Res Chem Intermed
https://doi.org/10.1007/s11164-018-3363-7

An eco-friendly synthesis of 4-aryl-substituted pyrano-fuzed coumarins as potential pharmacological active heterocycles using molybdenum oxide nanoparticles as an effective and recyclable catalyst

Yaghoub Pourshojaei[1,2] · Mohammad-Hossein Jadidi[1] · Khalil Eskandari[1] · Alireza Foroumadi[2,3] · Ali Asadipour[1]

Received: 25 October 2017 / Accepted: 1 March 2018

Abstract A green cascade three-component reaction between 4-hydroxycoumarin, malononitrile and a wide range of arylaldehydes by employing molybdenum oxide nanoparticles (MoO_3 NPs) is described. By this achievement, some medicinally important products have been successfully synthesized in a one-pot under green conditions. Obtaining good to excellent yields of products, environmentally benign procedure, being easily handled, availability of starting materials, use of non-toxic solvents, and high recyclability of nano-catalysts are the most important advantages of this methodology.

Keywords Pyrano-fuzed coumarins · Molybdenum oxide nanoparticles · Recyclable catalyst · Green protocol

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11164-018-3363-7) contains supplementary material, which is available to authorized users.

✉ Yaghoub Pourshojaei
y.pourshoja@kmu.ac.ir

✉ Khalil Eskandari
khalileskandari@yahoo.com

[1] Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutics Research Center, Kerman University of Medical Sciences, Kerman, Iran

[2] Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

[3] Drug Design and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran

Published online: 12 March 2018

Introduction

In the past decades, catalytic technologies have attracted much interest from chemists and industrialists, especially the use of heterogeneous recyclable eco-friendly catalysts considering the economic aspects, and from the green chemistry point of view [1, 2]. Based on the above, environmentally benign heterogeneous catalysts have been widely used in synthetic methodologies and their scope is being expanded [3]. Among them, metal oxides have attracted much interest and been broadly applied by chemists in different types of organic reactions [4–6]. The rate of reaction progress in the presence of heterogeneous catalysts directly depends on the total surface area of the catalysts, and also on the number of active sites on them. Therefore, it is obviously expected that good catalytic activity is achieved with smaller particle sizes and higher surface areas of the catalysts [7, 8].

Considering the above, using nano-sized heterogeneous, environmentally benign catalysts in synthetic protocols is of considerable importance. Among metal oxide nanoparticles, molybdenum oxide nanoparticles (MoO_3 NPs) is one of the most attractive nanomaterials which have extensively attracted the attraction of chemists because of its special chemical and physical properties. These NPs have been successfully applied as promising materials in broad areas, especially as reusable catalysts in synthetic methodologies [9, 10]. From the above, it can be seen that MoO_3 NPs can be successfully applied as heterogeneous Lewis catalysts in organic synthesis because of their special qualities, including easy separation from the reaction mixture by simple filtration, the capability for reuse in further cycles, not producing undesired side products, and thermal stability. In addition, nano-MoO_3 shows non-corrosivity and non-toxicity qualities which make it more important from the green chemistry point of view, and of benefit as an environmentally benign catalyst in the chemical industries and synthetic methodologies [11–13]. These important advantages encourage chemists to apply Mo-based heterogeneous catalysts in organic transformations. For instance, using supported molybdenum oxides for the fast pyrolysis of lignocellulosic biomass [14], ethanolysis of kraft lignin to platform chemicals over molybdenum-based catalysts [15], synthesis of indole alkaloids by employing nanocomposites of MoS_2–RGO [16], biodiesel synthesis by employing molybdenum dioxo catalyst [17], and also selective hydrodeoxygenation of 2-furancarboxylic acid over a molybdenum oxide-modified platinum catalyst [18] can be counted as recent developments in Mo-based heterogeneous catalysis.

In recent decades, the attention being paid to environmental pollution control programmes and policies and also to green chemistry aspects have led to using harmless and neat technologies in synthetic methodologies [19, 20]. One of the harmless and neat technologies is the use of aqueous medium in synthetic procedures, which can not only sometimes accelerate reaction progress but is also completely compatible with green chemistry aspects [21, 22]. Furthermore, running organic reactions in aqueous media has some other important advantages, such as using harmless, non-toxic, non-corrosive, inexpensive, and easily accessible solvents [21, 22].

The other noteworthy achievement in organic synthetic methodologies is loading reaction components in a one-pot. Running organic reactions in this way has some unique advantages which have resulted in attracting the interest of chemists. For instance, diminishing of reaction waste, saving in time, simplifying practical aspects and also having atom economy, step economy, and redox economy can be counted as advantages of one-pot reactions [23–25]. In addition, running in a one-pot, the economical point of view is important because complicated molecules can be obtained from simple starting materials, and can be easily separated from the reaction mixture, purified and characterized [26]. Coumarin, which may be classified as α,β-unsaturated δ-lactones [27] or benzopyrone analogous [28], is one of the important *O*-containing heterocycles which have been isolated from natural products [29], and have attracted great interest from chemists and pharmaceutics [30–34]. So far, a broad range of works on biological and pharmaceutical activities of coumarin and its derivatives have been published. For example, they have been shown to be anti-inflammatory [35], antitumor [36, 37], anticoagulant, anti-oxidant, antibacterial, and antiHIV [38] activities. Among coumarin analogous 4-hydroxycoumarins which have been found in numerous plants and natural products and which belong to a class of vitamin K antagonists, have increasingly attracted the interest of chemists and pharmacologists [39, 40]. For instance, 4-hydroxycoumarin and its derivatives have also shown antibacterial [41], antiHIV [42–44], antiviral [45], anti-oxidant [46], and anticoagulant [47] activities. To date, numerous types of biologically active products are recognized with 4-hydroxycoumarin's scaffold being observed in their chemical structures as an obvious motif (Fig. 1) [48]. All the

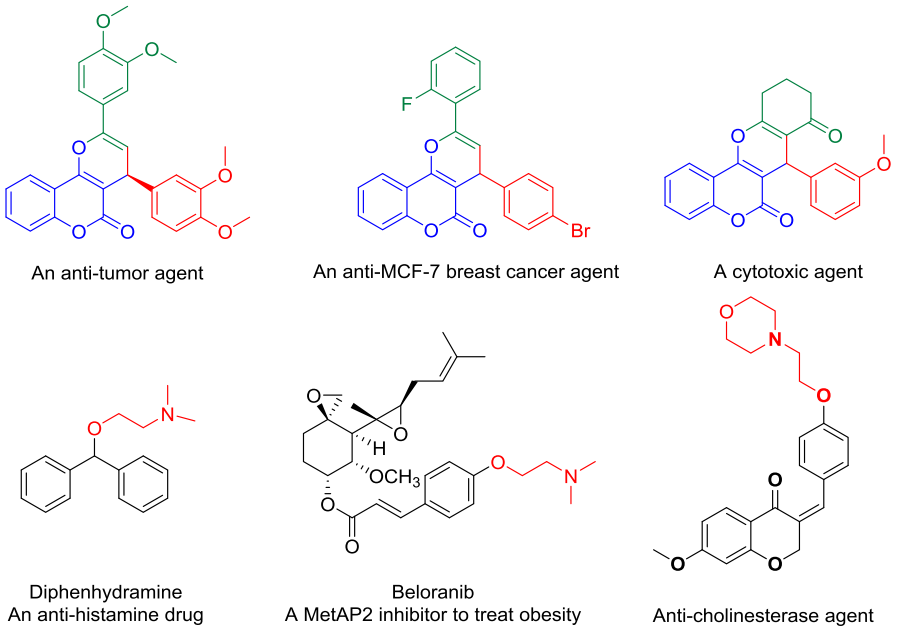


Fig. 1 Examples of some drugs and biologically active compounds containing 4-hydroxycoumarin or alkylamine ether motifs

