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# Synthesis Characterization and Antipyretic Evaluation of Some Novel Chalconesemicarbazone Derivatives

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**Abstract:** In the present study, researchers have used pharmacophore hybridization technique of drug design and designed a pharmacophore model chalconesemicarbazone which is having hydrogen acceptor site, hydrogen do nor site and lipophilic site, etc., using ligandscout-2.02 software. A series of 2-methyl pheny lsemicarbazone was synthesized and evaluated for their antipyretic activity using Brewe's yeast induced pyrexia in rats. Based on the results of an antipyretic study, compound 12 was the most active compound. When the phenyl group of aldehydic and acetophenic moiety of chalcone is substituted with hydroxy group, the compounds exhibited better activity in comparison to substitution with the other groups like p-dimethyl amino groups. The unsubstituted compounds showed very less protection against pyrexia in comparison to the substituted compounds. 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.

**Key words:** Hyperthermia, chalcone, ligandscout, brewer's yeast, pallas, synthesized

## 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-$\alpha$) which increase the synthesis of prostaglandin E2 (PGE2) 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., PGE2 (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, etc. (Singh *et al*., 2010a). 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, researchers have used pharmacophore hybridization technique of drug design and designed a pharmacophore model chalconesemicarbazone which is having hydrogen acceptor site, hydrogen donor site and lipophilic site, etc. (Fig. 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, researchers 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. *In silico* metabolism prediction of the synthesized compounds is shown in Fig. 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.

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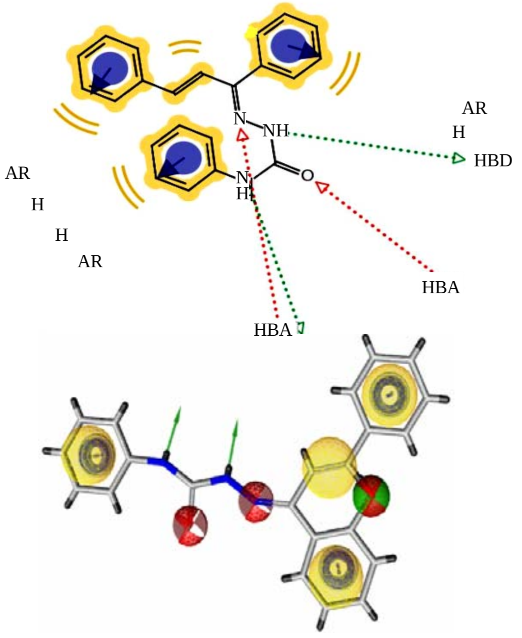

Fig. 1: Pharmacophore of the designed chalconesemicarbazone by ligandscout 2.02

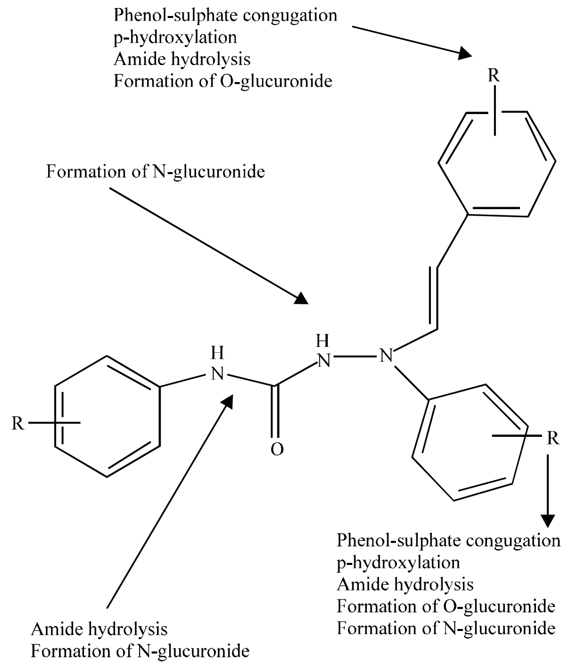

Fig. 2: *In silico* metabolism of the chalconesemicarbazone

## MATERIALS AND METHODS

**Chemistry:** Chalconesemicarbazones were synthesized according to synthetic scheme 1 (Fig. 3). 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 $D_2O$.

