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SYNTHESIS OF IMIDAZO[4,5-*C*] QUINOLINE DERIVATIVES *VIA* HOFMANN REARRANGEMENT IN THE PRESENCE OF IODOBENZENE DIACETATE AND ITS BIOLOGICAL EVALUATION

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Abstract
A new series of imidazo[4,5-*c*] quinoline derivatives were designed and synthesised using substituted amide derivatives of quinoline in the presence of iodobenzenediacetate as a catalyst *via* Hofmann rearrangement and intramolecular cyclization. The structures of the title compounds were confirmed by FT-IR, elemental analysis, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The newly synthesized compounds **4a-u** were evaluated for their *in vitro* antibacterial bioassay against a cluster of pathogenic strains of bacteria and fungi, *in vitro* antitubercular and antimalarial activity against *Mycobacterium tuberculosis* H37Rv strain and *Plasmodium falciparum* respectively. Compound **4s** exhibited excellent antitubercular and antimalarial potency.

Keywords
Imidazo[4,5-*c*] quinoline, Hofmann rearrangement and biological activity

Introduction

Malaria and tuberculosis are the world's most dangerous infectious diseases after HIV and Cancer. *P. falciparum* is considered as the most virulent form of the *Plasmodium* genus which is responsible for the infection of malaria. On the other hand, the emergence of *P. falciparum* conflict to antimalarial drugs is a serious cause for anxiety.[I-III] *Mycobacterium tuberculosis* is accountable for the occurrence of tuberculosis (TB). To overcome the threat of tuberculosis, there is a vital requirement of new drugs with divergent and unique structures and perhaps a different mechanism of action from that of the routine antitubercular drugs.[IV-V] Quinoline and its derivatives are the key structural motifs in heterocyclic chemistry and occupy a significant position in biological and medicinal chemistry.[VI] They exhibited a broad spectrum of pharmacological activities such as anticancer,[VII] analgesic,[VIII] anti-inflammatory,[IX] antimalarial,[X] antituberculosis[XI] and antifungal[XII] activities. Fluorine substituted quinoline derivatives such as norfloxacin, ofloxacin, ciprofloxacin, temafloxacin,

defloxacin, sparfloxacin, delafloxacin, lomefloxacin etc. are used clinically as they possess effective antibacterial potency.[XIII]

The imidazolone motif appears in many natural products,[XIV] which possess interesting biological activities. They were applied as intermediates in the synthesis of many natural products, such as biotin,[XV] slagenins,[XVI] axinohydantoins,[XVII] oroidin-derived alkaloids,[XVIII] aplysinopsins,[XIX] Lancetta-derived alkaloid carcaridine A,[XX] and others. Due to their importance many methods have been developed for construction of imidazole ring.[XXI]

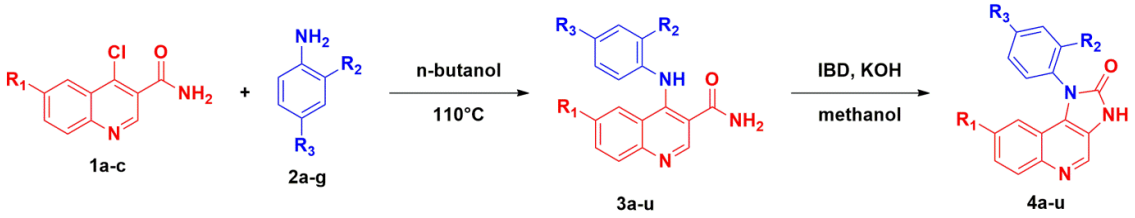
IBD is used as a catalyst for various reactions like oxidative rearrangements and fragmentations, oxidative functionalization of carbonyl compounds, alkenes, and arenes, oxidation of alcohols, cationic cyclization.[XXII-XXV] IBD can serve as excellent oxidants in Hofmann-type degradation of aliphatic or aromatic carboxamides to the respective amines.

In view of advantages of iodobenzenediacetate, we have chosen iodobenzenediacetate as a catalyst to synthesize imidazo[4,5-*c*]quinoline derivatives. It has been well-established that fusion of imidazole ring at 3rd and 4th position of quinoline moiety is highly active against *plasmodium falciparum* and plays a pivotal role in development of new antimalarial drugs[XXVI] and in consequence, emerged as a validated molecular target. Despite the immense pharmacological effects of imidazolone and quinoline, a modification on the imidazolone nucleus by substituted amines and at 6th position of quinoline nucleus may bring significant changes in pharmacological activities, and may provide new classes of therapeutically active compounds.

