An Efficient Green Approach for the Synthesis of Fluoroquinolones Using Nano Zirconia Sulfuric Acid as Highly Efficient Recyclable Catalyst in two Forms of Water

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ABSTRACT: *Various antibacterial fluoroquinolone compounds were prepared by the direct amination of 7-halo-6- fluoroquinolone-3-carboxylic acids with a variety of piperazine derivatives and (4aR,7aR)-octahydro-1H-pyrrolo[3,4-b] pyridine using Zirconia Sulfuric Acid (ZrSA) nanoparticle, as a catalyst in the presence of ordinary or magnetized water upon reflux condition. The results showed that ZrSA exhibited high catalytic activity towards the synthesis of fluoroquinolone derivatives in two forms of water. However, the magnetized water showed better results. Furthermore, the catalyst was recyclable and could be reused at least three 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 harmful organic solvents. This method, therefore, represents a significant improvement over the methods currently available for the synthesis of fluoroquinolone derivatives.*

KEYWORDS: *Fluoroquinolone derivatives; Antibacterial; Fast and green synthesis; Zirconia sulfuric acid (ZrSA); Ordinary or magnetized water.*

INTRODUCTION

Fluoroquinolones have been a class of important synthetic antibacterial agents which are widely used in the clinic for the treatment of infectious diseases [1, 2]. These compounds act with excellent activity against gram negative and comparatively moderate against gram-positive bacteria [3–7]. Mechanism of action of these compounds is based on the inhibition of an enzyme essential for bacterial DNA replication called DNA gyrase [8].

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It also appears that some fluoroquinolones possess anticancer and even anti-HIV activities [9–11].

Despite the fact that there are still certain undesired events in the usage of fluoroquinolones for 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 structural modification of the fluoroquinolone skeleton and in the development of its new derivatives with increasing efficacy to the prevention of hospital-acquired infections induced by fluoroquinolone-resistant pathogens [12–14]. 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 [15]. For example, piperazinyl moieties substitution at this position of fluoroquinolones which increase their basicity, lipophilicity and their ability to penetrate into cell walls which leads to a wide range of clinically beneficial fluoroquinolone such as ciprofloxacin, enrofloxacin, levofloxacin, etc. [16–18].

Many synthetic protocols have been developed to accelerate the rate of amination of fluoroquinolones and to improve the yield [19–29]. Major drawbacks of these procedures include expensive reagents, use of large amounts of toxic organic solvents, prolonged heating and side reactions or using the microwave. These disadvantages are not acceptable in the current pharmaceutical industry. Therefore, the development of a new greener and more convenient method for the synthesis of fluoroquinolones is highly desirable.

Acid-catalysts which are one of the most frequently applied processes in the chemical industry have been a major area of research interest [30–32]. Commonly, liquid inorganic acids including H_2SO_4, HCl, and H_3PO_4 are part of the homogeneous acid catalysts. Despite their application in the wide production of industrial chemicals, many disadvantages such as high toxicity, corrosive nature, hazards in handling and difficult separation from the products make them not so useful. Furthermore, the synthesis using homogeneous catalysts have a major problem of catalyst recovery and reuse. These difficulties are not in the range of green chemistry. According to these disadvantages, in order to improve drawbacks of these catalysts, replacement of them by novel, nontoxic, eco-friendly, recyclable heterogeneous catalysts with improved efficiency have been the important topics of researchers during the last decades. Heterogeneous catalysts show an important role in many aspects of environmental and economic in many industrial processes. They presented some excellence including great reactivity, operational simplicity, low toxicity, non-corrosive nature and the potential of the recyclability. Furthermore, most of the heterogeneous catalysts show better product selectivity, so that by-product can be easily separated [33–38]. One of the important routes for developing novel heterogeneous catalysts is immobilizing of homogenous precursors on solid support [39–43].

