HL
http://heteroletters.org

ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)
Vol. 2: (2), 2012, 168-173

SYNTHESIS OF (Z)-3-(3-CHLORO-2-OXO-4-PHENYLAZETIDIN-1-YL)-4-(2`-(4`-SUBSTITUTEDPHENYL) HYDRAZONO)-1-((5-THIOXO-4,5-DIHYDRO-1,3,4-OXADIAZOL-2-YL)METHYL))-1H-PYRAZOL-5(4H)-ONE DERIVATIVES

***Nagaraju G[1], Kishore Kumar k[1], Jayaveera K.N[1]and Ravindranath L.K[2].**

[1]Department of Chemistry, J.N.T.University, Anantapur, Andhrapradesh, India
[2]Department of Chemistry, S.K.University, Anantapur, Andhrapradesh, India
E-mail: nagarajuchemg@gmail.com

ABSTRACT
In present investigation, we have synthesised the Substituted 1, 3, 4-Oxadiazoles with oxophenylazetidine and pyrazoline ring systems to enhance the required biological activity. We have synthesised the required biologically active molecules by easily ongoing, cost effective, easily reproducible and feasible synthetic routs. Innovate synthetically most important and active molecules towards targeted diagnostic diseases and exhibit antibacterial, anticonvulsant, anticancer activities. The structures of all these compounds have been confirmed by IR, ^{1}HNMR, and elemental analysis.

KEYWORDS
1, 3, 4-Oxadiazoles, oxophenylazetidine and pyrazoline ring system.

INTRODUCTION
The activity of the 1,3,4-Oxadiazoles is attributed to the azetidine and pyrazoline ring systems. The synthesis of the (Z)-3-(3-chloro-2-oxo-4-phenyl azetidin-1-yl)-4-(2`-(4`-substituted phenyl) hydrazono)-1-((5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-pyrazol-5(4H)-one derivatives is carried out by easily applicable and synthetically most feasible routs.

Several synthesised derivatives of 5-substituted-1, 3, 4-Oxadiazoles[1] were reported to posses hypoglycaemic activity and found to be less toxic than the corresponding hydrazides. Some new adamantylthiazolyl -1,3,4-oxadiazoles[2] have posses *in vitro* antiproliferative activity and some symmetrical 2,5-disubstituted-1,3,4-Oxadiazoles have posses CNS depressant and anticonvulsant activities[3].H.S.Yathirajan et al[4] have synthesised new substituted 1,3,4-Oxadiazole derivatives bearing 6-bromonaphthalene moiety and tested for antimicrobial studies. Some 3-(substituted amino methyl)-5-(3, 5-dinitrophenyl)-1,3,4-Oxadiazol-2-thiones were screened for their cardiovascular and anti-inflammatory activity[5]. These compounds were found to be non-toxic and psychotropic in nature. Synthesis of 1,3,4-oxadiazoles linked to naptho[2,1-b]furan[6] are active towards antimicrobial and antiinflammatory.Antibacterial studies of 2-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-1,3,4-oxadiazole derivatives[7] have been carried out. Most of these compounds

were active against *E.coil, p.aeruginosa, B.subtilis and S.aureus.*In the present work we have synthesised

EXPERIMENTAL: Melting points were determined in open capillary tubes and are uncorrected (in degree Celsius).The Infrared spectra were recorded in KBr discs on Perkin-Elmer FT-IR(Spectrum ONE) spectrophotometer(vmax in cm-1).The 1HNMR spectra were recorded on a Bruker AMX (400 MHz) spectra photometer in DMSO-d6 with TMS as an internal standard (chemical shifts in δ).Mass Spectra were recorded on Shimazdu LCMS-QP8000.Silica gel chromatography using Merck silica gel 60ASTM(60-120 &230-400)mesh.

Preparation of the compounds from 2(a-f) to 7(a-f).
Preparation of the intermediate compounds from 2(a-f) to 7(a-f) have been reported by Ravindranath et al IPCBEE, vol 10, 80-85(2011).

