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Novel Anthracene-9-Sulfonyl Derivatives As Anticancer Agents: Synthesis And In Vitro Biological Evaluation

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Abstract

In this study, a new series of anthracene-9-sulfonyl derivatives incorporated with different heterocyclic moieties were synthesized and screened for their *in vitro* anticancer activity against colon carcinoma cell lines (HCT-116), hepatic carcinoma cell lines (HepG 2) and breast carcinoma cell lines (MCF-7). Among them, compound 4-acetylphenyl anthracene-9-sulfonate (**8**) showed selective high cytotoxic activity over colon carcinoma cell lines (HCT-116), also compounds 2-(anthracen-9-ylsulfonyl)malononitrile (**7**), *N*-(4-fluorophenyl)anthracene-9-sulfonamide (**5b**) and *N*-((1*H*-benzo[*d*]imidazol-2-yl)methyl)anthracene-9-sulfonamide (**10**) showed the significant selective cytotoxic effect over breast carcinoma cell lines (MCF-7). All the compounds are subjected to explore their safety on normal human skin cell lines (BJ-1), the results revealed that all the compounds are safe and have insignificant weak cytotoxicity over normal human cells.

Keywords: Anthracene-9-sulfonyl. Anticancer. HCT-116 cells. HepG 2 cells. MCF-7 cells.

1. Introduction

Anthracene is the simplest tricyclic aromatic compound, consisting of three fused benzene rings. Anthracene exhibit promising biological activities [1-4] .Anthracene derivatives have a broad range of biological activities for example, anti-inflammatory [5], antibacterial [6-9] ,antifungal [9] and anticancer activity [10-20]. Also anthracene was reported to be active against specific skin ailments [21]. Three-ring system of the anthracene has potential for overlapping with the DNA base pairs.[22]. Many-sided chemistry of anthracene provides a suitable route to synthesis a number of closely related derivatives [23]. In the present study, we studied the anticancer activity of synthesized compounds (1-13) against colon carcinoma cell lines (HCT-116), hepatic carcinoma cell lines (HepG 2) and breast carcinoma cell lines (MCF-7).

Experimental Section

Chemistry

All melting points are uncorrected and were taken in open capillary tubes using Electrothermal apparatus 9100. Elemental microanalyses were carried out at Microanalytical Unit, Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt, using VarioElementar and were found within ±0.4% of the theoretical values. Infrared spectra were recorded on

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a FT/IR- 4100 Jasco-Japan, Fourier transform, Infrared spectrometer at cm^{-1} scale using KBr disc technique at Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt. ^1H NMR and ^{13}C NMR spectra were determined by using a JEOL AS-500 NMR spectrometer at Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt. Varian Gemini200-Oxford 300 MHz and Merury Plus-Oxford 400 MHz at Ministry of defense, Chemical Warfare Department, The Main Chemical Warfare Laboratories, Cairo, Egypt. Chemical shifts were expressed in δ (ppm) downfield from tetramethylsilane as an internal standard. The mass spectra were measured with a GC MSQp1000EX Shimadzu, Cairo University, Cairo, Egypt, and with a Finnigan MAT SSQ-7000 mass spectrometer at Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt. Follow up of the reactions and checking the purity of the compounds were made by thin layer chromatography on silica gel-precoated aluminium sheets (Type 60, F 254, Merck, Darmstadt, Germany) using chloroform/methanol (20:2, v/v), and the spots were detected by exposure to UV lamp at λ254 nanometer for few seconds and by iodine vapor.

(Anthracen-9-ylsulfonyl)glycine (2)

To a mixture of 1 (2.76 g, 0.01 mol) and glycine (0.75 g, 0.01 mol) in dioxane (10 mL), aqueous saturated sodium carbonate was added drop wise until pH=7.5-8. After stirring for 0.5 h, the mixture was acidified with 1N hydrochloric acid and the precipitated solid was filtered and washed with water and recrystallized from DMF to give 2.

