

## Synthesis of mandelic acid derived phthalimides as a new class of anti-inflammatory and antimicrobial agents<sup>†</sup>

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Received 22 August 2007; accepted (revised) 8 April 2008

In the present study, a new series of 2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl) ethyl 2-hydroxy-2-(substituted phenyl) acetates **6a-e** have been synthesized from the combination of *N*-(2-hydroxy ethyl) phthalimide **5** and substituted mandelic acids **2a-e** which resulted in both anti-inflammatory and antimicrobial activity. These compounds have been characterized by IR, <sup>1</sup>H NMR, mass spectral and elemental analysis. Among the compounds tested for anti-inflammatory activity, compound **6b** and **6c** showed significant activity and compound **6d** showed potent antibacterial and antifungal activity. The anti-inflammatory activity has been determined by carrageenan induced acute paw oedema in rats. The results are discussed in the text. The *in vitro* antibacterial and antifungal activity of the compounds have been evaluated by paper disc diffusion method. The minimum inhibitory concentrations (MIC) of the compounds have also been determined by agar streak dilution method.

**Keywords:** Phthalimides, mandelic acids, antimicrobial and anti-inflammatory activity

Aromatic hydroxy acids and its derivatives or constituents thereof are important biologically active compounds and display a range of physiological effects. One such example is the application of mandelic acids in the production of  $\beta$ -lactam antibiotics<sup>1</sup>. A vast literature exists in which it is revealed that mandelic acid and its derivatives showed anti-oxidant<sup>2</sup>, urinary antiseptic<sup>3</sup>, anti-HIV<sup>4</sup>, anti-tumor<sup>5</sup>, antifungal<sup>6</sup>, anti-thrombic effects<sup>7</sup>. Among heterocyclic scaffolds, phthalimides are also of particular interest and have been reported as anti-psychotics<sup>8</sup>, anti-inflammatory agents<sup>9</sup>, herbicides<sup>10</sup>, and insecticides<sup>11</sup>. Phthalimide derivatives with phenyl acetic acid and phenyl propionic acid were found to possess anti-inflammatory and analgesic properties<sup>12</sup>.

