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Synthesis of some 4*H*-Pyran Derivatives Using Bio-synthesized ZnO Nanoparticles and the Evaluation of their Biological Activities

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ZnO Nanoparticles were simply synthesized by green biosynthesis method using ficus carica leaf extract. The structure of these nanoparticles was assigned using Fourier transform infrared spectroscopy (IR), Field emission-scanning electron microscopy (FE-SEM), and X-ray powder diffraction (XRD). The catalytic activity of these nanoparticles was studied for the synthesis of 4*H*-pyrans. A series of 4*H*-pyrans 3(a-l) were synthesized in good to high yields by reaction of corresponding α,α′-bis(substituted benzylidene) cycloalkanones and malononitrile in the presence of ZnO nanoparticles as a catalyst at 110 °C. This environmentally friendly method has some advantages such as high efficiency, use of available catalyst, solvent-free reaction conditions, and easy operation. The antibacterial activity of synthesized 4*H*-pyrans was also tested using Staphylococcus aureus and Escherichia coli bacterial strains.

Keywords: ZnO, 4*H*-pyrans, Catalyst, Malononitrile, Ficus carica leaves

INTRODUCTION

Recently, the synthesis of heterocyclic compounds due to their valuable properties has attracted much attention in organic chemistry and especially medicinal chemistry. 4*H*-pyrans are an important group of heterocyclic compounds that have shown specific pharmacological and biological activities such as anti-HIV [1], anti-cancer [2], antiallergic [3], antitumor [4], and antibacterial [5]. Also, 4*H*-pyrans are applied as potential biodegradable agrochemicals [6], photoactive materials [7], and pigments [8]. Several catalytic procedures have been reported for the synthesis of 4*H*-pyrans in the literature using two-component and three-component reactions. Various catalysts such as ammonia [9], tetrabutylammonium bromide [10], silica gel-supported polyphosphoric acid (PPA–SiO_2) [11], nanosized magnesium oxide [12] montmorillonite KSF [13], Piperazine-functionalized Fe_3O_4/SiO_2 magnetic nanoparticles [14], DABCO [15] Piperazine [16] and MgO nanostructures [17], have been used for these reactions. Although these methods have some advantages, they still have limitations such as difficult reaction conditions, long reaction time, low efficiency, use of toxic solvents, and expensive or unavailable reagents as part of our ongoing research into the development of simple and useful synthetic protocols including synthesis of pyran derivatives[16,17] and also due to application of nano ZnO in organic processes [18-23], herein, we wish to report an easy, effective, suitable method for the production of 4*H*-pyran derivatives from α,ά-bis(substituted benzylidene) cycloalkanones and malononitrile under solvent-free conditions using ZnO nanoparticles (NP-ZnO) as a heterogeneous catalyst (Scheme 1).

EXPERIMENTAL

Materials and Measurements

All Chemicals were purchased from Merck and Aldrich

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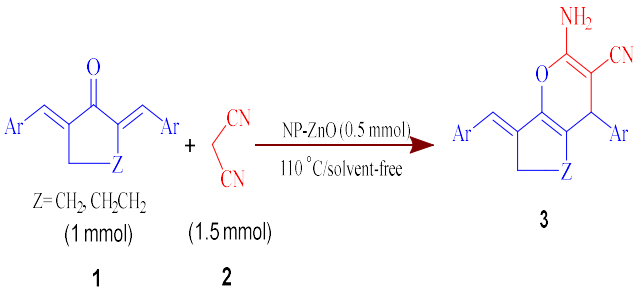


Scheme 1. The synthetic pathway of 4*H*-pyran derivatives

and used without further purification. All synthetic products were identified by comparing their physical constants as well as comparing their IR and NMR spectra with those reported in the literature. Melting points were measured by using electrothermal digital apparatus and are uncorrected. The progress of the reaction was performed by TLC. IR spectra were recorded using a JASCO4200 spectrometer in the KBr pellet. The powder X-Ray diffraction patterns were measured with a Philips X-pert diffractometer using Cr-Kα irradiation. FE-SEM coupled with EDAX was taken by a Zeiss/sigma vp-500 photograph to examine the shape and metallic composition of the samples. NMR spectra were recorded on a Brucker spectrophotometer (300 MHz) in DMSO using TMS as an internal standard.

