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Microwave-Assisted Synthesis and Biological Evaluation of Some Coumarin Hydrazides

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Abstract: In this work, 15 different coumarin hydrazides were successfully synthesized and screened for their antioxidant and antilipase activities. To do this, firstly, salicylaldehyde derivatives and Meldrum's Acid were reacted in absolute ethanol with catalytic amount of pyridine to obtain coumarin-3-carboxylic acid derivatives (**1a-e**). Then, these compounds were treated with 1H-benzotriazole in dichloromethane by using thionyl chloride to synthesize benzotriazole derivatives (**2a-e**). Then, compounds **2a-e** were reacted with three commercial hydrazides (nicotinic hydrazide, benzhydrazide,and phenyl acetichydrazide) in ethanol by using microwave irradiation and conventional heating procedures to obtain final products (**3-5a-e**). Finally, these compounds were tested for their anti-oxidant and anti-lipase activities. The structure of newly synthesized compounds was identified by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis data.

Keywords: Coumarin, Hydrazide, Porcine pancreatic lipase, Antioxidant.

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INTRODUCTION

Since the first publication on microwave synthesis in 1986, the use of microwave heating in organic synthesis has become so popular that it has been termed as the Bunsen burner of the 21st century. In many respects, this technique is superior to classical heating because it reduces the reaction time and provides higher yields and purity (1-5).

Coumarins (known as benzopyran-2-ones) are a family of lactones and they are the most abundant secondary metabolite. They show important biological activities such as antibacterial (6, 7), antifungal (8, 9), anti-tubercular (10, 11), antitumor (12), antioxidant (13), and anti-HIV (14). Also, coumarins are used as food additive and cosmetics industry (15). The general commercial application of coumarins is the use of dispersed fluorescent brightening agents and as dyes for tuning lasers (16-18). A few coumarin-based derivatives acenocoumarol, dicoumarolum, and hymecromone which are approved for therapeutic purposes in the clinic are given below (Figure 1.) (10). This broad spectrum of biological activities and successful usage of coumarin derivatives in medicinal and industrial chemistry have further inspired more research on coumarin derivatives. In addition to numerous activities of coumarin derivatives, some enzyme inhibitors were reported such as α-glucosidase, anti-lipase, carbonic anhydrase, urease and acetylcholinesterase (19-27).

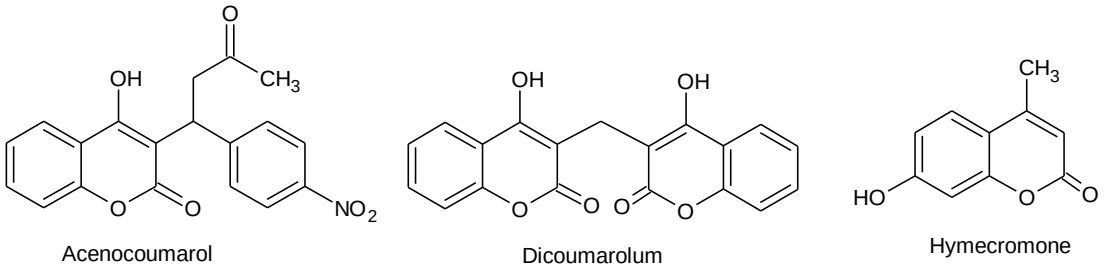


Figure 1. Acenocoumarol, Dicoumarolum,and Hymecromone.

Recent researches have proved that coumarin hydrazones have pharmacologically powerful properties. Nasr *et al*. reported *in vitro* anticancer activity of some coumarin hydrazide-hydrazone derivatives and found that one of the compounds could be a potent anticancer drug to overcome drug resistance in cancer (26, 28, 29). Also, Karatas *et al.* have showed that coumarins bind to the active pocket of the enzyme in a similar carbonic anhydrase enzyme study of coumarin by molecular docking study (19).

In our previous works, we have already synthesized coumarin-triazole and coumarin-quinazolinone hybrid molecules and investigated their biological activities. Some of the compounds showed potent antitumor, antilipase and α-glucosidase activities (26, 27). In these works, we have found that coumarin has a positive effect on antitumor, antilipase and α-

glucosidase activities. In the present study, we focused on the synthesis of coumarin hydrazides and investigation of their antioxidant and lipase inhibition activities (27, 30).

MATERIALS AND METHODS

Chemistry

All reaction progress was monitored by TLC on silica gel plates (Merck 60, F_{254}, 0.2 mm). The melting points were determined on capillary tubes on Stuart SMP30 melting point apparatus and are uncorrected. The FTIR spectra were recorded on a Perkin-Elmer 100 FTIR spectrometer as KBr pellets. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were obtained using a Varian-Mercury (tetramethylsilane as the internal standard) and the chemical shifts are expressed in δ values (ppm). The experiments were carried out in microwave process vials (30 mL) with control of the temperature by infrared detection temperature sensor. It was monitored by a computer and maintained at a constant value by a discrete modulation of delivered microwave power. After the completion of the reaction, the vial was cooled to 60 °C via air jet cooling.

EXPERIMENTAL SECTION

General procedure for the synthesis of compounds 1a-e

A solution of corresponding salicylaldehyde derivative (0.01 mol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (1.58 g, 0.011 mol) in absolute ethanol (50 mL) and pyridine (0.5 mL) was refluxed in a round-bottomed flask for 6 h. After the reaction was completed (monitored by TLC, eluent ethyl acetate–hexane, 4:1 v:v), the solvent was evaporated under reduced pressure. The obtained solid was washed with H_2O and recrystallized from a mixture of EtOH–H_2O, 3:2.

