International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.4, No.2, pp 634-639, April-June 2012

Synthesis of 2,6-diazido-1-(*N*-substituted phenyl)-1,4-dihydropyridine- 3,5-dicarbaldehydes and their transformation into multivariant functionalities.

A.P.Rajput* and P.D.Girase[1]

***P.G. Research Center, Department of Chemistry, Z.B.Patil College, Dhule-424002 (M.S.) India .**
[1]S.V.S's Dadasaheb Rawal College, Dondaicha, Dist. Dhule. (M.S.) India.

****Corres.author: aprajput@rediffmail.com***
Mobile: +919423491139 Fax: (+912562) 220678

Abstract: A series of new 2,7-diamino-9-(N-substituted phenyl)-9,10-dihydro-1,8,9-triaza-anthracene-3,6-dicarbonitriles 6a-d were prepared by condensation of malononitrile with 2,6-diamino derivatives 5a-d which have been prepared by the action of sodium dithionite on 2,6-diazido-1-(N-substituted phenyl)-1,4-dihydropyridine-3,5-dicarbaldehydes 4a-d which in turn were prepared by the treatment of sodium azide with 3a-d. The structures of the newly synthesized compounds have been confirmed on the basis of elemental analysis and spectral studies. The newly synthesized title compounds have been screened for their in *vitro* antimicrobial activities. Some of the compounds exhibited encouraging results.
Keywords:- Dihdropyridines, azides, dicarbonitriles, antimicrobial activity.

Introduction

Dihydropyridine represents one of the most active classes of heterocyclic compounds possessing a wide spectrum of biological activities. Dihydropyridines are reported as calcium and sodium channel blockers[1,2]. Dihydropyridines are clinically useful agents for the treatment of cardiovascular disease such as anginapectoris and hypertension[3]. These are also used as antioxidants and are useful for developing drugs[4].

Azides are considered very important compounds due to both their industrial as well as biological applications[5]. Azide derivatives have been used in rubber vulcanization, polymer crosslinking, dyes, tire cored adhesives, foaming of plastics, pharmaceuticals, pesticides and herbicides[5]. Many azide compounds have shown mutagenic activities[6-8].

The chemistry of azides has thus, attracted the attention of many chemists, since many of these compounds play an important role in organic chemistry[9-11].

Azides[12] present themselves as energy rich and flexible intermidiates among many synthetic precursors and have continued to attract immense interest. An azides can be considered as a masked amino group and is used for amine protection. Azides as dipoles undergo cycloaddition reactions with olefinic species popularly known as Huisgen reaction[13]. They are also important intermediates in Ugi-multicomponent reactions[14]. Literature survey reveals that dicarbinitriles have been found to be associated with diverse biological activities such as antioxidants, antihistaminic, anti-inflammatory, analgesic antibacterial and antifungal activities[15-20].

In view of the above and in continuation of our work in the synthesis of fused heterocyclic compounds[21-29], we herein report a new series of azides **4a-d,** 2,6-diamino derivatives **5a-d** and dicarbonitriles **6a-d (Scheme-II).**

Experimental

All melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on FT-IR spectrophotometer. ^{1}HNMR spectra were recorded on varian USA Mercury plus 300 MHz NMR spectrometer with DMSO-d_6 as a solvent using TMS as internal reference (chemical shift in δ ppm). The starting compounds were synthesized according to **scheme-I**. Glutaric acid **1** was converted into N-substituted phenyl glutarimides **2a-d** which were then diformylated using Vilsmeier-Haack reaction to form **3a-d.**

General procedure for synthesis of 2,6-diazido-1-(N-substituted phenyl)-1,4-dihydropyridine-3,5-dicarbaldehydes 4a-d.

To a solution of **3** (1mmole) in absolute ethanol (10ml), p-toluenesulphonic acid (2mmole) and sodium azide (3mmole) were added and the reaction mixture was heated under reflux for 3 hr. After completion of the reaction (monitored by TLC) the reaction mixture was poured into ice-cooled water and the resulting precipitate was filtered, dried and purified by recrystallisation from aq. ethanol which afforded pure 2,6-diazido-1-(N-substituted phenyl)-1,4-dihydropyridine-3,5-dicarbaldehydes **4a-d (Scheme-II).**

2,6-diazido-1-(phenyl)-1,4-dihydropyridine-3,5-dicarbaldehydes 4a:
M. F. $C_{13}H_9O_2N_7$; Yield 71%; faint yellow solid, mp 116-118^{0}C; IR (KBr): 2924(CH_2), 2852(CHO), 2120(N_3), 1664(C=O), 1442(ArC=C), 1249(C-N) cm^{-1}; ^{1}HNMR (DMSO-d6): δ 2.63(s, 2H, CH_2), 7.60-7.28 (m, Ar-H), 9.90 (s, 2H, 2CHO).