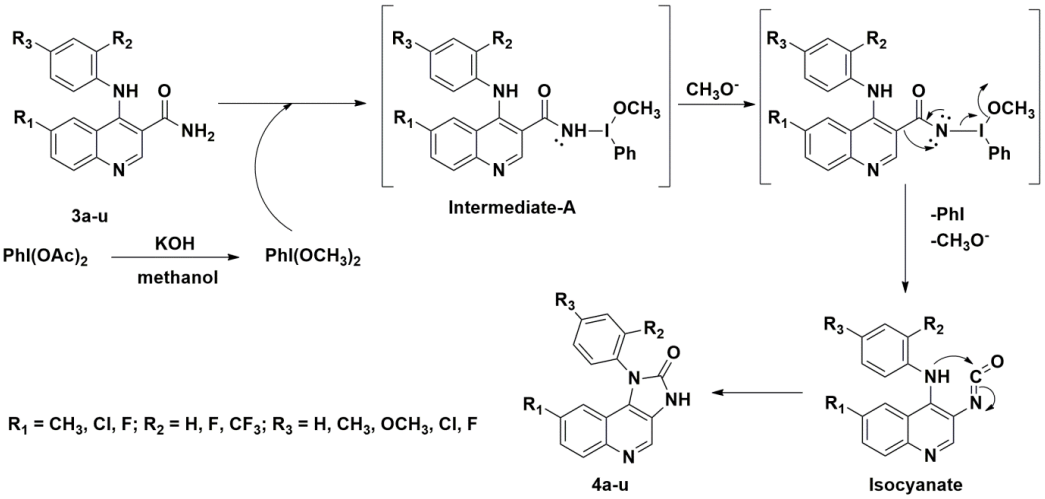
In continuation of our efforts to develop new synthetic methodologies for the preparation of quinolines incorporated motifs,[XXVII-XXXIV] we have synthesised imidazo[4,5-*c*]quinoline derivatives. An effort has been carried out to synthesis of quinoline-imidazole hybrid with the assumption that the inclusion of more than one bioactive moiety into a single scaffold may produce novel heterocycles with remarkable biological activities.

Results and Discussion

The synthetic approach implemented for the preparation of the targeted imidazo[4,5-*c*]quinolin-2(3*H*)-one derivative **4a-u** is illustrated in **Scheme 1**. 4-substituted aniline was reacted with diethyl ethoxymethylenemalonate in neat condition to give the corresponding diethyl 2-((4-substituted-phenyl-amino)methylene)malonate, which was then cyclised with polyphosphoric acid to give ethyl 6-substituted-4-oxo-1,4-dihydroquinoline-3-carboxylate. The compounds 4-chloro-6-substituted-quinoline-3-carboxamide was prepared by hydrolysis followed by amidation of compounds ethyl 6-substituted-4-oxo-1,4-dihydroquinoline-3-carboxylate. After this 4-chloro-6-substituted-quinoline-3-carboxamide **1a-c** and substituted aniline **2a-g** reacted through chloro-amine coupling reactions approach to obtain intermediate **3a-u**. Finally, the target compounds 1-and 8-substituted-1H-imidazo[4,5-c]quinolin-2(3H)-one derivative **4a-u** were successfully obtained from the reaction of intermediate **3a-u** *via* hofmann type rearrangement using iodobenzenediacetate as a catalyst. The chemical structures of these novel compounds were confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR, mass and elemental analysis.



Scheme 1. Synthesis of 1-and 8-substituted-1H-imidazo[4,5-c]quinolin-2(3H)-one [**4a-u**]



Scheme 2. Plausible mechanism for the hofmann type rearrangement in final step

A plausible mechanism for the final step of reaction is outlined in **Scheme 2**. Addition of iodobenzenediacetate to methanolic KOH leads to the formation of $PhI(OCH_3)_2$. Reaction of amide **3a-u** with $PhI(OCH_3)_2$ leads to the probable formation of the *N*-(phenyliodonio) Intermediate-A. Rearrangement of Intermediate-A leads to the formation of an isocyanate. After this isocyanate and secondary amine group intramolecularly react to form the final imidazo[4,5-c]quinolin-2(3*H*)-one derivative **4a-u**.

