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Synthesis and Antibacterial Study of Some New Benzimidazole Substituted Quinoline Derivatives

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ABSTRACT

As many scientific and technical observations are pouring informations about the activity and effectiveness of synthetic and semi synthetic derivatives related to quinolines and benzimidazoles it was concern to explore this two leads in a single molecular entity. The present study embodied the synthesis and evaluation of antibacterial activity of a series of benzimidazole substituted quinoline derivatives condensed with different amines. The derivatives were synthesized in moderate to good yields. The characterizations for the synthesized derivatives were done by IR, ^{1}H NMR and Mass spectral analysis. The compounds were then subjected for antibacterial screening, among them 4c and 4d showed appreciable activity against all the strains used. In the light of the results obtained from antibacterial studies, these derivatives can be further thoroughly investigated for future prospect.

Keywords: Benzimidazolo quinoline, antibacterial activity, cyclisation.

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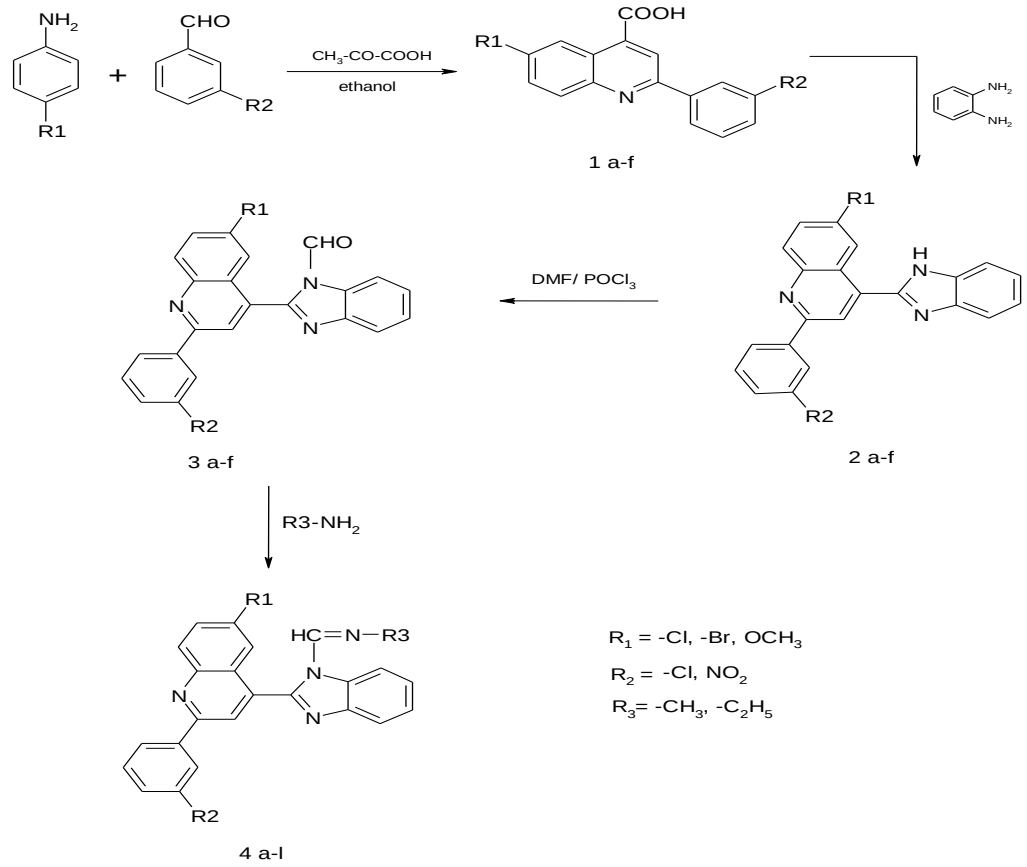
INTRODUCTION