2,6-diazido-1-(4-methylphenyl)-1,4-dihydro pyridine-3,5-dicarbaldehydes 4b:
M.F. $C_{14}H_{11}O_2N_7$; Yield 81%; dark brown solid, mp 86-88^{0}C; IR (KBr): 2924 (CH_2), 2854 (CHO), 2108(N_3), 1658 (C=O), 1442 (ArC=C), 1247(C-N) cm^{-1}; ^{1}HNMR (DMSO-d6): δ 2.31 (s, 3H, CH_3), 2.60 (s, 2H, CH_2), 7.41-7.09 (m, Ar-H), 10.0 (s, 2H, 2CHO).

2,6-diazido-1-(4-chlorophenyl)-1,4-dihydro pyridine-3,5-dicarbaldehydes 4c.
M.F. $C_{13}H_8O_2N_7Cl$; Yield 91%; reddish brown solid, mp 81-83^{0}C; IR (KBr): 2924 (CH_2), 2854 (CHO), 2108(N_3), 1726 (C=O),1492 (ArC=C), 1246 (C-N) cm^{-1}; ^{1}HNMR (DMSO-d6): δ 2.40 (s, 2H, CH_2), 7.63-7.32 (m, Ar-H), 9.86 (s, 2H, 2CHO).

2,6-diazido-1-(2-methylphenyl)-1,4-dihydrop yridine-3,5-dicarbaldehydes 4d:
M.F. $C_{14}H_{11}O_2N_7$; Yield 71%; yellow solid, mp 90-92^{0}C; IR (KBr): 2924 (CH_2), 2852 (CHO), 2108 (N_3), 1670 (C=O), 1460 (ArC=C), 1288(C-N) cm^{-1}; ^{1}HNMR (DMSO-d6): δ 2.40 (s, 3H, CH_3), 2.49 (s, 2H, CH_2), 7.49-7.03 (m, Ar-H), 10.07 (s, 2H, 2CHO).

General procedure for synthesis of 2,6-diamino-1-(N-substituted phenyl)-1,4-dihydropyridine-3,5-dicarbaldehydes 5a-d.

Sodium dithionite (6 mmole) was added in portions to a stirred solution of 2,6-diazido-1-(N-substituted phenyl)-1,4-dihydropyridine-3,5-dicarb aldehydes **4a-d** (1 mmole) in a mixture of methanol (15 ml) and water (5 ml). The solution was stirred at room temperature for 3-4 hrs. The reaction mixture was poured into ice cold water. The precipitated solid was collected by filtration, washed well with water, dried and recrystalized from ethanol to get a pure 2,6-diamino-1-(N-substituted phenyl)-1,4-dihydro-pyridine-3,5-dicarbaldehydes**5a-d (Scheme-II).**

2,6-diamino-1-(phenyl)-1,4-dihydropyridine-3,5-dicarbaldehydes 5a:
M.F. $C_{13}H_{13}O_2N_3$; Yield 85%; yellow solid, mp 192-194^{0}C; IR (KBr): 3325, 3138 (NH_2), 2924 (CH_2), 2852 (CHO), 1664 (C=O), 1442 (ArC=C), 1249 (C-N) cm^{-1}.

2,6-diamino-1-(4-methylphenyl)-1,4-dihydropyridine-3,5-dicarbaldehydes 5b:
M.F. $C_{14}H_{15}O_2N_3$; Yield 79%; yellow solid, mp 202-204^{0}C; IR (KBr): 3300, 3250 (NH_2), 2930 (CH_2), 2852 (CHO),1660 (C=O), 1450 (ArC=C), 1255 (C-N) cm^{-1}.

2,6-diamino-1-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarbaldehydes 5c:
M.F. $C_{13}H_{12}O_2N_3Cl$; Yield 84%; yellow solid, mp 172-174^{0}C; IR (KBr): 3320, 3210 (NH_2), 2923 (CH_2), 2857 (CHO), 1664 (C=O), 1475 (ArC=C), 1240 (C-N) cm^{-1}.

