Iranian Journal of Catalysis 8(1), 2018, 47-52

IRANIAN JOURNAL OF CATALYSIS

Nano-Fe_3O_4@ZrO_2-SO_3H as highly efficient recyclable catalyst for the green synthesis of fluoroquinolones in ordinary or magnetized water

Ahmad Nakhaei[a,*], Abolghasem Davoodnia[b], Sepideh Yadegarian[a]

[a]*Young Researchers and Elite Club, Mashhad Branch, Islamic Azad University, Mashhad, Iran*

[b]*Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran.*

Received 11 May 2017; received in revised form 18 October 2017; accepted 21 December 2017

ABSTRACT

Core–shell zirconia-coated magnetite nanoparticle bearing sulfonic acid groups (nano-Fe_3O_4@ZrO_2-H_3PO_4) have been prepared and used as an efficient acid catalyst in the synthesis of fluoroquinolons by the direct amination of 7-halo-6- fluoroquinolone-3-carboxylic acids with variety of piperazine derivatives and (4aR,7aR)-octahydro-1H-pyrrolo[3,4-b] pyridine. The reaction was carried out in the ordinary or magnetized water as a solvent. In the final outcomes, the nano-Fe_3O_4@ZrO_2-SO_3H showed good catalytic performance in the both forms of water. However, the magnetized water showed better results. Therefore, this new procedure provides prompt achievement to the appropriate products with acceptable yields in water as a green solvent at reflux situations with an easy work-up process. Furthermore, the catalyst was recyclable and could be reused at least three times without any discernible loss in its catalytic activity.

Keywords: *Fluoroquinolones, Fast and green synthesis, Fe_3O_4@ZrO_2-SO_3H, Ordinary water, Magnetized water.*

1. Introduction

The use of water as a green medium for organic synthesis has become the most important study area. In addition to the economical and environmental advantages, water shows unique physical and chemical properties which lead to exclusive reactivity and selectivity in comparison with organic solvents. Thus, extensive use of organic reactions in water medium is necessary these days [1].

Fluoroquinolones have been a class of important synthetic antibacterial agents which are widely used in clinics for the treatment of infectious diseases [2]. These compounds act excellently against gram-negative and moderately against gram-positive bacteria [3]. Mechanism of action of these compounds is based on inhibition of an enzyme called DNA gyrase which is essential for bacterial DNA replication [4]. It also appears some fluoroquinolones possess anticancer and even anti-HIV activities [5]. Despite that there are still certain undesired events in usage of fluoroquinolones for therapeutic purposes [6,7], fluoroquinolones are one of the most important antimicrobial agents with many advantages for clinical use [8,9].

Therefore, there has been a growing interest in the structure modification of the fluoroquinolone skeleton and in the development of its new derivatives with increasing efficacy in prevention of hospital-acquired infections induced by fluoroquinolone-resistant pathogens [10,11]. Recent studies have shown that substituents at the 7-position of the fluoroquinolone framework highly affect their biological activity, antimicrobial spectrum, strength and target preferences [12]. For example, piperazinyl moieties substitution at this position of fluoroquinolones increase their basicity, lipophilicity and their ability to penetrate cell walls which leads to a wide range of clinically beneficial fluoroquinolones such as ciprofloxacin, enrfoloxacin, levofloxacin, etc. [13-15].

In recent years, economic and environmental concerns encourage the application of heterogeneous catalysts to carry out various organic transformations [16]. These catalysts have very high catalytic activities due to their large specific surface area and make the processes clean,

---

[*]Corresponding author emails: nakhaei_a@yahoo.com
nakhaei_a@mshdiau.ac.ir
Tel./Fax: +98 51 3890 9410

safe, high-yielding and inexpensive [17]. Nowadays, application of magnetic nanocomposites as heterogeneous catalysts is an interesting research area. The surface functionalization of these materials is an elegant way to bridge the gap between heterogeneous and homogeneous catalysis [18].