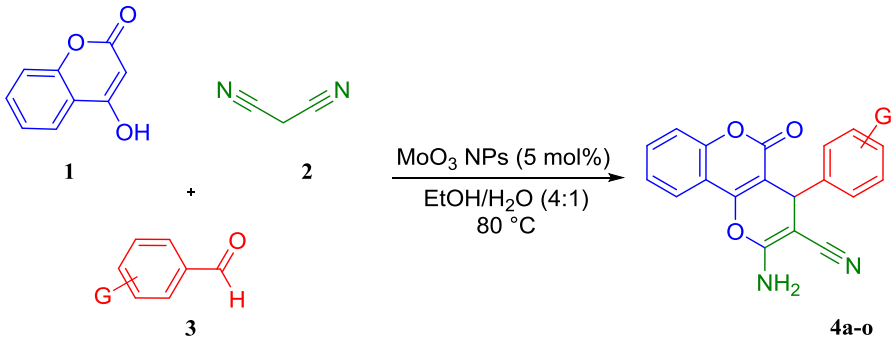
above-mentioned features about the biological and pharmaceutical activities of 4-hydroxycoumarin have encouraged chemists and pharmacologists to synthesize newly prepared heterocycles based on the 4-hydroxycoumarin framework [49–51]. In addition to the above-mentioned scaffolds, the alkylamine ether moiety has also been found in some important drugs and biologically active compounds (Fig. 1) [52–54].

These disclosed properties have encouraged chemists and pharmacologists to design synthetic routes to obtain newly prepared molecules exhibiting pharmacological and biological activities which may be applied in the future in the treatment of human disease as new medicines [43, 55, 56]. Based on the above, and in continuation of our research studies onthe catalytic synthesis of newly prepared potentially interesting biologically active heterocyclic compounds, [57–61], here we wish to report a green one-pot catalytic three-component reaction between 4-hydroxycoumarin (**1**), malononitrile (**2**), and a broad range of arylaldehydes (**3**) in the presence of catalytic amounts of MoO_3 NPs (Scheme 1)

It has been found that MoO_3 NPs not only efficiently catalyze the synthesis and cyclization of 4-phenyl-substituted pyrano-fuzed coumarins via a convenient work-up but also have some advantages, such as safety, capability for reuse, high stability, and easy handling. Therefore, in this work, the preparation, high activation, and regeneration of MoO_3 NPs as an eco-friendly and recyclable catalyst in the synthesis of some medicinally important heterocycles are explained. Furthermore, the efficiency of the catalyst in the synthesis of target products was compared with others. The structures of the target products (**4**) were deduced from and confirmed by FT-IR, FT-^{1}H and FT-^{13}C NMR spectroscopies and (C,H,N,) analyses.

Experimental

Chemicals were purchased from Merck and Sigma-Aldrich. An elecrtothermal IA9100 melting point apparatus fixed at 1 °C/min was used for melting point measurements. A Brucker FT-IR Tensor 27 infrared spectrophotometer with KBr as



Scheme 1 One-pot synthesis of 4-phenyl-substituted pyrano-fuzed coumarins catalyzed by MoO_3 NPs under green conditions

the matrix was applied for recording IR spectra, which were recorded in the range of 4000–400 cm^{-1}. A FT-NMR Bruker Avance Ultra Shield Spectrometer at 400.13 for ^{1}H NMR and at 100.62 MHz for ^{13}C NMR (In some cases, ^{1}H NMR 300 MHz and ^{13}C NMR 75 MHz, was applied) in DMSO as solvent was used for recording ^{1}H and ^{13}C NMR. Elemental analyses (C,H,N,S) were performed on a Heraeus Rapid analyzer and the results were found to be in good agreement with the calculated values (± 0.3%). TLC-Grade silica gel-G/UV (254 nm) plates were used for monitoring of the reaction progress using $CHCl_3/CH_3OH$ (10:1) as eluent.

Catalyst characterization

Scanning electron microscopy (SEM) evaluations of the nano-catalyst were performed on a JEOL JEM 3010 instrument operating at an accelerating voltage of 300 kV. An X-ray diffraction pattern for the characterization of the heterogeneous nano-catalyst was studied with XRD (D8 Avance; Bruker). EDAX analysis was carried out by NEWXL30 144-2.5 instrument in an active area of 10 mm^2. Thermogravimetric (TG) measurements were carried out using a thermal gravimetric analyzer (BAHR, STA 503) from room temperature to 1100 °C in air at a heating rate of 10 °C min^{-1}. Transmission electron microscopy (TEM) investigations of the nano-catalyst were performed on a JEOL JEM 3010 instrument operating at an accelerating voltage of 300 kV. The Brunauer–Emmett–Teller (BET) surface area was measured on a BELSORP-MR6 (Japan) at 77.4 K. All samples were first degassed in a vacuum at 100 °C for 4 h before analysis.

Typical procedure to prepare MoO_3 NPs

To synthesize MoO_3 NPs, to the stirred mixture of 2 g (1.6 mmol) ammonium heptamolybdate tetrahydrate ($(NH_4)_6Mo_7O_{24} \times 4H_2O$) dissolved in 5 mL ethanol and 15 mL of deionized water, at room temperature for 20 min, HNO_3 (2 M) was added dropwise until the pH of the mixture reached 1. Then, the formed clear solution was stirred under reflux conditions at 90 °C for 5 h. Next, the obtained light-blue precipitates were separated by filtration, washed several times with deionized water until the washing solution became neutral, and dried in an oven at 90 °C for 12 h. In the final step, the catalyst was calcined at 450 °C for 6 h in an electric furnace.

General procedure for the preparation of corresponding aldehydes

Corresponding aldehydes containing alkylamine ethers were synthesized according to the procedure, and the physical and chemical properties of obtained aldehydes were compared with those reported in the literature [61], and all their structures were confirmed. Also, *p*-benziloxybenzaldehyde derivatives were prepared by being treated with 4-hydroxybenzaldehyde with appropriate benzylchloride/bromide derivatives in the presence of K_2CO_3 as the catalyst. The physical and chemical properties of all the obtained substrates were compared with those reported in the literature and all their structures were confirmed [68, 69].

