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Synthesis and biological evaluation of some novel-3-(5-substituted benzimidazol-2-yl)-5-arylisoxazolines

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Abstract

The synthesis of a new series of 3-(5-substituted benzimidazol-2-yl)-5-arylisoxazolines (**6a–h**) was achieved in excellent yields by the condensation of 1-(1*H*-benzimidazol-2-yl)-3-(substituted phenyl)prop-2-en-1-ones (**5a–h**) with hydroxylamine at room temperature. These 1-(1*H*-benzimidazol-2-yl)-3-(substituted phenyl)prop-2-en-1-ones (**5a–h**) were obtained by the condensation of 2-acetyl benzimidazoles (**4a–d**) with different aromatic aldehydes, which in turn were obtained by the oxidation of 2-(α-hydroxy)ethyl benzimidazoles (**3a–d**) prepared by the reaction of *o*-phenylenediamines (**1a–d**) with α-hydroxy propionic acid **2**. The synthesized compounds were characterized by their IR, ^{1}H NMR and MS analyses. These compounds were screened for their antibacterial and antifungal activity by standard methods and found some of them active.

Keywords: Benzimidazolyl-5-arylisoxazolines; Antibacterial; Antifungal activity

Benzimidazoles are known to exhibit significant activity against several viruses such as human cytomegalovirus, HIV [1], herpes [2], RNA [3] and influenza [4]. In view of varied biological activities of benzimidazoles, their preparation has gained considerable attention in recent years and many strategies are reported [5–8]. Synthesis of isoxazoles [9,10] has been a developing field within the realm of heterocyclic chemistry. Isoxazoles are also equally important for their biological and pharamacological properties [11–18].

Inspired by the biological profile of benzimidazoles and isoxazoles and in connection of our work on the design and synthesis of biologically active and pharmacologically important new heterocycles [19], it was thought worthwhile to synthesize the new compounds. Containing two of the specified pharmacophores in order to obtain the molecules having enhanced biological activities and to evaluate them for their antimicrobial activity to begin with further it is also noted from the literature that there is no report, on the synthesis of 3-(5-substituted benzimidazol-2-yl)-5-arylisoxazolines.

The synthetic strategy developed Scheme 1 to obtain the 3-(5-substituted benzimidazol-2-yl)-5-arylisoxazoline **6** from 1-(1*H*-benzimidazol-2-yl)-3-(substituted phenyl)prop-2-en-1-one **5** with hydroxylamine hydrochloride. For the synthesis of target compounds, 2-(α-hydroxy)ethylbenzimidazole **3** was prepared from the reaction of substituted

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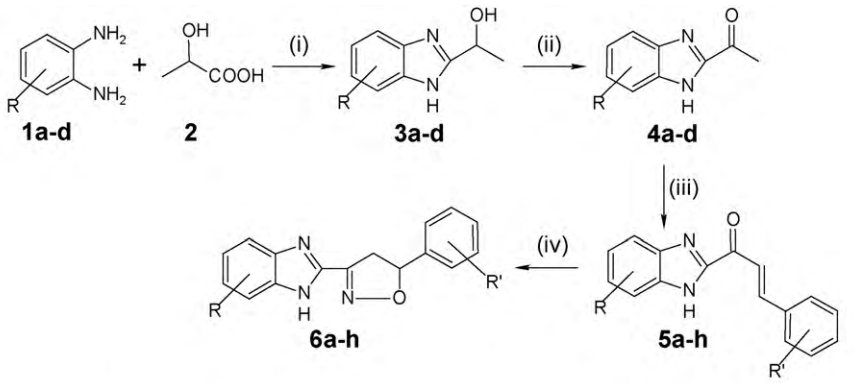

1/3/4 R = (a) -H; (b) -4-CH_3; (c) -4-Cl; (d) -4-NO_2; 5/6 R = (a) -H; (b) -H; (c) -H; (d) -4-CH_3; (e) -4-CH_3; (f) -4-Cl; (g) -4-Cl; (h) -4-NO_2;
5/6 R' = (a) -H; (b) -4-OCH_3; (c) -3,4-OCH_3; (d) -H; (e) -4-C_2H_5; (f) -4-C_2H_5; (g) -4-NO_2; (h) -4- C_2H_5.

