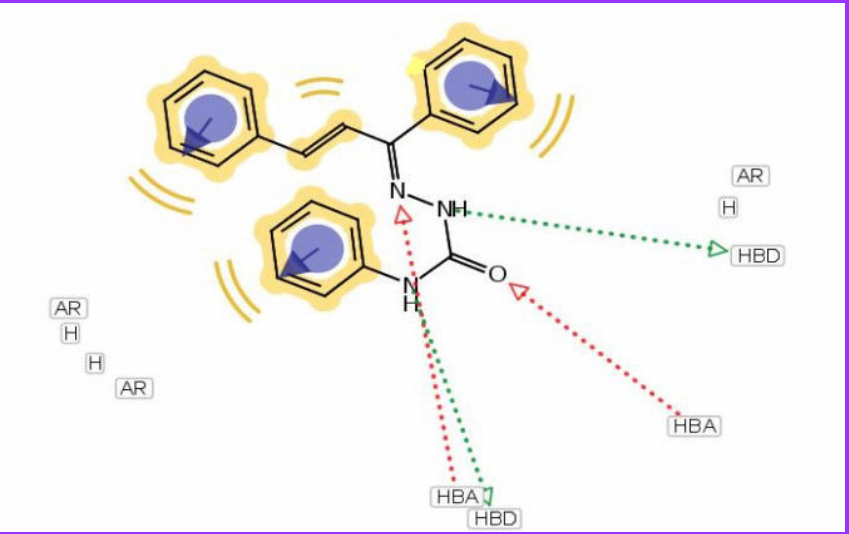

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Design synthesis and biological evaluation of 2-methylphenyl semicarbazone derivatives

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Abstract

We have used pharmacophore hybridization technique of drug design and designed a pharmacophore model 2-methylphenylsemicarbazone which is having hydrogen acceptor site, hydrogen donor site, lipophilic site etc using ligandscout-2.02 software. A series of 2-methylphenyl-semicarbazone was synthesized and evaluated for their antipyretic activity using boiled cow milk induced pyrexia in rabbits. Compound 11 was the most active compound. The possible metabolites of some selected synthesized chalconesemicarbazones were predicted by computational method using Pallas version-3.1 ADME-Tox prediction software. The major pathway of metabolism was found to be p-hydroxylation and amide hydrolysis.

Introduction

Pyrexia is caused as a secondary impact of infection, malignancy or other diseased states. It is the body's natural defense to create an environment where infectious agent or damaged tissue cannot survive (Gulcin et al., 2004). Normally the infected or damaged tissue initiates the enhanced formation of pro-inflammatory mediator's (cytokines like interleukins and TNF-α), which increase the synthesis of prostaglandin E_2 (PGE_2) near peptic hypothalamus area and thereby triggering the hypothalamus to elevate the body temperature (Gupta et al., 2003). High fever often increases faster disease progression by increasing tissue catabolism, dehydration and existing complaints, as found in HIV (Chattopadhyay et al., 2005). Most of the antipyretic drugs inhibit COX-2 expression to reduce the elevated body temperature by blocking the metabolism of arachidonic acid through the enzyme cyclooxygenase (COX) and thereby the production of prostaglandins, e.g. PGE_2 (McCormick and Contreras, 2001). Semicarbazone, themselves are of much interest due to a wide spectrum of pharmacological activities like antibacterial, antifungal (Dogan et al., 1999), anticonvulsant (Pandeya et al., 1998), antitubercular (Sriram et al., 2004), analgesic and anti-inflammatory (Singh et al., 2010) etc. 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 (Viana et al., 2003).

In the present study, we have used pharmacophore hybridization technique of drug design and designed a pharmacophore model 'semicarbazone', which is having hydrogen acceptor site, hydrogen donor site, lipophilic site, etc (Figure 1) using ligandscout 2.02 software by minimizing energy with MM3 force field, which may help in binding with receptors and plays an important role in pharmacological activities.