2-Oxo-2*H*-chromene-3-carboxylic acid (1a). Yield: 1.39 g (73%). M.P.: 189–190°C (M.P.: 188°C (31)).

6-Chloro-2-oxo-2*H*-chromene-3-carboxylic acid (1b). Yield: 1.57 g (70%). M.P.: 200-201 °C (M.P.: 198-199 °C (32)).

6-Bromo-2-oxo-2*H*-chromene-3-carboxylic acid (1c). Yield: 1.80 g (67%). M.P.: 195–196°C (M.P.: 194–196°C (33)).

6,8-Dichloro-2-oxo-2*H*-chromene-3-carboxylic acid (1d). Yield: 1.80 g (67%).M.P.: 225-226 °C (M.P.: 220-224 °C (34)).

7-diethylamino-2-oxo-2*H*-chromene-3-carboxylic acid (1e).Yield: 1.88 g (67%).M.P.: 225-226 °C (M.P.: 224-225 °C (35)).

General procedure for the synthesis of compounds 2a-e

Thionyl chloride (1.78 g, 0.015 mol) was added to a solution of 1*H*-benzotriazole (5.95 g, 0.05 mol) in CH_2Cl_2 (75 mL). The mixture was stirred for 30 min at room temperature. Then the corresponding coumarin-3-carboxylic acid **1a-e** (0.01 mol) was added and the reaction mixture was stirred for 12 hours at room temperature. The precipitate was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 (100 mL), and the solution was washed with 10% Na_2CO_3 solution (50 mL) and 4 N HCl (50 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave compounds **2a-e**, which were recrystallized from CH_2Cl_2–hexane, 1:1.

3-(1*H*-Benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-one (2a). Yield: 2.12 g (73%). M.P.: 179–180°C (M.P.: 176–177 °C (36)).

3-(1*H*-Benzotriazol-1-ylcarbonyl)-6-chloro-2H-chromen-2-on (2b) Yield: 2.20 g (63%).M.P.: 248–249 °C.

3-(1*H*-Benzotriazol-1-ylcarbonyl)-6-bromo-2*H*-chromen-2-one (2c). Yield 2.52 g (68%). M.P.: 250–251 °C.

3-(1*H*-Benzotriazol-1-ylcarbonyl)-6,8-dichloro-2H-chromen-2-on (2d). Yield: 2.34 g (65%).M.P.:263–264 °C.

3-(1*H*-Benzotriazol-1-ylcarbonyl)-7-diethylamino-2H-chromen-2-on (2e). Yield: 2.46 g (68%).M.P.:210–211°C (M.P.:212–214 °C (37)).

General procedure for the synthesis of compounds 3-5a-e

***Conventional method*:** A solution of compounds **2a-e** (0.01 mol) in absolute ethanol (15 mL) and corresponding hydrazide derivative (0.011 mol) was taken in a round-bottomed flask. The mixture was refluxed for 4h. After the completion of the reaction, the mixture was cooled to room temperature and the product appeared as a white solid. It was filtered and washed with ethanol to obtain the pure product.

***Microwave method*:** Compounds **2a-e** (0.01 mol) and corresponding hydrazide derivative (0.011 mol) were taken in a microwave process vial (30 mL) and dry ethanol (5 mL) was added. Then, the mixture was irradiated in microwave at 135 °C for 15 min at 200 W maximum power. After the completion of the reaction, the mixture was taken in the beaker with hot ethanol, and

a product appeared as a white solid. It was filtered and washed with ethanol to obtain the pure product.

***N*'-(2-Oxo-2*H*-1-benzopyran-3-ylcarbonyl)pyridine-3-carbohydrazide (3a):** M.P.: 269–270 °C (38), FTIR (KBr): 3365, 3232 (NH), 1709, 1681, 1640 (C=O), 1190 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 7.43 (s, 1H, Ar-H), 7.52 (d, J=6.4 Hz,1H, Ar-H), 8.00 (d, J=6.8 Hz,1H,Ar-H), 8.27 (d, J=9.2 Hz,1H,Ar-H), 8.75 (d, J=7.6 Hz,2H,Ar-H), 8.90 (d, J=8.4 Hz, 2H, Ar-H), 9.05 (s, 1H, coumarin C-4H), 10.61 (s, 1H, NH), 11.20 (s, 1H, NH). ^{13}C NMR (100MHz, DMSO-d_6):116.72, 118.74, 118.82, 124.11, 128.36, 130.86, 134.92, 135.81, 148.51, 149.03, 153.00 (coumarin C-3), 154.47 (coumarin C-4), 160.17 (C=O), 160.57 (C=O), 163.79 (C=O). Elemental Analysis: Calculated $C_{16}H_{11}N_3O_4$: C, 62.14; H, 3.58; N, 13.59. Found: C, 62.10; H, 3.51; N, 13.50.

***N*'-(6-Chloro-2-oxo-2*H*-1-benzopyran-3-ylcarbonyl)pyridine-3-carbohydrazide (3b):** M.P.:284–285 °C, FTIR (KBr): 3201, 3039 (NH), 1706, 1683 (C=O), 1192 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6):7.39 (s, 1H, Ar-H), 7.62 (d, J=6.0Hz, 1H, Ar-H),8.00 (d,J=6.0Hz,1H,Ar-H), 8.28 (d, J=9.2 Hz,1H, Ar-H), 8.69(d, J=7.6 Hz,1H,Ar-H), 8.96 (d, J=8.0 Hz, 2H, Ar-H), 9.03 (s, 1H, coumarin C-4H), 10.55 (s, 1H, NH), 11.24 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d6): 121.07, 121.18, 121.37, 124.11, 128.31, 128.75, 129.21, 133.48, 135.82, 146.84, 149.02, 153.0 (coumarin C-4), 158.76 (coumarin C-3), 160.11 (C=O), 163.94 (C=O), 165.79 (C=O). Elemental analysis: Calculated for $C_{16}H_{10}ClN_3O_4$: C, 55.91; H, 2.93; N, 12.23. Found: C, 55.93; H, 2.95; N, 12.27.

