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Synthesis, Characterization and Antimicrobial activity of some Quinolino-Benzimidazole analogues

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ABSTRACT

The research envisaged in the present study is the synthesis and evaluation of some quinolino-benzimidazole derivatives for antibacterial activity. The title compounds were synthesized in a good yield. The derivatives were characterized by their analytical data and IR, ^{1}H NMR & Mass spectral studies. All the compounds were subjected for antibacterial screening, among them 3a, 3b, 3c 3d showed good activity. The antibacterial activity studies suggest that these derivatives may be further investigated for optimization to modify them in a useful manner.

Keywords: *Quinolino analogues, Amino derivatives, Antimicrobial.*

INTRODUCTION

In the development of organic therapeutic agents scientists have explored numerous approaches to find and develop organic compounds that are now available to us in dosage forms suitable for the treatment of ours ills and often for the maintenance for our health. Pure organic compounds, natural or synthetic, are the chief source of the cure, the mitigation or the prevention of disease today. These remedial agents have had their origin in a number of ways, firstly from naturally occurring materials of both plant and animal origin and secondly from the synthesis of organic compounds whose structures are closely related to those of naturally occurring compounds that have shown to possess useful medicinal properties. Since ancient time the mankind have had a wide range of natural products that they use for medicinal purposes. These products, obtained from animal, vegetable and mineral sources, were sometimes very effective. However, many of the products were very toxic too. As medicine is an ever-changing science, success in the drug discovery is dependant on the ability to identify potent and novel compounds, colloquially as New Chemical Entities that have potential to treat a disease in a safe and effective manner. A thorough analysis of drug action can provide the basis for both the rational therapeutic use of a drug and the design of new and superior therapeutic agents. The discovery of a new drug not only requires its design and synthesis but also the development of testing methods and procedures, which are needed to establish how a substance operates in the body compartments and its suitability for use as a drug.

The current trend in the drug design is to develop new clinically effective agents through the structural modification of a lead nucleus. The lead is a prototype compound that has the desired biological or pharmacological activity but may have many undesirable characteristics like high toxicity, other biological activity, insolubility or metabolism problems. Such organic leads once identified, are easy to exploit.

Quinolones are one of the largest classes of antibacterial agent used worldwide with therapeutic indications having evolved from urinary tract infections in the early 1970s to infections of almost all the body parts till present time. This goal has been reached by a clear understanding of structure activity relationships for this group of drugs. This enormous knowledge has ultimately led to the development of different methodologies associated with synthesis of newer derivatives with a broad spectrum of activity and improved pharmacokinetic parameters. However all these efforts had their own limitation, an inevitable fact, i.e. the emergence of resistance [1-3]. Many technical reports are available till date about quinolones in terms of their development, characterization, susceptibility to the organisms and clinical efficacy and efficiency [4, 5]. But the scientific community now appears to take forward the caution or even restriction regarding the usage of these agents. The activity of quinolones arises primarily from the formation of complexes between DNA, type II topoisimerases (DNA gyrase) and topoisomerase IV. Both topoisomerase enzymes are essential for bacterial growth. Resistance to quinoline antibacterials can develop through a decrease in intrabacterial concentration of a drug and/or modifications in the target enzymes. A detailed survey of literature revealed that different structural modifications on quinoline nucleus resulted a diverse series of derivatives with a varying degree of effectiveness; however their clinical usefulness is still not established.

The benzimidazole heterocycle, a class of privileged entity, reported to find its use in different therapeutic measures, as antimicrobial [6], antibacterial [7], anti-inflammatory [8, 9], anti-anxiety [10] etc. Since quinoline and benzimidazole compounds have been found to have a range of pharmacological activities, therefore in our present study we synthesized a few quinolino-benzimidazole derivatives and evaluated them for anti bacterial activity.

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MATERIALS AND METHODS

All the chemicals used to synthesize the title compounds were of laboratory grade. Open capillary tube method was used to determine the melting point and is uncorrected. The IR spectra were recorded in the region of 5000-500 cm^{-1} in a Shimadzu 8400S FTIR spectrophotometer (KBr discs). NMR spectra were obtained on a Brukar Spectrospin 200 spectrometer (TMS as 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 monitor the progress of reaction as well as to check the purity of the compounds; Benzene: Chloroform: Ethyl acetate-1:1:1 as mobile phase was used.

