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A convenient synthesis, characterization and biological evaluation of novel schiff base heterocycles as potential antimicrobial, antitubercular agents and their structural activity relationship

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A B S T R A C T

A series of (E)-1-methyl-3-((substituted phenylimino)methyl)quinolin-2(^{1}H)-one schiff bases (**3a-j**) bearing quinoline moiety synthesized successfully in ethanol by condensation of starting material 1-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**1**) with various substituted anilines (**2a-j**). The structure of the newly synthesized compounds was confirmed by proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance spectroscopy, Fourier transformation infrared (FT-IR), Mass spectroscopic study and elemental analysis. The *in-vitro* antimicrobial activity of the synthesized compounds was undertaken by agar well diffusion method against gram positive bacteria (*Bacillus licheniformis* and *Bacillus cereus*) gram negative bacteria (*Escherichia coli* and *Acetobactor sp.)* and antifungal activity against (*Aspergillus Flavus* and *Pichnanomala*). Further the compounds which shows good activity (**3b**, **3c**, **3d**, **3f**, **3g** and **3j**) are screened for *in-vitro* antitubercular activity by Micro-plate alamar blue assay (MABA) method against *mycobacterium tuberculosis H37Rv* strain provided important information about activity against these strains. The structure activities of the synthesized compounds were also discussed. Compounds **3a**, **3c**, **3d**, **3f** and **3g** show good argument with the different substituent attached to the phenyl ring.

1. Introduction

The synthesis of new heterocyclic compounds is a significant aspect of medicinal chemistry due to the versatile importance recognized value of this type of compound in the development of new drugs. In this view quinoline and its derivatives are interesting frameworks owing to their established medicinal value. In recent years, quinoline bearing moiety has gathered enormous attention among the researchers, chemists as well as biologists. Quinoline is one of the key elements for naturally occurring molecules. The synthesis of quinoline with oxygen has been of considerable interest to researchers because these may contribute to significant antimalarial, antibacterial, antiasthamatic, antihypertensive, anti inflammatory and antiplatelet properties[1-3]. Among many antimicrobial agents, 2-quinolone is a significant and selective agent which has stimulated remarkable interest in the preparation of 2-quinolones bearing heterocycles utilized in the synthesis of commercial drugs and are easily accessible in the market[4-5]. In recent years tremendous bioactivities of 2-quinolones have been discussed as antimicrobial[6-7], Antioxidant and anti-inflammatory activities[8]. Antitubercular activity[9], Fornesy transferase inhibitor[10], and antiangiogenic activity[11]. Literature surveys exhibit various heterocycles[12-21] associated with biological activities. Different 2-quinolones have been found to report *in-vitro* and *in-vivo* growth inhibition activity against various bacterial and fungi stains. Quinolones are particularly known to inhibit DNA synthesis by cleavage of bacterial DNA gyrase nd type-IV topoisomerase, as a result in rapid bacterial death[22-26]. The regioselectivity of the [3+2] cycloaddition reactions between trans-β-nitrostyrene and C,Ndiarylnitryle imine analogues as three atom components (TACs) has been studied with the use of Conceptual Density Functional Theory in the framework of Molecular Electron

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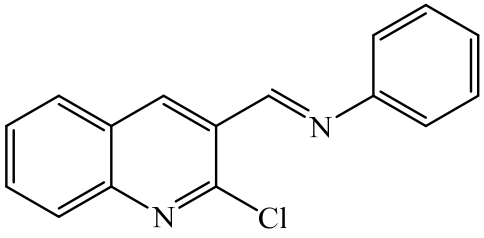
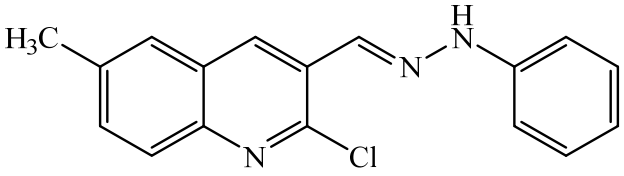
density Theory[27-31]. Heterocycles containing oxygen and nitrogen as donor atoms have attracted the attention of researchers and provoked the synthesis of schiff base derivatives which has been enhanced by the present advancements in the field of medicine[32] and organic chemistry. On the other hand, Schiff compounds with the structure -C=N- (azomethane group) are generally prepared by the reaction of primary amine and active carbonyl groups. Schiff base derivatives form an important class of compounds in the field of pharmaceuticals in medicinal chemistry. Since the discovery of schiff base[33], it has received more attention because of the easy tailoring possibility of the compounds by incorporating the different substituents in both amino and aldehydic active precursors, which gives the variation in the fundamental properties of the synthesized compounds. This brings the promising biological and therapeutic applications especially their antibacterial activities[34-37]. Schiff bases have a broad spectrum of bioactivity and are well known for their antitumor[38], antifungal[39], antiviral[40], antibacterial[41] and anticancer[42]. Literature studies reveal that the compounds (**Fig. 1**)[43-44] are significant molecules that possess a broad spectrum of biological activity. Inspired and motivated by these findings, in continuation of our interest in the exploration of new heterocyclic scaffolds our research focused on the synthesis of schiff base derivatives using simple and convenient methods. In this article we describe the design synthesis of (E)-1-methyl-3-((substituted phenylimino)methyl)quinolin-2(1H)-one schiff bases **(3a-j)** bearing quinoline moiety. Thus obtained molecules were characterised by ^{1}H, ^{13}C NMR, FT-IR, Mass spectral and elemental analysis. Obtained derivatives were subjected to antimicrobial activities and further investigated antitubercular activity against *mycobacterium tuberculosis H37Rv* strain.



