

## SYNTHESIS, CHARACTERIZATION AND DFT STUDIES OF SCHIFF BASES OF *p*-METHOXYSALICYLALDEHYDE

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(Received September 23, 2022; Revised December 5, 2022; Accepted December 16, 2022)

**ABSTRACT.** Five new Schiff bases synthesized by the reaction between 2-(methylthio)aniline derivatives and *p*-methoxysalicylaldehyde are presented as Mth-1 ( $R = H$ ), Mth-2 ( $R = CH_3$ ), Mth-3 ( $R = OCH_3$ ), Mth-4 ( $R = Cl$ ) and Mth-5 ( $R = Br$ ). They were characterized by CHNS analyses, NMR ( $^1H$ ,  $^{13}C$ , DEPT135, COSY and HSQC), FTIR and UV-Vis spectroscopic techniques. FT-IR, elemental analyses and NMR data supported the formation of the Schiff bases, with the chemical shifts of azomethine and phenol protons showing sensitivity to ring substitution. The crystal structure of Mth-1 featured the alignment of the phenyl rings to each other and to the C=N group with dihedral angles  $>170^\circ$ . The DFT calculations corroborated the bond lengths and angles of Mth-1. The HOMO-LUMO energies, dipole moments and other reactivity parameters were calculated. The methyl-substituted Mth-2 was the least polar of the compounds. With calculated energy band gaps of almost 4 eV, the compounds may have applications in the semiconductors field.

**KEY WORDS:** Schiff bases, *p*-methoxysalicylaldehyde, Crystal structure, Spectroscopic properties, DFT calculations

## INTRODUCTION

Research on Schiff bases continues to generate much attention because of their importance and myriad of possible complexes with metal ions [1-6]. Salicylaldehyde is an important precursor to useful organic compounds such as salicylaldoxime, catechol, benzofuran, and coumarins. Salicylaldehyde and its derivatives are useful in preparing Schiff bases with diverse structures by condensation reaction with compounds containing one or more amine groups. Owing to their relative ease of synthesis and flexible structural designs, many salicylaldehyde-based Schiff bases have shown applications in medicine and pharmacology [4-7], catalysis [8], as well as valuable functionality in structural and spectroscopic studies [6, 9-10]. They have been found relevant in electrochemical and optical, electrochemical and sensors research [1-3]. Various salicylaldehyde-based Schiff bases have been prepared, for example, the synthesis and structures of Schiff bases from 2-(methylthio)aniline and salicylaldehyde substituted with 3-OCH<sub>3</sub>, Br, Cl and di-*tert*-butyl groups and their ruthenium(II) complexes have been reported [11-14]. However, those prepared from *p*-methoxysalicylaldehyde and substituted 2-(methylthio)anilines are yet to be reported. The study of substitution effect on properties of organic compounds continues to increase the knowledge base. Density functional theory (DFT) at different levels of calculations has shown reliability in prediction of various properties such as geometry parameters, band gap energies, reactivity and quantum chemical descriptors in salicylaldehyde-based Schiff bases [1, 9-10]. We

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hereby report the synthesis, characterization and DFT studies of Schiff bases derived from *p*-methoxysalicylaldehyde and 2-(methylthio)anilines with *CH*<sub>3</sub>, *OCH*<sub>3</sub>, *Cl* and *Br* substitution. The detailed bulk compositions were confirmed by elemental analysis, NMR, FT-IR and UV-Vis spectroscopic techniques. Theoretical studies were conducted to measure and evaluate the geometry parameters, frontier molecular orbitals and chemical descriptors at the B3LYP6 level and 6-311++G(d,p) basis set. The single crystal suitable for X-ray diffraction could only be obtained for one Schiff base whose bond lengths and angles were compared with those calculated for all five compounds. The electronic effect of the substituents on the proton NMR spectra and the reactivity factors were highlighted and discussed.

## EXPERIMENTAL

### Materials and methods

The analytical grade chemicals and reagents from commercial suppliers were used as obtained. One- and two-dimensional NMR spectra (<sup>1</sup>H, <sup>13</sup>C, DEPT135, COSY and HSQC) were obtained in CDCl<sub>3</sub> solvent relative to tetramethylsilane on Bruker Avance 400 MHz NMR spectrometer. CHNS analyses were carried out on Elementar Analysensysteme varioMICRO V1.6.2 GmbH. Uncorrected melting points were obtained using the Galenkemp melting point apparatus. The infrared spectra were obtained as solids in the mid-IR (4000–650 cm<sup>-1</sup>) on PerkinElmer Spectrum 100 ATR-FTIR. The electronic spectra (200–600 nm) were obtained in dichloromethane solution on PerkinElmer Lambda 25 UV-VIS Spectrometer.

### General procedure for the synthesis of Schiff bases

The Schiff bases were prepared by refluxing measured amounts of 2-(methylthio)anilines and *p*-methoxysalicylaldehyde in 4 mL ethanol/dichloromethane mixture (1:1) for 6 h (Scheme 1). The solvent was reduced using a rotary evaporator and the precipitates were obtained by filtration, washed with ethanol and dried.

