SYNTHESIS OF NOVEL (E)-3-(1, 3-DIPHENYL-1H-PYRAZOLE-4-YL) PROPANOIC ACID DERIVATIVES AND BIOLOGICAL EVALUATION OF THEIR ANTI-INFLAMMATORY ACTIVITY

Dimple Pirgal [1] Konatham Teja Kumar Reddy[2]* Vijayakumar B [3], Amrutha S [4], Akshay Kumar. U[5], K.V. Vismaya[6]

[1]Assistant Professor Pharmaceutical Chemistry Department KLE college of pharmacy, Bengaluru -560010
[2]University college of Technology, Osmania University Main Rd, Amberpet, Hyderabad, Telangana 500007.
[3]Department of Pharmaceutical Chemistry, Grace College of Pharmacy, Palakkad-678004, Kerala, India
[4]Department of Pharmaceutical Chemistry and Analysis, Nehru College of Pharmacy, Thiruvilwamala, Thrissur – 680 588, Kerala, India.
[5] Department of Pharmaceutical Chemistry, Nitte College of Pharmaceutical Sciences, Bengaluru, Karnataka
[6] Department of Pharmaceutical Chemistry and Analysis, Nehru College of Pharmacy, Thiruvilwamala, Thrissur – 680 588, Kerala, India.
Correspondence Email : teja.konatham1704@gmail.com
ORCID ID: 0000-0003-0227-2248

ABSTRACT

Five derivatives 3-(1, 3- substituted diphenyl-1H-pyrazole-4-yl-) propionic acidswere synthesized by reduction of 3-(1,3-diphenyl-1H-pyrazole-4-yl-) acrylic acid in ethyl acetate was added in the presence of 20% palladium / charcoal with constant stirring. The reaction mixture was stirred for overnight and the excess of ethyl acetate was distilled off under reduced pressure. The precipitate obtained was filtered, dried and recrystallized from appropriate solventThe chemical structures of these compounds were confirmed by means of Physical data and IR spectral data. The compounds were assayed for anti-inflammatory activity.Among the compounds 4a and 4d showed significant anti-inflammatory activity, 4b and 4e showed moderate anti- inflammatory activity.

Keywords: Physical data, IR spectral data compounds, anti-inflammatory activity.
DOI Number: 10.14704/NQ.2022.20.12.NQ77083 **NeuroQuantology2022;20(12): 1021-1029**

INTRODUCTION

Pharmaceutical compounds which are predominantly heterocyclic compounds, have been an area of intensive research, due to their applicability in the prevention or treatment of various disorders. A large number of heterocyclic compounds, both synthetic and natural, are pharmacologically active and are in clinical use. Heterocyclic compounds are widely distributed in nature, which are essential to life. Various compounds such as alkaloids, antibiotics, essential amino acids, vitamins, hemoglobin ,hormones and a large number of synthetic drugs contain heterocyclic ring systems.Among the wide variety of heterocycles that have been explored for developing pharmaceutically important heterocycles for developing important molecules, pyrazoles have played an important role in medicinal chemistry.

