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SYNTHESIS, CHARACTERISATION OF COUMARIN DERIVATIVES AND THEIR ANTI CANCER ACTIVITIES

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ABSTRACT

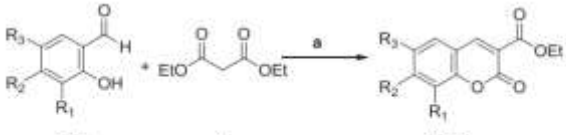
Two sets of coumarines were synthesised, and their IR, 1H, and 13C NMR and mass spectra were all very well characterised. Eight a and eight c, which contain coumarine with an amide-extended chromophore, have shown promise as anti-cancer agents. Our research may lead to more widespread use of coumarines for their potential cancer-fighting properties.

Keywords: *Coumarine, Synthesis, Characterisation and anti-cancer.*

INTRODUCTION

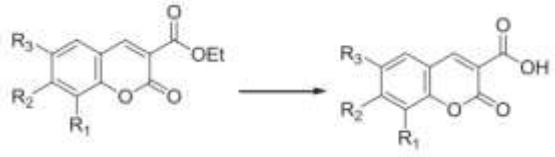
Cancer is one of the prominent causes of death in the world and based on World Health Organization (WHO) report, more than 13 million cancers death will happen in 2030. It was estimated that one in five people before age 75 will suffer from cancer during their lifetime. Most cancers are recognized by uncontrolled growth of cells without differentiation due to the deregulation of essential enzymes and other proteins controlling cell division and proliferation. Although many efforts for treatment of cancer diseases have been carried out and much progress have been eventuated from diagnosis to treatment of cancer, but some of cancer patients do not respond to therapy or recurrence subsequent initial response. Nevertheless, chemotherapy is a basic approach for the treatment of cancer diseases. One of the most important obstacles in chemotherapy is drug resistance to many anticancer agents. Drug-induced toxicities followed by administrating high doses of chemotherapeutic agents to overcome drug resistance were arisen. Accordingly, the discovery of new anticancer agent with promising activity and high therapeutic index is an urgent need. Coumarin (1, 2H-chromen-2-one or 2H-1-benzopyran-2-one) nucleus is a bicyclic heterocycle consisting of benzene and 2- pyrone rings (Fig. 1). Coumarins, a part of flavonoid group of plant secondary metabolite, are a wide class of natural and synthetic compounds that showed versatile pharmacological activities including anti-inflammatory, antioxidant, antinociceptive, hepatoprotective, antithrombotic, antiviral, antimicrobial, antituberculosis, anti-carcinogenic, antidepressant, antihyperlipidemic and anticholinesterase activities. Several natural and synthetic drugs containing coumarin scaffold are clinically well-known agents. For example, hymecromone (4-methylumbelliferone, 2) was used as choleretic and antispasmodic agent. Scopoletin (6-methoxy-7- hydroxycoumarin, 3) has been isolated from several plant species and has antioxidant, hepatoprotective, anti-inflammatory and antifungal properties. Carbochromen (4) has beneficial effect in coronary disease. 4-Hydroxycoumarin derivatives acenocoumarol (5), phenprocoumon (6), warfarin (7), difenacoum (8), and brodifacoum (9) are anticoagulant agents that act as vitamin K antagonists.

Synthetic Scheme:



1a-e 2 3a-e

1a;R_1=R_2=R_3=H
1b;R_1=OCH_3;R_2=R_3=H
1c;R_1=OC_2H_5;R_2=R_3=H
1d;R_1=R_2=H,R_3=Br



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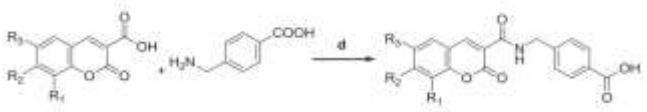


6a-d 7 8a-d

8a: $R_1=R_2=R_3=H$
8b: $R_1=OCH_3$; $R_2=R_3=H$
8c: $R_1=OCH_2CH_3$; $R_2=R_3=H$
8d: $R_1=R_3=H$; $R_2=OCH_3$

Scheme 1. Reagents and conditions: (a) Piperidine, EtOH, reflux; (b) NaOH (2 N), rt and then HCl (2 N); (c) CDI, THF, reflux; (ii) TFA, rt.

