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Novel amide-type ligand bearing bis-pyridine cores: Synthesis, spectral characterizations and X-ray structure analyses

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ABSTRACT

The novel salicylamide-type ligand containing bis-pyridine moieties, i.e. 2-((6-chloropyridin-3-yl)methoxy)-*N*-(2-((6-chloropyridin-3-yl)methylthio)phenyl)benzamide, which has been successfully synthesized and characterized by typical spectroscopic techniques mainly including IR, ^{1}H NMR and ESI-MS. The structure of target compound was further determined by single crystal X-ray diffraction method and which crystallized in the monoclinic system with space group *P*2(1)/c.

1. Introduction

Carboxamide scaffolds have been known for a few decades, which attracted great attention as versatile ligands in numerous applications. Many carboxamide derivatives have been widely used in the field of coordination chemistry, and most of which can interact with various biologically important ions [1–4]. Meanwhile, many synthetic carboxamides have also been applied in material chemistry, and the broad biological activities of carboxamide-type derivatives have also been known for a long time [5–15]. Nowadays, many carboxamides derivatives have been developed as commercial medicines (such as BMS-354825, Finasteride, Durasteride, and Lacosamide) and agrochemicals (such as Flonicamid, Tolfenpyrad, Chlorantraniliprole, Cyantraniliprole, Niclosamide, Penthiopyrad, Isotianil, Tiadinil, Mandipropamid, Mefenacet, and Propisochlor) (Fig. 1), and so which have played significantly important role in drug design and agrochemical industry.

Among these carboxamide skeletons, especially those multi-substituted salicylamide skeletons arouse many researchers' interest, which have been demonstrated to be important structural unit with diverse use in various biochemical process and coordination chemistry [16]. Up to now, many salicylamide derivatives have been demonstrated to present widely medicinal activities such as EGFR PTK inhibitors [17], antiviral activity [18], anti-tuberculosis activity [19], antibacterial activity [20], anti-inflammatory activities [21], antimycobacterial activity [22], cercaricidal activity [23], and aldose reductase inhibitors [24].

Thus, there is a great demand for the development of novel synthetic ligands capable of selective interaction with biomolecules or biologically important ions. In the present study, we focus on the synthesis and characterization of neotype salicylamide ligand bearing bis-pyridine moieties as shown in Scheme 1. Its structure was confirmed by typical spectroscopic methods mainly including IR, ^{1}H NMR, ESI-MS spectra, and single crystal X-Ray diffraction structural analysis has also been applied for further study on its detail structural information.

2. Experimental

2.1. Materials and general methods

All melting points (m.p.) were obtained using a digital model X-5 apparatus and are uncorrected. Infrared (IR) spectra in potassium bromide (KBr) were recorded on a Thermo Nicolet FT-IR Avatar 330 instrument. ^{1}H NMR spectra were recorded on a Bruker spectrometer at 600 MHz with $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per

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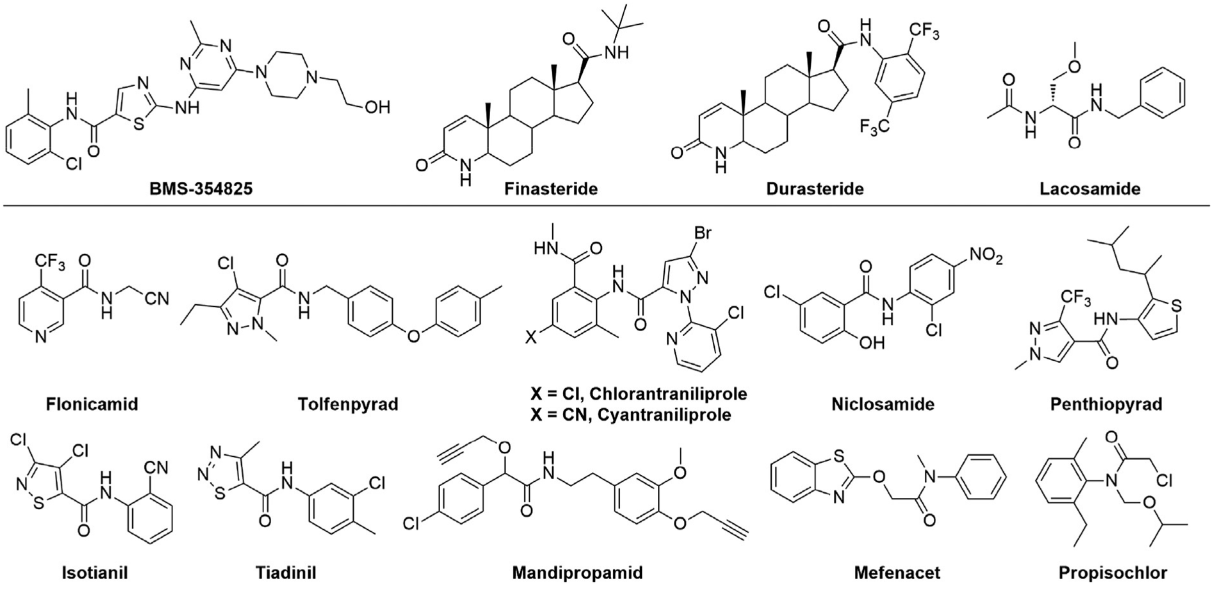
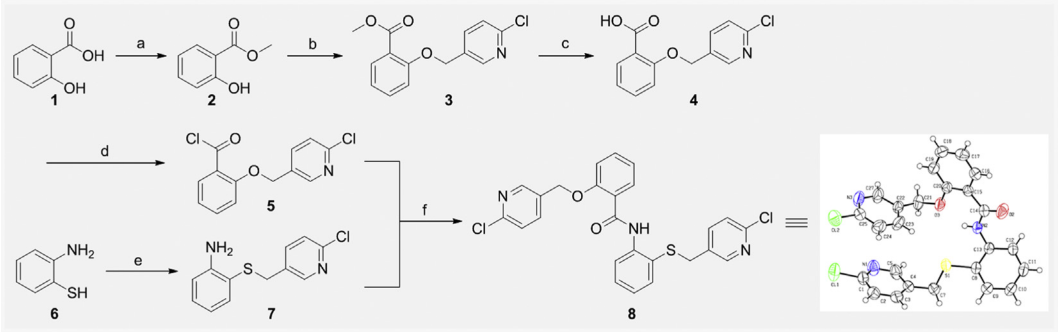


