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Expeditious multicomponent single stage reaction (MCSSRs) for the synthesis of 4-(3*H*)-Quinazolinones using ZrO_2 nano particle (NPs)

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Abstract: Expeditious multicomponent single stage reaction (EMCSSRs) for the synthesis of 4-(3*H*)-Quinazolinones using Zirconium nanoparticles (ZrO_2 NPs) with combination of water-ethanol as green solvent. ZrO_2 NPs gave good catalytic activity for the first five cycles of reactions. The expected results revels the catalytic activity, reaction time and the reusability of catalyst achieving by the cyclisation of 2-amino benzoic acid (Anthranilic acid), triethyl orthoformate or tri-ethoxy methane (TEM) and aliphatic and aromatic primary amines in presence of reported ZrO_2 NPs as a catalyst. This protocol offers several advantages such as a very short reaction time, reusability of catalyst and excellent yield of product. The final products were confirmed by spectral characterization data and comparing with its reported method. The synthesized ZrO_2 NPs were characterized by XRD, FTIR and UV-Visible spectra.

Keywords: Green Chemistry; ZrO_2 NPs; 2-amino benzoic acid; 4-(3*H*)-Quinazolinones; Multi-component single stage reaction.

Introduction

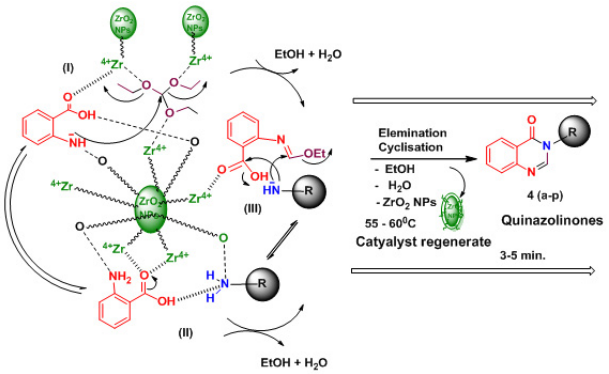
ZrO_2 NPs is more effective due to their reactivity and large surface area, being a dielectric material, ZrO_2 has a stable tetragonal phase structure and conductivity of this pure ZrO_2 material is only 10^{-7} s/cm at 1000 ºC, which is close to the conductivity of insulating material [1]. ZrO_2 NPs and water-ethanol found that best catalyst solvent combination for the some elementary organic transformations [2,3].

Nitrogen containing six members fused heterocyclic compound particularly Quinazolinones are biologically active with potential medicinal use as anticancer [4], antitubercular agent [5], anti-inflammatory and antioxidant [6], anticonvulsant agent [7],

antimicrobial [8], antitumor [9], ACHE inhibitor [10], antiviral [11] and catalytic activities [12,13].

Multicomponent single stage reactions (MCSSRs) are known tool for the synthesis of various products and intermediates in medicinal and combinatorial chemistry [14, 15] avoiding time consuming and multistep process [16, 17], have been proven to be smooth and shows advantage of an atom economy and high selectivity [18]. To owing these broad variety of Pharmacological importance and new catalytic method for preparation of Quinazolinones derivative starting from anthranilic acid, triethyl orthoformate and variety of primary amines. Previously reported of 4 (3*H*)-quinazolinones using catalysts reagents such as NH_4Cl [19], P-TSA [20], Iodine, [21], $Ce(CH_3SO_3).2H_2O$ [22], CAN [23], $SrCl_2.6H_2O$ [24], $Zn(ClO_4)$ [25], $NH_4(NO_3).9H_2O$ [26], heteropoly acids by MWI method [27] and Vitamin B1[28]. All these protocols suffer from some more disadvantages like longer reaction time, poor yield, tedious work-up protocol, toxic catalysts and solvents. Thus, we wish to developed a new methods for targeted 4-(3*H*)-quinazolinones by expeditious multicomponent single stage (MCSSRs) by using ZrO_2 NPs as reusable and heterogeneous catalyst in combination of water-ethanol as solvent, temperature at 55-60° C (**Scheme 1**).

Scheme 1. Multicomponent synthesis of 4-(3*H*)-quinazolinone derivatives at room temperature to 55-60° C in combination of ethanol-water as solvent.