- Infrared spectra are recorded on Perkin Elmer model 283B and nicolet 740 FT-IR. Instruments and values are given in cm-1
- Proton Nuclear Magnetic Resonance spectra are recorded on varianGemini-200, varianunity-200 and advance-400MHZ Bruker UX-NMRinstrument.The samples are made in chloroform-d(1:1) or/and DMSO-d6 using tetramethylsilane (MeSi) as the internal standard and are given in the d scale.
- ESI Mass spectra were recorded on a Micro mass Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector.
- High-resolution mass spectra (HRMS) were recorded on a QSTAR XL Hybrid MS– MS mass spectrometer.
- Elemental analysis is carried out on VARFIO EL, se Elementor.
- Analytical Thin-layer Chromatography (TLC) is performed on pre coated silica-gel-60 F
- All extracts are extracted with ethyl acetoacetate and water and concentrated at reduced pressure on Buchi-R-3000 rotary evaporated below 50°C.yields reported are isolated yields of materials judged homogenous by TLC and NMR spectroscopy.
- Employing TLC techniques using appropriate solvent system for development monitored all the reasons. Moisture sensitive reactions are carried out by standard syringe-septum techniques.Dry ether, dry toluene is made by distilling them from sodium benzophenone ketyl and dry methanol is prepared by using potassium hydroxide.
- 254(0.5mm) glass plates. Visualisation of the sports on TLC plates is achieved either to iodine vapour or UV light.
- Melting Points were recorded on Melter Fp-51 instrument and were uncorrected.

Experimental Procedure:

All reagents and solvents were purchased from Merck & Co., Inc. (Darmatadt, Germany) and Acros Organics (Thermofisher, Belgium) and used without further purification. Entinostat and vorinostat were purchased from EuroAsia Chemicals @(www.euroasiarnd.com). The progress of all reactions was monitored by thin-layer chromatography with 0.25 mm Silica gel plates (60 GF-254-Merck & Co (Darmatadt, Germany)) and visualized using UV light and iodine vapor. Melting points were measured with an electrothermal melting point apparatus (Stafford, UK) and were uncorrected. Infrared spectra were recorded on a Perkin Elmer Model 1420 spectrometer (KBr disks, Massachusetts, USA).1H NMR and 13CNMR spectra were determined at 300 MHz and 75 MHz, respectively (DMSO-d6, TMS) on a Bruker FT-300 MHz instrument (Karlsruhe, Germany). The chemical shifts (δ) and coupling constants (J) are expressed in parts per million and Hertz, respectively. Spin multiples are given as s (singlet), d (doublet), t (triplet), q (quartet), s (sextet), m (multiplet). Mass spectra were obtained from a 6410 Agilent LC-MS triple quadrupole mass spectrometer (LC-MS, Santa Clara, USA) with an electrospray ionization (ESI) interface. Elemental analyses were performed on a Cos-Tec model EAS 4010 instrument (Cernusco, Italy) and the results are within ±0.4% of the theoretical values. Cell lines, including HCT116, A2780, MCF7, A549, HL60, PC3 and Huvec purchased from Pasteur Institute Cell Bank of IRAN (Tehran, IRAN).

General procedure for the synthesis of ethyl 2-oxo-2H-chromene-3-carboxylates (3a-d)

Diethyl malonate (2.11 mmol) and piperidine (2 mL) were added to a solution of the appropriate salicylaldehyde derivatives (1a-d) (10 mmol) in ethanol (20 mL) and the resulting mixture was refluxed for 14–15 h until the disappearance of the starting materials (monitored by TLC). After cooling, the crude product was filtrated, washed with cold ethanol and recrystallized from ethanol.

General procedure for the synthesis of 2-oxo-2H-chromene-3-carboxylic acids (4a-d)

Esters (3a-v) were dissolved in aqueous sodium hydroxide (2 N, 20 mL) and were stirred at rt for 5–7 h. After cooling, solution was acidified with hydrochloric acid (2 N) until a white precipitate formed. The white solid was filtrated, washed with water and dried to yield acids (4a-d).

