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ANALGESIC ACTIVITY OF THIOSEMICARBAZONE & THIAZOLYL HYDRAZONE SCHIFF BASES OF 1-INDANONE

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ABSTRACT

Thiosemicarbazone and a series of Thiozolyl hydrazone of 1-indanone have been synthesized. Analgesic activity of the prepared derivatives was evaluated *in vitro* in comparison to standard drug (Aspirin) by tail flick method. Out of 13 synthesized compounds (**c1**- **c13**) 9 showed analgesic activity and 4 compounds (**c3**, **c6**, **c11** and **c13**) were found inactive. Out of 9 active compounds 3 compounds (**c7**, **c8** and **c12**) were found comparable with Aspirin from 30-90min. None of the compound was found more active than Aspirin.

INTRODUCTION

Indanone is an important scaffold in pharmaceutical research and found to be very useful in the synthesis of a variety of molecules having carbocyclic and heterocyclic systems which have been widely used in medicine, agriculture and in natural products synthesis and have shown a wide variety of biological activities. Extensive studies on bioactivity of Indanone derivatives open up more and more new possibilities of their utilization for various diseased conditions. In addition, structurally related Indanes has been considered as an ideal chemical entity which is related with numerous biological activities (Vinsova, Imramovsky et al. 2008). Moreover, Indane nucleus is an isostere of indole ring (Nigar, Hossan et al. 2015), which along with its various derivatives have already been established as drug molecule for various purposes.

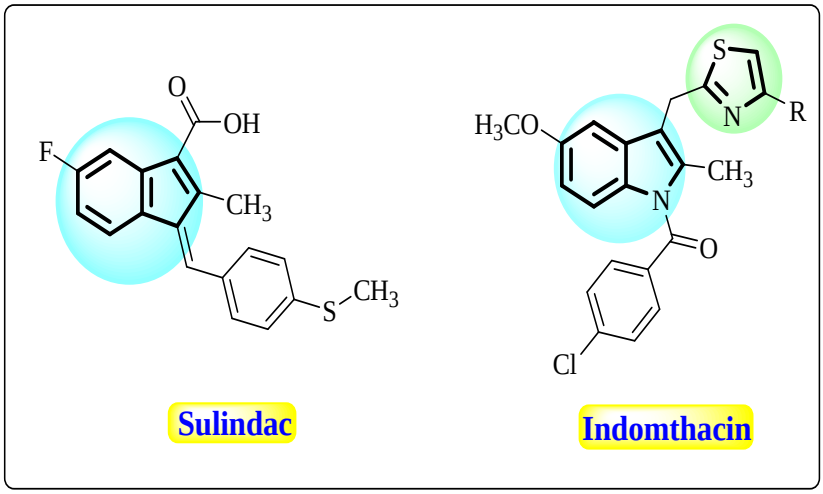


Figure 1: Indane and thiazole containing analgesic drugs.

Schiff bases are important class of organic molecules with imine or azomethine linkage formed by the condensation of compounds having primary amino group with aldehydes or ketones. The presence of different types of carbonyl and amine compounds provides the basis for the synthesis of Schiff's bases with varied structural properties which is responsible for a variety of biological activities. Many Schiff bases have potential biological values, being used successfully as biological compounds (Finkielsztein, Castro et al. 2008) including antioxidant (Glisoni, Cuestas et al. 2012, El-Sharief, Abbas et al. 2013), significant antibacterial, antifungal, anticancer and diuretic activities reported by Prakash et al in his review (Oshiro, Sakurai et al. 1991) as well as anti-inflammatory, antimalarial, antiproliferative, antiviral, antipyretic in naturally derived and synthetic compounds (Momeni, Nordström et al. 2005), antiplatelet aggregation (Mashayekhi, Tehrani et al. 2013, Tehrani, Sardari et al. 2013), CNS activities (as potentiation of pentobarbitone induce nercosis), analgesic, anticonvulsant, antidepressant, antimicrobial and anti-glycation activities (Ulanenko, Falb et al. 2006, Ugliarolo, Gagey et al. 2012).

