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RESEARCH ARTICLE

Nano-Fe_3O_4@ZrO_2-SO_3H as Highly Efficient Recyclable Catalyst for the Green Synthesis of Fluoroquinolones

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Abstract: Nano-Fe_3O_4@ZrO_2-SO_3H (n-FZSA), was utilized as a magnetic catalyst for the synthesis of various fluoroquinolone compounds. These compounds were prepared by the direct amination of 7-halo-6-fluoroquinolone-3-carboxylic acids with piperazine derivatives and (4aR,7aR)-octahydro-1H-pyrrolo[3,4-b] pyridine in water. The results showed that n-FZSA exhibited high catalytic activity towards the synthesis of fluoroquinolone derivatives, giving the desired products in high yields. Furthermore, the catalyst was recyclable and could be used at least seven times without any discernible loss in its catalytic activity. Overall, this new catalytic method for the synthesis of fluoroquinolone derivatives provides rapid access to the desired compounds in refluxing water following a simple work-up procedure, and avoids the use of organic solvents.

Keywords: Fluoroquinolones, fast synthesis, green solvent, Fe_3O_4@ZrO_2-SO_3H, catalyst, antibacterial agent.

1. INTRODUCTION

The use of water as a green media for organic synthesis has become the most important study area. In addition to the economical and environmental advantages, water shows single physical and chemical properties which lead to exclusive reactivity and selectivity in assessment with organic solvents [1].

Fluoroquinolones have been a class of important synthetic antibacterial agents which are widely used in clinic for the treatment of infectious diseases [2]. These compounds act with an excellent activity against gram-negative and comparatively moderate against gram-positive bacteria [3]. Mechanism of action of these compounds is based on inhibition of DNA gyrase, an enzyme essential for bacterial DNA replication [4]. It also appears that some fluoroquinolones possess anticancer and even anti-HIV activities [5].

Despite the side effects in therapeutic purposes, fluoroquinolones are one of the most important antimicrobial agents with many advantages for clinical use. 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 to prevention of hospital-acquired infections induced by fluoroquinolone-resistant pathogens [6, 7]. 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 [8]. For example, the substitution of piperazinyl moieties at this position of fluoroquinolones increases their basicity, lipophilicity and their ability to penetrate into cell walls which leads to a wide range of clinically beneficial fluoroquinolone such as ciprofloxacin, enrofoloxacin, levofloxacin, *etc*. [9-17].

The current presentation is the development of our earlier studies of reusable catalysts for the synthesis of organic compounds [18-32], and as a result of global interest in the ongoing research towards the development of environmentally friendly methods for the synthesis of organic compounds that are frequently used in current pharmaceutical industry. We report herein a facile and efficient green synthesis of fluoroquinolones as potential antibacterial with short reaction time by the two-component condensation for a variety amines and some 7-halo-6-fluoroquinolone-3-carboxylic acids using *n*-FZSA as heterogeneous catalyst (Scheme **1**). This method therefore represents a significant improvement over the methods currently available for the synthesis of fluoroquinolone derivatives [9-12].

2. RESULTS AND DISCUSSION

2.1. Characterization of the Catalyst

For our investigations, the *n*-FZSA catalyst was prepared according to the literature procedure [33]. The *n*-FZSA was

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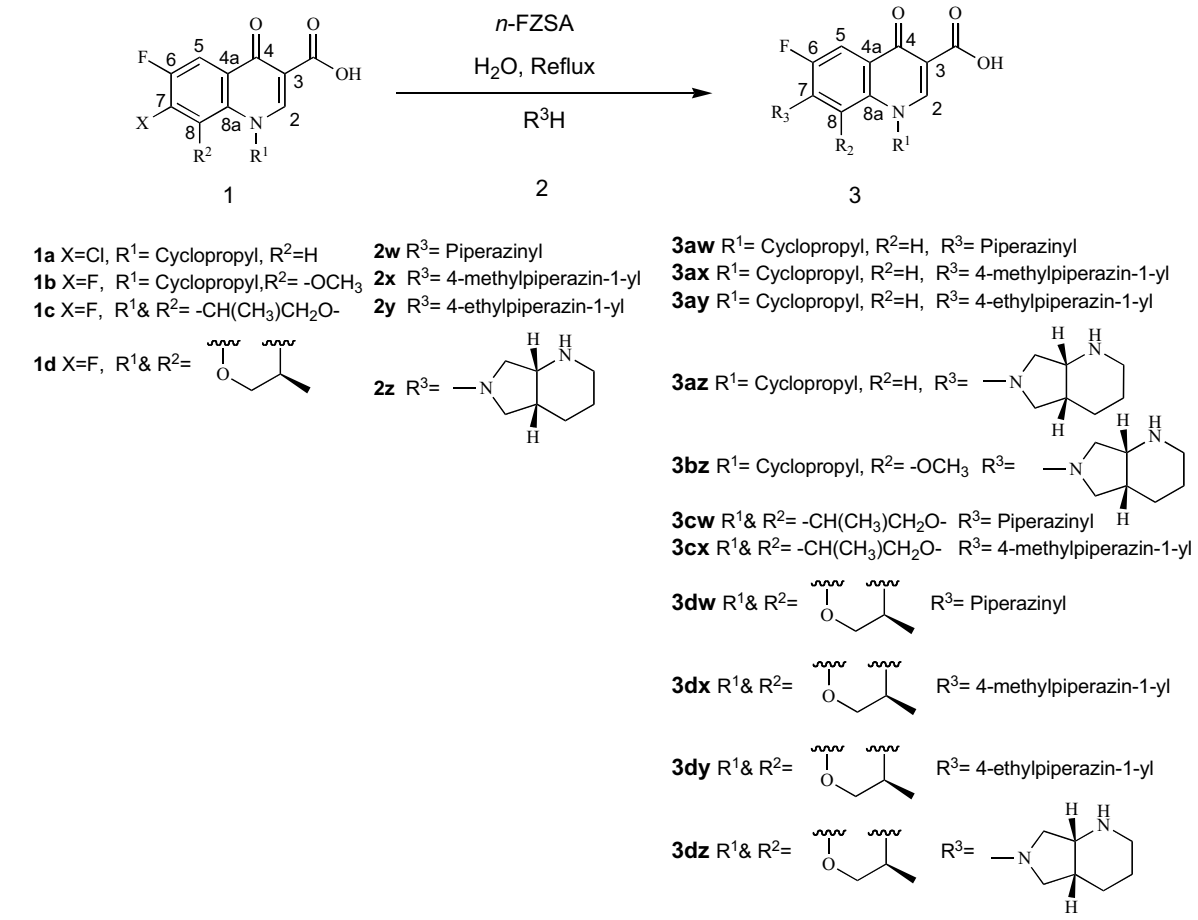


