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4-Methylphenylsemicarbazone Derivatives Inhibits Cow Milk Induced Pyrexia in Rabbits

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Abstract: A series of 4-methylphenylsemicarbazone was synthesized and investigated for their antipyretic activity using boiled cow milk induced pyrexia in rabbits. It was observed that the compound 4MS-8 exhibited maximum protection against pyrexia. Hydroxy substitution in aldehydic and acetophenic moiety of 4-methylphenylsemicarbazone derivatives significantly increased antipyretic activity.

Key words: Pyrexia, cow milk, antipyretic, 4-methylphenylsemicarbazone, derivatives

INTRODUCTION

Non Steroidal Anti-Inflammatory Drugs (NSAID's) are widely used in the treatment of pain, inflammation and fever. NSAID's reduce the fever by blocking the metabolism of arachidonic acid through the enzyme cyclooxygenase and thereby the production of prostaglandins (Singh *et al*., 2010). The semicarbazone, themselves are of much interest due to a wide spectrum of pharmacological activities. Recently some researchers had reviewed the bioactivity of semicarbazones and they have exhibited anticonvulsant (Pandeya *et al*., 2000), antitubercular (Sriram *et al*., 2004), antioxidant (Singhal and Paul, 2011a), analgesic, antipyretic, anti-inflammatory, etc. (Singh *et al*., 2010; Singhal and Paul, 2011b). The present study was aimed at investigating the antipyretic activity of synthesized 4-methylphenylsemicarbazone derivatives using cow milk induced pyrexia in rabbits.

MATERIALS AND METHODS

Chemistry: 4-Methylphenylsemicarbazones were synthesized (Singhal and Paul, 2011a) according to synthetic scheme as shown in Fig. 1. Melting points were measured in open capillary tubes on a Buchi 530 melting point apparatus and were uncorrected. Infrared (IR) and proton Nuclear Magnetic Resonance (1H NMR) spectra were recorded for the compounds on Jasco IR Report 100 (KBr) and Brucker Advance (300 MHz) instruments, respectively. Chemical shifts are reported in parts per million (ppm) using Tetramethylsilane (TMS) as an internal standard. All exchangeable protons were confirmed by addition of D_2O. Mass spectra were

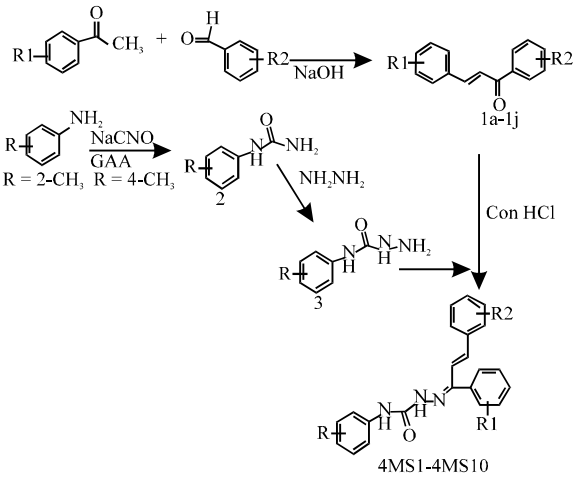

Fig. 1: Synthetic scheme for synthesizing the 4-methyphenylsemicarbazone derivatives

measured with a Shimadzu GC-MS-QP5000 spectrophotometer. Only molecular ions (M^+) and base peaks are given. Elemental analysis (C, H and N) were undertaken with a Perkin-Elmer Model 240C analyzer and all analyses were consistent with theoretical values (within 0.4%) unless indicated. The homogeneity of the compounds was monitored by ascending Thin-Layer Chromatography (TLC) on silica gel G (Merck) coated aluminum plates, visualized by iodine vapor. The structure (Fig. 2) and physicochemical properties of the synthesized title compounds are shown in Table 1.

Boiled cow milk induced pyrexia in rabbit (Singhal *et al*., 2011): Boiled cow milk induced pyrexia was used to evaluate the antipyretic activity of

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Table 1: Physicochemical data of 4-methylphenylsemicarbazone derivatives

Comp no.	R	R_1	R_2	Yield (%)	Mol wt.	Molecular formula	mp (°C)	Rf value
4MS-1	4-CH_3	H	H	52	371	$C_{23}H_{21}N_3O_2$	206	0.53
4MS-2	4-CH_3	H	4"-OH	65	387	$C_{23}H_{21}N_3O_3$	188	0.63
4MS-3	4-CH_3	H	4"-OCH_3	63	401	$C_{24}H_{23}N_3O_3$	204	0.70
4MS-4	4-CH_3	H	4"-$N(CH_3)_2$	64	414	$C_{25}H_{26}N_4O_2$	195	0.62
4MS-5	4-CH_3	4-OH	6"-OH	55	403	$C_{23}H_{21}N_3O_4$	178	0.58
4MS-6	4-CH_3	4-OH	4"-$N(CH_3)_2$	56	430	$C_{25}H_{26}N_4O_3$	185	0.66
4MS-7	4-CH_3	H	6"-OH	54	387	$C_{23}H_{21}N_3O_3$	180	0.69
4MS-8	4-CH_3	5-OH	6"-OH	67	403	$C_{23}H_{21}N_3O_4$	183	0.54
4MS-9	4-CH_3	5-OH	4"-OH	50	403	$C_{23}H_{21}N_3O_4$	165	0.59
4MS-10	4-CH_3	5-OH	4"-OCH_3	56	417	$C_{24}H_{23}N_3O_4$	172	0.77

