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Synthesis of New 3-heteroaryl-2-phenylquinolines and their Pharmacological Activity as Antimicrobial Agents

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Abstract: Some new unfused tricyclic aromatic systems containing various heterocyclic cores were synthesized. These compounds were prepared in good yields via appropriate routes using 6-methyl-2-phenylquinoline-3-carbaldehyde as a key intermediate. The antibacterial activity of the prepared compounds was evaluated against: *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia* and *Salmonella thipymurium* using the disk-diffusion method. The minimum inhibitory concentration (MIC) was determined for the tested compounds.

Keywords: 2-Phenylquinoline, heterocycles, crystal structure, antimicrobial activity, minimum inhibitory concentration.

Heterocyclic compounds have so far been synthesized mainly due to the wide range of biological activities. Much attention has been paid to the synthesis of heterocyclic compounds bearing nitrogen and oxygen containing ring system, like pyrazole, oxazole, coumarine, and pyrrole derivatives mainly due to their higher pharmacological activity [1]. At present, the role of heterocyclic compounds has become increasingly important in designing new class of structural entities of medicinal importance [2].

Quinoline derivatives have considerable interest since many years due to the presence of this skeleton in a large number of bioactive compounds and natural products [3]. Thus, a large variety of quinoline derivatives exhibit useful biological activities like antimalarial [4], anti-inflammatory [5], anticancer [6], antibiotic [7], antihypertensive [8], tyrokinase PDGF-RTK inhibiting agents [9], and anti HIV [10]. To improve the pharmacological profile of the quinoline moiety, a number of investigations have been carried out which involved there coupling with some various heterocyclic core [11]. The introduction of the quinoline nucleus has already been used successfully in a number of other cases [12].

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On the other hand, Denny *et al.* have demonstrated the efficacy of unfused tricyclic aromatic systems such as phenylquinolines and benzimidazoles as 'minimal intercalators' that have moderate binding affinity with DNA [13]. Other studies have showed that the presence of aryl ring at 2nd position of quinoline moiety gives a very good pharmacological activity to the target molecule [14]. The coupling of heterocyles entities with 2-phenylquinoline moiety might as well be envisioned to bring with some biological activities.

Following of our previous works related to the use of substituted 2-chloro-3-formylquinolines as precursors of different quinoline-containing heterocycles [15], we have recently reported preparations and antibacterial screening of series of compounds carrying diverse functionalities such as an amine, amide or ester group linked to the 2-phenylquinoline entity [16]. We wish to report herein our preliminary results concerning the synthesis of new 3-heteroaryl-2-phenylquinoline hybrids. The synthetic pathways adopted for the preparation of 2-phenylquinoline compounds linked to the heterocyclic nucleus are outlined in schemes **1–4**.

The key intermediate 6-methyl-2-phenylquinoline-3-carbaldehyde **2**, required for the preparation of the target compounds was obtained in two steps according to established methods [17]: first 6-methyl-2-chloroquinolyl-3-carbaldehyde **1** was prepared by condensation/cyclization of the corresponding anilide with phosphoryl chloride and DMF. Subsequent Suzuki-Miyaura reaction of **1** with phen-

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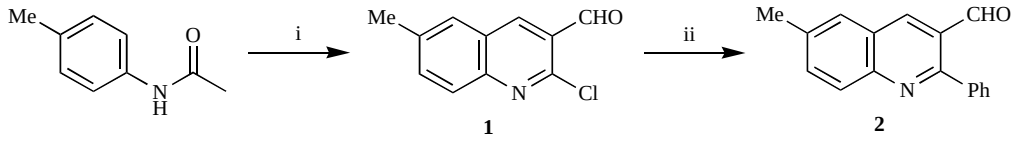
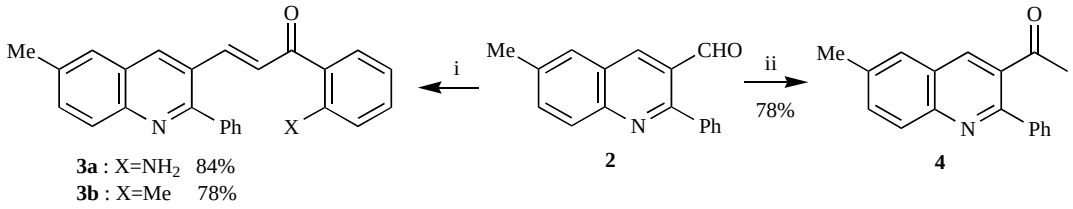


Scheme 1. Reagents and conditions: (i) $POCl_3$, DMF, 85°C, 18h; (ii) $Pd(PPh_3)_4$, $PhB(OH)_2$, Na_2CO_3 (2M), DME, reflux, 4h.



