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Green Synthesis of New Naphthospiro Chromanone Scaffolds and Their Antimicrobial Activity[1]

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Abstract—An efficient synthesis of new naphthospiro chromanone scaffolds using ionic liquids as a green solvent under microwave irradiation is presented. The reaction was also studied under conventional elevated temperature conditions. The structures of newly synthesized compounds have been elucidated by means of IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry data. All compounds were screened for their antimicrobial activity.

Keywords: spiro chromanone, green chemistry, ionic liquid, microwave irradiation, antimicrobial activity

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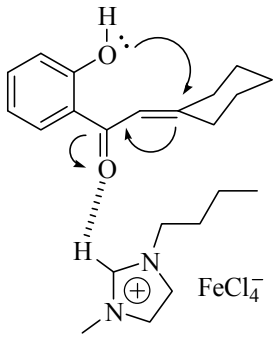
INTRODUCTION

Spiro compounds are elegant targets of organic synthesis due to their biological activity. The spiro-heterocyclic moiety is a key structural component of a variety of natural compounds and drugs. This class of compounds plays a distinctive role in the development of new heterocyclic scaffolds for medicine. The chromanone skeleton is often used for synthesis of compounds with diverse biological properties. They exhibit significant biological activities such as antibacterial [1], anticancer [2], antimalarial [3], antifungal [4], antioxidant [5], and antiviral [6]. Spiro chromanones are known for broad range of biological activities such as antiarrhythmic [7], acetyl CoA carboxylase (ACC)–Inhibitors [8], and Delta Opioid Receptor Agonists for pain relief [9]. Development of an ecologically friendly chemical process is the important target of the current study. Microwave induced organic reaction enhancement (MORE) chemistry is recognized as a nonconventional method for time efficient synthesis which could be an alternative to conventional methods. The former is believed to be a step toward green chemistry [10]. Ionic liquids are of considerable interest as environment friendly alternatives to conventional organic solvents due to very low vapor pressure, non-explosive character and thermal stability within a wide temperature range [11, 12]. In view of these advantages and as part of our research [13] on green synthesis of biologically active heterocyclic compounds, we present the synthesis of new naphthospiro chromanone scaffolds induced by microwave irradiation as an efficient alternative to conventional methods.

RESULTS AND DISCUSSION

Chemistry. The title compounds have been synthesized by the reaction of 2-acetyl naphthol/1-acetyl naphthol with various ketones, namely: cyclopentanone, cyclohexanone, cycloheptanone, 1-methylpiperidine-4-one, 1-benzylpiperidine-4-one, N–Boc-piperidine-4-one, in the presence of pyrrolidine [14] using an [bmim]Cl·$FeCl_3$ ionic liquid as a solvent under microwave irradiation. The highly acidic 2H proton of [bmim]Cl·$FeCl_3$ can activate the carbonyl carbon of both cycloalkanone and 2-hydroxy ketone, thus promote the formation of enamine and cyclization of an intermediate leading to the final product:



[1] The text was submitted by the authors in English.

Table 1. Physical data of naphtho spiro chromanone scaffolds

Comp. no.	Conventional		Microwave	
	time, h	yield, %	time, min	yield, %
IIIa	10	75	9	90
IIIb	12	77	10	88
IIIc	11	75	9	82
IIId	10	78	8	89
Va	11	78	9	87
Vb	10	77	9	90
Vc	12	78	8	90
VIIa	12	75	10	89
VIIb	12	78	10	87
VIIc	11	75	8	89
VIId	10	77	8	86
IXa	10	76	10	89
IXb	11	78	8	87
IXc	10	78	9	90

The ionic liquid [bmim]Cl·$FeCl_3$ is relatively air and moisture stable and an efficient solvent for a wide range of organic compounds. The products can be easily separated from the ionic liquid medium by simple extraction with ethylacetate. We have successfully recycled the ionic liquid up to three times without significant loss of activity. The synthesis of title compounds was also carried under elevated temperature. Under microwave irradiation the reaction completed within minutes with higher yield compared to the conventional synthesis that needed hours of heating (Table 1).

