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Synthesis of New Schiff Base of 1,3-Oxazine and 1,3-Thiazine Derivatives Derived from 4-Phenyl Substituted Chalcones and Evaluation of their Antibacterial Activity

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Oxazine and thiazine heterocycles have distinctive interests due to their important class of natural and non-natural products and exhibit high biological activities in the pharmaceutical and biological fields. This work was planned to synthesize Schiff base of 1,3-oxazine and 1,3-thiazine derivative from 4-phenyl substituted chalcones. The structures of the newly synthesized targeted compounds were established from UV, IR, ^{1}H NMR, ^{13}C NMR and DFT calculations. The molecular properties HOMO-LUMO energy, energy gap, softness and harness were calculated using DFT/B3LYP/6-311G (d,p) basis set. *in vitro* Antibacterial activities of Schiff bases of 1,3-oxazines and 1,3-thiazines derivatives were investigated against Gram-positive (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*) and compared with each other. It was found that thiazine derivatives showed higher activity.

Keywords: Schiff base, Chalcones, Spectral, DFT, Antibacterial studies.

INTRODUCTION

Chalcone compounds and their heterocyclic derivatives are known to possess important medicinal and pharmacological activities such as antibacterial, antifungal, anti-inflammatory, analgesic, antitubercular, antimalarial, antiviral, antioxidant, antiulcer and antihyperglycemic [1-4]. These properties of heterocyclic derivatives show great potential to be used as chemotherapeutic agents. Due to the increased resistance to antibiotics, there is a need to develop alternative medicines to fight the pathogenic microorganisms. In recent years there is immense focus on the medicinal properties (antifungal, antibacterial, cytotoxic, antiviral and analgesic) of the novel oxazine and thiazine derivatives of chalcones [5-7]. Oxazines and thiazines are heterocyclic compounds containing one nitrogen and one oxygen/sulfur in a six-membered ring. Three isomers are found depending on the relative position of the heteroatoms and double bonds [7].

Heterocyclic compounds are abundant in nature and have learned more significance because their structural subunits are exhibit in many natural products like vitamins, hormones, antibiotics, *etc.* 1,3-Thiazines-nitrogen and sulfur and 1,3-oxazine contains-nitrogen and oxygen in their six-membered heterocyclic ring (N-C-S, N-C-O linkage). The heterocyclic compounds which contain nitrogen, sulfur and oxygen possess vast significance in the field of medicinal chemistry [8]. Derivatives of thiazine and oxazine have various activities such as antifungal, anti-inflammatory, antitubercular, antibacterial, analgesic, anticancer, *etc*. A new series of biologically important Schiff bases were synthesized and substituted with an aromatic aldehyde to give substituted chalcones [9]. The compound 4-(4-bromophenyl)-6-(*N*,*N*-dimethylaminophenyl)-*N*-[(*E*)(4-chlorophenyl)methylidene]-6*H*-1,3-oxazin-2-amine was screened for its antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* and were found to be very active. Some of the reported oxazine derivatives showing chemotherapeutic properties include benzo-1,3-oxazines, efavirenz, a trifluoromethyl-1,3-oxazin-2-one and naphthoxazines [10-13]. Considering their antibacterial and antifungal activity, it would be exciting to explore more oxazines derivatives [11].

In present work, some new derivatives of Schiff bases derived from 1,3-thiazines, 1,3-oxazines are synthesized, characterized and also evaluated their potential as antibacterial agents and comparative kinetic stability. The derivative of chalcones is used as the starting material for the synthesis of thiazines,

oxazines and Schiff bases. The HOMO-LUMO energies, dipole moments, energy gap, softness and hardness were determined by the density functional theory (DFT) method.

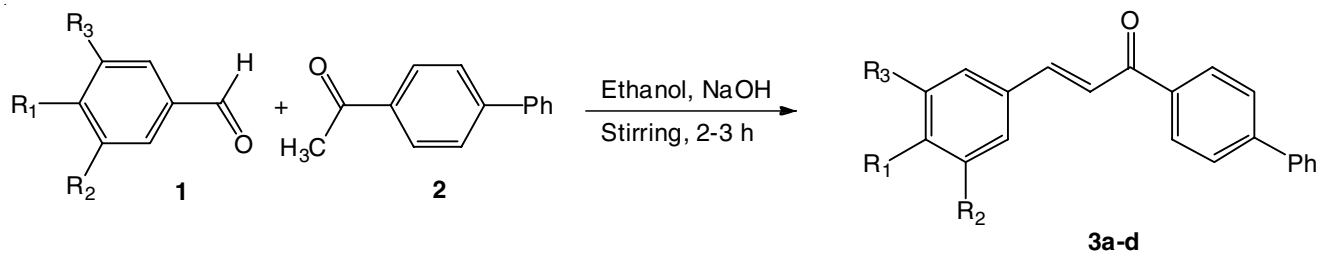
EXPERIMENTAL

Reagents and reactants were obtained from Sigma-Aldrich without purification. The purity of derivatives was monitored using thin-layer chromatography on silica gel-G with methanol and benzene mixture as mobile phase. The melting points of the compounds were measured in open capillaries, with digital scientific melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin Elmer SP-2 spectrophotometer by using KBr. ^{1}H & ^{13}C NMR spectra of the derivatives were recorded on Bruker (Avance II, Bruker 400MHz NMR spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm and elemental analyses were conducted on a Perkin-Elmer 2400 elemental analyzer.