Table 2: Effect of 4-methylphenylsemicarbazones on boil milk induced pyrexia in rabbits

		Rectal temperature (°F)*		Rectal temperature after administration of compound (°F)*		
Compound	Dose (mg kg^{-1})	Normal (A)	3 h after boil milk admin. (B)	1 h (C1)	2 h (C2)	3 h (C3)
Control	-	99.85±0.31	103.17±0.29	103.2±0.33	103.2±0.32	103.17±0.34
Aspirin	100	99.75±0.20	103.57±0.23	100.17±0.29 (89)[a]	99.85±0.18 (97.38)[a]	99.75±0.16 (100)[a]
4MS-1	30	99.55±0.26	103.35±0.13	102.55±0.19 (21.05)[d]	102.1±0.16 (32.89)[d]	101.57±0.17 (46.84)[a, d]
4MS-2	30	99.2±0.220	103.3±0.210	100.85±0.16 (59.76)[a, f]	100.2±0.13 (75.61)[a]	100±0.19 (80.49)[a, e]
4MS-3	30	98.67±0.15	102.72±0.16	100.67±0.2 (50.62)[c, d]	99.87±0.2 (70.37)[a, f]	99.47±0.13 (80.25)[a, e]
4MS-4	30	99.67±0.35	103.27±0.38	102.75±0.42 (14.44)[d]	102.12±0.46 (31.94)[d]	101.05±0.29 (61.67)[a, d]
4MS-5	30	99.15±0.17	103.3±0.170	99.45±0.2 (92.77)[a]	99.27±0.16 (97.11)[a]	99.22±0.14 (98.31)[a, f]
4MS-6	30	98.95±0.14	102.82±0.24	102.12±0.24 (18.09)[d]	101.5±0.29 (34.11)[d]	101.02±0.27 (46.51)[a, d]
4MS-7	30	99.12±0.12	103.2±0.130	100.67±0.15 (62.01)[a]	100.3±0.15 (71.08)[a]	99.95±0.1 (79.66)[a, e]
4MS-8	30	99.2±0.200	103.42±0.22	99.25±0.21 (98.81)[a]	99.22±0.21 (99.53)[a]	99.2±0.2 (100)[a]
4MS-9	30	98.77±0.18	102.87±0.19	98.9±0.19 (96.83)[a]	98.8±0.18 (99.27)[a]	98.8±0.18 (99.27)[a]
4MS-10	30	98.9±0.130	102.97±0.03	99.2±0.11 (92.63)[a]	99.05±0.13 (96.31)[a]	99.02±0.11 (97.05)[a]

Figures in parenthesis indicate inhibition (%) of temperature elevation; [a, c]$p<0.001$ and 0.05, respectively compared with control; [d, f]$p<0.001$, 0.01 and 0.05, respectively compared with standard; one way ANOVA test followed by Tukey test. *Each value is the mean±SD for 4 rabbits

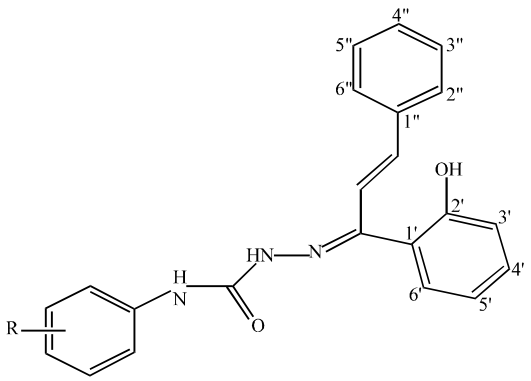

Fig. 2: Structure of synthesized 4-methylphenylsemi carbazone derivatives

synthesized compounds. Before experimentation rectal temperature of rabbits were recorded by inserting a well lubricated bulb of a thermometer in the rectum. Care was taken to insert it to the same depth each time (about 6 cm). Milk was collected from local cow had been boiled. When temperature of the boiled milk equilibrates to room temperature then rabbits were injected intraperitoneally boiled milk at the dose of 0.5 mL kg^{-1} body weight, to induce pyrexia. Induction of fever was taken about 2-3 h. Then, test animals were orally administered 30 mg kg^{-1} of the synthesized compounds, saline (control) or 100 mg kg^{-1} aspirin (reference drug). Finally, rectal temperatures were recorded 1 h intervals up to 3 h.

RESULTS AND DISCUSSION

The antipyretic activity of the synthesized 4-methylphenylsemicarbazone compounds was evaluated using boiled cow milk induced pyrexia in rabbits which is shown in Table 2. Comparison of the antipyretic activity of all tested compounds revealed that compound 4MS-8 was the most active compound. The order of activity regarding substitution on chalconyl group is OH>OCH_3>$(CH_3)_2$-N>H. The substitution with different substituent on the phenyl of the aldehydic and acetophenic group of chalcone moiety plays an important role in protection of the pyrexia.

Hydoxy substitution in the aldehydic and acetophenic moiety of chalcone significantly increased antipyretic potential. Methoxy substitution in the aldehydic moiety of chalcone also favors antipyretic activity. Bulkier substitution (p-dimethylamino) or unsubstituted compounds exhibited less antipyretic potential.

CONCLUSION

In this study, the substitution with different substituent on the phenyl of the aldehydic and acetophenic group of chalcone moiety plays an important role in protection of the pyrexia.

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