*Synthesis of (E)-5-methoxy-2-((2-(methylthio)phenyl)imino)methyl)phenol (MtH-1)*. MtH-1 was prepared from 2-(methylthio)aniline (0.250 g, 1.80 mmol) and *p*-methoxysalicylaldehyde (0.2700 g, 1.77 mmol). Brown solid, yield: 0.46 g (95%). M.p. 68–69 °C. *Anal.* % for C<sub>15</sub>H<sub>15</sub>NO<sub>2</sub>S (273.35): calcd. C 65.91, H 5.53, N 5.12, S 11.73; found C 65.80, H 5.24, N 5.13, S 11.42. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm = 2.47 (s, 3H, H8), 3.85 (s, 3H, H9), 6.50 (d, 1H, H15), 6.54 (s, 1H, H13), 7.17 (d, 1H, H6), 7.24 (s, 1H, H3), 7.25 (t, 1H, H5), 7.28 (t, 1H, H4), 7.30 (d, 1H, H16), 8.54 (s, 1H, H7), 13.65 (s, 1H, H1). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ ppm = 14.78 (C8), 55.54 (C9), 101.11 (C13), 107.13 (C15), 113.19 (C11), 117.03 (C6), 124.91 (C5), 125.26 (C4), 126.92 (C3), 133.55 (C16), 134.49 (C2), 145.39 (C1), 160.73 (C7), 163.66 (C12), 164.03 (C14). IR (cm<sup>-1</sup>): ν<sub>C-H</sub> (2929, 2840), ν<sub>C=N</sub> (1614), ν<sub>C=C</sub> (1611, 1576, 1466), δ<sub>O-H</sub> (1557), ν<sub>C-O</sub> (1336), ν<sub>C-N</sub> (1289), ν<sub>C-S</sub> (715, 682). UV, λ<sub>max</sub> (nm): 246, 273, 359.

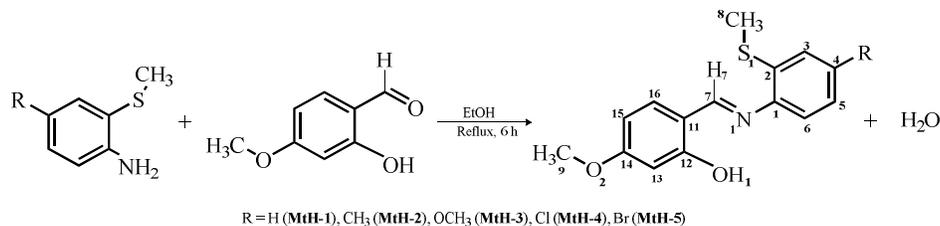
*Synthesis of (E)-5-methoxy-2-((4-methyl-2-(methylthio)phenyl)imino)methyl)phenol (MtH-2)*. MtH-2 was prepared from 4-methyl-2-(methylthio)aniline (0.202 g, 1.32 mmol) and *p*-methoxysalicylaldehyde (0.1126 g, 0.74 mmol). Yellow solid, yield: 0.18 g (85%). M.p. 72–73 °C. *Anal.* % for C<sub>16</sub>H<sub>17</sub>NO<sub>2</sub>S (287.38): calcd. C 66.87, H 5.96, N 4.87, S 11.16; found C 67.07, H 5.88, N 4.94, S 11.21. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm = 2.38 (s, 3H, H4), 2.46 (s, 3H, H8), 3.84 (s, 3H, H9), 6.49 (d, 1H, H15), 6.54 (s, 1H, H13), 6.98 (d, 1H, H5), 7.04 (s, 1H, H3), 7.07 (d, 1H, H6), 7.27 (d, 1H, H16), 8.53 (s, 1H, H7), 13.70 (s, 1H, H1). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ ppm = 14.94 (C8), 21.24 (C4), 55.44 (C9), 101.18 (C13), 107.04 (C15), 113.29 (C11), 116.68 (C6), 125.83 (C5), 126.10 (C3), 133.40 (C16), 134.25 (C2), 136.92 (C4), 143.00 (C1), 159.83

(C7), 163.68 (C12), 163.93 (C14). IR (cm<sup>-1</sup>):  $\nu_{\text{C-H}}$  (2917, 2839),  $\nu_{\text{C=N}}$  (1634),  $\nu_{\text{C=C}}$  (1607, 1587, 1462),  $\delta_{\text{O-H}}$  (1559),  $\nu_{\text{C-O}}$  (1339),  $\nu_{\text{C-N}}$  (1289),  $\nu_{\text{C-S}}$  (713, 680). UV,  $\lambda_{\text{max}}$  (nm): 247, 276, 363.

**Synthesis of (E)-5-methoxy-2-((4-methoxy-2-(methylthio)phenyl)imino)methyl)phenol (MtH-3).** MtH-3 was prepared from 4-methoxy-2-(methylthio)aniline (0.1134 g, 0.67 mmol) and *p*-methoxysalicylaldehyde (0.1134 g, 0.74 mmol). Yellow solid, yield: 0.0922 g (45%). M.p. 80-81 °C. *Anal.* % for C<sub>16</sub>H<sub>17</sub>NO<sub>3</sub>S (303.38): calcd. C 63.34, H 5.65, N 4.62, S 10.57; found C 63.38, H 6.06, N 4.66, S 10.72. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  ppm = 2.45 (s, 3H, H8), 3.83 (s, 3H, H4), 3.85 (s, 3H, H9), 6.48 (d, 1H, H15), 6.52 (s, 1H, H13), 6.69 (d, 1H, H5), 6.77 (s, 1H, H3), 7.13 (d, 1H, H6), 7.25 (d, 1H, H16), 8.50 (s, 1H, H7), 13.66 (s, 1H, H1). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  ppm = 14.80 (C8), 55.40 (C4), 55.50 (C9), 101.15 (C13), 106.91 (C15), 109.89 (C3), 111.16 (C5), 113.36 (C11), 117.31 (C6), 133.20 (C16), 136.45 (C2), 138.68 (C1), 158.69 (C7), 158.82 (C4), 163.34 (C12), 163.68 (C14). IR (cm<sup>-1</sup>):  $\nu_{\text{C-H}}$  (2911, 2839),  $\nu_{\text{C=N}}$  (1625),  $\nu_{\text{C=C}}$  (1603, 1588, 1467),  $\delta_{\text{O-H}}$  (1560),  $\nu_{\text{C-O}}$  (1338),  $\nu_{\text{C-N}}$  (1285),  $\nu_{\text{C-S}}$  (716, 684). UV,  $\lambda_{\text{max}}$  (nm): 244, 280, 367.

