Article

Three Multi-Components Reaction: Synthesis and X-Ray Single-Crystal of Hydroacridinone-Based Hydrazino-S-Triazine Derivative as a New Class of Urease Inhibitor

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Abstract: The one-pot fashion of three multi-component reaction provides the desired hydroacridinone-based hydrazino-s-triazine scaffold **4**. Compound **4** was crystallized in an orthorhombic crystal system and Pbc_a space group with $a = 11.6271(2)$ Å, $b = 18.2018(4)$ Å, $c = 32.4721(6)$ Å, and $\alpha = \beta = \gamma = 90^\circ$ with one formula unit per asymmetric unit and eight molecules per unit cell. Additionally, structural features, Hirshfeld surfaces, and DFT studies were also investigated. Its packing in the crystal is controlled by H...H (63.4%), O...H (12.7%), Cl...H (7.2%), N...H (4.7%), and C...H (10.2%) contacts, where the O...H and Cl...H contacts were found the strongest. In vitro urease inhibition evaluation showed that the hydroacridinone-based hydrazino-s-triazine is more active ($IC_{50} = 17.9 \pm 0.47$ µM) than the standard acetohydroxamic acid ($IC_{50} = 20.3 \pm 0.43$ µM).

Keywords: three-component reaction; hydroacridinone; hydrazino-s-triazine; urease inhibitors; DFT; Hirshfeld surfaces

1. Introduction

Urease is a metalloenzyme-containing nickel that frequently exists in various plants, bacteria, fungi, and algae and leads to the growing of different bacteria pathogen (e.g., *Helicobacter pylori*) in acidic condition inside the stomach. Several health complications including hepatic coma, urinary tract infections, gastric lymphoma, gastric ulcers, gastric carcinoma, pyelonephritis, and kidney stones proved to be related to these bacterial infections [1,2]. In spite of numerous compounds being well-known to have potential urease inhibition, few of them are in the market for urease treatment. Thus, the discovery of effective and safe urease inhibitors is a very important issue in pharmaceutical research due to the contribution of ureases in different pathological conditions.

On the other hand, acridine-based compounds have been proven to display different pharmaceutical targets including anti-protozoal drugs [3], anti-bacterial drugs [4], anti-malarial agents [5], anti-HIV drugs [6], anti-inflammatory drugs [7], and antiviral drugs [8], and are known as cytotoxic agents and fluorescent probes [9,10]. Several acridine-based heterocyclic compounds have previously been reported to have a wide range of biological and therapeutic activities [11–15].

Similarly, *s*-triazine is one of the constituent molecular scaffolds found in natural products and synthetic drugs [16,17]. The *s*-triazine ring-based compounds have been proven to display different pharmaceutical targets for example MAO inhibitors [18], anticancer [19], antiviral [20], drug delivery systems [21], antimalarial [22], antiprotozoal [23], antimicrobial [24], antifungal [25], and antileishmanial activity [26]. The *s*-triazine moiety linked with other groups is of a lipophilic character and is already reported to have remarkable antifungal and antibacterial activities [27–30].

According to our knowledge, the search of potent acridine-based *s*-triazine compounds as urease inhibitors is not reported so far. Accordingly, we synthesized a hydroacridinone-based hydrazino-*s*-triazine derivative via a one-pot multi-component reaction. The *in vitro* anti-urease inhibition of the hydroacridinone-based hydrazino-*s*-triazine was evaluated. In addition, its structural features, Hirshfeld surfaces, and DFT were demonstrated.

2. Materials and Methods

2.1. General Methods

All melting points were determined using Mel-Temp electrothermal apparatus (Electrothermal, Staffordshire, ST15, UK) and were uncorrected. Thin-layer chromatography (TLC) was conducted on silica gel (Kiesel gel G, Merck) and spots were detected under UV light at 254 nm. IR spectra were recorded in a KBr matrix with a Perkin Elmer, Spectrum 100 FT-IR spectrophotometer (FT-IR, Perkin Elmer, Waltham, MA, USA). Furthermore, ^1H and ^{13}C NMR spectra were recorded in CDCl_3 as solvent using JEOL 400 MHz (JEOL, Ltd, Tokyo, Japan), and the chemical shifts (δ) values were given in ppm. X-ray crystallographic analysis was collected by using Bruker SMART APEX II D8 Venture diffractometer at Karachi University.

2.2. Synthesis of Hydroacridinone Compound 4

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-10-((4-morpholino-6-(piperidin-1-yl)-1,3,5-triazin-2-yl)amino)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (4).

