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Research Article

Novel Coumarin-Indole Hybrids as Cytotoxic Candidates: Synthesis and Antiproliferative Activity

Sarah S. Ismael*, Noor Ahmed M. Waheed, Seema Mahmood Kasim, Yasser Fakri Mustafa

ABSTRACT

Cancer is regarded as a nightmare for humanity and a challenging task for medical professionals. Twelve hydrides (**2a**-**2l**), made of trifunctionalized coumarin and various substituted indoles, were created in an effort to realize the hope of a cancer cure. The 4,5-dimethoxysalicylaldehyde and ethyl acetoacetate were combined in a Knoevenagel reaction to create the coumarin component. The construction of the indole component involved converting various aminoindoles through diazotization and Sandmeyer reactions to twelve substituted indoles (**1a**-**1l**). These two components were combined through a Michael addition reaction to create the desired hybrids. Investigating their spectra released from various spectroscopical instruments allowed researchers to determine the 2D molecular frameworks of these hybrids. Studying the survival of nine tumor cell types after treatment with the synthesized hybrids enabled researchers to estimate there *in vitro* impact as cytotoxic candidates. By checking the cell viability using an MTT marker, it was possible to see that this effect was antiproliferative. The cytotoxicity measurements, IC_{50} scores, revealed a number of intriguing facts. To start, the synthetic hybrids displayed a relatively similar cytotoxic pattern against the cancerous cell lines under investigation. Second, compared to hybrids with chloride, hydroxyl, or methoxy substituents, fluorinated hybrids are more toxic to cancerous cells. Finally, hybrids with indole substituted at position-6 (**2i**-**2l**) have the highest cytotoxicity among those with indole functionalized at position-4 (**2a**-**2d**) or position-5 (**2e**-**2h**). From these facts, the authors concluded that hybrids with indole substituted at position-4 can represent potential candidates as antiproliferative applicants. Moreover, hybrid **2i** may serve as a valuable model for creating potent anti-breast cancer therapies.

Key words: Indole, Coumarin, Cytotoxicity, MTT, Michael addition, Anti-breast cancer.

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INTRODUCTION

Despite an abundance of trials to effectively fight cancer development, the mortality rate because of this sneaky and fatal anomaly is still terrifying.[1] These trials encompass searching for new cytotoxic substances found in nature,[2] structurally altering cytotoxic medications to increase their effectiveness,[3] and creating new chemical structures with anticancer effects.[4] The superiority of cancer over the approved medications comes from the poor selectivity of the cytotoxic agents and the development of many evasive mechanisms of resistance by cancerous cells.[5]

A conjugated aromatic oxygen-heterocycle, coumarin, was sequestered novally from Tonka beans in 1820 by A. Vogel of Munich, who misidentified it as benzoic acid at first. Since then, two approaches have been developed, leading to a boost in the number of coumarins.[6] The first is the isolation of coumarins from their natural sources, and the second is a lab synthesis of this molecular structure. The latter approach is highly advanced by discovering various related synthetic reactions, utilizing different modes of activating energy, and employing numerous green reaction conditions and catalysts.[7]

Indole is one of the most pervasive and prominent aromatic nitrogen-heterocycles that originally created in 1866 by Aldolf von Baeyer. Since it is the principal structural component of the vital amino acid tryptophan and the framework for many naturally occurring bioactive molecules, indole occupies a pivotal position in biochemistry.[8] In this regard, so many molecules, including naturally occurring proteins, enzymes, neurotransmitters, receptors, and hormones, hold this heterocycle in their molecular structures. Because of their potent anticancer properties, various indole-containing vinca alkaloids, particularly vincristine and vinblastine, have piqued investigators' intrigue in this chemical nucleus.[9]

The fact that oxygen and nitrogen heterocycles can resemble the structure of peptides and attach to vital proteins in a cyclical fashion makes them generally exhibit a wide range of bioactivity. When its substitutional groups are oriented in 3D-spaces, the aromatic polycyclic ring structure demonstrates a distinguishable rigorous conformation with exceptionally elevated specialty, which has attracted a lot of attention.[10] Indole-based derivatives have a distinct advantage in the biomedical field due to their favorable pharmacologic properties, which include antiviral, hypoglycemic, hypotensive, anti-inflammatory, hypolipidemic, anti-HIV, antidepressant, anti-asthmatic, and, most prominently, anticancer activity.[11] On the other hand, coumarin-derived compounds are unceasingly gaining attention due to their interesting therapeutic potentials, such as anti-Alzheimer's, anticancer, antimalarial, anti-HIV, and antioxidant. The working group has investigated many of these potentials for a vast variety of natural, semi-synthetic, and synthesized coumarins over the last decade.[12-14]

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The concept of molecular hybridization describes the cross-linking of two or three distinct biostructures to create hybridized molecules with promising biological profiles. The built frameworks can be intended to exploit two different receptors and/or enzymes at the same time, resulting in powerful mutual synergistic interactions.[15] As a result, a single hybridized molecule can afford more than one distinct mode of action, which is considered an advantage in cancer chemotherapy.[16] Because indole and coumarin biostructures have already shown potential as anticancer agents, the authors aimed to synthesize twelve hybrids involving these biostructures and investigate them as promising antiproliferative agents.

EXPERIMENTAL

Materials and analytical facilities

The employed tumorigenic lines and information about their contemporary framework were provided by Sigma-Aldrich. The necessary ingredients, solvents, and chemicals for catalytic reactions were supplied by a variety of external organizations, including Scharlau, Haihang, Labcorp, Chem-Lab, Sigma-Aldrich, and Bioworld. The thermal properties (mp) of novel coumarin-indole hybrids and their constructing units were calculated using the single-open capillary tube method by the electronic CIA 9300 research lab tool. The purification of the hybrids and their precursors was confirmed by the authors using thin-layer separatory chromatography (TSC), which allowed them to monitor the chemical alterations. In this methodology, the elevator was a $CHCl_3$-to-EtOH (4:1) blend, and the stationary phase was silica molecules supported on chromatographic aluminum paper.

