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Synthesis and characterization of new unsymmetrical bis-Schiff bases

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Abstract

The literature is replete with symmetrical tetradentate bis-Schiff bases of 1,2-diamines with o-hydroxy aldehyde or ketones, but less attention has been focused on the analogous unsymmetrical tetradentate ones. Unsymmetrical Schiff bases of aromatic diamines are very difficult to obtain and are not easily isolated. This class of Schiff bases have very simple synthetic procedure and versatile coordination behavior. Metal complexes containing these Schiff bases in their structure usually possess exceptional antibacterial, antifungal and antitumor activities including anti-HIV activity. In this regard, two new unsymmetrical bis-Schiff bases, (Z)-N-(2-nitrophenyl)-N'-(2-((Z)-(2-oxoindolin-3-ylidene)amino)phenyl)acetimidamide (1) and (Z)-N-(2-nitrophenyl)-N'-(Z)-N-(2-oxoindolin-3-ylidene)carbamimidoyl)acetimidamide (2), were prepared from the condensation reactions of 2'-nitroacetanilide and 1H-indole-2,3-dione with o-phenylenediamine and guanidinium ions in ethanol. The corresponding symmetrical bis-Schiff bases (Z,Z)-1,3-bis(2-oxoindolin-3-ylidene)guanidine (3) and N-((2-(1-iminoethyl)-2-(2-nitrophenyl)hydrazinyl)methyl)-N-(2-nitrophenyl)acetimidamide (4) were also prepared. The data obtained from the elemental, IR and NMR spectroscopic analyses were used to propose structures for the four compounds.

Keywords: Bis-Schiff bases, guanidinium ions, 2'-nitroacetanilide, 1H-indole-2,3-dione and o-phenylenediamine

Introduction

Synthetic chemists over the years continue to conduct research on the synthesis of new Schiff base ligands. Schiff base ligands have simple synthetic methods, with flexible coordination modes and more importantly they have exceptional antibacterial, antifungal and antitumor activities (Bagihali and Badami, 2008). The mechanism of the anti-

tumor activity of these Schiff bases is due to their ability to interact with DNA leading to DNA damage of cancer cells, and eventual blockage of division in cancer cells with overall result in cell death (Yin and Hong, 2012).

Schiff bases derived from 1H-indole-2,3-dione and its derivatives have been reported to display a broad range of biological activities including anticonvulsant, anti-depressant

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and sedative, antiviral, antibacterial, antifungal and anti-HIV activities (Pandeya and Witvrouw, 1999). 1H-indole-2,3-dione has also been used over the years as a raw material for drug synthesis and in the preparation of a large variety of heterocyclic compounds (Cerchiaro and Ferriera, 2004). Bis-Schiff bases readily form chelate rings with transition metal ions, and metal complexes of 1H-indole-2,3-dione derived bis-Schiff bases were reported to affect cell viability and also exhibited antimicrobial properties (Cerchiaro and Ferriera, 2005; Bacchi and Zani, 2005). Compounds incorporating the guanidine moiety have also been applied as antimicrobial, antiviral and antifungal agents (Mathias and Diop, 2008). Therefore, the synthesis of such compounds including their analogues or derivatives is considered an important approach to the production of new drugs.

There is increasing cases of resistance to the existing drugs by microbes in recent times; reports of screening of new potent and non-toxic antimicrobial drugs have therefore dominate the scientific literature. Hence our interest in the syntheses of new Schiff base ligands to serve as potential candidates in the design of new drugs.

Many symmetrical tetradentate Schiff bases of 1,2-diamines with *o*-hydroxy aldehyde or ketone have been prepared and studied intensely. However, less attention has been focused on unsymmetrical tetradentate Schiff bases derived from 1,2-diamines and different aldehydes. In particular, Schiff bases

derived from aromatic 1,2 diamines have been under-investigated. This research therefore, seeks to investigate some unsymmetrical tetradentate Schiff bases of aromatic diamines. It is worthwhile to mention here that unsymmetrical bis-Schiff bases are very difficult to obtain and are not easily isolated (Tan and Ang, 1988).

Materials and Methods

1H-indole-2,3-dione, 2'-nitroacetanilide, guanidinium chloride, *o*-phenylenediamine and potassium *tert*-butoxide (K-*t*BuO) were all commercially sourced from Sigma Aldrich and Merck. All the solvents were freshly distilled before use and the progress of the reactions were monitored by thin layer chromatography.

Synthesis of the bis-Schiff bases

The bis-Schiff bases were prepared by following modified literature procedures (Nagajothi and Parameswari, 2013). The ligands were synthesized by the condensation reaction of the diamine with the corresponding carbonyl compound(s) in ethanol under stirring, heat and reflux followed by isolation and purification.

