-containing pre-clinical kinase inhibitors.

Our interest in the 1,3-dimethylpiperazine moiety is part of our ongoing effort to investigate the biological activity of novel 1,2,6-thiadiazines. Non-S-oxidized 1,2,6-thiadiazines are relatively unexplored heterocycles that have applications as organic photovoltaics (OPVs) [11], liquid crystals [12], plant protectants [13–17], and potential anticancer agents [18]. The chemistry of non-S-oxidized 1,2,6-thiadiazines has recently been reviewed [19]. Currently, we are developing a series of new 1,2,6-thiadiazine building blocks to expand our library of drug-like compounds with potential kinome selectivity profiles. For this work, we investigated the 3-methylmorpholine moiety as a substituent on 4*H*-1,2,6-thiadiazin-4-one [7]. In continuation of this work, we decided to investigate the 1,3-dimethylpiperazine moiety, which we planned to introduce by a selective nucleophilic displacement of one chloride of dichlorothiadiazinone **5** by (*R*) and (*S*)-1,3-dimethylpiperazine to yield

3-methylmorpholine-substituted thiadiazines **6a** and **6b**, respectively (Scheme 1). This displacement can occur under mild conditions owing to the electrophilic nature of the starting thiadiazine.

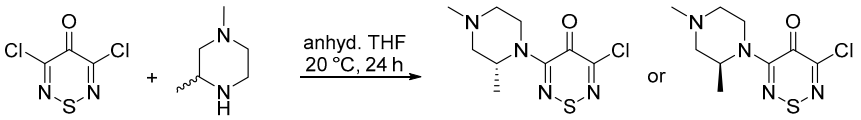


5 **6a,b**

Scheme 1. Planned synthesis of 1,3-dimethylpiperazine-substituted thiadiazines **6a** and **6b**.

2. Results and Discussion

We reacted 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**5**) [20] with 1 equiv. of 1,3-dimethylpiperazines in anhydrous tetrahydrofuran (THF), at 20 °C. The dibasic nature of piperazines means that no extra base or excess of piperazine reagent is required. Dilution of the reaction mixture with dichloromethane (DCM) saturated in ammonia, followed by column chromatography, led to the isolation of the desired products **6a** and **6b** as yellow oils in 70% and 68% yields, respectively (Scheme 2, see Supplementary Materials for NMR spectra). Compared to the analogous 3-methylmorpholine derivatives [7], the ^{1}H NMR spectra of the products **6a** and **6b** display increased line broadening, which can be attributed to decreased free rotation of the piperazine ring owing to a greater electron release into the thiadiazine. Similar hindered rotation phenomena of thiadiazines bound to secondary cyclic amines have been reported [21]. The optical rotation data showed that the two products were indeed enantiomers ($[\alpha]_D^{20}$ +65 and −64, respectively, for **6a** and **6b**, see Materials and Methods).



5 *R* or *S* (2 equiv) **6a**, 70% **6b**, 68%

Scheme 2. Synthesis of (*R*) and (*S*)-3-chloro-5-(2,4-dimethylpiperazin-1-yl)-4*H*-1,2,6-thiadiazin-4-one **6a** and **6b**.

We noted that the stereochemistry of the products **6a** and **6b** was attributed to the enantiomeric purity of the starting (*R*)- and (*S*)-1,3-dimethylpiperazines, $[\alpha]_D^{20}$ +6.5 (*c* 1, $CHCl_3$) and −6.0 (*c* 1, $CHCl_3$), respectively. To the best of our knowledge, and in particular, under the mild reaction conditions used for the above nucleophilic substitutions, chiral 1,3-dimethylpiperazines do not epimerize.

3. Materials and Methods

The reaction mixture was monitored by thin layer chromatography (TLC) using commercial glass-backed TLC plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. Tetrahydrofuran (THF) was distilled over CaH_2 before use. The UV-vis spectrum was obtained using a Perkin-Elmer Lambda-25 UV-vis spectrophotometer (Perkin-Elmer, Waltham, MA, USA) and inflections are identified by the abbreviation "inf". Optical rotation was determined in a JASCO P-2000 polarimeter. The IR spectrum was recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer (Shimadzu, Kyoto, Japan) with the Pike Miracle Ge ATR accessory (Pike Miracle, Madison, WI, USA) and strong, medium and weak peaks are represented by s, m and w, respectively. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 machine [at 500 and 125 MHz, respectively, (Bruker, Billerica, MA, USA)]. Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Attached proton test (APT) NMR studies were

used for the assignment of the ^{13}C peaks as CH_3, CH_2, CH, and Cq (quaternary). The MALDI-TOF mass spectrum (+ve mode) was recorded on a Bruker Autoflex III Smartbeam instrument (Bruker). 3,5-Dichloro-4*H*-1,2,6-thiadiazin-4-one (**5**) was prepared according to the literature procedure [20,22].