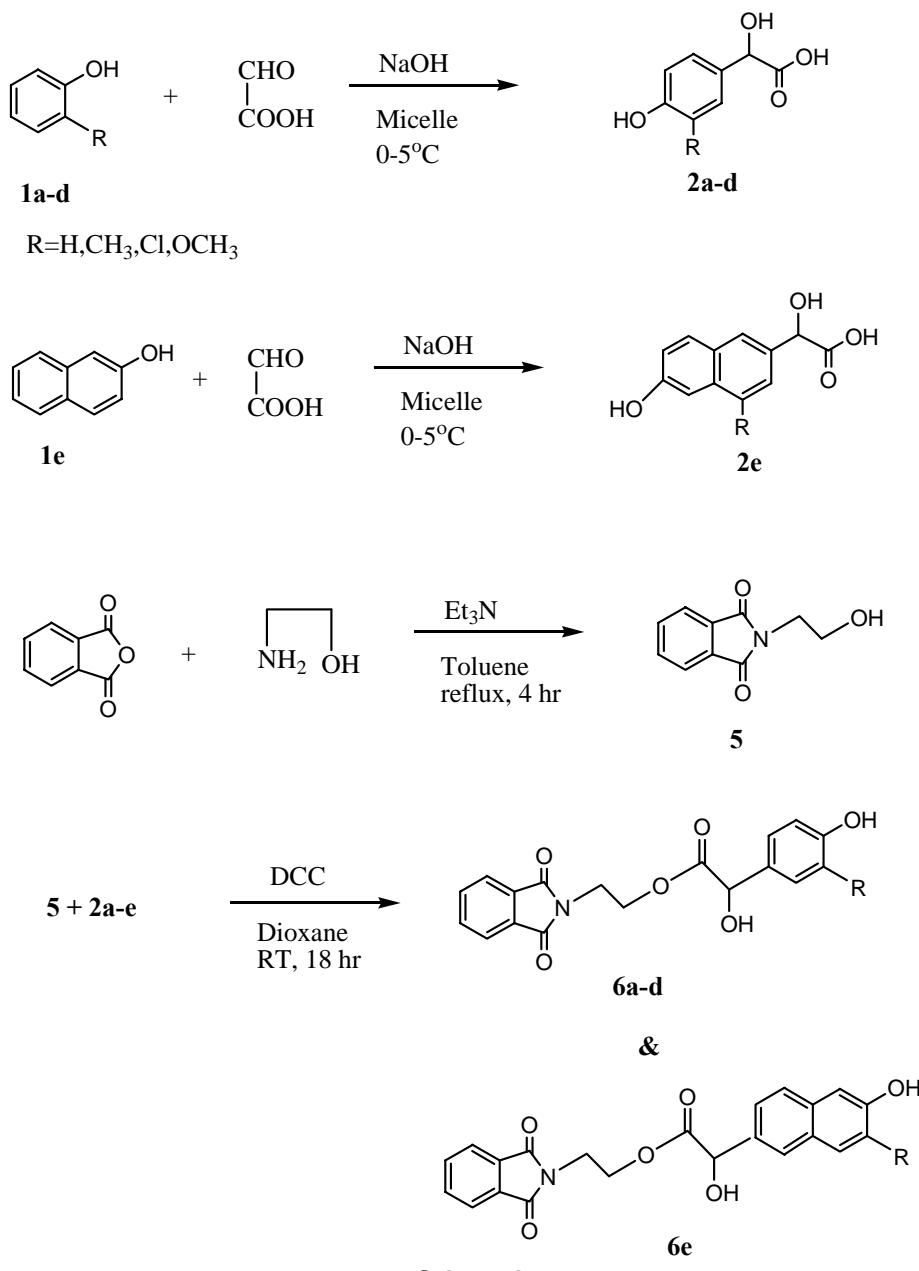
In continuation of the recent studies in synthesis of biologically active heterocycles<sup>13</sup>, it was therefore envisaged that a new series of 2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl) ethyl 2-hydroxy-2-(substituted) acetate resulting from the combination of *N*-(2-hydroxy ethyl) phthalimide **5**

and substituted mandelic acids **2a-e**, would result in compounds with potent antimicrobial and anti-inflammatory activity.

In the present study, substituted mandelic acids **2a-e** (**Scheme I**) were prepared by reacting a mixture of NaOH solution, corresponding substituted phenols and glyoxalic acid in the presence of a phase transfer catalyst (CTAB). *N*-(2-hydroxy ethyl) phthalimide **5** was prepared by treatment of phthalic anhydride with ethanolamine and triethyl amine in toluene. Compound **5** was allowed to condense with the above prepared substituted mandelic acids **2a-e** in the presence of dioxane/water to obtain the desired new series of 2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl) ethyl 2-hydroxy-2-(substituted) acetate **6a-e**.

The *in vitro* antibacterial (*Staphylococcus aureus* ATCC 9144, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 29665) and antifungal (*Candida albicans* ATCC 2091 and *Aspergillus niger* ATCC 9029) activity of the compounds were evaluated by paper disc diffusion method. The minimum inhibitory concentrations (MIC) of the compounds were also determined by agar streak dilution method (**Table I**).

<sup>†</sup> IICT Communication No. 070613

**Scheme I**

The *in vivo* anti-inflammatory activity of the synthesized compounds **6a-e** (Table II) was evaluated by carrageenan induced acute paw oedema in rats taking carrageenan as control and indomethacin as standard.

