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Research Article

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Synthesis, Characterization and Biological Evaluation of 9-Anthracenyl Chalcones as Anti-Cancer Agents

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ABSTRACT

The universal incidence and tremendous mortality ratio of cancer makes it a serious health affair especially in cancers progressive with inflammation. In view of this menace, consequential efforts are continuing to characterize new drugs or agents for therapeutic intervention against cancer. As a follow through, herein our study a series of 9-Anthracenyl chalcone derivatives (A1–A16) were designed, synthesized, characterized and evaluated for their anti-cancer activity against four human cancer cell lines HeLa, MIAPACA, U-87 and SIHA using an SRB assay. Among them we found that four of the compounds A7, A8, A10 and A11 have shown marked anti-cancer activity against HeLa, U-87, MIAPACA and SIHA with GI_{50} values of 5.18 µM, 4.04 µM, 5.31 µM and 4.02 µM respectively.

Keywords: Synthesis; Anthracenes; Chalcones; Anti-cancer activity

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INTRODUCTION

Cancer is a progressive fatal disease in that exemplified through a continual, aberrant along with uncontrolled cell proliferation, in the act of constant cellular deformity which goes on to the progeny leading to expansive masses that abort the neighboring normal tissue, as follows attacking the underlying organs. Being the second prevailing and the most potentially life threatening global disease, it bring about 8.2 million human deaths annually with an increasing incidence of at least 14.1 million new cases that may go up to 13 million deaths and 21.4 million new cases by 2030, thus enduring a great socioeconomic impact on humanity [1-5]. Many cancers are complex and heterogeneous emerge through a network of collective variations of elements ranging from tumor intrinsic genetic factors to extrinsic tumor microenvironmental factors. Abounding reports suggest that genetic alterations, epigenetic variations, diet, lifestyle, and chronic inflammation have the possibility for cancer influence. And also the wide acceptance that chronic inflammation due to infectious or immune diseases mark up with cancer risk in a variety of malignancies such as esophageal, gastric, hepatic, pancreatic and colorectal cancer [6,7]. Of particular, the inflammatory cells and the biological intermediators of inflammation are essential elements of all tumors microenvironment. Despite, the unresolved inflammation is able to decline the precised control in the immune response which disturbs the cellular microenvironment, preceded by cancer-related gene alteration, and posttranslational modification in key cell signaling proteins involved in cell cycle, DNA repair and apoptosis [8-11]. Importantly, a key inflammatory mediator deregulated or elevately expressed in many cancers is cyclooxygenase-2 (COX-2). The activated COX-2 associated pathway is important in cancer as they initiate many key steps involved in progression of the cancer including cell division, inhibition of cell death, angiogenesis, and metastasis. Also the epidemiological, clinical, and preclinical studies in the recent decades put forward that over-expression of this

