SYNTHESIS AND CHARACTERISATION OF NEW BENZOXAZOLE DERIVATIVES

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ABSTRACT:
Benzoxazole derivatives are very useful compounds with well-known biological activity and has promising activity as therapeutic agents. In the current research work, the twelve benzoxazole derivatives **3a-l** were synthesized by the cyclocondensation reaction of appropriate carboxylic acid with 2-amino phenol in $POCl_3$. All the synthesized benzoxazole derivatives were confirmed structurally by means of IR, ^1H NMR, ^{13}C NMR and Mass spectral analysis.

Keywords: Benzoxazole derivatives, carboxylic acid, 2-amino phenol, $POCl_3$

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INTRODUCTION:

Benzoxazoles are also known as benzo[*d*]oxazoles or 1,3-benzoxazoles **Fig. 1**, are an important class of π-electron-excessive, benzene-fused heterocyclic compounds found in natural products and display a wide range of pharmacological applications. It is therefore a widely used starting scaffold for drug and agrochemical discovery programs. [1] [2]

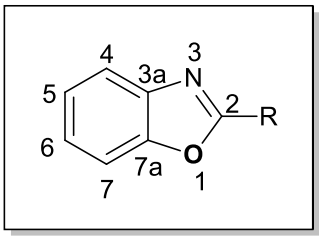


Fig. 1 Benzoxazole with numbering

The benzoxazole structure also been found in herbicides [3] [4] chiral auxiliaries in asymmetric thermal reactions (e.g. Rebek's imine) [5-7] and chiral receptors for the resolution of racemic mixtures. [8-11] The strong luminescent properties of the benzoxazole ring also means that it plays a big role in fluorescent whitening dyes [12] various photochromic materials [13] and mesogenic polymers / liquid crystalline networks.[14-16]

Recent observations suggest that targets containing benzoxazole moiety, have remarkable biological activities. For example, antimicrobial [17] [18], anti-inflammatory [19] [20], anti-viral [21], antihistaminic [22], herbicidal [23], anti-helminthic [24], anticancer [25], hypoglycemic [26], antiparasitics [27], antifungal [28], antitubercular [29], elastase inhibitors [30], protein kinase inhibitors [31], steroid sulfatase inhibitors [32]. The novel antibacterial agent containing benzoxazole system is Boxazomycin B [33]. Benzoxazole ring containing antibiotic calcymicin [34] and the anti-inflammatory agent Benzoxaprofen [35] are also obtained by synthetic methods. Zoxazolamine an α-amino-5-chlorobenzoxazole is reported to possess muscle relaxant, sedative and uricosuric effect. [36]

The significant biological activity and great utility of the heterocvclic scaffold fosters to synthesize benzoxazole derivatives. The present research work is focused on the development of alternative synthetic methods for nitrogen and oxygen containing heterocyclic compounds in order to enhance the significant effect on biological activity. The title compounds **3a-g** were synthesized by treating the 2-amino phenol with appropriate carboxylic acid in $POCl_3$.

1. EXPERIMENTAL SECTION:

All the compounds and reagents were commercially available without pre-treatment. All solvents and chemicals were obtained from Merck, Spectrochem or Aldrich and are of analytical grade, and were used immediately after opening. TLC was performed on the glass-backed silica gel sheets (Silica Gel-60 GF254) and visualized in UV light (254 nm). Melting points were recorded in open capillary tubes and were found uncorrected. 1H NMR and 13C NMR spectra were recorded on a Bruker AV- 400 spectrometer in CDCl3 using TMS as an internal standard. Infrared spectra were recorded on Thermo scientific spectrometer. Elemental analyses were obtained using a Thermo Finnigan Flash EA 1112 as an instrument. Mass spectrum was recorded with an Advion mass spectrometer of Micromax Company.

General procedure for the synthesis of substituted benzoxazole derivatives (3a-l):

An equimolar mixture of substituted carboxylic acids and 2-aminothiophenol in $POCl_3$ was heated at 70-80°C for 5-6 h. Then reaction mass was allowed to cool at room temperature and diluted with water and then reflux for 2 h. The reaction mass allowed to cool and basified with 50% NaOH to obtain differently substituted benzoxazole derivatives **3a-l**. The product was filtered and recrystallized from ethanol.