The ^{1}H NMR spectra of compounds **4a-u** shows signal of –NH proton as a sharp singlet around δ 11.55-11.91 ppm. The aromatic protons resonate as multiplets at around δ 6.49-8.96 ppm. The IR spectrum of compounds **4a-u** exhibited characteristic absorption band around 1645-1660 cm^{-1} and 1710-1728 cm^{-1} which was attributed to the presence C=O stretching of imidazolone ring. The absorption bands for all the compounds **4a-u** were observed in the range of 3290-3320 cm^{-1} corresponding to cyclic –NH of amide group. The absorption band around 2970-2990 cm^{-1} is due to aromatic C-H stretching. The mass spectrum of all the compounds showed molecular ion peak at M^+ corresponding to their molecular weights, which confirmed the respective chemical structures.

Biological section

Antibacterial activity

Broth micro dilution method was used for the *in vitro* antimicrobial screening of final compounds **4a-u** at minimal inhibitory concentration (MIC).[XXXV] The analysis of antibacterial screening data (**Table 1**) revealed that all the compounds **4a-u** showed moderate to very good inhibitory activity. The compound **4h** showed maximum activity i.e. 211 µM against *B. subtilis.* Majority of the compounds showed excellent activity against gram positive bacteria *B. subtilis* and *C. tetani* as compared to ampicillin (MIC = 715 µM), while compounds **4d**, **4f**, **4i**, **4p**, **4s**, **4t** and **4c**, **4f**, **4h**, **4k, 4m, 4p, 4s, 4t** showed similar activity as that of the standard drugs ampicillin against *B. subtilis* and *C. tetani* respectively. The compounds **4e** (213 µM) and **4u** (287 µM) displayed comparatively good activities against *S. pneumonia*.

In case of inhibiting gram negative bacteria, compounds **4e** and **4n** showed superior activity against *V. cholera* relative to ampicillin i.e. 287 µM and compound **4o** illustrated marvellous activity against *E. coli* as compared to ampicillin. Compounds **4g**, **4s** and **4a**, **4i**, **4l** showed the same inhibitory effects as that of the standard ampicillin against *E. coli* and *S. typhi*

respectively. In *V. cholera*, compounds **4s** and **4u** showed comparable activity to ampicillin. Remaining other compounds are moderate or less active against all gram positive and gram negative bacteria.

Table 1. *In vitro* antimicrobial activity (MIC, μM) of compounds **4a-u**.

Entry	Gram positive bacteria			Gram negative bacteria			Fungi	
	S.P.	B.S.	C.T.	E.C.	S.T.	V.C.	C.A.	A.F.
	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC
	1936	441	449	443	98	3906	227	3008
4a	454	**363**	**363**	726	**227**	908	3632	3632
4b	864	**345**	864	432	864	345	**864**	>3456
4c	818	818	**655**	655	655	818	>3275	818
4d	403	**645**	**403**	1614	1614	807	>1000	1614
4e	**213**	**340**	**426**	340	340	**170**	>3409	1704
4f	681	**681**	**681**	852	852	1704	**852**	3409
4g	582	728	1456	**291**	728	728	1456	2912
4h	845	**211**	**676**	676	676	676	1690	>3381
4i	807	**645**	807	807	**201**	807	1614	3228
4j	1534	767	1534	306	383	306	3069	1534
4k	1514	755	**605**	755	605	378	**755**	1514
4l	637	**398**	**398**	637	**199**	796	**796**	3187
4m	398	**318**	**637**	796	796	398	3187	1593
4n	549	1374	**549**	549	687	**171**	2749	1374
4o	716	1790	895	**179**	716	447	**895**	3580
4p	426	**681**	**681**	426	681	681	1704	1704
4q	322	**403**	**322**	645	322	807	**645**	1614
4r	318	**398**	796	318	637	796	3187	3187
4s	841	**672**	**672**	**210**	672	**210**	1682	1682
4t	841	**672**	**672**	672	336	1682	3364	3364
4u	**287**	1439	**287**	575	1799	**287**	**574**	2879
Ampicillin	286	715	715	286	286	286	n. t. [a]	n. t.
Chloramphenicol	154	154	154	154	154	154	n. t.	n. t.
Ciprofloxacin	150	301	150	075	075	075	n. t.	n. t.
Norfloxacin	031	156	310	031	031	031	n. t.	n. t.
Nystatin	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	107	107
Griseofulvin	n. t.	n. t.	n. t.	n. t.	n. t.	n. t.	1417	283

S.P.: *Streptococcus pneumoniae*, C.T.: *Clostridium tetani*, B.S.: *Bacillus subtilis*, S.T.: *Salmonella typhi*, V.C.: *Vibrio cholera*, E.C.: *Escherichia coli*, C.A.: *Candida albicans*, A.F.: *Aspergillus fumigatus*, MTCC: Microbial Type Culture Collection. A: Ampicillin, B: Chloramphenicol, C: Ciprofloxacin, D: Norfloxacin, E: Nystatin, F: Griseofulvin, [a]n.t.: not tested.

