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The Diverse supramolecular synthons formed by 2-subsituted 5-morpholinomethylphenyl Triazolo[1,5-a]pyridines in solid state

Yingying Chai [a, c, 1], Changfu Li [a, c, 1], Liying Meng [c], Xinglong Zhou [b], Zhenqiang Xia [a], Weimin Li [a, **], Yang He [a, c, *]

[a] Department of Respiratory and Critical Care Medicine, Targeted Tracer Research and Development Laboratory, West China Hospital of Sichuan University, Sichuan University, No. 37, Guo Xue Street, Chengdu, Sichuan, 610041, China
[b] School of Chemical Engineering, Sichuan University, Chengdu, Sichuan, 610065, China
[c] Institute for Nanobiomedical Technology and Membrane Biology, West China Hospital, West China Medicinal School, Sichuan University, No. 1, Keyuan 4th Road, Gaopengdadao, Chengdu, 610041, China

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ABSTRACT

1,2,4-Triazolo[1,5-a]pyridines emerge as promising pharmacophores whose properties depend critically on 2- and 5-positioned substituents. We synthesized three new 1,2,4-triazolo[1,5-a]pyridine derivatives with different 2-substituents in combination with a morpholinomethylphenyl group at 5-position. Due to their unique electronic and intermolecular interactional characteristics, 2-substituents exert distinct influences on their crystal structures by forming diverse supramolecular synthons. Within the triazolopyridine cores, two non-conventional types of intermolecular hydrogen bonds are adopted by compound **1**, bifurcated hydrogen bond motifs are formed through the two faces of 2-amino group substituted compound **2**, and an anti-parallel self-complementary pairwise hydrogen bond motif is formed by 2-nitro group substituted compound **3**. In the single crystal, compound **3** displays different conformational dynamics around the side chains compared to that of **1** and **2**. The elucidating and understanding of their structural chemistry information is valuable for both their pharmaceutical development and application in crystal engineering.

1. Introduction

1,2,4-Triazolo[1,5-a]pyridines represent a special class of heterocyclic compounds with a bridge-headed nitrogen atom, and have drawn much attention from a theoretical viewpoint and for their practical use as biologically active analogues and also for other industrial uses [1]. Following the synthesis of the first 1,2,4-triazolo [1,5-a]pyridine heterocyclic compound by T. Okamoto et al. [2], many derivatives have been constructed and have found various applications in medicinal chemistry [3]. Their pharmacological activities include antioxidant [4], mGlu modulation [5], PDE10 [6] and PHD-1 inhibition [7]. They were also employed as treatment of cardiovascular disorders [8], type 2 diabetes [9,10], hyperproliferative disorders [11], and as herbicidal agents [12]. Recently, they also emerged as promising pharmaceutical scaffolds with inhibitory activity against different kinases associated with various pathological conditions [13–16].

Our high throughput screening of the expression profile of kinases from clinical samples suggested that certain members of the Janus kinase (JAK) family could serve as new therapeutic targets in non-small cell lung cancer (NSCLC). This prompted us to investigate the potential of 1,2,4-triazolo[1,5-a]pyridine derivatives as novel anti NSCLC therapeutic agents. The difficulty of inhibiting JAK was reported to be associated with the risk of immune suppression. One option to overcome this challenge is to deconvolve the promiscuous inhibitory effects of 1,2,4-triazolo[1,5-a]pyridine derivatives through further modification of their exocyclic side chains. The crucial sites for modulating the activity and selectivity are the 2- and 5-positions. According to preliminary biological activity studies, our current chemical modifications were focused on 5-morpholinomethylphenyl derivatives with different 2-positioned substituents.

Although the 1,2,4-triazolo[1,5-a]pyridine scaffold has been

* Corresponding author.
** Corresponding author.
E-mail addresses: Weimin003@163.com (W. Li), heyangqx@scu.edu.cn (Y. He).
[1] These authors contributed equally to this work.

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investigated for years, surprisingly only very few single crystal structures have been reported [17]. The lack of their structural knowledge will hamper the optimization process for their future development. For this reason, we extensively investigated the molecular structure of a series of 1,2,4-triazolo[1,5-a]pyridine derivatives in single crystalline solid state. Previously, we have found the different 2-halogenated 5-morpholinomethylphenyl 1,2,4-triazolo[1,5-a]pyridines displayed different propensities to form either hydrogen bond (HB) or halogen bond (XB) [18]. However, the influences of other 2-substituents groups with distinct HB forming capabilities and inductive effects on the supramolecular synthons of this series of compounds have not been tackled yet. Amino group is an electron-donating group with HB donors and is a very important pharmacophore, and nitro group on the opposite is an electron-withdrawing group with HB acceptors. To elucidate their influences on the crystal structures for this series of compounds will not only provide pharmaceutical payoffs but also offer crucial structural information in other fields such as crystal engineering. Herein, we disclosed the synthesis of the 2-hydrogen (**1**), 2-amino (**2**) and 2-nitro (**3**), and compared their intriguing crystal structural features resulted from different supramolecular synthons (Fig. 1).

