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Spectroscopic characterization, antimicrobial activity, DFT computation and docking studies of sulfonamide Schiff bases

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ABSTRACT

Schiff bases synthesised from the condensation of 2-(hydroxy)naphthaldehyde and sulfonamides (sufathiazole (STZ), sulfapyridine (SPY), sulfadiazine (SDZ), sulfamerazine (SMZ) and sulfaguanidine (SGN)) are characterized by different spectroscopic data (FTIR, UV–Vis, Mass, NMR) and two of them, (E)-4-(((2-hydroxynaphthalen-1-yl)methylene)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (**1a**) and (E)-*N*-(diaminomethylene)-4-(((2-hydroxynaphthalen-1-yl)methylene)amino)benzenesulfonamide (**1e**) have been confirmed by single crystal X-ray structure determination. Antimicrobial activities of the Schiff bases have been evaluated against certified and resistant Gram positive (*Staphylococcus aureus*, *Enterococcus facelis*) and Gram negative (*Streptococcus pyogenes*, *Salmonella typhi*, *Shigella dysenteriae, Shigella flexneri, Klebsiella pneumonia*) pathogens. Performance of Schiff base against the resistant pathogens are better than standard stain and MIC data lie 32–128 μg/ml while parent sulfonamides are effectively inactive (MIC >512 μg/ml). The DFT optimized structures of the Schiff bases have been used to accomplish molecular docking studies with DHPS (dihydropteroate synthase) protein structure (downloaded from Protein Data Bank) to establish the most preferred mode of interaction. ADMET filtration, Cytotoxicity (MTT assay) and haemolysis assay have been examined for evaluation of druglike character.

1. Introduction

Sulfonamides are well known antibiotics for treatment of bacterial infection, malaria, leprosy etc. Sulpha drugs exert their bactericidal effect by inhibiting the metabolic pathway of the enzyme *Dihydropteroate synthetase* (DHPS). Folate, a vital agent for formation of nucleic acids (DNA, RNA) in the cells, is synthesised by direct participation of DHPS in a catalytic cycle [1–3]. Prolong consumption of sulfonamides shows some adverse reaction to liver, kidney, skin, lung, heart and blood [4,5]. These side effects have demanded world wide effort to search for new generation drugs. One of the simple ways of functionalization is the condensation of aliphatic/aromatic aldehydes/ketones with sulfonamides to synthesize sulfonamide-imines. Literature shows some publications on biological activities of sulfonamide-imines and their transition metal complexes [6–11]. For the last couple of years we have also been engaged in the synthesize of sulfonamide-imines [12,13], sulfonamide-azo [14] compounds and exploration of their medicinal activity and toxicity.

Schiff bases are one of the most widely used organic compounds and unveil a broad array of biological activities [15,16] including antifungal [17,18], antibacterial [19,20] antiproliferative, antimalarial [21,22] and antipyretic. Imine group also appears in many natural products [23] those are very important for their biological activity [24,25]. Again, phenols are one of the oldest antibacterial substances to destroy microorganism. Chlorooxyphenol (principal ingredient in Dettol), hexachlorophene, thymol, amyl-*m*-cresol (used in Strepsils) are basically aromatic phenol and commercially used disinfectant. As a part of continuous research, in this paper we have characterized Schiff bases obtained from 2-(hydroxy)naphthaldehyde and sulfonamides such as sufathiazole (STZ), sulfapyridine (SPY), sulfadiazine (SDZ), sulfamerazine (SMZ) and sulfaguanidine (SGN). Using different spectroscopic techniques Schiff bases have been characterized along with single crystal X-ray structures of two compounds. The DFT computation has been carried out to explain the electronic structure. Antimicrobial activity of the compounds has been evaluated against several standard and resistant Gram positive and Gram negative bacterial stain. Docking of Schiff bases with DHPS protein has been focused to investigate

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the most preferred binding mode and hence the mechanism of antimicrobial action might be rationalised. Docking is a growing *in-silico* technique useful for prediction of drug-likeness and toxicity (ADMET) of small molecules [26].

