Research Article

SYNTHESIS OF NOVEL BENZOPYRONE SUBSTITUTED BENZIMIDAZOLE ANALOGUES AS ANTIBACTERIAL AGENTS

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DOI: 10.7897/2230-8407.06231**ABSTRACT**

A large variety of scientific reviews and reports are providing informations about the effectiveness of synthetic and semi synthetic analogues of benzimidazoles and benzopyrones. It was our interest to explore the novel compounds containing these two fundamental heterocycles in one structure. The present study deals with the synthesis and determination of antibacterial activity of benzopyrone substituted benzimidazole derivatives. The derivatives were synthesized in a good to moderate yields. The structural analysis for the synthesized derivatives was done by IR, ¹HNMR and Mass spectral analysis. Further the compounds were subjected for antibacterial evaluation, among them 5a, 5b, 5g and 5h showed appreciable activity against the strains used. In view of the antibacterial studies, these derivatives can be further modified and investigated for future development.

Keywords: Benzimidazole benzopyrone, antimicrobial activity, condensation.

INTRODUCTION

In the development of effective therapeutic agents scientists have explored numerous approaches to find and develop compounds that are now available to us in dosage forms suitable for the treatment of diseases. Pure organic compounds, natural or synthetic, are the chief source for the mitigation or the prevention of disease today. These remedial agents have had their origin in a number of ways, from naturally occurring materials and from the synthesis of organic compounds whose structures are featured closely to the naturally occurring compounds. Benzimidazole analogues are an important class of bioactive molecules in the field of pharmaceuticals. These are very useful intermediates or subunits for the development of drugs. Benzimidazole is isosteric with indole and purine nuclei, which is present in a number of fundamental cellular components and bioactive compounds. A number of drug candidates used in different therapeutic areas contain the benzimidazole ring such as antihypertensives, proton pump inhibitors, anti histaminics, anti helminthics. Compounds bearing benzimidazole moiety are reported to possess a number of interesting biological activities such as anticancer¹⁻⁴, anthelmintic⁵⁻⁷, antiallergic⁸⁻⁹, antitubercular¹⁰⁻¹², antioxidant¹³⁻¹⁴, antihistaminic¹⁵⁻¹⁷ and antimicrobial¹⁸⁻²⁷ etc. There is a growing interest in the medicinal potential of natural products such as glycosides, alkaloids, flavones, coumarins etc. Benzopyrone class of compounds occurs in nature as flavones, isoflavones, neoflavones etc. Flavonoids are a group of naturally occurring low molecular weight compounds that are widely distributed in the plant kingdom and should represent a significant part of the average daily

diet. Members of the flavone class have been associated with a wide variety of biological activities and may be useful in the treatment of certain diseases. A lot of attentions have been drawn on the study of flavonoids as inhibitors of oxidative reactions²⁸⁻³¹ and as anti-inflammatory agents³²⁻³⁴. Compounds having Chromone moiety are associated with interesting physiological activities such as antibacterial, antiviral, anticancer, antioxidant, antifungal, anti cholesteremic, anti diabetic, anti allergic, diuretic etc³⁵. In view of the above observations it was speculated that as both benzimidazole and benzopyrone derivatives have been reported to possess antibacterial activity, presence of these two heterocycles in a single molecule should also have the desired antibacterial property. Hence it was our interest to synthesize some benzopyrone substituted benzimidazole analogues in this present investigation by convenient and effective method.

MATERIALS AND METHODS

Analytical grade chemicals were used to synthesize the title compounds. Melting points were determined by open capillary tube method and are uncorrected. The FT-IR spectra were recorded using KBr discs on a Shimadzu 8400 S FTIR spectrophotometer in the region of 4000-400 cm⁻¹. ¹HNMR spectra were recorded using TMS as internal standard in CDCl₃ at 60 MHz on a Bruker Spectrospin 200 spectrometer. Mass spectral studies were carried out using JEOL GC mate instrument. TLC studies for final compounds were performed using precoated Silica gel G plates (Toluene: Chloroform: Ethyl acetate= 1:1:1 as mobile phase).