The structures of products were elucidated by spectral methods. For example, the IR spectrum of **IIIb** contained a band at 1702 cm^{-1} characteristic for flavanone carbonyl group. In the ^1H NMR spectrum of **IIIb** was registered a singlet δ = 2.80 ppm (2H) assigned to methylene protons, that indicated the formation of flavanone structure. The multiplets δ = 1.30–1.40 ppm (1H) and δ = 1.50–1.68 ppm (5H) were assigned to 4'-H_a protons and 3'-$H_{a,e}$, 4'-H_e, 5'-$H_{a,e}$ protons respectively. A multiplet δ = 1.70–1.80 ppm (2H) was assigned to 2'-H_a, 6'-H_a. The multiplet δ = 2.02–2.18 ppm (2H) was assigned to 2'H_e, 6'H_e. In the ^{13}C NMR spectrum of **IIIb** were registered the following signals δ = 193.75 ppm (>C=O), 49.33 ppm (C_3) and 80.94 ppm (C_2). The mass spectra of **IIIb** contained the peak *m/z* = 267 (100%) $[M + H]^+$.

Table 2. Effect of solvents on the synthesis of naphthospiro chromanone scaffolds

Solvent	Conventional		Microwave	
	time, h	yield, %	time, min	yield, %
Ethanol	12–14	64–67	12–14	70–76
Dimethyl formamide	10–12	66–70	11–12	75–82
Ionic liquid [bmim]Cl·$FeCl_3$	10–12	75–80	8–10	82–90

Antibacterial activity. The synthesized compounds **IIIa–IIId, Va–Vc**, **VIIa–VIId, and IXa–IXc** (Table 3) were screened for antibacterial activity against different types of bacterial strains including Gram negative bacterial strains of *Escherichia coli* and *Pseudomonas aeruginosa*, and Gram positive bacterial strains of *Staphylococcus aureus* and *Bacillus subtilis* at a concentration of 100 μg/mL.

The zone of inhibition of the following compounds **IIIa, IIIc**, **Va–Vc**, **VIIa, VIIb, IXa,** and **IXb** demonstrated high activity against Gram positive bacterial strains of *Staphylococcus aureus,* and **IIIa, IIIc**, **Va**, **Vc**, **VIIa, VIIb**, **VIId**, **IXa,** and **IXb** against Gram positive bacterial strains of *Bacillus subtilis* compared to the standard drug Amoxicilin at a concentration 100 μg/mL.

The zone of inhibition of the following compounds **IIId**, **Va–Vc**, **IIIa, VIIa, VIIb, IXa, and IXb** were of high activity against Gram negative bacterial strains of *Escherichia coli,* and **IIIc**, **Va**, **Vc**, **VIIb**, **VIId** and **IXa** against Gram negative bacterial strains of *Pseudomonas aeruginosa* compared to standard drug Amoxicilin at concentration 100 μg/mL. The compounds **VIIb** and **IXb** exhibited broad spectrum of antibacterial activity against all tested strains.

Antifungal activity. The antifungal activity of syn-thesized compounds **IIIa–IIId, Va–Vc, VIIa–VIId** and **IXa–IXc** (Table 3) was tested against three pathogenic fungi, namely *Aspergillus nigerzeae, Pencillium italicum*, and *Fusarium oxysporum* at a concentration of 100 μg/mL. The zone of inhibition of compounds **IIIb**, **IIIc**, **IIIe**, **IIIf**, **VIIa**, **VIIb**, **VIIf,** and **IXc** exhibited high activity against *Aspergillus nigerzeae*, **IIIc, IIId, VIIb, VIIe,** and **IXb** against

Pencillium italicum, **IIIb–IIId**, **VIIb, VIId, VIIf, IXa,** and **IXc** against *Fusarium oxysporum* compared to standard drug Mycostatin at concentration 100 μg/mL. The compounds **IIIc** and **VIIb** demonstrated broad spectrum of antifungal activity against all tested strains.

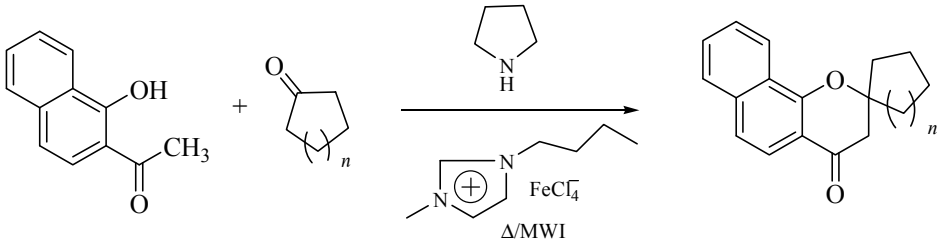
Antimicrobial activity. All products were screened for their antimicrobial activity [15] against two strains of Gram-positive bacteria (*Staphylococcus aureus, Bacillus subtilis*), two strains of Gram-negative bacteria (*Echerichia coli, Pseudomonas aeruginosa*), and three strains of fungi (*Aspergillus niger*, *Penicillium italicum* and *Fusarium oxysporum*). Standard antibiotic drugs *Amoxicillin* for bacteria and *Mycostatin* for fungi were used at concentration 100 μg/mL.