Synthesis of chalcones (3a-d): An equimolar amount of 4-phenyl acetophenone (0.02 mol) and substituted benzaldehyde (0.02 mol) were dissolved in absolute alcohol and 10 % KOH solution was added dropwise with stirring the reaction was continued for 2 h and left overnight. Then the mixture of the reaction was kept overnight in an ice-water to obtain the product. The crude product was recrystallized from ethanol to get the final product (**Scheme-I**).

Synthesis of oxazine derivatives (4a-d): An equimolar quantity of chalcones (**3a-d**) and urea was dissolved in ethanolic NaOH and was stirred for 2-3 h at room temperature. The reaction mixture was refluxed for 6 h and poured into cold water with continuous stirring for 2 h. The reaction mixture was kept overnight in an ice-water to obtain the product. The precipitate obtained was filtered, washed and recrystalized from ethanol to get the final product (**Scheme-II**).

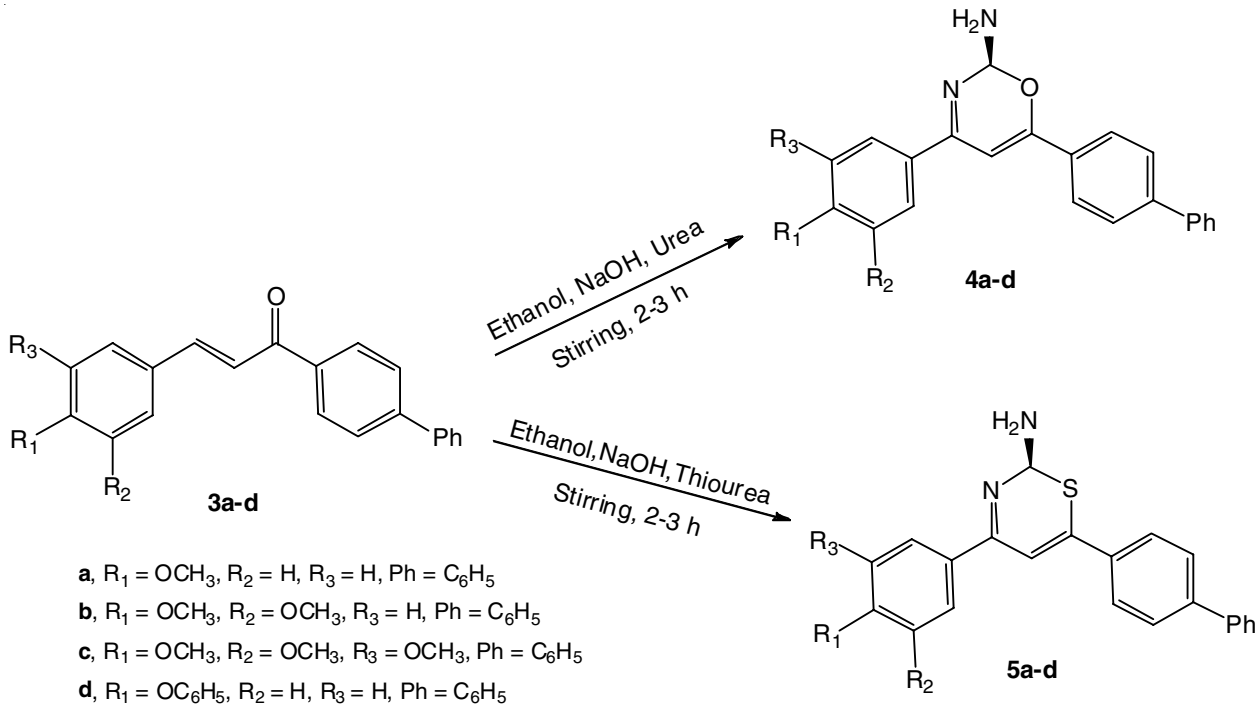
Synthesis of thiazine derivatives (5a-d): An equimolar quantity of chalcones (**3a-d**), thiourea was dissolved in ethanolic NaOH and was stirred for 2-3 h at room temperature in the presence of acetic acid. The reaction mixture was refluxed for 2-3 h and poured into cold water with continuous stirring for 1 h. The reaction mixture was kept overnight in an ice-water to obtain the product. The precipitate obtained was filtered,



