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Microwave assisted synthesis of 2-amino-6-methoxy-4*H*-benzo[*h*]chromene derivatives

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ABSTRACT

A convenient and efficient method using microwave assisted synthesis of 4*H*-benzo[*h*]chromenes (7 and 8), by the reaction of 4-methoxy-1-naphthol (1) with a mixture of aromatic aldehydes (2) and malononitrile (3) or ethyl cyanoacetate (5) and also, by the reaction of 4-methoxy-1-naphthol (1) with *α*-cyanocinnamonitriles (4) or ethyl *α*-cyanocinnamates (6) in ethanolic piperidine solution was examined. Structures of the newly synthesized compounds were established on the basis of spectral data, IR, ^{1}H NMR, ^{13}C NMR, ^{13}C NMR-DEPT and MS data.

1. Introduction

2-Aminochromenes are important class of heterocyclic compounds having important biological activities. During the last decade, such compounds have shown interesting pharmacological properties including, antimicrobial [1-5], antileishmanial [6-9], anticancer [10,11], antioxidant [12-15], hypertensive [16], antiproliferative [17], antitumor [18-27] effects and activities, as well as treatment of Alzheimer's disease [28] and Schizophrenia disorder [29]. Fused chromene ring systems have blood platelet antiaggregating [30], antihistaminic [31] and analgesic activities [32-36]. They also exhibit hypolipidemic activity [37], DNA breaking activities and mutagenicity [38].

Recently, several methods for the synthesis of 2-aminochromenes and 2-aminobenzochromenes have been described [10,39,40]. Various catalysts such as piperidine [41-44], morpholine [45], CTACl (Cetyltrimethylammonium chloride) [46], or CTABr (Cetyltrimethylammonium bromide) [47], *o*-quinone methides (*o*-QMs) [48,49] and alumina [50] have been used for the preparation of 2-aminochromenes and 2-aminobenzochromenes. However, most of the reported methods require prolonged reaction time, stoichiometric reagents, and toxic solvents but generate only moderate yields of the product.

Microwave heating has been known for accelerating the organic reactions [51-53]. Cyclocondensation reactions in "dry media" leading to heterocyclic systems have been performed under microwave irradiation [54-60]. The reactions were carried out in a neat, solvent-free state or in ethanol under microwave irradiation help to generate products not attainable through classical heating methods.

In continuation of our program on the chemistry of 4*H*-pyran derivatives [10,42,61-73], it seemed interesting to synthesize new 4*H*-benzo[*h*]chromene derivatives by using a mixture of aromatic aldehydes/malononitrile or *α*-cyano-cinnamonitriles and a mixture of aromatic aldehydes/ethyl cyanoacetate or ethyl *α*-cyanocinnamates aiming for evaluation of their antitumor activities and DNA extractions.

2. Experimental

2.1. Instrumentation

Melting points were determined with a Stuart Scientific Co. Ltd apparatus. IR spectra were determined as KBr pellets on a Jasco FT/IR 460 plus spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AV 500 MHz spectrometer using tetramethylsilane (TMS) as an internal reference and results are expressed as δ (ppm) values.

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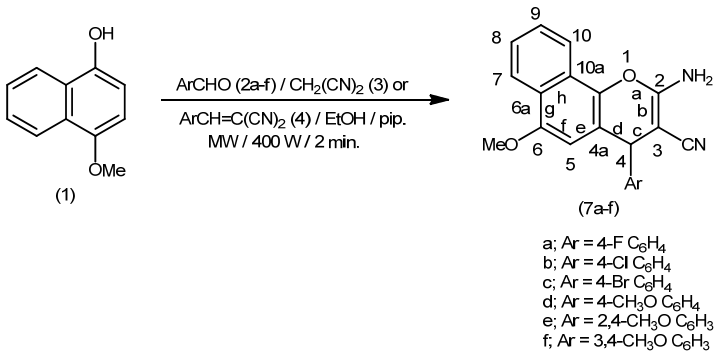


Scheme 1

^{13}C NMR spectra were obtained using distortionless enhancement by polarization transfer (DEPT), with this technique, the signals of CH and CH_3 carbon atoms appears normal (up) and the signal of carbon atoms in CH_2 environments appears negative (down). The Microwave apparatus used is Milestone Sr1, Microsynth. The MS were measured on a Shimadzu GC/MS-QP5050A spectrometer. Elemental analyses for C, H and N were performed on a Perkin-Elmer 240 microanalyser.