Pain which largely characterized into two classes, acute and chronic pain is a complex body response to noxious stimulus (Apkarian, Baliki et al. 2009). It is noticed that current drugs that produce analgesia such as opiates and NSAIDs (Non-steroidal anti-inflammatory drugs) are not successful in all cases, because of the high risk of adverse effects (Ahmadiani, Fereidoni et al. 1998). Due to these facts search of other alternatives appear necessary and favorable to get new and better analgesic agents with minimum adverse effects. In our present study Schiff base, Thiosemicarbazone was synthesized by condensing 1-Indanone with Thiosemicarbazide and then different Thiazolyl hydrazones of 1-Indanone were

synthesized by reacting Thiosemicarbazone with differently substituted Phenacyl bromide. The analgesic activity of all the derivatives was checked by Tail flick method.

MATERIALS AND METHODS

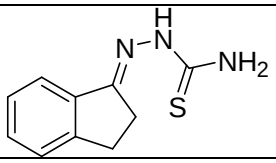
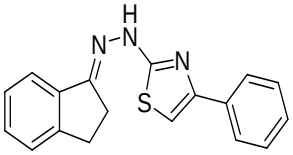
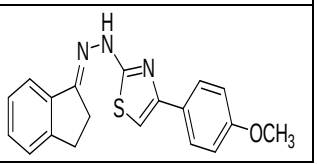
Chemicals and apparatus used in derivatization

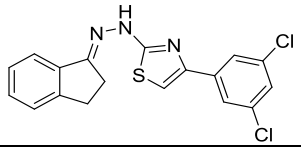
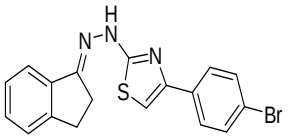
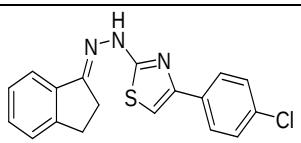
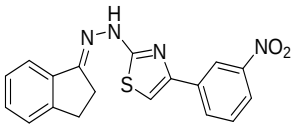
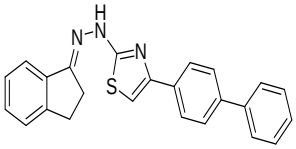
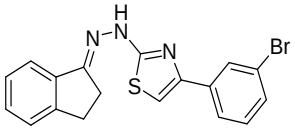
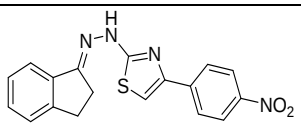
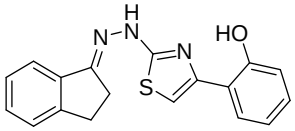
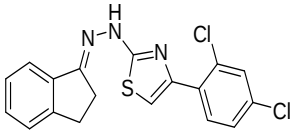
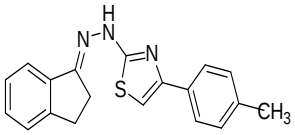
All reagents have been purchased from sigma-Aldrich chemical company and solvents; acetone, ethanol, methanol, THF, hexane, etc. used were of analytical grade. The purity of the products, progress of the reaction were checked on Merck silica gel 60 GF254 coated TLC plates and ultraviolet light at 254 and 366 nm and / or iodine spray vapors was used to visualize spots. The synthesized compounds were dried and kept in vacuum anhydrous condition. Fisher-Johns melting point apparatus was used for melting points which are uncorrected. For drying of compounds calcium sulfate and silica gel of E. Merck was used. Watt man's filter paper was used for filtration.

Derivatization

Thiazolyl hydrazones were synthesized by reacting 1 mmol of 1-indanone with thiosemicarbazide (1 mmol) in the presence of catalytic amounts of acetic acid in 10 mL of ethanol as solvent at 80^0C for 10-12 hrs to obtain intermediate thiosemicarbazone. The thiosemicarbazone (1 mmol) was then refluxed at 80^0C for 10-20 min in the presence of triethanol amine (TEA) with differently substituted phenacyl bromide (1 mmol) in the same solvent. All synthetic products were purified by washing with petroleum ether, hexane, and diethyl ether. The detail of synthesized derivatives are given in table-1.

Table 1: Name and Structure of derivatives c1 to c13.

