

## Synthesis and antimicrobial activity of 2-imino-4-(benzimidazol-2'-yl)-6-aryl-6H-2,3-dihydro-1,3-thia/oxazines

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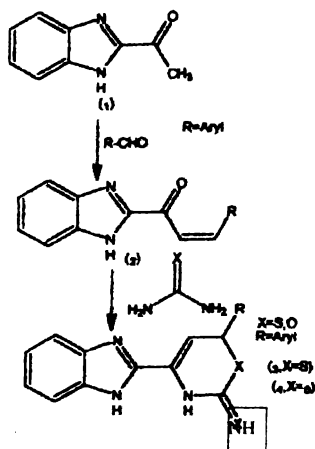
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Manuscript received 11 May 2001, revised 22 April 2002, accepted 17 August 2002

2-Acetylbenzimidazole (1) on condensation with various aldehydes yields the chalcones (2a-l) which on cyclization with thiourea/urea in alc. KOH furnish the corresponding 2-imino-4-(benzimidazol-2'-yl)-6-aryl-6H-2,3-dihydro-1,3-thiazines/1,3-oxazines (3a-l, 4a-l). The compounds have been evaluated for their antibacterial and antifungal activities.

Oxazines and thiazines<sup>1</sup> and benzimidazoles<sup>2</sup> possess various biological activities. These observation led us to synthesize some oxazine and thiazine derivatives bearing 2-acetylbenzimidazole moiety.

The basic nucleus 2-acetylbenzimidazole (1) was prepared by oxidation of hydroxyethylbenzimidazole with chromium trioxide. The reaction of 1 with different aryl aldehydes furnished the chalcone derivatives (2). The later (2) on cyclocondensation with thiourea/urea afforded thiazine/oxazine derivatives (3 and 4) (Scheme 1), respectively.



3,4 (a-l)

- |   |   |
|---|---|
| a C <sub>6</sub> H <sub>5</sub>                                       | 3i 3-CH <sub>3</sub> .C <sub>6</sub> H <sub>4</sub>                 |
| b 2-Cl.C <sub>6</sub> H <sub>4</sub>                                  | j 2-Cl.6-Br.C <sub>9</sub> H <sub>4</sub> N                         |
| c CH=CH.C <sub>6</sub> H <sub>5</sub>                                 | k 3-(OC <sub>6</sub> H <sub>5</sub> ).C <sub>6</sub> H <sub>4</sub> |
| d 3,4-(OCH <sub>3</sub> ) <sub>2</sub> .C <sub>6</sub> H <sub>3</sub> | l 4-Cl.C <sub>6</sub> H <sub>4</sub>                                |
| e 4-N(CH <sub>3</sub> ) <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>   | 4i 3-Br.C <sub>6</sub> H <sub>4</sub>                               |
| f 2-C <sub>4</sub> H <sub>9</sub> O                                   | j 3-Cl.C <sub>6</sub> H <sub>4</sub>                                |
| g 4-OCH <sub>3</sub> .C <sub>6</sub> H <sub>4</sub>                   | k 2-OCH <sub>3</sub> .C <sub>6</sub> H <sub>4</sub>                 |
| h 4-SCH <sub>3</sub> .C <sub>6</sub> H <sub>4</sub>                   | l 4-OH.C <sub>6</sub> H <sub>4</sub>                                |

Antibacterial activity was evaluated against *B. megaterium*, *E. coli*, *S. aureus* and *P. vulgaris* using ampicillin as standard. The presence of halogen at either 2, 3 or 4 position in 3b, 3c, 3d showed maximum activity towards *B.m* and *S.a*. The presence of methoxy at 4-position in 3l and 4k enhanced activity towards *E.c*. Compounds 3e, h, l and 4a, g, h, l showed maximum activity against *P.v*. 4a, e, g, j, l displayed highest activity against *B.m*. 3d, e, h, l and 4c, f, k, l exhibited significant activity against *B.m*, 3d, e, h, l and 4c, f, k, l exhibited significant activity against *A.n*. Antifungal activity was screened against *A. niger* using greseofulvin as standard. Compounds 3d, e, h, l and 4c, f, k, l showed significant activity.

### Experimental

All the m.ps. were determined in open capillary tubes and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer Spectrum GX spectrophotometer and <sup>1</sup>H NMR spectra (TFA) on Hitachi 1200 NMR CW (60 MHz) and Bruker (300 MHz) spectrophotometers using TMS as an internal reference.

**2-Acetylbenzimidazole (1)** : A solution of chromium trioxide (0.015 mol) in water (5 ml) was added dropwise to a solution of 2-1'-hydroxyethylbenzimidazole (0.02 mol) in a gl. acetic acid (15 ml) at 90°. The reaction mixture was heated at 100° for 5 min and then poured into ice-water and filtered. The filtrate was extracted with chloroform and the extract dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated. The residue was crystallized from benzene, (50%), m.p. 188–189°.