### Results and Discussion

All the compounds exhibited significant anti-inflammatory activity. Among the five compounds **6b** and **6c** at 200 mg/kg (p.o.) showed significant reduction in paw oedema, when compared to the compound **6a**, **6d** and **6e**. The compound **6b** and **6c**

showed 70% protection, compound **6d** showed 65% and compound **6a** and **6e** showed 60% protection. The standard indomethacin showed 75% protection. The compounds did not cause mortality up to 2000 mg/kg in acute oral toxicity studies (OECD-423 guidelines) and were considered as safe (X-unclassified). Moreover, all the compounds exhibited moderately potent antibacterial and antifungal activity. The compounds were active against all the tested micro-organisms compared to ciprofloxacin as standard and with MIC values of 30-35  $\mu$ g, 32-36  $\mu$ g, 32-35  $\mu$ g, 31-34  $\mu$ g, 15-35  $\mu$ g and 30-34  $\mu$ g against *S. aureus*, *B.*

**Table I** — Antimicrobial activity of the synthesized compounds **6a-e**  
*In vitro* activity Zone of inhibition (MIC)

	<i>B. cereus</i> (ATCC9144)	<i>S. aureus</i> (ATCC11778)	<i>K. pneumoniae</i> (ATCC25922)	<i>E. coli</i> (ATCC29665)	<i>C. albicans</i> (ATCC2091)	<i>A. niger</i> (ATCC9029)
<b>6a</b>	24(25)	24(25)	24(34)	25(34)	24(34)	17(33)
<b>6b</b>	27(26)	25(35)	26(32)	25(35)	25(33)	16(34)
<b>6c</b>	25(24)	23(33)	27(31)	28(35)	25(33)	16(35)
<b>6d</b>	32(22)	30(31)	28(31)	32(32)	28(30)	20(15)
<b>6e</b>	26(24)	25(30)	26(32)	26(33)	26(32)	18(15)
<b>Ciprofloxacin</b>	35(1.2) (-100 µg/disc)	32(1.4)	33(0.9)	36(1.2)	-	
<b>Ketaconazole</b>	-	-	-	-	-	33(2.2) (100 µg/disc)
						20(8.9)
Zone of inhibition in mm, MIC in µg mL <sup>-1</sup>						

**Table II** — Anti-inflammatory activity of the synthesized compounds **6a-e**  
*Carrageenan induced Paw Oedema*

Group	1 hr	2 hr	3 hr	4 hr	5 hr
Group I Control 1% CMC (1 ml/kg)	0.18 ± 0.003	0.26 ± 0.006	0.32 ± 0.005	0.36 ± 0.004	0.42 ± 0.005
Group II Compound – <b>6a</b> (200 mg/kg)	0.17 ± 0.003** (5.55%)	0.22 ± 0.007** (15.38%)	0.21 ± 0.003** (34.37%)	0.18 ± 0.005*** (50%)	0.16 ± 0.007*** (60%)
Group III Compound – <b>6b</b> (200 mg/kg)	0.17 ± 0.004** (5.55%)	0.21 ± 0.004** (19.53%)	0.18 ± 0.004*** (43.75%)	0.15 ± 0.006*** (58.33%)	0.12 ± 0.004*** (70%)
Group IV Compound – <b>6c</b> (200 mg/kg)	0.15 ± 0.002** (16.66%)	0.19 ± 0.007** (26.92%)	0.21 ± 0.003*** (50%)	0.13 ± 0.004*** (63.88%)	0.12 ± 0.004*** (70%)
Group V Compound – <b>6d</b> (200 mg/kg)	0.15 ± 0.004** (16.66%)	0.19 ± 0.004** (26.92%)	0.21 ± 0.004** (34.37%)	0.20 ± 0.003*** (44.44%)	0.16 ± 0.003*** (65%)
Group VI Compound – <b>6e</b> (200 mg/kg)	0.16 ± 0.004** (15.38%)	0.20 ± 0.003** (24.73%)	0.21 ± 0.004*** (38.54%)	0.15 ± 0.005*** (47.56%)	0.16 ± 0.004*** (60%)
Group VII Standard Indomethacin (20 mg/kg)	0.17 ± 0.003*** (5.55%)	0.19 ± 0.007*** (26.92%)	0.16 ± 0.005*** (50%)	0.1 ± 0.003*** (66.66%)	0.14 ± 0.002*** (75%)

All values are mean ± SEM values using 6 animals in each group.

