ARTICLE

Ecofriendly Synthesis of Biscoumarin Derivatives Catalyzed by Thiourea Dioxide -Modified Magnetic Animal Bone Meal Nanoparticles as Catalyst in Water

Ahmad Reza Momeni[*], **Jalal Albadi** and **Sadegh Bakhtiar**

Faculty of Sciences, University of Shahrekord, Shahrekord, Iran.

Abstract: Magnetic animal bone meal nanoparticels functionalized with thiourea dioxide (Fe$_3$O$_4$@ABM-TUD) were prepared as heterogeneous and green catalyst. The catalyst was characterized using several techniques, such as fourier transform infrared spectroscopy (FT-IR), thermogravimetric analysis (TGA), differential thermogravimetrics (DTG) and scanning electron microscopy (SEM). The catalytic activity of Fe$_3$O$_4$@ABM-TUD was evaluated on the synthesis of biscoumarins in water. The catalyst was magnetically recovered and reused for five cycles without any significant loss of efficiency.

Keywords: Green catalyst, Biscoumarin, Animal bone meal, Thiourea dioxide, Magnetic nanoparticels.

Introduction

Biscoumarin and its derivatives are significant due to their biological activities, such as urease inhibitors[1], HIV inhibitory activity[2], anticoagulant activity[3] and anti- inflammatory activity[4]. Recently, a number of methods have been reported for the synthesis of biscoumarins by reaction of 4-hydroxycoumarin and various aldehydes[5-16], but many of these methods have disadvantages, such as long reaction times, low yields, harsh reaction conditions, poor reusability and use of expensive and toxic catalysts. Therefore, in the last decade, the use of non-toxic and reusable catalysts have been developed. Natural catalysts, bio-base catalysts and solid supported catalysts are examples of this category[17]. Among them, solid supported catalysts have attracted much attention, because they have many advantages, such as ease of catalyst separation and high catalytic activity. Nanoparticles, especially core-shell magnetic nanoparticles, have been used as support for homogenous catalysts[18]. These magnetic catalytic systems have high surface area and can be separated from product solution by an external magnet. This can prevent the loss of solid catalyst that occurs in conventional separation methods[19,20].

Animal Bone Meal (ABM) as a natural catalyst has recently been used as heterogeneous catalyst for the thia-Michael addition[21], crossed-aldol condensation[22] and for synthesis of benzimidazoles, benzoxazoles and benzothiazoles[23]. The ABM as a natural, inexpensive and biocompatible inorganic solid is potentially useful for catalyst immobilization, which can contribute to the development of catalytic processes and reduced environmental problems.

Thiourea dioxide (TUD), as an efficient organocatalyst, has been successfully used in several kinds of organic reactions, such as the one-pot synthesis of heterocyclic compounds[24], hydrolysis of imines[25], synthesis of naphthopyran derivatives[26], oxidation of

alcohols[27], oxidation of sulfides to sulfoxides [28], synthesis of pyrano[4,3- b]pyrans[29] and as reducing agent in reduction of aldehydes[30]. TUD is not a dioxide, but instead is a derivative of a sulfinic acid, which can be readily prepared by the reaction of thiourea and hydrogen peroxide. TUD can activate organic substrates by hydrogen bonding. It can form strong hydrogen bonds, because it possesses two extra oxygen atoms and provides higher activation than the corresponding thiourea.

While the use of homogeneous and heterogeneous protic acids and Lewis acids is known in catalyzed organic reactions, most of these catalysts suffer from some disadvantages, such as use of expensive and corrosive reagents, toxic transition metals, sensitivity to moisture and non-availability[31]. It seems that TUD could be an environmental benign catalyst alternative for some hazardous catalysts in organic transformations. TUD is soluble in water and acts as a homogeneous catalyst. Heterogenization of TUD by immobilizing on a solid support could solve this problem.