**Synthesis of (E)-2-((4-chloro-2-(methylthio)phenyl)imino)methyl)-5-methoxyphenol (MtH-4).** MtH-4 was prepared from 4-chloro-2-(methylthio)aniline (0.1161 g, 0.67 mmol) and *p*-methoxysalicylaldehyde (0.1140 g, 0.75 mmol). Yellow solid, yield: 0.175 g (85%). M.p. 90-91 °C. *Anal.* % for C<sub>15</sub>H<sub>14</sub>ClNO<sub>2</sub>S (307.80): calcd. C 58.53, H 4.58, N 4.55, S 10.42; found C 57.94, H 4.95, N 4.49, S 9.85. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  ppm = 2.45 (s, 3H, H8), 3.83 (s, 3H, H9), 6.48 (d, 1H, H15), 6.51 (s, 1H, H13), 7.04 (d, 1H, H5), 7.10 (d, 1H, H6), 7.12 (s, 1H, H3), 7.25 (d, 1H, H16), 8.48 (s, 1H, H7), 13.34 (s, 1H, H1). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  ppm = 14.64 (C8), 55.43 (C9), 101.10 (C13), 107.27 (C15), 113.05 (C11), 117.76 (C6), 124.24 (C5), 124.99 (C3), 132.45 (C16), 133.68 (C2), 136.76 (C4), 143.74 (C1), 160.83 (C7), 163.51 (C12), 164.23 (C14). IR (cm<sup>-1</sup>):  $\nu_{\text{C-H}}$  (2915, 2834),  $\nu_{\text{C=N}}$  (1632),  $\nu_{\text{C=C}}$  (1605, 1576, 1462),  $\delta_{\text{O-H}}$  (1554),  $\nu_{\text{C-O}}$  (1340),  $\nu_{\text{C-N}}$  (1291),  $\nu_{\text{C-Cl}}$  (756),  $\nu_{\text{C-S}}$  (717, 688). UV,  $\lambda_{\text{max}}$  (nm): 247, 277, 364.

**Synthesis of (E)-2-((4-bromo-2-(methylthio)phenyl)imino)methyl)-5-methoxyphenol (MtH-5).** MtH-5 was prepared from 4-bromo-2-(methylthio)aniline (0.1143 g, 0.52 mmol) and *p*-methoxysalicylaldehyde (0.0881 g, 0.58 mmol). Yellow solid, yield: 0.165 g (89%). M.p. 94-95 °C. *Anal.* % for C<sub>15</sub>H<sub>14</sub>BrNO<sub>2</sub>S (352.25): calcd. C 51.15, H 4.01, N 3.98, S 9.10; found C 51.99, H 3.97, N 4.03, S 9.37. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  ppm = 2.45 (s, 3H, H8), 3.84 (s, 3H, H9), 6.48 (d, 1H, H15), 6.51 (s, 1H, H13), 6.98 (d, 1H, H6), 7.25 (d, 1H, H5), 7.25 (d, 1H, H16), 7.26 (s, 1H, H3), 8.48 (s, 1H, H7), 13.34 (s, 1H, H1). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  ppm 14.63 (C8), 55.40 (C9), 101.06 (C13), 107.23 (C15), 113.01 (C11), 118.06 (C6), 120.25 (C5), 126.98 (C3), 127.90 (C16), 133.68 (C2), 137.03 (C4), 144.12 (C1), 160.79 (C7), 163.48 (C12), 164.21 (C14). IR (cm<sup>-1</sup>):  $\nu_{\text{C-H}}$  (2911, 2839),  $\nu_{\text{C=N}}$  (1627),  $\delta_{\text{O-H}}$  (1545),  $\nu_{\text{C=C}}$  (1602, 1572, 1468),  $\nu_{\text{C-O}}$  (1342),  $\nu_{\text{C-N}}$  (1291),  $\nu_{\text{C-Br}}$  (746),  $\nu_{\text{C-S}}$  (715, 688). UV,  $\lambda_{\text{max}}$  (nm): 244, 277, 363.



Scheme 1. The synthesis scheme for the Schiff bases and the NMR atom labeling.

### *X-Ray crystallography data*

The crystallography data of the Schiff base Mt-1H was collected at 200 K on a Bruker KAPPA APEX II diffractometer (Mo- $K\alpha$  radiation,  $\lambda = 0.71073 \text{ \AA}$ ). The structure of MtH-1 was solved and refined by direct methods and least-squares procedures using SHELXL-2013 [15]. The non-hydrogen atoms were anisotropically refined. The position and isotropic temperature parameter of the phenolic hydrogen H1 were independently refined. The positions of all other hydrogen atoms were fixed relative to the positions of the bonded atoms but the isotropic temperature parameters were independently refined. The crystal structure diagrams were obtained using ORTEP-3 and Mercury [16, 17]. CCDC 890400 contains the supplementary crystallographic data for MtH-1, freely available at the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

### *Computational details*

DFT was employed to optimize the structures of the Schiff bases and all calculations were performed with the Gaussian 16 B.01 package [18] using B3LYP functional with 6-311++G(d,p) basis set [19-21]. GaussView 6.0.16 was used for modeling and for visualizing the resulting structures [22]. Gas-phase geometry optimization was employed to generate the structures which were used in calculations. Chem3D Ultra 10.0 was subsequently used for generating high resolution structures [23]. Single-point energy calculation for ultraviolet visible (UV-Vis), using the time-dependent density functional theory (TD-DFT) approach, was carried out in dichloromethane ( $\epsilon = 8.93$ ) over 50–500 nm range. All solvent calculations were done using the solvation model based on density (SMD).