As a part of our research in developing efficient methods of organic synthesis that involve reusable catalysts [19-23], we studied application of zirconia shell bearing sulfonic acid groups ($Fe_3O_4@ZrO_2–SO_3H$) as an efficient acid catalyst in the synthesis of some fluoroquinolones with short reaction time by the reaction of variety amines and some 7-halo-6-fluoroquinolone-3-carboxylic acids in the presence of ordinary water (OW) and also magnetized (MW) water as a solvent (Scheme 1). Nano-$Fe_3O_4@ZrO_2$-SO_3H (n-FZSA) could be readily separated from the reaction mixture by a permanent magnet and reused several times. The process is more effective than filtration and centrifugation in preventing loss of the solid catalyst. However, there were no reports on application of n-FZSA as an acidic heterogeneous catalyst in the synthesis of fluoroquinolones.

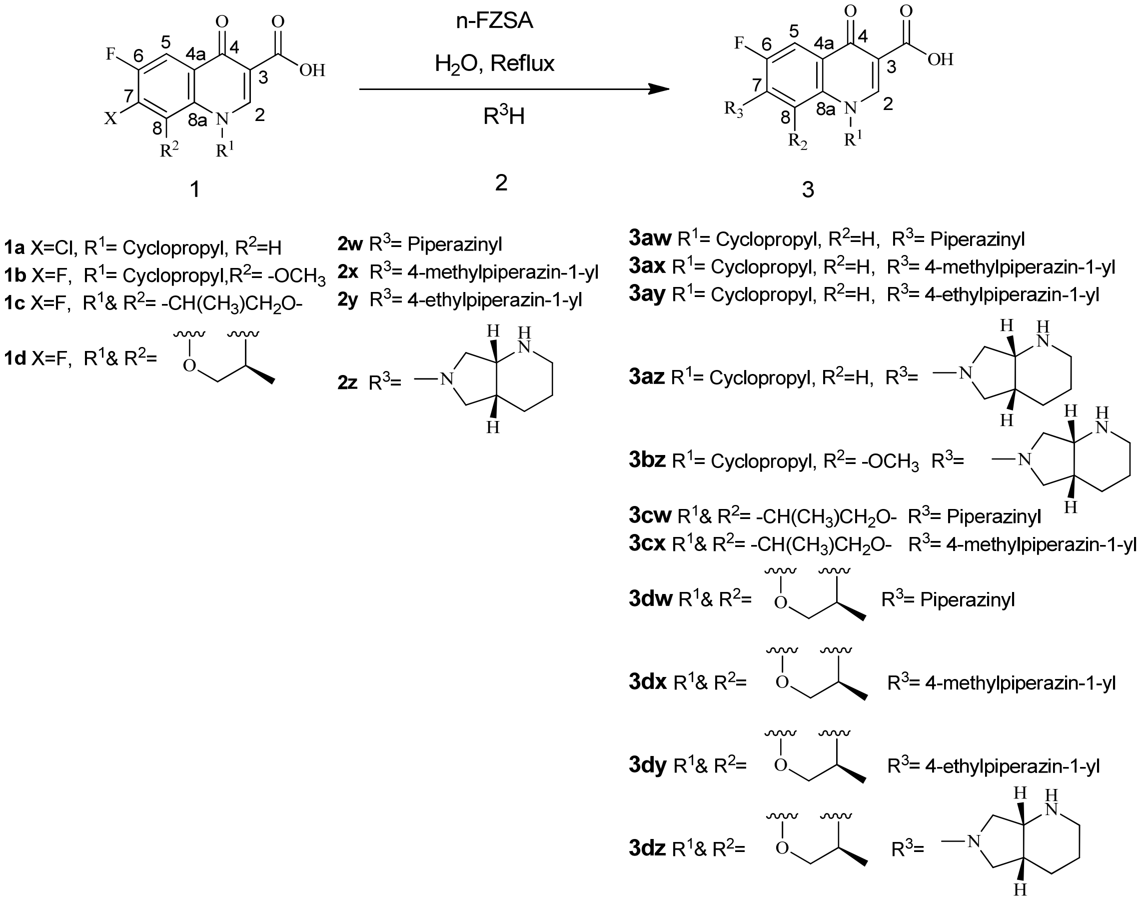
2. **Experimental**

2.1. Chemicals and apparatus

All chemicals were available commercially and used without additional purification. Melting points were recorded using a Stuart SMP3 melting point apparatus. The FT-IR spectra of the products were obtained with KBr disks using a Tensor 27 Bruker spectrophotometer. The ^{1}HNMR (300 MHz) and ^{13}CNMR (75 MHz) spectra were recorded using Bruker spectrometers.

