Synthesis, Characterization andAntimicrobial Activity of 2,5disubstituted-3-[5-(1H-indol-3-yl)-4,5-dihydro-1H-pyrazol/1H isoxazole-3-yl]-6-chloro-2-methyl-4-phenyl-quinoline

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Abstract

The present investigation is in the interest of some synthesized novel derivatives 2, 5-disubstituted-3-[5-(1H-indol-3-yl)-4,5-dihydro-1H-pyrazol-3-yl]-6-chloro-2-methyl-4-phenyl-quinoline **4(a-f)** and 2, 5 - disubstituted - 3 - [5-(1H-indol-3-yl) - 4, 5-dihydro-1 H- isoxazole - 3 - yl] - 6 - chloro - 2 – methyl - 4 - phenyl - quinoline**5 (a-c).**The core nucleus indolescaffold is incorporated with different biological active heterocycles such as indole, quinoline, pyrazoline/isoxazoline. The characterization of the synthesisedcompounds reported is based on IR, ^{1}H NMR, ^{13}CNMR and mass spectral data. All the synthesised compounds were screened for their antibacterial activity on four bacteria (two Gram positive Species *Bacillus subtilis, Staphylococcus aureus* and two Gram negative species, *Escherichia coli, Salmonella typhi*) and antifungal activity on two fungi species (*Aspergillusniger, Aspergillusfumigatus*).Ciprofloxacin is used as bacterial standards and Amphotericin B is used as fungal standards for references to evaluate the efficacy of the tested compounds. Amongst the biological evaluated synthesised compounds 4b,4e and 5b exhibited most potent antimicrobial activity.It was observed that the presence of electron withdrawing group at 2and 5 position of indoleremarkably enhanced the antimicrobial activity.

Keywords: Indole, pyrazoline, Isoxazoline, Quinolineand antimicrobial.

Introduction

The versatile nature of heterocycles has been known from the century since their direct involvement in natural products [1-4]. Particularly, the nitrogen based heterocyclesare omnipresent and play pivotal role in medicinal chemistry [5-11]. Amongst the various N-heterocycles, indole motifs have received significant attention due to their presence in proteins, amino acids, bioactive alkaloids, and drugs [12–23]. In this context, a large number of indole moieties have been investigated in the development of new efficient bioactive molecules with diverse pharmacological properties, such as antimicrobial, antiviral, anticancer, anti-

inflammatory, inhibitors, and antioxidant [24–47]. Generally, indoles substituted at 2ndor 3rdposition [48–50], are known to exhibit certain bioactivity.

The structural modifications in existing drugs have shown astounding results in the field of drug discovery. Searching for structure with significant bioactivity, we focused onto the development of molecules through combination of different active pharmacophores like quinolines, pyrazoline and isoxazole along with indole into one core structure. This may lead to compounds with improved antimicrobial activity.

The substituted quinoline derivatives are the focus of a large number of studies because of their wide range of biological applications [51]. The quinoline moiety constitutes the main framework of several natural products such as Monteluka[52]and Skimmianine [53]. Polysubstitutedquinolines in particular are very important compounds because of their medicinal applications as antimalarial, anti-inflammatory, antiasthmatic and antibacterial agents and they also have a wide array of industrial applications [54-56].

2-Pyrazoline derivatives have been reported to exhibit various pharmacological activities such as antimicrobial [57], anti-inflammatory [58], antihypertensive, anti-tumor [59, 60], and anticonvulsant [61]. In addition, pyrazolines are also reported to possess cytotoxic properties against human lung tumor cell line (A549) [62]. Nowadays some newly steroidal pyrazoline are also synthesized for finding a novel drug molecule [63].

Isoxazole being an azole with an oxygen atom next to the nitrogen, exhibits broad spectrum of biological activity and also forms a part of various biodynamic agents [64]. The substituted isoxazoles are also considered to be important synthons due to their versatility towards chemical transformations to useful synthetic intermediates. Isoxazole derivatives show hypoglcemic, analgesic, anti-inflammatory, antifungal, anti-bacterial and HIV-inhibitory activities [65]. Prompted by the above-mentioned observations, we have focused onto construct some new antimicrobial derivatives bearing quinoline, pyrazoline and isoxazoline scaffolds and study the structure activity relationship due to substituent variations.