Significant differences with respect to control group was evaluated by ANOVA, Dunnets 't' test. \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001.

$$\text{Percentage protection} = \frac{\text{control} - \text{test}}{\text{Control}} \times 100$$

The data are presented in the **Table II**.

*cereus*, *E. coli*, *K. pneumoniae*, *A. niger* and *C. albicans* respectively. Among the compounds **6d** showed potent antimicrobial activity.

### Experimental Section

The melting points were determined in open capillary tubes and are uncorrected. The IR spectra of the compounds were recorded on ABB Bomem FTIR spectrometer MB104 in KBr pellets. <sup>1</sup>H NMR spectra were recorded on 300 MHz Bruker DPX 200 spectrometer. The chemical shifts are reported in parts per million downfield from tetramethyl silane. Mass spectra were recorded on Shimadzu QP 5000 GC-MS.

Microanalyses for C, H, N were performed in Heraeus CHN Rapid Analyzer. All the compounds gave satisfactory chemical analyses (±0.4%). The homogeneity of the compounds was checked by TLC on aluminium foil backed precoated SiO<sub>2</sub> gel (HF254, 200 mesh) plates (E Merck) using *n*-hexane:ethyl acetate (8:2) as mobile phase and visualized by iodine vapors.

### General procedure for the synthesis of substituted mandelic acids, **2a-e**

To a mixture of 50 mL of NaOH solution (4 g, 100 mmol), substituted phenol (8.7 mL, 100 mmol) and

cetyl trimethyl ammonium bromide (CTAB – phase transfer catalyst) (2 mL, 0.005 mmol solution), glyoxalic acid (5.5 mL, 100 mmol) was added dropwise from an addition funnel for 1 hr at 0-5°C. The stirring was continued for 4-5 hr. Completion of the reaction was confirmed by TLC. The reaction mixture was acidified with HCl to pH 6 and extracted into benzene. The aqueous layer was further acidified by HCl to pH 2, saturated with brine solution and extracted into ethyl acetate, dried over anhydrous sodium sulphate and evaporated under reduced pressure. The obtained products **2a-e** were purified by recrystallization from benzene.

#### **2-(4'-Hydroxyphenyl)-2-hydroxyethanoic acid, 2a**

Off-white solid, Yield: 90%. m.p. 102-04°C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 3.65 (s, 1H, CHOH), 4.9 (s, 1H, CHOH), 6.61-6.78 (m, 2H, aromatic), 7.13-7.28 (m, 2H, aromatic), 7.82 (br s, 1H, OH Ar); IR (KBr): 3428, 3280, 2975, 1725 cm<sup>-1</sup>; MS: *m/z* (%) 168 (M<sup>+</sup>) (20), 123 (100), 95 (50), 77 (60). Anal. Calcd. C, 57.15; H, 4.80; O, 38.06; (for C<sub>8</sub>H<sub>8</sub>O<sub>4</sub>). Found C, 57.02; H, 4.92; O, 38.14%.

#### **2-(3'-Chloro-4'-hydroxyphenyl)-2-hydroxyethanoic acid, 2b**

Off-white solid, Yield: 85%, m.p. 119-22°C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.6 (s, 1H, CHOH), 4.9 (s, 1H, CHOH), 6.6-7.2 (m, 3H, aromatic), 9.0 (br, 1H, COOH); IR (KBr): 1720, 3285 cm<sup>-1</sup>; MS: *m/z* (%) 202 (M<sup>+</sup>) (10), 57 (70), 128 (30), 93 (20). Anal. Calcd. C, 47.43; H, 3.48; Cl, 17.50; O, 31.59; (for C<sub>8</sub>H<sub>7</sub>ClO<sub>4</sub>). Found C, 47.14; H, 3.56; Cl, 17.32; O, 31.78%.