2.2. Solvent magnetizing apparatus (SMA)

The permanent magnet in a compact form, a unit called "AQUA CORRECT", was used. This equipment is a coaxial static magnetic system with field strength of 0.6 Tor 6000 gauss (H.P.S Co., Germany). The equipment was connected from one end to the liquid pump and the other end to the pipelines of solvent reservoir. Solutions flowed through a coaxial static magnet and came back to the solvent reservoir. Therefore, solutions could pass through the field for many times, in a closed cycle (Fig. 1) [24].



Scheme 1. Synthesis of fluoroquinolone derivatives in the presence of n-FZSA under refluxing water.

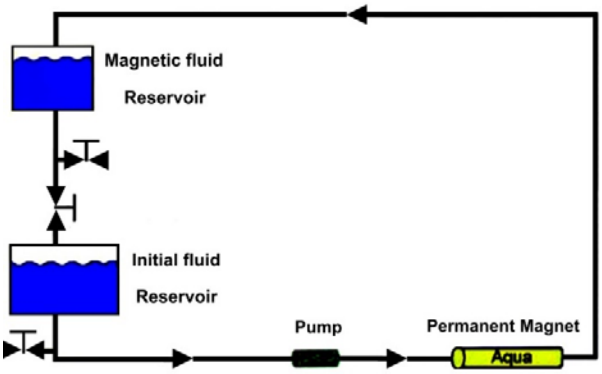


Fig. 1. The pilot of solvent magnetizing apparatus (SMA).

2.3. General experimental procedure

The catalyst was synthesized according to the literature [25]. A mixture of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **1a** (1 mmol) and *N*-ethylpiperazine **2y** (1.5 mmol) and n-FZSA (0.06 g) as catalyst in H_2O (5 ml) was heated under reflux for the appropriate time. The reaction was monitored by TLC. After the appropriate time, the catalyst was separated using an external magnet and washed with hot ethanol (5 mL). The reaction mixture was then cooled to room temperature. The precipitated solid was collected by filtration, and recrystallized from ethanol 96% to give the desired compound in high yields.

3. Results and Discussion

3.1. Characterization of the catalyst

The n-FZSA was characterized by FT-IR, X-ray diffraction (XRD), thermal gravimetric (TG), and pH analysis. The FT-IR spectrums of nano-ZrO_2, nano-Fe_3O_4, nano-Fe_3O_4@ZrO_2, and nano-Fe_3O_4@ZrO_2-SO_3H are shown in Fig. 2, curves a-d, respectively. In the curve a, the characteristic bands at 578 and 755 cm^{-1} were associated with stretching vibration of Zr–O, and also the band at 1627 cm^{-1} was attributed to the bending vibration of Zr–OH groups [26]. In curve b, the Fe_3O_4 shows the characteristic absorption band at 593 cm^{-1} relating to the Fe-O stretching vibration and a broad band attributed to the stretching vibrational of surface -OH groups at 3400-3600 cm^{-1} [27, 28]. The spectrum of the Fe_3O_4@ZrO_2 nanoparticles (Fig. 2(c)) shows a new absorption peak relating to the characteristic absorption of zirconia at 624 cm^{-1} which confirmed the successful formation of Fe_3O_4@ZrO_2 nanoparticles [29]. The FT-IR spectrum of the n-FZSA catalyst prepared in the current study revealed new bonds at 825–1325 and 2500–3500 cm^{-1} corresponding to the characteristic absorption of the O=S=O, S-O and O-H stretching vibration of the sulfonic groups, respectively [25].