Scheme (1). Synthesis of fluoroquinolone derivatives in the presence of *n*-FZSA under refluxing water.

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. (**1**). In Fig. (**1a**), the characteristic bands at 578 and 755 cm^{-1} is associated with the stretching vibration of Zr-O, as well as the band at 1627 cm^{-1} attributed to the bending vibration of Zr-OH groups [34]. The characteristic absorption band of Fe_3O_4 appears at 593 cm^{-1} in Fig. (**1b**). The spectrum of the Fe_3O_4@ZrO_2 nanoparticles (Fig. **1c**) shows a new absorption peak related to the characteristic absorption of zirconia at 624 cm^{-1} which confirmed the successful formation of Fe_3O_4@ZrO_2 nanoparticles [35]. 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 [33].

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. (**2**). In Fig. (**2a**), the signals at the values of 2θ equal to 30.23 (220), 35.10 (311), 43.26 (400), 53.51 (422), 56.06 (511) and 63.11 (440) corresponds to cubic structure of Fe_3O_4 and has good agreement with (JCPDS file PDF no. 65-3107) [36]. The XRD pattern of the nano-Fe_3O_4@ZrO_2 sample shows peaks at 31.02˚ and 36.23˚ belonging 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˚ are found which can be indexed to the diffraction of (112) and (211) planes of the standard data for ZrO_2 (JCPDS file no. 88-1007) [37]. The peaks position of nano-Fe_3O_4@ZrO_2-SO_3H unchanged during modification by chlorosulfonic acid showing that the crystalline structure of the core-shell nanomagnetic is essentially maintained after functionalization.

The TG curves of nano-Fe_3O_4@ZrO_2, and nano-Fe_3O_4@ZrO_2-SO_3H are shown in Fig. (**3**). In the TG curve of nano-Fe_3O_4@ZrO_2 (Fig. **3a**) two-stage decomposition is seen corresponding to different mass lose ranges. In the first region, a mass loss approximately 1% weight occurred below 120°C is attributable to the loss of trapped water, organic solvents, and surface hydroxyl groups. A mass loss of approximately 1% weight occurred lower than 750°C 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. **3a**) was divided into several regions relating to different mass lose ranges. The first region, which occurred below 136°C, shows a mass loss 2% weight that is attributable 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 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 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 [38]. From the TG, it can be concluded that the prepared catalyst could be safely used in organic reactions at temperatures up to 140 °C.

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.

2.2. Evaluation of Catalytic Activity of n-FZSA in the Synthesis of Fluoroquinolone Derivatives

The 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 and also under solvent-free conditions (Table **1**). Long reaction times and poor yields of the product **3ay** were obtained in the absence of the catalyst in all cases (entries 1-5). Also, low yields of the desired product were obtained under solvent-free conditions in the presence or absence of the catalyst (entries 4-6). The presence of temperature was necessary for all situations. Therefore, the best results were reached under catalytic condition upon refluxing solvents, preferably polar solvents (entries 12-16). According to the final outcomes, the reaction was more facile and proceeded to give the highest yield (97%), and short reaction time (19 min), using 0.06 g of *n*-FZSA in H_2O (5 ml) at reflux temperature (entry 12). Increase of the catalyst amount up to 0.08 g did not improve the product yield or shorten reaction time (entry 12).

To show the catalytic advantage of the *n*-FZSA for this reaction, we compared the activity of this catalyst with nano-Fe_3O_4, nano-ZrO_2, and nano-Fe_3O_4@ZrO_2 under optimized condition. According to the optimization experiments, all nano-catalysts involved demonstrated good catalytic effects in the model reaction but the *n*-FZSA catalyst promoted the reaction more efficiently than the others, leading to higher yields of **3ay** (Table **2**).