## RESULTS AND DISCUSSION

The stoichiometric formulas of the Schiff bases are proposed based on CHNS analysis which correspond closely with the calculated CHNS values. The compounds are soluble in dichloromethane and chloroform but insoluble in water, ethanol, DMSO or DMF, hence their antimicrobial activity could not be determined.

### *Crystallography data analysis*

The single crystal of MtH-1 was obtained from a dichloromethane-ethanol solvent mixture and crystallized in the monoclinic  $P2_12_12_1$  space group. Figure 1 shows the atom labeling of MtH-1 with ellipsoid at 50% probability, and the packing diagram depicting the intramolecular hydrogen bond. The crystallography data, and the lengths and angles of selected bonds are presented in Tables 1 and 2. The molecule contains two different carbon to nitrogen bonds. The azomethine N1=C7 bond length of 1.28 Å is shorter than N1-C1 bond distance of 1.41 Å [2, 24-25]. The doubly bonded aromatic C=C bond distances (1.37–1.41 Å) are also smaller than C7-C11 length (1.45 Å). The additional  $\pi$  electron density in the delocalized keto/enol double bonds draws the participating atoms together, shortening the bonds. Likewise, the bonds proximal to the aromatic rings, C14-O2 and S1-C2, are shorter than the corresponding C9-O2 and S1-C8 bonds. This results from the effect of  $\pi$ -electron delocalization in aromatic rings. The bonds, C12-O1, C14-O2, O2-C9, S1-C8 and S1-C2 show lengths of 1.34, 1.37, 1.42, 1.79, 1.76 Å, respectively, depicting the comparative polarity of C-O and C-S. The C-N, C-O and C-S bond lengths are within the limits of literature reports on related Schiff bases [11-13]. The aromatic C=C angles are in the range 118.07–121.92°, as expected for carbon atoms in trigonal planar  $sp^2$  arrangement. The atoms between the phenyl rings (C7-N1-C1, N1-C7-C11, N1-C7-H7, C11-C7-H7) share bond angles close to 120°, showing there is an extension of  $\pi$ -conjugation between the rings. The

distorted trigonal planar arrangement of the methoxy oxygen (C14–O2–C9) with an angle of  $117.97^\circ$  indicates the participation of its lone pairs in  $\pi$ -conjugation. S and O atoms in C2–S1–C8 ( $104^\circ$ ) and C12–O1–H1 ( $103^\circ$ ), retain the angular orientation, consistent with atoms containing two lone pairs of electrons [13, 26]. The phenyl rings are parallel to each other with a dihedral angle of  $176.82^\circ$  (C1–N1–C7–C11). The intramolecular interaction involving the imine nitrogen and phenolic OH (H–C=N $\cdots$ H–O) shows the H-bond distance of  $1.79 \text{ \AA}$  (N $\cdots$ H) and donor to acceptor distance of  $2.61 \text{ \AA}$  (N $\cdots$ O). The bond angle of  $154^\circ$  ( $< \text{N}\cdots\text{H}-\text{O}$ ) indicates the non-linearity of the hydrogen bonding to the imine nitrogen atom. These parameters are within the range reported for similar compounds [13, 27].

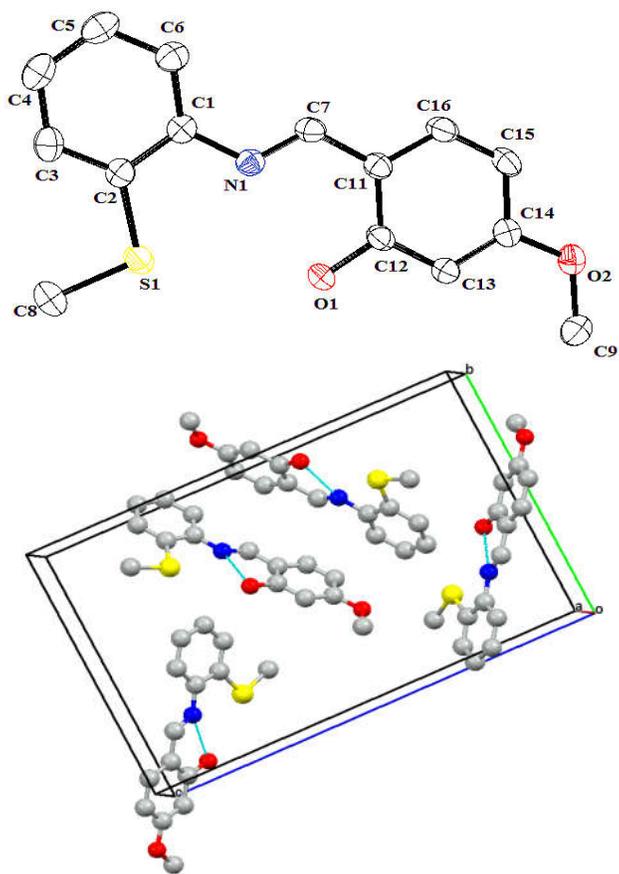


Figure 1. ORTEP drawing of Mth-1 with ellipsoid at 50% probability and the packing diagram of Mth-1 depicting intramolecular hydrogen bonds with green lines.