Descriptive spectrum analyzers were used to examine the chemical shifts of the magnetic resonance, wavenumbers of infrared, and maximum absorptive wavelengths for the synthesized hybrids and their precursors. These analytical tools are, in order, the Bruker-Avance III HD (DMSO-d_6, 600 MHz), the Bruker FTIR-ATR (α type), and the 1600PC UV/Vis.

Synthetic reactions

The follow-up steps employed for creating the coumarin-indole hybrids and their constructing units are displayed in Figure 1.

Synthesis of indole-constructing unites (1a-1l)

The fluorinated indoles (**1a**, **1e**, and **1i**) were formed using the technique described by Abdulaziz (2022),[17] while the chlorinated derivatives (**1b**, **1f**, and **1j**) were produced using the method as described by Waheed (2022).[18] Firas's procedure published in 2022 for generating methoxy congeners was followed to synthesize indoles **1c**, **1g**, and **1k**.[19] Finally, the hydroxy composites, including **1d**, **1h**, and **1l**, were created by using the method outlined by Kasim *et al.* in 2022.[20] The success of synthesizing the indole-constructing units was ascertained by comparing their physical and chemical characteristics with those reported in the literature.

One-pot synthesis of the coumarin-indole hybrids (2a-2l)

A mixture of ethyl acetoacetate (0.26 ml, 2 mmol), 4,5-dimethoxysalicylaldehyde (0.37 g, 2 mmol), and piperidine (30 ml, 0.3 mmol) was exposed to a 10-minute, 250 W microwave treatment.

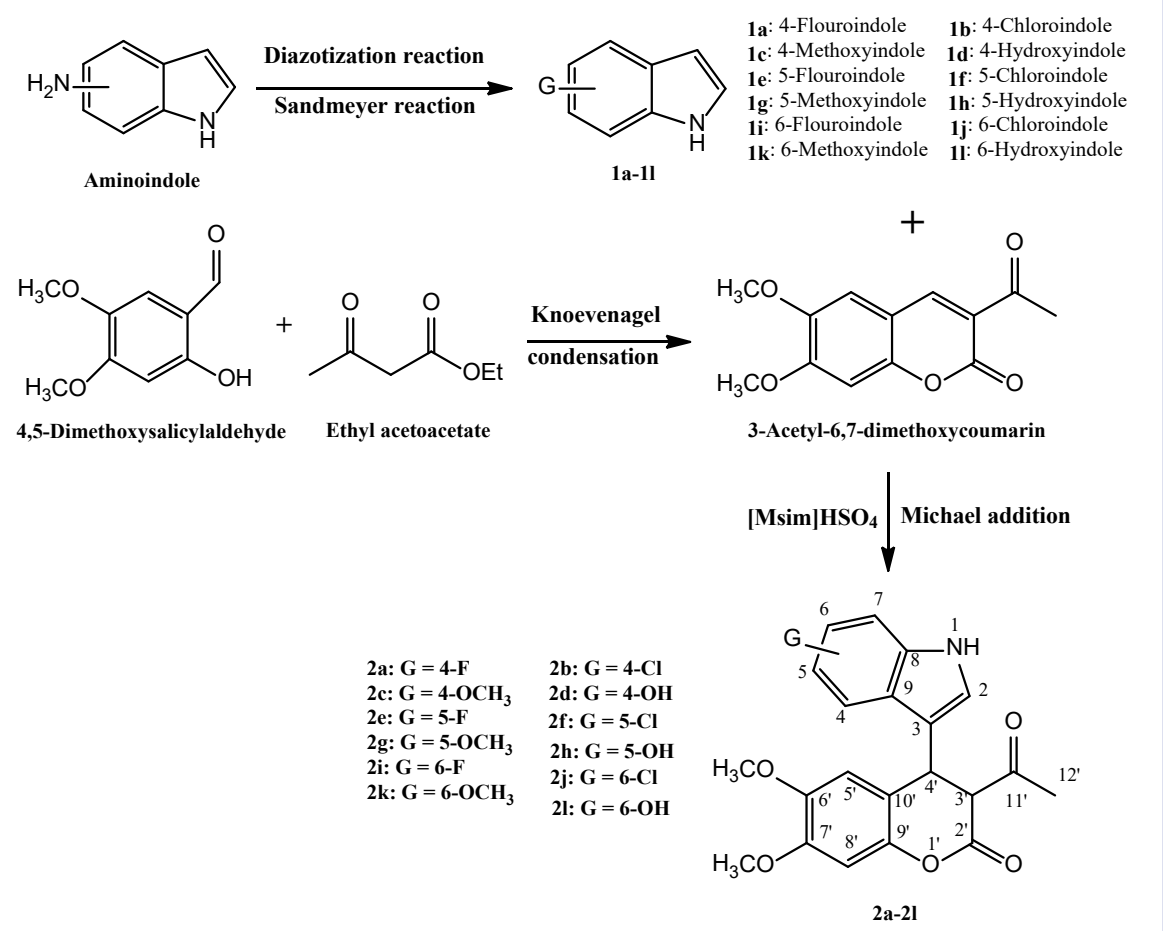

Figure 1: The synthetic pathway of the coumarin-indole hybrids and their constructing units.

Table 1: The cytotoxicity markers of the hybrids with 4-substituted indoles.

Tumor cell types	Positive control and the first part of our coumarin-indole hybrids IC_{50} (µg/ml) ± SD (n=3)				
	5-FU	2a	2b	2c	2d
MCF-7	12.46 ± 0.98	33.91 ± 1.03	38.24 ± 1.09	56.06 ± 1.02	59.78 ± 1.06
MDA-MB-231	30.11± 0.92	53.16 ± 0.94	54.91 ± 1.02	59.74 ± 0.88	63.10 ± 0.96
AR42J	20.45 ± 0.95	46.34 ± 0.96	56.32 ± 0.89	64.45 ± 1.04	66.83 ± 0.85
KYSE-30	28.08 ± 1.06	54.09 ± 1.02	62.14 ± 0.80	67.34 ± 0.98	71.11 ± 0.84
SK-OV-3	22.97 ± 1.01	50.50 ± 1.06	56.92 ± 0.87	63.17 ± 0.90	72.70 ± 0.96
HeLa	13.22 ± 1.09	39.34 ± 1.01	50.02 ± 0.96	58.21 ± 0.89	64.45 ± 0.89
AMN3	24.12 ± 1.04	52.46 ± 0.88	65.21 ± 0.90	65.41 ± 0.93	66.72 ± 1.03
AB12	19.62 ± 0.93	48.25 ± 0.86	52.90 ± 1.07	60.78 ± 0.98	61.94 ± 1.01
LC540	22.89 ± 0.91	42.57 ± 1.05	52.79 ± 0.93	53.95 ± 1.12	67.02 ± 1.05

Table 2: The cytotoxicity markers of the hybrids with 5-substituted indoles.