Synthetic strategies adopted to achieve the target compounds are depicted in Scheme 1.In the present investigation chalcones**3(a-c)** are obtained by the condensation of 1-(6-Chloro-2-methyl-4-phenyl-quinolin-3-yl)-ethanonewith various 2,5-disubstituted indole 3-carboxaldehyde in alcohol.The key chalcone derivatives are used as precursors for the synthesis of title compounds **4(a-f) and 5(a-c).** Compounds **3 (a-c)**were synthesized through the Claisen–Schmidt condensation of equimolar amounts of 1-(6-Chloro-2-methyl-4-phenyl-quinolin-3-yl)-ethanone and different derivatives of indole-3-carbaldehyde **2(a-c)** by stirring the reactants in aqueous alcoholic solution containing sodium hydroxide at room temperature. Compound **2(a-c)** isVilsmeier–Haack reactions adduct; it provides a vital and efficient intermediate for the synthesis of several new substituted heterocyclic analogues.Chalcone compounds **3 (a-c)**on cyclocondensation with hydrazine and hydroxyl amine hydrochloride resulted into final compounds.

Materials and Methods

Chemicals, Methods and Structural Studies

All the chemicals and solvents were of laboratory reagent grade and used as received from Sigma Aldrich and SD fine. Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by TLC using silica gel-G coated aluminum plates (Merck) and spots were visualized by exposing the dry plates to iodine vapors. The IR (KBr) spectra were recorded on a Perkin-Elmer spectrometer on FT-IR spectrometer. The 1H NMR (DMSO-d6) spectra recorded on a Bruker (400 MHz) and the chemical shifts were expressed in ppm (δ scale) downfield from TMS. Mass spectral data were recorded by electron impact method on JEOL GCMATE II GC-MS mass spectrometer. Elemental analysis was carried out using Flash EA 1112 series elemental analyzer. All the compounds gave C, H and N analysis within±0.5% of the theoretical values

Synthesis of 2,5-disubstituted indole-3- chalcone 3(a-c)

To a stirred solution of 2,5-disubstituted indole-3-carbaldehyde **2(a-c)** (**4**, 500 mg, 3.45 mmol) in absolute ethanol (25 ml) were added 1-(6-chloro-2-methyl-4-phenyl-quinolin-3-yl)-ethanone**(1)** (**3**, 1.018 g, 3.45 mmol) and 40% aqueous solution of KOH (25 ml) and the reaction mixture was refluxed for 16 hours. Reaction mixture was cooled to room temperature and pour into ice cold water. Precipitated brown solid was filtered and washed with cold H_2O. The crude product was purified by flash column chromatography on silica gel using gradiant hexane/EtOAc mixture to yield desired product as a brown solid.

Comp.No.3a

IR (KBr) (λmax in cm-1):1617(C=N**);** 1700(C=O**);** 3318(indoleN-H);1H NMR (400 MHz, $CDCl_3$) $^{\delta}$(ppm):8.85(br, s,1H, indole NH),2.75(s,3H),6.69-7.21(2H, CH=CH-),7.21-8.09(m,13ArH); LCMS: m/z = 422; Analysis: Calcd for ($C_{27}H_{19}ClN_2O$): C, (76.65); H, (4.55) N, (6.60) Found: C, 76.68; H, 4.53, N, 6.62.Brown crystals

Comp.No.3b

IR (KBr) (λmax in cm-1): 1624(C=N); 1701(C=O**);** 3388(indoleN-H);1H NMR (400 MHz, $CDCl_3$) $^{\delta}$(ppm): 8.75(br, s,1H, indole NH),2.75(s,3H),6.75 and 7.10 (2H, CH= CH-) 7.20-8.08(m,16ArH); LCMS: m, /z = 533;Analysis: Calcd for $C_{33}H_{22}Cl_2N_2O$ (397): C, (74.1); H, (4.13), N,(5.23). Found: C, 74.3; H, 4.16, N, 5.25. Yellow crystals

