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Synthesis, spectral studies and biological activity of novel *3H*-1,5-benzodiazepine derivatives

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Chlorination of 5-(2-ethoxyphenyl)-1-methyl-3-propyl-1, 6-dihydro-7*H*-pyrazolo [4, 3-d] pyrimidin-7-one **1** with $POCl_3$ affords 5-(2-ethoxyphenyl)-1-methyl-7-chloro-1*H*-pyrazolo [4, 3-d] pyrimidine **2**. Further compound **2** is condensed with different β-diketones / β-ketoesters**3a-e**, to obtain new β-diketones/β-ketoesters **4a-e.** The synthesized new β-diketones/β-ketoesters **(4a-e)** and *o*-phenylenediamine (*o*-PDA) gives biologically active *3H*-1,5-benzodiazepines **5a-e**. All the newly synthesized compounds are characterized by elemental analysis and spectral studies. The compounds **5a-e** have been screened for antimicrobial, antifungal and anthelmintic activity.

Keywords: Pyrazolo[4,3-d]pyrimidin-7-one, β-diketones/β-ketoesters, silica chloride, *o*-phenylenediamine, *3H*-1,5-benzodiazepines, antimicrobial, anthelmintic

Benzodiazepines have recently attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals. These compounds are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, hypnotic agents[1] as well as anti-inflammatory agents[2]. Other than their biological importance, benzodiazepines derivatives are also commercially used as dyes for acrylic fibres[3]. Moreover, 1,5-benzodiazepines derivatives are valuable synthons that can be used in the preparation of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano- benzodiazepines[4]. As a result, research in this area is still very active and is directed towards the synthesis of compounds with enhanced pharmacological activity.

The present work is focused on the synthesis of pyrazolo[4,3-d]pyrimidin-7-one containing 1, 5-benzo-diazepines due to the importance of this class of compounds which has recently found application in medicinal chemistry. Substituted pyrozolopyrimi-dinones are potent and selective inhibitors of type 5 cyclic gaunosine-3′,5′-monophosphate phospho-diesterase (cGMP) PDE-5 (ref. 5,6) which have utility in the treatment of male erectile dysfunction (MED) (ref. 7) and female sexual dysfunction (FSD). They have also found use in the treatment of impotence, one of male sexual dysfunction with reduced side effects[8]. Substituted pyrazolopyrimidinones are also useful as CNS stimulant, bronchodilator, cardiotonic[9], herbicide[10] and antiviral[11]agents.

Generally, benzodiazepines were synthesized by the condensation of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds[12], β-haloketones, or ketones[13]. A variety of reagents, such as BF_3-etherate, $NaBH_4$, polyphosphoric acid, or SiO_2, $MgO/POCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, Al_2O_3/P_2O_5, or AcOH under microwave irradiation and in the presence of ionic liquids[14] are utilized for condensation reactions. Most recently, this condensation has also been reported to proceed in the presence of CAN, (bromodimethyl)-sulfonium bromide, organic acids, and $AgNO_3$ (ref. 15). However, all of these methods have the common disadvantage of employing drastic reaction conditions and also producing several side-products. Surface-mediated solid phase reactions are of growing interest[16] because of their ease of execution and work-up, mild reaction conditions, faster rate of reaction, greater selectivity, high yields, absence of solvents and lower cost in comparison with their homogeneous counterparts. Efforts have been made to explore the utility of surface-mediated reactions[17-19] under microwave irradiation. Herein is reported a new method for the preparation of 1,5-benzodiazepine derivatives with β-diketones and β-ketoesters. It was found that a mixture of SiO_2-Cl / wet SiO_2 in solvent-

