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Note

Synthesis and characterization of benzimidazolyl-phenothiazine derivatives and a study of their antiviral and antifungal activities

Abha Bishnoi*, V K Pandey & Rashmi Saxena

Department of Chemistry,
University of Lucknow, Lucknow 226 007, India
and
M N Joshi & S K Bajpai

Department of Microbiology,
Central Drug Research Institute, Lucknow 226 001, India

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Reaction of phenothiazine with *p*-aminobenzoic acid and aromatic aldehydes in ethanol furnishes 10-(α-*p*-carboxyphenyl-aminobenzyl) phenothiazines **2** which on treatment with *o*-phenylene diamine in pyridine results in the formation of 10-(α-*p*-benzimidazolyl-aminobenzyl) phenothiazines **3** in the yields varying from 60-85%. Antiviral and antifungal activities of **3** are reported.

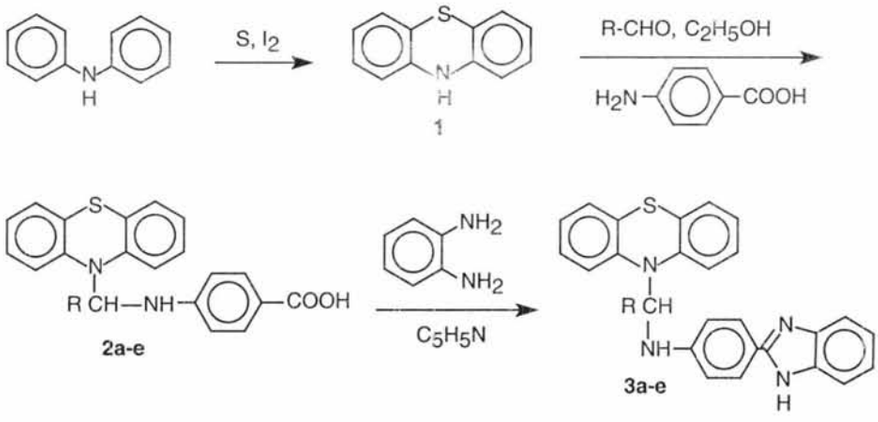
Phenothiazine derivatives possess varying degree of antiviral and antiparasitic properties. Further, the benzimidazolyl derivatives constitute an important class of compounds possessing diverse types of pharmacological activities including antiviral and antifungal activities. In addition, recently benzimidazole derivatives have been demonstrated to possess broad spectrum antiviral activity against *Encephalomyocarditis virus (EMCV), Japanese encephalitis virus (JEV),* and *Semiliki forest virus (SFV) in vitro* as well as *in vivo*[1,2].

Keeping in view of these valid observations and in continuation of our research for biologically active heterocycles, it was planned to synthesize some 10-(α-*p*-benzimidazolyl-aminobenzyl) phenothiazines **3** **(Scheme I)** and to evaluate their antiviral activity *in vitro* against *Japanese encephalitis virus (JEV)* and *Herpes simplex virus type-1 (HSV-1)* and antifungal activity against *Fusarium solani.*

Pharmacological activity

All the compounds were screened for their antiviral activity against *JEV* and *HSV-1 in vitro.* Cytotoxicity tests and antiviral assay of the compounds were performed by standard method of Sidwell *et al.*[3] *in vitro.* Virus was maintained by intracerebral passages in 1-3 days old suckling albino swiss mice. The brains of infected mice with specific paralytic symptoms were triturated and 10% homogenate (w/v) was made in phosphate buffered saline (PBS), *p*H 7.2. The mean lethal dose (LD_{50}) of the virus in mice was calculated before each experiment[4]. It was found that benzimidazolylphenothiazines exhibited varying degree of antiviral activity against *JEV* and *HSV-1.* The results of such activities are summarized in **Table I.** Most of the compounds showed significant antiviral activity.

All the compounds were evaluated for their antifungal activity against *Fusarium solani.* The antifungal data are recorded in **Table I.** The 10-(α-*p*-benzimidazolyl-aminobenzyl) phenothiazine 3e



Scheme I

Table I—Antiviral and antifungal activity data of 10-(α-*p*- benzimidazolyl-aminobenzyl) phenothiazines **3a-e**

Compd	Dose	CT_{50}	EC_{50}	TI	*% CPE Inhibition*		% Iinhibition in fungal zone
					JEV	HSV-1	
3a	500-4	500	15.6	32	75	18	50
3b	500-4	250	31.25	8	75	41	55
3c	500-4	250	31.25	8	-	41	65
3d	500-4	500	31.25	16	75	41	57
3e	500-4	500	15.6	32	50	60	70

showed the maximum activity against *F. solani*. It can be concluded that the presence of an electronegative group (*p*-chloro) in the aromatic ring is greatly responsible for causing enhanced antifungal activity.