Scheme 1. (i) 4N HCl, reflux, 24 h, (ii) $K_2Cr_20_7$, H_2SO_4, 2.5 h, (iii) Ar–CHO, EtOH, 60% KOH, 4 h, (iv) NH_2OH, EtOH, AcOH, NaOAc, reflux, 6 h.

o-phenylenediamine **1** with α-hydroxypropionic acid **2** in the presence of hydrochloric acid under reflux. It was followed by oxidation of compound **3** with potassium dichromate and sulfuric acid, at room temperature to get 2-acetyl benzimidazole **4** which on condensation reaction with aromatic aldehydes at room temperature in ethanol and 60% KOH gave benzimidazolyl propenone **5**. These chalcones on the cyclocondensation reaction with hydroxylamine in the presence of sodium acetate in ethanol and acetic acid afforded the title compound **6**. The synthetic route leading to the title compounds is summarized in Scheme 1. The newly synthesized compounds were characterized by their IR, ^{1}H NMR, and MS analyses and further the compounds were screened for their antibacterial and antifungal activity.

1. Antibacterial activity

The antibacterial activity of the synthesized compounds was evaluated against two Gram-positive bacteria viz., *Bacillus subtilis*, *Staphylococcus aureus* and two Gram-negative bacteria viz., *Escherichia coli* and *Klebsiella pneumoniae*, using streptomycin and benzyl penicillin as standard drugs, respectively by the 'Cup–plate method' [20] using DMSO as the solvent and the results are given in Table 1. It has been observed that the compounds exhibited interesting biological activity, however, with a degree of variation. Among all the compounds, compound **6c** displayed relatively high activity against *B. subtilis* and *S. aureus*, compounds **6d** and **6g** were also active against *S. aureus*.

Table 1
Antibacterial and antifungal activity of 3-(5-substituted benzimidazol-2-yl)-5-arylisoxazolines **6a–h**.

Compound	Antibacterial activity[a,b]				Antifungal activity[a,b]	
	B. subtilis	*S. aureus*	*E. coli*	*K. pneumoniae*	*F. oxysporum*	*A. niger*
6a	05/03	07/05	06/04	06/03	02/02	02/01
6b	12/11	12/11	08/07	08/08	05/03	05/02
6c	15/12	15/11	12/10	12/10	03/02	02/01
6d	13/11	15/13	13/10	13/10	05/02	03/02
6e	08/06	09/07	06/05	06/05	03/01	02/01
6f	12/12	12/11	05/03	05/03	00/00	00/00
6g	13/11	15/13	10/10	10/10	05/03	05/03
6h	08/06	09/07	05/04	05/04	03/02	03/02
Streptomycin[c]	–	–	16	16	–	–
Benzyl penicillin[c]	16	16	–	–	–	–
Fluconazole[c]	–	–	–	–	06	06

[a] Zone of inhibition in mm at 500 μg/mL concentration.
[b] Zone of inhibition in mm at 250 μg/mL concentration.
[c] Zone of inhibition in mm at 40 μg/mL concentration.

Compounds **6b** and **6f** showing reasonable activity against *B. subtilis* and *S. aureus* **6d** and **6g** were active against *B. subtilis*, whereas compounds **6c** and **6d** were active against *E. coli* and *K. pneumoniae*. The rest of the compounds showed low activity against all the organisms employed.

2. Antifungal activity

The newly prepared 3-(5-substituted benzimidazol-2-yl)-5(4-substiuted phenyl)- isoxazolines were also screened for their antifungal activity against two fungi viz., *F. oxysporum* and *Aspergillus niger* by the 'Cup–plate method' using fluconazole as a standard drug and DMSO as the solvent. It has been observed that the compounds exhibited good to excellent activity, with a degree of variation. Among all the compounds, compounds **6b**, **6d** and **6g** showed excellent activity against *F. oxysporum*, compounds **6b** and **6g** also have high activity against *A. niger*. Compound **6f** is inactive against both fungal organisms. The remaining compounds exhibited low to moderate activity against two organisms.