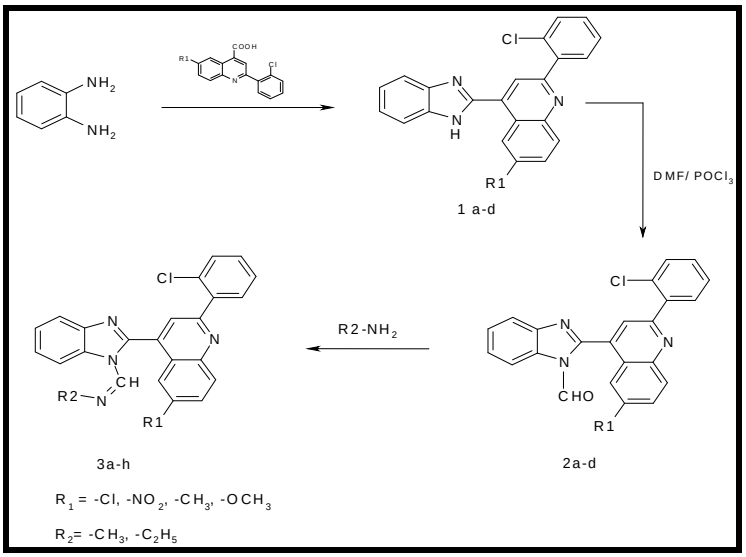
General procedure for the synthesis of quinolino-benzimidazole compounds (1a):

o-Phenylenediamine (0.08 mol) and quinoline-4-carboxylic acid (0.08 mol) were taken in a round bottomed flask and the mixture was heated at 100^{0}C for 3.5 hrs. The resulting solution was treated with sodium hydroxide to make it was just alkaline to litmus. The product was filtered and washed with ice-cold water. The crude product was treated with de-colorizing carbon. The quinolino-benzimidazole derivative (1a) precipitated after cooling. It was washed with cold water and dried. Yield 70%. In a similar manner compounds 1b-d were synthesized.

Reaction of quinolino-benzimidazole compounds with DMF-$POCl_3$ (2a):

The quinolino-benzimidazole compound (1a, 0.01mol) was carefully added to the Vilsmier Haac reagent at 0^0C by cooling the reaction vessel in an ice bath. The reaction mixture was then occasionally stirred at room temperature for 2 hr. Then it was treated with sodium carbonate solution and heated to 90^0C. The solution was then repeatedly extracted with chloroform. The chloroform layer was dried over anhydrous calcium chloride. The combined extracts were evaporated to dryness and purified by recrystallization from rectified spirit. Yield 50%. Compounds 2b-d was prepared similarly.

Scheme of synthesis:



General procedure for the synthesis of title compounds (3a):

2a (2.35mmol) and methyl amine (2.35mmol) was taken together in a conical flask and stirred in about 10 ml of water for 5 hrs at room temperature and kept aside for 48 hours at cold condition. The crystalline solid thus obtained was filtered and washed with ice-cold water and dried to give amino substituted quinolino-benzimidazole derivatives (3a). Then it was purified by recrystallization from ethanol. Compound 3b-h was prepared similar to this method. The physical data are reported in **Table 2**.

3a-IR (KBr, cm^{-1}): 3035 C-H str aromatic, 2927 C-H str aliphatic, 1678 C=N str, 1498 C=C str aromatic, 1337 C-H bending aliphatic, 1194 C-N str, 827 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ): 3.58 3H s N-CH_3, 5.85 1H s CH=N, 6.37-6.83 4H m Ar H, 6.96-7.27 3H m Ar H, 7.33-7.58 5H m Ar H. Mass (M+H): 432.71.

3b-IR (KBr, cm^{-1}): 3031 C-H str aromatic, 2934 C-H str aliphatic, 1671 C=N str, 1488 C=C str aromatic, 1341 C-H bending aliphatic, 1207 C-N str, 839 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ): 2.45-2.93 3H t CH_3, 3.42-3.67 2H m N-CH_2, 5.81 1H s CH=N, 6.39-6.68 4H m Ar H, 6.84-7.27 3H m Ar H, 7.35-7.59 5H m Ar H. Mass (M+H): 446.85.

3c-IR (KBr, cm^{-1}): 3032 C-H str aromatic, 2891 C-H str aliphati), 1685 C=N str, 1509 C=C str aromatic, 1348 C-H bending aliphatic, 1191 C-N str, 844 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ): 3.54 3H s N-CH_3, 5.74 1H s CH=N, 6.41-6.79 4H m Ar H, 6.91-7.25 3H m Ar H, 7.34-7.65 5H m Ar H. Mass (M+H): 442.43.