In medicinal chemistry there has been a widespread use of heterocyclic compounds which is increasing day by day because this kind of compounds are explored in many of the structures of bioactive molecules which are essential for life as well as many naturally occurring pigments, flavonoids, chlorophyll are also associated with this. Benzimidazole, the use of which dates centuries ago, is an important and privileged structure having varieties of biological and pharmacological activities. Moreover it is a structural isoster of naturally occurring purine; the antibacterial activity of derivatives of benzimidazoles was explained by the competitive inhibition for the synthesis of bacterial nucleic acids and proteins[1, 2, 3]. Besides benzimidazoles are very useful intermediates for the development of molecules of biological interest, some oxadiazol-1H-benimidazole has been reported to possess antimicrobial and antifungal activities[4]. Benzimidazole and their derivatives were reported to have wide range of biological activities like antifungal [5], antibacterial [6], anti-inflammatory[7, 8], antianxiety[9], inhibitors of gastric acid secretion [10] etc. On the other hand quinolones are a class of organic compound composed of benzene and a pyridine ring fused. Presence of a fluorine atom at 6- position of the quinoline ring system led to norfloxacin, which had a broad spectrum antibacterial activity. Different quinoline derivatives were found to be reported as antimicrobial[11], antimalarial[12, 13] , cytotoxic agents [14, 15], antitumors [16] etc. Since quinoline and benzimidazole derivatives are reported to have antimicrobial activity, it was of interest that the presence of both these two structures in a single molecule should also exhibit a good antimicrobial property. Therefore in this study we synthesized a few benzimidazole substituted quinoline derivatives as possible anti bacterial agents.

MATERIALS AND METHODS

The melting points of the synthesized compounds were determined by open capillary tube method and are uncorrected. The IR spectra were recorded in the region of 4000-400 cm^{-1} in a Shimadzu 8400S FTIR spectrophotometer using KBr discs. NMR spectra were recorded on a Brukar Spectrospin 200 spectrometer using TMS as an internal standard and the values are expressed in δ scale. Mass spectra were obtained by using JEOL GC mate instrument. Precoated Silica gel G plates were used to check the purity of the compounds; Benzene: Chloroform: Ethyl acetate= 1:1:1 as mobile phase was used; detections were carried out either in UV chamber or by using iodine vapour.

Scheme of synthesis



Synthesis of quinoline-4-carboxylic acid (1a)

m-chlorobenaldehyde (0.059 mol), freshly distilled pyruvic acid (0.0625 mol) and absolute alcohol (50ml) were placed in a round bottomed flask. The mixture was then heated on a water bath to boiling point and added slowly, a solution of p-chloro aniline (0.62 mol) in absolute ethanol. The mixture was then refluxed further for 3hrs and allowed to stand over-night in cold condition. The product was filtered off and washed with a little cold ether. Then it was recrystallized from ethanol. Yield 51%. Similarly compounds 1b-f were synthesized.

Synthesis of substituted quinolino benzimidazole compounds (2a)

To 0.08 mol of o-phenylenediamine was added quinoline-4- carboxylic acid (1a) (0.08 mol). The mixture was then heated at 100^0C for 4 hrs. To make it just alkaline to litmus the resulting solution was treated with sodium hydroxide. The product was filtered and washed with ice-cold water. The crude product was treated with de-colorizing carbon. The benzimidazole derivative (2a) appeared to precipitate after cooling. It was washed with cold water and dried at 100^0C. Yield 62%. In a similar manner compounds 2 b-f were synthesized.

Reaction of quinolino benzimidazole compounds with DMF-$POCl_3$ (3a)

The quinolino benzimidazole compound (2a) thus prepared (0.01mole) was added to DMF/$POCl_3$ (Vilsmier Haac reagent) at 0^0C. Then the reaction mixture was stirred at room

temperature for about 2.5 hr. Then it was treated with aqueous sodium carbonate and heated to 90^0C. Then the solution was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The combined extracts were evaporated to dryness and recrystallized from rectified spirit. Yield 47%. Compounds 3b-f was prepared following this method.

General method for the synthesis of title compounds (4a-l)

An equimolar mixture of 3a and methyl amine was stirred in 5 ml of water at room temperature for 5 hrs. The crystalline solid, obtained after keeping the solution at cold condition, was collected and washed with water and dried to give amino substituted quinolino benzimidazole derivatives (4a). Then it was recrystallized from ethanol. Compounds 4b-l were prepared similar to this method. The physical data are reported in table 1.