Comp.No 3c

IR (KBr) (λmax in cm-1): 1634(C=N); 1705(C=O); 3330 (indoleN-H); 1H NMR (400 MHz, $CDCl_3$) $^{\delta}$(ppm): 8.75(br, s,1H, indole NH),2.74(s,3H),6.7 - 7.1 (2H, CH= CH-) 7.12-8.08(m,16ArH); LCMS: m/z =513; Analysis: Calcd for$C_{34}H_{25}ClN_2O$: C, (79.62); H, (4.17),N, (5.45). Found: C, 79.60; H, 4.19, N, 5.46.Yellow crystals

Synthesis of 2,5- disubstituted-3-[5-(1H-indol-3-yl)-4,5-dihydro-1H-pyrazol-3-yl]-6-chloro-2-methyl-4-phenyl-quinoline. 4 (a-f)

The Chalcones**3(a-c)** (267 mg, 0.5 mmol) in ethanol (10 ml) was added hydrazine (0.4 ml) and the reaction mixture was refluxed for 24 h. Reaction mixture was concentrated, diluted with CH_2Cl_2, and washed with H_2O. Organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography on silica gel using gradiant hexane/EtOAc mixture to yield desired product as a yellow solid

Comp.No.4a

IR (KBr) (λmax in cm-1): 1577(C=C); 1616(C=N); 3406(indoleN-H); 3049(N-H (pyrazole)1H NMR (400 MHz, $CDCl_3$) $^{\delta}$(ppm): 2.82(s,3H),8.12(s,1H, indole NH),6.82(s,1H, pyrazole NH)7.1-8.02(m,12H, ArH), 4.97(t,1H),2.58-2.70(m,1H),2.71-2.74(t,1H);LCMS: m/z=436; Analysis: Calcd for: $C_{27}H_{21}ClN_4$;C, (74.20); H, (4.82);N, (12.79),Found: C, 74.22 ; H, 4.84, N, 12.80.Pale yellow crystals

Comp.No.4b

IR (KBr) (λmax in cm-1): 1572(C=C); 1650(C=N); 3427(indoleN-H); 3053(N-H (pyrazole)1H NMR (400 MHz, $CDCl_3$) $^{\delta}$(ppm): 2.90(s,3H),8.13(s,1H,indoleNH),6.82(s,1H, pyrazoleNH),7.18-8.06(m,16H, ArH),4.93-4.96(t,1H),2.67-2.73(t,1H),2.48-2.53(t,1H);LCMS: m/z = 547; Analysis: Calcd for: $C_{33}H_{24}Cl_2N_4$, C, (72.42); H, (4.41); N, (10.21), Found: C, 72.40; H, 4.42, N, 10.23. Dark yellow crystals

Comp.No.4c

IR (KBr) (λmax in cm-1): 1568(**C=C);** 1614(C=N); 3430(indoleN-H);3056(N-H (pyrazole)1H NMR (400 MHz, CDCl3) $^{\delta}$(ppm):2.864(s,3H),8.13(s, 1H,indoleNH), 2.735(s,3H), 6.831(s,1H,pyrazole NH)71.84-8.06(m,16H,ArH),4.932-4.962(t,1H),2.672—2.705(t,1H), 2.501-2.533(t,1H); LCMS: m/z=527; Analysis: Calcd for: $C_{34}H_{27}ClN_4$, C, (77.45); H, (5.14);N, ((10.61), Found: C, 77.48; H, 5.16 ;N, 10.63.Dark yellow crystals