3d-IR (KBr, cm^{-1}): 3028 C-H str aromatic, 2871 C-H str aliphatic, 1681 C=N str, 1489 C=C str aromatic, 1359 C-H bending aliphatic, 1218 C-N str, 831 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ): 2.54-2.77 3H t CH_3, 3.39-3.57 2H m N-CH_2, 5.81 1H s CH=N, 6.45-6.67 4H m Ar H, 6.74-7.19 3H m Ar H, 7.37-7.61 5H m Ar H. Mass (M+H): 456.67.

3e-IR (KBr, cm^{-1}): 3039 C-H str aromatic, 2935 C-H str aliphatic, 1672 C=N str, 1507 C=C str aromatic, 1357 C-H bending aliphatic, 1226 C-N str, 841 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ): 1.82 3H s CH_3, 3.47 3H s N-CH_3, 5.76 1H s CH=N, 6.45-6.77 4H m Ar H, 6.88-7.21 3H m Ar H, 7.35-7.59 5H m Ar H. Mass (M+H): 411.67.

3f-IR (KBr, cm^{-1}): 3031 C-H str aromatic, 2949 C-H str aliphatic, 1691 C=N str, 1498 C=C str aromatic, 1341 C-H bending aliphatic, 1199 C-N str, 842 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ): 2.01 3H s CH_3, 2.51-2.81 3H t CH_3, 3.42-3.54 2H m N-CH_2, 5.85 1H s CH=N, 6.35-6.72 4H m Ar H, 6.85-7.28 3H m Ar H, 7.34-7.59 5H m Ar H. Mass (M+H): 425.39

3g-IR (KBr, cm^{-1}): 3035 C-H str aromatic, 2938 C-H str aliphatic, 1691 C=N str, 1517 C=C str aromatic, 1339 C-H bending aliphatic, 1238 C-N str, 837 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ): 2.24 3H s OCH_3, 3.51 3H s N-CH_3, 5.81 1H s CH=N, 6.34-6.77 4H m Ar H, 6.91-7.25 3H m Ar H, 7.42-7.68 5H m Ar H. Mass (M+H): 427.81.

3h-IR (KBr, cm^{-1}): 3029 C-H str aromatic, 2870 C-H str aliphatic, 1678 C=N str, 1532 C=C str aromatic, 1341 C-H bending aliphatic, 1218 C-N str, 834 C-H bending aromatic. ^{1}HNMR ($CDCl_3$, δ): 2.22 3H s OCH_3, 2.42-2.51 3H t CH_3, 3.47-3.66 2H m N-CH_2, 5.83 1H s CH=N, 6.44-6.77 4H m Ar H, 6.83-7.28 3H m Ar H, 7.32-7.58 5H m Ar H. Mass (M+H): 441.76

Antibacterial screening: [11, 12]

All the synthesized title compounds were examined for their antibacterial activity by cup plate method (in DMF solution) against *Staphylococcus aureus, Pseudomonus aeruginosa, Bacillus subtilis and Escherichia coli*. Nutrient agar plates were prepared in petridishes by pouring melted agar media and allowed to solidify. Then it was inoculated over the surface with sterile cotton. With the help of a borer the cups were made and filled with solution of suitable concentration of sample and standard and incubated at 37^0C for 24 hours. The antimicrobial agents after incubation produced a characteristic zone of inhibition of the microbial growth which was then measured and represented (**Table 3**). Norfloxacin was used as a standard. The control ($CHCl_3$) with solvent (DMF) in identical condition showed no activity.

