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

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Abstract: Reaction of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one with (*R*) and (*S*)-3-methylmorpholines (2 equiv), in THF, at *ca.* 20 °C gave (*R*) and (*S*)-3-chloro-5-(3-methylmorpholino)-4*H*-1,2,6-thiadiazin-4-ones in 95 and 97% yields, respectively. The new compounds were fully characterized.

Keywords: substitution; heterocycle; thiadiazine; morpholine; chirality

1. Introduction

Morpholines are important saturated nitrogen-containing heterocycles and are utilized in a number of clinically used pharmaceuticals [1]. Among the nitrogen-containing heterocycles, morpholines rank as 17th in the most frequently used in U.S. FDA approved drugs [2], while other uses include insecticides [3] and corrosion inhibitors [4]. Examples of morpholine containing drugs include the analgesic phenadoxone, the analeptic doxapram, the β blocker timolol, and the Epidermal Growth Factor Receptor (EGFR) kinase inhibitor gefitinib [5] (Figure 1).

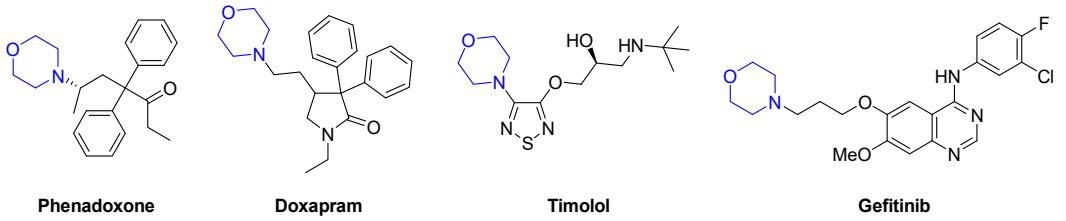


Figure 1. Morpholine containing drugs.

The further tuning of the morpholine's properties by using an asymmetric 3-methylmorpholine has been demonstrated to improve a compound's biological activity and enhance its physicochemical characteristics. There are a number of reports of 3-methylmorpholines, exhibiting a variety of biological activities, including anti-cancer [6], anti-HIV [7], and antidiabetic agents [8].

The introduction of 3-methylmorpholines in the design of kinase inhibitors can not only enhance the potency of a compound, but the methyl group can act as a steric handle to increase the torsion between adjacent ring systems. There are a number of examples in the literature where having a substituted methylmorpholine has enhanced the potency on target, as well as the selectivity profile over close kinome family members (Figure 2) [9–11]. The effects of introducing a methyl group are not always additive [12], and the precise addition of the stereochemistry can be critical [13]. These steric effects can also be achieved by fluorine [14], by adding a carbon spirocycle [15], or by altering the

electronics of the ring system [16]. There are even examples where manipulation of the atropisomerism can directly affect the kinome selectivity profile [17]. These methods all alter the electronics of the system and hence can radically influence the selectivity profile of the kinase inhibitor, while the addition of a methyl group is a more subtle modification with limited electronic character.

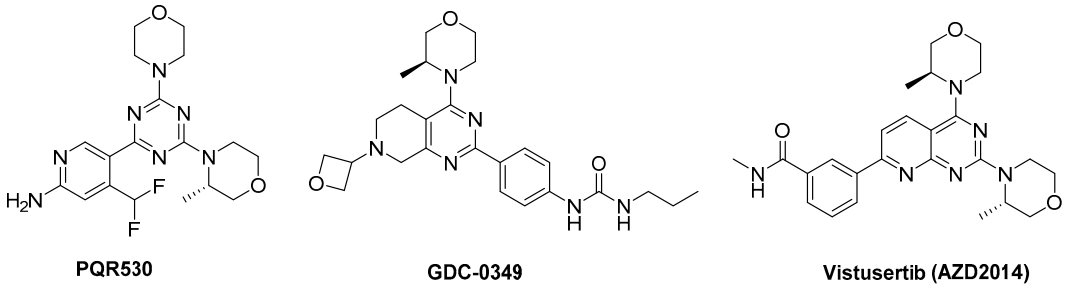
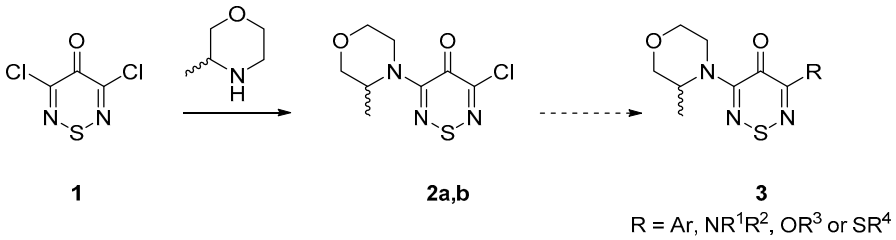


Figure 2. 3-Methylmorpholine containing pre-clinical kinase inhibitors.

