

ISSN 1996-5052

Current Research in
Chemistry

Efficient *p*-Amino Benzoic Acid Catalyzed Eco-friendly Synthesis of 1,5-benzodiazepines among Various Amino Acids under Solvent Free Conditions

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ABSTRACT

p-Amino benzoic acid was found to be the versatile acidic amino acid catalyst among various amino acids tested for the preparation of 1,5-benzodiazepines derivatives from a wide range of substituted *o*-phenylenediamines and ketones. The corresponding products were obtained in good isolated yields (85-92%) at room temperature under solvent free conditions. Simple and effective method, use of non-hazardous catalyst and good to excellent yields are the important features of this method.

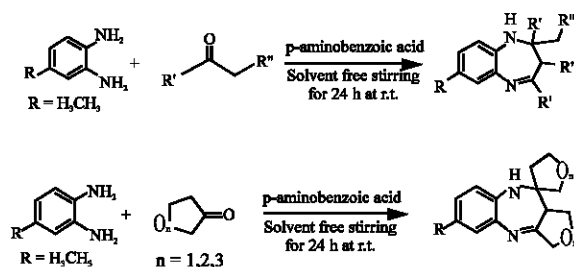
Key words: 1,5-benzodiazepines, acidic amino acid, *o*-phenylenediamines, ketones, *p*-amino benzoic acid, solvent free, non hazardous catalyst

INTRODUCTION

Benzodiazepines are privileged heterocyclic compounds because they belong to an important class of pharmacologically pre-eminent 1,5-benzodiazepines which have extensively used as anti-convulsant, anti-anxiety, analgesic, sedative, anti-depressant, hypnotic (Randall, 1974). Some heterocyclic compounds containing 1,5-benzodiazepines possess anti-inflammatory (Roma *et al.*, 1991), anti-viral (Kavali and Badami, 2000), anti-HIV (Di Braccio *et al.*, 2001), anti-microbial (Kumar and Joshi, 2007), anti-tumor activities (Kamal *et al.*, 2008). More recently their use has been extended to various diseases such as cancer, viral infections (non-nucleoside inhibitors of HIV-1 reverse transcriptase) and cardiovascular diseases (Varala *et al.*, 2007). Other than biological importance, they are valuable synthons for the preparation of fused ring compounds such as triazolo (El-Sayed *et al.*, 2007), oxadiazolo (Nagaraja *et al.*, 2006), oxazino (Nabih *et al.*, 2006), furano (Reddy *et al.*, 2000) benzodiazepines.

Due to their wide range of applications these compounds have received a great deal of attention in contrast with their literature. Although, there are few established synthetic routes to 1,5-benzodiazepines but the methodology is still underdeveloped in contrast to their wide applications of in pharmaceutical, industrial and synthetic field.

Amino acids are molecules containing an amine group, a carboxylic acid group and a side-chain that varies between different amino acids. The key elements of an amino acid are carbon, hydrogen, oxygen and nitrogen. They are particularly important in biochemistry, where the term



Scheme 1: Chemical reaction for the synthesis of 1,5-benzodiazepines using *p*-amino benzoic acid

usually refers to alpha-amino acids. The amine and carboxylic acid functional groups found in amino acids allow them to have amphiprotic properties. Carboxylic acid groups (-COOH) can be deprotonated to become negative carboxylates (-COO⁻) and α -amino groups (NH₂⁺) can be protonated to become positive a-ammonium groups (+NH₃⁺). Out of the essential and non-essential amino acids, some are acidic: aspartic acid, glutamic acid, anthranilic acid; basic: arginine, histidine, lysine; amidic amino acids: asparagine, glutamine; sulphur containing amino acids: cysteine, methionine etc. Out of these various uses as different precursors they are not being used in any synthesis except peptide synthesis. Hence this article is an effort to try catalytic capacity of amino acids in the synthesis of 1,5-benzodiazepines. In continuation with our research for the development of simple and novel methods for the synthesis of different 1,5-benzodiazepine derivatives, we have done comparative study on various acidic amino acids catalyzed synthesis of 1,5-benzodiazepines by condensation of *o*-phenylenediamine with acetophenone (model reaction) under solvent free conditions (Scheme 1). We are gratified to report a simple, efficient and practical method for 1,5-benzodiazepine synthesis using 10 mol% *p*-amino benzoic acid (PABA).