Scheme 2. Plausible mechanistic path for the synthesis of 4-(3*H*)-quinazolinone derivatives.

Results and discussion:

Catalysts characterization:

UV-Visible spectroscopy: The UV-Visible spectra of pure ZrO_2 NPs and ZrO_2 NPs after 8th cycle were recorded on Scinco UV–vis scanning spectrometer (ModelS-4100) with the wavelength λ= ~260 nm. UV near-band edge (NBE) emission of ZrO_2 was observed at range between 454 nm ~ 465 nm which was equivalent to band gap of 4.74 eV. The electronic band structure of ZrO_2 is strongly influenced by the hybridization of Zr-4d orbital and O-2p orbital [31]. Wavelength of pure ZrO_2 NPs before and after used in the reaction was same as 260 nm (Figure **1**). The interaction of quinazolinones with ZrO_2 NPs has noticeable effect in its band structure as revealed by UV–Vis spectroscopy.

FT-IR: Fourier transform infra-red spectra were recorded on a Perkin-Elmer FT Spectrophotometer in KBr disc. The FT-IR analysis of ZrO_2 NPs the stretching vibrations can be studied in terms of transmittance % against wave numbers. The distinctive band around 3300-3375 cm^{-1} can be seen which indicated the transmittance due to O-H absorptions. 935-948 cm^{-1} and a broad band near 1640-1649 cm^{-1} which are associated with the O–H modes of chemisorbed water and/ or terminated hydroxides at the surface. The intense absorbance band in FT-IR spectrum were observed in range between 490-498 cm^{-1}

and 440-458 cm^{-1} which were attribute to the Zr-O stretching vibrations (Figure **2**).

X-ray diffraction*:* The X-ray diffraction (XRD) patterns was characterized by Philips X'Pert Pro monochromatized diffractometer Cu-Kα radiation (λ = 1.54056 Å). By X-ray diffraction pattern (Figure **3**), we observed high intensity peak (103) assigned at 2θ = 30.5° (112) and (101) reflections are present at 2θ = 51.02° and 59.31° respectively. All the reflections are indexed to the characteristic planes of a major tetragonal phase in ZrO_2 crystal system (t-ZrO_2, space group P21/a, JCPDS card No. 37-1484 and 88-1007). Elsewhere, no extra peak was observed corresponding to monoclinic plane. A clear broad peak in powder X-ray diffraction confirmed the formation of nano-sized particles of ZrO_2 (Figure **4**). The crystallite sizes was estimated from the Debye–Scherrer equation $D = \frac{0.9\lambda}{\beta cos\theta}$; where λ is the wavelength of Cu-Kα radiation (1.54056 Å) and β is the full width of the (h k l) peak at the diffracting angle 2θ. The mean crystallite size was estimated between ~20 and ~30 nm from XRD data (Figure **3**, **4**).

Discussion: Previously literature survey tells that there is no any report for the synthesis of 4 (3*H*)-quinazolinone derivatives under the catalyst of zirconium oxide nano particle (NPs) selected as model reaction of 2-amino benzoic acid (1 mmol) **1**, triethyl orthoformate (1.2 mmol) **2**, primary amine (aniline) (1 mmol) **3** (Table **1**) stirred condition at r. t. to 60 ºC temperature. At first, we carry out the reaction without catalyst and solvent, reaction did not detected even after 60 min (**Table 1** entry 1). The same reaction was carried out in 10 mol % of ZrO_2 NPs, again solvent free condition there is very negligible effect on the yield of product (**Table 1** entry 2,3). If we used polar protic solvent in the same reaction yield of the product were increases drastically with reduced the time of reaction(**Table 1** entry 7-9), certainly yield of the product were increased by the combination of ethanol-water in the set of model reaction in 3 min (**Table 1** entry 12). If we increase the mole % of catalyst more than 10 mol % there is no increase the yield of product (**Table 1**, entry 13) due to the surface area of the NPs being more active in polar-protic solvents and presence of oxygen vacancies, which are responsible for stability and higher surface activity [32]. The important feature for these catalysts is; surface of catalyst contains active hydroxyl, oxide groups and Zr^{+4} act as Lewis acids and or base which are well reported [33].