2.2. General procedure for the preparation of 4H-benzo[h] chromene-3-carbonitrile derivatives (7a-f)

A solution of 4-methoxy-1-naphthol **1** (0.01 mmol) in EtOH (30 mL) and piperidine (0.5 mL) was treated with a mixture of aromatic aldehydes **2** (0.01 mmol) and malononitrile **3** (0.01 mmol) or *α*-cyanocinnamonitriles **4** (0.01 mmol). The reaction mixture was heated under microwave irradiation conditions for 2 min at 400 W / 140 °C. The solid product which formed was collected by filtration, washed with MeOH and recrystallized from ethanol. The physical and spectral data of compounds **7a-f** are as follows (Scheme 1):

2-Amino-4-(4-fluorophenyl)-6-methoxy-4H-benzo[h]chrome ne-3-carbonitrile (**7a**): Color: Pale yellow crystals. Yield: 89%. M.p.: 220-221 °C (M.p.: 218-219 °C [74]). FT-IR (KBr, υ, cm $^{-1}$): 3457, 3398, 3284 (NH_2), 3071, 3003, 2942, 2870 (CH str.), 2193 (CN). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 3.80 (s, 3H, CH_3O), 4.89 (s, 1H, H-4), 7.14 (s, 2H, NH_2), 8.21-6.51 (m, 9H, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 162.05 (2C), 151.19 (6C), 141.74 (10bC), 129.43 (10aC), 127.25 (9C), 126.23 (8C), 124.40 (6aC), 123.64 (7C), 121.63 (10C), 120.60 (4aC), 117.59 (CN), 103.29 (5C), 56.02 (3C), 55.98 (CH_3O), 40.65 (4C), 160.38, 136.82, 129.36, 115.49 (Ar-C). MS (EI, *m/z* (%)): 346 (M^+, 40.86), 251 (100). Anal. calcd. for $C_{21}H_{15}FN_2O_2$: C, 72.82; H, 4.37; N, 8.09. Found: C, 72.80; H, 4.34; N, 8.06 %.

