

SYNTHESIS OF BENZIMIDAZOLE-ISATIN DERIVATIVES FOR ANALGESIC ACTIVITY

SURESH.S*, BLESSI PRIYANKA.K, MAHARAJ.P, SRIKANTH.CH, KARTHIK.K, SAMMAIAH.G.

University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Email: priya_ashok85@yahoo.com

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ABSTRACT

A series of benzimidazole-isatin derivatives were prepared and profiled as analgesic compounds. All the synthesised compounds were analyzed by means of spectral data and are confirmed by ^1H NMR, IR and Mass. Compounds (R= H, 5-CH₃, 5-NO₂, 5-Cl, 5-Br) have been evaluated for their analgesic activity by using Diclofenac sodium as a standard. Compound (R= 5-NO₂) showed potent analgesic activity when compared to Diclofenac sodium.

Keywords: isatin derivatives, benzimidazole, analgesic.

INTRODUCTION

Indole is the most beneficial heterocyclic nucleus which has gained prominence in medicinal chemistry due to its diverse biological activities such as antimicrobial¹⁻⁷, anticancer, antioxidant⁸⁻¹², antipyretic, analgesic and anti-inflammatory¹³⁻¹⁶ activities. It is interesting to note from chemical literature that benzimidazole¹⁷⁻²³ exhibits spectrum of biological activities in different heterocyclic nuclei like antimicrobial¹⁷⁻²¹ anti-inflammatory^{22,23}. It is therefore thought worthwhile to synthesize some new indole derivatives by incorporating benzimidazole moiety in single molecular frame work with the hope to possess better antimicrobial, anti-inflammatory and antipyretic activity. In recent years, research is focused on existing molecules and their modifications in order to reduce their side effects and to explore other pharmacological and biological effects.

CHEMISTRY

Melting points of all the synthesized compounds were determined by open capillary tubes using Toshniwal & Cintex melting point apparatus. Expressed in °C and are uncorrected. The IR spectra (KBr pellets) were recorded on Elmer Spectrum BX-1 spectrometer for the compounds. ^1H NMR spectra were recorded for compounds on AV 300MHz NMR Spectrometer, using TMS as an internal standard. The Mass spectra were recorded on LCQ ion Mass spectrometer. The purity of the compounds were checked by Thin Layer Chromatography (TLC) on Merck Silica gel 60 F254 pre coated sheet using Petroleum Ether and Ethyl acetate in 1:1 % v/v.

EXPERIMENTAL SECTION

*Synthesis of Indole-2, 3-diones (Isatins, III)**Isonitrosoacetanilides (II) - General Procedure*

In a 5 lit. R.B. flask were placed chloral hydrate (0.54 mol) and 1200 ml of water. To this solution, were then added crystallized sodium sulphate (1300 g) followed by a solution of an appropriate aromatic amine in 300 ml of water and concentrated hydrochloric acid (0.52 mol). Finally, a solution of hydroxylamine HCl (1.58 mol) in 500ml of water was added. The contents of the flask were heated over a wire-gauge by a Mecker burner so that vigorous boiling begins in about 45 minutes. After 1 to 2 minutes of vigorous boiling the reaction was completed. During the heating period itself the crystals of isonitrosoacetanilides started separating out. On cooling under the current of water, the entire product was solidified. It was filtered under suction, air dried and purified by recrystallization from suitable solvent(s).

Indole-2, 3-dione¹⁵⁻¹⁷ (III) - General Procedure

Sulphuric acid (600g, d 1.84, 326 ml) was warmed at 50°C in a one liter RB flask fitted with an efficient mechanical stirrer and to this finely powdered appropriate isonitrosoacetanilide (II, 0.46 mol) was added at such a rate so as to maintain the temperature between 60°C to 70°C but not higher. External cooling was applied at this stage so that the reaction could be

carried out more rapidly. After the addition of isonitroso compound was completed the temperature of the solution was raised to 80°C and maintained at that temperature for 10 minutes to complete the reaction. Then the reaction mixture was cooled to room temperature and poured onto crushed ice (2.5 kg) while stirring. After standing for about half-an-hour, the product separated was filtered, washed several times with small portions of cold water and dried. Purification of the compound was effected by the recrystallization from methanol.