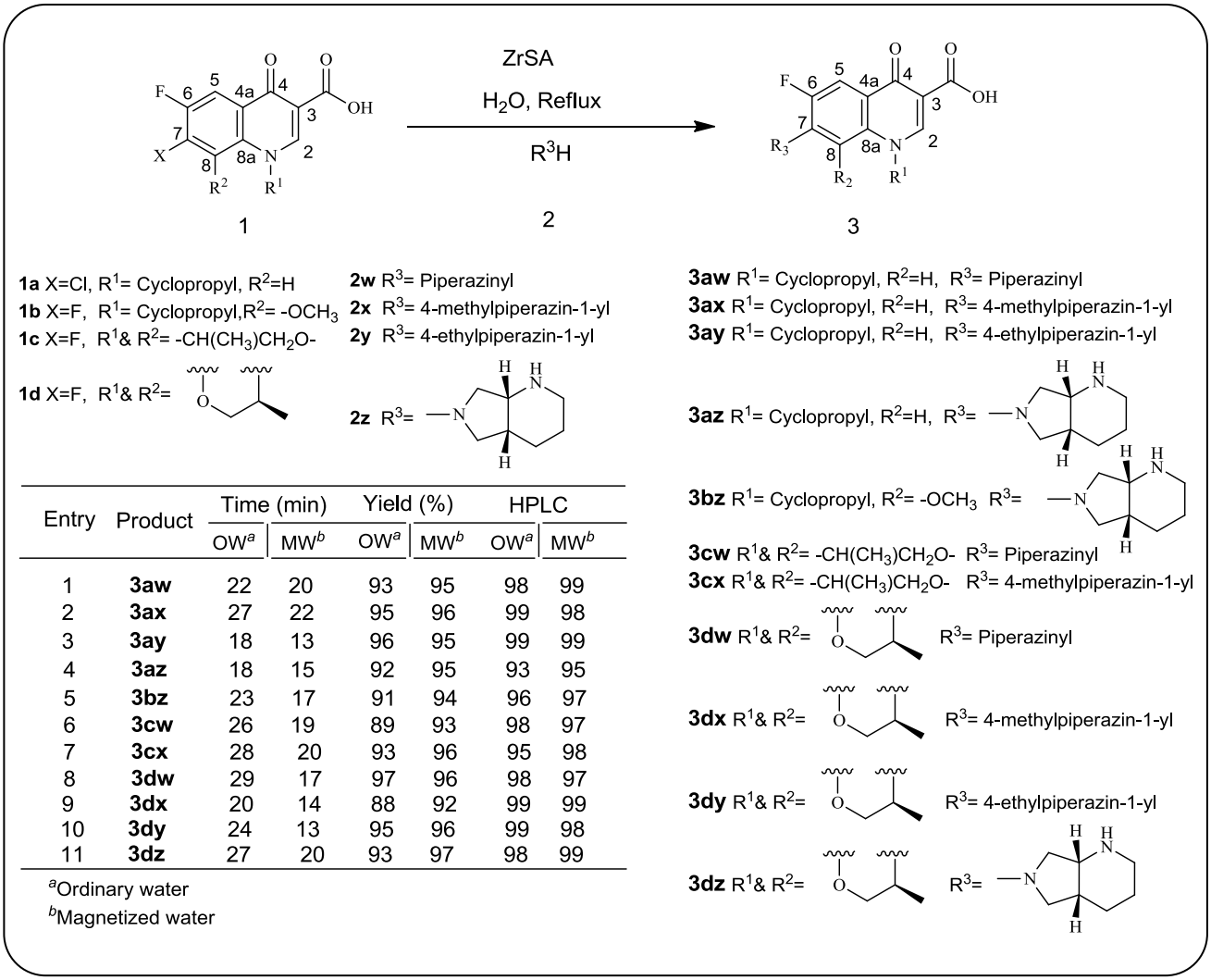
The metal oxide nanoparticles such as TiO_2, MgO, Al_2O_3, and ZnO are reported as useful heterogeneous catalyst agents in the synthesis of organic compounds [44-46]. Zirconia (ZrO_2) is one of the most important metal oxide nanoparticles with high surface area, mechanical strength, and thermal stability which have wide application in the chemical industry especially as a catalyst [47].

