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Facile Ionic Liquid-Mediated, Microwave Assisted Green Synthesis, and Antioxidant Studies of Novel Indolin-2-one Annulated Spirochromanone Conjugates[1]

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Abstract—A convenient and efficient synthetic protocol of ionic liquid, 1-*n*-butyl-3-methylimidazolium tetrachloroferrate, [bmim]Cl·$FeCl_3$ mediated synthesis of novel indolin-2-one annulated spirochromanone conjugates was described. These spirochromanone conjugates were efficiently synthesized by Kabbe condensation of substituted 3-[2-(5-acetyl-2,4-dihydroxyhenyl)-2-oxoethylidene]indolin-2-ones with various cycloalkanones catalyzed by pyrrolidine in ionic liquid [bmim]Cl·$FeCl_3$ under microwave irradiation. This approach offers the advantages of short reaction time, mild reaction conditions, high yields, convenient operation, and reuse of ionic liquid. The synthesized compounds were evaluated for their antioxidant activity. Among the compounds synthesized, **IVb** and **IVd** exhibited the highest antioxidant activity. The IC_{50} values for compounds **IVb** and **IVd** were found to be 1.25 and 1.74 μM, respectively, comparable to that of ascorbic acid (IC_{50} 8.64 μM), a standard antioxidant agent.

Keywords: spirochromanones, indolin-2-one, ionic liquid, Kabbe condensation, antioxidant activity, microwave irradiation

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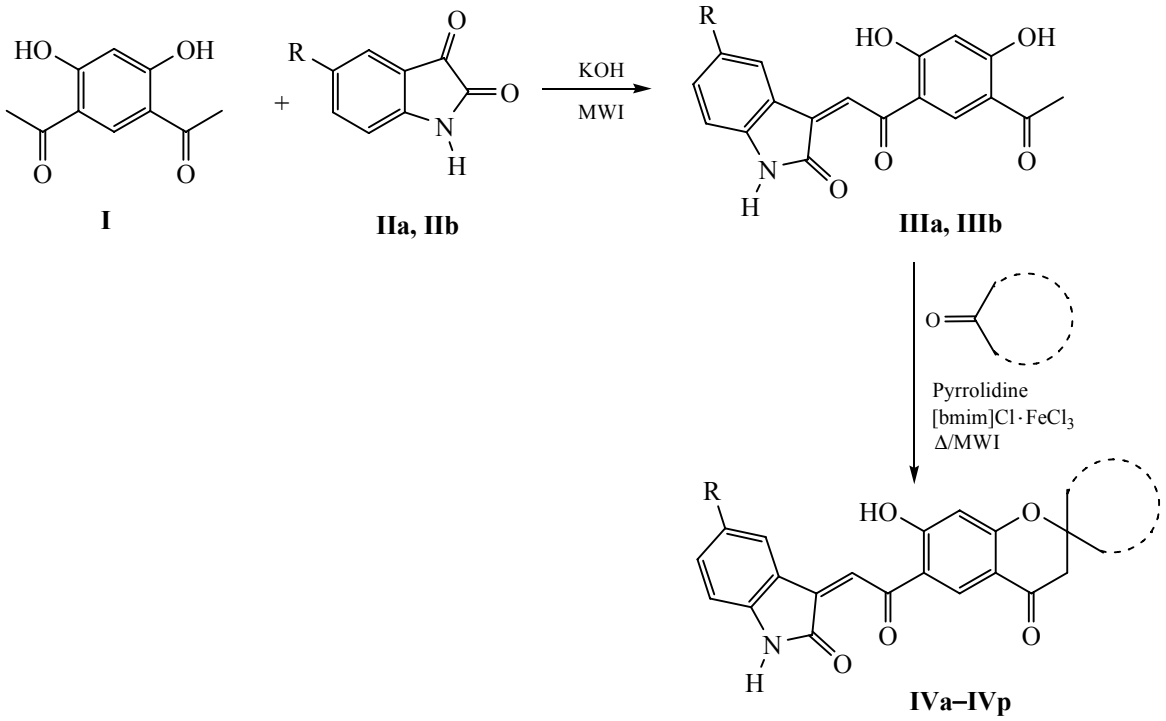
INTRODUCTION

Room temperature ionic liquids, especially those based on the 1-alkyl-3-methylimidazolium cation, have shown a great promise as attractive greener alternatives to classical volatile organic solvents in chemical transformations [1]. Interesting features of these ionic liquids are their ability to solvate a broad spectrum of both organic and inorganic compounds, low vapor pressure, recyclability, high thermal stability and ease of handling. For this reason, their use in organic synthesis has emerged as an important facet of green chemistry. Ionic liquids are also referred to as "designer solvents" [2], as their physical and chemical properties can alter by varying their structure, with respect to the choice of organic cations and anions, and side-chain attached to the organic cation.

Chromones, are important structural motifs found in a number of natural products like flavanoids, isoflavanoids, coumarins, homo-, iso, and neoflavonoids [3]. Aquiledine and Cheliensisine are the naturally occurring flavonones used for the treatment of pustulosis, necrotic boils, other infections [4] and neoplastic [5] respectively. These structural motifs have displayed a wide spectrum of potential biological activities such as antioxidant [6], antiarrhythmic [7], anticancer [8], antiestrogenic [9], anti-HIV [10], antimicrobial [11], antibacterial [12], antiinflammatory [13], and antidiabetic [14]. Indole derivatives have been found to possess wide range of biological activities such as anticonvulsant [15], antidepressant [16], antihistamine [17], antifungal, antitubercular [18], cardiovascular [19], antidiabetic [20], analgesic, anti-inflammatory [21], and anthelmintic activity. Microwave assisted organic synthesis has attracted considerable interest over the last few decades, leading often to remarkable decreases in reaction times, significant enhancement of yields, easier workups and better regioselectivity [22]. Inspired by the wide range of activities possessed by chromanone derivatives and

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

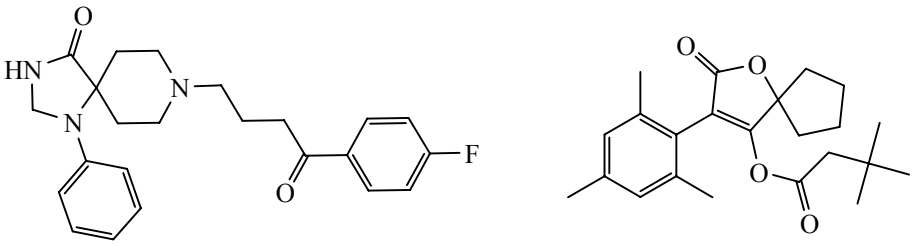
Scheme 1. Synthetic route for the indolin-2-one fused spirochromanone conjugates **IVa–IVp**



in continuation of our efforts in search of potential antioxidant agents, we report herein a ionic liquid mediated synthesis of novel indolin-2-one fused spirochromanone conjugates in microwave irradiation method and are evaluated as potent antioxidant agents (Fig. 1).

RESULTS AND DISCUSSION

Chemistry. The route for the synthesis of spirochromanones (**IVa–IVp**) starting from (**IIIa, IIIb**) and different cycloalkanones is illustrated in Scheme 1. All these syntheses involve the preliminary preparation of 3-[2-(5-acetyl-2,4-dihydroxyhenyl)-2-oxoethylidene]-5-substituted-indolin-2-ones (**IIIa, IIIb**). Initially the synthesis of (**IIIa, IIIb**) were carried out by the condensation of 5-substituted isatins and 4,6-diacetyl resorcinol stirred in alcoholic KOH for 8 h [23]. But this conventional method gave poor yields. Hence, we turned our attention towards microwave assisted synthesis, under microwave irradiation the yields were significantly improved and reaction completes in 5-6 min of shorter reaction time. The spirochromanones were synthesized by the Kabbe condensation of 3-[2-(5-acetyl-2,4-dihydroxyhenyl)-2-oxoethylidene]-5-substituted-indolin-2-ones-5-substituted-indolin-2-ones (**IIIa, IIIb**) with cycloalkanones in the presence of pyrrolidine in ionic liquid in conventional and microwave irradiation method. Microwave irradiation method predominantly gave higher



Spiperone (Schizophrenia) Spiromesifen (Acaricide)

Fig. 1. Biologically active spiro compounds on the market.

yields (76–89%) in 5–6 min of shorter reaction time. Formation of indolin-2-one fused spirochromanone (**IVa–IVp**) was confirmed by recording their IR, NMR and mass analyses.

IR spectrum of compound **IVa** showed absorption bands at 3439, 1686, 1599, and 1551 cm^{-1} which is due to the O–H, C=O, amide-C=O, and α,β-unsaturated C=O groups, respectively. The ^1H NMR spectrum of **IVa** showed a singlet at δ 12.74 ppm corresponding to O–H proton and a singlet at δ 10.21 ppm was due to N–H proton. A singlet was observed at δ 8.38 ppm was due to C=O flanked Ar-H. The appearance of doublets at δ 8.76 and 7.93 ppm were due to aromatic ring protons. The appearance of a triplet at δ 1.98 ppm and multiplet at δ 1.19 ppm was due to cyclic aliphatic $–CH_2$ protons.

Antioxidant activity. The antioxidant activity of synthesized compounds **IVa–IVp** was carried out by DPPH radical scavenging assay using ascorbic acid as standard antioxidant. The experiments were carried out at 500 μg/mL concentration. The compounds **IVa–IVp** showed promising DPPH free radical scavenging ability. The results reveal that, among the compounds tested, the compound **IVb** having cyclohexanone fused and **IVd** having *N*-carboxylate piperidone fused spirochromanone exhibited the highest radical scavenging ability at 1.25 and 1.74 μM, respectively, which exhibit more potent radical scavenging activity than the standard Ascorbic acid (IC_{50} 8.64 μM). The compound **IVc** having *N*-BOC piperidone fused spirochromanone exhibited IC_{50} value at 6.85 μM, still more potent than the standard and **IVf** having *N*-benzyl piperidone fused spirochromanone showed radical scavenging abilities as potent as standard at IC_{50} 8.12 μM.

The compounds **IVh** having fused bicyclo ketal annulated and **IVj** having 5-bromo substituted, cyclohexanone fused exhibited moderate scavenging activity, while remaining compounds showed poor radical scavenging abilities (47.46 to 61.16 μM) in comparison with the standard antioxidant. The presence of N-alkylated piperidone moiety enhances the radical scavenging activity, followed by cyclohexanone fused moiety, those which show more potent activity than the standard ascorbic acid.

EXPERIMENTAL

Materials and equipments. All chemicals and solvents were of commercially high-purity grade purchased from Sigma Aldrich Pvt. Ltd. and Merck Pvt. Ltd., India. TLC: silica gel (SiO_2; Merck 60 F254) coated on aluminum plates; visualization with UV and aqueous $KMnO_4$ solution. mp: Stuart SMP3 melting-point apparatus; uncorrected. Microwave reactions were carried out in milestone multi SYNTH microwave system. IR spectra: Shimadzu FTIR 8400 S spectrometer; KBr pellets; ν in cm^{-1}. NMR spectra: Bruker Avance-400 spectrometer, in DMSO-d_6; δ in ppm related to TMS as internal standard. Mass spectra: Finnigan MAT 1020 mass spectrometer; in *m/z*. Elemental analysis was determined by using Thermofinnigan CHNS analyzer.

General procedure for the synthesis of indolin-2-one fused spirochromanone conjugates (IVa–IVp). *Conventional method.* An equimolar mixture of 33-[2-(5-acetyl-2,4-dihydroxyhenyl)-2-oxoethylidene]-5-substituted-indolin-2-ones (**IIIa, IIIb**) (0.004 mol), substituted cycloalkanone (0.004 mol) and 2-3 drops of pyrrolidine in 1-*n*-butyl-3-methylimidazolium tetrachloroferrate, [bmim]Cl· $FeCl_3$ (2 mL) was stirred at 60°C for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with dichloro methane (3 × 10 mL). The combined extracts were concentrated in vacuo and the resulting product was directly charged on small silica gel column and eluted with a mixture of ethyl acetate : *n*-hexane (3 : 7, v/v) to afford pure product. The rest of the viscous ionic liquid was further washed with ether and dried at 80°C under reduced pressure to retain its activity in subsequent runs.

Microwave irradiation method. A mixture of 3-[2-(5-acetyl-2,4-dihydroxyhenyl)-2-oxoethylidene]-5-substituted-indolin-2-ones (**IIIa, IIIb**) (0.004 mol), substituted cycloalkanone (0.004 mol) and 2-3 drops of pyrrolidine in 1-*n*-butyl-3-methylimidazolium tetrachloroferrate, [bmim]Cl·$FeCl_3$ (1 mL) was subjected to microwave irradiation at 100 W for 5–6 min. After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with dichloro methane (3 × 10 mL). The combined extracts were concentrated in vacuo and the resulting product was directly charged on small silica gel column and eluted with a mixture of ethyl acetate : *n*-hexane (3 : 7 v/v) to afford pure product. The rest of the viscous ionic liquid was further washed with ether and dried at 80°C under reduced pressure to retain its activity in subsequent runs.

Table 1. Synthesis of novel indolin-2-one fused spirochromanone conjugates

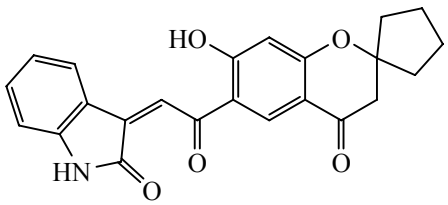
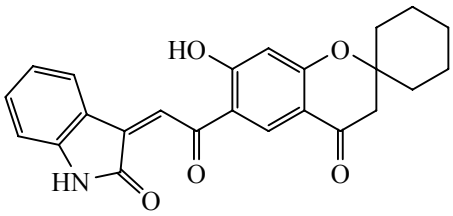
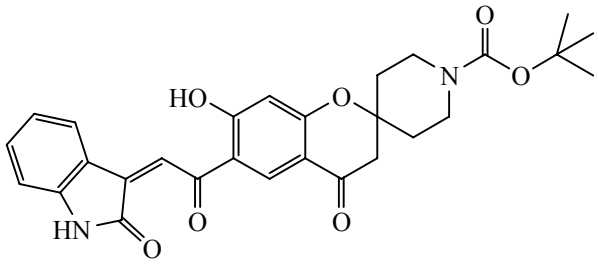
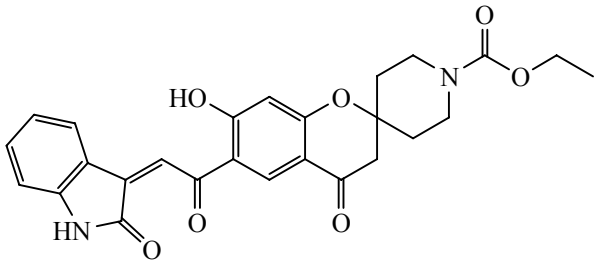
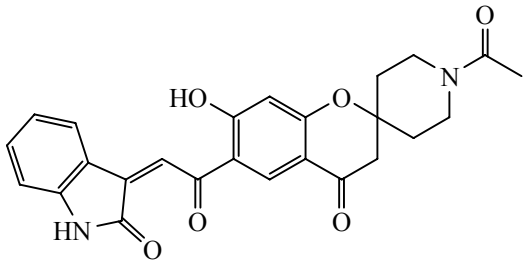
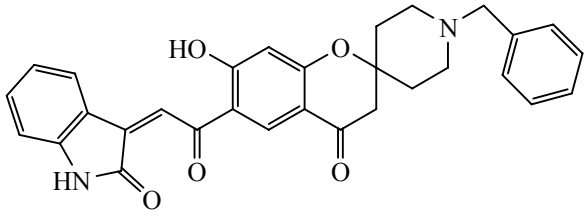
Comp. no.	Formula	Conventional method		Microwave irradiation	
		time, h	yield[a], %	time, min	yield, %
IVa		7	56	5	86
IVb		7	61	5	89
IVc		7	54	6	84
IVd		8	55	5	81
IVe		8	60	6	78
IVf		7	54	6	77

Table 1. (Contd.)

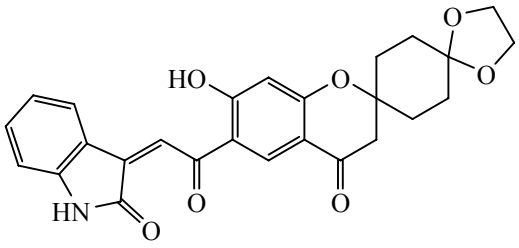
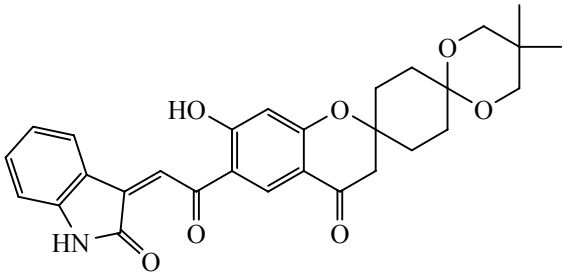
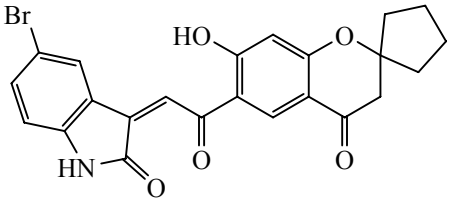
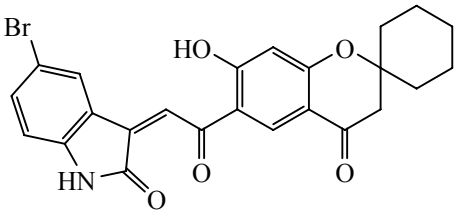
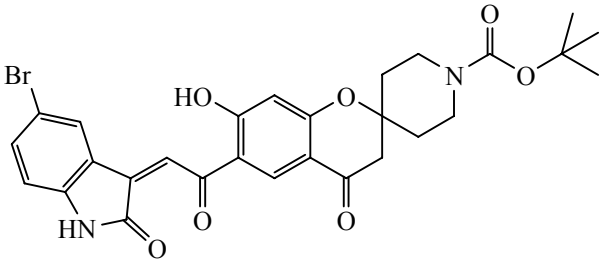
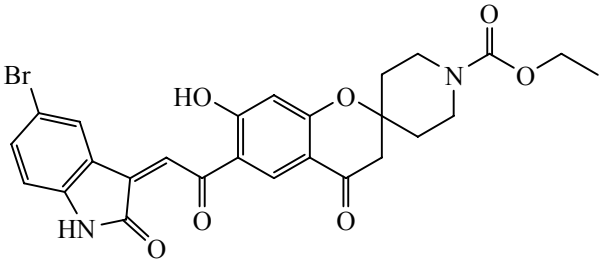
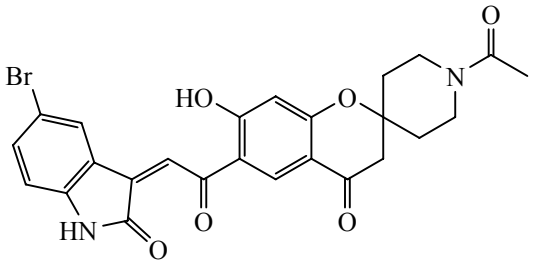
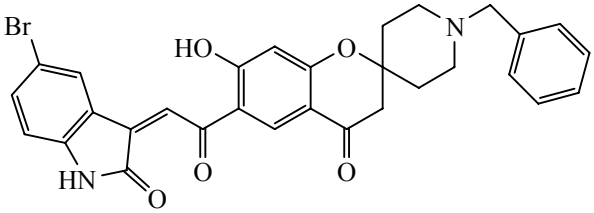
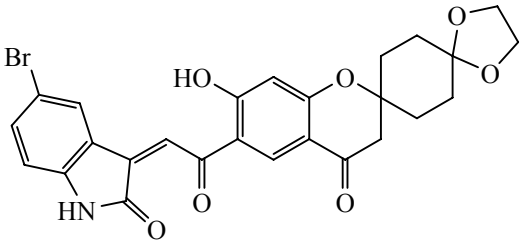
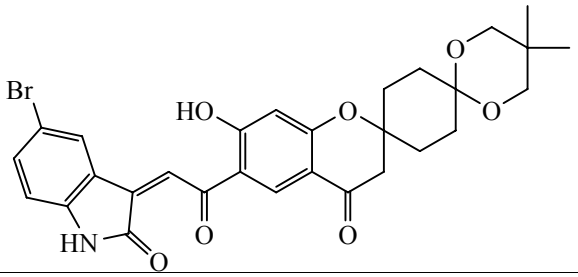
Comp. no.	Formula	Conventional method		Microwave irradiation	
		time, h	yield[a], %	time, min	yield, %
IVg		8	61	5	88
IVh		8	58	5	89
IVi		8	62	5	87
IVj		7	56	6	86
IVk		8	63	5	79
IVl		7	66	6	82

Table 1. (Contd.)

Comp. no.	Formula	Conventional method		Microwave irradiation	
		time, h	yield[a], %	time, min	yield, %
IVm		8	59	6	80
IVn		8	56	6	76
IVo		7	66	6	87
IVp		8	58	6	85

[a] Isolated yields.

Antioxidant assay. For the evaluation of antioxidant activity, we have used a stable-free radical α,α-diphenyl-β-picrylhydrazyl (DPPH), at the concentration of 0.2 mM in methanol [24]. To 0.1 mL of the test compound at 500 μg/mL, 1.5 mL of methanol and 0.5 mL of DPPH solution were added, mixed thoroughly and absorbance (OD) was read at 517 nm against the blank. The reduction percent of the free radical concentration (OD) with 500 μg/mL concentration of test compounds was calculated and was compared with standard Ascorbic acid. The results were expressed as IC_{50} values (the concentration of the test required to scavenge 50% free radicals). The antioxidant DPPH free radical scavenging activity of all the synthesized compounds performed using DPPH method results shown in Table 2.

Compound IVa. mp 223–226°C. IR spectrum, ν, cm^{-1}: 3439 (OH), 1686 (C=O), 1599 (amide C=O), 1551 (α,β-unsaturated C=O). ^{1}H NMR spectrum, δ, ppm: 12.74 s (1H, OH), 10.21 s (1H, NH), 8.76 d (1H, Ar-H, J = 8.4 Hz), 8.38 s (1H, C=O flanked Ar-H), 8.23 s (1H, COC=CH), 7.93 d (1H, Ar-H, J = 8.4 Hz), 7.72 t (1H, Ar-H), 7.51 t (1H, Ar-H), 6.43 s (1H, Ar-H), 2.85 s (2H, $COCH_2$), 1.98 t (4H, CH_2), 1.19 m (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 190.0

Table 2. DPPH radical scavenging activity of novel indolin-2-one fused spirochromanone conjugates

Comp. no.	IC_{50}, μM	Comp. no.	IC_{50}, μM
IVa	57.61	**IVj**	17.51
IVb	1.25	**IVk**	56.34
IVc	6.85	**IVl**	48.47
IVd	1.74	**IVm**	58.62
IVe	47.71	**IVn**	12.65
IVf	8.12	**IVo**	61.16
IVg	47.46	**IVp**	54.06
IVh	37.05	Ascorbic acid	8.64
IVi	53.29		

(C=O), 167.3 (amide C=O), 162.4 (α,β-unsaturated C=O), 156.0 (C–OH), 144.2 (spiro fused C), 130.3, 127.3, 126.4, 124.0, 115.6, 113.7, 113.4, 105.0, 90.4, 59.7 (CH_2), 45.9 (CH_2). Found, %: C 70.91; H 4.89; N 3.58. $C_{23}H_{19}NO_5$. Calculated, %: C 70.94; H 4.92; N 3.60. *M* 390 $[M + H]^+$.

Compound IVb. mp 231–235°C. IR spectrum, ν, cm^{-1}: 3436 (OH), 1689 (C=O), 1608 (amide C=O), 1571 (α,β-unsaturated C=O). ^1H NMR spectrum, δ, ppm: 12.73 s (1H, OH), 10.16 s (1H, NH), 8.69 d (1H, Ar-H, *J* = 9.2 Hz), 8.51 s (1H, C=O flanked Ar-H), 8.49 s (1H, COC=CH), 8.12 d (1H, Ar-H, *J* = 8.4 Hz), 7.88 t (1H, Ar-H), 7.72 t (1H, Ar-H), 6.46 s (1H, Ar-H), 2.75 s (2H, $COCH_2$), 1.32-1.25 m (10H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 189.4 (C=O), 167.3 (amide C=O), 164.4 (α,β-unsaturated C=O), 156.0 (C–OH), 144.5 (spiro fused C), 131.3, 130.3, 126.6, 124.0, 116.1, 113.4, 105.6, 90.4, 63.6 (CH_2), 44.6 (CH_2). Found, %: C 71.41; H 5.23; N 3.44. $C_{24}H_{21}NO_5$. Calculated, %: C 71.45; H 5.25; N 3.47. *M* 404 $[M + H]^+$.

Compound IVc. mp 212–216°C. IR spectrum, ν, cm^{-1}: 3441 (OH), 1690 (C=O), 1612 (amide C=O), 1576 (α,β-unsaturated C=O). ^1H NMR spectrum, δ, ppm: 12.69 s (1H, OH), 10.06 s (1H, NH), 8.68 d (1H, Ar-H, *J* = 9.2 Hz), 8.53 s (1H, C=O flanked Ar-H), 8.51 s (1H, COC=CH), 8.12 d (1H, Ar-H, *J* = 8.4 Hz), 7.87 t (1H, Ar-H), 7.71 t (1H, Ar-H), 6.61 s (1H, Ar-H), 3.36 t (4H, NCH_2), 2.75 s (2H, $COCH_2$), 1.41 s (9H, $C(CH_3)_3$), 1.26 t (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 189.4 (C=O), 166.8 (amide C=O), 164.8 (α,β-unsaturated C=O), 156.2 (C–OH), 144.4 (spiro fused C), 129.4, 127.3, 118.4, 114.3, 111.8, 105.0, 104.0, 85.4, 78.7, 53.3 (CH_2), 46.5 (CH_2). Found, %: C 66.61; H 5.56; N 5.51. $C_{28}H_{28}N_2O_7$. Calculated, %: C 66.66; H 5.59; N 5.55. *M* 505 $[M + H]^+$.

Compound IVd. mp 246–249°C. IR spectrum, ν, cm^{-1}: 3436 (OH), 1693 (C=O), 1622 (amide C=O), 1577 (α,β-unsaturated C=O). ^1H NMR spectrum, δ, ppm: 12.66 s (1H, OH), 10.11 s (1H, NH), 8.66 d (1H, Ar-H, *J* = 9.2 Hz), 8.51 s (1H, C=O flanked Ar-H), 8.47 s (1H, COC=CH), 8.12 d (1H, Ar-H, *J* = 8.4 Hz), 7.72 t (1H, Ar-H), 7.68 t (1H, Ar-H), 6.60 s (1H, Ar-H), 4.04 t (2H, O-CH_2), 3.21 t (4H, NCH_2), 2.83 s (2H, $COCH_2$), 1.65 s (3H, CH_3), 1.19 t (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 189.4 (C=O), 167.2 (amide C=O), 164.8 (α,β-unsaturated C=O), 155.9 (C–OH), 144.9 (spiro fused C), 139.4, 130.9, 127.8, 127.5, 126.9, 125.7, 123.0, 118.4, 114.3, 113.5, 104.9, 78.6, 60.7 (CH_2), 44.5 (CH_2). Found, %: C 65.52; H 5.05; N 5.83. $C_{26}H_{24}N_2O_7$. Calculated, %: C 65.54; H 5.08; N 5.88. *M* 477 $[M + H]^+$.

Compound IVe. mp 232–235°C. IR spectrum, ν, cm^{-1}: 3428 (OH), 1689 (C=O), 1624 (amide C=O), 1582 (α,β-unsaturated C=O). ^1H NMR spectrum, δ, ppm: 12.59 s (1H, OH), 10.02 s (1H, NH), 8.67 d (1H, Ar-H, *J* = 9.2 Hz), 8.50 s (1H, C=O flanked Ar-H), 8.45 s (1H, COC=CH), 8.12 d (1H, Ar-H, *J* = 8.4 Hz), 7.73 t (1H, Ar-H), 7.69 t (1H, Ar-H), 6.62 s (1H, Ar-H), 3.21 t (4H, NCH_2), 2.83 s (2H, $COCH_2$), 2.76 s (3H, CO-CH_3), 1.22 t (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 189.5 (C=O), 167.2 (amide C=O), 164.4 (α,β-unsaturated C=O), 162.5 (C–OH), 154.6; 144.6 (spiro fused C), 139.6, 131.4, 127.6, 127.4, 126.1, 124.9, 123.0, 118.4, 114.5, 113.5, 78.6, 60.7 (CH_2), 44.5 (CH_2). Found, %: C 67.23; H 4.95; N 6.23. $C_{25}H_{22}N_2O_6$. Calculated, %: C 67.26; H 4.97; N 6.27. *M* 447 $[M + H]^+$.

Compound IVf. mp 265–268°C. IR spectrum, ν, cm^{-1}: 3432 (OH), 1671 (C=O), 1628 (amide C=O), 1586 (α,β-unsaturated C=O). ^1H NMR spectrum, δ, ppm: 12.46 s (1H, OH), 10.11 s (1H, NH), 8.67 d (1H, Ar-H, *J* = 9.2 Hz), 8.52 s (1H, C=O flanked Ar-H), 8.43 s (1H, COC=CH), 8.12 d (1H, Ar-H, *J* = 8.4 Hz), 7.89–7.41 m (7H, Ar-H), 6.63 s (1H, Ar-H), 4.13 s (2H, $PhCH_2N$), 3.21 t (4H, NCH_2), 2.77 s (2H, $COCH_2$), 1.22 t (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 188.8 (C=O), 167.4 (amide C=O), 164.8 (α,β-unsaturated C=O), 155.8 (C–OH), 144.8 (spiro fused C), 132.9, 130.8, 128.9, 128.6, 127.4, 127.0, 125.8, 123.1, 118.1, 117.6, 114.5, 113.3, 105.1, 104.0, 76.7, 46.9

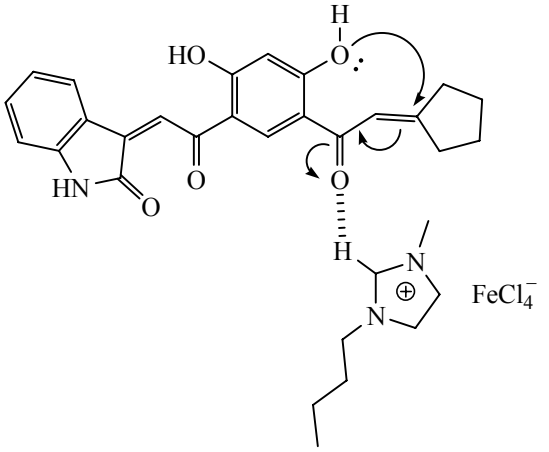


Fig. 2. [bmim]Cl·$FeCl_3$ mediated Kabbe condensation.

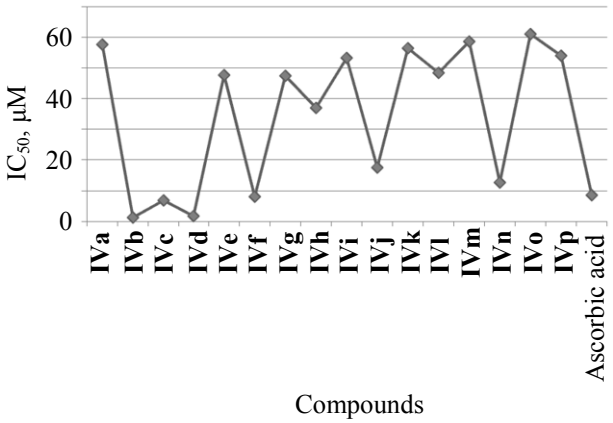


Fig. 3. Evaluation of DPPH radical scavenging activity of title compounds.

(CH_2), 44.5 (CH_2). Found, %: C 72.82; H 5.28; N 5.63. $C_{30}H_{26}N_2O_5$. Calculated, %: C 72.86; H 5.30; N 5.66. *M* 495 $[M + H]^+$.

Compound IVg. mp 252–254°C. IR spectrum, ν, cm^{-1}: 3437 (OH), 1685 (C=O), 1611 (amide C=O), 1576 (α,β-unsaturated C=O). ^1H NMR spectrum, δ, ppm: 12.73 s (1H, OH), 10.15 s (1H, NH), 8.66 d (1H, Ar-H, *J* = 9.2 Hz), 8.47 s (1H, C=O flanked Ar-H), 8.46 s (1H, COC=CH), 8.10 d (1H, Ar-H, *J* = 8.4 Hz), 7.85 t (1H, Ar-H), 7.68 t (1H, Ar-H), 6.58 s (1H, Ar-H), 3.88 s (4H, O-CH_2), 2.75 s (2H, $COCH_2$), 1.75 t (4H, CH_2), 1.26 t (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 189.7 (C=O), 167.5 (amide C=O), 164.8 (α,β-unsaturated C=O), 155.9 (C–OH), 144.8 (spiro fused C), 132.9, 130.8, 127.5, 126.8, 126.0, 123.1, 117.8, 117.1, 113.5, 112.1, 104.9, 79.4, 63.7 (CH_2), 44.6 (CH_2). Found, %: C 67.62; H 4.95; N 2.99. $C_{26}H_{23}NO_7$. Calculated, %: C 67.67; H 5.02; N 3.04. *M* 462 $[M + H]^+$.

Compound IVh. mp 247–249°C. IR spectrum, ν, cm^{-1}: 3429 (OH), 1681 (C=O), 1615 (amide C=O), 1576 (α,β-unsaturated C=O). ^1H NMR spectrum, δ, ppm: 12.71 s (1H, OH), 10.09 s (1H, NH), 8.66 d (1H, Ar-H, *J* = 9.2 Hz), 8.46 s (1H, C=O flanked Ar-H), 8.44 s (1H, COC=CH), 8.10 d (1H, Ar-H, *J* = 8.4 Hz), 7.84 t (1H, Ar-H), 7.67 t (1H, Ar-H), 6.56 s (1H, Ar-H), 3.84 s (4H, O-CH_2), 2.76 s (2H, $COCH_2$), 1.79 t (4H, CH_2), 1.44 s (6H, $C(CH_3)_2$), 1.25 t (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 189.4 (C=O), 167.5 (amide C=O), 164.8 (α,β-unsaturated C=O), 156.2 (C–OH), 144.4 (spiro fused C), 133.0, 131.0, 127.6, 125.6, 122.6, 117.7, 113.7, 112.1, 104.0, 79.9, 61.2 (CH_2), 48.5, 44.7 (CH_2). Found, %: C 69.13; H 5.76; N 2.74. $C_{29}H_{29}NO_7$. Calculated, %: C 69.17; H 5.80; N 2.78. *M* 504 $[M + H]^+$.

Compound IVi. mp 229–233°C. IR spectrum, ν, cm^{-1}: 3433 (OH), 1688 (C=O), 1591 (amide C=O), 1556 (α,β-unsaturated C=O). ^1H NMR spectrum, δ, ppm: 12.74 s (1H, OH), 10.18 s (1H, NH), 8.81 s (1H, Ar-H), 8.36 s (H, C=O flanked Ar-H), 8.21 s (1H, COC=CH), 7.75 d (1H, Ar-H, *J* = 8.4 Hz), 7.50 d (1H, Ar-H, *J* = 8.4 Hz), 6.42 s (1H, Ar-H), 2.88 s (2H, $COCH_2$), 1.89 t (4H, CH_2), 1.16 m (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 189.9 (C=O), 167.4 (amide C=O), 161.9 (α,β-unsaturated C=O), 156.4 (C–OH), 144.6 (spiro fused C), 131.0, 127.4, 126.4, 124.0, 115.6, 113.8, 113.1, 105.0, 89.4; 59.4 (CH_2), 45.6 (CH_2). Found, %: C 58.94; H 3.85; N 2.95. $C_{23}H_{18}BrNO_5$. Calculated, % : C 58.99; H 3.87; N 2.99. *M* 468 $[M + H]^+$.

Compound IVj. mp 216–219°C. IR spectrum, ν, cm^{-1}: 3439 (OH), 1691 (C=O), 1619 (amide C=O), 1574 (α,β-unsaturated C=O). ^1H NMR spectrum, δ, ppm: 12.73 s (1H, OH), 10.15 s (1H, NH), 8.78 s (1H, Ar-H), 8.48 s (1H, C=O flanked Ar-H), 8.36 s (1H, COC=CH), 7.82 d (1H, Ar-H, *J* = 9.2 Hz), 7.66 d (1H, Ar-H, *J* = 9.2 Hz), 6.44 s (1H, Ar-H), 2.76 s (2H, $COCH_2$), 1.32-1.23 m (10H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 190.4 (C=O), 167.5 (amide C=O), 164.7 (α,β-unsaturated C=O), 156.3 (C–OH), 144.8 (spiro fused C), 133.2, 131.6, 127.6, 124.5, 116.1, 113.4, 113.0, 105.4, 90.1, 64.0 (CH_2), 44.6 (CH_2). Found, %: C 59.73; H 4.15; N 2.87. $C_{24}H_{20}BrNO_5$. Calculated, %: C 59.76; H 4.18; N 2.90. *M* 482 $[M + H]^+$.

Compound IVk. mp 263–267°C. IR spectrum, ν, cm^{-1}: 3432 (OH), 1693 (C=O), 1616 (amide C=O),

1581 (α,β-unsaturated C=O). ^{1}H NMR spectrum, δ, ppm: 12.71 s (1H, OH), 10.06 (1H, NH), 8.70 s (1H, Ar-H), 8.51 s (1H, C=O flanked Ar-H), 8.47 s (1H, COC=CH), 7.76 d (1H, Ar-H, *J* = 9.2 Hz), 7.64 d (1H, Ar-H, *J* = 9.2 Hz), 6.62 s (1H, Ar-H), 3.37 t (4H, NCH_2), 2.75 s (2H, $COCH_2$), 1.39 s [9H, $C(CH_3)_3$], 1.25 t (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 189.6 (C=O), 166.8 (amide C=O), 164.4 (α,β-unsaturated C=O), 156.7 (C–OH), 144.4 (spiro fused C), 130.2, 128.3, 117.3, 114.7, 111.6, 105.2, 104.3, 85.4, 79.1, 53.6 (CH_2), 46.8 (CH_2). Found, %: C 57.61; H 4.64; N 4.75. $C_{28}H_{27}BrN_2O_7$. Calculated, %: C 57.64; H 4.66; N 4.80. *M* 583 $[M + H]^+$.

Compound IVl. mp 251–253°C. IR spectrum, ν, cm^{-1}: 3429 (OH), 1697 (C=O), 1619 (amide C=O), 1581 (α,β-unsaturated C=O). ^{1}H NMR spectrum, δ, ppm: 12.64 s (1H, OH), 10.04 s (1H, NH), 8.68 s (1H, Ar-H), 8.47 s (1H, C=O flanked Ar-H), 8.38 s (1H, COC=CH), 7.65 d (1H, Ar-H, *J* = 9.2 Hz), 7.48 d (1H, Ar-H, *J* = 9.2 Hz), 6.62 s (1H, Ar-H), 4.04 t (2H, O–CH_2), 3.25 t (4H, NCH_2), 2.81 s (2H, $COCH_2$), 1.62 s (3H, CH_3), 1.19 t (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 189.1 (C=O), 167.4 (amide C=O), 164.4 (α,β-unsaturated C=O), 161.6 (C–OH), 155.3, 144.6 (spiro fused C), 138.5, 130.9, 127.6, 127.5, 126.9, 125.7, 123.3, 117.7, 114.3, 113.8, 104.9, 78.9, 60.4 (CH_2), 44.1 (CH_2). Found, %: C 56.19; H 4.14; N 4.99. $C_{26}H_{23}BrN_2O_7$. Calculated, %: C 56.23; H 4.17; N 5.04. *M* 555 $[M + H]^+$.

Compound IVm. mp 227–230°C. IR spectrum, ν, cm^{-1}: 3425 (OH), 1689 (C=O), 1628 (amide C=O), 1584 (α,β-unsaturated C=O). ^{1}H NMR spectrum, δ, ppm: 12.54 s (1H, OH), 10.10 s (1H, NH), 8.70 s (1H, Ar-H), 8.47 s (1H, C=O flanked Ar-H), 8.42 s (1H, COC=CH), 7.66 d (1H, Ar-H, *J* = 9.2 Hz), 7.54 d (1H, Ar-H, *J* = 9.2 Hz), 6.64 s (1H, Ar-H), 3.21 t 4H, NCH_2), 2.84 s (2H, $COCH_2$), 2.73 s (3H, $COCH_3$), 1.21 t (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 190.2 (C=O), 167.2 (amide C=O), 164.7 (α,β-unsaturated C=O), 162.1 (C–OH), 154.5, 144.6 (spiro fused C), 139.6, 131.6, 127.7, 127.4, 126.1, 124.4, 123.0, 118.1, 114.4, 113.5, 78.6, 61.4 (CH_2), 44.8 (CH_2). Found, %: C 57.12; H 4.00; N 5.29. $C_{25}H_{21}BrN_2O_6$. Calculated, %: C 57.16; H 4.03; N 5.33. *M* 525 $[M + H]^+$.

Compound IVn. mp 219–221°C. IR spectrum, ν, cm^{-1}: 3430 (OH), 1665 (C=O), 1621 (amide C=O), 1573 (α,β-unsaturated C=O). ^{1}H NMR spectrum, δ, ppm: 12.41 s (1H, OH), 10.15 s (1H, NH), 8.73 s (1H, Ar-H), 8.50 s (1H, C=O flanked Ar-H), 8.41 s (1H, COC=CH), 7.77–7.34 m (7H, Ar-H), 6.64 s (1H, Ar-H), 4.10 s (2H, $PhCH_2N$), 3.24 t (4H, NCH_2), 2.77 s (2H, $COCH_2$), 1.21 t (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 189.2 (C=O), 167.4 (amide C=O), 164.6 (α,β-unsaturated C=O), 156.7 (C–OH), 144.4 (spiro fused C), 133.1, 130.8, 128.9, 128.4, 127.0, 125.6, 123.1, 117.2, 114.5, 113.3, 105.3, 104.0, 76.4, 46.5 (CH_2), 44.3 (CH_2). Found, %: C 62.80; H 4.34; N 4.84. $C_{30}H_{25}BrN_2O_5$. Calculated, %: C 62.84; H 4.39; N 4.89. *M* 573 $[M + H]^+$.

Compound IVo. mp 231–234°C. IR spectrum, ν, cm^{-1}: 3429 (OH), 1685 (C=O), 1615 (amide C=O), 1582 (α,β-unsaturated C=O). ^{1}H NMR spectrum, δ, ppm: 12.74 s (1H, OH), 10.15 s (1H, NH), 8.68 s (1H, Ar-H), 8.44 s (1H, C=O flanked Ar-H), 8.36 s (1H, COC=CH), 7.75 d (1H, Ar-H, *J* = 9.2 Hz), 7.66 d (1H, Ar-H, *J* = 9.2 Hz), 6.54 s (1H, Ar-H), 3.88 s (4H, O-CH_2), 2.75 s (2H, $COCH_2$), 1.77 t (4H, CH_2), 1.27 t (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 189.6 (C=O), 167.5 (amide C=O), 164.5 (α,β-unsaturated C=O), 155.9 (C–OH), 144.4 (spiro fused C), 133.4, 130.8, 127.7; 126.4, 126.0, 123.1, 117.4, 117.0, 113.3, 112.4, 104.8, 79.4, 63.6 (CH_2), 44.5 (CH_2). Found, %: C 57.72; H 4.05; N 2.53 $C_{26}H_{22}BrNO_7$. Calculated, %: C 57.79; H 4.10; N 2.59. *M* 540 $[M + H]^+$.

Compound IVp. mp 226–228°C. IR spectrum, ν, cm^{-1}: 3426 (OH), 1676 (C=O), 1601 (amide C=O), 1572 (α,β-unsaturated C=O). ^{1}H NMR spectrum, δ, ppm: 12.74 s (1H, OH), 10.04 s (1H, NH), 8.71 d (1H, Ar-H), 8.42 s (1H, C=O flanked Ar-H), 8.37 s (1H, COC=CH), 7.74 d (1H, Ar-H, *J* = 9.2 Hz), 7.62 d (1H, Ar-H, *J* = 9.2 Hz), 6.54 s (1H, Ar-H), 3.84 s (4H, OCH_2), 2.77 s (2H, $COCH_2$), 1.76 t (4H, CH_2), 1.43 s (6H, $C(CH_3)_2$), 1.22 t (4H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 190.4 (C=O), 167.6 (amide C=O), 164.4 (α,β-unsaturated C=O), 156.8 (C–OH), 144.8 (spiro fused C), 133.2, 131.0, 127.6, 125.6, 122.2, 117.4, 113.7, 112.0, 103.7, 79.6, 61.6 (CH_2), 48.5, 44.5 (CH_2). Found, %: C 59.74; H 4.81; N 2.35 $C_{29}H_{28}BrNO_7$. Calculated, %: C 59.80; H 4.85; N 2.40. *M* 582 $[M + H]^+$.

CONCLUSIONS

In this communication, we report a simple, economical, efficient, high yielding synthesis of novel indolin-2-one fused spirochromanone conjugates (**IVa**–**IVp**) by Kabbe condensation of substituted 3-[2-(5-acetyl-2,4-dihydroxyhenyl)-2-oxoethylidene]-5-substituted-indolin-2-ones with various cycloalkanones

in an ionic liquid. The remarkable key features of the reaction include the use of ionic liquid, 1-*n*-butyl-3-methylimidazolium tetrachloroferrate, [bmim]Cl·$FeCl_3$ as an inexpensive, environmentally benign reaction medium, easy isolation of the product and reuse of an ionic liquid and the synthesis of titled compounds under microwave irradiation method in shorter reaction time with good yields. Antioxidant activity screening results revealed that most of the compounds synthesized showed a better radical scavenging activity than that of the ascorbic acid.

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