Compounds	Name	Structure
c1	1-Indanone thiosemicarbazone	
c2	N-Indan-1-ylidene-N'-(4-phenyl-thiazol-2-yl)-hydrazine	
c3	N-Indan-1-ylidene-N'-[4-(4-methoxy-phenyl)-thiazol-2-yl]-hydrazine	

c4	N-Indan-1-ylidene-N'-[4-(3, 5-Dichloro-phenyl)-thiazol-2-yl]-hydrazine,	
c5	N-Indan-1-ylidene-N'-[4-(4-Bromo-phenyl)-thiazol-2-yl]-hydrazine	
c6	N-Indan-1-ylidene-*N*'-[4-(4-Chloro-phenyl)-thiazol-2-yl]-hydrazine	
c7	N-Indan-1-ylidene-N'-[4-(3-nitro-phenyl)-thiazol-2-yl]-hydrazine	
c8	N-Indan-1-ylidene-N'-(4-Biphenyl-4-yl-thiazol-2-yl)-hydrazine	
c9	N-Indan-1-ylidene-N'-[4-(3-Bromo-phenyl)-thiazol-2-yl]-hydrazine	
c10	N-Indan-1-ylidene-N'-[4-(4-nitro-phenyl)-thiazol-2-yl]-hydrazine,	
c11	N-Indan-1-ylidene-N'-[4-(2-hydroxy-phenyl)-thiazol-2-yl]-hydrazine	
c12	N-Indan-1-ylidene-N'-[4-(2, 4-Dichloro-phenyl)-thiazol-2-yl]-hydrazine	
c13	N-Indan-1-ylidene-N'-[4-(4-methyl-phenyl)-thiazol-2-yl]-hydrazine	

Analgesic Activity

Method of diStasi *et al.* was used to assess the antinociceptive effect against thermal stimuli (tail flick method) (Di Stasi, Costa et al. 1988). Male Albino mice having weights of between 20-30g, were used in the study. Before the experiment, same environmental conditions were given to the mice and provide them standard rodent diet for three days. Test Compounds were dissolved in water for injection/DMSO (30%), injected intraperitoneally(ip) to the test groups at the doses of 30 mg/kg body weight. Aspirin (as standard) was also administered at the same dose to the standard group. Control groups were supplied with only vehicle. After

administration of compounds, readings were taken after every 30 minutes(0-180 minutes), mean of the three readings was considered as the post drug reaction time. To measure the analgesia by test, control and standard drug (Aspirin), Tail flick latency difference (TFLD) or mean increase in latency were used.

The average latency time produced by the control animals (base line latency) and treated group (drug latency) were compared and expressed as percent analgesia by using formula:

$$\% \, Analgesia = \frac{Drug\ latency - Base\ line\ latency}{Base\ line\ latency} \, x\ 100$$

Statistical Analysis

By applying one way analysis of variance (ANOVA) analgesic activity was expressed as latency ± SEM in second. The differences between the means were tested using post hoc LSD and values of $p < 0.05$ were statistically measured as significant. SPSS for windows version 12 was used for the statistical analysis.

RESULTS

Table-2: Comparison of Mean ± 2SEM of 30 mg dose among Thiosemicarbazone and Thiazolyl Hydrazone Schiff Bases of 1-Indanone / Control / Aspirin from 0-180 min.