Experimental Section

General. IR spectra (KBr) were recorded on a Perkin-Elmer Grating 599B spectrophotometer and ^{1}H NMR spectra ($CDCl_3$) on a Varian EM 390 spectrometer. Melting points were determined in open capillaries and are uncorrected. Purity and homogeneity of the compounds were checked by TLC. Compounds **2a-e** gave satisfactory analytical results for C, H and N. Mass spectra of **3a** were recorded on a Hitachi-Elmer model RMV-7 spectrometer at 70eV.

Phenothiazine **1** was prepared according to the reported method[5].

10-(α-*p*-carboxyphenyl-aminobenzyl)phenothiazine 2a. A mixture of phenothiazine **1** (0.02 mole), benzaldehyde (0.02 mole) and *p*-aminobenzoic acid (0.02 mole) in ethanol (50mL) was heated under reflux for 4hr on a steam-bath. Subsequently, ethanol was distilled off and the pasty mass obtained, was triturated with petroleum ether (b.p. 60-80°C). The solid **2a**, which was isolated, was dried in vacuum desiccator. It was recrystallised from acetone, m.p. 115°C, yield 60%. Anal. for $C_{26}H_{20}N_2O_2S$. Calcd: N, 6.60. Found: N, 6.35%.

Similarly, other products **2b-e** were synthesized and their characterization data are represented as under.

2b (R = *p*-hydroxyphenyl) : m.p. 72°C, yield 90%.

2c (R = *o*-nitrophenyl): m.p. 120°C, yield 65%; IR: 3420 (NH Str.), 30.30 (CH Str.), 1690 (carboxylic CO), 1545 (Ar-NO_2), 1379 (C=N).

2d (R = *p*-methoxyphenyl): m.p. 90°C, yield 70%.

2e (R = *p*-chlorophenyl): m.p. 145°C, yield 50%.

10 -(α-*p*-Benzimidazolyl-aminobenzyl)phenothiazine 3a. A mixture of **2a** and *o*-phenylene diamine (in equimolar quantity) in anhydrous pyridine (30 mL) was heated under reflux for 6 hr on a sand-bath under anhydrous reaction conditions. Subsequently, the resultant solution was cooled to room temperature and poured into ice-cold water (100mL) containing conc. HCl (10mL). A solid separated out, which was allowed to settle down for 0.5hr. It was filtered and washed with water (4×25 mL). The crude product **3a** thus obtained, was recrystallised from dilute ethanol, m.p. 186°C, yield 85%. Anal. for $C_{32}H_{24}N_4S$. Calcd: N, 11.29. Found: N, 11.25%.

Similarly, other products **3b-e** were synthesized and their characterization data are represented as under.

IR: 1630 (C=N), 1610 (-NH), 1350cm^{-1} (C-N); ^{1}HNMR: δ 2.3-2.1 (s, 1H, CH), 5.3-5.1 (br, s, 1H, CH- N*H*-Ar), 6.6-6.2 (br, s, 1H, Ar-N*H*-Ar), 8.5-7.2 (m, 21H, Ar-H); Mass: m/z 496(M^+), 380, 118, 93, 298, 182, 106, 194, 174, 148, 123, 77, 51, 91, 65.

3b (R = *p*-hydroxyphenyl): m.p. 161°C, yield 80%.

3c (R = *o*-nitrophenyl): m.p. 195°C, yield 60%.

3d (R = *p*-methoxyphenyl): m.p. 200°C, yield 60%; ^{1}HNMR: δ 2.3-2.2 (s, 1H, CH), 3.1-2.9 (s, 3H, O-CH_3), 5.6-5.3 (br, s, 1H, CH-N*H*-Ar), 6.2-5.9 (br, s, 1H, Ar-N*H*-Ar), 8.6-7.1 (m, 21H, ArH).

3e (R = *p*-chlorophenyl): m.p. 100°C, yield 75%.

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