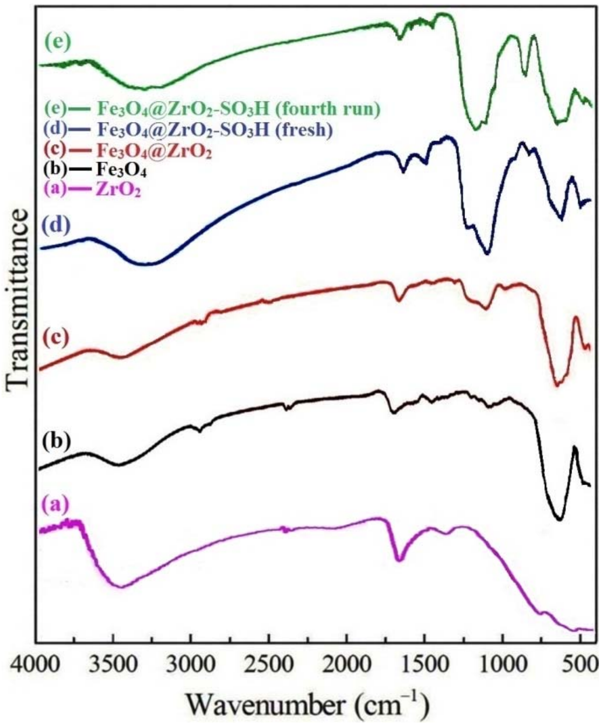


Fig. 2. FT-IR spectra of nano-ZrO_2 (a) nano-Fe_3O_4, (b) nano-Fe_3O_4@ZrO_2, (c) nano-Fe_3O_4@ZrO_2-SO_3H (first run (d)), nano-Fe_3O_4@ZrO_2-SO_3H (fourth run (e)).

The XRD patterns of the prepared nano-Fe_3O_4, nano-Fe_3O_4@ZrO_2, and nano-Fe_3O_4@ZrO_2-SO_3H are presented in Fig. 3. In Fig. 3(a), the signals at the values of 2θ which are equal to 30.23 (220), 35.10 (311), 43.26 (400), 53.51 (422), 56.06 (511) and 63.11 (440) correspond to the cubic structure of Fe_3O_4 and are good agreement with (JCPDS file PDF no. 65-3107) [30].

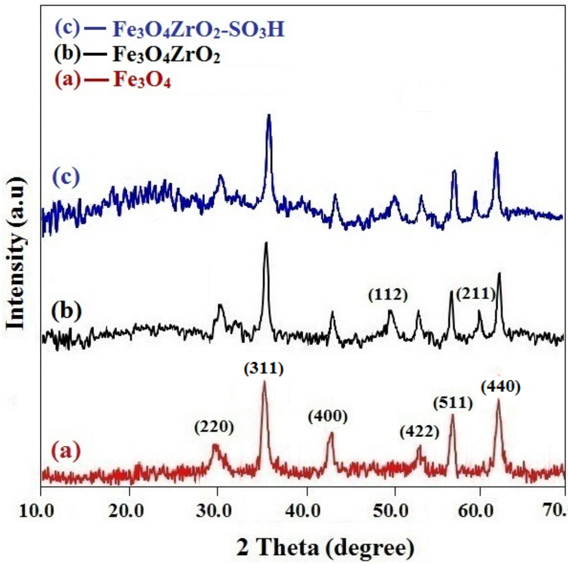


Fig. 3. XRD patterns of nano-Fe_3O_4 (a) nano-Fe_3O_4@ZrO_2 (b) nano-Fe_3O_4@ZrO_2-SO_3H (c)

The XRD pattern of the nano-Fe_3O_4@ZrO_2 sample shows that peaks at 31.02° and 36.23° belong to Fe_3O_4 which have shifted from 30.23° and 35.10°, respectively. Besides the peaks for Fe_3O_4, two small nonmagnetic related peaks located in 50.21° and 60.52°,can be indexed to the diffraction of (112) and (211) planes of the standard data for ZrO_2 (JCPDS file no. 88-1007) [31]. In the XRD patterns of nano-Fe_3O_4@ZrO_2-SO_3H, the peak positions are the same as those for the nano-Fe_3O_4@ZrO_2. Based on this observation, it can be concluded that after functionalization of the nano-Fe_3O_4@ZrO_2 support materials with chlorosulfonic acid, the core–shell crystalline structure of the nanomagnets essentially remains intact [25].