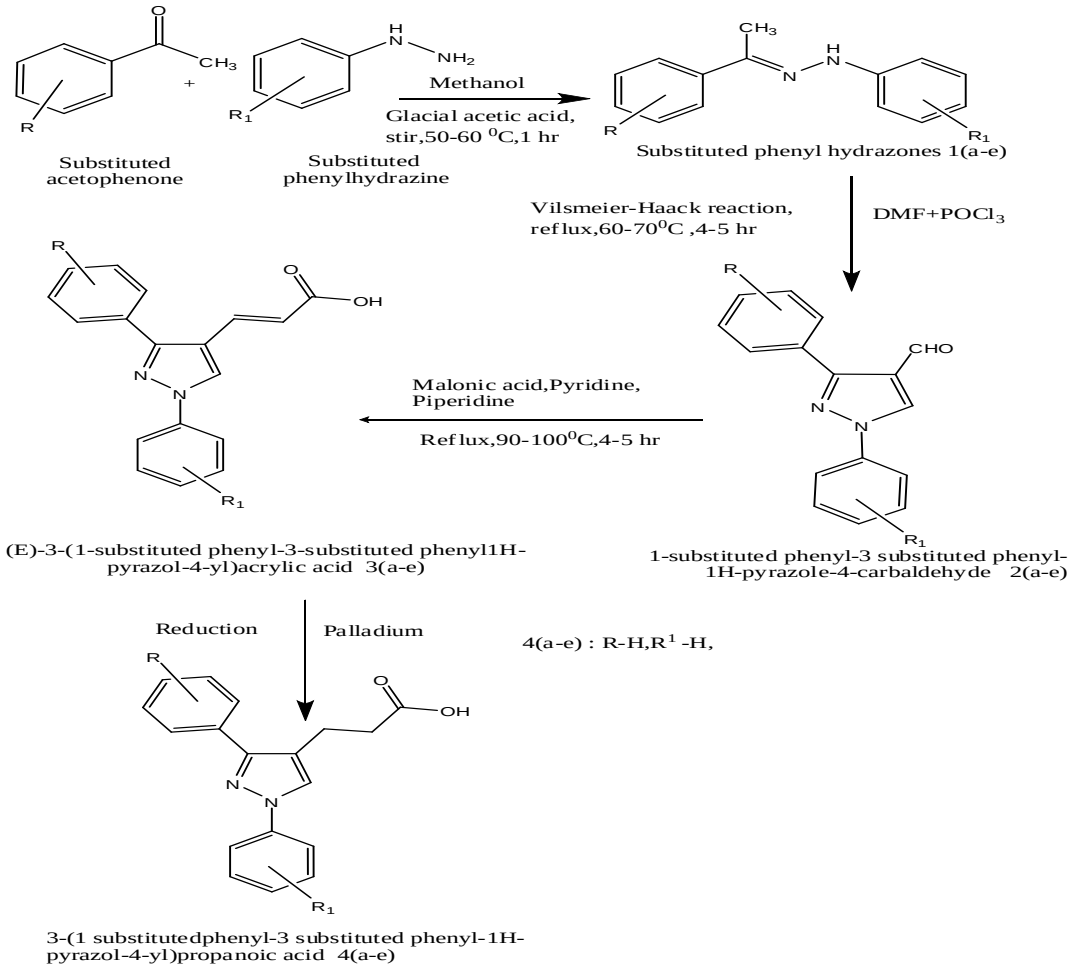
.

MATERIALS AND METHODS

All the chemicals and solvents used were of synthetic grade from Sd. fine chemicals Ltd. (Mumbai India), Merck, NR chem. Melting points were determined in open capillary tubes using SISCO melting point apparatus and are uncorrected. Purity of the compounds was verified by a single spot in TLC using E-Merck Silica Gel $F_{254,}$ 0.25mm aluminum plates. Visualization was accomplished with U.V light (254nm) and iodine chamber. The IR spectra were recorded on SCHIMADZU FT IR SPECTROPHOTOMETER by using 1% potassium bromide discs

eISSN 1303-5150

RESULTS &DISCUSSION



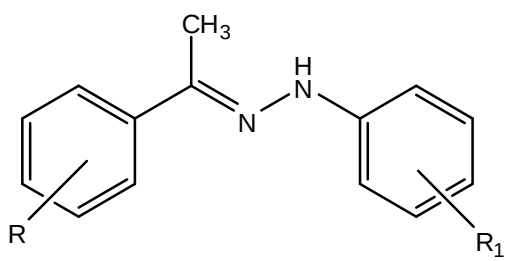
PHYSICAL AND SPECTRAL DATA OF THE COMPOUNDS :

Steps involved are:

Step 1:

In the above scheme, first step involves condensation reaction in which substituted acetophenones react with substituted phenyl hydrazines to give 1-phenyl ethanone phenyl hydrazones in the presence of methanol and catalytic amounts of glacial acetic acid. Homogeneity of the compound was checked by TLC(Solvent system - ethyl acetate :hexane 3:7).