***N*'-(6-Bromo-2-oxo-2*H*-1-benzopyran-3-ylcarbonyl)pyridine-3-carbohydrazide (3c):** M.P.: 289–290 °C, FTIR (KBr): 3363, 3282 (NH), 1739, 1694, 1662 (C=O), 1240 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 7.35 (s, 1H, Ar-H), 7.80 (d, J=6.4 Hz,1H,Ar-H), 8.03 (d, J=6.8 Hz, 1H, Ar-H), 8.20 (d, J=9.0 Hz, 1H, Ar-H), 8.73 (d, J=7.6 Hz, 1H, Ar-H), 8.80 (d, J=8.0 Hz, 2H, Ar-H), 9.05 (s, 1H, coumarin C-4H), 10.50 (s, 1H, NH), 11.20 (s, 1H, NH). ^{13}C NMR (100 MHz,DMSO-d_6): 117.17, 119.01, 120.63, 124.11, 128.34, 132.66, 135.82, 137.02, 147.68, 148.20, 149.02 (coumarin C-4), 155.64 (coumarin C-3), 156.31 (C=O), 160.35 (C=O), 163.90 (C =O). Elemental analysis: Calculated for $C_{16}H_{10}BrN_3O_4$: C, 49.51; H, 2.60; N, 10.83. Found: C, 49.55; H, 2.57; N, 10.76.

***N*'-(6,8-Dichloro-2-oxo-2*H*-1-benzopyran-3-ylcarbonyl)pyridine-3-carbohydrazide (3d):** M.P.:292–293 °C, FTIR (KBr): 3199, 3040 (NH), 1706, 1684 (C=O), 1192 (C-O) cm^{-1}. ^{1}H NMR (400 MHz,DMSO-d_6): 7.54 (s, 1H, Ar-H), 8.09-8.15 (m,2H,Ar-H), 8.25 (s, 1H, Ar-H), 8.56-8.76 (m,2H,Ar-H), 9.04 (s, 1H, coumarin C-4H), 10.60 (s, 1H, NH), 11.10 (s,1H,NH).^{13}C NMR (100 MHz, DMSO-d_6): 121.20, 121.37, 124.12, 128.12, 128.32, 128.75, 129.20, 133.49, 135.83, 146.82, 148.92, 149.02 (coumarin C-3), 153.04 (coumarin C-4), 158.75 (C=O), 160.14 (C=O), 163.95 (C=O). Elemental analysis: Calculated for $C_{16}H_9Cl_2N_3O_4$: C, 50.82; H, 2.40; N,

11.11. Found: C, 50.79; H, 2.37;N,11.11.

***N*'-[7-(diethylamino)-2-oxo-2*H*-1-benzopyran-3-carbonyl]pyridine-3-carbohydrazide (3e):** M.P.: 266–267 °C (266–267 °C (16)), FTIR (KBr): 3268 (NH), 1685,1644 (C=O), 1190 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 1.13 (t, J=6.8 Hz, 6H, CH_3), 3.90 (q, J=6.8 Hz, 4H, CH_2), 6.63 (s, 1H,Ar-H), 6.82 (d, J=6.4 Hz, 1H, Ar-H), 7.55 (d, J=6.8Hz, 1H, Ar-H), 7.73(d, J=9.2 Hz,1H,Ar-H),8.24(d, J=7.6 Hz, 1H, Ar-H), 8.74(d, J=8.4 Hz, 2H, Ar-H), 9.03 (s, 1H, coumarin C-4H), 10.47 (s, 1H, NH), 11.12 (s, 1H,NH).^{13}C NMR (100 MHz,DMSO-d_6):12.77 ($2CH_3$), 44.87 ($2CH_2$), 96.38, 108.13, 108.29, 110.81, 124.06, 128.45, 132.33, 135.79, 148.94, 149.01 (coumarinC-4), 152.90, 153.31 (coumarin C-3), 157.94 (C=O), 161.65 (C=O), 161.84 (C=O), 163.79 (C=O). Elemental analysis: Calculated for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.08; H, 5.25; N, 14.68.

***N*'-Benzoyl-2-oxo-2*H*-1-benzopyran-3-ylcarbohidrazide (4a):** M.P.: 239-240°C (38), FTIR (KBr): 3266, 3112 (NH), 1706, 1681 (C=O), 1188 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 7.42 (s, 1H, Ar-H), 7.54 (t, J=6.8 Hz, 1H, Ar-H), 7.61 (d, J=9.2 Hz, 2H, Ar-H), 7.73 (t, J=7.6 Hz, 2H, Ar-H), 8.00(d, J=8.4 Hz, 2H, Ar-H), 8.03 (s, 1H, Ar-H), 8.89 (s, 1H, coumarin C-4H), 10.57 (s, 1H, NH), 10.93 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 116.70, 118.73, 118.87, 125.68, 128.06 (2C), 128.94 (2C), 130.83, 132.42, 134.88, 148.53 (coumarin C-4), 154.43 (coumarin C-3), 160.21 (C=O), 160.62 (C=O), 165.32 (C=O). Elemental analysis: Calculated for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09. Found: C,66.29;H,3.82;N,9.00.