Table 1. Summary of crystallographic data for Schiff base MtH-1.

Chemical formula	C <sub>15</sub> H <sub>15</sub> NO <sub>2</sub> S
Molecular weight	273.34
Crystal system	Orthorhombic
Space group	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
<i>a</i> (Å)	5.63650(10)
<i>b</i> (Å)	12.2831(3)
<i>c</i> (Å)	19.3196(4)
$\alpha = \beta = \gamma$ (°)	90.00
Volume (Å <sup>3</sup> )	1337.57(5)
<i>Z</i>	4
Temperature (K)	200 (2)
Density <sub>calc</sub> (g/cm <sup>3</sup> )	1.357
Absorption coefficient (mm <sup>-1</sup> )	0.239
<i>F</i> (000)	576
$\theta$ Range for data collection (°)	1.96–28.00
Limiting indices	$-7 \leq h \leq 5, -16 \leq k \leq 16, -25 \leq l \leq 25$
Refinement method	<i>F</i> <sup>2</sup> Full-matrix least-squares on
Reflections collected	13256
Unique reflections ( <i>R</i> <sub>int</sub> )	3231(0.0154)
Absorption correction (Min., max.)	0.8295, 0.9696
Data/restraints/parameters	3231/0/192
Final <i>R</i> indices [ <i>I</i> > 4 $\sigma$ ( <i>I</i> )]	<i>R</i> <sub>1</sub> = 0.0268, <i>wR</i> <sub>2</sub> = 0.0718
<i>R</i> indices (all data)	<i>R</i> <sub>1</sub> = 0.0289, <i>wR</i> <sub>2</sub> = 0.0742
Goodness-of-fit on <i>F</i> <sup>2</sup>	1.050
Completeness to $\theta$	28.00 (99.9%)
Largest difference in peak and hole (e Å <sup>-3</sup> )	0.201 and -0.204
CCDC	890400

### NMR analysis

The atom labeling for <sup>1</sup>H and <sup>13</sup>C NMR spectra of Schiff bases MtH-1–MtH-5 is shown in Scheme 1. The proton NMR spectra show singlet peaks at 2.46  $\delta$  ppm and 3.84  $\delta$  ppm due to *SCH*<sub>3</sub> (H<sup>8</sup>) and phenyl *OCH*<sub>3</sub> (H<sup>9</sup>) proton absorptions, respectively [11]. The methyl- and methoxy-substituted compounds, MtH-2 and MtH-3, have additional singlet absorption at 2.38  $\delta$  ppm (R = *CH*<sub>3</sub>) and 3.83  $\delta$  ppm (R = *OCH*<sub>3</sub>), respectively, which are like chemical shifts recorded in related compounds [2]. The chemical shifts of the aromatic protons (H<sup>3</sup>, H<sup>5</sup>, H<sup>6</sup>, H<sup>13</sup>, H<sup>15</sup>, H<sup>16</sup>) are within the range of 6.48–7.30  $\delta$  ppm. These protons are typically deshielded. The singlet peaks of azomethine *N=C–H* (H<sup>7</sup>) and phenol *O–H* (H<sup>1</sup>) protons appear downfield in the ranges 8.48–8.54 and 13.34–13.70  $\delta$  ppm, respectively. The chemical shift of the latter has been attributed to the significant deshielding effect from hydrogen bonding [4, 12, 28]. Change of substituents on C4 affected the chemical shifts of the adjacent protons, H<sup>5</sup> and H<sup>6</sup>. The electron withdrawing *Br* and *Cl* atoms decrease the electron density of the surrounding nuclei leading to de-shielding effect (7.04–7.26  $\delta$  ppm) while the donating *CH*<sub>3</sub> and *OCH*<sub>3</sub> groups shield the neighboring nuclei resulting in the lower chemical shifts observed (6.69–7.04  $\delta$  ppm). The chemical shifts of azomethine and phenol protons are also sensitive to the nature of substituents; the increased electron density in MtH-2 and MtH-3 may be reinforcing the hydrogen bond, hence the higher chemical shifts observed (8.53, 13.70  $\delta$  ppm and 8.50, 13.66  $\delta$  ppm) compared to 8.48 and 13.34  $\delta$  ppm in MtH-4 and MtH-5 substituted with electron-withdrawing *Br* or *Cl* atoms. The <sup>13</sup>C chemical shifts for C<sup>8</sup> (*H*<sub>3</sub>C–*S*) are in the range 14.63–14.94  $\delta$  ppm [12]. The methyl and methoxy substituents (R) in MtH-2 and MtH-3 have <sup>13</sup>C shifts of 21.24  $\delta$  ppm and 55.50  $\delta$  ppm, respectively, the latter being close to that observed for *H*<sub>3</sub>C–*O* (C<sup>9</sup>) in the compounds [28]. The

high-frequency region contains the  $^{13}\text{C}$  shifts for the aromatic  $\text{C}^1\text{-C}^6$ ,  $\text{C}^{11}\text{-C}^{16}$  (101.06–164.23  $\delta$  ppm) and azomethine  $\text{C}^7$  (158.69–160.83  $\delta$  ppm).

Table 2. Bond lengths [ $\text{\AA}$ ] and angles [ $^\circ$ ] for the Schiff bases.