General procedure for the synthesis of 4-((2-oxo-2H-chromene-3-carboxamido) methyl) benzoic acid derivatives (6a-d) the corresponding 2-oxo-2H-chromene-3-carboxylic acids (3a-d, 5 mmol) was added to a suspension of 1, 1´-carbonyldimidazole (CDI, 25 mmol) in dry tetrahydrofuran(THF, 10 mL) and the mixture was stirred for 2 h at rt. Then 4-(aminomethyl) benzoic acid (5, 25 mmol) and trifluoroacetic acid (TFA, 1.2 mL) were added and stirred for additional 10 h at rt. The mixture was evaporated to remove THF and extracted with EtOAc, dried over anhydrous Na2SO4 and concentrated under reduced pressure. Further purification was done with preparative thin layer chromatography.

4-((2-oxo-2H-chromene-3-carboxamido) methyl) benzoic acid (6a)White solid; yield:78%; mp: 261–263 °C; Rf = 0.56 (petroleum ether: ethyl acetate = 3:1); IR (KBr): νmax (cm−1) 3312 (NH), 1709 1602 (CO); 1H NMR (300 MHz, DMSO-d6) δ 4.63 (d, 2H, J = 6.0 Hz,CH2), 7.44–7.54 (m, 4H, Ar-H), 7.77 (t, 1H, J = 6.0 Hz, Ar-H), 7.92 (d, 2H, J = 9.0 Hz, Ar-H), 7.99 (d, 1H, J = 9.0 Hz, Ar-H), 8.90 (s, 1H, CH), 9.23 (t, 1H, J = 6.0 Hz, NH); 13C NMR (75 MHz, DMSO-d6) δ 43.04, 116.62, 118.94, 119.57, 125.62, 127.78, 129.88, 130.06, 130.75, 134.61, 144.56, 148.08, 154.40, 160.73, 161.96, 167.60; Anal. calcd. for C18H13NO5: C, 66.87; H, 4.05; N, 4.33; found: C 66.80, H 4.09, N 4.24.

4-((8-methoxy-2-oxo-2H-chromene-3-carboxamido) methyl) benzoic acid (6b)White solid; yield: 73%; mp: 238–240 °C; Rf = 0.49 (petroleum ether: ethyl acetate = 3:1); IR (KBr): νmax (cm−1) 3347 (NH), 1712 &1606 (CO); 1H NMR (300 MHz, DMSO-d6) δ 3.95 (s, 1H, OCH3), 4.62 (d, 2H, J = 6.0 Hz, CH2), 7.35–7.54 (m, 5H, Ar-H),7.91 (d, 1H, J = 8.1 Hz, Ar-H), 8.85 (s, 1H, CH), 9.24 (t, 1H, J = 5.7 Hz, NH); 13C NMR (75 MHz, DMSO-d6) δ 43.05, 56.65, 116.53, 119.46, 119.57, 121.62, 125.54, 127.81, 129.36, 137.81, 143.69, 144.56, 146.73, 148.30, 160.44, 161.83, 167.60; Anal. calcd. for C19H15NO6: C, 64.59; H, 4.28; N, 3.96; found: C 64.66, H 4.20, N 4.05.

4-((8-ethoxy-2-oxo-2H-chromene-3-carboxamido) methyl) benzoic acid (6c) Pale yellow solid; yield: 79%; mp: 246–248 °C; Rf = 0.43 (petroleum ether: ethyl acetate = 3:1); IR (KBr): νmax (cm−1) 3335 (NH), 1707 and 1653 (CO); 1H NMR (300 MHz, DMSO-d6) δ 1.42 (t, 3H, J = 6.9Hz, CH3), 4.20 (q, 2H, J = 6.9Hz,OCH2), 4.62 (d, 2H, J = 6.0Hz, CH2), 7.34 (d, 1H, J = 7.5Hz, Ar-H), 7.42–7.48 (m, 3H, Ar-H), 7.52 (dd, 1H, J1 = 7.5Hz, J2 = 1.2Hz, Ar-H), 7.92 (d, 2H, J = 8.1Hz, Ar-H), 8.86 (s, 1H, CH), 9.23 (t, 1H, J = 6.0Hz, NH); 13C NMR (75 MHz, DMSO-d6) δ 15.04, 43.03, 65.02, 117.43, 119.56, 119.59, 121.62, 125.56, 127.82, 129.89, 137.82, 143.79, 144.63, 145.98, 148.37, 160.53, 161.96, 167.66; Anal. calcd. for C20H17NO6: C, 65.39; H, 4.66; N, 3.81; found: C 65.30, H 4.73, N 3.75.