Typical procedure to the synthesis of 4a

4-hydroxycoumarin (1 mmol, 0.162 g) was added to a stirred mixture of malononitrile (1.5 mmol 0.01 g), MoO_3 NPs (0.007 g, 5 mol%) and para-(4-morpholinoethoxy)-benzaldehyde (1 mmol, 0.235 g) in EtOH/H_2O (4:1). The mixture was heated at 80 °C for the times indicated in Table 2 (see "Results and discussion". After compilation of the reaction progress (which was controlled by TLC $CHCl_3$/CH_3OH (10:1) as eluent), the mixture was precipitated and then filtrated to separate the crude product., which was dissolved in boiling ethanol and filtrated to separate the catalyst. Finally, a crystalline pure product was obtained in solution and isolated by filtration.

Representative spectral data

*2-Amino-4-(4-(2-morpholinoethoxy)phenyl)-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile (**4a**)*

Light yellow crystals; m.p: 191–193 °C; FT-IR (KBr) (ν_{max}, cm^{-1}): 3413, 3272, 3148, 2937, 2860, 2189, 1729, 1679, 1605, 1375, 1171, 1110, 1035, 763. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.94 (d, 1H, J = 7.5 Hz, CH_{Ar}), 7.70 (t, 1H, J = 7.5 Hz, CH_{Ar}), 7.50–7.44 (m, 2H, CH_{Ar}), 7.38 (brs, 2H, NH_2), 7.15 (d, 2H, J = 8 Hz, CH_{Ar}), 6.86 (d, 2H, J = 8 Hz, CH_{Ar}), 4.38 (s, 1H, CH), 4.01 (t, 2H, J = 5.5 Hz, OCH_2), 3.56 (brs, 4H, $2CH_2$), 2.67 (brs, 2H, CH_2), 2.46 (brs, 4H, $2CH_2$); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 160.0, 158.4, 157.9, 153.6, 152.6, 135.9, 133.3, 129.2, 125.1, 122.9, 119.8, 117.0, 114.9, 113.5, 104.8, 66.5, 65.6, 58.9, 57.4, 53.9, 36.7. Anal Calcd. for ($C_{25}H_{23}N_3O_5$): C, 67.41; H, 5.20; N, 9.43; Found: C, 67.39; H, 5.15; N, 9.46%.

*2-Amino-5-oxo-4-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile (**4b**)*

Light yellow crystals; m.p: 185–186 °C; FT-IR (KBr) (ν_{max}, cm^{-1}): 3349, 3153, 2954, 2192, 1721, 1677, 1606, 1377, 1242, 1174, 1113, 1048, 766. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.91–7.89 (m, 1H, CH_{Ar}), 7.73–7.70 (m, 1H, CH_{Ar}), 7.51–7.42 (m, 4H, CH_{Ar}, NH_2), 7.20 (d, 2H, J = 8.5 Hz, CH_{Ar}), 6.93 (d, J = 8.5 Hz, 2H, CH_{Ar}), 4.41 (s, 1H, CH), 4.33 (brs, 2H, OCH_2), 2.95 (brs, 6H, $3CH_2$), 1.74–1.50 (m, 6H, $3CH_2$); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 160.0, 158.4, 157.1, 153.7, 152.6, 136.7, 133.4, 129.4, 125.2, 123.0, 119.8, 117.0, 115.1, 113.5, 104.6, 62.8, 58.5, 55.2, 53.1, 38.7, 22.9, 21.7; Anal Calcd. for ($C_{26}H_{25}N_3O_4$): C, 70.41; H, 5.68; N, 9.47; Found: C, 70.44; H, 5.59; N, 9.51%.

*2-Amino-4-(4-(3-morpholinopropoxy)phenyl)-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile (**4c**)*

Light yellow crystals; m.p: 170–173 °C; FT-IR (KBr) (ν_{max}, cm^{-1}): 3415, 3331, 3141, 2866, 2192, 1702, 1671, 1605, 1466, 1379, 1237, 1178, 1111, 767. ^{1}H NMR

(500 MHz, DMSO-d_6) δ (ppm): 7.90 (d, 1H, J = 8 Hz, CH_{Ar}), 7.71 (t, 1H, J = 8 Hz, CH_{Ar}), 7.51–7.42 (m, 4H, CH_{Ar}, NH_2), 7.17 (d, J = 8.5 Hz, 2H, CH_{Ar}), 6.87 (d, J = 8.5 Hz, 2H, CH_{Ar}), 4.40 (s, 1H, CH), 4.02 (t, 2H, J = 5 Hz, OCH_2), 3.92–3.78 (brs, 4H, $2CH_2$) 3.50 (brs, 2H, CH_2), 3.21 (brs, 2H, CH_2), 3.06 (brs, 2H, CH_2), 2.15 (brs, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 160.0, 158.4, 157.8, 153.6, 152.5, 136.2, 133.3, 129.2, 125.1, 123.0, 119.7, 117.0, 114.9, 113.4, 104.7, 65.4, 63.7,58.6, 54.0, 51.5, 36.6, 23.5; Anal Calcd. for ($C_{26}H_{25}N_3O_5$): C, 67.96; H, 5.48; N, 9.14; Found: C, 68.04; H, 5.41; N, 9.20%.

*2-Amino-4-(4-((4-bromobenzyl)oxy)phenyl)-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile (**4d**)*

Navajo white crystals; m.p: 249–250 °C; FT-IR (KBr) (ν_{max}, cm^{-1}): 3398, 3284, 3177, 2911, 2861, 2193, 1710, 1671, 1598, 1377, 1236, 1170, 1056, 1013, 873, 806, 757; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.91 (dd, 1H, ^1J = 6 Hz, ^2J = 3 Hz, CH_{Ar}), 7.75–7.64 (m, 1H, CH_{Ar}), 7.59 (dd, 2H, ^1J = 6 Hz, ^2J = 3 Hz, CH_{Ar}), 7.53–7.39 (m, 6H, CH_{Ar}, NH_2), 7.20 (d, 2H, J = 9 Hz, CH_{Ar}), 6.96 (d, J = 9 Hz, 2H, CH_{Ar}), 5.06 (s, 2H, CH_{2Bn}), 4.42 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 160.0, 158.4, 157.8, 153.6, 152.4, 137.1, 136.3, 133.3, 131.9, 130.2, 129.3, 125.1, 122.9, 121.4, 119.8, 117.0, 115.1, 113.5, 104.7, 68.9, 58.6, 36.7. Anal Calcd. for ($C_{26}H_{17}BrN_2O_4$): C, 62.29; H, 3.42; N, 5.59; Found: C, 62.34; H, 3.39; N, 5.63%.

*2-Amino-4-(4-((4-chlorobenzyl)oxy)phenyl)-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile (**4e**)*

Navajo white crystals, m.p: 246–148 °C; FT-IR (KBr) (ν_{max}, cm^{-1}): 3398, 3286, 3180, 2911, 2863, 2193, 1714, 1672, 1600, 1378, 1237, 1208, 756. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.92 (dd, 1H, ^1J = 6 Hz, ^2J = 3 Hz, CH_{Ar}), 7.75–7.69 (m, 1H, CH_{Ar}), 7.53–7.43 (m, 6H, CH_{Ar}), 7.39 (brs, 2H, NH_2), 7.21 (d, J = 9 Hz, 2H, CH_{Ar}), 6.97 (d, J = 9 Hz, 2H, CH_{Ar}), 5.08 (s, 2H, CH_{2Bn}), 4.42 (s, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 160.0, 158.4, 157.8, 153.6, 152.5, 136.6, 136.2, 133.3, 132.8, 129.9, 129.2, 128.9, 125.1, 122.9, 119.7, 117.0, 114.8, 113.4, 104.7, 68.8, 58.6, 36.6. Anal Calcd. for ($C_{26}H_{17}ClN_2O_4$): C, 68.35; H, 3.75; N, 6.13; Found: C, 68.33; H, 3.69; N, 6.15%.