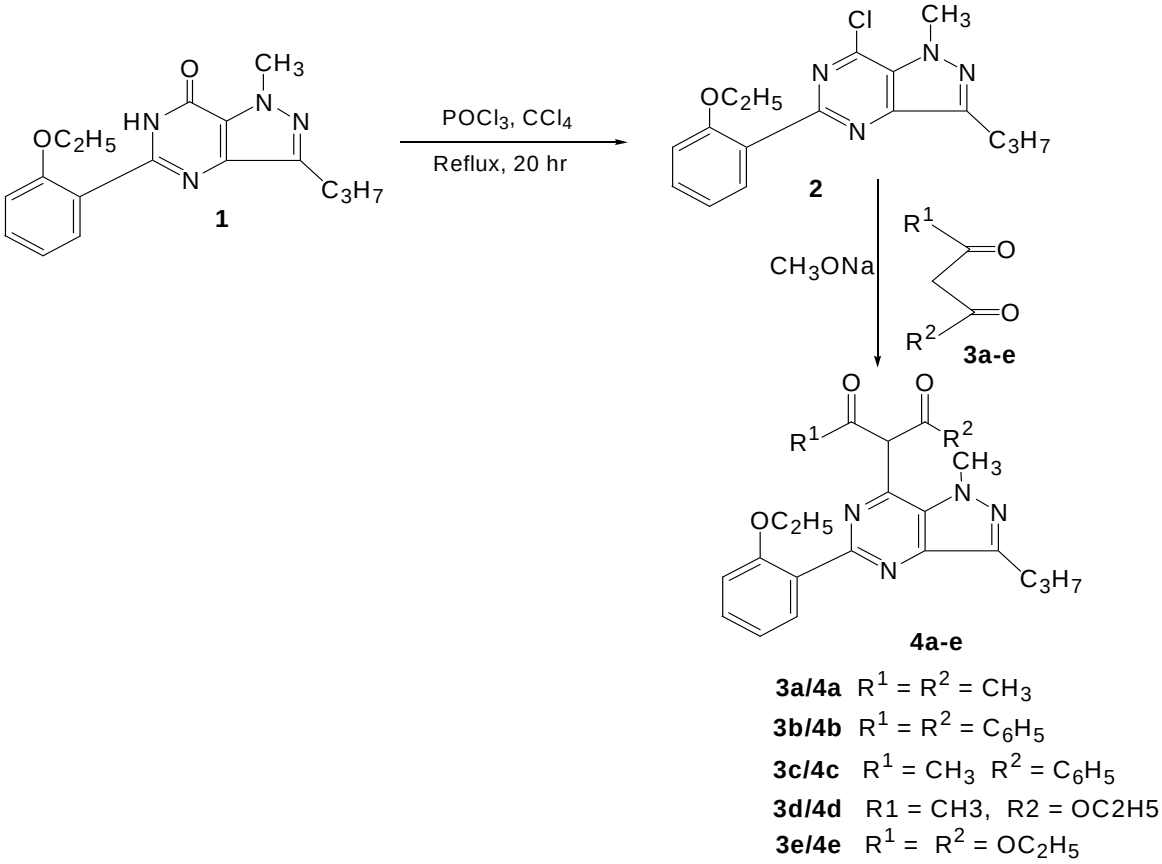
free conditions under microwave irradiation was capable of producing high yields of 1, 5-benzodiazepines **5a-e** by condensation of *o*-phenylenediamine with β-diketones and β-ketoesters **4a-e** under mild conditions in upto 90% yield.

Results and Discussion

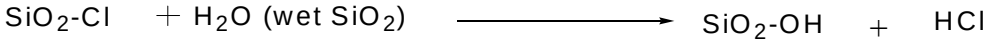
5-(2-Ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-d]pyrimidin-7-one was chlorinated with $POCl_3$. The chlorinated compound was condensed with different β-diketones /β-ketoesters in the presence of sodium methoxide (**Scheme I**). The condensation of newly synthesized β-diketones/β-ketoesters **4a-e** with *o*-phenylenediamine (*o*-PDA) in the presence of SiO_2-Cl / wet SiO_2, (**Scheme II** and **Scheme III**) under microwave irradiation gave *3H*-1,5-benzodiazepines **5a-e**. Silica chloride was synthesized according to the reported procedure[20,21].

