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ORIGINAL ARTICLE

# Synthesis, antimicrobial and cytotoxic activity of novel azetidine-2-one derivatives of 1*H*-benzimidazole

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**Abstract** A series of 1-methyl-*N*-[(substituted-phenylmethylidene)-1*H*-benzimidazol-2-amines **(4a–4g)** were prepared via the formation of 1-methyl-1*H*-benzimidazol-2-amine **(3)**, which was prepared by the cycloaddition of *o*-phenylenediamine **(1)** with cyanogen bromide in the presence of aqueous base followed by N-methylation with methyl iodide in the presence of anhydrous potassium carbonate in dry acetonitrile. Moreover, the four-membered β-lactam ring was introduced by the cycloaddition of **4a–4g** and chloroacetyl chloride in the presence of triethylamine catalyst to give 3-chloro-1-(1-methyl-1*H*-benzimidazol-2-yl)-(4′-substituted)-phenylazetidin-2-one **5a–5g**. A total of 14 compounds were synthesized and characterized by IR, $^1$H NMR, $^{13}$C NMR and Mass spectral technique, in addition they were evaluated for anti-bacterial and cytotoxic properties. Among the chemicals tested **4a**, **4b**, **5a**, **5b**, **5g** exhibited good antibacterial activity and **5f**, **5g** shown good cytotoxic activity in vitro.

## 1. Introduction

Despite numerous attempts to search and develop new structural prototype as effective antimicrobials, benzimidazoles still remain as potential class of compounds. Recently, the chemistry and biological profiles of various pharmacophores of N-1 substituted and 2-substituted benzimidazole derivatives have been worked out (Ansari and Lal, 2008). Effect of substituents on the benzimidazole ring exhibited correlated structure–activity relationship (Powers et al., 2006). Incorporation of an imidazole nucleus, a biologically active pharmacophore, in the benzimidazole molecule has made it a versatile heterocycle with wide spectrum of biological activity. Moreover, benzimidazole derivatives are structural isosteres of naturally occurring nucleotides, which allow them to interact easily with the biophores (Starcevic et al., 2007). Therefore, numerous biological activities of benzimidazoles derivatives have been described; antimicrobial (Kus et al., 2009), anticancer (Thimmegowda et al., 2008), anti inflammatory (Mader et al., 2008), antiviral (Vazquez et al., 2001),

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antiparasitic (Kazimierczuk et al., 2002), antiprotozoal (Gomez et al., 2008), antihelminitics (Dahiya and Pathak, 2007), protein kinase inhibitors (Bernatowicz et al., 2009) and $H^+/K^+$ ATPase inhibitors (Cho et al., 2001). Polyfunctionality of 2-aminobenzimidazole molecule resulting from the cyclic guanidine moiety has made it a building block for the synthesis of a large number of derivatives of pharmacological interest (Mavrova et al., 2007). Different substituted 2-aminobenzimidazoles have been found to possess in vivo and in vitro growth inhibition activity against various strains of bacteria, fungi and yeast.

On the other side, literature survey revealed that 2-azetidinones are associated with various pharmacological activities. A large number of 3-chloro monocyclic β-lactam having substitution at positions 1 and 4 possess powerful anti-bacterial, anti-microbial, sedative, anti-fungal and anti-tubercular activity (Kagan and Luche, 1968; Mohamed et al., 2006). With the above facts and in continuation of our research for newer anti-cancer and anti-microbial agents in the present study, we report here the synthesis of 2-azetidinone derivatives of 2-amino-1*H*-benzimidazoles to develop potential drug candidates of this class (Manjula et al., 2009; Badiger et al., 2006). These molecules operate by forming a covalent adduct with the membrane-bound bacterial transpeptidase, also known as penicillin binding proteins (PBPs), involved in the biosynthesis of cell walls. These mechanism-based inhibitors prevent the construction of cell wall and eventually lead to cell lysis and death (Halve et al., 2007).

## 2. Material and method

### 2.1. Chemistry

All chemicals and solvents were supplied by Merck, S.D. Fine-chem limited, Mumbai. All the solvents were distilled and dried before use. The reactions were monitored with the help of thin-layer chromatography using pre-coated aluminum sheets with $GF_{254}$ silica gel, 0.2 mm layer thickness (E. Merck). Various solvent systems used for developing the chromatograms were (a) chloroform/methanol (9:1), (b) chloroform/methanol (9.5:0.5), (c) ethyl acetate/pet-ether (2:1) and (d) chloroform/benzene (1:1). Columns of different sizes packed with G60 (70–230 mesh) silica gel was used for purification. Melting points of the synthesized compounds were recorded on the Veego (VMP-MP) melting point apparatus. IR spectrum was acquired on a Shimadzu Infra Red Spectrometer, (model FTIR-8400S). $^1H$ NMR spectra of the synthesized compounds were performed in DMSO with a Bruker Avance-II 400 NMR Spectrometer operating at 400 MHz in SAIF, Punjab University (Chandigarh). $^{13}C$ NMR spectra of the synthesized compounds were scanned with a Bruker Avance-II 400 NMR Spectrometer operating at 400 MHz in Regional Research Laboratory (RRL), Jammu Tawi. Chemical shifts are reported in $\delta$ scale (ppm). Mass spectra of the synthesized compounds were recorded at MAT 120 in SAIF, Punjab University, Chandigarh and Regional Research Laboratory (RRL), Jammu Tawi.