*2-Amino-4-(4-((3-chlorobenzyl)oxy)phenyl)-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile (**4f**)*

Navajo white crystals; m.p: 223–225 °C; FT-IR (KBr) (ν_{max}, cm^{-1}): 3393, 3325, 3197, 2922, 2853, 2201, 1711, 1672, 1605, 1490, 1380, 1264, 1173, 1052, 805, 757; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.92 (dd, 1H, ^1J = 6 Hz, ^2J = 3 Hz, CH_{Ar}), 7.76–7.71 (m, 1H, CH_{Ar}), 7.49–7.39 (m, 8H, $3CH_{Ar}$, NH_2), 7.26 (t, 1H, J = 9 Hz, CH_{Ar}), 6.92–6.86 (m, 3H, CH_{Ar}), 5.07 (s, 2H, CH_{2Bn}), 4.45 (s, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 160.0, 158.8, 158.5, 153.9, 152.6, 145.4, 136.4, 133.4, 132.8, 130.1, 130.0, 128.8, 125.1, 122.9, 120.7, 117.0, 114.8, 113.4,

104.3, 68.8, 58.3, 37.3. Anal Calcd. for ($C_{26}H_{17}ClN_2O_4$): C, 68.35; H, 3.75; N, 6.13; Found: C, 68.37; H, 3.80; N, 6.09%.

2-(4-((4-chlorobenzyl)oxy)benzylidene)malononitrile (int. **7e**) m.p. 174–176 °C; IR (KBr) (ν_{max}, cm^{-1}): 3032, 2924, 2853, 2221, 1603, 1582, 1433, 1274, 1178, 1013, 828, 798; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.41 (1H, s, $CH_{vinylic}$), 7.99 (2H, d, J = 9 Hz, CH_{Ar}), 7.53–7.46 (4H, m, CH_{Ar}), 7.27 (2H, d, J = 9 Hz, CH_{Ar}), 5.26 (2H, s, OCH_2). ^{13}CNMR (75 MHz, DMSO-d_6) δ (ppm): 163.6, 160.8, 135.5, 133.8, 133.2, 130.2, 129.0, 124.8, 116.4, 115.7, 115.2, 114.3, 77.6, 69.4. Anal. Calcd for ($C_{17}H_{11}ClN_2O$): C, 69.28; H, 3.76; N, 9.50; Found: C, 69.25; H, 3.77; N, 9.55.

Results and discussion

Characterization of catalyst

Molybdenum(VI) oxide nanoparticles were synthesized by a slight modification of the solvothermal method [62]. The functional groups of the MoO_3 with the best crystalline degree were identified by FT-IR (Supplementary materials: Fig. S29). The FT-IR spectrum of MoO_3 NPs shows three strong peaks at 990 cm^{-1} attributed to the stretching vibration of the terminal M=O bond with an indicator of the layered orthorhombic MoO_3 lattice, 855 cm^{-1} attributed to the stretching vibration of Mo–O–Mo bonds, and a broad band at 558 cm^{-1} corresponding to the bending stretching vibration of an oxygen atom linked to three Mo atoms [63, 64].

Figure 2 shows the X-ray diffraction pattern (XRD) of the MoO_3 NPs. In the XRD pattern, the distinguished diffraction peaks centered at $2\theta \sim$ 23.7°, 25.9°, 27.1°, 33.7°, 33.9°, 35.8°, 39.1°, and 49.2° related,respectively, to the (001), (011), (021), (101), (111), (121), (051) and (002) planes of the MoO_3 with an rutile phase which is in agreement with the standard data for the MoO_3 orthorhombic lattice structure (JCPDS: 05-0506) [9b].

Also, an EDAX study of the MoO_3 NPs showed peaks corresponding to molybdenum and oxygen only which proves that the catalyst is essentially pure (Fig. 3). Furthermore, to support the stability of the catalyst at higher temperatures, thermogravimetric analysis (TGA) of MoO_3 NPs was performed (Fig. 4). The TGA curve shows that the weight percent remains constant until about 780 °C. Therefore, it was found that the catalyst is stable at temperatures below 780 °C.

SEM was used to observe the morphology of MoO_3 NPs (Fig. 5). SEM images of MoO_3 NPs show that they have a diameter of about 40 nm without any amorphous or other kinds of crystallized phase particles. In addition, the TEM images of the nanoparticles were studied for more investigation of their morphology (Fig. 6) and showed the MoO_3 NPs have a homogeneous diameter size of about 40 nm.

Synthesis of pyrano-fuzed coumarins using MoO_3 NPs

Before running this three-component reaction, it was necessary to prepare benzaldehydes containing alkylamine ethers. For this aim, 4-hydroxybenzaldehyde

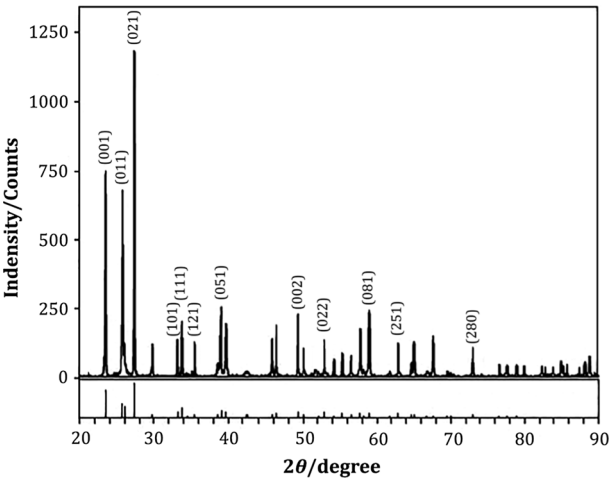


Fig. 2 X-ray diffraction pattern of the MoO_3 NPs

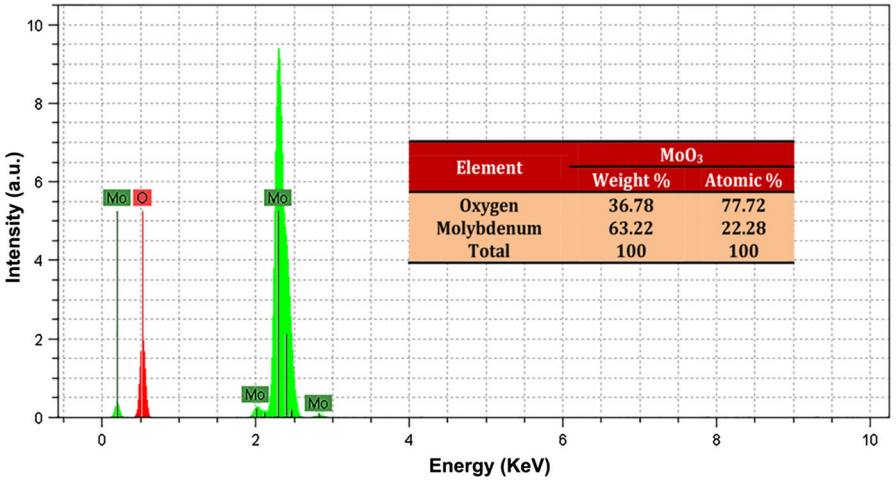


Fig. 3 EDAX spectrum of MoO_3 nanoparticles

was reacted with appropriate alkylhalides to obtain the desired aldehydes containing alkylamine ethers. This procedure was run according to a previously reported methodology [61], and the chemical structures of obtained aldehydes were strongly confirmed by comparing their physical and spectroscopic data with those reported in the literature [61].