2. CHARACTERISATION:

Compound 3c

Yield: 95%, MF: $C_{13}H_8N_2O_3$/ 240.21, Pale yellow solid; IR cm^{-1}: 3151, 1649.39, 1606, 1521, 1346, 1312, 1251.59, 1221, 766.37; ^{1}H NMR: ($CDCl_3$, 400MHz): δ= 7.48-7.52 (1H, dt, Ar-H), 7.56-7.61(1H, dt, Ar-H), 7.98-8.00(1H, d, J=8Hz, Ar-H), 8.15,-8.17(1H,d, J=8Hz, Ar-H), 8.29-8.31(2H,d, J=8Hz, Ar-H), 8.37-8.39 (2H,d, J=8Hz, Ar-H); ^{13}C NMR: ($CDCl_3$, 400MHz); δ= 121.84, 132.95, 124.31, 126.23, 126.92, 128.24, 135.50, 139.19, 149.06, 154.12, 164.83; MS: m/z 240.1

Compound 3d

Yield: 94%; MF: $C_{13}H_7N_3O_5$/ 285.21; Pale yellow solid; IR cm^{-1}: 3106.47, 1600, 1593.14, 1500.73, 1341.90, 726.84; ^{1}H NMR: ($CDCl_3$, 400MHz): δ= 7.55-7.63 (2H, m, Ar-H), 8.01-8.03 (1H, d, J=8Hz, Ar-H), 8.19-8.21(1H, d, J= 8Hz, Ar-H), 9.15 (1H, s, Ar-H), 9.26 (2H, s, Ar-H); ^{13}C NMR: ($CDCl_3$, 400MHz); δ= 119.82, 122.66, 124.32, 126.94, 127.40, 135.43, 137.20, 149.11, 153.87, 162.12; MS: m/z 284.98

Compound 3h

Yield: 91%; MF: $C_{15}H_{13}NO_2$/ 239.27; white solid; IR cm^{-1}: 3100, 2980.98, 1600, 1532.13, 1341.99; ^1H NMR: ($CDCl_3$, 400MHz): δ= 2.31 (3H, s, -CH_3), 5.49 (2H, s, -CH2), 6.95-6.98 (2H, d, Ar-H), 7.12-7.14 (2H, d, Ar-H), 7.40-7.44 (1H, t, Ar-H), 7.50-7.54 (1H, t, Ar-H), 7.90-7.92 (1H, d, Ar-H), 8.04-8.06 (1H, d, Ar-H); ^{13}C NMR: ($CDCl_3$, 400MHz); δ= 20.53, 68.02, 114.82, 121.83, 123.08, 125.21, 126.15, 130.12, 131.25, 135.05, 152.99, 155.75, 169.02; MS: m/z 239.01

Compound 3k

Yield: 92%; MF: $C_{14}H_{10}ClNO_2$/ 259.69; Pale yellow solid; IR cm^{-1}: 3106.47, 2920.14, 1539, 1033.29; ^1H NMR: ($CDCl_3$, 400MHz): δ= 5.49 (2H, s, -CH2), 6.98-7.01 (2H, d, J=8Hz, Ar-H), 7.27-7.29 (2H, d, J=8Hz, Ar-H), 7.42- 7.45 (1H, t, Ar-H), 7.51-7.53 (1H, t, Ar-H), 7.91-7.93 (1H, d, J=8Hz,Ar-H), 8.05-8.07 (1H, d, J=8Hz, Ar-H); ^{13}C NMR: ($CDCl_3$, 400MHz); δ= 68.13, 116.32, 121.83, 123.19, 125.40, 126.27, 126.93, 129.58, 135.04, 152.92, 156.42, 167.88.