Comp.No.4d

IR (KBr) (λmax in cm-1): 1579(**C=C);** 1618(C=N); 3420(indoleN-H); 1H NMR (400 MHz, $CDCl_3$) $^{\delta}$(ppm):2.91(s,3H),8.207(s, 1H, indoleNH),7.184-8.06(m,18H, ArH), 4.932-4.962(t,1H),2.702-2.735(t,1H),2.513-2.672(t,1H), LCMS: m/z= 513; Analysis: Calcd for: $C_{33}H_{25}ClN_4$, C, (77.24); H, (4.93);N, (10.94), Found: C, 77.26; H, 4.91; N, 10.92.Yellow crystals

Comp.No.4e

IR (KBr) (λmax in cm-1): 1560(**C=C);** 1608(C=N); 3428(indoleN-H); 1H NMR (400 MHz, $CDCl_3$) $^{\delta}$(ppm):2.91(s,3H),8.207(s, 1H, indoleNH),7.184-8.06(m,18H, ArH), 4.932-

4.962(t,1H),2.702-2.735(t,1H),2.513-2.672(t,1H), LCMS: m/z=622; Analysis: Calcd for: $C_{39}H_{28}Cl_2N_4$, C, ((75.25); H, (4.87);N, ((8.75), Found: C, 75.23; H, 4.89; N,8.77.Light yellow crystals.

Comp.No.4f

IR (KBr) (λmax in cm-1): 1580(**C=C);** 1613(C=N); 3425(indoleN-H); 1H NMR (400 MHz, $CDCl_3$)$^{\delta}$(ppm): 2.91(s,3H), 8.207(s,1H,indoleNH),7.184-8.06(m,18H,ArH),4.932-4.962(t,1H),2.702-2.735(t,1H),2.513-2.672(t,1H), LCMS: m/z= 602; Analysis: Calcd for: $C_{40}H_{31}ClN_4$, C,(79.63); H, (5.20);N, ((9.27), Found: C, 79.65; H, 5.18; N, 9.29. Yellow crystals

Synthesis of 2,5- disubstituted-3-[5-(1H-indol-3-yl)-4,5-dihydro-1H-isoxazole-3-yl]-6-chloro-2-methyl-4-phenyl-quinoline. 5(a-c)

The Chalcones**3(a-c)(**296 mg, 0.7 mmol) in ethanol (15 ml) was added hydroxylamine Hydrochloride (0.5 ml) and the reaction mixture was refluxed for 24 h. Reaction mixture was concentrated, diluted with CH_2Cl_2, and washed with H_2O. Organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography on silica gel using gradient hexane/EtOAc mixture to yield desired product as a yellow solid (0.131 g, 30%).

Comp.No.5a

IR (KBr) (λmax in cm-1): 1580(**C=C);**1650 (C=N);3431 (indoleN-H);1H NMR (400 MHz, $CDCl_3$) $^{\delta}$(ppm):2.8(s,3H), 8.03(s,1H, indole NH), 7.04-8.02 (m,13H, ArH), 4.94-4.97 (t,1H), 2.70-2.74(t,1H),2.58-2.67(t,1H).LCMS: m/z=437; Analysis: Calcd for: $C_{27}H_{20}ClN_3O$, C,(74.01); H, (4.58);N, (9.61), Found: C, 74.05; H, 4.60 , N, 9.60.Pale yellow crystals

Comp.No.5b

IR (KBr) (λmax in cm-1): 1568(C=C); 1658 (C=N); 3427 (indoleN-H); 1H NMR (400 MHz, $CDCl_3$) $^{\delta}$(ppm): 2.8(s,3H), 8.03(s,1H, indole NH), 7.04-8.02 (m,13H, ArH), 4.94-4.97 (t,1H), 2.70-2.74(t,1H),2.58-2.67(t,1H).LCMS: m/z=548; Analysis: Calcd for: $C_{33}H_{23}Cl_2N_3O$ C,(72.25); H, (4.21);N, ((7.65), Found: C, 72.27; H, 4.23 , N, 7.66. Darkyellow crystals

Comp.No.5c

IR (KBr) (λmax in cm-1): 1572(C=C); 1648 (C=N); 3423 (indoleN-H); 1H NMR (400 MHz, $CDCl_3$) $^{\delta}$(ppm): 2.8(s,3H), 8.03(s,1H, indole NH), 7.04-8.02 (m,13H, ArH), 4.94-4.97 (t,1H), 2.70-2.74(t,1H),2.58-2.67(t,1H).LCMS: m/z=528;Analysis: Calcd for:$C_{34}H_{26}ClN_3O$, C,(77.32); H, (4.95);N, ((7.95), Found: C, 77.34; H, 4.96 , N, 7.96.Brownish yellow crystals.