a, $R_1 = OCH_3$, $R_2 = H$, $R_3 = H$, $Ph = C_6H_5$ **c**, $R_1 = OCH_3$, $R_2 = OCH_3$, $R_3 = OCH_3$, $Ph = C_6H_5$

b, $R_1 = OCH_3$, $R_2 = OCH_3$, $R_3 = H$, $Ph = C_6H_5$ **d**, $R_1 = OC_6H_5$, $R_2 = H$, $R_3 = H$, $Ph = C_6H_5$

Scheme-I: Synthesis of chalcone derivatives (**3a-d**)



a, $R_1 = OCH_3$, $R_2 = H$, $R_3 = H$, $Ph = C_6H_5$

b, $R_1 = OCH_3$, $R_2 = OCH_3$, $R_3 = H$, $Ph = C_6H_5$

c, $R_1 = OCH_3$, $R_2 = OCH_3$, $R_3 = OCH_3$, $Ph = C_6H_5$

d, $R_1 = OC_6H_5$, $R_2 = H$, $R_3 = H$, $Ph = C_6H_5$

Scheme-II: Synthesis of 1,3-oxazine derivatives (**4a-d**) and 1,3-thiazine derivatives (**5a-d**)

washed and recrystallized from ethanol to get the final product (**Scheme-II**).

Synthesis of Schiff base of 1,3-oxazine derivatives 6(a-d): An equimolar quantity of oxazine derivatives **(4a-d)** and substituted benzaldehyde were dissolved in absolute ethanolic and were refluxed for 3-4 h on a water bath and reduced the volume up to 25%. The mixture of the reaction was kept overnight to obtain the product (**Scheme-III**). The precipitate obtained was filtered, washed and recrystalized from ethanol to get the final product and the completion of the reaction was observed by TLC.

Spectral data

(*E*)-2-(((6-([1,1'-Biphenyl]-4-yl)-4-(4-methoxyphenyl)-2*H*-1,3-oxazin-2-yl)imino)-methyl)-6-methoxyphenol (6a): Black solid; Yield: 80%; m.p. 130-132 ºC. Elemental analysis of $C_{31}H_{26}N_2O_4$ calcd. (found) %: C, 75.90 (875.95); N, 5.71 (5.70); H, 5.34 (5.32). IR (KBr, ν_{max}, cm^{-1}): 3432 (OH), 2920 (Ar-H, stretching), 1540 (C=N, stretching in ring), 1106 (C-O, stretching in ring), 1630 (C=N, stretching), 1640 (CH=CH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.56 (s, Ar-OH), 8.82 (s, 1H, CH=N), 6.86-7.60 (m, 16H, Ar-H), 5.32 (s, CH, oxzrine), 6.76 (s, 1H, αCH), 3.78 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 75.12 (C5), 114.80 (Cα), 156.44 (C4); 160.10 (C6), 150.22 (C-OH), 162.80 (CH=N), 55.80 (OCH_3).

(*E*)-2-(((6-([1,1'-Biphenyl]-4-yl)-4-(3,4-dimethoxyphenyl)-2*H*-1,3-oxazin-2-yl)-imino)methyl)-6-methoxyphenol (6b): Brown solid; Yield: 72%; m.p. 138-140 ºC. Elemental analysis of $C_{32}H_{28}N_2O_5$ calcd. (found) %: C, 73.83 (74.01); N, 5.38 (5.35); H, 5.42 (5.44). IR (KBr, ν_{max}, cm^{-1}): 3425 (OH), 2922 (Ar-H, stretching), 1550 (C=N, stretching in ring), 1098 (C-O, stretching in ring), 1626 (C=N, stretching), 1645 (CH=CH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.50 (s, Ar-OH), 8.90 (s, 1H, CH=N), 6.86-7.65 (m, 15H, Ar-H), 5.30 (s, CH, oxazine), 6.78 (s, 1H, αCH), 3.80 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 74.24 (C5), 114.66 (Cα), 156.40 (C4); 160.00 (C6), 151.12 (C-OH), 55.22 (OCH_3).

