Indian J Physiol Pharmacol 1999; 43 (1) : 143–145

LETTER TO THE EDITOR

ANALGESIC AND SEDATIVE EFFECT OF THIOUREIDO DERIVATIVES OF ACETOPHENONE SEMICARBAZONES

Sir,

(Received on May 21, 1998)

Several synthetic compounds like thiobisformamidine, dithiobiurets and thiobiurets posses a significant analgesic property (1). Some of them (isothiobiurets, thiobiurets) also potentiate the barbiturate hypnosis and this has generally been linked to an enhanced lipophilic property due to the introduction of sulphur. Partition coefficient (a lipophilic parameter for π-value) is considered to influence the biological activity. Since acetaminophen is a suitable substitute of aspirin as far as analgesic/antipyretic property is concerned, a series of thioureido derivatives of acetophenone semicarbazones, that are closely related to acetaminophen, with an extra atom of sulphur incorporated in the molecule were synthesized (2). We describe here the analgesic properties of these compounds and their effect on the barbiturate induced hypnosis.

Fourteen compounds were synthesized and tested. Their chemical structure is shown in Fig. 1. Methods described by Dimmock et al (3) and Ram et al (4) were used to obtain the semicarbazones/ thiosemicarbazones and thioureido derivatives respectively. The characterization of the compounds was done using CHN analysis, IR UV and ^{1}H NMR spectral analysis which confirmed the structure. Test drugs were dissolved in polyethylene glycol and administered by intraperitoneal (ip) route. Aspirin (Reckitt & Colman) and pentobarbitone sodium (May & Baker) were dissolved in distilled water.

Analgesic studies were done in albino rats weighing 100 to 130 g using the hot wire technique (tail flick response) as described by Pandeya et al (5). The tail was subjected to radiant heat and the time to withdrawl (or flick) was noted before and 30 min after the administration of drugs. The cut-off value was one minute i.e. tail was withdrawn after one minute. All the test compounds were administered in a dose of 10 mg/kg, ip. Compound I was also tested at 5 mg/kg, ip. Six animals were used in each group and significance was analysed by Student's 't' test.

Effect of the test drugs (20 mg/kg, ip) was also observed on pentobarbitone (30 mg/ kg, ip) induced sleep in albino mice of either sex, weighing 25 to 30 g and fasted for 12h before experimentation. Percent change in sleeping time was determined by comparing the sleeping time of the test group with that of control. Significance of the difference noted, was evaluated using Student's 't' test.

All test compounds showed a significant analgesic activity at 10 mg/kg. Majority of the compounds were more active than aspirin (10 mg/kg). Introduction of sulphur, however, reduced the analgesic activity. Introduction of thioureido moiety gave

TABLE I : Analgesic/sedative activity of the tested compounds. For analgesic activity, all compounds were administered in a dose of 10 mg/kg. For compound I, 5 mg/kg dose was also tried. For pentobarb sleep all compounds were administered in a dose of 20 mg/kg to mice.

Compound No.	*Partition Co-efficient (25°C)*	*Analgesic activity (Tail Flick Latencies in seconds) (Mean±SEM; n=6)*		*Change in Sleeping Time in minute (Mean±SEM; n=6)*	*Hypnosis Potentiation (%)*
		Control	*Treated*		
I	4.55	7.00 ± 1.12 6.16 ± 0.76	68.66 ± 3.86*** b 53.83 ± 2.58***	a	
II	1.94	4.16 ± 0.79	16.16 ± 2.84**	274.16 ± 1.50***	+ 299.53
III	3.54	6.43 ± 0.22	8.53 ± 0.49**	a	
IV	2.12	6.66 ± 0.76	47.83 ± 1.90***	a	
V	1.94	6.16 ± 0.54	54.16 ± 1.72***	62.16 ± 3.79	– 9.41
VI	2.12	5.83 ± 0.60	46.83 ± 1.93***	59.50 ± 2.62	– 13.29
VII	1.08	6.16 ± 0.35	31.16 ± 1.72***	270.00 ± 9.69***	+ 293.47
VIII	3.16	9.50 ± 0.50	26.50 ± 0.67***	71.50 ± 1.88	+ 4.19
IX	1.63	5.66 ± 0.59	29.33 ± 1.02***	75.66 ± 2.04	+ 10.24
X	1.5	7.33 ± 0.41	26.50 ± 0.76***	77.66 ± 3.07	+ 13.17
XI	1.38	6.86 ± 0.92	8.23 ± 1.29**	a	
XII	1.77	5.41 ± 0.15	7.23 ± 0.28***	a	
XIII	2.57	5.19 ± 0.54	6.22 ± 0.89	69.33 ± 2.83	+ 2.85
XIV	2.33	6.29 ± 0.41	7.30 ± 0.61	66.66 ± 2.83	– 1.03
Aspirin		6.03 ± 0.23	10.22 ± 0.33		
Pentobarbitone sodium (30 mg/kg)				68.62 ± 4.95	
Control (PEG 200)				67.66 ± 1.02	

Partition Co-efficient :- At 25°C; pH 7.4 $CHCl_3$: Phosphate buffer system. + increase; -decrease; Drug dissolved in polyethylene glycol (PEG 200)
a-Antagonise the effect of pentobarbitone (did not sleep). b, 5 mg/kg
**P<0.01; ***P<0.001

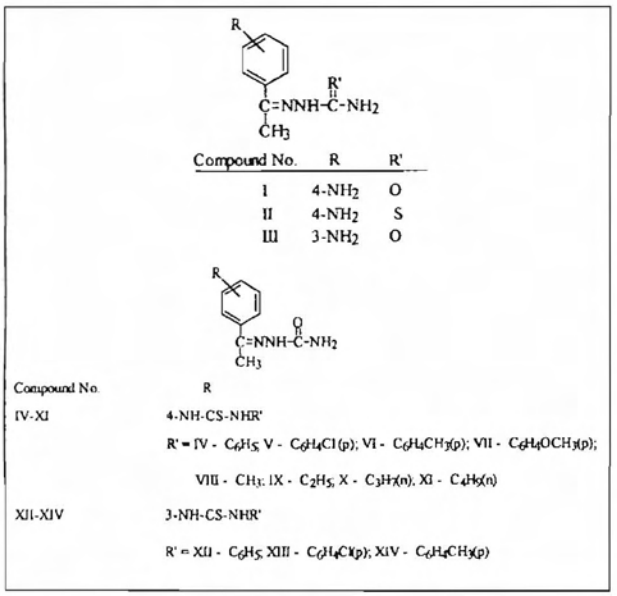

Fig. 1 : Structure of derivatives of acetophenone semicarbazones

potent analgesic compounds but the meta-substituted compounds (XII and XIV) are less active than para-substituted derivatives (compounds V, VI, and VII).

Compound V, VI, VIII, IX, XIII and XIV had no effect in pentobarbitone induced sleep. Compounds II and VII potentiated the pentobarbitone induced sleep. While, I, III, IV, XI and XII antagonised the effect of pentobarbitone. It is concluded that compound I with a maximum partition coefficient possesses a significant analgesic activity at 5 mg/kg dose and has no sedative effect. I can thus serve as a lead compound for future synthesis of useful analgesic drugs.

ACKNOWLEDGEMENTS

One of the authors (VM) is grateful to U.G.C., New Delhi for providing financial assistance for pursuing the work.

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