According to these results, and to generalize this model reaction, we developed the reaction of **1a-d** with a range of various amines **2w-z** under the optimized reaction conditions (Table **3**). The condensation of **1a-d** and **2w-z** afforded the products **3** in refluxing water. The *n*-FZSA efficiently catalyzed the reactions, giving the desired products in high yields over relatively short reaction times. Easy separation of obtained products from the catalyst makes this method useful for the synthesis of fluoroquinolones. Purity checks with melting points, TLC, HPLC (>91%), and the ^{1}H NMR spectroscopic data reveal that only one product is formed in all cases and no undesirable side-products are observed. The structures of all known products **3** were deduced and compared with those of authentic samples from their melting points, ^{1}H NMR, ^{13}C NMR, and FT-IR spectral data [10-17].

Table 1. Optimization of reaction conditions for the synthesis of compound 3ay catalyzed by *n*-FZSA[*].

Entry	Catalyst (g)	Solvent	T/°C	Time/min	Isolated Yield/%
1	-----	EtOH	Reflux	135	32
2	-----	H_2O	Reflux	135	44
3	-----	H_2O	r.t.	180	34
4	-----	-----	100	150	16
5	-----	-----	120	150	19
6	0.06	-----	120	100	31
7	0.02	H_2O	Reflux	60	76
8	0.04	H_2O	Reflux	40	88
9	0.06	H_2O	80	45	89
10	0.06	H_2O	r.t.	30	78
11	0.08	H_2O	Reflux	20	96
12	**0.06**	**H_2O**	**Reflux**	**19**	**97**
13	0.06	EtOH	Reflux	25	83
14	0.06	MeOH	Reflux	40	63
15	0.06	CH_3CN	Reflux	50	51
16	0.06	CH_2Cl_2	Reflux	60	41

[*]Reaction conditions: Ethyl 7-chloro-6-fluoroquinolone-3-carboxylic acids **1a** (1 mmol) and *N*-ethylpiperazine **2y** (1.5 mmol).

Table 2. Catalytic activity of *n*-FZSA compared with the other catalysts under optimized condition.

Entry	Catalyst	Time/min	Isolated Yield/%
1	FZSA	19	97
2	Fe_3O_4@ZrO_2	20	90
3	Fe_3O_4	30	86
4	ZrO_2	30	85

Table 3. *n*-FZSA catalyzed synthesis of fluoroquinolones[a].

Entry	Product	Time (min)	Yield (%)
1	**3aw**	22	94
2	**3ax**	25	91
3	**3ay**	19	97
4	**3az**	18	91
5	**3bz**	25	96
6	**3cw**	27	94
7	**3cx**	25	89
8	**3dw**	29	97
9	**3dx**	22	96
10	**3dy**	24	95
11	**3dz**	27	93

[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.

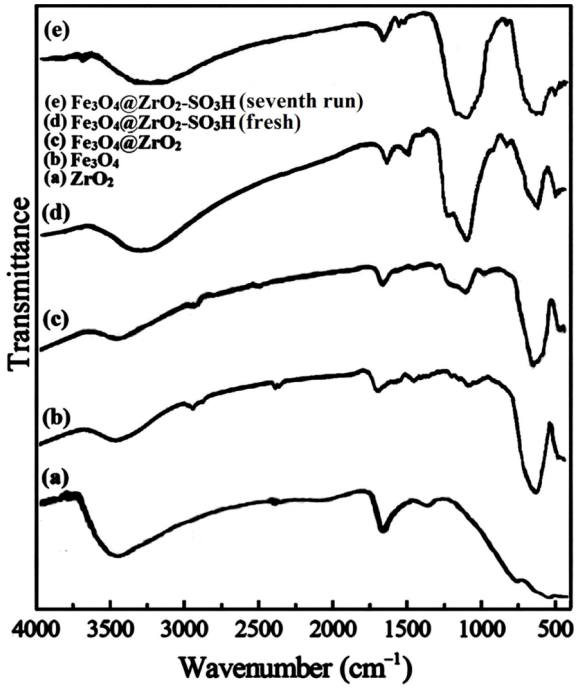


Fig. (1). FT-IR spectra of nano-ZrO_2 (**a**) nano-Fe_3O_4 (**b**) nano-Fe_3O_4@ZrO_2 (**c**) nano-Fe_3O_4@ZrO_2-SO_3H (first run (**d**)) nano-Fe_3O_4@ZrO_2-SO_3H (seventh run (**e**)).

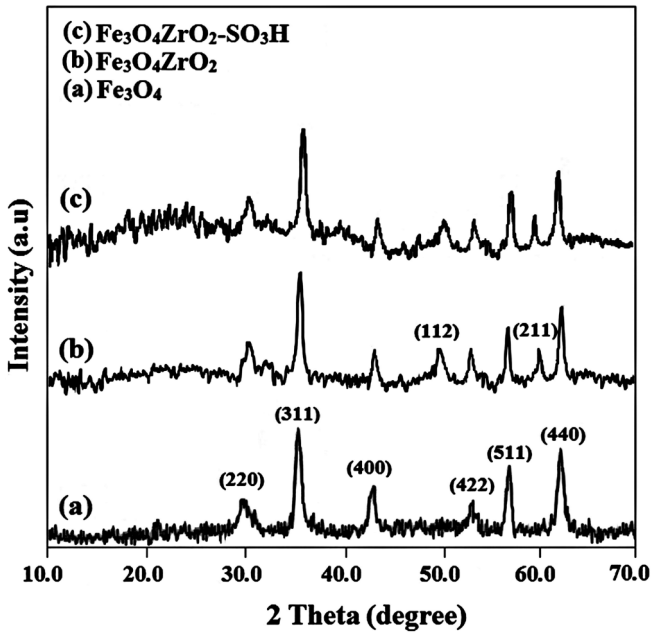


Fig. (2). XRD patterns of nano-Fe_3O_4 (**a**) nano-Fe_3O_4@ZrO_2 (**b**) nano-Fe_3O_4@ZrO_2-SO_3H (**c**).