4-((7-methoxy-2-oxo-2H-chromene-3-carboxamido) methyl) benzoic acid (6d) Light brown; yield: 89%; mp: 242–244 °C; Rf = 0.46 (petroleum ether: ethyl acetate = 3:1); IR (KBr): νmax (cm−1) 3346 (NH), 1701, 1659 &1614 (CO); 1H NMR (300 MHz, DMSO-d6) δ 3.89 (s, 3H, OCH3), 4.62 (d, 2H, J = 6.0Hz, CH2), 7.02 (dd, 1H, J1 = 8.7Hz, J2 = 2.4Hz, Ar-H), 7.09 (d, 1H, J = 2.1Hz, Ar_H), 7.45 (d, 2H, J = 8.1Hz, Ar-H), 7.90 (m, 3H, Ar-H), 8.83 (s, 1H, CH), 9.17 (t, 1H, J = 6.0Hz, NH), 12.91 (brs, 1H, OH); 13C NMR (75 MHz, DMSO-d6) δ 42.98, 56.67, 100.69, 112.54, 114.05, 115.16, 127.77, 129.84, 129.90, 131.99, 144.77, 148.47, 156.64, 161.24, 162.20, 164.90, 167.65; Anal. calcd. for C19H15NO6: C, 64.59; H, 4.28; N, 3.96; found: C 64.48, H 4.34, N 3.89.

N-(4-((2-aminophenyl) carbamoyl) benzyl)-2-oxo-2H-chromene-3-carboxamide (8a) White solid; yield: 90%; mp: 207–209 °C; Rf = 0.76 (petroleum ether: ethyl acetate = 3:2); IR (KBr): νmax (cm−1) 3404 and 3322 (NH and NH2), 1720, 1653 and 1609 (CO); 1H NMR (300 MHz, DMSO-d6) δ 4.64 (d, 2H, J = 6.0 Hz, CH2), 4.90 (s, 2H, NH2, D2O exchangable), 6.62 (t, 1H, J = 6.6 Hz, Ar-H), 6.79 (d, 1H, J = 7.5 Hz, Ar-H), 6.93 (t, 1H, J = 7.5 Hz, Ar-H), 7.18 (d, 1H, J = 6.0 Hz, Ar-H), 7.48–7.55 (m, 4H, Ar-H), 7.75 (t, 1H, J = 6.0 Hz, Ar-H), 7.98 (m, 2H, Ar-H), 8.90 (s, 1H, CH), 9.22 (t, 1H, J = 6.0 Hz, NH, D2O exchangable), 9.64 (s, 1H, NH, D2O exchangable); 13C NMR (75 MHz, DMSO-d6) δ 43.03, 116.63, 116.79, 118.95, 119.58, 123.70, 125.63, 126.93, 127.05, 127.63, 128.36, 129.93, 130.75, 133.75, 134.62, 143.00, 148.05, 154.39, 160.78, 161.91, 165.53; LCMS(ESI, m/z): (M+1)+ 414.0, [2 M + 1]+ 827.2; Anal. calcd. for C24H19N3O4: C, 69.72; H, 4.63; N, 10.16; found: C 69.78, H 4.69, N 10.06.

N-(4-((2-aminophenyl) carbamoyl) benzyl)-8-methoxy-2-oxo-2H-chromene-3-carboxamide (8b)