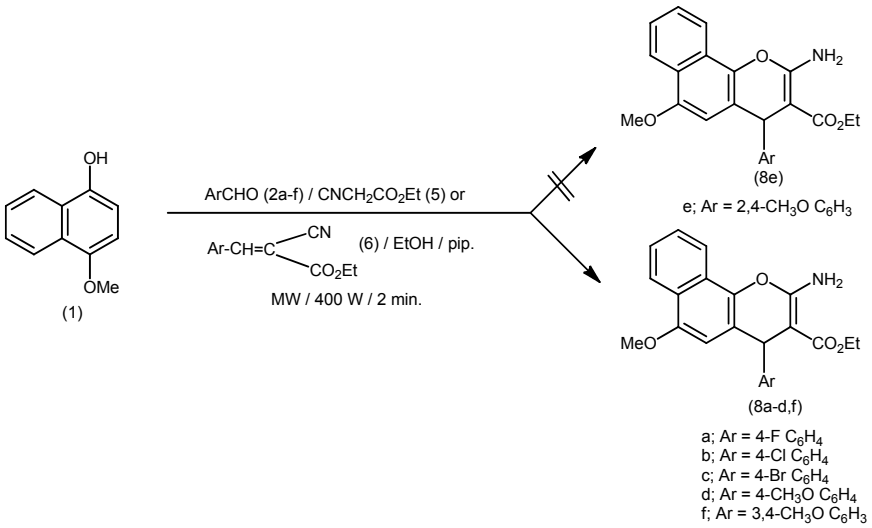
2-Amino-4-(4-chlorophenyl)-6-methoxy-4H-benzo[h]chrome ne-3-carbonitrile (**7b**): Color: Colourless needles. Yield: 91 %. M.p.: 218-219 °C (M.p.: 218-219 °C [75]). FT-IR (KBr, υ, cm $^{-1}$): 3466, 3330, 3199 (NH_2), 3080, 3000, 2962, 2810 (CH str.), 2194 (CN). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 3.81 (s, 3H, CH_3O), 4.89 (s, 1H, H-4), 7.15 (bs, 2H, NH_2, cancelled by D_2O), 8.21-6.52 (m, 9H, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 160.41 (2C), 151.23 (6C), 144.47 (10bC), 131.48 (10aC), 127.30 (9C), 126.31 (8C), 123.62 (6aC), 121.65 (7C), 120.61 (10C), 120.48 (4aC), 117.27 (CN), 103.27 (5C), 55.72 (CH_3O), 55.67 (3C), 40.74 (4C), 136.87, 129.39, 128.67, 124.43 (Ar-C). ^{13}C NMR-DEPT (125 MHz, DMSO-d_6, δ, ppm, 135° CH, CH_3 (↑), CH_2 (↓)): 129.39 (↑ Ar-CH), 128.67 (↑ Ar-CH), 127.30 (↑ 9CH), 126.31 (↑ 8CH), 121.65 (↑ 7CH), 120.61 (↑ 10CH), 103.27 (↑ 5CH), 55.72 (↑CH_3O), 40.74 (↑ 4CH). ^{13}C NMR-DEPT (125 MHz, DMSO-d_6, δ, ppm, 90° CH (↑)): 129.39 (↑ Ar-CH), 128.67 (↑ Ar-CH), 127.30 (↑ 9CH), 126.31 (↑ 8CH), 121.65 (↑ 7CH), 120.61 (↑ 10CH), 103.27 (↑ 5CH), 40.74 (↑ 4CH). ^{13}C NMR-DEPT (125 MHz, DMSO-d_6, δ, ppm, 45° CH, CH_2, CH_3 (↑)): 129.39 (↑ Ar-CH), 128.67 (↑ Ar-CH), 127.30 (↑ 9CH), 126.31 (↑ 8CH), 121.65 (↑ 7CH), 120.61 (↑ 10CH), 103.27 (↑ 5CH), 55.72 (↑CH_3O), 40.74 (↑ 4CH). MS (EI, *m/z* (%)): 364 (M^++2, 4.31), 362 (M^+, 18.7), 75 (100). Anal. calcd. for $C_{21}H_{15}ClN_2O_2$: C, 69.52; H, 4.17; N, 7.72. Found: C, 69.80; H, 4.22; N, 7.79 %.

2-Amino-4-(4-bromophenyl)-6-methoxy-4H-benzo[h]chrome ne-3-carbonitrile (**7c**): Color: Colourless crystals. Yield: 88 %. M.p.: 230-231 °C. FT-IR (KBr, υ, cm $^{-1}$): 3456, 3335, 3255 (NH_2), 3070, 3008, 2973, 2875 (CH str.), 2191 (CN). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.82 (s, 3H, CH_3O), 4.75 (bs, 2H, NH_2), 4.78 (s, 1H, H-4), 8.20-6.18 (m, 9H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 159.16 (2C), 152.44 (6C), 137.50 (10bC), 128.34 (10aC), 126.31 (9C), 125.49 (8C), 124.11 (6aC), 122.27 (7C), 121.35 (10C), 120.49 (4aC), 116.10 (CN), 102.74 (5C), 60.53 (3C), 55.68 (CH_3O), 41.52 (4C), 143.37, 131.98, 129.76, 119.76 (Ar-C). MS (EI, *m/z* (%)): 408 (M^++2, 43.63), 406 (M^+, 44.27), 250 (100). Anal. calcd. for $C_{21}H_{15}BrN_2O_2$: C, 61.93; H, 3.71; N, 6.88. Found: C, 61.52; H, 4.21; N, 6.12 %.