As part of our research program on the development of convenient methods using reusable catalysts for the synthesis of organic compounds [48–56], and as a result of global interest in the ongoing research towards the development of environmentally friendly methods for the synthesis of organic compounds, we report herein facile and efficient green synthesis of fluoroquinolones as potential antibacterial with short reaction time by the two- component condensation of variety amines and some 7-halo-6-fluoroquinolone-3-carboxylic acids using Zirconia Sulfuric Acid (ZrSA), as heterogeneous catalysts with high catalytic activity under reflux condition in ordinary or magnetized water. In the final, both forms of water exhibited excellent outcomes, but the magnetized water showed higher yields in shorter reaction times (Scheme 1).

EXPERIMENTAL SECTION

Chemicals and apparatus

All chemicals were available commercially and used without additional purification. The catalyst was synthesized according to the literature [57]. 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 ^1H NMR (300 MHZ) and ^{13}C NMR (75 MHZ) spectra were recorded using Bruker spectrometers.



Entry	Product	Time (min)		Yield (%)		HPLC	
		OW[a]	MW[b]	OW[a]	MW[b]	OW[a]	MW[b]
1	**3aw**	22	20	93	95	98	99
2	**3ax**	27	22	95	96	99	98
3	**3ay**	18	13	96	95	99	99
4	**3az**	18	15	92	95	93	95
5	**3bz**	23	17	91	94	96	97
6	**3cw**	26	19	89	93	98	97
7	**3cx**	28	20	93	96	95	98
8	**3dw**	29	17	97	96	98	97
9	**3dx**	20	14	88	92	99	99
10	**3dy**	24	13	95	96	99	98
11	**3dz**	27	20	93	97	98	99

[a]Ordinary water
[b]Magnetized water

Scheme 1: Synthesis of fluoroquinolone derivatives in the presence of ZrSA under refluxing ordinary or magnetized water.

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 the solvent reservoir. Solutions flow through a coaxial static magnetic and come back to the solvent reservoir. Therefore, the solution could pass through the field many times, in a closed cycle [59].

General

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 ZrSA (0.08 g) as catalyst in 5 ml of H_2O (ordinary or magnetized) was heated under reflux for the appropriate time. The reaction was monitored by TLC. After completion of the transformation, the catalyst was removed by filtration and then the reaction mixture was allowed to cool down into room temperature. finally, the crude product was collected by filtration and washed with H_2O and recrystallized from ethanol to give the desired compound **3ay**.

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

m.p.: 254-256 °C (lit. [23] 255-257 °C); FT-IR (ν, cm^{-1} KBr disc): 3533, 3335, 3033, 2912, 1705, 1623, 1494, 1447, 1383, 1271, 1144, 1024, 804; ^1H 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, $2CH_2$), 3.22 (t, *J* = 6.0 Hz, 4H, $2CH_2$), 3.75-3.85 (m, 1H, CH), 7.47 (d, *J* = 9.0 Hz, 1H, C8H), 7.75 (d, *J* = 15.0 Hz, 1H, C5H), 8.58 (s, 1H, C2H); ^{13}C NMR (75 MHz, DMSO-d_6): 7.9 (CH_2), 36.2 (NCH), 45.8 ($2NCH_2$), 51.1 ($2NCH_2$), 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); 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.

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

m.p.: 245-247 °C (lit. [22] 248-250 °C); FT-IR (ν, cm^{-1} KBr disc): 3428, 3093, 2935, 1729, 1626, 1507, 1469, 1378, 1299, 1142, 1007, 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, NCH_3), 2.20-2.35 (m, 4H, $2CH_2$), 3.00-3.10 (m, 4H, $2CH_2$), 3.75-3.85 (m, 1H, CH), 7.47 (d, *J* = 6.0 Hz, 1H, C8H), 7.75 (d, *J* = 12.0 Hz, 1H, C5H), 8.62 (s, 1H, C2H); ^{13}C NMR (75 MHz, DMSO-d_6): 8.0 ($2CH_2$), 31.2 (NCH_3), 36.3 (NCH), 45.9 ($2NCH_2$), 49.4 ($2NCH_2$), 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.