***N*'-Benzoyl-6-chloro-2-oxo-2*H*-1-benzopyran-3-ylcarbohydrazide (4b):** M.P.:266–267 °C, FTIR (KBr): 3326, 3184 (NH), 1688, 1648 (C=O), 1135 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 7.49 (s, 2H,Ar-H), 7.55 (d, J=6.6Hz, 2H, Ar-H), 7.90 (d, J=9.2 Hz, 2H, Ar-H), 8.74 (d, J=8.4 Hz,2H, Ar-H), 8.82 (s, 1H, coumarin C-4H), 10.47 (s, 1H, NH), 10.96 (s,1H,NH).^{13}C NMR (100 MHz, DMSO-d_6): 121.20, 121.36, 128.06, 128.73 (2C), 128.95 (2C), 129.19, 132.45, 133.45, 146.73, 148.90 (coumarin C-4) (coumarin C-3), 158.76 (C=O), 160.17 (C=O), 165.34 (C=O). Elemental analysis: Calculated for $C_{17}H_{11}ClN_2O_4$: C, 59.57; H, 3.23; N, 8.17. Found: C, 59.65; H, 3.29; N, 8.11.

***N*'-Benzoyl-6-bromo-2-oxo-2*H*-1-benzopyran-3-ylcarbohydrazide (4c):** M.P.: 258–259 °C (Cas No: 322414-14-2), FTIR (KBr): 3320, 3085 (NH), 1715, 1654 (C=O), 1190 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6):7.47 (d, J=6.6 Hz, 2H, Ar-H), 7.21 (d, J=6.0 Hz ,2H, Ar-H), 7.70 (d, J=9.2Hz, 1H, Ar-H), 8.10 (d, J=7.6 Hz, 1H, Ar-H), 8.76 (d, J=8.4 Hz, 2H, Ar-H), 8.82 (s, 1H, coumarin C-4H), 10.48 (s, 1H, NH), 10.95 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d6): 117.18, 118.98, 120.98, 121.14, 121.60, 128.05 (2C), 128.93 (2C), 132.44, 132.63, 136.97, 147.11 (coumarin C-4), 153.48 (coumarin C-3), 159.68 (C=O), 160.37 (C=O), 165.31 (C=O). Elemental analysis: Calculated for $C_{17}H_{11}BrN_2O_4$: C, 52.74; H, 2.86; N, 7.24. Found: C, 52.70;

H, 2.80; N, 7.21.

***N*'-Benzoyl-6,8-dichloro-2-oxo-2*H*-1-benzopyran-3-ylcarbohydrazide (4d):** M.P.: 269–271 °C, FTIR (KBr): 3156, 3030 (NH), 1723, 1645 (C=O), 1190 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 7.54 (s, 1H, Ar-H), 8.11 (d, J=6.0 Hz, 2H, Ar-H), 8.25 (d, J=9.2 Hz, 1H, Ar-H), 8.74-8.82 (m, 3H, Ar-H), 9.05 (s, 1H, coumarin C-4H), 10.15 (s,1H,NH), 11.11 (s,1H,NH).^{13}C NMR (100 MHz, DMSO-d6): 121.18, 121.36, 124.11 (2C), 128.31 (2C), 128.73, 129.18, 133.47, 135.81, 146.80 148.90, 148.99 (coumarin C-4), 153.02 (coumarin-C-3), 158.73 (C=O), 160.12 (C=O), 163.93 (C=O). Elemental analysis: Calculated for $C_{17}H_{10}Cl_2N_2O_4$: C, 54.13; H, 2.67; N, 7.43. Found: C, 54.10; H, 2.61; N, 7.39.

N'-Benzoyl-7-(diethylamino)-2-oxo-2H-chromen-3-ylcarbohydrazide (4e): M.P.: 263–264 °C, (263–264 °C (16)), FTIR (KBr): 3326, 3264 (NH), 1688, 1648 (C=O), 1191 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6): 1.12 (t, J=6.8 Hz, 6H, CH_3), 3.48 (q, J=6.8 Hz, 4H, CH_2), 6.62 (s, 1H, Ar-H), 6.81 (d, J=6.8 Hz, 1H, Ar-H), 7.49 (t, J=7.2 Hz, 2H, ArH), 7.57 (d, J=7.2 Hz, 1H, Ar-H), 7.72 (d, J=6.8 Hz, 1H, ArH), 7.92 (d, J=6.8 Hz, 2H, Ar-H), 8.70 (s, 1H, coumarin C-4H), 10.40 (s, 1H, NH), 10.85 (s,1H,NH). ^{13}C NMR (100 MHz,DMSO-d_6): 12.75 ($2CH_3$), 44.87 ($2CH_2$), 96.36, 108.11, 108.41, 110.79, 128.01 (2C), 128.91 (2C), 132.31, 132.66, 148.89 (coumarin C-4), 153.28 (coumarin C-3), 157.91 (C=O), 161.76 (C=O), 165.27 (C=O). Elemental analysis: Calculated for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.08. Found: C, 66.39; H, 5.50; N, 11.01.

2-Oxo-*N*'-(phenylacetyl)-2*H*-1-benzopyran-3-ylcarbohydrazide (5a): M.P.: 253–254 °C (Cas No: 505065-35-0), FTIR (KBr): 3231, 3048 (NH), 1703, 1664 (C=O), 1206 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 3.58 (s, 2H, CH_2), 7.22 (s, 1H, Ar-H), 7.39 (s,2H, Ar-H, 7.72 (d, J=9.2 Hz, 2H, Ar-H), 7.80 (d, J=7.6 Hz, 2H, Ar-H), 8.00 (d, J=8.4 Hz, 2H, Ar-H), 8.87 (s, 1H, coumarin C-4H), 10.68 (s, 1H, NH), 11.04 (s,1H,NH).^{13}C NMR (100 MHz, DMSO-d_6): 40.23 (CH_2), 116.68, 118.43, 125.67, 127.02, 128.66 (2C), 128.96 (2C), 129.44, 129.52, 130.78, 134.85, 136.00, 148.36 (coumarin C-4), 154.36 (coumarin C-3), 158.83 (C=O), 160.34 (C=O), 167.88 (C=O). Elemental analysis: Calculated for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.01; H, 4.33; N, 8.62.

