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ORIGINAL RESEARCH

Green synthesis of pyrano [3,2-b]pyran derivatives using nano Si–Mg–fluorapatite catalyst and the evaluation of their antibacterial and antioxidant properties

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Abstract

In this study, we synthesize 2-amino-4-alkyl/aryl-6-(hydroxymethyl)-8-oxopyrano[3,2-b] pyran-3-carbonitriles derivatives using a multicomponent reaction featuring aromatic or aliphatic aldehydes, kojic acid, and malononitrile catalyzed by nano fluoroapatite doped with Si and Mg (Si–Mg–FA). All reactions were carried out in EtOH as the solvent under reflux and green condition. The process demonstrates various advantages, including high yields, short reaction times, and simple workup. In addition, toxic organic solvent is not used, nor is chromatographic purification of products required. We characterized the synthesized compounds by Fourier transform infrared, ^{13}CNMR, and ^{1}HNMR spectroscopies. Additionally, the antibacterial properties of the pyrano[3,2-b]pyran derivatives were evaluated by determining the minimum inhibitory concentration on two gram-positive and gram-negative bacteria using the macro dilution method and compared with Penicillin and Tetracycline at the same conditions. The 2-amino-4-(2,4-dichlorophenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile and the 2-amino-4-hexyl-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile show the best antibacterial activity with a MIC value of 62.5 µg/ml against *Staphylococcus aureus* (ATCC 25923). Moreover, the antioxidant properties of the pyrano [3,2-b] pyrans derivatives were evaluated. It is notable that pyrano[3,2-b] pyrans derivatives, synthesized with substituent groups on benzaldehyde such as-NO_2, -$COOCH_3$, -OMe show the best antioxidant activity measured by DPPH radical-scavenging method.

Keywords Pyrano[3,2-b]pyran · Multi-component reaction · Antibacterial · Antioxidant · Kojic acid

Introduction

Kojic acid, 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one, and its derivatives are an important class of natural/synthetic compounds, showing a wide range of biological activity, such as anti-melanogenic (Rho et al. 2008) and tyrosinase inhibitory (Noh et al. 2007), antimicrobial (Aytemir et al. 2004), and anti-inflammatory (Rho et al. 2010). Thus, the synthesis of these compounds is of a great interest to the organic and medicinal chemistry. One of the most fascinating compounds derived from kojic acid is chromene and its derivatives, which have shown various pharmacological and therapeutic properties, such as antibacterial (Kumar et al. 2009), anticancer (Shestopalov et al. 2012), anticonvulsant (Angelova et al. 2016) activities. Moreover, chromenes are cognitive enhancers used in the treatment of Alzheimer's, Parkinson's, and Huntington's diseases (Konkoy et al. 2001; Balalaie et al. 2007). The synthesis of 2-amino-6-(hydroxymethyl)-8-oxo-4-aryl-4,8-dihydropyrano [3,2-b]pyranes is interesting because these compounds fuse two useful scaffolds composed of 2-amino-4H-pyran, which is a core structure of many pharmacological agents, and kojic acid derivatives, in a single molecular entity. Nevertheless, only a few methods have been reported for the synthesis of 2-amino-6-(hydroxymethyl)-8-oxo-4-aryl-4,8-

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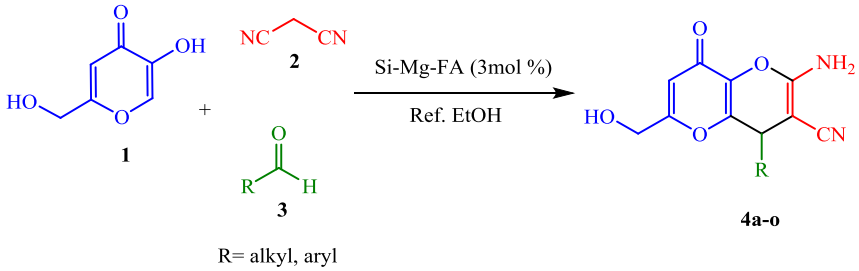


Scheme 1 Synthesis of 2-amino-4-alkyl/aryl-6 (hydroxymethyl)-8-oxo-pyrano [3,2-b]pyran-3-carbonitrile derivatives using a three-component reaction

dihydropyrano[3,2-b]pyranes (Banitaba et al. 2013; Li et al. 2013; Sadeghi et al. 2014; Sarrafi et al. 2015; Zirak et al. 2017).

Green chemistry is the design of chemical processes to minimize waste levels in the process and eliminates the use and generation of hazardous substances (Kidwai 2001). Along the multiple stages of a synthetic route, waste in many forms is often generated besides the target compounds. One of the best waste prevention strategies in the design phase of a synthetic procedure is to reduce the number of steps required to synthesize the target product. The Multicomponent Reactions (MCRs) is a method designed for the overall waste reduction of a process by incorporating a highly resource efficient step in the synthesis and through shortening the total synthetic sequence with the positive ecological consequences (Cioc et al. 2014). The development of a facile, efficient, and convenient synthetic procedure MCRs have played a fundamental role in organic and medicinal chemistry (Kappe 2000; Simon et al. 2004). Moreover, MCRs have several advantages, including a decreased number of reaction steps and times, lower energy consumption and waste (Ramón and Yus 2004; Ulaczyk-Lesanko and Hall 2005) and high purity and excellent yields (Touré and Hall 2009).Thus this methodology can enable the synthesis of bioactive and complex molecules in an efficient, facile, and rapid manner, with minimal workup (Nefzi et al. 1997; Thompson 2000; Dömling 2002).

Among the different starting materials for the synthesis of heterocyclic compounds, especially oxygen-containing molecules, which due to their physicochemical characteristics are an important and essential category of heterocycles (Okasha et al. 2016). Consequently, the development of a facile, efficient, and convenient synthetic procedure for the preparation of these compounds is highly desirable.

