One-pot, three component approach to synthesis of multipart fused heterocyclic compounds: Synthesis of fused pyran-2-ones

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Abstract
An efficient, three-component synthesis of novel class of dihydropyran-2-ones which are fused with coumarin rings, from reaction between Meldrum's acid, aryl aldehydes and 5,7-dihydroxy-4-methyl (and phenyl) coumarin was described. In this research 9,10-dihydropyrano[2,3-h]benzopyrone-8-ones in the presence of catalytic amount of piperidine as organo basic catalyst were obtained in good to excellent yields under refluxing methanol for the time.

Keywords: Heterocycles, lactones, aldehydes, fused-ring systems, nucleophilic addition

Introduction

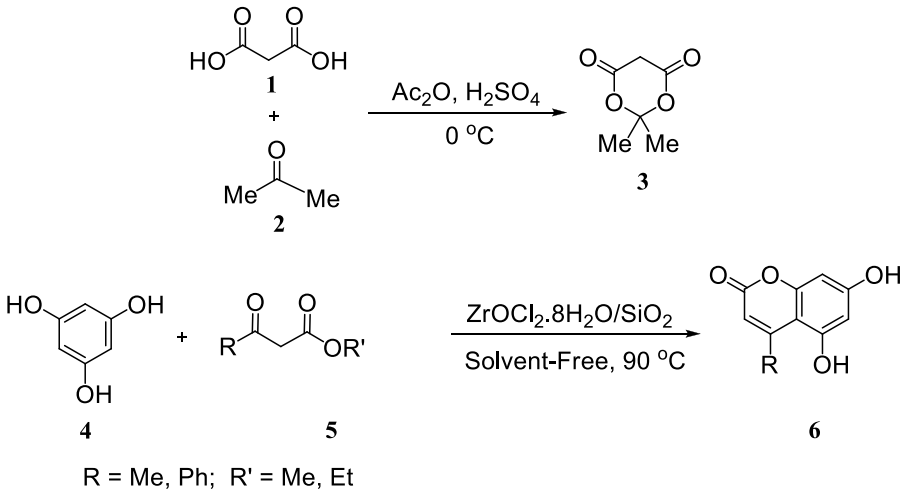
Multicomponent reactions (MCRs) are masterpieces of synthetic efficiency and reaction design that play an important role in organic synthesis. MCRs are general defined as reactions where more than two starting materials react to form a novel and senior molecules in one pot. Furthermore, multicomponent and multistep reactions have been designed to produce biologically active compounds. [1]

The scaffolds of dihydropyran-2-ones have appeared as a fragment in many natural products. These structures can exhibit a wide range of biological activities.[2,3] These type of compounds are an important class of heterocyclic structures, that can be applied in drug and pharmaceutical fields.[4] These compounds have attracted scientific interest because of their biological actions such as antimicrobial activity through DNA gyrase-B,[5] antioxidant activity against superoxide and hydroxyl radicals, antimicrobial activity against *E. coli* and *S. aureus*, antibiotic and cytotoxic activities, antiinflammatory, antiaging, and anticancer activity.[4] Furthermore, they can act as potent nonpeptidic inhibitors of HIV protease.[6] Coumarins are the benzo-2-pyrone derivatives mainly found in plants of the family of Rutaceae and Umbelliferae.

They exhibit a broad range of biological activities including anticoagulation, antifungal, anti-psoriasis, and *etc*.[7]