Tumor cell types	Positive control and the second part of our coumarin-indole hybrids IC_{50} (µg/ml) ± SD (n=3)				
	5-FU	2e	2f	2g	2h
MCF-7	12.46 ± 0.98	24.16 ± 0.92	29.16 ± 0.90	46.15 ± 1.01	50.14 ± 0.89
MDA-MB-231	30.11± 0.92	42.93± 1.03	44.80 ± 1.04	51.29 ± 1.05	53.70 ± 0.95
AR42J	20.45 ± 0.95	35.12 ± 1.02	48.01 ± 0.93	55.77 ± 0.87	59.02 ± 0.98
KYSE-30	28.08 ± 1.06	44.06 ± 1.04	54.28 ± 0.83	53.16 ± 0.92	59.34 ± 0.98
SK-OV-3	22.97 ± 1.01	43.24 ± 1.00	49.67 ± 0.99	55.34 ± 0.99	63.78 ± 0.90
HeLa	13.22 ± 1.09	27.12 ± 0.96	39.45 ± 0.89	47.32 ± 0.84	53.31 ± 0.83
AMN3	24.12 ± 1.04	42.98 ± 0.91	56.71 ± 0.91	55.81 ± 0.89	61.92 ± 0.86
AB12	19.62 ± 0.93	39.83 ± 0.91	42.04 ± 0.96	49.11 ± 1.08	53.45 ± 1.07
LC540	22.89 ± 0.91	35.01 ± 1.11	45.55 ± 1.12	45.41 ± 0.93	58.69 ± 0.97

Table 3: The cytotoxicity markers of the hybrids with 6-substituted indoles.

Tumor cell types	Positive control and the third part of our coumarin-indole hybrids IC_{50} (µg/ml) ± SD (n=3)				
	5-FU	2i	2j	2k	2l
MCF-7	**12.46 ± 0.98**	**14.33 ± 1.01**	24.37 ± 0.98	43.27 ± 1.22	44.52 ± 1.08
MDA-MB-231	**30.11± 0.92**	**32.78± 1.09**	39.71 ± 1.00	48.69 ± 1.06	46.48 ± 1.01
AR42J	20.45 ± 0.95	31.09 ± 0.98	43.84 ± 1.01	52.38 ± 0.94	55.86 ± 0.90
KYSE-30	28.08 ± 1.06	40.21 ± 1.01	50.56 ± 0.90	58.04 ± 1.00	56.16 ± 0.95
SK-OV-3	22.97 ± 1.01	38.06 ± 1.03	46.49 ± 0.95	53.33 ± 0.91	59.92 ± 0.92
HeLa	13.22 ± 1.09	22.54 ± 1.02	35.21 ± 0.97	44.12 ± 1.03	49.47 ± 0.95
AMN3	24.12 ± 1.04	38.11 ± 0.98	52.46 ± 1.11	54.89 ± 0.87	60.42 ± 0.98
AB12	19.62 ± 0.93	35.01 ± 0.94	39.63 ± 0.87	46.45 ± 1.02	49.06 ± 1.02
LC540	22.89 ± 0.91	29.29 ± 1.05	41.63 ± 0.92	48.02 ± 1.06	54.47 ± 1.15

As the temperature of the reacted mixture dropped to that of the room, it was diluted with 2 ml of acetonitrile before being combined with an indole-based derivative (2 mmol) and [Msim]HSO_4 (0.2 mmol, 52 mg) as a catalyst. Based on the TSC results, the final solution was blended for 4-6 hours at room temperature before being poured onto a 250 ml solution of ice and water. The precipitated crude underwent filtering and recrystallization from ethyl acetate for purification.[21]

2a: 3'-Acetyl-4'-(4-fluoro-1*H*-indol-3-yl)-6',7'-dimethoxychroman-2'-one. mp 154-156°C; Yield 80.77% (0.62 g); λ_{max} (MeOH) 326 nm; R_f 0.62; FTIR (solid state, str., cm^{-1}): 3409, 3346 (N-H, 2nd amine, H-bounded), 3034 (olefin C-H, indole), 2956, 2861 (alkane C-H), 1733 (C=O, lactonic ester), 1690 (C=O, ketone, H-bounded), 1633 (C=C, olefin), 1560 (C=C, aryl), 1255, 1260 (ether of asymmetrical aryl-methyl C-O-C), 1112 (aryl C-F); Proton NMR (ppm): δ 9.88 (1H, singlet, NH-1), 7.35 (1H, doublet, H-7, Coupling constant (Hz)=6), 7.12 (1H, singlet, H-2), 7.03 (1H, triplet, H-6, Coupling constant (Hz)=6), 6.97 (1H, singlet, H-5′ '), 6.90 (1H, doublet, H-5, Coupling constant (Hz)=6), 6.76 (1H, singlet, H-8'), 4.94 (1H, singlet, H-4'), 4.00 (1H, singlet, H-3'), 3.87 (6H, singlet, OCH_3-6' and OCH_3-7'), and 2.35 (3H, singlet, H-12'); Carbon NMR (ppm): δ 207.1 (C, C-11'), 173.0 (C, C-2'), 158.1 (C, C-4), 151.4 (C, C-7'), 150.5 (C, C-6'), 146.3 (C, C-9'), 142.1 (C, C-8), 133.3 (C, C-10'), 128.2 (CH, C-2), 125.8 (CH, C-6), 122.6 (C, C-9), 119.9 (CH, C-5), 119.4 (C, C-3), 111.8 (CH, C-5'), 110.7 (CH, C-7), 108.4 (CH, C-8'), 73.1 (CH, C-3'), 60.1 (CH_3, OCH_3-6' and OCH_3-7'), 45.3 (CH, C-4'), and 32.4 (CH_3, CH_3-12').