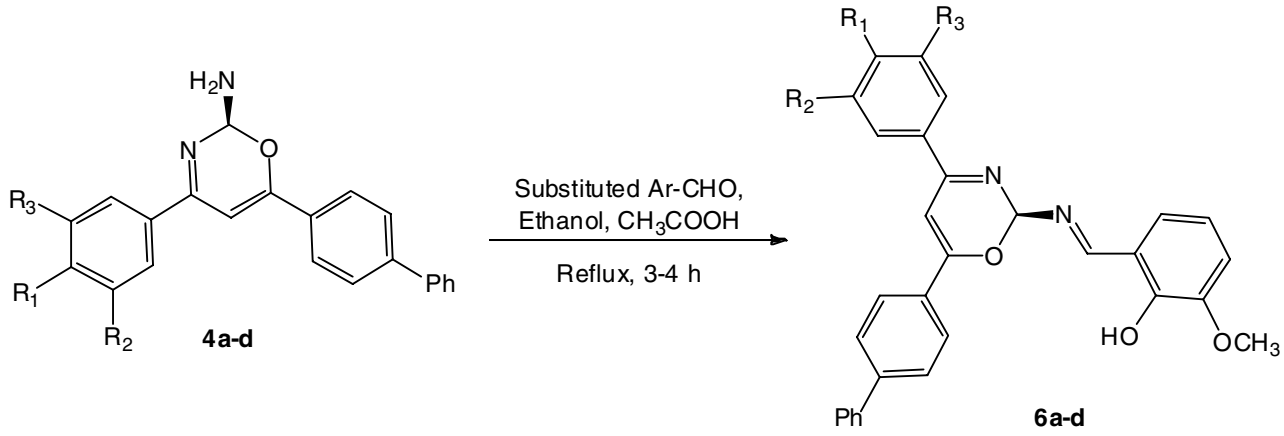
(*E*)-2-(((6-([1,1'-Biphenyl]-4-yl)-4-(3,4,5-trimethoxyphenyl)-2*H*-1,3-oxazin-2-yl)imino)methyl)-6-methoxyphenol (6c): Dark brown solid; Yield: 78%; m.p. 128-130 ºC. Elemental analysis of $C_{33}H_{30}N_2O_6$ calcd. (found) %: C, 71.99 (71.60); N, 5.09 (5.01); H, 5.49 (5.46). IR (KBr, ν_{max}, cm^{-1}): 3424 (OH), 2930 (Ar-H, stretching), 1552 (C=N, stretching in ring), 1100 (C-O, stretching in ring), 1634 (C=N, stretching), 1644 (CH=CH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.52 (s, Ar-OH), 8.88 (s, 1H, CH=N), 6.85-7.62 (m, 14H, Ar-H), 5.32 (s, CH, oxazine), 6.80 (s, 1H, αCH), 3.84 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 75424 (C5), 115.02 (Cα), 156.28 (C4); 161.20 (C6), 154.12 (C-OH), 56.52 (OCH_3).

(*E*)-2-(((6-([1,1'-biphenyl]-4-yl)-4-(4-phenoxyphenyl)-2*H*-1,3-oxazin-2-yl)imino)methyl)-6-methoxyphenol (6d): Yellow solid; Yield: 70%; m.p. 95-96 ºC. Elemental analysis of $C_{36}H_{28}N_2O_4$ calcd. (found)%: C, 78.24 (78.65); N, 5.07 (5.02); H, 5.11 (5.06). IR (KBr, ν_{max}, cm^{-1}): 3464 (OH), 2928 (Ar-H, stretching), 1565 (C=N, stretching in ring), 1120 (C-O, stretching in ring), 1630 (C=N, stretching), 1638 (CH=CH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.70 (s, Ar-OH), 8.82 (s, 1H, CH=N), 6.80-7.70 (m, 21H, Ar-H), 5.30 (s, CH, oxazine), 6.68 (s, 1H, αCH), 3.80 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 74.24 (C5), 114.95 (Cα), 156.08 (C4); 160.42 (C6), 154.28 (C-OH), 56.68 (OCH_3).

Synthesis of Schiff base of 1,3-thiazine derivatives (7a-d): An equimolar quantity of thiazine derivatives (**5a-d**) and substituted benzaldehyde were dissolved in absolute ethanolic, refluxed for 3-4 h on a water bath and reduced the volume up to 25%. The mixture of the reaction was kept overnight to obtain the product. The precipitate obtained was filtered, washed and recrystallized from ethanol to get the final product and the completion of the reaction was observed by TLC (**Scheme-IV**).

