International Journal of Drug Development & Research
| Jan-March 2010 | Vol. 2 | Issue 1 |
ISSN 0975-9344
Available online http://www.ijddr.com

Original Research Manuscript

PHARMACOLOGICAL STUDY OF BIOTRANSFORMATION OF SUBSTITUTED AND UNSUBSTITUTED INDANONE ACETIC ACID ADDUCT WITH PYRAZOLONE RING FOR ANALGESIC ACTIVITY *IN-VIVO*

NIRALI A PASSI*, MAULIK K PRAJAPATI, PROF DR DHRUBO JYOTI SEN AND PROF DR INDERMEET SINGH ANAND

DEPARTMENT OF PHARMACEUTICAL CHEMISTRY AND PHARMACOLOGY, SHRI SARVAJANIK PHARMACY COLLEGE, HEMCHANDRACHARYA NORTH GUJARAT UNIVERSITY, ARVIND BAUG, MEHSANA-384001, GUJARAT, INDIA

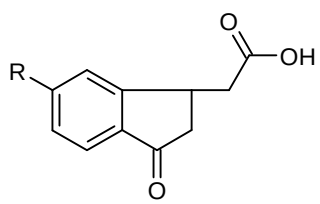
PHONE: 00-91-2762-247711, FAX: 00-91-2762-247712, EMAIL: DHRUBOSEN69@YAHOO.COM

ABSTRACT

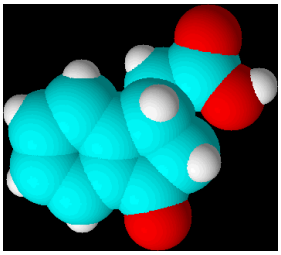
Substituted and unsubstituted indanone acetic acids have been synthesized and conjugated with carboxy-pyrazolone to get indanone-pyrazolone adduct. The antiinflammatory activity has been screened for Indanone acetic acid, Indanone-Pyrazolone adduct and Carboxy Pyrazolone by rat paw edema method with reference standard drug Indomethacin which is bioisosteres with indanone acetic acid ring. It has been observed that all the test compounds have anti-inflammatory activity and 70% inhibition of edema persists for 3 hours in the case of Indanone acetic acids and for Carboxy pyrazolone and 60-70% inhibition of edema persists for 5 hours in the case of Indanone-pyrazolone adduct. Indanone has non-heterocyclic fused ring having six membered benzene ring and five membered cyclopentane ring where as pyrazolone has five membered heterocyclic ring substituted with six membered benzene ring. The adduct of indanone acetic acid and carboxy pyrazolone joins with amide linkage which has free carboxy group which is present in the both Indanone acetic acid and Carboxy pyrazolone. Indanone-pyrazolone adduct shows high lipid solubility by partition coefficient rather than the other two compounds which shows the same % inhibition of edema and longer duration of analgesic activity which is equal to the other test compounds. It proves that the Indanone-Pyrazolone adduct shows activity for a certain period and then releases the two factors Indanone acetic acid and Carboxy Pyrazolone after hydrolysis of amide linkage by biotransformation in-vivo and the activity becomes prolonged but the % inhibition remains the same due to the in-vivo synergism appears and the combination activity of the three shows more prolonged action with longer duration by competitive inhibition of arachidonic acid pathway which has also free carboxylic acid group.

Introduction:

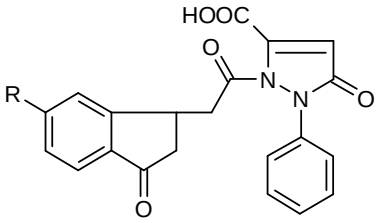
DESIRED PRODUCTS



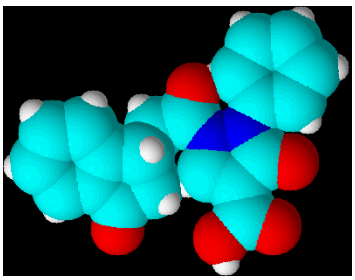
Indanone acetic acid



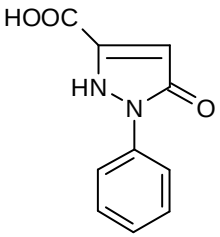
3D-View



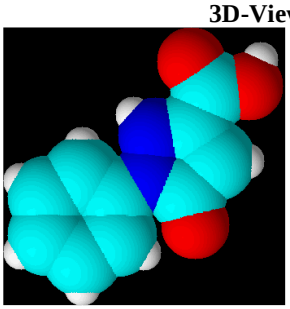
Indanone-pyrazolone adduct



3D-View

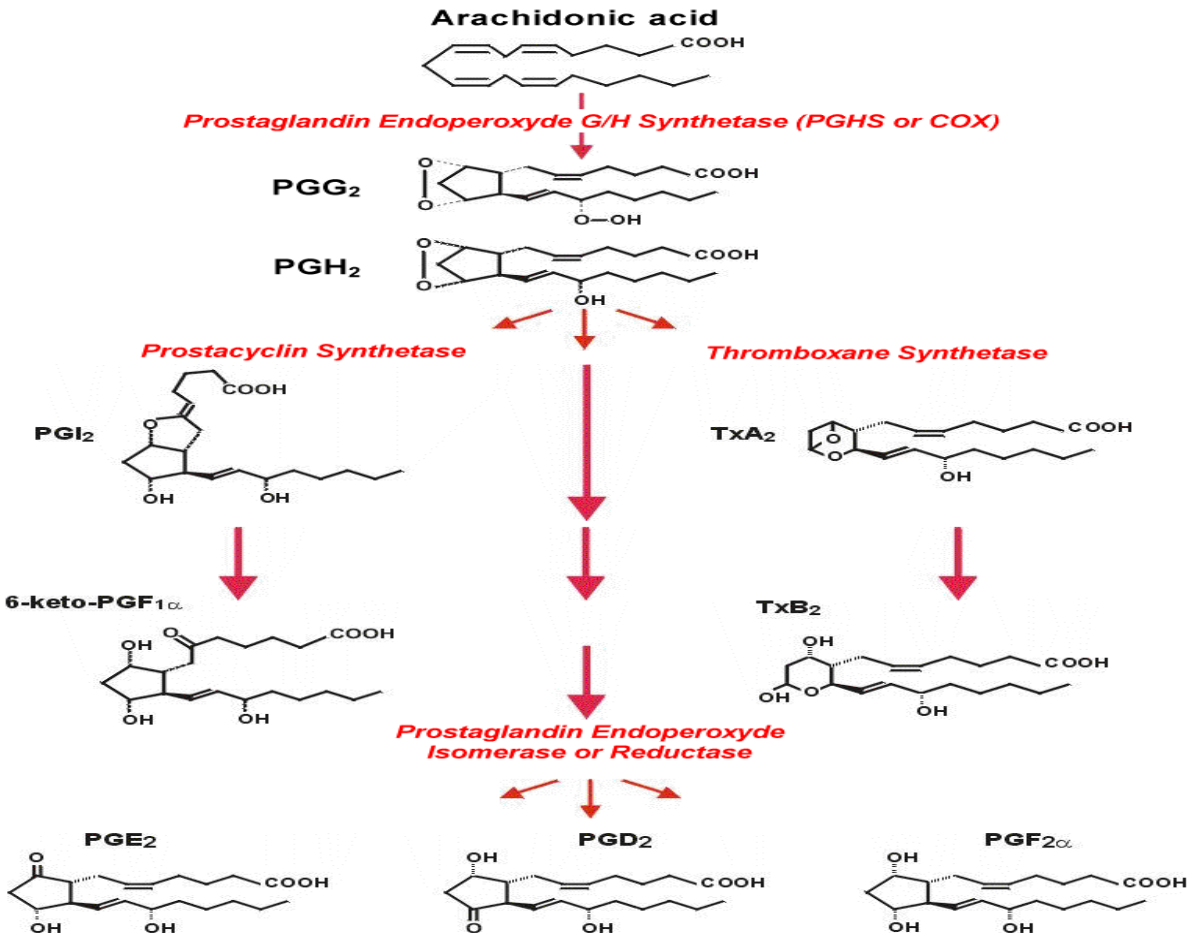


Carboxy pyrazolone

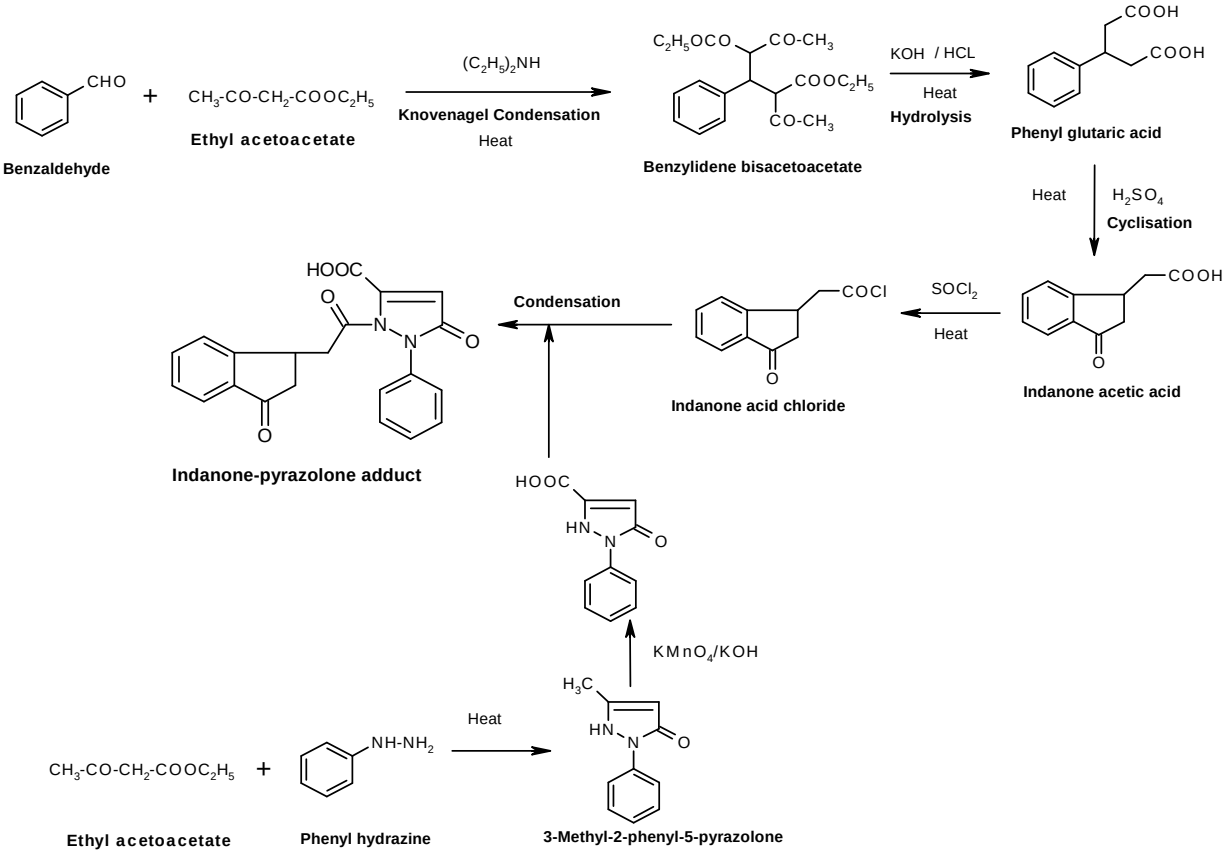


3D-View

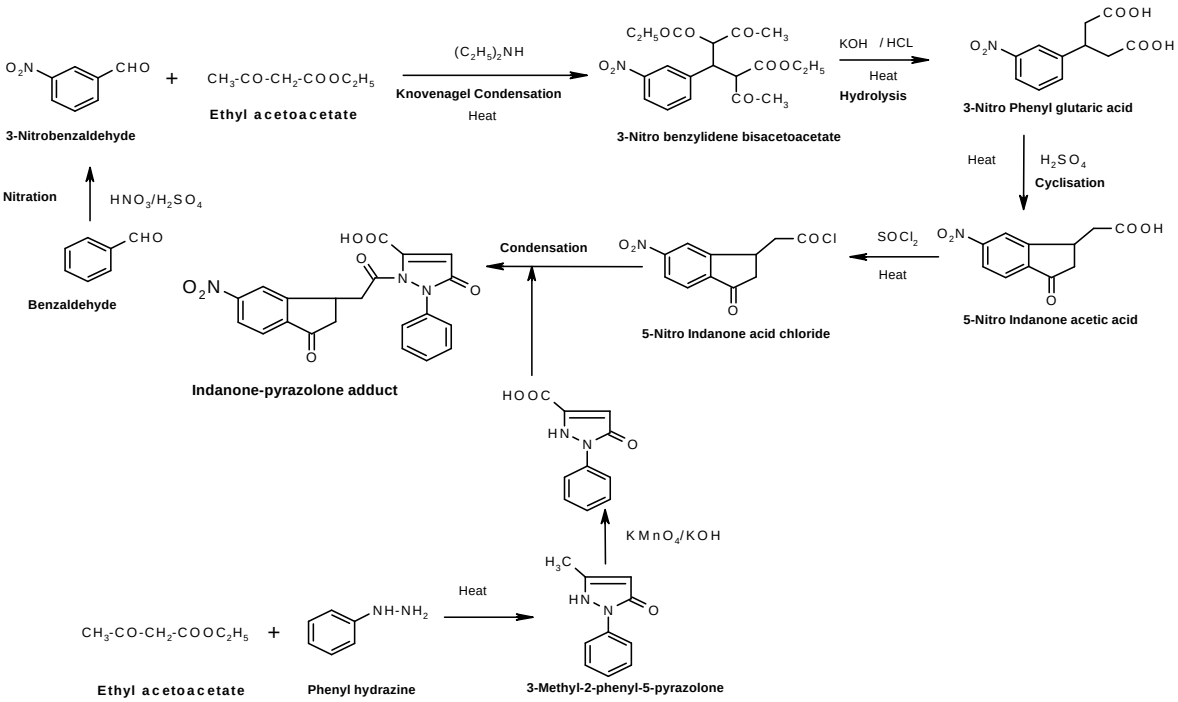
CYCLOOXYGENASE PATHWAY



SYNTHESIS SCHEME I



SCHEME-II



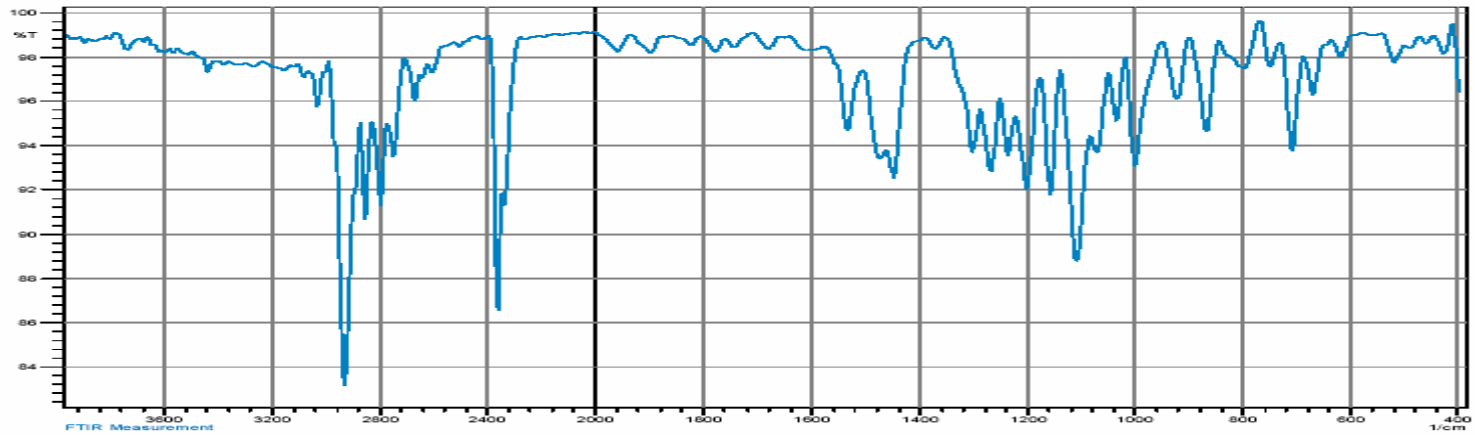
CHEMISTRY

Substituted and unsubstituted indanone acetic acids has been synthesized; where R=NO2 and R=H. Substituted and unsubstituted aromatic aldehyde followed the Knovenagel condensation by ethyl acetoacetate as β-ketoester in presence of secondary amine to form a bisacetoacetate, which on alkaline hydrolysis and subsequent ring cyclisation by dehydrating agent produced the Indanone acetic acid (R=NO2: 5-Nitro indanone acetic acid and R=H: Indanone acetic acid) [1,2].

Condensation of phenyl hydrazine with ethyl acetoacetate as β-ketoester produced methyl substituted pyrazolone and oxidizing the methyl group to carboxylic acid by alkaline potassium hydroxide produced Carboxy pyrazolone. The free carboxy group of indanone acetic acids (R= NO2 and H) have been converted into acid chloride and condensing with free imino group of carboxy pyrazolone to achieve the desired product Indanone-pyrazolone adduct. All the three different components (Indanone acetic acids: R=NO2 and R=H, Indanone-pyrazolone adduct and Carboxy pyrazolone) were characterized by spectroscopy and N% [3,4].