White solid; yield: 80%; mp: 213–215 °C; Rf = 0.65 (petroleum ether: ethyl acetate = 3:2); IR (KBr): νmax (cm−1) 3402 and 3342 (NH and NH2), 1701, 1659 and 1601 (CO); 1H NMR (300 MHz, DMSO-d6) δ 3.95 (s, 3H, OCH3), 4.58 (d, 2H, J = 6.0 Hz, CH2), 4.95 (s, 2H, NH2),6.64 (t, 1H, J = 6.0 Hz, Ar-H), 6.79 (d, 1H, J = 6.6 Hz, Ar-H), 6.97 (t, 1H, J = 6.6 Hz, Ar-H), 7.15 (d, 1H, J = 6.6 Hz, Ar-H), 7.30–7.50 (m, 5H, Ar-H), 7.95 (d, 2H, J = 6.6 Hz, Ar-H), 8.87 (s, 1H, CH), 9.23 (t, 2H, J = 6.0 Hz, NH), 9.66 (s, 1H, NH); 13C NMR (75 MHz, DMSO-d6) δ 43.04, 56.69, 116.59, 116.80, 119.51, 119.70, 121.66, 123.71, 125.58, 126.93, 127.04, 127.66, 128.36, 133.76, 142.99, 143.41, 143.72, 146.77, 148.27, 160.49, 161.88, 161.93, 165.59; LCMS(ESI, m/z): [M+1]+ 444.0, (2 M + 1)+ 887.3; Anal. calcd. for C25H21N3O5: C, 67.71; H, 4.77; N, 9.48; found: C 67.82, H 4.82, N 9.56.

N-(4-((2-aminophenyl) carbamoyl) benzyl)-8-ethoxy-2-oxo-2H-chromene-3-carboxamide (8c) White solid; yield: 87%; mp: 218–220 °C; Rf = 0.46 (petroleum ether: ethyl acetate = 3:2); IR (KBr): νmax (cm−1) 3400 and 3326 (NH and NH2), 1720, 1653 and 1613 (CO); 1H NMR (300 MHz, DMSO-d6) δ 1.43 (t, 3H, J = 6.9 Hz, CH3), 4.23 (q, 2H, J = 6.9 Hz, OCH2), 4.63 (s, 2H, J = 5.4 Hz, CH2), 4.92 (s, 2H, NH2), 6.61 (t, 1H, J = 6.9 Hz, Ar-H), 6.78 (d, 1H, J = 6.9 Hz, Ar-H), 7.00 (t, 1H, J = 6.9 Hz, Ar-H), 7.17 (d, 1H, J = 7.2 Hz, Ar-H), 7.33–7.54 (m, 5H, Ar-H), 7.95 (d, 2H, J = 8.1 Hz, Ar-H), 8.87 (s, 1H, CH), 9.24 (t, 1H, J = 6.0 Hz, NH), 9.66 (s, 1H, NH); 13C NMR (75 MHz, DMSO-d6) δ 15,04, 43.01, 65.00, 116.56, 116.74, 117.37, 119.60, 121.61, 123.65, 123.76, 125.58, 126.95, 127.15, 127.65, 128.36, 133.76, 143.00, 143.50, 143.76, 145.98, 148.35, 160.57, 161.90, 165.61; LCMS(ESI, m/z): 458.0 [M+1]+, 915.1 [2 M + 1]+; Anal. calcd. for C26H23N3O5: C, 68.41; H, 5.07; N, 9.19; found: C 68.29, H 5.01, N 9.05.

N-(4-((2-aminophenyl)carbamoyl)benzyl)-7-methoxy-2-oxo-2H-chromene-3- carboxamide (8d) Yellow solid; yield: 92%; mp: 212–214 °C; Rf = 0.53 (petroleum ether: ethyl acetate = 3:2); IR (KBr): νmax (cm−1) 3402 and 3342 (NH and NH2), 1701, 1659 and 1601 (CO); 1H NMR (300 MHz, DMSO-d6) δ 3.91 (s, 3H, OCH3), 4.62 (d, 2H, J = 5.4Hz, CH2), 4.94 (brs, 2H, NH2), 6.61 (t, 1H, J = 7.2Hz, Ar-H), 6.78 (d, 1H, J = 7.8Hz, Ar-H), 7.00 (t, 1H, J = 7.2Hz, Ar-H), 7.05 (m, 3H, Ar-H), 7.48 (d, 2H, J = 8.4Hz, Ar-H), 7.95 (m, 3H, Ar-H), 8.87 (s, 1H, CH), 9.19 (t, 1H, J = 5.4Hz, NH), 9.66 (s, 1H, NH); 13C NMR (75 MHz, DMSO-d6) δ 42.85, 56.75, 100.78, 112.62, 114.14, 115.32, 116.59, 116.79, 123.68, 126.95, 127.07, 127.61, 128.36, 132.07, 133.70, 143.12, 143.42, 148.48, 156.70, 161.26, 162.19, 164.94, 165.53; LCMS(ESI, m/z): 444.0 [M+1]+, 887.3 [2 M + 1]+; Anal. calcd. for C25H21N3O5: C, 67.71; H, 4.77; N, 9.48; found: C 67.86, H 4.63, N 9.59.