inducible enzyme and its principle metabolic product prostaglandin E2 (PGE-2) may have increased possibility of exposure to many cancer types such as pancreatic gastric, breast, lung, colon, oesophageal, prostate, hepatocellular skin, cervical, bone etc. and their inhibition has the potential to reduce the risk of developing certain cancers [7,12-16]. Thus the fact of interrelationship between inflammation and carcinogenesis affiliated with COX-2 over-expression makes this enzyme an attractive molecular target. In light of these circumstances, immense efforts on the effective prevention of cancer are of clinical importance with the targeted management of inflammation in daily practice, in an attempt to obtain new effective anticancer compounds [12-16]. Concurrently, explorations in a search for compounds with anti-cancer activity, α,-unsaturated carbonyl system based derivatives such as chalcones are of great interest as they have been used as a combinatorial starting point for novel medicinal entities and may also contribute to their antitumor properties. Also, chalcones have been proved to be having promising therapeutic efficacy in the management of many human cancers [1,17-19]. Chalcones are the compounds with 1,3-diphenylprop-2-en-1-one unsaturated carbonyl moiety, belonging to the flavonoid family, that encompass a broad range of natural as well as synthetic molecules [20,21]. They have been reported with varied pharmacological practice including antibacterial, anti-inflammatory, antioxidant, anti-tumor, antifungal, antimalarial and anti-invasive [22-29]. Recent studies make evident the absorbance of chalcones in the daily diet which appear to be promising as potential chemopreventive and chemotherapeutic compounds [30,31]. Chalcones exert their cytotoxic activities through multiple mechanisms from the very early stages to the very late stages. In the early stages, they inhibit tumor initiation via lowering the promotion, progression; angiogenesis and invasion there by decline the late stage of metastasis. Also they are predominant in the negative regulation of cell cycle progression that favors apoptosis mechanism in the transformed cells. Association of chalcones in these moderation processes is in consistence with their significance in the network of inflammatory cell-signaling pathways affiliated with tumor promotion. Besides these in comparison with the currently useful anticancer drugs that exhibit genotoxic effects via interacting with the nucleic acid amino groups, chalcones are unlike to react with the amino and hydroxyl groups on nucleic acids and thus would unlikely induce mutagenicity and carcinogenicity commonly associated with alkylating agents used in cancer chemotherapy. Also chalcones have the advantages of being inexpensive, available, safety profile, less toxic, oral administration and the ease of synthesis, thus making these compounds as an exceptional chemical template [32-34]. However, the various classes of chalcone derivatives with their anti-cancer activities were reported in the literature but 9-anthracenyl–chalcone derivatives with their anticancer activities are not explored much.

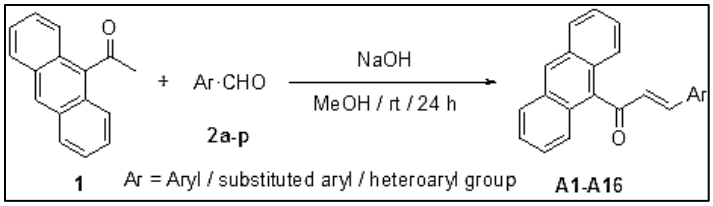
In order to explore diverse class of chalcone scaffolds, herein we report the design and synthesis of a series of 9-Anthracenyl chalcone derivatives (A1-A16) and examined there *in vitro* anti-cancer activity against four human cancer cell lines HeLa, MIAPACA, U-87 and SIHA.

EXPERIMENTAL SECTION

All commercially available chemicals, reagents and solvents were used as received. For thin layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by Iodine and or by UV light. All melting points were recorded on an IKON melting point apparatus and are uncorrected. Purity of the all synthesized 9-Anthracenyl chalcone products were confirmed by Binary Gradient HPLC-3000 system. IR spectra were recorded on JASCO FT/IR-5300. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded at Bruker 400 MHz and 500 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS (d = 0) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (d = 77.0) for ^{13}C NMR. High-resolution mass spectra were recorded on micromass ESI-TOF MS.

Synthesis

To a mixture of 9-Acetyl anthracene (2 mmol), benzaldehyde (2 mmol) in methanol solution (5 mL) was added a catalytic amount of NaOH and the reaction mixture was stirred at room temperature for 24 hours. The progress of the reaction was monitored by thin layered chromatography (TLC) and after completion of the reaction was added ice cold water. The solid product was collected by filtration method and at that moment the product was washed with water (3-4 times) and finally washed with methanol to obtain the pure product. The same synthetic protocol was followed for the synthesis of all other 9-Anthracenyl Chalcone derivatives (Scheme 1 and Table 1).



Scheme 1: Synthesis of 9-anthracenyl chalcone derivatives (A1-A16)

Table 1: Synthesis of 9-anthracenyl chalcone derivatives (A1-A16)[a]