The importance of developing new environmentally benign methods led us to consider TUD as an eco-friendly compound and ABM as an inexpensive and available support for the preparation of a green heterogeneous organocatalyst. Therefore, in continuation of our researche on the performance of different nanocatalysts on the organic reactions[32-35], herein, we report the preparation of TUD incorporated on a surface of ABM magnetite nanoparticles, as a non-toxic and recyclable catalyst, which catalyzed the synthesis of biscoumarins in water as solvent. The magnetic catalyst could be easily isolated from the reaction mixture by an external magnet and reused several times without significant decrease in its activity.

Experimental

Materials and Apparatus

All chemicals, including $FeCl_3 \cdot 6H_2O$, (3-chloropropyl) trimethoxysilane (CPTMS), thiourea, aldehyde derivatives and 4-hydroxycumarine, were purchased with high purity from Fluka and Merck (Darmstadt, Germany). All materials were of commercial reagent grade. FT-IR spectra were obtained with potassium bromide pellets in the range 400–4000 cm^{-1} with a JASCO 6300 spectrometer. The morphology of the catalyst was studied by a scanning electron microscope (HITACHI S-4160) operated at a 30 kV accelerating voltage. Thermogravimetric analysis (TGA/DTA) was carried out under N_2 atmosphere with a heating rate of 10 °C/min with a Mettler SF1 thermogravimetric analyzer.

Synthesis of Magnetic Fe_3O_4 Nanoparticles ($Fe3O4$-MNPs)

Magnetite nanoparticles (Fe_3O_4-MNPs) were synthesized according to the reported procedure [36]. $FeCl_3.6H_2O$ (2.35 g, 8.7 mmol) and $FeCl_2.4H_2O$ (0.86 g, 4.3 mmol) were dissolved in 40 mL deionized water. The resultant solution was stirred for 30 min at 80 °C. Then, 5 mL of NH_4OH solution were added with vigorous stirring to produce a black solid and the resultant mixture was stirred for another 30 min and then cooled to room temperature. The black magnetic nanoparticles were isolated by magnetic decantation, washed several times with deionized water and then dried in an oven at 80 ˚C.

Surface modification of Fe_3O_4 -NPs with ABM

Animal bone meal was prepared according to the reported procedure[22].

The magnetite particles obtained in the previous step were covered with a layer of ABM. For this purpose, a suspension of ABM and magnetite nanoparticles (1:1 w/w) in ethanol was prepared. The mixture was ultrasonicated for 20 min. After ultrasonication, the mixture was stirred for 12 hours at reflux conditions under Ar atmosphere. Then, the mixture was cooled to room temperature and ABM-coated magnetic nanoparticles were separated by an external magnet, washed with ethanol and dried at 80°C.

Preparation of Fe_3O_4@ABM-TUD

The magnetic nanoparticles modified with thiourea dioxide were prepared according to the following procedure. TUD was synthesized according to the reported procedure with minor modifications [24]. Thiourea (5.0 g) was dissolved in hot water (40 mL) at 40 °C and the solution was cooled to RT. Then, 30% aqueous hydrogen peroxide (30 mL) was added drop-wise to ice-cooled thiourea solution, maintaining the temperature below 10 °C. The reaction was stirred for 2 h. The mixture was then cooled to 0°C, filtered and dried at 50 °C. After this, Fe_3O_4@ABM (2 g) was added to the solution of

3-(chloropropyl) trimethoxysilane (2 mL) in ethanol (50 mL) and the resultant mixture was refluxed under Ar atmosphere for 12 h. Fe_3O_4@ABM-Cl particles were separated by a magnet, washed with ethanol and dried at 80°C for 8 h. Finally, the prepared Fe_3O_4@ABM-Cl (5 g), triethylamine (6 ml) and TUD (5 g) were dispersed in anhydrous toluene with vigorous stirring. The mixture was refluxed for 12 h. The resulting solid (Fe_3O_4@ABM-TUD) was separated by an external magnet, washed with ethanol and dried under vacuum at 60 °C.