2b: 3'-Acetyl-4'-(4-chloro-1*H*-indol-3-yl)-6',7'-dimethoxychroman-2'-one. mp 136-138°C; Yield 83.14% (0.66 g); λ_{max} (MeOH) 320 nm; R_f 0.63; FTIR (solid state, str., cm^{-1}): 3411, 3332 (N-H, 2nd amine, H-bounded), 3031 (olefin C-H, indole), 2950, 2867 (alkane C-H), 1732 (C=O, lactonic ester), 1688 (C=O, ketone, H-bounded), 1641 (C=C, olefin), 1576 (C=C, aryl), 1253, 1257 (ether of asymmetrical aryl-methyl C-O-C), 1065 (aryl C-Cl); Proton NMR (ppm): δ 9.91 (1H, singlet, NH-1), 7.46 (1H, doublet, H-7, Coupling constant (Hz)=6), 7.20 (1H, doublet, H-5, Coupling constant (Hz)=6), 7.11 (1H, singlet, H-2), 6.99 (1H, triplet, H-6, Coupling constant (Hz)=6), 6.94 (1H, singlet, H-5′ '), 6.77 (1H, singlet, H-8'), 4.95 (1H, singlet, H-4'), 4.00 (1H, singlet, H-3'), 3.88 (6H, singlet, OCH_3-6' and OCH_3-7'), and 2.33 (3H, singlet, H-12'); Carbon NMR (ppm): δ 207.3 (C, C-11'), 173.1 (C, C-2'), 151.4 (C, C-7'),

150.5 (C, C-6'), 146.6 (C, C-9'), 143.8 (C, C-8), 133.1 (C, C-10'), 130.7 (C, C-4), 129.5 (C, C-9), 128.2 (CH, C-2), 126.9 (CH, C-6), 124.2 (CH, C-5), 119.4 (C, C-3), 113.2 (CH, C-7), 111.8 (CH, C-5'), 108.4 (CH, C-8'), 73.1 (CH, C-3'), 60.1 (CH_3, OCH_3-6' and OCH_3-7'), 44.5 (CH, C-4'), and 32.5 (CH_3, CH_3-12').

2c: 3'-Acetyl-4'-(4-methoxy-1*H*-indol-3-yl)-6',7'-dimethoxychroman-2'-one. mp 160-162°C; Yield 80.02% (0.63 g); λ_{max} (MeOH) 323 nm; R_f 0.68; FTIR (solid state, str., cm^{-1}): 3410, 3335 (N-H, 2nd amine, H-bounded), 3033 (olefin C-H, indole), 2978, 2857 (alkane C-H), 1732 (C=O, lactonic ester), 1687 (C=O, ketone, H-bounded), 1640 (C=C, olefin), 1574 (C=C, aryl), and 1250, 1246 (ether of asymmetrical aryl-methyl C-O-C); Proton NMR (ppm): δ 9.90 (1H, singlet, NH-1), 7.18 (1H, doublet, H-7, Coupling constant (Hz)=6), 7.12 (1H, singlet, H-2), 6.94 (1H, triplet, H-6, Coupling constant (Hz)=6), 6.86 (1H, singlet, H-5′ '), 6.76 (1H, singlet, H-8'), 6.66 (1H, doublet, H-5, Coupling constant (Hz)=6), 4.94 (1H, singlet, H-4'), 3.98 (1H, singlet, H-3'), 3.90 (3H, singlet, OCH_3-4), 3.81 (6H, singlet, OCH_3-6' and OCH_3-7'), and 2.35 (3H, singlet, H-12'); Carbon NMR (ppm): δ 207.2 (C, C-11'), 173.4 (C, C-2'), 160.9 (C, C-4), 151.3 (C, C-7'), 150.3 (C, C-6'), 146.5 (C, C-9'), 143.8 (C, C-8), 133.7 (CH, C-6), 132.1 (C, C-10'), 129.6 (C, C-9), 128.2 (CH, C-2), 119.5 (C, C-3), 111.7 (CH, C-5'), 108.3 (CH, C-8'), 107.4 (CH, C-7), 105.3 (CH, C-5), 73.1 (CH, C-3'), 63.5 (CH_3, OCH_3-4), 60.1 (CH_3, OCH_3-6' and OCH_3-7'), 45.6 (CH, C-4'), and 32.4 (CH_3, CH_3-12').

2d: 3'-Acetyl-4'-(4-hydroxy-1*H*-indol-3-yl)-6',7'-dimethoxychroman-2'-one. mp 183-186°C; Yield 78.15% (0.60 g); λ_{max} (MeOH) 337 nm; R_f 0.48; FTIR (solid state, str., cm^{-1}): 3402, 3338 (N-H, 2nd amine, H-bounded), 3221 (O-H, phenolic, H-bounded), 3031 (olefin C-H, indole), 2968, 2877 (alkane C-H), 1733 (C=O, lactonic ester), 1687 (C=O, ketone, H-bounded), 1638 (C=C, olefin), 1562 (C=C, aryl), and 1254, 1262 (ether of asymmetrical aryl-methyl C-O-C); Proton NMR (ppm): δ 9.85 (1H, singlet, NH-1), 7.14 (1H, doublet, H-7, Coupling constant (Hz)=6), 7.06 (1H, singlet, H-2), 6.95 (1H, singlet, H-5′ '), 6.88 (1H, triplet, H-6, Coupling constant (Hz)=6), 6.78 (1H, singlet, H-8'), 6.64 (1H, doublet, H-5, Coupling constant (Hz)=6), 5.39 (1H, singlet, OH-4), 4.95 (1H, singlet, H-4'), 4.02 (1H, singlet, H-3'), 3.86 (6H, singlet, OCH_3-6' and OCH_3-7'), and 2.33 (3H, singlet, H-12'); Carbon NMR (ppm): δ 207.0 (C, C-11'), 173.2 (C, C-2'), 155.4 (C, C-4), 151.1 (C, C-7'), 150.2 (C, C-6'), 146.3 (C, C-9'), 145.1 (C, C-8), 133.6 (C, C-10'), 129.0 (CH, C-2), 128.4 (CH, C-6), 124.8 (C, C-9), 119.7 (C, C-3), 111.6 (CH, C-5'), 109.3 (CH, C-5), 107.7 (CH, C-7), 106.4 (CH, C-8'), 73.1 (CH, C-3'), 60.0 (CH_3, OCH_3-6' and OCH_3-7'), 45.6 (CH, C-4'), and 32.4 (CH_3, CH_3-12').

