

Synthesis and biological evaluation of 3-(phthalimidoethyl)-4-substituted cinnamoyl substituted benzanilides

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Abstract : 3-Phthalimidoethyl substituted benzoic acids (2) were prepared by refluxing *N*-hydroxyethyl phthalimide (1) with substituted benzoic acids. The corresponding acid chlorides (3) were condensed with 4-aminoacetophenone in anhydrous potassium carbonate to give 3-phthalimidoethyl-4-acetyl substituted benzanilides (4). The substituted benzanilide derivatives (4) were condensed with diverse aryl aldehydes to afford the title compounds (5). Compounds (5) were screened for their possible hypoglycemic and *in vitro* antibacterial activities.

Keywords : Benzanilides, hypoglycemic activity, antibacterial activity.

The phthalimide compounds and their derivatives are reported to show diverse biological activities^{1,2}. In continuation of our earlier work³, we report herein the synthesis of a series of new phthalimide compounds and evaluation of their possible hypoglycemic and *in vitro* antibacterial activities.

Results and discussion

The Na CMC suspension of title compounds were shown to produce reduction in the blood glucose concentration between 8 h of administration in two methods, normoglycemic rats⁴ and alloxan induced hyperglycemic rats⁵ at tested dose of 250 mg/kg of body weight. When compared with reference glibenclamide administered at a dose of 2.5 mg/kg, the compounds **5a₂**, **a₄**, **a₅**, **b₂** and **b₅** exhibited moderate hypoglycemic activity.

The antibacterial activity of the title compounds were determined by agar cup-plate method⁶. Among the compounds, **5b₂**, **b₄** and **b₅** were found to be most active against all the tested strains i.e. *Staphylococcus aureus*, *Actinomyces pyogenus*, *Escherichia coli* and *Klebsiella aerogenus*. However, all the rest compounds were less active in comparison to ampicillin trihydrate which was taken as the standard drug.

Experimental

Melting points were determined in open capillaries

and were uncorrected. Purity of the compounds were checked by TLC. IR spectra (KBr) were recorded on a Jasco FT/IR 410 spectrophotometer (ν_{\max} in cm^{-1}). ¹H NMR (CDCl_3) on a Bruker DPX-300 MHz spectrometer using TMS as internal reference (chemical shift in δ ppm). C, H and N analyses were carried out on a Euro EA (Italy) analyzer.

N-Hydroxyethylphthalimide (1) : About (0.12 mol, 19.1 g) of phthalic anhydride and 2-amino ethanol (0.12 mol, 7.32 ml) were heated together in an oil bath at 100° for 2 h. Subsequently the content was cooled and dilute HCl (50 ml) was added slowly with constant stirring. A white mass was separated out which was crystallized from ethanol (70%), m.p. 135° (Found : C, 62.53; H, 5.2; N, 7.5. $\text{C}_{10}\text{H}_9\text{NO}_3$ calcd. for : C, 62.82; H, 4.71; N, 7.32%); ν_{\max} 3447 (OH stretching), 3058 (C-H stretching), 1776 (C=O cyclic), 1607 (aromatic hydrocarbon), 1426 cm^{-1} (C-N stretching in primary aromatic ring); δ 4.3 (2H, t, CH₂), 4.5 (2H, t, CH₂), 5.1 (1H, broaden, OH), 7.2-8.3 (4H, m, ArH).

3-Phthalimidoethyl substituted benzoic acids (2) : To a solution of substituted benzoic acids (0.04 mol) dissolved in ethanol (50 ml) was added with a hot solution of compound 1 (0.04 mol) in ethanol (50 ml) slowly with constant stirring followed by concentrated HCl (5 drops) and the mixture was kept under reflux on a water-bath for 4 h. On cooling, the separated solid was dried and

crystallized from acetone **2a** (63%), m.p.120° (Found : C, 64.51; H, 4.18; N, 3.89. C₁₉H₁₅NO₆ calcd. for : C, 64.58; H, 4.24; N, 3.96%); ν_{\max} 3045 (C-H stretching), 1779, 1767 (amide carbonyl), 1697 (-COOH stretching), 1606 (aromatic hydrocarbon), 1428 cm⁻¹ (C-N stretch-

ing in primary aromatic ring); δ 2.1 (3H, s, -C-CH₃), 4.2 (2H, t, CH₂), 4.3 (2H, t, CH₂), 7.0-8.1 (7H, m, ArH), 12.2 (1H, s, COOH); **2b** (64%), m.p. 118 °C (Found : C, 54.19; H, 3.31; N, 3.86. C₁₆H₁₂NO₄Br calcd. for : C, 54.39; H, 3.39; N, 3.96%).