Preparation of (Z)-2-((Z)-3-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-4-(2-(4`-substituted phenyl) hydrazono)-5-oxo-4, 5-dihydro-1H-pyrazol-1-yl)-N`-(1`-(4-substitutedphenyl) ethy lidene) acetohydrazide.8 (a-j).
To solution of (7e) (0.01 mol) in hot methanol (25ml), acetophenone (0.01 mol) and a drop of glacial acetic acid were added. The solid that separated on refluxing for 3 hrs was filtered, wash with cold methanol and recrystallized from methanol to give (8e) with yield 83%.The above reaction of (7e) with acetophenone has been extended to p–methyl acetophenone, p–chloroacetophenone, p-methoxyacetophenone and p–nitroacetophenone.

^{1}HNMR (DMSO-d_6: δppm) of **8e:** 1.69 (s, 3H,CH_3), 4.06 (s,2H, NCH_2CO), 12.15(s, 1H, -CONH), 11.21 (s, 1H, Ar-NH), 5.14 (d,1H,3-CH),4.56(d,1H,4-CH), 6.72(m,2H,Ar-H), 7.16 (m,3H,Ar-H),7.37(m,2H,Ar-H),7.53 (m,2H, Ar-H),7.78(m,3H,Ar-H),8.03 (m,2H,Ar-H). ^{13}CNMR (DMSO-d_6 ;δppm):14.2,54.4,54.9,117.8,124.5, 126.8,127.4,128.6,128.9,131.3,134.2,141.8, 143.3,165.7, 168.7,168.9,170.3,171.2. EI ms: (M+1): 577.04; Anal. Calcd.for C28H23Cl2N7O3 (576.43) C:58.34;H:4.02;N:17.01; Found:C:58.84; H:3.89;N:17.12.

^{1}HNMR(DMSO-d6;δppm) of **8g:**3.21(s,3H,Ar-CH_3),1.75(s,3H,CH3),4.03(s,2H,NCH_2 CO) ,12.21 (s, 1H,-CONH), 11.41 (s, 1H, Ar-NH), 5.16(d,1H,3-CH),4.47(d,1H,4-CH),6.72(m,2H,Ar-H),7.17(m,3H,Ar-H),7.20(m,2H,Ar-H) ,7.32(m,2H,Ar-H),7.53(m,2H,Ar-H), 7.86 (m,2H,Ar-H). ^{13}CNMR (DMSO-d_6;δppm):14.2,24.8,54.4,62.2,117.9,124.7,126.9,127.5,128.4, 129.1,129.9, 131.4,140.8,143.8,163.4,166.0,167.8,168.9,176.7. EI ms: (M+1):591.09; Anal. Calcd.for C29H25Cl2N7O3(590.46) C:58.99;H:4.27;N:16.61; Found:C:59.17;H:4.28;N:16.32.

^{1}HNMR(DMSO-d6;δppm) of **8h:**1.78 (s, 3H, CH_3), 4.43 (s,2H, NCH_2CO), 12.21 (s,1H,-CONH),11.46 (s,1H,Ar-NH), 5.18(d,1H,3-CH),4.48(d,1H,4-CH),6.82(m,2H,Ar-H),7.18 (m, 3H,Ar-H), 7.37(m,2H,Ar-H),7.52(m,2H,Ar-H),7.82(m,2H,Ar-H),7.99(m,2H,Ar-H). ^{13}CNMR (DMSO-d_6;δppm):13.9,54.2,54.8,62.6,117.9,124.8,126.8,127.7,128.5,129.3,129.8,130.9,132.8, 136.9,141.2,143.8,163.6,166.2,167.9,168.8,177.0. EI ms: (M+1):611.01; Anal. Calcd.for C28H22Cl3N7O3(610.88) C:55.05;H:3.63;N:16.05; Found:C:55.19;H:3.94;N:15.58.