Synthesis of (Z)-N-(2-nitrophenyl)-N'-(2-((Z)-(2-oxoindolin-3-ylidene)amino)phenyl) acetimidamide (1):

A solution of *o*-phenylenediamine (10 mmol, 1.08 g) in 10 mL absolute ethanol was combined with a mixture of ethanolic solutions of 2'-nitroacetanilide (10 mmol, 1.80 g) and 1H-indole-2,3-dione (10 mmol, 1.47 g). The mixture was

stirred in a round-bottomed flask and heated under reflux over a water bath for 3 hours. The mixture was cooled in a cold water bath. The yellow precipitate formed was filtered, washed with cold ethanol and dried over CaCl₂ in a desiccator. Some difficulty was experienced in the purification of the compound. It was found that repeated recrystallization from ethanol failed to remove contamination. Yield: 3.43 g (78.85%); mol wt.: 399.40 g mol⁻¹; m.p.: 268 °C; IR (KBr) (cm⁻¹): ν(C=O) 1721, ν(C=N) 1610, ν(N-H) 3475, 3428, ν(C-NO₂) 1565; ¹HNMR (DMSO-*d*₆), δ (ppm): 2.5 (s, -CH₃), 7-8.5 (m, phenyl protons), 12.0 (s, -NH); Anal. Calcd for C₂₂H₁₇N₅O₃: C, 66.16; H, 4.29; N, 17.53. Found: C, 70.89; H, 4.01; N, 15.03.

Synthesis of (Z)-N-(2-nitrophenyl)-N'-((Z)-N-(2-oxoindolin-3-ylidene)carbamimidoyl) acetimidamide (2):

Guanidinium chloride (0.96 g, 10 mmol) in 10 mL ethanol was combined with an ethanolic solution (10 mL) of potassium tert-butoxide (1.12 g, 10 mmol). The white solid precipitate (KCl) obtained was filtered off and washed with ethanol (1 mL). To the combined solution, 1H-indole-2,3-dione (1.47 g, 10 mmol) in 15 mL of ethanol and 2'-nitroacetanilide (1.80 g, 10 mmol) also in 15 mL of ethanol were added. The resulting clear solution was heated under reflux for 3 hours and allowed to cool to room temperature. The solid suspension formed was filtered and washed with ethanol to give compound **2** as a yellow crystalline solid.

Yield: 2.74 g (59.43%); mol wt.: 396.33 g mol⁻¹; m. p.: 376 °C; IR (KBr) (cm⁻¹): ν(C=O)1725, ν(C=N)1664, ν(N-H)3472, 3414, ν(N-O) 1586; ¹HNMR (DMSO-*d*₆), δ(ppm): 2.5 (s, -CH₃), 6.8 - 7.8 (m, phenyl protons), 12.0 (s, -NH); Anal. Calcd for C₁₇H₁₄N₆O₃.C₂H₅OH: C, 60.94; H, 5.34; N, 22.45. Found: C, 64.05; H, 4.03; N, 22.31.

Synthesis of (Z,Z)-1,3-bis(2-oxoindolin-3-ylidene) guanidinium ion (3):

The guanidinium ion was obtained from its hydrochloride salt, guanidinium chloride, as described for **2**. The filtrate was then combined with an ethanolic solution of 1H-indole-2,3-dione (20 mmol, 2.94 g) in a round-bottomed flask. The mixture was stirred and heated under reflux in a water bath for 3 hours after which the mixture was allowed to cool in a cold water bath. The light brown precipitate was filtered, washed with cold ethanol, dried and then stored in a desiccator over CaCl₂. Yield: 1.83 g (42.93%); mol wt.: 317.30 g mol⁻¹; m. p.: 363°C; IR (cm⁻¹): ν(C=O) 1730, ν(C=N) 1600, ν(N-H) 3400; Anal. Calcd for C₁₇H₁₁N₅O₂: C, 64.35; H, 3.47; N, 22.08. Found: C, 64.05; H, 3.43; N, 22.31.

Synthesis of (1E,1'E)-N',N''-(iminomethylene)bis(N-(2-nitrophenyl)acetimidamide) (4):

The free guanidinium ion was obtained from its hydrochloride salt as described for **2** and then combined with an ethanolic solution of 2'-nitroacetanilide (20 mmol, 3.60 g) in a round-bottomed flask. The mixture was stirred and

heated under reflux for 3 hours after which the reaction mixture was cooled in a cold water bath. The orange crystalline product was filtered and dried over CaCl₂. Some difficulty was experienced in the purification of the compound as it was soluble in most common solvents. Yield: 2.07 g, 41.96 %; mol wt.: 429.36 g mol⁻¹, m. p.: 78 - 80°C; IR (KBr) (cm⁻¹): ν(C=O) absent, ν(C=N) 1631, ν(N-H) 3475, 3350; Anal. Calcd for C₁₇H₁₉N₇O₄.C₂H₅OH: C, 52.85; H, 4.47; N, 22.71. Found: C, 52.22; H, 4.24; N, 20.48.