2-Amino-4-(4-methoxyphenyl)-6-methoxy-4H-benzo[h]chro mene-3-carbonitrile (**7d**): Color: Colourless needles. Yield: 87%. M.p.: 180-181 °C. FT-IR (KBr, υ, cm $^{-1}$): 3443, 3332, 3207 (NH_2), 3079, 3029, 2995, 2947, 2895, 2839 (CH str.), 2193 (CN). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 3.81 (s, 3H, OCH_3), 3.72 (s, 3H, CH_3O), 4.80 (s, 1H, H-4), 7.07 (bs, 2H, NH_2, cancelled by D_2O), 8.11-6.52 (m, 9H, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 160.25 (2C), 151.10 (6C), 137.64 (10bC), 128.56 (10aC), 128.30 (9C), 127.17 (6aC), 126.10 (8C), 124.33 (7C), 123.66 (10C), 121.61 (4aC), 118.09 (CN), 103.44 (5C), 56.43 (3C), 55.64 (CH_3O), 54.96 (CH_3O), 40.70 (4C), 158.12, 136.74, 128.77, 114.00 (Ar-C). MS (EI, *m/z* (%)): 358 (M^+, 13.92), 251 (100). Anal. calcd. for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.79; H, 5.11; N, 7.89 %.

2-Amino-4-(2,4-dimethoxyphenyl)-6-methoxy-4H-benzo[h] chromene-3-carbonitrile (**7e**): Color: yellow needles. Yield: 81%. M.p.: 218-219 °C. FT-IR (KBr, υ, cm $^{-1}$): 3481, 3436, 3332 (NH_2), 3001, 2936, 2837 (CH str.), 2186 (CN). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 3.73 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 5.13 (s, 1H, H-4), 6.97 (bs, 2H, NH_2), 8.19-6.47 (m, 8H, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 161.01 (2C), 151.01 (6C), 136.93 (10bC), 127.09 (10aC), 125.94 (9C), 125.57 (6aC), 124.18 (8C), 123.58 (7C), 121.53 (10C), 120.72 (4aC), 118.33 (CN), 105.37 (5C), 55.68 (3C), 55.50 (CH_3O), 55.19 (CH_3O), 55.11(CH_3O), 40.03 (4C), 159.40, 157.22, 129.28, 120.49, 102.96, 98.67 (Ar-C). MS (EI, *m/z* (%)): 388 (M^+, 30.38), 374 (100). Anal. calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.21; H, 5.45; N, 7.22 %.

2-Amino-4-(3,4-dimethoxyphenyl)-6-methoxy-4H-benzo[h] chromene-3-carbonitrile (**7f**): Color: Pale yellow crystals. Yield: 83%. M.p.: 205-206 °C.



Scheme 2

FT-IR (KBr, υ, cm $^{-1}$): 3386, 3331, 3215 (NH_2), 3062, 3004, 2970, 2939, 2903, 2828 (CH str.), 2193 (CN). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 3.82 (s, 3H, CH_3O), 3.72 (s, 3H, CH_3O), 3.71 (s, 3H, CH_3O), 4.79 (s, 1H, H-4), 7.05 (bs, 2H, NH_2), 8.21-6.58 (m, 8H, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 161.08 (2C), 151.77 (6C), 138.71 (10bC), 127.88 (10aC), 126.82 (9C), 125.04 (6aC), 124.35 (8C), 122.33 (7C), 121.31 (10C), 120.27 (4aC), 118.73 (CN), 104.19 (5C), 56.85 (3C), 56.40 (CH_3O), 56.23 (CH_3O), 56.15 (CH_3O), 41.72 (4C), 149.43, 148.47, 137.36, 121.43, 112.71, 112.11 (Ar-C). MS (EI, *m/z* (%)): 388 [M$^+$, 21.23] with a base peak at 64 (100). Anal. calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.19; H, 5.32; N, 7.38 %.