^{1}HNMR(DMSO-d6;δppm) of **8i:**3.86 (s,3H,O – CH_3), 1.73 (s,3H, CH3), 4.21(s,2H, NCH_2CO), 12.10 (s,1H,-CONH), 11.32 (s,1H,Ar-NH),5.20(d,1H,3-CH),4.51(d,1H,4-CH),6.65(m, 2H,Ar-H),7.05(m,2H,Ar-H),7.20 (m,3H,Ar-H), 7.32(m,2H,Ar-H),7.54(m,2H,Ar-H),7.79(m,2H,Ar-H). ^{13}CNMR (DMSO-d_6;δppm):13.8,54.3,54.9,56.8,62.9,114.7,117.8,124.5, 126.3,126.8,127.4, 128.6,129.9,141.4,143.7,163.2,164.5,167.1,168.7,176.8.EI ms: (M+1):607.08; Anal. Calcd.for C29H25Cl2N7O4(606.46) C:57.43;H:4.16;N:16.17; Found:C:57.84;H:4.19; N:16.03.
^{1}HNMR(DMSO-d6;δppm) of **8j:**1.73 (s,3H, CH3), 4.12 (s,2H, NCH_2CO), 12.21 (s,H, NH), 11.04 (s, H, Ar-NH),5.16(d,1H,3-CH),4.48(d,1H,4-CH),6.72(m,2H,Ar-H),7.19(m,3H,Ar-H),7.36(m,2H,Ar-H),7.59(m,2H,Ar-H),8.12(m,2H,Ar-H),8.48(m,2H,Ar-H). ^{13}CNMR (DMSO-d_6 ;δppm):13.9,54.4,54.7,62.8,117.9,121.5,124.8,126.7,127.2,128.8,129.8,130.8,140.3,141.8,143.6, 150.9,163.8,164.6,168.5,168.9,177.0. EI ms: (M+1):622.01; Anal. Calcd.for C28H22Cl2N8O5 (621.43) C:54.12;H:3.57;N:18.03; Found:C:54.68;H:3.75;N:17.94.

Preparation of (Z)-1-((4-acetyl-5``-(4-substitutedphenyl)-5``-methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-3-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-4-(2-(4`-substitutedphenyl) hydrazono)-1H-pyrazol-5(4H)-one. 9(a-j).

A mixture of **(8e)** (0.01 mole) and excessive acetic anhydride (10 ml) was refluxed for 2 hours. The excessive acetic anhydride was distilled off and the residue was poured on to crushed ice. The solid thus obtained was filtered, washed with water and recrystallized from aqueous methanol to furnish **(9e)** with 63% yield. The cyclization reaction was extended to other hydrazones **9(b–j)** and in each case the respective (substituted) R_1 = p–$CH_3C_6H_4$, p–ClC_6H_4, p–$OCH_3C_6H_4$, p–$NO_2C_6H_4$ was isolated in 76 – 52% yields.

^{1}HNMR (DMSO-d_6;δppm) of **9e:** 1.89(s,3H,-CH_3),2.46(s,3H,-$COCH_3$),3.78(s,2H,NCH_2), 11.21 (s, 1H, Ar-NH), 5.14 (d,1H,3-CH),4.56 (d,1H,4-CH), 6.72(m,2H,Ar-H), 7.16 (m,3H, Ar-H), 7.37 (m,2H, Ar-H),7.53(m,2H,Ar-H),7.78(m,3H,Ar-H), 8.03(m,2H, Ar-H). ^{13}CNMR (DMSO-d_6;δppm):23.9, 28.3,49.9, 54.4, 62.8,77.8, 117.8,124.9,126.8,127.2,128.9, 129.9,141.6, 142.7, 143.8,162.8, 164.1, 168.3, 168.8, 169.9. EI ms: (M+1):619.08; Anal. Calcd.for C30H25Cl2N7O4 (618.47) C: 58.26; H: 4.07; N: 15.85; Found: C: 59.01; H: 3.91; N: 15.59.