Scheme of synthesis

Synthesis of benzopyrone-3-carboxylate (1a)

Substituted salicylaldehyde (0.01 mol) and diethyl malonate (0.01 mol) were placed into a flask on a magnetic stirrer. To this mixture added 4 ml of ethanol, 1.5 ml piperidine and 5 drops of glacial acetic acid. The solution was then refluxed for 4 hours with continuous stirring. Then the reaction mixture was cooled to room temperature followed by cooling in an ice bath. Crystals were then collected by filtration and recrystallized from 95 % ethanol. Melting point 93°C , yield 59 %. In a similar manner compounds 1b-d were synthesized. IR (KBr, cm^{-1}): 3580 (O-H str), 3024 (C-H str aromatic), 2895 (C-H str aliphatic), 1718 (C=O str ketone), 1747 (C=O str ester), 1468 (C=C str aromatic), 1362 (C-O str). ^1H NMR (CDCl_3 , δ): 2.1 3H t CH_3 , 2.95 2H m $-\text{CH}_2-$, 5.17 1H s C-4 H, 6.1-6.18 1H d Ar H, 6.68-6.81 2H m Ar H, 10.87-10.93 1H s OH. Mass ($M+1$): 235

Preparation of benzopyrone-3-carboxylic acid (2a)

Benzopyrone-3-carboxylate (1a) (0.1 mol) and a solution of 8gm of sodium hydroxide in 50 ml of water were heated under reflux. After around 2 hours the reaction was diluted with equal volume of water and cooled. Then it was poured with stirring into 30 ml of concentrated hydrochloric acid containing ice. The product was collected by filtration. Yield 59 %, M.P 188°C . Similarly compounds 2b-d was synthesized. IR (KBr, cm^{-1}): 3593 (O-H str), 3027 (C-H str aromatic), 1727 (C=O str), 1473 (C=C str aromatic), 1355 (C-O str). ^1H NMR (CDCl_3 , δ): 5.34 1H s C-4 H, 6.24-6.31 1H d Ar H, 6.68-6.81 2H m Ar H, 10.6-10.7 1H s OH, 11.43-11.97 1H -COOH. Mass ($M+1$): 207

Synthesis of benzopyrone substituted benzimidazole analogues (3a)

o-Phenylenediamine (0.08 mol) and benzopyrone-3-carboxylic acid (2a) (0.08 mol) were heated at 100°C for 5 h. Then it was treated

with sodium hydroxide till alkaline to litmus. The product was filtered and washed with ice-cold water. After treating with decolorizing carbon the benzopyrone substituted benzimidazole derivative (3a-d) appeared to precipitate while cooling. It was washed with cold water and dried at 100°C . Yield 70 %, M.P 167°C . In a similar manner compounds 3b-d were synthesized. IR (KBr, cm^{-1}): 3615 (O-H str), 3493 (N-H str), 3039 (C-H str aromatic), 1725 (C=O str), 1657 (C=N str), 1529 (N-H bending), 1481 (C=C str aromatic), 1359 (C-O str), 1327 (C-H bending aliphatic), 1237 (C-N str), 794 (C-H bending aromatic). ^1H NMR (CDCl_3 , δ): 2.95 1H NH, 5.37 1H s C=C, 6.18-6.21 1H d Ar H, 6.54-6.67 2H m Ar H, 6.71-6.98 4H m Ar H, 10.64-10.73 1H s OH. Mass ($M+1$): 279³⁶

General procedure for the synthesis of title compounds (5a-h)