Table 1: Data of the synthesized derivatives

Compound code	Mol. Formula	Mol. Wt	Melting point (^{0}C)	R_f value	Yield (%)
4a	$C_{24}H_{16}Cl_2N_4$	431	192	0.64	51
4b	$C_{25}H_{18}Cl_2N_4$	445	183	0.58	49
4c	$C_{24}H_{16}ClN_5O_2$	441	181	0.61	51
4d	$C_{25}H_{18}ClN_5O_2$	455	189	0.56	53
4e	$C_{24}H_{16}BrClN_4$	475	179	0.65	53
4f	$C_{25}H_{18}BrClN_4$	489	185	0.59	51
4g	$C_{24}H_{16}BrN_5O_2$	486	174	0.64	54
4h	$C_{24}H_{17}BrN_5O_2$	487	158	0.53	58
4i	$C_{25}H_{19}ClN_4O$	426	175	0.63	59
4j	$C_{26}H_{21}ClN_4O$	440	169	0.58	58
4k	$C_{25}H_{19}N_5O_3$	437	181	0.62	56
4l	$C_{26}H_{21}N_5O_3$	451	173	0.69	57

Antibacterial screening[17, 18]

The title compounds were subjected to screen for their antibacterial activity by cup plate Agar diffusion method against *Pseudomonus aeruginosa, Escherichia coli, Staphylococcus aureus* and *Bacillus subtilis*. Nutrient agar plates were prepared by pouring melted agar media onto the petridishes which was allowed to solidify. Then it was inoculated over the surface with sterile cotton. The cups were then made with the help of borer and filled with sample solution and standard and incubated at 37^0C for 24 hours. The antimicrobial agents diffused through the agar media around the cups and produced zone of inhibitions of the microbial growth (Table 2). The control ($CHCl_3$) with solvent (DMF) in identical condition showed no activity. Norfloxacin was used as a standard.

Table 2: Antibacterial activity

Compound code	Zone of inhibition			
	S. aureus	*P. aeruginosa*	*B. subtilis*	*E. coli*
4a	+	++	+	+
4b	+	-	+	+
4c	+++	++	+++	+++
4d	++	+++	++	+++
4e	+	+	+	-
4f	-	+	+	++
4g	+	+	-	+
4h	+	++	+	+
4i	+	+	+	+
4j	-	+	+	+
4k	+	+	+	-
4l	+	-	+	++

- = inactive, + = weakly active (10-13 mm), ++ = moderately active (14-17 mm), +++ = highly active (18-23 mm)

RESULTS AND DISCUSSION

Structural variations of benzimidazole substituted quinoline derivatives were carried out by substituting 3a-f with two amines. The derivatives were synthesized successfully in a moderate yield. The structures of the synthesized compounds (4a-l) were confirmed by IR, ^{1}H NMR and Mass spectral studies. The IR spectra of the title compounds (4a-l) shown the absorption band around 3027-3038 cm^{-1} for C-H stretching aromatic, around 2865-2957 cm^{-1} for C-H stretching aliphatic, C=N str around 1669-1689 cm^{-1}, C=C str aromatic around 1475-1534 cm^{-1}, C-H bending aliphatic around 1327-1354 cm^{-1} and C-N str around 1192-1231 cm^{-1}. The presence of a singlet peak at 10.25 in the proton NMR spectrum of 1a revealed the presence of the acidic proton at the 4th position of the quinoline ring system confirming the cyclisation of aldehyde, amine and pyruvic acid. In the subsequent step this proton signal (for acidic hydrogen) of 1a disappeared in the ^{1}H NMR spectrum of 2a and a NH proton signal was appeared which was identified of benzimidazole ring, thus confirming the cyclisation of the quinoline4-carboxylic acid with o-phenylene diamine to give benzimidazole substituted quinoline moiety (2a). A carefully observed ^{1}H NMR spectrum of 3a identified the presence of a singlet which was noticed at far downfield around δ 9.9; later this was characterized as the aldehydic proton. The aldehydic proton was appeared at downfield because electronegative oxygen with π electrons made this particular proton to be acidic enough to be appear at higher δ value. A thorough examination of ^{1}H NMR spectrum of 4a revealed a signal for three methyl protons (N-CH_3)