Preparation of ZnO nanoparticles (NP-ZnO)

A mixture of de-ionized water (75 ml), ethanol (25 ml), and grinded Ficus carica leaves (10 g) was refluxed for 2 h. The resulting extract was filtered to separate the solid materials. Subsequently, two different solutions were prepared: Solution A: ficus carica leaves extract (25 ml) and n-hexane (30 ml) was added to a solution of $Zn(CH_3COO)_2.2H_2O$ (25 mmol) in water (50 ml). Solution B: a solution of ammonium carbonate (70 mmol) in 25 ml of ficus carica leaves extract. Solution B was then added dropwise to solution A while stirring by magnetic stirring and the resulting precipitate was filtered, washed with water (10 ml) several times, dried, and calcinated at 500 °C for 2 h.

General Procedure for Preparation of α,α′-Bis (substituted Benzylidene) Cycloalkanones

According to the reported method [24], a mixture of cycloalkanone (5 mmol), aromatic aldehyde (10 mmol), KOH (0.11 g), and ethanol (10 ml) were magnetically stirred at 40 °C. After completion of the reaction (monitored by TLC) the reaction mixture was cooled to room temperature and the obtained solid product was filtered and air dried, which was then recrystallized from ethanol to give the pure product.

General Procedure for Preparation of 4*H*-Pyran Derivatives

A mixture of α,α′-bis (substituted benzylidene) cycloalkanones 1 (1 mmol), malononitrile 2 (1.5 mmol), and ZnO nanoparticles (0.50 mmol) was stirred at 110 °C under solvent-free conditions for a preferred time as given in Table 3. After completion of the reaction, followed by TLC (n-hexane/ethyl acetate 7:3) and hot ethanol (5 ml) were added and cooled to room temperature. Then water (10 ml) was added and the product was filtered and dried. Finally, the solid product obtained was dissolved in N,N-dimethylformamide (DMF) to separate the heterogeneous catalyst and evaporate the solvent. The product was recrystallized from ethanol to give a pure product.

Selected Data for 4*H*-pyran Derivatives

(E)-2-Amino-8-benzylidene-4-phenyl-5,6,7,8-tetra-hydro-4*H*-chromene-3-carbonitrile (3a). Yield: 90%, Mp: 234-236 °C, white crystals. IR (KBr, cm^{-1}): ν = 3431, 3340, 3179, 3024, 2920, 2850, 2192, 1675, 1616, 1590, 1575, 1490, 1450, 1420, 1262, 1150, 1138, 1041, 878, 699.

(E)-2-Amino-8-(2-chlorobenzylidene)-4-(2-chloro-phenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (3b). Yield: 87%, Mp: 239-241 °C, Light yellow crystals. IR (KBr, cm^{-1}): ν = 3468, 3343, 3261, 3213, 3062, 2918, 2829, 2192, 1676, 1636, 1592, 1477, 1440, 1413, 1381, 1256, 1130, 1038, 872, 751, 694, 567.

(E)-2-Amino-8-(2-bromobenzylidene)-4-(2-bromophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (3c). IR (KBr, cm^{-1}): *v* = 3462, 3347, 3251, 3208, 3051, 2919, 2834, 2195, 1672, 1633, 1594, 1463, 1405, 1334, 1250, 1213, 1019, 884, 746, 665. ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ = 7.48 (d, *J* = 8.4 Hz ,1H, ArH), 7.41(d, *J* = 7.8 Hz, 1H, ArH), 7.17-7.26 (m, 3H, NH_2, ArH), 6.99-7.09 (m, 3H, ArH), 6.75 (d, *J* = 6.3 Hz, 3H, ArH, C=CH), 4.39 (s, 1H, CH), 2.10-2.22 (m, 2H, CH_2), 1.84-1.90 (m, 1H, CH_2), 1.49-1.54 (m, 1H, CH_2), 1.27-1.33 (m, 2H, CH_2). ^{13}C NMR (DMSO, 75 MHz, ppm): δ = 160.49, 141.08, 137.09, 133.09, 132.92,131.47, 131.13, 129.60, 129.46, 129.20, 127.86, 124.15, 123.64, 122.29, 120.63, 120.51, 115.96, 115.93, 55.18, 42.52, 27.02, 26.88, 22.16. Anal. Calcd. for $C_{23}H_{18}Br_2N_2O$: C, 55.45; H, 3.64; N, 5.62. Found: C, 55.49; H, 3.41; N, 5.81.

(E)-2-Amino-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbo-nitrile (3d). Yield: 85%, Mp: 205-207 °C, Light yellow crystals. IR (KBr, cm^{-1}): *v* = 3462, 3347, 3251, 3208, 3051, 2919, 2834, 2195, 1672, 1633, 1594, 1463, 1405, 1334, 1250, 1213, 1019, 884, 746, 665.