Recent studies have reported a new nano cooperative catalyst (Ahmadi et al. 2014) composed of $Ca_{9.5}Mg_{0.5}(PO_4)_{5.5}(SiO_4)_{0.5}F_{1.5}$ (Si–Mg–FA), synthesized through the simultaneous incorporation and doing of F, Mg, and Si into hydroxyapatite, that demonstrates greatly enhanced biological, mechanical, physical, and chemical properties (Ahmadi et al. 2014; Khazdooz et al. 2017, 2018).

Here, we develop environmentally benign methods to synthesis 2-amino-4-alkyl/aryl-6(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile derivatives using a three-component reaction. We use a one-pot three-component reaction of kojic acid, aldehyde, and malononitrile in the presence of $Ca_{9.5}Mg_{0.5}(PO_4)_{5.5}(SiO_4)_{0.5}F_{1.5}$ (Si–Mg–FA) as a nano-biocatalyst under mild and heterogeneous conditions (Scheme 1). Moreover, our method involves reduced amount of hazardous and harmful organic solvents used by employing the biocatalyst with a reduced time needed for reaction workup, which makes it an excellent and green method for synthesis of pyrano[3,2-b]pyran derivatives.

Material and methods

All reagents were purchased from Merck and Sigma Aldrich with more than 98% purity and used without further purification. Products were characterized by Fourier transform infrared, ^{1}HNMR, and ^{13}CNMR spectroscopies and compared with those obtained from the literature. All melting points were taken on an Electro Thermal Amstead 9200 apparatus and are uncorrected. ^{1}HNMRspectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz in DMSO-d6 as the solvent. FT-IR Spectra were obtained using an AnalystData PerkinElmer. The nano powder fluorapatite doped with Si and Mg (Si–Mg–FA) was synthesized according to previous works (Khazdooz et al. 2017, 2018). The absorption was monitored by a unico 2100 UV–VIS spectrometer.

General procedure for the synthesis of pyrano[3,2-b] pyrans

A mixture of aldehyde (1 mmol), malononitrile (1 mmol), and kojic acid (1 mmol) in the presence of $Ca_{9.5}Mg_{0.5}(PO_4)_{5.5}(SiO_4)_{0.5}F_{1.5}$ (0.03 g, 3 mol%) as a catalyst was added in 5 ml of EtOH and stirred under reflux conditions. After completion of the reaction, as monitored by thin layer chromatography (ethyl acetate, n-hexane 25:75), the mixture was cooled and cold distilled water (5 ml) was added. The solid product was filtered, and then recrystallized in EtOH/H_2O (9:1) to separate the catalyst.

Spectral data of synthesized pyrano[3,2-b]pyran derivatives

2-amino-4-(phenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile (4a): White solid; m.p. 222–224 °C; IR (KBr, ν): 3373, 3313, 3197, 3067, 2864, 2197, 1646, 1592, 1445, 1217 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 7.53–7.25$ (5H, m, Ar-H), 7.40 (2H, s, NH_2), 6.42 (1H, s, H-7), 5.76 (1H, t, $J = 6.0$ Hz, OH), 4.91 (1H, s, H-4), 4.26 (1H, dd, $J = 6.0$, 16.0 Hz, CH_2), 4.17 (1H, dd, $J = 6.0$, 16.0 Hz, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 169.1$, 168.2, 158.7, 148.2, 140.1, 136.4, 129.7, 128.5, 127.5, 118.4, 111.3, 59.1, 55.2, 45.3 ppm.

2-amino-4-(4-chlorophenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile (4b): White solid; m.p. 216–218 °C; IR (KBr, ν): 3376, 3305, 3188, 3080, 2863, 2193, 1638, 1597, 1487, 1208 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 7.48$ (2H, d, $J = 8.0$ Hz, Ar-H), 7.35 (2H, d, $J = 8.0$ Hz, Ar-H), 7.41 (2H, s, NH_2), 6.38 (1H, s, H-7), 5.78 (1H, t, $J = 6.0$ Hz, OH), 5.45 (1H, s, H-4), 4.29 (1H, dd, $J = 6.0$, 16.0 Hz, CH_2), 4.21(1H, dd, $J = 6.0$, 16.0 Hz, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 169.5$, 165.4, 159.2, 148.5, 139.9, 136.1, 132.5, 129.7, 128.9, 119.1, 113.7, 59.5, 55.3, 37.2 ppm.

2-amino-4-(4-fluoro-phenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile (4c): White solid; m.p. 240–243 °C; IR (KBr, ν): 3393, 3303, 3187, 2925, 2192, 1672, 1637, 1595, 1508, 1207 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 7.43 – 7.46$ (2H, m, Ar-H), 7,36 (2H, s, NH_2), 7.30 – 7.32 (2H, m, Ar-H), 6.43 (1H, s, H-7), 5.79 (1H, t, $J = 6.0$ Hz, OH), 4.95 (1H, s, H-4), 4.31 (1H, dd, $J = 6.0$. 16.0 Hz, CH_2), 4.22 (1H, dd, $J = 6.0$. 16.0 Hz, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta =$ 177.8, 169.0, 164.0, 143.8, 137.9, 130.3, 128.3, 125.7, 117.8, 115.5, 111.4, 59.2, 55.4 ppm.

2-amino-4-(3-bromophenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile (4d): White solid; m.p. 238–240 °C; IR (KBr, ν): 3420, 3323, 3208, 2911, 2863, 2196, 1642, 1593, 1408, 1226 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 7.67 – 7.60$ (2H, m, Ar-H), 7.46 (1H, t, $J = 8$ Hz, Ar-H), 7.39–7.40(3H, m, NH_2, Ar-H), 6.43 (1H, s, H-7), 5.78 (1H, t, $J = 6.0$ Hz, OH), 4.95 (1H, s, H-4), 4.30 (1H, dd, $J = 6.0$. 16.0 Hz, CH_2), 4.22 (1H, dd, $J = 6.0$. 16.0 Hz, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 176.9$, 169.4, 168.3, 159.1, 143.6, 142.9, 136.0, 131.6, 130.7, 130.3, 127.2, 122.0, 119.1, 114.3, 59.1, 55.2 ppm.