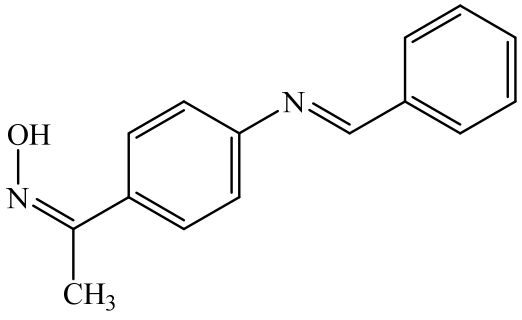
(*E*)-1-(2-chloroquinolin-3-yl)-*N*-phenyl methanimine

1



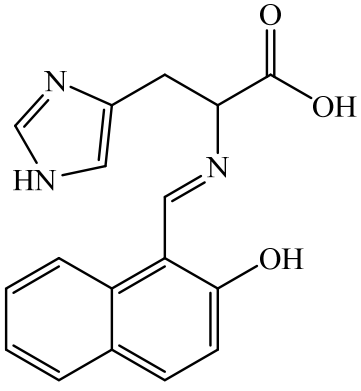
1-(2-Chloro-6-methyl quinolin-3-yl)methylene-2-phenyl hydrazine

2



(*Z*)-1-(4-(((*E*)-benzylidene)amino)phenyl)ethan-1-one oxime

3



(*E*)-2-(((2-hydroxynaphthalen-1-yl)methylene)amino)-3-(1*H*-imidazol-4-yl)propanoic acid

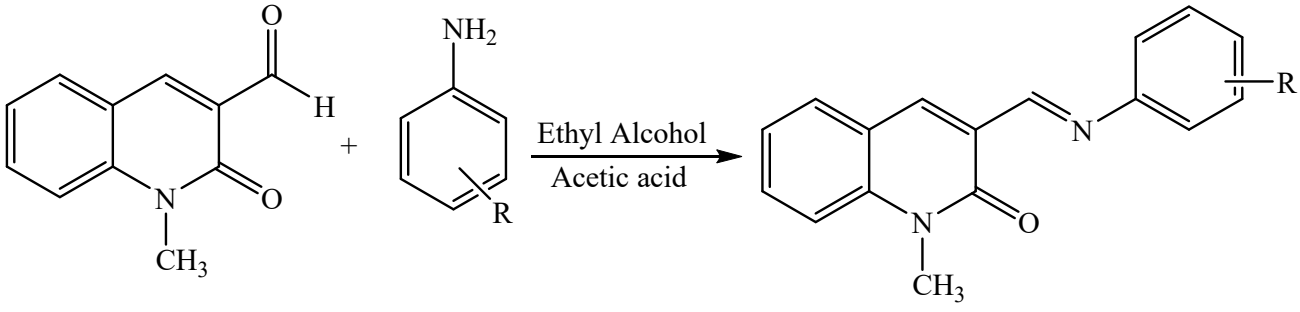
4

2. Results and Discussion

2.1. Synthesis and characterisation

The formation of schiff base from an aldehyde is an irreversible reaction, generally this reaction takes place under acid or base catalysis. The formations of schiff base are by separation of the product or removal of water molecules or both. The acid concentration must be low because amines are basic in nature. If the amines are protonated it becomes non-nucleophile, equilibrium pulled towards left and carbinolamine formation does not occur. Because of this, schiff bases are carried out at low or mild pH. In the present study, the starting key material 1-methyl-2-oxo-1, 2-dihydroquinoline-3-carbaldehyde (**1**) was synthesized by the reaction of vilsmeier Haack reaction of N-methyl acetanilide according to available protocol[45], and all the (E)-1-methyl-3-((substituted phenylimino)methyl)quinolin-2(1H)-one schiff bases (**3a-j**) were obtained in a good yield by refluxing key intermediate with different substituted anilines (**2a-j**) in the presence of alcohol with catalytic amount

of glacial acetic acid. The course of the complete reaction followed by thin layer chromatography. The synthetic route as shown in **scheme 1**. The identification of structure of the newly synthesized compounds was carried out by ^{1}H, ^{13}C, FT-IR and mass spectroscopic method and physical data mentioned in the characterization section. The elemental analysis details provide us with good agreement between the theoretically calculated values and the experimentally determined values within the permissible error. All the assignments of proton and carbon NMR peaks were found in their expected region. The ^{1}H NMR spectra of the synthesized compounds, for example **3a** the imine proton (-CH=N-) resonates at δ 8.68 as s singlet, and absence of aldehyde peak at δ 8 to 10 ppm, which confirms the formation of schiff base. The aromatic protons of the phenyl ring were observed in between δ 7.71 and δ 7.76 ppm. The terminal methyl group protons appeared at δ 3.71 ppm as a triplet. In the ^{13}C NMR spectrum, quinoline of the compound **3a** observed at δ 160.78. The peak at δ 157.43 ppm corresponds to imine carbon (-CH=N-). The aromatic carbons resonated at δ 157.43 to δ 114.90 ppm. The NMR spectral data of the synthesized compounds match with the literature values. In the FT-IR spectra the synthesized compounds show vibration signals at expected frequencies for the suitable functional group and chromospheres, for example compound **3a** shows stretching frequency at 1643.35 cm^{-1} due to the imine (-CH=N-) linkage. The vibration of C=O seen around 3462.22 cm^{-1}. In the FT-IR spectra there is no characteristic signal to the -NH_2 of the primary amine which indicates the formation of schiff base compounds successfully. The mass spectra of the synthesized compounds show molecular ion peaks corresponding to the molecular weight, which is also strong evidence for the formation of schiff base compounds.



1 **(2a-j)** **(3a-j)**

R= 3-Cl, 3, 4-Cl, 4-Cl, 4-NO_2, 4-Br, 3-Cl 4-NO_2, 4-Cl, 3, 4-CH_3, 3, 5-Cl in (**2a-j**) and (**3a-j**).

Scheme 1: synthesis of schiff bases (3a-j)

2.2. Biological activity

2.2.1. Antimicrobial activity

Antibacterial activities of the newly synthesized compounds were screened against gram positive bacteria (*Bacillus licheniformis* and *Bacillus cereus*) gram negative bacteria (*Escherichia coli* and *Acetobactor sp.*) and antifungal activities were screened against *Aspergillus Flavus* and *Pichnanomala*. The results exhibited good to moderate antibacterial activity for all the strains, compared with the standard drugs *Ciprofloxacin*. Compounds **3b**, **3c**, **3d**, **3f**, **3g** and **3j** exhibited excellent activity against tested microorganisms of both gram positive and gram-negative bacterial strain in comparison with the standard reference drug. Compound **3a** and **3i** were significantly active and remaining compounds showed good to moderate activity against the bacterial strains. Antifungal activity among the synthesized compounds **3b**, **3c**, **3d**, **3f**, **3g** and **3j** shows potential antifungal activity. Compounds **3a** and **3e** exhibit good activity and the remaining compounds display moderate to good antifungal activity against tested microorganisms in comparison with the standard reference drug *fluconazole*. The results of the zone of inhibition values and minimum inhibition concentration of the tested compounds are illustrated in Table **1** and **Table 2** respectively. An examination of the values (**Table 1**) reveals that among the molecules (**3a-j**).