Spectral data

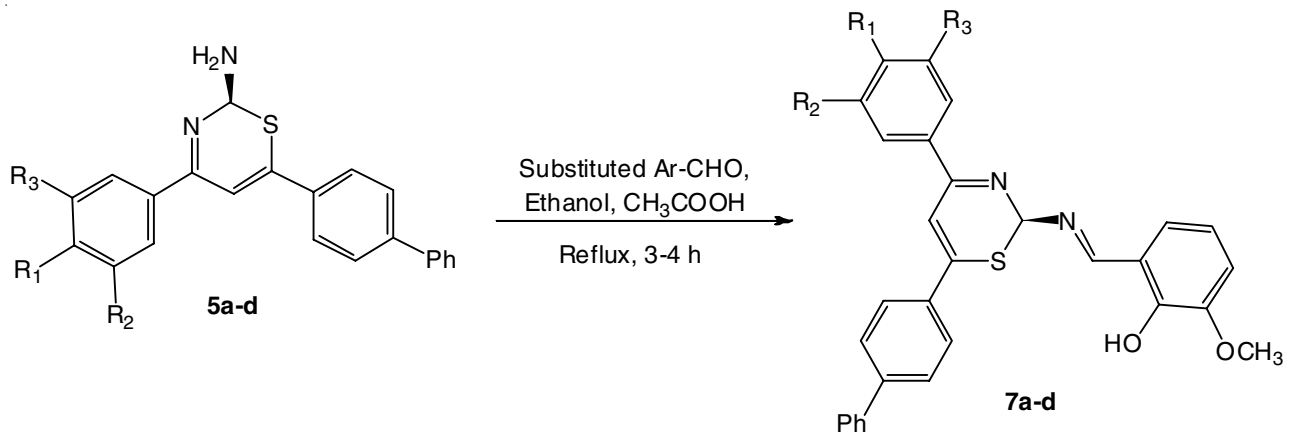
(*E*)-2-(((6-([1,1'-Biphenyl]-4-yl)-4-(4-methoxyphenyl)-2*H*-1,3-thiazin-2-yl)imino)-methyl)-6-methoxyphenol (7a): Yellow solid; Yield: 70%; m.p. 95-96 ºC. Elemental analysis of $C_{31}H_{26}N_2O_3S$ calcd. (found) %: C, 73.49 (73.60); S, 6.33 (6.28); N, 5.53 (5.50); H, 5.17 (5.15). IR (KBr, ν_{max}, cm^{-1}): 3380 (OH), 2932 (Ar-H, stretching), 1540 (C=N, stretching in ring), 868 (C-S, stretching in ring), 1632 (C=N, stretching),



a, $R_1 = OCH_3$, $R_2 = H$, $R_3 = H$, $Ph = C_6H_5$ **c**, $R_1 = OCH_3$, $R_2 = OCH_3$, $R_3 = OCH_3$, $Ph = C_6H_5$

b, $R_1 = OCH_3$, $R_2 = OCH_3$, $R_3 = H$, $Ph = C_6H_5$ **d**, $R_1 = OC_6H_5$, $R_2 = H$, $R_3 = H$, $Ph = C_6H_5$

Scheme-III: Sythetic route of Schiff bases from 1,3-oxazine derivatives (**6a-d**)



a, $R_1 = OCH_3$, $R_2 = H$, $R_3 = H$, $Ph = C_6H_5$ **c**, $R_1 = OCH_3$, $R_2 = OCH_3$, $R_3 = OCH_3$, $Ph = C_6H_5$

b, $R_1 = OCH_3$, $R_2 = OCH_3$, $R_3 = H$, $Ph = C_6H_5$ **d**, $R_1 = OC_6H_5$, $R_2 = H$, $R_3 = H$, $Ph = C_6H_5$

Scheme-IV: Synthetic route of Schiff bases from 1,3-thiazine derivatives (**7a-d**)

1644 (CH=CH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.68 (s, Ar-OH), 8.78 (s, 1H, CH=N), 6.75-7.68 (m, 16H, Ar-H), 5.82 (s, CH, oxazine), 6.40 (s, 1H, αCH), 3.80 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 95.20 (C5), 85.68 (Cα), 157.62 (C4); 152.88 (C6), 150.62 (C-OH), 55.66 (OCH_3).

(*E*)-2-(((6-([1,1'-Biphenyl]-4-yl)-4-(3,4-dimethoxyphenyl)-2*H*-1,3-thiazin-2-yl)imino)methyl)-6-methoxyphenol (7b): Yellow solid; Yield: 82%; m.p. 130-132 ºC. Elemental analysis of $C_{32}H_{28}N_2O_4S$ calcd. (found) %: C, 71.62 (71.80); S, 5.98 (5.90); N, 5.22 (5.16); H, 5.26 (5.24). IR (KBr, ν_{max}, cm^{-1}): 3392 (OH), 2938 (Ar-H, stretching), 1546 (C=N, stretching in ring), 8672 (C-S, stretching in ring), 1630 (C=N, stretching), 1642 (CH=CH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.76 (s, Ar-OH), 8.82 (s, 1H, CH=N), 6.68-7.68 (m, 15H, Ar-H), 5.80 (s, CH, oxazine), 6.34 (s, 1H, αCH), 3.80 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 96.52 (C5), 85.46 (Cα), 156.42 (C4); 152.74 (C6), 151.22 (C-OH), 57.56 (OCH_3).