(E)-2-Amino-8-(3-nitrobenzylidene)-4-(3-nitrophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbo-nitrile (3e). Yield: 86%, Mp: 241-243 °C, Orange powder. IR (KBr, cm^{-1}): *v* = 3443, 3334, 3260, 3219, 2932, 2855, 2192, 1678, 1641, 1606, 1580, 1520, 1416, 1354, 1135, 1038, 808, 734, 674.

(E)-2-Amino-8-(4-nitrobenzylidene)-4-(4-nitrophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbo-nitrile (3f). Yield: 81%, Mp: 217-219 °C, Orange powder. IR (KBr, cm^{-1}): *v* = 3466, 3369, 3260, 3202, 2920, 2846, 2192, 1675, 1635, 1591, 1540, 1514, 1423, 1337, 1262, 1130, 1102, 855, 705.

(E)-2-Amino-8-(4-methylbenzylidene)-4-(p-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (3g). Yield: 66%, Mp: 162-163 °C, Very light yellow crystals. IR (KBr, cm^{-1}): *v* = 3449, 3320, 3260, 3219, 2926, 2851, 2189, 1664, 1644, 1601, 1514, 1405, 1267, 1119, 1038, 878, 814, 671, 516.

(E)-2-Amino-8-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (3h). Yield: 53%, Mp: 222-224 °C, Cream crystals. IR (KBr, cm^{-1}): *v* = 3466, 3369, 3219, 3167, 2926, 2893, 2192, 1670, 1635, 1606, 1509, 1405, 1302, 1243, 1170, 1135, 1038, 872, 616.

(E)-2-Amino-7-benzylidene-4-phenyl-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carbonitrile (3i). Yield: 79%, Mp: 224-226 °C, white crystals. IR (KBr, cm^{-1}): *v* = 3449, 3334, 3249, 3202, 2920, 2850, 200, 1611, 1646, 1595, 1496, 1452, 1405, 1382, 1107, 919, 872, 767, 705.

(E)-2-Amino-7-(2-bromobenzylidene)-(2-bromophenyl)-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carbonitrile (3j). Yield: 84%, Mp: 211-213 °C, Light yellow crystals. IR (KBr, cm^{-1}): v = 3414, 3299, 3179, 3061, 2912, 2850, 2195, 1681, 1623, 1469, 1375, 1314, 1256, 1094, 1019, 953, 863, 663. ^{1}H-NMR (DMSO-d_6, 300 MHz, ppm): δ = 7.37-7.47 (m, 3H, NH_2, ArH), 6.93-7.24 (m, 7H, ArH), 6.44 (s, 1H, C=CH), 4.61 (s, 1H, CH), 2.55-2.61 (m, 2H, CH_2), 1.75-1.79 (m, 1H, CH_2), 0.95-1.00 (m, 1H, CH_2). ^{13}C NMR (DMSO-d6, 75 MHz, ppm): δ = 161.60, 146.30, 140.06, 136.49, 133.29, 129.76, 129.31, 129.12, 128.95, 128.23, 125.96, 123.91, 123.38, 120.71, 118.95, 115.71, 115.43, 11.18, 60.23, 55.07, 27.82, 26.38. Anal. Calcd. for $C_{22}H_{16}Br_2N_2O$: C, 54.57; H, 3.33; 8.81; N, 5.79. Found: C, 54.71; H, 3.26; N, 6.01.

(E)-2-Amino-7-(4-chlorobenzylidene)-4-(4-chlorophenyl)-4,5,6,7-etrahydrocyclopenta[b]pyran-3-carbonitrile (3k). Yield: 81%, Mp: 223-225 °C, Yellow crystals. IR (KBr, cm^{-1}): *v*= 3462, 3333, 3254, 3202, 2926, 2852, 2197, 1678, 1629, 1590, 1494, 1414, 1380, 1256, 1150, 1906, 1009, 955, 820, 514.

(E)-2-Amino-7-(3-nitrobenzylidene)-4-(3-nitrophenyl)-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carbonitrile (3l). Yield: 80%, Mp: 245-247 °C, Orange powder. IR (KBr, cm^{-1}): *v* = 3414, 3322, 3252, 3208, 3050, 2920, 2850, 2192, 1681, 1629, 1601, 1532, 1490, 1465, 1349, 1244, 1187, 1107, 900, 808, 746, 665.