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

m.p.: 218-220 °C (lit. [22] 219-221 °C); FT-IR (ν, cm^{-1} KBr disc): 3533, 3335, 3033, 2912, 1738, 1627, 1470, 1381, 1337, 1254, 1154, 1022, 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, $2CH_2$), 2.42 (q, *J* = 6.0 Hz, 2H, NCH_2), 2.50-2.60 (m, 8H, $4CH_2$, overlapped with solvent), 3.75-3.85 (m, 1H, CH), 7.55 (d, *J* = 6.0 Hz, 1H, C8H), 7.88 (d, *J* = 15.0 Hz, 1H, C5H), 8.65 (s, 1H, C2H), 15.23 (s br., 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6): 8.0 ($2CH_2$), 12.4 (CH_3), 36.2 (NCH), 40.7 (NCH_2), 49.8-52.4 ($4NCH_2$), 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); 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.

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 (lit. [24] 256-258 °C); FT-IR (ν, cm^{-1} KBr disc): 3504, 3308, 3076, 2938, 1719, 1629, 1549, 1509, 1412, 1336, 1180, 1108, 888; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10-1.35 (m, 4H, $2CH_2$), 1.55-1.70 (m, 4H, $2CH_2$), 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, $2CH_2$), 3.63-3.75 (m, 1H, CH), 6.91 (d, *J* = 6.0 Hz, 1H, C8H), 7.65 (d, *J* = 15.0 Hz, 1H, C5H), 8.49 (s, 1H, C2H); 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.

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 (lit. [29] 238-242 °C); FT-IR (ν, cm^{-1} KBr disc): 3529, 3470, 3033, 2929, 1708, 1624, 1517, 1457, 1353, 1324, 1186, 1047, 805; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.81-1.25 (m, 4H, $2CH_2$), 1.63-1.85 (m, 4H, $2CH_2$), 2.60-2.70 (m, 2H, CH_2), 3.10-3.20 (m, 1H, CH), 3.37 (s, 3H, OCH_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* = 12.0, 3.0 Hz, 1H, C5H), 8.64 (s, 1H, C2H), 15.15 (s br., COOH); ^{13}C NMR (75 MHz, DMSO-d_6): 8.8 ($2CH_2$) 10.0 (CH_2), 17.2 (CH_2), 20.9 (CH), 34.6 (NCH_2), 39.1 (NCH), 41.1 (NCH_2), 41.8 (NCH), 54.4 (NCH_2), 62.3 (OCH_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); 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.

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 (lit. [27] 257-260 °C); FT-IR (ν, cm^{-1} KBr disc): 3255, 3092, 2968, 1723, 1573, 1454, 1392, 1254, 1023, 1011, 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, $2CH_2$), 3.18-3.25 (m, 4H, $2CH_2$, 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* = 12.0, 6.0 Hz, 1H, C5H), 8.91

(s, 1H, C2H); ^{13}C NMR (75 MHz, DMSO-d_6): 18.4 (CH_3), 46.6 ($2NCH_2$), 52.0 ($2NCH_2$), 55.2 (NCH), 68.4 (OCH_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); 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.

*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.: 253-255 °C (lit. [27] 250-257 °C); FT-IR (ν, cm^{-1} KBr disc): 3419, 3335, 3043, 2968, 1714, 1622, 1523, 1469, 1371, 1255, 1146, 1056, 804; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.44 (d, *J* = 9.0 Hz, 3H, CH_3), 2.22 (s, 3H, NCH_3), 2.35-2.50 (m, 4H, $2CH_2$), 3.20-3.40 (m, 4H, $2CH_2$), 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* = 12.0 Hz, 1H, C5H), 8.95 (s, 1H, C2H), 15.17 (s br., 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6): 18.4 (CH_3), 46.5 (NCH_3), 50.5 ($2NCH_2$), 55.2 ($2NCH_2$), 55.7 (NCH), 68.4 (OCH_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); 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.