Table 1. Antimicrobial activity of synthesized compounds by agar well diffusion method (ZIC values in mm)

Compound	Antibacterial				Antifungal	
	B.licheniformis	*B.cereus*	*E. coli*	*A. sp*	*Flavus*	*Pichnanomala*
3a	16	16	16	28	24	21
3b	18	23	31	32	30	31
3c	20	14	33	30	30	31
3d	22	21	31	31	31	33
3e	12	15	25	21	16	23
3f	08	12	26	23	21	21
3g	21	22	31	30	29	29
3h	13	14	16	26	14	21
3i	12	10	21	29	19	16
3j	19	24	33	29	31	34
Ciprofloxacin	23	26	34	31	-	-
fluconazole	-	-	-	-	33	36

Table 2. Minimum inhibitory concentration of the compounds at 100 µg/mL

Compound	Antibacterial				Antifungal	
	B.licheniformis	*B.cereus*	*E. coli*	*A. sp*	*Flavus*	*Pichnanomala*
3a	56	75	74	82	76	52
3b	100	98	88	100	100	100
3c	98	34	94	97	99	94
3d	100	99	100	96	84	75
3e	75	76	75	48	83	88
3f	100	96	98	78	98	63
3g	100	98	89	88	100	73
3h	56	88	58	68	89	64
3i	76	86	74	74	56	72
3j	100	56	98	98	58	88
Ciprofloxacin	12.5	25	25	12.5	-	-
fluconazole	-	-	-	-	12.5	12.5

2.2.3. Antimycobacterial activity

The result from the antimicrobial studies reveals that the compounds **3b**, **3c**, **3d**, **3f**, **3g** and **3j** shows potential microbial activity, this report provoked and encourage us to go for preliminary screening for their antituberculosis activity against *M. tuberculosis* H37Rv (ATCC- 27294) strain. The bioassay results of the synthesized compounds, **3b, 3c, 3d, 3f, 3g and 3j** are summarized in Table **3.** The outcome of the analyzed results shows that the compounds possess less potential against the *M. tuberculosis H37Rv* strain compared standard reference drugs Isoniazid-1.6 µg/ml, Ethambutol-1.6 µg/ml, Pyrazinamide-3.125µg/ml, Rifampicin-0.8 µg/ml and Streptomycin-0.8µg/ml.

Table 3. Antimycobacterial activity Minimum Inhibition Concentration in µg/mL of the compounds **3b**, **3c**, **3d**, **3f**, **3g**, and **3j** (R- Resistant, S- Sensitive)

Compound	**0.8**	**1.6**	**3.12**	**6.25**	**12.5**	**25**	**50**	**100**
3b	R	R	R	R	R	R	R	S
3c	R	R	R	R	R	R	R	S
3d	R	R	R	R	R	R	R	S
3f	R	R	R	R	R	R	R	S
3g	R	R	R	R	R	R	R	S
3j	R	R	R	R	R	R	S	S

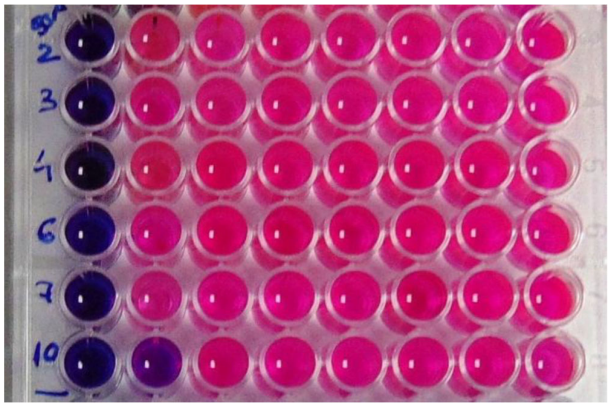
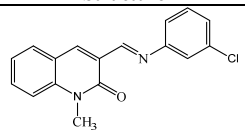
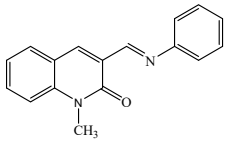
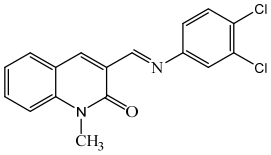
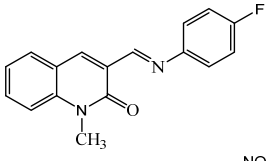
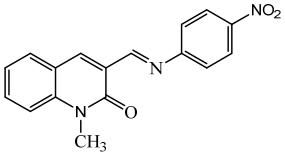
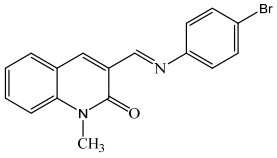
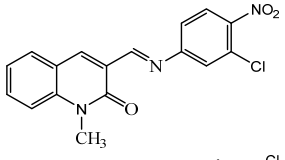
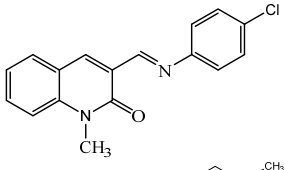
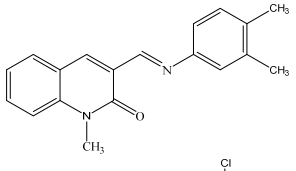
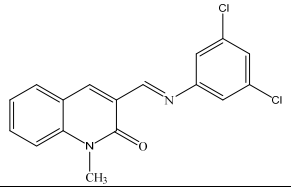


Fig. 1. Pictorial view of the well plate for MABA assay against *Mycobacterium tuberculosis*

2.2.4. Structral activity relationship studies

As a continuation of this study and according to the biological activity presented in **Table 1** and **Table 2**, the structure-activity relationships (SAR) were reported here. The study reveals that, different electron withdrawing groups and electron donating groups are attached to the phenyl ring as substituents were linked to azomethane group. The close observation of antimicrobial potential identified that the inhibition values of the synthesized compounds exhibited a varied range of antimicrobial activities against the tested microorganisms. The compound **3a** had the electron withdrawing group at position **3** exhibit more potency against microorganisms. Similarly compound **3c** shows similar potential against the strains. This indicates the electron withdrawing groups at any position in the phenyl ring enhance the activity. The compounds **3d**, **3e**, and **3f** containing fluro, nitro and bromo respectively of phenyl ring also enhanced the microbial activity. The compound **3b** which does not have any substituent to the phenyl ring shows less activity against the tested microorganisms. The compound **3g**, electron withdrawing group as well as electron donating group at different positions in the phenyl ring exhibit excellent potential of antimicrobial activity.