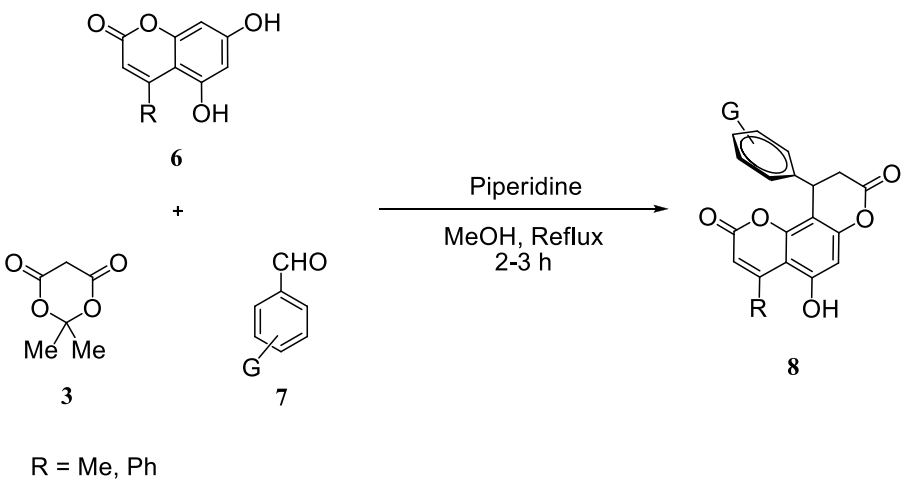
It is well-known that the Meldrum's acid can react with aromatic and heteroaromatic aldehydes to produce corresponding arylidene derivatives.[8] arylidene Meldrum's acids are important intermediates in the synthesis of other heterocyclic compounds with new and extensive structures.[9]

The scope of our study is in the dominion of heterocyclic compounds,[10] herein, we wish to report the one-pot, three-component synthesis of dihydropyran-2-one derivatives which are fused with coumarin rings. In this work, we found a synthetic route for the preparation of a new class of pyrane-2-ones that can be utilized in biochemistry, pharmacology and medicine applications. For this purpose, firstly Meldrum's acid **3** and 5,7-dihydroxy-4-methyl (and phenyl) coumarin **6** were prepared (Scheme 1).



Scheme 1. Synthesis of Meldrum's acid and 5,7-dihydroxy-4-methyl (and phenyl) coumarins.

Meldrum's acid, according to the reported method by McNab, was prepared from the malonic acid **1** and acetone **2** in the presence of acetic anhydride and sulfuric acid.[8] On the other hands, 5,7-dihydroxy-4-methyl coumarin was synthesized from the phloroglucinol **4** and ethyl acetoacetate **5** by the use of Lewis acid catalyst under thermal and solvent-free conditions. Also, for the synthesis of 5,7-dihydroxy-4-phenyl coumarin, ethyl benzoylacetate was handled.[10a]



Scheme 2. Synthesis of 10-aryl substituted-9,10-dihydropyrano [2,3-h]chromene-2,8-diones.

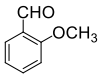
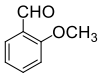
Three-component reaction was carried out by using Meldrum's acid **3**, 5,7-dihydroxy-4-substituted coumarin **6** and aromatic aldehyde **7** in the presence of piperidine as an organocatalyst under refluxing in methanol to obtain 10-aryl substituted-9,10-dihydropyrano[2,3-h]chromene-2,8-dione **8** (Scheme 2).

Results and Discussion

It is known that, the presence of a hydroxyl group on the aromatic rings, is a key factor for the activation of ring in its ortho and para positions towards electrophiles such as arylidene Meldrum's acid. Here, two hydroxyl groups on the aromatic ring of coumarin activate this ring towards arylidene Meldrum's acid (formed from condensation of Meldrum's acid with aldehydes) as nucleophile reagent. As it was expected, this reagent can activate ortho and para position of the aromatic ring and can react with arylidene Meldrum's acid as a nucleophile.

By this achievement, several 4-aryl substituted dihydropyran-2-ones which are fused with coumarin ring were obtained with good to excellent yields (Table 1).