6-Chloro-2-oxo-*N*'-(phenylacetyl)-2*H*-1-benzopyran-3-ylcarbohydrazide (5b): M.P.:253–254°C, FTIR (KBr): 3238, 3054 (NH), 1702, 1681 (C=O), 1189 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6): 3.56 (s,2H,CH_2), 7.22-7.31 (m,5H,Ar-H), 8.10 (m, 2H, Ar-H), 8.81 (s, 1H, coumarin C-4H), 10.59 (s, 1H, NH), 11.03 (s, 1H, NH). ^{13}C NMR (100 MHz,DMSO-d_6):39.32 (CH_2), 120.71, 121.18, 121.35, 127.02, 128.68, 128.72, 129.22 (2C), 129.52 (2C), 133.43, 135.94, 146.61 (coumarin C-4), 148.79 (coumarin C-3), 158.41 (C=O), 158.92 (C=O), 168.01 (C=O). Elemental analysis: Calculated for $C_{18}H_{13}ClN_2O_4$: C,60.60;H,3.67;N,7.85. Found:C,60.53;H,3.60;N,7.76.

6-Bromo-2-oxo-*N*'-(phenylacetyl)-2*H*-1-benzopyran-3-ylcarbohydrazide (5c): M.P.: 250–252 °C (Cas No: 353473-63-9), FTIR (KBr): 3274, 3100 (NH), 1715, 1680 (C=O), 1187 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 3.33 (s, 2H, CH_2), 7.22-7.33(m, 4H, Ar H), 7.48 (s, 1H, Ar-H), 7.88 (d, J=9.2 Hz,1H, Ar-H), 8.23 (d, J=7.6 Hz,2H, Ar-H), 8.82 (s, 1H, coumarin C-4H), 10.59 (s, 1H, NH), 11.17 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 39.33 (CH_2), 117.18, 119.72, 120.61, 127.02, 128.72 (2C), 129.51 (2C), 132.59, 135.98, 136.94, 146.95 (coumarin C-4), 153.40 (coumarin C-3), 158.62 (C=O), 159.81 (C=O), 167.93(C=O). Elemental analysis: Calculated for $C_{18}H_{13}BrN_2O_4$: C,53.89; H,3.27; N,6.98. Found: C,53.81; H, 3.20; N, 6.91.

6,8-Dichloro-2-oxo-*N*'-(phenlacetyl)-2*H*-1-benzopyran-3-ylcarbohydrazide (5d): M.P.: 250–252 °C, FTIR (KBr): 3187, 3056 (NH), 1700, 1685 (C=O), 1190 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 3.56 (s, 2H, CH_2), 7.22-7.33 (m, 5H, Ar-H), 7.46 (d, J=6.8 Hz,1H, Ar-H), 7.89 (d, J=9.6 Hz, 1H, Ar-H), 8.82 (s, 1H, coumarin C-4H), 10.64 (s, 1H, NH), 11.03 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 40.36 (CH_2), 116.67, 118.41, 118.73, 125.66, 127.00, 128.70, 129.51 (2C), 130.77 (2C), 134.83, 135.99, 148.35 (coumarin C-4), 154.34 (coumarin C-3), 158.82 (C=O), 160.32 (C=O), 167.87 (C=O). Elemental analysis: Calculated for $C_{18}H_{12}Cl_2N_2O_4$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.20; H, 3.03; N, 7.11.

7-(Diethylamino)-2-oxo-*N*'-(phenylacetyl)-2*H*-1-benzopyran-3-ylcarbohydrazide (5e): M.P.: 263–264 °C, FTIR (KBr): 3362, 3300 (NH), 1697, 1672 (C=O), 1199 (C-O) cm^{-1}. 1H NMR (400 MHz, DMSO-d_6): 1.11 (t, J=6.8 Hz, 6H, CH_3), 3.43 (q, J=6.8 Hz, 4H, CH_2), 3.56 (s, 2H, CH_2), 6.59 (s, 1H, Ar-H), 6.78 (d, J=8.8 Hz, 1H, Ar-H), 7.23-7.31 (m, 4H, ArH), 7.66 (s, 1H, Ar-H), 7.89 (d, J=6.8 Hz, 1H, ArH), 8.66 (s, 1H, coumarin C-4H), 10.55 (s, 1H, NH), 10.95 (s, 1H, NH).^{13}C NMR (100 MHz, DMSO-d_6): 12.74 (CH_3), 39.32 (CH_2), 44.85 (CH_2), 96.34, 108.11, 108.13, 110.75, 126.97, 128.69 (2C), 129.49 (2C), 132.21, 136.11, 148.60 (coumarin C-4), 153.19, 157.80 (coumarin-C-3), 159.99 (C=O), 161.82 (C=O), 167.66 (C=O). Elemental analysis: Calculated for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, 67.11; H, 5.80 N, 10.62.