Yield: 85%; M.p. 130-132°C. IR spectrum (KBr, ν, cm^{-1}): 3407 (OH), 3044 (NH), 1679 (C=O). ^1H NMR (DMSO-d_6) δ: 4.6 (s, 2H, CH_2), 7.1-8.1 (m, 9H, Ar-H), 9.3 (s, 1H, 1NH, D_2O exchangeable), 13.0 (s, 1H, 1OH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 20.5, 20.5, 48.2, 124.5, 124.7, 124.7, 126.1, 126.1, 126.1, 126.1, 126.8, 126.8, 131.3, 131.3, 132.6, 170.3. MS: m/z = 315 (10%) ($M^{\cdot+}$); Anal. Calcd. For $C_{16}H_{13}NO_4S$ (315.34): C, 60.94; H, 4.16; N, 4.44 %; found: C, 58.54; H, 5.13; N, 3.99%.

1-(Anthracen-9-ylsulfonyl)-2-thioxoimidazolidin-4-one (3)

A mixture of 2 (6.3 g, 0.02 mol), acetic anhydride (6.1 mL, 0.06 mol), anhydrous pyridine (15 mL) and ammonium thiocyanate (2.2 g, 0.03 mol) was heated to 110 °C for 1 h. The volatiles were removed and the residue was suspended in water (100 mL) and stirred for 1 h. The soild formed was filtered, washed with water and recrystallized from DMF/ H_2O to give 3.

Yield: 70%; M.p. 255-257°C. IR spectrum (KBr, ν, cm^{-1}): 3222 (NH), 1691 (C=O). ^1H NMR (DMSO-d_6) δ: 4.2 (s, 2H, CH_2), 7.3-7.9 (m, 9H, Ar-H), 12.0 (s, 1H, 1NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 20.1, 20.3, 48.5, 124.2, 124.6, 124.7, 124.9, 126.2, 126.3, 126.4, 127.1, 127.5, 131.2, 132.6, 137.5, 174.5, 175.6. MS: m/z = 356 (9%) ($M^{\cdot+}$); Anal. Calcd. For $C_{17}H_{12}N_2O_3S_2$ (356.41): C, 57.29; H, 3.39; N, 7.86%; found: C, 57.03; H, 3.15; N, 7.61%.

(Anthracen-9-ylsulfonyl)glycinoyl chloride (4)

A mixture of compound 2 (0.31 g, 0.001 mol) and an excess of thionyl chloride (10 mL) was refluxed for 1 h, then the excess thionyl chloride was evaporated. The solid obtained was collected, washed several times with dry benzene and recrystallized from acetone to give 4.

Yield: 60%; M.p. > 300°C. IR spectrum (KBr, ν, cm^{-1}): 3223 (NH), 1689 (C=O). ^1H NMR (DMSO-d_6) δ: 4.3 (s, 2H, CH_2), 7.5-8.6 (m, 9H, Ar-H), 9.3 (s, 1H, 1NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 21.1, 21.3, 45.6, 123.7, 123.7, 125.9, 125.8, 125.6, 126.5, 126.8, 129.1, 129.3, 131.3, 131.4, 133.0, 162.5. MS: m/z = 333 (4%) ($M^{\cdot+}$), m/z = 335 (6%) ($M^{\cdot+}$+2); Anal. Calcd. For $C_{16}H_{12}ClNO_3S$ (333.79): C, 57.57; H, 3.62; N, 4.20%; found: C, 57.45; H, 3.35; N, 5.13%.

N-(substituted)anthracene-9-sulfonamide 5(a, b)

A mixture of 1 (2.76 g, 0.01 mol) and derivatives of amines namely: *4-aminoantipyrine* and *4-fluoroaniline* (0.01 mol) in absolute ethanol (20 mL) containing triethylamine (1 mL) was stirred for 3 h at room temperature. The formed precipitate was filtered off, washed with water, dried and recrystallized from ethanol-dioxane mixture to give 5(a, b).

N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)anthracene-9-sulfonamide (5a).

Yield: 80%; M.p. 159-161°C. IR spectrum (KBr, ν, cm^{-1}): 3185 (NH), 1692 (C=O). ^1H NMR (DMSO-d_6) δ: 2.2 (s, 3H, CH_3), 3.2 (s, 3H, CH_3 of N-CH_3), 7.1-8.5 (m, 14H, Ar-H), 9.1 (s, 1H, 1NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 13.3, 33.9, 114.5, 122.4, 123.4, 123.9, 124.2, 124.5, 124.6, 124.8, 127.3, 127.5, 127.6, 127.8, 128.2, 128.6, 129.1, 129.2 , 129.7 , 130.9, 132.1, 132.6 , 133.3 , 136.5, 161.6. MS: m/z = 443 (20%) ($M^{\cdot+}$); Anal. Calcd. For $C_{25}H_{21}N_3O_3S$ (443.52): C, 67.70; H, 4.77; N, 9.47%; found: C, 67.52; H, 4.26; N, 9.24%.