2.3. General procedure for the preparation of ethyl 4H-benzo[h]chromene-3-carboxylate derivatives (8a-d,f)

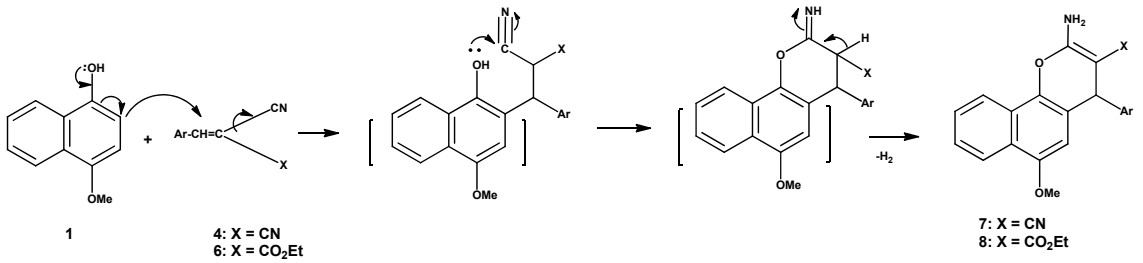
A solution of 4-methoxy-1-naphthol **1** (0.01 mmol) in EtOH (30 mL) and piperidine (0.5 mL) was treated with a mixture of aromatic aldehydes **2** (0.01 mmol) and ethyl cyanoacetate **5** (0.01 mmol) or ethyl α-cyanocinnamates **6** (0.01 mmol). The reaction mixture was heated under microwave irradiation conditions for 2 min at 400 W / 140 °C. The solid product which formed was collected by filtration, washed with MeOH and recrystallised from ethanol or ethanol/benzene. The physical and spectral data of compounds **8a-d**,**f** are as follows (Scheme 2):

Ethyl 2-amino-4-(4-fluorophenyl)-6-methoxy-4H-benzo[h] chromene-3-carboxylate (**8a**): Color: Pale yellow crystals. Yield: 75 %. M.p.: 162-163 °C (M.p.: 162-163 °C [76]). FT-IR (KBr, υ, cm $^{-1}$): 3408, 3302 (NH_2), 3065, 3020, 2978, 2935, 2896 (CH str.) 1668 (CO). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 1.19 (t, *J* = 7 Hz, 3H, CH_3CH_2), 3.88 (s, 3H, CH_3O), 4.10 (q, *J* = 7 Hz, 2H, CH_3CH_2), 4.99 (s, 1H, H-4), 7.49 (bs, 2H, NH_2), 8.17-6.34 (m, 9H, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 169.42 (*CO*), 162.31 (2C), 151.97 (6C), 137.31 (10bC), 129.33 (10aC), 126.94 (9C), 125.70 (6aC), 125.05 (8C), 124.24 (7C), 122.11 (10C), 120.53 (4aC), 103.42 (5C), 78.87 (3C), 59.47 (CH_3CH_2), 55.59 (CH_3O), 40.73 (4C), 14.37 (CH_3CH_2), 160.37,143.33, 129.55, 114.96 (Ar-*C*). MS (EI, *m/z* (%)): 393 (M$^+$, 81.4) with a base peak at 298 (100). Anal. calcd. for $C_{23}H_{20}FNO_4$: C, 70.22; H, 5.12; N, 3.56. Found: C, 70.30; H, 5.48; N, 3.41%.