EXPERIMENTAL

Mesearuments. Melting points were measured in open capillary tubes. Purity of the compounds was tested routinely by TLC on silica gel F_{254} (Merck). Element analysis was carried out with Thermofinnigan CHNS analyzer. NMR spectra were measured with Bruker Avance–300 NMR spectrometer, and Mass spectra were recorded by Shimadzu mass spectrometer. IR spectra were recorded with Shimadzu FTIR 8400s spectrophotometer. Microwave reactions were carried out in Milestone multi SYNTH microwave system. All compounds and solvents were reagent grade. Technical grade ethyl acetate and petroleum ether were used for column chromatography and distilled prior to use. Column chromatography was carried out using silica gel (60–120 mesh) packed in glass columns. The reaction pathway is presented by Schemes 1–4.

Synthesis of spiro[benzo(*h*)chromene-2,1'-cycloalkan]-4(3*H*)-ones and spiro[benzo(*f*)chromene-3,1'-cycloalkan-1(2*H*)-ones *(general procedure). a. Conventional method.* An equimolar mixture of 2-acetyl naphthol/1-acetyl naphthol (0.0026 mol), pyrrolidine (0.0026mol), cycloalkanone (0.0026 mol) and ionic liquid [bmim]Cl·$FeCl_3$ (10 mL) was stirred at 90–95°C for 10–12 h. Progress of the reaction was monitored by TLC. After completion of the reaction, it was extracted with ethylacetate (3 × 10 mL). The combined extract was concentrated under vacuum and the residue was subjected to column chromatography using EtOAc: Pet ether (v/v 1 : 4). The product was recrystallized from chloroform. The mother liquor was dissolved in acetonitrile, treated with charcoal and filtered. The filterate was evaporated and the IL was dried under vacuum at 65°C for 10 h. The IL was reused for further reactions.

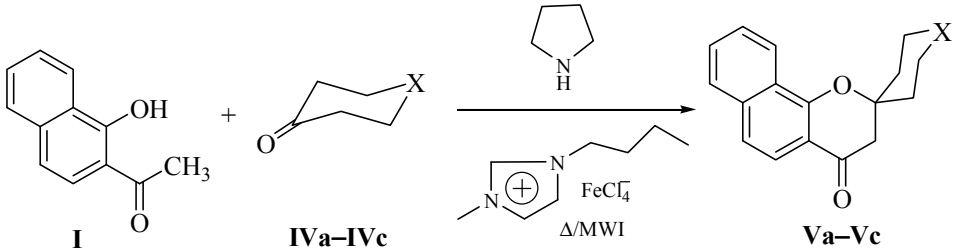
Scheme 1.



I **IIa–IId** **IIIa–IIId**

n = 1 (**a**), 2 (**b**), 3 (**c**), 4 (**d**).

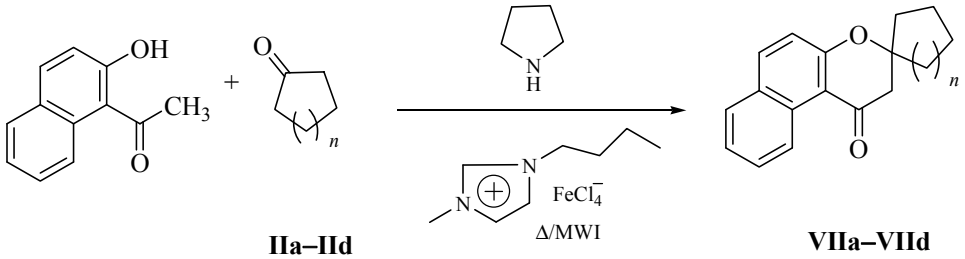
Scheme 2.



I **IVa–IVc** **Va–Vc**

X = N– (**a**), N–Bn (**b**), N–Boc (**c**).