Antifungal activity

The result of antifungal study (**Table 1**) of the synthesized imidazo[4,5-*c*]quinoline derivatives revealed that all the compounds have poor activity against *A. fumigates*. Where as in comparison with standard fungicidal griseofulvin (MIC = 1417 μM), compounds **4q** and **4u** contributed excellent antifungal activity i.e. 645 μM and 574 μM respectively against *C. albicans.* While compounds **4b**, **4f**, **4k**, **4l** and **4o** showed same potency against *C. albicans*. All other compounds showed weak antifungal potency than nystatin and griseofulvin.

Antituberculosis activity

The inspiring results from the antibacterial activity motivated us to decide screening of the title compounds for their *in vitro* antituberculosis activity against *M. Tuberculosis H37Rv* strain using Lowenstein-Jensen medium (conventional method) as described by Rattan.[XXXVI] The bioassay results achieved for the convenience of all the synthesized analogues against *M. tuberculosis* H37Rv is summarized in **Table 2**. Rifampicin and Isoniazid were used as the reference drugs. The outcome of the result revealed that, compounds **4a**, **4d**, **4f**, **4l**, **4p** and **4s** were found to possess outstanding activity (i.e. 98%, 94%, 97%, 98%, 97% and 99% at 250 μg/mL respectively) against *M. tuberculosis* H37Rv.

Table 2. *In vitro* antituberculosis activity (% Inhibition) of imidazo[4,5-c]quinoline derivatives **4a-u** against *M. tuberculosis* H37Rv (at concentration 250 μg/mL).

Entry	% Inhibition	MIC (μM)	Entry	% Inhibition	MIC (μM)
4a	**98**	**181**	4m	45	n. t.
4b	12	n. t.	4n	38	n. t.
4c	35	n. t.	4o	12	n. t.
4d	**94**	**322**	**4p**	**97**	**213**
4e	63	n. t.	4q	81	n. t.
4f	**97**	**170**	4r	25	n. t.
4g	79	n. t.	**4s**	**99**	**42**
4h	20	n. t.	4t	67	n. t.
4i	70	n. t.	4u	85	n. t.
4j	33	n. t.	Rifampicin	98	48
4k	45	n. t.	Isoniazid	99	1
4l	**98**	**79**			

The compound **4s** shows high potency against *M. tuberculosis* i.e. MIC = 42 μM as compared to rifampicin i.e. MIC = 48 μM at 99% inhibition. Compound **4l** MIC = 79 μM exhibited better inhibition at 98%. Also, compounds **4a** MIC = 181 μM, **4d** MIC = 322 μM, **4f** MIC = 170 μM and **4p** MIC = 213 μM displayed moderate inhibition compared to reference drugs (**Table 2**). Compound **4s** was emerging out as the most potent member of the series and opens up a new access to optimize this series for new class of antituberculer agent.

Antimalarial activity

All the synthesized compounds **4a-u** was evaluated for their *in vitro* antimalarial activity against chloroquine and quinine sensitive strain of *P. falciparum*. All experiments were performed in duplicate and a mean value of IC_{50} is mentioned in **Table 3**. The active compounds were found to have IC_{50} in the range of 0.093 to 0.735 μM against *P. falciparum* strain. These compounds displayed excellent activity against *P. falciparum* strain as compared to quinine IC_{50} = 0.826 μM. Furthermore compounds **4n** was found to possess moderate activity i.e. IC_{50} = 0.093 μM as compared to chloroquine. Remaining all other compounds was found to be less active against *P. falciparum* strain. Compound **4n** was emerging out as the most potent member of the series and opens up a new access to optimize this series for new class of antimalarial agent.[XXXVII-XXXIX]

Table 3. *In vitro* antimalarial activity of compounds 4a-u

Entry	IC_{50} (μM)	Entry	IC_{50} (μM)
4a	3.897	4m	2.263
4b	6.186	**4n**	**0.093**
4c	3.357	**4o**	**0.257**
4d	**0.735**	4p	1.943

4e	**0.194**	**4q**	**0.278**
4f	**0.201**	4r	4.749
4g	3.582	**4s**	**0.225**
4h	**0.524**	**4t**	**0.111**
4i	**0.184**	**4u**	**0.659**
4j	3.321	**Chloroquine**	0.062
4k	4.452	**Quinine**	0.826
4l	1.976		

Experimental Section

Synthesis of 4-(substituted-phenylamino)-6-sustituted-quinoline-3-carboxamide 3a-u

A mixture of compounds **1a-c** and various amines **2a-g** in n-butanol were charged in a 50 mL round bottom flask with mechanical stirrer and condenser. The reaction mixture was heated at 110°C for 1 h and the progress of the reaction was monitored by TLC. After the completion of reaction (as evidenced by TLC), the reaction mixture was cooled to room temperature and separated precipitates of compounds **3a-u** were filtered, dried, and recrystallized from methanol.