Table 4. Structures of the synthesized compounds pointing position of the substituent

Compound	Mol. Formula	Substituent	Structure
3a	$C_{17}H_{13}ClN_2O$	3-Cl	
3b	$C_{17}H_{14}N_2O$	-	
3c	$C_{17}H_{12}Cl_2N_2O$	3, 4-Cl	
3d	$C_{17}H_{13}FN_2O$	4-F	
3e	$C_{17}H_{13}N_3O_3$	4-NO_2	
3f	$C_{17}H_{13}BrN_2O$	4-Br	
3g	$C_{17}H_{12}ClN_3O$	3-Cl, 4-NO_2	
3h	$C_{17}H_{13}ClN_2O$	4-Cl	
3i	$C_{19}H_{18}N_2O$	3-CH_3, 4-CH_3	
3j	$C_{17}H_{12}Cl_2N_2O$	3-Cl, 5-Cl	

3. Conclusions

In conclusion we have designed and synthesized schiff bases **(3a-j)** bearing quinoline moiety successfully. The reaction proceeds quickly and there are no observations of any undesirable side reactions. The main advantage of this reaction is use of simple starting key material, simple procedure, easy to workup, without need of any chromatographic purification process, and significant yield. All the synthesized compounds were characterized by ^{1}H, ^{13}C NMR, and FT-IR and Mass

spectral analysis. The *in-vitro* antimicrobial activity of the synthesized compounds were undertaken by agar well diffusion method against gram positive bacteria (*Bacillus licheniformis* and *Bacillus cereus*) gram negative bacteria (*Escherichia coli* and *Acetobactor sp.)* and antifungal activity against (*Aspergillus Flavus* and *Pichnanomala*). Whereas the antimycobacterial activity of the selected compounds was examined by the MABA method. Among the synthesized compounds some of them show a broad spectrum of antimicrobial activity, particularly compounds **3b**, **3c**, **3d**, **3f**, **3g** and **3j** show significant activity of both antibacterial and antifungal assay. Further the compounds which show good activity (**3b**, **3c**, **3d**, **3f**, **3g** and **3j**) are screened for *in-vitro* antitubercular activity by Micro-plate alamar blue assay (MABA) method against *mycobacterium tuberculosis H37Rv* strain, the results show less activity for the tested microorganisms. In conclusion the targeted compounds seemed to be promising pharmacophores.

Acknowledgements

The authors are grateful to Davangere University for encouraging research activities and also thankful to NMR Instrument Centre, Mangalore University Mangalagangothri, India, for carrying out the spectral analysis.

4. Experimental

4.1. Materials and methods

S.D Fine-Chem. Limited, Mumbai supplied all the necessary chemicals and solvents. All chemicals have been used without further refinement. The reactions were monitored with the help of thin-layer chromatography using precoated aluminum sheets with GF-254 silica gel, 0.2 mm layer thickness (E-Merck). The melting points were analyzed using Veego (VMP-MP) melting point apparatus and are uncorrected. The IR spectra of the synthesized compounds were analyzed using KBr on Shimadzu IR-AFFINITY-1. The ^{1}H NMR spectra of the synthesized compounds were recorded on Bruker Avance II 400 NMR spectrometer (with TMS as an internal standard) at NMR Instrument Centre, Mangalore University Mangalagangothri, India. Chemical shifts are reported in δ ppm units with respect to TMS as an internal standard. Mass spectra were recorded on Waters, Q-TOF Micromass (LCMS). Preliminary analysis (CHNS) was achieved employing a CHN EA-99 mth tool. The compounds were analyzed for elemental analysis and the percentages of elements were found to be very near to that of the calculated values.

4.2. General procedure for the synthesis of 1-methyl-2-oxo-1, 2-dihydroquinoline-3-carbaldehyde (1)

The starting material as well as key intermediate for the preparation of final schiff base derivatives 1-methyl-2-oxo-1, 2-dihydroquinoline-3-carbaldehyde **(1)** were synthesized by the reaction of vilsmeier Haack reaction of N-methyl acetanilide according to available protocol method. In this contribution to a stirred solution of *N*, *N*-dimethyl formamide 12 ml (0.164 mol) in a 500 mL round bottom flask equipped with a drying tube at 0 ^{0}C. To this added phosphorus oxychloride 18 mL, (0.11 mol) drop wise with constant stirring. To this solution, N-Methyl acetanilide 5 g (0.034 mol) was added and after 5 min the reaction mixture was refluxed for 4-5h. The completion of reaction was monitored by TLC (Ethyl acetate and Hexane as an eluent). The reaction mixture was allowed to room temperature and poured into 500 g of crushed ice under constant stirring. The reaction mixture was neutralized with 10 % sodium bicarbonate solution, the obtained solid was filtered, washed well with water and dried under vacuum until complete dry then recrystallization using ethyl acetate.

4.3. General procedure for the synthesis of schiff base derivatives (3a-j)

A 15 mL of ethanolic solution of aniline **2a** (10 mmol) was added slowly to 15 ml ethanolic solution of 1-methyl-2-oxo-1, 2-dihydroquinoline-3-carbaldehyde **(1)**. The reaction mixture is acidified with a few drops of glacial acetic acid and refluxed for three to four hours. The progress of the reaction was monitored by thin layer chromatography. After the confirmation of completion of the reaction with TLC (Chloroform and methanol as an eluent) the reaction mixture allowed to cool room temperature, the precipitate, which formed after a certain time. Then filtered off, washed with diethyl ether followed by chloroform and cold absolute alcohol. Similarly, the remaining compounds **(3b-j)** were synthesized and purified by recrystallization using absolute ethanol. The prepared compounds yield, molecular formula, molecular weight, melting points and analytical data were provided in the data section.

4.4. Physical and spectral data

4.4.1. (E)-3-(((3-chlorophenyl)imino)methyl)-1-methylquinolin-2(1H)-one (3a)

Solid Yield 78 %, m.p 293 ^{o}C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.68 (s, 1H), 7.98 (dd, J = 7.9, 1.4 Hz, 1H), 7.71-7.76 (m, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.45-7.49 (m, 1H), 7.33-7.37 (m, 3H), 7.23-7.26 (m, 1H), 3.71 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.78, 157.43, 153.07, 140.68, 137.31, 133.66, 132.58, 130.93, 130.73, 125.49, 125.24, 122.64, 120.74, 119.96, 119.34, 114.90, 29.39; IR (KBr) cm^{-1} 3462.22 (-O-H), 2920.23-2868.38 (Ar-CH), 1965.21

(aliphatic-CH), 1643.35 (-C=O), LCMS *m/z*: 297.01; Anal. Calcd. (%) for $C_{17}H_{13}ClN_2O$. C, 68.89; H, 4.42, N, 9.44. Found: C, 68.94; H, 4.47, N, 9.51.