3-Phthalimidoethyl substituted benzoyl chlorides (3) : A mixture of compound **2** (8 g) and thionyl chloride (6 ml) in dry benzene was refluxed on a water-bath for 2.5 h under anhydrous condition. The solvent was then removed under reduced pressure to yield the compounds, **3a** (61%), m.p. 125° (Found : C, 61.33; H, 3.72; N, 3.72. C₁₉H₁₄NO₅Cl calcd. for : C, 61.37; H, 3.76; N, 3.76%); ν_{\max} 3045 (C-H stretching), 1768, 1698 (amide carbonyl), 1606 (aromatic hydrocarbon), 1428 cm⁻¹ (C-N stretching in primary aromatic ring); δ 2.0 (3H, s,

-C-CH₃), 4.1 (2H, t, CH₂), 4.3 (2H, t, CH₂), 7.1-8.3 (7H, m, ArH); **3b** (60%), m.p. 124° (Found : C, 53.12; H, 2.81; N, 3.65. C₁₇H₁₁NO₃BrCl calcd. for : C, 53.19; H, 2.86; N, 3.63%).

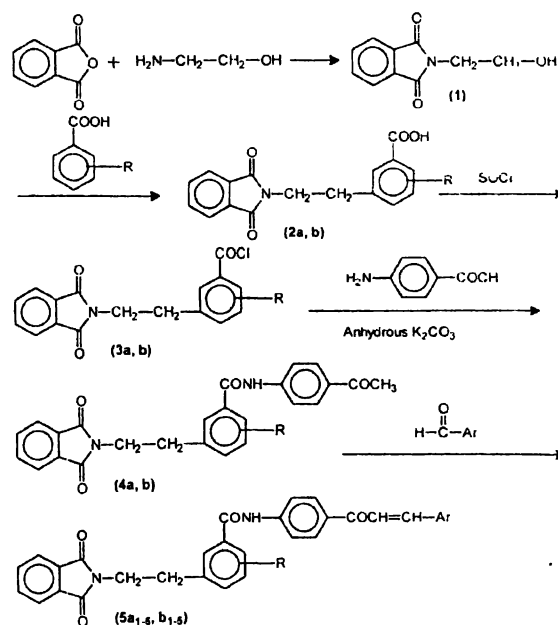
3-Phthalimidoethyl-4-acetyl substituted benzanilides (4) : A mixture of compound **3** (0.2 mol), 4-aminoacetophenone (0.2 mol) and anhydrous K₂CO₃ (2.2 g) in carbon tetrachloride (100 ml) was refluxed for 4 h on a water-bath under anhydrous condition. The solvent was distilled off and the separated solid was crystallized from ethanol, **4a** (65%), m.p. 110° (Found : C, 68.89; H, 4.60; N, 5.71. C₂₇H₂₂N₂O₆ calcd. for : C, 68.93; H, 4.68; N, 5.95%); ν_{\max} 3335 (N-H stretching), 3027 (C-H stretching), 1768, 1698 (amide carbonyl), 1593 (aromatic hydrocarbon), 1429 cm⁻¹ (C-N stretching in pri-

mary aromatic ring); δ 2.1 (3H, s, -C-CH₃), 4.2 (2H, t, CH₂), 4.4 (2H, t, CH₂), 5.7 (1H, s, NH), 7.1-8.2 (11H, m, ArH); **4b** (69%), m.p. 108° (Found : C, 62.20; H, 3.91; N, 5.78. C₂₅H₁₉N₂O₄Br calcd. for : C, 62.24; H, 3.94; N, 5.80%).