MATERIALS AND METHODS

This study was carried out from 10th September 2011 to 30th October 2011 in the Pharmaceutical Chemistry Division, Shivalik College of Pharmacy, Nangal, Punjab, India.

The melting points were determined on Veego-programmable melting point apparatus (microprocessor based) and are uncorrected. Proton (1H) nuclear magnetic resonance spectra were obtained using Bruker AC-400 F, 400 MHz spectrometer and are reported in parts per million (ppm), downfield from Tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra were obtained with Perkin Elmer 882 Spectrum and RXI, FT-IR model using potassium bromide pellets (in cm⁻¹). Carbon-13 magnetic resonance were obtained using Bruker AC-400 F, 400 MHz spectrometer and are reported in parts per million (ppm). Reactions were monitored and the homogeneity of the products was checked by TLC which were prepared with silica gel G and activated at 110°C for 30 min. The plates were developed by exposure to iodine vapours. Anhydrous sodium sulphate was used as drying agent.

General procedure for the preparation of 2, 3-dihydro-1H-1, 5-benzodiazepines: *o*-phenylenediamine (1 mmole), *p*-amino benzoic acid (10 mol% or 0.1 mmole) and various ketone (2.5 mmole) were taken in RBF and stirred for 24 h at room conditions. After completion of the reaction [monitored via TLC using CHCl₃ and MeOH (9.5:0.5 mL) as eluent], the reaction mass was poured into crushed ice and basified with ammonia solution, if required. The precipitated solid was separated, washed thoroughly with water and dried. The residue was subjected to column chromatography to get the desired compound.

2,2,4-Trimethyl-2,3-dihydro-1H-1,5-benzodiazepine: Entry 1

IR (KBr): 3292 cm^{-1} (NH), 2955 cm^{-1} (Aromatic CH), 1631 cm^{-1} (Alkene C = C), 1474 cm^{-1} (Aromatic C = C).

$^1\text{H-NMR}$ (CDCl_3): δ 1.3 (s, 6H, $-\text{CH}_3$), δ 2.2 (s, 2H, $-\text{CH}_2$), δ 2.4 (s, 3H, $-\text{CH}_3$), δ 6.7-7.2 (m, 4H, ArH).

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_2$: C, 76.55; H, 8.57; N, 14.88; Found: C, 76.51; H, 8.52; N, 14.92.

2,3-Dihydro-2-methyl-2,4-diphenyl-1H-1,5-benzodiazepine: Entry 2

IR (KBr): 3277 cm^{-1} (Sec N-H), 3061 cm^{-1} (Aromatic C-H), 2972 cm^{-1} (Aliphatic C-H), 1559 cm^{-1} (Aromatic C = C).

$^1\text{H-NMR}$ (CDCl_3): δ 1.8 (s, 3H, $-\text{CH}_3$), δ 3 (d, 1H, $-\text{CH}$), δ 3.2 (d, 1H, $-\text{CH}$), δ 6.8-7.7 (m, 14H, ArH).

Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_2$: C, 84.58; H, 6.45; N, 8.97; Found: C, 84.60; H, 6.42; N, 8.94.

2,4-Dimethyl-2-ethyl-2,3-dihydro-1H-1,5-benzodiazepine: Entry 3

IR (KBr): 3338 cm^{-1} (Sec N-H), 3058 cm^{-1} (Aromatic C-H), 2968 cm^{-1} (Aliphatic C-H), 1639 cm^{-1} (C = N), 1472 cm^{-1} (Aromatic C = C), 1252 cm^{-1} (C-N).

$^1\text{H-NMR}$ (CDCl_3): δ 0.8 (t, 3H, $-\text{CH}_3$), δ 1.3 (t, 3H, $-\text{CH}_3$), δ 1.3 (s, 3H, $-\text{CH}_3$), δ 1.7 (q, 2H, $-\text{CH}_2$), δ 2.2 (m, 2H, $-\text{CH}_2$), δ 2.6 (q, 2H, $-\text{CH}_2$), δ 3.3 (brs, 1H, NH), δ 6.5-7.3 (m, 4H, ArH).