N-(4-fluorophenyl)anthracene-9-sulfonamide (5b).
Yield: 70%; M.p. 244-246°C. IR spectrum (KBr, ν, cm^{-1}): 3222 (NH). ^{1}H NMR (DMSO-d_6) δ: 6.8-7.9 (m, 13H, Ar-H), 10.2 (s, 1H, 1NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 114.3, 114.9, 117.2, 117.6, 123.2, 123.4, 123.8, 123.9, 126.4, 126.5, 126.6, 126.8, 127.3, 127.8, 129.8, 132.0, 132.3, 133.9, 136.8, 156.5. MS: m/z = 351 (89%) ($M^{\cdot+}$); Anal. Calcd. For $C_{20}H_{14}FNO_2S$ (351.40): C, 68.36; H, 4.02; N, 3.99%; found: C, 68.26; H, 3.85; N, 3.70%.

Anthracene-9-sulfonohydrazide (6)
A mixture of 1 (2.76 g, 0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (30 mL) was refluxed for 8 h. The solid formed after cooling was filtered off and recrystallized from DMF to give 6.
Yield: 65%; M.p. 213-215°C. IR spectrum (KBr, ν, cm^{-1}): 3405, 3286 (NH_2), 3185 (NH). ^{1}H NMR (DMSO-d_6) δ: 3.7 (s, 2H, NH_2, D_2O exchangeable), 6.9-7.9 (m, 9H, Ar-H), 11.2 (s, 1H, 1NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 20.2, 20.3, 125.1, 125.8, 125.7, 125.6, 125.4, 127.6, 127.5, 129.8, 129.8, 131.8, 131.9, 134.2. MS: m/z = 272 (19%) ($M^{\cdot+}$); Anal. Calcd. For $C_{14}H_{12}N_2O_2S$ (272.32): C, 61.75; H, 4.44; N, 10.29%; found: C, 61.50; H, 5.10; N, 10.08%.

2-(Anthracen-9-ylsulfonyl)malononitrile (7)
A mixture of 1 (2.76 g, 0.01 mol) and malononitrile (0.6 g, 0.01 mol) in dry ethanol (20 mL) containing triethylamine (1 mL) was refluxed for 3 h. The solid formed was filtered off, washed with water, dried and recrystallized from DMF/ EtOH to give 7.
Yield: 85%; M.p. > 300°C. IR spectrum (KBr, ν, cm^{-1}): 2261, 2209 (2C≡N). ^{1}H NMR (DMSO-d_6) δ: 5.1 (s, 1H, CH), 7.1-8.1 (m, 9H, Ar-H). ^{13}C NMR (DMSO-d_6): δ 55.2, 114.5, 114.9, 124.2, 124.3, 124.6, 124.8, 127.2, 127.3, 127.5, 127.6, 128.5, 128.9, 130.6, 131.5, 131.6, 134.9. MS: m/z = 306 (14%) ($M^{\cdot+}$); Anal. Calcd. For $C_{17}H_{10}N_2O_2S$ (306.34): C, 66.65; H, 3.29; N, 9.14%; found: C, 66.48; H, 3.13; N, 9.05%.

4-Acetylphenyl anthracene-9-sulfonate (8)
A mixture of 1 (2.76 g, 0.01 mol) and p-hydroxyacetophenone (1.36 g, 0.01 mol) in pyridine (40 mL) was heated under reflux for 5 h. The mixture was poured into ice water containing few drops of HCL. The solid product was filtered and recrystallized from ethanol to give 8. Yield: 75%; M.p. 243-245°C. IR spectrum (KBr, ν, cm^{-1}): 1663 (C=O). ^{1}H NMR (DMSO-d_6) δ: 2.6 (s, 3H, CH_3), 7.1-8.1 (m, 13H, Ar-H). ^{13}C NMR (DMSO-d_6): δ 27.6, 126.2, 126.3, 126.5, 126.8, 128.3, 128.3, 128.4, 128.6, 128.7, 128.9, 129.2, 129.5, 129.6, 129.7, 130.6, 133.4, 133.6, 137.8, 142.3, 147.3, 198.1. MS: m/z = 376 (18%) ($M^{\cdot+}$); Anal. Calcd. For $C_{22}H_{16}O_4S$ (376.43): C, 70.20; H, 4.28%; found: C, 69.89; H, 4.14%.