After the MoO_3 NPs, and desired aldehydes were prepared and characterized, they were applied to the synthesis of 4-phenyl-substituted pyrano-fuzed coumarins via a green, one-pot reaction (Scheme 1).

Before starting to expand and examine the scope of the reaction, compound **4g** was selected as model to find best conditions for running the reaction (Table 1).

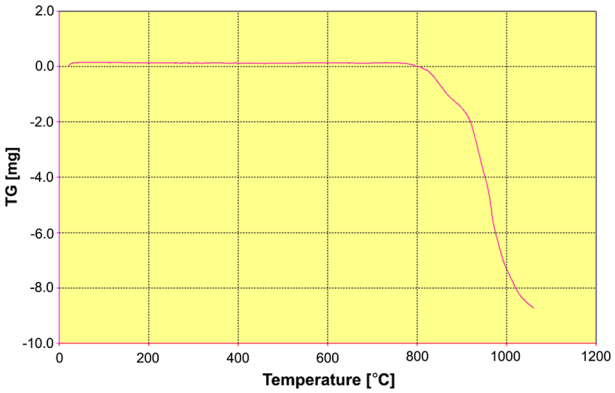


Fig. 4 Thermogravimetric analysis of MoO_3 NPs

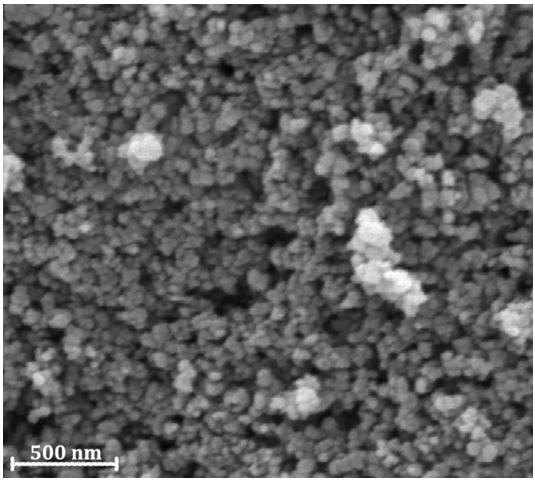


Fig. 5 Scanning electron microscopy of MoO_3 NPs

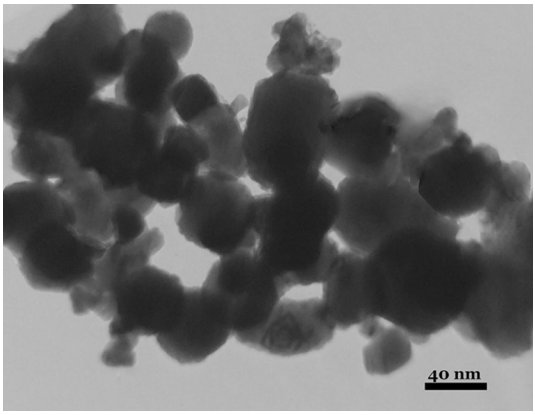


Fig. 6 TEM image of MoO_3 NPs

At first, the reaction was loaded in catalyst-free condition. It was observed that no remarkable target product was obtained. Also, among the examined acidic and basic catalysts, MoO_3 NPs showed better efficiency than the others. Furthermore, the mix of EtOH and H_2O with a 1:1 ratio was not only more effective than other pure solvents such as EtOH, H_2O, CH_3CN, CH_2Cl_2 or $CHCl_3$ but also showed more efficiency than other ratios of mixed EtOH and H_2O. Among different examined conditions, the use of MoO_3 NPs in aqueous medium [EtOH/H_2O (4:1)] at 80 °C disclosed the best efficiency tofor the synthesis of the product (Table 1).

On the other hand, further investigations to find the optimum amounts of the required catalyst im the model reaction revealed that the yield of the product was at a maximum (90%) when 5 mol% of MoO_3 NPs was used, while using another amounts of the catalyst (for instance 3, 4, 6 and 7 mol%) did not lead to maximum yield.

From the above, it was decided to carry out the reaction in aqueous medium [EtOH/H_2O (4:1)] in the presence of MoO_3 NPs (5 mol%) at 80 °C. To examine the generality of the reaction, compound **3** as one of the starting materials in this three-component reaction was exchanged to lead to the synthesis of some novel and known heterocycles with good to excellent yields. The results are summarized in Table 2 [65–67].

As can be seen from Table 2, the use of aryl aldehydes bearing either electron-donating or electron-withdrawing groups leads to obtaining products with good to excellent yields without remarkable differences in the yields. However, for compounds **4a**–**c**, the yields of cproducts are slightly less than others in which aryl aldehydes bearing alkyl amine side chains have been used.

Table 1 Effect of different conditions to the synthesis of **4g**

Entry	Conditions[a]	Yield[b] (%)
1	Catalyst-free, EtOH, reflux	Trace
2	MoO_3 NPs, EtOH, r.t.	37
3	MoO_3 NPs, EtOH, reflux	82
4	MoO_3 NPs, H_2O, reflux	68
5	MoO_3 NPs, EtOH/H_2O (1:1), 80 °C	70
6	MoO_3 NPs, EtOH/H_2O (2:1), 80 °C	79
7	MoO_3 NPs, EtOH/H_2O (4:1), 80 °C	90
8	MoO_3 NPs, EtOH/H_2O (5:1), 80 °C	84
9	SSA, EtOH/H_2O (4:1), 80 °C	83
10	*p*-TSA, EtOH/H_2O (4:1), 80 °C	73
11	*p*-TSA, CH_3CN, reflux	50
12	SSA, CH_3CN, reflux	57
13	SSA, CH_2Cl_2, reflux	Trace
14	$In(OTf)_3$, $CHCl_3$, reflux	37
15	Na_2CO_3, CH_2Cl_2, reflux	Trace
16	Na_2HPO_4, $CHCl_3$, reflux	30

[a]Reaction time: 30 min; catalyst amount: 5 mol%; amount of solvent: 10 mL

[b]Isolated yield

This innovation in the synthesis of different kinds of potentially interesting biologically active heterocycles which were obtained by the exchange of two starting materials may attract the attention of pharmacologists and pharmacists in the future, especially when these products show important biological and pharmacological activities. It is believed that these compounds will be biologically active because there is strong evidence that their analogues are biologically active [35–38].