Scheme 2. Reagents and conditions: (i) 2-methylacetophenone or 2-aminoacetophenone, NaOH, EtOH, rt; (ii) (a) MeI, Mg, Et_2O; (b) PCC, CH_2Cl_2, rt.

ylboronic acid affords the 6-methyl-2-phenyl-3-formylquinoline **2** in 79% of yield (Scheme **1**).

Chalcones derivatives **3a** or **3b** were easily prepared in good yields by aldol condensation reaction of 6-methyl-2-phenylquinoline-3-carbaldehyde **2** with 2-methylacetophenone and 2-aminoacetophenone respectively which were pure enough for use in subsequent steps. The reaction of **2** with methyl magnesium iodide afforded the secondary alcohol intermediate. Oxidation of this latter with pyridinium chlorochromate gives the corresponding 1-(6-methyl-2-phenylquinolin-3-yl)ethanone **4** (Scheme **2**). Both ^1H and ^{13}C NMR spectra of compounds **3** and **4** were in full agreement with the proposed structures.

The X-ray crystallographic analysis of single crystals of **3b** and **4** confirmed their respective structural assignments (Figs. **1**, **2**).

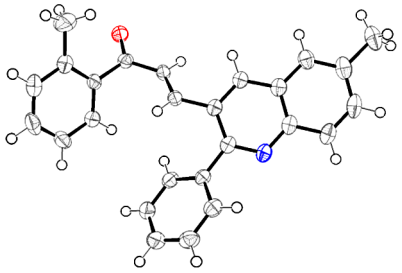


Fig. (1). ORTEP plot of the X-ray crystal structure of **3b**. Displacement ellipsoids are drawn at the 50% probability level [18].

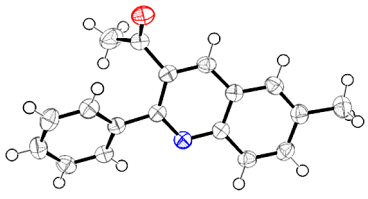


Fig. (2). ORTEP plot of the X-ray crystal structure of **4**. Displacement ellipsoids are drawn at the 50% probability level [18].

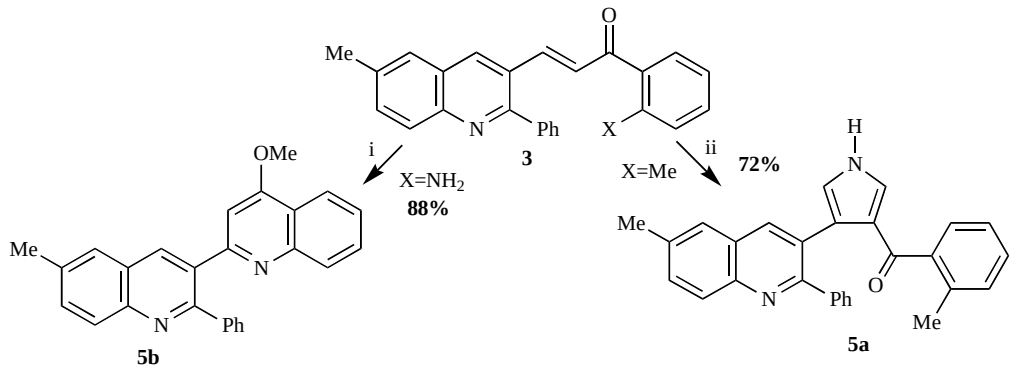
The structure of **3b** contains a quinoline unit linked to an aryl ketone α,β-unsaturated at C_3 and phenyl ring at C_2. The dihedral angle between the quinoline ring system and the linked phenyl ring is 37.38 (8) and, this value is 41.05 (8) between the quinoline entity and the second phenyl *o*-tolyl ring. The crystal packing can be described by layers parallel to (100) crystallographic plane. It is stabilized by C-H...O and C-H...π interactions and π...π stacking interactions.

In the title compound, **4**, the quinoline ring system is approximately planar with a dihedral angle of 2.05 (5)° and forms a dihedral angle of 65.32(6)° with the phenyl ring. The crystal packing can be described as parallel layers to the (010) plane. It features C-H···π interactions and strong π-π stacking interactions. These interactions link the molecules within the layers and also link the layers together, reinforcing the cohesion of the structure.

