DESIGN, MOLECULAR DOCKING OF SYNTHESIZED SCHIFF-BASED THIAZOLE/ PYRIDINE DERIVATIVES AS POTENT ANTIBACTERIAL INHIBITOR

Article *in* INDIAN DRUGS · December 2019

CITATIONS
9

READS
645

4 authors, including:

Chita Ranjan Sahoo

57 PUBLICATIONS **602** CITATIONS

SEE PROFILE

Rabindra N Padhy

Siksha O Anusandhan University

227 PUBLICATIONS **3,277** CITATIONS

SEE PROFILE

Sudhir Kumar Paidesetty

Siksha O Anusandhan University

100 PUBLICATIONS **1,360** CITATIONS

SEE PROFILE

ORIGINAL RESEARCH ARTICLES

DESIGN, MOLECULAR DOCKING OF SYNTHESIZED SCHIFF-BASED THIAZOLE/ PYRIDINE DERIVATIVES AS POTENT ANTIBACTERIAL INHIBITOR

Sahoo C. R.[a,b], Patro R.[b], Sahoo J.[c], Padhy R. N.[a] and S. K. Paidesetty[b]*

(Received 16 July 2019) (Accepted 07 October 2019)

ABSTRACT

A series of *N*-(substituted benzylidene) thiazol-2-amines (3a-3d) and *N*-(substituted benzylidene) pyridyl-2-amines (3A-3D) were synthesized and individual structures were confirmed by several spectral techniques. Antibacterial activity of synthesized Schiff-base derivatives were performed by agar-diffusion method. These compounds were screened by *in vitro* antibacterial activity against uropathogenic bacteria, *Escerichia coli* and *Klebsiella pneumoniae*. The compounds 3a, 3B and 3d had the best inhibititory activity against *K. pneumonia,* whereas, the other derivatives had moderate activity. The compounds, 3A and 3D exhibited significant inhibitions against *E.coli,* while other compounds were resisted by both pathogens. It is probable that the presence of 4-nitrophenyl substituted and azomethine functionality having been connected either to thiazole or pyridine nucleus might have contributed to the antibacterial activities of the derivatives. Those were computationally assessed for drugable properties with molecular docking using *E.coli* DNA gyrase, PDBID-1KZN and Lipinski's rule of five (RO5).

Keywords: Thiazole/pyridine, schiffbase, antibacterial, spectral analysis

INTRODUCTION

Nowadays, most antibiotics are resisted by bacterial pathogens, and the developement of newer effective antibacterial drug candidates for controlling infections has become a dire necessity. Thiazole and pyridine are examples of nitrogenous heterocyclic organic compounds, thiazole and derivatives have showed with antimycobacterial[1] and anti-inflammatory[2] and analgesic activities[3]. Likewise, the nuclueus pyridine and its derivatives have showed broad biological action[4]. The Schiff-based thiazole/pyridine compounds have potent synergistic antibacterial action. Compounds with –CH=N– azomethine functional group play a unique organic sython for the synthesis of new molecules. Those molecules have been known with a range of biological activities such as anticancerous[5], anti-mycobacterial[6-7] antiviral[8], anti HIV[9], antioxidant[10,11] and antibacterial activities[12].

Schiff bases are important because of an inherent flexibility and structural similarity with some natural biological substances due to presence of imine (-N=CH-). Substitution at C-2 by thiazole/ pyridine is essential for bolstering biological actions from which, azomethine derivatives had been used in medicinal chemistry. The azomethine group has the ablity to form stable complexes with transition metal ions. Moreover, recent medicinal chemistry approaches for synthesis of potent and novel biological active molecules are the call of the day[13-14]. Bacterial topoisomerases are vital enzymes and performing negative supercoiling of chromosome, which act as acting antibacterial inhibitor[15].