It is believed that demonstrating the biological and pharmacological activities of these compounds is appropriate because there are proven biologically active fragments in their chemical structures.

Investigation of reaction mechanism

An admissible mechanism for the synthesis of phenyl-substituted pyranocoumarins is given in Scheme 2. In this proposed pathway, in a first step, malononitrile (**2**) and aldehyde (**3**) are reacted together in the presence of MoO_3 NPs to give intermediate (**7**). In the next step, 4-hydroxycoumarin is attacked to (**7**) and followed by an enol-keto tautomerization, Intermediate (**8**) is formed. Finally, (**8**) is converted to product (**4**) by the attack of enolic OH to the nitrile group via an intramolecular cyclization procedure. It can be obviously seen from the reaction mechanism that MoO_3 NPs play a key role in the activation of reactants to interact with each other in all the steps that subsequently lead to accelerating the reaction progress.

In addition, before adding 4-hydroxycoumarin to the reaction mixture, intermediate (**7e**) was separated as the sole material and successfully characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis (see representative spectral data and supplementary materials: Figs. S27, S28). This observation strongly confirms the above proposed reaction mechanism.

Investigation of catalyst recycling

In the other investigation, as one of the noteworthy aspects of this methodology is the capability of catalyst to be reused which makes it industrially and economically important, the recyclability of MoO_3 NPs was also evaluated on a model reaction (Fig. 7). This investigation reveals that MoO_3 NPs can efficiently catalyze the reaction up to six times without remarkable loss of its activity.

In addition, the BET method was applied to identify the specific surface area (S_{BET}) of the catalyst before the first and after the sixth runs, respectively (Supplementary materials, Figs S30, S31). The BET analysis ofthe catalyst before the first run showed a specific surface area of 47 $m^2\ g^{-1}$. Also, this analysis of the specific surface area of the catalyst after the sixth run was 41 $m^2\ g^{-1}$. Therefore, the results from the BET analyses revealed that there is no significant decline in the surface area of the catalyst before and after use, which results are completely compatible with those obtained from the reusability of catalyst. Furthermore, the TEM image and XRD pattern of the catalyst after use clearly demonstrated that no remarkable agglomeration or changes in the crystalline phase have occurred over each run (Supplementary materials, Figs S32, S33). From both these observations, it

Table 2 Investigations of the scope of substrates to the synthesis of 4-phenyl-substituted pyrano-fuzed coumarins[a]

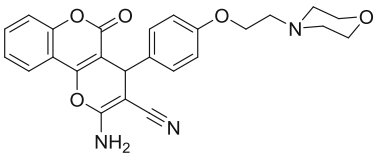
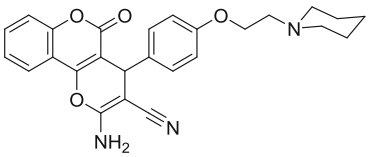
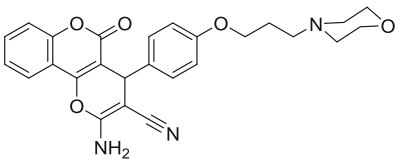
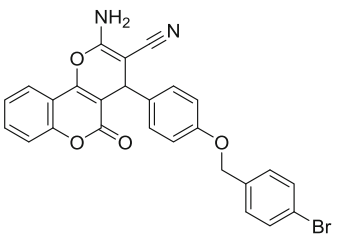
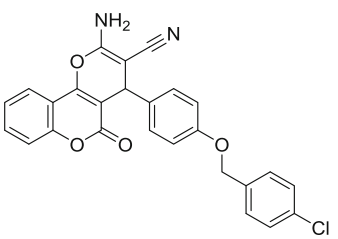
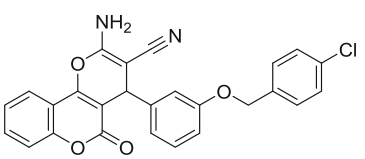
Entry	Product	Time (min)	Yield[b] (%)	M.P. (lit.)
1	 **4a**	45	88	191–193[c]
2	 **4b**	50	87	185–186[c]
3	 **4c**	50	88	170–173[c]
4	 **4d**	40	93	249–250[c]
5	 **4e**	40	90	246–248[c]
6	 **4f**	40	92	223–225[c]

Table 2 continued

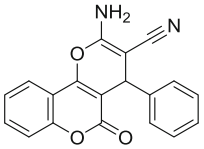
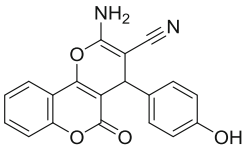
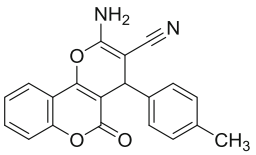
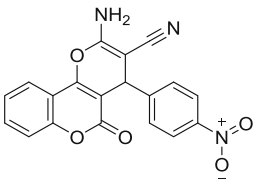
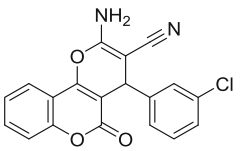
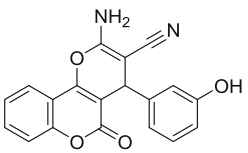
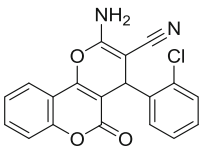
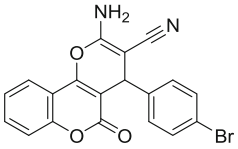
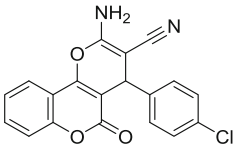
Entry	Product	Time (min)	Yield[b] (%)	M.P. (lit.)
7	 **4g**	30	90	260–262 (261–263) [65]
8	 **4h**	35	88	259–260 (258–260) [65]
9	 **4i**	30	90	253–256 (257–259) [65]
10	 **4j**	30	95	251–254 (250–252) [65]
11	 **4k**	30	91	247–249 (248–249) [66]
12	 **4l**	45	89	269–270 (266–267) [67]
13	 **4m**	30	93	273–275 (274–275) [66]

Table 2 continued

Entry	Product	Time (min)	Yield[b] (%)	M.P. (lit.)
14	 **4n**	30	95	256–257 (255–257) [66]
15	 **4o**	30	91	264–265 (265–267) [65]

[a]Reaction conditions: 4-hydroxycoumarin **1** (1 mmol), malononitrile **2** (1.5 mmol), appropriate aldehyde **3** (1 mmol), MoO_3 NPs (5 mol%), EtOH/H_2O (4:1) at 80 °C