2e: 3'-Acetyl-4'-(5-fluoro-1*H*-indol-3-yl)-6',7'-dimethoxychroman-2'-one. mp 142-144°C; Yield 76.22% (0.58 g); λ_{max} (MeOH) 327 nm; R_f 0.62; FTIR (solid state, str., cm^{-1}): 3406, 3349 (N-H, 2nd amine, H-bounded), 3035 (olefin C-H, indole), 2955, 2862 (alkane C-H), 1733 (C=O, lactonic ester), 1693 (C=O, ketone, H-bounded), 1636 (C=C, olefin), 1562 (C=C, aryl), 1256, 1257 (ether of asymmetrical aryl-methyl C-O-C), 1114 (aryl C-F); Proton NMR (ppm): δ 9.80 (1H, singlet, NH-1), 7.58 (1H, doublet, H-7, Coupling constant (Hz)=6), 7.10 (1H, singlet, H-2), 7.00 (1H, doublet, H-6, Coupling constant (Hz)=6), 6.95 (1H, singlet, H-5′ '), 7.44 (1H, singlet, H-4), 6.79 (1H, singlet, H-8'), 4.94 (1H, singlet, H-4'), 4.04 (1H, singlet, H-3'), 3.80 (6H, singlet, OCH_3-6' and OCH_3-7'), and 2.36 (3H, singlet, H-12'); Carbon NMR (ppm): δ 207.2 (C, C-11'), 173.1 (C, C-2'), 163.6 (C, C-5), 151.4 (C, C-7'), 150.5 (C, C-6'), 146.4 (C, C-9'), 138.5 (C, C-8), 133.2 (C, C-10'), 128.2 (CH, C-2), 125.0 (C, C-9), 121.1 (CH, C-6), 119.2 (C, C-3), 118.5 (CH, C-7), 115.7 (CH, C-4), 111.8 (CH, C-5'), 108.4 (CH, C-8'), 73.3 (CH, C-3'), 60.1 (CH_3, OCH_3-6' and OCH_3-7'), 45.4 (CH, C-4'), and 32.5 (CH_3, CH_3-12').

2f: 3'-Acetyl-4'-(5-chloro-1*H*-indol-3-yl)-6',7'-dimethoxychroman-2'-one. mp 118-120°C; Yield 78.01% (0.62 g); λ_{max} (MeOH) 316 nm; R_f 0.63; FTIR (solid state, str., cm^{-1}): 3410, 3336 (N-H, 2nd amine, H-bounded), 3035 (olefin C-H, indole), 2946, 2862 (alkane C-H), 1732 (C=O, lactonic ester), 1692 (C=O, ketone, H-bounded), 1642 (C=C, olefin), 1580 (C=C, aryl), 1255, 1252 (ether of asymmetrical aryl-methyl C-O-C), 1069 (aryl C-Cl); Proton NMR (ppm): δ 9.92 (1H, singlet, NH-1), 7.66 (1H, singlet, H-4), 7.54 (1H, doublet, H-7, Coupling constant (Hz)=6), 7.30 (1H, doublet, H-6, Coupling constant (Hz)=6), 7.10 (1H, singlet, H-2), 6.94 (1H, singlet, H-5′ '), 6.78 (1H, singlet, H-8'), 4.95 (1H, singlet, H-4'), 4.04 (1H, singlet, H-3'), 3.89 (6H, singlet, OCH_3-6' and OCH_3-7'), and 2.37 (3H, singlet, H-12'); Carbon NMR (ppm): δ 207.0 (C, C-11'), 173.3 (C, C-2'), 151.2 (C, C-7'), 150.6 (C, C-6'), 146.6 (C, C-9'), 134.8 (C, C-9), 133.1 (C, C-10'), 131.6 (C, C-5), 130.6 (C, C-8), 128.2 (CH, C-2), 126.1 (CH, C-4), 124.6 (CH, C-6), 120.1 (CH, C-7), 118.8 (C, C-3), 111.5 (CH, C-5'), 108.4 (CH, C-8'), 73.1 (CH, C-3'), 60.1 (CH_3, OCH_3-6' and OCH_3-7'), 44.5 (CH, C-4'), and 32.4 (CH_3, CH_3-12').

2g: 3'-Acetyl-4'-(5-methoxy-1*H*-indol-3-yl)-6',7'-dimethoxychroman-2'-one. mp 131-133°C; Yield 74.27% (0.59 g); λ_{max} (MeOH) 326 nm; R_f 0.68; FTIR (solid state, str., cm^{-1}): 3412, 3338 (N-H, 2nd amine, H-bounded), 3036 (olefin C-H, indole), 2974, 2853 (alkane C-H), 1733 (C=O, lactonic ester), 1685 (C=O, ketone, H-bounded), 1642 (C=C, olefin), 1576 (C=C, aryl), and 1254, 1241 (ether of asymmetrical aryl-methyl C-O-C); Proton NMR (ppm): δ 9.93 (1H, singlet, NH-1), 7.62 (1H, singlet, H-4), 7.49 (1H, doublet, H-7, Coupling constant (Hz)=6), 7.11 (1H, singlet, H-2), 6.95 (1H, singlet, H-8'), 6.88 (1H, singlet, H-5′ '), 6.74 (1H, doublet, H-6, Coupling constant (Hz)=6), 4.93 (1H, singlet, H-4'), 4.04 (1H, singlet, H-3'), 3.91 (3H, singlet, OCH_3-5), 3.80 (6H, singlet, OCH_3-6' and OCH_3-7'), and 2.36 (3H, singlet, H-12'); Carbon NMR (ppm): δ 207.0 (C, C-11'), 173.4 (C, C-2'), 160.3 (C, C-5), 151.1 (C, C-7'), 150.3 (C, C-6'), 148.2 (C, C-8), 146.5 (C, C-9'), 135.0 (C, C-10'), 132.7 (C, C-9), 128.1 (CH, C-2), 119.5 (C, C-3), 118.2 (CH, C-6), 115.1 (CH, C-4), 116.1 (CH, C-7), 111.8 (CH, C-5'), 108.3 (CH, C-8'), 73.1 (CH, C-3'), 63.6 (CH_3, OCH_3-5), 60.1 (CH_3, OCH_3-6' and OCH_3-7'), 45.6 (CH, C-4'), and 32.5 (CH_3, CH_3-12').