TABLE 1: ***Physical data of 1-phenyl ethanone phenyl hydrazone derivatives(1a-1e):***



eISSN 1303-5150

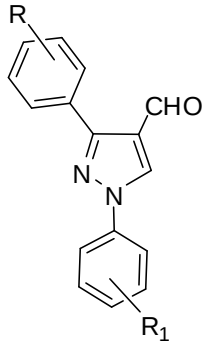
S.No	Compd	R	R^1	Molecular formula	Molecular weight	M.P(^{0}C)	Yield (%)
1	1a	H	H	$C_{14}H_{14}N_2$	210	125-130	93
2	1b	2-Cl	H	$C_{14}H_{13}ClN_2$	244	119-125	93
3	1c	4-Cl	H	$C_{14}H_{13}ClN_2$	244	118-122	91
4	1d	4-CH_3	H	$C_{15}H_{16}N_2$	224	117-122	93
5	1e	4-CH_3	2-CH_3	$C_{16}H_{18}N_2$	238	121-125	92

(1a-1e)

Step2:

Different substituted phenyl hydrazones when subjected to Vilsmeier -Haack reaction under reflux at 60-70 ^{0}C for 4-5 hr yielded pyrazole-4-carbaldehydes. Progress of the reaction was monitored by TLC. Purity of the compounds (2a-2e) was monitored by melting point and a single spot in TLC. The structures of the compounds were confirmed by physical and spectral data

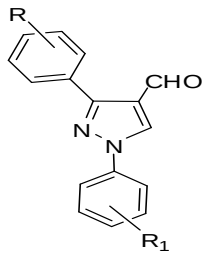
Table 2 Physical data of 3-(1,3-diphenyl)-1-H-pyrazole-4-carbaldehydes(2a-2e):



(2a-2e)

S.No	compd	R	R^1	Molecular formula	Molecular weight	M.P(^{0}C)	Yield(%)
1	2a	H	H	$C_{16}H_{12}N_2O$	248	138-140	88
2	2b	2-Cl	H	$C_{16}H_{11}ClN_2O$	282	142-145	89
3	2c	4-Cl	H	$C_{16}H_{11}ClN_2O$	282	138-142	88
4	2d	4-CH_3	H	$C_{17}H_{14}N_20$	262	137-139	86
5	2e	4-CH_3	2-CH_3	$C_{18}H_{16}N_20$	276	141-143	87

Table 3: Spectral data of the compounds(2a-2e)



(2a-2e)

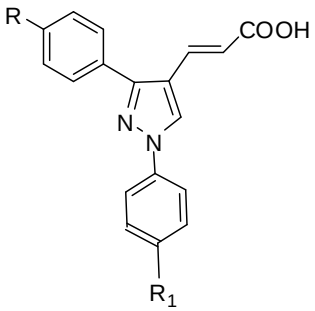
eISSN 1303-5150

Comp	***R***	***R^1***	***IR(KBr disc) in cm^{-1}***
2a	H	H	1674.1 (C=O str of CHO), 3055.54(Ar C-H str),2929 (C-H str of CHO),1591.16 (C=N str)
2b	2-Cl	H	1670.24 (C=O str of CHO), 3060.61 (Ar C-H str), 2858 (C-H str of CHO)1596.65 (C=N str),754.12 (C-Cl str).
2c	4-Cl	H	1670.24 (C=O str of CHO), 3061.78 (Ar C-H str), 2921 (C-H str of CHO),1597.91 (C=N str),753.15 (C-Cl str).
2d	4-CH_3	H	1670.24(C=O str of CHO), 2825 (C-H str of CHO),3058.68(ArC-H str), 1596.95(C=N str)
2e	4-CH_3	2-CH_3	1671.20(C=O of CHO), 2819 (C-H str of CHO),3121.57(Ar-C-H str), 1604.66(C=N str). 2930.63 (C-H str of CH_3)

STEP 3:

The above substituted pyrazole-4-carbaldehydes were condensed with malonic acid in pyridine and catalytic amounts of piperidine under reflux for 4-5 hr to form corresponding acrylic acids (3a-h). The structures of the compounds were confirmed by physical and spectral data