**3-(Benzimidazol-2'-yl)-1-aryl-1-propene-3-ones (2)** : A solution of 1 (0.01 mol) and 4-methoxybenzaldehyde (0.01 mol) in ethanol and 40% NaOH (2–3 drops) was stirred for 24 h at room temperature. The resulting solid was crystallized from ethanol to give 2 (R = 4-OCH<sub>3</sub>.C<sub>6</sub>H<sub>4</sub>; 68%), m.p.

## Note

225° (Found : C, 73.36; H, 5.03; N, 10.10.  $C_{17}H_{14}N_2O_2$  reqd. : C, 73.38; H, 5.03; N, 10.07%);  $\nu_{max}$  3435 (NH), 3050 (CH=CH), 1652 (C=O), 1516  $cm^{-1}$  (C=N);  $\delta$  (300 MHz) (TFA) 3.63 (3H, s, Ar-OCH<sub>3</sub>), 6.89 (2H, d, CH=CH), 7.60 (2H, d, ArH), 7.66 (2H, dd, benzimidazole(c,d)), 7.67 (2H, d, ArH(para)), 7.85 (2H, dd, benzimidazole(b,e)), 8.01 (1H, s, NH).

The other chalcones (**2**) were similarly derived from 2-acetylbenzimidazole and substituted aryl aldehydes.

**2-Iminothiazine-4-(benzimidazol-2'-yl)-6-aryl-6H-2,3-dihydro-1,3-thiazine/1,3-oxazines (3 and 4)** : A mixture of **2** (0.01 mol) and thiourea/urea (0.01 mol) in alc. KOH (15 ml) was refluxed for 10 h. It was then poured onto crushed ice and neutralized with conc. HCl. The resulting solid was crystallized from ethanol to furnish **3** and **4** : **3a** m.p. >290°, 0.69,  $\delta$  7.1–8.5 (ArH), 9.10–9.21 (s, NH); **3b** 275d, 0.65,  $\delta$  6.9–8.5 (ArH), 9.10–9.23 (s, NH); **3c** >290, 0.55,  $\delta$  6.2–8.2 (ArH + CH=CH), 9.12–9.18 (s, NH); **3d** >290, 0.39,  $\delta$  (s, OCH<sub>3</sub>), 4.0 (s, OCH<sub>3</sub>), 7.6–8.3 (ArH), 9.11–9.16 (s, NH); **3e** >290, 0.50,  $\delta$  3.4 (s, NCH<sub>3</sub>), 3.5 (s, NCH<sub>3</sub>), 7.0–8.2 (ArH), 9.13–9.18 (s, NH); **3f** >290, 0.40,  $\delta$  6.1–8.4 (ArH), 9.15–9.21 (s, NH); **3g** >290, 0.66,  $\delta$  3.9 (s, OCH<sub>3</sub>), 6.6–8.4 (ArH), 9.13–9.20 (s, NH); **3h** >290, 0.67,  $\delta$  2.5 (s, SCH<sub>3</sub>), 6.7–8.4 (ArH), 9.14–9.25 (s, NH); **3i** >290, 0.48,  $\delta$  2.3 (s, CH<sub>3</sub>), 6.5–8.2 (ArH), 9.12–9.18 (s, NH); **3j** >290, 0.45,  $\delta$

6.6–8.5 (ArH), 9.5–9.23 (s, NH); **3k** >290, 0.70,  $\delta$  7.3–8.5 (ArH), 9.12–9.20 (s, NH); **3l** >290, 0.65,  $\delta$  6.8–8.9 (ArH), 9.10–9.19 (s, NH).

**4a** m.p. >175°, 0.35,  $\delta$  7.51–7.82 (ArH), 9.0 (s, NH); **4b** 175, 0.48,  $\delta$  6.80–7.95 (ArH), 9.2 (s, NH); **4c** 128, 0.52,  $\delta$  6.75–8.00 (ArH + CH=CH), 9.2 (s, NH); **4d** 193,  $\delta$  4.0 (s, 6H), 7.6–8.2 (ArH), 9.2 (s, 1H); **4e** 195, 0.51,  $\delta$  3.5 (s, 6H), 6.90–7.89 (ArH), 9.2 (s, 1H); **4f** >280, 0.39,  $\delta$  6.9–7.9 (ArH), 9.1 (s, 1H); **4g** 220, 0.55,  $\delta$  4.0 (s, 3H), 7.0–8.3 (ArH), 9.2 (s, 1H); **4h** 128, 0.47,  $\delta$  2.55 (s, 3H), 6.9–8.5 (ArH), 9.2 (s, 1H); **4i** 182, 0.41,  $\delta$  7.67–8.21 (ArH), 9.1 (s, NH); **4j** 190, 0.32,  $\delta$  7.00–8.33 (ArH), 9.2 (s, NH); **4k** 195, 0.71,  $\delta$  4.0 (s, 3H), 7.1–8.2 (ArH), 9.2 (s, 1H); **4l** 110, 0.45,  $\delta$  7.0–7.93 (ArH), 9.1 (s, 1H).

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