Compounds	Latency Time						
	0min	30 min	60 min	90 min	120 min	150 min	180min
c1	0.95 ± 0.01**( )	1.55 ± 0.04**(**)	2.25 ± 0.18**(**)	2.61 ± 0.14**(**)	2.85 ± 0.16**(**)	2.30 ± 0.21** ( )	1.77 ± 0.15** ( )
c2	0.96 ± 0.01**( )	2.00 ± 0.09**	2.49 ± 0.07**(**)	2.88 ± 0.07**(**)	2.9 ± 0.07**(**)	2.50 ± 0.07**	1.42 ± 0.04**(**)
c3	0.94 ± 0.015**( )	1.27 ± 0.12**(**)	2.12 ± 0.21**(**)	2.33 ± 0.15**(**)	1.99 ± 0.20**(**)	1.66 ± 0.21**	1.18 ± 0.09**(**)
c4	1.00 ± 0.016**( )	2.24 ± 0.09**(**)	2.57 ± 0.14**(**)	2.92 ± 0.12**(**)	2.56 ± 0.14**(**)	2.30 ± 0.12**	1.44 ± 0.07**(**)
c5	0.91 ± 0.01**( )	2.15 ± 0.12**(*)	2.55 ± 0.10**(**)	3.16 ± 0.12**(**)	2.94 ± 0.09**(**)	2.38 ± 0.12**	1.64 ± 0.22**( )
c6	0.94± 0.02**( )	1.58 ± 0.21**(**)	1.92 ± 0.10**(**)	2.20 ± 0.06**(**)	2.09 ± 0.07**(**)	1.56 ± 0.03**	1.26 ± 0.06**(**)
c	0.93± 0.01**( )	2.30 ± 0.21**(**)	2.91 ± 0.16**( )	3.19 ± 0.17**(**)	2.84 ± 0.18**(**)	2.09± 0.11**( )	1.26 ± 0.06**(**)
c8	0.96± 0.00**(*)	2.32 ± 0.05**(**)	3.01 ± 0.10**( )	3.29 ± 0.19**(**)	2.61 ± 0.36**(**)	2.16 ± 0.24**( )	1.40 ± 0.12**(**)
c9	0.93 ± 0.01**( )	2.13 ± 0.12**(*)	2.34 ± 0.10**(**)	2.45 ± 0.07**(**)	2.46 ± 0.20**(**)	1.99 ± 0.16**( )	1.35 ± 0.15**(**)
c10	0.99 ± 0.01**(*)	1.49 ± 0.05**(**)	2.46 ± 0.20**(**)	3.35 ± 0.29**(*)	3.10 ± 0.24**( )	2.23 ± 0.07**(*)	1.35 ± 0.04**(**)
c11	0.94± 0.009**( )	1.44 ± 0.03**(**)	2.33 ± 0.11**(**)	2.81 ± 0.24**(**)	2.81 ± 0.29**(*)	2.03 ± 0.13**( )	1.23 ± 0.06**(**)
c12							
c13							
Control							
Aspirin							

	0.98± 0.01**(*) 0.94 ± 0.01*( ) 0.87 ± 0.03 0.91±0.02	2.26 ± 0.03**(**) 1.63 ± 0.17**(**) 0.89 ± 0.04 1.98±0.03	2.92 ± 0.22**( ) 2.25± 0.18**(**) 0.99 ± 0.03 2.91± 0.03	3.16 ± 0.13**(**) 2.61 ± 0.14**(**) 1.05 ± 0.05 3.71±0.07	2.60 ± 0.12**(**) 2.85 ± 0.16**(**) 1.04 ± 0.055 3.15±0.021	2.18 ± 0.06**( ) 2.05 ± 0.15**( ) 0.99 ± 0.04 2.136±0.040	1.26 ± 0.03**(**) 1.28 ± 0.04**(**) 0.97 ± 0.04 1.68±0.038

* is the significant (p-value) and indicates that difference is significant between control and corresponding drug category at 0.05 level of significance.

** is the significant (p-value) and indicates that difference is significant among control and corresponding drug category at 0.01 level of significance.

(*) is the significant (p-value) and indicates that difference is significant between aspirin and corresponding drug category at 0.05 level of significance.

(**) is the significant (p-value) and indicates that difference is significant between aspirin and corresponding drug category at 0.01 level of significance

( ) shows that there is no significant difference between aspirin and the corresponding drug at 0.05 and 0.01 level of significance.

Latency time of control (n=90) and treated groups (n=15), which are mean ± SEM of animals in three independent experiment.

Table 3: Percentage Analgesia of Thiosemicarbazone and Thiazolyl Hydrazone Schiff Bases of 1-Indanone and Aspirin (Standard).