2,6-diamino-1-(2-methylphenyl)-1,4-dihydropyridine-3,5-dicarbaldehydes 5d:
M.F. $C_{14}H_{15}O_2N_3$; Yield 80%; yellow solid, mp 180-182^{0}C; IR (KBr): 3300, 3205 (NH_2), 2940 (CH_2), 2858 (CHO), 1670 (C=O), 1480 (ArC=C), 1248 (C-N) cm^{-1}.

General procedure for synthesis of 2,7-diamino-9-(N-substituted phenyl)-9,10-dihydro-1,8,9-triaza-anthracene-3,6-dicarbonitriles 6a-d.

Triethylamine (4 mmole, 0.40 gm) was added to a solution of 2,6-diamino-1-(*N*-substituted Phenyl)-1,4-dihydropyridine-3,5-dicarbaldehydes **5a-d**

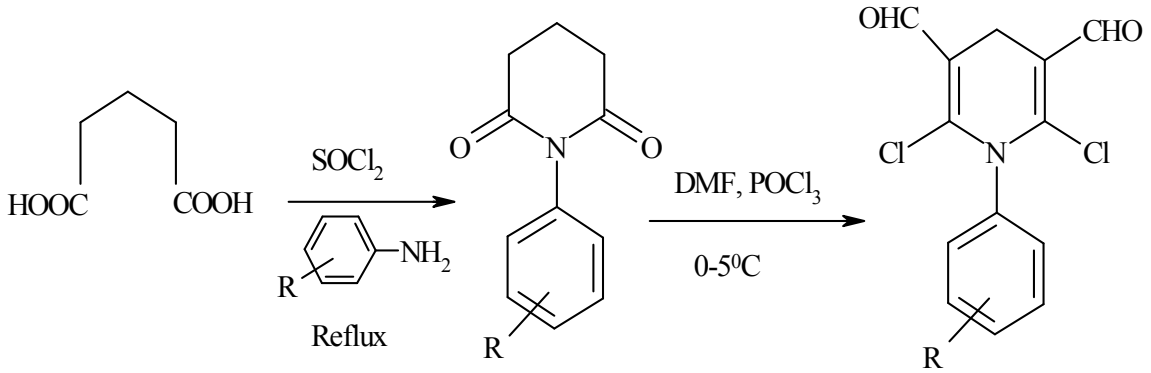
(1mmole) and malononitrile (2.5 mmole) in absolute ethanol (10 ml). The solution was stirred at room temperature for 3 hrs. The resulting solid product was collected by filtration, dried and recrystalized from ethanol to afford a pure 2,7-diamino-9-(N-substituted phenyl)-9,10-dihydro-1,8,9-triaza-anthracene-3,6-dicarbonitrile **6a-d (Scheme-II).**

2,7-diamino-9-(phenyl)-9,10-dihydro-1,8,9-triaza-anthracene-3,6-dicarbonitriles 6a:
Yield 74%; yellow crystals, mp 210-212^{0}C; IR (KBr): 3322, 3215 (NH_2), 2925 (CH_2), 2220 (CN), 1475 (ArC=C), 1260 (C-N) cm^{-1}; ^{1}HNMR (DMSO-d6): δ 3.81 (s, 2H, CH_2), 4.0 (s, 4H, $2NH_2$), 7.01-6.46 (m, ArH), 7.79 (s, 2H, 2CH), Anal.Calcd. for $C_{19}H_{13}N_7$: C, 67.24; H, 3.86; N, 28.89. Found: C, 67.02; H, 3.70; N, 28.76.

2,7-diamino-9-(4-methylphenyl)-9,10-dihydro-1,8,9-triaza-anthracene-3,6-dicarbo nitriles 6b: Yield 78%; yellow crystals, mp 197-199^{0}C; IR (KBr): 3320, 3250 (NH_2), 2920 (CH_2), 2228 (CN), 1470 (ArC=C), 1242 (C-N) cm^{-1}; ^{1}HNMR (DMSO-d6): δ 2.26 (s, 3H, CH_3), 3.55 (s, 2H, CH_2), 4.2 (s, 4H, $2NH_2$), 7.10-6.50 (m, ArH), 7.80 (s, 2H, 2CH), Anal.Calcd. for $C_{20}H_{15}N_7$: C, 67.97; H, 4.27; N, 27.74. Found: C, 67.79; H, 4.05; N, 27.60.