It has been reported thats, azomethine bearing heterocyclic moiety shows several biological activities. Thus, synthesis of thiazole/pyridine Schiff-base derivatives were validated by their binding affinity, prediction of biological actions, druglikeness properties and toxicity profiles by applying logistic computational tools. The

[a] Central Research Laboratory, Institute of Medical Sciences & Sum Hospital, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar - 751 003, Odisha, India

[b] Department of Medicinal Chemistry, School of Pharmaceutical Sciences, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar - 751 003, Odisha, India

[c] Department of Pharmaceutics, School of Pharmacy, Arka Jain University, Gamharia, Mohanpur, Seraikela Kharsawan - 832 108, Jharkhand India

* For Correspondence E-mail: psudhirkumar@soa.ac.in

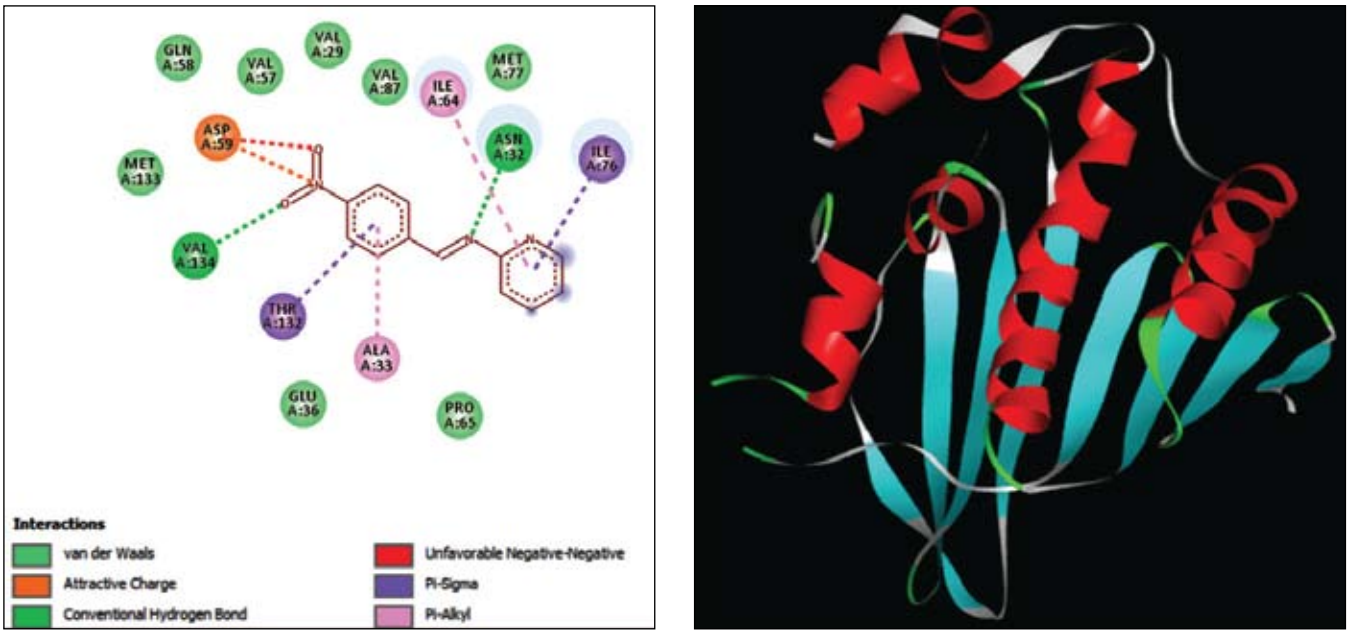


Fig.1: Ligand (3D) interactions of amino acids with target *E.coli* bacterial DNA gyrase

obtained molecules were monitored by *in vitro* antibacterial action against uropathogenic bacteria. Furthermore, those compounds were docked with bacterial DNA gyrase PDBID: 1KZN (*E.coli*).

MATERIALS AND METHODS

Instruments

Synthetic grade chemicals (Merck) were used in the present studies. Functional groups of products were characterized by FT/IR with a JASCO FT/IR4100 spectrophotometer using KBr disc; the number of envirormental protons also detected by ^{1}H NMR with Bruker^{1}H NMR 400MHz using TMS is an internal standard. The melting points were measured by Elico melting point apparatus.

Synthesis of *N*-(subst. benzylidene) thiazol-2-amine 3a-3d & *N*-(subst. benzylidene) pyridyl-2-amine 3A-3D

Schiff-base derivatives were prepared by the condensation of equimolar solutions of appropriate aldehyde (0.818 mol) with amines with both 2-amino thiazole or 2-amino pyridine (0.818 mol) separately in a 2 mL volume of glacial acetic acid and the reaction mixture was stirred at the ambient temperature and the mixture was kept under reflux for 2h. the reaction was monitored by TLC Plate with the solvent system (*n*-hexane: ethyl acetate) and the derivatives were recrystallized from hot ethanol.