*Preparation of N-[6-(propylsulfanyl)-1H-benzimidazole-2-yl]**Hydrazinecarboxamide (V)*

A mixture of methyl [6-(propylsulfanyl)-1H-benzimidazol-2-yl] carbamate (albendazole IV, 0.1 moles) hydrazine hydrate 99% (0.2 moles) in 20 ml of methanol was refluxed for 2 hrs. The solvent was evaporated and the product obtained was filtered, washed with cold water and dried. Melting point: 180 °C, Yield: 90%.

General procedure for the preparation of 2(2-oxo-1, 2-dihydro-indole-3-ylidene)-N-[6(propylsulfanyl)-1H-benzimidazole-2-yl] hydrazine Carboxamide (VI)

A mixture of N-[6-(Propylsulfanyl)-1H-benzimidazole-2-yl] hydrazine carboxamide (V, 0.01 mole) and an appropriate isatin (III, 0.01 mole) were dissolved in methanol (20 ml). The reaction mixture was refluxed for 5-6 hrs. The preparation was poured onto crushed ice. The product obtained was filtered, washed with cold water then recrystallized with suitable solvent

SPECTRAL DATA

Compound VIa (R= H): %yield 90, mp: 245-248

IR: 3179.88 (NH), 1733.81 (C = O), 1351.43 (C=N), 1528.49 (CONH). ^1H NMR (400MHz, DMSO): δ [ppm]: 1.0 (t, 3H, CH₃), 1.6 (m, 2H, CH₂), 2.9 (t, 2H, CH₂), 6.9-7.8 (m, 7H, Ar-H), 8.0 (s, 1H, benzimidazole NH), 8.8 (s, 1H, NH), 10.6 (s, 1H, CONH) 11.6 (s, 1H, Indole NH). MASS: Its mass spectrum exhibited molecular ion (M+1) peak at m/z 395 (100%) as a base peak. It also showed peak at m/z 234, this may be fragment ion obtained due to cleavage of CONH.

Compound VIb (R= 5-Cl): %yield 84, mp: 259-261

IR 3179.88 (NH), 1733.81 (C = O), 1351.43 (C=N), 1528.49 (CONH). ^1H NMR (400 MHz, DMSO): δ [ppm]: 1.0 (t, 3H, CH₃), 1.6 (m, 2H, CH₂), 2.9 (t, 2H, CH₂), 7.1-7.9 (m, 6H, Ar-H), 8.1 (s, 1H, benzimidazole NH), 8.9 (s, 1H, NH), 10.6 (s, 1H, CONH) 11.6 (s, 1H, Indole NH). MASS: Its mass spectrum exhibited molecular ion (M+1) peak at m/z 428.7 (100%) as a base peak.

Compound VIc (R= 7-Cl): %yield 86, mp: 259-261

IR: 3179.88 (NH), 1733.81 (C = O), 1351.43 (C=N), 1528.49

(CONH).¹H NMR (400 MHz, DMSO): δ [ppm]: 1.0 (t,3H,CH₃), 1.6 (m,2H,CH₂), 2.9 (t,2H,CH₂), 7.1-7.9 (m,6H,Ar-H), 8.1 (S,1H,benzimidazole NH), 8.9 (S,1H,NH), 10.6(S,1H, CONH) 11.6 (S,1H, Indole NH). MASS: Its mass spectrum exhibited molecular ion (M+1) peak at m/z 428(100%) as a base peak.

Compound VId (5-Br): %yield 75, mp 260-262.

IR: 3179.88 (NH), 1733.81 (C = O), 1351.43 (C=N), 1528.49 (CONH).¹H NMR (400 MHz, DMSO): δ [ppm]: 1.0 (t,3H,CH₃), 1.6(m,2H,CH₂), 2.9(t,2H,CH₂), 7.1-8.0 (m,6H,Ar-H), 8.1(S, 1H, benzimidazole NH), 8.9 (S, 1H, NH), 10.6 (S, 1H, CONH) 11.6 (S, 1H, Indole NH).MASS: Its mass spectrum exhibited molecular ion (M+1) peak at m/z 474.9 (100%) as a base peak.

