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New spiro-oxindole constructed with pyrrolidine/thioxothiazolidin-4-one derivatives: Regioselective synthesis, X-ray crystal structures, Hirshfeld surface analysis, DFT, docking and antimicrobial studies

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ABSTRACT

In this work, polycyclic heterocycles containing spirooxindole, pyrrolidine, and thioxothiazolidin-4-one rings have been synthesized *via* the regioselective 1,3-dipolar cycloaddition of azomethine ylide, which is generated in situ by the condensation of the dicarbonyl compound isatin and the secondary amino acid (L-proline), with 5-arylidine-2-thioxothiazolidin-4-one as the dipolarophile. The structure of the synthesized compounds **4a** and **4b** were determined by using X-ray single crystal diffraction, and also, Hirshfeld surface analysis were reported. Their geometric parameters were calculated using density functional theory at the B3LYP/6-311G (d,p) level of theory. Both compounds showed antimicrobial and antifungal activity better than selected standards (ampicillin and gentamicin in case of antibacterial activity and Amphotericin A and fluconazole in case of antifungal activity). Molecular docking study of the synthesized compounds indicated that phenyl group plays an important role in determination of compound interaction inside the receptors.

1. Introduction

The spirocyclic ring structure is a unique feature of a number of natural and synthetic products that possess interesting biological activities. The potential use of spiro derivatives in medicinal chemistry has been well recognized owing to their anti-mycobacterial, antitumor, antiproliferative, and anti-tuberculosis activities [1–15]. Similarly, the 4-thiazolidinone moiety has been utilized for the synthesis of a variety of useful heterocyclic products including drugs [16,17], dyes, and intermediates such as thioflavin T., thiazole yellow, and thidiazuron [18]. Furthermore, 4-thiazolidinone derivatives have been used as insecticides [19,20] and herbicides [21] owing to their low toxicity toward human beings and excellent biological activity. The thiazolidinone moiety is also associated with a broad spectrum of biological activities including antidiabetic [22], antifungal, antibacterial, anti-inflammatory, anticonvulsant, hypnotic, anti-tuberculosis, antihistaminic, antiviral, cardiovascular, anthelmintic, and anticancer properties [23,24]. A number of 4-thiazolidinone derivatives have been investigated for their inhibitory effect on the oxidation of β-hydroxybutyrate substrate by rat brain homogenates and in the tricarboxylic acid cycle during respiratory activity [25]. Therefore, development of new spiro-heterocycles having oxindole, pyrrolidine, or thiazolidinone rings is worthwhile from the perspective of medicinal chemistry.

Recently, several methods have been reported in literature for the synthesis of oxindole derivatives with spiro heterocycles [26,27]. Generally, isatin and its derivatives have been employed as the starting materials for 1,3-dipolar cycloaddition reactions that yield the spirooxindole core owing to the facile preparation of the corresponding azomethine ylides in the presence of α-amino acids

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[28–33]. Ponnala et al. have reported an example of 1,3-dipolar cycloaddition reactions with olefins that proceed regio- and stereoselectively to furnish the novel dispiropyrrolidine scaffold [34]. Liu et al. have developed an efficient three-component reaction of 5-arylidene-4-thioxo-1,3-thiazolidine-2-one or 5-arylidene-1,3-thiazolidine-2,4-dione, sarcosine, and isatin for the synthesis of dispiropyrrolidine derivatives in ethanol under ultrasound irradiation [35]. Another example reported by Prasad and coworkers is a facile method for the syntheses of pyrrolizidine-substituted benzo [*h*]quinoline, quinoline, dispiropyrrolidine, and thiapyrrolizidine compounds in good yields *via* multicomponent 1,3-dipolar cycloaddition reactions of azomethine ylide [36]. However, to the best of our knowledge, there are no reports on the synthesis of this regioisomers and diastereoisomers of dispiro compounds containing rhodanine.

In this work, the synthesis and X-ray crystal structures of diastereomerically pure spiro-oxindole, pyrrolidine, and thiazolidinone rings have been reported for the first time. Moreover, the antimicrobial activities and molecular docking study as well was addressed on this work.

2. Materials and methods

2.1. General remarks

"All chemicals were purchased from Aldrich, Sigma-Aldrich, and Fluka and used without further purification, unless otherwise stated. All melting points were measured on a Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer. NMR spectra were recorded on a Varian Mercury Jeol-400 NMR spectrometer. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) were measured in deuterated dimethyl sulfoxide (DMSO-d_6). Chemical shifts (δ) are in ppm, and *J*-coupling constants are given in Hz. Mass spectra were recorded on a Jeol JMS-600 H instrument. Elemental analysis was carried out on an Elmer 2400 Elemental Analyzer in CHN mode. For X-ray diffraction analysis, data were collected on a Bruker APEX-II D8 Venture diffractometer with an area detector".

2.2. General procedure for the synthesis of **4a**,**b** (GP1)

A stirred mixture of isatin **2** (74 mg, 0.5 mmol), L-proline **3** (57.5 mg, 0.5 mmol), and 5-benzylidene-2-thioxothiazolidin-4-one **1a**,**b** (0.5 mmol) in MeOH (10 mL) was heated under reflux conditions for the specified period of time. After completion of the reaction was indicated by TLC, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography using petroleum ether–ethyl acetate (3:1) as the eluent.