S. No.	Compound	Ar-CHO	Yields (%)	Mp (°C)
1	A1	Benzaldehyde	86	186-189
2	A2	p-Chlorobenzaldehyde	90	157-160
3	A3	p-Fluorobenzaldehyde	88	109-112
4	A4	p-Bromobenzaldehyde	80	167-170
5	A5	p-Methylbenzaldehyde	85	114-116
6	A6	m-Chlorobenzaldehyde	86	145-148
7	A7	p-Nitrobenzaldehyde	73	159-162
8	A8	p-Cyanobenzaldehyde	80	130-133
9	A9	m-Fluorobenzaldehyde	84	165-168
10	A10	m-Nitrobenzaldehyde	75	169-172
11	A11	p-Dimethylaminobenzaldehyde	80	171-174
12	A12	Furfuraldehyde	75	119-122
13	A13	3,4,5-Trimethoxybenzaldehyde	90	150-153
14	A14	3,4-Dimethoxybenzaldehyde	88	104-107
15	A15	4-Methoxybenzaldehyde	86	100-103
16	A16	Pyridine-4-carboxaldehyde	73	160-163

Note: [a] Reaction Conditions: 9-Acetyl Anthracene (2 mmol); Ar-CHO (2 mmol); NaOH in Methanol 24 h at RT

Spectral Characterization

(E)-1-(anthracen-9-yl)-3-phenylprop-2-en-1-one (A1)

Bright yellow solid, yield: 86%, m.p. 186-189°C, IR(KBr) cm^{-1} 3132 (Aromatic C-H), 1639 (C=O), 1520 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, Ar-H), 8.08 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.97 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.50 –7.45 (m, 4H, Ar-H), 7.46 –7.44 (m, 2H, Ar-H, =CH), 7.3–7.32 (m, 4H, Ar-H), 7.2–7.25 (m, 1H, =CH). ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.19, 147.90, 134.62, 134.29, 131.17, 131.01, 129.19, 128.95, 128.69, 128.65, 128.45, 126.60, 126.66, 125.55, 125.31. HRMS (m/z) 309.1273 (M+1) observed for $C_{23}H_{16}O$.

(E)-1-(anthracen-9-yl)-3-(4-chlorophenyl)prop-2-en-1-one (A2)

Pale yellow solid, yield: 90%, m.p. 157-160°C, IR(KBr) cm^{-1} 3049 (Aromatic C-H), 1629 (C=O), 1577 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, Ar-H), 8.08 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.92 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.51 – 7.49 (m, 5H, Ar-H), 7.37 (d, *J* = 7.4 Hz, 1H, =CH), 7. 32 (d, *J* = 7.4 Hz, 1H, =CH), 7.28 – 7.25 (m, 1H, Ar-H), 7.24 –7.22 (m, 1H, Ar-H), 7.20 – 7.18 (m, 1H, Ar-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.87, 146.13, 136.96, 134.35, 132.78, 131.14, 129.75, 129.51, 129.22, 128.70, 128.56, 128.39, 126.72, 125.55, 125.17. HRMS (m/z) 343.0882 (M+1) observed for $C_{23}H_{15}ClO$.

(E)-1-(anthracen-9-yl)-3-(4-fluorophenyl)prop-2-en-1-one (A3)

Orange yellow solid, yield: 88%, m.p. 109-112°C, IR(KBr) cm^{-1} 3059 (Aromatic C-H), 1629 (C=O), 1587 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, Ar-H), 8.09 – 8.06 (m, 2H, Ar-H), 7.94 – 7.70 (m, 2H, Ar-H), 7.53 – 7.42 (m, 6H, Ar-H), 7.23 – 7.22 (m, 2H, =CH), 7.06 – 7.01 (m, 2H, Ar-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.00, 165.56, 163.04, 146.49, 134.45, 131.14, 130.66, 130.57, 130.50, 128.92, 128.49, 128.31, 126.69, 125.55, 125.22, 116.25. HRMS (m/z) 327.1183 (M+1) observed for $C_{23}H_{15}FO$.