Antibacterial evaluation by using disc agar diffusion method[15]

The antimicrobial activity of the synthesized molecules (**3a-3d** and **3A-3D**) were monitored by agar well diffusion method. The lowest concentration of the test compounds inhibited the visible growth on the respective seeded medium for bacteria were termed as minimum inhibitory concentration (MIC). Test solutions of synthesized molecules were prepared by two-fold dilution method at a concentration level ranging from 20-100 μgmL^{-1} to evaluate the MIC.

Computational study

Eight of thiazole/pyridine derivatives (**3a-3d** and **3A-3D**) were virtually designed by employing the connect

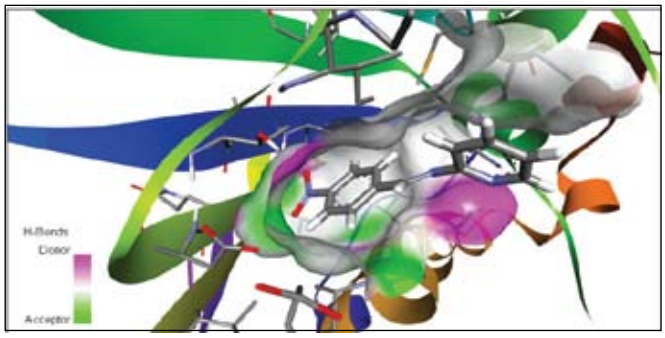


Fig. 2: Visualization during molecular docking on interaction of compound 3D with target bacterial DNA gyrase

between either thiazole or pyridine rings with some derivatives of aldehyde through azomethine functional group. Two dimensional (2D) structures of these designed derivatives were drawn and errors of the same was checked and optimized by Chemdraw Ultra software. Those structures were energy minimized by Open Babel Program. The druglikeness parameter of these derivatives were predicted with the Lipinski's Role of five (RO5) by Molinsperation software, and possible biological action was assessed by PASS predictions. Furthermore, toxicity profile of each designed molecule was predicted with desired class and lethal doses $_{50}$ (LD_{50}) values were calculated by ProTox Software. Furthermore, these desired compounds were virtually subjected to molecular docking against the target, bacterial dihydrofolate synthetase, with crystal structure PDB ID: 1KZN (2.5 A^0 resolution) having been retrieved from protein data bank (www.rscb.org/pdb). During molecular docking, deletion of nonproteinous and transitional metal ions and water molecules in the structure of protein was done. Furthermore, the molecular docking study was carried out using AUTO-DOCK Tools 4.2, protein-ligand interaction visualization by Discovery Studio R2 2017 and outcomes were interpreted by PyMOL program.

Spectral characterisation of Schiff-based thiazole/ pyridine derivatives (3a-3d & 3A-3D)

(E)-N-(3,4-dimethoxybenzylidene)thiazol-2-amine (3a)

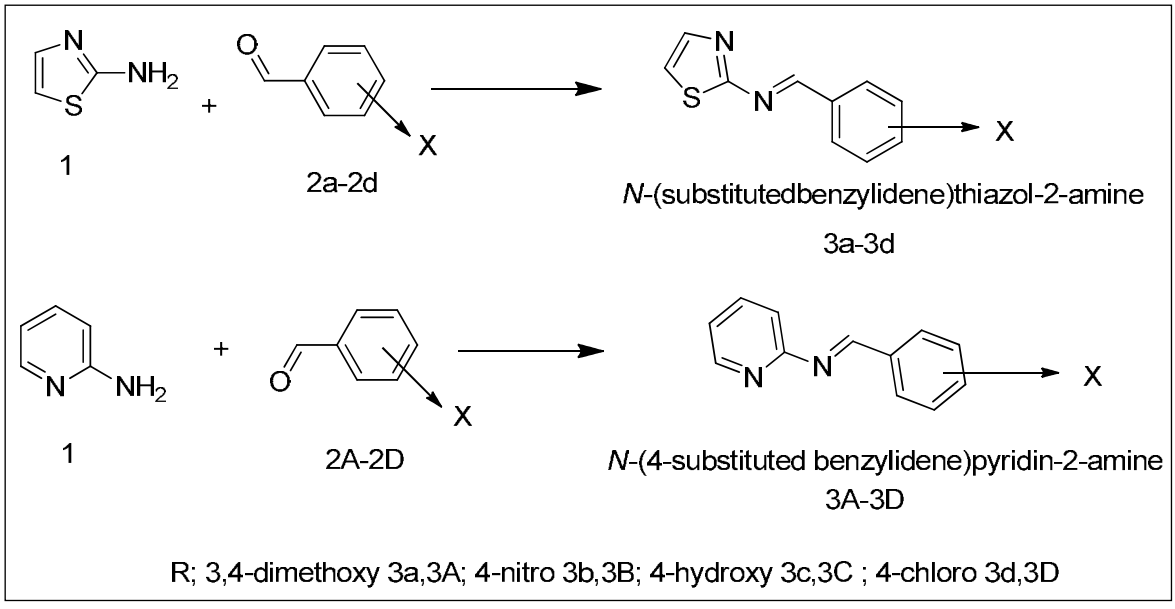
Colouress solid. (99%). m.p.: 192-94°C. ; IR (KBr,cm^{-1}): 3072 (CHstr.), 2875 (CH_2 str.), 1635(C=NH str.) 1614, 1558 (C=Cstr.),1197, 1247(C-OCH_3str.), 767 (Trisubst. of phenyl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H, -N=CH), 6.98-7.42 (m, 3H, Ar-H), 7.87 (d, 1H, thiazole H-4), 7.65 (d, 1H, thiazole H-5), 3.91 (s, 6H, 2xOCH_3); ESI-HRMS (m/z): *Anal.* Calcd. for $C_{12}H_{12}N_2O_2S$ [M + H]$^+$ 248.067; found: 248.085; Elemental analytical Calcd. % for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28; S, 12.91. Found: C, 57.85; H, 4.93; N, 11.22; S, 13.54.