Parameters	X-ray	B3LYP/6-311++G(d,p)				
	MtH-1	MtH-1	MtH-2	MtH-3	MtH-4	MtH-5
N1–C7	1.280(17)	1.278	1.278	1.278	1.279	1.279
N1–C1	1.415(15)	1.400	1.400	1.400	1.398	1.397
C12–O1	1.344(15)	1.354	1.354	1.355	1.354	1.354
C14–O2	1.366(15)	1.359	1.360	1.360	1.358	1.358
O2–C9	1.421(18)	1.424	1.424	1.424	1.424	1.424
S1–C2	1.762(13)	1.781	1.782	1.780	1.778	1.778
S1–C8	1.795(14)	1.823	1.823	1.823	1.823	1.823
C11–C7	1.450(2)	1.460	1.460	1.460	1.459	1.459
C4–R	0.951	1.084	1.510	1.368	1.763	1.922
N1–C7–C11	121.55(12)	126.21	126.21	126.18	126.39	126.24
N1–C7–H7	119.21	120.40	120.44	120.52	120.40	120.36
C7–N1–C1	123.50(11)	119.84	119.88	120.07	119.91	119.91
C3–C2–S1	124.37(11)	124.53	124.46	124.09	124.07	124.07
C1–C2–S1	116.39(9)	116.30	116.20	116.26	116.46	116.32
C2–S1–C8	103.77(7)	102.47	102.54	102.40	102.49	102.50
C14–O2–C9	117.97(11)	118.72	118.70	118.68	118.77	118.78
C7–N1–C1–C2	172.68(1)	-139.37	-140.82	-143.41	-140.25	-139.89
N1–C7–C11–C16	-176.18(1)	-176.35	-176.60	-176.66	-176.27	-176.35
C8–S1–C2–C1	177.30(1)	-179.50	-179.55	-179.86	-179.49	-179.42
C1–N1–C7–C11	-175.97	-176.55	-176.51	-176.56	-176.45	-176.43

#### Infrared and UV-Vis spectra

The experimental infrared spectra of MtH-1–MtH-5 show the aldimine C–H asymmetric (2929–2911  $\text{cm}^{-1}$ ) and symmetric (2840–2834  $\text{cm}^{-1}$ ) stretches [29]. The azomethine C=N stretch appears as a strong band in the region 1630  $\text{cm}^{-1}$ . The aromatic  $\nu(\text{C}=\text{C})$  bands are observed in the ranges 1611–1602, 1588–1572, 1468–1462  $\text{cm}^{-1}$ , of medium or strong intensity [30, 31]. The spectra for all the compounds do not show a sharp, distinct or a significantly noticeable band for  $\nu(\text{O-H})$  but rather very weak bands due to the keto/enol tautomerism experienced by this class of Schiff bases. A prominent band was observed at  $\sim 1550$   $\text{cm}^{-1}$  and has been assigned to the contribution by the phenolic  $\delta(\text{O-H})$  of the enol tautomer. Vibrational bands around 1342–1336  $\text{cm}^{-1}$  and 1291–1285  $\text{cm}^{-1}$  are attributed to the phenol  $\nu(\text{C-O})$  and  $\nu(\text{C-N})$ . The weak bands around 715 and 685  $\text{cm}^{-1}$  are assigned to asymmetric and symmetric  $\nu(\text{S-C-S})$ . Medium bands in the spectra of MtH-4 and MtH-5 at 756/746  $\text{cm}^{-1}$  have been attributed to the C–Cl/Br stretching vibrations, respectively [31].

The UV spectra (Figure 2) of the compounds have two absorptions at approximately 245 nm and 280 nm, assigned to  $\pi \rightarrow \pi^*$  transitions of their phenyl rings. Organic compounds demonstrate intra-ligand absorptions in the ultraviolet region with wavelengths between 200 and 400 nm while longer wavelengths are shown by highly conjugated compounds. The third band appearing in the range 359–367 nm is attributed to  $n \rightarrow \pi^*$  transition of imine C=N group [32].

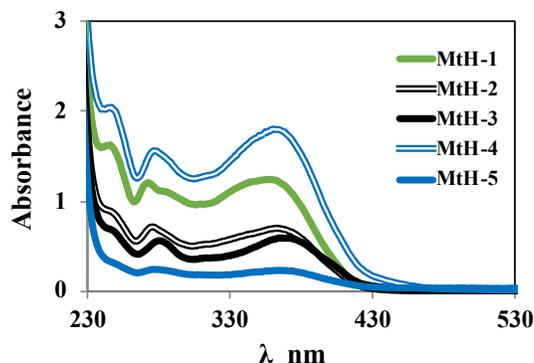


Figure 2. The UV spectra of the Schiff bases.

#### *DFT studies*

##### *Geometry parameters*

The bond lengths, angles and dihedral angles of MtH-1 atoms were calculated using B3LYP/6-311++G(d,p) method and recorded in Table 2. The results showed corroboration between the X-ray measurements and DFT calculations for bond lengths. The largest difference of 0.02-0.03 Å was found for C–S distances, which concurs with findings reported for similar structures showing a discrepancy of between 0.03 and 0.04 Å [33]. The inductive effect of the electron withdrawing -CH<sub>3</sub> on the sulfur atom was not accounted for and may contribute to the difference in experimental and computed C–S bond lengths. The largest variations between the experimental and calculated angles for MtH-1 were from the imine carbon (N1-C7-C11, 4.7°) and torsion of the imine moiety relative to the thiophenyl ring (C7–N1–C1–C2, ~43°). This may arise from differing imine group conformations in the DFT optimized and X-ray crystal structures. The geometry parameters calculated for MtH-2 to MtH-5 compounds were comparable with those derived for MtH-1, showing the reliability of the DFT method employed (Table 2). The calculated C4-R bond length follows the order, C4–H < C4–OCH<sub>3</sub> < C4–CH<sub>3</sub> < C4–Cl < C4–Br, in accordance with the QSAR substituent constants [34]. This may indicate the origin of the strength of the substituted carbon bond in the molecules.