Synthesis of 1-and 8-substituted-1H-imidazo[4,5-c]quinolin-2(3H)-one 4a-u

A solution of KOH (1.3 mmol) in methanol was portion-wise added to a stirred solution of compounds **3a-u** (1 mmol) in 5 mL methanol at 10-15°C. After add the IBD (iodobenzenediacetate) (1.2 mmol) to reaction mixture and reaction mixture was stirred at room temperature for 1h. After the completion of reaction (as evidenced by TLC), the solvent was distilled off to get compounds **4a-u** and recrystallized from chloroform: methanol (1:1). The physicochemical data of the synthesized compounds **4a-u** are given below.

*8-methyl-1-phenyl-1H-imidazo[4,5-c]quinolin-2(3H)-one **4a***

Yield 76%; m.p. 257-259°C; IR (ν_{max}, cm^{-1}): 3310, 2981, 1716, 1652; ^{1}H NMR (400 MHz, DMSO-d_6): 2.44 (s, 3H), 7.22-8.97 (m, 9H), 11.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.5, 116.8, 119.8, 121.4, 126.3, 127.5, 128.0, 128.9, 129.5, 134.2, 142.7, 147.8, 150.5, 158.7, 162.6; ESI-MS (m/z): Calcd. 275.30, found 275.45 (M^+); Anal. Calcd. (%) for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.48; H, 4.89; N, 14.97.

*8-methyl-1-(p-tolyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one **4b***

Yield 78%; m.p. 280-282°C; IR (ν_{max}, cm^{-1}): 3317, 2972, 1713, 1649; ^{1}H NMR (400 MHz, DMSO-d_6): 2.34 (s, 3H), 2.45 (s, 3H), 7.25-8.76 (m, 8H), 11.64 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.3, 21.7, 115.8, 120.8, 121.4, 126.4, 127.8, 128.5, 128.7, 129.2, 133.9, 136.9, 142.6, 148.2, 151.4, 157.5, 162.1; ESI-MS (m/z): Calcd. 289.33, found 289.40 (M^+); Anal. Calcd. (%) for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.55; H, 5.47; N, 14.39.

*1-(4-methoxyphenyl)-8-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one **4c***

Yield %; m.p. 274-276°C; IR (ν_{max}, cm^{-1}): 3305, 2988, 1719, 1645; ^{1}H NMR (400 MHz, DMSO-d_6): 2.45 (s, 3H), 3.84 (s, 3H), 7.26-8.74 (m, 8H), 11.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.2, 55.6, 118.5, 119.5, 121.6, 122.6, 125.8, 126.6, 127.4, 128.5, 129.9, 130.3, 134.4, 139.7, 149.9, 150.3, 159.6, 162.6; ESI-MS (m/z): Calcd. 305.33, found 305.40 (M^+); Anal. Calcd. (%) for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.98; H, 5.15; N, 13.58.

*1-(4-chlorophenyl)-8-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one **4d***

Yield %; m.p. 269-271°C; IR (ν_{max}, cm^{-1}): 3311, 2990, 1725, 1657; ^{1}H NMR (400 MHz, DMSO-d_6): 2.36 (s, 3H), 7.29-8.81 (m, 8H), 11.64 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.5, 117.4, 120.6, 122.8, 126.5, 127.8, 128.5, 129.7, 133.9, 134.3, 136.8, 142.5, 148.3, 158.1, 161.9; ESI-MS (m/z): Calcd. 309.75, found 309.92 (M^+); Anal. Calcd. (%) for $C_{17}H_{12}ClN_3O$: C, 65.92; H, 3.90; N, 13.57. Found: C, 65.68; H, 4.17; N, 13.71.