2,7-diamino-9-(4-chlorophenyl)-9,10-dihydro-1,8,9-triaza-anthracene-3,6-dicarbo nitriles 6c: Yield 68%; yellow crystals, mp 168-170^{0}C; IR (KBr): 3325, 3220 (NH_2), 2920 (CH_2), 2225 (CN), 1472 (ArC=C), 1244 (C-N) cm^{-1}; ^{1}HNMR (DMSO-d6): δ 3.72 (s, 2H, CH_2), 4.1 (s, 4H, $2NH_2$), 7.10-6.70 (m, ArH), 7.78 (s, 2H, 2CH), Anal.Calcd. for $C_{19}H_{12}N_7Cl$: C, 61.05; H, 3.23; N, 26.22. Found: C, 60.80; H, 3.11; N, 26.10.

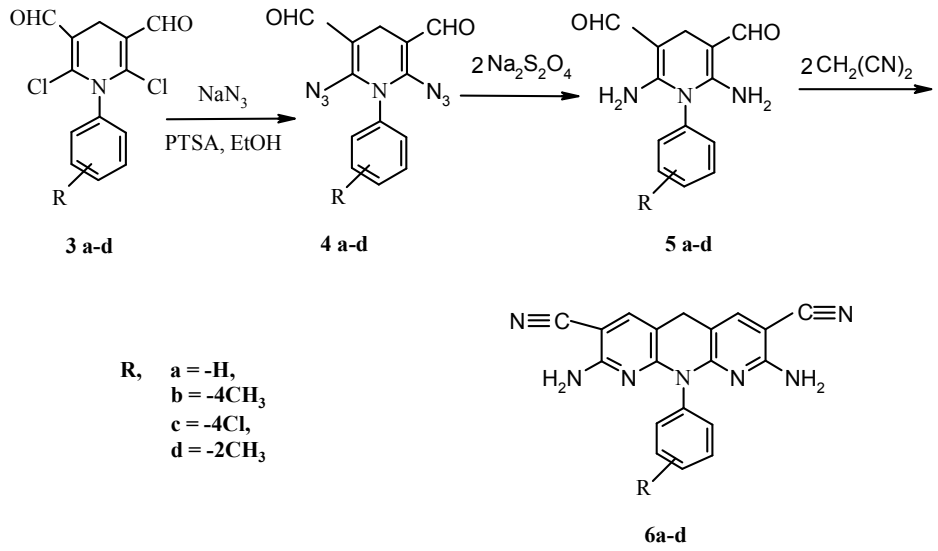
2,7-diamino-9-(2-methylphenyl)-9,10-dihydro-1,8,9-triaza-anthracene-3,6-dicarbo nitriles 6d: Yield 72%; yellow crystals, mp 162-164^{0}C; IR (KBr): 3322, 3215 (NH_2), 2924 (CH_2), 2230 (CN), 1485 (ArC=C), 1255 (C-N) cm^{-1}; ^{1}HNMR (DMSO-d6): δ 2.30 (s, 3H, CH_3), 3.81 (s, 2H, CH_2), 4.0 (s, 4H, $2NH_2$), 7.02-6.46 (m, ArH), 7.79 (s, 2H, 2CH), Anal.Calcd. for $C_{20}H_{15}N_7$: C, 67.97; H, 4.27; N, 27.74. Found: C, 67.83; H, 4.12; N, 27.59.



1 **2 a-d** **3 a-d**

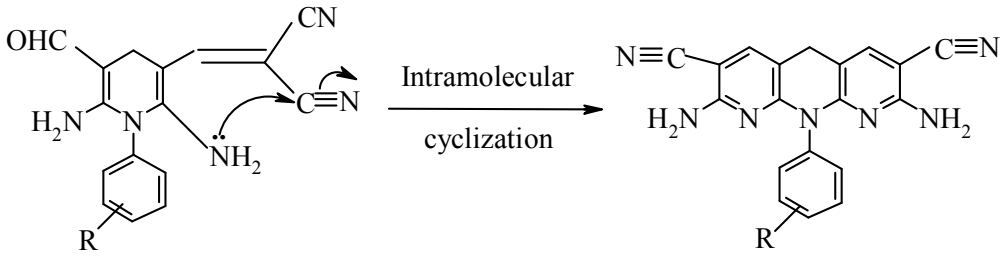
R, a = -H, b = -4Me, c = -4Cl, d = -2Me

(Scheme- I)