Our interest in the 3-methylmorpholine 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 plant protectants [18–22], liquid crystals [23], organic photovoltaics (OPVs) [24], and potential anti-cancer agents [25]. The chemistry of non-S-oxidized 1,2,6-thiadiazines has recently been reviewed [26]. Currently, we are developing a series of new 1,2,6-thiadiazine building blocks to expand our library of a drug like compounds with potential kinome selectivity profiles. For this work, we investigated the 3-methylmorpholine moiety as a substituent of 4*H*-1,2,6-thiadiazin-4-one. We planned to introduce this moiety by a selective nucleophilic displacement of the first chloride of dichlorothiadiazinone **1** by 3-methylmorpholine to yield 3-methylmorpholine-substituted thiadiazines **2a** and **2b**. This displacement could occur under mild conditions owing to the electrophilic nature of the starting thiadiazine.

In the future, we plan to further elaborate thiadiazines **2a** and **2b** by introducing a second substituent via displacement of the remaining chloride. The second substituent could be either an aryl, amino, alkoxy, or thioaryl group (Scheme 1). Substitutions with alkoxy or thioaryl groups on chlorothiadiazines are known [27], while Pd catalysis can be used to introduce aryl (Suzuki or Stille [28–30]) or amino groups (Buchwald [31]).

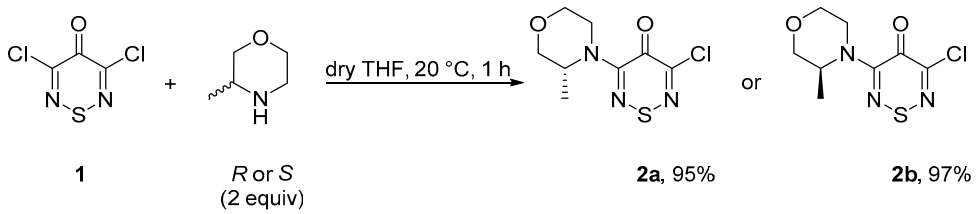


Scheme 1. Planned synthesis of 3-methylmorpholine-substituted thiadiazines **2a** and **2b** and structures of potential derivatives **3**.

2. Results and Discussion

We reacted 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**1**) with 1 equiv. of 3-methylmorpholines and 1 equiv. of 2,6-lutidine in EtOH at *ca.* 20 °C [25]. While both reactions led to complete consumption of the starting thiadiazine **1** to give the desired products, we noted problems with the isolation and stability of products. In particular, the crude product from both reactions after purification by dry flash column chromatography showed the presence of unreacted morpholine. This led to the degradation of the thiadiazines **2** in a solution that was clearly shown by decoloration of the yellow solution. To avoid this problem, we altered the reaction conditions to use 2 equiv. of 3-methylmorpholine [27] in dry tetrahydrofuran (THF), at *ca.* 20 °C, which led to complete consumption of the starting thiadiazinone **1**

after 1 h. Dilution of the reaction mixture with dichloromethane (DCM), followed by extraction with 1 M HCl to remove unreacted morpholine, led to the isolation of the desired products **2a** and **2b** as yellow oils in 95 and 97% yields, respectively (Scheme 2, see SI for NMR spectra in Supplementary Materials). The products, which were isolated without the need for chromatography, were free of any residual amines and showed improved stability both neat and in solution. The optical rotation data showed that the two products were indeed enantiomers ($[\alpha]_D^{20}$ −31 and +32, respectively, for **2a** and **2b**, see Materials and Methods).



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

We noted that the stereochemistry of the products **2a** and **2b** was attributed to the enantiomeric purity of the starting (*R*)- and (*S*)-3-methylmorpholines, $[\alpha]_D^{20}$ −13.8 (*c* 1, $CHCl_3$) and +13.4 (*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 3-methylmorpholines do not epimerize. The possibility of hindered rotation of the methylmorpholino group and the thiadiazine C(5) position, which could lead to atropoisomerism and mixtures of diastereoisomers, was not observed by NMR: each compound showed only five narrow C-signals in the ^{13}C NMR spectra, representative of a rapidly rotating 3-methylmopholino substituent.

This synthetic effort successfully gave the chiral (*R*) and (*S*) 3-methylmorpholines **2a** and **2b**, which can be of interest to the medicinal and materials science sectors. The chemistry of these two aminothiadiazines will be further investigated to assess the potential applications.

3. Materials and Methods

The reaction mixture was monitored by TLC using commercial glass-backed thin layer chromatography (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 were 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 Pike Miracle Ge ATR accessory (Pike Miracle, Madison, WI, USA), and strong, medium, and weak peaks were represented by s, m, and w, respectively. ^1H 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 were 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). (*R*)- and (*S*)-3-methylmorpholine were purchased from Combi-Blocks (San Diego, CA, USA), and their optical rotation values were $[\alpha]_D^{20}$ −13.8 (*c* 1, $CHCl_3$) and +13.4 (*c* 1, $CHCl_3$), respectively. 3,5-Dichloro-4*H*-1,2,6-thiadiazin-4-one (**1**) was prepared according to the literature procedure [27,32].

(R)-3-Chloro-5-(3-methylmorpholino)-4H-1,2,6-thiadiazin-4-one (**2a**). To a stirred mixture of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**1**) (91.5 mg, 0.500 mmol) in THF (1 mL) at *ca.* 20 °C, was added in one portion (*R*)-3-methylmorpholine (101 mg, 1 mmol). The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until the complete consumption of the starting material (TLC, 1 h).