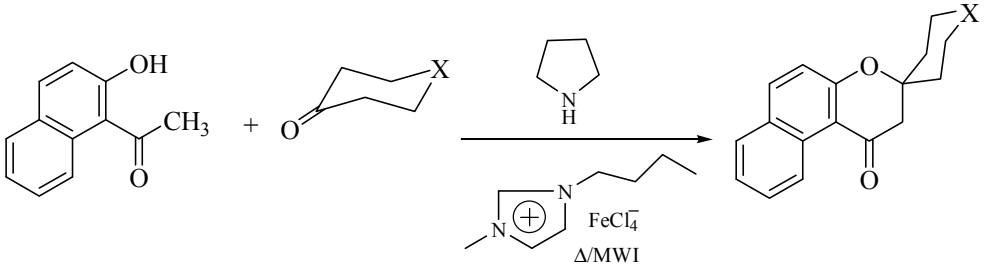
Scheme 3.



IIa–IId **VIIa–VIId**

n = 1 (**a**), 2 (**b**), 3 (**c**), 4 (**d**).

Scheme 4.



VI **IVa–IVc** **IXa–IXc**

X = N– (**a**), N–Bn (**b**), N–Boc (**c**).

b. Microwave irradiation method. An equimolar mixture of 2-acetyl naphthol/1-acetyl naphthol (0.0026 mol), pyrrolidine (0.0026 mol), cycloalkanone (0.0026 mol), and ionic liquid [bmim]Cl·$FeCl_3$ (5 mL) was taken in a quartz tube and inserted into Teflon vial with screw cap and subjected to microwave irradiation at 160 W for 8–10 min. Progress of the reaction was monitored by TLC. After completion of the reaction, it was extracted with ethylacetate (3 × 10 mL). The combined extract was concentrated under vacuum and the residue was subjected to column chromatography using EtOAc: Pet ether (v/v 1 : 4). The product was recrystallized from chloroform. The mother liquor was dissolved in acetonitrile, treated with charcoal and filtered. The filterate was evaporated and the IL was dried under vacuum at 65°C for 10 h. The IL was reused for further reactions.

Spiro(benzo[*h*]chromene-2,1'-cyclopentan)-4(3*H*)-one (IIIa). mp 130–132°C. IR spectrum ν, cm^{-1}: 1695 (>C=O). ^{1}H NMR spectrum, δ, ppm: 9.44 d (1H, *J* = 7.6 Hz, aromatic), 8.90 d (1H, *J* = 7.6 Hz, aromatic), 7.75 d (1H, *J* = 7.8 Hz, aromatic), 7.58–7.65 m (1H, H_6 aromatic), 7.35–7.44 m (1H, H_7 aromatic), 7.05 d (1H, *J* = 7.6 Hz, aromatic), 2.90 s (2H, $COCH_2$), 2.10–2.22 m (2H, cyclopentyl), 1.79–1.94 m (2H, cyclopentyl), 1.60–1.76 m (4H, cyclopentyl). ^{13}C NMR spectrum, δ, ppm: 193.78 (>C=O), 161.71, 137.36, 132.38, 129.37, 128.80, 127.27, 125.45, 124.32, 120.45, 112.93, 81.90, 49.32, 34.32, 25.26 and 21.54; LCMS: $[M + H]^+$ *m/z*= 253 (90%). Found, %: C 80.98; H 6.38. $C_{17}H_{16}O_2$. Calculated, %: C 80.95; H, 6.34.

Spiro(benzo[*h*]chromene-2,1'-cyclohexan)-4(3*H*)-one (IIIb). mp 162–164°C. IR spectrum ν, cm^{-1}: 1702 (>C=O). ^{1}H NMR spectrum, δ, ppm: 9.42 d (1H, *J* = 7.6 Hz, H_5 aromatic), 7.88 d.d (1H, *J* = 7.8 Hz, 7.6 Hz, H_6 aromatic), 7.80 d (1H, *J* = 7.8 Hz, H_7 aromatic), 7.60 d.d (1H, *J* = 7.6 Hz, 7.8 Hz, H_8 aromatic), 7.40 d.d (1H, *J* = 7.8 Hz, 7.6 Hz, H_9 aromatic), 7.10 d (1H, *J* = 7.6, H_{10} aromatic), 2.80 s (2H, $COCH_2$), 2.02–2.18 m (2H, 2'-H_e, 6'-H_e, cyclohexyl), 1.70–1.80 m (2H, 2'-H_a, 6'-H_a, cyclohexyl), 1.50–1.68 m (5H, 3'-$H_{a,e}$, 4'-H_e, 5'-$H_{a,e}$, cyclohexyl), 1.30–1.40 m (1H, 4'-H_a, cyclohexyl). ^{13}C NMR spectrum, δ, ppm: 193.75 (>C=O), 161.69, 137.32, 131.38, 129.47, 128.82, 128.27, 125.55, 124.47, 119.45, 111.93, 80.94, 49.33, 34.45, 25.25, 21.69 and 21.54; LCMS $[M + H]^+$ at *m/z* =267 (100 %). Found, %: C 81.19; H 6.78. $C_{18}H_{18}O_2$. Calculated, %: C 81.20; H 6.76.