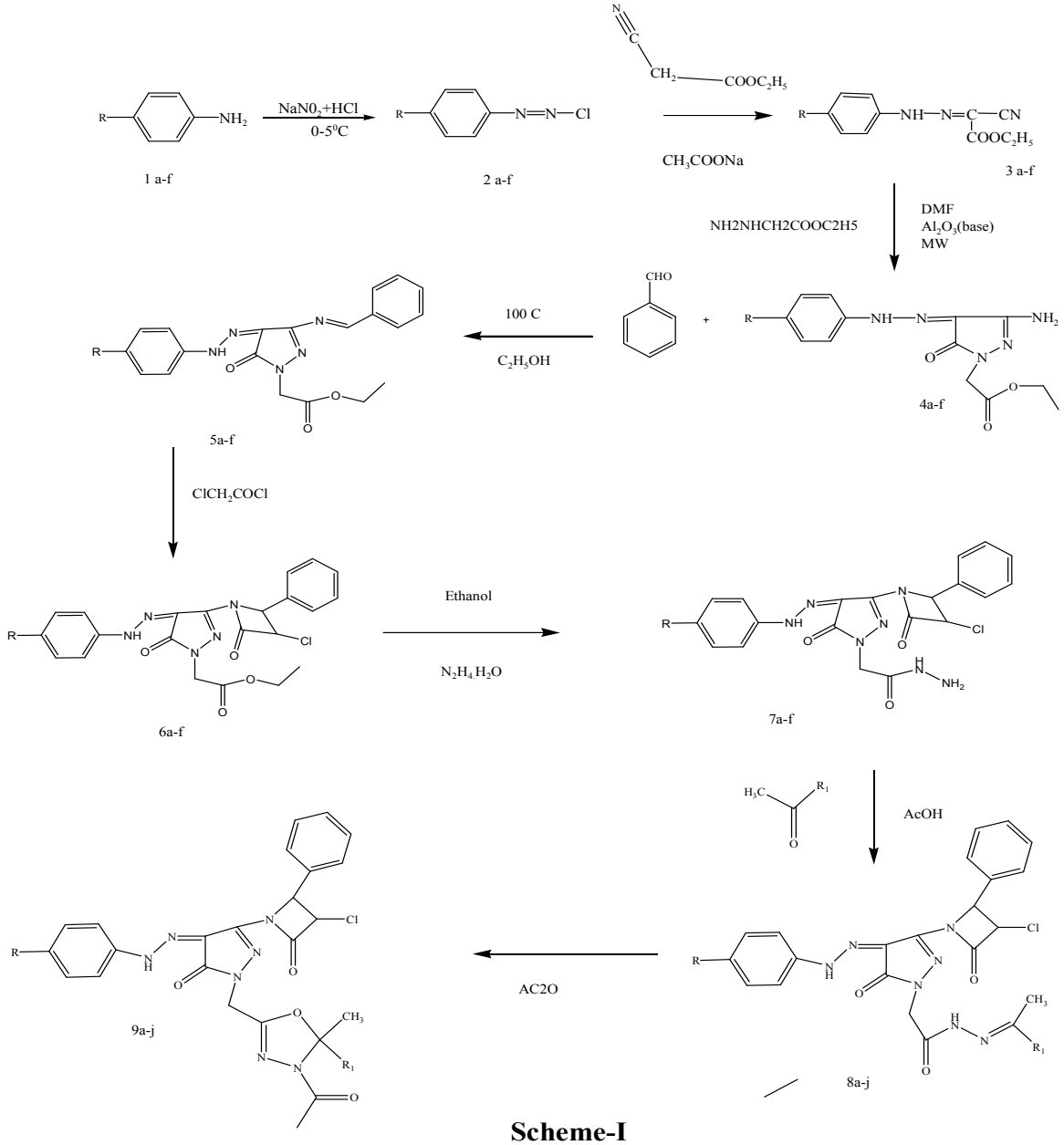
^{1}HNMR (DMSO-d_6;δppm) of **9g:** 3.11(s,3H,Ar-CH_3),1.93(s,3H,-CH3),2.49(s,3H,-$COCH_3$), 3.82(s,2H, NCH_2), 11.41 (s, 1H, Ar-NH), 5.16 (d,1H, 3-CH),4.47(d,1H,4-CH),6.72 (m,2H,Ar-H) , 7.17(m,3H, Ar-H),7.20(m,2H,Ar-H) ,7.32(m,2H,Ar-H), 7.53 (m,2H, Ar-H), 7.86 (m,2H,Ar-H). ^{13}CNMR (DMSO-d_6;δppm):23.9,24.6,28.2,54.8,62.9,77.8,117.9,124.5,126.8,127.4, 128.9, 129.8,136.6,139.7,141.5,143.9,163.1,164.4,168.4,168.9,169.7. EI ms: (M+1):633.05; Anal. Calcd.for C31H27Cl2N7O4(632.5) C:58.87;H:4.30;N:15.50; Found:C:58.96;H:4.52; N:15.21.