*(E)-N-(*4-nitrobenzylidene)thiazol-2-amine (3b)

Yellow solid. (95%). m.p.: 189-92 °C. ; IR (KBr,cm^{-1}): 3088 (CHstr.), 1455, 1532 (NO_2 str.), 1637(C=NH str.) 1615, 1558 (C=Cstr.), 1066 (C-Sstr.), 752 (disubst. of phenyl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H, -N=CH), 7.45-7.85 (m, 4H, Ar-H), 7.92 (d, 1H, thiazole H-4), 7.63 (d, 1H, thiazole H-5); ESI-HRMS (m/z): *Anal.* Calcd. for $C_{10}H_7N_3O_2S$ [M + H]$^+$ 233.067; found: 233.081; Elemental analytical Calcd. % for $C_{10}H_7N_3O_2S$: C, 51.49; H, 3.02; N, 18.02; S, 13.75; Found: C, 51.56; H, 2.95; N, 18.00; S, 13.77

(E)-4-((thiazol-2-ylimino)methyl)phenol (3c)

White solid. (98%). m.p.: 159-62 °C.; IR (KBr,cm^{-1}): 3115 (OHstr.), 1638(C=NH str.) 1615, 1558 (C=Cstr.), 1192 (C-Ostr.), 756 (disubst. of phenyl);^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H, -N=CH), 6.98-7.63 (m, 4H, Ar-H), 7.86 (d, 1H, thiazole H-4), 7.77 (d, 1H, thiazole H-5); ESI-HRMS (m/z): *Anal.* Calcd. for $C_{10}H_8N_2OS$ [M + H]$^+$ 204.087; found: 204.091; Elemental analytical Calcd. % for $C_{10}H_8N_2OS$: C, 58.80; H, 3.95; N, 13.72; S, 15.70; Found: C, 58.75; H, 4.11; N, 13.77; S, 15.63



Scheme-1

Table I: Physiological activity related druglikness properties of thiazole/pyridine derivatives

Deriva-tives	Lipinski rule of five (RO5)						Predicted lethal doses, toxicity class		Docking Score Kcal/mol (1KZN)
	MW (≤ 500 g/mol)	No. of H-ba (≤10)	No. of H-bd (≤10)	cLogP value (≤5)	tPSA (Å)	% ABS	LD_{50} (mg/kg)	Class	
3a	248.06	5	0	2.78	34.11	97.23	1500	4	-6.2
3b	233.03	5	0	2.45	57.11	89.30	180	3	-6.7
3c	204.04	4	1	2.46	36.46	96.42	1000	4	-6.3
3d	222.00	3	0	3.43	18.84	102.50	300	3	-6.2
3A	242.11	4	0	2.59	33.24	97.53	2000	4	-6.8
3B	227.07	4	0	2.26	56.24	89.60	1500	4	-7.2
3C	198.08	3	1	2.27	35.60	96.72	2000	4	-6.9
3D	216.05	2	0	3.25	17.98	102.80	2000	4	-6.9

Table II: *In vitro* antibacterial activity of thiazole/pyridine derivatives with zone of inhibition (mm) and MIC (µg/mL) against both gram positive and negative bacterial strains.