Table 4.1.4: Physical data of 3-(1,3-diphenyl-1H-pyrazol-4-yl)acrylic acids(3a-3e)

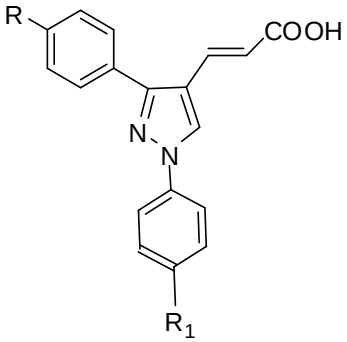


(3a-3e)

S.no	***Comp***	***R***	***R^1***	***Mol.formula***	***Mol.wt***	***M.P(^{0}C)***	***Yield(%)***
1	3a	H	H	$C_{18}H_{14}N_2O_2$	290	208-210	84
2	3b	2-Cl	H	$C_{18}H_{13}ClN_2O_2$	324	218-224	83
3	3c	4-Cl	H	$C_{18}H_{13}ClN_2O_2$	324	216-220	81
4	3d	4-CH_3	H	$C_{19}H_{16}N_2O_2$	304	210-215	82
5	3e	4-CH_3	2-CH_3	$C_{20}H_{18}N_2O_2$	318	214-217	81

Table 4: Spectral data of compounds (3a-3e)

eISSN 1303-5150



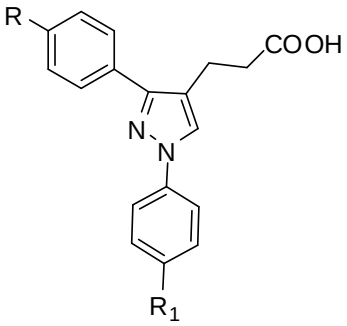
(3a-3e)

Compd	***R***	***R^1***	***IR(KBr disc) in cm^{-1}***
3a	H	H	1691.48 (C=O str of COOH), 1618.17 (C=N str), 3392.91 (O-H str)
3b	2-Cl	H	1683.74(C=O str of COOH),1620.09(C=N str),3427.27 (O-H str)
3c	4-Cl	H	1683.74 (C=O str of COOH), 1627.81(C=N str), 3407.29(O-H str)
3d	4-CH_3	H	1685.67 (C=O str of COOH), 1620.09(C=N str),3427.27(O-H str)
3e	4-CH_3	2-CH_3	1687.60 (C=O str of COOH), 1610.28 (C=N str) ,3326.01(O-H str)

Step 4:

The above pyrazole-acrylic acids were reduced by diimide method using hydrazine hydrate and hydrogen peroxide. The reduction was also tried with palladium/charcoal in ethyl acetate and ammonium formate by stirring for overnight at room temperature. The structures of the compounds were confirmed by physical and spectral data .

Table .6:Physical of 3-(1,3-substituted diphenyl-1H-pyrazol-4-yl)propanoic acids(4a-4e):



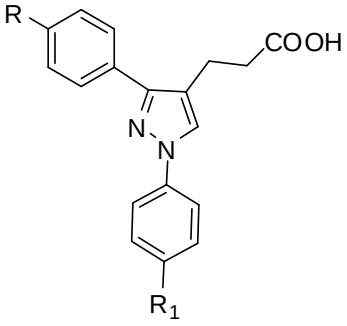
(4a-4e)

;

S.No	***Compd***	***R***	***R^1***	***Mol.formula***	***Mol.wt***	***M.P(^{0}c)***
1	4a	H	H	$C_{18}H_{16}N_2O_2$	292	99-103
2	4b	2-Cl	H	$C_{18}H_{15}ClN_2O_2$	326	97-100
3	4c	4-Cl	H	$C_{18}H_{15}ClN_2O_2$	326	93-95
4	4d	4-CH_3	H	$C_{19}H_{18}N_2O_2$	308	91-95
5	4e	4-CH_3	2-CH_3	$C_{20}H_{20}N_2O_2$	322	92-96