2-amino-4-(3-nitrophenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile (4e): Yellow solid; m.p. 255–257 °C; IR (KBr, ν): 3529, 3377, 3318, 3207, 3082, 2867, 2188, 1643, 1592, 1531, 1438, 1349, 1217 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta =$ 8.31–8.27 (2H, m, Ar-H), 7.91 (1H, d, $J = 8$ Hz, Ar-H), 7.79–7.83 (1H, t, $J = 8$ Hz, Ar-H), 7.49 (2H, s, NH_2), 6.44 (1H, s, H-7), 5.78 (1H, t, $J = 6.0$ Hz, OH), 5.23 (1H, s, H-4), 4.30 (1H, dd, $J = 6.0$. 16.0 Hz, CH_2),4.22 (1H, dd, $J =$ 6.0. 16.0 Hz, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 170.5$, 168.9, 160.1, 148.6, 147.9, 143.2, 137.0, 135.3, 131.4, 123.6, 122.8, 119.5, 112.3, 59.5, 55.4 ppm.

2-amino-4-(4-nitrophenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile (4f): Yellow solid; m.p. 230–232 °C; IR (KBr, ν): 3535, 3451, 3327, 3173, 3082, 2944, 2907, 2871, 2194, 1649, 1590, 1520, 1446, 1349, 1261, 1204 ppm. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 8.35$ (2H, d, $J = 8.8$ Hz, Ar-H), 7.72 (2H, d, $J = 8.8$ Hz, Ar-H), 7.48 (2H, s, NH_2), 6.441 (1H, s, H-7), 5.78 (1H, t, $J = 6.0$ Hz, OH), 5.173 (1H, s, H-4), 4.29 (1H, dd, $J = 6.0$. 16.2 Hz, CH_2), 4.21 (1H, dd, $J = 6.0$ 16.2 Hz, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 170.5$, 168.8, 160.9, 149.2, 148.0, 143.8, 129.8, 124.1, 118.5, 117.0, 114.6, 112.5, 59.8, 54.4 ppm.

2-amino-4-(4-cyano-phenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran3-carbonitrile (4g): Light yellow solid; m.p. 234–237 °C; IR (KBr, ν): 3578, 3429, 3332, 3218, 2900, 2192, 1626, 1592, 1420, 1199 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 7.97$ (2H, d, $J = 8.4$ Hz, Ar-H), 7.62 (2H, d, $J = 8.4$ Hz, Ar-H), 7.45 (2H, s, NH_2), 6.44 (1H, s, H-7), 5.78 (1H, t, $J = 6.0$ Hz, OH), 4.28 (1H, s, H-4), 4.29 (1H, dd, $J = 6.0$. 16.2 Hz, CH_2), 4.21 (1H, dd, $J = 6.0$. 16.2 Hz, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 170.1$, 168.8, 160.1, 148.4, 146.9, 137.5, 133.2, 129.1, 119.2, 118.9, 112.0, 111.3, 59.5, 55.20 ppm.

2-amino-4-(2,4-dichlorophenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile (4h): White solid; m.p. 244–245 °C; IR (KBr, ν): 3578, 3429, 3332, 3218, 2900, 2192, 1626, 1592, 1420, 1199 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 7.80$ (1H, d, $J = 2.4$ Hz, Ar-H), 7.61 (1H, dd, $J = 2.4$ 8.4 Hz, Ar-H), 7.55 (1H, d, $J = 8.4$ Hz, Ar-H), 7.46 (2H, s, NH_2), 6.46 (1H, s, H-7) 5.80 (1H, t, $J = 6.0$ Hz, OH), 5.40 (1H, s, H-4), 4.31 (1H, dd, $J = 6.0$ 15.6 Hz, CH_2), 4.23 (1H, dd, $J =$ 6.0 15.6 Hz, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 169.8$, 168.7, 159.9, 148.0, 137.6, 137.1, 134.3, 133.8, 133.0, 129.7, 128.9, 119.5, 111.7, 59.5, 56.1, 38.4 ppm

Methyl 4-(2-amino-3-cyano-4,8-dihydro-6-(hydroxymethyl)-8-oxopyrano[3,2-b]pyran-4-yl)benzoate (4i) (new compound): White solid; m.p. 249–250 °C; IR (KBr, ν): 3303, 3187, 3077, 2948, 2870, 2192, 1728, 1635, 1597, 1441, 1274, 1208 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 8.10$ (2H, d, $J = 8.4$ Hz, Ar-H), 7.57 (2H, d, $J = 8.4$ Hz, Ar-H), 7.43 (2H, s, NH_2), 6.44 (1H, s, H-7), 5.79 (1H, t, $J = 6.0$ Hz, OH), 5.06 (1H, s, H-4), 4.30 (1H, dd, $J = 6.0$

16.4 Hz, CH_2), 4.22 (1H, dd, $J = 6.0$ 16.4 Hz, CH_2), 3.96 (3H, s, OCH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta =$ 169.5, 168.3, 165.6, 159.3, 148.2, 145.9, 136.5, 130.5, 129.9, 129.8, 129.2, 128.3, 119. 1, 111.4, 59.0, 55.0, 52.6, 52.2 ppm. Analytical calculated for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98; N, 7.91. Found C, 61.13 H, 4.07, N, 7.98.

2-amino-4-(2methoxyphenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile (4j) (new compound): White solid; m.p. 238–240 °C; IR (KBr, ν): 3338, 3276, 3190, 3011, 2932, 2853, 2201, 1655, 1598, 1492, 1258, 1203 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 7.39$ (1H, td, $J = 8.0$ 1.6 Hz, Ar-H), 7.23 (1H, dd, J = 7.6 1.6 Hz, Ar-H), 7.20 (2H, s, NH_2), 7.14 (1H, d, $J = 8$ Hz, Ar-H), 7.05 (1H, t, $J = 7.6$ Hz, Ar-H), 6.41 (1H, s, H-7), 5.76 (1H, t, $J = 6.0$ Hz, OH), 5.09 (1H, s, H-4), 4.29 (1H, dd, $J = 6.0$ 16.0 Hz, CH_2),4.19 (1H, dd, $J = 6.0$ 16.0 Hz, CH_2), 3.85 (3H, s, OCH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 170.9, 169.0, 163.7, 144.5, 138.0, 129.3, 127.9, 126.4, 118.2, 112.1, 111.2, 59.3, 56.2, 55.4, 37.8 ppm. Analytical calculated for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found C, 62.44, H, 4.24, N, 8.65.