appeared at 3.57 which is generally a bit higher δ value than the normal alkyl protons; this deshielding can be attributed to the direct attachment of the -CH_3 group with nitrogen. It was further confirmed that the CH=N proton (4a) appeared at somewhat up field direction. The ^{1}H NMR spectrum of 4i to 4l showed a sharp singlet appeared at around δ 2.24-2.29; this particular resonance was confirmed for the presence of 3 -OCH_3 protons; presence of electronegative oxygen and direct attachment of -OCH_3 to the aromatic ring made these protons to appear at a relatively downfield value. Compounds 4b, 4d, 4f, 4h, 4j and 4l were prepared by using ethyl amine. The protons associated with amino moiety of the aforesaid derivatives were appeared at δ 2.51-2.95 for -CH_3 and δ 3.37-3.63 for –CH_2. The mutual coupling of these protons resulted in the splitting of signals, thus 2 protons of –CH_2 appeared as multiplets and 3 protons of –CH_3 appeared as a triplet. All the other aromatic and aliphatic protons were appeared for their characteristic shielding and deshielding. It was nice to note that two of the synthesized compounds like 4c and 4d were appreciably active against all the strains of microorganisms used. The results of the antibacterial activity showed that compounds 4f & 4l and 4a & 4h were moderately active against *E.coli* and *P. aeruginosa* respectively. Remaining compounds were weakly active or inactive.

4a-IR (KBr, cm^{-1}): 3032 (C-H str aromatic), 2930 (C-H str aliphatic), 1678 (C=N str), 1489 (C=C str aromatic), 1336 (C-H bending aliphatic), 1192 (C-N str), 827 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 3.57 3H s N-CH_3, 5.84 1H s CH=N, 6.37-6.81 4H m Ar H, 6.94-7.23 3H m Ar H, 7.32-7.61 5H m Ar H. Mass (M+H): 432.51

4b-IR (KBr, cm^{-1}): 3030 (C-H str aromatic), 2934 (C-H str aliphatic), 1680 (C=N str), 1487 (C=C str aromatic), 1341 (C-H bending aliphatic), 1207 (C-N str), 836 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 2.67-2.91 3H t CH_3, 3.39 2H m CH_2, 5.85 1H s CH=N, 6.41-6.75 4H m Ar H, 6.81-7.28 3H m Ar H, 7.32-7.59 5H m Ar H. Mass (M+H): 446.68

4c-IR (KBr, cm^{-1}): 3030 (C-H str aromatic), 2926 (C-H str aliphatic), 1679 (C=N str), 1515 (C=C str aromatic), 1335 (C-H bending aliphatic), 1198 (C-N str), 847 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 3.54 3H s N-CH_3, 5.78 1H s CH=N, 6.35-6.81 4H m Ar H, 6.92-7.29 3H m Ar H, 7.37-7.64 5H m Ar H. Mass (M+H): 442.38

4d-IR (KBr, cm^{-1}): 3027 (C-H str aromatic), 2881 (C-H str aliphatic), 1675 (C=N str), 1487 (C=C str aromatic), 1354 (C-H bending aliphatic), 1215 (C-N str), 824 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 2.52-2.78 3H t CH_3, 3.37 2H m CH_2, 5.81 1H s CH=N, 6.43-6.71 4H m Ar H, 6.77-7.19 3H m Ar H, 7.41-7.62 5H m Ar H. Mass (M+H): 456.48

4e-IR (KBr, cm^{-1}): 3035 (C-H str aromatic), 2943 (C-H str aliphatic), 1675 (C=N str), 1495 (C=C str aromatic), 1344 (C-H bending aliphatic), 1231 (C-N str), 841 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 3.45 3H s N-CH_3, 5.74 1H s CH=N, 6.41-6.74 4H m Ar H, 6.84-7.29 3H m Ar H, 7.32-7.61 5H m Ar H. Mass (M+H): 476.67