4.4.2. (E)-1-methyl-3-((phenylimino)methyl)quinolin-2(1H)-one (3b)

Solid Yield 73%, m.p 289 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.73 (s, 1H), 8.01 (dd, J = 7.9, Hz, 2H), 7.76-7.79 (m, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 2.3 Hz, 1H), 7.35-7.39 (m, 1H), 7.33 (dd, J = 8.4, Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.75, 158.06, 151.39, 140.89, 137.61, 132.71, 131.69, 131.1, 130.73, 125.01, 122.82, 122.68, 121.73, 114.01, 40.19, 38.89, 29.43; IR (KBr) cm^{-1} 3433.29 (-O-H), 2921.63-2868.37 (Ar-CH), 1943.29 (aliphatic-CH), 1643.35 (-C=O), LCMS *m/z*: 263.11; Anal. Calcd. (%) for $C_{17}H_{14}N_2O$. C, 77.84; H, 5.38, N, 10.68. Found: C, 77.79; H, 5.43, N, 10.63.

4.4.3. (E)-3-(((3,4-dichlorophenyl)imino)methyl)-1-methylquinolin-2(1H)-one (3c)

Solid Yield 79%, m.p 296 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 8.72 (s, 1H), 8.00 (dd, J = 7.8, 1.5 Hz, 1H), 7.73-7.78 (m, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.35-7.39 (m, 1H), 7.31 (dd, J = 8.5, 2.4 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.76, 158.04, 151.49, 140.76, 137.57, 132.72, 131.68, 131.15, 130.79, 125.18, 122.84, 122.69, 121.74, 114.96, 40.12, 38.87, 29.42; IR (KBr) cm^{-1} 3462.22 (-O-H), 2921.60-2868.38 (Ar-CH), 1956.21 (aliphatic-CH), 1656.85 (-C=O), LCMS *m/z*: 332.03; Anal. Calcd. (%) for $C_{17}H_{12}Cl_2N_2O$. C, 61.65; H, 3.65, N, 8.46. Found: C, 61.70; H, 3.70, N, 8.51.

4.4.4. (E)-3-(((4-fluorophenyl)imino)methyl)-1-methylquinolin-2(1H)-one (3d)

Solid Yield 78 %, m.p 289 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6; δ 10.31 (s, 1H), 8.53 (s, 1H), 7.95-8.11 (m, 3H), 7.79-7.83 (m, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.30-7.40 (m, 1H), 6.74 (d, J = 9.3 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 190.04, 160.81, 141.78, 141.16, 134.05, 131.90, 126.36, 124.71, 122.78, 118.73, 115.12, 112.33, 40.12, 39.91, 39.70, 39.28, 29.08; IR (KBr) cm^{-1} 3379.29 (-O-H), 2924.31-2867.37 (Ar-CH), 1886.24 (aliphatic-CH), 1651.07 (-C=O), LCMS *m/z*: 281.10; Anal. Calcd. (%) for $C_{17}H_{13}FN_2O$. C, 72.85; H, 4.67, N, 9.99. Found: C, 72.90; H, 4.72, N, 9.94.

4.4.5. (E)-1-methyl-3-(((4-nitrophenyl)imino)methyl)quinolin-2(1H)-one (3e)

Solid Yield 77 %, m.p 284 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6; δ 10.32 (s, 1H), 8.51 (s, 1H), 7.93-8.09 (m, 3H), 7.77-7.81 (m, 1H), 7.61 (d, J = 8.3 Hz, 2H), 7.29-7.39 (m, 1H), 6.73 (d, J = 9.2 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 190.1, 160.79, 141.73, 141.11, 134.15, 131.93, 126.33, 124.73, 122.77, 118.71, 115.11, 112.31, 40.11, 39.89, 39.89, 39.27, 29.11; IR (KBr) cm^{-1} 3483.44 (-O-H), 2924.33-2867.39 (Ar-CH), 1863.26 (aliphatic-CH), 1643.35 (-C=O), LCMS *m/z*: 308.10; Anal. Calcd. (%) for $C_{17}H_{13}N_3O_3$. C, 66.44; H, 4.26, N, 13.67. Found: C, 66.45; H, 4.31, N, 13.72.

***4**.4.6. (E)-3-(((4-bromophenyl)imino)methyl)-1-methylquinolin-2(1H)-one (3f)*

Solid Yield 81%, m.p 289 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6; δ 8.80 (s, 1H), 8.68 (s, 1H), 7.97 (dd, J = 7.8, 1.1 Hz, 1H), 7.69-7.74 (m, 1H), 7.58-7.61 (m, 3H), 7.31-7.35 (m, 1H), 7.21-7.25 (m, 2H), 3.69 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.73, 158.11, 151.48, 140.73, 137.56, 132.73, 131.66, 131.11, 130.76, 125.11, 122.83, 122.0, 121.73, 114.93, 40.11, 38.86, 29.39; IR (KBr) cm^{-1} 3448.72 (-O-H), 2823.31-2656.3 (Ar-CH), 1836.26 (aliphatic-CH), 1649.14 (-C=O), LCMS *m/z*: 342.02; Anal. Calcd. (%) for $C_{17}H_{13}BrN_2O$. C, 59.84; H, 3.84, N, 8.21. Found: C, 59.89; H, 3.89, N, 8.26.

4.4.7. (E)-3-(((3-chloro-4-nitrophenyl)imino)methyl)-1-methylquinolin-2(1H)-one (3g)

Solid Yield 81%, m.p 289 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6; δ 10.30 (s, 1H), 8.52 (s, 1H), 8.02 (dd, J = 7.9, 1.4 Hz, 1H), 7.79-7.83 (m, 2H), 7.63 (d, J = 8.7 Hz, 2H), 7.35-7.39 (m, 2H), 3.69 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 190.88, 160.84, 141.81, 141.21, 134.11, 131.93, 129.15, 124.73, 122.84, 118.75, 115.15, 40.12, 39.91, 39.71, 39.29, 38.87, 29.12; IR (KBr) cm^{-1} 3456.36 (-O-H), 2920.23-2863.26 (Ar-CH), 1856.56 (aliphatic-CH), 1643.35 (-C=O), LCMS *m/z*: 342.02; Anal. Calcd. (%) for $C_{17}H_{12}ClN_3O_3$. C, 59.75; H, 3.54, N, 12.30. Found: C, 59.70; H, 3.49, N, 12.25.