^{1}HNMR (DMSO-d_6;δppm) of **9h:** 1.88(s,3H,-CH_3),2.49(s,3H,-$COCH_3$),3.81(s,2H, NCH_2), 11.46(s,1H, Ar-NH),5.18(d,1H,3-CH),4.48(d,1H,4-CH), 6.82 (m,2H, Ar-H),7.18 (m, 3H,Ar-H), 7.37 (m,2H, Ar-H), 7.52(m,2H,Ar-H),7.82(m,2H,Ar-H), 7.99 (m,2H, Ar-H). ^{13}CNMR (DMSO-d_6;δppm):23.8,28.4,49.9,54.9,62.7,77.8,117.8, 124.3,126.9, 127.3,128.8,129.8,132.6,140.9, 141.7,143.8,163.4,164.7,165.1,168.3,168.9.EI ms: (M+1): 653.02; Anal. Calcd.for C30H24Cl3N7O4(652.92) C:55.19;H:3.71;N:15.02; Found:C:55.53; H:3.87;N:15.01.

^{1}HNMR (DMSO-d_6;δppm) of **9i:** 3.86(s,3H,O – CH_3),1.93(s,3H,-CH3),2.47(s,3H,-$COCH_3$), 3.84(s,2H, NCH_2), 11.32(s, 1H,Ar-NH), 5.20(d,1H,3-CH),4.51 (d,1H,4-CH), 6.65(m, 2H,Ar-H),7.05 (m,2H, Ar-H),7.20 (m,3H, Ar-H), 7.32(m,2H,Ar-H),7.54(m,2H, Ar-H),7.79 (m,2H,Ar-

H). ^{13}CNMR (DMSO-d_6;δppm):23.9,28.2,49.4,54.6,56.3,62.6,77.8,114.7,117.9,124.5, 126.8, 127.3,128.1,128.9,129.8,134.8,141.4,143.7,158.9,163.5,164.6,167.7,168.2,168.8. EI ms: (M+1): 649.08; Anal. Calcd. For $C_{31}H_{27}Cl_2N_7O_5$(648.5) C:57.41;H:4.20;N:15.12; Found: C:57.52; H:4.28;N:15.01.

^{1}HNMR (DMSO-d_6;δppm) of **9j:** 1.93(s,3H,CH3),2.46(s,3H,-$COCH_3$), 3.83(s,2H, NCH_2),11.04 (s, H,Ar-NH), 5.16(d,1H,3-CH) ,4.48(d,1H,4-CH), 6.72(m,2H,Ar-H), 7.19(m,3H, Ar-H),7.36(m,2H, Ar-H), 7.59(m,2H,Ar-H), 8.12 (m,2H,Ar-H),8.48(m,2H, Ar-H). ^{13}CNMR (DMSO-d6;δppm):23.9,28.3,49.6,54.8,62.8,77.5,117.6,120.9,124.8,126.9,127.2,127.9 ,128.7, 129.8,141.4,143.8,146.7,148.9,163.7,164.6,167.5,168.2,168.7. EI ms: (M+1): 664.04; Anal. Calcd. For $C_{30}H_{24}Cl_2N_8O_6$(663.47) C:54.31;H:3.65;N:16.89; Found:C:54.68;H:3.78;N:16.51.



Scheme-I

RESULTS AND DISCUSSION:

Our preparation of 9(a-j) followed the classic synthesis of 8(a-j), utilising the reaction of 7(a-f) with acetophenone derivatives. The pyrazol acetate 6(a-f) and hydrazine hydrate, both required for preparation of precursor 7(a-f), were prepared as follows. Starting from commercially available p-substituted aniline moieties 1(a-f), the pyrazol acetate 6(a-f) were prepared by diazotisation of 1(a-f) with $HCl/NaNO_2$,followed by in-situ coupling with ethyl 2-cyanoacetate and sodium acetate mixture at 0-5°c in minimum amount of water and ethanol to afford cyanoacetate 3(a-f) (in 89% yield),followed by condensation with ethyl 2-hydrazinylacetate and DMF under micro wave conditions intermittently at 30 sec intervals for 2-4 min to give 78% - 85% of 4(a-f).The coupling of 4(a-f) with benzaldehyde and ring formation with 2-chloroacetyl chloride afforded 6(a-f) with 43%-61% yield. The precursor 7(a-f) was prepared by the reaction of 6(a-f) with hydrazine hydrate in ethanol, the compound 8(a-j) was prepared by the reaction of 7(a-f) (0.01 mol) in hot methanol (25ml), acetophenone (0.01 mol) and a drop of glacial acetic acid. A mixture of 8(a-j) (0.01 mole) and excessive acetic anhydride (10 ml) was refluxed for 2 hours afforded 9(a-j).

The maintenance of 0-5°c in diazotisation step is very important and also critical, because diazonium salt won`t form if we cooled the reaction mass to < -10°c, and slow addition of ethyl 2-cyano acetate is preferable. The conversion of 4(a-f) in to 5(a-f) has two possibilities of ethyl 2-chloroacetate addition to the reactant molecule, one at amide nitrogen and second at amine nitrogen, but it could be controlled by the very slow addition of ethyl 2-chloroacetate and DMF mixture. The yield of the precursor 7(a-f) could be increased with substituted benzaldehyde moieties. The formation of 8(a-j) was varied from electron rich acetophenone derivatives to electron deficient acetophenone moieties; the electron rich acetophenone moieties have high reactivity than electron deficient.

Sl. No.	R	R_1	Compound	Time (h)	Temp °C	Yield (%)
1	H	C_6H_5	8a	3	80	80
2	CH_3	C_6H_5	8b	3-4	80	63
3	OCH_3	C_6H_5	8c	2.5-3	80	74
4	OC_2H_5	C_6H_5	8d	2-3	80	61
5	Cl	C_6H_5	8e	3.5-4	80	66
6	Br	C_6H_5	8f	3.5-4	80	67
7	Cl	$CH_3C_6H_4$	8g	3-4	80	72
8	Cl	ClC_6H_4	8h	3.5-4.5	80	63
9	Cl	$OCH_3C_6H_4$	8i	3 -4	80	71
10	Cl	$NO_2C_6H_4$	8j	3.5-5	80	64
11	H	C_6H_5	9a	2-2.5	Reflux	63
12	CH_3	C_6H_5	9b	2-3	Reflux	66
13	OCH_3	C_6H_5	9c	2-2.5	Reflux	71
14	OC_2H_5	C_6H_5	9d	2	Reflux	76
15	Cl	C_6H_5	9e	2.5-3.5	Reflux	52
16	Br	C_6H_5	9f	2.5-3	Reflux	65
17	Cl	$CH_3C_6H_4$	9g	2-3	Reflux	62
18	Cl	ClC_6H_4	9h	3-4	Reflux	63
19	Cl	$OCH_3C_6H_4$	9i	2-3	Reflux	65
20	Cl	$NO_2C_6H_4$	9j	3-4.5	Reflux	61

REFERENCES:

1. T. Kurihara, H. Takada, TIto and K. Sagawa, Tohoku Yakka Daigaku Kenkyu Nempo,.17, 43 (1970);
2. Maryam Zahid, Khawaja A. Yasin, Tashfeen Akhtar Nasim H. Rama, Shahid Hameed, Najim A. Al-Masoudi, Roberta Loddo, and Paolo La Colla., ARKIVOC 2009 (xi) 85-93
3. B. L. Sharma and S. K. Tandon, Pharmazie,. 39 (H-12), 858 (1984);
4. International Journal of Chemistry Vol 2, No 1, p- 38-54., 2010
5. DR. Nigam's. Swarup, V.K. Saxena and K.C. Singh, J. Ind. Chem. Soc,.69, 692 (1992).
6. Ravindra et al *Indian J. Chem.,* **45B**, 2506-2511 (2006).
7. Zhang, Y.; Qian, R. Z.; Xu, P. F.; Zhang, Z. Y.; Wang, Q.; Mao, L. M.; Yu,. K. B. J. Chin. Chem. Soc. 2002, 49, 369–373.

Received on February 3, 2012.