Antimicrobial and anthelmintic activities of compounds 5a-e

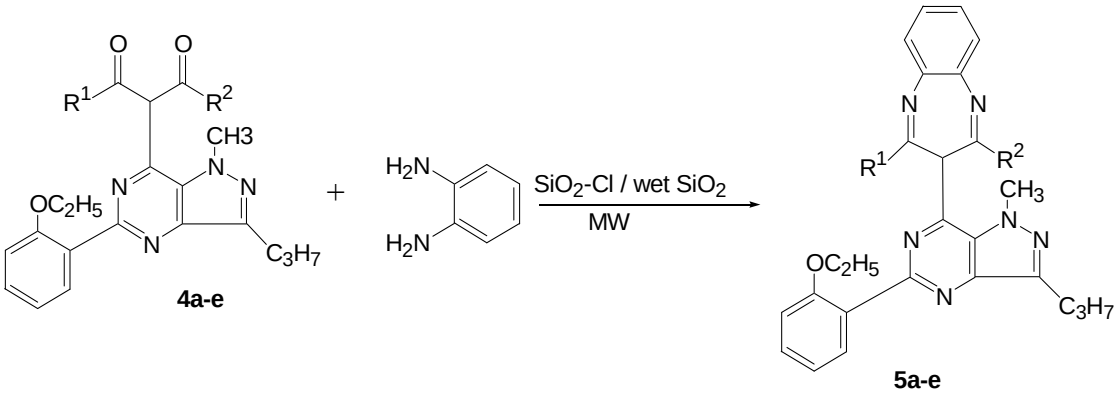
The newly synthesized benzodiazepine compounds have been screened for antibacterial activity against *Staphylococcus aurens* and *Klebsiella pneumoniae* as well as antifungal activity against *Aspergillus niger* and *Candida albicans* by cup-plate method[22,23]. Crofloxin and Ciclopiroxolamine were used as standards for comparison of antibacterial and antifungal activity, respectively. The results indicate that these compounds were active against all the four organisms. The anthelmintic activity was carried out on earth worms *Pherituma posthuma,* by a technique described by Bagavant *et al.*[24] with slight modification. Piperazine citrate was used as standard drug. The results of antimicrobial and anthelmintic activity were recorded in **Table I**. The compound **5c** exhibited higher antimicrobial and antifungal activity than the



Scheme I



Scheme II



5a $R^1 = R^2 = CH_3$
5b $R^1 = R^2 = C_6H_5$
5c $R^1 = CH_3$ $R^2 = C_6H_5$
5d $R^1 = CH_3$, $R^2 = =O$
5e $R^1 =$ $R^2 = =O$

Scheme III

Table I — Antimicrobial and anthelmintic activity of compounds **5a-e**

Compd	Antibacterial activity zone of inhibition (in mm)		Antifungal activity zone of inhibition (in mm)		Anthelmintic activity (in min)	
	A. aurens	*K. pneumoniae*	*A. niger*	*C. albicans*	Paralysis	Death
5a	11	10	15	18	95	90
5b	10	10	16	17	90	120
5c	22	24	25	28	105	112
5d	12	15	15	11	102	124
5e	14	09	10	**19**	105	129
Std	24	26	22	24	100	125

standard drug but compounds **5d** and **5e** showed significant anthelmintic activity.

Experimental Section

All melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on a Nicolet-Megna-FT-IR-550 spectrometer in KBr pellets. ^1H and ^{13}C NMR spectra were run on model DRX 300 at 300.13 and 75 MHz using $CDCl_3$ as solvent and TMS as an internal standard and mass spectra on a LCMS instrument. The homogeneity of the newly synthesized compounds was checked by TLC. Satisfactory elemental analyses were obtained for all the compounds.