The TG curves of nano-Fe_3O_4@ZrO_2, and nano-Fe_3O_4@ZrO_2-SO_3H are shown in Fig. 4. In the TG curve of nano-Fe_3O_4@ZrO_2 (Fig. 4(a)) a two-stage decomposition is seen, corresponding to different mass loss ranges. In the first region, a mass loss, approximately 1% of weight, occurred below 120 °C is attributed to the loss of trapped water, organic solvents, and surface hydroxyl groups. A mass loss of approximately 1% weight occurred lower than 750 °C, this possibly related to the slow mass loss of dehydroxylation of ZrO_2. The TG curve of nano-Fe_3O_4@ZrO_2-SO_3H (Fig. 4(b)) was divided into several regions relating to different mass lose ranges. The first region, which occurred below 136 °C, showed a mass loss (2% weight) that is attributed to the evaporation of the H_2O, and organic solvents molecules adsorbed onto the surface and the release of the structural water resulted from the bonded hydroxyl groups. The mass loss of approximately 3% weight which occurred between 145 and 360 °C is related to the slow mass loss of SO_3H groups. Finally, the mass loss of approximately 22 % weight which occurred between 500 and 700 °C is related to the sudden loss of SO_3H groups. This mass loss confirms the coating of sulfonic acid groups on ZrO_2 [32]. From the TG, it can be concluded that the prepared catalyst could be safety used in organic reactions at temperatures up to 140 °C.

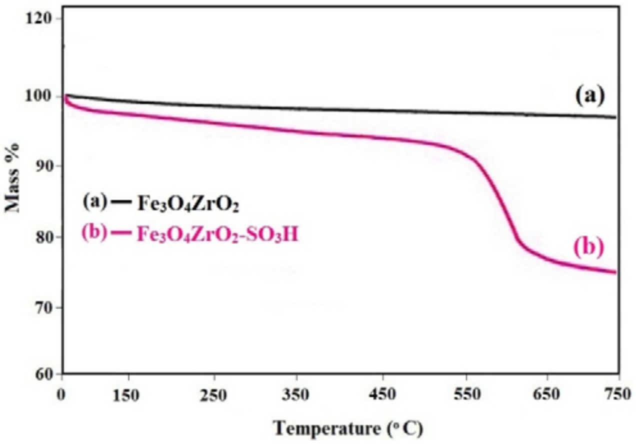


Fig. 4. Thermal gravimetric (TG) analysis of the n-FZSA.

The density of the SO_3H groups was measured using NaOH (0.1 N) as titrant by acid-base potentiometric titration. The amount of SO_3H in the catalyst was 4.83 mmol/g.

3.2. Evaluation of catalytic activity of n-FZSA in the synthesis of fluoroquinolone derivatives

Catalytic activity of this material was evaluated in the synthesis of fluoroquinolone derivatives. Synthesis of compound **3ay** was selected as a model reaction for optimizing the reaction conditions. The reaction was carried out with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **1a** (1 mmol) and *N*-ethylpiperazine **2y** (1.5 mmol) in the presence of different amounts of *n*-FZSA, and in various solvents such as H_2O, EtOH, MeOH, CH_3CN, CH_2Cl_2, and also under solvent-free conditions at different temperatures. Poor yield (below 40 %) of the product **3ay** was obtained in the absence of the catalyst in all cases. On the other hand, different amounts of the catalyst (0.02, 0.04, 0.06, and 0.08 g) in a solvent or under solvent-free condition at various temperatures improved the yields and time of the reaction. The best results under catalytic conditions (0.06 g of the catalyst) were reached upon refluxing in polar solvents, preferably water. Therefore, water has been selected as the preferred solvent. Two forms of water (ordinary or magnetized) were used for this reaction. In the final outcomes, the magnetized water showed better yield in shorter reaction time at the same conditions. Increase of the catalyst amount up to 0.08 g did not improve the product yield or shorten reaction time in both forms of water. All subsequent reactions were carried out under these optimized conditions (see Table 1).

n-FZSA efficiently catalyzed the reaction, giving the products **3** in high yields over relatively short reaction time in ordinary and also magnetized water as solvents. Overall, all prepared products displayed higher yields in shorter reaction times in the presence of magnetized water. Easy separation of obtained products from the catalyst made this method useful for the synthesis of fluoroquinolones. Purity of all products in the both forms of water as solvent was higher than 90% (HPLC). Melting points of the products **3** were close to those reported earlier [14, 33-38] and their structures were confirmed by FT-IR, ^1H and ^{13}C NMR spectra.