Table:5: Spectral data of compounds (4a-4e)

eISSN 1303-5150



(4a-h)

Cpd	*R*	*R[1]*	*IR(KBrdisc) stretching*
4a	H	H	1708.81 (C=O str of COOH), 1596.95 (C=N str),3438(O-H str)
4b	2-Cl	H	1714.60(C=O str of COOH),3367(O-H str) , 756.04(C-Cl str)
4c	4-Cl	H	1706.88 (C=O str of COOH),3438(O-H str)754.17 (C-Cl str)
4d	4-CH_3	H	1711.71(C=O str of COOH),2927 (C-H str of $CH_{3),}$ 3243.08(0-H str)
4e	4-CH_3	2-CH_3	1707.85(C=O str of COOH), 2917.74(C-H str of CH_3), 3405(O-H str)

Anti-inflammatory Studies

INFLAMMATION:

Inflammation is a tissue reaction to infection, irritation or foreign substance. It is a part of host defensemechanism. During these tissue reactions the permeability of the vasculature is increased and leads to extrusion of cells and cellular fluid into the extra vascular ares which results in the formation of edema.

The complete process of inflammation generally consists of three phases:

1) Dilation and increased permeability of small blood vessels resulting in edema and swelling.
2) Emigration of leucocytes from venules and capillaries, cellular infiltration and a general mopping up reaction.
3) Proliferation of fibroblasts and synthesis of new connective tissue to repair the injury.

Inflammation may be acute or chronic.

- **Acute inflammation** is usuallycharacterized by fundamental symptoms like redness, swelling, pain and loss of function at the injured area depending upon site and extent of injury.
- **Chronic inflammation** usually occurs when acute inflammation remains unresolved. It is associated with many inflammatory diseases e.g. rheumatoid arthritis, hepatitis etc.

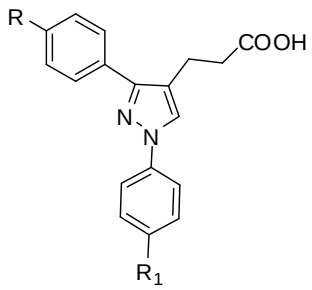
In human beings, inflammation occurs in vascular tissues and is primarily a local vascular response, where rich fluid and cells are brought to the site of injury to neutralize the damaging agent. The damage may be due to variety of causes such as mechanical (cuts, blows, etc), chemical (acids, alkalis, toxins etc), radiation, burns, bacteria, viruses, parasites and may be antigen antibody reactions. At a microscopic level, the response is usually accompanied by the familiar clinical sign of erythema, edema, tenderness and pain. The inflammation mediators are histamine, serotonin, prostaglandins, leukotrienes etc. Models for the acute inflammation involve the measurement of the cardinal signs of inflammation such as edema.

eISSN 1303-5150

Many acute inflammatory models involve the injection of irritants into the hind paw of the rat to induce edema. A famous and good irritant known was carrageenan. The volume of hind paw is measured prior and after inducing the inflammation by using plethysmometer. The amount of inflammation in untreated animals and animals treated with test drugs were measured. If the inflammation in the treated animals is less than that in untreated animals, then the drug is considered to possess anti-inflammatory activity.

Plethysmometer technique is based on the principle of mercury displacement. It is a simple apparatus, which consists of two glass arms containing mercury in one of the arm, and on the other arm a scale is fixed. The mercury displacement due to dipping of the paw can be directly read from the scale attached to the mercury column. The net edema volume can be calculated by subtracting paw volume before the induction of edema from the paw volume after the inflammation.