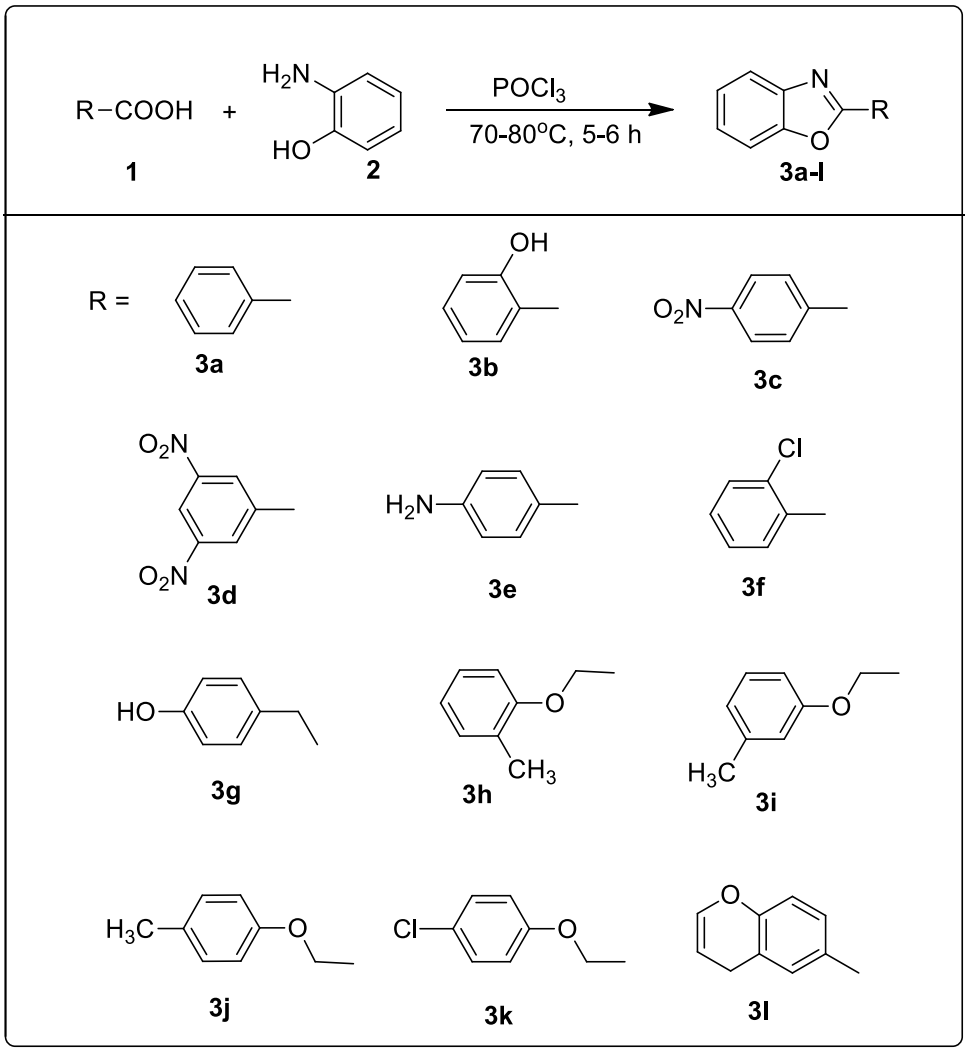
Compound 3l

Yield: 88%; MF: $C_{16}H_{11}N_2$/ 249.26; Yellow solid; IR cm^{-1}: 3058.50, 2971.54, 1692.27, 1588.54, 1513.57, 1488.72; ^1H NMR: ($CDCl_3$, 400MHz): δ= 4.42-4.47 (2H, dd, -CH_2), 5.66-5.68 (1H, dd, olefinic -CH), 6.92-6.99 (3H, m, Ar-H), 7.09-7.11 (1H, m, olefinic –CH), 7.42-7.44 (1H, t, Ar-H), 7.46-7.52 (1H, t, Ar-H), 7.54-7.56 (1H, d, Ar-H), 7.93-7.95 (1H, d, Ar-H); ^{13}C NMR: ($CDCl_3$, 400MHz); δ= 67.10, 73.45, 117.53, 117.63, 121.89, 122.09, 122.32, 123.31, 125.45, 126.36, 134.95, 142.36, 143.08, 153.67, 167.72; MS: m/z 249.50.