Spiro(benzo[*h*]chromene-2,1'-cycloheptan)-4(3*H*)-one (IIIc). mp 170–172°C. IR spectrum ν, cm^{-1}: 1666 (>C=O). ^{1}H NMR spectrum, δ, ppm: 9.41 d (1H, *J* = 7.6 Hz, aromatic), 7.90 d (1H, *J* = 7.6 Hz, aromatic),

7.72 d (1H, J = 7.6 Hz, aromatic), 7.58–7.62 m (1H, aromatic), 7.36–7.41 m (1H, aromatic), 7.05 d (1H, J = 7.6 Hz, aromatic), 2.85 s (2H, $COCH_2$), 1.52–2.21 m (12H, cycloheptyl). ^{13}C NMR spectrum, δ, ppm: 193.8 (>C=O), 161.8, 137.3, 131.3, 129.4, 128.7, 128.2, 125.5, 124.4, 119.5, 111.9, 84.4, 50.1, 37.8, 29.5 and 22.0; LCMS $[M + H]^+$ at m/z =281 (100 %). Found, %: C 81.44, H 7.18. $C_{19}H_{20}O_2$. Calculated, %: C 81.42; H 7.14.

Spiro(benzo[*h*]chromene-2,1'-cyclooctan)-4(3*H*)-one (IIId). mp 172–174°C. IR spectrum ν, cm^{-1}: 1678 (>C=O). ^1H NMR spectrum, δ, ppm: 9.41 d (1H, J = 7.6 Hz, aromatic), 7.90 d, (1H, J = 7.6 Hz, aromatic), 7.75 d (1H, J = 7.6 Hz, aromatic), 7.58–7.62 m (1H, aromatic), 7.36–7.42 m (1H, aromatic), 7.04 d (1H, J = 7.6 Hz, aromatic), 2.83 s (2H, $COCH_2$), 1.4–2.15 m (14H, cyclo octyl). ^{13}CNMR, δ, ppm: 193.7 (>C=O), 162.7, 138.2, 130.7, 129.6, 127.4, 127.9, 126.7, 125.9, 120.5, 110.9, 86.4, 53.5, 37.9, 29.7, 23.1 and 22.4; LCMS $[M + H]^+$ at m/z =295 (85 %). Found, %: C 81.65, H 7.51. $C_{20}H_{22}O_2$. Calculated, %: C 81.63; H 7.48.

1'-Methylspiro(benzo[*h*]chromene-2,4'-piperidin)-4(3*H*)-one (Va). mp 168–170°C. IR spectrum ν, cm^{-1}: 1672 (>C=O). ^1H NMR spectrum, δ, ppm: 9.42 d (1H, J = 7.6 Hz, aromatic), 7.93 d (1H, J = 7.6 Hz, aromatic), 7.76 d (1H, J = 7.6 Hz, aromatic), 7.58–7.65 m (1H, aromatic), 7.38–7.44 m (1H, aromatic), 7.10 d (1H, J = 7.6 Hz, aromatic), 2.82 s (2H, $COCH_2$), 2.40–2.65 m (4H, piperidinyl), 2.38 s (3H, N–CH_3) 1.80–2.20 m (4H, Piperidinyl). ^{13}C NMR spectrum, δ, ppm: 193.5 (>C=O), 162.8, 137.8, 132.7, 130.4, 129.7, 128.7, 126.5, 125.2, 120.5, 112.9, 85.4, 53.1, 47.3 and 33.0; LCMS (*m/z*): 282 (100%); Found, % : C 76.84; H 6.78; N 4.99. $C_{18}H_{19}NO_2$: Calculated, %: C 76.86; H 6.76; N 4.98.