We also used the model reaction under optimized reaction conditions to evaluate the reusability of the *n*-FZSA

catalyst. After completion of the reaction, the catalyst was recovered as described in the experimental section. The separated catalyst was washed with hot ethanol and subsequently dried at 50°C under vacuum for 1 h before being reused in a similar reaction. The catalyst could be used at least four times without significant reduction in its activity (97, 95, 95, 94, 93, 93, 91 % yields in first to seventh use, respectively) which clearly demonstrates the practical reusability of this catalyst. Furthermore, the FT-IR spectra of the seventh run recovered catalysts (Fig. **1e**) were almost identical to the spectrum of the fresh catalyst (Fig. **1d**), indicating that the structure of the catalyst was unchanged by the reaction.

Probably the catalyst could act as a Brönsted acid related 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 (Scheme **2**).

3. EXPERIMENTAL SECTION

3.1. Chemicals and Apparatus

All chemicals were commercially available and used without additional purification. The catalyst was synthesized according to the literature [33]. 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}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using Bruker spectrometers.

3.2. General Experimental Procedure

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) were heated under reflux for the appropriate time. The reaction was monitored by TLC. After 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 desired compound in high yields.

3.2.1. 1-Cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (3aw)

M.p: 254-256°C; FT-IR (ν, cm^{-1} KBr disc): 3335, 3033, 2912, 1623, 1447, 1271, 1144, 804; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.15-1.20 (m, 2H, CH_2), 1.30-1.35 (m, 2H, CH_2), 2.90 (t, J = 6.0 Hz, 4H, CH_2 ×2), 3.22 (t, J = 6.0 Hz, 4H, CH_2 ×2), 3.75-3.85 (m, 1H, CH), 7.47 (d, J_{HF} = 9.0 Hz, 1H, H-8), 7.75 (d, J_{HF} = 15.0 Hz, 1H, H-5), 8.58 (s, 1H, H-2); ^{13}C NMR (75 MHz, DMSO-d_6): 7.9 (CH_2), 36.2 (CH), 45.8 (CH_2 ×2), 51.1 (CH_2 ×2), 106.9 (C3), 107.1 (C8), 111.4 (C5), 118.7 (C4a), 139.6 (C8a), 146.1 (C7), 148.2 (C2), 154.0 (C6), 165.6 (COOH), 176.6 (C4); HPLC Purity: 96.52%; Anal. Calc. for $C_{17}H_{18}FN_3O_3$ (%): C, 61.62; H, 5.48; N, 12.68. Found: C, 61.54; H, 5.37; N, 12.62.

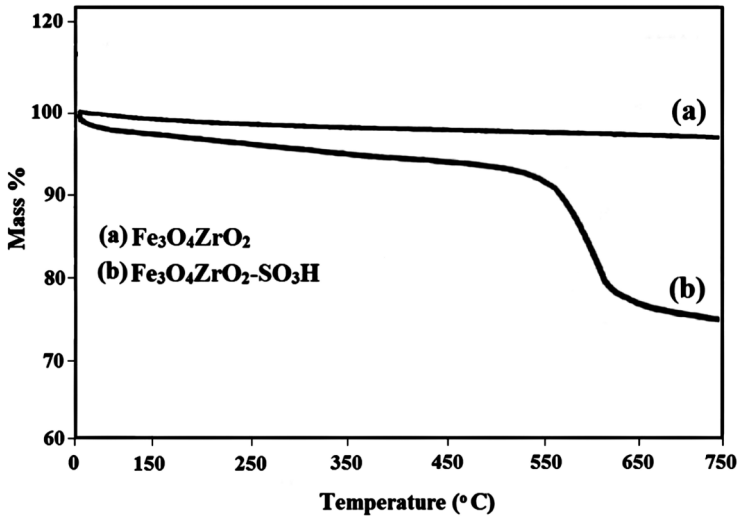
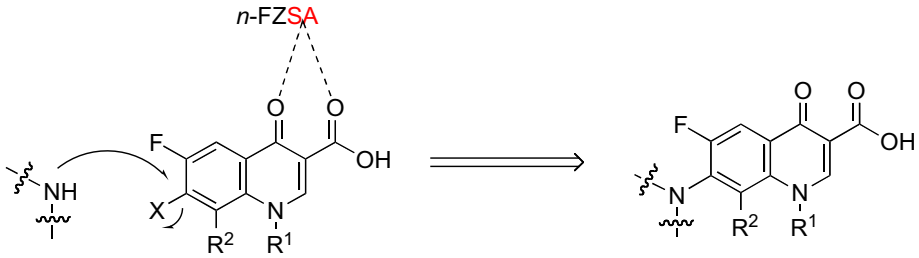


Fig. (3). Thermal gravimetric (TG) analysis of the *n*-FZSA.



Scheme (2). Plausible mechanism for the n-FZSA catalyzed formation of fluoroquinolones.

