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ORIGINAL ARTICLE

Synthesis, characterization and pharmacological screening of novel benzimidazole derivatives

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Abstract In present study *o*-phenylenediamine and phenoxyacetic acid were used as starting material through series of steps 2-[2-(phenoxymethyl)-1*H*-benzimidazol-1-yl]acetohydrazide **5** was obtained. Various derivatives of 2-[2-(phenoxymethyl)-1*H*-benzimidazol-1-yl]-N′-[(Z)-phenylmethylidene]acetohydrazide and some compounds containing oxadiazole bearing benzimidazole were synthesized by using various aromatic aldehyde, cyanogens bromide and carbon disulfide/potassium hydroxide. These were elucidated by IR, NMR and elemental analysis and their *in vivo* anticonvulsant screening was performed using MES and scPTZ. Two compounds **7g** and **j** were found to be potent in both the screens and their protective index was found to be better than standard drugs used.

1. Introduction

All the heterocyclic compounds are of great interest in pharmaceutical chemistry. Out of these heterocyclic compounds the benzfused heterocyclic compound, i.e. benzimidazole and its derivatives have wide variety of biological activities like antimicrobial activity (Kumar et al., 2006; Afaf et al., 2000; kazimierczuk et al., 2002; Shetgiri and Kokitkar, 2001; Ansari and Lal, 2009), antiinflammatory-analgesic (Khan and Nandan, 1997; Evans et al., 1996; Taha, 2005), anticancer (Demirayak et al., 2002), CNS depressant (Sharma et al., 1999), androgen receptor antagonist (Raymond et al., 2007), antitubercular (Kaghthara et al., 1999; Foks et al., 2006) and anticonvulsant (Chmirri et al., 1989, 2002; Vostrova et al., 1986; Singh, 1969, 1970). In addition the benzimidazole have played a very important role in the development of theory in heterocyclic chemistry and also extensively in organic synthesis. Benzimidazole nucleus is present in vitamin-B_{12} (Merck index 2001), albendazole, mebendzole and thiabendazole. In this present study some novel derivatives of schiff bases containing benzimidazole nucleus and oxadiazole bearing benzimidazole

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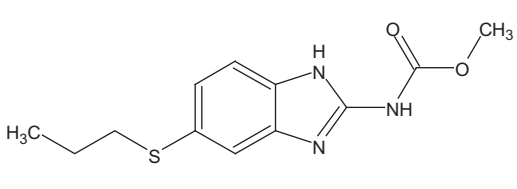
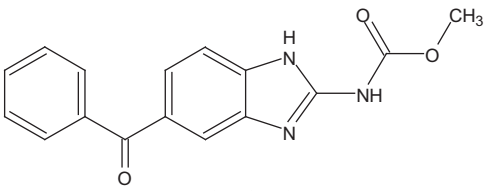
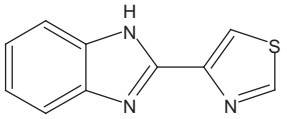
derivatives have been synthesized and their antimicrobial and anticonvulsant activity have been established.



Albendazole



Mebendazole



Thiabendazole

2. Experimental

2.1. Instrumentation

The entire chemical reagents which are used in the study were procured locally. The completion of reaction is monitored thin layer chromatography (TLC) using toluene:ethyl acetate:formic acid (5:4:1) and benzene:acetone (9:1) as solvent system. The product is purified by recrystallisation and purity of the compounds was checked by thin layer chromatography (TLC) using silica gel G plates (Merck). The spots were developed in iodine chamber and viewed under UV lamp. Melting points were determined in an open capillary using melting point apparatus and are uncorrected. The proton magnetic resonance (^{1}H NMR) spectra were recorded on a Brucker 300 MHz instrument in DMSO-d_6 using tetramethylsilane as internal standard. The infrared spectra of compounds were recorded in KBr on a Bio Rad FTIR Spectrophotometer.

2.1.1. Procedure for the synthesis of 2-(phenoxymethyl)-1H-benzimidazole (3)

A mixture of *o*-phenylenediamine **1** (0.05 mol; 5.40 g) and phenoxyacetic acid **2** (0.05 mol; 7.60 g) in round bottom flask and refluxed in 4 N HCl for 3 h on water bath. After completion of the reaction, the solution was poured onto crushed ice, NaOH solution was added drop wise to neutralize and the resulting solid was filtered, washed with cold water, dried and recrystallized. Yield 80%; m.p. 160–164 °C, IR (KBr) cm^{-1}: 1240 (C—O), 1540 (C═N), 3450 (N—H): ^{1}H NMR (DMSO-d_6) δ ppm: 5.29 (s, 2H, OCH_2), 6.85–7.70 (m, 9H, aromatic), 12.31 (s, 1H, NH). Anal. Cacd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49; O, 7.13. Found: C, 75.0; H, 5.35; N, 12.45; O, 7.10%.