	Latency time						
Compounds	**0min**	**30 min**	**60 min**	**90 min**	**120 min**	**150 min**	**180min**
c1	9.195402299	74.15730337	127.2727273	148.5714286	174.0384615	132.3232323	82.4742268
c2	10.34482759	124.7191011	151.5151515	174.2857143	178.8461538	152.5252525	46.39175258
c3	8.045977011	42.69662921	114.1414141	121.9047619	91.34615385	67.67676768	21.64948454
c4	14.94252874	151.6853933	159.5959596	178.0952381	146.1538462	132.3232323	48.45360825
c5	4.597701149	141.5730337	157.5757576	200.952381	182.6923077	140.4040404	69.07216495
c6	8.045977011	77.52808989	93.93939394	109.5238095	100.9615385	57.57575758	29.89690722
c7	6.896551724	158.4269663	193.9393939	203.8095238	173.0769231	111.1111111	29.89690722
c8	10.34482759	160.6741573	204.040404	213.3333333	150.9615385	118.1818182	44.32989691
c9	6.896551724	139.3258427	136.3636364	133.3333333	136.5384615	101.010101	39.17525773
c10	13.79310345	67.41573034	148.4848485	219.047619	198.0769231	125.2525253	39.17525773
c11	8.045977011	61.79775281	135.3535354	167.6190476	170.1923077	105.0505051	26.80412371
c12	12.64367816	153.9325843	194.9494949	200.952381	150	120.2020202	29.89690722
c13	8.045977011	83.14606742	127.2727273	148.5714286	174.0384615	107.0707071	31.95876289
Aspirin	4.597701149	122.4719101	193.9393939	253.3333333	202.8846154	115.7575758	73.19587629

Percent protection from centrally mediated pain of control (n=90) and treated groups (n=15)

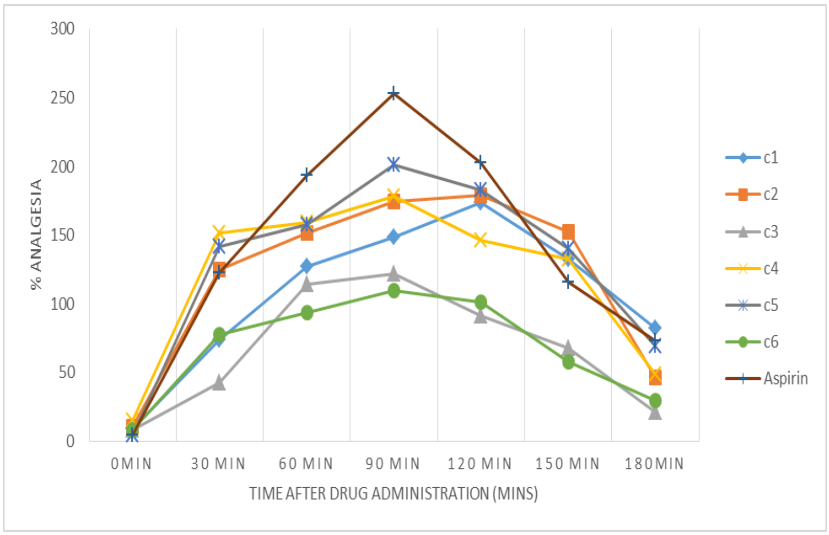


Figure 2: Percent analgesia of synthesized compounds c1-c6 and aspirin.

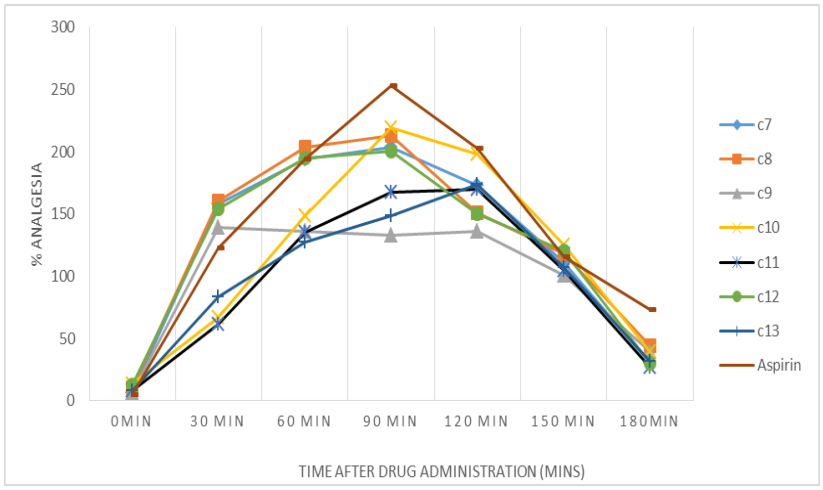


Figure 3: Percent analgesia of synthesized compounds c7-c13 and aspirin.