(E)-1-(anthracen-9-yl)-3-(4-bromophenyl)prop-2-en-1-one (A4)

Pale yellow solid, yield: 80%, m.p. 167-170°C, IR(KBr) cm^{-1} 3054 (Aromatic C-H), 1634 (C=O), 1582 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H, Ar-H), 8.09 – 8.06 (m, 2H, Ar-H), 7.93 – 7.90 (m, 2H, Ar-H), 7.54 – 7.44 (m, 7H, Ar-H), 7.33 – 7.25 (m, 3H, Ar-H, =CH). ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.86, 134.34, 134.10, 133.20, 132.19, 131.13, 129.93, 129.59, 128.72, 128.59, 128.40, 126.74, 125.57, 125.36, 125.17. HRMS (m/z) 388.0409 (M+1) observed for $C_{23}H_{15}BrO$.

(E)-1-(anthracen-9-yl)-3-(p-tolyl)prop-2-en-1-one (**A5)**
Bright orange solid, yield: 85%, m.p. 114-116°C, IR(KBr) cm^{-1} 3044 (Aromatic C-H), 1629 (C=O), 1580 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, Ar-H), 8.08 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.93 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.52 – 7.45 (m, 5H, Ar-H), 7.37 – 7.33 (m, 2H, Ar-H), 7.26 (d, *J* = 7.3 Hz, 1H, =CH), 7.25 – 7.18 (m, 1H, Ar-H), 7.15 (d, *J* = 7.3 Hz, 1H, =CH), 2.35 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.26, 131.56, 131.15, 129.80, 129.68, 129.23, 128.68, 128.62, 128.41, 128.30, 128.09, 127.95, 126.55, 125.50, 125.36, 21.51. HRMS (m/z) 323.1435 (M+1) observed for $C_{24}H_{18}O$.

(E)-1-(anthracen-9-yl)-3-(3-chlorophenyl)prop-2-en-1-one (**A6)**
Bright orange solid, yield: 86%, m.p. 145-148°C, IR(KBr) cm^{-1} 3054 (Aromatic C-H), 1629 (C=O), 1562 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, Ar-H), 8.08 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.91 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.53 – 7.47 (m, 5H, Ar-H), 7.42 (d, *J* = 7.6 Hz, 1H, =CH), 7.36 – 7.25 (m, 4H, Ar-H, =CH). ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.84, 145.89, 144.49, 136.12, 135.00, 134.20, 133.54, 131.13, 130.73, 130.13, 128.73, 128.38, 127.97, 126.77, 126.64, 125.55, 125.11. HRMS (m/z) 343.0882 (M+1) observed for $C_{23}H_{15}ClO$.

(E)-1-(anthracen-9-yl)-3-(4-nitrophenyl)prop-2-en-1-one (**A7)**
Yellow solid, yield: 73%, m.p. 159-162°C, IR(KBr) cm^{-1} 3039 (Aromatic C-H), 1639 (C=O), 1539 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H, Ar-H), 8.17 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.08 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.91 – 7.80 (m, 2H, Ar-H), 7.59 – 7.55 (m, 2H, Ar-H), 7.53 – 7.48 (m, 4H, Ar-H), 7.34 (d, *J* = 7.6 Hz, 1H, =CH), 7.28 (d, *J* = 7.6 Hz, 1H, =CH). ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.34, 148.72, 143.87, 140.39, 133.75, 132.35, 131.11, 129.11, 128.99, 128.84, 128.39, 126.98, 125.66, 124.91, 124.07. HRMS (m/z) 354.1120 (M+1) observed for $C_{23}H_{15}NO_3$.

(E)-4-(3-(anthracen-9-yl)-3-oxoprop-1-en-1-yl)benzonitrile (**A8)**
Bright orange solid, yield: 80%, m.p. 130-133°C, IR(KBr) cm^{-1} 3054 (Aromatic C-H), 2228 (CN), 1644 (C=O), 1598 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H, Ar-H), 8.01 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.88 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.64 – 7.61 (m, 2H, Ar-H), 7.55 – 7.49 (m, 6H, Ar-H), 7.36 – 7.22 (m, 2H, =CH). ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.45, 144.51, 138.58, 132.58, 131.78, 131.11, 128.92, 128.85, 128.81, 128.38, 127.22, 126.93, 125.63, 124.93, 118.19, 113.88. HRMS (m/z) 334.1223 (M+1) observed for $C_{24}H_{15}NO$.