Biological Activity

Anticancer activity has been carried out for the synthesized compounds using MDAMB (breast cancer) cell line by MTT Assay. Cell proliferation and viability was determined by 3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide (MTT) assay [60]. The pale yellow colored tetrazolium salt (MTT) reduces to a dark blue water-insoluble formazan by metabolically active cells and that is measured quantitatively after soluble in DMSO. The absorbance of the soluble formazan is directly proportional to the number of viable cells. Cells were seeded at a density of 1×104 cells in 200 µL of medium per well of 96-well plate. The 96-well microtiter plates were incubated for 24 h prior to addition of the experimental compounds. Cells were treated with vehicle alone (0.4% DMSO) or compounds (drugs were dissolved in DMSO previously) at different concentrations (1, 10 and 25µM) of test compounds for 48 hours. The assay was completed with the addition of MTT (5 %, 10µL) and incubated for 60 min at 37°C. The supernatant was aspirated and plates were air dried and the MTT-formazan crystals dissolved in 100 µL of DMSO. The optical density (O.D.) was measured at 560 nm using TECAN multimode reader. The

growth percentage of each treated well of 96 well plate have been calculated based on test wells relative to control wells [61].

The cell growth inhibition was calculated by generating dose response curves as a plot of the percentage of surviving cells versus drug concentration. Anti-proliferative activity of the cancer cells to the test compounds was expressed in terms of IC50value, which defines as a concentration of compound that produced 50% absorbance reduction relative to control.

Results:

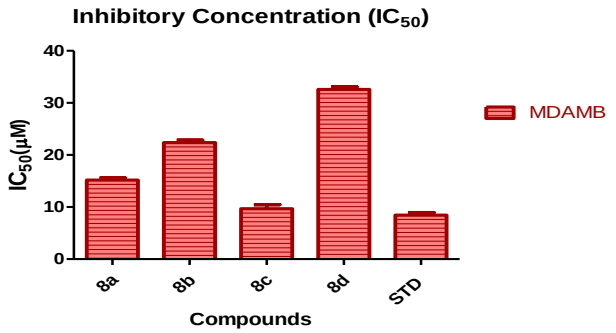
The compounds 8a and 8c showed strong potent activity with IC50 values around 9.68 and 15.2 µg/ml against MDAMB cell lines where as 8b and 8d were showed poor inhibition activity.

Table 5:IC50 (µM) for the synthesized compounds and (STD) on the cells MDAMB (breast cancer) determined by MTT assay:

Compound code	MDAMB (breast cancer)
8a	15.2 ± 0.39
8b	22.39 ± 0.47
8c	9.68 ± 0.78
8d	32.57 ± 0.53
STD	8.45 ± 0.49

STD= Fluorouracil

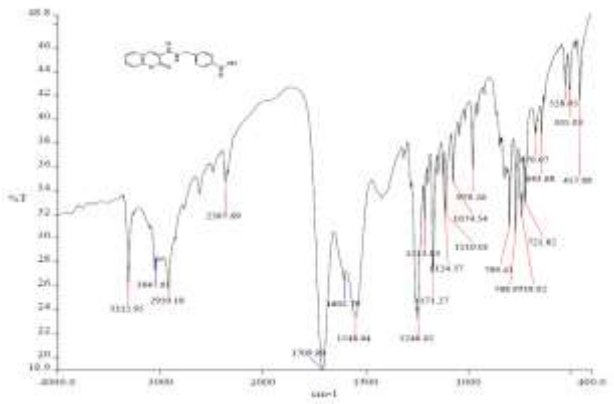
Data represented as mean ± standard deviation