Antibacterial Atudy

Determination of Minimum Inhibitory Concentration (MIC). The standard method was used to determine the minimum inhibitory concentration (MIC) of synthesized 4*H*-pyrans 3(a-l) with some modifications [25]. In summary, 25.6 mg of synthesized compounds 3(a-l) was dissolved in 1 ml DMSO and this solution was added to 99 ml of sterile Mueller-Hinton broth medium (Scharlau, Spain). The concentration of synthesized compounds 3(a-l) at this stage was found to be 256 µg ml^{-1}. Then, 1 ml of Mueller-Hinton broth medium was added into 10 sterilized glass tubes. 1 ml of synthesized compounds 3(a-l) solution was added to the first tube and serial dilutions were prepared. 1 ml of bacterial suspension with 0.5 McFarland turbidity was inoculated into each tube and all of them were incubated (37 °C, 24 h). After the end of the incubation period, the lack of turbidity in glass tubes was described as the antibacterial activity of the synthesized compounds 3(a-l). The minimum concentration of synthesized compounds 3(a-l) showing no turbidity was considered as the MIC. The strains used to determination of MIC values were Staphylococcus aureus (ATCC 35933) and Escherichia coli (ATCC 25922). The MICs of all compounds were determined and repeated three times.

RESULTS AND DISCUSSION

ZnO nanoparticles were synthesized by a green biosynthesis and comfortable method with using of ficus carica leaves extract as stabilizing agent, $Zn(CH_3COO)_2.2H_2O$ as basic materials, and ammonium carbonate as a precipitating agent. Zinc oxide is an ionic compound (Zn^{2+}–O^{2-}) and amphoteric oxide, this means that ZnO has Lewis base positions (O^{2-}) and Lewis acid positions (Zn^{2+}). Therefore, this property of zinc oxide was used for the synthesis of 4*H*-pyran derivatives. Lewis base position (O^{2-}) of NP-ZnO can abstract the acidic proton of malononitrile, and the Lewis acid (Zn^{2+}) of NP-ZnO may activate the carbonyl group of ketone for the Michael addition reaction. The structure of ZnO nanoparticles was approved using IR, XRD, FE-SEM, and EDX techniques. The FT-IR analysis of ZnO nanoparticles is shown in Fig. 1. The IR absorption

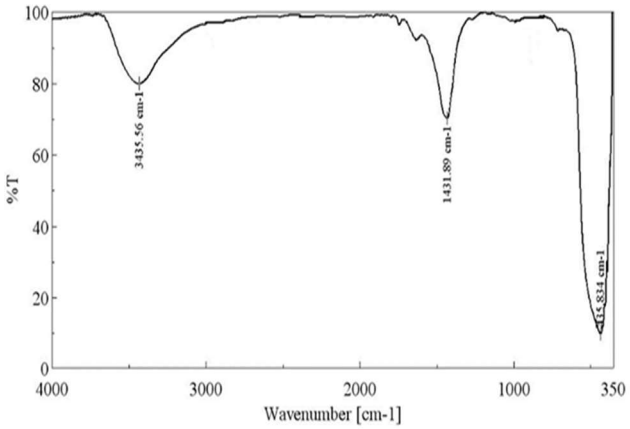


Fig. 1. The FT-IR spectrum of zinc oxide nanoparticles.

bands at 3435 and 1413 cm^{-1} ares are due to the stretching and bending vibrations mode of the hydroxyl (OH) group of atmospheric moisture and hydroxyl (OH) groups on the surface of zinc oxide nanoparticles [26-28]. The absorption band 435 cm^{-1} is assigned to the stretching vibrations of the (Zn-O) bond.

The XRD pattern of ZnO nanoparticles is presented in Fig. 2. This pattern shows six determined peaks at 2θ = 48.0°, 52.1°, 54.9°, 73.7°, 89.7° and 101.7°, which are related to the (100), (002), (101), (102), (110), (103) planes of ZnO, respectively. These results show that prepared ZnO

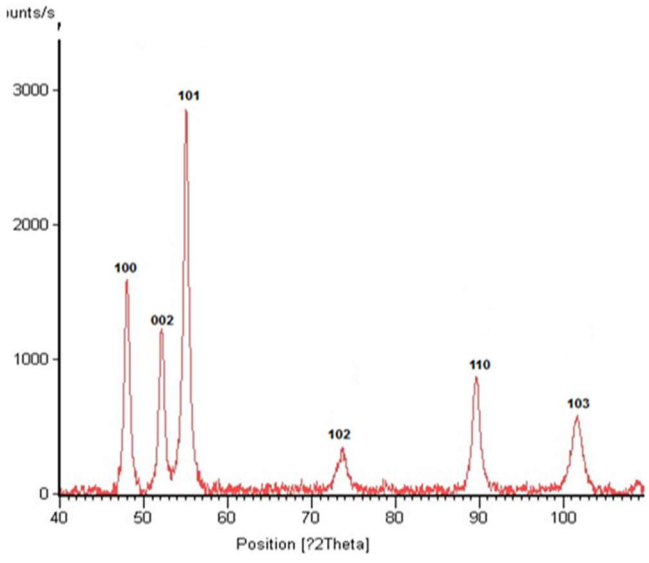


Fig. 2. The XRD pattern of zinc oxide nanoparticles.