2-amino-4-(4-methylphenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran3-carbonitrile (4k): Light yellow solid; m.p. 219–220 °C; IR (KBr, ν): 3357, 3303, 3185, 3060, 2931, 2860, 2196, 1630, 1598, 1510, 1208, 1098, cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta =$ 7.45 (4H, bs, Ar-H), 7.41 (2H, s, NH_2), 6.42 (1H, s, H-7), 5.78 (1H, t, $J = 6.0$ Hz, OH), 4.73 (1H, s, H-4), 4.29 (1H, dd, $J = 6.0$ 16.1 Hz, CH_2), 4.19 (1H, dd, $J = 6.0$ 16.1 Hz, CH_2), 2.33 (3H, s, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 170.1$, 168.8, 159.1, 148.9, 137.6, 137.1, 136.2, 129.7, 127.5, 119.1, 111.2, 59.5, 55.7, 21.1 ppm.

2-amino-4-(4-(2-amino-3-cyano)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyrene-4-yl)phenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile(4l): White solid; m.p. 266–267 °C; IR (KBr, ν): 3329, 3186, 2868, 2195, 1642, 1593, 1408, 1206 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 7.40$ (4H, s, Ar-H), 7.36 (4H, s, NH_2), 6.43 (2H, s, H-7), 5.79 (2H, t, $J = 6.0$ Hz, OH), 4.91 (2H, s, H-4), 4.31 (2H, dd, $J = 6.0$ 16.1 Hz, CH_2), 4.23 (2H, dd, $J = 6.0$ 16.1 Hz, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 170.2$, 168.8, 160.0, 149. 1, 140.9, 137.1, 129.0, 119.6, 111.9, 59.6, 55.8 ppm.

2-amino-4-(thiophen-2-yl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile (4m): Light yellow solid; m.p. 226–228 °C; IR (KBr, ν): 3532, 3319, 3170, 2913, 2856, 2198, 1636, 1594, 1444, 1213 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 7.56$ (1H, dd, $J = 1.2$ 5.6 Hz, Ar-H), 7.38 (2H, s, NH_2), 7.13 (1H, d, $J = 5.6$ Hz, Ar-H), 7.06 (1H, m, Ar-H), 6.39 (1H, s, H-7), 5.78 (1H, t, $J = 6.0$ Hz, OH), 5.21 (1H, s, H-4), 4.31 (1H, dd, $J = 6.0$ 15.6 Hz, CH_2), 4.24 (1H, dd, $J = 6.0$ 15.6 Hz, CH_2) ppm.^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 166.3$, 159.3, 148.4, 144.9, 135.7, 127.3, 126.4, 126.0, 119.1, 111.4, 100.5, 59.1, 55.7, 35.5 ppm.

2-amino-4-(pyridine-3-yl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile (4n): Light yellow solid; m.p. 248–250 °C IR (KBr, ν): 3362, 3310, 3261, 3187, 2922, 2835, 2198, 1627, 1595, 1508, 1426, 1218 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 8.64$–8.62 (2H, m, Ar-H), 7.82 (1H, dt, $J = 2.0$ 8.0 Hz, Ar-H), 7.54–7.51 (1H, m, Ar-H), 7.45 (2H, s, NH_2), 6.43 (1H, s, H-7), 5.78 (1H, t, $J = 6.0$ Hz, OH), 5.04 (1H, s, H-4), 4.30 (2H, dd, $J = 6.0$ 16.0 Hz, CH_2), 4.21 (2H, dd, $J =$ 6.0 16.0 Hz, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 170.0$, 168.5, 159.6, 149.3, 149.0, 145.5, 142.1, 136.6, 136.1, 124.3, 119.1, 111.2, 59.5, 54.6 ppm.

2-amino-4-hexyl-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile (4o) (new compound): White solid; m.p. 130–132 °C; IR (KBr, ν): 3423, 3324, 2930, 2857, 2197, 1644, 1594, 1412, 1207 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 7.23$ (2H, s, NH_2), 6.47 (1H, s, H-7), 5.89 (1H, t, $J = 6.0$ Hz, OH), 4.44 (2H, d, $J =$ 6 Hz, CH_2), 3.79 (1H, t, $J = 4.8$, H-4), 1.48-1.23 (8H, m, CH_2 (C1′-C4′)), 0.96 (3H, *t*, $J = 6.8$ Hz, CH_3-C5′) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 168.1$, 160.1, 156.5, 150.3, 138.9, 137.2, 119.5, 111.3, 59.2, 53.6, 35.4, 27.4, 24.5, 17.6, 13.8 ppm. Analytical calculated for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found C, 61.91, H, 6.32, N, 9.56.

