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4-Methylumbelliferone and Its Derived Compounds: A Brief Review of Their Cytotoxicity

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Abstract

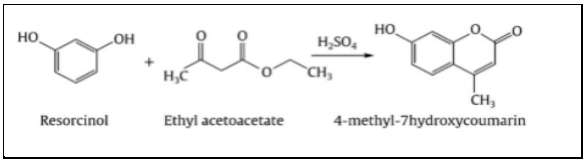
Many efforts have been directed toward the isolation of natural products, and using them to synthesize new chemical agents, and explore their cytotoxic attributes. However, finding new chemotherapeutic agents with towering potentials in the terms of high activity and target-selectivity, as well as minimal side effects is still out of hand. To satisfy that, medicinal chemists directed much of their research toward screening the cytotoxic activity of the isolated products and synthetic compounds. One of the most investigated bands of compounds is those belong to coumarin-family. Although most of these family members exhibited characteristic cytotoxic attributes, the compound termed 4-methylumbelliferone and chemically named 7-hydroxy-4-methylcoumarin showed, with its derived compounds, an exceptional activity in cancer therapy. This effect included the ability of these compounds to counteract the mechanisms of the multidrug-tumor resistance, cover the side potentials of the currently used chemotherapeutic drugs, and boost the tumor sensitivity to phototherapy. In this report, we browsed the literature to report the recent advances for the application of 4-methylumbelliferone and its derived compounds as cytotoxic agents and identify the structural requirements for the maximum selectivity versus each cancer-phenotype. The outcomes of this report may help in the direction of research toward designing and synthesizing new 4-methylumbelliferone-derived products exhibiting the best selectivity and green-side potentials.

Keywords: Chemotherapy; Synthetic coumarins; Cytotoxicity; 4-Methylumbelliferone ; Coumarin.

1. Introduction

Coumarins represent a major class of bicyclic compounds which contain oxygen within the benzopyrone family of compounds [1]. Many coumarin-based compounds, whether natural, semisynthetic or synthetic have a multitude of biological actions [2]–[11] such as antimicrobial [12], [13], antioxidant [14], [15], anti-inflammatory [16], anti-Alzheimer [17], anticoagulant [18], cardiotonic [19], and antitumor activities [20]–[22]. Several mechanisms have been implicated in the antitumor action of coumarin-based compounds against various tumor cell lines depending on the distribution of the versatile functional groups attached to the basic coumarin nucleus [23-26].

One of the examples of synthetic coumarins is 4-methylumbelliferone. Pechmann condensation is the primary source for the synthesis of 4-methylumbelliferone and is carried out by reacting resorcinol with ethyl acetoacetate, as shown in Scheme 1. Homogenous or heterogeneous catalysts may be used in this synthesis. Heating, ultrasound or microwave radiation can be employed as an energy source for the [23], [24].



Scheme 1: Synthetic scheme for the preparation of 7-hydroxy-4-methylcoumarin (4-methylumbelliferone) utilizing a Pechmann reaction [23, 24].

Among several thousands of synthetic coumarins, 4-methylumbelliferone has attracted much attention [25]. The compound's potential in the photo- and

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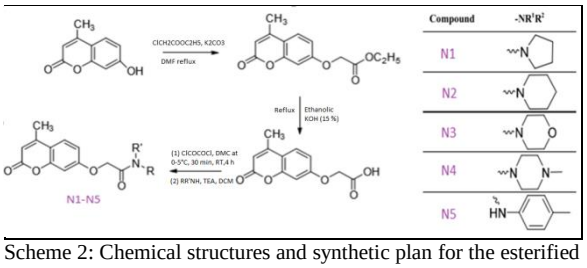
chemotherapy of various cancer types is behind this interest [26]. In this concern, it was concluded that the antitumor activity of 4-methylumbelliferone can be enhanced by the incorporation of specific functional groups at defined positions. Based on this finding, 4-methylumbelliferone can serve as a template for the preparation of more potent and selective coumarin-derived antitumor agents with minimal side effects [3]. Therefore, this review is aimed at exploring the antitumor potential of different compounds derived from 4-methylumbelliferone.