1-(4-fluorophenyl)-8-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4e***
Yield %; m.p. 266-268°C; IR (ν_{max}, cm^{-1}): 3298, 2974, 1722, 1648; ^1H NMR (400 MHz, DMSO-d_6): 2.36 (s, 3H), 7.28-8.82 (m, 8H), 11.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.3, 115.7, 117.8, 120.8, 121.9, 124.5, 127.3, 128.9, 130.2, 132.5, 133.9, 137.5, 142.7, 147.7, 162.9, 163.2; ESI-MS (m/z): Calcd. 293.30, found 293.41 (M^+); Anal. Calcd. (%) for $C_{17}H_{12}FN_3O$: C, 69.62; H, 4.12; N, 14.33. Found: C, 69.91; H, 4.26; N, 14.05.
1-(2-fluorophenyl)-8-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4f***
Yield %; m.p. 260-263°C; IR (ν_{max}, cm^{-1}): 3306, 2985, 1728, 1653; ^1H NMR (400 MHz, DMSO-d_6): 2.35 (s, 3H), 7.25-8.78 (m, 8H), 11.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.3, 115.6, 117.8, 120.4, 121.4, 126.3, 127.8, 128.5, 129.2, 129.7, 134.2, 138.5, 140.3, 144.6, 147.8, 162.8, 163.6; ESI-MS (m/z): Calcd. 293.30, found 293.45 (M^+); Anal. Calcd. (%) for $C_{17}H_{12}FN_3O$: C, 69.62; H, 4.12; N, 14.33. Found: C, 69.85; H, 4.29; N, 14.21.
8-methyl-1-(2-(trifluoromethyl)phenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4g***
Yield %; m.p. 256-258°C; IR (ν_{max}, cm^{-1}): 3313, 2977, 1718, 1658; ^1H NMR (400 MHz, DMSO-d_6): 2.36 (s, 3H), 7.23-8.81 (m, 8H), 11.66 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.5, 115.8, 120.1, 120.9, 124.5, 125.9, 126.6, 127.9, 128.4, 129.0, 129.8, 132.2, 134.3, 136.4, 142.8, 147.7, 152.4, 162.5; ESI-MS (m/z): Calcd. 343.30, found 343.80 (M^+); Anal. Calcd. (%) for $C_{18}H_{12}F_3N_3O$: C, 62.97; H, 3.52; N, 12.24. Found: C, 63.15; H, 3.85; N, 12.05.
8-chloro-1-phenyl-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4h***
Yield %; m.p. 250-252°C; IR (ν_{max}, cm^{-1}): 3298, 2983, 1712, 1660; ^1H NMR (400 MHz, DMSO-d_6): 7.30-8.89 (m, 9H), 11.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 115.1, 116.5, 122.1, 124.2, 127.0, 128.3, 128.7, 129.1, 129.5, 133.7, 136.9, 143.1, 147.5, 158.3, 161.5; ESI-MS (m/z): Calcd. 295.72, found 295.90 (M^+); Anal. Calcd. (%) for $C_{16}H_{10}ClN_3O$: C, 64.98; H, 3.41; N, 14.21. Found: C, 64.65; H, 3.29; N, 14.42.
8-chloro-1-(p-tolyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4i***
Yield %; m.p. 268-270°C; IR (ν_{max}, cm^{-1}): 3290, 2979, 1719, 1645; ^1H NMR (400 MHz, DMSO-d_6): 2.30 (s, 3H), 7.28-8.85 (m, 8H), 11.64 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.3, 115.1, 116.4, 122.2, 124.3, 126.9, 128.3, 128.7, 129.3, 129.7, 132.9, 133.9, 136.8, 143.2, 147.7, 158.2, 161.7; ESI-MS (m/z): Calcd. 309.75, found 310.05 (M^+); Anal. Calcd. (%) for $C_{17}H_{12}ClN_3O$: C, 65.92; H, 3.90; N, 13.57. Found: C, 65.68; H, 3.98; N, 13.72.
8-chloro-1-(4-methoxyphenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4j***
Yield %; m.p. 246-248°C; IR (ν_{max}, cm^{-1}): 3295, 2970, 1720, 1648; ^1H NMR (400 MHz, DMSO-d_6): 3.81 (s, 3H), 7.23-8.81 (m, 8H), 11.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 55.8, 114.5, 115.3, 116.5, 122.1, 125.2, 128.3, 128.5, 129.2, 132.4, 135.0, 136.2, 143.1, 147.8, 158.3, 158.9, 161.9; ESI-MS (m/z): Calcd. 325.75, found 325.80 (M^+); Anal. Calcd. (%) for $C_{17}H_{12}ClN_3O_2$: C, 62.68; H, 3.71; N, 12.90. Found: C, 62.97; H, 3.85; N, 12.78.
8-chloro-1-(4-chlorophenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4k***
Yield %; m.p. 254-256°C; IR (ν_{max}, cm^{-1}): 3304, 2982, 1728, 1653; ^1H NMR (400 MHz, DMSO-d_6): 7.29-8.87 (m, 8H), 11.64 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 115.1, 117.0, 123.2, 123.5, 126.2, 128.4, 129.0, 132.1, 133.4, 136.1, 137.2, 142.9, 146.9, 158.0, 162.3; ESI-MS (m/z): Calcd. 330.17, found 330.51 (M^+); Anal. Calcd. (%) for $C_{16}H_9Cl_2N_3O$: C, 58.20; H, 2.75; N, 12.73. Found: C, 58.39; H, 2.82; N, 12.61.
8-chloro-1-(4-fluorophenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4l***
Yield %; m.p. 252-255°C; IR (ν_{max}, cm^{-1}): 3290, 2974, 1710, 1651; ^1H NMR (400 MHz, DMSO-d_6): 7.28-8.90 (m, 8H), 11.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 114.9, 115.7, 116.5, 122.1, 122.7, 123.2, 128.3, 129.8, 132.5, 143.1, 147.7, 158.3, 161.5, 162.9; ESI-MS (m/z): Calcd. 313.71, found 313.98 (M^+); Anal. Calcd. (%) for $C_{16}H_9ClFN_3O$: C, 61.26; H, 2.89; N, 13.39. Found: C, 61.06; H, 2.93; N, 13.50.
8-chloro-1-(2-fluorophenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4m***