On these observations, we have designed a synthetic scheme to synthesize this pharmacophore, and also synthesize some lead compounds. The possible metabolites of some selected synthesized compounds were predicted by computational method using Pallas version 3.1 ADME-Tox prediction (Mexalert/RetroMex) software.

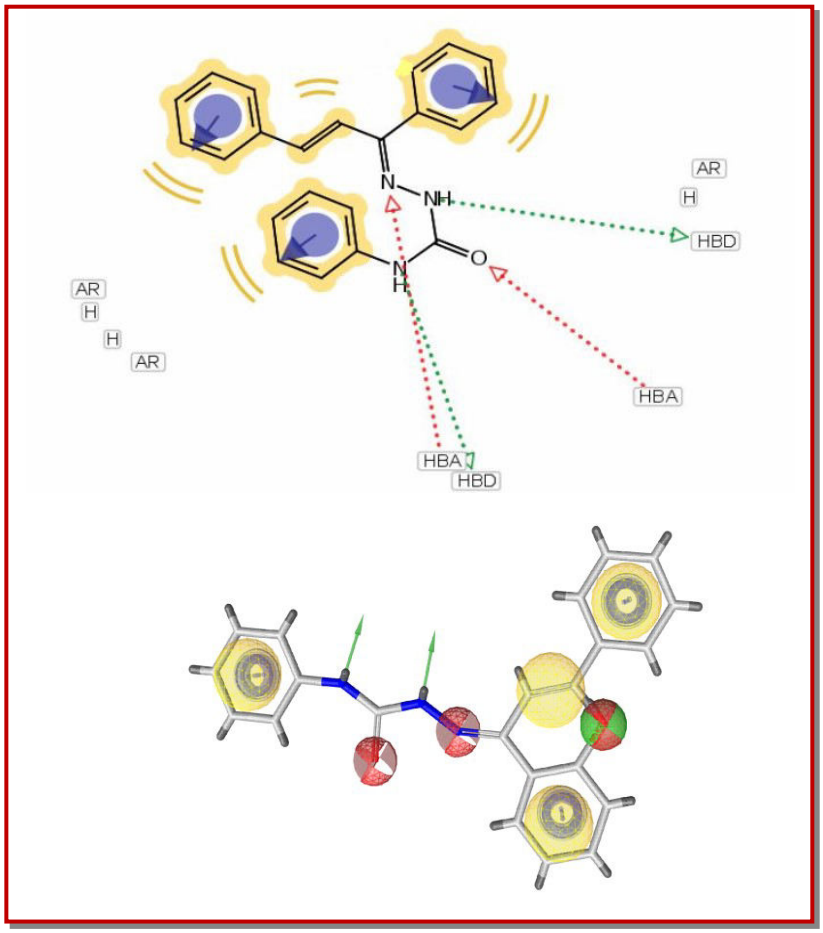


Figure 1: Pharmacophore of the designed chalconesemicarbazone by ligandscout 2.02