A mixture of 5,5-dimethylcyclohexane-1,3-dione (dimedone, **1**) (2 mmol, 280 mg), *p*-chlorobenzaldehyde **2** (1 mmol, 141 mg), **3** (1 mmol, 279 mg), and glacial acetic acid (5 mL) was heated under reflux overnight. The solid product was isolated by simple filtration. Compound **4** was obtained in 85% yield as yellow powder, m.p: 275–286 °C. IR (KBr, cm^{-1}): 3292, 2959, 2934, 2856, 1640, 1581, 1520, 1498, 1444, 1365; ^1H -NMR (CDCl_3): δ 7.37–7.15 (m, 4H, Ph), 4.7 (s, 1H, PhCH), 3.85–3.71 (m, 12H, morpholino & piperidiny), 2.44 (s, 4H, CH_2 hydroacridinone), 2.20 (s, 2H, CH_2 hydroacridinone), 2.15 (s, 2H, CH_2 hydroacridinone), 1.52 (m, 7H, piperidiny and amino), 1.23 (s, 12H, 4 CH_3); ^{13}C -NMR (CDCl_3): δ 196.3, 195.5, 195.4, 162.4, 150.4, 142.7, 131.7, 130.0, 129.9, 129.8, 129.6, 128.2, 127.9, 127.8, 115.3, 114.7, 66.5, 50.7, 50.2, 50.0, 44.7, 44.5, 44.0, 41.3, 40.9, 38.8, 38.5, 38.1, 33.3, 32.7, 32.4, 32.0, 31.5, 30.0, 29.7; GC/MS (EI+): 645.3; Anal. for $\text{C}_{35}\text{H}_{44}\text{ClN}_7\text{O}_3$; Calcd: C, 65.05; H, 6.86; N, 15.17; Found: C, 65.25; H, 6.99; N, 15.35.

Single crystals were obtained from ethanol-diethyl ether (1:2) by slow evaporation at room temperature.

2.3. Single-Crystal X-ray Diffraction Analysis

Single-crystal X-ray diffraction analysis of compound **4** was carried out by mounting an appropriate crystal with dimensions $0.15 \times 0.09 \times 0.07 \text{ mm}^3$ on a Bruker D8 Venture equipped with CCD Photon II detector and graphite monochromator having Cu K α radiation ($\lambda = 1.54178 \text{ \AA}$) at $T = 173 \text{ K}$ for data collection. For the integration and reduction of data, SAINT (Bruker 1998) program was used [31]. The structure solution was done by direct method and Fourier transformation techniques, and further refined by full-matrix least-squares techniques on F^2 using SHELXL-2018 program. PLATON (Spek 2008) [32] and SHELXL (Sheldrick 2015) [33] programs were employed for the final refinement of the solved structure (Table 1). CCDC 1967280 contains supplementary crystallographic data for this

paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union 26 Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; email: deposit@ccdc.cam.ac.uk or at <http://www.ccdc.cam.ac.uk>.

Table 1. Summary of data collection and structure refinements of crystal of **4**.

Identification Code	4
Empirical formula	C ₃₅ H ₄₄ Cl N ₇ O ₃
Formula weight	646.22
Temperature	173(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 11.6271(2) Å α = 90°. b = 18.2018(4) Å β = 90°. c = 32.4721(6) Å γ = 90°.
Volume	6872.2(2) Å ³
Z	8
Density (calculated)	1.249 Mg/m ³
Absorption coefficient	1.343 mm ^{−1}
F(000)	2752
Crystal size	0.150 × 0.090 × 0.070 mm ³
Theta range for data collection	2.721° to 68.235°.
Index ranges	−14 ≤ h ≤ 14, −20 ≤ k ≤ 21, −39 ≤ l ≤ 38
Reflections collected	51121
Independent reflections	6266 [R(int) = 0.0788]
Completeness to theta = 67.679°	99.9%
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	6266 / 0 / 423
Goodness-of-fit on F ²	1.026
Final R indices [I > 2σ(I)]	R1 = 0.0561, wR2 = 0.1457
R indices (all data)	R1 = 0.0814, wR2 = 0.1630
Largest diff. peak and hole	0.278 and −0.418 e.Å ^{−3}
CCDC No.1967280	

2.4. Hirshfeld Surface Analysis

The topology analyses based on CIF data were performed using Crystal Explorer 17.5 program [34] in order to determine the percentages of the different intermolecular interactions in the crystal structure of the studied compound.

2.5. Computational Methods

All DFT calculations were performed using Gaussian 09 software package [35,36]. The optimized geometry in gas phase was calculated using B3LYP/6-31G(d,p) method. The starting input was the X-ray structure coordinates. No imaginary frequencies were obtained indicating a real energy minimum.