1'-Benzylspiro(benzo[*h*]chromene-2,4'-piperidin)-4(3*H*)-one (Vb). mp 158–160°C. IR spectrum ν, cm^{-1}: 1693 (>C=O). ^1H NMR spectrum, δ, ppm: 9.42 d (1H, J = 7.6 Hz, aromatic), 7.95 d (1H, J = 7.6 Hz, aromatic), 7.75 d (1H, J = 7.6 Hz, aromatic), 7.58–7.64 m (1H, aromatic), 7.38–7.42 m (1H, aromatic), 7.42–7.38 m (5H, aromatic), 7.12 d (1H, aromatic), 3.56 s (2H, N–CH_2), 2.84 s (2H, $COCH_2$), 2.60–2.72 m (2H, piperidinyl), 2.40–2.58 m (2H, piperidinyl), 2.10–2.20 m (2H, piperidinyl), 1.80–1.90 m (2H, piperidinyl). ^{13}C NMR spectrum, δ, ppm: 192.8 (>C=O), 163.7, 142.7, 138.7, 136.5, 132.4, 129.6, 129.9, 128.3, 127.2, 126.9, 120.8, 118.7, 116.9, 112.7, 86.4, 54.8, 47.8 and 35.0. LCMS $[M + H]^+$ at m/z = 358(100%). Found, %: C 80.66; H 6.46; N 3.95.$C_{24}H_{23}NO_2$. Calculated. %: C 80.67; H 6.44; N 3.92.

***tert*-Butyl-4-oxo-3,4-dihydrospiro(benzo[*h*]chromene-2,4'-piperidine)-1'-carboxylate (Vc).** mp 188–190°C. IR spectrum ν, cm^{-1}: 1675 (>C=O). ^1H NMR spectrum, δ, ppm: 9.42 d (1H, J = 7.6 Hz, aromatic), 7.95 d (1H, J = 7.6 Hz, aromatic), 7.75 d (1H, J = 7.6 Hz, aromatic), 7.58–7.64 m (1H, aromatic), 7.38–7.46 m (1H, H_7 aromatic), 7.12 d (1H, J = 7.6 Hz, aromatic), 3.80–3.85 m (2H, N–CH_2, eq.), 3.20–3.35 m (2H, N–CH_2, ax.), 2.82 s (2H, $COCH_2$), 2.08–2.20 m (2H, CH_2–C–CH_2, eq.), 1.50–1.65 m (2H, CH_2–C–CH_2, ax.) 1.45 s (9H, *t*-butyl). ^{13}C NMR spectrum, δ, ppm: 192.6 (>C=O), 161.0, 154.7, 137.7, 131.2, 129.7, 129.0, 128.3, 125.0, 124.0, 119.0, 112.0, 79.8, 78.0, 76.7, 49.1, 39.3, 33.7, 28.4. LCMS $[M + H]^+$ at m/z = 368 (80%). Found, %: C 71.90; H, 6.87; N 3.83. $C_{22}H_{25}NO_4$. Calculated, %: C 71.93; H, 6.81; N 3.81.

Spiro(benzo[*f*]chromene-3,1'-cyclopentan)-1(2*H*)-one (VIIa). mp 124–126°C. IR spectrum ν, cm^{-1}: 1695 (>C=O). ^1H NMR spectrum, δ, ppm: 8.30 d (1H, J = 7.6 Hz, aromatic), 7.75–7.85 m (2H, aromatic), 7.42–7.62 m (2H, aromatic), 7.38 d (1H, J = 7.8 Hz, aromatic), 2.95 s (2H, $COCH_2$), 2.15–2.3 m (2H, cyclopentyl), 1.80–1.85 m (2H, cyclopentyl), 1.65–1.69 m (4H, cyclopentyl). ^{13}C NMR spectrum, δ, ppm: 190.5 (>C=O), 165.4, 127.9, 115.8, 105.7, 90.9, 46.7, 37.5, 23.7. LCMS: $[M + H]^+$ m/z= 253 (90%). Found, %: C 81.30; H 6.41. $C_{17}H_{16}O_2$. Calculated, %: C 81.27; H 6.37.

Spiro(benzo[*f*]chromene-3,1'-cyclohexan)-1(2*H*)-one (VIIb). mp 163–165°C. IR spectrum ν, cm^{-1}: 1698 (>C=O). ^1H NMR spectrum, δ, ppm: 8.31 d (1H, J = 7.6 Hz, aromatic), 7.76–7.83 m (2H, aromatic), 7.43–7.61 m (2H, aromatic), 7.36 d (1H, J = 7.80 Hz, aromatic), 2.82 s (2H, $COCH_2$), 2.16–2.24 m (2H, cyclohexyl), 1.80–1.85 m (4H, cyclohexyl), 1.65–1.69 m (4H, cyclohexyl). ^{13}C NMR spectrum, δ, ppm: 190.5 (>C=O), 165.4, 127.9, 115.8, 105.7, 85.9, 46.7, 37.5, 23.7, 21.3. LCMS: $[M + H]^+$ m/z= 267 (93%). Found, %: C 81.24; H 6.79. $C_{18}H_{18}O_2$. Calculated, %: C 81.20; H 6.76.

Spiro(benzo[*f*]chromene-3,1'-cycloheptan)-1(2*H*)-one (VIIc). mp 169–172°C. IR spectrum ν, cm^{-1}: 1676 (>C=O). ^1H NMR spectrum, δ, ppm: 8.38 d (1H, J = 7.6 Hz, aromatic), 7.82 d (1H, J = 7.6 Hz, aromatic), 7.78 d (1H, J = 7.6 Hz, aromatic), 7.58–7.60 m (1H, aromatic), 7.51–7.53 m (1H, aromatic), 7.36 d (1H, J = 7.80 Hz, aromatic), 2.82 s (2H, $COCH_2$), 2.20–2.30 m (2H, cycloheptyl), 1.65–1.80 m (8H, cycloheptyl),

Table 3. Antimicrobial activity of naphtho spiro chromanones **IIIa–IIId, Va–Vc, VIIa–VIId,** and **IXa–IXc**

Comp. no.	Zone of inhibition, mm						
	gram-positive bacteria		gram-negative bacteria		fungi		
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*A. nigerzeae*	*P. italicum*	*F. oxysporum*
IIIa	22	10	22	07	06	09	12
IIIb	15	07	18	06	07	07	16
IIIc	22	08	24	08	09	07	22
IIId	18	12	20	09	11	08	16
Va	22	15	22	08	07	09	20
Vb	22	07	25	06	09	06	24
Vc	20	08	23	09	09	06	22
VIIa	20	10	24	06	10	08	14
VIIb	15	10	20	08	08	07	16
VIIc	11	08	10	06	08	08	14
VIId	20	11	14	08	09	07	14
IXa	20	08	26	06	07	06	18
IXb	24	10	24	07	07	08	16
IXc	16	07	14	06	08	06	18
Standard A[a]	30	12	30	10	–	–	–
Standard B[b]	–	–	–	–	12	10	25

[a] Standard A: Amoxicilin; reference drug for Gram-positive and Gram-negative bacteria. [b] Standard B: Mycostatin; reference drug for fungi

1.43–1.60 m, (2H, cycloheptyl). ^{13}C NMR spectrum, δ, ppm: 192.3 (>C=O), 157.7, 137.7, 129.4, 127.8, 126.0, 125.4, 123.5, 121.5, 120.1, 114.9, 85.2, 48.6, 38.2, 29.1, 22.1. LCMS $[M + H]^+$ at *m/z* =281 (100 %). Found, %: C 81.44; H 7.16. $C_{19}H_{20}O_2$. Calculated, %: C 81.42; H 7.14.

Spiro(benzo[*f*]chromene-3,1'-cyclooctan)-1(2*H*)-one (VIId). mp 176–178°C. IR spectrum ν, cm^{-1}: 1676 (>C=O). ^{1}H NMR spectrum, δ, ppm: 8.41 d, (1H, *J* = 7.6 Hz, aromatic), 7.86 d (1H, *J* = 7.6 Hz, aromatic), 7.81 d (1H, *J* = 7.6 Hz, aromatic), 7.60–7.62 m (1H, aromatic), 7.55–7.58 m (1H, *J* = 7.6 Hz, aromatic), 7.39 d (1H, *J* = 7.80 Hz, aromatic), 2.80 s (2H, $COCH_2$), 2.22–2.30 m (2H, cyclooctyl), 1.65–1.80 m (10H, cycloctyl), 1.42–1.61 m (2H, cycloctyl). ^{13}C NMR spectrum, δ, ppm: 192.7 (>C=O), 158.1, 136.9, 129.9, 128.3, 126.8, 125.9, 123.8, 121.7, 120.3, 115.3, 83.1, 47.9, 38.4, 28.9, 28.8, and 22.1. LCMS $[M + H]^+$ at *m/z* =295 (100 %). Found, %: C 81.43; H 7.49. $C_{20}H_{22}O_2$. Calculated, %: C 81.63; H 7.48.

1'-Methylspiro(benzo[*f*]chromene-3,4'-piperidin)-1(2*H*)-one (IXa). mp 169–170°C. IR spectrum ν, cm^{-1}: 1682 (>C=O). ^{1}H NMR spectrum, δ, ppm: 8.42 d (1H, *J* = 7.6 Hz, aromatic), 7.84 d (1H, *J* = 7.6 Hz, aromatic), 7.81 d (1H, *J* = 7.6 Hz, aromatic), 7.59–7.62 m (1H, aromatic), 7.50–7.52 m (1H, aromatic), 7.38 d (1H, *J* = 7.80 Hz, aromatic), 2.84 s, (2H, $COCH_2$), 2.42–2.64 m (4H, CH_2-N–CH_2), 2.40 s (3H, N–CH_3) 1.83–2.21 m (4H, CH_2–C–CH_2). ^{13}C NMR spectrum, δ, ppm: 192.5 (>C=O), 156.5, 137.5, 129.8, 126.2, 126.5, 125.2, 124.1, 120.5, 120.0, 114.7, 85.5, 54.9, 48.2, and 32.2. LCMS $[M + H]^+$ at *m/z* =282 (100 %). Found, %: C 76.86; H 6.82; N 5.10. $C_{18}H_{19}NO_2$. Calculated, %: C 76.86; H 6.76; N 4.98.

1'-Benzylspiro(benzo[*f*]chromene-3,4'-piperidin)-1(2*H*)-one (IXb). mp 156–158°C. IR spectrum ν, cm^{-1}: 1671 (>C=O). ^{1}H NMR spectrum, δ, ppm: 8.32 d (1H, *J* = 7.6 Hz, aromatic), 7.78–7.84 m (2H, aromatic), 7.50–7.70 m (2H, aromatic), 7.24–7.40 m (5H, aromatic), 7.12–7.21 m (1H, aromatic), 3.60 s (2H, CH_2–N–CH_2),

2.80 s (2H, $COCH_2$), 2.61–2.70 m (2H, N–CH_2, eq.), 2.42–2.55 m, (2H, N–CH_2, ax.), 2.08–2.23 m (2H, CH_2–C–CH_2, eq.), 1.81–1.95 m (2H, CH_2–C–CH_2, ax.). ^{13}C NMR spectrum, δ, ppm: 192.8 (>C=O), 158.5, 141.2, 138.0, 129.5, 126.7, 126.4, 125.3, 124.1, 123.8, 120.5, 120.0, 118.3, 116.9, 115.8, 85.8, 53.9, 48.8, 32.8. LCMS $[M + H]^+$ at m/z = 358(90%). Found, %: C 80.65; H 6.52; N 3.93. $C_{24}H_{23}NO_2$. Calculated, %: C 80.67; H 6.44; N 3.92.

***tert*-Butyl 1-Oxo–1,2-dihydrospiro(benzo[*f*]chromene-3,4'-piperidine]-1'-carboxylate (IXc).** mp 192–194°C. IR spectrum ν, cm^{-1}: 1675 (>C=O). ^{1}H NMR spectrum, δ, ppm: 8.37 d (1H, J = 7.6 Hz, aromatic), 7.78–7.80 m (2H, aromatic), 7.50–7.65 m (1H, aromatic), 7.40 d (1H, aromatic), 7.14 d (1H, J = 7.80 Hz, aromatic), 3.90–4.10 m (2H, N–CH_2, eq.), 3.20–3.40 m (2H, N–CH_2, ax.), 2.82 s (2H, $COCH_2$), 2.15–2.24 m (2H, CH_2–C–CH_2 eq.), 1.60–1.80 m (2H, CH_2–C–CH_2, ax.) 1.45 s (9H, *t*-butyl); ^{13}C NMR spectrum, δ, ppm: 192.8 (>C=O), 161.6,154.4, 138.1, 132.7, 130.5, 129.8, 128.7, 125.4, 124.8, 120.0, 114.1, 80.1, 79.0, 76.6, 49.3, 39.5, 33.8, and 28.7; LCMS $[M + H]^+$ at m/z = 368(90%). Found, %: C 71.93; H, 6.86; N 3.82. $C_{22}H_{25}NO_4$. Calculated, %: C 71.93; H, 6.81; N 3.81.

Antimicrobial activity. The biological activity of the products has been evaluated by filter paper disc method [15] in DMF solution, concentration 100 μg/mL. The inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were measured in millimeters at the end of incubation period of 3 days at 37°C for *Echerichia coli* and at 28ºC for other bacteria and fungi, DMF alone showed no inhibation zone (Table 3).

CONCLUSIONS

We have synthesized a series of naphthospiro chromanone scaffolds using ionic liquids as green solvents under microwave irradiation and conventional methods. Ionic liquids increased reaction rates, products yield, made workup procedures less complex. Ionic liquids were recycled and reused. The microwave irradiation process using an ionic liquid as a solvent proved to be a simple environmentally friendly method leading to high yields and short reaction time.

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