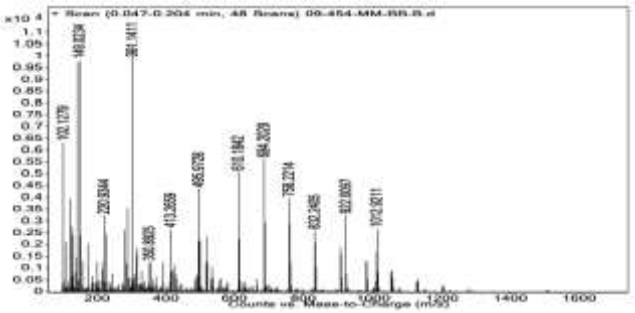


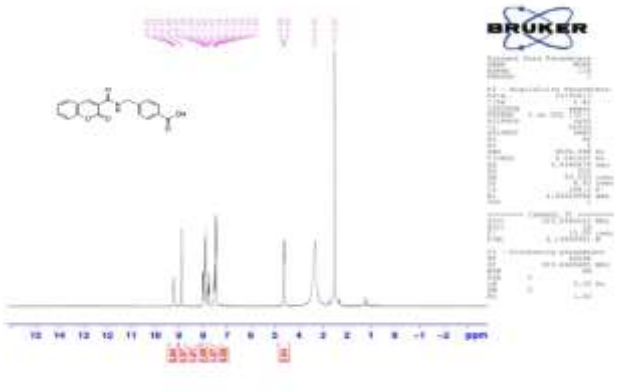
Graph 1: Comparison of IC50 (µM) for the synthesized compounds and (STD) on the MDAMB cells

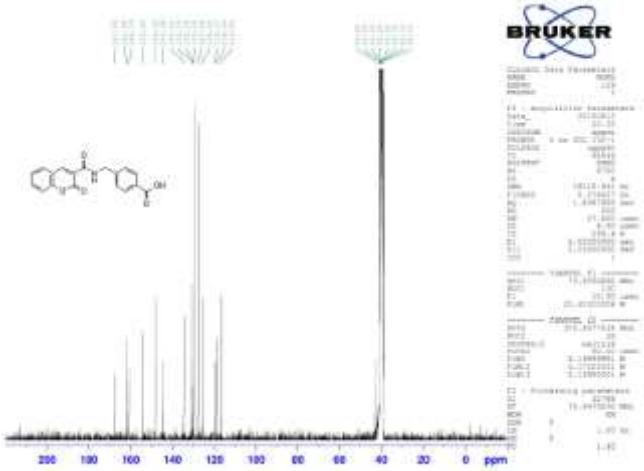
Conclusion

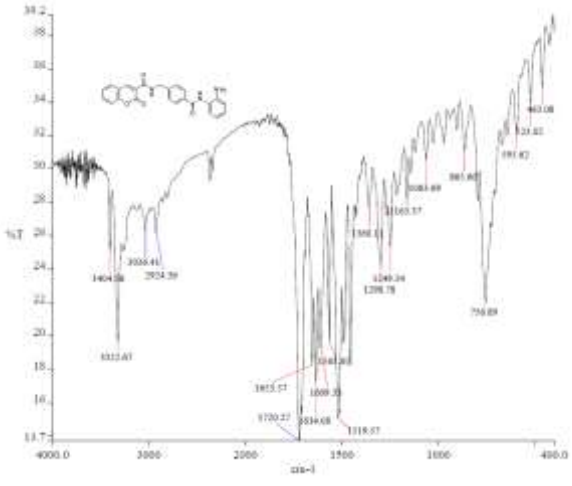
Thus the coumarin derivatives 8a and 8c serve as good leads for further studies to develop potent cytotoxic agents.