Mice were used by Bhattacharyya et al. to study the antitumor effects of 4-methylumbelliferone versus papilloma. Their results showed a beneficial effect of 4-methylumbelliferone in the translation of several signal-related proteins. In their conclusions, the authors stated that this coumarin derivative could be an up-regulator of the proteins responsible for apoptosis and a down-regulator of the proteins involved in the suppression of this vital process. Accordingly, the authors concluded that the skeleton of this synthetic compound may offer a new scaffold that can be implemented in designing new chemotherapeutic agent for papilloma [27].

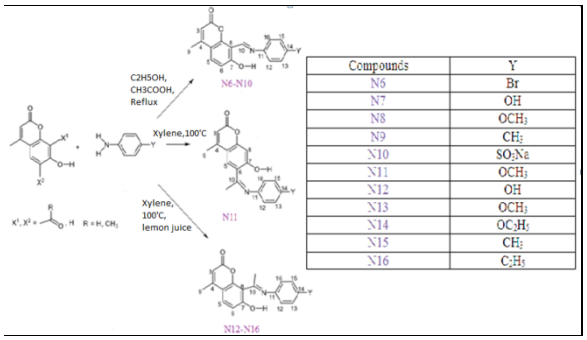
Prostate cancer cell line was another type of cancers against which the potential of 4-methylumbelliferone was investigated by Lokeshwar et al. The study found that this synthetic coumarin has good oral bioavailability and a promising antitumor effect mediated by suppressing the expression of hyaluronic acid receptors, Hyaluronan synthase 2 (HAS2), and protein kinase B /PKB, also known as Akt kinase [28].

Shah et al. synthesized five derivatives of 7-coumarinyl-oxyacetamides, herein called N1-N5, starting from 4-methylumbelliferone (Scheme 2). The antitumor activity of the prepared compounds was tested using two cancer cell-lines. The synthetic coumarin derivatives in this study showed a satisfying antitumor attribute against the test line A549 cells (specific line acquired from lung cancer). Additionally, compound N4 showed an outstanding activity against A375 cells (special cell line attained from melanoma) [29].



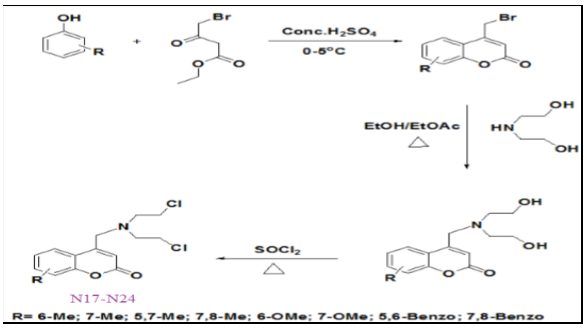
Scheme 2: Chemical structures and synthetic plan for the esterified compounds as displayed via Shah et al [29].

Eighteen coumarin-Schiff base conjugates, of which eleven were novel, were synthesized by Hejchman et al., as shown in Scheme 3. These novel synthetic compounds (for the purposes of this review are termed N6-N16 were derived from aldehyde- or ketone-based 4-methylumbelliferone derivatives substituted with 6-acetyl, 8-acetyl, or 8-formyl functional groups. The antitumor effect of compounds N6-N16 was evaluated against two cancer cell lines, CFPAC (human pancreatic cells) and HeLa (cervical) cells. Four-methylumbelliferone-based derivatives showed higher selectivity for cancer cells than non-malignant cells, with the best anticancer effect exhibited by compounds N8 and N12 [30].



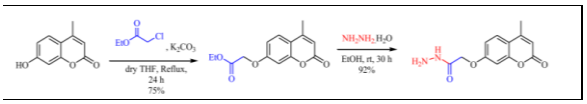
Scheme 3: Chemical structures and synthetic plan for the products synthesized via Hejchman et al [30].