(Scheme-II)

Mechanism for the formation of 2,7-diamino-9-(N-substituted phenyl)-9,10-dihydro-1,8,9-triaza-anthracene-3,6-dicarbonitriles 6a-d (Scheme-III) :-



(Scheme-III)

Antimicrobial activity:

The compounds **4a-d** were screened for their *in vitro* antimicrobial activities against *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus, Aspergillus niger* and *Candida albicans*. The agar diffusion assay (Well method, Disc size 6mm, Hi media) was used. The compounds were tested at the concentration of 100µg/ml in DMF. The results were compared with respective standards Nystatin and Chloramphenicol. All the compounds showed moderate to good antimicrobial activity.

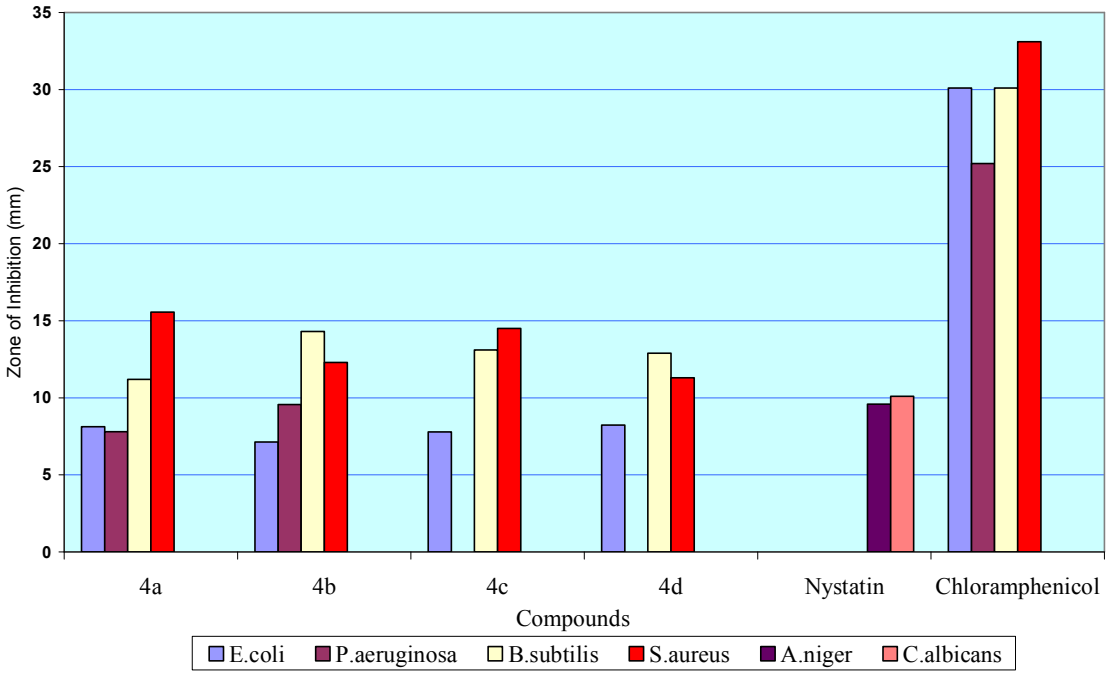
Table-1: Biological activities of Compounds 4a-d

Compound	***E. coli***	***P. aeruginosa***	***B. subtilis***	***S. aureus***	***A. niger***	***C. albicans***
4a	8.13	7.8	11.2	15.56	-	-
4b	7.13	9.56	14.3	12.3	-	-
4c	7.78	-	13.1	14.5	-	-
4d	8.23	-	12.9	11.3	-	-
Nystatin 100U/disc)	NA	NA	NA	NA	9.59	10.1
Chlora-mphenicol (10mcg/disc)	30.1	25.2	30.1	33.1	NA	NA

Diameter in mm calculated by Digital Vernier Calliper.

"-" means "no zone of inhibition", "NA" means "Not Applicable"

Fig.- 1 Biological activities of compounds 4a-d



Conclusion

In summary, an entire new series of azide derivatives containing dihydropyridine nucleus have been synthesized in one pot and in facile manner from 2,6-dichloro-1-(N-substituted phenyl)-1,4-di hydro pyridine-3,5-dicarbaldehydes in good yields. The synthetic strategy is straightforward and much more simple. This protocol offers the flexibility of transformation of 2,6-dichloro and 3,5-di formyl groups into different functionalities.