3.2.2. 1-Cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3ax)

HPLC Purity: 96.22%; m.p: 245-247°C; FT-IR (ν, cm^{-1} KBr disc): 3428, 3093, 2935, 1626, 1469, 1299, 1142, 885; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (s, 2H, CH_2), 1.32 (d, J = 9.0 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3), 2.20-2.35 (m, 4H, CH_2 ×2), 3.00-3.10 (m, 4H, CH_2 ×2), 3.75-3.85 (m, 1H, CH), 7.47 (d, J_{HF} = 6.0 Hz, 1H, H-8), 7.75 (d, J_{HF} = 12.0 Hz, 1H, H-5), 8.62 (s, 1H, H-2); ^{13}C NMR (75 MHz, DMSO-d_6): 8.0 (CH_2 ×2), 31.2 (CH_3), 36.3 (CH), 45.9 (CH_2 ×2), 49.4 (CH_2 ×2), 106.0 (C3), 107.1 (C8), 111.0 (C5), 118.0 (C4a), 139.6 (C8a), 146.1 (C7), 148.3 (C2), 151.0 (C6), 166.3 (COOH), 176.7 (C4); Anal. Calc. for $C_{18}H_{20}FN_3O_3$ (%): C, 62.60; H, 5.84; N, 12.17; Found: C, 62.53; H, 5.78; N, 12.11.

3.2.3. 1-Cyclopropyl-7-(4-ethylpiperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3ay)

M.p: 218-220°C; FT-IR (ν, cm^{-1} KBr disc): 3335, 3033, 2912, 1627, 1470, 1254, 1154, 803; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.05 (t, J = 7.0 Hz, 3H, CH_3), 1.10-1.35 (m, 4H, CH_2 ×2), 2.42 (q, J = 6.0 Hz, 2H, CH_2), 2.50-2.60 (m, 8H, CH_2 ×4, overlapped with solvent), 3.75-3.85 (m, 1H, CH), 7.55 (d, J_{HF} = 6.0 Hz, 1H, H-8), 7.88 (d, J_{HF} = 15.0 Hz, 1H, H-5), 8.65 (s, 1H, H-2), 15.23 (s br., 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6): 8.0 (CH_2 ×2), 12.4 (CH_3), 36.2 (CH), 40.7 (CH_2), 49.8-52.4 (CH_2 ×4), 106.5 (C3), 107.1 (C8), 111.3 (C5), 118.8 (C4a), 139.5 (C8a), 145.5 (C7), 148.1 (C2), 155.0 (C6), 166.3 (COOH), 176.5 (C4); HPLC Purity: 97.65%; Anal. Calc. for $C_{19}H_{22}FN_3O_3$ (%): C, 63.50; H, 6.17; N, 11.69; Found: C, 63.41; H, 6.09; N, 11.62.

3.2.4. 1-Cyclopropyl-6-fluoro-7-((4aR,7aR)-hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3az)

M.p: 258-260°C; FT-IR (ν, cm^{-1} KBr disc): 3308, 3076, 2938, 1629, 1412, 1336, 1180, 888; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10-1.35 (m, 4H, CH_2 ×2), 1.55-1.70 (m, 4H, CH_2 ×2), 1.88 (m, 1H, CH), 2.08 (m, 1H, CH), 2.50-2.60 (m, 1H, CH), 3.33 (t, J = 6.0 Hz, 2H, CH_2), 3.30-3.55 (m, 4H, CH_2 ×2), 3.63-3.75 (m, 1H, CH), 6.91 (d, J_{HF} = 6.0 Hz, 1H, H-8), 7.65 (d, J_{HF} = 15.0 Hz, 1H, H-5), 8.49 (s, 1H, H-2); HPLC Purity: 95.21%; Anal. Calc. for $C_{20}H_{22}FN_3O_3$ (%): C, 64.68; H, 5.97; N, 11.31; Found: C, 64.61; H, 5.59; N, 11.25.

3.2.5. 1-Cyclopropyl-6-fluoro-7-((4aR,7aR)-hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-8 methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3bz)

M.p: 239-241°C; FT-IR (ν, cm^{-1} KBr disc): 3470, 3033, 2929, 1624, 1457, 1324, 1186, 805; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.81-1.25 (m, 4H, CH_2 ×2), 1.63-1.85 (m, 4H, CH_2 ×2), 2.60-2.70 (m, 2H, CH_2), 3.10-3.20 (m, 1H, CH), 3.37 (s, 3H, CH_3), 3.60-3.65 (m, 1H, CH), 3.70-3.80 (m, 1H, CH), 3.80-3.97 (m, 2H, CH_2), 4.04-4.19 (m, 2H, CH_2), 7.63 (dd, J_{HF} = 12.0, 3.0 Hz, 1H, H-5), 8.64 (s, 1H, H-2), 15.15 (s br., COOH); ^{13}C NMR (75 MHz, DMSO-d_6): 8.8 (CH_2 ×2) 10.0 (CH_2), 17.2 (CH_2), 20.9 (CH), 34.6 (CH_2), 39.1 (CH), 41.1 (CH_2), 41.8 (CH), 54.4 (CH_2), 62.3 (CH_3), 106.8 (C3), 117.6 (C5), 134.9 (C4a), 137.1 (C8), 140.6 (C8a), 150.8 (C7), 151.7 (C2), 154.0 (C6), 166.3 (COOH), 176.4 (C4); HPLC Purity: 91.89%; Anal. Calc. for $C_{21}H_{24}FN_3O_4$ (%): C, 62.83; H, 6.03; N, 10.47; Found: C, 62.78; H, 5.94; N, 10.41.