Thus, all examples were tested practicallygood to the excellent yields in ethanol water (4:1) at 10 mol % of catalyst (Table **2**, Scheme **1**). The catalytic activity of catalyst was explored by checking its reusability, after each cycle, the ZrO_2 NPs were recovered by centrifugation, washed with methanol, dried and reused for successive reactions. First four cycles gave better yield and then gradually decreases (Table **3**, Figure **5**).

The possible mechanism for the synthesis of *4 (3H)-quinazolinones derivatives*has been described the reactionbetween anthranilic acid **1**, triethyl orthoformate **2**, primary amine **3,** theelimination and cyclization has been successfully carried out by using active hydroxyl and Zirconium ion of ZrO_2 NPs as catalyst (**Scheme 2**).

Table 1. Screening of catalyst with solvents, reaction time, and yield for the synthesis 4 (3H)-quinazolinone**.**

Entry	Catalyst	Solvent	Time (min)	Yield[a] (%)
1	Without	Solvent free	60	0
2	ZrO_2 NPs (10 mol %)	Solvent free	10,15,30	00,30,30
3	ZrO_2 NPs (15 mol %)	Solvent free	15,30	35,35
7	ZrO_2 NPs (10 mol %)	H_2O	3,5,7	20,53,53
8	ZrO_2 NPs (10 mol %)	MeOH	3,5,7	42,58,58

9	ZrO_2 NPs (10 mol %)	EtOH	3,5,7	50,63,63
10	ZrO_2 NPs (10 mol %)	EtOH:H_2O (6:1)	5,7	68,68
11	ZrO_2 NPs (10 mol %)	EtOH:H_2O (4:2)	5,7	73,73
12	ZrO_2 NPs (10 mol %)	EtOH:H_2O (**4:1**)	2,**3**	82,**98**
13	ZrO_2 NPs (15 mol %)	EtOH:H_2O (4:1)	3,5	98,98

Reaction conditions: anthranilic acid 1 (1mmol), triethyl orthoformate 2 (1.2mmol), primary amine 3 (1mmol) and ZrO_2 NPs in 6 ml of solvent (4-1) was stirred at 50-60°C temperature; [a]Isolated yield.

Finally the structures of the compounds **4a** were confirmed by spectral data. For example, in the The ^{1}HNMR spectrum of compound gave singlet at δ = 8.39 (s, 1H, -CH=CN), δ = 7.40 (d, 2H, Ar-CH), δ = 7.40 (t, 2H, Ar-CH), δ = 7.20 (t, 1H, Ar-CH), and δ at 7.62-7.70 (3H, m, Ar-CH), 8.05 (d, 1H, Ar-CH) and 7.30-7.62 (m, 5H, Ar-H). ^{13}CNMRδ at 160.2, 148.3, 147.1, 137.2, 133.6, 128.9, 128.7, 128.3, 128.0, 127.9, 127.4, 126.7, 126.2, 120.2.; Mass spectrometry: MS (m/z, %): 223.07 [M+H].