The benzopyrone substituted benzimidazole compound (3a) (0.01mole) was added at 0°C to the Vilsmier Haac reagent. The reaction mixture was then stirred at room temperature for 3.5 h followed by treating with cold aqueous sodium carbonate solution and warmed to 90°C . After cooling to room temperature the solution was extracted with chloroform. The chloroform layer was dried. The combined extracts were evaporated to dryness and purified by recrystallization from rectified spirit. Yield 49 %, M.P 172°C . Compounds 4b-d were prepared by this method.³⁷ IR (KBr, cm^{-1}): 3621 (O-H str), 3027 (C-H str aromatic), 1731 (C=O str), 1661 (C=N str), 1487 (C=C str aromatic), 1337 (C-O str), 1314 (C-H bending aliphatic), 1273 (C-N str), 794 (C-H bending aromatic). ^1H NMR (CDCl_3 , δ): 5.39 1H s C=C, 6.21-6.28 1H d Ar H, 6.48-6.62 2H m Ar H, 6.69-6.94 4H m Ar H, 9.97 1H s CHO, 10.63 1H s OH. Mass ($M+1$): 307. A mixture of 4a (2.35 mmol) and methyl amine (2.5 mmol) was stirred in about 5 ml of ethanol at room temperature for 7.5 h and kept for 48 hours at cold condition. The crystalline solid obtained was collected and washed with ice-cold water and dried to give the title compound (5a). Then it was recrystallized from water ethanol mixture (1:1). Compounds 5b-h was prepared similar to this method. The physical data are reported

in Table 1. IR (KBr, cm^{-1}): 3617 (O-H str), 3022 (C-H str aromatic), 2895 (C-H str aliphatic), 1735 (C=O str), 1672 (C=N str), 1491 (C=C str aromatic), 1341 (C-O str), 1309 (C-H bending aliphatic), 1243 (C-N str), 789 (C-H bending aromatic). ^1H NMR (CDCl_3 , δ): 3.57 3H s N-CH₃, 5.48 1H s C=C, 5.89 1H s N=CH, 6.29-6.35 1H d Ar H, 6.4-6.6 2H m Ar H, 6.61-6.89 4H m Ar H, 10.74 1H s OH. Mass (M+1): 320

Antibacterial screening

All the synthesized title compounds were subjected to screen for their antibacterial activity by cup plate Agar diffusion method. The

organisms used were *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Escherichia coli*. Agar plates were prepared by pouring melted agar media onto the petridishes and allowed to solidify. Then it was inoculated over the surface with sterile cotton. The cups were made with the help of borer and filled with the solution of suitable concentration of sample and standard and incubated at 37°C for 24 hours. The antimicrobial agents diffuse around the cups and produce a characteristic zone of inhibition of the microbial growth which was then measured (Table 2). Under identical condition the control (CHCl_3) with solvent (DMF) showed no activity. Norfloxacin was used as a standard.³⁸⁻⁴⁰

Table 1: Data of the synthesized derivatives

Compound code	Mol. Formula	Mol. Wt	Melting point ($^{\circ}\text{C}$)	R _f value	Yield (%)
5a	$\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_3$	319	151	0.52	58
5b	$\text{C}_{19}\text{H}_{15}\text{N}_3\text{O}_3$	333	167	0.62	51
5c	$\text{C}_{19}\text{H}_{15}\text{N}_3\text{O}_2$	317	180	0.67	54
5d	$\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_2$	331	192	0.74	57
5e	$\text{C}_{19}\text{H}_{15}\text{N}_3\text{O}_3$	333	154	0.56	52
5f	$\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_3$	347	178	0.59	59
5g	$\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_4$	348	190	0.68	50
5h	$\text{C}_{19}\text{H}_{14}\text{N}_4\text{O}_4$	362	153	0.53	56

Table 2: Antibacterial activity of the synthesized compounds

Compound code	Zone of inhibition			
	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>B. subtilis</i>	<i>E. coli</i>
5a	++	++	+++	+++
5b	++	++	++	+++
5c	-	+	++	+
5d	+	++	-	+
5e	+	-	+	+
5f	-	+	+	+
5g	++	++	++	+++
5h	+++	+++	++	++