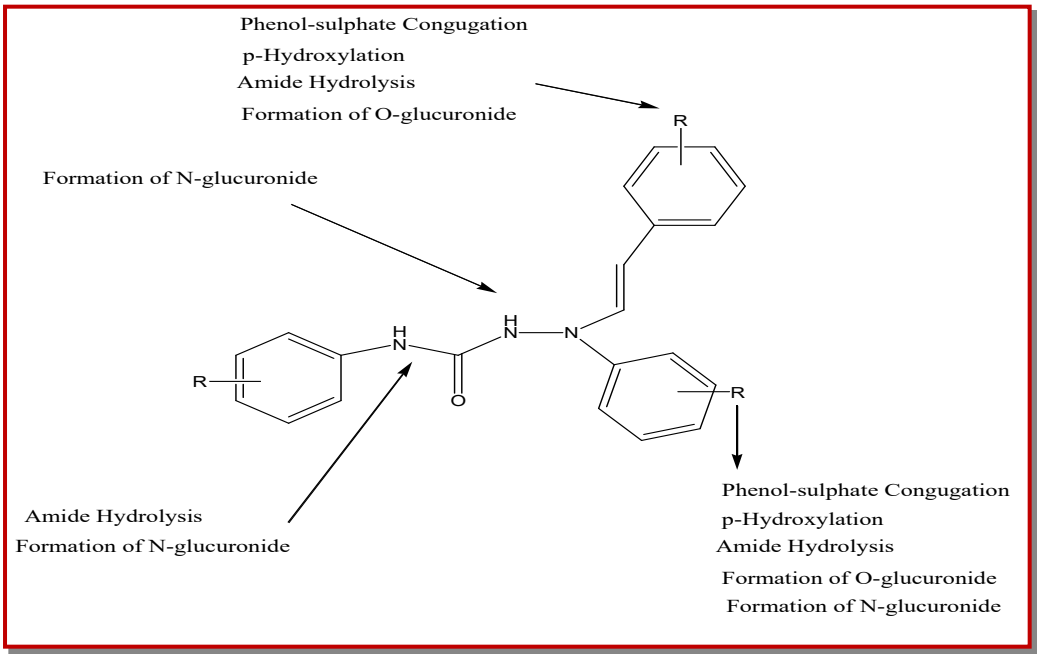
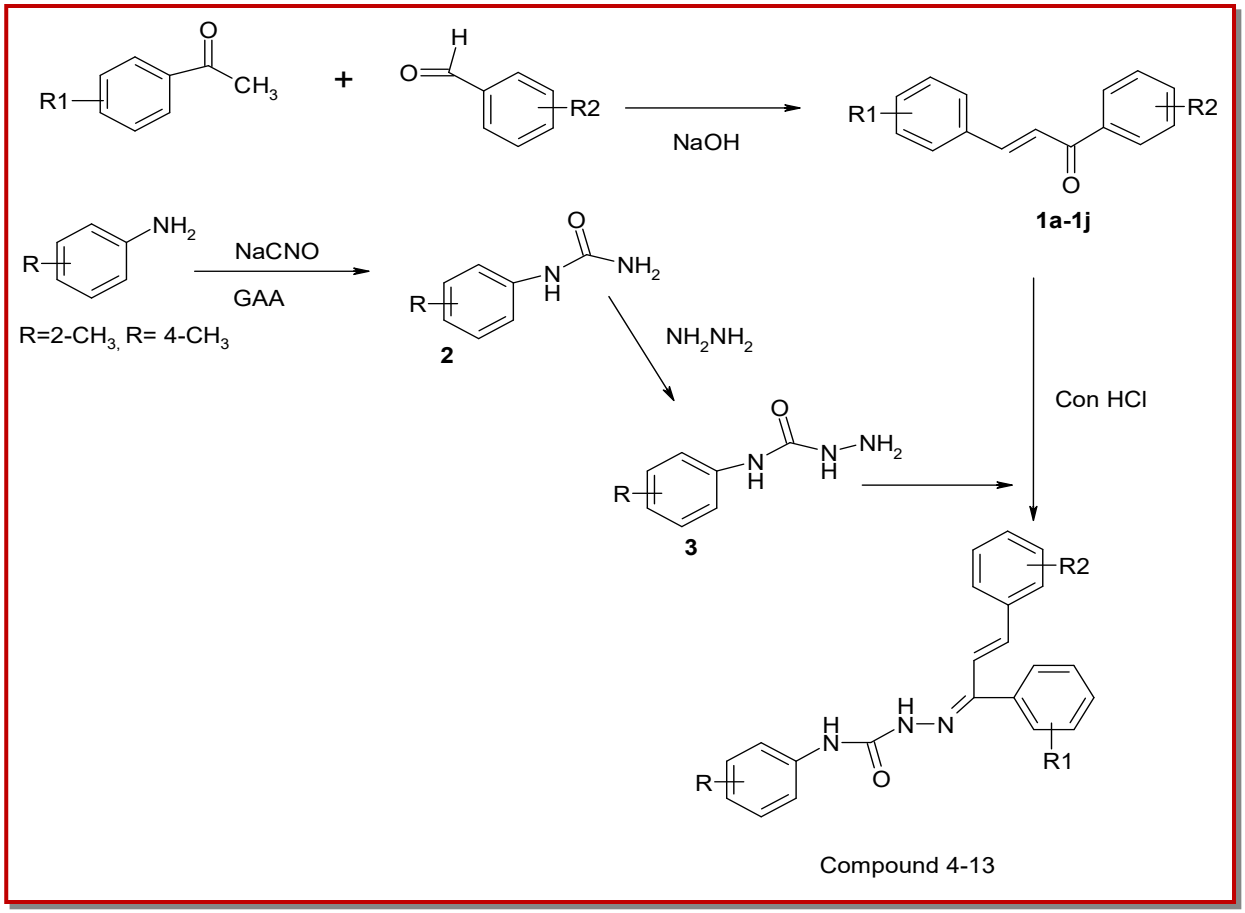