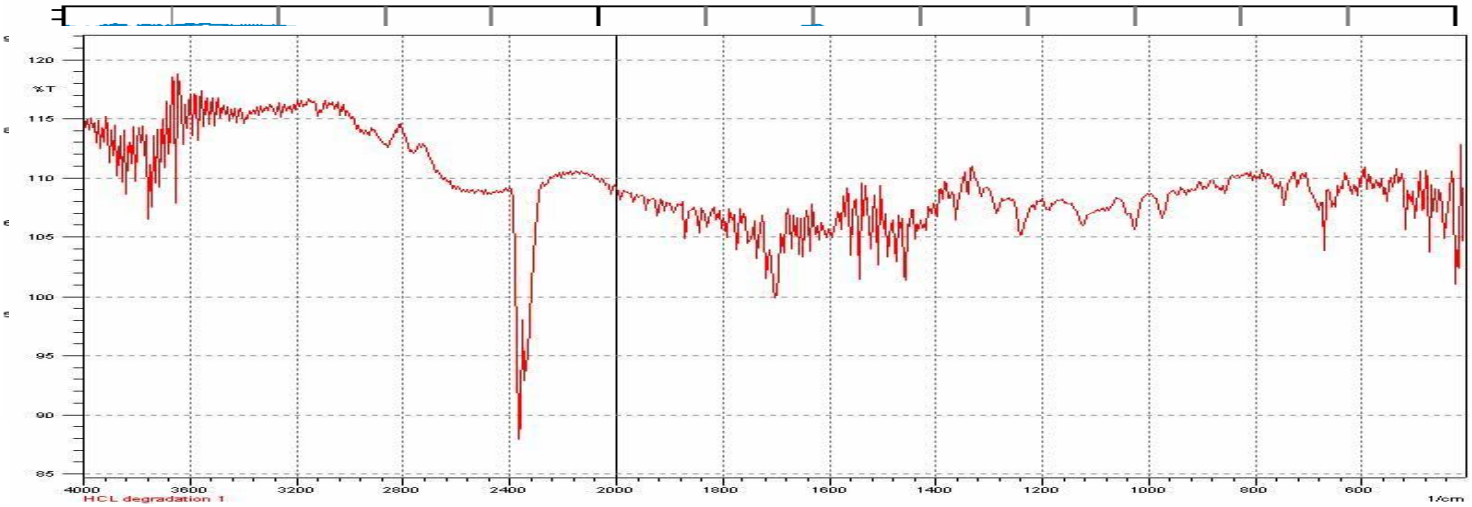
INFRARED SPECTROSCOPY OF SYNTHESISED COMPOUNDS