Synthesis of 5-[2-ethoxyphenyl]-1-methyl-7-chloro-1*H*-pyrazolo[4,3-d] pyrimidine, 2

3.12 g (0.01 mol), 5-[2-Ethoxyphenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrimidin-7-one was placed into a two neck round bottom flask, diluted with CCl_4 and $POCl_3$ added drop wise at 0°C. After completion of addition, the reaction mixture was heated on a water bath for 20 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, unreacted $POCl_3$ was removed under reduced pressure. The reaction mass was poured in ice and was extracted by chloroform. Chloroform layer was evaporated to get a white solid compound. The product was purified by column chromatography over silica gel using pet ether:ethyl acetate (50:50) as eluent. It was purified by recrystallization from methanol. Homogeneity of the compound was checked by TLC using ethyl acetate:acetone (8:2) system as mobile phase (m.p. 165°C, yield 2.5 g, 70%).

Synthesis of 3-[5-(2-ethoxyphenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-7-yl-]-1,3-dimethyl/1,3-diphenyl/1-phenyl,3-methyl/1-methyl,3-ethoxy / 1,3-diethoxy propane-1,3-dione, 4a-e

Sodium methoxide (0.54 g, 0.01 mol) and different β-diketones/β-ketoesters (0.01 mol) **3a-e** were placed in a dry round bottom flask and the mixture stirred for

1 hr on a magnetic stirrer at 50°C after which a creamy mass was obtained. The chloride derivative **2** (3.19 g, 0.01 mol) was then added and dry toluene was added as solvent to effect proper stirring of the reaction mass. The reaction mixture was heated for 8 hr at 80°C with stirring. The progress of the reaction was monitored by TLC. On completion of the reaction, the mass was cooled and toluene was removed. The reaction mixture was extracted using chloroform and washed with water to remove the salt.

The chloroform layer was dried using anhydrous sodium sulphate. Chloroform was evaporated to obtain the solid compound. The product was purified by column chromatography over silica gel using pet ether:ethyl acetate (50:50) as eluent. It was purified by recrystallization from ethyl acetate and acetone mixture. Homogeneity of the compound was checked by TLC using 7:2:1 (benzene:ethanol:ammonia) upper layer as mobile phase.

Microwave assisted synthesis of *3H*-1, 5-benzodiazepines, 5a-e

β-Diketones/β-ketosters (10 mmol) were placed along with silica chloride (1 g) and wet SiO_2 (50% w/w) (1 g) in a conical flask and mixed well. *o*-Phenylenediamine (10 mmol) was added after irradiation at 300 W for 5 min. The solid product was washed with dry diethyl ether to remove unreacted β-diketones/β-ketoesters. Then, the crude product was extracted in dichloromethane and the solvent evaporated on a water bath. The product was dried *in vacuo* and purified by recrystallization from acetone. The product was purified by column chromatography over silica gel using pet ether:ethyl acetate (60:40) as eluent.

Analytical and spectral characterization data

3-[5-(2-ethoxyphenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-7-yl]-2,4- dimethyl-*3H*-1,5-benzodiazepine, 5a. m.p. 183°C, yield 85.7%; IR (KBr): 3060, 2945, 1590, 1480, 1250, 1020 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03 (t, *J* = 8.46, 3H), 1.60 (m, *J* = 7.25, 2H), 1.64 (t, *J* = 6.98,3H), 2.30 (s, 6H), 2.55 (t, *J* = 8.34, 2H), 3.80 (s, 3H), 4.40 (q, *J* = 8.12, 2H), 6.05 (s, 1H), 7.4-8.0 (m, *J* = 7.36, 8H); ^{13}C NMR ($CDCl_3$): δ 162.56, 149.94, 132-128, 75.32, 67.85, 53.20, 40.37, 29.26, 15.85, 14.70; LCMS: *m/z* 455 ($M+H^+$). Anal. Calcd. for $C_{27}H_{30}N_6O$: C, 71.37; H, 6.61; N, 18.50. Found: C, 71.26; H, 6.60; N, 18.49%.