2h: 3'-Acetyl-4'-(5-hydroxy-1*H*-indol-3-yl)-6',7'-dimethoxychroman-2'-one. mp 198-200°C; Yield 72.46% (0.55 g); λ_{max} (MeOH) 339 nm; R_f 0.47; FTIR (solid state, str., cm^{-1}): 3402, 3336 (N-H, 2nd amine, H-bounded), 3220 (O-H, phenolic, H-bounded), 3033 (olefin C-H, indole), 2969, 2870 (alkane C-H), 1733 (C=O, lactonic ester), 1686 (C=O, ketone, H-bounded), 1637 (C=C, olefin), 1560 (C=C, aryl), and 1256, 1264 (ether of asymmetrical aryl-methyl C-O-C); Proton NMR (ppm): δ 9.89 (1H, s, NH-1), 7.43 (1H, doublet, H-7, Coupling constant (Hz)=6), 7.08 (1H, singlet, H-2), 6.95 (1H, singlet, H-5′ '), 6.72 (1H, doublet, H-6, Coupling constant (Hz)=6), 6.60 (1H, singlet, H-8'), 7.47 (1H, singlet, H-4), 5.40 (1H, singlet, OH-5), 4.96 (1H, singlet, H-4'), 4.02 (1H, singlet, H-3'), 3.88 (6H, singlet, OCH_3-6' and OCH_3-7'), and 2.35 (3H, singlet, H-12'); Carbon NMR (ppm): δ 207.4 (C, C-11'), 173.6 (C, C-2'), 158.4 (C, C-5), 151.1 (C, C-7'), 150.0 (C, C-6'), 148.3 (C, C-9'), 146.6 (C, C-8), 136.1 (C, C-9), 133.6 (C, C-10'), 129.2 (CH, C-2), 122.7 (CH, C-6), 119.7 (C, C-3), 116.5 (CH, C-7), 111.6 (CH, C-5'), 109.6 (CH, C-4), 106.5 (CH, C-8'), 73.1 (CH, C-3'), 60.2 (CH_3, OCH_3-6' and OCH_3-7'), 45.6 (CH, C-4'), and 32.4 (CH_3, CH_3-12').

2i: 3'-Acetyl-4'-(6-fluoro-1*H*-indol-3-yl)-6',7'-dimethoxychroman-2'-one. mp 176-178°C; Yield 83.56% (0.64 g); λ_{max} (MeOH) 329 nm; R_f 0.63; FTIR (solid state, str., cm^{-1}): 3412, 3352 (N-H, 2nd amine, H-bounded), 3039 (olefin C-H, indole), 2958, 2860 (alkane C-H), 1733 (C=O, lactonic ester), 1694 (C=O, ketone, H-bounded), 1638 (C=C, olefin), 1564 (C=C, aryl), 1257, 1262 (ether of asymmetrical aryl-methyl C-O-C), 1115 (aryl C-F); Proton NMR (ppm): δ 9.94 (1H, singlet, NH-1), 8.05 (1H, doublet, H-4, Coupling constant (Hz)=6), 7.36 (1H, singlet, H-7), 7.14 (1H, singlet, H-2), 6.97 (1H, singlet, H-5′ '), 6.80 (1H, doublet, H-5, Coupling constant (Hz)=6), 6.62 (1H, singlet, H-8'), 4.94 (1H, singlet, H-4'), 4.02 (1H, singlet, H-3'), 3.89 (6H,

singlet, OCH_3-6' and OCH_3-7'), and 2.40 (3H, singlet, H-12'); Carbon NMR (ppm): δ 207.1 (C, C-11'), 173.0 (C, C-2'), 164.9 (C, C-6), 152.4 (C, C-7'), 150.5 (C, C-6'), 146.3 (C, C-9'), 143.3 (C, C-8), 140.4 (C, C-9), 133.3 (C, C-10'), 128.2 (CH, C-2), 124.2 (CH, C-4), 119.4 (C, C-3), 113.0 (CH, C-7), 111.8 (CH, C-5'), 108.4 (CH, C-8'), 102.6 (CH, C-5), 73.1 (CH, C-3'), 60.1 (CH_3, OCH_3-6' and OCH_3-7'), 45.3 (CH, C-4'), and 32.4 (CH_3, CH_3-12').