3.2.6. 9-Fluoro-3-methyl-7-oxo-10-(piperazin-1-yl)-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (3cw)

M.p: 258-260°C; FT-IR (ν, cm^{-1} KBr disc): 3255, 3092, 2968, 1723, 1454, 1254, 1023, 805; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.44 (d, J = 6.0 Hz, 3H, CH_3), 2.80-2.85 (m, 4H, CH_2 ×2), 3.18-3.25 (m, 4H, CH_2 ×2, overlapped with solvent), 4.37 (d, J = 12.0 Hz, 1H, CH_2, diastereotopic proton), 4.58 (d, J = 12.0 Hz, 1H, CH_2, diastereotopic proton), 4.85-4.95 (m, 1H, CH), 7.51 (dd, J_{HF} = 12.0, 6.0 Hz, 1H, H-5), 8.91 (s, 1H, H-2); ^{13}C NMR (75 MHz, DMSO-d_6): 18.4 (CH_3), 46.6 (CH_2 ×2), 52.0 (CH_2 ×2), 55.2 (CH), 68.4 (CH_2), 103.6 (C5), 107.1 (C3), 120.0 (C4a), 125.2 (C8a), 132.3 (C7), 140.5 (C8), 146.5 (C2), 154.0 (C6), 166.5 (COOH), 176.7 (C4); HPLC Purity: 96.91%; Anal. Calc. for $C_{17}H_{18}FN_3O_4$ (%): C, 58.78; H, 5.22; N, 12.10; Found: C, 58.72; H, 5.17; N, 10.36.

3.2.7. 9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (3cx)

m.p: M.p: 253-255°C; FT-IR (ν, cm^{-1} KBr disc): 3335, 3043, 2968, 1622, 1469, 1255, 1146, 804; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.44 (d, J = 9.0 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.35-2.50 (m, 4H, CH_2 ×2), 3.20-3.40 (m, 4H, CH_2 ×2), 4.35 (dd, J = 12.0, 3.0 Hz, 1H, CH_2, diastereotopic proton), 4.59 (dd, J = 12.0, 3.0, 1H, CH_2, diastereotopic proton), 4.85-4.98 (m, 1H, CH), 7.52 (d, J_{HF} = 12.0 Hz, 1H, H-5), 8.95 (s, 1H, H-2), 15.17 (s br., 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6): 18.4 (CH_3), 46.5 (CH_3), 50.5 (CH_2 ×2), 55.2 (CH_2 ×2), 55.7 (CH), 68.4 (CH_2), 103.5 (C5), 107.0 (C3), 119.8 (C4a), 125.2 (C8a), 132.5 (C7), 140.5 (C8), 146.5 (C2), 154.2 (C6), 166.5 (COOH), 176.7 (C4); HPLC Purity: 92.63%; Anal. Calc. for $C_{18}H_{20}FN_3O_4$ (%): C, 59.83; H, 5.58; N, 11.63; Found: C, 59.77; H, 5.08; N, 11.58.

3.2.8. (S)-9-Fluoro-3-methyl-7-oxo-10-(piperazin-1-yl)-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (3dw)

M.p: 260-262°C; FT-IR (ν, cm^{-1} KBr disc): 3255, 3092, 2968, 1723, 1454, 1254, 1023, 805; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.45 (d, J = 6.0 Hz, 3H, CH_3), 2.75-2.85 (m, 4H, CH_2 ×2), 3.15-3.25 (m, 4H, CH_2 ×2, overlapped with solvent), 4.30-4.40 (m, 1H, CH_2, diastereotopic proton), 4.52-4.62 (m, 1H, CH_2, diastereotopic proton), 4.85-4.95 (m, 1H, CH), 7.51 (d, J_{HF} = 12.0 Hz, 1H, H-5), 8.92 (s, 1H, H-2); ^{13}C NMR (75 MHz, DMSO-d_6): 18.4 (CH_3), 45.8 (CH_2 ×2), 51.0 (CH_2 ×2), 55.2 (CH), 68.5 (CH_2), 103.6 (C5), 107.2 (C3), 120.2 (C4a), 125.2 (C8a), 132.3 (C7), 140.5 (C8), 146.5 (C2), 154.2 (C6), 166.5 (COOH), 176.7 (C4); HPLC Purity: 94.96%; Anal. Calc. for $C_{17}H_{18}FN_3O_4$ (%): C, 58.78; H, 5.22; N, 12.10; Found: C, 58.70; H, 4.93; N, 11.51.