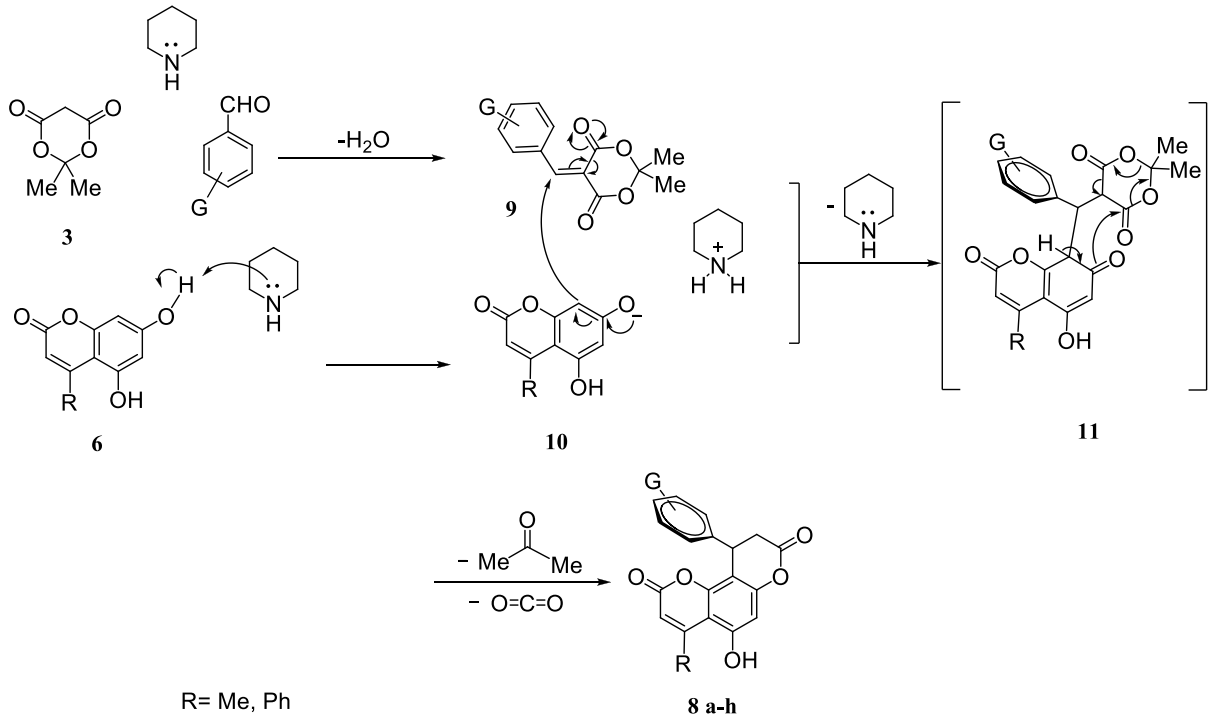
Table 1. Synthesis of 4-aryl substituted pyran-2-one[2,3-*h*] chromene-2,8-dione derivatives

Product **8**	Aldehyde	R	Yield (%)[a]	Mp (°C)
a		Me	82	333 dec.
b		Me	90	328 dec.
c		Me	85	337 dec.
d		Me	85	350 dec.
e		Ph	82	276-277
f		Ph	87	298-300
g		Ph	80	288-290
h		Ph	80	285-286

[a]Refers to isolated yields

The structures of compounds **8** were deduced from ^{1}H NMR, ^{13}C NMR, FT-IR spectra and elemental analysis data. The suggested mechanism for the synthesis of product **8** is shown in Scheme 3. As can be seen from this Scheme, firstly, Knoevenagel condensation between Meldrum's acid and aldehyde will occur and arylidene Meldrum's acid **9** is formed. From Michael type nucleophilic attack of intermediate **10** (that was obtained from the reaction of 5,7-dihydroxy-4-methyl (phenyl) coumarin with piperidine) to arylidene Meldrum's acid **9**, intermediate **11** was obtained.

This intermediate is unstable, and readily tautomerized to its enol type. Due to the tautomerization of ketone to enol type, this causes the ring to be aromatic and would be stable. Lastly, intramolecular nucleophilic attack of enol type intermediate **11** after releasing the acetone and carbon dioxide, dihydropyran-2-one ring was formed and product **8** was obtained (Scheme 3).



Scheme 3. The suggested mechanism for the synthesis of 10-aryl substituted-9,10-dihydropyrano [2,3-*h*]chromene-2,8-dione.

In another variation, we tried to synthesize of 10-alkyl substituted-9,10-dihydropyrano[2,3-h]chromene-2,8-diones by using aliphatic aldehydes and ketones, but the progress of the reactions were unsuccessful.