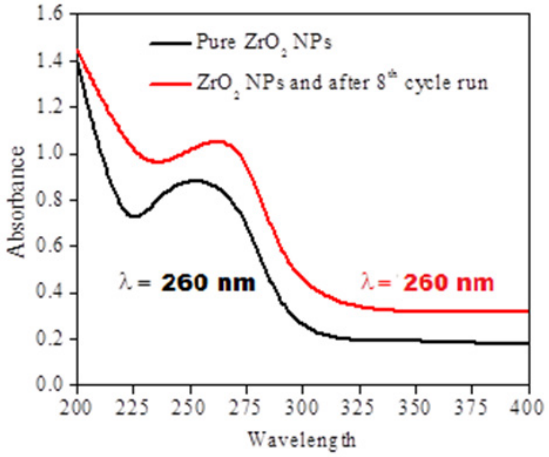


Figure 1: UV-Visible spectra of pure ZrO_2 NPs and after 8th cycle

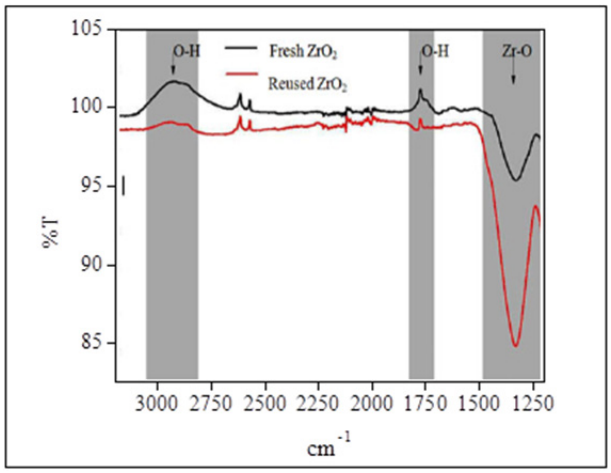


Figure 2: FT-IR spectra of fresh (black line) and reused (red line) ZrO_2 NPs

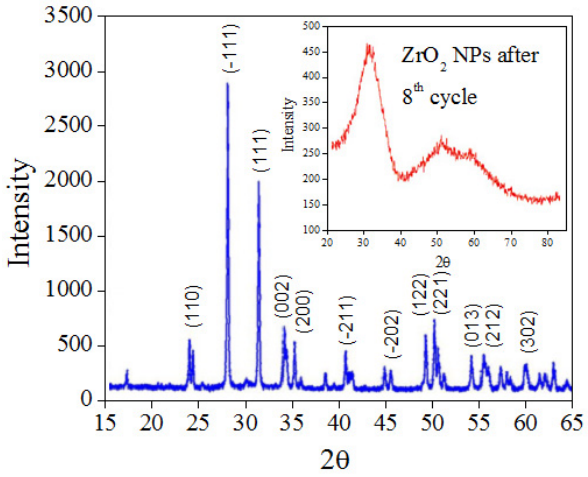


Figure 3: Powder XRD pattern of monoclinic ZrO_2 NPs and ZrO_2NP_S after 8th cycle

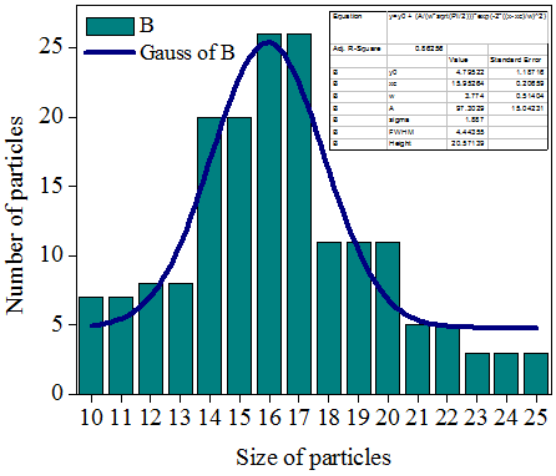
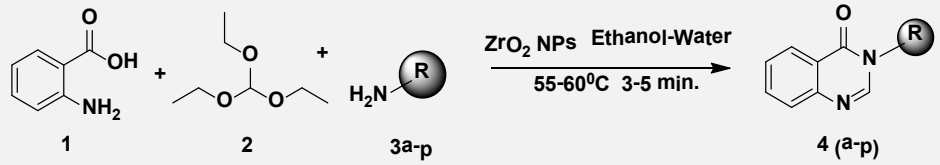
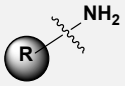
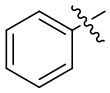
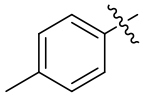
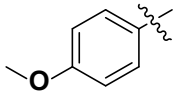
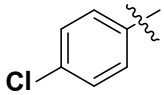
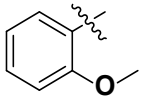
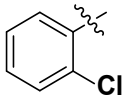
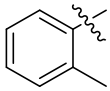
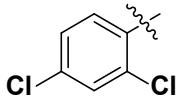
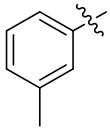
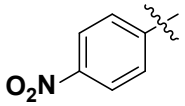
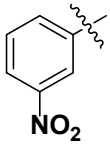