(*E*)-2-(((6-([1,1'-Biphenyl]-4-yl)-4-(3,4,5-trimethoxyphenyl)-2*H*-1,3-thiazin-2-yl)-imino)-methyl)-6-methoxyphenol (7c): Yellowish brown solid; Yield: 82%; m.p. 135-136 ºC. Elemental analysis of $C_{33}H_{30}N_2O_5S$ calcd. (found) %: C, 69.94 (70.18); S, 5.66 (5.60); N, 4.94 (4.96); H, 5.34 (5.30). IR (KBr, ν_{max}, cm^{-1}): 3390 (OH), 2940 (Ar-H, stretching), 1544 (C=N, stretching in ring), 892 (C-S, stretching in ring), 1635 (C=N, stretching), 1640 (CH=CH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.70 (s, Ar-OH), 8.98 (s, 1H, CH=N), 6.78-7.60 (m, 14H, Ar-H), 5.82 (s, CH, oxazine), 6.30 (s, 1H, αCH), 3.82 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 96.88 (C5), 85.66 (Cα), 156.02 (C4); 152.70 (C6), 150.82 (C-OH), 56.88 (OCH_3).

(*E*)-2-(((6-([1,1'-Biphenyl]-4-yl)-4-(4-phenoxyphenyl)-2*H*-1,3-thiazin-2-yl)imino)-methyl)-6-methoxyphenol (7d): Yellow solid; Yield: 70%; m.p. 95-96 ºC. Elemental analysis $C_{36}H_{28}N_2O_3S$ of calcd. (found) %: C, 76.03 (76.30); S, 5.64 (5.60); N, 4.93 (4.94); H, 4.96 (4.94). IR (KBr, ν_{max}, cm^{-1}): 3460 (OH), 2930 (Ar-H, stretching), 1560 (C=N, stretching in ring), 1110 (C-O, stretching in ring), 1635 (C=N, stretching), 1640 (CH=CH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.80 (s, Ar-OH), 8.90 (s, 1H, CH=N), 6.70-7.62 (m, 21H, Ar-H), 6.30 (s, CH, oxazine), 5.88 (s, 1H, αCH), 3.84 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 95.42 (C5), 86.84 (Cα), 156.20 (C4); 152.60 (C6), 150.82 (C-OH), 56.16 (OCH_3).

Computational details: All quantum chemical calculations were performed with the Gaussian 05W computational package [14]. The pre and post-processing of data were carried out with Gauss View [15]. The HOMO and LUMO energy of the molecules studied were optimized without constraints of any sort, using Becke's three-parameter Lee-Yang-Parr (B3LYP) DFT functional [16].

Biological activity assay: Antibacterial activity of Schiff bases of 1,3-oxazine and 1,3-thiazine heterocyclic (**6a-d** and **7a-d**) have been carried out against two bacterial strains like, (*S. aureus*) Gram-positive and (*E. coli*) Gram-negative using nutrient agar medium *via* disc diffusion method [17]. Synthesized heterocyclic derivatives were dissolved in DMSO at 100 µg/mL concentration and incubated at 35 ºC for 24 h. After the incubation period, the inhibition zones were measured in mm and antibiotics like ampicillin as a standard drug was used for the comparison at the same concentration.

RESULTS AND DISCUSSION

The target Schiff bases of oxazine and thiazine derivatives were synthesized in three steps of the chemical reaction. In step 1, a number of substituted chalcones were synthesized by condensing with 4-phenylacetophenone and substituted benzaldehyde in the presence of base-catalyzed. In step 2, the substituted chalcone derivatives were condensed with urea/thiourea in the presence of a catalytic amount of NaOH yielded as substituted oxazine and thiazine derivatives. In step 3, the various substituted oxazine and thiazine derivatives were reacted with substituted benzaldehyde in presence of acetic acid, which yielded 1,3-oxazine derivatives (**6a-d**) and 1,3-thiazine derivatives (**7a-d**) of Schiff base compounds.

UV absorption and FTIR spectra of Schiff bases of 1,3-oxazine derivatives (**6a-d**) have been provided a preliminary idea for the formation of the product. According to the UV spectrum, the presence of peaks at 206 ± 5 and 302 ± 8 nm

clearly showed that compounds have been related to the aromatic double bond (π-π* transition) and heteroatom (n-π* transition), respectively. According to the FT-IR spectra data, the presence of absorption peak at ~1580 cm^{-1} has clearly noticed the utilization of starting chalcone derivatives transforms into the cyclic products. Further, the corresponding peaks at ~3350, ~2960, ~1150, ~1640, 1450 and ~781 cm^{-1} have been related to –OH, C-H aromatic, C-O, aromatic C=C, C-N and C-H out plane bending vibration, respectively in the compounds. Similarly, proton NMR strongly invested in the formation of the product by its δ value at ~δ 11.50, 6.70-7.65, 5.80-5.31, 4.59 and 3.75 ppm corresponding to the O-H, Ar-H, -C=CH, -CH and OCH_3 protons.