*(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 (lit. [29] 263-265 °C); FT-IR (ν, cm^{-1} KBr disc): 3255, 3092, 2968, 1723, 1573, 1454, 1392, 1254, 1023, 1011, 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, $2CH_2$), 3.15-3.25 (m, 4H, $2CH_2$, 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* = 12.0 Hz, 1H, C5H), 8.92 (s, 1H, C2H); ^{13}C NMR (75 MHz, DMSO-d_6): 18.4 (CH_3), 45.8 ($2NCH_2$), 51.0 ($2NCH_2$), 55.2 (NCH), 68.5 (OCH_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); 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.

*(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 (lit. [25] 225-226 °C); FT-IR (ν, cm^{-1} KBr disc): 3251, 3079, 2973, 1721, 1539, 1517, 1439, 1394, 1289, 1087, 1004, 801; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.44 (d, *J* = 6.0 Hz, 3H, CH_3), 2.22 (s, 3H, NCH_3), 2.35-2.50 (m, 4H, $2CH_2$), 3.20-3.30 (m, 4H, $2CH_2$), 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* = 12.0 Hz, 1H, C5H), 8.94 (s, 1H, C2H), 15.15 (s br., 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6): 18.4 (CH_3), 46.5 (NCH_3), 50.5 ($2NCH_2$), 55.2 ($2NCH_2$), 55.7 (NCH), 68.4 (OCH_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); 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.

*(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 (lit. [26] 229-230 °C); FT-IR (ν, cm^{-1} KBr disc): 3432, 3042, 2975, 1714, 1623, 1529, 1478, 1306, 1243, 1200, 1010, 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, $2CH_2$), 3.15-3.20 (m, 4H, $2CH_2$), 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* = 12.0 Hz, 1H, C5H), 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 ($2NCH_2$), 53.4 ($2NCH_2$), 55.3 (NCH), 68.5 (OCH_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); 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.

*(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 (lit. [24] 265-268 °C); FT-IR (ν, cm^{-1} KBr disc): 3319, 3044, 2932, 1719, 1622, 1527, 1472, 1357, 1191, 1087, 1045, 862; ^{1}H NMR (300 MHz,

DMSO-d_6): δ 1.30-1.70 (m, 4H, $2CH_2$), 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, $2CH_2$), 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), 7.4 (d, *J* = 15 Hz, 1H, C5H), 8.85 (s, 1H, C2H); 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.

RESULTS AND DISCUSSION

Characterization of the catalyst

For our investigations, the catalyst ZrO_2–SO_3H (ZrSA) was prepared according to the literature procedure [57]. The ZrSA catalyst was characterized by FT-IR and pH analysis. The FT-IR spectrum of the nano-ZrO_2 and ZrO_2–SO_3H are shown in Fig. 1(1) and (2), respectively. In Fig. 1(1), the characteristic vibrational bands of the Zr–O appears at 576 and 752 cm^{-1}, as well band belonging to the Zr–OH group at 1627 cm^{-1}. The FT-IR spectrum of the catalyst which contained absorbance band at 3421 cm^{-1}, indicated the presence of water. These observations proved nano-ZrO_2 structures which are consistent with the previously reported evidence [57, 58]. The FT-IR spectrum of the ZrSA catalyst prepared in the current study (Fig. 1(2)) revealed new bonds at 820-890 and 1060–1180 cm^{-1} which are related to the O=S=O asymmetric and symmetric stretching vibration and S–O stretching vibration of the sulfonic groups (–SO_3H), respectively. The appeared broadband around 2700–3600 cm^{-1} related to the OH stretching absorption of the SO_3H group. All these specifications acknowledge nano-ZrO_2 structure that has functionalized with sulfonic acid groups. 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 2.45 mmol/g.