(**E)-1-(anthracen-9-yl)-3-(3-fluorophenyl)prop-2-en-1-one** (**A9)**
Bright orange solid, yield: 84%, m.p. 165-168°C, IR(KBr) cm^{-1} 3065 (Aromatic C-H), 1634 (C=O), 1582 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H, Ar-H), 8.09 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.90 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.55 – 7.46 (m, 4H, Ar-H), 7.35 – 7.30 (m, 2H, Ar-H), 7.28 (d, *J* = 7.6 Hz, 1H, =CH), 7.22 (d, *J* = 7.6 Hz, 1H, =CH), 7.18 – 7.15 (m, 1H, Ar-H), 7.10 – 7.06 (m, 1H, Ar-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.89, 161.97, 146.11, 134.23, 134.12, 131.13, 130.49, 130.49, 130.42, 130.18, 128.63, 128.39, 128.20, 127.97, 127.29, 126.75, 124.58, 123.86, 122.43. HRMS (m/z) 327.1180 (M+1) observed for $C_{23}H_{15}FO$.

(**E)-1-(anthracen-9-yl)-3-(3-nitrophenyl)prop-2-en-1-one** (**A10)**
Bright orange solid, yield: 75%, m.p. 169-172°C, IR(KBr) cm^{-1} 3054 (Aromatic C-H), 1639 (C=O), 1520 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H, Ar-H), 8.26 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.20 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.12 – 8.06 (m, 2H, Ar-H), 7.92 – 7.80 (m, 2H, Ar-H), 7.79 – 7.76 (m, 1H, Ar-H), 7.57 – 7.47 (m, 5H, Ar-H), 7.36 (d, *J* = 7.2 Hz, 1H, =CH), 7.27 (d, *J* = 7.3 Hz, 1H, =CH). ^{13}C NMR (400 MHz, $CDCl_3$) δ 119.53, 148.62, 114.23, 136.05, 133.85, 133.75, 131.45, 131.11, 129.97, 128.93, 128.83, 128.38, 128.31, 126.95, 125.64, 125.00, 123.05. HRMS (m/z) 354.1134 (M+1) observed for $C_{23}H_{15}NO_3$.

(**E)-1-(anthracen-9-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one** (**A11)**
Bright orange solid, yield: 80%, m.p. 171-174°C, IR(KBr) cm^{-1} 3054 (Aromatic C-H), 2362 (N-CH), 1630 (C=O), 1572 (olefinic C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H, Ar-H), 8.06 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.98 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.51 – 7.44 (m, 4H, Ar-H), 7.33 – 7.28 (m, 2H, =CH), 7.15 (d, *J* = 7.4 Hz, 2H, , Ar-H), 6.60 (d, *J* = 7.4 Hz, 2H, Ar-H), 3.00 (s, 6H, CH_3). ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.85, 152.32, 149.18, 135.62, 134.10, 133.56, 130.65, 128.48, 128.44, 127.81, 127.23, 126.27, 128.73, 125.73, 124.37, 111.72, 40.02. HRMS (m/z) 374.1521 (M+23) observed for $C_{25}H_{21}NO$.

(E)-1-(anthracen-9-yl)-3-(furan-2-yl)prop-2-en-1-one (A12)
Bright yellow solid, yield: 75%, m.p. 119-122°C, IR(KBr) cm^{-1} 3106 (Aromatic C-H), 1618 (C=O), 1541 (olefinic C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H, Ar-H), 8.08 – 8.04 (m, 2H, Ar-H), 7.94 – 7.91 (m, 2H, Ar-H), 7.54 – 7.45 (m, 5H, Ar-H), 7.16 (d, *J* = 8.4 Hz, 1H, =CH), 6.95 (d, *J* = 8.4 Hz, 1H, =CH), 6.54 – 6.51 (m, 1H, Ar-H), 6.45 (dd, *J* = 6.4 Hz, *J* = 2.7 Hz, 1H, Ar-H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.53, 150.79, 145.67, 134.46, 133.63, 131.13, 128.40, 128.34, 127.23, 126.67, 126.39, 125.51, 125.32, 116.98, 112.80. HRMS (m/z) 321.0890 (M+23) observed for $C_{21}H_{14}O_2$.