#### 2.1.1. Synthesis of 2-aminobenzimidazoles (2)

*o*-Phenylenediamine **1** (43.2 g, 0.4 mol) was stirred with water (400 mL) in an ice-bath and cyanogen bromide (35.5 g, 0.333 mol) was added drop wise during 1 h. The mixture was stirred for 3 h, filtered, and made basic with aqueous sodium hydroxide, the base being precipitated and filtered off. The solid obtained was filtered, and crystallized from water to give **2**, yield 70.1%, mp 226–228 °C, $\lambda_{max}$ (methanol) 212 nm; IR (KBr, $v$, $cm^{-1}$): 3383 and 3060 (–NH, –$NH_2$), 1168 and 1568 (NH bend), 1269 and 1313 (–C–N); $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 5.6 (s, 2H, $NH_2$), 6.7 (s, 1H, NH), 7.10–7.28 (m, 4H, Ar-H); $^{13}C$NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): Benzimidazole C: [154.63 (C), 138.48 (C), 134.89 (C), 122.67 (CH), 116.29 (CH), 118.54 (CH)]; HRMS calcd for $C_3H_7N_3$: 133.1511, found 133.1592.

#### 2.1.2. Synthesis of 1-methyl-1H-benzimidazol-2-amine (3)

Compound **2** (2.6 g, 0.02 mol) and potassium carbonate (2.6 g, 0.02 mol), acetonitrile (30 mL) methyl iodide (0.75 mL, 0.01 mol) were refluxed under nitrogen overnight at 50 °C then added water and extracted with ethyl acetate. Dried with $MgSO_4$ and recrystallized from ethanol to give compound **3**, yield 78%, mp 201–203 °C (in water), 209–210 °C (in acetone), $\lambda_{max}$ (methanol) 211 nm; IR (KBr, $v$, $cm^{-1}$): 3374 (–NH, –$NH_2$), 2921 and 2849 (C–$CH_3$), 1314 and 1270 (C–N); $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 3.9 (s, 2H, $NH_2$), 3.5 (s, 3H, $CH_3$), 7.20–7.48 (m, 4H, Ar-H); $^{13}C$NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): Benzimidazole C: [153.67 (C), 139.47 (C), 132.27 (C), 121.34 (CH), 116.29 (CH), 111.25 (CH)], 27.89 (N–$CH_3$); HRMS calcd for $C_8H_9N_3$: 147.1771, found 147.1751

#### 2.1.3. General procedure for the synthesis of compounds (**4a–4g**)

The 2-amino-1-methyl benzimidazole **3** (0.01 mol) was added to a solution of the different substituted benzaldehydes (0.012 mol) in dry ethanol 40 mL in RBF. Dry benzene (10 mL) and two drops of glacial acetic acid were also added to the above mixture. The mixture was refluxed for 8–20 h and at the end of the reaction; solvents were partially evaporated then poured into water. The precipitates were collected by filtration, washed with ether, dried and compounds **4a–4g** were synthesized and recrystallized from the appropriate solvent like ethanol or ethanol–water.

*2.1.3.1. N-[(4-Chlorophenyl) methylidene]-1-methyl-1H-benzimidazol-2-amine (**4a**).* This was prepared and purified as per the above mentioned procedure: yield 58%, mp 216–218 °C, $\lambda_{max}$ (methanol) 208.4 nm; IR (KBr, $v$, $cm^{-1}$): 1432 (–N=CH), 1092 (Ar-Cl), 2925 and 2869 (N–$CH_3$); $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 2.46 (s, 3H, N–$CH_3$), 7.35–7.82 (4H, Ar-H), 7.11–7.30 (m, 4H, Ar-H), 9.3 (s, 1H, N=CH); $^{13}C$NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): Benzimidazole C: [151.14 (C), 140.47 (C), 134.2 (C), 120.98 (CH), 114.25 (CH), 111.25 (CH)], Arom-C: [135.66 (C), 133.57 (C), 131.67 (CH), 130.76 (CH)], 156.67 (N=CH), 26.18 (N–$CH_3$); HRMS calcd for $C_{15}H_{12}ClN_3$: 269.7291, found 269.7234.

*2.1.3.2. 1-Methyl-N-[(4-nitrophenyl) methylidene]-1H-benzimidazol-2-amine (**4b**).* This was prepared and purified as per the above mentioned procedure: yield 58.9%, mp 248–250 °C, $\lambda_{max}$ (methanol) 208.5 nm; IR (KBr, $v$, $cm^{-1}$): 1432 (N=CH), 1515 (–N=O), 1342 (–N=O), 855 and 834 (–C–NO), 2929 and 2849 (N–$CH_3$); $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 2.42 (s, 3H, –N–$CH_3$), 7.62–8.34 (4H, Ar-H), 7.14–7.43 (m, 4H, Ar-H), 9.53 (s, 1H, –N=CH); $^{13}C$ NMR (400 MHz, DMSO-$d_6$) $\delta$