3. Experimental

All reagents and solvents were purchased and used without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were obtained on a Perkin Elmer BX serried FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a varian 300 MHz spectrometer for ^{1}H NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

*3.1. 2-(α-Hydroxy)ethyl benzimidazoles **3a–d***

o-Phenelenediamine (0.01 mol) was mixed with lactic acid (0.01 mol) added to 4N-hydrochloric acid (5 mL) and refluxed for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled and neutralized with NH_3 solution. The solid was separated through filter and recrystallized from ethanol.

*3.2. 2-Acetyl benzimidazoles **4a–d***

To a solution of 2-(α-hydroxy)ethyl benzimidazoles **3** (0.01 mol) in dil. H_2SO_4 (25%, 40 mL) was dropwise added the solution of $K_2Cr_2O_7$ (0.15 mol) and H_2SO_4 (5%, 80 mL) with constant stirring at room temperature over a period of 20 min. Further the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was neutralized with NH_3 solution (1:1) and resultant orange solid was filtered, washed with water and dried, recrystallized from ethyl acetate.

*3.3. 1-(1H-Benzimidazol-2-yl)-3-(substituted phenyl) prop-2-en-1-ones **5a–h***

2-Acetyl benzimidazoles **4** (0.01 mol) and appropriately substituted benzaldehydes (0.01 mol) were mixed in ethanol (20 mL) containing 60% aq. KOH (5 mL) and stirred constantly at room temperature for 4 h. After completion of the reaction (monitored by TLC), the reaction mixture ethanol was removed mostly and residue poured into ice-cold water and neutralized with dil. HCl solution. The solid formed was filtered and dried, recrystallized from absolute ethanol.

*3.4. 3-(5-Substituted benzimidazol-2-yl)-5-arylisoxazolines **6a–h***

A mixture of **5** (0.01 mol) was dissolved in ethanol (15 mL) and anhydrous sodium acetate (0.01 mol) in acetic acid (10 mL) was added. It was followed by a solution of hydroxylamine hydrochloride (0.01 mol) in ethanol (10 mL). Then the reaction mixture was refluxed for 7–8 h. After completion of reaction (monitored by TLC), the reaction mixture was poured into ice-cold water and the solid separated was filtered and dried, recrystallized from ethyl acetate.

3.5. Some selected product characterization data

3a: Yellow solid, yield 90%, mp 180–182 °C; IR (KBr): 2971, 1623, 1458, 1215, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.30 (bs, 1H), 7.52 (d, 2H, J = 7.8 Hz), 7.32 (d, 2H, J = 1.9 Hz), 4.8 (s, 1H), 3.05 (q, 1H, J = 7.4 Hz), 1.62 (d, 3H, J = 7.2 Hz); MS: m/z 163.4 (M^++1).

4a: Yellow solid, yield 78%, mp 189–191 °C; IR (KBr): 3289, 3059, 3015, 1674, 1580, 1445, 1235, 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 13.02 (s, 1H), 7.85 (d, 1H, J = 7.8 Hz), 7.52 (d, 1H, J = 7.6 Hz), 7.32 (t, 2H, J = 7.4 Hz), 2.74 (s, 3H); MS: m/z 161.3 (M^++1).

5a: Pale yellow solid, yield 69%, mp 162–164 °C; IR (KBr): 3276, 2856, 1589, 1487, 1238 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.11 (d, 3H, J = 12.8 Hz), 7.76 (dd, 3H, J = 2.8, 7.2 Hz), 7.43 (d, 2H, J = 12.9 Hz), 7.23 (dd, 2H, J = 2.4, 7.6 Hz), 6.90 (d, 1H, J = 13.1 Hz); MS: m/z 249.3 (M^++1).

6a: Colorless solid, yield 75%, mp 216–218 °C; IR (KBr): 3370, 3025, 2210, 1560, 1425, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.17 (s, 1H), 7.50 (dd, 2H, J = 9.3, 16.0 Hz), 7.40 (d, 2H, J = 11.5 Hz), 7.17 (d, 2H, J =11.8 Hz), 7.14 (dd, 2H, J = 9.2, 15.6 Hz), 7.12 (dd, 1H, J = 9.2, 15.8 Hz), 5.62 (d, 1H, J = 12.4 Hz), 3.89 (d, 2H, J = 12.9 Hz); MS: m/z 264.3 (M^++1).

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