3-[5-(2-ethoxyphenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-7-yl]-2,4-diphenyl-*3H*-1,5-benzodiazepine, 5b. m.p. 219°C, yield 86.3%; IR (KBr): 3040, 2900, 1585, 1492, 1240, 1010 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03 (t, *J* = 8.45, 3H), 1.65 (m, *J* = 7.86, 2H), 2.55 (t, *J* = 7.46, 2H), 1.65 (t, *J* = 6.95,3H), 4.42 (q, *J* = 8.75, 2H), 3.80 (s, 3H), 6.0 (s, 1H), 7.6-8.1 (m, *J* = 7.66,18H); ^{13}C NMR ($CDCl_3$): δ 157.50, 148.95, 132-127, 76.37, 66.36, 54.20, 41.25, 29.50, 15.84, 14.64; LCMS: *m/z* 579($M+H^+$). Anal. Calcd. for $C_{37}H_{34}N_6O$: C, 77.35; H, 6.09; N, 14.63. Found: C, 76.99; H, 6.10; N, 14.59%.

3-[5-(2-ethoxyphenyl)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-7-yl-2-methyl-4-phenyl-*3H*-1,5-benzodiazepine, 5c. m.p. 211°C, yield 83.7%; IR(KBr): 3050, 2930, 1585, 1260, 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03 (t, *J* = 8.32,3H), 1.65 (m, *J* = 7.85, 2H), 1.69 (t, *J* = 9.05, 3H), 2.55 (t, *J* = 7.65, 2H), 3.80 (s, 3H), 4.42 (q, *J* = 8.75, 2H), 6.0 (s, 1H), 2.35 (s, 3H), 7.6-8.1 (m, *J* = 7.95,13H); ^{13}C NMR ($CDCl_3$): δ 157.23, 149.90,132-128, 75.34, 68.36, 54.03, 40.32, 29.54, 15.84, 14.66 ; LCMS: *m/z* 517($M+H^+$). Anal. Calcd. for $C_{32}H_{32}N_6O$: C, 74.41; H, 6.02; N, 16.27. Found: C, 74.31; H, 6.15; N, 16.10%.

3-[5-(2-ethoxyphenyl)}-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-7-yl]-4-methyl-1,3-dihydro-*3H*-1,5-benzodiazepine-2-one, 5d. m.p. 189°C, yield 82.3%; IR (KBr): 3040, 2900, 1580, 1490, 1260, 1045 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03 (t, *J* = 8.37, 3H), 1.60(t, *J* = 8.23, 3H), 1.65 (m, *J* = 8.15, 2H), 2.55 (t, *J* = 7.95, 2H), 2.50 (s, 3H), 3.80 (s, 3H), 4.44 (q, *J* = 7.65, 2H), 5.8 (s, 1H), 7.3-8.0 (m, *J* = 7.65, 4H), 8.75 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 165.34, 158.454, 149.12, 134-126, 75.85, 68.34, 54.37, 40.35, 28.60, 15.74, 14.47; LCMS: *m/z* 457($M+H^+$). Anal. Calcd. for $C_{26}H_{28}N_6O_2$: C, 68.12; H, 6.11; N, 18.34. Found: C, 68.10; H, 6.03; N, 18.29%.

3-[5-(2-ethoxyphenyl)}-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-7-yl]-1,5-dihydro-*3H*-1,5-benzodiazepine-2,4-dione, 5e. m.p. 203°C, yield 85.4%; IR (KBr): 3050, 2920, 1560, 1490, 1250, 1030 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.02 (t, *J* = 8.35, 3H), 1.64(t, *J* = 7.65, 1.70 (m, *J* = 7.95,2H), 2.55 (t, *J* = 6.98, 2H), 3.80 (s, 3H),4.40 (q, *J* = 7.35, 2H), 6.10 (s, 1H), 7.5-8.0 (m, *J* = 7.85, 8H), 8.65 s, 2H); ^{13}C NMR ($CDCl_3$): δ 165.5, 157.56, 145.8,133-128, 75.37, 68.39, 54.34, 40.34, 29.57, 15.81, 14.66; LCMS: *m/z* 443($M+H^+$). Anal. Calcd. for $C_{25}H_{26}N_6O_2$: C, 65.50; H, 5.69; N, 18.34. Found: C, 65.49; H, 5.61; N, 8.17%.

