INTERNATIONAL RESEARCH JOURNAL OF PHARMACY **ISSN 2230 – 8407**
Available online http://www.irjponline.com
Research Article

ANTIINFLAMMATORY ACTIVITY OF SOME NOVEL METHYLPHENYL SEMICARBAZONE DERIVATIVES

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Article Received on: 12/03/2011 Revised on: 29/04/2011 Approved for publication: 12/05/2011

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ABSTRACT
In the present study a series of methylphenylsemicarbazones was synthesized and evaluated for their anti-inflammatory activities by cotton pellet induced granuloma, formalin induced paw edema and carrageenan induced paw edema in rats. Most of the compounds were found to be more or comparable potent than the reference standard drug in all the three animal models. Based on the results of anti-inflammatory study it was found that chloro substitution in the aldehydic moiety and amino substitution in acetophenic moiety of chalcone (compound 28) exhibited better activity. Lengthening of carbon chain also favor anti-inflammatory activity.
KEYWORDS: Chalcones, Anti-inflammatory, formalin induced paw edema, carrageenan induced paw edema, cotton pellet induced granuloma

INTRODUCTION

Non steroidal anti-inflammatory drugs (NSAID's) are widely used in the treatment of pain and inflammation. NSAID's reduce the pain and swelling associated with arthritis by blocking the metabolism of arachidonic acid (AA) through the enzyme cyclooxygenase (COX) and thereby the production of prostaglandins, e.g. PGE2, which sensitizes nociceptors at nerve fiber terminals[1]. The semicarbazides, which are the raw material of semicarbazones, have been known to have biological activity against many of the most common species of bacteria[2]. Semicarbazone, themselves are of much interest due to a wide spectrum of antibacterial and antifungal activities[2,3]. Recently some workers had reviewed the bioactivity of semicarbazones and they have exhibited anticonvulsant[3-5], antitubercular[6] analgesic, anti-inflammatory etc[7]. There are several reports about the synthesis and pharmacological evaluation of new bioactive Naroylarylhydrazones acting at the AA cascade enzyme level and chalcones are also having analgesic and anti-inflammatory activity[8,9]. As a part of ongoing research program to find novel anti-inflammatory compounds, herein, we have fused these both active moiety and design a scheme for synthesizing these compounds[7,10,11].

MATERIALS AND METHODS

Methylphenyl semicarbazones were previously synthesized and characterized[12]. 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 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 (figure 1) and physicochemical properties of the synthesized title compounds are given in table 1.

Anti-Inflammatory Activity

The synthesized Chalconesemicarbazones were screened for their anti-inflammatory activities using the cotton pellet induced granuloma, formalin induced paw edema

and carrageenan induced paw edema in rats. All the protocols for animal experimentation were approved by Institutional Animal Ethics Committee (IAEC). Protocol approval reference number is PBRI/IAEC/10/PN-118.

In the cotton pellet granuloma, 30 mg of cotton pellet were surgically inserted into the groin of animals for 7 days with the administration of Chalconesemicarbazones (30 mg/Kg), Saline or aspirin (100mg/kg) once a day for the 7 days period. On the eighth day animals were sacrificed with an overdose of ether. The cotton pellets with the attached granuloma were dissected out, dried and the weights of the dried granuloma were determined. The mean of the granuloma formed in each animal was determined[13].

In the formalin induced paw edema, Just before injection of the test compounds the volume of the paw was measured plethysmographically. Animals were pretreated of either test compounds (30mg/kg, p.o.) or aspirin (100mg/kg, p.o.). The control group received the same volume of the vehicle. Edema was induced after one hour by subplanter injection of 0.05 ml of a 2.5% solution of formalin into the left hind paw. The increase in paw volume was determined 4 h after injection of the phlogistic agent. The percentage anti-inflammatory activity was calculated by the formula: anti-inflammatory activity=(1-dt/dc)/100 where dt is the difference of paw volume in drug treated groups and dc is the difference in paw volume of the control group[13].

In the carrageenan-induced rat paw edema test acute inflammation was produced by sub-planter injection of 0.1ml of freshly prepared 1% suspension of carrageenan (Sigma-Aldrich, Dorset, UK) in the right hind paw of the rats 1 h after i.p. administration of the compounds and paw volume was measured plethysmometrically at 0 hr and 3hr. The test compounds (30mg/kg) was administered i.p. in DMSO, standard group was treated with diclofenac (50mg/kg) i.p. 1 hrs before by the injection and control group received only DMSO. Anti-inflammatory activity was expressed as percent of inhibition of the edema when compared with the control group[14].

RESULTS AND DISCUSSION

The Anti-inflammatory activity of the synthesized methylphenyl semicarbazone compounds was evaluated using cotton pellet induced granuloma, formalin induced paw edema and carrageenan induced paw edema in rats which is summarized in **table 2**, **3** and **4** respectively.

As from the tables it could be seen that most of the compounds showed significant activity comparable to the reference drug. Among the synthesized compounds, compound 28 was the most potent anti-inflammatory agent against all the three animal models. Compound 25, 26, 27 and 28 showed the better or comparable activity in comparision to the standard drug in cotton pellet induced granuloma and carrageenan induced paw edema method. Compound 24 showed intermediate anti-inflammatory activity. Compound 4 and 14 exhibited minimal anti-inflammatory activity.