Compound VIe (R=5-NO₂):%yield 80, mp 261-263.

IR: 3179.88 (NH), 1733.81(C = O), 1351.43 (C=N), 1528.49 (CONH).¹H NMR (400 MHz, DMSO): δ [ppm]: 1.0 (t,3H,CH₃), 1.6(m,2H,CH₂), 2.9(t,2H,CH₂), 6.9-7.8(m,7H,Ar-H), 8.0 (S,1H,benzimidazole NH), 8.8 (S,1H,NH), 10.6 (S,1H, CONH) 11.6 (S,1H, Indole NH). MASS: Its mass spectrum exhibited molecular ion (M+1) peak at m/z 441(100%) as a base peak.

Compound VI f (R= 7-NO₂):%yield 82, mp 254-256.

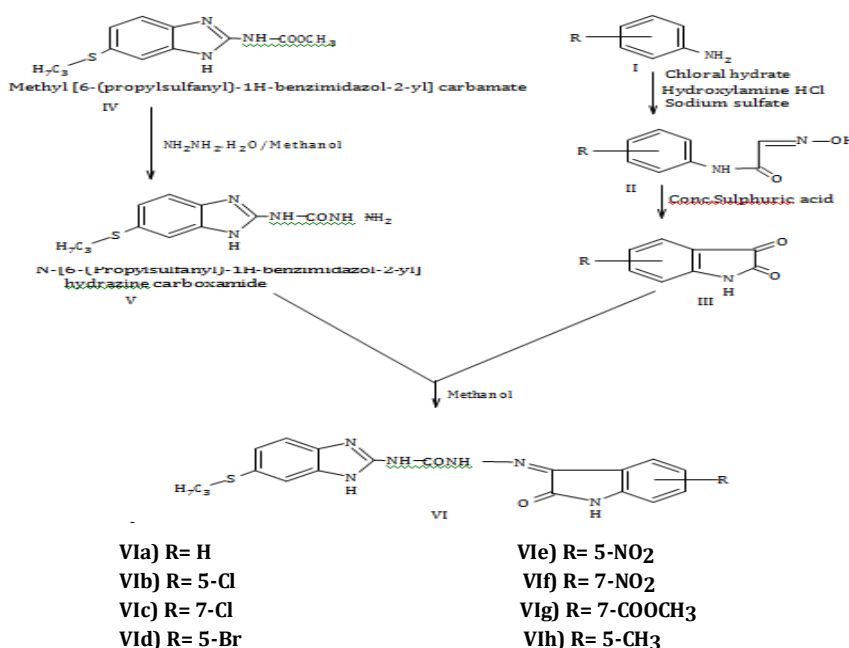
IR: 3179.88 (NH), 1733.81(C = O), 1351.43 (C=N), 1528.49 (CONH).¹H NMR (400 MHz, DMSO): δ [ppm]: 1.0 (t,3H,CH₃), 1.6(m,2H,CH₂), 2.9(t,2H,CH₂), 6.9-7.8(m,7H,Ar-H), 8.0 (S,1H,benzimidazole NH), 8.8 (S,1H,NH), 10.6 (S,1H, CONH) 11.6 (S,1H, Indole NH). MASS: Its mass spectrum exhibited molecular ion (M+1) peak at m/z 441(100%) as a base peak.

Compound VIg (R= 7-COOCH₃):%yield 85, mp 252-254.