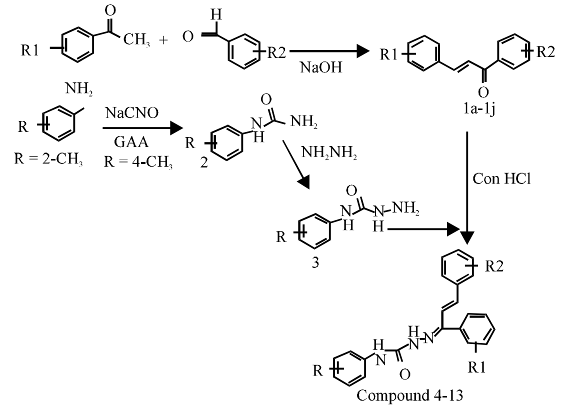

Fig. 3: Synthetic scheme for synthesizing the semicarbazone derivatives

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.

**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 h). 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 shown in Table 1.

Table 1: Physico-chemical 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 |

**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 h 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 con. hydrochloric acid was added and continuously stirred for 4-5 h. The reaction mixture was poured into ice and precipitate so obtained was filtered, washed with sodium acetate (0.005 mol, 0.41 g) in 2 mL water. The crude solid was dried and recrystallized with hot ethanol. The structures and physicochemical properties of the synthesized title compounds are shown in Table 2 (Fig. 4).

**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$_2$O exchangeable), 9.42 (s, 1H, CONH, D$_2$O 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).

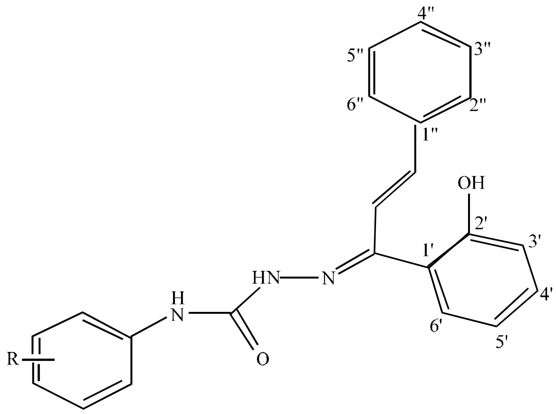

Fig. 4: Structure of synthesized semicarbazone derivatives

**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$_2$O exchangeable), 9.8 (s, 1H, CONH, D$_2$O 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$_2$O exchangeable), 9.86 (s, 1H, CONH, D$_2$O 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

Table 2: 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 |

(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).

**Yeast induced hyperthermia in rats:** Yeast induced pyrexia (Fadeyi *et al*., 2004) was used to evaluate the antipyretic activity of synthesized compounds. The protocol for animal experimentation was approved by Institutional Animal Ethics Committee. Protocol approval reference number is PBRI/IAEC/10/PN-118. Before experimentation basal rectal temperature of rats were recorded by inserting a well lubricated bulb of a thermometer in the rectum. Rats were injected subcutaneously with 10 mL $kg^{-1}$ body weight brewer's yeast suspension (15% in 0.5% w/v methylcellulose) to induce pyrexia. Total 19 h after yeast injection, the rectal temperature was recorded again and animals showing a rise in temperature of <0.6°C were discarded. Thereafter, treatment was carried out. Test animals were orally administered 30 mg $kg^{-1}$ of the synthesized compounds, saline (10 mL $kg^{-1}$; p.o.; control) or 100 mg $kg^{-1}$ Aspirin (Reference drug). Finally, rectal temperatures were recorded by digital thermometer at 1, 2 and 3 h intervals after administration of compounds[14,15]. Percentage inhibition of elevated temperature (pyrexia) was calculated using equation:

$$\text{Percentage of inhibition of elevated temperature (pyrexia)} = \frac{(B-A)-(C-A)}{(B-A)} \times 100$$

Where:

A = Norman temperature
B = Temperature after 19 h of brewer's yeast administration
C = Temperature at different time interval after Standard/Synthesized compounds administered

All the data were given as mean±SD for 6 rats. The $p<0.001$, 0.01 and 0.05 were considered significant. Mean difference in temperature elevation was measured statistically by one way ANOVA followed by Turkey test.