Fig. 1. Representative structure of drugs and pesticides containing amide units.



Scheme 1. Reagents and conditions: a. MeOH, Conc. H_2SO_4; b. 2-Chloro-5-(chloromethyl)pyridine, K_2CO_3, MeCN, r.t. to reflux for 10–12 h; c. NaOH, methanol/H_2O, rt to 50 °C for 5–7 h; d. $SOCl_2$, reflux for 4–6 h; e. 2-Chloro-5-(chloromethyl)pyridine, K_2CO_3, MeCN, r.t.; f. Et_3N, DMAP, DCM, r.t. for 2–5 h.

million) values. Coupling constants ^{n}J are reported in Hz. Mass spectra were performed on a WATERS ACQUITY UPLC® H-CLASS PDA (Waters®) instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates, and spots were visualized with ultraviolet light. All chemicals or reagents used for syntheses were commercially available, were of AR grade, and were used as received. All anhydrous solvents were dried according to standard methods. All other solvents and reagents were analytical reagent and used directly without purification.

2.2. Syntheses of target molecule **8**

2.2.1. General synthetic procedure for 2-((6-chloropyridin-3-yl)methoxy)benzoic acid **4** and 2-((6-chloropyridin-3-yl)methoxy)benzoyl chloride **5**

The key intermediate 2-((6-chloropyridin-3-yl)methoxy)benzoic acid **4** and 2-((6-chloropyridin-3-yl)methoxy)benzoyl chloride **5** was routinely prepared via multi-steps according to document method [25,26].

2.2.2. General synthetic procedure for 2-((6-chloropyridin-3-yl)methylthio)aniline **7**

To a solution of 2-aminobenzenethiol (1.25 g, 10 mmol) and K_2CO_3 (1.52 g, 11 mmol) in MeCN (25 mL) was added 2-chloro-5-(chloromethyl)pyridine (1.62 g, 10 mmol). The resultant mixture was stirred at room temperature for sever hours, which was detected by TLC. Then the mixture was charged with water and extracted with ethyl acetate, the organic phase was separated and dried over anhydrous Na_2SO_4. After filtered and concentrated, the organic residue is purified by silica gel column-chromatography.

2.2.3. General synthetic procedure for the target compound **8**

The typical process of synthesis of novel salicylamide derivative containing 2-chloro-5-pyridyl moiety **8** is shown as following: The freshly formed acylchloride **5** (2.2 mmol) dissolved in dry dichloromethane was added dropwise to a solution of the substituted aniline **7** (2 mmol), Et_3N (2.5 mmol), and catalytic amount of DMAP in dry dichloromethane under ice-bath. The resultant solution was stirred at room temperature for 2–5 h, which was detected by TLC. Then the mixture was washed to neutral with water and dried via anhydrous Na_2SO_4. After filtered and concentrated, the organic residue is purified by silica gel column-chromatography (ethyl acetate/petroleum ether) or recrystallization to give white solid or crystal. Their physico–chemical properties and the spectra data are as follows: 2-((6-chloropyridin-3-yl)methoxy)-*N*-(2-((6-chloropyridin-3-yl)