N'-isonicotinoylanthracene-9-sulfonohydrazide (9)
A mixture of 1 (2.76 g, 0.01 mol) and isonicotinic hydrazide (1.37 g, 0.01 mol) in absolute ethanol (20 mL) containing triethylamine (1 mL) was stirred for 3 h at room temperature. The formed precipitate was filtered, washed with water, dried and recrystallized from DMF to give 9. Yield: 85%; M.p. 164-166°C. IR spectrum (KBr, ν, cm^{-1}): 3100, 3045 (2NH), 1661 (C=O). ^{1}H NMR (DMSO-d_6) δ: 6.8-7.9 (m, 13H, Ar-H), 9.1, 11.3 (2s, 2H, 2NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 121.5, 121.6, 124.3, 124.4, 124.5, 124.6, 127.2, 127.3, 127.5, 127.6, 127.8, 127.9, 129.1, 131.3, 131.5, 136.5, 139.3, 149.7, 149.8, 165.8. MS: m/z = 377 (8%) ($M^{\cdot+}$); Anal. Calcd. For $C_{20}H_{15}N_3O_3S$ (377.42): C, 63.65; H, 4.01; N, 11.13%; found: C, 63.48; H, 4.65; N, 10.89%.

N-((1H-benzo[d]imidazol-2-yl)methyl)anthracene-9-sulfonamide (10)
Solution of 4 (0.33 g, 0.001 mol) in dry benzene (20 mL) and o-phenylenediamine (0.10 g, 0.001 mol) were refluxed for 30 min. The solid obtained was filtered and washed with cold water and then recrystallized from ethanol-dioxane mixture to give 10.
Yield: 85%; M.p. 198-200°C. IR spectrum (KBr, ν, cm^{-1}): 3288, 3200 (2NH). ^{1}H NMR (DMSO-d_6) δ: 4.1 (s, 2H, CH_2), 6.9-8.1 (m, 13H, Ar-H), 10.5, 12.1 (2s, 2H, 2NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 43.2, 116.3, 116.5, 122.2, 122.6, 124.2, 124.3, 124.5, 124.6, 127.3, 127.4, 127.6, 127.8, 127.9, 128.0, 129.3, 131.6, 131.7, 136.5, 137.4, 137.8, 142.5. MS: m/z = 387 (8%) ($M^{\cdot+}$); Anal. Calcd. For $C_{22}H_{17}N_3O_2S$ (387.46): C, 68.20; H, 4.42; N, 10.85%; found: C, 68.09; H, 4.20; N, 10.74%.

N,N'-(1,4-phenylene)bis(2-(anthracene-9-sulfonamido)acetamide) (11)
Solution of 4 (0.66 g, 0.002 mol) in dry benzene (20 mL) and benzene-1,4-diamine (0.10 g, 0.001 mol) were refluxed for 30 min. The solid obtained was filtered and washed with cold water then recrystallized from DMF to give 11.
Yield: 70%; M.p. 105-107°C. IR spectrum (KBr, ν, cm^{-1}): 3225, 3200, 3190, 3150 (4NH), 1687, 1675 (2C=O). ^{1}H NMR (DMSO-d_6) δ: 4.1 (s, 4H, $2CH_2$), 7.1-8.9 (m, 22H, Ar-H), 9.5, 10.0 (2s, 2H, 2NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 43.5, 44.1, 122.3, 122.4, 122.5, 122.7, 123.3, 123.4, 123.5,

123.6, 123.7, 123.8, 123.9, 124.1, 126.1, 126.2, 126.3, 126.3, 126.4, 126.5, 126.5, 126.7, 128.1, 128.4, 128.4, 128.6, 129.7, 129.8, 133.2, 133.6, 132.7, 132.7, 134.2, 134.2, 136.8, 136.9, 167.5, 167.5. MS: m/z = 702 (29%) ($M^{\cdot+}$); Anal. Calcd. For $C_{38}H_{30}N_4O_6S_2$ (702.80): C, 64.94; H, 4.30; N, 7.97%; found: C, 64.82; H, 4.17; N, 7.83%.