## RESULTS AND DISCUSSION

The antipyretic activity of the synthesized chalconesemicarbazone compounds was evaluated using Brewer's yeast induced pyrexia in rats which is shown in Table 3. As from the Table 3, 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 12 was the most active compound in the synthesized chalconesemicarbazone series. The order of activity regarding substitution on chalconyl group is OH> $OCH_3$>$(CH_3)_2$-N>H (Singh *et al*., 2010b;

Table 3: Effect of chalcone semicarbazones on yeast induced hyperthermia in rats

| Compound | Dose (mg kg$^{-1}$) | Rectal temperature (°C)* | | Rectal temperature after administration of compound (°C)* | | |
|---|---|---|---|---|---|---|
| | | Normal (A) | 19 h after yeast admin (B) | 20 h (C1) | 21 h (C2) | 22 h (C3) |
| Control | - | 100.75±0.23 | 103.88±0.12 | 103.95±0.1 | 103.97±0.08 | 103.95±0.13 |
| Aspirin | 100 | 100.7±0.14 | 103.97±0.06 | 102.15±0.11 (55.66)$^{a}$ | 101.42±0.24 (77.98)$^{a}$ | 100.95±0.19 (92.35)$^{a}$ |
| 4 | 30 | 100.8±0.14 | 103.97±0.16 | 103.3±0.18 (21.14)$^{d}$ | 103.07±0.22 (28.39)$^{a, d}$ | 102.95±0.13 (32.18)$^{a, d}$ |
| 5 | 30 | 100.37±0.11 | 103.63±0.09 | 102.6±0.09 (31.8)$^{a, f}$ | 102.25±0.11 (42.51)$^{a, d}$ | 102.13±0.09 (45.87)$^{a, d}$ |
| 6 | 30 | 100.53±0.16 | 103.78±0.13 | 102.72±0.13 (32.92)$^{a, f}$ | 102.32±0.15 (45.23)$^{a, d}$ | 102.18±0.15 (49.23)$^{a, d}$ |
| 7 | 30 | 100.72±0.16 | 103.93±0.1 | 103.45±0.16 (15.22)$^{d}$ | 103.28±0.12 (20.19)$^{d}$ | 103±0.19 (29.19)$^{a, d}$ |
| 8 | 30 | 100.37±0.14 | 103.53±0.12 | 102±0.1 (48.58)$^{a}$ | 101.52±0.12 (63.72)$^{a}$ | 101.25±0.08 (72.24)$^{a, f}$ |
| 9 | 30 | 100.38±0.11 | 103.6±0.11 | 102.85±0.11 (23.29)$^{c, d}$ | 102.57±0.13 (32.3)$^{a, d}$ | 102.45±0.11 (35.7)$^{a, d}$ |
| 10 | 30 | 100.22±0.28 | 103.57±0.23 | 102.38±0.13 (35.22)$^{a, f}$ | 101.78±0.13 (53.13)$^{a, e}$ | 101.82±0.16 (52.24)$^{a, d}$ |
| 11 | 30 | 100.3±0.17 | 103.62±0.17 | 101.7±0.14 (57.83)$^{a}$ | 101.17±0.24 (73.79)$^{a}$ | 101.02±0.21 (78.31)$^{a}$ |
| 12 | 30 | 100.42±0.11 | 103.6±0.11 | 101.73±0.13 (58.49)$^{a}$ | 101.17±0.1 (76.41)$^{a}$ | 101.1±0.08 (78.62)$^{a}$ |
| 13 | 30 | 100.35±0.13 | 103.55±0.12 | 101.9±0.07 (51.56)$^{a}$ | 101.5±0.09 (64.06)$^{a}$ | 101.35±0.1 (68.75)$^{a, e}$ |

Figures in parenthesis indicate inhibition (%) of temperature elevation; $^{a,c}p<0.001$ and 0.05 compared with control; $^{d\text{-}f}p<0.001$, 0.01 and 0.05, respectively compared with standard; one way ANOVA test followed by Turkey test. *Each value is the mean±SD for 6 rats

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 is 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, 17) 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, 11-13 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

In summary, most of the synthesized compounds were potential lead for antipyretic activity. On the bases 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.