(E)-1-(anthracen-9-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (A13)
Yellow solid, yield: 90%, m.p. 150-153°C, IR(KBr) cm^{-1} 3059 (Aromatic C-H), 1629 (C=O), 1572 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, Ar-H), 8.10 – 8.07 (m, 2H, Ar-H), 7.94 – 7.91 (m, 2H, Ar-H), 7.54 – 7.47 (m, 4H, Ar-H), 7.23 (d, *J* = 8.9 Hz, 1H, =CH), 7.14 (d, *J* = 8.9 Hz, 1H, =CH), 6.68 (s, 2H, Ar-H), 3.86 (s, 3H, OCH_3), 3.82 (s, 6H, OCH_3). ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.08, 153.50, 153.44, 148.06, 140.86, 134.64, 131.26, 131.16, 129.62, 128.70, 128.63, 128.42, 128.30, 126.64, 125.33, 60.96, 56.17. HRMS (m/z) 421.1418 (M+23) observed for $C_{26}H_{22}O_4$.

(E)-1-(anthracen-9-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (A14)
Pale yellow solid, yield: 88%, m.p. 104-107°C, IR(KBr) cm^{-1} 2992 (Aromatic C-H), 1624 (C=O), 1598 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H, Ar-H), 8.08 – 8.06 (m, 2H, Ar-H), 7.96 – 7.94 (m, 2H, Ar-H), 7.55 – 7.45 (m, 6H, Ar-H), 7.20 (s, 1H, Ar-H), 7.18 (d, *J* = 9.1 Hz, 1H, =CH), 6.99 (d, *J* = 9.1 Hz, 1H, =CH), 3.89 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3). ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.04, 151.84, 149.29, 148.09, 131.17, 128.83, 128.60, 128.40, 128.19, 127.28, 126.77, 126.54, 125.51, 125.33, 1233.50, 11.06, 110.18, 55.99, 55.89. HRMS (m/z) 391.1310 (M+23) observed for $C_{25}H_{20}O_3$.

(E)- 1-(anthracen-9-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (A15)
Pale yellow solid, yield: 86%, m.p. 100-103°C, IR(KBr) cm^{-1} 3059 (Aromatic C-H), 1629 (C=O),1567 (olefinic C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H, Ar-H), 8.08 – 8.05 (m, 2H, Ar-H), 7.96 – 7.94 (m, 2H, Ar-H), 7.52 – 7.46 (m, 4H, Ar-H), 7.40 (d, *J* = 9.4 Hz, 2H, Ar-H), 7.21 – 7.19 (m, 2H, =CH), 7.85 (d, *J* = 9.4 Hz, 2H, Ar-H), 3.81 (s, 3H, OCH_3). ^{13}C NMR (500 MHz, $CDCl_3$) δ 200.15, 162.07, 147.95, 134.12, 131.16, 130.49, 128.61, 128.41, 128.07, 127.23, 127.08, 126.52, 125.50, 125.35, 114.42, 55.40. HRMS (m/z) 361.1203 (M+23) observed for $C_{24}H_{18}O_2$.

(E)-1-(anthracen-9-yl)-3-(pyridin-4-yl)prop-2-en-1-one (A16)
Dark orange solid, yield: 73%, m.p. 160-163°C, IR(KBr) cm^{-1} 3049 (Aromatic C-H), 1634 (C=O), 1582 (olefinic C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.57 (m, 3H, Ar-H), 8.08 – 8.07 (m, 2H, Ar-H), 7.89 – 7.87 (m, 2H, Ar-H), 7.51 – 7.48 (m, 2H, Ar-H), 7.40 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.27 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.25 – 7.15 (m, 2H, =CH). ^{13}C NMR (400 MHz, $CDCl_3$) δ 119.56, 150.56, 144.04, 141.49, 132.65, 131.09, 128.98, 128.81, 128.39, 127.20, 126.96, 125.64, 124.91, 122.05. HRMS (m/z) 332.1054 (M+23) observed for $C_{22}H_{15}NO$.

