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Application of ZrO_2–SO_3H as highly efficient recyclable nano-catalyst for the green synthesis of fluoroquinolones as potential antibacterial

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*

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Abstract

Various antibacterial fluoroquinolone compounds were prepared 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 using Zirconia Sulfuric Acid (ZrSA) nanoparticle, as a catalyst in refluxing water. The results showed that ZrSA exhibited high catalytic activity towards the synthesis of fluoroquinolone derivatives, with the desired products being formed in high yields. 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).

Introduction

Fluoroquinolones have been a class of important synthetic antibacterial agents which are widely used in clinic for the treatment of infectious diseases [1,2]. These compounds act with an excellent activity against gram-negative and comparatively moderate against gram-positive bacteria [3–7]. Mechanism of action of these compounds is based on inhibition of an enzyme essential for bacterial DNA replication called DNA gyrase [8]. 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 structure modification of the fluoroquinolone skeleton and in the development of its new derivatives with increasing efficacy to prevent hospital-acquired infections induced by

*Corresponding author: Ahmad Nakhaei
Tel: +98 (51) 38909410, Fax: +98 (51) 38909410
E-mail: nakhaei_a@yahoo.com, nakhaei_a@mshdiau.ac.ir

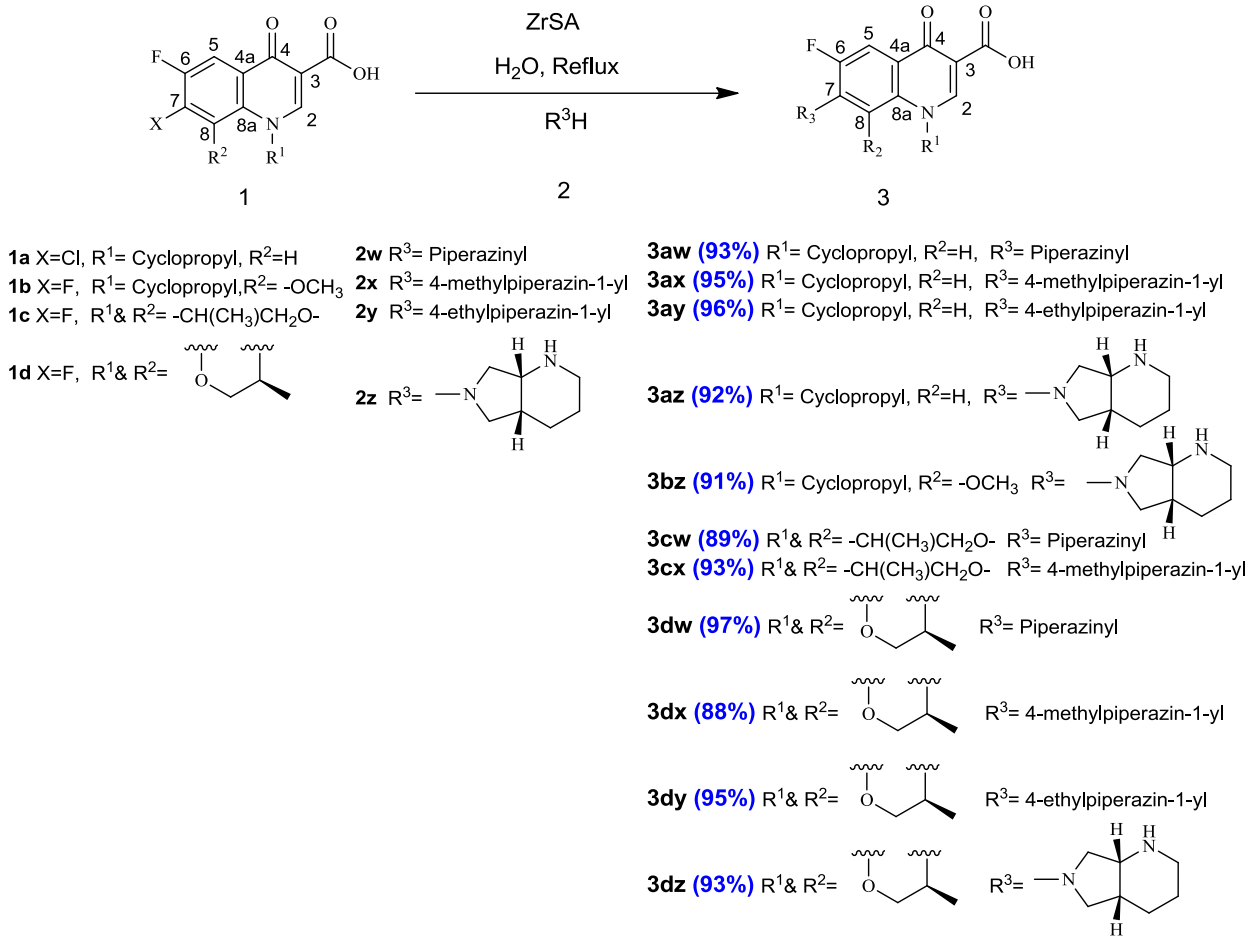
fluoroquinolone-resistant pathogens [12–14]. Recent studies have shown that substituents at the 7-position of the fluoroquinolone framework highly affect their biological activity, antimicrobial spectrum, strength and target preferences [15]. For example, piperazinyl moieties substitution at this position of fluoroquinolones which increase their basicity, lipophilicity and their ability to penetrate into cell walls leads to a wide range of clinically beneficial fluoroquinolone such as ciprofloxacin, enrfoloxacin, 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 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 chemical industry have been a major area of research interest [30–32]. Heterogeneous catalysts show 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 a 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 which (ZrO_2) is one of the most important metal oxide nanoparticles with high surface area, mechanical strength and thermal stability has wide applications in chemical industry especially as catalyst [47].