General Procedure

A mixture of 4-hydroxycoumarin (2.0 mmol), aldehyde (1.0 mmol), Fe_3O_4@ABM-TUD (0.01 g) as catalyst in water (5 mL) was heated under reflux condition for the appropriate time. After completion of the reaction (monitored by TLC), the catalyst was removed by an external magnet and the reaction mixture was allowed to cool to room temperature. Then, the obtained solid was

filtered and recrystallized from ethanol to afforded pure product.

Results and Discussion

Catalyst Characterization

Fe_3O_4 magnetic nanoparticles (MNPs) were prepared by chemical co-precipitation from Fe^{2+} and Fe^{3+} in ammonia solution. The chemical stability of magnetic nanoparticles was improved by coating their surface with animal bone meal. Then, chloro-coated Fe_3O_4 nanoparticles were obtained by coordination bond formation between the 3-(chloropropyl) trimethoxysilane with ABM surface. Subsequently, Fe_3O_4@ABM-TUD was prepared by substitution reaction of amino-groups of TUD with chloro-groups of Fe_3O_4@ABM-Cl (Scheme 1). The prepared catalyst was characterized by FT-IR, TGA and scanning electron microscopy (SEM).

Scheme 1. Preparation of Fe_3O_4@ABM-TUD.
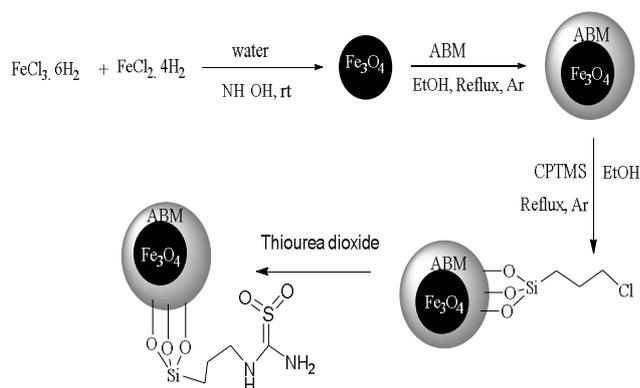
The FT-IR spectra of the animal bone meal, TUD, Fe_3O_4@ABM and Fe_3O_4@ABM-TUD are shown in Fig. 1. FT-IR spectrum as shown in Fig. 1a showed the characteristic absorption peaks of sample TUD[27]. The bonds at 3272 and 3049 cm^{-1} were attributable to the stretching vibration of NH and OH, respectively. The characteristic bonds for S=O, C=S and C-S appear at 1068, 1000 and 735 cm^{-1}. In the spectrum of ABM, the bond at 3571 cm^{-1} was attributable to the stretching vibration of the lattice OH^- and the medium sharp peak at 633 cm^{-1} was assigned for the OH deformation mode. The characteristic bonds for PO_4^{3-} appear at 570, 603, 962, 1049 and 1091 cm^{-1} (Fig. 1b)[37]. Stretching mode of Fe–O appears at 570 cm^{-1}

(Fig. 1c, d). In the spectrum of Fe_3O_4@ABM-TUD, the characteristic absorption bands appear at 3616, 1673, 1068 and 3419 cm^{-1} which, confirmin the successful bonded TDU on the magnetite nanoparticles surface (Fig. 1d).

The morphology and size distribution of Fe_3O_4@ABM and Fe_3O_4@ABM-TUD were examined by scanning electron microscopy (SEM) (Figure 2). Scanning electron microscopy (SEM) revealed that Fe_3O_4@ABM particles have a nearly spherical shape (Figure 2a). Fe_3O_4@ABM-TUD exhibits smooth surface morphology as shown in Figure 2b.