Figure 2: *In silico* metabolism of the chalconesemicarbazone



Scheme 1: Synthetic scheme for synthesizing the semicarbazone derivatives

Table I

Physicochemical properties of chalcone derivatives

Comp No.	R_1	R_2	Molecular formula	mp (°C)	Yield (%)	Rf value
1a	H	H	$C_{15}H_{12}O_2$	89	85	0.80
1b	H	4″-OH	$C_{15}H_{12}O_3$	164	85	0.83
1c	H	4″-OCH_3	$C_{16}H_{14}O_3$	135	85	0.82
1d	H	4″-$N(CH_3)_2$	$C_{17}H_{17}NO_2$	155	85	0.78
1e	4′-OH	6″-OH	$C_{15}H_{12}O_4$	216	90	0.85
1f	4′-OH	4″-$N(CH_3)_2$	$C_{17}H_{17}NO_3$	174	90	0.81
1g	H	6″-OH	$C_{15}H_{12}O_3$	166	85	0.86
1h	5′OH	6″-OH	$C_{15}H_{12}O_4$	218	85	0.84
1i	5′OH	4″-OH	$C_{15}H_{12}O_4$	208	85	0.87
1j	5′OH	4″-OCH_3	$C_{16}H_{14}O_4$	152	85	0.79

Table II

Physicochemical data of semicarbazone derivatives

Comp No.	R	R_1	R_2	Yield (%)	Mol Wt.	Molecular formula	mp (°C)	Rf Value
4	2-CH_3	H	H	57	371	$C_{23}H_{21}N_3O_2$	150	0.78
5	2-CH_3	H	4″-OH	66	387	$C_{23}H_{21}N_3O_3$	145	0.71
6	2-CH_3	H	4″-OCH_3	65	401	$C_{24}H_{23}N_3O_3$	135	0.65
7	2-CH_3	H	4″-$N(CH_3)_2$	58	414	$C_{25}H_{26}N_4O_2$	148	0.57
8	2-CH_3	4-OH	6″-OH	57	403	$C_{23}H_{21}N_3O_4$	142	0.60
9	2-CH_3	4-OH	4″-$N(CH_3)_2$	50	430	$C_{25}H_{26}N_4O_3$	160	0.67
10	2-CH_3	H	6″-OH	63	387	$C_{23}H_{21}N_3O_3$	140	0.55
11	2-CH_3	5-OH	6″-OH	61	403	$C_{23}H_{21}N_3O_4$	135	0.63
12	2-CH_3	5-OH	4″-OH	56	403	$C_{23}H_{21}N_3O_4$	120	0.69
13	2-CH_3	5-OH	4″-OCH_3	57	417	$C_{24}H_{23}N_3O_4$	126	0.51

In silico metabolism prediction of the synthesized compounds is given in Figure 2. The major pathway of metabolism was found to be p-hydroxylation and amide hydrolysis however in some compounds glucuronide and sulfate conjugation may also occur.