As a 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 especially compounds that are frequently used in current pharmaceutical industry, we report herein a facile and efficient green synthesis of fluoroquinolones as a potential antibacterial with short reaction time having 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 high yield (Scheme 1).



Scheme 1. Synthesis of fluoroquinolone derivatives in the presence of ZrSA under refluxing water

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 ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using Bruker spectrometers.

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 ZrSA (0.08 g) as catalyst in H_2O (5 mL) was heated under reflux for the appropriate time. The reaction was monitored by TLC. Upon completion of the transformation, hot ethanol was added and the catalyst filtered through sintered glass Büchner funnel under hot conditions. The catalyst was washed with a small portion of hot ethanol. After cooling, the combined filtrate was allowed to stand at room temperature. The precipitated solid was collected by filtration, and recrystallized from ethanol to give compound **3ay** in high yields.

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

HPLC Purity: 98.59%; Yield: 93%; 21 min; 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; ^{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, $2CH_2$), 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)

HPLC Purity: 97.28%; Yield: 95%; 27 min; 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)

HPLC Purity: 98.97%; Yield: 96%; 18 min; 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)

HPLC Purity: 92.96%; Yield: 91%; 18 min; 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)

HPLC Purity: 95.86%; Yield: 91%; 23 min, 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)

HPLC Purity: 97.29%; Yield: 89%; 26 min; 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)

HPLC Purity: 94.78%; Yield: 93%; 28 min; 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)

HPLC Purity: 98.32%; Yield: 97%; 29 min; 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)

HPLC Purity: 99.97%; Yield: 88%; 20 min; 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)

HPLC Purity: 99.25%; Yield: 95%; 24 min; 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)

HPLC Purity: 98.96%; Yield: 93%; 27 min; 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), 7.47 (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

In this research work, the catalyst ZrO_2–SO_3H (ZrSA) was prepared according to the literature procedure [57]. The ZrSA catalyst was characterized by FT-IR, XRD, and pH analysis. The FT-IR spectrum of the nano-ZrO_2 and ZrO_2–SO_3H are shown in Figure 1(1) and (2), respectively. In Figure 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 evidences [57, 58]. The FT-IR spectrum of the ZrSA catalyst prepared in the current study (Figure 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 broad band 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 XRD pattern of ZrSA nanoparticles is shown in Figure 2. The following peak intensities (011), (110), (111), (111), (-111), (002), (200), (021), (211), (-102), (121), (-112), (202), (220), (-202), (013), (113), (311), (222), (-222), (-132) have good agreement with the previous reported evidence [57] which confirm the formation of ZrSA nano-catalyst.

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 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 suitable reaction conditions. The reaction was carried out by 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) in the presence of different amounts of ZrSA, and various solvents such as EtOH, H_2O, MeOH, CH_3CN, CH_2Cl_2, and also under solvent-free conditions at different temperature (Table 1). 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 (Entries 1-5). 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 other non-polars. Also, the best yields and short reaction times were obtained in 0.08 g of the catalyst in water at different temperature. Besides, 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 (96%), and short reaction time (18 min), using 0.08 g of ZrSA in H_2O (5 mL) at reflux temperature (Entry 12). All subsequent reactions were carried out in these optimized conditions.