3.2.9. (S)-9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (3dx)

M.p: 225-227°C; FT-IR (ν, cm^{-1} KBr disc): 3251, 3079, 2973, 1721, 1439, 1289, 1087, 801; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.44 (d, *J* = 6.0 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.35-2.50 (m, 4H, CH_2 ×2), 3.20-3.30 (m, 4H, CH_2 ×2), 4.36 (dd, *J* = 12.0, 3.0 Hz, 1H, CH_2, diastereotopic proton), 4.59 (dd, *J* = 12.0, 3.0 Hz, 1H, CH_2, diastereotopic proton), 4.85-4.95 (m, 1H, CH), 7.48 (d, J_{HF} = 12.0 Hz, 1H, H-5), 8.94 (s, 1H, H-2), 15.15 (s br., 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6): 18.4 (CH_3), 46.5 (CH_3), 50.5 (CH_2 ×2), 55.2 (CH_2 ×2), 55.7 (CH), 68.4 (CH_2), 103.8 (C5), 107 (C3), 120 (C4a), 125.2 (C8a), 132.3 (C7), 140.4 (C8), 146.5 (C2), 154.2 (C6), 166.5 (COOH), 176.7 (C4); HPLC Purity: 99.01%; Anal. Calc. for $C_{18}H_{20}FN_3O_4$ (%): C, 59.83; H, 5.58; N, 11.63; Found: C, 59.78; H, 5.50; N, 11.56.

3.2.10. (S)-10-(4-Ethylpiperazin-1-yl)-9-fluoro-3-methyl-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (3dy)

M.p: 230-232°C; FT-IR (ν, cm^{-1} KBr disc): 3432, 3042, 2975, 1623, 1478, 1243, 1200, 743; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.05 (t, *J* = 6.0 Hz, 3H, CH_3), 1.45 (d, *J* = 9.0 Hz, 3H, CH_3), 2.35-2.40 (m, 2H, CH_2, overlapped with solvent), 2.40-2.60 (m, 4H, CH_2 ×2), 3.15-3.20 (m, 4H, CH_2 ×2), 4.37 (d, *J* = 12.0 Hz, 1H, CH_2, diastereotopic proton), 4.57 (d, *J* = 9.0 Hz, 1H, CH_2, diastereotopic proton), 4.91 (d, 1H, *J* = 6.0 Hz, CH), 7.56 (d, J_{HF} = 12.0 Hz, 1H, H-5), 8.94 (s, 1H, C2H); ^{13}C NMR (75 MHz, DMSO-d_6): 12.2 (CH_3), 18.4 (CH_3), 46.5 (NCH_2), 50.5 (CH_2 ×2), 53.4 (CH_2 ×2), 55.3 (CH), 68.5 (CH_2), 103.0 (C5), 107.0 (C3), 125.2 (C4a), 126.8 (C8a), 132.3 (C7), 140.0 (C8), 146.7 (C2), 154.0 (C6), 166.5 (COOH), 176.6 (C4); HPLC Purity: 95.21%; Anal. Calc. for $C_{19}H_{22}FN_3O_4$ (%): C, 60.79; H, 5.91; N, 11.19; Found: C, 60.72; H, 5.84; N, 11.11.

3.2.11. (S)-9-Fluoro-10-((4aR,7aR)-hexahydro-1H-pyrrolo-[3,4-b]pyridin-6(2H)-yl)-3-methyl-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (3dz)

M.p: 265-267°C; FT-IR (ν, cm^{-1} KBr disc): 3319, 3044, 2932, 1622, 1472, 1191, 1087, 862; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.30-1.70 (m, 4H, CH_2 ×2), 1.45 (d, *J* = 6.0 Hz, 3H, CH_3), 2.10-2.20 (m, 1H, CH), 2.80-2.90 (m, 1H, CH), 3.15-3.40 (m, 4H, CH_2 ×2), 4.00-4.15 (m, 2H, CH_2), 4.23 (d, *J* = 12.0 Hz, 1H, CH_2, diastereotopic proton), 4.59 (d, *J* = 12.0 Hz, 1H, CH_2, diastereotopic proton), 4.80-4.92 (m, 1H, CH), 7.47 (d, J_{HF} = 15 Hz, 1H, H-5), 8.85 (s, 1H, H-2); HPLC Purity: 97.23%; Anal. Calc. for $C_{20}H_{22}FN_3O_4$ (%): C, 62.01; H, 5.72; N, 10.85; Found: C, 61.96; H, 5.74; N, 10.78.