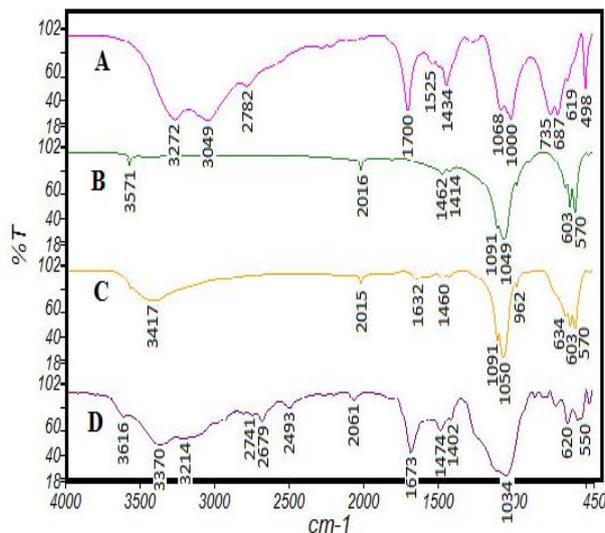**Figure 1.** FT-IR spectra of (A) TUD, (B) ABM, (C) Fe_3O_4@ABM and (D) Fe_3O_4@ABM-TUD.
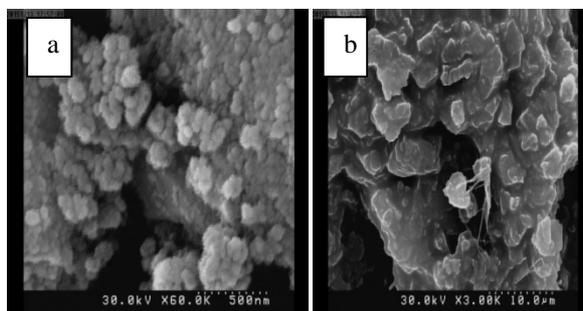
Figure 2. The SEM image of (a) Fe_3O_4@ABM and (b) Fe_3O_4@ABM-TUD.

Thermal stability of Fe_3O_4@ABM-TUD was determined by TGA/DTA analysis (Figure 3). A decrease in the weight percentage of Fe_3O_4@ABM-TUD at about 150 $°C$ is related to desorption of water molecules from the catalyst surface and the percentage of the mass loss is 0.92%. The weight loss from 200 to 550 $°C$ was attributed to the decomposition of organic groups, which indicates that the amount of organic component was about 54 % by weight.
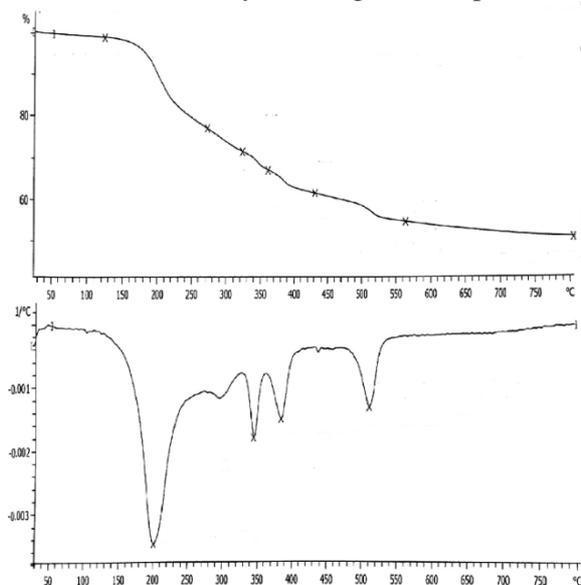
Figure 3. TGA/DTG curves of Fe_3O_4@ABM-TUD.

Catalytic Activity

The catalytic activity of the synthesized Fe₃O₄@ABM-TUD was investigated in the synthesis of biscoumarins (Scheme 2). Initially, the condensation reaction of 4-nitrobenzaldehydes with 4-hydroxycoumarin in the presence of a catalytic amount of Fe₃O₄@ABM-TUD under solvent-free conditions was chosen as a model reaction. Interestingly, the corresponding biscoumarin was obtained in good yield. In order to optimize the reaction conditions for the synthesis of biscoumarins, the effects of solvent, temperature and the amount of catalyst were investigated. The model reaction was carried out in the various solvents and solvent-less conditions (Table 1, entries 1-7). The results showed that