Conclusions

In summary, a new series of 10-aryl substituted-9,10-dihydropyrano[2,3-h]benzopyrone-8-ones have been synthesized via a MCR approach and were characterized by elemental and spectral analysis. This synthetic strategy allows formation of the complicated oxygen containing fused heterocyclic systems. As well as, the introduction of various aromatic substituents into the 4-position of pyran-2-one systems was obtained. By this development, the scope of heterocyclic compounds was increased. These types of compounds can be applied in medicine and pharmacy, and can be considered by chemists in the future works.

Experimental Section

General. Solvents were purified and dried by standard procedures and distilled prior to use. Commercially available reagents were purchased from Merck Chemical Co. Melting points were measured on an elecrtothermal KSB1N apparatus. IR spectra were recorded in the matrix of KBr with JASCO FT-IR-680 plus spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a FT-NMR Bruker Avance Ultra Shield Spectrometer at 400.13 and 100.62 MHz in DMSO-d_6 as solvent. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values. TLC was performed on TLC-Grade silica gel-G/UV 254 nm plates. Chemicals were purchased from Fluka and Merck chemical companies and were used without further purification.

General process for the preparation of Meldrum's acid in excellent yield (compound 3)
To stirred mixture of malonic acid (52 g) and acetic anhydride (60 mL) in the presence of catalytic amount of sulfuric acid (1.5 mL), 40 mL of acetone in ice bath is added and is allowed the reaction mixture to reach at room temperature. After 2 h stiring at this condition, the reaction components are allowed to stand together for the time (12 h) in cool place to appear crystalline product. Then crystals were filtrated and were washed with very cool water and recrystallized from hot acetone to give the pure product **3.**

Typical procedure for the synthesis of 5,7-dihydroxy-4-methyl (or phenyl) coumarin (compound 6): Ethylacetoacetate (or benz-oyl acetic acid ethyl ester) (1mmol) was added to a mixture of phloroglucinol (1mmol) and $ZrOCl_2.8H_2O/SiO_2$ (0.27 g, 10 mol%) in a screw-cap vial. The reaction mixture was stirred in a preheated oil bath (90 °C). After the completion of the reaction, the solid product was suspended in water (20 mL). The resulting crude product was filtered off and recrystallized from hot EtOH to give the pure product **6**.

General procedure for synthesis of 10-arylsubstituted-9,10-dihydropyrano[2,3-h] chromene-2,8-dione (Compounds 8a-h)
For the preparation of these products, for example compound **8b**, to a stirred solution of the 1 mmol Meldrum's acid (0.144 g) and 1 mmol 2-chlorobenzaldehyde (0.140 g) in 10 mL methanol, in the presence of basic catalytic amount of piperidine (1-2 drops), the 1 mmol 5,7-dihydroxy-4-methyl coumarin (0.192 g) under reflux condition was added. The reaction progress was controlled by TLC (*n*-hexane/ethyl acetate, 1:1). After 2 h, the reaction was completed and the residue was filtered. The crude product recrystallized from ethanol to yield pure product **8b** in 92% yield.

5-Hydroxy-4-methyl-10-phenyl-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (8a). White solids, mp 333 °C (decomposed); yield 0.28 g, 88%; IR (KBr) (ν_{max}, cm^{-1}): 3255, 1782, 1694, 1628, 1605, 1382, 1337, 1125, 1094, 847, 736, 700. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ_H 2.51 (s, 3H, CH_3), 2.95 (d, *J* 16 Hz, 1H, CH), 3.38 (dd, $^{2}J_{HH}$ 16.0 Hz, $^{3}J_{HH}$ 7.2 Hz, 1H, CH), 4.73 (d, $^{3}J_{HH}$ 6.0 Hz, 1H, CH), 6.09 (s, 1H, CH), 6.60 (s, 1H, CH), 7.11 (d, $^{3}J_{HH}$ 7.6 Hz, 2H, aromatic

CH), 7.24 (t, $^{3}J_{HH}$ 6.8 Hz, 1H, aromatic CH), 7.32 (t, $^{3}J_{HH}$ 7.2 Hz, 2H, aromatic CH), 11.15 (s, 1H, OH). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ_C 24.07, 34.37, 37.26, 99.98, 106.56, 111.76, 126.96, 127.67, 127.94, 129.44, 141.67, 152.54, 154.40, 155.51, 159.62, 167.24. Anal. Calcd for $C_{19}H_{14}O_5$ (322.31): C, 70.80; H, 4.38. Found: C, 70.68; H, 4.55.