Biological Activity
The human cancer cell lines HeLa, MIAPACA, U-87 and SIHA, used in this study were purchased from the American Type Culture Collection (ATCC, United States) and were maintained in Dulbecco's modified Eagle's medium (containing 10% FBS in a humidified atmosphere of 5% CO_2 at 37°C). The synthesized test compounds were evaluated for their *in vitro* anti-proliferative activity in these four different human cancer cell lines compared with the standard drug Nocodazole. A protocol of 48 h continuous drug exposure was used and an SRB cell proliferation assay was used to estimate cell viability or growth. All the cell lines were grown in Dulbecco's modified Eagle's medium (containing 10% FBS in a humidified atmosphere of 5% CO at 37°C). Cells were trypsinized when sub-confluent from T25 flasks/60 mm dishes and seeded in 96-well plates in 100 mL aliquots at plating densities depending on the doubling time of individual cell lines. The microtiter plates were incubated at 37°C, 5% CO_2, 95% air, and 100% relative humidity for 24 h prior to the addition of experimental drugs and were incubated for 48 h with different doses (0.01, 0.1, 1, 10, 100 mM) of the prepared derivatives. After incubation at 37°C for 48 h, the cell monolayers were fixed by the addition of 10% (wt/vol) cold trichloroacetic acid and incubated at 4°C for 1 h and were then stained with 0.057% SRB dissolved in 1% acetic acid for 30 min at room temperature. Unbound SRB was washed with 1% acetic acid. The protein-bound dye was dissolved in 10 mM Tris base solution for OD determination at 510 nm using a microplate reader (Enspire, Perkin Elmer, USA). Using the

seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth was calculated at each of the drug concentrations levels.
Percentage growth inhibition was calculated as:
[(Ti-Tz)/(C-Tz)] x 100 for concentrations for which Ti >/= Tz
[(Ti-Tz)/Tz] x 100 for concentrations for which Ti < Tz.
The dose response parameter, growth inhibition of 50% (GI was calculated from [(Ti-Tz)/ (CTz)] × 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Values were calculated for this parameter if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested.

RESULTS AND DISCUSSION

Chemistry

In the current work a series of 9-Anthraacenyl chalcones were designed and synthesized by Claisen-Schmidt condensation reaction from commercially available 9-acetyl anthracene with various aromatic/heteroaromatic aldehydes catalyzed by sodium hydroxide in methanol solution at room temperature for 24 hours and afforded desired 9-Anthraacenyl chalcone derivatives (Scheme 1). Practically all 9-Anthraacenyl chalcone derivatives (A1-A16) were synthesized by using aforementioned conditions and the results show that the condensation reaction proved to be general and quit efficient synthetic protocol for aryl, hereto aryl and tolerated a verity of functional groups on the phenyl ring regardless whether electron-donating or electron-withdrawing in character. The chemical structures of 9-Anthraacenyl chalcone products are summarized in Figure 1.

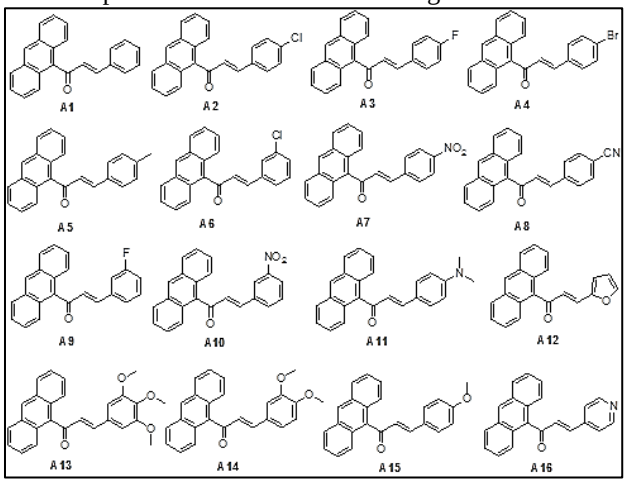


Figure 1: Structures of the synthesized 9-anthracenyl chalcones (A1-A16)