IR: 3179.88 (NH), 1733.81 (C = O), 1351.43 (C=N), 1528.49 (CONH).¹H NMR (400 MHz, DMSO): δ [ppm]: 1.0 (t,3H,CH₃), 1.6 (m,2H,CH₂), 2.9(t,2H,CH₂), 6.9-7.8(m,7H,Ar-H),8.0 (S,1H,benzimidazole NH), 8.8 (S,1H,NH), 10.6 (S,1H, CONH) 11.6

Analgesic activity of 2(2-oxo-1,2-dihydro-indole-3-ylidene)-N-[6(Phenylsulfanyl)-1H-benzimidazole-2-yl] hydrazine carboxamide (VIa-VIj)

Control (DMSO)	Standard (Diclofenac)	T ₁ (R=H)	T ₂ (R=5-NO ₂)	T ₃ (R=5-CH ₃)	T ₄ (R=5- Cl)	T ₅ (R=5- Br)
6	14	9	12	11	9	7
5	13	12	11	9	12	9
8	13	13	13	6	10	8
4	12	8	10	8	11	7
Pvalue	0.0003	0.0176	0.0017	0.087	0.0044	0.0871



(S,1H, Indole NH). MASS: Its mass spectrum exhibited molecular ion (M+1) peak at m/z 454 (100%) as a base peak.

Compound VIh (R= 5-CH₃):%yield 84, mp 259-261.

IR: 3179.88 (NH), 1733.81(C = O), 1351.43 (C=N), 1528.49 (CONH).¹H NMR (400 MHz, DMSO): δ [ppm]:1.0(t,3H,CH₃),1.6(m,2H,CH₂),2.9(t,2H,CH₂),6.9-7.8(m,7H,Ar-H),8.0 (S,1H,benzimidazole NH), 8.8 (S,1H,NH), 10.6 (S,1H, CONH) 11.6 (S,1H, Indole NH). MASS: Its mass spectrum exhibited molecular ion (M+1) peak at m/z 410(100%) as a base peak.

EXPERIMENTAL PROCEDURE

Analgesic activity

All the experiments were carried out using male Albino mice (25-30g). On arrival these animals were placed at random and allocated polypropylene cages with paddy husk as bedding. Animals were housed at a temperature of 24 ± 2°C and relative humidity of 30-70%. A 12:12 light:day cycle was followed. All animals were allowed free access to water with standard commercial chaw pellets. All the experimental procedures and protocols used in this study were reviewed by the Institutional Animal Ethics Committee.

Each group of four (n=4) mice were selected for the present study. One group served as control and received the vehicle, and the other group received the standard drug Diclofenac sodium (2.5mg/kg, i.p.).The drug concentration of 10mg in 25 ml DMSO (30%) was administered i.p. to the other groups. The mice were placed on Eddy's hot plate kept at a temperature of 55 ± 0.5°C for a maximum time of 15sec. Reaction time was recorded when the animals licked their fore-and hind paws and jumped, at 0,15,30,60 minutes. The relative potencies to diclofenac sodium were determined. In Statistical analysis, all the data was analysed by using student *t*-test (Table-II). P values<0.05 were considered as statistically significant.

Synthesized compounds (R= H, 5-CH₃, 5-NO₂, 5-Cl, 5-Br) tested for analgesic activity by using Diclofenac Sodium as a standard. At the first 15th minute the compounds exhibited potent analgesic effect when compared with the standard. At the 30th minute the test compounds retained the analgesic effect. At the 60th, 90th minute the test compounds exhibited reduction in the analgesic effect. Compound (R= 5-NO₂) showed potent analgesic activity among the tested compounds when compared to standard Diclofenac sodium. Compound(R=5-CH₃) showed less analgesic activity, and the compounds (R= H, 5-Cl, 5-Br) showed moderate analgesic activity when compared to standard Diclofenac Sodium.

CONCLUSION

All the compounds were analyzed by means of spectral data and are confirmed by NMR, IR and Mass. Compounds (R= H, 5-CH₃, 5-NO₂, 5-Cl, 5-Br) have been evaluated for their analgesic activity by using Diclofenac sodium as a standard. Compound (R=5-NO₂) showed potent analgesic activity when compared to Diclofenac Sodium. Compound(R= 5-CH₃) showed less analgesic activity and the compounds (R= H, 5-Cl, 5-Br) showed moderate analgesic activity when compared to Diclofenac Sodium as a standard.

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