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Research Article

SYNTHESIS OF SOME SUBSTITUTED BENZIMIDAZOLE DERIVATIVES FOR ANTIBACTERIAL ACTIVITY

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ABSTRACT

In the present study synthesis and evaluation of antibacterial activity of various substituted benzimidazole derivatives condensed with different amines was undertaken. The derivatives were synthesized in moderate to good yields. The synthesized compounds were characterized by IR, ^{1}H NMR and Mass spectral studies. All the compounds were subjected for antibacterial screening, among them 3a, 3b, 3g and 3h showed appreciable activity against the organisms used. The antibacterial activity studies suggested that these derivatives may be further investigated for future drug development.

Keywords: Quinolino, Condensation, Antibacterial Activity

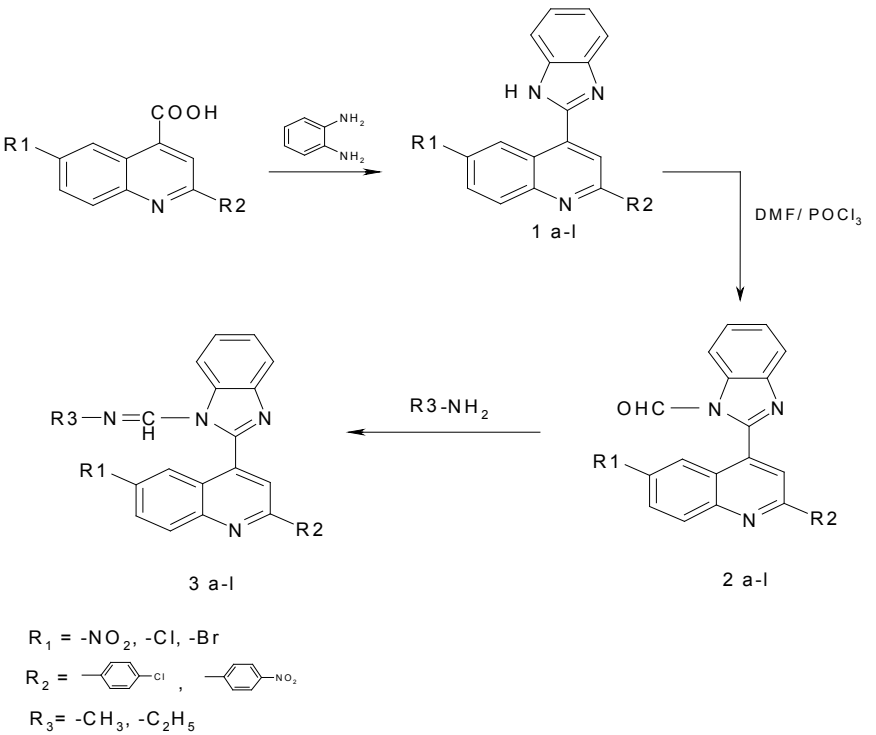
INTRODUCTION

Heterocyclic compounds have occupied a prominent place among various classes of organic drug candidates by virtue of their diverse biological activities. Hence the design, synthesis optimization and large scale production of new molecules for human welfare have been a concern in recent years. Despite significant progress in antimicrobial therapy, infectious diseases caused by bacteria and fungi remain a major worldwide health problem due to the rapid development of resistance to the existing antimicrobial drugs. In other words, the indiscriminate use of existing antimicrobial drugs has resulted in the development of resistant pathogens. Every type of biological action detected, irrespective of the compounds involved in its induction, there presents a potential lead. The interest in the chemistry and biological activities of benzimidazole derivatives dates back to the early sixties; since then hundreds of compounds endowed with several pharmacological activities have been reported. It may provide scaffolds on which pharmacophores can be arranged to yield potent and selective drug. Benzimidazoles and its derivatives represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities and these are well-documented in literature. The benzimidazole derivatives with their fused ring system bear different functional substituents and this leads to essential modifications of the physico-chemical, metabolic and pharmacokinetic properties of drugs containing benzimidazole moiety. The literature survey shows that in past recent years large number of compounds with different structures has been reported which exhibited antimicrobial activity. However, their clinical usefulness is still restricted because of their side effects. Synthesis of benzimidazole compound is emerged as essential need for development of new pharmaceutical entity. Benzimidazole is isosteric with indole and purine nuclei, which are present in a number of fundamental cellular components and bioactive compounds. This heterocycle may represent a kind of privileged substructure, which may interact with different proteins and enzymes. Indeed, a number of important drugs used in different therapeutic areas contain the benzimidazole ring, as antihypertensives[1], antihelmintics[2], anti-protozoal[3], antiulcer[4], analgesic[5], antimicrobial[6], antiallergic[7], antioxidant[8] as well as several other kinds of still investigational therapeutic agents including antibacterial, antitumor and anti viral. In recent years, attention has increasingly been given to the synthesis of benzimidazole derivatives as a source of new antimicrobial agents. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. Recent observations suggest that substituted benzimidazoles and heterocycles, which are the structural isosters of nucleotides owing fused heterocyclic nuclei in their structures that allow them to interact easily with the biopolymers, possess potential activity with lower toxicities in the chemotherapeutic approach in man. In addition, benzimidazole derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis. Since benzimidazole compounds have been found to have a broad range of pharmacological and biological activities, it was assumed that substitution of the aforesaid lead nucleus with quinolino system should also have appreciable antimicrobial property. Therefore in our present study we synthesized a few benzimidazole derivatives substituted with quinoline as possible anti bacterial agents.