Compound	*S. aureus* (MTCC7443)		*E. coli* (MTCC614)	
	(mm)	(µg/mL)	(mm)	(µg/mL)
3a	12	60	13	40
3b	09	100	10	80
3c	13	40	13	40
3d	11	80	12	60
3A	16	20	15	40
3B	10	80	10	80
3C	11	60	12	60
3D	17	20	16	20
Amoxycillin (Standard)	-	20	-	20

Table III: Aminoacid residues interaction with bacterial protein PDB ID:1KZN

Compound	Schiff base derivatives bearing two substract	Amino acid interactions of the bacterial protein target with ligand of Schiff base derivatives
3a	2-amino thiazole + veratraldehyde	Glu36,Ile64,Ala33,Val134, Val29,Thr132
3b	2-amino thiazole + 4-nitro benzaldehyde	Val134,Asp59,Ala33,Thr132,Asn32,Ile76,Ile64
3c	2-amino thiazole +4-hydroxy benzaldehyde	Val134,Val29,Ala33,Thr132,Val57,Glu36,Ile64
3d	2-amino thiazole + 4-chloro benzaldehyde	Val29,Ala33,Val57,Val134,Thr132,Ile76,Ile64
3A	2-amino pyridine + veratraldehyde	Ile64,Glu36,Ala33
3B	2-amino pyridine + 4-nitro benzaldehyde	Asp59,Val134,Thr134,Ala33,Asn32,Ile76
3C	2-amino pyridine + 4-hydroxy benzaldehyde	Ala33,Val134,Thr132,Asn32,Ile64,Ile76
3D	2-amino pyridine + 4-chloro benzaldehyde	Asn32,Ile76,Ile64,Thr132,Ala33,Val134,Val29.

(E)-N-(4-chlorobenzylidene)thiazol-2-amine (3d)

White solid. (98%). m.p.: 166-68 °C.; IR (KBr,cm^{-1}): 3071 (CHstr.), 1634(C=NH str.) 1615, 1558 (C=Cstr.), 742 (C-Clstr.), 753 (disubst. of phenyl);^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H, -N=CH), 7.43-7.89 (m, 4H, Ar-H), 7.86 (d, 1H, thiazole H-4), 7.64 (d, 1H, thiazole H-5); ESI-HRMS (m/z): *Anal*. Calcd. for $C_{10}H_7ClN_2S$ [M + H]$^+$ 222.087; found: 222.103; Elemental analytical Calcd. % for $C_{10}H_7ClN_2S$: C, 53.93; H, 3.17; Cl, 15.92; N, 12.58; S, 14.40; Found; C, 53.99; H, 3.12; Cl, 15.88; N, 12.55; S, 14.32.

(*E)-N*-(3,4-dimethoxybenzylidene)pyridin-2-amine (3A)

Colouress solid. (99%). m.p.: 194-96 °C. ; IR (KBr,cm^{-1}): 3072 (CHstr.), 2890 (CH_2 str.), 1638(C=NH str.) 1619, 1555 (C=Cstr.),1197, 1246(C-OCH_3str.), 764 (Trisubst. of phenyl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H, -N=CH), 6.95-7.42 (m, 3H, Ar-H), 7.00-8.22 (m, 4H, pyridine H), 3.92 (s, 6H, 2xOCH_3); ESI-HRMS (m/z): *Anal*. Calcd. for $C_{14}H_{14}N_2O_2$ [M + H]$^+$ 242.167; found: 242.185; Elemental analytical Calcd. % $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56; Found: C, 69.39; H, 5.85; N, 11.52

(E)-N-(4-nitrobenzylidene)pyridin-2-amine (3B)

Yellow solid. (97%). m.p.: 187-90 °C. ; IR (KBr,cm^{-1}): 3076 (CHstr.), 1453, 1532 (NO_2 str.), 1636(C=NH str.) 1615, 1558 (C=Cstr.), 1066 (C-Sstr.), 754 (disubst. of phenyl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H, -N=CH), 7.45-7.85 (m, 4H, Ar-H), 6.95-8.43 (m, 4H, pyridine H-4); ESI-HRMS (m/z): *Anal*. Calcd. for $C_{12}H_9N_3O_2$; [M + H]$^+$ 227.077; found: 227.081; Elemental analytical Calcd. % $C_{12}H_9N_3O_{22}$ C, 63.43; H, 3.99; N, 18.49; Found: C, 63.44; H, 4.09; N, 18.47.