2j: 3'-Acetyl-4'-(6-chloro-1*H*-indol-3-yl)-6',7'-dimethoxychroman-2'-one. mp 154-156°C; Yield 86.59% (0.59 g); λ_{max} (MeOH) 318 nm; R_f 0.65; FTIR (solid state, str., cm^{-1}): 3410, 3338 (N-H, 2nd amine, H-bounded), 3038 (olefin C-H, indole), 2951, 2869 (alkane C-H), 1732 (C=O, lactonic ester), 1694 (C=O, ketone, H-bounded), 1640 (C=C, olefin), 1570 (C=C, aryl), 1251, 1255 (ether of asymmetrical aryl-methyl C-O-C), 1070 (aryl C-Cl); Proton NMR (ppm): δ 9.93 (1H, singlet, NH-1), 8.01 (1H, doublet, H-4, Coupling constant (Hz)=6), 7.69 (1H, singlet, H-7), 7.26 (1H, doublet, H-5, Coupling constant (Hz)=6), 7.14 (1H, singlet, H-2), 6.95 (1H, singlet, H-5′ '), 6.80 (1H, singlet, H-8'), 4.95 (1H, singlet, H-4'), 4.02 (1H, singlet, H-3'), 3.88 (6H, singlet, OCH_3-6' and OCH_3-7'), and 2.33 (3H, singlet, H-12'); Carbon NMR (ppm): δ 207.0 (C, C-11'), 173.7 (C, C-2'), 151.4 (C, C-7'), 150.4 (C, C-6'), 146.6 (C, C-9'), 143.9 (C, C-8), 140.4 (C, C-9), 136.2 (C, C-6), 133.5 (C, C-10'), 128.2 (CH, C-2), 126.2 (CH, C-4), 124.3 (CH, C-5), 119.8 (C, C-3), 116.9 (CH, C-7), 111.3 (CH, C-5'), 108.4 (CH, C-8'), 73.2 (CH, C-3'), 60.1 (CH_3, OCH_3-6' and OCH_3-7'), 44.5 (CH, C-4'), and 32.7 (CH_3, CH_3-12').

2k: 3'-Acetyl-4'-(6-methoxy-1*H*-indol-3-yl)-6',7'-dimethoxychroman-2'-one. mp 171-173°C; Yield 81.19% (0.64 g); λ_{max} (MeOH) 325 nm; R_f 0.72; FTIR (solid state, str., cm^{-1}): 3414, 3337 (N-H, 2nd amine, H-bounded), 3032 (olefin C-H, indole), 2975, 2852 (alkane C-H), 1732 (C=O, lactonic ester), 1689 (C=O, ketone, H-bounded), 1644 (C=C, olefin), 1576 (C=C, aryl), and 1250, 1244 (ether of asymmetrical aryl-methyl C-O-C); Proton NMR (ppm): δ 9.90 (1H, singlet, NH-1), 7.96 (1H, doublet, H-4, Coupling constant (Hz)=6), 7.22 (1H, singlet, H-7), 7.11 (1H, singlet, H-2), 6.86 (1H, singlet, H-5′ '), 6.76 (1H, singlet, H-8'), 6.52 (1H, doublet, H-5, Coupling constant (Hz)=6), 4.95 (1H, singlet, H-4'), 3.96 (1H, singlet, H-3'), 3.80 (3H, singlet, OCH_3-6), 3.70 (6H, s, OCH_3-6' and OCH_3-7'), and 2.35 (3H, singlet, H-12'); Carbon NMR (ppm): δ 207.2 (C, C-11'), 173.6 (C, C-2'), 161.5 (C, C-6), 151.3 (C, C-7'), 150.0 (C, C-6'), 146.5 (C, C-9'), 143.6 (C, C-8), 137.1 (C, C-9), 132.0 (C, C-10'), 128.5 (CH, C-2), 124.8 (CH, C-4), 119.2 (C, C-3), 114.1 (CH, C-5), 111.9 (CH, C-5'), 108.3 (CH, C-8'), 100.2 (CH, C-7), 73.3 (CH, C-3'), 63.5 (CH_3, OCH_3-6), 60.1 (CH_3, OCH_3-6' and OCH_3-7'), 45.6 (CH, C-4'), and 32.5 (CH_3, CH_3-12').

2l: 3'-Acetyl-4'-(6-hydroxy-1*H*-indol-3-yl)-6',7'-dimethoxychroman-2'-one. mp 207-209°C; Yield 75.25% (0.57 g); λ_{max} (MeOH) 336 nm; R_f 0.46; FTIR (solid state, str., cm^{-1}): 3400, 3332 (N-H, 2nd amine, H-bounded), 3220 (O-H, phenolic, H-bounded), 3034 (olefin C-H, indole), 2965, 2874 (alkane C-H), 1733 (C=O, lactonic ester), 1688 (C=O, ketone, H-bounded), 1634 (C=C, olefin), 1561 (C=C, aryl), and 1253, 1260 (ether of asymmetrical aryl-methyl C-O-C); Proton NMR (ppm): δ 9.80 (1H, singlet, NH-1), 7.85 (1H, doublet, H-4, Coupling constant (Hz)=6), 7.13 (1H, singlet, H-7), 7.00 (1H, singlet, H-2), 6.88 (1H, singlet, H-5′ '), 6.70 (1H, singlet, H-8'), 6.53 (1H, doublet, H-5, Coupling constant (Hz)=6), 5.44 (1H, singlet, OH-6), 4.93 (1H, singlet, H-4'), 4.02 (1H, singlet, H-3'), 3.86 (6H, singlet, OCH_3-6' and OCH_3-7'), and 2.35 (3H, singlet, H-12'); Carbon NMR (ppm): δ 207.5 (C, C-11'), 173.1 (C, C-2'), 161.9 (C, C-6), 151.4 (C, C-7'), 150.2 (C, C-6'), 146.3 (C, C-9'), 144.0 (C, C-8), 137.4 (C, C-9), 133.7 (C, C-10'), 129.0 (CH, C-2), 125.2 (CH, C-4), 119.7 (C, C-3), 115.9 (CH, C-5), 111.6 (CH, C-5'), 106.5 (CH, C-8'), 101.8 (CH, C-7), 73.2 (CH, C-3'), 60.0 (CH_3, OCH_3-6' and OCH_3-7'), 45.6 (CH, C-4'), and 32.5 (CH_3, CH_3-12').