2. Experimental

2.1. Materials and methods

Sufathiazole (STZ), sulfapyridine (SPY), sulfadiazine (SDZ), sulfamerazine (SMZ) and sulfaguanidine (SGN) Sufathiazole (STZ) were purchased from Hi-Media, and 2-hydroxynaphthyldehyde was prepared from 2-naphthol following Duff reaction [27]. All other chemicals and solvents were of analytical grade and used without any purification.

Melting points were determined on a melting Point apparatus using open capillary and the reported values are uncorrected. The FTIR spectra (in KBr pellets) were recorded on a RX-1 Perkin Elmer spectrophotometer in the range 4000–400 cm^{-1}. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker 300 MHz FT-NMR spectrometer using TMS as internal standard. The mass spectra were recorded on a Water HRMS model XEVO-G2QTOF#YCA351 spectrometer. UV–Vis spectra were recorded on Lambda 25 Perkin Elmer spectrophotometer. Elemental analyses were performed using a Perkin-Elmer 2400 Series-II CHN analyzer, Perkin Elmer, USA elemental analyzer.

2.1.1. Synthesis of (E)-4-(((2-hydroxynaphthalen-1-yl)methylene) amino)-N-(thiazol-2-yl)benzenesulfonamide (**1a**)

2-(Hydroxy)naphthaldehyde (0.2 g, 1.16 mmol) was dissolved in 25 ml of super dry ethanol followed by the dropwise addition of sulfathiazole (STZ) (0.3 g, 1.18 mmol in 10 ml ethanol) with constant stirring for 30 min. The mixture was then refluxed for 2.5 h. The solution was then cooled to room temperature and allowed to evaporate slowly in air; an orange coloured crystals of (E)-4-(((2-hydroxynaphthalen-1-yl)methylene)amino)-*N*-(thiazol-2-yl)benzenesulfonamide (**1a**) deposited on the wall of the beaker. The crystals were filtered and further recrystallized from hot ethanol. The purity of the product was checked by TLC; yield, 0.32 g (66%).

All other Schiff-bases (**1b**-**1e**) were prepared by identical procedure with the yield of 60–75%.

1a: Mp., 264(2)°C. HRMS (ESI) *m/z*: $[M+H]^+$ at 410.0928 (calcd 410.48); FTIR (ν, cm^{-1}): ν(OH), 3455 and 3163; ν(C=N), 1624; ν(SO_2), 1590, 1528, 1350 (-S=O of SO_2 anti), 1280, 1141 (-S=O of SO_2 sym), 1087, 840, 832, 568. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.74 (1H, s, OH), 9.64 (1H, s,11-H); 8.49 (1H, d, J = 8.6, 3-H); 7.96 (1H, d, J = 9.1, 8-H); 7.92 (2Hs, d, J = 8.4, 14-H, 16-H); 7.79(1H, d, J = 7.7, 4-H), 7. 74 (2Hs, d, J = 8.4, 13-H, 17-H); 7.54 (1H, t, J = 7.3, 7-H); 7.35 (1H, t, J = 7.3, 6-H); 7.26 (1H, d, J = 6.0, 5-H); 7.01 (1H, d, J = 9.1, 20-H); 6.84(1H, d, J = 4.5, 19-H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 171.3, 169.4, 164.4, 157.1, 147.6, 140.0, 138.0, 133.5, 129.7, 129.5, 128.8, 127.8, 125.0, 122.6, 120.9, 119.2, 112.9, 109.3. UV–Vis (λ_{max}, nm (ε, 10^3 M^{-1} cm^{-1}) in acetonitrile): 462 (13.8), 442 (14.7), 370 (11.3), 318 (15.3). Anal. Calcd. for $C_{20}H_{15}N_3O_3S_2$ (407): C, 58.66; H, 3.69; N, 10.26%. Found: C, 60.02; H, 3.78; N, 10.35%.