carrying out the reaction in H_2O gave the highest yield for the desired product (Table 1, entry 6). The effect of temperature was studied by carrying out the model reaction at different temperatures in water (room temperature, 40, 80 °C and reflux conditions), and the best result was obtained at reflux conditions (Table 1, entries 13-16). In the room temperature, the reaction did not take place and no formation of the respective product was detected after 1 h, (Table1, entry 13). Afterwards, the influence of the catalyst amount in this reaction was investigated. The reaction was performed with 0.005-0.03 g of Fe₃O₄@ABM-TUD as catalyst. It was observed that the best amount of Fe₃O₄@ABM-TUD is 0.01 g which afforded the desired product in 95 % yields (Table1, entry 10). Increasing amounts of catalyst did not improve the yield or reaction rate (Table 1, entries 11 and 12).

Scheme 2. Synthesis of biscoumarin derivatives using Fe₃O₄@ABM-TUD as catalyst.

R=Alkyl or Aryl

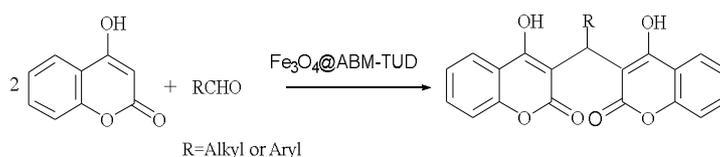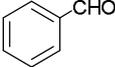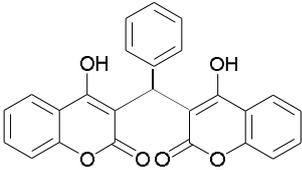**Table 1. Optimization of reaction conditions for the synthesis of biscoumarin.[a]**

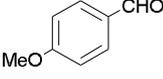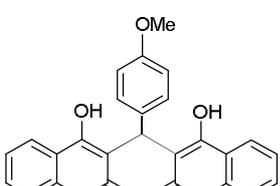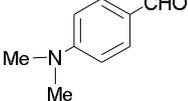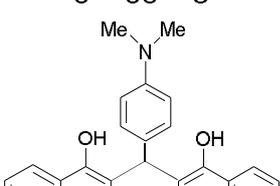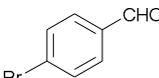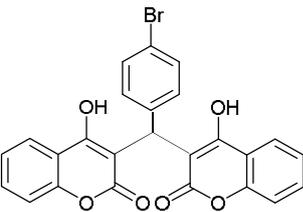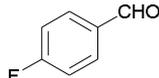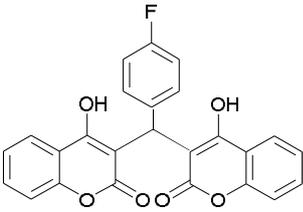| Entry	Catalyst (g)	Temperature (°C)	Solvent	Time (min.)	Yield (%)[b]
1	0.01	Reflux	EtOH	90	60
2	0.01	Reflux	CH_3CN	150	70
3	0.01	Reflux	n-Hexane	150	50
4	0.01	Reflux	CH_2Cl_2	150	40
5	0.01	Reflux	H_2O/EtOH(1:1)	30	90
6	0.01	Reflux	H_2O	15	95
7	0.01	100	Solvent-free	45	70
8	0.005	Reflux	H_2O	20	80
9	0.008	Reflux	H_2O	15	80
10	0.01	Reflux	H_2O	15	95
11	0.02	Reflux	H_2O	15	92
12	0.03	Reflux	H_2O	15	92
13	0.01	rt	H_2O	60	-
14	0.01	40	H_2O	15	57
15	0.01	80	H_2O	15	62
16	0.01	Reflux	H_2O	15	95

Based on the above observations, a wide variety of aromatic aldehydes, containing both electron-withdrawing and electron-donating groups (Table 2, entries 1–10), 2-furylcarbaldehyde as heteroaromatic aldehyde (Table 2, entry 11) and aliphatic aldehyde derivatives, such as cinnamaldehyde (Table 2, entry 12), were treated with 4-hydroxycoumarin to give the corresponding biscoumarin products. As shown in Table 2, a wide range of aldehydes could react with 2-hydroxycoumarin and regardless of the nature of the substituents on the aromatic ring, the biscoumarin derivatives were obtained in good to excellent yields. The type of aldehyde has no significant effect on the reaction.