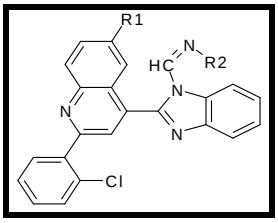
RESULTS AND DISCUSSION

Modifications in the structures of quinolino-benzimidazole derivatives were carried out. o-phenylene diamine was treated with quinoline-4-carboxylic acid, where cyclisation took place between the carboxylic acidic group of quinoline and two amino groups of the former. This is general kind of reaction for the synthesis of benzimidazoles. The reaction progressed with a good yield of the product. Proceeding to the next step the Vilsmier Haac reagent reacted with the amino group of benzimidazole part and consequently an aldehydic group was introduced (2a-d). Further these compounds were allowed to react with suitable primary amines and the final products were formed with the liberation of a molecule of water. The derivatives were synthesized successfully in a feasible yield. The structural analysis and confirmations thereby were carried out for all of the synthesized compounds (3a-h) by

their IR, ^{1}H NMR and Mass spectral studies. The IR spectra of the title compounds (3a-h) shown the characteristic absorption bands for C-H stretching aromatic, C-H stretching aliphatic, C=N str, C=C str aromatic, C-H bending aliphatic and C-N vibrations at around 3028-3039 cm^{-1}, 2870-2949 cm^{-1}, 1671-1691 cm^{-1}, 1488-1532 cm^{-1}, 1337-1359 cm^{-1} and 1191-1238 cm^{-1} respectively. In the ^{1}H NMR spectrum of 2a a singlet peak was appeared at δ 10.17, which was identified as the proton of aldehydic group, thus confirming the reaction of 1a-d with DMF/$POCl_3$. The aldehydic proton, being deshielded enough by oxygen atom with π electrons, was appeared at higher δ value. The disappearance of this particular peak in the NMR spectra of 3a-h confirmed the condensation of amines with 2a-d. A further examination (NMR spectrum of 3a) revealed that the 3 protons of the methyl group of amine were appeared at δ 3.58; the nitrogen atom being electronegative resulted these 3 protons to be appeared at this downfield vale. The CH=N proton (3a-h) was appeared at around δ 5.74-5.85. This (-CH=) methylene proton was deshielded by a triple effect, for say, by a doubly bonded nitrogen, a π electron framework and on another side a single bonded imidazole ring nitrogen. The ^{1}H NMR spectrum of 3g and 3h showed a sharp singlet resonated at around δ 2.22-2.24; this particular peak was confirmed for 3 -OCH_3 protons; being deshielded due to electronegative oxygen and direct attachment to the aromatic ring made these protons to appear at downfield value. The protons, associated with amino moiety of the compounds which were prepared by using ethyl amine, appeared as a result of their mutual coupling and thus splitting of signals, 2 protons of –CH_2 as multiplets and 3 protons of –CH_3 as triplets. All the other protons were appeared due to their characteristic shielding and deshielding effect.

It was observed that four of the synthesized compounds namely 3a, 3b, 3c and 3d showed good activity against the bacterial strains. This was might be due to the presence of chloro and nitro group in the structures of 3a-d. Remaining compounds were weakly active or inactive.

Table No. 1: Structure of various analogues



Compound code	R1	R2
3a	Cl	CH_3
3b	Cl	C_2H_5
3c	NO_2	CH_3
3d	NO_2	C_2H_5
3e	CH_3	CH_3
3f	CH_3	C_2H_5
3g	OCH_3	CH_3
3h	OCH_3	C_2H_5

Table No. 2: Data of the synthesized derivatives

Compound code	Mol. Formula	Mol. Wt	Melting point (°C)	R_f value	Yield (%)
3a	$C_{24}H_{16}Cl_2N_4$	431	181	0.62	48
3b	$C_{25}H_{18}Cl_2N_4$	445	176	0.53	41
3c	$C_{24}H_{16}Cl_2N_5O_2$	441	186	0.59	52
3d	$C_{25}H_{18}Cl_2N_5O_2$	455	168	0.56	54
3e	$C_{25}H_{19}ClN_4$	410	182	0.61	53
3f	$C_{26}H_{21}Cl_2N_4$	424	171	0.58	50
3g	$C_{25}H_{19}ClN_4O$	426	177	0.62	44
3h	$C_{26}H_{21}ClN_4O$	440	159	0.55	47

Table No. 3: Antibacterial activity of the synthesized compounds

Compound code	Zone of inhibition			
	S. aureus	*P. aeruginosa*	*B. subtilis*	*E. coli*
3a	++	+	+	++
3b	++	+	++	+
3c	+	++	++	+
3d	++	+	+	+
3e	-	+	+	+
3f	+	+	-	+
3g	+	-	+	-
3h	+	+	-	+

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

CONCLUSION

Some of the quinolino-benzimidazole derivatives showed good antibacterial activity against the organisms. But as a fact that bacteria are smarter than humans, both fundamental and practical approaches are the need of the hour in this regard for developing more effective antibacterial agents.

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