Determination of minimum inhibitory concentration (MIC)

We determined the minimum inhibitory concentrations (MIC) of the synthesized pyrano[3,2-b]pyrans against a panel of bacteria strains by the macro-dilution method. Brain Heart Infusion (BHI) was used as a medium to grow and dilute the compound suspension for the bacterial tests. To compare the efficacy of synthesized pyrano[3,2-b]pyrans with common antibacterial; drugs, we purchased Penicillin V and Tetracycline tablets from a local pharmacy (Isfahan, Iran) and used with the same concentration as standard antibacterial. First, colonies grown over night on an agar plate were inoculated into BHI (0.5 ml) in sterile conditions. Then the tube was incubated for 24 h at 37 °C. Due to the growth of bacteria the solution became turbid. This turbidity was measured by the spectrophotometric device after first zeroing the instrument against pure BHI solution, then the bacteria (0.5 ml) inoculated into BHI tube and was compared against 0.5 Mc Farland turbidity standard. Absorption in the range of (0.08–0.1) suggests 0.5 McFarland standard that, this range equals concentration 1.5×10^8 cuf/ml. In the following, synthesized pyrano[3,2-b]pyrans and also standard antibacterial drugs, Penicillin V and Tetracycline, (0.04 g) were dissolved in dimethyl sulfoxide (DMSO) (2 ml) and the solution was diluted with BHI (2 ml) to

Table 1 Optimization of the reaction conditions for the synthesis of 2-amino-4-(4-chlorophenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano [3,2-b]pyran-3-carbonitrile

Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	–	EtOH	Reflux	150	17
2	2	EtOH	Reflux	60	77
3	2	H_2O	Reflux	60	50
4	3	EtOH	Reflux	35	91
5	4	EtOH	Reflux	40	90
6	3	H_2O/ EtOH	Reflux	60	68

Reaction conditions: 4-chlorobenzaldehyde (1 mmol), malononitrile (1 mmol) and kojic acid (1 mmol). The yields refer to the isolated pure products

prepare samples and controls with the same concentration (2000 µg/ml). Further progressive serial dilution was performed to obtain the required concentrations of 1000, 500, 250. 125, 62.5, 31.25, 15.6, 7.8, 3.9, 1.9 (µg/ml). Then to each of the tubes were inoculated 100 µl of prepared bacterium suspension and incubated at 37 °C for 24 h. At the end of the incubation period, the MIC values were recorded as the lowest concentration of the pyrano[3,2-b]pyrans and Penicillin V and Tetracycline that had no visible turbidity.

Antioxidant activity

The free radical scavenging activity of the pyrano[3,2-b] pyrans derivatives and ascorbic acid (as a standard) was determined using the 1,1-diphenyl-2-picryl hydrazyl (DPPH) assay according to a literature method with some modifications (Kumar et al. 2010; Kadhum et al. 2011). In this test, the antioxidants reduce the 1,1-diphenyl-2-picryl hydrazyl ($DPPH^{\bullet}$) having a violet to a yellow color of diphenylpicrylhydrazine (DPPH-H). For the analysis, we prepared a DPPH solution in methanol (0.004% w/v) with an absorbance range between 0.8 and 1.2 at a wavelength of 517 nm. Several pyrano [3,2-b]pyran derivative solutions (1.5 ml; 100, 200, 300 µg/ml in methanol) were prepared and DPPH solution (3 ml, in methanol) was added to each. The resulting solutions were shaken vigorously and all tubes were left at ambient temperature for 30 min in the dark. The control was prepared with 1.5 ml of methanol and 3 ml of DPPH solution. The absorbance of the solutions were read at 517 nm using the UV/VIS–UV spectrophotometer. The percentage of free radical scavenging activity was calculated according to the following equation:

$$\% \text{ scavenging activity} = [(\text{Ac} - \text{As})/\text{Ac}] \times 100.$$

In which Ac is the absorbance of the control, and As is the absorbance of the sample.

Result and discussion

In continuation of our investigations of the application of Nano Si–Mg–Fluorapatite in organic synthesis (Khazdooz et al. 2017, 2018) we demonstrate the synthesis of pyrano [3,2-b]pyrans derivatives by the three-component condensation of 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one (kojic acid) **1**, malononitrile **2** and an aliphatic or aromatic aldehyde **3** in the presence of Si–Mg–FA as catalyst (Scheme 1).

Optimization of solvent and catalyst (Si–Mg–FA) amount

We optimized the conditions for the model reaction of 4-chloro-benzaldehyde (1 mmol), malononitrile (1 mmol), and kojic acid (1 mmol) to prepared 2-amino-4-(4-chlorophenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano [3,2-b]pyran-3-carbonitrile. The results are summarized in Table 1. When this one pot reaction was carried out in the absence of the catalyst, the corresponding product was obtained in low yield after lengthy reaction time (Table 1, entry 1). By increasing the catalyst amount to 3 mol%, the reaction was carried out in 35 min and with 91% yield. However, further increase of the catalyst amount did not improve the yield of the reaction (Table 1, entry 5). Therefore, we found that the best results were obtained when the reaction was carried out in EtOH reflux using 3 mol% of the catalyst (Table 1, entry 4).

Investigation of synthesized derivatives

After optimizing the reaction conditions, we studied the generality of this method. Using this procedure, different kinds of aromatic, aliphatic, and heterocyclic aldehydes were treated with kojic acid and malononitrile for the synthesis of the corresponding pyrano[3,2-b]pyran derivatives in good to high yields (Table 2). As can be seen in Table 2, aromatic aldehydes with different functional groups were employed to the condensation reaction and the resulting products were synthesized in good to high yields (82–93%) and short reaction time. The substituent of the aromatic aldehyde dramatically influences in the reaction time. Aromatic aldehydes with electron-withdrawing groups (such as halide, cyano and nitro; Table 2, entries 2–9) required shorter reaction times and provided higher yields than aldehydes that featured

Table 2 The synthesis of pyrano[2,3-b]pyran derivatives using various aldehydes, kojic acid, and malononitrile in the presence of Si–Mg–FA catalyst