Yield %; m.p. 258-260°C; IR (ν_{max}, cm^{-1}): 3299, 2978, 1726, 1649; ^{1}H NMR (400 MHz, DMSO-d_6): 7.26-8.89 (m, 8H), 11.64 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 115.0, 115.5, 119.1, 121.9, 122.3, 124.6, 126.4, 128.0, 129.1, 129.8, 130.1, 138.5, 144.0, 148.1, 157.9, 162.5; ESI-MS (m/z): Calcd. 313.71, found 314.10 (M^+); Anal. Calcd. (%) for $C_{16}H_9ClFN_3O$: C, 61.26; H, 2.89; N, 13.39. Found: C, 61.36; H, 2.78; N, 13.52.

8-chloro-1-(2-(trifluoromethyl)phenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4n***

Yield %; m.p. 262-264°C; IR (ν_{max}, cm^{-1}): 3312, 2981, 1710, 1660; ^{1}H NMR (400 MHz, DMSO-d_6): 7.29-8.91 (m, 8H), 11.67 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 115.3, 120.1, 121.4, 122.3, 124.6, 125.1, 126.5, 127.8, 128.0, 129.3, 129.9, 130.5, 132.2, 143.1, 147.9, 158.4, 162.3; ESI-MS (m/z): Calcd. 363.72, found 364.08 (M^+); Anal. Calcd. (%) for $C_{17}H_9ClF_3N_3O$: C, 56.14; H, 2.49; N, 11.55. Found: C, 56.35; H, 2.59; N, 11.47.

8-fluoro-1-phenyl-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4o***

Yield %; m.p. 274-276°C; IR (ν_{max}, cm^{-1}): 3309, 2985, 1717, 1652; ^{1}H NMR (400 MHz, DMSO-d_6): 7.25-8.79 (m, 9H), 11.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 103.5, 115.4, 116.7, 117.2, 122.2, 126.4, 128.0, 130.1, 133.9, 144.0, 154.3, 158.0, 160.9, 163.8; ESI-MS (m/z): Calcd. 279.27, found 279.90 (M^+); Anal. Calcd. (%) for $C_{16}H_{10}FN_3O$: C, 68.81; H, 3.61; N, 15.05. Found: C, 68.67; H, 3.52; N, 15.32.

8-fluoro-1-(p-tolyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4p***

Yield %; m.p. 278-281°C; IR (ν_{max}, cm^{-1}): 3320, 2986, 1722, 1657; ^{1}H NMR (400 MHz, DMSO-d_6): 2.32 (s, 3H), 7.28-8.79 (m, 8H), 11.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.3, 103.4, 115.0, 118.1, 119.3, 122.4, 126.7, 129.8, 132.9, 136.8, 144.0, 154.1, 158.3, 160.8, 163.4; ESI-MS (m/z): Calcd. 293.30, found 293.55 (M^+); Anal. Calcd. (%) for $C_{17}H_{12}FN_3O$: C, 69.62; H, 4.12; N, 14.33. Found: C, 69.38; H, 4.19; N, 14.51.