CONCLUSION

In this work 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 refluxing water. This method provided these products in high yields over short reaction time, following a facile work-up process. The catalyst is inexpensive and easily obtained, stable and storable. Also, easy magnetic separation makes this catalyst attractive in view of green chemistry and catalysis science.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Breslow, R. *Acc. Chem. Res*., **1991**, *24*(6), 159-164.
[2] Fernandes, P.B.; Shipkowitz, N.; Bower, R.R.; Jarvis, K.P.; Weisz, J.; Chu, D.T. *J. Antimicrob. Chemother*., **1986**, *18*(6), 693-701.
[3] Fujimaki, K.; Noumi, T.; Saikawa, I.; Inoue, M.; Mitsuhashi, S. *Antimicrob. Agents Chemother*., **1988**, *32*(6), 827-833.
[4] Llorente, B.; Leclerc, F.; Cedergren, R. *Bioorg. Med. Chem*., **1996**, *4*(1), 61-71.
[5] Oh, Y.-S.; Lee, C.-W.; Chung, Y.-H.; Yoon, S.-J.; Cho, S.-H. *J. Heterocycl. Chem*., **1998**, *35*(3), 541-550.
[6] Aubry, A.; Pan, X.-S.; Fisher, L.M.; Jarlier, V.; Cambau, E. *Antimicrob. Agents Chemother*., **2004**, *48*(4), 1281-1288.
[7] Gootz, T.D.; Zaniewski, R.; Haskell, S.; Schmieder, B.; Tankovic, J.; Girard, D.; Courvalin, P.; Polzer, R.J. *Antimicrob. Agents Chemother*., **1996**, *40*(12), 2691-2697.
[8] Mitscher, L.A. *Chem. Rev*., **2005**, *105*(2), 559-592.
[9] Dubar, F.; Anquetin, G.; Pradines, B.; Dive, D.; Khalife, J.; Biot, C. *J. Med. Chem*., **2009**, *52*(24), 7954-7957.
[10] Shindikar, A.V.; Viswanathan, C.L. *Bioorg. Med. Chem. Lett*., **2005**, *15*(7), 1803-1806.
[11] Sriram, D.; Aubry, A.; Yogeeswari, P.; Fisher, L.M. *Bioorg. Med. Chem. Lett*., **2006**, *16*(11), 2982-2985.
[12] Kumar, Y.R.; Prasad, R.V.V.N.K.V.; Kumar, R.R.; Eswaraiah, S.; Mukkanti, K.; Suryanarayana, M.V.; Reddy, M.S. *J. Pharm. Biomed. Anal*., **2004**, *34*(5), 1125-1129.
[13] Guruswamy, B.; Arul, R. *Lett. Drug Des. Discov*., **2013**, *10*(1), 86-93.
[14] Hayakawa, I.; Hiramitsu, T.; Tanaka, Y. *Chem. Pharm. Bull*., **1984**, *32*(12), 4907-4913.
[15] Grohe, K.; Heitzer, H. *Liebigs Ann. Chem*., **1987**, *1987*(1), 29-37.
[16] Kawakami, K.; Namba, K.; Tanaka, M.; Matsuhashi, N.; Sato, K.; Takemura, M. *Antimicrob. Agents Chemother*., **2000**, *44*(8), 2126-2129.
[17] Reddy, P.G.; Baskaran, S. *Tetrahedron Lett*., **2001**, *42*(38), 6775-6777.
[18] Nakhaei, A.; Yadegarian, S.; Davoodnia, A. *Heterocycl. Lett*., **2016**, *6*(3), 329-339.
[19] Nakhaei, A.; Hosseininasab, N.; Yadegarian, S. *Heterocycl. Lett*., **2017**, *7*(1), 81-90.
[20] Nakhaei, A.; Farsinejad, S.; Ramezani, S. *Curr. Green Chem*., **2017**, *4*(3), 130-136.
[21] Nakhaei, A.; Davoodnia, A.; Yadegarian, S. *Heterocycl. Lett*., **2016**, *6*(4), 601-608.
[22] Nakhaei, A.; Davoodnia, A.; Yadegarian, S. *Heterocycl. Lett*., **2017**, *7*(1), 35-44.
[23] Nakhaei, A.; Davoodnia, A.; Yadegarian, S. *Russ. J. Gen. Chem*., **2016**, *86*(12), 2870-2876.
[24] Nakhaei, A.; Davoodnia, A.; Morsali, A. *Res. Chem. Intermediat*., **2015**, *41*(10), 7815-7826.
[25] Nakhaei, A.; Davoodnia, A. *Chin. J. Catal*., **2014**, *35*(10), 1761-1767.

[26] Davoodnia, A.; Yadegarian, S.; Nakhaei, A.; Tavakoli-Hoseini, N. *Russ. J. Gen. Chem*., **2016**, *86*(12), 2849-2854.
[27] Davoodnia, A.; Nakhaei, A.; Tavakoli-Hoseini, N. *Z. Naturforsch. B,* **2016**, *71*(3), 219-225.
[28] Davoodnia, A.; Nakhaei, A. *Synth. React. Inorg. M*., **2016**, *46*(7), 1073-1080.
[29] Ahmadi, T.; Davoodnia, A.; Pordel, M.; Fattahi, M.; Ebrahimi, M.; Tavakoli-Hoseini, N.; Nakhaei, A. *Heterocycl. Lett*., **2017**, *7*(1), 27-34.
[30] Yadegarian, S.; Davoodnia, A.; Nakhaei, A. *Orient. J. Chem*., **2015**, *31*(1), 573-579.
[31] Rohaniyan, M.; Davoodnia, A.; Nakhaei, A. *Appl. Organomet. Chem*., **2016**, *30*(8), 626-629.
[32] Mirzaie, Y.; Lari, J.; Vahedi, H.; Hakimi, M.; Nakhaei, A.; Rezaei-fard, A. *J. Mex. Chem. Soc*., **2017**, *61*(1), 35-40.
[33] Hosseini, M.M.; Kolvari, E. *Chem. Lett*., **2017**, *46*(1), 53-55.
[34] Platero, E.E.; Mentruit, M.P. *Catal. Lett.,* **1994**, *30*(1), 31-39.
[35] Sarkar, A.; Biswas, S.K.; Pramanik, P. *J. Mater. Chem*., **2010**, *20*(21), 4417-4424.
[36] Li, G.-Y.; Jiang, Y.-R.; Huang, K.-L.; Ding, P.; Yao, L.-L. *Colloid Surf. A Physicochem. Eng. Asp.,* **2008**, *320*(1-3), 11-18.
[37] Kumar, A.P.; Kim, J.H.; Thanh, T.D.; Lee, Y.-I. *J. Mater. Chem. B,* **2013**, *1*(38), 4909-4915.
[38] Navarra, M.A.; Croce, F.; Scrosati, B. *J. Mater. Chem*., **2007**, *17*(30), 3210-3215.