Table 2. Fe₃O₄@ABM-TUD catalyzed synthesis of biscoumarins in water.ᵃ

Entry	Substrate	Product	Time (min.)	Yield (%)[b]	Mp (°C) Found	Mp (°C) Reported [6,8]
1			5	94	226-228	228-230
2			15	95	234-236	232-234
3			15	87	234-236	234-236
4			20	93	251-253	254-256
5			20	92	223-225	218-220
6			15	92	251-253	254-256
7			20	82	245-246	242-244
8			15	87	221-222	222-224
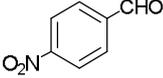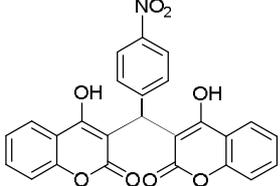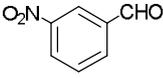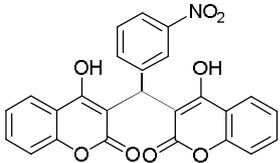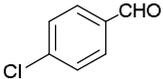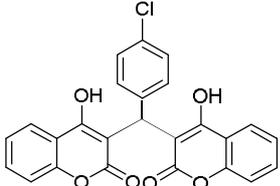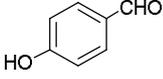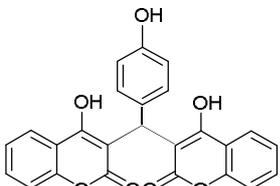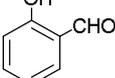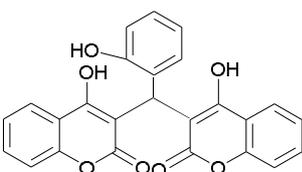
Entry	Substrate	Product	Time (min.)	Yield (%)[b]	Mp (°C) Found	Mp (°C) Reported [6,8]
9			15	87	264-265	266-268
10			15	82	212-213	212-214
11			15	85	194-196	198-200
12			15	93	225-227	228-230
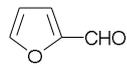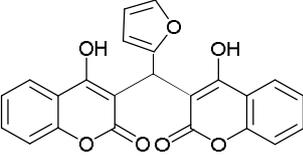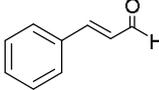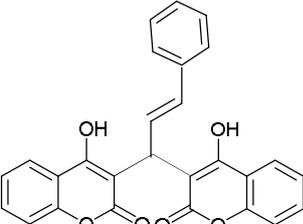
[a] Reaction conditions: Aldehyde (1 mmol), 4-hydroxycoumarin (2 mmol), Fe_3O_4@ABM-TUD (0.01 g) and water (3 ml) at reflux temperature. [b] Isolated yields.

Reusability of the catalyst was studied through a condensation reaction of 4-nitrobenzaldehyde with 4-hydroxycoumarin under optimized conditions. The recovered Fe_3O_4@ABM-TUD can be washed with ethanol and used again at least five times without any significant loss of catalytic activity (Figure 4).
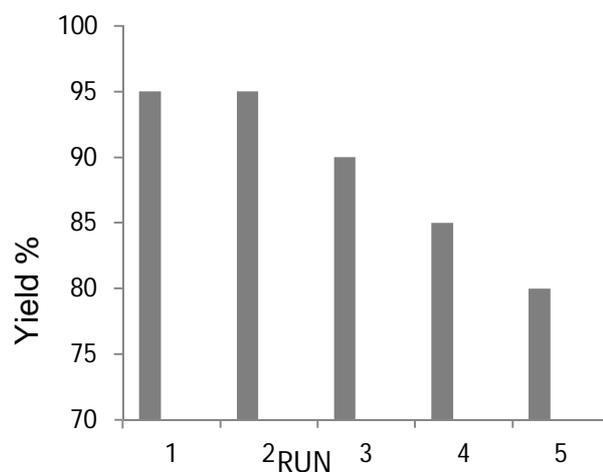

Figure 4. Reuse of Fe_3O_4@ABM-TUD.