Investigating the antiproliferative activity

For each of the investigated coumarin-indole hybrids as well as the FDA-approved antiproliferative drug, 5-fluorouracil (5-FU), a source solution was prepared by dissolving 1 mg of the investigated in 1 ml of DMSO. From this solution, an addition of ten sub-source solutions (500-0.98 μg/ml) was prepared using DMSO as a concentration attenuator. The examined cancerous-10^4 line's cells were then packed above an expansion form of media for each well of a 96-well layout and allowed to multiply for 24 hr. Per well, was then individually confronted with one of the concentrations that had been made earlier. After 72 hr of onset, the expansive material was thrown away, and the colored probe (MTT, 28 μl, 3.25 mM) was incorporated to test the cell viability. The confronted cells were then kept at 37°C for a supplementary 1.5 hr. Using a digital microplate-reader that was calibrated at a wavelength of 492 nm, the absorption spectrum of each well was scored. The abbreviations of Ac and Au, in the order, represented the absorption sores of confronted and unconfronted cells. The proliferation retarding percent (PR%) was computed by applying the mathematical equation, which is PR% = (Au-Ac/Au)×100. To establish the IC_{50} marks in nonlinear regression, the PR% values were sketched against the logarithmic concentration range. The protocol steps were tripled throughout in order to optimize the performance.[22]

RESULTS AND DISCUSSION

Chemistry

The availability of various aminosalicylaldehydes in our stock and the expensive pricing of the indole-constructing unites (**1a**-**1l**) encouraged the research team to synthesize them. The synthesis was accomplished by applying the diazotization that was followed by Sandmeyer reactions. On the other hand, the coumarin component of the hybrids, 3-acetyl-4,5-dimethoxycoumarin, was synthesized *in situ* via the Knoevenagel condensation reaction. In this case, the utilization of microwave irradiation results in maximizing the yield, minimizing the side reaction and shortening the reaction time.[23] Then, afterward, the formed trifunctionalized coumarin derivative was reacted individually with the synthesized indole-constructing unites via a Michael addition reaction, creating the target hybrids in a good yield. The accuracy of our synthetic effort was validated by analyzing the spectra of the generated hybrids discharged from various spectrophotometers.

Antiproliferative activity

To fully achieve our aim, the potential of the synthesized coumarin-indole hybrids as cytotoxic candidates was investigated, utilizing MTT as a coloring probe to identify the survival of the cells under investigation. In this *in vitro* assay, the cytotoxicity of our hybrids was studied versus nine tumor cell types, employing 5-FU and the utilized solvent, in this order, as positive and negative controls. These types included in this assay were MCF-7, MDA-MB-231, AR42J, KYSE-30, SK-OV-3, HeLa, AMN3, AB12, and LC540.

From the cytotoxicity markers recorded in Tables 1, 2 and 3, several shining spotlights are indicated. First, the cytotoxicity of our coumarin-indole hybrids was less than that of the 5-FU against the tumor cell types being studied in a relatively comparable way. Second, hybrids with fluoride functionality were more potent as cytotoxic agents than those with chloride, hydroxyl, or methoxy moieties.[22,24] Third, the cytotoxicity of the hybrids bearing indole substituted at position-6 (**2i**-**2l**) was up-scored relative to those with indole functionalized at position-4 (**2a**-**2d**) or position-5 (**2e**-**2h**). Also, the latter hybrids have the lowest levels of cytotoxicity indicators.[25,26] The steric hindrance of the indole substitute received the attention from the authors; it is present to the greatest extent in the hybrids **2a**–**2d**, then degrades in the hybrids **2e**–**2h**, and finally declines in the hybrids **2i**-**2l**. Finally, the

cytotoxicity of the **2i** hybrid was outstanding and approached that of the 5-FU against the two breast cancer cell types under study, MCF-7 and MDA-MB-231 (27,28). The authors hypothesized that this hybrid is a possible candidate to function as an anti-breast cancer agent in light of this heralding discovery.

CONCLUSION

In this study, the effective synthesis of twelve coumarin-indole hybrids and the characterization of their 2D molecular structures were reported. The authors concluded that hybrids with an indole substitution at position-4 can reflect viable candidates as antiproliferative applications after investigating their antiproliferative capabilities and analyzing the obtained results. Furthermore, because of its highly potent activity against the investigated breast cancer cell types, hybrid **2i** might be a valuable paradigm for developing heralding and strong anti-breast cancer treatments.

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APPROVAL BY THE ETHICS COMMITTEE

The research was authorized by the department of pharmaceutical chemistry's ethics committee at session number 6 on 20-2-2019.

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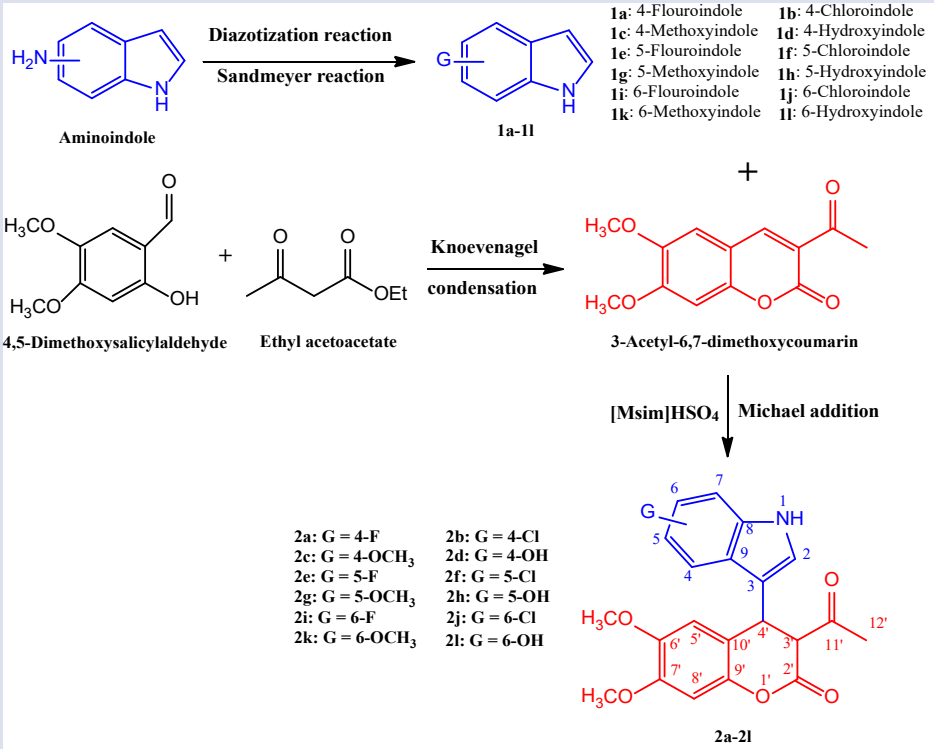
GRAPHICAL ABSTRACT



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