4.4.8. (E)-3-(((4-chlorophenyl)imino)methyl)-1-methylquinolin-2(1H)-one (3h)

Solid Yield 73 %, m.p 291 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.63 (s, 1H), 7.66 (dd, J = 7.8, 1.4 Hz, 1H), 7.73-7.79 (m, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.43-7.47 (m, 1H), 7.31-7.35 (m, 3H), 7.21-7.23 (m, 1H), 3.77 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 161.77, 156.41, 151.11, 141.67, 136.33, 133.65, 131.56, 131.99, 129.71, 125.56, 123.23, 121.61, 120.73, 120.93, 120.33, 115.91, 29.38; IR (KBr) cm^{-1} 3464.15 (-O-H), 2923.21-2858.66 (Ar-CH), 1956.36 (aliphatic-CH), 1651.07 (-C=O), LCMS *m/z*: 297.11; Anal. Calcd. (%) for $C_{17}H_{13}ClN_2O$. C, 68.89; H, 4.42, N, 9.45. Found: C, 68.84; H, 4.38, N, 9.40.

4.4.9. (E)-3-(((3,4-dimethylphenyl)imino)methyl)-1-methylquinolin-2(1H)-one (3i)

Solid Yield 69%, m.p 296 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.76 (s, 1H), 8.11 (dd, J = 7.8, Hz, 2H), 7.71-7.76 (m, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.36-7.38 (m, 3H), 7.36 (dd, J = 8.5, Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.73, 159.66, 151.37, 141.86, 137.63, 136.21, 132.73, 131.68, 131.23, 131.71, 126.11, 123.89, 122.63, 121.75, 115.11, 40.20, 39.66, 38.86, 29.44; IR (KBr) cm^{-1} 3450.65 (-O-H), 2926.61-2856.33 (Ar-CH), 1956.32 (aliphatic-CH), 1645.28 (-C=O), LCMS *m/z*: 291.15; Anal. Calcd. (%) for $C_{19}H_{18}N_2O$. C, 78.59; H, 6.25, N, 9.65. Found: C, 78.66; H, 6.30, N, 9.70.

4.4.10. (E)-3-(((3,5-dichlorophenyl)imino)methyl)-1-methylquinolin-2(1H)-one (3j)

Solid Yield 80%, m.p 297 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.74 (d, J = 11.7 Hz, 1H), 8.53 (s, 1H), 8.01-8.04 (m, 1H), 7.75-7.83 (m, 1H), 7.58-7.65 (m, 2H), 7.33-7.39 (m, 2H), 3.70 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 190.04, 160.80, 159.54, 141.78, 141.15, 134.05, 131.90, 131.00, 126.61, 125.89, 124.70, 122.78, 120.34, 118.72, 115.12, 114.98, 40.12; IR (KBr) cm^{-1} 3439.08 (-O-H), 2856.63-2834.56 (Ar-CH), 1936.56 (aliphatic-CH), 1656.85 (-C=O), LCMS *m/z*: 331.01; Anal. Calcd. (%) for $C_{17}H_{12}Cl_2N_2O$. C, 61.65; H, 3.65, N, 8.46. Found: C, 61.70; H, 3.70, N, 8.51.

5. Biology

5.1. In-vitro antibacterial assay

Antibacterial activity of the synthesized compounds was determined by agar well diffusion technique (Zhang *et al*., 2009) with some modifications. The pure cultures of bacterial strains were procured from National Collection of Industrial Microorganisms, (Pune, India). Initially the petri dishes were prepared by adding 20 mL of sterilized nutrient agar media under aseptic conditions and allowed to cool and get solid. After the formation of solid media 100 µL of standardized gram-positive bacteria *Bacillus licheniformis* (MTCC-2465)*, Bacillus cereus* (MTCC-430) and gram-negative bacteria *Escherichia coli* (MTCC-7410)*, Acetobactor sp* (MTCC-3245) were spread uniformly using sterile cotton swabs. Wells were created using a sterile cork borer. Standard reference drug Ciprofloxacin was used as a positive control and DMSO used as a negative control. Then keep it at 4 ºC for about 4 hours for the diffusion of antibacterial metabolites, further the plates were incubated at room temperature for about one day and then the plates were examined for the formation of zone of inhibition. The zone of a inhibition was measured in millimeters (mm). Single inhibition zone was measured three repeated times to get the average values.

5.2. In-vitro antifungal assay

Antifungal activity of the synthesized compounds was determined by agar well diffusion technique (Zhang *et al*., 2009) with some modifications. The pure cultures of bacterial strains were procured from National Collection of Industrial Microorganisms, (Pune, India). Initially the petri dishes were prepared by adding 20 mL of sterilized potato dextrose agar media under aseptic conditions and allowed to cool and get solid. After the formation of solid media 100 µL of standardized *Aspergillus Flavus* (MTCC-2465) and *Pichnanomala* (MTCC-237) were spread uniformly. Wells were created using a sterile L-shaped loop. Standard reference drug *fluconazole* was used as a positive control and DMSO used as a negative control. Then keep it at 4 ºC for about 4 hours for the diffusion of antibacterial metabolites, further the plates were incubated at room temperature for about one day and then the plates were examined for the formation of zone of a inhibition. The zone of inhibition was measured in millimeters (mm). Single inhibition zone was measured three repeated times to get the average values.

5.3. In-vitro antituberculosis assay

Antituberculosis activity and drug susceptibility of the synthesized compounds were determined against *Mycobacterium tuberculosis H37Rv* (ATCC-27294) strain, procured from National Collection of Industrial Microorganisms, (Pune, India). The activity was done in the Maratha Mandal's Central Research Laboratory, Maratha Mandal's NGH Institute of Dental Sciences and Research Centre, R. S. No. 47A/2, Bauxite Road, Belgaum - 590 010. The activity of the synthesized compounds **3b**, **3c**, **3d**, **3f**, **3g** and **3j** was examined by adopting microplate Alamar Blue assay (MABA) technique. Which shows good correlation with proportional and BACTEC radiometric methods and it is non toxic, uses a thermally stable reagent. 20µl of sterile deionized water was added to all outer perimeter wells of sterile 96 wells plate to minimize evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µl of the Middle brook 7H9 broth and serial dilutions of compounds were made directly on plate. The final drug concentrations examined were 100 to 0.2 µg/mL. Plates were incubated at 37 ºC for five days and parafilm is used to cover and seal. Then After, 25µl of freshly prepared 1:1 mixture of Alamar Blue reagent and 10% tween 80 was added to the plate and incubated for one day. A blue colour in the well was interpreted as no bacterial growth, and pink colour was scored as growth. The MIC was defined as the lowest drug concentration which prevented the changing of the colour from blue to pink.