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References

1 (a) Schutz H, *Benzodiazepines* (Springer, Heidelberg), **1982**; (b) Landquist J K, in *Comprehensive Heterocyclic Chemistry*, Vol. 1, Katritzky A R & Rees C W (Pergamon, Oxford), **1984,** 166-170; (c) Fryer R I, Bicyclic Diazepines, in *Comprehensive Heterocyclic Chemistry*, edited by Taylor E C, Vol. 50, Chapter II, (Wiley, New York), **1991**; (d) Randall L O & Kappel B, in *Benzodiazepines*, edited by Garattini S, Musini E & Randall L O (Raven Press, New York), **1973**, p27.

2 De Baun J R, Pallos F M & Baker D R, *US Patent* 3,978,227, 1**976**; *Chem Abstr*, 86, **1977**, 5498d.

3 Haris R C & Straley J M, *US Patent* 1,537,757, **1968**; *Chem Abstr,* 73, **1970,** 100054w.

4 (a) Aversa M C, Ferlazzo A, Gionnetto P & Kohnke F H, *Synthesis,* **1986**, 230; (b) Essaber M, Hasnaoui A, Benharref A & Lavergne J P, *Synth Commun*, 28, **1998**, 4097; (c) EI-Sayed A M, Abdel-Ghany H & EI-Saghier A M M, *Synth Commun*, 29, **1999**, 3561; (d) Chimirri A, Grasso S, Ottana R, Romeo G & Zappala M, *J Heterocycl Chem*, 27, **1990**, 371.

5 Bunnage M K, Mathias J P, Street S D A & Wood A, *PCT Int Appl WO* 9954, 333, (ClCO7D, 487/14), 28 Oct, **1999**; *GB Appl* **1998**/14, 187, 30 Jun. **1998**, 221pp; *Chem Abstr,* 131, **1999**, 310644f.

6 Bell A S & Terrett N K, *Eur Pat EP* 526, 004 (Cl. CA7D, 487/04), 03 Feb. **1993**, *GB Appl* 01/14, 760, 9 Jul **1991**, 34 pp; *Chem Abstr,* 118, **1993**, 254957c.

7 Doherty P C, Place V A Jr & Smith W L, *PCT Int Appl WO* 9921, 558 (Cl. A61K 31/485) 6 May **1999**, *US Appl* 181, 070, 27 Oct. **1998**, 31 pp; *Chem Abstr*, 130, **1999,** 332908d.

8 Yoo M, Kim W, Chang M S, Lim J I, Kim D S, Kim I Y, Lim T K, Ann B O, Kang K K, Son M, Doh H, Kim S, Shim H, Oh T, Kim H & Kim D G, *PCT Int Appl WO* 0027, 848 (Cl. CO7D, 487/14) 18 May **2000**, *KR Appl* 9, 949, 9 Nov. **1999**; *Chem Abstr,* 132, **2000**, 334469z.

9 Warner-Lambert Co, *Jpn Kokai Tokkyo Koho JP* 61, 236, 778 [86, 236, 778] (Cl. CO7D 87/010, 22 Oct. **1986**; *US Appl* 720, 437, 05 Apr. **1985**; *Chem Abstr,* 106, **1987,** 101967h.

10 Lindell S D, Moloney B A, Hewitt B D, Earnhaw C G, Philip P J & Dancer J E, *Bioorg Med Chem Lett*, 9(14), **1999,** 1985.

