International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol. 3, No.3, pp 1485-1489, July-Sept 2011

Synthesis and Analgesic activity of Methylphenyl Semicarbazone derivatives

Manmohan Singhal*[1], Arindam Paul[2]

[1]School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India
[2]G D Memorial College of Pharmacy, Jodhpur, Rajasthan, India

*Corres. author: manu.research2@gmail.com
Phone no: +91-9829153193*

Abstract: In the present study a series of methylphenylsemicarbazones was synthesized and evaluated for their analgesic activities by writhing, hot plate and formalin induced paw licking animal model. 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 analgesic study It was found that chloro substitution in the aldehydic moiety and amino substitution in acetophenic moiety of chalcone exhibited better activity. Lengthening of carbon chain also favor analgesic activity.
Keywords: Chalcones, Analgesic activity, Hot plate, writhing, formalin induced paw licking.

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 activity[8-15]. As a part of ongoing research program to find novel analgesic compounds, herein, we have fused these both active moiety and design a scheme for synthesizing these[16-18]. The analgesic (anti-nociceptive) of synthesized compounds was performed using writhing, hot plate and formalin induced paw licking methods.

Materials and Methods

Chalconesemicarbazones[19] were synthesized according to synthetic scheme as shown in figure 1.

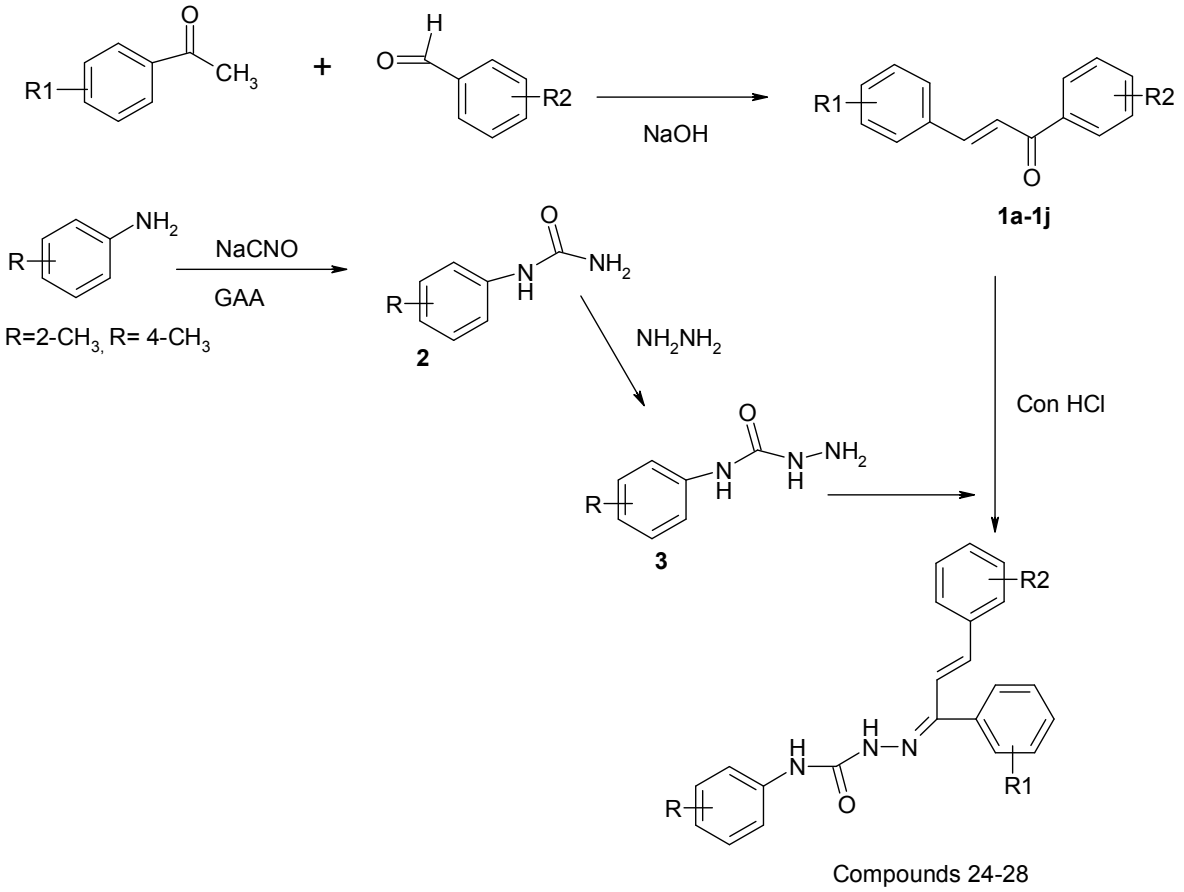

Figure 1: Synthetic scheme for synthesizing the Chalconesemicarbazone compounds

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 D2O. 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 Physicochemical properties of the synthesized title compounds are given in table 1.