Acknowledgement

This work was supported by The principal, Z. B. Patil college Dhule, The principal S.V.S's Dadasaheb Rawal college Dondaicha, The principal R. C. Patel college, Shirpur and Universal Starch Chem. Allied Ltd. Dondaicha. Spectroscopic data were obtained from IIT Mumbai and Cadila Pharmaceutical Ahemadabad,India.

References:

1. Kamail,S.Atwal;Brian,N. Swanson;J.Med.Chem. 1991,34,No.2,806.
2. Winter,S.Bevan;Campbell,E.A. British J.o f Ane - sthesia, 1995,75,157.
3. Robert,J.Chorvat;Kurt,J.Rorig J.Org.Chem.1988,53,5779.
4. Takeshi,Kolke.Chem.Pharm.Bull.2001,49(5),558.
5. Scriven, E. F. V. Azides and Nitrenes: Reactivity and Utility; Academic Press: Orlando, Fla., 1984.
6. Sander, C.; Muehlbour, F. J.; Enviromental Exp. Bot. 1977, 17, 43.
7. Nilan, R. A.; Sideris, E. G.; Kleinhofs A.; Nilan, R. A. Mut. Res. 1973, 17, 142.
8. Owais, W.; Rosichan, J. L.; Roland, R. C.; Kleinhofs, A., Nilan, R. N. Mut. Res. 1983, 118, 299.
9. Scriven, E. F. V.; Turnbull, K. Chem. Rev. 1983, 88, 35.
10. Patai, S. "The Chemistry of the Azide Group", Interscience Publishers: New York, 1971; pp. 331.
11. Ridois, N. A. J. Heterocycl. Chem.1984, 21, 1169.
12. Brase, S.; Gil, C.; Knepper, K. and Zimmermann, V. Angew Chem. Int. Ed. 2005, 44, 5188.
13. Huisgen, R.; Knorr, R.; Mobius, L. and Szeimies, G. Chem. Ber. 1965, 98, 4014.
14. Domling, A. Chem. Rev. 2006,106, 17.
15. Eisner, U.; Kuthan, J. Chem. Rev. 1972, 72, 1.
16. Ouintela, J. M.; Peinador, C.; Botana, L.; Estevez, M.; Reiguera, R. Bioorg. Med. Chem.1997, 5, 1543.

17. Monna, F.; Chimenti, F.; Balasco, A.; Bizzarri, B.; Filippelli ,W. A.; Gagliardi, L. Eur. J. Med. Chem. 1999, 34, 245.
18. Ueno, K.; Sasaki, A.; Kawano, K.; Okabe, T.; Kitazawa, N.; Takahashi, K.; Yamamoto,Y.; Suzuki, Y. 15 Apr 1999 Int. Appl. WO 99 180 77; ref. Chem. Abstr. 1999, 130 , 311813b.
19. Elderfied, R. C.; King, T. P. J. Am. Chem. Soc. 1954, 76, 5439.
20. Hosni, H. M.; Abdulla, M. M. Acta Pharm. 2008, 58, 175.
21. Rajput A. P. and Rajput S. S., Asian J. Chem., 2007, Vol.19 No.6, 4939.
22. Rajput A. P. and Girase P. D., Abstract. No.B-70 in Tenth Tetrahedron Symposium, Challenges in Organic and Bioogranic Chemistry, 23-26 June 2009 Paris, France.
23. Pawar R. A. and Rajput A. P., Indian J. Chem., 1989, 28B, 866.
24. Rajput A. P. and Rajput S. S., Int. J. PharmTech. Res., 2009, Vol.3, 900.
25. Rajput A. P. and Rajput S. S., Int. J. PharmTech. Res., 2009, Vol.4, 1605.
26. Rajput A. P. and Girase P. D., Indian J. Heterocyclic Chem., July-Sept. 2010, Vol.20, 87.
27. Rajput A. P. and Girase P. D., Int. J. Chem. Res., 2011, Vol.2, Issue 4, 38.
28. Rajput A. P. and Girase P. D., Int. J. Pharm Pharm Sci, 2011, Vol.3, Suppl 4, 214.
29. Rajput A. P. and Girase P. D., Int. J. PharmTech. Res., 2011, 3(4), 2111.

*****