Table 1. *n*-FZSA catalyzed synthesis of fluoroquinolones.[a]

Entry	Product	Time (min)		Yield (%)		HPLC	
		OW[b]	MW[c]	OW[b]	MW[c]	OW[b]	MW[c]
1	**3aw**	22	20	94	95	96	95
2	**3ax**	25	19	91	94	96	97
3	**3ay**	19	16	97	97	97	96
4	**3az**	18	19	91	96	95	96
5	**3bz**	25	20	96	95	92	95
6	**3cw**	27	25	94	95	97	97
7	**3cx**	25	23	89	91	92	96
8	**3dw**	29	20	97	96	95	94
9	**3dx**	22	20	96	96	99	98
10	**3dy**	24	19	95	94	95	97
11	**3dz**	27	21	93	95	97	96

[a]Reaction conditions: 7-halo-6- fluoroquinolone-3-carboxylic acids, piperazine derivatives or (4aR,7aR)-octahydro-1H-pyrrolo[3,4-b] pyridine, and *n*-FZSA (0.06 g) in refluxing water.

[b]Ordinary water.

[c]Magnetized water.

The model reaction under optimized reaction conditions was used for evaluating reusability of *n*-FZPA catalyst. Upon completion of the reaction, the catalyst was recovered as described in the experimental section. The catalyst could be used at least four times without significant reduction in its activity. The results of the catalyst recovery in the presence of ordinary water were as 97, 95, 94, 94 % yields in the first to fourth use, respectively. FT–IR spectra of the catalyst after the fourth run (Fig. 2, curve **d**) was almost identical to the spectrum of the freshly prepared catalyst (Fig. 2, curve **e**). The magnetized water showed the same results.

Probably, the catalyst could act as a Brönsted acid relating to the $-SO_3H$ group and therefore promote the reactions. The catalyst would play a significant role in increasing the electrophilic character of the electrophiles in the reaction.

4. Conclusions

In this paper, we developed the synthesis of fluoroquinolone derivatives in the presence of n-FZSA as a highly effective heterogeneous catalyst for the direct amination of 7-halo-6-fluoroquinolone-3-carboxylic acids with several amines in ordinary or magnetized water as solvent. This method provided these products in high yields over short reaction time in the both forms of water, but the magnetized water showed better yields in the shorter reaction times. The catalyst is inexpensive and easily obtained, stable and storable. In addition, easy magnetic separation makes this catalyst attractive in view of green chemistry and catalysis science.

Acknowledgements

This research project is dedicated to (late) Dear Ardavan Mir.

References

[1] R. Breslow, Acc. Chem. Res. 24 (1991) 159-164.

[2] P.B. Fernandes, N. Shipkowitz, R.R. Bower, K.P. Jarvis, J. Weisz, D.T. Chu, J. Antimicrob. Chemother. 18 (1986) 693-701.

[3] K. Fujimaki, T. Noumi, I. Saikawa, M. Inoue, S. Mitsuhashi, Antimicrob. Agents Chemother. 32 (1988) 827-833.

[4] B. Llorente, F. Leclerc, R. Cedergren, Bioorg. Med. Chem. 4 (1996) 61-71.

[5] Y.-S. Oh, C.-W. Lee, Y.-H. Chung, S.-J. Yoon, S.-H. Cho, J. Heterocycl. Chem. 35 (1998) 541-550.

[6] R. Stahlmann, H. Lode, Drugs 58 (1999) 37-42.

[7] B.A. Lipsky, C.A. Baker, Clin. Infect. Dis. 28 (1999) 352-361.

[8] D.C. Hooper, J.S. Wolfson, N. Engl. J. Med. 324 (1991) 384-394.

[9] J.S. Wolfson, D.C. Hooper, Clin. Microbiol. Rev. 2 (1989) 378-424.