nanoparticles are pure and have a wurtzite hexagonal structure and match well with standard zinc oxide (JCPDS card No.01-080-0074). The crystallite size of the ZnO nanoparticles was calculated with Debye-Scherrer's formula ($D = 0.9\lambda/\beta\cos\theta$), where D is the crystal size, λ- the wavelength of the X-ray radiation (k = 0.229 nm) for CrKα and β- the full width at half maximum (FWHM). The obtained crystallite size from the highest peak of (101) was found to be 37.5 nm.

The size and morphology of zinc oxide nanoparticles were investigated by Field Emission Scanning Electronic Microscopy (FE-SEM) (Fig. 3). This image shows that the morphology of zinc oxide nanoparticles is spherical. The results showed average nanoparticle size was equal to 32-50 nm. The elemental analysis of ZnO nanoparticles, was determined by EDX studies (Fig. 4). The EDX spectrum indicates that there are two elemental Zinc and Oxygen with no other impurities present in the prepared ZnO nanoparticles.

To investigate the effects of zinc oxide nanoparticles as a catalyst for the synthesis of 4*H*- pyrans under solvent-free conditions, the reaction between 2,6-di-benzylidene cyclohexanone with malononitrile was selected as a model. For optimization of conditions, the model reaction was carried out in the presence of different amounts of catalyst at different temperatures and using various solvents/or solvent-free. The solvent-free medium at 110 °C and the use of 0.5 mmol catalyst was found the best conditions for this reaction (Table 1. entry 5). Under optimal conditions, the Bulk-ZnO catalyst showed less activity than ZnO nanoparticles (Table 1, entry 6).

After optimizing the reaction conditions, different 4*H*-pyrans with electron donor and electron-withdrawing groups were synthesized using α,ά-bis(substituted benzylidene) cycloalkanones and malononitrile with good to high yields (Table 2). Benzylidines with electron-withdrawing groups participated in the reaction in shorter times and had better efficiencies than benzilidines with electron-donating groups.

The proposed mechanism for the synthesis of 4*H*-pyrans from α,ά-bis(substituted benzylidene) cycloalkanones, and malononitrile in the presence of ZnO nanoparticles is given in Scheme 2. Initially, the acidic proton of malononitrile is abstracted by the Lewis base site (O^{2-}) of NP-ZnO, Also Lewis acid sites (Zn^{2+}) of NP-ZnO activate the

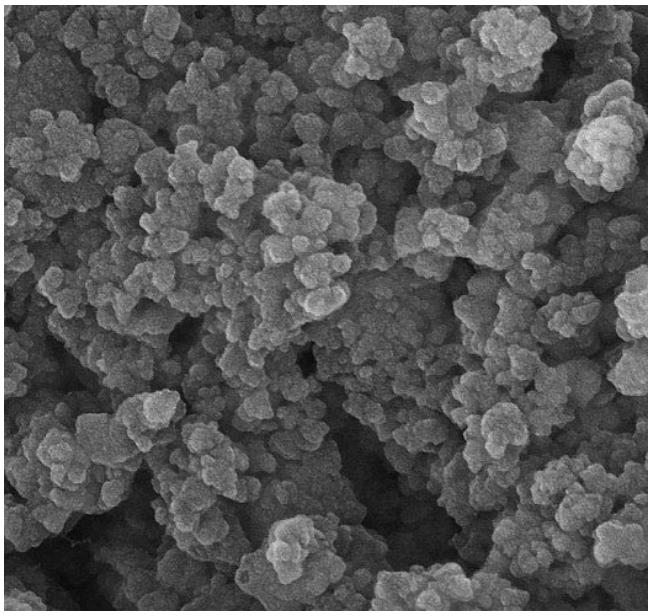


Fig. 3. The FE-SEM micrographs of zinc oxide nanoparticles.