2.2.1. (1′R,7a'R)-2″-thioxo-2'-(p-tolyl)-5′,6′,7′,7a'-tetrahydro-2′H-dispiro[indoline-3,3′-pyrrolizine-1′,5″-thiazolidine]-2,4″-dione, **4a**

IR (KBr, ν, cm^{-1}): 3246, 1722, 1618, 1595, 1515, 1471; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.80 (bs, 1H, NH), 9.86 (bs, 1H, NH), 7.84–7.66 (m, 8H, Ar–H), 5.49–5.41 (d, J = 9.3 Hz, 1H), 4.10 (m, 2H), 2.91 (t, 2H), 2.28 (m, 2H), 2.10 (s, 3H), 1.12 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 26.9, 30.6, 47.3, 51.5, 54.9, 63,6, 71.5, 73.7, 107.4, 111.9, 113.3, 122.2, 129.7, 131.5, 136.4, 144.2, 162.0, 170.2, 174.2, 178.1; HRMS *(m/z)* calculated for $[M+1]^+$ $C_{23}H_{21}N_3O_2S_2$ 435.11, found: 436.11. Elemental Analysis: C, 63.42; H, 4.86; N, 9.65; S, 14.72; found C, 63.45; H, 4.85; N, 9.70; S, 14.71.

2.2.2. (1′R,7a'R)-2′-phenyl-2″-thioxo-5′,6′,7′,7a'-tetrahydro-2′H-dispiro[indoline-3,3′-pyrrolizine-1′,5″-thiazolidine]-2,4″-dione, **4b**

IR (KBr, ν, cm^{-1}): 3340, 1710, 1610, 1466; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.81 (bs, 1H, NH), 9.91 (bs, 2H, NH), 7.98–7.70 (m, 8H, Ar–H), 5.55–5.51 (d, J = 9.3 Hz, 1H), 4.12 (m, 2H), 2.95 (t, 2H), 2.29 (m, 2H), 1.17 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 26.5, 48.0, 53.8, 56, 67.8, 72.6, 79.6, 83.4, 100.5, 108.3, 111.0, 122.4, 129.8, 131.4, 139.3, 144.0, 162.3, 170.0, 174.1, 178.0; HRMS *(m/z)* calculated for $C_{22}H_{19}N_3O_2S_2$ $[M+1]^+$: 421.09, found: 422.09; Elemental Analysis: C, 62.69; H, 4.54; N, 9.97; S, 15.21; found: C, 62.71; H, 4.55; N, 10.00; S, 15.22.

2.3. Computational details

The X-ray structures of the studied compounds were optimized by using the Gaussian 09 program [37,38]. For this task, the B3LYP method and 6-311G(d,p) basis sets were used for all atoms. Frequency calculations gave no imaginary frequencies, indicating that the optimized structure is an energy minimum as there were no negative modes.

2.4. Hirshfeld surface analysis

Hirshfeld surfaces (HSs) and 2D fingerprint plots (FPs) were generated by using the Crystal Explorer 3.1 software [39]. The crystallographic information files (CIF) obtained from the X-ray single crystal measurements were used for performing the HS analysis. The HSs and FPs were constructed based on the electron distribution calculated as the sum of spherical atom electron densities [40–47].

2.5. Agar diffusion well method to determine the antimicrobial activity

2.5.1. Antibacterial activity of compound **4a**,**b**

"Antibacterial activities were investigated by using agar well diffusion method, against the *Staphylococcus pneumonia* (RCMB 010010) and *Bacillus subtilis* (RCMB 010067) (as Gram-positive bacteria) and *Pseudomonas aeruginosa* (RCMB 010043) and *Escherichia coli* (RCMB 0100052) (as Gram-negative bacteria). The solution of 10 mg/mL of compound in DMSO was prepared for testing against bacteria. Centrifuged pellets of bacteria from 24 h old culture containing approximately 10^4–10^6 CFU (colony forming unit) per mL were spread on the surface of nutrient agar (type tone 1%, yeast extract 0.5%, NaCl 0.5%, agar, and 1000 mL of distilled water, pH 7.0) which was autoclaved under 121 °C for at least 20 min. Wells were created in medium with the help of sterile metallic bores and then cooled down to 45 °C. The activity was determined by measuring the diameter of the inhibition zone (in mm). A volume of 100 μL of the tested sample (10 mg/mL) was loaded into the wells of the plates. A solution of the compound was prepared in DMSO, while DMSO was also loaded as control. The plates were kept for incubation at 37 °C for 24 h and then the plates were examined for the formation of zones of inhibition. Each inhibition zone was measured three times by caliper to get an average value. The test was performed three times for each bacterium and the average was taken. Ampicillin and Gentamicin were used as antibacterial standard drugs" [48].

2.5.2. Antifungal activity of compound **4a**,**b**

Tested sample was screened *in vitro* for its antifungal activity against various fungi, namely, *Aspergillus fumigatus* (RCMB 002568), *Syncephalastrum racemosum* (RCMB 016001) *Geotricum candidum* (RCMB 05097) and *Candida albicans* (RCMB 05036). The antifungal activity was performed by agar well diffusion method