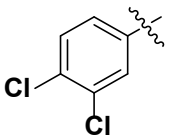
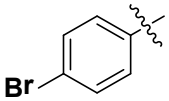
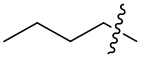
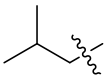
Figure 4: Size distribution of ZrO_2 nanoparticles

Table 2. ZrO_2 nano particle catalyzed synthesis of 4-(3*H*)-Quinazolinones derivatives



1 2 3a-p 4 (a-p)

Entry	R(2) 	Product	Time (min)	Yield (%)	m.p. (°C)		Ref.
					Reported	Found	
1		4a	3	98	139-141	140	[29]
2		4b	3	94	145-148	146	[30]
3		4c	3	92	133-135	132	[30]
4		4d	3	90	122-124	120	[30]
5		4e	3	92	150-153	152	[30]
6		4f	3	90	117-118	118	[30]
7		4g	3	92	157-159	158	[30]
8		4h	3	90	230-234	229	[29]
9		4i	3	93	138-140	140	[30]
10		4j	3	94	165-166	164	[30]
11		4k	3	92	154-156	155	[30]

12		4l	3	90	160-164	162	[29]
13		4m	3	93	147-149	148	[30]
14		4n	5	-	-	-	[28]
15		4o	5	-	-	-	-
16		4p	5	-	-	-	-

[a]**Reaction conditions:** anthranilic acid **1** (1mmol), triethyl orthoformate **2** (1.2mmol), variety of primary amine **3** (1mmol) and (10 mol %) of ZrO_2 NPs of ethanol-water (4-1) 6 ml was stirred at 50-60°C temperature; [a]Isolated yield,

Table 3. Recyclability of ZrO_2 NPs for the synthesis of 4-(3H)-quinazolinone (4)

No. of Cycle	Time (min)	Yield (%)
I	**3**	**98**
II	**3**	**97**
III	**3**	**97**
IV	**3**	**96**
V	**3**	**93**
VI	**3**	**89**
VII	**5**	**86**
VIII	**5**	**79**

[a]**Reaction conditions:** anthranilic acid **1** (1mmol), triethyl orthoformate **2** (1.2mmol), primary amine (aniline)**3** (1mmol) and (10 mol %) of ZrO_2 NPs of ethanol-water (4-1) 6 ml was stirred at 50-60°C temperature; [a]Isolated yield,

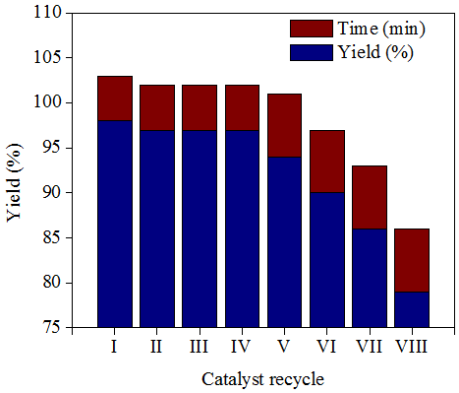


Figure 5: Recyclability of ZrO_2 NPs for the synthesis of 4-(3*H*)-quinazolinone (4)

Experimental

General

Allchemicals with high purity and catalyst ZrO_2 NPs were purchased from Sigma-Aldrich and an appropriate molar proportion of starting reactants was taken and the protocols of standard techniques were followed for the multi-component single path synthesis of functionalized quinazolinonesusing zirconium nanoparticles. The ZrO_2 NPs catalyst was characterized by UV-Visible (Figure **1**.), FT-IR (Figure **2**.) and X-ray diffraction (Figure **3**&**4**).Melting points of synthesized product were recorded on OptiMELT digital melting point apparatus and were uncorrected. IR spectra were recorded on a FT-IR (Bruker). ^{1}H NMR spectra were recorded on a 400 MHz Bruker spectrometer in solvent DMSO as part per million (ppm) downfield from a tetra methylsilane TMS internal standard. Mass spectra were recorded on water UPLC TQD Mass spectrometer, showing M^+ peak. Spectral data for the entire synthesized product (**4a-4p**) as depicted in Table 2 (Ref.) and in discussion part.