To show the merit of the present work in comparison with previously reported results in the literature, we summarized some of results for the synthesis of biscoumarin derivatives in Table 3. As shown in Table 3, Fe_3O_4@ABM-TUD can act as effective catalyst with respect to reaction times and yields.

Table 3. Comparison results of Fe_3O_4@ABM-TUD with some of other catalysts reported in literature for the synthesis of biscoumarin derivatives.

Entry	Conditions	Catalyst	Time (min)	Yield (%)	Reference
1	Water, 80 °C	PTTH	7-10	80-95	[6]
2	Toluene, 90 °C	[P4VPy–BuSO$_3$H]HSO$_4$	36-60	90-95	[7]
3	Ethanol, reflux	[TBA]$_2$[W$_6$O$_{19}$]	5-10	85-92	[5]
4	CH$_2$Cl$_2$, 40 °C	Nano silica chloride	1-5.5 h	68-95	[8]
5	H$_2$O, Reflux	SBPDSA	5-15	80-95	[9]
6	H$_2$O, Reflux	Fe_3O_4@ABM-TUD	5-20	82-95	This work

Conclusions

Fe_3O_4@ABM-TUD was prepared as an environmentally friendly organocatalyst and used in water for the synthesis of biscoumarins. This procedure is clean, simple and safe. The catalyst was magnetically recovered and recycled for several runs without any significant loss of efficiency. These advantages make it an attractive catalyst for this process.

Acknowledgements

References

[1] Khan, K. M.; Iqbal, S.; Lodhi, M. A.; Maharvi, G. M.; Choudhary, M. I.; Perveen, S. *Bioorg. med. chem.* **2004**, *12*, 1963-1968.

[2] Manian, R. D. R.; Jayashankaran, J.; Raghunathan, R. *Tetrahedron lett.* **2007**, *48*, 1385-1389.

[3] Manolov, I.; Maichle-Moessmer, C.; Nicolova, I.; Danchev, N. *Arch. Pharm.* **2006**, *339*, 319-326.

[4] Kontogiorgis, C.; Hadjipavlou-Litina, D. *J. Enzym. Inhib. Med. Ch.* **2003**, *18*, 63-69.

[5] Zolfigol, M. A.; Moosavi-Zare, A. R.; Zarei, M. *CR. Chimie* **2014**, *17*, 1264-1267.

[6] Rezaei, R.; Moezzi, F.; Doroodmand, M. M. *Chinese Chem.Lett.* **2014**, *25*, 183-186.

[7] Boroujeni, K. P.; Ghasemi, P.; Rafienia, Z., *Monatsh. Chem.* **2014**, *145*, 1023-1026.

[8] Mehrabi, H.; Abusaidi, H. *J. Iran. Chem. Soc.* **2010**, *7*, 890-894.

[9] Niknam, K.; Sajadi, S. A.; Hosseini, R.; Baghernejad, M. *Iran. J. Catal.* **2014**, *4*, 163-173.

[10] Khan, K. M.; Rahim, F.; Wadood, A.; Kosar, N.; Taha, M.; Lalani, S.; Khan, A.; Fakhri, M. I.; Junaid, M.; Rehman, W. *Eur. j. med. chem.* **2014**, *81*, 245-252.

[11] Wang, J.; Shi, D.; Zhuang, Q.; Wang, X.; Tu, S. *Chinese J. Org. Chem.* **2005**, *25*, 926-929.

[12] Kidwai, M.; Bansal, V.; Mothsra, P.; Saxena, S.; Somvanshi, R. K.; Dey, S.; Singh, T. P. *J. Mol. Catal. A-Chem.* **2007**, *268*, 76-81.

[13] Khurana, J. M.; Kumar, S. *Tetrahedron Lett.* **2009**, *50*, 4125-4127.