(E)- N-4-((pyridin-2-ylimino)methyl)phenol (3C)

White solid. (98%). m.p.: 158-60 °C.; IR (KBr,cm^{-1}): 3120 (OHstr.), 1635(C=NH str.) 1615, 1558 (C=Cstr.), 1243 (C-Ostr.), 753 (disubst. of phenyl);^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H, -N=CH), 6.94-7.55 (m, 4H, Ar-H), 6.87-7.86 (m, 4H, pyridineH); ESI-HRMS (m/z): *Anal*. Calcd. for $C_{12}H_{10}N_2O$ [M + H]$^+$ 198.097; found: 198.11; Elemental analytical Calcd. % $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13;Found: : C, 72.67; H, 4.88; N, 14.03.

(E)-N-(4-chlorobenzylidene)pyridin-2-amine (3D)

White solid. (98%). m.p.: 176-78 °C.; IR (KBr,cm^{-1}): 3071 (CH str.), 1639(C=NH str.) 1615, 1558 (C=Cstr.), 744 (C-Clstr.), 758 (disubst. of phenyl);^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H, -N=CH), 7.43-7.89 (m, 4H, Ar-H), 6,87-7.86 (m, 4H, pyridine H); ESI-HRMS (m/z): *Anal*. Calcd. for $C_{12}H_9ClN_2$ [M + H]$^+$ 216.087; found: 216.103; Elemental analytical Calcd. % $C_{12}H_9ClN_2$: C, 66.52; H, 4.19; Cl, 16.36; N, 12.93;Found: C, 66.44; H, 4.22; Cl, 16.28; N, 12.88.

RESULTS AND DISCUSSION

A series of compounds bearing thiazole or pyridine (**3a-3b** & **3A-3D**) with functional azomethine were synthesized by the reaction of individual appropriate amines with aldehydes in glacial acetic acid (**Scheme-1).** All the synthesized compounds have shown sharp absorption peaks in FTIR spectra at of the range of 1634-1643 cm^{-1}, which attributed to azomethine functional group. Several peaks too were observed in the range of 2990-3050 cm^{-1} that are assigned to as aromatic hydrocarbon, thiazole and pyridine nucleus for those compounds with respective vibrational frequencies. The precursor amines (1a and 1A) appeared stretching frequency for the –NH_2 group, while reaction was completed those substituted amines frequency disappeared and appeared as new –N=CH stretching vibration that are assigned to as Schiff-base. Furthermore, ^{1}HNMR spectra of the synthesized compounds exhibited sharp singlets appearing at a range of δ 8.34-8.42 ppm corresponding to azomethine protons (**3a-3d** & **3A-3D**); thus the formation of Schiff-base derivatives was confirmed. Compounds **3a** and **3A** exhibited three singlets peaks at δ 3.92, 7.55 and 8.37 ppm, which were assigned to methoxy, azomethine and aromatic phenyl protons, respectively. These compounds were subjected to molecular docking with bacterial DNA gyrase with PDB ID:1KZN and the obtained results indicate that the compound **3D** had comparatively better binding affinity than the other derivatives. Other essential computational parameters were also carried out and their results are depicted in Table I & III. Consequently, *in vitro* antibacterial activities were performed and amongst all compounds, two compounds **3A** and **3D** were detected as more potent against both pathogenic bacterial *S. aureus* and *E. coli* with compare to standard drug Amoxycillin (Table II).

CONCLUSION

In conclusion, a series compounds containing thiazole or pyridine moiety with azomethine functionality were designed, synthesized and screened for inherent antibacterial activities. These compounds exhibited moderate contolling activity against both the pathogenic bacterial strains, *S aureus* and *E. coli*, whereas the compounds **3b** and **3B** had significant antibacterial action

with the standard antibiotic amoxycillin. Concomitantly, those compounds were docked with bacterial DNA gyrase and virtually it could be proved that all these compounds had significant binding affinity and with their drugable characters assessed through advanced computational tools. Furthermore, studies on the antibacterial mechanism of action of these potent molecules against target could be developed in future.