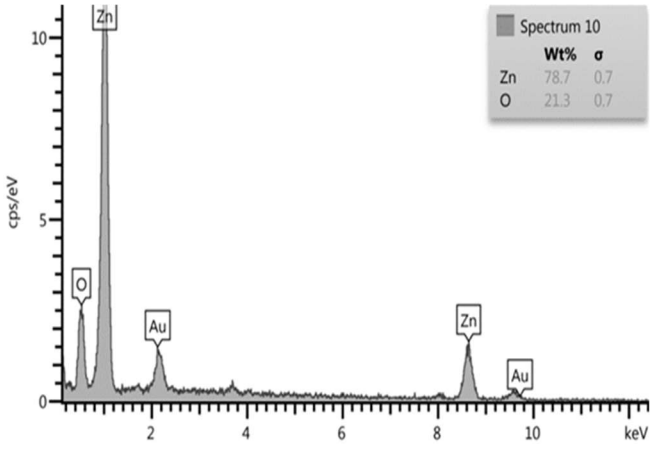


Fig. 4. The EDX analysis of zinc oxide nanoparticles.

carbonyl group of benzylidine. The created malononitrile carbanion reacts with the benzylidine compound via a Michael addition to give intermediate I, which could cyclize by nucleophilic attack of the OH group on the CN group. Finally, through tautomerization, the main product is obtained.

For the probe of the recycling and reusability of the catalyst, the reaction between α,ά-bis(substituted benzylidene) cycloalkanones (1 mmol) and malononitrile

Table 1. Optimization Conditions for the Reaction of 2,6-Dibenzylidenecyclohexanone with Malononitrile in the Presence of NP-ZnO Catalyst

Entry	Catalyst	T (°C)	Solvent	Time (min)	Yield (%)[a]
1	NP-ZnO (0.1 mmol)	110	Free	120	78
2	NP-ZnO (0.2 mmol)	110	Free	105	81
3	NP-ZnO (0.3 mmol)	110	Free	95	90
4	NP-ZnO (0.4 mmol)	110	Free	110	78
5	NP-ZnO (0. 5 mmol)	110	Free	80	90
6	Bulk-ZnO (0.5 mmol)	110	Free	210	69
7	NP-ZnO (0.5 mmol)	90	Free	120	75
8	NP-ZnO (0.5 mmol)	100	Free	80	80
9	NP-ZnO (0.5 mmol)	110	Free	80	90
10	NP-ZnO (0.5 mmol)	120	Free	75	80
11	NP-ZnO (0.5 mmol)	r.t	EtOH	24h	-
12	NP-ZnO (0.5 mmol)	Reflux	EtOH	5h	45
13	NP-ZnO (0.5 mmol)	Reflux	Toluene	5h	<10
14	NP-ZnO (0.5 mmol)	Reflux	CH_3CN	5h	18
15	NP-ZnO (0.5 mmol)	Reflux	CH_2Cl_2	5h	12
16	NP-ZnO (0.5 mmol)	Reflux	n-Hexane	5h	-
17	NP-ZnO (0.5 mmol)	Reflux	H_2O	5h	-
18	NP-ZnO (0.5 mmol)	Reflux	H_2O/EtOH(1:1)	5h	-

Table 2. Synthesis of 4*H*-Pyran Derivatives 3(a-l) in the Presence of NP-ZnO Catalyst

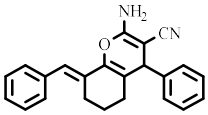
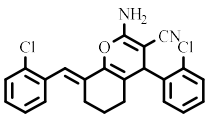
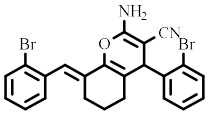
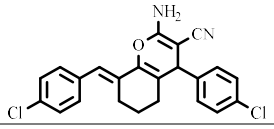
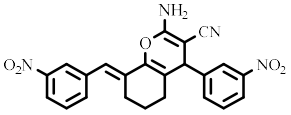
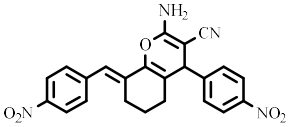
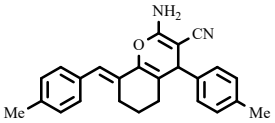
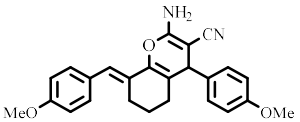
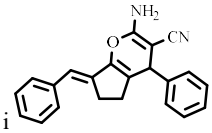
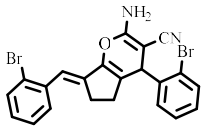
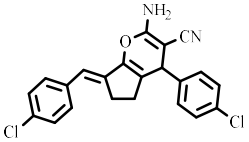
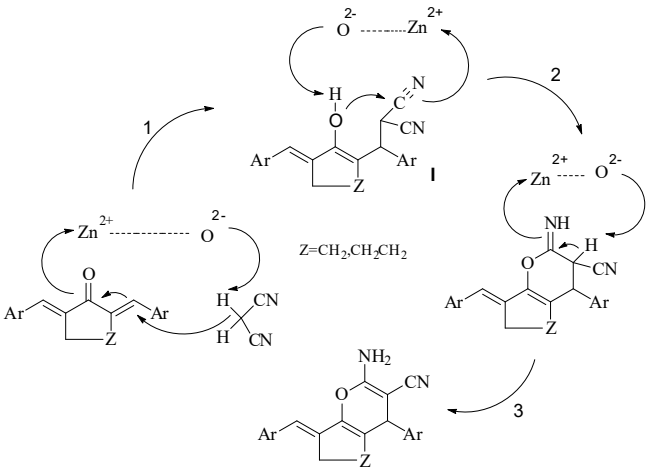
Entry	Ar	Z	Product (3)	Time (min)	Yield (%)	M.p. (°C)		Ref.
						Found	Reported	
1	C_6H_5	CH_2CH_2	a 	80	90	234-236	232-234	[15]
2	2-ClC_6H_4	CH_2CH_2	b 	85	87	239-241	238-240	[15]
3	2-BrC_6H_4	CH_2CH_2	c 	90	85	205-207	-	