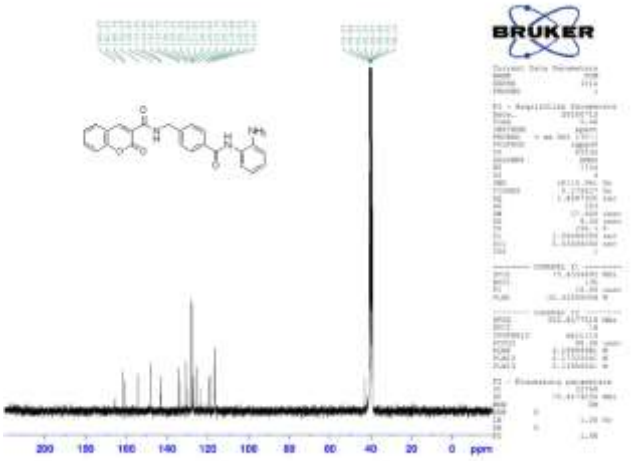


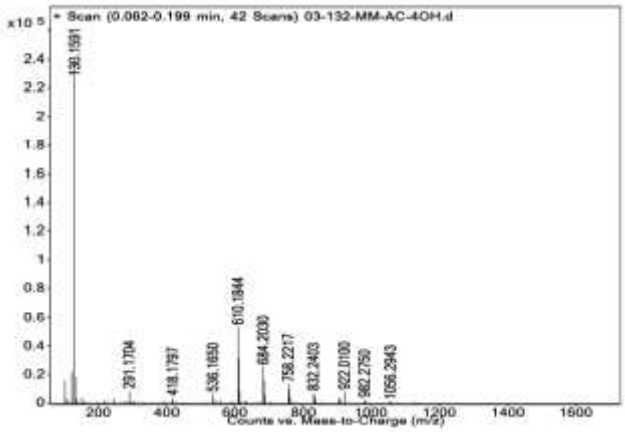


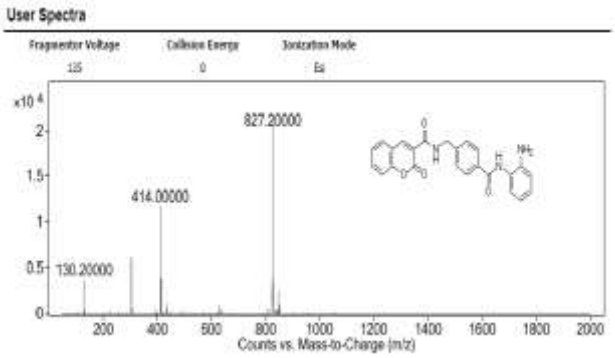


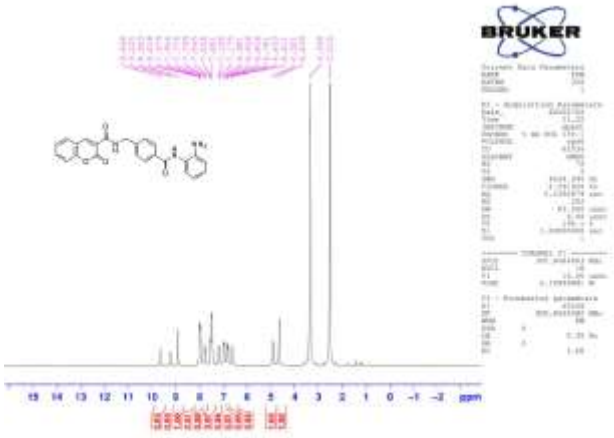


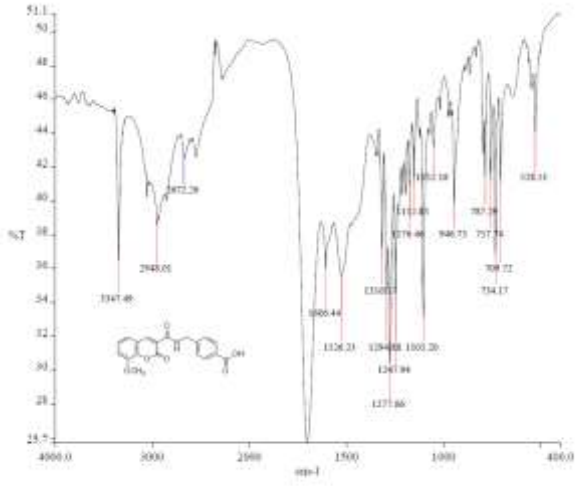












CONCLUSION

An effective review of literature had been done on coumarines; synthesized two sets of coumarines and well characterize by IR, 1H & 13C NMR, Mass Spectra. 8a and 8c were found to be potential towards anti-cancer activity because of coumarine with an extended chromophore by amide linkage. We hope our study would be an expansion of anti-cancer activity of coumarines.

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