Anti-cancer Activity

The *in vitro* anti-proliferative activity of the synthesized compounds were evaluated against a panel of four different human cancer cell lines, HeLa, MIAPACA, U-87 and SIHA. The results for compounds A1–A16 are shown as GI_{50} values calculated using SRB assay are tabulated in Table 2. The GI_{50} concentration for each compound was calculated with reference to a control sample, which represents the concentration that results in a 50% decrease in cell growth/proliferation after 48 h incubation in the presence of drug. The cytotoxic activities of synthesized compounds were compared with the activity exhibited by the reference drug Nocodazole. Based on the data obtained, most of the compounds possess GI_{50} values were at the 4.02 µM to 19.57 µM range. Among all the synthesized 9-Anthracenyl chalcones, compounds **A7**, **A8**, **A10** and **A11** were found to be the most potent against all the four human cancer cell lines with the GI values below 10 µM. ranging from 5.18 to 8.41, 4.04 to 7.24, 5.31 to 7.16 and 4.02 to7.03 µM respectively.

Table 2: Anti-cancer activities of synthesized 9-anthracenyl chalcone derivatives A1-A16 against human cancer cell lines

Compound	HELA GI50(μM)	U-87 GI50(μM)	MIAPACA GI50(μM)	SIHA GI50(μM)
A1	12.3 ± 0.05	14.44 ± 0.07	11.39 ± 0.06	16.25 ± 0.07
A2	17.06 ± 0.07	15.10 ± 0.05	13.06 ± 0.07	14.50 ± 0.06
A3	16.10 ± 0.07	13.10 ± 0.05	16.4 ± 0.06	15.22 ± 0.07
A4	11.02 ± 0.05	14.80 ± 0.06	15.34 ± 0.03	13.44 ± 0.06
A5	18.50 ± 0.06	17 ± 0.06	12.10 ± 0.06	18.29 ± 0.05
A6	11.06 ± 0.06	13.48 ± 0.07	15.55 ± 0.08	14.08 ± 0.05
A7	5.18 ± 0.05	6.18 ± 0.06	8.41 ± 0.06	7.06 ± 0.06
A8	6.47 ± 0.06	4.04 ± 0.06	5.46 ± 0.05	7.24 ± 0.06
A9	14.06 ± 0.06	15.06 ± 0.06	12.52 ± 0.06	19.57 ± 0.07
A10	6.65 ± 0.05	7.16 ± 0.06	5.31 ± 0.05	6.16 ± 0.06
A11	5.65 ± 0.07	7.03 ± 0.07	6.44 ± 0.05	4.02 ± 0.07
A12	13.35 ± 0.06	12.55 ± 0.07	12.36 ± 0.08	14.28 ± 0.06
A13	12.30 ± 0.6	10.86 ± 0.08	14.31 ± 0.08	11.53 ± 0.05
A14	13.08 ± 0.06	14.33 ± 0.05	11.30 ± 0.05	15.02 ± 0.08
A15	16.89 ± 0.05	13.65 ± 0.06	18.05 ± 0.05	19.43 ± 0.08
A16	15.44 ± 0.05	11.43 ± 0.07	12.64 ± 0.06	17.62 ± 0.07
Nocodazole	0.567 ± 0.2	0.667 ± 0.3	0.782 ± 0.2	0.884 ± 0.1

CONCLUSION

The present study described the synthesis, characterization and evaluation of 9-Anthracenyl chalcone derivatives for their anticancer activity. We have identified the compounds **A7**, **A8**, **A10** and **A11** as effective considering their significant cytotoxic activity against the four human cancer cell lines HeLa, MIAPACA, U-87 and SIHA. Further these observations may facilitate a promising approach to design novel anticancer agents based on the potent compound by structural modifications of these series of 9-Anthracenyl chalcones can lead to discover better anti-cancer agents as clinical candidates.

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