N,N'-([1,1'-biphenyl]-4,4'-diyl)bis(2-(anthracene-9-sulfonamido)acetamide) (12)

Solution of 4 (0.66 g, 0.002 mol) in dry benzene (20 mL) and benzidine (0.18 g, 0.001 mol) were refluxed for 30 min. The solid obtained was filtered and washed with cold water and then recrystallized from DMF to give 12.

Yield: 65%; M.p. 209-211°C. IR spectrum (KBr, ν, cm^{-1}): 3083, 3033, 3000, 2920 (4NH), 1691, 1687 (2C=O). ^{1}H NMR (DMSO-d_6) δ: 4.3 (s, 4H, $2CH_2$), 6.9-8.4 (m, 26H, Ar-H), 8.9, 11.0 (2s, 2H, 2NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 44.4 , 44.5 , 118.2, 118.3, 118.3, 118.5, 124.2, 124.3, 124.5, 124.5, 124.6, 124.6, 124.7, 124.9, 127.1, 127.1, 127.3, 127.4, 127.4, 127.5, 127.6, 127.6, 127.7, 127.8, 127.8, 127.8, 127.9, 127.9, 128.1, 128.1, 129.4, 129.6 , 131.5, 131.6, 131.7, 131.7, 135.6, 135.7, 135.8, 135.8, 138.2, 139.2, 169.1, 169.2. MS: m/z = 779 (35%) ($M^{\cdot+}$+1); Anal. Calcd. For $C_{44}H_{34}N_4O_6S_2$ (778.90): C, 67.85; H, 4.40; N, 7.19%; found: C, 67.74; H, 4.28; N, 7.09%.

2-(Anthracene-9-sulfonamido)-N-(4-sulfamoylphenyl)acetamide (13)

Solution of 4 (0.33 g, 0.001 mol) in dry benzene (20 mL) and 4-aminobenzenesulfonamide (0.17 g, 0.001 mol) were refluxed for 30 min. The solid obtained was filtered and washed with cold water then recrystallized from dioxane to give 13.

Yield: 70%; M.p. 210-212°C. IR spectrum (KBr, ν, cm^{-1}): 3405, 3286 (NH_2), 3185, 3100 (2NH), 1691 (C=O). ^{1}H NMR (DMSO-d_6) δ: 4.1 (s, 2H, CH_2), 6.8 (s, 2H, NH_2, D_2O exchangeable), 6.9-7.8 (m, 13H, Ar-H), 9.2, 10.1 (2s, 2H, 2NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 45.2, 118.2, 118.6, 124.2, 124.3, 124.6, 124.7, 127.2, 127.4, 127.6, 127.8, 128.1, 128.8, 129.3, 129.4, 129.9, 133.2, 133.5, 135.6, 137.2, 141.5, 169.3. MS: m/z = 469 (26%) ($M^{\cdot+}$); Anal. Calcd. For $C_{22}H_{19}N_3O_5S_2$ (469.53): C, 56.28; H, 4.08; N, 8.95%; found: C, 56.08; H, 3.99; N, 8.65%.

Pharmacology (Cell lines):

Colon carcinoma cell lines (HCT-116), hepatic carcinoma cell lines (HepG 2), breast carcinoma cell lines (MCF-7) and BJ-1 "A telomerase-immortalized normal foreskin fibroblast cell line were obtained from Karolinska Center, Department of Oncology and Pathology, Karolinska Institute and Hospital, Stockholm, Sweden.