Results/Discussion

The isolated compounds were stable in air with sharp melting points and they were poorly soluble in most common organic solvents except compound **4** which practically dissolves in almost all the solvents. Elemental analysis indicates that compounds **2** and **4** have one molecule of ethanol each in their structure.

The 1H-indole-2,3-dione molecule possesses two different C=O bonds at the C-2 and C-3 positions with C=O stretching vibrations appearing around 1721 and 1760 cm⁻¹ at these two positions respectively while the C=O vibration is usually observed around 1701 cm⁻¹ in the free 2'-nitroacetanilide molecule (Fletton and Lancaster, 1986). The IR spectrum of compound **1** has characteristic ν(C=O) band of the C-3 still at 1721 cm⁻¹ an indication that this group on 1H-indole-2,3-dione is not involved in the reaction. The ν(C=O) bands at 1760 and 1701 cm⁻¹ in 1H-indole-2,3-dione and 2'-

nitroacetanilide respectively were not observed in the IR spectrum of the Schiff base **1** suggesting that these groups were involved in the Schiff base formation. A new band was observed at 1610 cm⁻¹ and was attributed to the formation of the characteristic azomethine C=N bonds in compound **1**. The ¹H NMR Spectrum of **1** (Fig. 1) contained reasonably well defined resonances in good agreement with the formation of the unsymmetrical Schiff base. The aromatic protons were observed as a multiplet between 7 – 8.5 ppm and a singlet at 2.5 ppm was attributed to the three methyl protons in 2'-nitroacetanilide. The singlet at 3.3 ppm was assigned to the residual protons from the (DMSO) solvent while the signal at 12 ppm was attributed to the NH from 1H-indole-2,3-dione (Jarrahpour and Brunel, 2007). Also, the N-H vibrations of observed around 3354 cm⁻¹ and 3386 cm⁻¹ in the free *o*-phenylenediamine molecule were not observed in the IR spectrum of the Schiff base **1**. This was attributed to the formation of the C=N bond at these positions with the C=O groups in 1H-indole-2,3-dione and 2'-nitroacetanilide molecules.

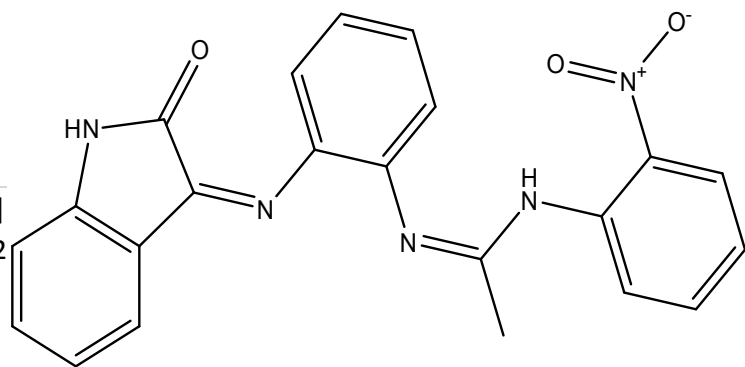


Fig. 1: Proposed structure of **1**.

Free guanidine ions were obtained from its hydrochloride salt *in situ* by addition of solution of the base potassium *tert*-butoxide in ethanol to the reaction mixture. The unsymmetrical Schiff base **2** was then prepared by the condensation reaction between the free guanidine ion, 1H-indole-2,3-dione and 2'-nitroacetanilide. The bands due to the C=O group in both C-2 position in 1H-indole-2,3-dione and 2'-nitroacetanilide were not observed in the IR spectrum of **2** indicating the involvement of this group in the formation of the Schiff base. The N-H vibrations observed around 3400 cm^{-1} in the free guanidine experienced a shift to 3414 cm^{-1} in the Schiff base **2** suggesting that some of the N-H bonds had been used up in the formation of the Schiff base.

This compound was soluble in DMF and DMSO and the ^1H NMR was therefore recorded in DMSO. The aryl protons were observed as a multiplet between 6.8 – 7.8 ppm and a singlet signal appearing at 2.5 ppm was attributed to the three methyl protons from 2'-nitroacetanilide as in compound **1**.

The signals around 8 – 9.5 ppm may be due to the presence of impurities which makes purification of this compound to be very difficult. This actually affected the accuracy of the elemental analysis data. The signal at 12 ppm was attributed to the NH group in 1H-indole-2,3-dione. The proposed structure for **2** based on the analytical and spectroscopic data is shown in Fig. 2.