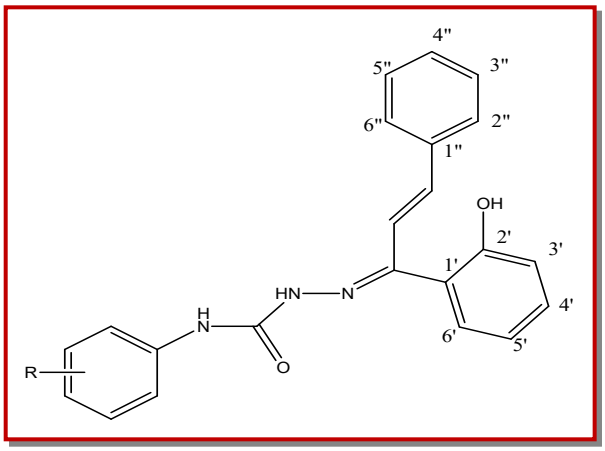


Figure 3: Structure of synthesized semicarbazone derivatives

Materials and Methods

Chemistry

Chalconesemicarbazones were synthesized according to synthetic Scheme 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 (^{1}H 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 24°C 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.

Synthesis of substituted chalcone derivatives

Substituted benzaldehydes (0.012 mol) were added to a mixture of substituted acetophenones (0.01 mol) in 25 mL of ethanol in a 200 mL beaker. The content of the beaker was mixed well and to that 10 mL of 10% potassium hydroxide solution was added and stirred vigorously at 25°C until the mixture was so thick that stirring was no longer effective (3-4 hours). After the completion of the stirring, the reaction mixture was kept in a refrigerator overnight. The reaction mixture was then diluted with ice-cold water (50 mL), acidified with 10% aqueous hydrochloric acid to precipitate the chalcones. The product was filtered with suction on a Buchner funnel, washed with cold water until the washings were neutral to litmus and then washed with 10 mL of ice-cold rectified spirit. The dried product was recrystallized from chloroform. The physicochemical properties of the synthesized chalcone derivatives are given in Table I.

Synthesis of methyl phenyl urea (2)

Substituted aniline (0.1 mol) was dissolved in 20 mL of glacial acetic acid and 10 mL of water. To this, 0.1 mol of sodium cyanate (6.5 g) in 80 mL of warm water was added with continuous stirring. The reaction mixture was allowed to stand for 30 min and then cooled in ice. The crude solid, thus obtained was filtered, dried and recrystallized with boiling water to yield methyl phenyl urea.

Synthesis of substituted phenyl semicarbazide (3)

Equimolar quantities (0.05 mol) of above phenyl urea (**2**) and hydrazine hydrate (2.5 mL) in ethanol were refluxed for 27 hours with continuous stirring. The two-third volume of ethanol was distilled by vacuum distillation unit and then poured into ice. The resultant crude solid was filtered, washed with water and dried. The obtained solid was recrystallized with 50 mL of 90% alcohol.