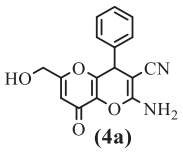
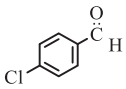
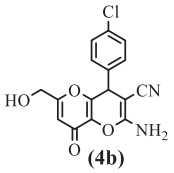
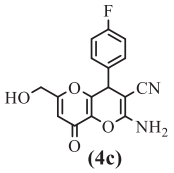
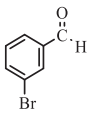
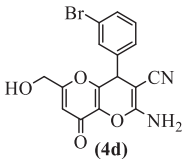
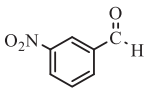
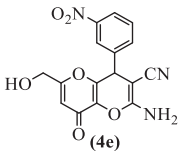
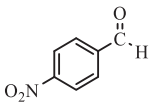
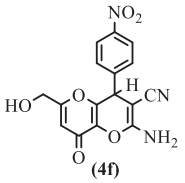
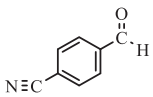
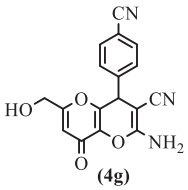
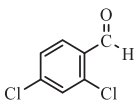
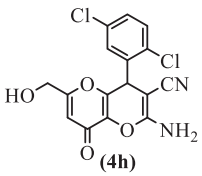
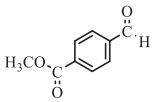
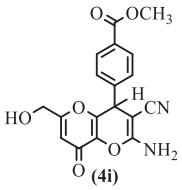
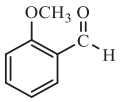
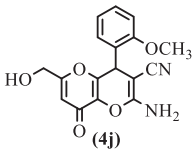
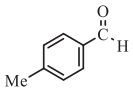
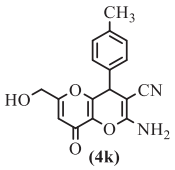
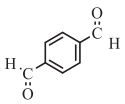
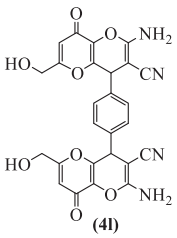
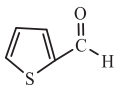
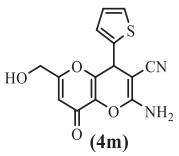
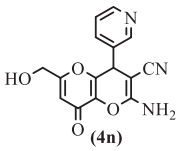
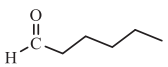
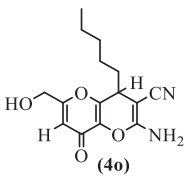
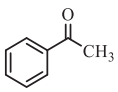
Entry	Aldehyde	Product	Time (min)	Yield (%)[a]	M.P. (°C)	
					Found	Reported (Ref.)
1		 **(4a)**	50	85	222–224	220–222 (Banitaba et al. 2013)
2		 **(4b)**	35	91	216–218	219–221 (Li et al. 2013)
3		 **(4c)**	30	88	240–243	247–249 (Sarrafi et al. 2015)
4		 **(4d)**	40	90	238–240	242–244 (Banitaba et al. 2013)
5		 **(4e)**	15	93	255–257	258–260 (Sadeghi et al. 2014)
6		 **(4f)**	20	91	230–232	230–232 (Sarrafi et al. 2015)
7		 **(4g)**	15	92	234–237	239–241 (Sadeghi et al. 2014)
8		 **(4h)**	45	91	244–245	240–242 (Banitaba et al. 2013)

Table 2 (continued)

Entry	Aldehyde	Product	Time (min)	Yield (%)[a]	M.P. (°C)	
					Found	Reported (Ref.)
9		 **(4i)**	15	92	249–250	–
10		 **(4j)**	60	86	238–240	–
11		 **(4k)**	60	86	219–220	221–223 (Sarrafi et al. 2015)
12		 **(4l)**	50	81	266–267	270–272 (Sarrafi et al. 2015)
13		 **(4m)**	90	87	226–228	231–233 (Zirak et al. 2017)
14		 **(4n)**	50	85	248–250	251–253 (Banitaba et al. 2013)
15		 **(4o)**	50	82	130–132	–
16		–	180	0	–	–

[a]The yields refer to the isolated pure products

Scheme 2 Suggested mechanism for the synthesis of pyrano[3,2-b]pyran catalyzed by Si–Mg–FA

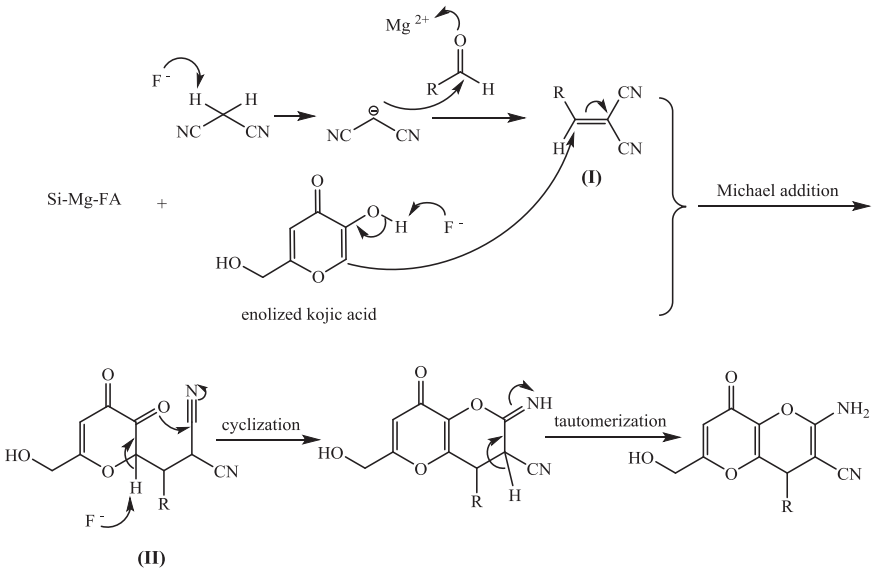


Table 3 Comparison of Si–Mg–FA with different catalysts for the synthesis of 2-amino-4-(3-nitro-phenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile

Entry	Catalyst	Amount of catalyst	Conditions	Time (min)	Yield (%)	Ref.
1	Fe_3O_4@SiO_2-IL-Fc	0.040 g	EtOH/H_2O (70:30),)))	10	96	(Teimuri-Mofrad et al. 2017)
2	$SnCl_4/SiO_2$ NPs	0.004 g	Solvent-free/70 °C	10	95	(Molaei et al. 2017)
3	Fe_3O_4@SiO_2-BenzIm-Fc[Cl]/$ZnCl_2$	0.008 g	EtOH/H_2O (2:1),)))	8	95	(Gholamhosseini-Nazari et al. 2019)
4	MCM-41-SO_3H	0.030 g	H_2O (90 °C)	35	98	(Sarrafi et al. 2015)
5	Nano SiO_2–OSO_3H	0.060 g	H_2O (reflux)	15	96	(Sadeghi et al. 2014)
6	Nano ZnO	0.06 g	EtOH (reflux)	120	95	(Zirak et al. 2017)
7	b-cyclodextrin	20 mol%	H_2O (70 °C)	60	92	(Kataev et al. 2016)
8	Imidazole	20 mol%	EtOH (reflux)	60	89	(Khan et al. 2014)
9	Si–Mg–FA	3 mol%	EtOH/H_2O (reflux)	15	93	This work

electron-donating groups (such as methyl and methoxy; Table 2, entries 10,11). It is worth noting that the steric effects of ortho substitutions on the aromatic aldehydes increased the reaction times (Table 2, entries 8,10). The notable advantage of this method is that heterocyclic aldehydes, such as thiophene-2-carbaldehyde and pyridine-3-carbaldehyde, were converted to the corresponding products with good yields without making any side products (Table 2, entries 13,14). Furthermore, unlike most reported methods, by employing this procedure, aliphatic aldehydes were easily converted to the corresponding pyrano[3,2-b]pyran products in suitable yields (Table 2, entry 15). However, we note that this method is not suitable for the conversion of ketones (e.g., acetophenone) to the corresponding pyrano[3,2-b]pyran derivatives due to the low electrophilicity and high hindrance of the carbonyl group of ketones compared with aldehydes (Table 2, entry 16).

Based on the results, we suggest a mechanism for the synthesis of these various pyrano[3,2-b]pyran derivatives via the condensation reaction of the aldehyde, malononitrile, and kojic acid catalyzed by Si–Mg–FA (Scheme 2). In the Si–Mg–FA catalyst structure, F^- can be used as a Brønsted base and Mg^{2+} as a Lewis acid. As a hard acid, Mg^{2+} can be coordinated by the oxygen lone pair electrons of the aldehyde and kojic acid in the reaction (Khazdooz et al. 2017, 2018). Intermediate (I) can be prepared when aldehyde reacted with malononitrile. After the Michael addition between the enolized kojic acid and intermediate (I), the intermediate (II) is formed. Finally by cyclization and tautomerization intermediate (II) the product is made.

To better elucidate the efficacy of our method, we compared the catalytic activity of the Si–Mg–FA with few catalysts reported in the literature for the synthesis of 2-amino-4-(3-nitro-phenyl)-4,8-dihydro-6-(hydroxymethyl)-

8-oxo-pyrano[3,2-b]pyran-3-carbonitrile. As shown in Table 3, Si–Mg–FA is comparable with the other reported catalysts with respect to yield, reaction time and reaction conditions. In addition, the other advantages of the present work are the use of nontoxic solvent, mild reaction conditions, and one-pot procedure. Moreover, our method involves reduced amount of hazardous and harmful organic solvents used by employing a biocatalyst in a one-pot synthesis with a reduced time needed for reaction workup which makes it an excellent and green method for the synthesis of pyrano[3,2-b]pyran derivatives.

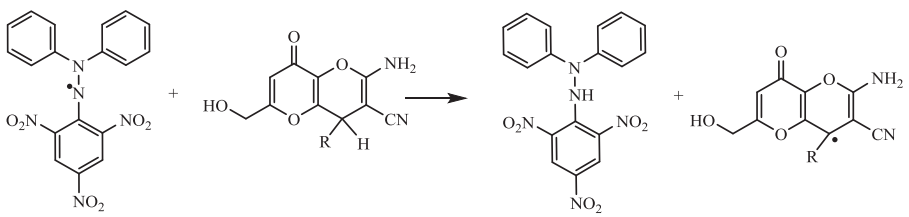
Investigation of the minimal inhibitory concentration (MIC) of pyrano[3,2-b]pyran derivatives

We evaluated the in vitro antibacterial activity of the synthesized pyrano[3,2-b]pyran compounds against *Staphylococcus aureus* (ATCC25923) and *Staphylococcus epidermidis* (ATCC12228) as examples of gram-positive bacteria and *Pseudomonas aeruginosa* (ATCC27853) and *Escherichia coli* (ATCC25912) as examples of gram-negative bacteria. Penicillin and tetracycline were used as reference drugs. The MIC measurements (mg/ml) were determined for the compounds using a two-fold serial dilution method (El-Batanony 2017). The results shown in Table 4 revealed that most of the tested compounds displayed variable inhibitory effects on the growth of the tested gram-positive and gram-negative bacterial strains. In general, the MIC of pyrano[3,2-b]pyran derivatives for the gram-positive bacteria growth was greater than the gram-negative bacteria. The results reported in Table 4 indicate that among all the screened derivatives, both compound **4h** and **4o** featured good antibacterial activity, with an MIC value of 62.5 µg/ml against gram-positive bacteria, such as *Staphylococcus aureus* (ATCC 25923), compared with Penicillin and Tetracycline (Table 4. Entry 8,15,16,17). Among these compounds, **4o** also showed the most significant antibacterial activity, with an MIC value of 100 µg/ml (compared with penicillin, 80 µg/ml) against another

Table 4 Antimicrobial activity (MIC values; µg/ml) of the synthesized pyrano[3,2-b]pyrans derivatives

Entry	Compound	Gram-positive bacteria		Gram-negative bacteria	
		Staphylococcus aureus ATCC 25923	Staphylococcus Epidermidis ATCC 12228	Pseudomonas aeruginosa ATCC 27853	Escherichia coli ATCC 25922
1	4a	250	300	135	125
2	4b	250	270	150	125
3	4c	250	270	150	135
4	4d	260	250	150	135
5	4e	260	260	150	125
6	4f	260	150	150	125
7	4g	300	200	150	125
8	4h	62.5	250	150	135
9	4i	250	300	150	135
10	4j	250	270	150	135
11	4k	250	250	150	125
12	4l	300	300	150	125
13	4m	250	250	150	125
14	4n	260	300	150	135
15	4o	62.5	100	150	125
16	Penicillin	35	80	35	62.5
17	Tetracycline	15	3.9	70	3.9