Anti-lipase activity

Lipase inhibition potential of synthesized compounds was investigated according to the method described previously (39, 40) against porcine pancreatic lipase using 4-nitrophenylpalmitate as the substrate. Enzyme and compounds (10 µM) were preincubated for 20 minutes at 37 °C in 50 mM pH 7.5 phosphate buffer containing 5mM sodium deoxycholate and 1 mg/mL gum arabic. Then,substrate (0.1 mM) was added to the reaction mixture and after 15-minute incubation, the amount of *p*-nitrophenol released was measured at 410 nm. Orlistat was used as positive control

and ethanol was used as the negative control. %lipase inhibition was calculated using the following equation:

$$\text{Lipase inhibition (\%)} = 100\ (A - B) - (C - D) / (A - B)$$

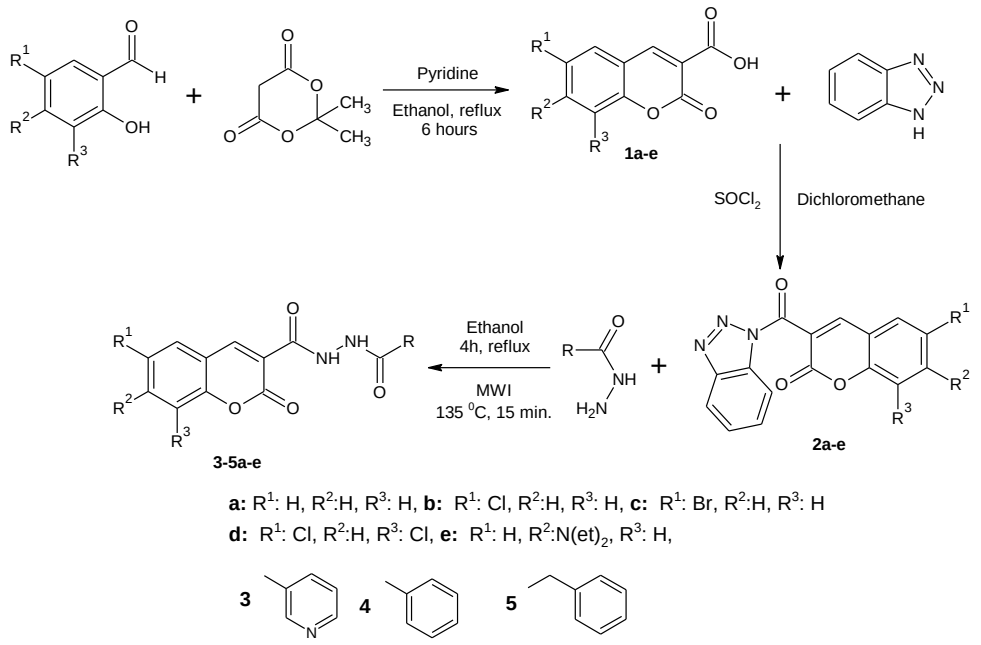
where A is the activity in the absence of inhibitor, B is the negative control in the presence of inhibitor, Cistheactivity presence inhibitor, and D is the negative control in the presence of inhibitor.

Cupric ion reducing antioxidant capacity (CUPRAC)

1 mL of 10 mM Cu (II) Cl, 1 mL of 7.5 mM neocuproine, 1 mL of 1 M NH_3COOCH_3 pH 7 buffer and 20 µL of compounds solution were mixed in test tubes. The final volume in the test tubes was adjusted to 4.1 mL by adding distilled water. After 45 min incubation period at room temperature, the absorbances were recorded at 450 nm against a blank containing no compound (41) used as a standard. The CUPRAC of compounds was expressed as milligrams of Trolox per 1 mg synthesized compound. Trolox® (Sigma Chemical Co, USA) was also tested under the same conditions as a standard antioxidant compound. The standard curve was linear between 8 mg/mL and 0.125 mg/mL trolox (r^2 =0.998). CUPRAC values were expressed as mg Trolox equivalent of 1 mg synthesized compound.

RESULTS AND DISCUSSION

In this study, a convenient method has been used for the synthesis of coumarin hydrazides **(3-5a-e)**. The synthesis of the target *compounds* **(3-5a-e)** was performed by the reaction of 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-ones **(2a-e) and corresponding hydrazide derivatives.** Coumarin-3-carboxylic acid derivatives **1a-e** were obtained from the treatment of corresponding salicylic aldehydes and Meldrum's acid in absolute ethanol with catalytic amount of pyridine. Then, compounds **1a-e** were treated with 1*H*-benzotriazole in the presence of $SOCl_2$ to synthesize compounds **2a-e** (Scheme 1.).



Scheme 1. Synthetic route of target compounds.

In the literature, it is found that benzotriazole group offers some advantages in organic synthesis. Moreover, we have seen that compound **2a** has been used for the preparation of some biologically active compounds in literature. Especially, this compound was reacted with some type of molecules like amino acids, thioles and peptides to synthesize some coumarin-hybrid compounds. However, many of these reactions have required long reaction time, hard purification technique, and expensive catalyst requirement. Therefore, microwave heating was used for a short reaction time and a catalyst-free synthesis of compounds (**3-5a-e**). By this time, these compounds were synthesized with conventional heating for compotation with microwave heating (Table 1.).

Table 1. Comparison of yield and reaction times of compounds **3-5a-e.**

Compound	Conventional Heating		Microwave Irradiation	
	Time (h)	Yield (%)	Time (min.)	Yield (%)
3a	4	70	15	74
3b	4	67	15	70
3c	4	71	15	69
3d	4	74	15	75
3e	4	67	15	70
4a	4	69	15	70
4b	4	71	15	72
4c	4	72	15	75
4d	4	59	15	65
4e	4	72	15	77
5a	4	76	15	80
5b	4	74	15	82
5c	4	75	15	78
5d	4	76	15	82
5e	4	68	15	75

In literature, some of the obtained compounds were previously synthesized from the reaction of coumarin-3-acylchloride and hydrazide derivatives (42-45). However, these reactions were not performed under microwave irradiation. Also, the microwave irradiation technique was not suitable for this type of reaction because, in this type of reactions, the discharge of HCl gas causes the increase of reaction pressure and that is very dangerous. Therefore, we have chosen to synthesize coumarin-benzotriazole derivative instead of acyl chloride derivative because benzotriazole derivatives are more stable and benzotriazole is an easy leaving group (26, 30, 37).