#### **2-(3'-Methyl-4'-hydroxyphenyl)-2-hydroxyethanoic acid, 2c**

Off-white solid, Yield: 75%. m.p. 78-80°C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.15 (s, 3H, CH<sub>3</sub>), 4.86 (s, 1H, CHOH), 5.2 (s, 1H, OH), 6.68-7.069 (m, 3H, aromatic), 7.63 (br s, 1H, OH), 8.706 (1H, COOH); IR (KBr): 3378, 3280, 1750 cm<sup>-1</sup>; MS: *m/z* (%) 182 (M<sup>+</sup>) (25), 138 (100), 110 (20), 91 (35). Anal. Calcd. C 59.34, H 5.53, O 35.13 (for C<sub>9</sub>H<sub>10</sub>O<sub>4</sub>). Found C, 59.18; H, 5.60; O, 35.21%.

#### **2-(6'-Hydroxynaphthyl)-2-hydroxyethanoic acid, 2d**

Light yellow solid, Yield: 62%. m.p. 116-18°C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 5.56 (s, 1H, CHOH), 5.95 (br

s, 1H, OH), 7.10-8.12 (m, 6 H), 9.6 (br s, 1H, COOH); IR (KBr): 3395, 3238, 1727 cm<sup>-1</sup>; MS: *m/z* (%) 218 (M<sup>+</sup>) (40), 173 (100), 144 (45), 127 (90). Anal. Calcd. C, 66.05; H, 4.62; O, 29.33 (for C<sub>12</sub>H<sub>10</sub>O<sub>4</sub>). Found C, 66.23; H, 4.80; O, 29.08%.

#### **2-Hydroxy-2-(4-hydroxy-3-methoxyphenyl)acetic acid, 2e**

Off-white solid, Yield: 65%. m.p. 121-23°C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 3.84 (s, 1H, OCH<sub>3</sub>), 4.92 (1H, CHOH), 5.25 (br s, 1H, OH), 6.72-6.93 (m, 3H, aromatic), 9.9 (br, 1H, COOH); IR (KBr): 3365, 3240, 1720 cm<sup>-1</sup>; MS: *m/z* (%) 198. Anal. Calcd. C, 54.55; H, 5.09; O, 40.37 (for C<sub>9</sub>H<sub>10</sub>O<sub>5</sub>). Found C, 54.43; H, 5.18; O, 39.98%.

#### **General procedure for the synthesis of N-(2-hydroxy ethyl)phthalimide 5**

A mixture of phthalic anhydride (7.0 g, 42.29 mmol) and ethanolamine (3.75 g, 42.42 mmol) and triethyl amine (0.7 mmol) in toluene (500 mL) was heated under reflux for 4 hr and azeotropic removal of water using Dean-Stark apparatus. The reaction mixture was then concentrated under reduced pressure. Ethyl acetate was added to the residue and the organic phase was washed with 1*N* HCl solution (20 mL) to eliminate the unreacted triethylamine, dried over anhydrous MgSO<sub>4</sub> and concentrated to yield the *N*-(2-hydroxy ethyl)phthalimide **5** as a white crystalline solid.

#### **2-(2-Hydroxyethyl)-1,3-isoindolinedione, 5**

Yield: 95%, white crystalline solid. m.p. 126-28°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.96-8.00 (m, 2H), 8.05-8.08 (m, 2H), 3.87-3.98 (m, 4H); IR (KBr): 3472, 1767, 1697, 1428, 1057, 725 cm<sup>-1</sup>; EI-MS: *m/z* (M<sup>+</sup>) 191, 160, 148, 105, 77. Anal. Calcd. C, 62.82; H, 4.74; N, 7.33; O, 25.11 (for C<sub>10</sub>H<sub>9</sub>NO<sub>3</sub>). Found C, 61.98; H, 4.86; N, 7.40; O, 25.03%.