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_2$: C, 77.18; H, 8.97; N, 13.85; Found: C, 77.25; H, 8.88; N, 14.01.

11-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-1H-dibenzo [b,e][1,4] diazepine: Entry 4

IR (KBr): 3278 cm^{-1} (Sec. NH), 3059 cm^{-1} (Aromatic CH), 2858 cm^{-1} (Alkane CH), 1634 cm^{-1} (Imine C = N), 1481 cm^{-1} (Aromatic C = C), 751 cm^{-1} (ortho substituted oop).

$^1\text{H-NMR}$ (CDCl_3): d 1.2-1.9 (m, 16H, $-\text{CH}_2$), d 2.3-2.6 (m, 3H, $-\text{CH}$), d 4.5 (1H, br, NH), d 6.8-7.9 (m, 4H, ArH).

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{N}_2$: C, 80.55; H, 9.01; N, 10.44; Found: C, 80.62; H, 9.05; N, 10.54.

10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydrobenzo[b]cyclohepta[e] [1,4] diazepine: Entry 5

IR (KBr): 3266 cm^{-1} (Sec N-H), 2916 cm^{-1} (Aromatic C-H), 2972 cm^{-1} (Aliphatic C-H), 1633 cm^{-1} (Alkene C = C), 1484 cm^{-1} (Aromatic C = C).

$^1\text{H-NMR}$ (CDCl_3): δ 1.5-2.4 (m, 20H, $-\text{CH}_2$), δ 2.4 (s, NH, 1H), δ 2.6 (m, 2H, $-\text{CH}_2$), δ 2.8 (m, 1H, $-\text{CH}$), δ 6.6-7.4 (m, 4H, ArH).

Anal. Calcd. for $\text{C}_{20}\text{H}_{28}\text{N}_2$: C, 81.03; H, 9.52; N, 9.45; Found: C, 81.15; H, 9.56; N, 9.54.

2,2,4-Trimethyl-2,3-dihydro-8-methyl-1H-1,5-benzodiazepine: Entry 6

IR (KBr): 3454 cm^{-1} (Sec. NH), 2924 cm^{-1} (Aromatic CH), 2853 cm^{-1} (Alkane CH), 1437 cm^{-1} (Aromatic C = C), 1236 cm^{-1} (C-N), 946 (1,2,4-substituted oop).

$^1\text{H-NMR}$ (CDCl_3): δ 1.2 (s, 6H, $-\text{CH}_3$), δ 1.35 (s, 3H, $-\text{CH}_3$), δ 2.3 (s, 3H, $-\text{CH}_3$), δ 2.3 (d, 1H, $-\text{CH}$), δ 2.3(d, 1H, $-\text{CH}$), δ 6.5-7.0 (m, 3H, ArH).

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_2$: C, 77.18; H, 8.97; N, 13.85; Found: C, 77.22; H, 8.91; N, 13.93.

2,3-Dihydro-2,8-dimethyl-2,4-diphenyl-1H-1,5-benzodiazepine: Entry 7

IR (KBr): 3335 cm^{-1} (Sec. NH), 3057 cm^{-1} (Aromatic CH), 2969 cm^{-1} (Alkene CH), 2858 cm^{-1} (Alkane CH), 1612 cm^{-1} (Imine C = N), 1493 cm^{-1} (Aromatic C = C), 1328 cm^{-1} (C-N), 758 cm^{-1} (Ortho substituted oop).

$^1\text{H-NMR}$ (CDCl_3): δ 1.75 (s, 3H, $-\text{CH}_3$), δ 2.6 (s, 3H, $-\text{CH}_3$), δ 2.9 (d, 1H, $-\text{CH}$), δ 3.1 (d, 1H, $-\text{CH}$), δ 7.2-7.9 (m, 14H, ArH), δ 2.6 (br, 1H, NH).