INDANONE ACETIC ACID



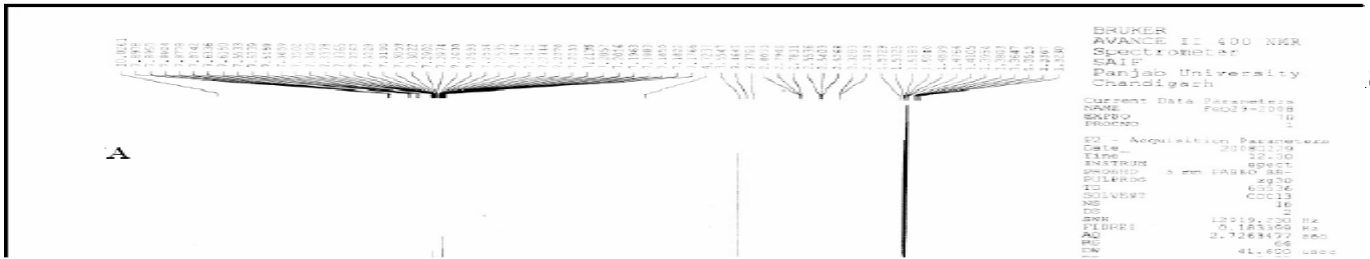
INDANONE-PYRAZOLONE ADDUCT

PYRAZOLONE CARBOXYLIC ACID

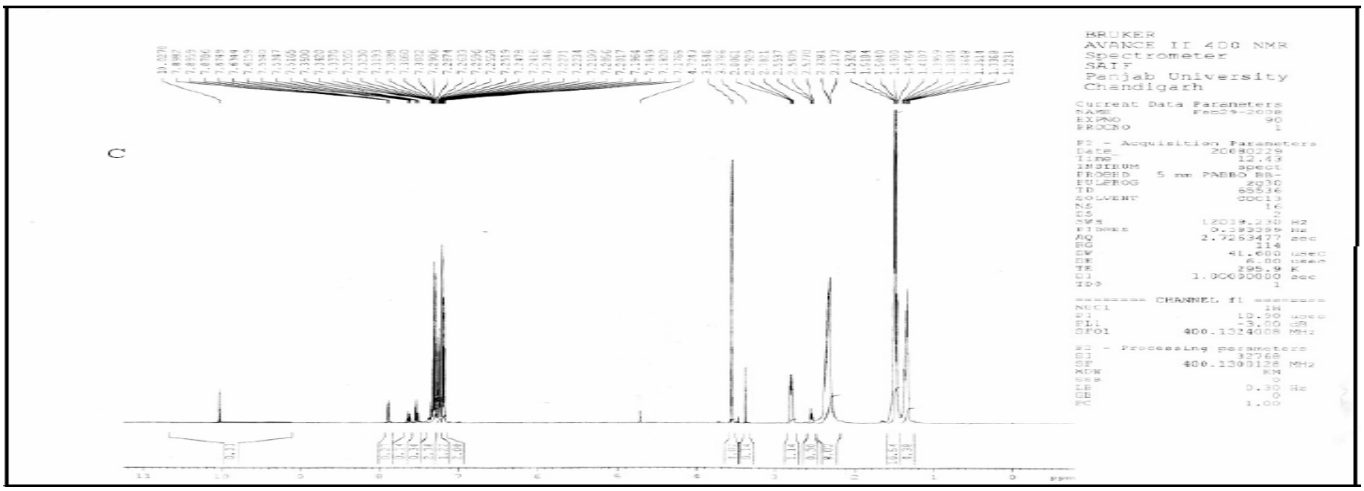


NMR SPECRTAS OF SYNTHESISED COMPOUNDS

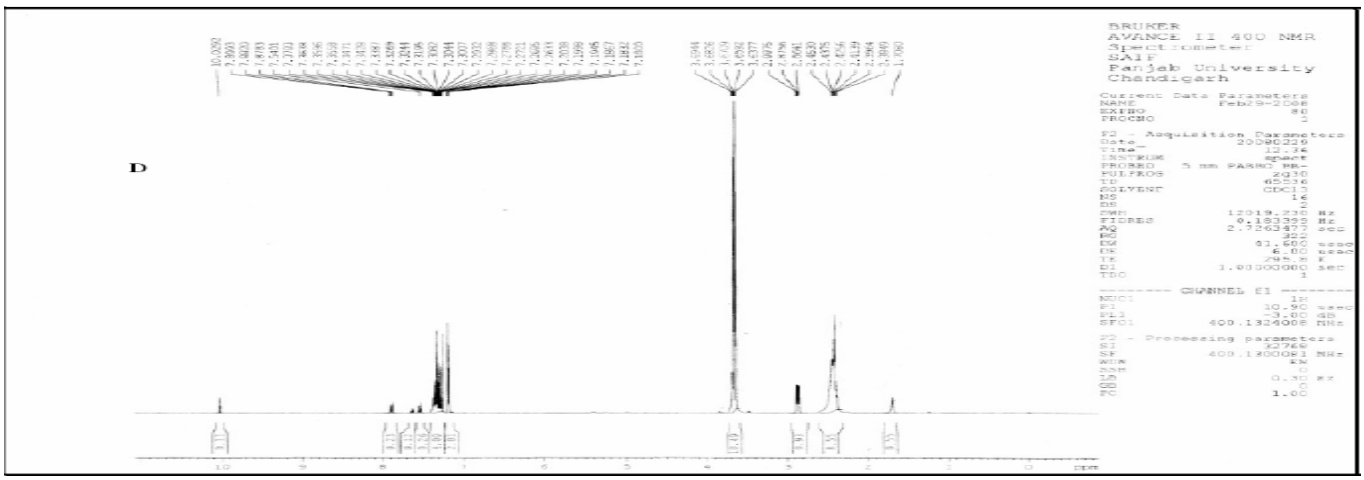
INDANONE ACETIC ACID



INDANONE-PYRAZOLONE ADDUCT



PYRAZOLONE CARBOXYLIC ACID



PHYSICOCHEMICAL PARAMETERS

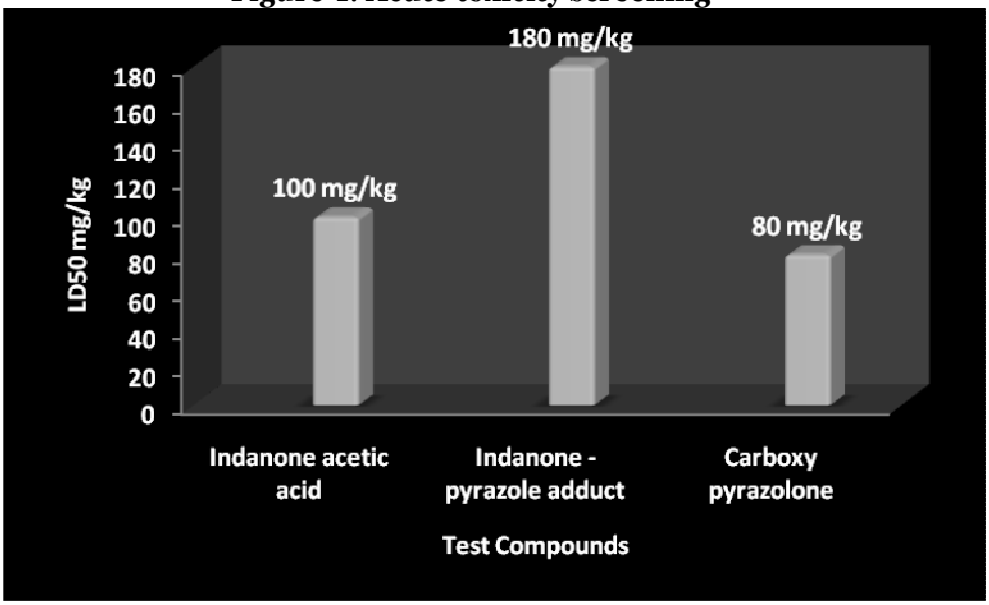
Table-1

COMPOUNDS	% YIELD	M.P.	POLARITY	MOL. FORMULA	N% CALCD	N% FOUND

Indanone acetic acid	54	134	Semipolar	$C_{11}H_{10}O_3$	Nil	Nil
5-Nitro Indanone acetic acid	48	142	Nonpolar	$C_{11}H_9O_5N$	5.95	6.12
Indanone-pyrazolone adduct	62	156	Nonpolar	$C_{21}H_{16}O_5N_2$	7.44	7.52
5-Nitro Indanone-pyrazolone adduct	58	176	Nonpolar	$C_{21}H_{15}O_7N_3$	9.97	10.12
Pyrazolone carboxylic acid	74	120	Semipolar	$C_{10}H_8O_3N$	7.36	7.48

PHARMACOLOGY

Figure-1: Acute toxicity screening