11 Sanghvi Y S, Larson S B, Smee D F, Revankar G R & Robins R K, *Nucleosides Nucleotides*, 10(6), **1991,** 1417.

12 Stahlhofen P & Ried W, *Chem Ber*, 90, **1957**,815.

13 Ried W & Torinus E, *Chem Ber*, 92, **1959**, 2902.

14 (a) Balakrishna M S & Kaboudin B, *Tetrahedron Lett*, 42, **2001**, 1127; (b) Curini M, Epifano F, Marcotullio M C & Rosati O, *Tetrahedron Lett*, 42, **2001**, 3197; (c) Sabita G, Reddy G S K, Reddy K B, Reddy N M & Yadav J S, *Adv Synth Catal,* 346, **2004**, 921; (d) Kaboudin B & Naveen K, *Heterocycles,* 55, **2001**, 1443; (e) Pozaretzi M, Stephanatou J S & Tsoleridis C A, *Tetrahedron Lett*, 43, **2002**,1755; (f) Reddy B M & Sreekant P M, *Tetrahedron Lett*, 44, **2003**, 4447; (g) Yadav J S, Reddy B V S, Eshwaraiah B & Auradha K, *Green Chem*, 4, **2002**, 592; (h) Jarikote D V, Siddiqui S A, Rajagapol R, Daniel T, Lahoti R J & Srinivasan K V, *Tetrahedron Lett*, 44, **2003**, 1835; (i) De Surya K & Gibbs R A, *Tetrahedron Lett*, 46, **2005**, 1811.

15 (a) Yadav J S, Reddy B V S, Praveenkumar S & Nagaiah K, *Synthesis,* **2005**, 480; (b) Das B, Ramu R, Ravikanth B & Reddy V S, *J Mol Catal A Chem,* 76, **2006**, 246; (c) Thakuria H, Pramanik A, Borah B M & Das G, *Tetrahedron Lett*, 47, **2006**, 3135; (d) Varala R, Enugala R, Nuvula S & Adapa S R, *Synlett,* **2006**, 1009; (e) Kumar R, Chaudhary P, Nimesh S, Verma A K & Chandra R, *Green Chem*, 8, **2006**, 519.

16 (a) Fadel A, Yefash R & Saluan J, *Synthesis*, **1987**, 37; (b) Rosini G, Galarini R, Marotta E & Righi R, *J Org Chem*, 55, **1990,** 781; (c) Kodomari M, Sakamoto T & Yoshitomi S, *J Chem Soc Chem Commun*, **1990,** 701; (d) Kropp P J, Duas K A, Crawford S D, Tubergren M W, Kepler K D, Craig S L & Wilson, V P, *J Am Chem Soc*, 112, **1990**, 7433; (e) Hondrogiannis G, Pagni R M, Kabalka G W, Anisoki P & Kurt R, *Tetrahedron Lett*, 31, **1990,** 5433; (f) Pantney H K, *Tetrahedron Lett*, 32, **1991**, 2259; (g) Pauter F & Daudon M, *Tetrahedron Lett*, 32, **199**1, 1457.

17 Sardarian A R & Kaboudin B, *Synth Commun*, 27, **1997,** 543.

18 Sardarian A R & Kaboudin B, *Tetrahedron Lett*, 38, **1997**, 2543.

19 Kaboudin B, *J Chem Rev*, **1999,** 402.

20 Mohanazadeh F, Momeni A R & Rangbar Y, *Tetrahedron Lett*, 33, **1994**, 6127.

21 Firouzabadi H, Iranpoor N, Karimi B & Hazarkhani H, *Synlett*, **2000**, 263.

22 Sundane A R, Rudresh K, Satynarayan N D & Hiremath S P, *Indian J Pharm Sci*, 60, 1989, 379.

23 Giand K N, Dar R N, Chopra B M & Kaul R N, *Indian J Pharm Sci,* 27, **1965,** 141.

24 Bagvant G, Gole S R, Joshi V & Soni S B, *Indian J Pharm Sci,* 56, **1994**, 80.