Anal. Calcd. for $\text{C}_{23}\text{H}_{22}\text{N}_2$: C, 84.63; H, 6.79; N, 8.58; Found: C, 84.68; H, 6.84; N, 8.45.

11-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-8-methyl-1H-dibenzo[b,e][1,4]diazepine: Entry 8

IR (KBr): 3351 cm^{-1} (Sec. NH), 2930 cm^{-1} (Alkene CH), 2857 cm^{-1} (Alkane CH), 1633 cm^{-1} (Imine C = N), 1484 cm^{-1} (Aromatic C = C).

$^1\text{H-NMR}$ (CDCl_3): δ 1.7-2.5 (m, 18H, $-\text{CH}_2$), δ 3.0 (s, 3H, $-\text{CH}_3$), δ 3 (t, 1H, $-\text{CH}$), δ 7.3-7.9 (m, 3H, ArH).

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_2$: C, 80.80; H, 9.28; N, 9.92; Found: C, 80.86; H, 9.34; N, 9.98.

10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydro-8-methylbenzo[b]cyclo hepta [e] [1,4]diazepine: Entry 9

IR (KBr): 3327 cm^{-1} (Sec N-H), 3060 cm^{-1} (Aromatic C-H), 2922 cm^{-1} (Alkene C-H), 2852 cm^{-1} (Aliphatic C-H), 1617 cm^{-1} (Alkene C = C), 1492 cm^{-1} (Aromatic C = C).

$^1\text{H-NMR}$ (CDCl_3): δ 1.6 (m, 22H, $-\text{CH}_2$), δ 2.2 (s, 3H, $-\text{CH}_3$), δ 3.1 (br, 1H, $-\text{NH}$), δ 3.1 (s, 1H, $-\text{CH}$), δ 6.5-7.1 (m, 3H, $-\text{CH}$).

Anal. Calcd. for $\text{C}_{21}\text{H}_{30}\text{N}_2$: C, 81.24; H, 9.74; N, 9.02; Found: C, 81.29; H, 9.79; N, 9.15.

RESULTS AND DISCUSSION

Due to their wide range of applications of 1, 5 benzodiazepines, these compounds have received a great deal of attention in contrast with their literature. The 1,5-benzodiazepine can be prepared by multicomponent condensation of *o*-phenylenediamine with α , β unsaturated carbonyl compounds, β -haloketones or ketones in the presence of a variety of catalysts e.g., *p*-toluenesulfonic acid (Pasha and Jayashankara, 2006), silica sulfuric acid (Ahmad and Ali, 2007), sulfanilic acid

(Sangshetti *et al.*, 2007), sulfamic acid (Li *et al.*, 2007), 2,4,6-trichloro-1,3,5-triazine (Kuo *et al.*, 2008), heteropoly acid (HPA) catalysts (Heravi *et al.*, 2008), Yb(OPf)₃ (Yi and Cai, 2008), ZOC (Baseer and Khan, 2011) etc. However, in spite of their utility, many of these methods suffer major or minor limitations like tedious work up procedure, the necessity of neutralization of strong acidic media, producing undesired washes, applications of expensive and hazardous catalyst and reagents, long reaction times, unsatisfactory yields, require separation of the catalyst from the product and formation of side products. In last few years, there has been growing interest in the use of organo catalyst owing to their eco-friendliness and can proceed under aerobic atmosphere, other notable advantages are, usually less expensive and commercially available (Peter and Moisan, 2001).

Recently Varala *et al.* (2007) have studied the catalytic activity of various organo acids and found *p*-nitrobenzoic acid as the efficient acid among them. But they use 100 mol% of *p*-nitrobenzoic acid for excellent yield. On the same pattern our study is an effort to try catalytic capacity of various amino acids in the synthesis of 1,5-benzodiazepines. Among the various amino acids screened, *p*-amino benzoic acid (PABA) was found to be the best catalyst at 10 mol% in terms of yields (entry 3, Table 1). To the best of our knowledge, there are no earlier reports on the preparation of 1,5-benzodiazepines using *p*-amino benzoic acid.