Table 2. Continued

4	4-ClC_6H_4	CH_2CH_2	d 	110	83	213-215	215-216	[29]
5	3-$NO_2C_6H_4$	CH_2CH_2	e 	130	86	241-242	237	[30]
6	4-$NO_2C_6H_4$	CH_2CH_2	f 	150	81	217-219	216-218	[31]
7	4-MeC_6H_4	CH_2CH_2	g 	180	66	162-163	261-262	[29]
8	4-$MeOC_6H_4$	CH_2CH_2	h 	200	53	222-224	220-222	[29]
9	C_6H_5	CH_2	 i	140	79	224-226	227-228	[31]
10	2-BrC_6H_4	CH_2	j 	100	84	211-213	-	
11	4-ClC_6H_4	CH_2	k 	125	81	223-224	224-226	[32]

[an] Isolated yield. Reaction conditions: α,α′-bis (substituted benzylidene) cycloalkanones (1 mmol), malononitrile (1.5 mmol), solvent-free, 110 °C.



Scheme 2. The Proposed mechanism for the formation of 4*H*-pyrans in the presence of ZnO nanoparticles

(1.5 mmol) under solvent-free conditions at 110 °C using ZnO nanoparticles (0.5 mmol) was examined. After the completion of the reaction, DMF (5 ml) was added and the heterogeneous catalyst was separated by simple filtration and washed with DMF and ethanol, dried in the oven, and reused without loss in activity after four runs (Fig. 5a). After four times the recycled catalyst was studied by XRD pattern (Fig. 5b), FT-IR spectra (Fig. 5c), and SEM analysis (Fig. 5d) found no obvious change in structure and characteristic bands of ZnO nanoparticles.

The applicability and the efficiency of the ZnO nanoparticle catalyst for the synthesis of 4*H*-pyran derivatives with those reported in the literature are compared (Table 3). As the results show, ZnO nanoparticles are a comparable, desirable, and effective catalyst for the synthesis of the desired 4*H*-pyrans under green conditions. The