Conflict of interest

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

References

1. Maguire M. P., Sheets K. R., McVety K., Spada A. P., and Zilberstein A. (**1994**) A new series of PDGF receptor tyrosine kinase inhibitors: 3-Substituted quinoline derivatives. *J. Med. Chem*., 37 (14) 2129-2137.
2. Malkov A. V., Kabeshov and Bella M. (**2007**) Vicinal amino alcohols as organocatalysts in asymmetric cross-aldol reaction of ketones: application in the synthesis of convolutamydine A^+. *Org. Lett*., 9 (26) 5473-5476.
3. Shaban M. A. E., Taha M. A. M., and Sharshira E, M. (**1991**) Synthesis and biological activities of Condensed heterocyclo [n,m-*a*,*b*, or *c*]quinazolines. *Adv. in Heter. Chem*., 52 1-153.
4. Thomas K. (**1999**) The pyrano route to 4-hydroxy-2-quinolone and 4-hydroxy- 2-pyridones. *IL farmaco*., 54 309-315.
5. Girish B., Manjunatha S. K., and Mamledesai S, N. (**2012**) Synthesis and antimicrobial activity of 4-hydroxy-1methyl/phenyl-3-(substituted anilinoacetyl) quinolin-2(1H)-one. *RGUHS J. Pharm. Sci*., 02 60-66.
6. Joseph P., Charles B., and Gladys D. (**2001**) Refomatsky reactions with N-arylpyrrolidine-2-thiones: Synthesis of tricyclic analogues of quinoline antibacterial agents. *Tetrahedron*., 57 9635 9648.
7. El-Dine S. A., and El-Khawass S. M. (**1979**) Synthesis of 4-[(2-alkylaryl or arylalkyl) amino-1,3,4-thiadiazol-5-yl]-2-synthesized quinolines and compounds reasonable antifungal and antimicrobial activity. *Pharmazie*., 34 537-538.
8. Anastasia D., Dionysia B., and Kyriakos, C. P. (**2007**) Design and synthesis of novel quinolinone-3-aminoamides and their α-lipoic acid adducts as antioxidant and anti-infl ammatory agents. *J. Med. Chem*., 50 2450-2458.
9. Joseph S., and Francis D. (**2002**) Aryl-2-quinolone derivatives having in vivo and in vitro antitumour activity. *J. Med.* Chem., 45 2543.
10. Qun L. I., Keith L. W. W., and Weibo. (**2005**) Design, synthesis, and activity of achiral analogs of 2-quinolones and indoles as non-thiol farnesyltransferase inhibitors. *Bioorg. Med. Chem.* Lett., 15 2033-2039.
11. Gisela C. M., Mariela B., and Ana M. B. (**2006**) Evaluation of antiparasitic, antituberculosis and antiangiogenic activities of 3-aminoquinolin-2-one derivatives. *J. Chil. Chem.* Soc., 51 859-863.
12. Uppar V., Chandrashekharappa S., Basarikatti A. I., Banuprakash G., Mohan M. K., Chougala M., Mudnakudu-Nagaraju K. K., Ningegowda R., and Padmashali B. (**2020**) Synthesis, antibacterial, and antioxidant studies of 7-amino-3-(4-fluorobenzoyl)indolizine-1-carboxylate derivatives. *J. Appl. Pharmaceut. Sci*., 10 (02) 077–085.
13. Uppar V., Chandrashekharappa S., Venugopala K. N., Gleiser R. M., Garcia D., Odhav B., Mohan M. K., Deb P. K., Venugopala R., and Padmashali B. (**2020**) Synthesis and characterization of pyrrolo [1, 2-a] quinoline derivatives for their larvicidal activity against Anopheles arabiensis. *Struct. Chem*., 17 1-20.
14. Uppar V., Mudnakudu-Nagaraju K. K., Basarikatti A. I., Chougala M., Chandrashekharappa S., Mohan M. K., Banuprakash G., Venugopala K. N., Ninge gowda R., and Padmashali B. (**2020**) Microwave induced synthesis, and pharmacological properties of novel 1-benzoyl-4-bromopyrrolo [1, 2-a] quinoline-3-carboxylate analogues. *Chem. Data. Collect.,* 25 100316.
15. Nandeshwarappa B. P., Chandrashekharappa S., Prakash G. K., and Prasannakumar J. K. (**2020**) Efficient synthesis and characterization of novel 2H-[1,4]oxaselenepino[5,6-*b*]quinolin-3(5H)-ones derivatives. *Chem. Data. Collect.*, 100446.
16. Nandeshwarappa B. P., Chandrashekharappa S., and Sadashiv S. O. (**2020**) Synthesis and antibacterial evaluation of 3-acetyl-2*H*-selenopyrano[2,3-*b*]quinolin-2-ones. *Chem. Data. Collect*., 100484.
17. Nandeshwarappa B. P., Chandrashekharappa S., and Sadashiv S. O. (**2020**) Synthesis and characterization of novel ethyl 2-oxo-2H-selenopyrano [2, 3-b] quinoline-3-carboxylates and studied their antimicrobial activities. *Chem. Data. Collect*., 100466.
18. Nandeshwarappa B. P., Prakash G. K., and Sadashiv S. O. (**2020**) Synthesis and Antimicrobial Activities of Dihydroazeto[2,3:4,5]seleno[2, 3-b] quinolines. *IntechOpen Book, Chapter-1*., 1-6.
19. Nandeshwarappa B. P., Chandrashekharappa S., and Raghu Ninge Gowda. (**2020**) Selenium-containing heterocycles: Synthetic investigation of some new series 3-(5-mercapto-1, 3, 4-oxadiazol-2-yl)-2H-selenopyrano [2, 3-b] quinolin-2-ones. *Chem. Data. Collect*., 29 100510.
20. Nandeshwarappa B. P., Chandrashekharappa S., and Prakash G. K., (**2020**) Nitrogen and selenium containing heterocycles: Part-1: Synthesis of some new substituted 3-(5-(2-oxopropylthio)-1, 3, 4-oxadiazol-2-yl)-2H-selenopyrano [2, 3-b] quinolin-2-ones. *Chem. Data. Collect*., 29 100534.
21. Nandeshwarappa B. P., Sandeep Chandrashekharappa., and Raghu Ningegowda., (**2021**) Design and synthesis of novel substituted 3-(2-(1, 3, 4-thiadiazol-2-ylamino) acetyl)-2H-selenopyrano [2, 3-b] quinolin-2-ones. *Chem. Data. Collect*., 35 100748.
22. Wolfson J., and Hooper D. C. (**1989**) Fluoroquinolone Antimicrobial agents, *Clini Microbio Rev* 2., 378-424.
23. Hooper D. C. (**1995**) Quinolones, In: Mandell, Douglas and Bennett's principles and practice of infectious diseases. 4th edition, New York: *Churchill Livingstone Inc*., 364-375.
24. Hooper D. C. (**1998**) Clinical applications of quinolones. *Biochim. Biophys. Acta*., 45-61.