Evaluation of the catalytic activity of ZrSA in the synthesis of fluoroquinolone derivatives

The catalytic activity of this material was evaluated in the synthesis of fluoroquinolone derivatives. At first, the synthesis of compound **3ay** was selected as a model reaction to determine the most suitable reaction conditions. The reaction was carried out by the mixture of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **1a** (1 mmol) and

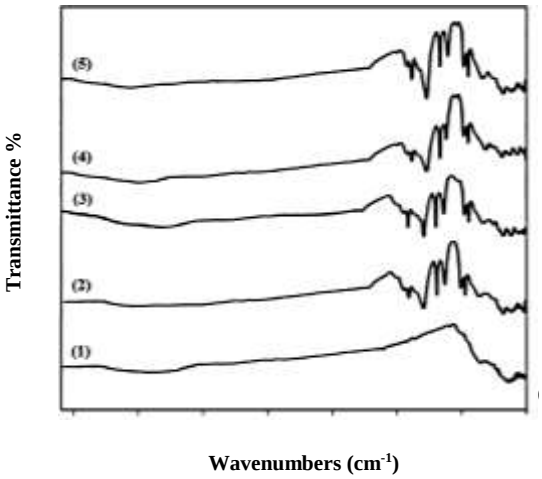


Fig. 1: FT-IR spectra of ZrO_2 (1), fresh catalyst ZrSA ((2), first run), and recovered catalysts (3-5).

N-ethyl piperazine **2y** (1.5 mmol) in the presence of different amounts of ZrSA, and various solvents such as EtOH, H_2O, $MeOHCH_3CN$, CH_2Cl_2, and also under solvent-free conditions at a different temperature. Long reaction times (>130 min) and not so good yields (< 40 %) of the product **3ay** were 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, 0.08, and 0.1) in the presence of the solvents or solvent-free condition in various temperatures caused to improve the yields and times of the reaction. Moreover, the best results in the presence of different amounts of catalyst were in refluxing solvents. These outcomes show that catalyst, solvent, and temperature are necessary for this reaction it is worth mentioning that polar solvents were better than non-polar. Solvents. Also, the best yields and short reaction times were obtained in 0.08 g of the catalyst in water at different temperature. Besides, a further increase in catalyst amount to 0.1 g, did not improve the product yield and reaction time. Among the tested solvents and also solvent-free conditions and various amounts of the catalyst, the reaction was more facile and proceeded to give the highest yield, and short reaction time, using 0.08 g of ZrSA in 5 ml of H_2O at reflux temperature. All subsequent reactions were carried out in these optimized conditions.

According to these results, and in order 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. The condensation of **1a-d** and **2w-z** afforded the products **3** in high yields over relatively

short reaction times in refluxing of two forms of water. But, in the final outcomes, the magnetized water exhibited higher yields in shorter reaction times for all of the desired products.

The ZrSA 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 (>93%), 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 [18–29]. We also used the model reaction under optimized reaction conditions to evaluate the reusability of the ZrSA 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 five times without significant reduction in its activity (97, 96, 94, 94, 93 % yields in first to fourth use, respectively) which clearly demonstrates the practical reusability of this catalyst. Furthermore, the FT-IR spectra of the recovered catalysts (Fig.1 (3)–(5)) were almost identical to the spectrum of the fresh catalyst (Fig.1(2)), indicating that the structure of the catalyst was unchanged by the reaction.

Although we did not investigate the reaction mechanism, the ZrSA could act as Brönsted acid and therefore promote the necessary reactions. The catalyst would play a significant role in increasing the electrophilic character of the electrophiles in the reaction.

CONCLUSIONS

In conclusion, in this paper we developed the synthesis of fluoroquinolone derivatives **3aw, 3ax, 3az, 3bz, 3cw, 3cx, 3dw, 3dx, 3dy, and 3dz** in the presence of Zirconia Sulfuric Acid (ZrSA) as a highly effective heterogeneous catalyst for the direct amination of 7-halo-6-fluoroquinolone-3-carboxylic acids **1a-d** with several amines **2w-z** in refluxing ordinary or magnetized water. This method provided these products in high yields over short reaction time in both forms of water, following a facile work-up process. However, the magnetized water showed better results. The catalyst is inexpensive and easily obtained, stable and storable, easily recycled and reused for several cycles with consistent activity.

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