Cell viability assay:

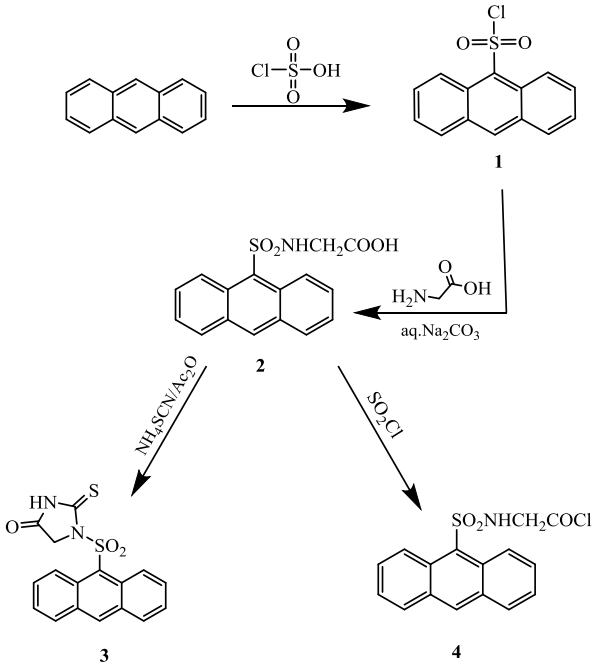
Procedure was done according to [24] , the cells were seeded at concentration of $10x10^3$ cells per well in case of HepG 2 and MCF-7 , $20x10^3$ cells/well in case of HCT-116 cell lines and 40 $x10^3$ cells/well in a fresh complete growth medium in case of BJ-1 using 96-well microtiter plastic plates at 37 ºC for 24 hours under 5% CO_2 in a water jacketed carbon dioxide incubator. DMSO was used as negative control, Doxorubicin as positive control. After 48 hours' incubation, the medium was aspirated and then MTT salt were added to each well and incubated for further four hours at 37 ºC under 5% CO_2. To stop the reaction and dissolve the formed crystals, 10% sodium dodecyl sulphate (SDS) was added to each well and incubated overnight at 37 ºC. The absorbance was measured using a microplate multi-well reader at 595 nm and a reference wave length of 690 nm. Cell viability was assessed according to the mitochondrial- dependent reduction of yellow MTT (3-(4, 5-dimethylthiazol-2-yl)-2, 5- diphenyl tetrazolium bromide) to purple formazan.

Results and discussion

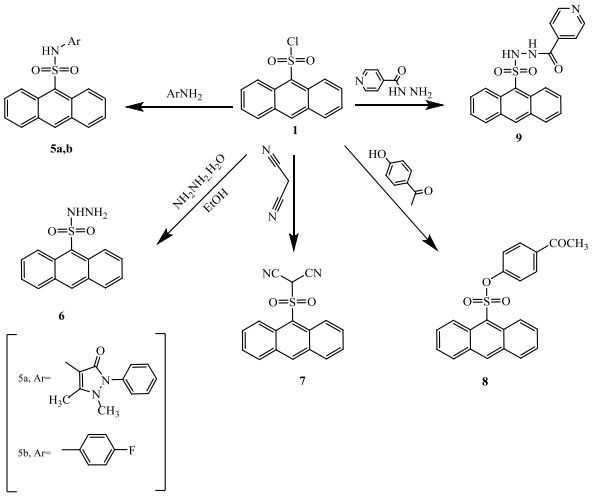
Chemistry

Anthracene-9-sulfonyl chloride **1** synthesized as the reported method [25]. Acylation of glycine with compound **1** in the presence of aqueous saturated sodium carbonate gave Compound **2** according to the method [26]. (**Scheme 1**). ^{1}H NMR for compound **2** confirmed the proposed structure due to the appearance of a singlet at 9.3 and 13.0 due to NH and OH in compound **2**, respectively. Treatment of the latter compound with ammonium thiocyanate and acetic anhydride in the presence of anhydrous pyridine led to the formation of compound **3** according to the method [26]. Also compound **2** reacted with acetic anhydride and thionyl chloride to give compound **4** as the reported method [27]. (**Scheme 1**). Characteristic IR bands provide significant indication for the formation of compounds **3** and **4**, for example the disappearance of (OH)

indicates the formation of compounds **3** and **4**. Compounds **(5a, b), 6, 7** and **9** prepared by the reaction of compound **1** with *4-aminoantipyrine*, *4-fluoroaniline*, hydrazene hydrate, malononitrile and **isonicotinic hydrazide**, respectively, according to the method [28]. (**Scheme 2**).