The anti-inflammatory screening of the all compounds were performed on rat by plethismometer using rat-paw edema method by treating Indanone acetic acid/5-Nitro Indanone acetic acid to the first group and Indanone-pyrazolone carboxylic acid to the second group having four animals each at 20mg/kg dose intraperitoneally4. Next group of four animals received the same compounds with indomethacin at the same dose and % inhibition of paw edema has been noted at one-hour interval for six hours. Indomethacin and the vehicle propylene glycol have been used for the two sets of animal for standard and control group.

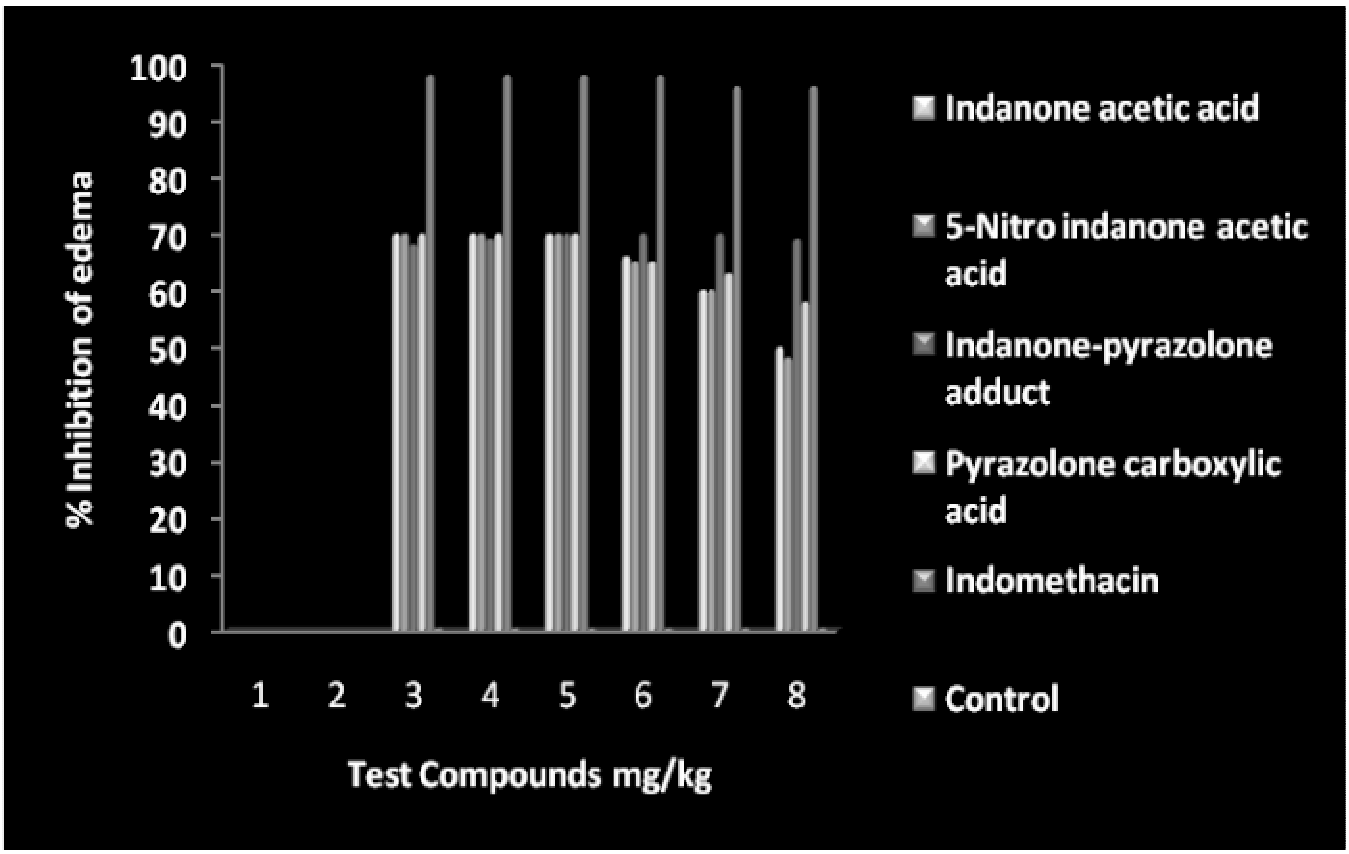
The analgesic activity of all the test compounds has been screened intraperitoneally by carrageenan induced rat paw edema method with Indomethacin as standard[5]. The % edema has been calculated by %=[(Control-Test)÷Control]×100. All the observations were calculated with statistical parameters by following Student's-t test for the authenticity of the experiment [6].