Table No : 6 Anti –Inflammatory data of 3-(1,3-substituted diphenyl-1H-pyrazole-4-yl) propionic acids (4a-4e)



Treatment	R	R^1	Dose mg/kg	MEAN EDEMA VOLUME(ml)				
	–			30 min	1 hr	2hr	3hr	4hr
Control	–	–		0.20±0.018	0.38±0.045	0.72±0.021	0.92±0.056	0.90±0.018
Diclofenac (standard)	_	_	100	0.12±0.011	0.22±0.011	0.32±0.01	0.25±0.018	0.33±0.01
4a	H	H	100	0.10±0.011	0.16±0.011	0.28±0.01	0.20±0.017	0.38±0.01
4b	2-Cl	H	100	0.15±0.012	0.23±0.019	0.39±0.018	0.32±0.019	0.50±0.018
4c	4-Cl	H	100	0.16±0.013	0.21±0.018	0.22±0.016	0.38±0.017	0.58±0.018
4d	4-CH_3	H	100	0.15±0.018	0.19±0.015	0.25±0.019	0.30±0.010	0.37±0.014
4e	4-CH_3	2-CH_3	100	0.16±0.013	0.26±0.018	0.28±0.016	0.30±0.017	0.42±0.018

eISSN 1303-5150

Edema volume = (mean ± SEM)

Table: 7Percentage protection against edema formation

Treatment	R	R^1	Dose mg/kg	% protection				
				30min	1 hr	2 hr	3hr	4hr
Diclofenac (standard)	**–**	**–**	**100**	**40**	**43.8**	**55.55**	**72.6**	**65.1**
4a	H	H	100	**13.5**	**56.7**	**52.5**	**70.3**	**38.3**
4b	2-Cl	H	100	**25**	**42.6**	**51.8**	66.3	**32.6**
4c	4-Cl	H	100	**20.7**	**47.6**	**51.4**	64.6	**31.8**
4d	4-CH_3	H	100	**25.8**	**46.7**	**53.8**	**67.8**	**37.2**
4e	4-CH_3	2-CH_3	100	**20.2**	**47.8**	**53.7**	66.7	**39.8**

DISCUSSION:

Five synthesized compounds 4a, 4b, 4c, 4d and4e were screened for anti-inflammatory activity by carrageenan induced paw edema method. Diclofenac was used as a standard. From the data obtained, the mean edema volume and percentage reduction in edema was calculated. From the tested compounds **4a & 4d** showed significantactivity and the results are comparable to the standard drug Diclofenac.

CONCLUSION

- Eight derivatives of 3-(1,3- substituted diphenyl -1H-pyrazol-4-yl) propanoic acids have been synthesized in high purity and in good yields.
- The chemical structures of the synthesized compounds were confirmed on the basis of physical and IR data .
- In the last step, the reduction of pyrazole acrylic acids was carried out by using palladium/charcoal method.
- The compounds were screened anti inflammatory activity was carried out using carrageenan induced rat paw edema method
- The compounds **(4a)& 4(d)** exhibited significant protection against the edema formation at a concentration of 100 mg/kg and the results are comparable with the standard drug, Diclofenac (100mg/kg). The activity may be attributed to the presence of chloro, methyl, substitutions on the phenyl ring.
- Suitable molecular modifications and QSAR studies of the compounds may generate more potent anti inflammatory agents.

REFERENCES:

1. Wilson & Gisvolds *Textbook Of Organic Medicinal and Pharmaceutical Chemistry* JH Block , JM Beale Jr, Lippincott Williams &Wilkins 11th Edition,3-5.2004.
2. Burger, J.Abraham, Burgers Medicinal Chemistry and drug Discovery, 6th edition,vol.1:Drug discovery 1-42
3. Igor G.Safonov, Dirt A. Heerding, Richard M.Keenan, Alan T.Price, Connie L.Levin, Kennet A.Lord and Peter M. Tapley,*Bioorganic and Medicinal Chemistry Letters* ,2006,16, 1212-1216
4. Jin Hee Ahn, Seung Jun Kim, Woul Seong Park, Sung Yun Cho, Jae Du Ha, Sung Soo Kim, Seung Kyu Kang, Dae Gwin Jeong, Suk-Kyeong Jung, Sang-Hyeup Lee, Hwan Mook Kim, Song Kyu Park, Ki HoLee, Chang Woo Lee, Chang Woo Lee, Seong Eon Ryu and Joong-Kwon Choi, *Bioorganic and Medicinal*