5-Hydroxy-4-methyl-10-(2-chlorophenyl)-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (8b). White solids, mp 328 °C (decomposed); yield 0.33 g, 92%; IR (KBr) (ν_{max}, cm^{-1}): 3219, 1797, 1680, 1625, 1605, 1136, 1097, 852 and 548. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ_H 2.56 (s, 3H, CH_3), 2.83 (dd, $^{2}J_{HH}$ 16 Hz, $^{3}J_{HH}$ 1.6 Hz, 1H, CH), 3.47 (dd, $^{2}J_{HH}$ = 16 Hz, $^{3}J_{HH}$ 7.2 Hz, 1H, CH), 5.05 (d, $^{3}J_{HH}$ 6.4 Hz, 1H, CH), 6.08 (s, 1H, CH), 6.63 (s, 1H, CH), 6.70 (dd, $^{3}J_{HH}$ 7.8 Hz, $^{4}J_{HH}$ 1.2 Hz, 1H, aromatic CH), 7.22 (m, 1H, aromatic CH), 7.31 (m, 1H, aromatic CH), 7.56 (q, $^{3}J_{HH}$ 8.0 Hz, $^{4}J_{HH}$ 1.2 Hz, aromatic CH), 11.24 (s, 1H, OH). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ_C 23.50, 31.70, 35.01, 99.36, 102.27, 106.16, 111.52, 127.30, 127.97, 129.33, 130.22, 132.22, 137.77, 151.90, 154.37, 154.72, 157.54, 158.82, 166.05. Anal. Calcd for $C_{19}H_{13}ClO_5$ (356.76): C, 63.97; H, 3.67. Found: C, 64.08; H, 3.75.

5-Hydroxy-4-methyl-10-(2-methoxyphenyl)-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (8c). White solids, mp 337 °C (decomposed); yield 0.315 g, 90%; IR (KBr) (ν_{max}, cm^{-1}): 3271, 1778, 1688, 1628, 1605, 1133, 1095, 851, 547. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ_H 2.54 (s, 3H, CH_3), 2.80 (dd, $^{2}J_{HH}$ 15.2 Hz, $^{3}J_{HH}$ 0.8 Hz, 1H, CH), 3.31 (dd, $^{2}J_{HH}$ = 16.2 Hz, $^{3}J_{HH}$ 8 Hz, 1H, CH), 3.81 (s, 3H, CH_3) 4.82 (d, $^{3}J_{HH}$ 7.2 Hz, 1H, CH), 6.05 (s, 1H, CH), 6.57 (s, 1H, CH), 6.74 (dd, $^{3}J_{HH}$ 7.4 Hz, $^{4}J_{HH}$ 1.6 Hz, 1H, aromatic CH), 6.81 (t, $^{3}J_{HH}$ 7.2 Hz, 1H, aromatic CH), 7.03 (d, $^{3}J_{HH}$ 8 Hz, 1H, aromatic CH), 7.24 (m, 1H, aromatic CH), 11.09 (s, 1H, OH). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ_C 23.52, 30.30, 34.57, 55.07, 99.18, 102.60, 105.89, 111.26, 120.38, 127.45, 128.51, 128.70, 152.07, 154.25, 154.82, 156.45, 157.02, 159.05, 166.47. Anal. Calcd for $C_{20}H_{16}O_6$ (352.34): C, 68.18; H, 4.58. Found: C, 68.26; H, 4.62.