Table 1. Optimization of reaction conditions for the synthesis of compound 3ay catalyzed by ZrSA

Entry	Catalyst (g)	Solvent	T/°C	Time/min	Isolated Yield/%
1	None	EtOH	Reflux	135	29
2	None	H_2O	Reflux	135	39
3	None	H_2O	r.t.	160	34
4	None	Solvent-free	100	150	17
5	None	Solvent-free	120	150	19
6	0.06	Solvent-free	120	100	26
7	0.08	Solvent-free	120	100	32
8	0.08	Solvent-free	100	100	26
9	0.02	H_2O	Reflux	80	61
10	0.04	H_2O	Reflux	33	74
11	0.06	H_2O	Reflux	20	90
12	0.08	H_2O	Reflux	18	96
13	0.08	H_2O	80	37	90
14	0.08	H_2O	r.t.	40	82
15	0.1	H_2O	Reflux	30	96
16	0.04	EtOH	Reflux	62	57
17	0.06	EtOH	Reflux	53	71
18	0.08	EtOH	Reflux	42	84
19	0.08	EtOH	r.t.	50	75
20	0.06	MeOH	Reflux	58	65
21	0.08	MeOH	Reflux	53	81
22	0.08	MeOH	r.t.	61	74
24	0.06	CH_3CN	Reflux	69	49
25	0.08	CH_3CN	Reflux	65	78
25	0.08	CH_3CN	r.t.	73	66
26	0.06	CH_2Cl_2	Reflux	72	45
27	0.08	CH_2Cl_2	Reflux	60	56
28	0.08	CH_2Cl_2	r.t.	79	49

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

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 water. 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 (96, 95, 94, 94 % 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 (Figure 1(3)–(5)) were almost identical to the spectrum of the fresh catalyst (Figure 1(2)), indicating that the structure of the catalyst was unchanged by the reaction.

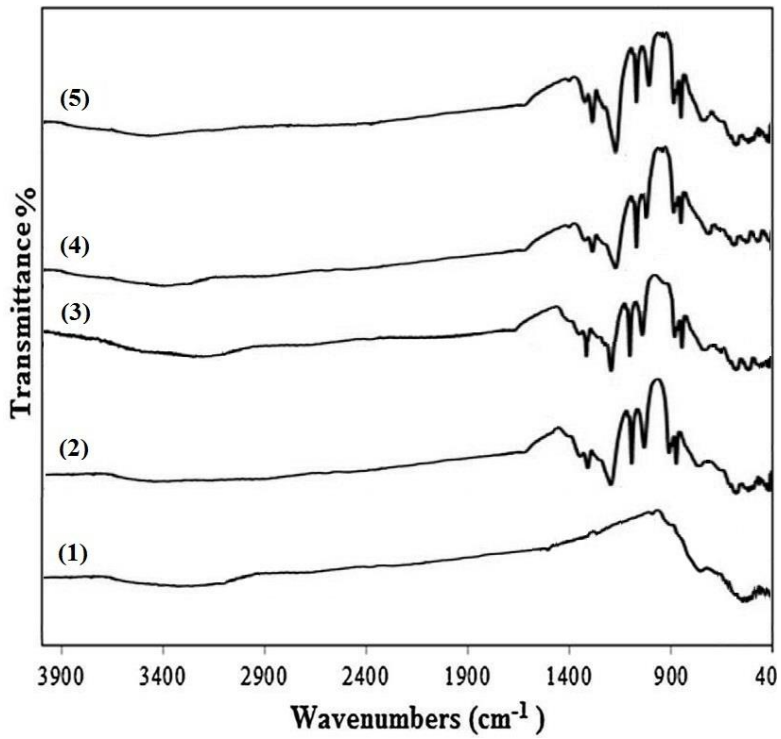


Figure 1. FT-IR spectra of ZrO_2 (1), fresh catalyst ZrSA ((2), first run), and recovered catalysts (3-5)

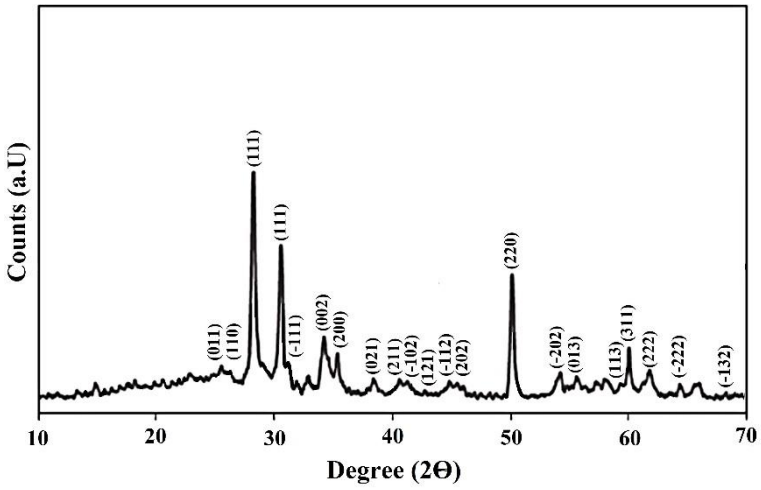


Figure 2. XRD pattern of ZrSA nanoparticles

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.

Conclusion

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 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, easily recycled and reused for several cycles with consistent activity.

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