MV et al. started the synthesis of 4-((Bis (2-chloroethyl) amino)) methyl-coumarins from 4-bromomethyl coumarin, as shown in Scheme 4. These compounds are referred to as N17-N24 for the purposes of this review. Their cytotoxic potential was evaluated against MCF-7 (breast cancer) and HeLa (cervix cancer) cells. The results revealed that these synthetic coumarin derivatives had an acceptable antitumor property against the tested cell lines, mainly through apoptosis induction [31].

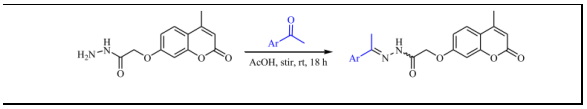


Scheme 4: Synthetic plan as depicted by MV et al [31].

Duangdee et al. reported the design and synthesis of 4-methylumbelliferone-hydrazide hybrids, as shown in Schemes 5 and 6. These compounds, herein referred to as N25-N31 (Fig. 1), were investigated for antitumor attribute, versus three common human cancer lines; hepatocellular (HepG2), breast (SKBR-3), and colorectal (Caco-2) cancer phenotypes. The investigations revealed that the hybrid N28 exhibited the highest antitumor activity against HepG2 cells, whereas the hybrid N30 showed the best cytotoxic effect against SKBR-3 line cells. Based on these results, it was concluded that the potent antitumor effect of these hybrids could be related to the presence of specific substituents on the para position of the phenyl ring [32].



Scheme 5: Synthesis of the hydrazide part as described via Duangdee et al [32].



Scheme 6: Condensation reaction applied to prepare the compounds titled N25-N31[32].

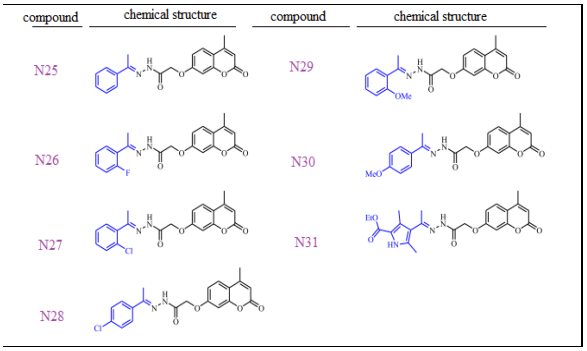


Fig. 1. Chemical structures of the compounds synthesized via Duangdee et al [32].

Nofal et al. fabricated a group of novel 4-methylumbelliferone-based compounds. The antitumor effect of these compounds was tested against Ehrlich ascites cancer. A cytotoxic effect was produced by some of the derivatives, with the highest antitumor activity exhibited by the compound here in termed N32 with the chemical structure shown in Fig. 2 [33].

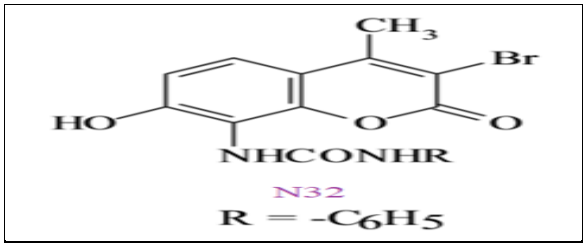


Fig. 2. Chemical structure of the product titled N32 [33].

Musa et al. have analyzed the antitumor activity of a panel consisting of eight coumarin conjugates that are closely similar to 4-methylumbelliferone regarding the building precursor, for the purposes of this review are called N33-N40 (Fig. 3). The cytotoxicity analysis was performed with two human cancer cell lines, which are prostate and breast cell lines. The analysis showed that compound N38 displayed the highest selectivity and antitumor property against prostate carcinoma cell line. Among the conclusions draw in this study, it was assumed that substitution of the p-methyl sulfonyl phenyl group at carbon 3 of the coumarin backbone may enhance the antitumor attribute of these conjugates [34].