2.1.2. Procedure for the synthesis of ethyl [2-(phenoxymethyl)-1H-benzimidazol-1-yl] acetate (4)

To a mixture of 2-(phenoxymethyl)-1*H*-benzimidazole **3** (0.05 mol; 11.2 g) in dry acetone (100 ml), and potassium carbonate (4 g), ethylchloro acetate was added drop wise at room temperature for a period of 20–30 min. The reaction mixture was stirred at room temperature for 10–15 h. The solid thus obtained was filtered off and filtrate was concentrated under reduced pressure. Yield 70%; m.p. 88–92 °C, IR (KBr) cm^{-1}: 1240 (C—O), 1540 (C═N), 1645 (C═O): ^{1}H NMR (DMSO-d_6) δ ppm: 5.29 (s, 2H, OCH_2), 6.70–7.83 (m, 9H, aromatic), 4.17 (m, 2H, CH_2), 1.65 (m, 3H, CH_3). Anal. Cacd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03; O, 15.47. Found: C, 69.65; H, 5.82; N, 9.01; O, 15.42%.

2.1.3. Procedure for the synthesis of 2-[2-(phenoxymethyl)-1H-benzimidazol-1-yl]aceto hydrazide (5)

To a mixture of ethyl [2-(phenoxymethyl)-1*H*-benzimidazol-1-yl]acetate **4** (0.01 mol; 3.10 g) and hydrazine hydrate 98% (0.01 mol; 0.49 ml) in alcohol was added and the reaction mixture was refluxed for 4 h. the reaction mixture was cooled and the solid so obtained was filtered, washed with cold water and recrystallized from ethanol. Yield 80%; m.p. 178–180 °C, IR (KBr) cm^{-1}: 1030 (N—N), 1242 (C—O), 1600 (C═N), 1656 (C═O), 3034 (CH—Ar), 3287 (N—H); ^{1}H NMR (DMSO-d_6) δ ppm: 2.52 (s, 1H, NH_2), 4.90 (s, 2H, CH_2), 5.48 (s, 2H, OCH_2), 6.92–7.69 (m, 9H, aroamtic), 9.43 (s, 1H, CONH). Anal. Cacd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91; O, 10.80. Found: C, 64.86; H, 5.42; N, 18.89; O, 10.77%.

2.1.3.1. Procedure for the synthesis of 5-{[2-(phenoxymethyl)-1H-benzimidazol-1-yl]methyl}-1,3,4-oxadiazol-2-amine (6).

A methanolic solution of 2-[2-(phenoxymethyl)-1*H*-benzimidazol-1-yl]acetohydrazide **5** (0.0016 mol; 0.4938 g) and cyanogen bromide (0.03 mol; 3.15 g) was refluxed approximately for 5 h. After completion of the reaction, the reaction mixture was cooled at room temperature and poured onto crushed ice. On basification with sodium bicarbonate (5%), a solid mass so separated was washed with water and recrystallized from ethanol. Yield 75%; m.p. 80–84 °C, IR (KBr) cm^{-1}: 1022 (N—N), 1240 (C—O), 1600 (C═N), 3063 (CH—Ar), 3144 (N—H). ^{1}H NMR (DMSO-d_6) δ ppm: 3.63 (s 2H, NH_2), 5.29 (s, 2H, CH_2), 5.39 (s, 2H, OCH_2), 6.94–7.68 (m, 7H, aromatic). Anal. Cacd for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79; O, 9.96. Found: C, 63.51; H, 4.67; N, 22.79; O, 9.97%.

2.1.4. General procedure for the Synthesis of 2-[2-(phenoxymethyl)-1H-benzimidazol-1-yl]-N'-[substituted phenyl methylidene]acetohydrazide (7a–j)

A mixture of 2-[2-(phenoxymethyl)-1*H*-benzimidazol-1-yl]acetohydrazide **(5)** (0.0025 mol; 0.738 g) and benzaldehyde

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