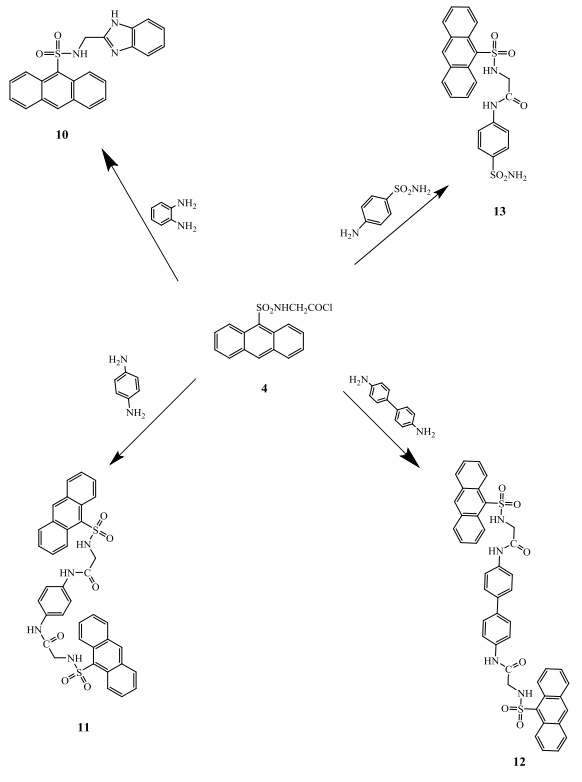


Scheme 1. Synthesis of anthracene-9-sulfonyl derivatives **1-4**



Scheme 2. Synthesis of anthracene-9-sulfonyl derivatives 5-**9**

Also compound **8** prepared by the reaction of compound **1** with p-hydroxyacetophenone as the reported method. [29]. (**Scheme 2**). ^{1}H NMR for compounds **(5a, b)** and **6** confirmed the proposed structure due to the appearance of a singlet at 9.1, 10.2 and 11.2 due to NH, respectively. IR spectrum of compound **7** showed band at 2261, 2209 due to the presence of (2C≡N). Also the appearance of the characteristic band at 1663 and 1661 due to the presence of (C=O) in compounds **8** and **9**, respectively. Condensation of **4** with *o*-phenylenediamines gave compound **10** as reported method [27] where 2NH proton resonated at 10.5 and 12.1 ppm. (**Scheme 3**). Treatment of acid chloride **4** with benzene-1,4-diamine and/or benzidine gave the corresponding derivatives **11** and **12** according to the method. [27]. (**Scheme 3**).



Scheme 3. Synthesis of anthracene-9-sulfonyl derivatives **10-13**

Confirmation of the synthesized compounds **11** and **12** was done using ^{1}H NMR spectroscopic data. For example appearance of a multiplet at 7.1-8.9 and 6.9-8.4 due to 22H and 26H of Ar-H in compounds **11** and **12**, respectively. When acid chloride **4** was treated with sulfanilamide, it gave the corresponding

Table 1: *In vitro* cytotoxicity percent of 14 compounds, at concentration 100 μg/ml. the result is an average of 3 replicate.

Compounds	HepG2	HCT-116	MCF-7
1	3.8 %	34.2%	64.1%
2	3.5%	31.8%	45.9%
3	12.9%	53.3%	68.8%
4	9.6%	8.3%	59.7%
5a	4.8%	23.9%	63.4%
5b	29%	25%	89.8%
6	10.7%	43.2%	37.5%
7	3.5%	34.3%	93.4%
8	3.5%	72%	43.4%
9	40.7%	36.1%	46.2%
10	6.51%	40.8%	85.6%
11	17.9%	2.6%	15.7%
12	20.8%	7.9%	39.3%
13	5.6%	39%	57.7%
Doxorubicin	99.5%	98%	99%

sulfanilamide **13** as reported method [27]. (**Scheme 3**). Characteristic IR bands provide significant indication for the formation of compound, the appearance of the characteristic band at 3405, 3286 due to the presence of (NH_2) in compound **13**.