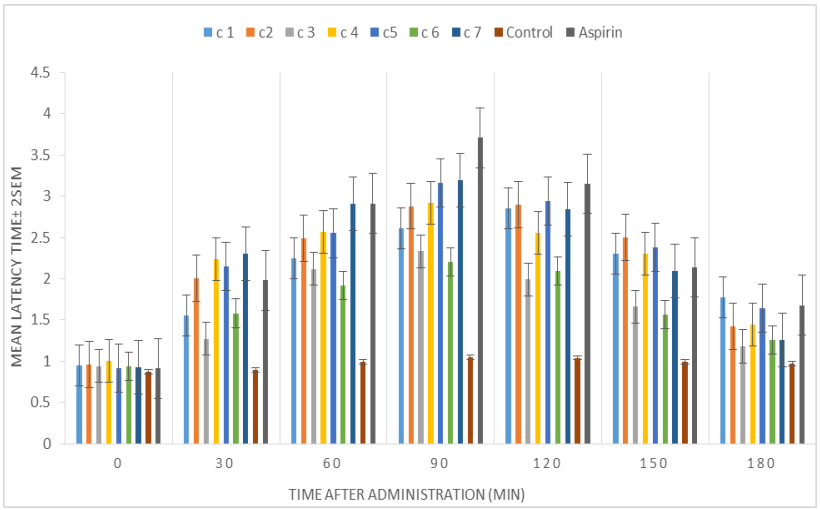


Figure 4: Error bar of mean latency time ± 2SEM of 30 mg dose from c1 to c7/Control/ Aspirin.

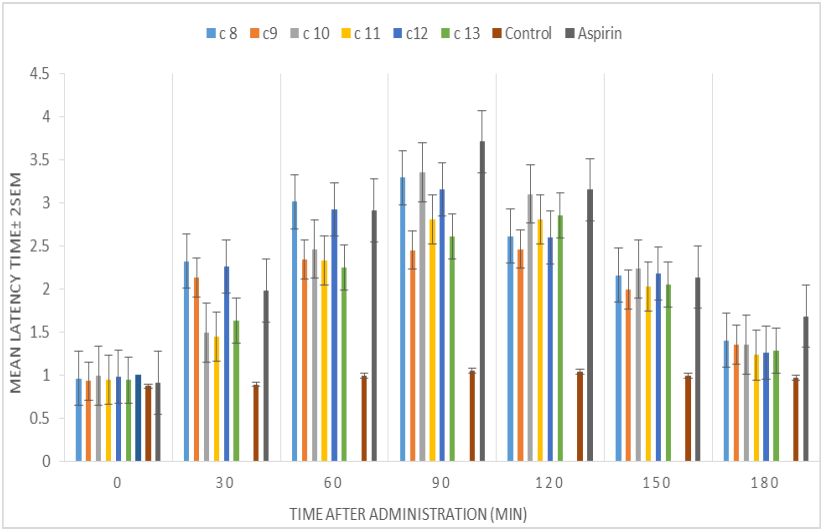


Figure 5: Error bar of mean latency time ± 2SEM of 30 mg dose from c8 to c13/Control/Aspirin.

DISCUSSION

Indane ring containing molecules, especially having a carboxylic acid moiety, generally found to show anti-inflammatory activity. Among Indane derivatives 1H-Indene-3-acetic acid-5-fluoro-2- indan-1,3-dione are well known anti-inflammatory agents (Shen 1972). Juby *et al*. (Juby, Goodwin et al. 1972) proved significant anti-inflammatory activity in many substituted Indan-1-carboxylic acids. Moreover, a number of methoxy indan-1-alkanoic acids with considerable anti-inflammatory properties were previously reported (Mukhopadhyay and Lahiri 1992). Indane derivatives, with a halo-substituted indanyl group were found to possess analgesic and anti-inflammatory activities (Roy, Gupta et al. 1983, Roy and Lahiri 1985, Ray and Lahiri 1990, Bachar and Lahiri 2004) It was observed that aromatic halogen substitution could be a reasonable means of increasing the analgesic and anti-inflammatory activities and widening the margin of safety (Bachar and Lahiri 2004). 1-Indanone is a ketones of Indane and Schiff bases have also be reviewed in literature having analgesic activity (Rana, Pandurangan et al. 2012) therefore Schiff bases of 1-Indanone were evaluated to possess analgesic activity.