UV absorption and FTIR spectra of Schiff bases of 1,3-thiazine derivatives (**7a-d**) have provided a preliminary idea in confirmation of the formation of the product. According to the UV spectrum of compounds **7a-d**, the presence of peaks at 240 and 318 nm has been related to the aromatic double bond (π-π* transition) and heteroatom (n-π* transition), respectively [18]. According to the FTIR, peaks around at 3320, 2930, 1645, 1550, 1452 and 870 cm^{-1} for Ar-OH aromatic, C-H aromatic stretching, C=N (*endo*-cyclic), C=C (*endo*-cyclic), C-N, C-S stretching vibrations, respectively. Similarly, proton NMR strongly supported the formation of the compounds by their value at ~δ 9.39, 6.55-7.87, 5.42-5.48, 3.08-3.87and 2.30 ppm corresponding to the O-H, Ar-H, C-H, CH_2 and $CO-CH_3$ protons of compounds **7a-d**. In ^{13}C NMR spectra, compound **7a-d** exhibited a peak at 185.7 ppm for the C=O group and appeared two peaks at 128.6 ppm and 131.8 ppm, respectively for carbons of alkene CH=CH but these peaks were disappeared from spectra of other derivatives of oxazine and thiazine and a new absorption band appeared at around 160 ppm for the carbon of imine group (C=N) [19]. Aromatic carbon signals have appeared in the expected region. All such spectral data and absorption peaks have also been supported for the formation of the targeted compounds.

Frontier molecular orbital analysis: The electron donor and accepting the power of a molecule can be distinct with help of HOMO and LUMO energy. These molecular orbitals play an important role in optical and electronic properties and pharmaceutical studies as well as provide information on biological mechanisms [20]. HOMO-LUMO energy gap informs about the kinetic stability and chemical reactivity of the molecules. A molecule is more polarizable with a small HOMO-LUMO energy gap and is generally associated with a high chemical reactivity and low kinetic stability [21]. Furthermore, the FMO's helps for predicting the most reactive position of the molecules. The calculated energy value of HOMO and LUMO orbitals are given in Table-1. The FMO's energy gap (E_{HOMO}-E_{LUMO}) of the Schiff base compounds **6a**, **6d**, **7a** and **7d** were found to be 4.641, 4.328, 3.236 and 3.219 eV, respectively. The HOMO and LUMO energy, energy gap (ΔE), chemical hardness (η), electronegativity (χ), global softness (S) and global electrophilicity index (ω), of compounds **6a**, **6d**, **7a** and **7d** have been calculated by B3LYP/6.311G(d,p) level of theory and reported in Table-1. The lower value of the HOMO-LUMO energy gap and the high value of electrophilicity index showed that the **7d** molecule has high chemical reactivity and biological activity. The HOMO-LUMO orbital distribution of the compounds **6a**, **6d**, **7a** and **7d** are shown in Fig. 1. The calculated value of the electrophilicity index for the compounds **6a**, **6d**, **7a** and **7d** was found to own 11.08, 11.56, 12.46 and 12.52 eV, respectively. The electrophilicity index of a molecule is given information about the binding ability of a compound with biomolecules [22]. The higher value of the electrophilicity index of the molecule showed that it has a higher binding capacity with biomolecules. Furthermore, HOMO orbitals have mostly localized on the hetero atom and partially located on the oxazine and thiazine ring (Fig. 1). While, LUMO orbitals were located on the whole molecule, but mostly located near the sulfur atom, nitrogen atom and azomethine group attached benzene ring.

TABLE-1
CALCULATED ENERGY PARAMETERS OF **6a**, **6d**, **7a** AND **7d** COMPOUNDS

Parameters	Compounds			
	6a	**6d**	**7a**	**7d**
Energy (kcal/mol)	37.151	32.119	31.924	27.049
HOMO (eV)	-9.493	-9.236	-7.969	-7.959
LUMO (eV)	-4.852	-4.908	-4.733	4.740
Energy gap (eV)	4.641	4.328	3.236	3.219
Electronegativity ($\chi = E_{LUMO} + E_{HOMO}/2$)	7.173	7.072	6.351	6.349
Hardness ($\eta = E_{LUMO} - E_{HOMO}/2$)	2.321	2.164	1.618	1.610
Softness, $S = 1/2\eta$	0.220	0.230	0.309	0.311
Electrophilicity index $\omega = (-\chi)^2/2\eta$	11.08	11.56	12.46	12.52