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

RESULTS AND DISCUSSION

The structural variations of benzopyrone substituted benzimidazole analogues were carried out. The salicylaldehyde on treatment with diethyl malonate gave the benzopyrone-3-carboxylate (1a-d) which was hydrolyzed to give the corresponding benzopyrone-3-carboxylic acids (2a-d). Reaction of these acids with o-phenylene diamine has undergone cyclisation (3a-d) between the two amino groups and the carboxylic acid group of the former. The reaction progressed with a moderate to good yield of the product. In the very next step the Vilsmeier Haas reagent was allowed to react with benzimidazole analogues whereby an aldehydic group was introduced to the structures (4a-d). The title compounds (5a-h) were then synthesized by reacting two amines (methyl amine and ethyl amine) with 4a-d. The structural characterization and therein confirmations were carried out for the synthesized title compounds (5a-h) by their IR, ^1H NMR and Mass spectral studies. A in-detailed study of the IR spectra of the title compounds (5a-h) revealed the characteristic absorption bands for O-H stretching, C-H stretching aromatic, C-H stretching aliphatic, C=N str, C=C str aromatic, C-H bending aliphatic and C-N vibrations were appeared at around 3587-3617 cm^{-1} , 3022-3039 cm^{-1} , 2895-2941 cm^{-1} , 1671-1681 cm^{-1} , 1488-1522 cm^{-1} , 1309-1338 cm^{-1} and 1196-1243 cm^{-1} respectively. Careful observations of the ^1H NMR spectrum of 1a revealed that the alkyl protons of the terminal ethyl group was appeared at δ 2.1 for three hydrogen atoms as a triplet and at δ 2.95 for two hydrogen atoms as

multiplet. The two hydrogen atoms ($-\text{CH}_2-$) were resonated at a little higher δ value than expected; attachment of the carbonyl group of ester may have caused this deshielding. Subsequent analysis of the ^1H NMR spectrum of 2a disclosed that these aliphatic protons were disappeared, thus confirming the hydrolysis of the ester to give corresponding acid (2a-d). The acidic proton being highly deshielded and as expected was appeared at around δ 11.5. Proceeding to the next step this acidic proton of 2a-d were absent along with the appearance of a proton signal at around δ 2.95 in the ^1H NMR spectrum of 3a-d, which represented the NH proton of benzimidazole moiety as well as the cyclisation between o-phenylene diamine and benzopyrone-3-carboxylic acids (2a-d). Reaction of 3a-d with DMF/ POCl_3 introduced one aldehydic group. Thus the ^1H NMR spectra of 4a-d were characterized by the absence of NH proton of benzimidazole ring and appearance of an aldehydic proton at around δ 9.9; the greater δ value of these protons can be attributed to the higher electronegativity and thereby deshielding capacity of oxygen than carbon. A thorough observation of the ^1H NMR spectrum of the title compounds revealed that these aldehydic protons got disappeared from their respective δ values, in stead one proton was appeared at δ 5.89 (5a), an up-field shift compared to aldehydic proton, as singlet which was confirmed as the N=CH proton, thus confirming the condensation of 4a-d with amines to give 5a-h. A further scrutiny ascertained that the alkyl protons ($-\text{CH}_3$ group) of 5a appeared at a little downfield value, this is due to the direct attachment of $-\text{CH}_3$ protons to nitrogen. The

CH=N proton was resonated around δ 5.89 (5a); this deshielding is due to the fact that electronegative nitrogen on both side of that particular carbon atom along with a pair of π electrons made this proton to be appeared to a much downfield value compared to normal alkyl protons. It was rather interesting to note that four of the synthesized compounds namely 5a, 5b, 5g and 5h showed good activity against the microorganisms. This was might be due to the presence of hydroxyl and nitro group in their structures. Remaining compounds were weakly active or inactive.

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