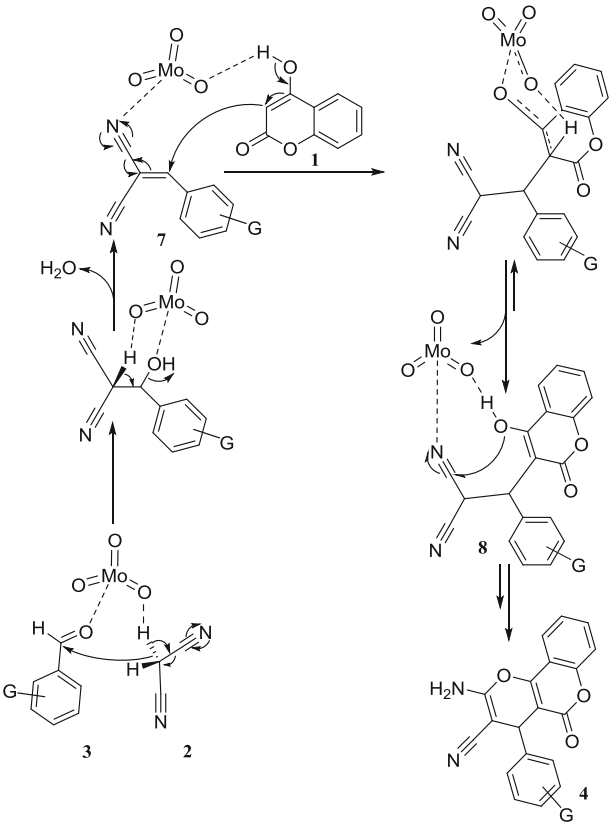
[b]Isolated yield

[c]Novel compound

can be better understood that reuse of MoO_3 NPs over six successive runs furnished (**4g**) in comparable yields to that obtained with a freshly prepared catalyst.

Conclusion

In summary, a green nanocatalytic approach for the synthesis of newly prepared potentially interesting and biologically active heterocycles has been described by the use of MoO_3 NPs as a highly efficient nano-catalyst, and in addition the scope of potentially biologically active heterocycles was developed. By this procedure, some novel products were obtained which can be candidates for medicinally important compounds or even important drugs in the future. It is believed that this methodology will attract the interest of chemists, biologists and pharmacologists in the future. Also, a new application of MoO_3 NPs as an eco-friendly, highly efficient, recyclable, and easily handled nano-catalyst for the synthesis of heterocyclic compounds has been introduced. The merit of this protocol is the synthesis of new kinds of organic compounds by the use of an efficient nano-Lewis acid catalyst and environmentally benign conditions with good to excellent yields.



Scheme 2 A proposed mechanism for the catalytic synthesis of product (**4**) by MoO_3 NPs

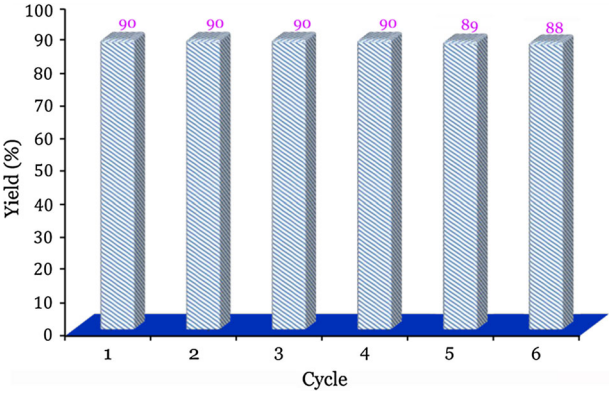


Fig. 7 Reusability of MoO_3 NPs over six runs

Acknowledgement The authors gratefully thank the Pharmaceutics Research Center, Institute of Neuropharmacology and Research Central Labratory, Kerman University of Medical Sciences for supporting this work.

References

1. A.K. Dalai, J.A. Kozinski, N. Abatzoglou, M. Azhar-Uddin, Catal. Today **291**, 1 (2017)
2. Y. Wu, Z. Fu, D. Yin, Q. Xu, F. Liu, C. Lu, L. Mao, Green Chem. **12**, 696 (2010)
3. K. Eskandari, B. Karami, S. Khodabakhshi, Catal. Commun. **54**, 124 (2014)
4. N. Salehi, B.B.F. Mirjalili, RSC Adv. **7**, 30303 (2017)
5. K. Eskandari, B. Karami, S. Khodabakhshi, Chem. Heterocycl. Compd. **50**, 1658 (2015)
6. K. Eskandari, B. Karami, Comb. Chem. High Throughput Screening **19**, 728 (2016)
7. T. Wanga, C. Li, L. Zhao, J. Zhanga, S. Li, G. Zenga, Appl. Surf. Sci. **400**, 227 (2017)
8. K. Yin, S. Mahamulkar, J. Xie, H. Shibata, A. Malek, L. Li, C.W. Jones, P. Agrawal, R.J. Davis, Appl. Catal. A Gen. **535**, 17 (2017)
9. F. Wang, W. Ueda, Chem. Eur. J. **15**, 742 (2009)
10. N.R. Dighore, P.L. Anandgaonker, S.T. Gaikwad, A.S. Rajbhoj, Mater. Sci. Pol. **33**, 163 (2015)
11. K. Murugappan, C. Mukarakate, S. Budhi, M. Shetty, M.R. Nimlos, Y. Roman-Leshkov, Green Chem. **18**, 5548 (2016)
12. M. Zare, Z. Moradi-Shoeili, F. Ashouri, M. Bagherzadeh, Catal. Commun. **88**, 9 (2017)
13. K. Ding, A. Gulec, A.M. Johnson, T.L. Drake, W. Wu, Y. Lin, E. Weitz, L.D. Marks, P.C. Stair, ACS Catal. **6**, 5740 (2016)
14. K. Murugappan, C. Mukarakate, S. Budhi, M. Shetty, M.R. Nimlos, Y. Román-Leshkov, Green Chem. **18**, 5548 (2016)
15. X. Ma, R. Ma, W. Hao, M. Chen, F. Yan, K. Cui, Y. Tian, Y. Li, ACS Catal. **5**, 4803 (2015)
16. A. Bahuguna, S. Kumar, V. Sharma, K.L. Reddy, K. Bhattacharyya, P.C. Ravikumar, V. Krishnan, ACS Sustain. Chem. Eng. **5**, 8551 (2017)
17. A.R. Mouat, T.L. Lohr, E.C. Wegener, J.T. Miller, M. Delferro, P.C. Stair, T.J. Marks, ACS Catal. **6**, 6762 (2016)
18. T. Asano, M. Tamura, Y. Nakagawa, K. Tomishige, ACS Sustain. Chem. Eng. **4**, 6253 (2016)
19. J.H. Clark, Nat. Chem. **1**, 12 (2009)
20. K. Eskandari, B. Karami, M. Farahi, V. Mouzari, Tetrahedron Lett. **57**, 487 (2016)
21. A. Gupta, S.R. Chaphalkar, J. Herbmed. Pharmacol. **5**, 7 (2016)
22. K. Eskandari, B. Karami, S. Khodabakhshi, J. Chem. Res. **38**, 600 (2014)
23. A.V. Ivachtchenko, Y.A. Ivanenkov, V.M. Kysil, M.Y. Krasavin, A.P. Ilyin, Russ. Chem. Rev. **79**, 787 (2010)
24. V. Nair, B.P. Babu, V. Varghese, C.R. Sinu, R.R. Paul, E.R. Anabha, E. Suresh, Tetrahedron Lett. **50**, 3716 (2009)
25. S. Khodabakhshi, B. Karami, K. Eskandari, Heterocycles **89**, 1670 (2014)
26. R. Bharti, T. Parvin, RSC Adv. **5**, 66833 (2015)
27. K. Eskandari, M. Rafieian-Kopaei, Chem. Heterocycl. Compd. **52**, 158 (2016)
28. N.O. Zarmouh, S.K. Eyunni, K.F.A. Soliman, BMC Complement. Altern. Med. **17**, 34 (2017)
29. M.R. Khazdair, M.H. Boskabady, J. HerbMed Pharmacol. **4**, 40 (2015)
30. K. Eskandari, B. Karami, Monatsh. Chem. **147**, 2119 (2016)
31. L. Chen, J. Lin, B. Chen, L. Zhao, Res. Chem. Intermed. **43**, 6691 (2017)
32. H. Kiyani, M. Tazari, Res. Chem. Intermed. **43**, 6639 (2017)
33. K. Eskandari, B. Karami, S. Khodabakhshi, M. Farahi, J. Chin. Chem. Soc. **62**, 473 (2015)
34. S. Rahmani-Nezhad, L. Khosravani, M. Saeedi, K. Divsalar, L. Firoozpour, Y. Pourshojaei, Y. Sarrafi, H. Nadri, A. Moradi, M. Mahdavi, A. Shafiee, A. Foroumadi, Synth. Commun. **45**, 741 (2015)
35. A. Witaicenis, L.N. Seito, A.S. Chagas, L.D.A. Junior, A.C. Luchini, P. Rodrigues-Orsi, Phytomedicine **21**, 240 (2014)
36. T. Nasr, S. Bondock, M. Youns, Eur. J. Med. Chem. **76**, 539 (2014)
37. J. Bronikowska, E. Szliszka, D. Jaworska, Z.P. Czuba, W. Krol, Molecules **17**, 6449 (2012)
38. C. Canning, S. Sun, X. Ji, S. Gupta, K. Zhou, J. Ethnopharmacol. **147**, 259 (2013)