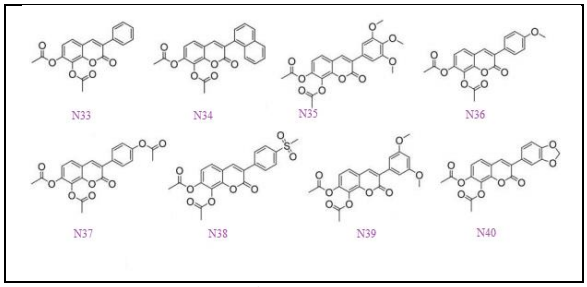
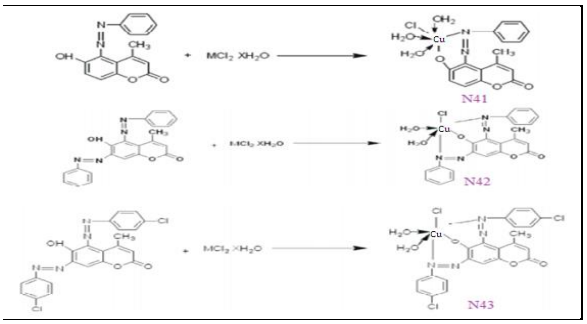


Fig. 3. Chemical structures of the conjugates synthesized via Musa et al [34].

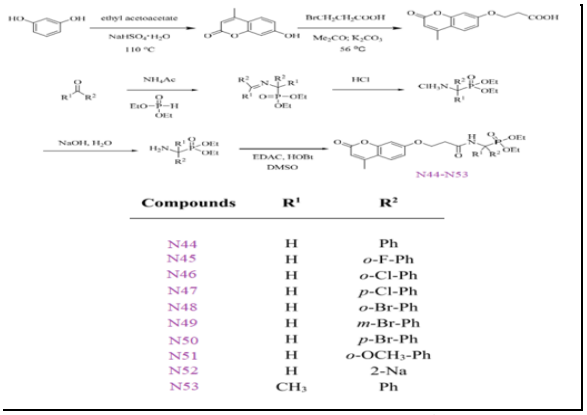
The interaction between copper and coumarin derivatives, as illustrated in Scheme 7 was reported by Ibrahim et al. The resultant three novel complexes, herein called N41-N43, were investigated as antitumor agents versus two cancer cell lines, namely A549 (lung cancer) and MCF-7 (breast cancer). The

results revealed that complexes N41 and N42 showed potent anticancer property against the breast cancer cell lines, while complex N43 exhibited the highest anticancer attribute versus the lung cancer cell line. These results led to the conclusion that the presence of the coumarin backbone and the copper metal in the same plane is required for the tested activity. Also, the electron transfer capability of the utilized coumarins is an additional important contributing factor [35].



Scheme 7: Synthesis of the coumarin-copper complexes that were synthesized via Ibrahim et al [35].

Li et al. synthesized a series of ten novel 4-methylumbelliferone-derived α-amino phosphonates, as presented in Scheme 8. The cytotoxic activities of these conjugates, called N44-N53 for the purposes of this review, was analyzed versus three human cancer cell lines; HCT-116 (colorectal carcinoma), KB (nasopharyngeal carcinoma), and MGC-803(lung adenocarcinoma) cell lines. These compounds have shown a higher anticancer property in comparison with the parent compound, 4-methylumbelliferone. Besides, compound N53 exhibited the best antitumor activity which was assumed to result from the induction of apoptosis [36].



Compounds	R^1	R^2
N44	H	Ph
N45	H	*o*-F-Ph
N46	H	*o*-Cl-Ph
N47	H	*p*-Cl-Ph
N48	H	*o*-Br-Ph
N49	H	*m*-Br-Ph
N50	H	*p*-Br-Ph
N51	H	*o*-OCH_3-Ph
N52	H	2-Na
N53	CH_3	Ph

Scheme 8: Synthesis and chemical structures of the compounds synthesized via Li et al [36].