MATERIALS AND METHODS

All the chemicals utilized were of analytical grade. Melting points were determined with an electro thermal melting point apparatus and are uncorrected. Progress of reaction and the purity of the synthesized compounds were monitored by thin layer chromatography on Silica Gel G precoated plates and visualization of spot was done by exposure to iodine vapour or in UV chamber. ^{1}HNMR was recorded on Brukar Spectrospin 200 spectrometer using $CDCl_3$ as solvent where tetramethyl silane served as an internal standard. IR spectra were recorded as KBr discs with a Shimadzu 8400 S FT-IR spectrophotometer. Mass spectra were obtained by using JEOL GC mate instrument.

Scheme of synthesis



Synthesis of the starting material

In a round bottomed flask, equipped with a reflux condenser, 6.25 g (6 ml, 0.059 mol) of purified Benzaldehyde, 5.5 g (0.0625 mol) of freshly distilled Pyruvic acid and 50 ml of absolute ethanol were placed. The mixture was then heated to the boiling point on a water bath and added slowly, with frequent shaking, a solution of 5.75 g (5.6 ml, 0.62 mol) of pure aniline in 25 ml of absolute ethanol for about 1 h. The mixture was then refluxed on water bath for 3 h and allowed to stand over-night. The product was filtered off and washed with a little cold ether. Then it was recrystallized from ethanol Yield 53 %.

Synthesis of substituted benzimidazole compounds (1a)

o-Phenylenediamine 6.75 g (0.0625 mol) was taken in a 250 ml round bottomed flask and added 4.375 g of quinoline-4- carboxylic acid. The mixture was then heated on water bath at 100^0C for 2 h. Then 10 per cent sodium hydroxide solution was slowly added, with constant shaking until the mixture was just alkaline to litmus. The product was filtered and washed with ice-cold water. The crude product was dissolved in 100 ml of boiling water and treated for 15 minutes with de-colorizing carbon. Then it was filtered and the filtrate was cooled. The benzimidazole derivative appeared to precipitate. Then it was washed with 7 ml of cold water and dried at 100^0C Yield 70 %. In a similar manner compounds 1b-l were synthesized.

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

The substituted quinolino benzimidazole compound (0.01 mol) was added to the Vilsmier Haac reagent [prepared by adding phosphorous oxy chloride (2.5 ml) in DMF (7.5 ml) at 0^0C] at 0^0C. Then the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then poured in to cold aqueous sodium carbonate solution (10 %) and stirred at 90^0C for 2 h. After cooling down to room temperature the solution was extracted with chloroform. The chloroform layer was washed repeatedly with water and dried over anhydrous sodium sulfate. The combined extracts were evaporated to dryness and purified by recrystallization from rectified spirit Yield 50 %. Similarly compounds 2b-l were synthesized

Synthesis of the title compounds (3a-l)

A mixture of aldehyde substituted quinolino benzimidazole compound (2.35 mmol) and methyl amine (2.35 mmol) was stirred in a small amount of water (5 ml) at room temperature for 5 h and kept over-night at cold condition. The crystalline solid obtained was collected by filtration, washed with ice-cold water and dried to give amino substituted quinolino benzimidazole derivative. Then it was recrystallized from ethanol Yield 49 %. Similarly other derivatives were prepared.