39. B. Karami, S. Khodabakhshi, K. Eskandari, Lett. Org. Chem. **10**, 105 (2013)
40. B. Karami, S. Khodabakhshi, K. Eskandari, Synlett **24**, 998 (2013)
41. P.P. Ghosh, A.R. Das, Tetrahedron Lett. **53**, 3140 (2012)
42. S. Hesse, G. Kirsch, Tetrahedron Lett. **43**, 1213 (2002)
43. B. Karami, K. Eskandari, S. Khodabakhshi, J. Iran. Chem. Soc. **11**, 631 (2014)
44. S. Khodabakhshi, B. Karami, K. Eskandari, Res. Chem. Intermed. **41**, 7263 (2015)
45. B.H. Lee, M.F. Clothier, F.E. Dutton, G.A. Conder, S.S. Johnson, Bioorg. Med. Chem. Lett. **8**, 3317 (1998)
46. J.C. Jung, Y.J. Jung, O.S. Park, Synth. Commun. **31**, 1195 (2001)
47. G. Melagraki, A. Afantitis, O. Igglessi-Markopoulou, A. Detsi, M. Koufaki, C. Kontogiorgis, D.J. Hadjipavlou-Litina, Eur. J. Med. Chem. **44**, 3020 (2009)
48. S. Yang, L. Shen, Y.J. Kim, J.H. Jeong, Org. Biomol. Chem. **14**, 623 (2016)
49. U. Kayal, R. Karmakar, D. Banerjee, G. Maiti, Tetrahedron **70**, 7016 (2014)
50. T. Balalas, A. Abdul-Sada, D.J. Hadjipavlou-Litina, K.E. Litinas, Synthesis **49**, 2575 (2017)
51. R. Porta, F. Coccia, R. Annunziata, A. Puglisi, ChemCatChem. **7**, 1490 (2015)
52. A. Banerji, A.A. Long, C.A. Camargo, Allergy Asthma Proc. **28**, 418 (2007)
53. D.D. Kim, J. Krishnarajah, S. Lillioja, F. Looze, J. Marjason, J. Proietto, S. Shakib, B.G.A. Stuckey, J.E. Vath, T.E. Hughes, Diabetes Obes. Metab. **17**, 566 (2015)
54. Y. Pourshojaei, A. Gouranourimi, S. Hekmat, A. Asadipour, S. Rahmani-Nezhad, A. Moradi, H. Nadri, F. Homayouni-Moghadam, S. Emami, A. Foroumadi, Eur. J. Med. Chem. **97**, 181 (2015)
55. B. Karami, R. Ferdosian, K. Eskandari, J. Chem. Res. **38**, 41 (2014)
56. B. Karami, K. Eskandari, Z. Zare, S. Gholipour, Chem. Heterocycl. Compd. **49**, 1715 (2014)
57. M.R. Saidi, Y. Pourshojaei, F. Aryanasab, Synth. Commun. **39**, 1109 (2009)
58. A. Asadipour, Z. Shams, K. Eskandari, M.H. Moshafi, E. Faghih-Mirzaei, Y. Pourshojaei, Res. Chem. Intermed. (2017).
59. A.Z. Halimehjani, Y. Pourshojaei, M.R. Saidi, Tetrahedron Lett. **50**, 32 (2009)
60. S. Rahmani-Nezhad, M. Safavi, M. Pordeli, S. Kabudanian-Ardestani, L. Khosravani, Y. Pourshojaei, M. Mahdavi, S. Emami, A. Foroumadi, A. Shafiee, Eur. J. Med. Chem. **86**, 562 (2014)
61. F. Mehrabi, Y. Pourshojaei, A. Moradi, M. Sharifzadeh, L. Khosravani, R. Sabourian, S. Rahmani-Nezhad, M. Mohammadi-Khanaposhtani, M. Mahdavi, A. Asadipour, H.R. Rahimi, S. Moghimi, A. Foroumadi, Future Med. Chem. **9**, 659 (2017)
62. P. Wongkrua, T. Thongtem, S. Thongtem, J. Nanomater. **2013**, 1 (2013)
63. Y. Chen, C. Lu, L. Xu, Y. Ma, W. Hou, J. Zhu, Cryst. Eng. Commun. **12**, 3740 (2010)
64. A. Klinbumrung, T. Thongtem, S. Thongtem, J. Nanomater. **2012**, 5 (2012)
65. M.G. Dekamin, M. Eslami, A. Maleki, Tetrahedron **69**, 1074 (2013)
66. Y. Wang, J. Luo, T. Xing, Z. Liu, Monatsh. Chem. **144**, 1871 (2013)
67. H. Kiyani, M.S. Jalali, Comb. Chem. High Throughput Screening **19**, 275 (2016)
68. H.M.H.G. Albers, L.J.D. Hendrickx, R.J.P. Van-Tol, J. Hausmann, A. Perrakis, H. Ovaa, J. Med. Chem. **54**, 4619 (2011)
69. R. Carrasco-Gomez, S. Keppner-Witter, M. Hieke, L. Lange, G. Schneider, M. Schubert-Zsilavecz, E. Proschak, B. Spankuch, Bioorg. Med. Chem. Lett. **24**, 5063 (2014)