2.1.2. (E)-4-(((2-hydroxynaphthalen-1-yl)methylene)amino)-N-(pyridin-2-yl) benzenesulfonamide (**1b**)

1b: Orange solid; yield 65%; Mp., 282(2)°C. HRMS (ESI) *m/z*: $[M+H]^+$ at 404.5531 (calcd 404.10); FTIR (ν, cm^{-1}): ν(-SO_2NH), 3461; ν(OH), 3152; ν(C=N), 1619; ν(SO_2), 1580, 1357 (-S=O of SO_2 anti), 1273, 1133 (-S=O of SO_2 sym), 1082, 960, 781, 634, 569. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.07 (1H, s, OH), 9.6 (1H, s,11-H); 8.48 (1H, d, J = 8.5, 3-H); 8.00(1H, s, 22-H), 7.94 (3Hs, d, J = 9.0, 14-H, 16-H and 8-H); 7.76(4Hs, 13H, 17-H, 4-H, 20-H); 7.53 (1H, t, J = 7.35, 7-H); 7.35 (1H, t, J = 7.32, 6-H); 7.20 (1H, d, J = 8.2, 19-H); 7.0 (1H, d, J = 9.2, 5-H); 6.86(1H, s, 21-H). ^{13}C NMR (300 MHz, DMSO-d_6): δ171.5, 164.4, 157.1, 153.2, 152.8, 147.6, 133.5, 129.7, 129.5, 129.3, 128.7, 127.2, 124.7, 124.3, 122.6, 121.25, 121.0, 119.2, 112.6, 109.3. UV–Vis (λ_{max}, nm (ε, 10^3 M^{-1} cm^{-1}) in methanol): 462 (16.3), 442 (17.3), 370 (14.8), 317 (23.4). Anal. Calcd. for $C_{22}H_{17}N_3O_3S$ (403.45): C, 65.49; H, 4.25; N, 10.42%. Found: C, 65.60; H, 4.40; N, 10.50%.

2.1.3. (E)-4-(((2-hydroxynaphthalen-1-yl)methylene)amino)-N-(pyrimidin-2-yl) benzenesulfonamide (**1c**)

1c: Orange solid; yield 62%; M.p., 272(2)°C. HRMS (ESI) *m/z*: $[M+H]^+$ at 405.3291 (calcd 405.09); FTIR (ν, cm^{-1}): ν(-SO_2NH), 3415; ν(OH), 3036; ν(C=N),1622; ν(SO_2), 1587, 1333 (-S=O of SO_2 anti), 1157 (-S=O of SO_2 sym), 1093, 946, 840, 630, 573. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.82 (1H, s, OH), 9.6 (1H, s,11-H); 8.52 (3Hs, m, 19-H, 21-H and 3-H); 8.06 (2Hs, d, J = 8.7, 14-H and 16-H), 7.96 (1H, d, J = 9.0, 8-H); 7.78 (3Hs, m, 13-H, 17-H, 4-H); 7.54 (1H, t, J = 7.3, 7-H); 7.35 (1H, t, J = 7.6, 6-H); 7.07 (1H, m, 20-H); 7.0 (1H, d, J = 6.0, 5-H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 171.6, 158.9, 157.7, 157.1, 153.5, 148.2, 138.9, 137.8, 130.3, 129.5, 128.8, 127.3, 124.7, 124.3, 122.6, 121.1, 119.2, 109.3. UV–Vis (λ_{max}, nm (ε, 10^3 M^{-1} cm^{-1}) in methanol): 462 (18.6), 442 (19.8), 369 (15.6), 316 (21.9). Anal. Calcd. for $C_{21}H_{16}N_4O_3S$ (404.44): C, 62.36; H, 3.99; N, 13.85%. Found: C, 62.45; H, 4.12; N, 13.57%.