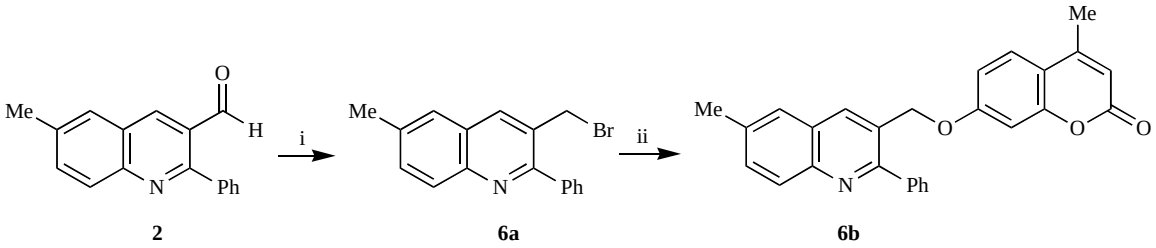
The pyrrole compound **5a** was prepared by stirring chalcone 3b with TosMic in the presence of *t*-BuOK in THF at room temperature [19]. The oxidation of 2'-aminochalcone **3a** using $FeCl_3.6H_2O$ in MeOH [20] gives the corresponding 4-methoxy-2-(6-methyl-2-phenylquinolin-3-yl) quinoline **5b** in good yields (Scheme **3**).

The conversion of **2** into the corresponding bromide **6a** was accomplished via a reduction/ substitution sequence. The reaction of **6a** with 7-hydroxy-4-methylcoumarin in the presence of cesium carbonate gave the quinoline **6b** in 88% of yields (Scheme **4**).

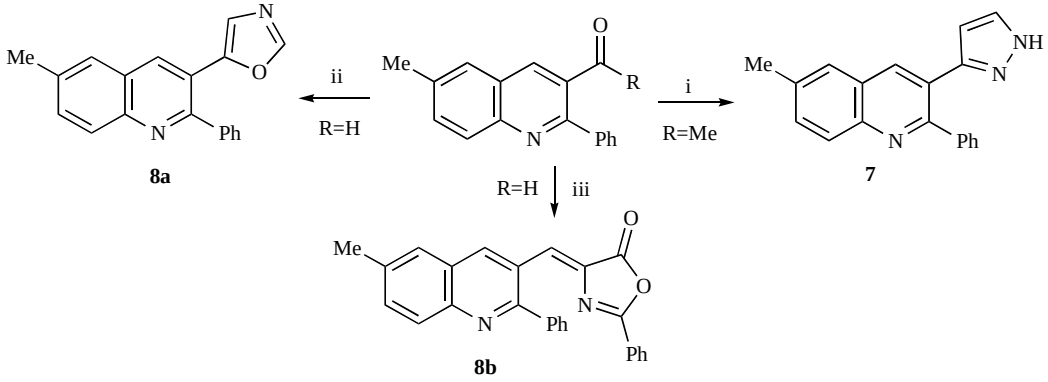
Next, we expanded this work to the preparation of heterocycles containing two heteroatoms such as pyrazole and oxazole coupled 2-phenylquinoline unit. The reaction of the resulting enamine obtained from the condensation of **4** with dimethylformamid dimethyl acetal, and hydrazine hydrate gave 6-methyl-2-phenyl-3-(1*H*-pyrazol-3-yl)quinoline **7** in good yields (65%) [21]. TosMic reacts with 6-methyl-2-phenylquinolin-3-carbaldehyde **2** in the presence of potassium carbonate in MeOH [22], giving the corresponding 6-methyl-3-(oxazol-5-yl)-2-phenylquinoline **8a** in 82% of yields [23]. The Erlenmeyer-Plöchl azlactone synthesis [24] of oxazolone **8b** was achieved in good yield (75%) after purification by column chromatography using CH_2Cl_2 as eluent, by addition of a slight excess of hippuric acid (*N*-benzoylglycine) to 6-methyl-2-phenylquinolin-3-carbaldehyde **2** in presence of acetic anhydride and anhy-



Scheme 3. Reagents and conditions: (i) $FeCl_3.6H_2O$, MeOH, reflux; (ii) TosMIC, *t*-BuOK, THF, 0°C to rt.



Scheme 4. Reagents and conditions: (i) (a) $NaBH_4$, MeOH, rt; (b) PBr_3, CH_2Cl_2, rt; (ii) 7-hydroxy-4-methyl-2H-chromen-2-one, Cs_2CO_3, acetone, rt.