Biological Activities

Antimicrobial Activity

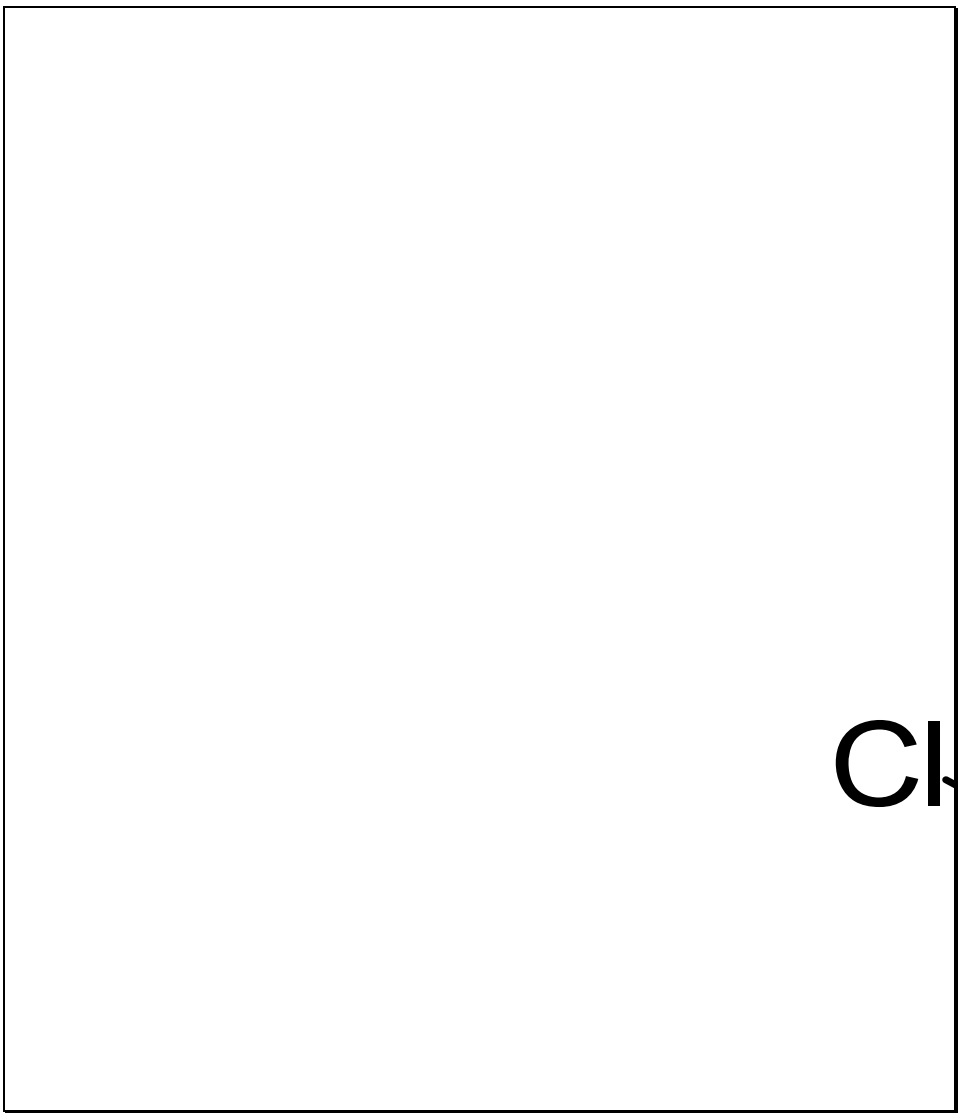
The antibacterial activities of compounds 4(a-f) and 5(a-c), were carried out using the cup plate diffusion method [66-67]. This method depends on the diffusion of the antibiotic from a cavity through the solidified agar layer in a petri dish to an extent such that the growth of the added