25. Hardman G. J., Limbird E. L., Molinoff P. B., and Goodman & Gilman's. (**2002**) The Pharmacological Basis of Therapeutics. 9 th edition, *McGraw-Hill Publication*., 1065.
26. Hosseini S. A., Samadzadeh P., Mirzaahmadi A. A., Khandar A. A., and Mahmoudi G. (**2010**) Synthesis, crystal structures, spectroscopic and electrochemical studies on Cu(II) and Ni(II) complexes with compartmental nitrogen-oxygen mixed donor ligands. *Polyhedron*., 80 41.
27. Sadowski M., Utnicka J., Wójtowicz A., and Kula K. (**2023**). The global and local Reactivity of C,N-diarylnitryle imines in [3+2] cycloaddition processes with trans-β-nitrostyrene according to Molecular Electron Density Theory: A computational study. *Curr. Chem. Lett*., 12(2) 421-430.
28. Kula K., and Zawadzińska K. (**2021**) Local nucleophile-electrophile interactions in [3+2] cycloaddition reactions between benzonitrile N-oxide and selected conjugated nitroalkenes in the light of MEDT computational study. *Curr. Chem. Lett*., 10 (1) 9-16.
29. Zawadzińska K., Ríos-Gutiérrez M., Kula K., Woliński P., Mirosław B., Krawczyk T., and Jasiński R. (**2021**) The participation of 3,3,3-trichloro-1-nitroprop-1-ene in the [3+2] cycloaddition reaction with selected nitrile N-oxides in the light of the experimental and MEDT quantum chemical study. *Molecules*., 26 (22) 6774.
30. Kula K., Kącka-Zych A., Łapczuk-Krygier A., Wzorek Z., Nowak A. K., and Jasiński R. (**2021**) Experimental and theoretical mechanistic study on the thermal decomposition of 3,3-diphenyl-4-(trichloromethyl)-5-nitropyrazoline. *Molecules*., 26 (5) 1364.
31. Kula K., Łapczuk A., Sadowski M., Kras J., Zawadzińska K., Demchuk O. M., Gaurav G. K., Wróblewska A., and Jasiński R. (**2022**) On the Question of the Formation of Nitro-Functionalized 2,4-Pyrazole Analogs on the Basis of Nitrylimine Molecular Systems and 3,3,3-Trichloro-1-Nitroprop-1-Ene. *Molecules*., 27 8409.
32. Boguszewska-Czubara A., Kula K., Wnorowski A., Biernasiuk A., Popiołek Ł., Miodowski D., Demchuk O. M., and Jasiński R. (**2019**) Novel functionalized β-nitrostyrenes: Promising candidates for new antibacterial drugs. *Saudi Pharm. J*., 27 (4) 593-601.
33. Schiff H. (**1864**) Schiff Base Reaction. *Justus Liebigs Annalen der Chemie*., 131 118-119.
34. Joseph J., Nagashri K., and Rani B. (**2013**) Synthesis, Characterization and Antimicrobial Activities of Copper Complexes Derived from 4-Aminoantipyrine Derivatives. *J. Saudi Chem. Soci*., 17 285-294.
35. Rao P. (**2019**) A Review on Versatile Applications of Novel Schiff Bases and Their Metal Complexes. *Lett. in Appl. Nano BioSci*., 8 675 681.
36. Rani A., Kumar M., Khare R., and Tuli S. (**2015**) Schiff Bases as an Antimicrobial Agent: A Review. *J. Bio and Chem.* Sci., 2 62-91.
37. Hameed A., Al-Rashida., Uroos M., Abid A. S., and Khan S. M. (**2017**) Schiff Bases in Medicinal Chemistry: A Patent Review (2010-2015). *Expert Opinion on Therapeutic Patents*., 27 63-79.
38. Chen J., Gu B., LeBoeuf E. J., Pan H., Dai S., Tumer M., Koksal H., Serin S., and Digrak M. (**1999**) Spectroscopic characterization of the structural and functional properties of natural organic matter fractions. *Transit. Met. Chem*., 24 13-17.
39. Walsh O. M., Meegan M. J., Prendergast R. M., Nakib T. A. (**1996**) Synthesis of 3-acetoxyazetidin- 2-ones and 3-hydroxyazetidin-2-ones with antifungal and antibacterial activity. *Eur. J.Med. Chem*., 31 989-1000.
40. Da Silva C. M., Da Silva C. L., Modolo L. V., Alves R. B., De Resende M. A., Martins C. V. B., and De Fatima A. (**2011**) Schiff bases: a short review of their antimicrobial activities. *J. Adv. Res*., 1-8.
41. Pandeya S. N., Sriram D., Nath G., and DeClercq E. (**1999**) Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff and Mannich bases derived from isatin derivatives and N-[4-(4' chlorophenyl)thiazol-2-yl] thiosemicarbazide. *Eur. J. Pharmacol*., 9 25-31.
42. Zhang B., Luo H., Xu Q., Lin L., and Zhang B. (**2017**) Antitumor activity of a Transthiosemicarbazone schiff base palladium (II) complex on human gastric adenocarcinoma cells. *Oncotarget*., 8 13620-1363.
43. Nandeshwarappa B. P., Manjappa S., and Kishore B. (**2011**) A novel approach toward the synthesis of azetidinones derivatives. *J. Sul. Chem*., 32 (5) 475-481.
44. Manjunatha S. K., Jennifer F., Shivalingrao M., Sujatha M. L., Rekha L., and Girish B. (**2019**) *INNOSC Theranostics and Pharm. Sci*., 2 14-18.
45. Praveen Kumar. C. H., Manjunatha S. K., and Nandeshwarappa B. P. (**2022**) *Chem. Data. Collect*., 42 100955.