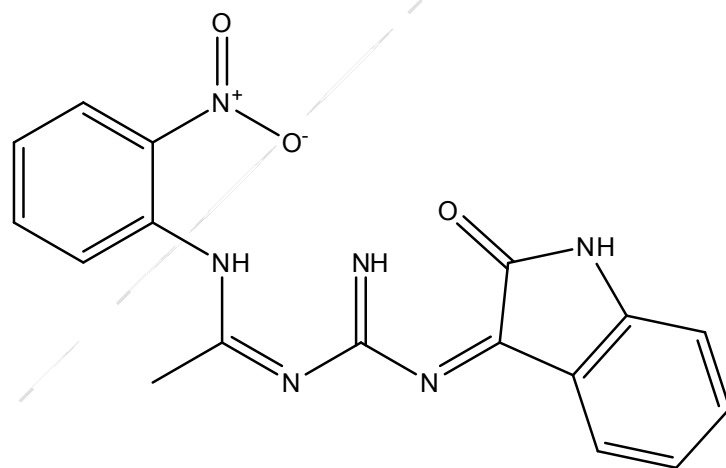


Fig. 2. Proposed structure of **2**

The Schiff base **3** was obtained by the condensation reaction between the generated free guanidine ion and 1H-indole-2,3-dione. This compound was poorly soluble in most common solvents including DMSO and DMF; therefore its NMR could not be recorded. The IR spectrum of **3** is characterized by a complete disappearance of bands due to C=O groups usually observed at 1760 cm^{-1} in free 1H-indole-2,3-dione molecule. The other C=O band appearing at 1721 cm^{-1} shifted to 1730 cm^{-1} in **3**. The disappearance of the N-H vibrations that normally appears around 3450 cm^{-1} in 1H-indole-2,3-

dione was observed at 3400 cm^{-1} in **3**. A new band was observed around 1600 cm^{-1} attributable to C=N vibrations suggesting the formation of the expected Schiff base **3** as

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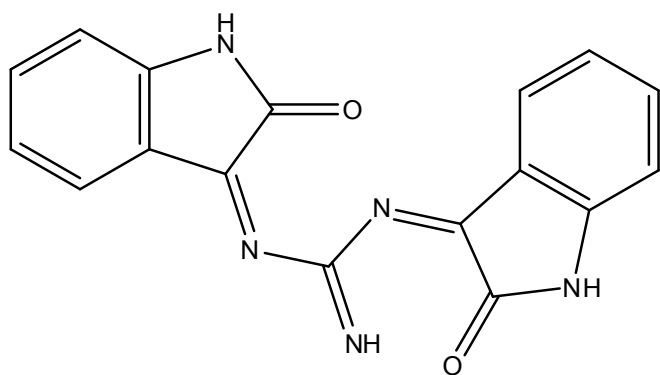


Fig. 3: Proposed structure of **3**

The Schiff base **4** was prepared by the condensation reaction of free guanidine ion with two equivalent of 2'-nitroacetanilide. This compound was also poorly soluble in all the common solvents and therefore its NMR could not be recorded. Some observed spectral changes in the IR spectra of the starting materials were attributed to formation of the Schiff base **4**. The C=O band observed around 1701 cm^{-1} in the free 2'-nitroacetanilide did not appear in the IR spectrum of **4**. The N-H vibrations observed in the IR spectrum of free guanidinium chloride were absent in **6**. Instead, these bands were shifted to around 3475 and 3350 cm^{-1} an indication that these groups were involved in the reaction leading to the formation of the Schiff base **4**. A new band at 1631 cm^{-1} was

assigned to the azomethine C=N band. The following structure was proposed for **4** based on the analytical and spectroscopic data:

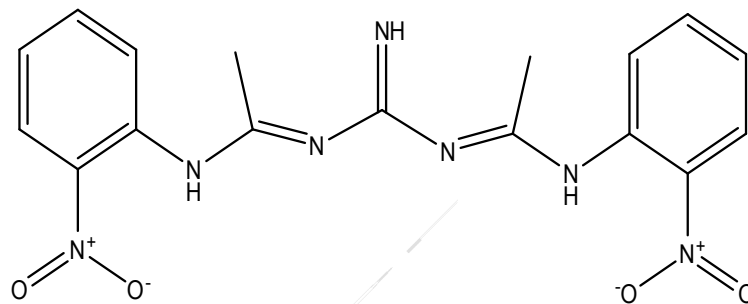


Fig. 4: Proposed structure of **4**

Conclusions

Symmetrical and asymmetrical bis-Schiff bases were synthesized using *o*-phenylenediamine and the less commonly applied guanidine as skeleton. Deviations of analytical and spectroscopic data of the compounds from those of the corresponding starting materials suggest the formation of new compounds. All the four compounds were air and moisture stable with two -C=NR functional groups and two possible O donor sites in their structures. The two asymmetrical Schiff bases **1** and **2** are novel and work is ongoing to characterize them further possibly to obtain their single crystals and determine their X-ray molecular structures.

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