microorganism is prevented in a circular zone around the cavity containing a solution of the antibiotic. For antibacterial activity, antibacterial species used are two Gram negative species, *Escherichia coli* (ATCC 9637), *Salmonella typhi* (ATCC 6539) and two Gram positive species, *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 29737). Two fungal strains *Aspergillusniger* (ATCC 16509), *Aspergillusfumigatus* (ATCC16406) were used for antifungal activity. Solution of each compound at a concentration of 1000µg/ml in DMSO was prepared and the inhibition zone diameter in millimeter was used as the criterion for measuring the microbial activity after 24h for bacteria and 72h for fungi. Ciprofloxacin is used as bacterial standards and Amphotericin B is used as fungal standards for references to evaluate the efficacy of the tested compounds under the same conditions. DMSO used as control and solvent to prepare compound solutions. Measurements of results are shown in table 1

Table 1.Antimicrobial activity results of 4(a-f),5(a-c)

Zone of inhibition in mm.						
Compound	**Antibacterial activity**				**Antifungal activity**	
	Gram positive		Gram negative			
	B.subtilis	*S.aureus*	*E. coli*	*S. typhi*	*A.fumigatus*	*A.niger*
4a	8+0.166	10+0.296	12+0.185	11+0.26	12+0.203	10+0.145
4b	**22+0.167**	**20+0.29**	**24**+0.251	**21**+0.173	**20**+0.145	**18**+0.203
4c	12+0.133	13+0.166	**22**+0.173	**18**+0.296	12+0.24	12+0.176
4d	16+0.233	17+0.305	**19**+0.153	**18**+0.145	12+0.26	12+0.145
4e	**23+0.066**	**24**+0.29	**27**+0.12	**21**+0.153	**18**+0.202	**18**+0.116
4f	16+0.2	17+0.296	15+0.145	15+0.233	12+0.088	12+0.033
5a	11+0.267	10+0.29	12+0.203	14+0.24	11+0.26	11+.145
5b	**20+0.134**	**21**+0.305	**24**+0.24	**22**+0.176	**20**+0.033	**20**+0.186
5c	13+0.167	13+0.317	14+0.26	17+0.203	13+0.12	13+0.173
Ciprofloxacin	26	28	30	26		
Amphotericin B					28	30

Note: Values are expressed in mean±SD (n=3)



Scheme 1: Synthesis of compounds 4 (a-f) and 5 (a-c)

Results and Discussion

Chemistry

In the present investigation chalcones**,3(a-c)** are obtained by the condensation of 1-(6-Chloro-2-methyl-4-phenyl-quinolin-3-yl)-ethanone with various 2,5-disubstituted indole 3-carboxaldehyde in alcohol.The IR spectrum of the chalcone**(3b)** exhibited characteristic absorption peaks at 3388 cm^{-1}corresponding to indole NH, and appearance of strong carbonyl absorption around 1700cm^{-1}corresponding to α, β unsaturated carbonyl group.The ^{1}H NMR spectrum of compound **3b** has shown a singlet downfield at δ 8.75 (s, 1H, NH) integrating for single proton due to more deshielded indole NH, singlet at δ2.75 (s,3H) due to methyl protons. The deshielded protons present on the α, β carbons of the chalcones appeared at δ 6.75 and δ 7.10(2H, -CH=CH-) respectively.The ^{13}C NMR