REFERENCES

1. Makam P. and Kannan T.: 2-Aminothiazole derivatives as antimycobacterial agents: Synthesis, characterization, in vitro and in silico studies, **Eur. J. Med. Chem**., 2014, 87, 643-656.
2. Helal M. H., Salem M. A., El-Gaby M. S. and Aljahdali M.: Synthesis and biological evaluation of some novel thiazole compounds as potential anti-inflammatory agents, **Eur. J. Med. Chem**., 2013, 65, 517-26.
3. Abdelazeem A. H., El-Saadi M. T., Safi El-Din A. G., Omar H. A. and El-Moghazy S. M.: Design, synthesis and analgesic/ anti-inflammatory evaluation of novel diarylthiazole and diarylimidazole derivatives towards selective COX-1 inhibitors with better gastric profile, **Bioorg. Med. Chem**., 2017, 25, 665-676.
4. Chaubey A. and Pandeya S. N.: Pyridine a versatile nucleuse in pharmaceutical field, **Asian J Pharm Clin Res.**, 2011, 4, 5-8.
5. Dhanya S., Isloor A. M., Shetty P., Nayak P. G. and Pai K. S. R.: *In vivo* anticancer and histopathology studies of Schiff bases on Ehrlich ascitic carcinoma cells, **Arabian J. Chem**, 2013, 4, 25-33.
6. Aboul-Fadl T., Bin-Jubair F. A. S. and Aboul-Wafa O.: Schiff bases of indoline-2,3-dione (isatin) derivatives and nalidixic acid carbohydrazide, synthesis, antitubercular activity and pharmacophoric model building, **Eur. J. Med. Chem**., 2010, 45,4578-4586.
7. Hearn M. J., Cynamon M. H. and M. F. Chen M. F., Coppins R., Davis J., Kang, H. J. O., Noble A., Tu-Sekine B., Terrot M. S., Trombino D. and Thai M.: Preparation and antitubercular activities *in vitro* and *in vivo* of novel Schiff bases of isoniazid, **Eur. J. Med. Chem**., 2009., 44, 4169-4178.
8. Kumar K. S., Ganguly S., Veerasamy R. and De Clercq E.: Synthesis, antiviral activity and cytotoxicity evaluation of Schiff bases of some 2-phenyl quinazoline-4(3)H-ones, **Eur. J. Med. Chem**., 2018, 45, 5474-5479.
9. Patel R. N., Patel P. V., Desai K. R., Purohit P. Y., Nimavat K. S. and Vyas K. B.: Synthesis of new heterocyclic schiff base, thiazolidinone and azetidinone compounds and their antibacterial activity and anti-hiv activities, **Heterocyclic Lett**., 2012, 2, 99-105.
10. Sashidhara K. V., Rosaiah J. N., Bhatia G. and Saxena J. K.: Novel keto-enamine Schiffs bases from 7-hydroxy-4-methyl-2- oxo-2H-benzo[h] chromene-8,10-dicarbaldehyde as potential antidyslipidemic and antioxidant agents, **Eur. J. Med. Chem**., 2008, 43, 2592-2596,.
11. Sahoo J. and Paidesetty S.K.: Biological investigation of novel metal complexes of 2-amino-4-substituted phenylthiazole Schiff bases, J Taibah Univ Med Sci, 2018, 13(2), 142-155.
12. Malladi S., Isloor A. M., Isloor S. and Akhila D. S.: Synthesis, characterization and antibacterial activity of some new pyrazole based Schiff bases, **Arabian J. Chem**., 2013, 6, 335-340.
13. Sahoo C. R., Paidesetty, S. K. and Padhy, R. N.: Norharmane as a potential chemical entity for development of anticancer drugs, **Eur. J. Med. Chem**., 2019, 162, 752-764.
14. Sahoo C. R., Paidesetty, S. K. and Padhy, R. N.: Nornostocine congeners as potential anticancer drugs: An overview, **Drug Dev. Res.,** DOI: 10.1002/ddr.21577.
15. Kathiravan M. K., Khilare M. M., Nikoomanesh K., Chothe A. S., and Jain K. S.: Topoisomerase as target for antibacterial and anticancer drug discovery, **J. Enzyme Inhib. Med. Chem**., 2012, 17, 419-435.
16. Baral N., Mohapatra S., Raiguru B. P., Mishra N. P., Panda P., Nayak S., Pandey S. K., Kumar., P. S. and Sahoo, C. R.: **J. Heterocycl. Chem**., 2019, 56, 552-565.