Pharmacology

According to our results, all the compounds gave weak cytotoxic effects on the hepatic cell lines (HepG 2) ranged from 3.5-40.7%. While compound **8** showed selective high cytotoxic activity (72%) over colon carcinoma cell lines (HCT-116), while the rest of the compounds had weak to moderate activity ranged from 2.6- 53.3%. For breast carcinoma cell lines (MCF-7), compounds **7**, **5b**, and **10** showed the significant selective cytotoxic effect with 93.4, 89.8 and 85.6% respectively as shown in **Table 1** & **Figure 1**. All the compounds are subjected to explore their safety on normal human skin cell lines (BJ-1), the results revealed that all the compounds (**1-13**) are safe and have insignificant weak cytotoxicity over normal human cells. Compounds **7**, **5b**, **10**, and **8** which possessed high cytotoxic activity over 70% were further screened at different concentrations at their corresponding cell line ranged from (100-12.5 ppm) to calculate their LC_{50} values as shown in **Figure 2** & **3**.

From **Figures 2** & **3**, compounds **7**, **5b**, and **10** showed significant potentiality in a dose-dependent manner with LC_{50} 34.7±0.4, 49.6±0.7 and 20±.06, respectively. Where, Doxorubicin LC_{50} on MCF-7 = 26.1(±1.3). While compound **8** showed LC_{50} 68±1.2 on colon HCT-116 cell lines **Figure 3.** While, Doxorubicin LC_{50} = 37.6(±1.5).

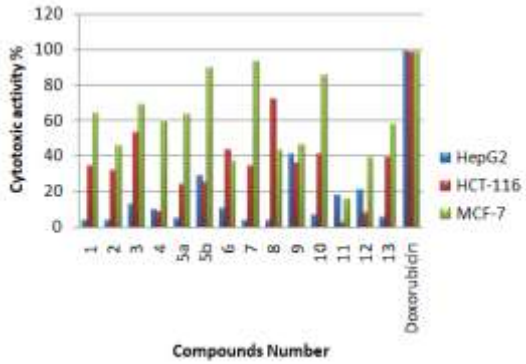


Fig 1: Anticancer activity of novel compounds

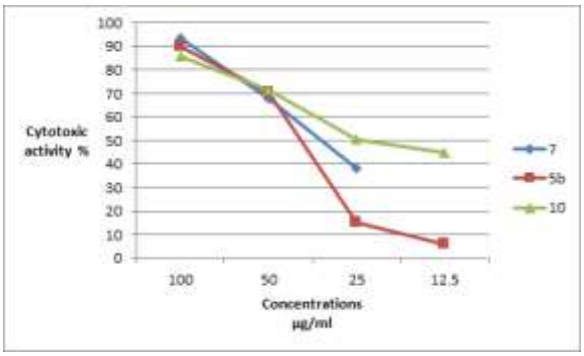


Fig 2: Compounds **7**, **5b** and **10** cytotoxic activities over breast carcinoma cell lines (MCF-7) at different concentrations, the result is an average of 3 replicate.

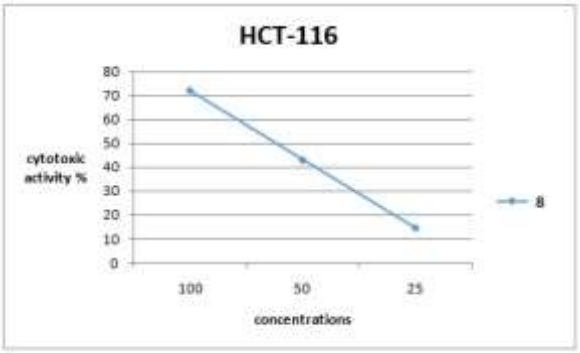


Fig 3: Compound **8** cytotoxic activity over colon carcinoma cell lines (HCT-116) at different concentrations, the result is an average of 3 replicate.

Conclusion

The purpose of the present work is the synthesis of new anthracene-9-sulfonyl derivatives, which are projected to show potent anticancer activity. Thus, the parent anthracene-9-sulfonyl chloride **1** was subjected to a series of various reactions to get the target compounds. *In vitro* cytotoxic evaluation of all the novel anthracene-9-sulfonyl derivatives against colon carcinoma cell lines (HCT-116), hepatic carcinoma cell lines (HepG 2) and breast carcinoma cell lines (MCF-7). The activity profile revealed that the compounds containing p-acetyl phenyl-sulfonate, cyano group, p-flurophenyl and benzimidazole ring have exerted a highly potent activity.

Conflict of interests: The authors declare that they have no conflict of interest

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