2.6. Urease Inhibition

The urease inhibition assay was performed spectrophotometrically. The final volume of the reaction mixture was 200 µL, comprising 25 µL of urease enzyme solution (1 U/well is defined as the release of 1 µM of substrate per unit time under the specified conditions). This mixture was incubated with 5 µL of test compound (500 µM) for 15 min at 30 °C (urease enzyme was prepared in phosphate buffer pH 6.8, concentration 4 mM). Thereafter, 55 µL of urea (substrate) at a concentration of 100 mM was added, and the plate was again incubated for 15 min at 30 °C. After incubation, 45 µL of phenol reagents (1% w/v phenol and 0.005% w/v sodium nitroprusside), and 70 µL of alkali reagents (0.5% w/v

sodium hydroxide and 0.1% sodium hypochlorite) were added to each well. The plate was re-incubated for 50 min at 30 °C. The continuous production of ammonia by urease was monitored following the Weatherburn method, and absorbance was recorded at 630 nm on an ELISA plate reader (Spectra Max M2, Molecular Devices, CA, USA). Acetohydroxamic acid was used as a reference compound (Standard Drug, available under the brand name Lithostate) [37,38].

3. Results and Discussion

3.1. Chemistry

The synthesis of **4** was outlined in Scheme 1, where the starting material including dimedone **1**, *p*-chlorobenzaldehyde **2**, and 4-(4-hydrazinyl-6-(piperidin-1-yl)-1,3,5-triazin-2-yl)morpholine **3** in acetic acid under reflux applying the one-pot fashion multi-component approach [39]. The structural feature of the desired hydroacridinone-based hydrazino-*s*-triazine was assigned based on sets of spectroscopic tools including FT-IR, mass spectroscopy (MS), nuclear magnetic resonance (NMR), and single-crystal X-ray diffraction technique.

Scheme 1. Synthetic route for the hydroacridinone-based hydrazino-*s*-triazine, **4**.

The ¹H-NMR spectra are consistent with the assigned structure of **4**. A multiplet signal was shown at δ 7.37–7.15 ppm and the singlet at δ 4.7 ppm could be assigned for the aromatic protons and the benzylic proton, respectively. In the aliphatic chemical shift region, a multiplet at δ 3.85–3.71 ppm for the morpholino and piperidinyl moieties protons was observed. The hydroacridinone proton was detected at δ 2.44–2.15 ppm. Additionally, the signal δ 1.52 ppm could be assigned to 7H of the piperidinyl ring (3CH₂), which overlays with the NH proton. Finally, the singlet signal assigned to the four methyl groups with 12 protons was detected at δ 1.23 ppm. ¹³C-NMR spectrum and MS are matching with the expected product.

3.2. Crystal Structural Description

The 3D structure of compound **4** was represented by the ORTEP diagram (Figure 1). Structurally, compound **4** was found to be comprised of 1,8-dioxo-decahydroacridine (N1/O1-O2/C1-C13) moiety substituted with planar *p*-chlorophenyl ring (C11/C15-C20) at C7 and dimethyl groups (C21-C22/C23-C24) at C2 and C11 atom, linked via N1-N2 linkage to planar *s*-triazine ring (N3-N5/C30-C32). The piperidinyl ring (N6/C25-C29) was found in twist-boat conformation at C30 and morpholino moiety (N7/O3/C33-C36) in a chair conformation at C32 atom, respectively. The torsion angle between N1/N2/C6/C31 was found to be 112.8(2)°. A list of dihedral angles is given in Table S1 (Supplementary Data).

Figure 2. Crystal packing diagram of compound 4. (a) The most important hydrogen bonding interaction (N-H...O) is presented as dotted turquoise line. (b) The weak C-H... π interactions are also presented in the same color in the lower part of this illustration.

3.4. Hirshfeld Analysis of Molecular Packing

In Hirshfeld surface analysis, the d_{norm} is a normalized contact distance as defined by Equation (1). The d_i is normalized by the van der Waals radius of the atoms involved; d_e is similarly normalized,

and the sum of these two quantities is the d_{norm} property. Where atoms make intermolecular contacts closer than the sum of their van der Waals radii, these contacts will be highlighted in red on the d_{norm} surface. Longer contacts are blue and contacts around the sum of van der Waals radii are white [41].

$$d_{norm} = \frac{d_i - r_i^{vdW}}{r_i^{vdW}} + \frac{d_e - r_e^{vdW}}{r_e^{vdW}} \quad (1)$$

Hirshfeld surfaces for compound **4** are shown in Figure 3. The decomposed fingerprint plots indicated that the most common contacts are H...H (63.4%), O...H (12.7%), Cl...H (7.2%), N...H (4.7%), and C...H (10.2%) as shown in Figure 4. Among them, the O...H and Cl...H contacts appeared as intense and faded red spots in the d_{norm} maps, respectively, while the rest of other contacts appeared as blue regions. From this point of view, the O...H and Cl...H contacts are considered the strongest among the others. These interactions appeared as relatively sharp spikes in the fingerprint (FP) plots (Figure 5). The intermolecular distances are 1.831 Å and 2.791 Å for the O1...H1 and Cl1...H28A, respectively.