In our present study out of 13 compounds (**c1- c13**) 9 showed analgesic activity and 4 compounds (**c3**, **c6**, **c11** and **c13**) were found inactive (Table-2, 3; Fig-4, 5). Out of 9 active compounds 3 compounds (**c7**, **c8** and **c12**) were found comparable with Aspirin from 30-90min (Table-3; Fig-4, 6). None of the compound was found more active than Aspirin.

Compound **c1** showed analgesic activity only after 150min (Table-3). Compound **c2, c4, c5** and **c9** showed maximum activity at 30 min and then their activity gradually decreased with increasing time (Table-3). Compound **c10** was found inactive up to 120min and its activity appeared at 150min (Table-1, 2; Fig-4, 5).

Regarding structure activity relationship presence of electron withdrawing groups Nitro (**c7**), Phenyl (**c8)** and di-Chloro (**c12**) reduce the electron density of the aromatic ring and make it more suitable for receptor interaction to give analgesic activity. Compounds **c3**, **c6**, **c11** and **c13** which generally have electron donating groups such as Methyl (CH_3), Hydroxyl (OH) and Methoxy (OCH_3) did not show any analgesic activity which may be due to increase in the electron density around the aromatic ring which can reduce its interaction with the receptor to produce analgesic activity. The compounds which have moderate density of electrons around the aromatic ring like **c2** generally showed activity at 30 or 60min and then their activity is decreased with time.

CONCLUSION

All synthesized compounds except 4 compounds **c3**, **c6**, **c11** and **c13** displayed significant inhibition of pain. Out of 9 active compounds 3 compounds (**c7**, **c8** and **c12**) were found comparable with Aspirin from 30-90 min. Due to their promising results can be selected for relieving pain**.** None of the compound was found more active than Aspirin.

REFERENCES

1. Ahmadiani, A., M. Fereidoni, S. Semnanian, M. Kamalinejad and S. Saremi. Antinociceptive and anti-inflammatory effects of Sambucus ebulus rhizome extract in rats. *J. Ethnopharmacol.*, 1998; 61(3): 229-235.
2. Apkarian, A. V., M. N. Baliki and P. Y. Geha. Towards a theory of chronic pain. *Prog Neurobiol*, 2009; 87(2): 81-97.
3. Bachar, S. and S. Lahiri. Synthesis of chloro and bromo substituted 5-(indan-1′-yl) tetrazoles and 5-(indan-1′-yl) methyltetrazoles as possible analgesic agents. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, 2004; 59(6): 435-438.
4. Di Stasi, L. C., M. Costa, S. L. Mendaçolli, M. Kirizawa, C. Gomes and G. Trolin. Screening in mice of some medicinal plants used for analgesic purposes in the state of Sao Paulo. *J. Ethnopharmacol.*, 1988; 24(2-3): 205-211.