Spectral investigations of compounds **3-5a-e** are suitable with the proposed structures. FTIR spectra of each compounds have two NH signals 3300-3200 cm^{-1} and three C=O signals at about 1700-1600 cm^{-1}. In ^{1}H NMR spectra of compounds **3-5a-e** , two NH signals were obtained at about 11.50 and 10.00 ppm. In ^{13}C NMR spectra of compounds **3-5a-e** , three C=O were found at about 164.00 (hydrazide), 159.00 (hydrazide) and 158.00 ppm (coumarin C-2), while coumarin C-3 and coumarin C-4 were shown at about 155.00 and 148.00 ppm. The FTIR, ^{1}H NMR and ^{13}C NMR (APT) spectra of compounds **5e** are given in Figure 1,2, and 3. Also, ın ^{13}C NMR spectra the number of aromatic carbons was suitable with the structure.

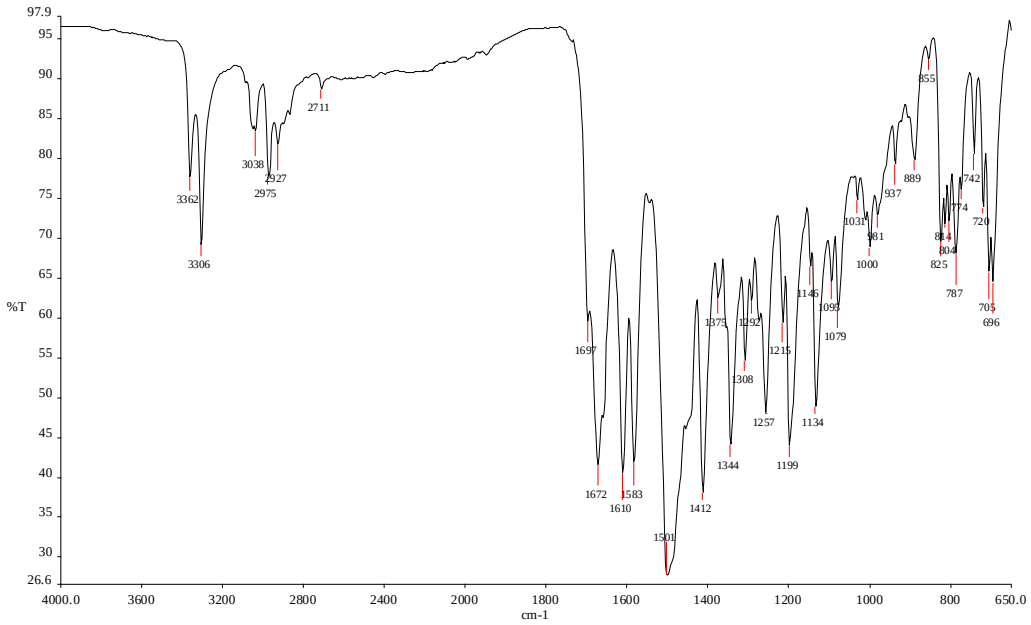


Figure 1. FTIR spectra of compound **5e.**

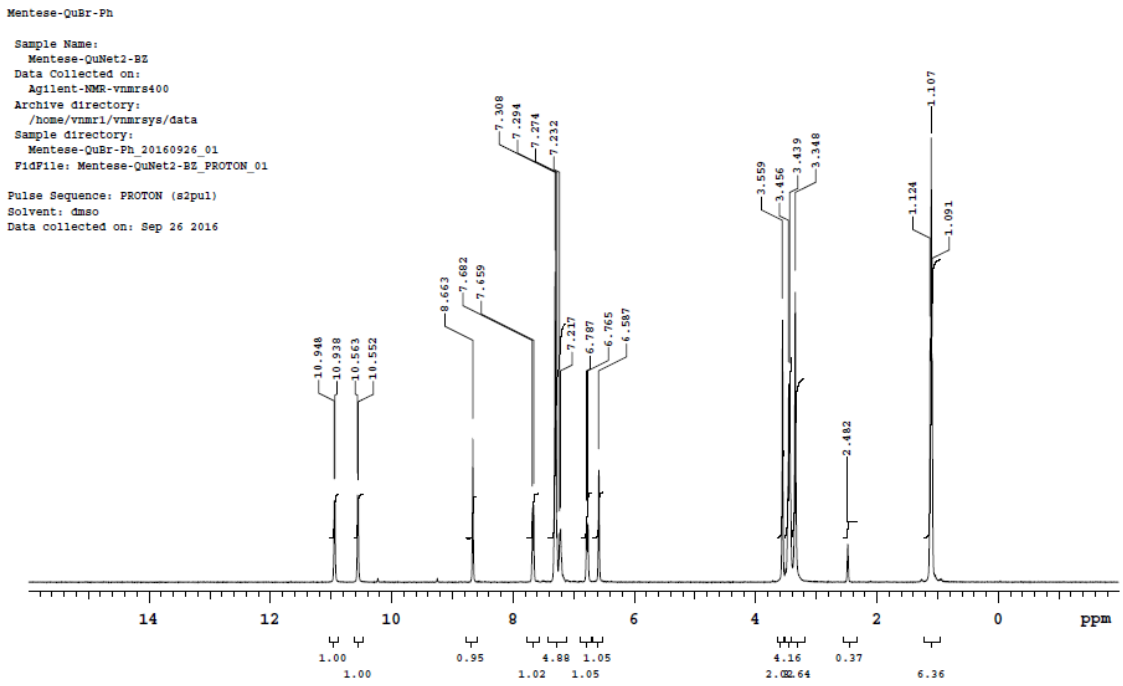


Figure 2. ^{1}H NMR spectra of compound **5e.**

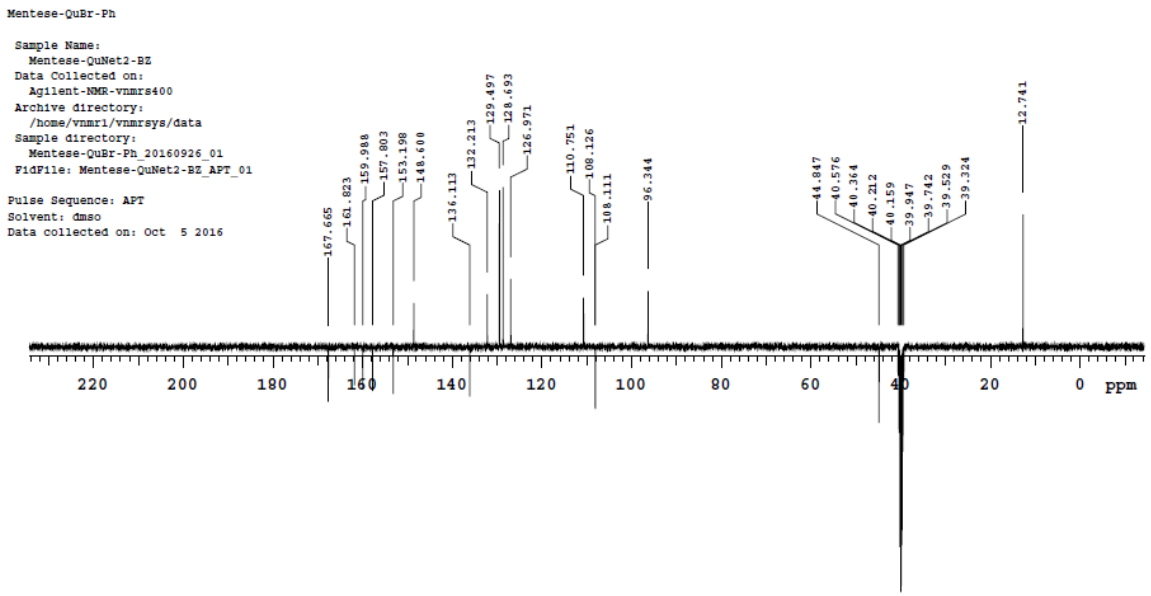


Figure 3. ^{13}C NMR (APT) spectra of compound **5e.**

Lipase Inhibition

Compounds **3-5a-e** were evaluated for their lipase inhibitory potential against porcine pancreatic lipase. All compounds except **3d, 3e, 4d** and **4e** inhibited porcine pancreatic lipase at different ratios. Compounds **5d, 5e** and **3b** presented greatest lipase inhibitory activity by 46.31±3.55, 42.96±3.75 and 42.50±3.62, respectively. Compound **5d** was determined to be the most effective lipase inhibitor among studied compounds. There is no inhibitory effect for the compounds **4a** and **4b**. Orlistat, a known anti-obesity drug approved by European Medical Association (46), showed 97.97±0.15 inhibition at 300 nM (Tablo 2.).

Table 2. Lipase inhibitory activities of the synthesized compounds **3-5a-e** at 10 μM final concentration against porcine pancreatic lipase.