3. RESULT AND DISCUSSION:

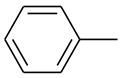
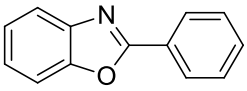
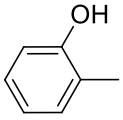
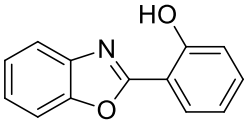
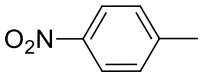
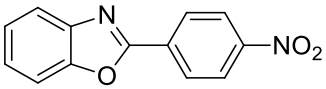
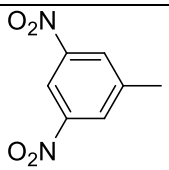
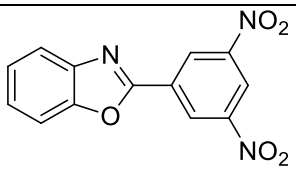
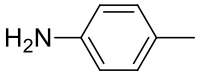
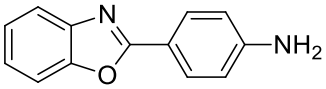
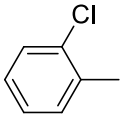
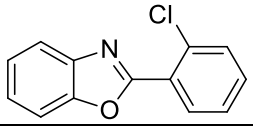
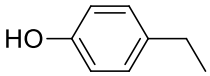
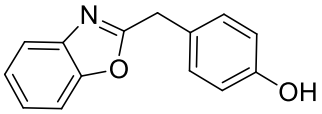
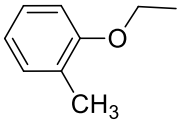
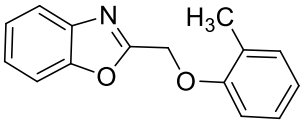
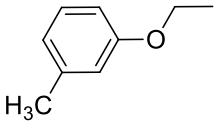
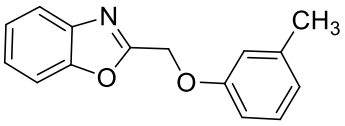
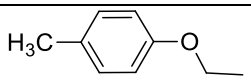
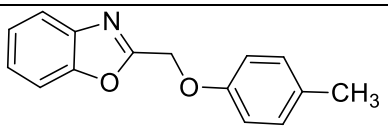
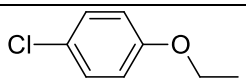
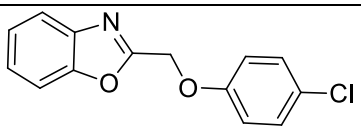
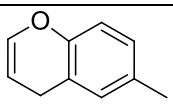
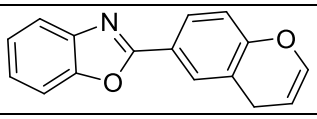
3.1CHEMISTRY:

In the present investigation, the benzoxazole derivatives **3a-g (Table 1)** were synthesized by the cyclocondensation reaction of appropriate carboxylic acid with 2-amino phenol in $POCl_3$.This intermediate was confirmed by TLC and characterized by IR, ^1H NMR and Mass Spectroscopy. All the synthesized compounds were characterized by IR, ^1H NMR, ^{13}C NMR and Mass Spectroscopy.



Reagents and conditions: $POCl_3$, reflux at 70-80 ºC, 5-6 h

Table 1: Synthesized benzoxazole derivatives (3a-g)

Entry	R	Structure of products	Yield %
3a			90
3b			82
3c			95
3d			94
3e			91
3f			92
3g			82
3h			91
3i			93
3j			91
3k			92
3l			88

IR spectrum of benzoxazoles showed disappearance of carbonyl and hydroxyl stretch of carboxylic acid indicates that conversion of carboxylic acids to benzoxazoles. The IR absorbtion bands at ~ 3100, ~2980, ~1600-1650 and ~1530-1590 cm^{-1} due to presence of aromatic (C-H), aliphatic (C-H), (C=N) and (C=C) respectively.

^1H NMR spectrum of substituted benzoxazoles shows that all the Ar-H protons resonated in range δ ~ 7.0 - 9.20 ppm. Besides these the peaks at δ ~2.30-2.50 ppm (s, 3H, Ar-CH_3) while sp^3 hybridized methylene protons resonated at δ ~5.48 ppm.

All the carbons resonated in range δ ~114-170 ppm while in case of some of the derivatives methylene carbon i.e. sp3 hybridized carbon resonated between δ 65-70 ppm also it shows downward peak in DEPT. The methyl carbon i.e. sp3 hybridized carbon resonated at δ ~20 ppm. The mass spectra of corresponding benzoxazoles derivatives showed

their molecular formula weight and are found to be in agreement with the literature.

4. CONCLUSION:

As bezoxazoles display a wide range of pharmacological applications, we have efficiently designed and synthesized the twelve benzoxazole derivatives **3a-l.** In this work, we achieved a new approach of $POCl_3$ mediated synthesis in which cyclocondensation reaction of appropriate carboxylic acid with 2-amino phenol gave excellent yields without formation of any side products.

ACKNOWLEDGEMENT:

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ABBREVIATIONS USED:

HIV = Human Immunodeficiency Virus; rt = room temperature; h = hour; IR = Infrared; ^{1}H NMR = Hydrogen-1Nuclear Magnetic Resonance;, ^{13}C NMR = Carbon-13 Nuclear Magnetic Resonance; Mol. Wt. = Molecular Weight; M.P. = Melting Point; TLC = Thin Layer Chromatography; TMS = Tetramethyl silane; LCMS = Liquid Chromatography Mass Spectroscopy; MHz = Megahertz

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