General procedure for synthesis of 4 (3H)-quinazolinones derivatives

General procedure for the synthesis of compounds (4a-p):

A mixture of 2-amino benzoic acid (1 mmol), triethyl orthoformate (1.2 mmol), variety of amine (1 mmol) in and ZrO_2 NPs (10 mol %) in 6 ml ethanol water (4:1) was stirred at double at of room temperature for 4-5 min until the reaction mixture solidified. The progress of the reaction was monitored by TLC. After completion of reaction, the solvent was removed under reduced pressure; crude product was stirred with 4-5 ml methanol at 60 ºC for 4-5 min followed by the simple centrifugation to expel catalyst out from reaction. Then methanol was removed under reduced pressure and the solid product was extracted by dichloromethane and filtered compound was purified by recrystallization from absolute ethanol to give product with an excellent yield (90-98 %). The products were confirmed by spectral characterization data and melting point and compared with reported method [29, 30] (**Table 2**).

Method for the preparation of tetragonal ZrO_2 NPs:

ZrO_2 nanoparticles (NPs) have been synthesized by dissociation of $ZrO_2Cl_2.8H_2O$ in a basic medium (pH ~9 to 11) at low temperature without adding any stabilizer. For the synthesisof ZrO_2 NPs, 40 ml of 0.05*M* NaOH solution in distilled water was slowly added in 100 ml 0.01*M* solution of $ZrO_2Cl_2.8H_2O$ in methanol-water (1:1) at ~0 to ~5 $^\circ$C with continuous stirring. After completion of the reaction (~50-60 min) the sol solution was refluxed at 100^{o}C for over a day with vigorous stirring. Sequentially, the solid and solution phases were separated by centrifugation and the solids were washed with dilute solution of NH_4NO_3 until negative test for chloride ion followed by washed with de-ionized water (2x20 ml) and ethanol (2x5 ml). Prepared solids were dried well and then calcinated at 500^{o}C for 5 hours. The formation of Nano-sized particles was confirmed by powder XRD studies.

Reusability of the catalyst: Procedure: The recovered catalyst from the reaction mixture during the synthesis of quinazolinones derivatives was then washed with methanol (8-9

ml) followed by ethanol (6 ml) and finally dried well and reused for subsequent runs.The better catalytic activity of ZrO_2 NPs for first 5thcycles, further cycle of reaction the yield of products were decreases even after increasing the time of reaction (**Table 3**, Figure **5**).

Conclusions

In conclusion we developed anexpeditious multicomponent single stage for the synthesis of 4-(3*H*)-quinazolinones in catalyzed by ZrO_2NPs as with combination of ethanol-water (4:1) at the stirringconditiontemperature at 50-60°C,starting from easily available reactants. Benefit of this methodology over other existing one is excellent yield within very short time of reaction and simple reaction procedure. This protocol provides extensive choice of access to compounds that are useful in medicinal and heterocyclic intermediate.