3a-IR (KBr, cm^{-1}): 3029 (C-H str aromatic), 2921 (C-H str aliphatic), 1679 (C=N str), 1494 (C=C str aromatic), 1334 (C-H bending aliphatic), 1194 (C-N str), 824 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 3.59 3H s N-CH_3, 5.87 1H s CH=N, 6.35-6.82 4H m Ar H, 6.97-7.29 3H m Ar H, 7.31-7.54 4H m Ar H. Mass (M+H): 442.91

3b-IR (KBr, cm^{-1}): 3031 (C-H str aromatic), 2932 (C-H str aliphatic), 1680 (C=N str), 1484 (C=C str aromatic), 1341 (C-H bending aliphatic), 1204 (C-N str), 836 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 2.6-2.9 3H t CH_3, 3.45 2H m N-CH_2, 5.85 1H s CH=N, 6.39-6.72 4H m Ar H, 6.81-7.26 3H m Ar H, 7.33-7.57 4H m Ar H. Mass (M+H): 456.98

3c-IR (KBr, cm^{-1}): 3030 (C-H str aromatic), 2894 (C-H str aliphatic), 1685 (C=N str), 1505 (C=C str aromatic), 1340 (C-H bending aliphatic), 1198 (C-N str), 847 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 3.58 3H s N-CH_3, 5.79 1H s CH=N, 6.37-6.84 4H m Ar H, 6.94-7.29 3H m Ar H, 7.33-7.61 4H m Ar H. Mass (M+H): 453.47

3d-IR (KBr, cm^{-1}): 3028 (C-H str aromatic), 2876 (C-H str aliphatic), 1677 (C=N str), 1489 (C=C str aromatic), 1351 (C-H bending aliphatic), 1210 (C-N str), 824 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 2.51-2.74 3H t CH_3, 3.39 2H m N-CH_2, 5.81 1H s CH=N, 6.41-6.69 4H m Ar H, 6.79-7.17 3H m Ar H, 7.35-7.59 4H m Ar H. Mass (M+H): 467.48

3e-IR (KBr, cm^{-1}): 3036 (C-H str aromatic), 2935 (C-H str aliphatic), 1675 (C=N str), 1498 (C=C str aromatic), 1349 (C-H bending aliphatic), 1223 (C-N str), 841 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 3.48 3H s N-CH_3, 5.76 1H s CH=N, 6.42-6.75 4H m Ar H, 6.87-7.19 3H m Ar H, 7.33-7.58 4H m Ar H. Mass (M+H): 432.37

3f-IR (KBr, cm^{-1}): 3034 (C-H str aromatic), 2947 (C-H str aliphatic), 1681 (C=N str), 1494 (C=C str aromatic), 1334 (C-H bending aliphatic), 1194 (C-N str), 837 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 2.51-2.83 3H t CH_3, 3.41-3.53 2H m N-CH_2, 5.85 1H s CH=N, 6.37-6.71 4H m Ar H, 6.82-7.24 3H m Ar H, 7.37-7.58 4H m Ar H. Mass (M+H): 446.39

3g-IR (KBr, cm^{-1}): 3031 (C-H str aromatic), 2934 (C-H str aliphatic), 1684 (C=N str), 1506 (C=C str aromatic), 1339 (C-H bending aliphatic), 1232 (C-N str), 831 (C-H bending aromatic).. ^{1}HNMR ($CDCl_3$, δ): 3.51 3H s N-CH_3, 5.87 1H s CH=N, 6.31-6.74 4H m Ar H, 6.91-7.27 3H m Ar H, 7.41-7.64 4H m Ar H. Mass (M+H): 442.91

3h-IR (KBr, cm^{-1}): 3029 (C-H str aromatic), 2861 (C-H str aliphatic), 1675 (C=N str), 1527 (C=C str aromatic), 1348 (C-H bending aliphatic), 1214 (C-N str), 824 (C-H bending aromatic).. ^{1}HNMR ($CDCl_3$, δ): 2.49-2.71 3H t CH_3, 3.46-3.64 2H m N-CH_2, 5.83 1H s CH=N, 6.41-6.74 4H m Ar H, 6.81-7.22 3H m Ar H, 7.31-7.52 4H m Ar H. Mass (M+H): 456.97