[10] A. Aubry, X.-S. Pan, L.M. Fisher, V. Jarlier, E. Cambau, Antimicrob. Agents Chemother. 48 (2004) 1281-1288.

[11] T.D. Gootz, R. Zaniewski, S. Haskell, B. Schmieder, J. Tankovic, D. Girard, P. Courvalin, R.J. Polzer, Antimicrob. Agents Chemother. 40 (1996) 2691-2697.

[12] L.A. Mitscher, Chem. Rev. 105 (2005) 559-592.

[13] F. Dubar, G. Anquetin, B. Pradines, D. Dive, J. Khalife, C. Biot, J. Med. Chem. 52 (2009) 7954-7957.

[14] A.V. Shindikar, C.L. Viswanathan, Bioorg. Med. Chem. Lett. 15 (2005) 1803-1806.

[15] D. Sriram, A. Aubry, P. Yogeeswari, L.M. Fisher, Bioorg. Med. Chem. Lett. 16 (2006) 2982-2985.

[16] I.W. Davies, L. Matty, D.L. Hughes, P.J. Reider, J. Am. Chem. Soc. 123 (2001) 10139-10140.

[17] M. Ledoux, C. Pham-Huu, Catal. Today 15 (1992) 263-284.

[18] C.S. Gill, B.A. Price, C.W. Jones, J. Catal. 251 (2007) 145-152.

[19] A. Nakhaei, A. Davoodnia, S. Yadegarian, Heterocycl. Lett. 7 (2017) 35-44.

[20] A. Nakhaei, A. Davoodnia, S. Yadegarian, Russ. J. Gen. Chem. 86 (2016) 2870-2876.

[21] A. Nakhaei, A. Davoodnia, A. Morsali, Res. Chem. Intermed. 41 (2015) 7815-7826.

[22] A. Nakhaei, A. Davoodnia, Chin. J. Catal. 35 (2014) 1761-1767.

[23] A. Nakhaei, Russ. J. Gen. Chem. 87 (2017) 1850-1856.

[24] M. Bakherad, A. Keivanloo, M. Gholizadeh, R. Doosti, M. Javanmardi, Res. Chem. Intermed. 43 (2017) 1013-1029.

[25] M.M. Hosseini, E. Kolvari, Chem. Lett. 46 (2017) 53-55.

[26] E.E. Platero, M.P. Mentruit, Catal. Lett. 30 (1994) 31-39.

[27] C. Garkoti, J. Shabir, S. Mozumdar, New J. Chem. 41 (2017) 9291-9298.

[28] P.L. Patnam, M. Bhatt, R. Singh, S. Saran, S.L. Jain, RSC Adv. 6 (2016) 60888-60895.

[29] A. Sarkar, S.K. Biswas, P. Pramanik, J. Mater. Chem. 20 (2010) 4417-4424.

[30] G.-Y. Li, Y.-R. Jiang, K.-L. Huang, P. Ding, L.-L. Yao, Colloid. Surf. A 320 (2008) 11-18.

[31] A.P. Kumar, J.H. Kim, T.D. Thanh, Y.-I. Lee, J. Mater. Chem. B 1 (2013) 4909-4915.

[32] M.A. Navarra, F. Croce, B. Scrosati, J. Mater. Chem. 17 (2007) 3210-3215.

[33] P.G. Reddy, S. Baskaran, Tetrahedron Lett. 42 (2001) 6775-6777.

[34] K. Kawakami, K. Namba, M. Tanaka, N. Matsuhashi, K. Sato, M. Takemura, Antimicrob. Agents Chemother. 44 (2000) 2126-2129.

[35] K. Grohe, H. Heitzer, Liebigs Ann. Chem. 1987 (1987) 29-37.

[36] I. Hayakawa, T. Hiramitsu, Y. Tanaka, Chem. Pharm. Bull. 32 (1984) 4907-4913.

[37] B. Guruswamy, R. Arul, Lett. Drug Des. Discov. 10 (2013) 86-93.

[38] Y.R. Kumar, V.V.N.K.V. Prasad Raju, R.R. Kumar, S. Eswaraiah, K. Mukkanti, M.V. Suryanarayana, M.S. Reddy, J. Pharm. Biomed. Anal. 34 (2004) 1125-1129.