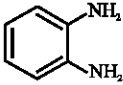
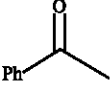
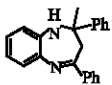
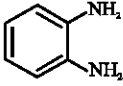

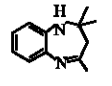
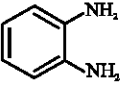
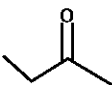
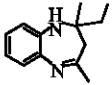
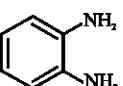

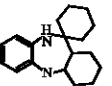
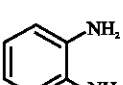

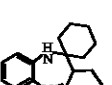
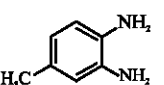

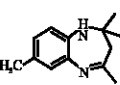
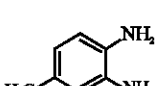
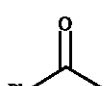
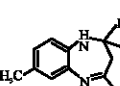
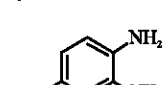

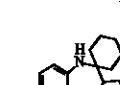
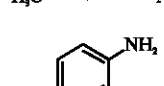

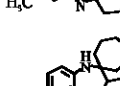
Initially we studied the influence of *p*-amino benzoic acid for the synthesis of 1,5-benzodiazepine using *o*-phenylenediamine and acetophenone as a model and varying the amount of *p*-amino benzoic acid by simple optimization study (Table 3). The investigation was initiated with *o*-phenylenediamine, acetophenone (1:2.5) and *p*-amino benzoic acid 15 mol% under solvent free conditions on continuous stirring for 24 hrs and 1,5-benzodiazepine was isolated in 92% yields (entry 2, Table 2). Further, the catalyst quantity was optimized to 10 mol% of *p*-amino benzoic acid and excellent results were achieved. Using less amount of catalyst, i.e., 5 mol% resulted in the decrease of product yield. Increasing the amount of catalyst (i.e., 20 mol%) did not show any significant effect on the reaction rate as well as yields. However, this reaction yielded a trace amount of product (difficult to isolate) in the absence of catalyst after stirring for more than 36 hrs showing the influence of *p*-amino benzoic acid as reaction catalyst. Similarly, other 1,5-benzodiazepine derivatives have been synthesized from *o*-phenylenediamines and ketones in 85-92% yields (Table 1). Diamines with electron releasing group (entry 6-9) also reacted smoothly with ketones to afford products in good yields. Both of the linear and cyclic ketones react with the diamines without any significant difference, to give the corresponding 1,5-benzodiazepine derivatives in quantitative yields. Easy work-up of the reaction was also the advantageous aspect of this method. It includes the pouring the reaction mixture in water which on filtration gave the corresponding 1,5-benzodiazepines. This method was superior in regards with yield and reaction time than the previously reported methods.

The proposed mechanism of the reaction (Scheme 2) involves an intramolecular imine enamine cyclization promoted by *p*-amino benzoic acid. Amine of *o*-phenylenediamine attacks carbonyl group

Table 1: Reaction of *o*-phenylenediamine with acetophenone promoted by amino acids in 1,5-benzodiazepines synthesis

Entry	Amino acid	Time (h)	Yield (%)
1	Aspartic acid	24	72
2	Glutamic acid	24	78
3	<i>p</i> -amino benzoic acid	24	92
4	Glycine	24	82
5	Anthranilic acid	24	88

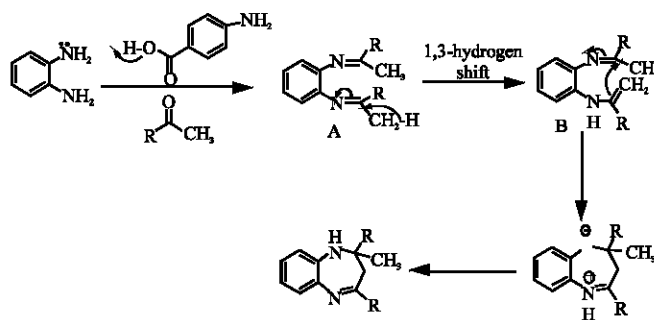
Table 2: Condensation of *o*-phenylenediamine with various ketones catalyzed by *p*-amino benzoic acid