#### **General method of synthesis 6a-e**

A mixture of substituted mandelic acid (3.5 g, 20 mmol) and *N*-(2-hydroxy ethyl) phthalimide (4.0 g, 20 mmol) in 1,4-dioxan (20 mL) were taken in a round bottomed flask under nitrogen. *N,N*-dicyclohexyl carbodiimide (4.5 g, 20 mmol) was added to the mixture at RT and the mixture was stirred at that temperature for 48 hr. The by-product was precipitated out and then filtered. The filtrate thus obtained was extracted with chloroform. The

combined layer was concentrated on a rotary thin film evaporator under reduced pressure. The obtained product was purified by recrystallization from ethyl acetate, and formation of the desired product was confirmed by TLC (**Scheme I**).

**2-(1,3-Dioxo-2,3-dihydro-1*H*-2-isoindolyl) ethyl 2-hydroxy-2-(4-hydroxy phenyl) acetate, 6a:** Yield: 62%. m.p. 104-06°C.  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.98 (t, 2H, CH<sub>2</sub>), 4.12 (t, 2H), 4.91 (s, 1H, CHOH), 6.65-7.32 (m, 4H), 7.98-8.01 (m, 2H), 8.12-8.20 (m, 2H); IR (KBr): 3418, 3263, 2857, 1767, 1682, 759  $\text{cm}^{-1}$ ; MS:  $m/z$  (%) 341, 248, 211, 160, 148, 104, 77, 45. Anal. Calcd. C, 63.34; H, 4.43; N, 4.10; O, 28.12 (for C<sub>18</sub>H<sub>15</sub>NO<sub>6</sub>). Found C, 63.18; H, 4.52; N, 3.98; O, 28.03%.

**2-(1,3-Dioxo-2,3-dihydro-1*H*-2-isoindolyl) ethyl 2-(3-chloro-4-hydroxyphenyl)-2-hydroxy acetate, 6b:** Yield: 60%. m.p. 108-10°C.  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.08 (s, 1H, CHOH), 4.02 (t, 2H, CH<sub>2</sub>), 4.16 (t, 2H); 5.20 (s, 1H, CHOH), 6.68-7.23 (m, 3H), 7.98-8.10 (m, 2H), 8.15-8.22 (m, 2H); IR (KBr): 3426, 3287, 2857, 1760, 1694, 759, 793  $\text{cm}^{-1}$ ; MS:  $m/z$  (%) 375, 341, 281, 241, 207, 174, 147, 107, 73, 55. Anal. Calcd. C, 57.54; H, 3.76; Cl, 9.43; N, 3.73; O, 25.55 (for C<sub>18</sub>H<sub>14</sub>ClNO<sub>6</sub>). Found C, 57.60; H, 3.80; Cl, 9.28; N, 3.79; O, 24.98%.

**2-(1,3-Dioxo-2,3-dihydro-1*H*-2-isoindolyl) ethyl 2-hydroxy-2-(4-hydroxy-3-methyl phenyl) acetate, 6c:** Yield: 58%. m.p. 116-18°C.  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.14 (s, 3H), 3.94 (t, 2H, CH<sub>2</sub>), 4.07 (t, 2H, CH<sub>2</sub>), 4.90 (s, 1H, CHOH), 6.68-7.10 (m, 3H) 8.00-8.20 (m, 4H); IR (KBr): 3470, 3365, 2855, 1781, 1713, 755  $\text{cm}^{-1}$ ; MS:  $m/z$  (%) 339. Anal. Calcd. C, 67.25; H, 5.05; N, 4.13; O, 23.57 (for C<sub>19</sub>H<sub>17</sub>NO<sub>5</sub>). Found C, 67.32; H, 5.10; N, 4.08; O, 23.70%.