Figure 3. Hirshfeld (a) d_{norm} , (b) shape index, and (c) curvedness maps for compound **4**.

Figure 4. The intermolecular contacts in 4 and their percentages.

Figure 5. The d_{norm} maps (left) and FP plots (right) of the O1 ... H1 (1.831 Å) and Cl1 ... H28A (2.791 Å) contacts in the studied molecule.

3.5. Geometric Parameters

The crystal structure was left to relax using DFT B3LYP/6-31G(d,p) method and the resulting optimized structure is presented in Figure 6. Bond distances and angles are given in Table S2 (Supplementary Materials). Figure 7 showed the good correlations between the calculated and experimental bond distances ($R^2 = 0.973$), and angles ($R^2 = 0.952$). The presence of many polar atoms related to the highly electronegative atoms such as oxygen, nitrogen, and chlorine leads to a polar molecule with a high dipole moment of 9.268 Debye. The natural atomic charges and the direction of the dipole moment vector are given in Table S3 (Supplementary Materials) and Figure 6, respectively. The dipole moment vector is oriented toward the most polar region in the molecule, which is the carbonyl oxygen atoms.

Figure 6. Optimized molecular structure showing the dipole moment vector of **4**; C: Grey, N: blue, O: red and H: white.

Figure 7. The calculated versus experimental (a) bond distances and (b) angles.

On the other hand, the HOMO (−5.722 eV) and LUMO (−1.516 eV) orbitals are distributed over the π -system of the fused ring (Figure 8). The energy of the HOMO–LUMO intramolecular charge transfer is calculated to be 4.206 eV. The reactivity indices [42–50] of the studied compound such as ionization potential (I), electron affinity (A), chemical potential (μ), hardness (η), softness (S), and electrophilicity

(ω) were calculated based on the HOMO and LUMO energies to be 5.722, 1.516, −3.619, 4.206, 0.238, and 1.557, respectively. These descriptors are important for the biological reactivity of the compounds.

Figure 8. HOMO and LUMO of 4.

3.6. Biological Activity

In a recent publication [51], we reported the synthesis of several hydrazone derivatives based on *s*-triazine and their corresponding anti-proliferative activities. Of these derivatives, only three inhibited the growth of lung carcinoma A549 and hepatocyte carcinoma HepG2 cells. Our results showed the combination of morpholino and piperidinyl moieties conferred greater selectivity for A549 cells and had a reasonable inhibitory effect on HepG2 cells [52].

Based on the previous results [52,53], 4-(4-hydrazinyl-6-(piperidin-1-yl)-1,3,5-triazin-2-yl)morpholine **3** was used as an example for the synthesis of hydroacridinone-based hydrazino-*s*-triazine **4**. Compound **4** was evaluated in vitro against-urease inhibition and the results are shown in Table 3. The desired compound exhibited high efficacy compared to acetohydroxamic acid ($IC_{50} = 20.3 \pm 0.43 \mu M$), where the IC_{50} is equal to $17.9 \pm 0.47 \mu M$ (Table 3). The structure of the compound consists of hydroacridinone-based hydrazino-*s*-triazine having lipophilic moieties like morpholine and piperidine provided high potency, which can be considered as a lead compound to discover new drugs as urease inhibitor.

Table 3. Result of in vitro urease enzyme inhibition potential.

Compound	Urease Inhibition $IC_{50} \pm SEM (\mu M)$
4	17.9 ± 0.47
Acetohydroxamic Acid	20.3 ± 0.43

4. Conclusions

The present report describes the design and synthesis of hydroacridinone-based ydrazine-*s*-triazine derivative as a promising anti-urease agent. The synthesized hydroacridinone based hydrazino-*s*-triazine derivative (**4**) showed more potency than acetohydroxamic acid as reference. Thus, the hydroacridinone-based *s*-triazine could be considered as a compound of potential lead for further optimization and drug discovery in future work. Hirshfeld analysis indicated the importance of the H...H (63.4%), O...H (12.7%), Cl...H (7.2%), N...H (4.7%), and C...H (10.2%) in the molecular packing of **4**. DFT calculations indicated that **4** is polar compound with a total dipole moment of 9.268 Debye. Its reactivity indices were computed using the frontier molecular orbital energies. The computed bond distances and angles were found in good correlations with the experimental results.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4352/10/1/14/s1>: Figure S1, The atom numbering of the calculated molecular structure of the studied compound; Table S1, The

calculated bond distances and angles of the studied organic compound compared to the experimental X-ray structure data; Table S2, The natural atomic charge analysis of the studied compound.

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