5-Hydroxy-4-methyl-10-(naphthalen-1-yl)-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (8d). White solids, mp 350 °C (decomposed); yield 0.325 g, 88%; IR (KBr) (ν_{max}, cm^{-1}): 3226, 1784, 1678, 1624, 1606, 1170, 1134, 1097, 853, 781, 551. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ_H 2.59 (s, 3H, CH_3), 2.90 (d, $^{3}J_{HH}$ 15.6 Hz, 1H, CH), 3.52 (dd, $^{2}J_{HH}$ 16 Hz, $^{3}J_{HH}$ 7.2 Hz, 1H, CH), 5.60 (d, $^{3}J_{HH}$ 6.8 Hz, 1H, CH), 6.06 (s, 1H, CH), 6.69 (s, 1H, CH), 6.74 (d, $^{3}J_{HH}$ 6.8 Hz, 1H, aromatic CH), 7.33 (t, $^{3}J_{HH}$ 7.6 Hz, 1H, aromatic CH), 7.63 (t, $^{3}J_{HH}$ 7.6 Hz, 1H, aromatic CH), 7.71 (t, $^{3}J_{HH}$ 7.6 Hz, 1H, aromatic CH), 7.85 (d, $^{3}J_{HH}$ 8 Hz, 1H, aromatic CH), 8.02 (d, $^{3}J_{HH}$ 8 Hz, 1H, aromatic CH), 8.39 (d, $^{3}J_{HH}$ 8.8 Hz, 1H, aromatic CH), 11.23 (s, 1H, OH). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ_C 23.55, 30.46, 36.43, 99.42, 103.41, 106.19, 111.43, 122.96, 123.11, 125.49, 126.15, 126.89, 128.01, 129.05, 129.95, 133.85, 136.40, 151.92, 154.62, 154.87, 157.35, 158.96, 166.39. Anal. Calcd for $C_{23}H_{16}O_5$ (372.37): C, 74.19; H, 4.33. Found: C, 74.19; H, 4.32.

5-Hydroxy-4-phenyl-10-phenyl-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (8e). Pale yellow solids, mp 276-277 °C; yield 0.32 g, 85%; IR (KBr) (ν_{max}, cm^{-1}): 3330, 1789, 1732, 1691, 1624, 1601, 1437, 1375, 1332, 1172, 1126, 1090, 767, 699, 611. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ_H 2.99 (d, $^{3}J_{HH}$ 16.0 Hz, 1H, CH), 3.44 (m, 1H, CH), 4.81 (d, $^{3}J_{HH}$ 6.4 Hz, 1H, CH), 6.00 (s, 1H, CH), 6.50 (s, 1H, CH), 7.18 (d, $^{3}J_{HH}$ 7.6 Hz, 2H, aromatic CH), 7.27 (t, $^{3}J_{HH}$ 7.2 Hz, 1H,

aromatic CH), 7.33-7.40 (m, 7H, aromatic CH), 10.76 (s, 1H, OH). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ_C 34.46, 37.20, 100.02, 104.36, 105.00, 113.53, 127.03, 127.74, 127.85, 127.89, 128.53, 129.49, 139.48, 141.63, 152.71, 154.84, 156.08, 156.80, 159.42, 167.18. Anal. Calcd for $C_{24}H_{16}O_5$ (384.38): C, 74.99; H, 4.20. Found: C, 74.75; H, 4.36.

5-Hydroxy-4-phenyl-10-(2-chlorophenyl)-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (8f). Pale yellow solids, mp 298-300 °C; yield 0.37 g, 90%; IR (KBr) (ν_{max}, cm^{-1}): 3353, 3067, 1778, 1734, 1692, 1621, 1603, 1434, 1375, 1349, 1179, 1136, 1120, 1090, 764, 738, 705, 464. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ_H 2.88 (d, $^3J_{HH}$ 15.6 Hz, 1H, CH), 3.51 (dd, $^2J_{HH}$ 16.0 Hz, $^3J_{HH}$ 7.6 Hz, 1H, CH), 5.14 (d, $^3J_{HH}$ 6.8 Hz, 1H, CH), 5.99 (s, 1H, CH), 6.54 (s, 1H, CH), 6.79 (d, $^3J_{HH}$ 7.6 Hz, 1H, CH), 7.26 (t, $^3J_{HH}$ 7.6 Hz, 1H, aromatic CH), 7.32-7.41 (m, 6H, aromatic CH), 7.59 (d, $^3J_{HH}$ 7.6 Hz, 1H, aromatic CH), 10.86 (s, 1H, OH). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ_C 32.28, 35.56, 99.96, 102.92, 105.17, 113.63, 127.86, 127.90, 128.53, 128.56, 129.88, 130.77, 132.75, 138.27, 139.38, 152.63, 155.38, 155.94, 157.20, 159.20, 166.52. Anal. Calcd for $C_{24}H_{15}ClO_5$ (418.83): C, 68.82; H, 3.61. Found: C, 68.76; H, 3.68.