Table 1: Physicochemical data of methyl semicarbazones

Comp no.	R	R1	R2	Yield (%)	Mol Wt.	Mol Formula	mp (ºC)	Rf Value
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

ANALGESIC ACTIVITY

The synthesized Chalconesemicarbazones were screened for analgesic activities using the writhing, hot plate test and the formalin induced paw licking test.
In the Hot plate (Eddy's Hot Plate; Techno, India) test animals were orally administered 30 mg/Kg of the Compound, saline (control) or 100 mg/Kg Aspirin (Reference drug). The animals were each placed on a hot plate (maintained at 55 ± 1oC) after 60 min of the administration of the Compound, drug or Saline and the time (Reaction time) it takes each of the animals to jump off the hot plate was noted and cut off period of 15 sec.The mean of the responses for the animals (6 per group) administered each compound was compared with the control group[20].

In the Formalin test, the paws of the animals were injected with 100 µL of 3% formalin after one hour of the oral administration of Compound (30 mg/Kg), saline or Aspirin (!00mg/kg. The licking time in the first phase (0 - 5 min post formalin injection) and in the second phase (20 – 30 min post formalin injection) was noted and the mean for each group was determined and compared with the control group[21,22].

In writhing method, Swiss albino mice of either sex weighing between 25-30 gm were randomly distributed in six groups of six mice each. The first group served as control and the animals of that group were administered 1% v/v acetic acid (1 ml/100 g) intraperitoneally. The onset and the number of writhing were recorded for a period of 10 min for each animal of the group. The second group of animals administered aspirin (50 mg/kg, i.p.) and 30 min later, acetic acid was administered to the animals of that group. The onset and the frequency of writhing response were observed[7]. The animals of remaining groups were treated with drug in DMSO 30 mg/kg and the acetic acid-induced writhing were recorded as described for group 1 and 2. Percent protection against acetic acid induced writhing was calculated using the formula:
% protection = (Nc - Nt / Nc) x 100
where Nt and Nc are the mean values of number of writhing in the test and control group, respectively.

RESULTS AND DISCUSSION

The Analgesic activity of the synthesized methylphenyl semicarbazone compounds was evaluated using Hot plate, Formalin induced paw licking method in rats and acetic induced writhing method in mice which is summarized in table 2, 3 and 4 respectively.

Table 2: Evaluation of Analgesic activity of the synthesized methylphenyl semicarbazones by hot plate test in rats

Compound	Dose mg/kg	Reaction time in seconds (Mean ± SD)[a]	% increase in pain Threshold
Control	----	3.82 ± 0.159	----
Aspirim	100	9.45 ± 0.245*	147.38
Compound 24	30	7.93±0.157* [b]	107.59
Compound 25	30	9.56±0.15*	150.26
Compound 26	30	8.47±0.189* [b]	121.73
Compound 27	30	9.14±0.211*	139.27
Compound 28	30	7.97±0.161* [b]	108.64

[a]Each value is the mean±SEM for 6 rats. *P < 0.001 compared with control; [b]P<0.001compared with standard; One way ANOVA test followed by turkey test.

As from the tables it could be seen that most of the compounds showed significant analgesic activity comparable to the reference drug. 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 algesia.

The chlorine substitution in the aldehydic moiety (compound 24, 26, 28) and amino substitution in acetophenic moiety (compound 26, 27, 28) is favorable for the anti-nociceptive activity and it increases the analgesic activity of the compounds. The lengthening of carbon chain i.e. cinnameldehyde (compound 25) is also favorable for analgesic activity. 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.

Table 3: Effects of the synthesized chalconesemicarbazones on formalin induced paw licking in rat

Compound	**Dose (mg/kg)**	**Formalin induced paw licking**			
		Early phase (seconds)[a]	**Early phase (seconds)[a]**	**% inhibition Early phase (seconds)**	**% inhibition Early phase (seconds)**
Control	--	122.5±10.37	101.67±6.95	----	----
Aspirin	50	31.17±5.46*	20.33±4.55*	74.56	80
Compound 24	30	55.83±4.55* [b]	32.17±6.87*	54.42	68.36
Compound 25	30	48.67±5.87*[c]	42.5±6.66* [b]	60.27	58.2
Compound 26	30	44.83±6.19*	36.5±7.19*	63.4	64.1
Compound 27	30	38.83±7.07*	30.67±5.61*	68.3	69.83
Compound 28	30	62.67±6.34* [b]	47.33±7.42* [b]	48.84	51.96
[a]Each value is the mean ±S.D. for 6 rats. *P < 0.001 compared with control; [b,c]P < 0.001 and 0.01 respectively compared with standard; One way ANOVAfollowed by turkey test.					

Table 4: Effect of the synthesized chalcone semicarbazones on acetic acid induced writhing in mice

Compound	Dose mg/kg	Number of writhings (mean ± SD)[a]	% inhibition of writhing
Control	----	83 ± 6.72	----
Aspirim	50	24.75 ± 2.66*	70.18
Compound 24	30	45.25± 5.32* [b]	45.48
Compound 25	30	36.75± 3.81*	55.72
Compound 26	30	38.5± 6.72*	53.61
Compound 27	30	45.75± 6.30*[b]	44.84
Compound 28	30	32.25 ± 4.48*	61.64
[a]Each value is the mean ±S.D. for 6 mice. *P < 0.001 compared with control; [b]P < 0.001 compared with standard; One way ANOVA test followed by turkey test.			