4f-IR (KBr, cm^{-1}): 3038 (C-H str aromatic), 2951 (C-H str aliphatic), 1679 (C=N str), 1485 (C=C str aromatic), 1327 (C-H bending aliphatic), 1198 (C-N str), 842 (C-H bending aromatic).. ^{1}HNMR ($CDCl_3$, δ): 2.52-2.84 3H t CH_3, 3.43-3.56 2H m CH_2, 5.87 1H s CH=N, 6.35-6.70 4H m Ar H, 6.83-7.28 3H m Ar H, 7.32-7.59 5H m Ar H. Mass (M+H): 490.39

4g-IR (KBr, cm^{-1}): 3031 (C-H str aromatic), 2938 (C-H str aliphatic), 1681 (C=N str), 1505 (C=C str aromatic), 1341 (C-H bending aliphatic), 1230 (C-N str), 837 (C-H bending aromatic).. ^{1}HNMR ($CDCl_3$, δ): 3.51 3H s N-CH_3, 5.87 1H s CH=N, 6.33-6.75 4H m Ar H, 6.94-7.29 3H m Ar H, 7.42-7.69 5H m Ar H. Mass (M+H): 487.51

4h-IR (KBr, cm^{-1}): 3035 (C-H str aromatic), 2865 (C-H str aliphatic), 1675 (C=N str), 1529 (C=C str aromatic), 1352 (C-H bending aliphatic), 1217 (C-N str), 828 (C-H bending aromatic).. ^{1}HNMR ($CDCl_3$, δ): 2.51-2.75 3H t CH_3, 3.45-3.63 2H m CH_2, 5.84 1H s CH=N, 6.42-6.78 4H m Ar H, 6.84-7.28 3H m Ar H, 7.34-7.57 5H m Ar H. Mass (M+H): 488.77

4i-IR (KBr, cm^{-1}): 3027 (C-H str aromatic), 2925 (C-H str aliphatic), 1675 (C=N str), 1534 (C=C str aromatic), 1341 (C-H bending aliphatic), 1248 (C-N str), 842 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 2.24 3H s OCH_3, 3.49 3H s N-CH_3, 5.76 1H s CH=N, 6.44-6.75 4H m Ar H, 6.98-7.24 3H m Ar H, 7.31-7.5 5H m Ar H. Mass (M+H): 427.71

4j-IR (KBr, cm^{-1}): 3029 (C-H str aromatic), 2934 (C-H str aliphatic), 1678 (C=N str), 1495 (C=C str aromatic), 1328 (C-H bending aliphatic), 1195 (C-N str), 837 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 2.29 3H s OCH_3, 2.65-2.95 3H t CH_3, 3.45-3.62 2H m CH_2, 5.84 1H s CH=N, 6.33-6.75 4H m Ar H, 6.74-7.21 3H m Ar H, 7.44-7.61 5H m Ar H. Mass (M+H): 441.87

4k-IR (KBr, cm^{-1}): 3035 (C-H str aromatic), 2946 (C-H str aliphatic), 1669 (C=N str), 1475 (C=C str aromatic), 1349 (C-H bending aliphatic), 1207 (C-N str), 832 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 2.26 3H s OCH_3, 3.57 3H s N-CH_3, 5.82 1H s CH=N, 6.36-6.87 4H m Ar H, 6.95-7.26 3H m Ar H, 7.38-7.61 5H m Ar H. Mass (M+H): 438.58

4l-IR (KBr, cm^{-1}): 3030 (C-H str aromatic), 2957 (C-H str aliphatic), 1675 (C=N str), 1513 (C=C str aromatic), 1347 (C-H bending aliphatic), 1231 (C-N str), 841 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 2.24 3H s OCH_3, 2.61-2.76 3H t CH_3, 3.46-3.61 2H m CH_2, 5.88 1H s CH=N, 6.31-6.62 4H m Ar H, 6.79-7.24 3H m Ar H, 7.23-7.52 5H m Ar H. Mass (M+H): 452.78

CONCLUSION

As assumed previously, the benzimidazole substituted quinoline derivatives showed appreciable antibacterial activity against the organisms. But a thorough investigation is required in this regard to derive more effective antibacterial agents.

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