Scheme 3 DPPH radical scavenging by pyrano[3,2-b] pyrans as an antioxidant



gram-positive bacterium, *Staphylococcus Epidermidis* (ATCC 12228) (Table 4. Entry 15). Additionally, compound **4a** demonstrated good antibacterial activity against *Pseudomonas aeruginosa* bacterium (ATCC 27853; gram-negative), with a MIC value of 135 µg/ml compared with the control drugs (Table 4. Entry 1). Finally, all the compounds showed good antibacterial activity against *Escherichia coli* bacterium (ATCC25922; gram-negative) all of the compounds, with MIC values of 125 or 135 µg/ml compared with the controls. Based on these results, we believe these synthesized pyrano[3,2-b]pyrans derivatives demonstrate strong potential for further studies in antibiotic medicine research.

Table 5 The percent DPPH radical scavenging ability of the synthesized pyrano[3,2-b]pyrans

Entry	Compound	Concentration (µm/ml)		
		100	200	300
1	4a	3	5	7
2	4b	9	17	17
3	4c	1	3	13
4	4d	9	11	11
5	4e	3	9	19
6	4f	17	49	50
7	4g	7	7	11
8	4h	19	21	27
9	4i	13	27	54
10	4j	54	54	41
11	4k	1	2	5
12	4l	15	23	29
13	4m	1	11	17
14	4n	1	1	5
15	4o	5	23	13
Ascorbic acid	–	96	97	98

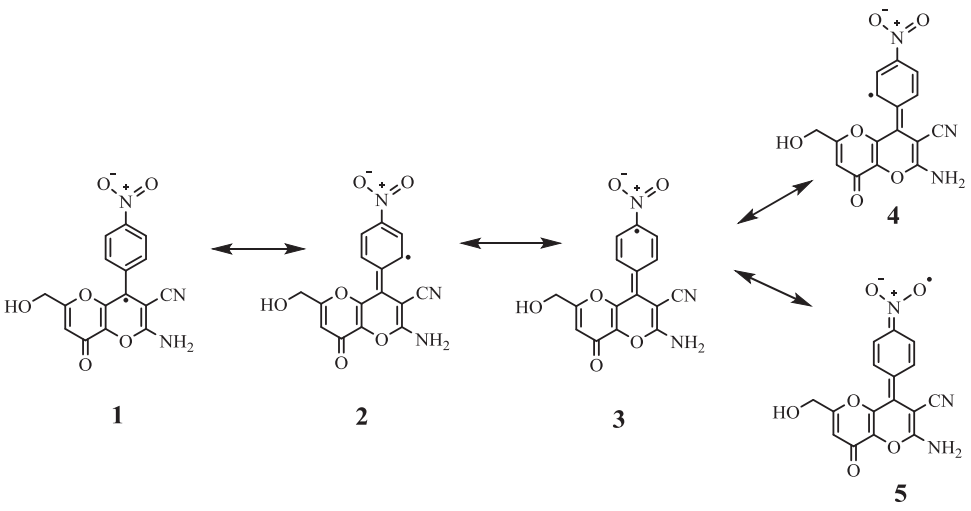
Investigation of antioxidant properties

We evaluated the in vitro antioxidant activity of the pyrano[3,2-b]pyrans derivatives using the DPPH radical-scavenging method. Antioxidant compounds scavenge DPPH radicals by either hydrogen-donation or electron donation (Scheme 3), and the purple color of the DPPH assay solution becomes light yellow. The color change can be quantified by measuring the decrease of the absorbance at 517 nm (Kumar et al. 2010; Kadhum et al. 2011).

Table 5 summarizes the results of the DPPH radical scavenging assay. All the pyrano[3,2-b]pyrans derivatives demonstrate antioxidant activity, likely due to benzyl hydrogen atoms of these molecules. In addition, their activity gradually increases with their concentration. It is interesting that some substituent groups (such as $–NO_2$, $–COOCH_3$, -OMe) on benzaldehyde (4f, 4i, 4j), which increase the resonance effect in the benzylic position, improve the antioxidant activity of the pyrano[3,2-b]pyrans derivatives. Moreover it is notable that **4f** shows more antioxidant activity than **4e**. This may be due to the presence of the nitro group in the *para* position of phenyl ring in **4f**, which can better stabilize the corresponding formed radical through the increase of the resonance effect. These resonance forms are showed in Scheme 4. When nitro is in the *para* position of phenyl ring in **4f**, the antioxidant compound has five resonance forms, while when it is in the *meta* position phenyl ring (**4e**), the antioxidant compound has only four resonance forms.

Conclusion

In conclusion, we have developed an efficient, clean, one-pot and three-component synthesis of pyrano[3,2-b]pyrans in ethanol under mild conditions with Si–Mg–FA catalyst.



Scheme 4 Resonance forms of the 2-amino-4-(4-nitrophenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile radical

The different advantages of this method include its operational simplicity, good yields, and simple workup procedures. We also evaluated the synthesized pyrano[3,2-b] pyran compounds for their in vitro antibacterial activity against *Staphylococcus aureus* (ATCC25923) and *Staphylococcus epidermidis* (ATCC12228) as examples of gram-positive bacteria and *Pseudomonas aeruginosa* (ATCC27853) and *Escherichia coli* (ATCC25912) as gram-negative bacteria. The results showed that these compounds had good and acceptable antibacterial properties. Moreover, the antioxidant properties of pyrano[3,2-b] pyrans derivatives were evaluated. Among these synthesized derivative 2-amino-4-(4-nitrophenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile, 2-amino-4-(2-methoxyphenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxo-pyrano[3,2-b]pyran-3-carbonitrile and Methyl 4-(2-amino-3-cyano-4,8-dihydro-6-(hydroxymethyl)-8-oxopyrano[3,2-b]pyran-4-yl)benzoate showed the maximum antioxidant properties.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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