Ethyl 2-amino-4-(4-chlorophenyl)-6-methoxy-4H-benzo[h] chromene-3-carboxylate (**8b**): Color: Colorless crystals. Yield: 79 %. M.p.: 160-161 °C (M.p.: 160-161 °C [75]). FT-IR (KBr, υ, cm $^{-1}$): 3408, 3302 (NH_2), 3406, 3330 (NH_2), 3030, 3010, 2981, 2938, 2899 (CH str.), 1666 (CO). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.13 (t, *J* = 7.5 Hz, 3H, CH_3CH_2), 3.78 (s, 3H, CH_3O), 4.02 (q, *J* = 7.5 Hz, 2H, CH_3CH_2), 4.91 (s, 1H, H-4), 6.30 (bs, 2H, NH_2, cancelled by D_2O), 8.10-6.27 (m, 9H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 168.08 (*CO*), 161.09 (2C), 151.18 (6C), 146.58 (10bC), 128.30 (10aC), 127.07 (9C), 125.93 (8C), 124.18 (6aC), 121.62 (7C), 120.59 (10C), 120.36 (4aC), 103.79 (5C), 76.00 (3C), 58.62 (CH_3CH_2), 55.72 (CH_3O), 40.08 (4C), 14.30 (CH_3CH_2), 136.90, 130.53, 129.13, 128.14 (Ar-*C*). ^{13}C NMR-DEPT (125 MHz, 125 MHz, $CDCl_3$, δ, ppm, 135° CH, CH_3 (↑), CH_2 (↓)): 129.13 (↑ Ar-*CH*), 128.14 ((↑ Ar-*CH*), 127.07 (↑ 9*CH*), 125.93 (↑ 8*CH*), 121.62 (↑ 7*CH*), (↑ 10*CH*), 103.79 (↑ 5*CH*), 58.62 (↓ CH_3CH_2), 55.72 (↑ CH_3O), 40.08 (↑ 4*CH*), (↑ CH_3CH_2). ^{13}C NMR-DEPT (125 MHz, $CDCl_3$, δ, ppm, 90° CH (↑)): 129.13 (↑ Ar-*CH*), 128.14 (↑ Ar-*CH*), 127.07 (↑ 9*CH*), 125.93 (↑ 8*CH*), 121.62 (↑ 7*CH*), 120.59 (↑ 10*CH*), 103.79 (↑ 5*CH*), 40.08 (↑ 4*CH*). ^{13}C NMR-DEPT (125 MHz, $CDCl_3$, δ, ppm, 45° CH, CH_2, CH_3 (↑)): 129.13 (↑ Ar-*CH*), 128.14 (↑ Ar-*CH*), 127.07 (↑ 9*CH*), 125.93 (↑ 8*CH*), 121.62 (↑ 7*CH*), 120.59 (↑ 10*CH*), 103.79 (↑ 5*CH*), 58.62 (↓ CH_3CH_2), 55.72 (↑ CH_3O), 40.08 (↑ 4*CH*), 14.30 (↑ CH_3CH_2). MS (EI, *m/z* (%)): 411 (M$^+$+2, 5.31), 409 (M$^+$, 19.38), 75 (100). Anal. calcd. for $C_{23}H_{20}ClNO_4$: C, 67.40; H, 4.92; N, 3.42. Found: C, 67.74; H, 4.42; N, 3.49 %.

Ethyl 2-amino-4-(4-bromophenyl)-6-methoxy-4H-benzo[h] chromene-3-carboxylate (**8c**): Color: Colorless needles. Crystallization: From ethanol/benzene. Yield: 79 %. M.p.: 165-166 °C. FT-IR (KBr, υ, cm $^{-1}$): 3404, 3301 (NH_2), 3010, 2981, 2939, 2899 (CH str.), 1666 (CO). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.20 (t, *J* = 7 Hz, 3H, CH_3CH_2), 3.84 (s, 3H, CH_3O), 4.10 (q, *J* = 7 Hz, 2H, CH_3CH_2), 4.97 (s, 1H, *H*-4), 6.41 (bs, 2H, NH_2), 8.17-6.33 (m, 9H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 169.31 (*CO*), 160.23 (2C), 152.01 (6C), 137.34 (10bC), 126.98 (10aC), 125.76 (9C), 125.08 (6aC), 124.21 (8C), 122.13 (7C), 120.52 (10C), 119.91 (4aC), 103.30 (5C), 78.52 (3C), 59.52 (CH_3CH_2), 55.60 (CH_3O), 40.98 (4C), 14.38 (CH_3CH_2), 146.57,131.21, 129.75, 119.66 (Ar-*C*). MS (EI, *m/z* (%)): 455 (M$^+$+2, 14.22), 453 (M$^+$, 15.99), 298 (100). Anal. calcd. for $C_{23}H_{20}BrNO_4$: C, 60.81; H, 4.44; N, 3.08. Found: C, 60.85; H, 4.21; N, 3.12 %.