2.1.4. (E)-4-(((2-hydroxynaphthalen-1-yl)methylene)amino)-N-(4-methylpyrimidin-2-yl)benzenesulfonamide (**1d**)

1d: Orange solid; yield 65%; Mp., 246(2)°C. HRMS (ESI) *m/z*: $[M+H]^+$ at 419.0718 (calcd 419.11); FTIR (ν, cm^{-1}): ν(-SO_2NH), 3457; ν(OH), 3029; ν(C=N), 1625; ν(SO_2), 1589, 1444, 1354 (-S=O of SO_2 anti), 1143 (-S=O of SO_2 sym), 1082, 961, 872, 753, 569.^{1}H NMR (300 MHz, DMSO-d_6): δ 11.77 (1H, s, OH), 9.64 (1H, s,11-H); 8.49 (1H, d, J = 8.4 3-H); 8.33 (1H, d, J = 8.7, 19-H), 8.06 (2Hs, d, J = 8.5, 14-H, 16-H); 7.95 (2Hs, d, J = 9.2, 8-H); 7.74 (3Hs, m, 13-H, 17-H, 4-H); 7.56 (1H, t, J = 7.7, 7-H); 7.35 (1H, t, J = 7.5, 6-H); 7.0 (1H, d, J = 9.0, 20-H); 6.92(1H, d, J = 6.0, 5-H); 2.33(1H, s, -CH_3 C-21). ^{13}C NMR (300 MHz, DMSO-d_6): δ171.8, 164.3, 157.4, 156.9, 153.4, 148.0, 138.9, 133.6, 130.5, 129.5, 128.8, 127.3, 125.4, 124.7, 122.6, 121.0, 119.2, 112.4. UV–Vis (λ_{max}, nm (ε, 10^3 M^{-1} cm^{-1}) in methanol): 464 (10.1), 442 (10.9), 368 (8.3), 316 (12.2). Anal. Calcd. for $C_{22}H_{18}N_4O_3S$ (404.44): C, 63.14; H, 4.34; N, 13.39%. Found: C, 63.05; H, 4.46; N, 13.28%.

2.1.5. (E)-N-(diaminomethylene)-4-(((2-hydroxynaphthalen-1-yl) methylene) amino) benzenesulfonamide (**1e**)

1e: Orange solid; yield 75%; Mp., 238(2)°C. HRMS (ESI) *m/z*: $[M+H]^+$ at 369.1024 (calcd 369.09); FTIR (ν, cm^{-1}): ν(-SO_2NH), 3445; ν(OH), 3152; ν(C=N), 1629; ν(SO_2), 1544, 1355 (-S=O of SO_2 anti), 1264, 1135 (-S=O of SO_2 sym), 1092, 825, 739, 642, 588. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.66 (1H, s,11-H); 8.50 (1H, d, J = 8.4 3-H); 7.96 (1H, d, J = 9.1, 8-H), 7.81(3Hs, m, 14-H, 16-H and 4-H); 7.78 (2Hs, d, J = 8.3, 14-H and 16-H); 7.54 (1H, t, J = 7.1, 7-H); 7.35 (1H, t, J = 7.2, 6-H); 7.02 (1H, d, J = 9.1, 5-H). 6.73 (4Hs, bs, -NH_2). ^{13}C NMR (300 MHz, DMSO-d_6): δ171.4, 158.6, 156.9, 146.8, 142.4, 138.9, 133.6, 131.3, 129.7, 129.3, 128.7, 122.6, 121.0, 120.9, 112.8, 109.2. UV–Vis (λ_{max}, nm (ε, 10^3 M^{-1} cm^{-1}) in methanol): 461 (10.7), 442 (12.4), 368 (10.0), 316 (13.8). Anal. Calcd. for $C_{18}H_{16}N_4O_3S$ (368.09): C, 58.68; H, 4.38; N, 15.21%. Found: C, 58.45; H, 4.45; N, 15.20%.

2.2. X-ray crystal structures

The single crystals of **1a** (0.11 × 0.13 × 0.18 mm^3) and **1e** (0.10 × 0.13 × 0.16 mm^3) were obtained by slow diffusion of dichloromethane solution to hexane (1:3, v/v). The X-ray crystal