Scheme 5. Reagents and conditions: (i) (a) $Me_2NCH(OMe)_2$, reflux; (b) $H_2NNH_2.H_2O$, EtOH, reflux; (ii) TosMic, K_2CO_3, MeOH, reflux; (iii) hippuric acid, AcONa, Ac_2O, MW.

drous sodium acetate under microwave irradiation (Scheme **5**).

Single crystals of **8a** were grown by evaporation of a CH_2Cl_2 solution and an X-ray crystallographic analysis confirmed the structural assignment (Fig. **3**).

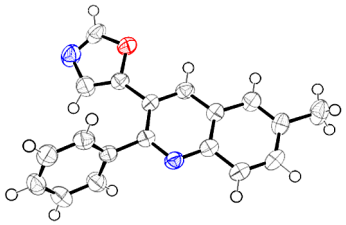


Fig. (3). ORTEP plot of the X-ray crystal structure of **8a**. Displacement ellipsoids are drawn at the 50% probability level [18].

In structure of **8a**, quinoline ring form a dihedral angle of 37.44(4)° and 52.80(7)° with phenyl ring and heterocyclic ring respectively. The crystal packing can be described as parallel layers to the (013) plane. Intermolecular interactions of C-H...π and π-π stacking connect the molecules together reinforcing the cohesion between the layers of the structure.

Numerous studies have demonstrated that the nature of substituents and substitution pattern on the quinoline unit may have a considerable impact on the pharmacological activities [25]. In this context, the prepared tricyclic aromatic systems containing various heterocyclic cores were evaluated for their antibacterial activities.

Almost prepared compounds were submitted for preliminary evaluation of their *in vitro* activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATCC-27853), *Klebsiella pneu-*

Table 1. *In vitro* Antibacterial Activity and MIC of Compounds

Compounds	Yield[a] (%)	MIC(µg/ml) (Zones of Inhibition in mm)*				
		Escherichia coli	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Salmonella typhimurium*
5a	72	100 (08)	50 (12)	No inhibition	>200 (10)	>200 (08)
5b	88	<25 (16)	<25 (32)	100 (12)	200 (ND)	No inhibition
6b	88	50 (16)	<25 (20)	200 (08)	100 (08)	>200 (08)
7	65	50 (14)	<25 (18)	100 (10)	100 (10)	No inhibition
8a	82	50 (10)	50 (15)	>200 (08)	>200 (10)	No inhibition
8b	75	<25 (15)	50 (17)	200 (10)	200 (ND)	No inhibition
Gentamicin		< 4 (25)	< 4 (21)	< 4 (25)	< 4 (15)	< 4 (20)
Chloramphenicol		< 8 (30)	< 8 (18)	ND	< 8 (20)	< 8 (25)

*Charge of disk 50μg.
[a]Isolated pure product
ND : Not determined

moniae (ATCC-700603) and *Salmonella typhimurium* (ATCC-07095) **E** using the disk-diffusion method [26]. Paper disks (6mm) were charged with 50µg of tested compounds (**5a-8b**). To confirm the antibacterial activities of synthesized compounds, the MICs tests were carried out. Bacterial inoculums were prepared by dilution of an overnight broth culture to give the equivalent of 10^6 cell/mL approximately. The MICs values (µg/mL) of each compound after 1 day of exposure are shown in Table **1**. Gentamicin and Chloramphenicol were chosen as standard drugs. The results of the antibacterial screening of the tested compounds are summarized in Table **1**.

Most of the tested compounds were found active against *Staphylococcus aureus* and *Escherichia coli*, however, in most cases, moderate activities were observed against *Pseudomonas aeruginosa* or *Klebsiella pneumoniae*. The compounds **5b**, **7, 8a** and **8b** don't show any inhibitory activity against *Salmonella typhimurium*. The best results were observed with compounds **5b, 6b, 8a** and **8b** which have shown a significant inhibition effect (MIC< 25 µg/mL) in the growth of Gram positive bacteria like *Staphylococcus aureus* (compounds **5b, 6b** and **7**) and *Escherichia coli* as Gram negative bacteria (**5b** and **8b**). Compounds **5a** and **6b** showed a moderate to good activity with broad antibacterial spectrum, and the quinoline compound **5b** is the most promising antibacterial agent.