## REFERENCES

Chattopadhyay, D., G. Arunachalam, L. Ghosh, K. Rajendran, A.B. Mandal and S.K. Bhattacharya, 2005. Antipyretic activity of *Alstonia macrophylla* Wall ex A. DC: An ethnomedicine of Andaman Islands. Pharm. Pharm. Sci., 8: 558-564.

Deshpande, S.R. and K.V. Pai, 2010. Synthesis, antibacterial and analgesic activities of 4-[1-Oxo-3-(substituted aryl)-2-propenyl]-3-(4-methylphenyl) sydnones. E-J. Chem., 7: 59-64.

Dogan, H.N., A. Duran and E. Yemni, 1999. Synthesis and antibacterial activity of 1-(3-hydroxy-2-naphthoyl)-4-substituted thiosemicarbazides. Drug Metabol. Drug Interact., 15: 187-195.

Fadeyi, O.O., C.A. Obafemi, C.O. Adewunmi and E.O. Iwalewa, 2004. Antipyretic, analgesic, antiinflammatory and cytotoxicity effect of four derivative of salicylic acid and anthranillic acid in mice and rat. Afr. J. Biotechnol., 3: 426-431.

Gulcin, I., O.I. Kufrevioglu, M. Oktay and M.E. Buyukokuroglu, 2004. Antioxidant antimicrobial antiulcer and analgesic activities of nettle (*Urtica dioica* L.). J. Ethnopharmacol., 90: 205-215.

Gupta, M., U.K. Mazumder, L. Manikandan, P.K. Haldar, S. Bhattacharya and C.C. Kandar, 2003. Antibacterial activity of *Vernonia cinerea*. Fitoterapia, 74: 148-150.

Keri, R.S., K.M. Hosamani and M.H. Hugar, 2010. Synthesis, anlgesic and anti-pyretic activity of *Pyrimidine derivatives* containing a coumarin moiety. Eur. J. Med. Chem., 45: 2597-2605.

Lin, C.N., T.H. Lee, M.F. Hsu, J.P. Wang, F.N. Ko and C.M. Teng, 1997. 2, 5'-dihydroxychalcone as a potent chemical mediator and cyclooxygenase inhibitor. J. Pharm. Pharmacol., 49: 530-536.

McCormick, D.A. and D. Contreras, 2001. On the cellular and network bases of epileptic seizures. Ann. Rev. Physiol., 63: 815-846.

Pandeya, S.N., V. Misra, P.N. Singh and D.C. Rupainwar, 1998. Anticonvulsant activity of thioureido derivatives of acetopheonone semicarbazones. Pharmacology, 37: 17-22.

Singh, H.P., C.S. Chauhan, S.N. Pandeya, C.S. Sharma, B. Srivastava and M. Singhal, 2010a. Synthesis and pharmacological screening of some novel chloro chalconesemicarbazone derivatives. Der Pharma Chem., 2: 343-351.

Singh, H.P., C.S. Chauhan, S.N. Pandeya, C.S. Sharma, B. Srivastava and M. Singhal, 2010b. Design, synthesis, analgesic and anti-inflammatory activity of some novel chalcone semicarbazone derivatives. Der Pharm. Lett., 2: 460-262.

Sriram, D., P. Yogeeswari and R.S. Thirumurugan, 2004. Antituberculous activity of some aryl semicarbazone derivatives. Bioorg. Med. Chem. Lett., 14: 3923-3924.

Taranalli, A.D., A.R. Bhat, S. Srinivas and E. Saravanan, 2008. Antiinflammatory, analgesic and antipyretic activity of certain thiazolidinones. Ind. J. Pharm. Sci., 70: 159-164.

Viana, G.S.B., M.A.M. Bandeira and F.J.A. Matos, 2003. Analgesic and anti-inflammatory effects of chalcones isolated from *Myracrodruon urundeuva* Allemao. Phytomedicine, 10: 189-195.