##### *Quantum chemical descriptors*

The maps for lowest unoccupied molecular orbitals (LUMO) and the highest occupied molecular orbitals (HOMO) of the Schiff bases are presented in Figure 3. These orbitals determine the way molecules interact with receptors, either biological targets or metal ions. The HOMO was observed to have contributions from the phenyl rings, sulfur and imine groups, while the more significant contributions are from the imine moiety and methylthio-phenyl ring. These groups are responsible for providing the electron density that formed the HOMO map. The phenyl rings and the imine group contribute to the LUMO.

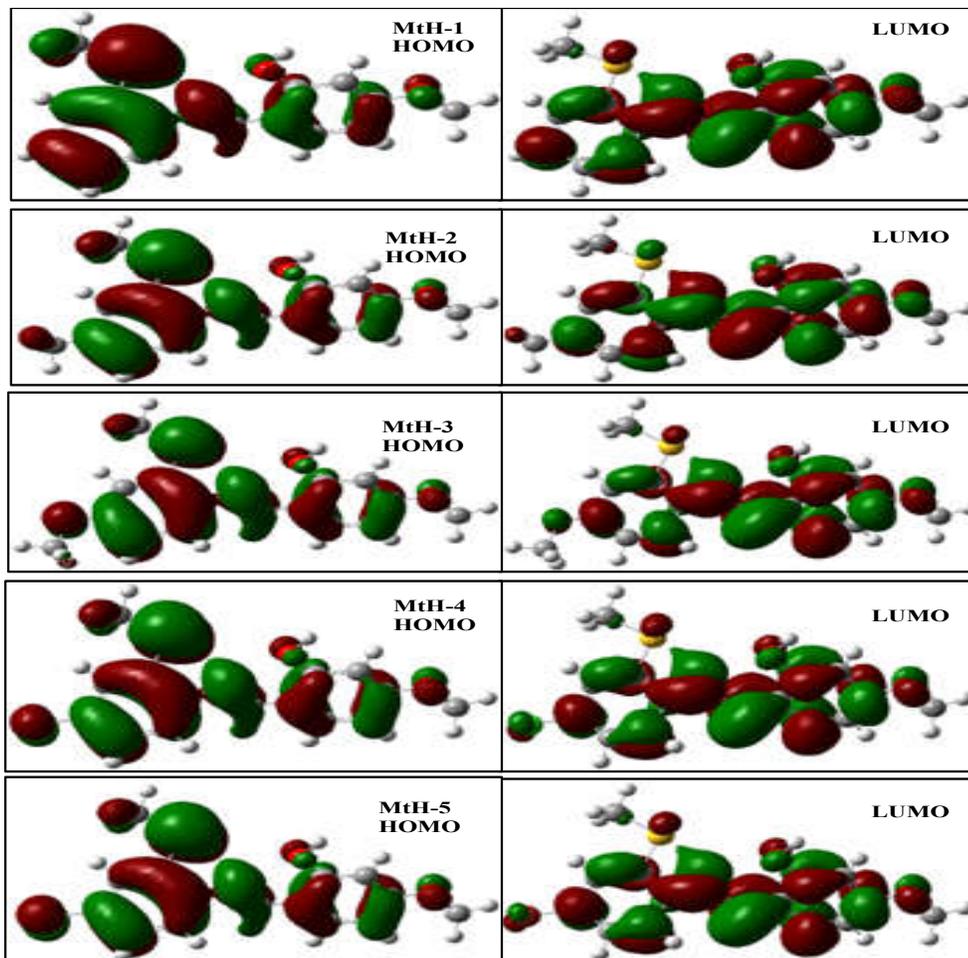


Figure 3. Frontier molecular orbitals for the optimized structures of Schiff bases.

Tables 3 and 4 contain the HOMO and LUMO energies,  $\Delta E$  (energy gap =  $E_{\text{LUMO}} - E_{\text{HOMO}}$ ) and reactivity indexes of the optimized molecular structures, which summarize their chemical properties. The donor capacity of a molecule is measured by  $E_{\text{HOMO}}$  [35, 36], and the larger the  $E_{\text{HOMO}}$ , the smaller the ionization potential. The relative ease of electron donation by the Schiff bases to a suitable metal vacant orbital decreases in the order: MtH-3 ( $R = \text{OCH}_3$ ,  $E_{\text{HOMO}} = -5.39$  eV) > MtH-2 ( $R = \text{CH}_3$ ,  $E_{\text{HOMO}} = -5.48$  eV) > MtH-1 ( $R = \text{H}$ ,  $E_{\text{HOMO}} = -5.56$  eV) > MtH-4/MtH-5 ( $R = \text{Cl/Br}$ ,  $E_{\text{HOMO}} = -5.65$  eV). MtH-4 and MtH-5 may be classified as better electron acceptors with lower  $E_{\text{LUMO}}$  (-1.68, -1.69 eV), larger electronegativity (3.67 eV) and electrophilicity (3.38, 3.40 eV) values.  $\Delta E$  is a measure of reactivity or stability, the smaller the energy gap, the softer and more reactive the molecule [37, 38]. MtH-3 and MtH-2 molecules are expected to show more reactivity ( $\Delta E = 3.88, 3.97$  eV;  $\delta = 0.51$  eV) compared to other Schiff bases. A small energy gap has been predicted to result into increased chemical potential [36], correspondingly, MtH-3 ( $C_p =$

-3.46 eV) is predicted as the most reactive compound while MtH-4, will be most stable and unreactive [5, 35, 36]. For the presented compounds, relatively small  $\Delta E$  in the range 3.88–3.97 eV suggest possible biological applications in lipophilic systems [39, 40]. Polarity arises from difference in electronegativity of bonding atoms and may be calculated in terms of dipole moments. The Schiff bases have dipole moments in the range 3.63 – 6.57 D, MtH-5 and MtH-4 being most polar, probably based on the large sizes and electronegativity of their Br and Cl atoms which create polar bonds. Lower polarity in MtH-2 is favorable in biological activity test for lipid layers, as the lipophilicity feature increases. The chemical potentials (-3.45 eV to -3.67 eV) demonstrate the compounds are stable and will not undergo spontaneous decomposition [41].