2. Experimental section

2.1. General methods

The chemicals and reagents used here are of analytical grade and were used as received. Thin-layer chromatography (TLC) was performed on aluminum sheet covered with silica gel 60 F254 (0.2 mm, Merck, Germany). Flash column chromatography (FC): silica gel 60 (Haiyang chemical company, P. R. China) at 0.4 bar. The NMR samples were dissolved in deuterated solvents, ^{1}H NMR and ^{13}C NMR spectra were recorded on an AV II (Bruker, Germany) spectrometer, the δ values in ppm are relative to tetramethylsilane as the internal standard. High resolution mass spectra were measured with mass analyzer (Q-TOF, Bruker, Germany) and equipped with an electrospray ionization (ESI) source; The DSC were measured on DSC 1 (METTLER TOLEDO), in the range of 25–220 °C, at a scan rate of 10 °C·min^{-1}.

2.2. Single crystal X-ray diffraction

Single crystal X-ray diffraction measurements were conducted on a Bruker APEX-II CCD diffractometer using Mo-Kα radiation ($\lambda = 0.71073$ Å) with a graphite monochromator at 170(3) K and 293(5) K in scan mode. Collected data and cell refinement were reduced using SAINT v7.68A (Bruker, 2012) and SADABS was used for absorption correction. The structures were solved with the SHELXL (Sheldrick, 2015) structure solution program using Intrinsic Phasing and refined with the SHELXL (Sheldrick, 2015) refinement package using full-matrix least-squares on F^2. All hydrogen atoms were refined isotropically, and the heavy atoms were refined with anisotropically. The amino hydrogens were found in the difference-Fourier map and refined with isotropic displacement parameters.

2.3. Synthesis and crystal growth

5-Bromo- [1,2,4]triazolo[1,5-a]pyridine (6). Conc. H_2SO_4 (100 ml), $NaNO_2$ (69.0 mg, 1.0 mmol) were dropwise added to a suspension of 5-bromo- [1,2,4]triazolo[1,5-a]pyridin-2-ylamine **5** (105.0 mg, 0.50 mmol) in 5 ml dioxane, and stirred under ice-water for 15 min. Then, the suspension was brought to room temperature and kept stirring for 24 h. As the reaction progressed, the suspension turned from colourless to red color. At the end point of reaction, the mixture was neutralized by NaOH (1 M) solution, and then transferred into CH_2Cl_2 (3 × 10 ml), dried ($MgSO_4$), filtered, and concentrated under vacuum. The product (80.0 mg, 82%) was isolated via column chromatography (silica gel 5 g, eluent: CH_2Cl_2) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, $J = 7.3$ Hz, 1H), 7.36 (dd, $J = 8.8$, 7.5 Hz, 1H), 7.70 (d, $J = 8.9$ Hz, 1H), 8.35 (s, 1H). ^{13}C NMR

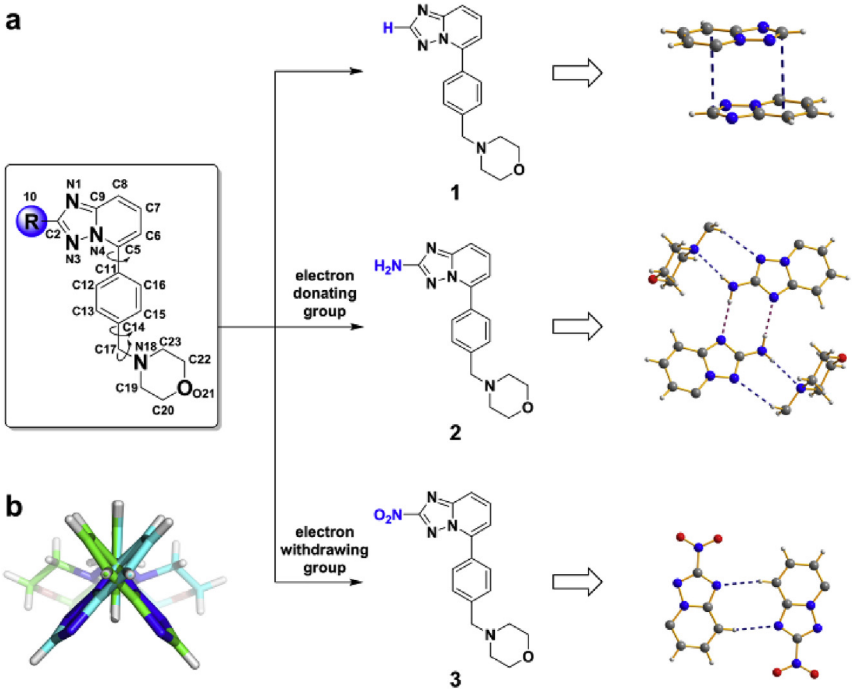

Fig. 1. a) Schematic illustration of the 2-subsituted triazolopyridines with crystallographic numbering and some selected intermolecular interactions in their crystal structures. Atoms are coded as follows: red, oxygen; blue, nitrogen; gray, carbon; white, hydrogen. b) The top view of the overlay graph on the benzene rings of the conformational enantiomeric pairs **1**-**A1**/**1**-**A2** of compound **1**. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)