5. El-Sharief, M. A. S., S. Y. Abbas, K. A. El-Bayouki and E. W. El-Gammal. Synthesis of thiosemicarbazones derived from N-(4-hippuric acid) thiosemicarbazide and different carbonyl compounds as antimicrobial agents. *Eur. J. Med Chem.,* 2013; 67: 263-268.
6. Finkielsztein, L. M., E. F. Castro, L. E. Fabián, G. Y. Moltrasio, R. H. Campos, L. V. Cavallaro and A. G. Moglioni. New 1-indanone thiosemicarbazone derivatives active against BVDV. *Eur. J. Med., Chem.,* 2008; 43(8): 1767-1773.
7. Glisoni, R. J., M. L. Cuestas, V. L. Mathet, J. R. Oubiña, A. G. Moglioni and A. Sosnik. Antiviral activity against the hepatitis C virus (HCV) of 1-indanone thiosemicarbazones and their inclusion complexes with hydroxypropyl-β-cyclodextrin. *Eur. J. Pharm. Sci.,* 2012; 47(3): 596-603.
8. Juby, P., W. Goodwin, T. Hudyma and R. Partyka. Antiinflammatory activity of some indan-1-carboxylic acids and related compounds. *J. Med. Chem.,* 1972; 15(12): 1297-1306.
9. Mashayekhi, V., K. H. M. E. Tehrani, S. Amidi and F. Kobarfard. Synthesis of novel indole hydrazone derivatives and evaluation of their antiplatelet aggregation activity. *Chem. Pharm. Bull.,* 2013; 61(2): 144-150.
10. Momeni, N., B. M. Nordström, V. Horstmann, H. Avarseji and B. V. Sivberg. Alterations of prolyl endopeptidase activity in the plasma of children with autistic spectrum disorders. *BMC psychiatry,* 2005; 5(1): 27.
11. Mukhopadhyay, A. and S. Lahiri. Evaluation of some newer non-steroidal anti-inflammatory indan-1-acids in various biological systems. *Indian J. Exp. Biol.,* 1992; 30(7): 583-586.
12. Nigar, S. T., M. M. Hossan and S. C. Bachar. Synthesis and Biological Activity Evaluation of Indan-1-Carboxylic Acid-3-Semicarbazone and Indan-1-Acetic Acid-3-Semicarbazone. *Lat. Am. J. Pharm.,* 2015; 34(1): 116-123.
13. Oshiro, Y., Y. Sakurai, T. Tanaka, T. Kikuchi, T. Hirose and K. Tottori. Novel cerebroprotective agents with central nervous system stimulating activity. 2. Synthesis and pharmacology of the 1-(acylamino)-7-hydroxyindan derivatives. *J. Med. Chem.,* 1991; 34(7): 2014-2023.
14. Rana, K., A. Pandurangan, N. Singh and A. K. Tiwari. A systemic review of schiff bases as an analgesic, anti-inflammatory. *Int. J. Curr. Pharm. Res.,* 2012; 4(2): 5-11.
15. Ray, S. and S. Lahiri. Studies on 5-(Indan-1′-yl) tetrazoles as Potential Non-Steroidal Antiinflammatory Agents. *Chem. Inform.,* 1990; 21(46): no-no.

16. Roy, A., J. Gupta and S. Lahiri. SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF A FEW 5-(INDAN-1′-YL) METHYLTETRAZOLES. *Chemischer Informationsdienst*, 1983; 14(49).
17. Roy, A. and S. Lahiri. Studies on two novel anti-inflammatory indanylmethyltetrazoles. *Indian J. Pharmacol.*, 1985; 17(1): 63.
18. Shen, T. Perspectives in nonsteroidal anti-inflammatory agents. *Angew. Chem. Int. Ed.*, 1972; 11(6): 460-472.
19. Tehrani, K. H. M. E., S. Sardari, V. Mashayekhi, M. E. Zadeh, P. Azerang and F. Kobarfard. One pot synthesis and biological activity evaluation of novel Schiff bases derived from 2-hydrazinyl-1, 3, 4-thiadiazole. *Chem. Pharm. Bull.*, 2013; 61(2): 160-166.
20. Ugliarolo, E. A., D. Gagey, B. Lantaño, G. Y. Moltrasio, R. H. Campos, L. V. Cavallaro and A. G. Moglioni. Synthesis and biological evaluation of novel homochiral carbocyclic nucleosides from 1-amino-2-indanols. *Bioorganic Med. Chem.*, 2012; 20(19): 5986-5991.
21. Ulanenko, K., E. Falb, H. E. Gottlieb and Y. Herzig. Novel 5-dimethylamino-1-and 2-indanyl uracil derivatives. *J. Org. Chem.*, 2006; 71(18): 7053-7056.
22. Vinsova, J., A. Imramovsky, J. Jampilek, J. F. Monreal and M. Dolezal. Recent advances on isoniazide derivatives. *Anti-Infective Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Infective Agents)*, 2008; 7(1): 12-31.