3-(Phthalimidoethyl)-4-substituted cinnamoyl substituted benzanilides (5) : To compound **4** (0.1 mol) dissolved in absolute ethanol (50 ml) was added a solution

of aryl aldehydes (0.1 mol) in ethanol (50 ml) followed by triethylamine (2 ml). The reaction mixture was refluxed on a water-bath for about 5 h, ethanol was distilled off and the crude residue was treated with petroleum ether (60-80°). The product was crystallized from acetone (yields 61-73%); **5a₁**, m.p.169°; **a₂**, 179°; **a₃**, 180°; **a₄**, 186°; **a₅**, 177°; **b₁**, 167°; **b₂**, 158°; **b₃**, 171°; **b₄**, 173°; **b₅**, 169°; **5a₃** (Found : C, 71.03; H, 4.51; N, 4.83. C₃₄H₂₆N₂O₇ calcd. for : C, 71.08; H, 4.52; N, 4.87%); ν_{\max} 1777 (C=O acyclic), 1663 (aromatic hydrocarbon), 1429 (C-N stretching in primary aromatic ring), 755 cm⁻¹ (monosubstituted benzene); δ 7.8 (1H,

d, CH), 7.9 (1H, d, CH), 2.1 (3H, s, -C-CH₃), 4.3 (2H, t, CH₂), 4.4 (2H, t, CH₂), 5.8 (1H, s, NH), 6.6-8.6 (15H, m, ArH); **5a₅** (Found : C, 70.02; H, 4.33; N, 5.01. C₃₂H₂₄N₂O₇ calcd. for : C, 70.07; H, 4.37; N, 5.10%); ν_{\max} 1775 (C=O acyclic), 1677 (aromatic hydrocarbon), 1393 (C-N stretching in primary aromatic ring), 756 cm⁻¹ (monosubstituted benzene); **5b₁** (Found : C, 67.27; H, 4.00; N, 4.93. C₃₂H₂₃N₂O₄Br calcd. for :



2,3,4,5a: R = 2-OCOCH₃

b, R = 4-Br

5a₁, b₁: Ar = Phenyl

a₂, b₂: Ar = 4-OCH₃ Phenyl

a₃, b₃: Ar = 2-OH Phenyl

a₄, b₄: Ar = 4-N(CH₃)₂ Phenyl

a₅, b₅: Ar = 2-Furyl

C, 67.36; H, 4.03; N, 4.91%); ν_{\max} 1776 (C=O acyclic), 1652 (aromatic hydrocarbon), 1359 (C-N stretching in primary aromatic ring), 752 cm^{-1} (monosubstituted benzene); **5b₂** (Found : C, 66.09; H, 4.06; N, 4.69. $\text{C}_{33}\text{H}_{25}\text{N}_2\text{O}_5\text{Br}$ calcd. for : C, 66.0; H, 4.16; N, 4.66%); ν_{\max} 1773 (amide carbonyl), 1659 (aromatic hydrocarbon), 1359 (C-N stretching in primary aromatic ring), 721 (monosubstituted benzene), 563 cm^{-1} (C-Br stretching); δ 7.7 (1H, d, CH), 7.8 (1H, d, CH), 3.6 (3H, s, OCH_3), 4.1 (2H, t, CH_2), 4.5 (2H, t, CH_2), 5.6 (1H, s, NH), 7.2-7.8 (15H, m, ArH).

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References

1. D. Bhatta, K. P. Satpathy and M. Swain, *J. Indian Chem. Soc.*, 1996, **73**, 616.
2. M. Patra and B. Dash, *J. Indian Chem. Soc.*, 1978, **55**, 587.
3. S. K. Sahu, S. K. Mishra, S. P. Mohapatra, D. Bhatta and C. S. Panda, *J. Indian Chem. Soc.*, 2004, **81**, 258.
4. M. Perfumi and R. Tacconi, *J. Int. Pharmacy*, 1996, **34**, 41.
5. P. T. C. Ponnachan, C. S. Paulose and K. R. Panikkar, *Indian J. Expt. Biol.*, 1993, **32**, 345.
6. Anonymous, "British Pharmacopoeia", University Press, Cambridge, London, 1953.