Ethyl 2-amino-4-(4-methoxyphenyl)-6-methoxy-4H-benzo[h] chromene-3-carboxylate (**8d**): Color: Colorless needles. Crystallization: From ethanol/benzene. Yield: 72 %. M.p.: 159-160 °C. FT-IR (KBr, υ, cm $^{-1}$): 3414, 3300 (NH_2), 3014, 2997, 2963, 2875 (CH str.), 1682 (CO).



Scheme 3

MS (EI, *m/z* (%)): 405 (M^+, 29.33), 299 (100). Anal. calcd. for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 71.15; H, 5.73; N, 3.49 %.

Ethyl 2-amino-4-(3,4-dimethoxyphenyl)-6-methoxy-4H-benzo [h]chromene-3-carboxylate (**8f**): Color: Light green crystals. Yield: 69%. M.p.: 185-186 °C. FT-IR (KBr, υ, cm $^{-1}$): 3412, 3310 (NH_2), 3064, 2937, 2901, 2833 (CH str.), 1676 (CO). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.16 (t, *J* = 7 Hz, 3H, CH_3CH_2), 3.66 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 4.02 (q, *J* = 7 Hz, 2H, CH_3CH_2), 4.99 (s, 1H, *H*-4), 7.72 (bs, 2H, NH_2), 8.27-6.68 (m, 8H, Ar-*H*). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 168.33 (*CO*), 161.16 (2C), 151.04 (6C), 136.85 (10bC), 126.93 (10aC), 125.70 (9C), 124.03 (6aC), 123.65 (8C), 121.59 (7C), 120.53 (10C), 119.00 (4aC), 104.01 (5C), 76.49 (3C), 58.55 (CH_3CH_2), 55.70 (CH_3O), 55.46 (CH_3O), 55.37 (CH_3O), 39.93 (4C), 14.36 (CH_3CH_2), 148.25, 147.08, 140.27, 121.30, 111.87, 111.53 (Ar-*C*). MS (EI, *m/z* (%)): 435 (M^+, 14.9), 299 (100). Anal. calcdç for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79; N, 3.22. Found: C, 68.96; H, 5.67; N, 3.28 %.

3. Results and discussion

3.1. Synthesis

Treatment of 4-methoxy-1-naphthol (**1**) with a mixture of aromatic aldehydes (**2**) and malononitrile (**3**) or *α*-cyano cinnamonitriles (**4**) in ethanolic piperidine solution under microwave irradiation conditions for 2 min at 140 °C afforded 2-amino-4-aryl-6-methoxy-4*H*-benzo[*h*]chromene-3-carbonitrile **7a-f** (Scheme 1). The reactions were controlled using TLC technique.

In a similar manner, treatment of 4-methoxy-1-naphthol (**1**) with aromatic aldehydes (**2**) and ethyl cyanoacetate (**5**) or with ethyl *α*-cyanocinnamates (**6**) under the same conditions afforded ethyl 2-amino-4-aryl-6-methoxy-4*H*-benzo[*h*] chromene-3-carboxylate **8a-d**, **f** (Scheme 2). The reactions were controlled using TLC technique. The maximum power of microwave irradiation was optimized by carrying out the same reaction at different Watt powers. Microwave radiations at 400 W gave the highest yield, and therefore microwave power of 400 W was chosen as the optimum power.