[14] Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1996**, *6*, 1257-1266.

[15] Hagiwara, H.; Fujimoto, N.; Suzuki, T.; Ando, M. *Heterocycles* **2000**, *53*, 549-552.

[16] Hagiwara, H.; Miya, S.; Suzuki, T.; Ando, M.; Yamamoto, I.; Kato, M. *Heterocycles* **1999**, *51*, 497-500.

[17] Anastas, P. T.; Bartlett, L. B.; Kirchhoff, M. M.; Williamson, T. C. *Catal. Today* **2000**, *55*, 11-22.

[18] Dam, B.; Nandi, S.; Pal, A. K. *Tetrahedron Lett.* **2014**, *55*, 5236-5240.

[19] Ghahremanzadeh, R.; Rashid, Z.; Zarnani, A. H.; Naeimi, H. Appl. Catal. A- Gen. **2013**, *467*, 270-278.

[20] Saikia, P. K.; Sarmah, P. P.; Borah, B. J.; Saikia, L.; Saikia, K.; Dutta, D. K. *Green Chem.* **2016**, *18*, 2843-2850.

[21] Riadi, Y.; Mamouni, R.; Abrouki, Y.; El Haddad, M.; Saffaj, N.; El Antri, S.; Routier, S.; Guillaumet, G.; Lazar, S. *Lett. Org. Chem.* **2010**, *7*, 269-271.

[22] Riadi, Y.; Mamouni, R.; Azzalou, R.; Boulahjar, R.; Abrouki, Y.; El Haddad, M.; Routier, S.; Guillaumet, G.; Lazar, S. *Tetrahedron Lett.* **2010**, *51*, 6715-6717.

[23] Riadi, Y.; Mamouni, R.; Azzalou, R.; El Haddad, M.; Routier, S.; Guillaumet, G.; Lazar, S. *Tetrahedron Lett.* **2011**, *52*, 3492-3495.

[24] Verma, S.; Kumar, S.; Jain, S. L.; Sain, B. *Org. biomol. chem.* **2011**, *9*, 6943-6948.

[25] Kumar, S.; Jain, S. L.; Sain, B. *RSC Adv.* **2012**, *2*, 789-791.

[26] Verma, S.; Jain, S. L. *Tetrahedron Lett.* **2012**, *53*, 6055-6058.

[27] MohanáBahuguna, G. *RSC Adv.* **2013**, *3*, 4184-4188.

[28] Kumar, S.; Verma, S.; Jain, S. L.; Sain, B. *Tetrahedron lett.* **2011**, *52*, 3393-3396.

[29] Ghashang, M.; Mansoor, S. S.; Aswin, K. *Chinese J.Catal.* **2014**, *35*, 127-133.

[30] Sambher, S.; Baskar, C.; Dhillon, R. S. *Synth. Commun.* **2008**, *38*, 2150-2157.

[31] Ma, J.; Zhong, L.; Peng, X.; Sun, R. *Green Chem.* **2016**, *18*, 1738-1750.

[32] Albadi, J.; Alihoseinzadeh, A.; Razeghi, A. *Catal. Commun.* **2014**, *49*, 1-5.

[33] Albadi, J.; Alihosseinzadeh, A.; Jalali, M.; Shahrezaei, M.; Mansournezhad, A. *Mol. Catal.* **2017**, *440*, 133-139.

[34] Albadi, J.; Alihosseinzadeh, A.; Mardani, M. *Chinese J. Catal.* **2015**, *36*, 308-313.

[35] Albadi, J.; Keshavarz, M.; Shirini, F.; Vafaie-nezhad, M. *Catal. Commun.* **2012**, *27*, 17-20.

[36] Safari, J.; Zarnegar, Z. *J. Mol. Catal. A-Chem.* **2013**, *379*, 269-276.

[37] Tahriri, M.; Solati-Hashjin, M.; Eslami, H. *Iran. J. Pharm. Sci.* **2008**, *4*, 127-134.