The substitution with different substituent on the phenyl of the aldehydic and acetophenic group of chalcone moiety plays an important role in the protection of the inflammation.

The amino substitution in acetophenic moiety (compound 26, 27, 28) and chlorine substitution in the aldehydic moiety (compound 24, 26, 28) is favorable for the anti-inflammatory. The lengthening of carbon chain i.e. cinnameldehyde (compound 25) is also favorable for the activity. It was observed that amino substitution in acetophenic moiety significantly increased anti-inflammatory activity as compared to unsubstituted acetophenic moiety. No exact mechanism study were done on molecular level but further studies were in process in our lab for searching the exact mechanism of action of these compounds, which may support the showing activities of the synthesized compounds. The compounds with no substitution (compound 4, 14) were showed very less protection against inflammation in comparison to the substituted compounds.

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Table 1: Physicochemical data of methylphenyl semicarbazones

Comp no.	R	R1	R2	Yield (%)	Mol Wt.	Mol Formula	mp (ºC)	Rf Value
4	2- CH_3	H	H	57	371	$C_{23}H_{21}N_3O_2$	150	0.78
14	4-CH_3	H	H	52	371	$C_{23}H_{21}N_3O_2$	206	0.53
24	2- CH3	H	p-Cl	65	389.88	C23H20ClN3O	115	0.49
25	2-CH3	H	Cinnamaldehyde	73	381.47	C25H23N3O	126	0.51
26	2-CH3	p-NH2	p-Cl	61	404.89	C23H21ClN4O	192	0.73
27	4-CH3	p-NH2	H	63	370.45	C23H22N4O	180	0.68
28	4-CH3	p-NH2	p-Cl	63	404.89	C23H21ClN4O	173	0.72

Table 2: Effects of the chalcone semicarbazones on cotton pellet induced granuloma in rats

Compounds	Dose (mg/kg, p.o.)	Increase in weight of Pellet[a]	Inhibition (%)
Control	----	0.69±0.022	----
Aspirin	100	0.11±0.01*	84.05
4	30	0.53±0.039*[b]	23.19
14	30	0.58±0.022*[b]	15.94
24	30	0.41±0.049*[b]	40.57
25	30	0.193±0.021*	72.02
26	30	0.178±0.069*	74.2
27	30	0.189±0.034*	72.6
28	30	0.14±0.022*	79.71
[a] Each value is the mean±SEM for 4 rats. [b]P<0.001 compared with standard; *P<0.001 compared with control; One way ANOVA followed by Turkey Test			

Table 3: Effects of the chalcone semicarbazones on formalin induced paw edema in rats

Group	Dose (mg/kg, p.o.)	Thichness variation (mm)[a]	Inhibition (%)
Control	----	0.26±0.012	----
Aspirin	100	0.07±0.015*	73.08
4	30	0.2±0.016*[c]	23.08
14	30	0.21±0.016[bc]	19.23
24	30	0.20±0.032*[c]	23.08
25	30	0.14±0.018*[c]	46.15
26	30	0.15±0.025*[c]	42.31
27	30	0.12±0.032*[d]	53.85
28	30	0.1±0.016*	61.54
[a] Each value is the mean±SEM for 6 rats. *, [b]P<0.001 & 0.01compared with control respectively; [c, d]P<0.001 & 0.01 compared with standard; One way ANOVA followed by Turkey Test			

Table 4: Anti-inflammatory activity of compounds in carrageenan induced paw edema method

Group	Dose (mg/kg)	Thichness variation (mm)[a]	Inhibition (%)
Control	----	0.950±.122	----
Diclofenac sodium	50	0.160±.010*	83.15
4	30	0.545±.095*[b]	42.63
14	30	0.576±.023*[b]	39.36
24	30	0.391±.021*[b]	58.84
25	30	0.154±.023*	83.78
26	30	0.149±.095*	80
27	30	0.143±.021*	84.94
28	30	0.130±.024*	86.31
[a] Each value is the mean±SEM for 4 rats. * P<0.001 compared with control; [b]P<0.001 compared with standard; One way ANOVA followed by turkey test			

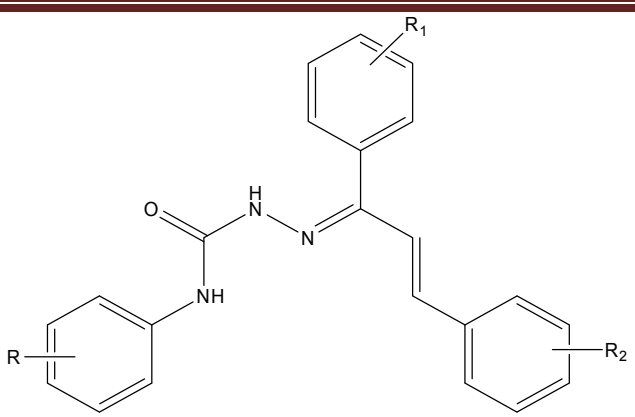

Figure 1: Structure of synthesized title compounds

Source of support: Nil, Conflict of interest: None Declared