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Fluorescent and antioxidant studies of effectively synthesized isochromenopyrrolone analogues

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An efficient strategy for the synthesis of 3-acetyl-2-methyl-1-phenylisochromeno [4,3-*b*] pyrrol-5(1*H*)-ones **4a–f** have been developed using montmorillonite K10 as a catalyst. The reaction proceeded from acetyl acetone, substituted primary amines and ninhydrin *via* acidic media under solvent-free conditions. Compounds **4a–c** exhibit green fluorescence under UV light, and their fluorescent properties in the liquid state were investigated. All the synthesized compounds were subjected for the evaluation of their free radical scavenging activity. Among all the tested compounds **4a** and **4c** exhibited good percentage inhibition in comparison with the standard, *i.e.* ascorbic acid.

1. Introduction

Aromatic heterocyclic compounds are known to show a wide range of ecotoxic effects, *e.g.* acute toxicity, cytotoxicity,[1] photo-induced toxicity,[2] mutagenicity[3] and carcinogenicity.[4] New efficient methods for the synthesis of heterocycles are a topic of major interest in modern synthetic organic chemistry.[5] Among the heterocycles isocoumarin represents the foremost class of naturally occurring lactones that display a wide range of biological activities such as protease inhibitor properties, antifungal, cytotoxic, anti-allergic, antimicrobial and antimalarial effects.[6–10] Isocoumarins are a class of natural products with a broad spectrum of biological activity,[11,12] including antioxidative,[13] antiangiogenic,[14] antifungal,[15,16] anti-allergic and antimicrobial[8–10] activities. They are also important in medicinal chemistry as building blocks for bioactive compounds.[17,18] In addition to its natural occurrence,[19,20] various synthetic methodologies for construction of isocoumarins have been demonstrated.[11] Note that isocoumarins are useful synthetic precursors to other heterocyclic and carbocyclic compounds.[21,22]

Free radicals oxidatively damage lipids, proteins and genomic DNA integrity, and they are widely recognized as the root cause of numerous degenerative diseases including cancer.[23] Antioxidants are potent scavengers of free radicals and serve as inhibitors of neoplastic processes.[24] Vegetables, fruits and their seeds are rich sources of vitamins C, E, β-carotene and other compounds that might protect the organism against free radical induced injury and diseases.[25,26] There has been an increasing interest in the use of natural antioxidants, such as tocopherols, flavonoids for the preservation of food materials.[27] These natural antioxidants avoid the toxicity problems, which may arise from the use of synthetic antioxidants such as butylated hydroxy anisole (BHA), butylated hydroxy toluene (BHT) and propyl gallate (PG). Due to the complexity of antioxidant activity in foods, the evaluation of synthetic heterocyclic compounds has been widely focused on recently.[28]

In this paper, synthesis of isochromenopyrrolone analogues using MK-10 under solvent-free conditions as an approach for organic synthesis is described, which involves microwave exposure of the neat reactants. The synthesis of 3-acetyl-2-methyl-1-phenylisochromeno [4,3-*b*] pyrrol-5(1*H*)-ones **4a–f** were carried out using MK-10 as a catalyst was found to be more efficient with high yields compared to conventional synthesis methods.[29]

2. Results and discussion

2.1 Chemistry

In this work, we have reported the synthesis of a novel series of 3-acetyl-2-methyl-1-phenylisochromeno [4,3-*b*] pyrrol-5(1*H*)-ones **4a–f** using MK-10 as a catalyst. The antioxidant activity and fluorescence properties of these 3-acetyl-2-methyl-1-phenyl-isochromeno [4,3-*b*] pyrrol-5(1*H*)-ones **4a–f** have also been reported.

The formation of **4a–f** was confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. FT-IR data of compound **4a** shows an absorption peak at 1462 cm^{-1}, indicating benzene C=C stretching, a peak at 1668 cm^{-1}, indicating alkene C=C stretching, a peak at 1732 cm^{-1}, indicating C=O stretching, and peaks at 3199–3057 cm^{-1}, indicating sp^{3} C–H stretching. ^{1}H-NMR data of compound **4a** confirms the existence of one methyl of pyrrole ring, one methyl group of the acetyl group and two methyl groups of substituted amine groups at δ 1.04, 1.04, 2.32, 2.79 ppm respectively, as well as two methylene protons of

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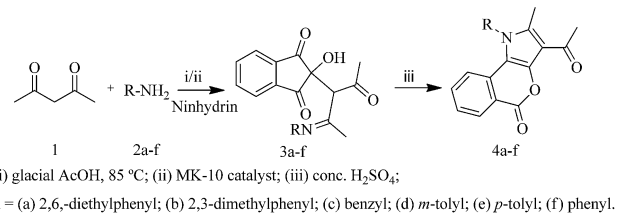

(i) glacial AcOH, 85 °C; (ii) MK-10 catalyst; (iii) conc. H_2SO_4;

R = (a) 2,6,-diethylphenyl; (b) 2,3-dimethylphenyl; (c) benzyl; (d) *m*-tolyl; (e) *p*-tolyl; (f) phenyl.

Scheme 1 Synthesis of 3-acetyl-2-methyl-1-phenylisochromeno [4,3-*b*] pyrrol-5(1*H*)-ones **4a–f**.

the ethyl groups at δ 2.26 and the seven aromatic protons that exist between δ 6.2 to 8.36 ppm. ^{13}C-NMR data of compound **4a** confirms the existence of six aliphatic carbons at δ 12.26–31.30 ppm, sixteen aromatic carbons between δ 110.4–142.1 ppm and two carbonyl groups at δ 161.99 (–C═O of isocoumarin ring) and 193.66 (–C═O of the acetyl group) (Scheme 1).

2.2 Fluorescence studies

For the fluorescence studies, we found that the compound **4c** exhibits a strong emission at 464 nm, the compound **4b** shows emission at 462 nm, which is similar to that of **4c**, and the compound **4a** shows weak emission at 456 nm.

2.3 Hydrogen peroxide scavenging assay

In the present study, hydrogen peroxide scavenging assay was performed for isochromenopyrrolones **4a–f**. The absorbance of the standard (ascorbic acid) and the compounds **4a–f** was measured at 230 nm, and the results were tabulated in Table 1. The percentage inhibition of the target molecules **4a–f** has been plotted against the various concentrations of the standard (ascorbic acid) and the test solutions (Fig. 1). All readings were obtained in triplicate to check their accuracy.

2.4 DPPH assay

In the present study, the DPPH assay was performed for the isochromenopyrrolones **4a–f**. The absorbance of the standard (ascorbic acid), and compounds **4a–f** were measured at 520 nm, and the results are listed in Table 2. The percentage inhibition of the target molecules have been plotted against the various concentrations of the standard (ascorbic acid) and the test solutions **4a–f** (Fig. 2). All readings were obtained in triplicate to check their accuracy.

Table 1 Percentage inhibition of H_2O_2 assay of 3-acetyl-2-methyl-1-phenylisochromeno [4,3-*b*] pyrrol-5(1*H*)-ones **4a–f**

	% Inhibition					
Conc. μL	4a	4b	4c	4d	4e	4f
10	41.63	40.62	40.81	11.07	22.61	10.54
20	50.85	45.68	48.14	20.84	31.74	18.19
30	58.38	53.64	54.76	32.42	48.89	32.16
50	84.46	83.82	74.05	52.68	72.14	52.05
100	88.70	87.64	83.64	76.21	82.38	74.89
IC_{50}	**1.84**	**2.07**	**2.07**	**2.46**	**2.90**	**2.38**

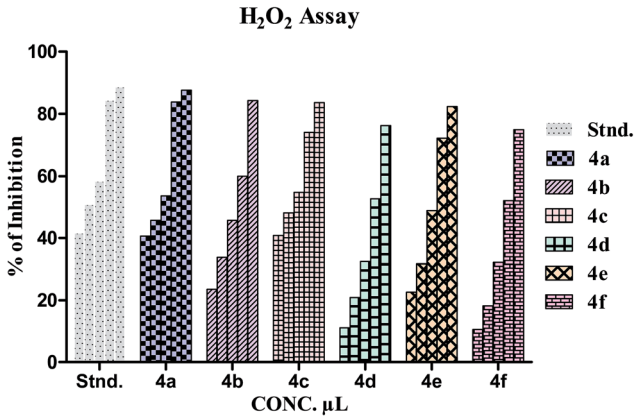

Fig. 1 Comparison of the percentage inhibition of H_2O_2 assay of 3-acetyl-2-methyl-1-phenylisochromeno [4,3-*b*] pyrrol-5(1*H*)-ones **4a–f**.

Table 2 Percentage inhibition of DPPH assay of 3-acetyl-2-methyl-1-phenylisochromeno [4,3-*b*] pyrrol-5(1*H*)-ones **4a–f**

	% Inhibition						
Conc. μL	4a	4b	4c	4d	4e	4f	4a
10	24.96	21.62	22.13	18.70	17.28	19.15	16.78
50	55.73	51.89	50.20	54.00	48.55	52.26	41.51
100	92.77	88.15	85.73	86.92	67.35	85.09	64.42
IC_{50}	1.76	1.88	1.91	1.90	2.22	1.93	2.38

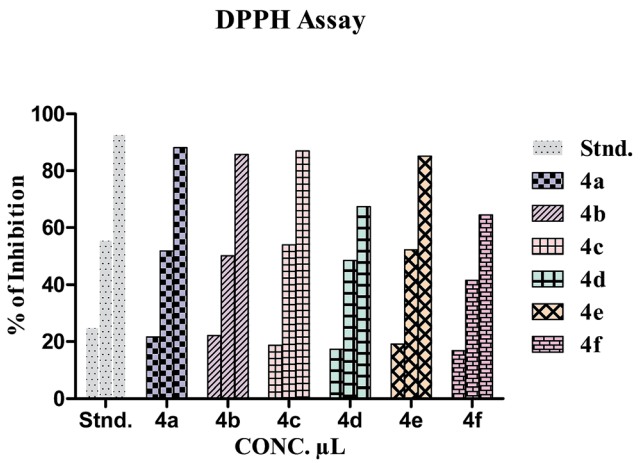

Fig. 2 Comparison of the percentage inhibition of DPPH assay of 3-acetyl-2-methyl-1-phenylisochromeno [4,3-*b*] pyrrol-5(1*H*)-ones **4a–f**.

3. Experimental

Solvents and reagents were commercially sourced and used without further purification. Thin-layered chromatography

(TLC) was performed on preparative plates of silica gel. Visualization was made using a UV chamber. Column chromatography was performed by using silica gel (60–120 mesh). Melting points were measured on a Elchem Microprocessor-based DT apparatus using an open capillary tube, and they are corrected with the standard, *i.e.* benzoic acid. IR spectra were obtained on a Nucon infrared spectrophotometer (KBr disc). UV-vis spectrum was obtained on UV-2550, Shimadzu Corporation, Kyoto, Japan. The NMR spectrum was recorded on a Bruker Avance III-400 & 500 MHz spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts were reported in δ units (ppm). GC-MS spectra were recorded on a Perkin Elmer spectrophotometer, GC model: clarus 680, mass spectrometer model: clarus 600 (EI). The fluorescence spectra were obtained on Hitachi F-7000 FL spectrophotometer.

3.1 General procedure for the synthesis of 3-acetyl-2-methyl-1-phenylisochromeno [4,3-*b*] pyrrol-5(1*H*)-one (4f)

Method A: (E)-2-hydroxy-2-(2-oxo-4-(phenylimino)pentan-3-yl)-1*H*-indene-1,3(2*H*)-dione (3f). A mixture of acetyl acetone **1** (1.1 mmol) and aniline **2f** (1.1 mmol) were heated at 85 °C for 15–30 min. Then, the reaction mixture was added to a solution of ninhydrin (1.1 mmol) in acetic acid (10 mL), and stirred at room temperature until the reactants disappeared. The progress of the reaction was monitored by TLC. After the completion, the reaction mixture was cooled to room temperature, and then this mixture was quenched using crushed ice. The solid formed was allowed to stand for 30 min and then filtered. Compound **3f** was recrystallized by mixture of acetone and hexane (2 : 8) to afford the crystals of intermediate compound **3f**.

3-Acetyl-2-methyl-1-phenylisochromeno [4,3-*b*]pyrrol-5(1*H*)-one (4f). About 0.5 mL of conc. H_2SO_4 was added to a solution of 200 mg of compound **3** in 10 mL of acetic acid. The reaction mixture was heated on a water bath at 85 °C for about 30–45 min. The initial pale green color of the solution was intensified to brown, which indicated the conversion of product **4a**. The progress of the reaction was monitored by TLC. Then, the reaction mixture was cooled to room temperature and poured into crush ice with continuous stirring. The precipitated solid was allowed to stand for 30 min and then filtered. Then, the solid obtained was purified by column chromatography using petroleum ether: ethyl acetate (8 : 2) as the eluent to afford the reddish brown crystals of isochromenopyrrolone **4a**.

Method-B: 3-acetyl-2-methyl-1-phenylisochromeno[4,3-*b*]-pyrrol-5(1*H*)-one (4f). Acetyl acetone **1** (1.1 mmol), aniline **2f** (1.1 mmol), ninhydrin (1.1 mmol), followed by addition of MK-10 (10 mg) were introduced in an Erlenmeyer flask. This mixture was subjected to microwave irradiation for sufficient intervals of time using resting intervals of 1 min after every 30 s of irradiation. The progress of the reaction was monitored by TLC. After cooling, the reaction mixture became sticky, and the sticky solid was then triturated to afford the product. The product was recrystallized by mixture of acetone and hexane (2 : 8) to afford the crystals of compound **4f**. Optimization of 3-acetyl-2-methyl-1-phenylisochromeno [4,3-*b*]pyrrol-5(1*H*)-one **4a–f** was performed by comparing the yield of the conventional and microwave irradiation methods. The results of the comparison are listed in Table 3.

3-Acetyl-1-(2,6-diethylphenyl)-2-methylisochromeno [4,3-*b*] pyrrol-5(1*H*)-one (4a). Pale brown solid, mol. formula: $C_{24}H_{23}NO_3$, exact mass: 373.1678, mol. wt.: 373.4443, yield 82%, m. pt. 209–211 °C. FT-IR (KBr pellets, cm^{-1}): 3388.93, 3199.91, 3057.17, 2966.52, 1732.08, 1668.43, 1462.04. 1H NMR (500 MHz, $CDCl_3$): δ = 8.35–8.36 (1H, dd, J_1 = 1.5 Hz J_2 = 1 Hz, –CH), 7.55–7.57 (1H, t, –CH), 7.34 (2H, m, –CH), 7.30 (1H, d, -CH), 7.28 (1H, d, -CH), 6.27–6.28 (1H, d, J = 5 Hz, –CH), 2.79 (3H, s, $-CH_3$), 2.32 (3H, s, $-CH_3$), 2.23 (2 × 2H, m, 2-CH_2) of Et, 1.01–1.05 (2 × 3H, t, 2-CH_3) of Et. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.6, 161.9, 142.1, 141.0, 138.8, 134.9, 133.8, 131.7, 130.6, 130.5, 2 × 127.1, 2 × 125.6, 117.8, 117.7, 111.5, 110.4, 31.3, 2 × 23.7, 2 × 13.7, 12.2. Mass: m/z 373.21.

3-Acetyl-1-(2,3-dimethylphenyl)-2-methylisochromeno[4,3-*b*] pyrrol-5(1*H*)-one (4b). Pale brown solid, mol. formula: $C_{22}H_{19}NO_3$, exact mass: 345.1365, mol. wt.: 345.3912, yield 84%, m. pt. 202–204 °C. FT-IR (KBr pellets, cm^{-1}): 3201.83, 1761.65, 1664.57. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.85 (3H, s, $-CH_3$), 2.36 (3H, s, $-CH_3$), 2.43 (3H, s, $-CH_3$), 2.77 (3H, s, $-CH_3$), 6.28–6.30 (1H, d, J = 10 Hz, –CH), 7.14–7.16 (1H, d, J = 10 Hz, –CH), 7.33 (3H, m, –CH), 7.44–7.46 (1H, d, J = 10 Hz, –CH), 8.36–8.35 (1H, d, J = 5 Hz –CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3, 13.8, 20.5, 31.4, 110.25, 117.8, 118.0, 125.7, 126.1, 2 × 127.2, 130.8, 131.8, 131.9, 2 × 135.0, 135.5, 136.0, 139.2, 139.5, 162.1, 193.9. GC-MS (EI): 345.26.

3-Acetyl-1-benzyl-2-methylisochromeno[4,3-*b*]pyrrol-5(1*H*)-one (4c). Pale brown solid, mol. formula: $C_{21}H_{17}NO_3$, exact mass: 331.1208, mol. wt.: 331.3646, yield 95%, m. pt. 182 °C[29] (lit. 182). FT-IR (KBr pellets, cm^{-1}): 3194.12, 3126.61, 2968.45, 2877.79, 1722.43, 1666.50, 1612.49. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.67 (3H, s, $-CH_3$), 2.74 (3H, s,$-CH_3$), 5.57 (2H, s, $-CH_2$), 7.07 (2H, d, J = 10 Hz, –CH), 7.34 (4H, m, –CH), 7.44–7.46 (1H, d, J = 10 Hz, –CH), 7.54 (1H, m, –CH), 8.39 (1H, m, –CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.4, 31.6, 48.6, 110.4, 111.6, 117.9, 118.8, 125.5, 126.7, 2 × 128.2, 129.3, 129.5, 130.4, 132.3, 135.1, 135.2, 139.1, 141.1, 161.9, 193.8. Mass: m/z 331.17.

3-Acetyl-2-methyl-1-*m*-tolylisochromeno[4,3-*b*]pyrrol-5(1*H*)-one (4d). Pale brown solid, mol. formula: $C_{21}H_{17}NO_3$, exact mass: 331.1208, mol. wt.: 331.3646, yield 88%, m. pt. 185–187 °C. FT-IR (KBr pellets, cm^{-1}): 2918.30, 2848.86, 1772.58,

Table 3 Reaction parameters of 3-acetyl-2-methyl-1-phenyl-isochromeno [4,3-*b*] pyrrol-5(1*H*)-ones **4a–f**

		Time		Yield (%)		
Entry	Product	CH[a] (h)	MW[b] (min)	CH[a]	MW[b]	M.P. (°C)
1	4a	2.45	1.20	79	82	209
2	4b	2.40	1.10	78	84	202
3	4c	2.50	1.40	86	95	180[29]
4	4d	2.45	1.20	83	88	187
5	4e	2.45	1	85	89	194
6	4f	3.05	1.10	82	85	245[29]

[a] Conventional heating–stirring, 85 °C, gla. AcOH, conc. H_2SO_4. [b] Microwave irradiated, MK-10.

1699.29, 1633.71. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48 (3H, s, $-CH_3$), 2.56 (3H, s, $-CH_3$), 2.82 (3H, s, $-CH_3$), 6.50–6.48 (1H, d, J = 8 Hz, –CH), 7.25 (1H, s, –CH), 7.35 (1H, s, –CH), 7.43–7.41 (1H, d, J = 8 Hz, –CH), 7.54 (1H, s, –CH), 7.59–7.58 (2H, d, J = 4 Hz, –CH), 8.43–8.41 (1H, d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 13.7, 20.5, 96.11, 112.5, 117.4, 117.5, 124.5, 126.5, 126.8, 131.2, 131.6, 131.8, 133.3, 134.5, 136.0, 137.4, 139.0, 142.5, 163.2, 190.4. Mass: m/z 331.18.

3-Acetyl-2-methyl-1-*p*-tolylisochromeno[4,3-*b*]pyrrol-5(1*H*)-one (4e). Pale brown solid, mol. formula: $C_{21}H_{17}NO_3$, exact mass: 331.1208, mol. wt.: 331.3646, yield 89%, m. pt. 192–194 °C. FT-IR (KBr pellets, cm^{-1}): 3199.91, 2966.52, 1786.08, 1670.35, 1606.70. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.40 (3H, s, $-CH_3$), 2.55 (3H, s, $-CH_3$), 2.74 (3H, s, $-CH_3$), 6.47–6.45 (1H, dd, J_1 = 4.4 Hz, J_2 = 1.4 Hz,–CH), 7.29 (3H, m, –CH), 7.38 (1H, m, –CH), 7.44–7.42 (2H, d, J = 8 Hz, –CH), 8.35–8.33 (1H, d, J = 8 Hz, –CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 13.7, 20.5, 96.11, 112.5, 117.4, 117.5, 124.5, 126.5, 126.8, 131.2, 131.6, 131.8, 133.3, 134.5, 136.0, 137.4, 139.0, 142.5, 163.2, 190.4. Mass: m/z 331.18.

3-Acetyl-2-methyl-1-phenylisochromeno[4,3-*b*]pyrrol-5(1*H*)-one (4f). Pale brown solid, mol. formula: $C_{20}H_{15}NO_3$, exact mass: 317.1052, mol. wt.: 317.3380, yield 85%, m. pt. 245–247 °C[29] (lit. 248). FT-IR (KBr pellets, cm^{-1}): 3057.17, 2918.30, 1712.79, 1612.49, 1494.33. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.38 (3H, s, $-CH_3$), 2.73 (3H, s, $-CH_3$), 6.36 (1H, s, –CH), 7.26 (1H, s, –CH), 7.31–7.29 (2H, t, d, J = 8 Hz, –CH), 7.44–7.42 (3H, d, J = 8 Hz, –CH), 7.64 (1H, s, –CH), 8.35–8.33 (1H, d, J = 8 Hz, –CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 31.6, 118.2, 124.0, 124.4, 125.0, 125.9, 126.9, 127.3, 130.4, 130.7, 131.9, 132.0, 134.9, 135.7, 136.8, 139.0, 139.3, 190.4, 201.3. Mass: m/z 317.26.

3.2 Antioxidant assay

Preparation of stock solution. A solution of hydrogen peroxide (40 mM) was prepared in phosphate buffer saline (PBS) at pH 7.4. A stock solution (1 mg mL^{-1}) was prepared for the synthesized compounds **4a–f** in methanol and subsequently diluted as 10, 20, 30, 50 and 100 μL.

Hydrogen peroxide scavenging anti-oxidant activity. Antioxidant activity was measured by a previously reported methodology.[30] For the present study, the samples were prepared by taking 1 mg of the compounds **4a–f** dissolved in 1 mL of AR grade methanol. The samples 10, 20, 30, 50 and 100 μL were taken in different test tubes, to which 20 μL of hydrogen peroxide was added and made up to 2 mL using phosphate buffer and incubated at room temperature for 10 min. The absorbance of the incubated solutions and the blank solution (phosphate buffer without hydrogen peroxide) were recorded against ascorbic acid. The absorbance was measured at 230 nm using a UV-vis spectrophotometer. Radical scavenging capacity (RSC) in percent was calculated by the following equation:

$$\%\ \text{of RSC}\ (\%) = [(A_b - A_s)/A_b] \times 100$$

where

RSC = radical scavenging capacity

A_s = absorbance of sample

A_b = absorbance of blank

DPPH radical scavenging assay. Radical scavenging activity of the compounds against stable DPPH (2,2-diphenyl-2-picrylhydrayl hydrate) was determined spectrophotometrically. When DPPH reacts with an antioxidant compound, which can donate hydrogen, DPPH is reduced. The changes in colour (from deep-violet to light yellow) were measured at 520 nm on a UV-vis spectrophotometer. A solution of DPPH was mixed with the synthesized compounds **4a–f** gives rise to the reduced form with the loss of violet color.

$$\text{DPPH}^{\cdot} + \text{RH} = \text{DPPH} + \text{R}^{\cdot}$$

where RH is the reduced form and R$^{\cdot}$ is free radical.

The DPPH radical scavenging activities of all the synthesized compounds **4a–f** and ascorbic acid were determined according to the reported method.[31] Initially, 1 mg mL^{-1} of the test material solutions and the standard (ascorbic acid) at a concentration of 10, 50 and 100 μg mL^{-1}, respectively, were added to 1 mL of 0.2 mM freshly prepared solution of DPPH in ethanol. The reaction mixture was stirred vigorously and allowed to stand for 30 min at room temperature under dark conditions. The absorbance of each reaction mixture was measured at 520 nm. The percentage of DPPH radical scavenging activity (%) of the sample was calculated as follows:

$$\%\ (\text{Inhibition}) = [(A_b - A_s)/A_b] \times 100$$

where

A_b = absorption of blank sample

A_s = absorption of sample

3.3 Fluorescence studies

UV-vis spectra. The UV absorption spectrum of compound **4a** in various solvents, such as DMF, ethanol and DMSO solution, were recorded in the range of 200–800 nm. The excitation peaks appears at 314 nm and 365 nm (Fig. 3a).

Fluorescence spectra. The fluorescence emission spectra of the synthesized compounds **4a–c** were recorded in DMSO with excitation wavelength at 365 nm. The fluorescence emission spectra of the compounds **4a–c** are shown in Fig. 3b.

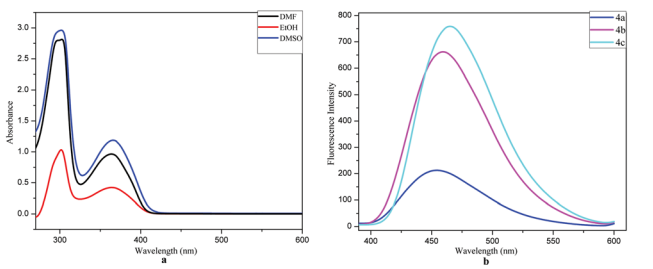

Fig. 3 3[a] Comparison of the UV-vis spectrum (DMF, ethanol and DMSO) of **4a**. [b] Fluorescence emission spectra of compounds **4a–c**.

Conclusions

In the present study, we report an efficient one-pot MK-10-catalysed synthesis of fused isochromenopyrrole-5(1*H*)-ones, which gave an enhanced yield with reduced time compared to conventional heating methods. Among the synthesized compounds, **4c** and **4b** exhibits strong fluorescence emission. The synthesized compounds were successfully screened for the free radical scavenging activity by H_2O_2 and DPPH assay method. Compounds **4a**, **4b** and **4c** showed a high percentage of inhibition similar to that of the standard, *i.e.* ascorbic acid.

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