5-Hydroxy-4-phenyl-10-(2-methoxyphenyl)-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (8g). Yellow solids, mp 288-290 °C; yield 0.35 g, 86%; IR (KBr) (ν_{max}, cm^{-1}): 3310, 3065, 2839, 1780, 1733, 1697, 1623, 1600, 1493, 1372, 1349, 1245, 1184, 1130, 1101, 1090, 1023, 887, 845, 756, 733, 700, 613. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ_H 2.85 (d, $^3J_{HH}$ 16.4 Hz, 1H, CH), 3.35 (dd, $^2J_{HH}$ 16.4 Hz, $^3J_{HH}$ 8.0 Hz, 1H, CH), 3.84 (s, 3H, OCH_3), 4.90 (d, $^3J_{HH}$ 7.6 Hz, 1H, CH), 5.96 (s, 1H, CH), 6.48 (s, 1H, CH), 6.86 (d, $^3J_{HH}$ 4.8 Hz, 2H, aromatic CH), 7.06 (d, $^3J_{HH}$ 8.4 Hz, 1H, aromatic CH), 7.25-7.29 (m, 1H, aromatic CH), 7.35-7.43 (m, 5H, aromatic CH), 10.71 (s, 1H, OH). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ_C 31.03, 35.08, 55.56, 99.78, 103.22, 104.91, 111.82, 113.32, 120.94, 127.83, 127.88, 128.18, 128.49, 129.07, 129.26, 139.50, 152.83, 155.26, 156.08, 156.69, 157.01, 159.41, 166.91. Anal. Calcd for $C_{25}H_{18}O_6$ (414.41): C, 72.46; H, 4.38. Found: C, 72.33; H, 4.45.

5-Hydroxy-4-phenyl-10-(naphthalen-1-yl)-9,10-dihydropyrano[2,3-*O*]chromene-2,8-dione (8h). Orange solids, mp 285-286 °C; yield 0.36 g, 84%; IR (KBr) (ν_{max}, cm^{-1}): 3337, 3062, 1783, 1732, 1697, 1622, 1603, 1437, 1357, 1240, 1166, 1129, 1090, 1014, 889, 855, 776, 703, 615, 593, 458. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ_H 2.97 (d, $^3J_{HH}$ 15.6 Hz, 1H, CH), 3.56 (dd, $^2J_{HH}$ 16.0 Hz, $^3J_{HH}$ 7.2 Hz, 1H, CH), 5.70 (d, $^3J_{HH}$ 6.8 Hz, 1H, CH), 5.99 (s, 1H, CH), 6.61 (s, 1H, CH), 6.84 (d, $^3J_{HH}$ 7.2 Hz, 1H, aromatic CH), 7.36-7.41 (m, 6H, aromatic CH), 7.65 (t, $^3J_{HH}$ 7.6 Hz, 1H, aromatic CH), 7.74 (t, $^3J_{HH}$ 7.2 Hz, 1H, aromatic CH), 7.88 (d, $^3J_{HH}$ 8.0 Hz, 1H, aromatic CH), 8.04 (d, $^3J_{HH}$ 8.0 Hz, 1H, aromatic CH), 8.44 (d, $^3J_{HH}$ 8.8 Hz, 1H, aromatic CH), 10.86 (s, 1H, OH). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ_C 31.07, 36.98, 100.03, 104.04, 105.22, 113.52, 123.60, 123.65, 126.04, 126.69, 127.43, 127.87, 127.92, 128.58, 129.60, 130.49, 134.40, 136.88, 139.47, 152.66, 155.66, 156.10, 157.05, 159.34, 166.87. Anal. Calcd for $C_{28}H_{18}O_5$ (434.44): C, 77.41; H, 4.18. Found: C, 77.37; H, 4.23.

Acknowledgements

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