In conclusion, as demonstrated herein, the approaches developed in this work allow an efficient access to new 3-heterocycle-2-phenylquinoline hybrids using appropriate synthetic routes. These approaches allow a diverse range of compounds to be prepared in good yields. All the target compounds were evaluated for their *in vitro* antimicrobial activity, and most of them proved to be active against Gram positive or Gram negative bacteria pathogens selected in this study. It was observed that the antimicrobial activity in these various classes of 2-phenylquinoline depends on the nature of heterocycles at C-3.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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[18] Crystal structure analysis for **3b**: $C_{26}H_{21}NO$, Mr = 363.44 g mol^{-1}, mp. 198 °C, orthorhombic, space group P 2_1nb, a = 7.4462(2) Å, b = 14.6709(5) Å, c = 17.7923(5) Å, V = 1943.67(10) $Å^3$, Z= 4. Crystal structure analysis for **4**: $C_{18}H_{15}NO$, Mr = 261.31 g mol^{-1}, mp. 175 °C, monoclinic, space group $P2_1/n$, a = 5.9353(2) Å, b = 12.2766(7) Å, c = 19.0972(8) Å, β = 91.926(2)°, V = 1390.74(11) $Å^3$, Z= 4. Crystal structure analysis for **8a:** $C_{19}H_{14}N_2O$, Mr = 286.32 g mol^{-1}, mp. 182 °C, orthorhombic, space group P 2_1nb, a = 5.656(5) Å, b = 14.110(4) Å, c = 18.390(5) Å, V = 1467.6(14) $Å^3$, Z=4. The structures were solved by direct methods and refined by full-matrix least squares analysis on F^2 using SHELXL. Hydrogen atoms were refined on the riding model with isotropic thermal parameters set twenty percent greater than those of their bonding partners. All other atoms were refined anisotropically. Crystallographic data (excluding structure factors) for compounds **3b**, **4** and **8a** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 861478 for **3b**, CCDC 861479 for **4** and CCDC 861480 for **8a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif./cif.

[19] Procedure for the synthesis of **5a**: To a solution of chalcone **3b** (1mmol) and tosylmethyl isocyanide (1mmol) in distilled tetrahydrofuran (5mL), was added *t*-BuOK (2 mmol) at 0°C. The reaction mixture was then stirred at room temperature for 2h. After removal of the solvent the residue was poured into water and extracted with CH_2Cl_2 (10 mL). The aqueous phase was further extracted with CH_2Cl_2 (2x10mL). The organic phases were combined, dried ($MgSO_4$), filtered and the filtrate was concentrated. The crude product was then purified by column chromatography on silica gel using Et_2O/PE as eluent. Selected data for **5a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.15 (br, 1H), 7.99 (s, 1H), 7.96 (d, J=8.6 Hz, 1H), 7.50 (s, 1H), 7.45-7.38 (m, 2H), 7.14-7.10 (m, 5H), 7.01 (d, *J*=7.4 Hz, 1H), 6.93 (t, *J*=7.4 Hz, 1H), 6.67-6.60 (m, 2H), 6.45-6.42 (m, 1H), 2.46 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.3, 158.7, 145.6, 141.3, 140.1, 136.6, 136.1, 135.9, 131.4, 130.4, 129.9, 129.2, 2x128.8, 2x128.0, 127.9, 127.5, 127.4, 127.2, 126.1, 124.5, 2x124.3, 119.9, 117.9, 21.6, 19.4. Anal. Calcd. For $C_{28}H_{22}N_2O$: C, 83.63; H, 5.25; N, 6.72; Found: C, 83.56; H, 5.51; N, 6.96.

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[23] Procedure for the synthesis of **8a**: To a mixture of 6-methyl-2-phenylquinoline-3-carbaldehyde **2** (1 mmol) and tosylmethyl isocyanide (1 mmol) in 10 mL of MeOH was added K_2CO_3 (1 mmol). The solution was refluxed for 2 h and the solvent was removed under reduced pressure. The residue was poured into ice-water and extracted with ether (20 mL). The organic layer was washed with saturated sodium hydrogen carbonate solution (10 mL) and dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the product is purified by column chromatography on silica gel using Et_2O/PE as eluent. Selected data for **8a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.88 (d, *J*= 8.6 Hz, 1H), 7.71 (s, 1H), 7.44 (s, 1H), 7.42 (dd, *J*=8.6, 1.7 Hz, 1H), 7.35-7.30 (m, 5H), 6.18 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 150.5, 149.1, 145.7, 140.5, 137.3, 133.9, 132.8, 129.1, 2x128.8, 2x128.7, 128.5, 126.7, 126.5, 125.4, 120.7, 21.6. Anal. Calcd. For $C_{26}H_{18}N_2O_2$: C, 79.70; H, 4.93; N, 9.78; Found: C, 79.55; H, 4.91; N, 9.43.

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