***in vitro* Antibacterial activity:** Newly synthesized compounds (**6a-d** and **7a-d**) were tested for their antibacterial activity against two organisms, namely *S. aureus* (Gram-positive) and *E. coli* (Gram-negative). The agar disc diffusion method was used for studying the activities of those heterocyclic compounds. Streptomycin used as a positive control and DMSO used as a negative control. The zone of inhibition (mm) of synthesized compounds against *S. aureus* and *E. coli* are shown in Table-2. Compound **7d** exhibits significant antibacterial activity compared to standard antibiotic drug against the tested organisms. The antibacterial activity of compounds may be

TABLE-2
ANTIBACTERIAL ACTIVITY OF SCHIFF BASES OF 1,3-OXAZINES AND 1,3-THIAZINES DERIVATIVES AT 100 µg/mL CONCENTRATION

Compounds	Zone of inhibition (mm)	
	E. coli	*S. aureus*
6a	7 ± 0.25	10 ± 0.22
6b	11 ± 0.56	14 ± 0.12
6c	10 ± 0.92	14 ± 0.32
6d	15 ± 0.45	18 ± 0.16
7a	14 ± 0.50	16 ± 0.75
7b	18 ± 0.12	20 ± 0.55
7c	19 ± 0.55	18. ± 0.15
7d	21 ± 0.22	32 ± 0.20
Ampicillin	22 ± 0.42	26 ± 0.25
DMSO	0	0

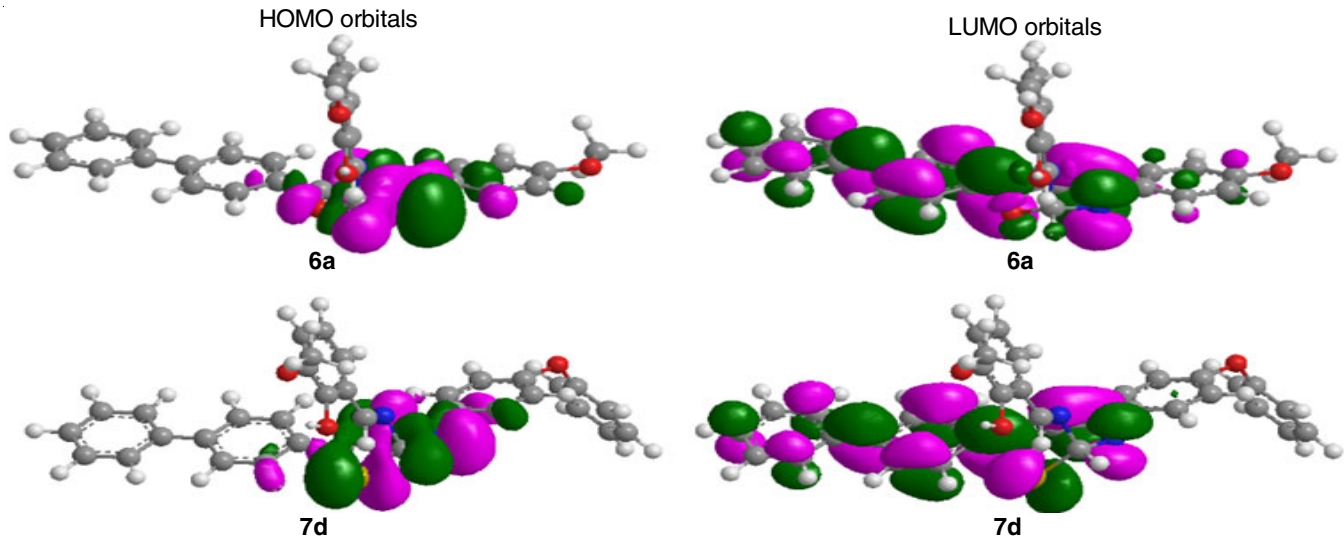


Fig. 1. Frontier molecular orbitals distribution of **6a** and **7d** compounds

increase due to the increase in lipophilicity and affects the partitioning of molecules into membranes and facilitates hydrophobic interactions of the molecules with specific binding sites on either proteins or enzymes. The antibacterial result reveals that all the synthesized compounds showed good antimicrobial activity when tested against antibacterial strains such as *S. aureus* and *E. coli*. The important conclusion is that the biological effectiveness of the best in the compounds of thiazine derivatives because its constituents including an organic heterocyclic ring containing sulfur atom.

Conclusion

In this study, heterocyclic Schiff bases of 1,3-oxazines and 1,3-thiazines (**6a-d** and **7a-d**) have been synthesized and characterized by analytical techniques. The calculated HOMO-LUMO energies show the high chemical reactivity of the molecules and support the high bioactivity of the heterocyclic derivatives. *in vitro* Antibacterial activity revealed that the synthesized compounds (**6a-d** and **7a-d**) possess potent antibacterial activities toward bacteria and compound **7d** shows potent activity compared to standard drug ampicillin.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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