J. Indian Chem. Soc.,
Vol. 96, January 2019, pp. 19-22

One-pot synthesis of modified 4-aryl-4*H*-chromenes and their preliminary anti-cancer studies

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Manuscript received online 29 August 2018, accepted 09 October 2018

The target substituted chromene molecule **4a-c** were prepared by simple one-pot synthesis using substituted benzaldehyde, malononitrile and 3-(dimethylamino)phenol. Fluoro-substituted (**4a**) possess high anti-oxidant property. The same compound shows good activity towards MCF-7 and BT-549 cell line analyses.

Keywords: 4-Aryl-4*H*-chromenes, one-pot synthesis, heterocyclic molecules, anti-oxidant, anti-cancer.

Introduction

Synthesizing biologically active compounds is one among the main focuses in medicinal chemistry. Among all known compounds, chromenes and its derivatives possess a unique importance as it shows wide range of biological[1] and pharmacological properties which includes diuretic, anticoagulant, and anti-cancer activity[2–7]. Besides, many substituted benzo-chromenes were employed in the treatment of various immune system diseases and diabetics[8].

The present attention in 2-amino-4*H*-chromenes rises from their utility towards healing of various human inflammations like rheumatoid, psoriatic arthritis and cancer therapy[9–12].

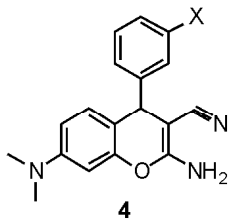

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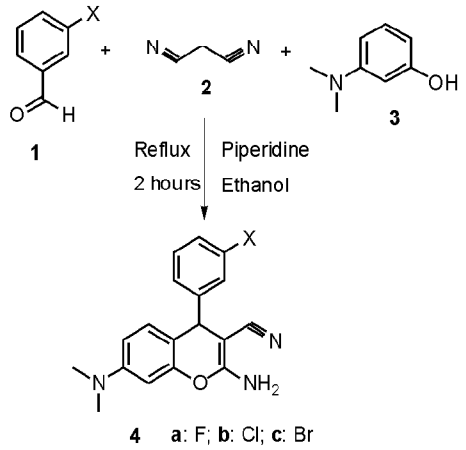
Fig. 1. Modified chromene.

There exist various protocols to prepare modified chromenes by utilizing several catalysts/bases[13–17]. However, all these protocols require either long duration time or lack in general applicability. Based on the previous report on *in silico* target profiling, a series of molecules were identified targeting estrogen receptor (ER), TNFR and tubulin which contains chromene unit[18,19]. The present research work illustrates the synthesis and preliminary biological studies of **4**.

Chemistry:

The target **4a-c** were prepared by using 3-(dimethylamino) phenol, 3-halobenzaldehyde and malonitrile (Scheme 1) which proceeds via Knoevenagel condensation followed by dehydration yields α,β-conjugated enone. The anionic compound of malononitrile added to the carbonyl carbon of the benzaldehyde leads to the formation of benzylidene malononitrile.



Scheme 1. Synthesis of substituted chromene molecule **4a-c**.

The reactants **1**, **2** and **3** were dissolved in ethanol along with few drops of piperidine and refluxed for two hours. The reaction was monitored via TLC, solid obtained after completion of reaction was filtered and purified by column chromatography.

Results and discussion

In vitro antioxidant studies:

The key feature of any antioxidant molecule is their capacity to capture radicals. The *in vitro* antioxidant potential of **4a-c** was assessed by 1,1-diphenyl-2-picrylhydrazyl (DPPH) and nitric oxide scavenging methods.

The DPPH methodology involves the contribution of a proton from a suitable hydrogen atom donor forming the reduced DPPH which was measured at various concentrations (between 10 and 50 μg/ml) in 517 nm wavelength. All the compounds **4a-c** exhibits almost equal activity (Table 1) with an IC_{50} value of 23.79, 23.23 and 23.35 μg/ml for **4a, 4b** and **4c** respectively.

Table 1. DPPH radical scavenging activity

Concentration	% Inhibition ± SEM		
(μg/ml)	**4a**	**4b**	**4c**
10	26.82±0.14	25.29±0.35	26.22±0.68
20	44.13±0.099	46.46±0.48	45.61±0.43
30	55.5±0.12	56.54±0.96	57.42±0.62
40	65.42±0.27	67.68±0.62	66.47±0.64
50	72.69±0.09	71.72±0.23	70.64±0.54

Nitric oxide is a significant chemical mediator produced by endothelial cells, neurons and involved in regulating various physiological processes. As evident from Table 2, **4a** (IC_{50} = 25.81 μg/ml) showed potent antioxidant ability comparable to that of ascorbic acid (IC_{50} = 27.2 μg/ml).

Table 2. Nitric oxide scavenging activity

Concentration	**%** Inhibition ± SEM		
(μg/ml)	**4a**	**4b**	**4c**
10	25.46±0.067	23.03±1.27	22.53±1.03
20	42.75±0.063	46.80±0.90	45.56±0.66
30	56.35±0.058	56.06±1.11	57.28±1.02
40	65.35±0.09	67.01±0.33	65.11±0.70
50	71.83±0.087	73.56±0.42	74.99±1.27

Cytotoxicity analysis:

The mitochondrial TCA cycle plays a vital role in the process of tumorigenesis. The *in vitro* anticancer screening of **4a-c** was performed by MTT assay on MCF-7 and BT-549 cell lines (Figs. 2 and 3).

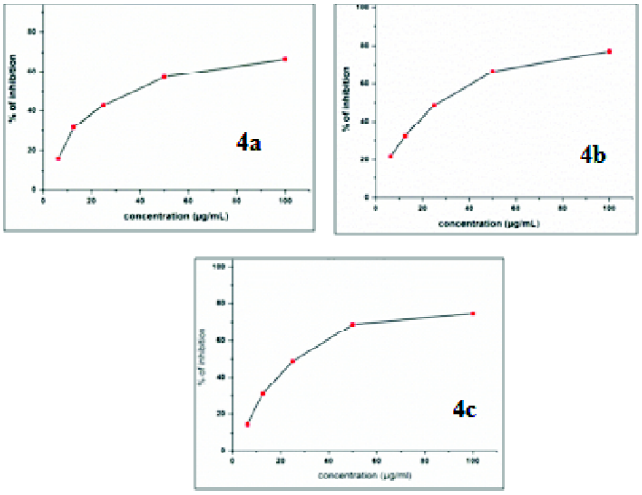


Fig. 2. CTC_{50} of **4a-c** on MCF-7 cell lines.

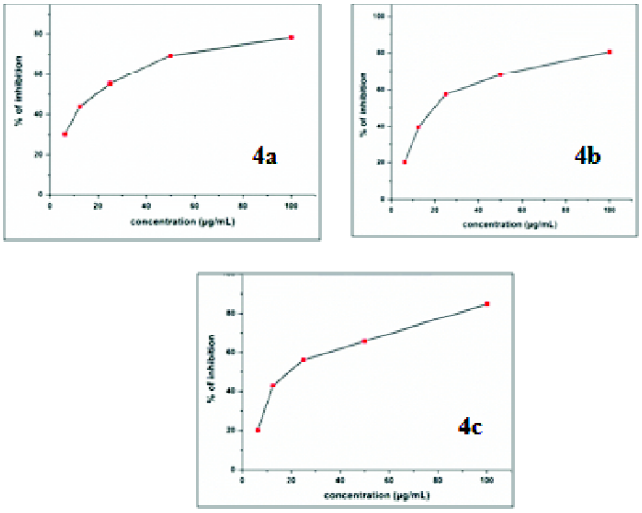


Fig. 3. CTC_{50} of **4a-c** on BT-549 cell lines.

The compounds **4a-c** exhibited moderate to potent cytotoxic activity. Among all, **4a** exhibited maximum activity in both cell lines with CTC_{50} of 28.81 μg/ml in MCF-7 cell line and 16.8 μg/ml in BT-549 cell line which could be due to presence of electronegative fluorine. Such an explanation is plausible due to similar finding by other research groups in

revealing the superiority of the fluorine atom over a variety of electron withdrawing groups as well as in recognizing the importance of fluorine substitution in the *para* regiochemistry[20,21] in the context of both breast and colon cancers.

Summary

Substituted 2-amino-4*H*-chromene (**4a-c)** was successfully synthesized using 3-(dimethylamino)phenol, 3-halobenzaldehyde and malonitrile in a good yield. The biological analyses show that compounds possess high antioxidant and anti-cancer activities. Synthesized substituted 4-aryl-4*H*-chromenes could find wide applications in drug discovery and syntheses of various substituted chromenes are under way in our laboratory.

Experimental

All chemicals used in the reactions were purchased from Sigma-Aldrich (Bangalore, India) or Fluka. All reactions were performed under nitrogen atmosphere. NMR (^{1}H/^{13}C) spectra were recorded on Bruker AXS (400 MHz) instrument. IR spectra were recorded on Shimadzu FT-IR spectrophotometer. MS data were obtained using Waters 2695-3100 LC/MS equipped with ESI source.

General procedure:

Two drops of piperidine were added to a mixture of substituted benzaldehyde (1 mmol), malononitrile (1 mmol), and substituted phenol (1 mmol) in ethanol (3 mL) and was heated to 60–80°C for 3 h and monitored by TLC (hexane:EtOAc = 7:3). The precipitate formed was filtered and washed with cold ethanol containing trace of water.

*2-Amino-7-(dimethylamino)-4-(3-fluorophenyl)-4H-chromene-3-carbonitrile (**4a**):* Yellowish pink solid (85%), ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.31 (t, 1H), 7.22 (m, 1H), 7.12 (d, 1H), 7.1 (d, 1H), 6.70 (s, 2H), 6.80 (d, 1H), 6.4 (dd, 1H), 6.21 (d, 1H), 4.8 (s, 1H), 3.12 (s, 6H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ: 161.49, 151.31, 149.11, 147.92, 132.07, 130.51, 129.35, 127.0, 126.6, 126.3, 120.9, 109.1, 109.5, 98.8, 55.2, 45.9, 46.43; MS (ESI, *m/z*): 310.2 (M+1). m.p. 109–112°C.

*2-Amino-4-(3-chlorophenyl)-7-(dimethylamino)-4H-chromene-3-carbonitrile (**4b**):* Yellow solid (78%), ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.34 (t, *J* 7.6 Hz, 1H), 7.27 (m, 1H), 7.18 (d, *J* 1.6 Hz, 1H), 7.13 (d, *J* 7.6 Hz, 1H), 6.90 (s, 2H), 6.80 (d, *J* 8.4 Hz, 1H), 6.47 (dd, *J* 2.4, 8.4 Hz, 1H), 6.23 (d, *J* 2.4 Hz, 1H), 4.66 (s, 1H), 3.33 (s, 6H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ: 160.49, 150.31, 149.12, 148.92, 133.07, 130.51, 129.37, 127.04, 126.56, 126.13, 120.59, 109.61, 109.45, 98.48, 55.72, 45.94, 45.43; MS (ESI, *m/z*): 326.3 (M+1), 328 (M+2, Cl isotopic peak); IR (KBr): 3419 and 3287 (N-H str. of 1° amine), 3082 (arom. -CH str.), 2214 (C≡N str.), 1631 (C=C ring str.), 1284 (C-N str. of -NH_2), 759 (C-Cl str.). m.p. 87–92°C.

*2-Amino-4-(3-bromophenyl)-7-(dimethylamino)-4H-chromene-3-carbonitrile (**4c**):* Yellow solid (75%), ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.14 (t, 1H), 7.20 (m, 1H), 7.28 (d, 1H), 7.19 (d, 1H), 6.98 (s, 2H), 6.72 (d, 1H), 6.51 (dd, 1H), 6.43 (d, 1H), 4.52 (s, 1H), 3.47 (s, 6H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ: 162.12, 151.31, 149.12, 148.92, 132.07, 131.51, 129.37, 128.04, 127.56, 126.13, 120.59, 109.61, 109.45, 98.48, 55.72, 45.94, 45.43; MS (ESI, *m/z*): 370.14 (M+1). m.p. 118–122°C.

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