DCM (10 mL) was then added, and the organic phase washed with 1 M aqueous HCl (2 × 5 mL) and then with H_2O (5 mL), dried over Na_2SO_4, and evaporated in vacuo to give the title compound **2a** (118 mg, 95%) as a yellow oil; R_f 0.34 (*n*-hexane/DCM, 50:50); $[\alpha]_D^{20}$ −31 (*c* 1, $CHCl_3$); (found: C, 38.57; H, 3.93; N, 16.86. $C_8H_{10}ClN_3O_2S$ requires C, 38.79; H, 4.07; N, 16.96%); λ_{max}(DCM)/nm 276 (log ε 3.70), 314 (3.89), 324 (3.87), 413 (3.51); v_{max}/cm^{-1} 2982w and 2884w (C-H), 1630s, 1626s, 1493s, 1439m, 1431m, 1427m, 1391w, 1371w, 1317m, 1296m, 1236m, 1196m, 1142m, 1092w, 1076w, 1059w, 1018w, 997w, 983w, 966m, 910m, 889m, 874m, 856m, 822m, 723m; δ_H(500 MHz; $CDCl_3$) 4.84 (1H, br s, C*H*O), 4.48 (1H, d, *J* 12.8, C*H*O), 3.93 (1H, dd, *J* 11.6, 3.4, C*H*O), 3.76-3.69 (2H, m, C*H*O & C*H*N), 3.61 (1H, ddd, *J* 12.1, 12.1, 2.9, C*H*N), 3.39 (1H, ddd, *J* 12.4, 12.4, 3.7, C*H*N), 1.36 (3H, d, *J* 6.7, CH_3); δ_C(125 MHz; $CDCl_3$) 158.7 (Cq), 152.5 (Cq), 145.2 (Cq), 70.8 (CH_2O), 66.8 (CH_2O), 49.5 (CHN), 41.2 (CH_2N), 14.9 (CH_3); *m*/*z* (MALDI-TOF) 250 (MH^+ + 2, 7%), 248 (MH^+, 19), 215 (32), 201 (67), 173 (85), 129 (100).

(S)-*3-Chloro-5-(3-methylmorpholino)-4H-1,2,6-thiadiazin-4-one* (**2b**). To a stirred mixture of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**1**) (91.5 mg, 0.500 mmol) in THF (1 mL) at *ca.* 20 °C, was added in one portion (*S*)-3-methylmorpholine (101 mg, 1 mmol). The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until the complete consumption of the starting material (TLC, 1 h). DCM (10 mL) was then added, and the organic phase washed with 1 M aqueous HCl (2 × 5 mL) and then with H_2O (5 mL), dried over Na_2SO_4, and evaporated in vacuo to give the title compound **2b** (120 mg, 97%) as a yellow oil; R_f 0.34 (*n*-hexane/DCM, 50:50); $[\alpha]_D^{20}$ +32 (*c* 1, $CHCl_3$); (found: C, 38.62; H, 3.99; N, 16.79. $C_8H_{10}ClN_3O_2S$ requires C, 38.79; H, 4.07; N, 16.96%); λ_{max}(DCM)/nm 276 (log ε 3.73), 313 (3.91), 323 (3.88), 413 (3.50); v_{max}/cm^{-1} 2967w and 2864w (C-H), 1632s, 1626s, 1493s, 1439m, 1431m, 1427m, 1391w, 1371w, 1317m, 1296m, 1236m, 1196m, 1140m, 1092w, 1076w, 1059w, 1018w, 997w, 982w, 966m, 908s, 889m, 876m, 855m, 820m, 725m; δ_H(500 MHz; $CDCl_3$) 4.85 (1H, br s, C*H*O), 4.48 (1H, d, *J* 12.8, C*H*O), 3.94 (1H, dd, *J* 11.6, 3.4, C*H*O), 3.76-3.69 (2H, m, C*H*O & C*H*N), 3.61 (1H, ddd, *J* 12.1, 12.1, 2.9, C*H*N), 3.39 (1H, ddd, *J* 12.4, 12.4, 3.7, C*H*N), 1.37 (3H, d, *J* 6.7, CH_3); δ_C(125 MHz; $CDCl_3$) 158.7 (*Cq*), 152.5 (*Cq*), 145.2 (*Cq*), 70.8 (CH_2O), 66.8 (CH_2O), 49.5 (CHN), 41.3 (CH_2N), 14.9 (CH_3); *m*/*z* (MALDI-TOF) 249 (MH^+ + 2, 11%), 247 (MH^+, 23), 242 (100), 215 (16), 201 (83), 173 (44), 129 (87).

4. Conclusions

(*R*) and (*S*)-3-chloro-5-(3-methylmorpholino)-4*H*-1,2,6-thiadiazin-4-ones were prepared in high yields from 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one and are the first non-*S*-oxidized 1,2,6-thiadiazines containing a chiral center.

Supplementary Materials: Supplementary Materials are available online, mol file and ^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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Conflicts of Interest: The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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