eISSN 1303-5150

Medicinal Chemistry Letters ,2006, 16, 2996-2999

5. G Rainer ..*Chemical Abstracts*, 91(1979)2046y, U..Spat.4,4146, 721.
6. G Rainer. Krutgen , Artaneium Forsch,U.Klemn, G.*Chemical Abstracts*.1981,31,649.
7. EI –emary .J.I , Bakhite , *.pharmazie , 1999, 54, 106-111.*
8. Wallace T. Ashton Clark, Linda L, Chang, Wayne, William .J Greenlee, Teaneck, Steven. M. Hutchins , Iselin, U.S.5,262,412.,1993.
9. S. T. Heller, S. R. Natarajan, *Org. Lett.*, 2006, *8*, 2675-2678.
10. F. Gosselin, P. D. O'Shea, R. A. Webster, R. A. Reamer, R. D. Tillyer, E. J. J. Grabowski, *Synlett*, 2006, 3267-3270.
11. M. S. M. Ahmed, K. Kobayashi, A. Mori, *Org. Letters.*, 2005, *7*, 4487-4489
12. X. Deng, N. S. Mani, *Org. Lett.*, 2008, *10*, 1307-1310.
13. Goverdhan Mehta,Narinder Mohal, *Tetrahedron .Letter*,1998,39,3287-89.
14. N. Nakamichi , Yuka Kawashita, Masahiko Hayashi, *synthesis* 2004,1015-1020.
15. K.Mogilaiah, K.Vidya, S.Kavitha &K.Shiva Kumar, *Indian Journal of Chemistry*,.48 B,Feb. 2009,282-285.
16. B C Gourdarshi Vannanavar, H Jayadevappa & K M Mahadevan *,Indian Journal of Chemistry,48 B, Oct.2009,1419-1423*
17. Shasikant R Pattan,Jayashri S Pattan,AA Bukitagar,V S Wakale & D S Husmade *,Indian J. Chem,.48 B,Oct2009,1453-1456*
18. K.Mogilaiah, K.Jagadeeshwar& R.Shiva prasad, *, Indian J. Chem* ,48 B,Oct-2009,1466-1469
19. Vijai Pathak,Rahul Joshi,Supreet Chabra,Ranjana Tiwari,Jaimala Sharma & Neetu Gupta,*Indian journal of heterocyclic chemistry,*.17,Oct-Dec.,2007,139-144.
20. S.N.Thore and Ashwini Kumar Gupta*, Indian journal of heterocyclic chemistry*,.19,Apr-June,2010 ,329-332
21. S.N.Thore and Ashwini Kumar Gupta, *Indian journal of heterocyclic chemistry*,19,Apr-June,2010 ,373-376.
22. S.K.Nawarde, S.B.Kale and B.K.Karale, Indian journal of hete S.N.Thore and Ashwini Kumar Gupta, *Indian journal of heterocyclic chemistry*,16,Jan-march 2007, 275-278.
23. Om Prakash ,Rashmi Pundeer,Pooja Ranjan,Kamaljeet Pannu,Yogita Dhingra &K,R Aneja, *Indian journal of heterocyclic chemistry*,48B,Apr-2009,563-568
24. Jaishree D Mahale, SC Manoja,NG Belsare and PR Rajput,*Indian journal of heterocyclic chemistry*,49B,Apr-2010,505-511
25. DI Brahma Bhatt , Ankit R Kaneria,Anil K Patel &Niraj H Patel*, Indian Journal of chemistry,*49B,July2010,971-977
26. D.R.Nagargoje, A.R.Ghawalkar, G.R.Jadhav, M.V.Shaikh, S.D.Diwakar, M.S.Shingare and C.H.Gill, *Indian J. HeterocyclicChemistry,* 18, July-Sept., 2008, 53-56.
27. B.Djerrari,J Fifani,NH Ahabchane,EM Essassi,B Garrigues and M Pierrot,*Indian journal of chemistry*,42 B,october 2003,2558-2562
28.

eISSN 1303-5150