Attempts to react 4-methoxy-1-naphthol (**1**) with 2,4-dimethoxybenzaldehyde (**2e**) and ethyl cyanoacetate (**5**) or with ethyl *α*-cyanocinnamate (**6e**) in ethanolic piperidine solution under microwave irradiation conditions for 2-5 min was unsuccessful, the ethyl 2-amino-4-(2,4-dimethoxyphenyl)-6-methoxy-4*H*-benzo[*h*]chromene-3-carboxylate (**8e**) was not formed. This may be due to the steric hindrance of the methoxy group at position 2 of the 2,4-dimethoxy-benzaldehyde.

The formation of compounds **7** and **8** indicates that the naphtholate anion (C-2) of compound **1** attack at the *β*-carbon of compound **4** and **6** to yield an acyclic Michael adduct, which underwent cyclization to give compound **7** or **8** (Scheme 3).

The structures of compounds **7** and **8** were established on the basis of spectral data. The IR spectra of compounds **7a-f** showed the appearance of the a NH_2 stretch at υ 3480-3386, 3398-3329, 3284-3199 cm,$^{-1}$ a CN stretch at υ 2194-2186 cm,$^{-1}$ while a NH_2 stretch at υ 3414-3404, 3330-3300 cm^{-1} and a CO stretch at υ 1682-1666 cm^{-1} for compounds **8a-d**,**f**. The ^{1}H and ^{13} C NMR spectra of compounds **7a-f** and **8a-d**,**f** revealed the presence of 4*H* signals at δ 5.13-4.78 (s, 1H, H-4) and 41.52-39.93 ppm (C-4). In compounds **8a-c**,**f** the ester group gave ^{1}H signals at 4.10-4.02 (q, *J* = 7.0-7.5 Hz, 2H, CH_2), 1.20-1.13 (t, *J* = 7.0-7.5 Hz, 3H, CH_3) with the corresponding signals in the ^{13}C spectra at 59.52-58.55 (CH_2) and 14.38-14.30 ppm (CH_3) respectively. The ^{13}C NMR-DEPT spectra at 45°, 90° and 135° and ^{13}C NMR-APT spectra of compounds **7** and **8** provided additional evidence in support of the proposed structures. The ^{13} C NMR-DEPT spectrum of compound **7b** at 135° CH, CH_3 [positive (up)], CH_2 [negative (down)], revealed the following signals at δ 55.72 (CH_3 ↑), 40.74 (C-4 ↑), while at 90° only CH signals are positive (up) and showed δ 40.74 (C-4 ↑) and at 45° (CH, CH_2 and CH_3 positive) revealed signals at δ 55.72 (CH_3 ↑), 40.74 ppm (C-4 ↑). The ^{13} C NMR-DEPT spectrum of compound **8b** at 135° CH, CH_3 [positive (up)], CH_2 [negative (down)], revealed the following signals at δ 58.62 (CH_2 ↓), 40.08 (C-4 ↑), 14.30 (CH_3↑), while at 90° only CH signals are positive (up) and showed δ 40.08 ppm (C-4 ↑) and at 45° (CH, CH_2 and CH_3 positive) revealed signals at δ 58.62 (CH_2 ↑), 40.08 (C-4 ↑), 14.30 ppm (CH_3 ↑). In addition, the ^{1}H NMR spectra for compounds **7a** and **8a** showed NH_2 protons resonated at 7.14 (sharp singlet) and 7.49 (broad singlet lower field). This deshielding is a result of replacement of CN group in compound **7a** by C=O group in compound **8a** whose C=O anisotropy would deshield these protons and in addition of the involvement of these protons in hydrogen bonding with the C=O group. This was supported by X-ray single crystal data [74,76]. The mass spectra of compounds **7** and **8** gave also additional evidences for the proposed structures.

4. Conclusions

In this article, we report the synthesis of some 4*H*-benzo[*h*]chromene derivatives under Microwave irradiation conditions. The structures of these compounds were elucidated on the basis of spectral data, IR, ^{1}H NMR, ^{13}C NMR, ^{13}C NMR-DEPT and MS data. The newly synthesized compounds **7** and **8** will be tested against tumor cell lines, also for DNA extractions and will be published later.

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