Entry	Diamine	Ketone	Product	Yield (%)	Time (h)	M.P.(°C)	M.P. ^{lit} (°C)
1				92	24	149-150	151-152 ^a
2				90	24	138-139	137-139 ^a
3				85	24	138-139	137-138 ^a
4				87	24	137-138	138-139 ^b
5				90	24	133-134	136-137 ^b
6				89	24	126-128	127-128 ^c
7				87	24	91-92	92-93 ^c
8				91	24	140-142	142-143 ^c
9				85	24	121-122	124-125 ^c

The reported melting points are referred from ^aJarikote *et al.* (2003), ^bAhmad and Ali (2007) and ^cDas *et al.* (2006)

Table 3: Optimization of concentration of *p*-amino benzoic acid for the synthesis of 1,5-benzodiazepines under solvent-free condition

Amount of catalyst mol (%)	Time (h)	Yield (%)
20	24	92
15	24	92
10	24	92
5	24	88



Scheme 2: Proposed mechanism and possible intermediates

of ketone giving the intermediate diimine A. A 1,3-hydrogen shift of the attached methyl group then occurs to form an isomeric enamine B, which cyclize to afford seven membered ring.

CONCLUSION

In conclusion, we have reported an efficient, inexpensive, non-hazardous ecofriendly new catalyst *p*-amino benzoic acid for the one pot synthesis of 1,5-benzodiazepines under solvent free condition at room conditions. The solvent-free green procedure as well as high yield and selectivity, makes this protocol an attractive and user friendly alternative for the synthesis of 1,5-benzodiazepines.

ACKNOWLEDGMENTS

The authors are thankful to Management, Shivalik College of Pharmacy, Nangal for providing the necessary laboratory facilities. The authors are thankful to Punjab State Council for Science and Technology (PSCST), Punjab for providing partial financial support for this research work. The authors are also thankful to SAIF, Panjab University, Chandigarh for cooperation in getting the spectral data.

REFERENCES

- Ahmad, S. and M. Ali, 2007. A fast and efficient method for the synthesis of 1,5-benzodiazepine derivatives under solvent-free conditions. *Iran. J. Chem. Eng.*, 26: 92-97.
- Baseer, M.A. and A.J. Khan, 2011. Citric acid catalyzed solvent free, an efficient one-pot synthesis of 2,3-dihydro-1H-1,5-benzodiazepines derivatives. *Resent Res. Sci. Technol.*, 3: 101-103.
- Das, B., R. Ramu, B. Ravikanth and V.S. Reddy, 2006. (Bromodimethyl) sulfonium bromide: An efficient catalyst for solvent-free synthesis of 1,5-benzodiazepines. *J. Mol. Catal.*, 246: 76-78.
- Di Braccio, M., G. Grossi, G. Roma, L. Vargiu, M. Mura and M.E. Marongiu, 2001. 1,5-Benzodiazepines. Part XII. Synthesis and biological evaluation of tricyclic and tetracyclic 1,5-benzodiazepine derivatives as nevirapine analogues. *Eur. J. Med. Chem.*, 36: 935-949.
- El-Sayed, A.M., A. Khodairy, H. Salah and H. Abdel-Ghany, 2007. Part 7: Synthesis of some new 1,5-benzodiazepines fused with different heterocyclic moieties. *Phosphorous Sulphur Silicon Relat. Elem.*, 182: 711-722.
- Heravi, M.M., S. Sadjadi, H.A. Oskooie, R. Hekmatshoar and F.F. Bamoharram, 2008. An efficient synthesis of 3H-1,5-benzodiazepine derivatives catalyzed by heteropolyacids as a heterogeneous recyclable catalyst. *J. Chinese Chem. Soc.*, 55: 842-845.
- Jarikote, D.V., S.A. Siddiqui, R. Rajagopal, T. Daniel, R.J. Lahoti and K.V. Srinivasan, 2003. Room temperature ionic liquid promoted synthesis of 1,5-benzodiazepine derivatives under ambient conditions. *Tetrahedron Lett.*, 44: 1835-1838.
- Kamal, A., N. Shankaraiah, S. Prabhakar, C.R. Reddy, N. Markandeya, K.L. Reddy and V. Devaiah, 2008. Solid-phase synthesis of new pyrrolobenzodiazepine-chalcone conjugates: DNA-binding affinity and anticancer activity. *Bioorg. Med. Chem. Lett.*, 18: 2434-2439.
- Kavali, J.R. and B.V. Badami, 2000. 1,5-benzodiazepine derivatives of 3-arylsydnonones: Synthesis and antimicrobial activity of 3-aryl-4-[2'-aryl-2',4',6',7'-tetrahydro-(1'H)-1',5'-benzodiazepine-4'-yl]sydnonones. *Farmaco*, 55: 406-409.
- Kumar, R. and Y.C. Joshi, 2007. Synthesis spectral studies and biological activity of 3H-1,5-benzodiazepine derivatives. *Arkivoc*, 13: 142-149.
- Kuo, C.W., C.C. Wang, V. Kavala, C.F. Yao, 2008. Efficient TCT-catalyzed synthesis of 1,5-benzodiazepine derivatives under mild conditions. *Molecules*, 13: 2313-2325.