General method for the synthesis of substituted phenyl chalconesemicarbazone

To a solution of above **(3)** (0.005 mol) in 25 mL of ethanol added an equimolar quantity of the appropriate chalcone derivative previously dissolved in ethanol. Then few drops of concentrated hydrochloric acid was added and continuously stirred for 4-5 hours. The reaction mixture was poured into ice and precipitate, so obtained was filtered, washed with sodium acetate (0.005 mol, 0.4 g) in 2 mL water. The crude solid was dried and recrystallized with hot ethanol. The structures (Figure 3) and physicochemical properties of the synthesized title compounds are given in Table II**.**

1-[1-(2-hydroxyphenyl)-3-phenylallylidene]-4-(2-methylphenyl) semicarbazide (4): 1H-NMR (δ/ppm in $CDCl_3$): 2.12 (s, 3H, Ar-CH_3), 4.83 (s, 1H, 2-OH), 7.11-7.64 (m, J= 8.32 Hz, 12H, Ar-H) 7.7 (s, 1H, –CH=CH–), 7.9 (s, 1H, –CH=CH–), 8.34 (s, 1H, ArNH, D_2O exchangeable), 9.42 (s, 1H, CONH, D_2O exchangeable); IR (KBr/cm^{-1}): 3450 (NH), 3480 (–OH), 3300–3240 (CONH), 1670 (–CH=CH–), 1590 (C-N), 1616, 1558 (aromatic), 754, 697 (monosubstituted benzene); MS, *m/z* 370; Elemental analysis calculated/found (%) C (74.37/74.26), H (5.70/5.48), N (11.31/11.12).

1-[1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)allylidene]-4-(2-methylphenyl) semicarbazide (5): 1H-NMR (δ/ppm in $CDCl_3$): 2.18 (s, 3H, Ar-CH_3), 4.9 (s, 1H, 2-OH), 5.2 (s, 1H, 4-OH), 7.3-7.64 (m, J= 8.4 Hz, 11H, Ar-H) 7.8 (s, 1H, –CH=CH–), 8.0 (s, 1H, –CH=CH–), 8.44 (s, 1H, ArNH, D_2O exchangeable), 9.8 (s, 1H, CONH, D_2O exchangeable); IR (KBr/cm^{-1}): 3455 (NH), 3475 (–OH), 3310–3245 (CONH), 1675 (–CH=CH–),1594 (C-N), 1615, 1556 (aromatic), 750, 695 (monosubstituted benzene); MS, *m/z* 386; Elemental analysis, cal/fou (%) C (71.30/71.24), H (5.46/5.35), N (10.85/10.47).

1-[1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)allylidene]-4-(2-methylphenyl) semicarbazide (6): 1H-NMR (δ /ppm in $CDCl_3$): 2.16 (s, 3H, Ar-CH_3), 4.7 (s, 1H, 2-OH), 3.88 (s, 3H, 4-OCH_3), 7.12-7.85 (m, J= 8.3 Hz, 11H, Ar-H), 7.98 (s, 1H, –CH=CH–), 8.35 (s, 1H, –CH=CH–), 8.87 (s, 1H, ArNH, D_2O exchangeable), 9.86 (s, 1H, CONH, D_2O exchangeable); IR (KBr/cm^{-1}): 3458 (NH), 3478 (–OH), 3310–3243 (CONH), 1677 (–CH=CH–),1587 (C-N), 1626, 1555 (aromatic), 758, 687 (monosubstituted benzene); MS, *m/z* 400; Elemental analysis cal/fou (%) C (71.80/71.57), H (5.77/5.48), N (10.47/10.36).

1-[1-(2,4-dihydroxyphenyl)-3-(2-hydroxyphenyl)allylidene]-4-(2-methylphenyl) semicarbazide (9): 1H-NMR (δ /ppm in $CDCl_3$): 2.48 (s, 3H, Ar-CH_3), 5.1 (s, 1H, 2-OH), 5.3 (s, 1H, 4-OH), 6.4 (s, 1H, 6-OH), 7.22-7.58 (m, J= 8.5 Hz, 10H, Ar-H) 7.88 (s, 1H, –CH=CH–), 8.4 (s, 1H, –CH=CH –), 8.77 (s, 1H, ArNH, D_2O exchangeable), 9.85 (s, 1H, CONH, D_2O exchangeable); IR (KBr/cm^{-1}): 3453 (NH), 3482 (–OH), 3314–3242 (CONH), 1667 (–CH=CH–), 1594 (C-N), 1618, 1552 (aromatic), 758, 687 (monosubstituted benzene); MS, *m/z* 402; Elemental analysis cal/fou (%) C (68.47/68.44), H (5.25/5.16), N (10.42/10.37).