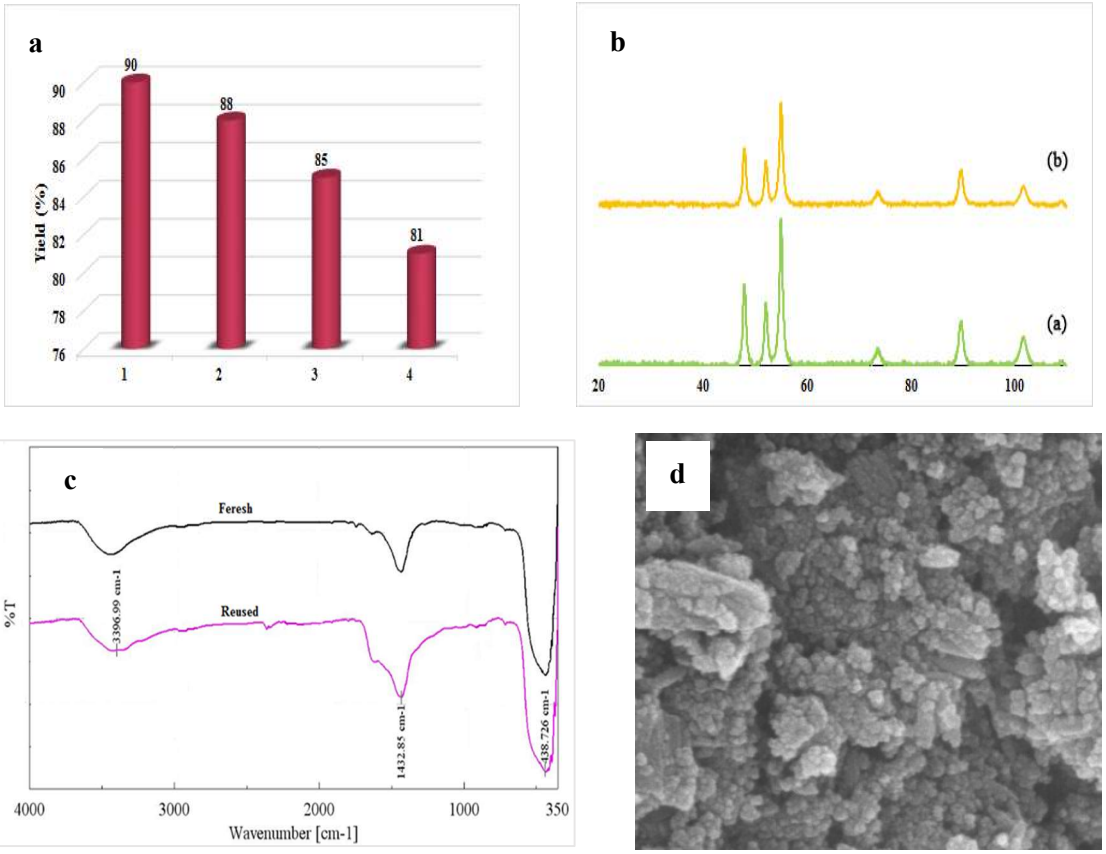


Fig. 5. The investigation of recyclability and reusability of ZnO nanoparticles (a), XRD patterns of reused and fresh ZnO nanoparticles (b), FT-IR spectra of reused and fresh ZnO nanoparticles (c), and SEM image of reused ZnO nanoparticles (d), after four runs.

Table 3. Various Catalysts are Used to Synthesize 4*H*-Pyran Derivatives

Entry	Catalyst	T (°C)	Solvent	Time (min)	Yield (%)	Ref
1	Piperidine (10 mol%)	Microwave irradiation	EtOH	5	80	[33]
2	K_2CO_3 (5 mol%)	Reflux	EtOH	10	95	[29]
3	DABCO (10 mol%)	Reflux	EtOH	5	95	[15]
4	Piperazine (10 mol%)	Reflux	EtOH	150	80	[16]
5	HTMAB (10 mol%)	110	H_2O	480	93	[31]
6	KF-Al_2O_3 (500 mg)	r.t	DMF	600	93	[34]
7	NP-ZnO (0.5 mmol)	110	Free	80	90	This work

porosity and high surface area of the nanostructure as well as the acidity of the zinc ions increase the catalytic activity of this catalyst.

The MIC value of the compound of 3f was concomitantly minimum (0.25 µg ml^{-1}) on the S. aureus and E.coli in comparison to other compounds. There was not any antimicrobial effect of the compound of 3b on E.coli but, surprisingly, the antimicrobial effect on S.aureus was confirmed as the MIC value of 0.25 µg $ml^{-1}$was reported (Table 4).

Table 4. Minimum Inhibitory Concentration (MIC) of 4*H*-Pyran Derivatives 3(a-l)

Compound 3	MIC values (µg ml^{-1})[a]	MIC values (µg ml^{-1})[b]
a	1	0.25
b	No antibacterial activity	0.25
c	8	4
d	8	0.25
e	64	4
f	0.25	0.25
g	32	0.25
h	32	0.25
i	64	0.5
j	8	0.25
k	32	0.25
l	64	0.25

[a]Bacterial strain = E.coli (ATCC 25922). [b]Bacterial strain = S.aureus (ATCC 35933).

The antibacterial results demonstrated that the antimicrobial effect of this synthesized 4*H*-pyran derivatives on gram-positive bacteria was more effective than gram-negative bacteria, due to the presence of more peptidoglycan. The MIC value of these compounds on S. aureus was approximately lower than E.coli.

CONCLUSIONS

In this research, an effective and green method for the preparation of 4*H*-pyran derivatives in the presence of ZnO nanoparticles under solvent-free conditions was reported. This method has some advantages such as short reaction times, high product yields, and the non-toxicity of the catalyst converted into a useful method compared to other 4*H*-pyrans synthesis methods. Other advantages of this method are solvent-free, easy recycling, and reusability of the catalyst.

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