8-fluoro-1-(4-methoxyphenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4q***

Yield %; m.p. 270-272°C; IR (ν_{max}, cm^{-1}): 3315, 2979, 1713, 1660; ^{1}H NMR (400 MHz, DMSO-d_6): 3.81 (s, 3H), 7.28-8.87 (m, 8H), 11.64 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 55.8, 103.8, 114.5, 122.1, 126.4, 128.0, 129.1, 130.1, 136.2, 144.1, 156.2, 158.0, 158.9, 160.6, 163.9; ESI-MS (m/z): Calcd. 309.29, found 309.70 (M^+); Anal. Calcd. (%) for $C_{17}H_{12}FN_3O_2$: C, 66.02; H, 3.91; N, 13.59. Found: C, 66.29; H, 3.75; N, 13.41.

1-(4-chlorophenyl)-8-fluoro-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4r***

Yield %; m.p. 266-268°C; IR (ν_{max}, cm^{-1}): 3295, 2983, 1714, 1646; ^{1}H NMR (400 MHz, DMSO-d_6): 7.26-8.90 (m, 8H), 11.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 103.8, 115.0, 118.2, 122.2, 129.3, 131.2, 133.3, 135.0, 136.8, 144.0, 154.1, 158.0, 160.9, 163.6; ESI-MS (m/z): Calcd. 313.71, found 314.05 (M^+); Anal. Calcd. (%) for $C_{16}H_9ClFN_3O$: C, 61.26; H, 2.89; N, 13.39. Found: C, 61.47; H, 2.78; N, 13.28.

8-fluoro-1-(4-fluorophenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4s***

Yield %; m.p. 270-273°C; IR (ν_{max}, cm^{-1}): 3297, 2989, 1720, 1649; ^{1}H NMR (400 MHz, DMSO-d_6): 7.27-8.75 (m, 8H), 11.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 103.9, 115.5, 116.8. 117.1, 122.5, 129.7, 131.6, 133.6, 134.1, 141.8, 154.0, 158.2, 160.7, 161.5, 164.0; ESI-MS (m/z): Calcd. 297.26, found 298.05 (M^+); Anal. Calcd. (%) for $C_{16}H_9F_2N_3O$: C, 64.65; H, 3.05; N, 14.14. Found: C, 64.94; H, 3.12; N, 13.85.

8-fluoro-1-(2-fluorophenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4t***

Yield %; m.p. 278-280°C; IR (ν_{max}, cm^{-1}): 3307, 2984, 1716, 1654; ^{1}H NMR (400 MHz, DMSO-d_6): 7.27-8.90 (m, 8H), 11.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 103.8, 115.4, 116.1, 116.9, 121.8, 122.7, 129.4, 131.3, 134.0, 135.2, 141.6, 154.0, 158.3, 160.6, 161.5, 163.9; ESI-MS (m/z): Calcd. 297.26, found 298.05 (M^+); Anal. Calcd. (%) for $C_{16}H_9F_2N_3O$: C, 64.65; H, 3.05; N, 14.14. Found: C, 64.85; H, 2.97; N, 14.31.

8-fluoro-1-(2-(trifluoromethyl)phenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one ***4u***
Yield %; m.p. 272-274°C; IR (ν_{max}, cm^{-1}): 3312, 2990, 1728, 1658; ^1H NMR (400 MHz, DMSO-d_6): 7.30-8.91 (m, 8H), 11.66 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 103.6, 116.4, 120.2, 122.3, 124.5, 126.8, 127.6, 129.0, 132.1, 133.9, 141.8, 153.9, 158.2, 160.8, 164.2; ESI-MS (m/z): Calcd. 347.27, found 347.55 (M^+); Anal. Calcd. (%) for $C_{17}H_9F_4N_3O$: C, 58.80; H, 2.61; N, 12.10. Found: C, 59.07; H, 2.47; N, 12.19.

Conclusion

The aim of the present study was to design and synthesize new imidazo[4,5-*c*]quinoline derivatives through hofmann type rearrangement and to test for their *in vitro* antimicrobial, antituberculosis and antimalarial activity. The spectral data supported the structures of all newly synthesized compounds. This synthetic strategy allows the assembly of relatively complicated nitrogen containing heterocyclic system as well as the introduction of diverse aromatic substitutions into imidazolone ring. Compounds **4a**, **4d**, **4f**, **4l**, **4p** and **4s** displayed moderate inhibition against antitubercular activity as compared to standard drugs. Majority of the compounds displayed good antimalarial activity. The present library model can be further explored to design the new class of antimicrobial, antitubercular and antimalarial agents.

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