3i-IR (KBr, cm^{-1}): 3032 (C-H str aromatic), 2921 (C-H str aliphatic), 1676 (C=N str), 1531 (C=C str aromatic), 1336 (C-H bending aliphatic), 1241 (C-N str), 842 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 3.49 3H s N-CH_3, 5.79 1H s CH=N, 6.41-6.72 4H m Ar H, 6.97-7.22 3H m Ar H, 7.29-7.47 4H m Ar H. Mass (M+H): 476.81

3j-IR (KBr, cm^{-1}): 3031 (C-H str aromatic), 2932 (C-H str aliphatic), 1669 (C=N str), 1494 (C=C str aromatic), 1330 (C-H bending aliphatic), 1192 (C-N str), 839 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 2.67-2.98 3H t CH_3, 3.47-3.61 2H m N-CH_2, 5.84 1H s CH=N, 6.34-6.72 4H m Ar H, 6.79-7.26 3H m Ar H, 7.41-7.57 4H m Ar H. Mass (M+H): 490.87

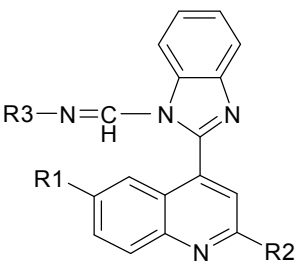
3k-IR (KBr, cm^{-1}): 3030 (C-H str aromatic), 2946 (C-H str aliphatic), 1678 (C=N str), 1485 (C=C str aromatic), 1342 (C-H bending aliphatic), 1197 (C-N str), 827 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 3.58 3H s N-CH_3, 5.81 1H s CH=N, 6.34-6.85 4H m Ar H, 6.94-7.21 3H m Ar H, 7.35-7.57 4H m Ar H. Mass (M+H): 487.38

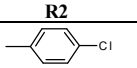
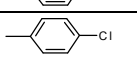
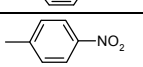
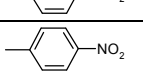
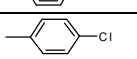
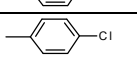
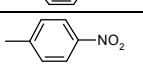
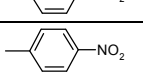
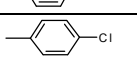
3l-IR (KBr, cm^{-1}): 3035 (C-H str aromatic), 2958 (C-H str aliphatic), 1672 (C=N str), 1517 (C=C str aromatic), 1337 (C-H bending aliphatic), 1218 (C-N str), 836 (C-H bending aromatic). ^{1}HNMR ($CDCl_3$, δ): 2.59-2.77 3H t CH_3, 3.45-3.62 2H m N-CH_2, 5.87 1H s CH=N, 6.29-6.62 4H m Ar H, 6.75-7.18 3H m Ar H, 7.28-7.49 4H m Ar H. Mass (M+H): 501.38

Antibacterial screening

All the benzimidazole derivatives were subjected to screen for their antibacterial activity in DMF solution by Agar diffusion method against *Bacillus subtilis, Pseudomonus aeruginosa, Staphylococcus aureus* and *Escherichia coli*. Agar plates were prepared by pouring melted agar media onto the sterilized petridishes and allowed to solidify. Then inoculation was accomplished over the surface of agar media with sterile cotton. The cups were then made with the help of a borer and filled with solution of suitable concentration of sample and standard and incubated at 37^0C for 24 hours. Through the agar media the antimicrobial agents diffuse around the cups made and produce a characteristic zone of inhibition of the microbial growth which was then measured and represented (Table 3) as the diameter of the inhibited zone in microbial growth. The control ($CHCl_3$) with solvent (DMF) in identical condition showed no activity. Norfloxacin was used as a standard.