References

1. McCormick D.A., Contreras D., On the cellular and network bases of epileptic seizures, Ann. Rev. Physiol., 2001, 63, 815-846.
2. Dogan H.N., Duran A., Yemni E., Synthesis and antibacterial activity of 1-(3-hydroxy-2-naphthoyl)-4-substituted thiosemicarbazides, Drug Metabol. Drug Interact., 1999, 15(2-3), 187-195.
3. Pandeya S.N., Dimmock J.R., Recent evaluations of thiosemicarbazones and semicarbazones and related compounds for antineoplastic and anticonvulsant activities, Pharmazie, 1993, 48(9), 659-666.
4. Pandeya S.N., Misra V., Singh P.N., Rupainwar D.C., Anticonvulsant activity of thioureido derivatives of acetopheonone semicarbazones, Pharmacol. Res., 1998, 37, 17-22.
5. Pandeya S.N., Yogeeswari P., Stables J.P., Synthesis and anticonvulsant activity of 4-bromophenyl substituted aryl semicarbazones, Eur. J. Med. Chem., 2000, 35, 879-886.
6. Sriram D., Yogeeswari P., Thirumurugan R.S., Antituberculous activity of some aryl semicarbazone derivatives, Bioorg. Med. Chem. Lett., 2004, 14, 3923-24.
7. Singh H.P., Chauhan C.S., Pandeya S.N., Sharma C.S., Srivastava B., Singhal M., Design, Synthesis, Analgesic and Anti-Inflammatory Activity of Some novel Chalcone semicarbazone derivatives, Der Pharmacia Lettre, 2010, 2(2), 460-462.
8. Meador K.J., Newer anticonvulsants: Dosing strategies and cognition in treating patients with mood disorders and epilepsy, J. Clin. Psychiatry, 2003, 64, 30-34.
9. Lin Z., Kadaba P.K., Molecular targets for the rational design of antiepileptic drugs and related neuroprotective agents, Med. Res. Rev., 1997, 17, 537-572.
10. Yogeeswari P., Raghavendran J., Thirumurugan R., Saxena A., Sriram D., Sodium valproate stimulates potassium and chloride urinary excretion in rats: gender differences, Curr. Drug Targets, 2004, 5, 553-568.
11. Dimmock J.R., Elias D.W., Beazely M.A., Kandepu N.M., Bioactivities of chalcones, Curr. Med. Chem., 1999, 6, 1125-1149.
12. Ni L Meng C.Q., Sikorski J.A., Recent advances in therapeutic chalcones, Expert Opin. Ther. Pat., 2004, 14, 1669-1691.
13. Mokle S.S., Sayyed M.A., Kothawar, Chopde, Studies on Synthesis and Antimicrobial activity of some new Iodochalcones, Flavones and Flavonols, Int. J. Chem. Sci., 2004, 2(1), 96-100.
14. Hsieh H.K., Tsao L.T., Wang J.P., Lin C.N., Synthesis and anti-inflammatory effect of chalcones, J. Pharm. Pharmacol., 2000, 52, 163–171.
15. Viana G.S., Bandeira M.A., Matos F.J., Analgesic and anti- inflammatory effects of chalcones isolated from Myracrodruon urundeuva Allemao, Phytomedicine, 2003, 10, 189-195.
16. Zhao L.M., Jin H.S., Sun L.P., Piao H.R., Quan Z.S., Synthesis and evaluation of antiplatelet activity of trihydroxychalcone derivatives, Bioorg. Med. Chem. Lett., 2005, 15, 5027–5029.
17. Dimmock J.R., Sidhu K.K., Thayer R.S., Mack P., Dutty M.J., Reid R.S., Quail J.W., Anticonvulsant activities of some aryl semicarbazones displaying potent oral activity in the maximal electroshock screen in rats accompanied by high protection indices, J. Med. Chem., 1993, 36, 2243–2252.
18. Pandeya S.N., Ponnilavarasan I., Pandey A., Lakhan R., Stables J.P., Evaluation of p-nitrophenyl substituted semicarbazones for anticonvulsant properties. Pharmazie, 1999, 54, 923–925.
19. Singhal M., Paul A., Singh H.P., Nitric oxide scavenging activity of synthesized methyl semicarbazone derivatives, Der Pharma Chemica, 2011, 3(2), 460-467.
20. Gupta R.K., Tandon V.R., Antinociceptive activity of Vitex negundo Linn. Leaf extract, Indian J. Physiol. Pharmacol., 2005, 49(2), 163-170.
21. Hunskaar S., Hole K., The formalin test in mice-dissociation between inflammatory and non inflammatory pain, Pain, 1997, 30,103–114.
22. Owoyele B.V., Soladoye A.O., Analgesic and anti-inflammatory activity of ethanolic *e*xtract of Chromolaena odorata leaves, Recent Progr. Med. Plants, 2007, 18, 397-406.

*****