1-[1-(2-hydroxyphenyl)-3-(2-hydroxyphenyl)allylidene]-4-(2-methylphenyl) semicarbazide (11): 1H-NMR (δ /ppm in $CDCl_3$): 2.24 (s, 3H, Ar-CH_3), 5.1 (s, 1H, 2-OH), 5.3 (s, 1H, 2, 4-OH), 7.2-7.78 (m, J= 8.35 Hz, 11H, Ar-H) ,7.8 (s, 1H, –CH=CH–), 8.2 (s, 1H, –CH=CH–), 8.78 (s, 1H, ArNH, D_2O exchangeable), 9.84 (s, 1H, CONH, D_2O exchangeable); IR (KBr/cm^{-1}): 3462 (NH), 3488(–OH), 3300–3240 (CONH), 1666 (–CH=CH–),1593 (C-N), 1618, 1554 (aromatic), 753, 694 (monosubstituted benzene); MS, *m/z* 386; Elemental analysis cal/fou (%) C (71.30/71.17), H (5.46/5.37), N (10.85/10.66).

1-[1-(2,5-dihydroxyphenyl)-3-(4-hydroxyphenyl)allylidene]-4-(2-methylphenyl) semicarbazide (13): 1H-NMR (δ /ppm in $CDCl_3$): 2.16 (s, 3H, Ar-CH_3), 5.4 (s, 1H, 2-OH) 5.2 (s, 1H, 4-OH), 5.6 (s, 3H, 5-OH) 7.22-7.88 (m, J= 8.6 Hz, 10H, Ar-H), 7.84 (s, 1H, –CH=CH–), 8.4 (s, 1H, –CH=CH–), 8.82 (s, 1H, ArNH, D_2O exchangeable), 9.96 (s, 1H, CONH, D_2O exchangeable); IR (KBr/cm^{-1}): 3456 (NH), 3482 (–OH), 3310–3245 (CONH), 1667 (–CH=CH–), 1593 (C-N), 1615, 1552 (aromatic), 755, 693 (monosubstituted benzene); MS, *m/z* 402; Elemental analysis cal/fou (%) C (68.47/68.28), H (5.25/5.17), N (10.42/10.08).

Boiled cow milk induced pyrexia in rabbit

Boiled cow milk induced pyrexia was used to evaluate the antipyretic activity of 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 body weight, to induce pyrexia. Induction of fever was taken about two to three hours. Then test animals were orally administered 30 mg/kg of the synthesized compounds, saline (control) or 100 mg/kg aspirin (reference drug). Finally, rectal temperatures were recorded 1 hour intervals up to 3 hours (Khan et al., 2007).