Table 1: Structure of various derivatives



Compound code	R1	R2	R3
3a	NO_2		CH_3
3b	NO_2		C_2H_5
3c	NO_2		CH_3
3d	NO_2		C_2H_5
3e	Cl		CH_3
3f	Cl		C_2H_5
3g	Cl		CH_3
3h	Cl		C_2H_5
3i	Br		CH_3

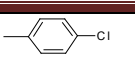
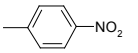
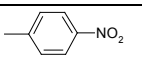
3j	Br		C_2H_5
3k	Br		CH_3
3l	Br		C_2H_5

Table 2: Physical data of the synthesized derivatives

Compound code	Mol. Formula	Mol. Wt	Melting point (^{0}C)	R_f value	Yield (%)
3a	$C_{24}H_{16}ClN_5O_2$	441.88	157	0.53	49
3b	$C_{25}H_{18}ClN_5O_2$	455.91	163	0.59	48
3c	$C_{24}H_{16}N_6O_4$	452.43	178	0.62	56
3d	$C_{25}H_{18}N_6O_4$	466.46	184	0.68	51
3e	$C_{24}H_{16}Cl_2N_4$	431.33	159	0.57	55
3f	$C_{25}H_{18}Cl_2N_4$	445.36	185	0.59	61
3g	$C_{24}H_{16}ClN_5O_2$	441.88	192	0.64	54
3h	$C_{25}H_{18}ClN_5O_2$	455.91	156	0.53	57
3i	$C_{24}H_{16}BrClN_4$	475.78	176	0.65	61
3j	$C_{25}H_{18}BrClN_4$	489.81	183	0.58	58
3k	$C_{24}H_{16}BrN_5O_2$	486.33	198	0.61	53
3l	$C_{25}H_{18}BrN_5O_2$	500.36	164	0.69	56

Table 3: Antibacterial activity of the synthesized compounds

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

-

- = inactive, + = weakly active (9-12 mm), ++ = moderately active (13-16 mm), +++ = highly active (17-22 mm)

RESULTS AND DISCUSSION

The starting material i.e. substituted quinoline4-carboxylic acid was conveniently prepared from benzaldehyde, pyruvic acid and aniline. The derivatives (3a-l) were synthesized in a moderate to good yield after condensing aldehyde substituted quinolino benzimidazole derivatives (2a-l) with different amines. The structures of all the synthesized compounds were confirmed by their IR, NMR and Mass spectral data. The IR spectra of the starting material showed the presence of a broad absorption band in the range of 3418 cm^{-1} and a strong peak at around 1700 cm^{-1}; the former was confirmed to be due to -OH group of carboxylic acid and the latter was the C=O group. Further the appearance of a strong carbonyl stretching vibration, later identified due to the presence of –CHO group, around 1730 cm^{-1} in the IR spectra of 2a-l confirmed the reaction of 1a-l with DMF/$POCl_3$. The disappearance of the aforesaid peak and the appearance of C=N absorption band around 1669-1685 cm^{-1} revealed the condensation of the suitable amines with 2a-l. The NMR spectra of the title compounds (3a-l) showed characteristic peaks for aromatic protons around δ 7-8. A careful observation and analysis thereon revealed that the aliphatic protons of 3a, 3c, 3e, 3g, 3i and 3k were appeared at more downfield value as singlets; this phenomenon can be explained by the fact that amino nitrogen being electronegative deshielded the aliphatic 3 methyl protons and as a result they appeared at little higher value than its normal range. Likewise the NMR spectra of 3b, 3d, 3f, 3h, 3j and 3l where ethyl amine was used for condensation, the 5 alkyl protons appeared as triplets and multiplets again at a more downfield value. The appearance of a sharp singlet at around δ 5.76-5.87 confirmed the presence of the CH=N proton; here this particular proton is attached with a carbon which having a π bond further attached with nitrogen atom. This dual electronegative effect resulted the CH=N proton to resonate at a much higher δ value. From the characteristic M+H peaks appeared in the Mass spectra, the molecular weights of the compounds were confirmed. It was very interesting to observe that some of the synthesized compounds showed good antibacterial activity when subjected for screening; compounds 3a, 3b, 3g and 3h showed appreciable activity. Other derivatives were weakly active or inactive.

CONCLUSION

It can be concluded that the some of the benzimidazole derivatives synthesized, showed appreciable antibacterial activity against the organisms. Further a thorough study is required to design these compounds for the potential of structural modifications to produce antibacterial agents more effectively.

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