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REFERENCES

1. Jiafeng Ding, Xinmei Li, Jian Cao, Liyuan Sheng, Linzi Yin and Xuemei Xu, Sensors and Actuators B. (2014)202, 232–239.
2. L. Nakka, J.E. Molinari and I.E. Wachs, *Journal of the American Chemical Society*. (2009)131, 42, 15544-15554.
3. K. Tomishige, Y. Ikeda, T. Sakaihori and K. Fujimoto, *Journal of Catalysis*. (2000)192, 2, 355-362.
4. G.H. Zang, W.B. Xue, Y.F. Wang, F.Y. An, J.M. Yuan,J.K. Qin, C.X. pan, G.F. Su, *Eur. J. Med. Chem.* (2015)95, 377-387.
5. W. Lu, I.A. Baig, H.J. Sun, C.J. Cui, R. Guo, I. P. Jung, D. Wang, M. Dong, M.Y. Yoon, J.G. Wang, *Eur. J. Med. Chem*. (2015)94, 298-305.
6. K.P. Rakesh, H.M. Manukumar, D.C. Gowada, *Bioorg. Med. Chem. Lett.* (2015)25, 1072-1077.
7. H.S. A. Alsalem, G.H. Hegazy, K.E.H. El-Taher, S.M. El-Messery, A.M. Al-Obid, H.I. Subbagh, *Bioorg. Med. Chem. Lett*. (2015)25, 1490-1499.
8. D.R. Patel, K.C. Patel, J. Saudi Chem. Soc. (2015)19, 347-359.
9. R. Venkatesh, M.J. Ramaiah, H.K. Gaikawad, S. Janardhan, R. Bantu, L. Nagarapu, G.N. Sastry, A.R. Ganesh, M. Bhadra, *Eur. J. Med. Chem.* (2015) 94, 87-101.
10. N.J. Liverton, D.J. Armstrong, D.A. Claremon, D.C. Remy, J.J Baldvin, R.J Lynch, G. Zhang, R.J. Gould, *Bioorg. Med. Chem*. (1998)8, 483-486.
11. J. Ma, P. Li, X. Li, Q. Shi, Z. Wan, D. Hu, L. Jin, B.Song, *J. Agric. Food Chem*. (2014)62, 8928-8934.
12. I. Shcherbakova, M.F. Balandrin, J. Fox, A. Ghatak, W.L. Heaton, R.L. Conklin, *Bioorg. Med. Chem. Lett*. (2005) 15, 1557-1560.
13. S.L. Cao, Y.P. Feng, Y.-Y.Jiang, S.-Y. Liu, G.Y. Ding, R.T. Li, *Bioorg. Med. Chem. Lett*. (2005)15, 1915-1917.
14. (a) J. Diego, Ramon, M. Yus, *AngewandteChemie International Edition*. (2005)44, 11, 1602-1634.
15. A. Domling, *Chemical Review*. (2006)106, 17-89.
16. D. Rocchi, J. Francisco Gonzalez and J. Carlos Menendez, *Green Chemistry*.(2013)15, 511-517.
17. L.F. Tietze, *Chemical Review*. (1996)96,1, 115-136.
18. C.C.A. Cariou, G.J. Clarkson, M. Shipman, *Journal of Organic Chemistry*. (2008)73, 24, 9762-9764.
19. G. Huang, B. Liu, M. Teng, Y. Chen, *Synth. Commun.* (2014)44, 1786-1794.
20. M. Narasimhulu, K.C. Mahesh, T.S. Reddy, K. Rajesh, Y. Venkateswarlu, *Tetrahedron Lett*. (2006) 47, 4381-4383.
21. H.S. Wang, J.E. Zeng, *Chin.J. Chem*. (2008)26, 175-178.
22. M. Wang, Z.G. Song, T.T. Zhang, *Monatsh. Chem*. (2010)141, 993-996.
23. M. Wang, Z.G. Song, T.T. Zhang, *Chem. Heterocycl. Compd*. (2010)46, 581-584.
24. M. Wang, Z.G. Song, T.T. Zhang, *Chin. Chem. Lett.* (2010)21, 1167-1170.
25. X.B. Jing, Z. Li, X. Pan, Y.C.A. Shi, *J. Chin. Chem.Soc.* (2008)55, 1145-1149.
26. M. Wang, Z. Song, T. Zhang, *Synth. Commun*. (2011)41, 385-391.
27. K. Ighilahriz, B. Boutemeur, F. Chami, C. Rabia, M. Hamdi, M.S. Hamdi, *Molecules*. (2008)13, 779-789.
28. D.S. Kawade and M.S. Shingare et al. Iranian *Journal of Catalysis*(2016) 6, 4 313-318
29. K. Ighilahriz, B. Boutemeur, F. Chami, C. Rabia, M. Hamdi, M.S. Hamdi, *Molecules*(2008)13, 779-789.
30. M. Wang, Z.G. Song, T.T. Zhang, *Org. Prep. Proc. Int.* (2010)42, 169-173.
31. QuaziArif Islam, Mirwasim Raja, ChiranjibSatra and Rajendra NathBasu.*Bulletine of Materials Science,* (2015)38, 6, 1473–1478.
32. E. Karapetrova, R. Platzer, J.A. Gardner, J.A. Sommers and W.E. Evenson, *Journal of the American Ceramic Society*. (2001)84, 1, 65-70.
33. Yubao Zhao, Wei Li, Minghui Zhang and Keyi Tao, *Catalysis Communications*. (2002)3, 239-245.