**2-(1,3-Dioxo-2,3-dihydro-1*H*-2-isoindolyl)ethyl 2-hydroxy-2-(6-hydroxy-2-naphthyl) acetate 6d:** Yield: 67%. m.p. 106-08°C.  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.01 (t, 2H, CH<sub>2</sub>), 4.22 (t, 2H, CH<sub>2</sub>), 5.60 (s, 1H, CHOH), 6.12 (br s, 1H, CHOH), 7.12-7.18 (m, 3H), 7.86-8.02 (m, 2H), 8.13-8.25 (m, 2H); IR (KBr): 3471, 3360, 2859, 1780, 1703, 755  $\text{cm}^{-1}$ ; MS:  $m/z$  (%) 391, 226, 154, 136, 107, 98, 77, 51. Anal. Calcd. C, 61.46; H, 4.61; N, 3.77; O, 30.16 (for C<sub>22</sub>H<sub>17</sub>NO<sub>6</sub>). Found C, 61.23; H, 4.72; N, 3.94; O, 29.82%.

**2-(1,3-Dioxo-2,3-dihydro-1*H*-2-isoindolyl) ethyl 2-hydroxy-2-(4-hydroxy-3-methoxyphenyl) ace-**

**tate, 6e:** Yield: 55%. M.p. 123-25°C.  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.84 (s, 3H), 3.97 (t, 2H, CH<sub>2</sub>), 4.09 (t, 2H), 5.30 (br s, 1H, CHOH), 6.72-7.01 (m, 3H), 7.98-8.22 (m, 4H); IR (KBr): 755, 1703, 2855, 3471  $\text{cm}^{-1}$ ; MS:  $m/z$  (%) 355. Anal. Calcd. C, 64.22; H, 4.82; N, 3.94; O, 27.01 (for C<sub>19</sub>H<sub>17</sub>NO<sub>7</sub>). Found C, 64.08; H, 4.95; N, 3.75; O, 27.23%.

### *In vitro* Antimicrobial Activity

All the synthesized compounds were tested for their antimicrobial activity against two Gram +ve (*S. aureus* and *B. cereus*), two Gram -ve (*E. coli* and *K. pneumoniae*) bacteria and two fungal strains (*C. albicans* and *A. niger*) at a concentration of 200  $\mu\text{g}/\text{mL}$  using paper disc diffusion method<sup>14</sup>. Ciproflaxacin (100  $\mu\text{g}/\text{disc}$ ) was used as reference standard for antibacterial activity and Ketoconazole (100  $\mu\text{g}/\text{disc}$ ) was used as reference standard for antifungal activity. Compound **6d** showed potent antimicrobial activity when compared to all the synthesized compounds. Minimum Inhibitory Concentrations (MIC) of the test compounds were determined by agar streak dilution method<sup>15</sup>. The observed MIC values for all the synthesized compounds are presented in **Table I**.

### Pharmacology

The synthesized compounds were evaluated for anti-inflammatory activity by using carrageenan induced acute paw oedema method. Acute oral toxicity tests were performed for all the synthesized compounds as per organization of economic co-operation and development (OECD) guidelines. Statistical analysis (ANOVA followed by Dunnett's test) was performed for anti-inflammatory activity to ascertain the significance of the exhibited activity. The test compounds and the standard drugs were administered in the form of a suspension (1% w/v of Tween-80 as vehicle). Inbred Wistar rats weighing 150-250 g were used. Acute oral toxicity<sup>16</sup> was determined as per OECD guidelines (acute toxic class method).

### Anti-inflammatory Activity

The anti-inflammatory activity<sup>17</sup> was determined by carrageenan-induced acute paw oedema in rats. Wistar rats of either sex selected by random sampling technique were used for the study. Indomethacin 20 mg/kg was administered as standard drug for

comparison. The test compounds were administered orally by intragastric tube. After half an hour of administration of test compounds, 0.1 mL of carrageenan was injected into the lateral malleolus of the sub plantar region of the left hind paw. The inflammation of the paw was measured for all the animals by using Plathysmograph before the administration of the carrageenan and after the administration of the carrageenan at 60, 120, 180, 240 and 300 min. The percentage protection of the compounds was calculated as follows (**Table II**).

The observed MIC is presented in **Table I**.

### Acknowledgements

R. Varala and M. M. Alam are thankful to the Director, IICT Hyderabad, Dr. J. S. Yadav and also to CSIR, India for the award of fellowship.

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