Table-2: Antiinflammatory activity screening

Compounds	Hours					
	1st Hour	2nd Hour	3rd Hour	4th Hour	5th Hour	6th Hour
Indanone acetic acid	70%	70%	70%	66%	60%	50%
5-Nitro Indanone acetic acid	70%	70%	70%	65%	60%	48%
Indanone Pyrazolone Adduct	68%	69%	70%	70%	70%	69%
Pyrazolone carboxylic acid	70%	70%	70%	65%	63%	58%
Indomethacin	98%	98%	98%	98%	96%	96%

Control	00%	00%	00%	00%	00%	00%

Figure-2: % Inhibition of rat paw edema



CONCLUSION

It has been observed that all the test compounds have anti-inflammatory activity and 70% inhibition of edema persists for 3 hours in the case of Indanone acetic acids and for Carboxy pyrazolone and 60-70% inhibition of edema persists for 5 hours in the case of Indanone-pyrazolone adduct. Indanone has non-heterocyclic fused ring having six membered benzene ring and five membered cyclopentane ring where as pyrazolone has five membered heterocyclic ring substituted with six membered benzene ring. The adduct of indanone acetic acid and carboxy pyrazolone joins with amide linkage which has free carboxy group which is present in the both Indanone acetic acid and Carboxy pyrazolone. Indanone-pyrazolone adduct shows high lipid solubility by partition coefficient rather than the other two compounds which shows the same % inhibition of edema and longer duration of analgesic activity which is equal to the other test compounds. It proves that the Indanone-pyrazolone adduct shows activity for a certain period and then releases the two factors Indanone acetic acid and Carboxy pyrazolone after hydrolysis of amide linkage by biotransformation in-vivo and the activity becomes prolonged but the % inhibition remains the same due to the in-vivo synergism appears and the combination activity of the three shows more prolonged action with longer duration by competitive inhibition of arachidonic acid pathway which has also free carboxylic acid group.

Acknowledgement: The author Nirali A Passi is thankful to the coresearcher Mr Maulik K Prajapati (M.Pharm.) and the research group of Shri Sarvajanik Pharmacy College, Mehsana, Gujarat, India for providing the necessary equipments, chemicals, instruments, animals and library facility for performing this project successfully under the guidance of Prof. Dr. Dhrubo Jyoti Sen who has guided nicely these synthetic as well as pharmacological experiments under his expertise. The

author is also thankful to Panjab University, Chandigarh for NMR and Mass Spectras of the synthesised compounds. This project work has been presented by the author in **42nd IUPAC Congress, 2-7 August 2009, SECC, Glasgow, United Kingdom** sponsored by the Royal Society of Chemistry of Great Britain.

References:

1. *S.C. Lahiri and J.K. Gupta, J.Indian Chem.Soc., 53, 1041 (1976).*
2. *C.A. Winter. et al., J.Pharmac.Exp.Ther, 141, 369-376 (1963).*
3. *Roy et al., Indian J.Physiol. Pharmac., 24, 369-372 (1980).*
4. *D.J. Sen, PhD Thesis, Jadavpur University, Kolkata, (2000).*
5. *Vogel; Vogel's Textbook of Practical Organic Chemistry; 5th edition, Prentice Hall, India, 1989.*
6. *S.N. Abramson and P.B. Molinoff, Molecular Pharmacology, 31, 103-111(1987).*
7. *M.L. Capone, S. Tacconelli et al; Circulation. 30; 109(12): 1468-71, (2004).*

****

Article History:----------

Date of Submission: 21-02-10

Date of Acceptance: 23-03-10

Conflict of Interest: NIL

Source of support: NONE