Spectrum of the compound **(3b)** has shown peaks at δ 25.82 due to methyl group, at δ198 due to carbonyl carbon. The 1H NMR spectrum of one of the target compound **(4b)** has exhibited a singlet at δ 8.13 due to indole NH, singlet at δ 6.82 corresponds to pyrazoline NH, singlet at 2.90 due to three protons of methyl group. The existence of methylenic protons of pyrazoline ring as dd, clearly indicates the magnetic non-equivalence of these two protons, which have chemical shift at δ 2.48-2.53 centered at δ 2.50 and δ2.67-2.73 centered at δ 2.70, the CH proton appeared as triplet at δ 4.93-4.96 centered at δ 4.94 due to vicinal coupling with two protons of methylene.The ^{13}C NMR Spectrum of the compound **(4b)** has shown peaks at δ26 due to carbon of methyl group, δ42.93 corresponding to methylinic carbon atom of pyrazoline ring, δ 46 due to CH of pyrazoline ring. The disappearance of the^{13}C peak at δ 198 confirms the cyclisation mechanism to form pyrazoline ring. Furthermore, the mass spectrum of **(4b)** has exhibited molecular ion peak at m/z 546(100%), corresponding to the molecular weight of the compound ,548(60%) and 550(10%) corresponding to isotopic peaks of the compound containing two chlorine atoms., the 3 peaks are formed in the ratio of 9:6:1.

Antimicrobial Activity

All the synthesised compounds were subjected for antimicrobial activity. In vitro antibacterial activities of the synthesized compounds were evaluated utilizing Bacillus subtilis, Staphylococcus aureus, Escherichia coli and Salmonella typhi, antifungal activity against*Aspergillus niger* and*Aspergillus fumigatus* by cup plate method. The bioactivity of the synthesised compounds depicts that activity depends on the nature of the substituent. The electronic nature of the substituent groups leads to significant discrepancy in antimicrobial activity. The presence of chloro group on the aromatic ring at 5th position and also the phenyl ring at 2nd position amplified the antimicrobial activity of the compounds compared to electron donating CH_3 group. They showed good activity against gram –ve bacteria. The compounds with no substitution at 2nd and 5th position showed minimum activity. 4e has exhibited highest antimicrobial activity amongst other synthesised analogues. All the test were performed in triplicate. Obtained bioactivity results were compared with commercially available drugs, Ciprofloxacin and Amphotericin B. However, none of the compounds exhibited zone of inhibition more than that of standard.

Conclusion

The synthesis of 2,5 disubstituted--3-[5-(1H-indol-3-yl)-4,5-dihydro-1H-pyrazol-3-yl]-6-chloro-2-methyl-4-phenyl-quinoline **4(a-f**) was prepared by cyclocondensation of chalcones **3 (a-c)** with hydrazine hydrate and phenyl hydrazine in ethanol, similarly 2, 5 - disubstituted - 3 - [5-(1H-indol-3-yl) - 4, 5-dihydro-1 H- isoxazole - 3 - yl] - 6 - chloro - 2 – methyl - 4 - phenyl - quinoline **5 (a-c)** were obtained by the cyclocondensation of chalcones with Hydroxylamine.

The structures of synthesised Novel Indole derivatives were confirmed by their IR,^{1}H NMR, ^{13}C NMR, Mass spectral and analytical data. Synthesised compounds **4b, 4e and 5b,** have shown maximum zone of inhibition against *Bacillus subtilis* (ATCC 6633),*Staphylococcus aureus* (ATCC 29737), *Escherichia coli* (ATCC 9637), and *Salmonella typhi*(ATCC 6539) rest of the compounds showed moderate to less activity.

Declaration of Competing Interest

With reference to the manuscript entitled "Synthesis, Characterization and antimicrobial activity of 2,5 disubstituted-3-[5-(1H-indol-3-yl)-4,5-dihydro-1H-pyrazol/1H isoxazole-3-yl]-6-chloro-2-methyl-4-phenyl-quinoline." All the authors have read, approved and made substantial contributions for the manuscript. None of the original material contained in this manuscript has been previously published nor is currently under review for publication elsewhere. The authors Pushpa and Sharangouda J. Patil having no conflict of interest.

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