Miri et al. reported the synthesis of multiple 4-alkylcoumarin derivatives and analyzed their cytotoxicity against three cancer cell lines; chronic myelogenous leukemia (K562), colorectal cancer (LS180), and breast cancer (MCF-7). These compounds (Fig. 4), herein named N54-N80, including 4-methylumbelliferone have shown an acceptable antitumor activity with those having the highest lipophilic character exhibiting the best effect. Better penetration to the target cells brought about by longer alkyl chains at carbon atom number 3 of the coumarin backbone was speculated by the authors to be the main factor contributing to the cytotoxic activity. [37].

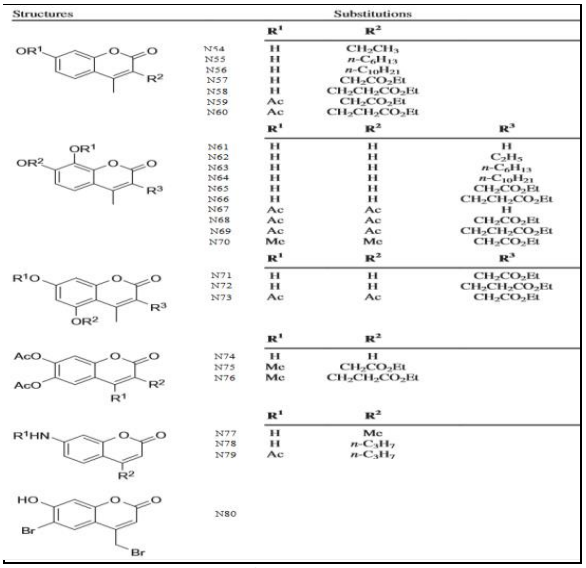
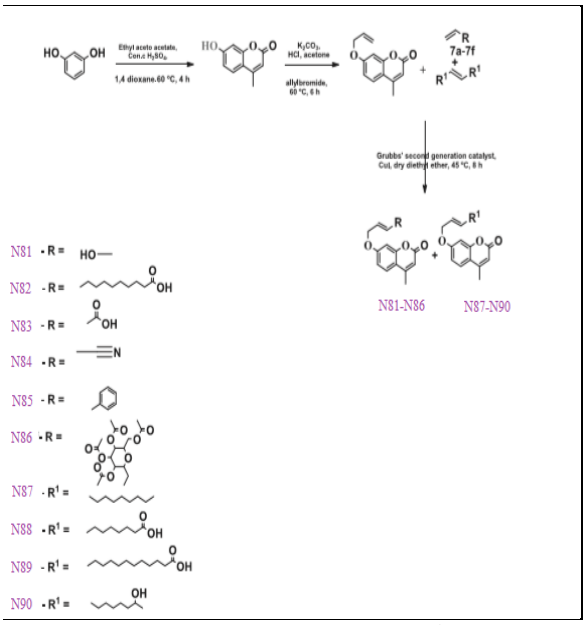


Fig. 4 Chemical structures of the compounds synthesized via Miri et al [37].

Yelchuri et al. reported the synthesis of ten new 4-methylumbelliferone derivatives, named N81-N90 herein as shown in Scheme 9. The authors achieved the synthesis by the condensation of 4-methylumbelliferone with various molecules such as acrylic acid, acrylo-nitrile, benzyl, allyloxy, and others. Compounds N81-N90 were tested for their antitumor attribute against four cancer cell lines, namely MDA-MB 231 (human breast), DU145 (prostate), SKOV3 (ovarian), HepG2 (hepatic). The results of cytotoxicity study revealed that substitution with nitrile, glycosidic, and hydroxyl groups would lead to good antitumor effect, and thus could serve as a potential scaffold for the design of new anticancer agents [38].



Scheme 9: Synthesis and chemical structures of the conjugates synthesized via Yelchuri et al [38].

Kawase et al. have investigated forty-four 4-methylumbelliferone-derived molecules, herein named N91-N134 (Fig. 5), for their ability to reverse tumor multidrug resistance and for cytotoxic activity. Fourteen compounds were able to reverse multidrug resistance with compound N124 scoring the best in this aspect that it was comparable to verapamil. