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Synthesis and Antioxidant Activity of Some 2-Amino-4-aryl-3-cyano-7-(dimethylamino)-4*H*-chromenes

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A new series of 2-amino-4-aryl-3-cyano-7-(dimethylamino)-4*H*-chromenes was synthesized by the condensation of 3-(dimethylamino)phenol, an aromatic aldehyde and malonitrile in ethanol containing piperidine. The assignments of the structure of all the newly synthesized compounds were based on elemental analysis and spectral data (IR, Mass, ^{1}H NMR). The antioxidant activity of the synthesized compounds was determined by Ferric Reducing Antioxidant Power (FRAP) and DPPH free radical scavenging methods. Several compounds showed significant antioxidant activity.

Key Words: Synthesis, Antioxidants, 4-Aryl-4*H*-chromenes.

INTRODUCTION

A growing amount of research in biology and medicine has been dedicated to free radicals such as Reactive Oxygen Species (ROS). ROS are required in many living tissues for normal metabolic processes, *e.g.*, phagocytosis, antiinflamation, cell division, and synthesis of collagen[1-3]. However, there is now considerable evidence that ROS induce oxidative damage in biomolecules especially in proteins, lipids and DNA. This damage causes various degenerative disorders, such as cardiovascular disease, aging, and neurodegenerative disease, like Alzheimer's disease, Parkinson's disease, mutation and cancer[4,5]. In view of the biological importance of dietary antioxidants in chemoprevention of these diseases, in an effort to develop a novel antioxidant, we have synthesized a series of 4-aryl-4*H*-chromenes and evaluated their antioxidant activities.

4-Aryl-4*H*-chromenes have been identified as novel anticancer agents by potent apoprosis inducing activity[6,7], but to the best of our knowledge, the 4-aryl-4*H*-chromenes have not been studied for their antioxidative activity.

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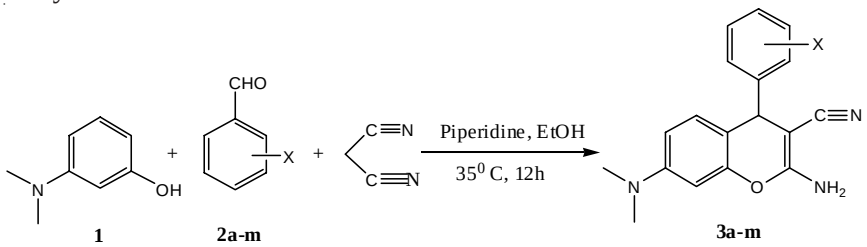
EXPERIMENTAL

2-Amino-3-cyano-7-(dimethylamino)-4-(substituted phenyl)-4*H*-chromenes (**3a-m**) were synthesized by the condensation of 3-(dimethylamino)phenol (**1**), a substituted benzaldehyde (**2**) and malonitrile in ethanol in the presence of piperidine (**Scheme-1**). The synthesized compounds were characterized by IR, ^{1}H NMR, mass spectral data and elemental analysis.



Scheme-1

Compounds **3a-m** were screened for their antioxidant activity using ferric reducing antioxidant power (FRAP) and DPPH free radical scavenging methods.

The melting points were taken on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrophotometer (KBr disks). ^{1}H NMR spectra were recorded on a Bruker FT-80 NMR spectrophotometer using $CDCl_3$ as solvent and TMS as an internal standard. The purity of the compounds was monitored by thin layer chromatography.

2-Amino-3-cyano-7-(dimethylamino)-4-(substituted phenyl)-4*H*-chromenes (3a-m): (General procedure): Piperidine (10 mmol) was added to a mixture of 3-dimethylaminophenol (**1**, 5 mmol), substituted benzaldehyde (**2**, 5 mmol) and malonitrile (5 mmol) in ethanol (20 mL). The reaction mixture was stirred at 35°C for 12 h. After cooling, the precipitated solid was filtered, washed with cold ethanol and crystallized from the same solvent.

2-Amino-4-(2,3-dimethoxyphenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (3a): Yield 56 %; m.p. 157-158° C; m.f. $C_{20}H_{21}N_3O_3$ IR (KBr, cm^{-1}): 3416, 3313 ν(NH_2), 2176 ν(CN); ^{1}H NMR ($CDCl_3$, 80 MHz) δ 7.10-6.90 (m,1H, aromatic), 6.89-6.60 (m, 3H, aromatic), 6.55-6.33 (m, 2H, aromatic), 4.96(s, 1H, 4H-chromene), 4.42 (brs, 2H, NH_2), 3.78(s, 3H), 3.75 (s, 3H), 2.88 (s, 6H, NMe_2); Ms (m/z, %): 351(M^+, 50), 321(30), 214(100), 198(17), 168(7).

2-Amino-4-(2,4-dimethoxyphenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (3b): Yield 40 %; m.p. 145-146°C; m.f. $C_{20}H_{21}N_3O_3$ IR (KBr, cm^{-1}):3400, 3318 ν(NH_2), 2187 ν(CN); ^{1}H NMR

($CDCl_3$, 80 MHz) δ: 7.04-6.78 (m, 2H, aromatic), 6.75-6.22 (m, 4H, aromatic), 5.06 (s, 1H, 4H-chromene), 4.47 (brs, 2H), 3.81 (s, 3H, OMe), 3.76 (s, 3H, OMe), 2.90 (s, 6H, NMe_2); Ms (m/z, %): 351(M^+, 100), 334(28), 276(13), 214(90), 198(88), 170(30), 138(16).

2-Amino-4-(2,5-dimethoxyphenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (3c): Yield 48%; m.p. 160-162°C; m.f. $C_{20}H_{21}N_3O_3$ IR (KBr, cm^{-1}):3400, 3298 ν(NH_2), 2182 ν(CN); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.00-6.65 (m, 3H, aromatic), 6.65-6.20 (m, 3H, aromatic), 5.12 (s, 1H, 4H-chromene), 4.50 (brs, 2H, NH_2), 3.80 (s, 3H, OMe), 3.69 (s, 3H, OMe), 2.91 (s, 6H, NMe_2); Ms (m/z, %): 351 (M^+, 35), 320(22), 214(100), 198(17), 167.9(8).

2-Amino-4-(3,4-dimethoxyphenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (3d): Yield 42%; m.p. 160-161°C; m.f. $C_{20}H_{21}N_3O_3$ IR (KBr, cm^{-1}):3467, 3324 ν(NH_2), 2187 ν(CN); ^1H NMR ($CDCl_3$, 80 MHz) δ: 6.95-6.61 (m, 3H, aromatic), 6.55-6.45 (m, 1H, aromatic), 6.40-6.29 (m, 2H, aromatic), 4.59 (s, 1H, 4H-chromene), 4.53 (brs, 2H, NH_2), 3.84 (s, 3H, OMe), 3.83 (s, 3H, OMe), 2.93 (s, 6H, NMe_2); Ms (m/z, %): 351(M^+, 93), 334 (14), 276(8), 236(16), 214(100), 198(59), 170(16), 137(20), 97(15), 83(90), 47.1(29).

2-Amino-4-(3,5-dimethoxyphenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (3e): Yield 38%; m.p. 170-171°C; m.f. $C_{20}H_{21}N_3O_3$ IR (KBr, cm^{-1}):3450, 3325 ν(NH_2), 2185 ν(CN); ^1H NMR (DMSO-d_6, 80 MHz) δ: 6.90-6.46 (m, 3H, aromatic), 6.40-6.35 (m, 1H, aromatic), 6.30-6.20 (m, 2H, aromatic), 4.50 (s, 1H, 4H-chromene), 4.33(brs, 2H, NH_2), 3.68 (s, 6H, OMe), 2.88 (s, 6H, NMe_2); Ms (m/z, %): 351(M^+, 80), 214(100), 198(9).

2-Amino-4-(2,3,4-trimethoxyphenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (3f): Yield 48%; m.p. 137-138°C; m.f. $C_{21}H_{23}N_3O_4$ IR (KBr, cm^{-1}): 3416, 3324 ν(NH_2), 2187 ν(CN); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.01-6.21 (m, 5H, aromatic), 4.91 (s, 1H, 4H-chromene), 4.51 (brs, 2H, NH_2), 3.95-3.70 (m, 9H, OMe), 2.90 (s, 6H, NMe_2); Ms (m/z, %): 381(M^+, 60), 350(67), 214(100), 198(30).

2-Amino-4-(3,4,5-trimethoxyphenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (3g): Yield 74%; m.p. 177-179°C; m.f. $C_{21}H_{23}N_3O_4$ IR (KBr, cm^{-1}): 3452, 3329 ν(NH_2), 2197 ν(CN); ^1H NMR ($CDCl_3$, 80 MHz) δ: 6.90-6.70 (m, 1H, aromatic), 6.65-6.20 (m, 4H, aromatic), 4.57 (brs, 3H, 4H-chromene and NH_2), 3.81 (s, 9H, OMe), 2.93 (s, 6H, NMe_2); Ms (m/z, %): 381 (M^+, 88), 214(100), 198(50).

2-Amino-4-(2-bromophenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (3h): Yield 49%; m.p. 197-198°C; m.f. $C_{18}H_{16}N_3OBr$ IR (KBr, cm^{-1}): 3462, 3318 ν(NH_2), 2202 ν(CN); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.6-7.5 (m, 1H, aromatic), 7.21-7.01 (m, 3H, aromatic), 7.00-6.71 (m,

1H, aromatic), 6.61-6.21 (m, 2H, aromatic), 5.31 (s, 1H, 4H-chromene), 4.58 (brs, 2H, NH_2), 2.91 (s, 6H, NMe_2); Ms (m/z, %): 371 (M^++2, 13), 369 (M^+, 13), 214(100), 198(15).

2-Amino-4-(3-bromophenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (3i): Yield 67 %; m.p. 178-180°C; m.f. $C_{18}H_{16}N_3OBr$ IR (KBr, cm^{-1}): 3457, 3349 ν(NH_2), 2192 ν(CN); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.32-7.05 (m, 3H, aromatic), 6.91-6.68 (m, 1H, aromatic), 6.54-6.20 (m, 3H, aromatic), 4.59 (brs, 3H, 4H-chromene and NH_2), 2.92 (s, 6H, NMe_2); Ms (m/z, %): 371(M^++2, 95), 369 (M^+, 98), 368 (56), 354(15), 214(100), 198(15), 170(30), 144(50).

2-Amino-4-(2,3-dichlorophenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (3j): Yield 67%; m.p. 207-208°C; m.f. $C_{18}H_{15}N_3OCl_2$ IR (KBr, cm^{-1}): 3452, 3334 ν(NH_2), 2192 ν(CN); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.24-7.15 (m, 1H, aromatic), 7.15-6.98 (m, 2H, aromatic), 6.90-6.65 (m, 1H, aromatic), 6.60-6.45 (m, 1H, aromatic), 6.47-6.25 (m, 1H, aromatic), 4.60 (m, 3H, 4H-chromene and NH_2), 2.94 (s, 6H, NMe_2); Ms (m/z, %): 363 (M^++4, 1), 361 (M^++2, 6), 359 (M^+, 8), 214(100), 198(14).

2-Amino-4-(2,6-dichlorophenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (3k): Yield 61%; m.p. 255-256°C; m.f. $C_{18}H_{15}N_3OCl_2$ IR (KBr, cm^{-1}): 3421, 3329 ν(NH_2), 2187 ν(CN); ^1H NMR (DMSO-d_6, 80 MHz) δ: 7.5-7.28 (m, 1H, aromatic), 7.28-6.92 (m, 2H, aromatic), 6.82-6.58 (m, 1H, aromatic), 6.5-6.15 (m, 2H, aromatic), 5.81 (s, 1H, 4H-chromene), 5.28 (brs, 2H, NH_2), 2.91 (s, 6H, NMe_2); Ms (m/z, %): 363 (M^++4, 4), 361 (M^++2, 24), 359 (M^+, 37), 279(9), 214(100), 198(57), 170(15), 143(8).

2-Amino-7-(dimethylamino)-4-(2,4-dimethylphenyl)-4*H*-chromene-3-carbonitrile (3l): Yield 32%; m.p. 100-101°C; m.f. $C_{20}H_{21}N_3O$ IR (KBr, cm^{-1}): 3477, 3313 ν(NH_2), 2192 ν(CN); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.05-6.80 (m, 3H, aromatic), 6.8-6.6 (m, 1H, aromatic), 6.55-6.22 (m, 2H, aromatic), 4.92 (s, 1H, 4H-chromene), 4.48 (brs, 2H, NH_2), 2.92 (s, 6H, NMe_3), 2.34 (s, 3H, Me), 2.26 (s, 3H, Me); Ms (m/z, %): 319 (M^+, 25), 214(100), 198(10).

2-Amino-4-biphenyl-4-yl-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (3m): Yield 79%; m.p. 216-218°C; m.f. $C_{23}H_{21}N_3O$ IR (KBr, cm^{-1}): 3462, 3308 ν(NH_2), 2187 ν(CN). ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.7-7.1 (m, 9H, aromatic), 6.84 (d, J=8.8, 1H, aromatic), 6.56-6.28 (m, 2H, aromatic), 4.68 (s, 1H, 4H-chromene), 4.54 (brs, 2H, NH_2), 2.92 (s, 6H, NMe_2); Ms (m/z, %): 367(M^+, 25), 214(100), 198(9).

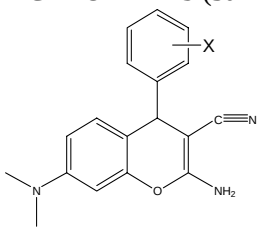
RESULTS AND DISCUSSION

In the present study, two commonly used antioxidant evaluation methods, Ferric Reducing Antioxidant Power (FRAP) and the DPPH (1,1-diphe-

nyl-2-picrylhydrazyl) radical scavenging methods, were chosen to determine the antioxidant potential of the compounds.

FRAP assay: The antioxidant capacity of the synthesized compounds was measured using FRAP method[8]. According to the method, reduction of ferric to ferrous ion at law pH cases a coloured ferrous-tripyridyltriazine complex to form. FRAP values are obtained by comparing the absorbance change at 593 nm in test reaction mixtures with those containing ferrous ions in known concentration (Table-1). According to the data presented in Table-1, compound **3k** having 2,6-dichloro substituent showed the most antioxidant power in FRAP assay.

TABLE-1
ANTIOXIDANT ACTIVITY OF 2-AMINO-3-CYANO-7-(DIMETHYLAMINO)-4-(SUBSTITUTED PHENYL)-4*H*-CHROMENES (**3a-m**)



Comp.	X	FRAP values (μM)[a]	DPPH IC_{50} (μM)[a]
3a	2,3-Di CH_3O	27.43 ± 1.41	93.8 ± 0.84
3b	2,4-Di CH_3O	26.23 ± 1.05	66.73 ± 0.48
3c	2,5-Di CH_3O	24.78 ± 0.95	424.89 ± 1.28
3d	3,4-Di CH_3O	25.46 ± 0.93	148.30 ± 0.69
3e	3,5-Di CH_3O	9.38 ± 0.38	179.61 ± 2.11
3f	2,3,4-Tri CH_3O	25.80 ± 0.55	81.90 ± 0.91
3g	3,4,5-Tri CH_3O	33.25 ± 1.07	109.83 ± 0.54
3h	2-Br	33.82 ± 0.89	186.94 ± 1.34
3i	3-Br	33.46 ± 1.04	> 500
3j	2,3-Di Cl	30.24 ± 0.47	237.22 ± 1.58
3k	2,6-Di Cl	35.30 ± 1.03	681.69 ± 1.50
3l	2,4-Di CH_3	33.46 ± 1.21	307.04 ± 2.74
3m	4-Ph	25.43 ± 0.93	> 500
Trolox®		50.28 ± 0.54	36.27 ± 0.49

[a]Values are expressed as mean ± SEM for three independent experiments.

DPPH assay: DPPH radical scavenging activity of the sythensized compounds was determined by the method described by Lamaison *et al.*[9], based on the reduction of methanolic solution of the colored DPPH radical. From the IC_{50} values (Table-1), compound **3b** having 2,4-dimethoxy group showed significant DPPH scavenging activity (IC_{50} = 66.73 μm) in comparison to Trolox, a hydrophilic analogue of vitamin E (IC_{50} = 36.27 μm).

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