- Li, Z., Y. Sun, X. Ren, W. Li, Y. Shi and P. Ouyang, 2007. Efficient synth 1,5-benzodiazepine mediated by sulfamic acid under neat or in solution. *Synth. Commun.*, 37: 1609-1615.
- Nabih, K., A. Baouid, A. Hasnaoui and A. Kenz, 2006. Highly region and diastereoselective 1,3-dipolar cycloaddition of nitrile oxides to 2,4-dimethyl-3H-1,5-benzodiazepines: Synthesis of bis[1,2,4-oxadiazolo]-[1,5]benzodiazepine derivatives. *Synth. Commun.*, 30: 1825-1836.
- Nagaraja, G.K., V.P. Vaidya, K.S. Rai and K.M. Mahadevan, 2006. An Efficient synthesis of 1,5-thiadiazepines and 1,5-benzodiazepines by microwave-assisted heterocyclization. *Phosphorous Sulphur Silicon Relat. Elem.*, 181: 2797-2806.
- Pasha, M.A. and V.P. Jayashankara, 2006. An expeditious of 1,5-benzodiazepine catalyzed by *p*-toluenesulfonic acid. *J. Pharmacol. Toxicol.*, 1: 573-578.
- Peter, P.I.D. and L. Moisan, 2001. Enantioselective Organocatalysis. *Angew. Chem., Int. Ed.*, 40: 3726-3748.
- Randall, L.O., 1974. *Psychopharmacological Agents*. Academic Press, New York, pp: 175-281.
- Reddy, K.V.V., P.S. Rao and D. Ashok, 2000. A facile synthesis of 2-benzoyl-6-hydroxy-3-methyl-5-(2-substituted-2,3-dihydro-1H-1,5-benzodiazepin-4-yl) benzo[*b*] furans. *Synth. Commun.*, 30: 1825-1836.
- Roma, G., G.C. Grossi, M. Di Braccio, M. Ghia and F. Mattioli, 1991. 1,5-Benzodiazepines IX. A new route to substituted 4H-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-5-amines with analgesic and/or anti-inflammatory activities. *Eur. J. Med. Chem.*, 26: 489-496.
- Sangshetti, J.N., N.D. Kokare and D.B. Shinde, 2007. Sulfanilic acid catalyzed solvent-free synthesis of 1,5-benzodiazepine derivatives. *Chinese Chem. Lett.*, 18: 1305-1308.
- Varala, R., R. Enugala and Srinivas R. Adapa, 2007. *p*-nitrobenzoic acid promoted synthesis of 1,5-benzodiazepine derivatives. *J. Braz. Chem. Soc.*, 18: 291-296.
- Yi, W.B. and C. Cai, 2008. ChemInform abstract: Ytterbium Perfluorooctanes catalyzed synthesis of 1,5-benzodiazepine derivatives in fluorous solvents. *Synth. Commun.*, 39: 3827-3829.