Compound (10μM)	% Pancreatic lipase inhibition
3a	35.00±2.41
3b	42.50±3.62
3c	27.50±1.25
4a	11.25±1.66
4b	8.08±1.08
4c	26.67±1.98
5a	20.61±2.00
5d	46.31±3.55
5e	42.96±3.75
Orlistat (300 nM)	97.97±0.15

Cupric ion reducing antioxidant capacity (CUPRAC)

In CUPRAC method bis (2,9-dimethyl-1,10-phenanthroline: neocuproine) Cu(II) chelate cation is used as the chromogenic oxidant. Antioxidants reduce neocuproine to the cuprous neocuproine

chelate [Cu(I)-Nc] which shows maximum absorption at 450 nm (41). All studied compounds reduced cupric ions at different ratios (Table 3.). The highest cupric ion reducing activity was observed for compound **4e**. When compared with other studied compounds, compound **3c** showed the least antioxidant power.

Table 3. Antioxidant capacities of the synthesized compounds **3-5a-e.**

Compounds	CUPRAC method (mg TEAC/mg compound)
3a	1.23±0.02
3b	1.51±0.08
3c	0.80±0.01
3d	1.09±0.02
3e	1.34±0.03
4a	1.23±0.02
4b	1.57±0.04
4c	1.38±0.03
4d	1.65±0.05
4e	1.82±0.08
5a	1.46±0.05
5b	1.51±0.06
5c	1.48±0.02
5d	1.68±0.05
5e	1.38±0.03

CONCLUSION

This study reports the synthesis of novel coumarin hydrazide derivatives from 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-ones **2a-e** and hydrazide derivatives by using microwave heating and conventional heating procedures. Microwave heating procedure has shown some advantages on classical heating with short reaction times, easy work-up, and the less quantity of organic solvent. In anti-lipase inhibition study, compound **5d** showed the highest activity among the synthesized compounds with 46.31±3.55% pancreatic lipase inhibition. In antioxidant activity study, all compounds showed the activity, while compound **4e** showed the best antioxidant capacity.

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