Table 3. The frontier molecular orbitals energies in DCM (in eV).

Compounds	$E_{\text{HOMO}}$	$E_{\text{LUMO}}$	$\Delta E$
MtH-1	-5.56	-1.59	3.97
MtH-2	-5.48	-1.55	3.93
MtH-3	-5.39	-1.51	3.88
MtH-4	-5.65	-1.68	3.97
MtH-5	-5.65	-1.69	3.96

Table 4. Calculated quantum chemical descriptors for the Schiff bases.

Compounds	I	A	$\eta$	$\delta$	$\chi$	$C_p$	$\omega$	$\mu_D$
MtH-1	5.56	1.59	1.98	0.50	3.58	-3.58	3.22	4.24
MtH-2	5.48	1.55	1.97	0.51	3.52	-3.52	3.15	3.63
MtH-3	5.39	1.51	1.94	0.51	3.45	-3.45	3.07	4.59
MtH-4	5.65	1.68	1.99	0.50	3.67	-3.67	3.38	6.52
MtH-5	5.65	1.69	1.98	0.50	3.67	-3.67	3.40	6.57

All units are in eV except  $\mu_D$  (Debye). A: Electron affinity, I: Ionization potential,  $\eta$ : Global hardness,  $\delta$ : Global softness,  $\chi$ : Electronegativity,  $C_p$ : Electronic chemical potential,  $\omega$ : Global electrophilicity,  $\mu_D$ : Dipole moment.

#### Molecular electrostatic potential (MEP)

The molecular electrostatic potential (MEP) plots of the Schiff bases are presented in Figure 4. MEP features the distribution of electron cloud over the functional groups, in a new cubic contour. MEP is useful in understanding the electron-deficient sites responsible for potential electrophilic attacks and nucleophilic reaction in a molecule during drug-protein interaction [42, 43]. The red color represents the electron-rich region and negative potential of the molecules. This zone features the nitrogen, phenol oxygen and sulfur atoms, which demonstrate nucleophilic reactivity in possible coordination towards metal ions. The phenolic proton occupies the blue-colored, electron-deficient site accountable for electrophilic attack and represents the positive potential region. The region with zero potential appears as pale green color, comprising the phenyl rings, the alkyl fragments and the substituents.

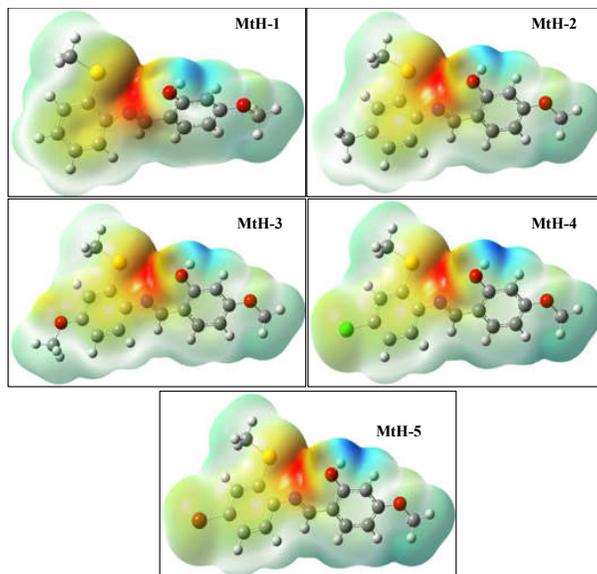


Figure 4. Molecular electrostatic potential plots.

### CONCLUSION

Five new Schiff bases were synthesized from the reflux reaction between 2-(methylthio)anilines and *p*-methoxysalicylaldehyde. The compounds were characterized by CHNS analysis, NMR, FT-IR and UV-Visible spectroscopic methods. The effect of ring substitution was observed in the  $^1\text{H}$  NMR chemical shifts. The crystal structure of MtH-1 was obtained and showed the phenyl rings were almost parallel to each other through the rigid imine bond. Theoretical studies of the compounds employing the B3LYP/6-311++G(d,p) basis set was used to predict the bond distances and angles of the Schiff bases. The HOMO-LUMO energy gaps calculated for these molecules are within the range for semi-conductors, and, also suggest possible biological applications in lipophilic systems. Predicted high reactivity was obtained for MtH-2 and MtH-3, possessing electron-donating  $-\text{CH}_3$  and  $-\text{OCH}_3$  substituents, respectively. The electrostatic potential plots of the molecules suggested nucleophilic reactivity of the Schiff bases towards metal ions through the nitrogen, phenol oxygen and sulfur donor atom.

### ACKNOWLEDGEMENTS

One of the authors (TE Olalekan) thanks the Organization of Women in Science for the Developing World (OWSD) and Rhodes University for providing a Research Fellowship and academic bursary, respectively.

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