*(R)-3-Chloro-5-(2,4-dimethylpiperazin-1-yl)-4*H*-1,2,6-thiadiazin-4-one* (**6a**)

To a stirred mixture of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**5**) (91.5 mg, 0.500 mmol) in THF (1 mL) at ca. 20 °C, was added in one portion (*R*)-1,3-dimethylpiperazine (57.0 mg, 0.500 mmol). The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until complete consumption of the starting material (TLC, 24 h). DCM saturated with NH_3 (10 mL) was then added, the mixture adsorbed onto silica and chromatography (DCM/*t*-BuOMe 50:50) gave the *title compound* **6a** (91.7 mg, 70%) as a yellow oil; R_f 0.48 (DCM/*t*-BuOMe, 50:50); $[\alpha]_D^{20}$ +65 (*c* 1.0, $CHCl_3$); (found: C, 41.57; H, 4.93; N, 21.46. $C_9H_{13}ClN_4OS$ requires C, 41.46; H, 5.03; N, 21.49%); λ_{max}(DCM)/nm 269 (log ε 3.13), 313 (3.36), 322 (3.34), 410 (2.96); υ_{max}/cm^{-1} 2970w, 2941w, 2843w and 2793w (C-H), 1630s, 1495s, 1462m, 1433m, 1404w, 1383w, 1339w, 1323w, 1298m, 1281m, 1229m, 1194m, 1169w, 1146m, 1096w, 1076w, 1049m, 997w, 978w, 964w, 939w, 918w, 903m, 891m, 870m, 854m, 845m, 800m, 725m; δ_H(500 MHz; $CDCl_3$) 4.98 (1H, br s, C*H*N), 4.61 (1H, br s, C*H*N), 3.41 (1H, dd, *J* 11.1, 11.1, C*H*N), 2.98 (1H, br s, C*H*N), 2.82 (1H, d, *J* 9.2, C*H*N), 2.37 (4H, br s, C*H*N & NCH_3), 2.25 (1H, br s, C*H*N), 1.42 (3H, d, *J* 6.6, CHCH_3); δ_C(125 MHz; $CDCl_3$) 158.7 (Cq), 152.5 (Cq), 145.2 (Cq), 59.2 (CH_2N), 54.8 (CH_2N), 49.0 (CHN), 45.7 (NCH_3), 40.5 (CH_2N), 16.1 ($CHCH_3$); *m/z* (MALDI-TOF) 263 (MH^++2, 31%), 261 (MH^+, 77), 177 (100), 142 (21), 113 (37).

*(S)-3-Chloro-5-(2,4-dimethylpiperazin-1-yl)-4*H*-1,2,6-thiadiazin-4-one* (**6b**)

To a stirred mixture of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**5**) (91.5 mg, 0.500 mmol) in THF (1 mL) at ca. 20 °C, was added in one portion (*S*)-1,3-dimethylpiperazine (57.0 mg, 0.500 mmol). The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until complete consumption of the starting material (TLC, 24 h). DCM saturated with NH_3 (10 mL) was then added, the mixture adsorbed onto silica and chromatography (DCM/*t*-BuOMe 50:50) gave the *title compound* **6b** (89.2 mg, 68%) as a yellow oil; R_f 0.48 (DCM/*t*-BuOMe, 50:50); $[\alpha]_D^{20}$ −64 (*c* 1.0, $CHCl_3$); (found: C, 41.52; H, 4.88; N, 21.33. $C_9H_{13}ClN_4OS$ requires C, 41.46; H, 5.03; N, 21.49%); λ_{max}(DCM)/nm 270 (log ε 3.13), 313 (3.35), 321 (3.33), 410 (2.96); υ_{max}/cm^{-1} 2974w, 2940w, 2845w and 2795w (C-H), 1630s, 1495s, 1462m, 1433m, 1404w, 1383w, 1339w, 1323w, 1298m, 1281m, 1229m, 1194m, 1169w, 1146m, 1096w, 1076w, 1049m, 997w, 978w, 963w, 939w, 918w, 903m, 893m, 870m, 854m, 845m, 802m, 727m; δ_H(500 MHz; $CDCl_3$) 4.97 (1H, br s, C*H*N), 4.60 (1H, br s, C*H*N), 3.38 (1H, ddd, *J* 13.0, 13.0, 2.7, C*H*N), 2.95 (1H, d, *J* 11.0, C*H*N), 2.77 (1H, d, *J* 11.4, C*H*N), 2.38 (4H, br s, C*H*N & NCH_3), 2.21 (1H, dd, *J* 11.2, 11.2, C*H*N), 1.40 (3H, d, *J* 6.8, CHCH_3); δ_C(125 MHz; $CDCl_3$) 158.7 (Cq), 152.5 (Cq), 145.1 (Cq), 59.4 (CH_2N), 54.9 (CH_2N), 49.1 (CHN), 46.0 (NCH_3), 40.6 (CH_2N), 16.0 ($CHCH_3$); *m/z* (MALDI-TOF) 263 (MH^++2, 29%), 261 (MH^+, 100), 225 (30), 142 (50), 112 (10).

4. Conclusions

(*R*) and (*S*)-3-chloro-5-(2,4-dimethylpiperazin-1-yl)-4*H*-1,2,6-thiadiazin-4-ones were prepared in good yields from 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one. These compounds can be of interest to the medicinal and materials science sectors, this work provides a valuable route to these intermediates. The chemistry of these two aminothiadiazines will be further investigated to assess their potential applications.

Supplementary Materials: The following are available online, mol file, ^1H and ^{13}C NMR spectra.

Author Contributions: P.A.K., C.R.M.A. and A.S.K. conceived the experiments; A.S.K. designed and performed the experiments, analyzed the data and wrote the paper; P.A.K. and C.R.M.A. edited the paper. All authors have read and agreed to the published version of the manuscript.

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