Table III

Effect of chalcone semicarbazones on boil milk induced pyrexia in rabbits

Compound	Dose (mg/kg)	Rectal temperature (°F)*		Rectal temperature after administration of compound (°F)*		
		Normal (A)	3 hours after boil milk administration (B)	1 hour (C1)	2 hours (C2)	3 hours (C3)
Control	----	99.9 ± 0.3	103.2 ± 0.3	103.2 ± 0.3	103.2 ± 0.3	103.2 ± 0.3
Aspirin	100	99.8 ± 0.2	103.6 ± 0.2	100.2 ± 0.3 (89)[a]	99.9 ± 0.2 (97.4)[a]	99.8 ± 0.2 (100)[a]
4	30	99.9 ± 0.4	103.4 ± 0.3	102.95 ± 0.31 (13.4)[d]	102.6 ± 0.3 (24.9)[d]	102.0 ± 0.3 (40)[a,d]
5	30	98.7 ± 0.2	102.8 ± 0.2	101.3 ± 0.1 (35.9)[d]	100.5 ± 0.1 (55.4) [a,d]	99.9 ± 0.2 (69.5)[a,d]
6	30	99.2 ± 0.2	103.3 ± 0.1	101.0 ± 0.2 (56.3)[a,f]	100.5 ± 0.2 (67.9) [a,f]	100.2 ± 0.2 (75.3)[a,d]
7	30	99.8 ± 0.4	103.7 ± 0.4	103.3 ± 0.4 (10.4)[d]	102.8 ± 0.4 (23.5)[d]	102.3 ± 0.4 (34.7)[b,d]
8	30	99.2 ± 0.2	103.1 ± 0.2	100.5 ± 0.2 (66.8)[a]	100.2 ± 0.1 (74.3) [a]	100.1 ± 0.2 (76.8)[a,d]
9	30	98.7 ± 0.2	102.7 ± 0.1	102.0 ± 0.1 (17.8)[d]	101.5 ± 0.1 (31.4)[d]	101.0 ± 0.1 (43.2)[a,d]
10	30	99.2± 0.1	103.2 ± 0.1	101.1 ± 0.3 (52.2)[b,e]	100.4 ± 0.2 (69.7) [a,f]	100.1 ± 0.1 (77.6)[a,d]
11	30	98.8 ± 0.2	102.9 ± 0.2	99.3 ± 0.2 (86.3)[a]	99.1 ± 0.2 (92.8) [a]	98.9 ± 0.2 (95.9)[a]
12	30	99.2 ± 0.2	103.2 ± 0.2	100.4 ± 0.1 (70.2)[a]	100.1 ± 0.2 (77.6) [a]	100.0 ± 0.2 (79.6)[a,e]
13	30	98.3 ± 0.2	103.0 ± 0.2	100.2 ± 0.3 (60.2)[a]	99.9 ± 0.2 (65.5) [a]	99.7 ± 0.2 (69.8)[a,d]

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

Results and Discussion

The antipyretic activity of the synthesized methyl semicarbazone compounds was evaluated using boiled cow milk induced pyrexia in rabbits which is summarized in Table III. As from the tables it could be seen that most of the compounds showed significant antipyretic activity comparable to the reference drug. Comparison of the antipyretic activity of all tested compounds revealed that compound **11** was the most active compound in the synthesized chalcone-semicarbazone series. The order of activity regarding substitution on chalconyl group is OH> OCH_3> $(CH_3)_2$-N>H (Singh et al., 2008; Taranalli et al., 2008). 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.

When the phenyl group of aldehydic and acetophenic moiety of chalcone was substituted with –OH group (compound- **11**, **12**) the compounds exhibited better activity in comparison to substitution with the other groups like p-dimethyl amino groups (compound **7**, **9**), may be due to increased hydrogen bonding interactions with the receptors. Hydroxyl substitution on both moieties of chalcone has more protection against pyrexia than substitution on any one moiety. Methoxy substitution in the aldehydic moiety of chalcone also favors antipyretic activity.

Among the synthesized compounds, compound **8**, **11**, **12** and **13** showed the better or comparable activity in comparision to the standard drug. In case of bulkier substitution (compound **7**, **9**) the substitution decrease the activity which may be due to the improper attachment with the receptor as compared to hydroxyl or methoxy substitution. The compounds with no substitution (compound **4**) or less substitution were showed very less protection against pyrexia in comparison to the substituted compounds (Deshpande and Pai, 2010; Keri et al., 2010; Lin et al., 1997).

Conclusion

Most of the synthesized compounds were potential lead for antipyretic activity. On the basis of observed results, it may be concluded that the substitution favors the activity, but the bulkier substitution may also disfavors the activity, may be due to the improper attachment with binding site. The hydroxyl substitution increases

the activity of the compounds, may be due to increased hydrogen bonding with the binding site.

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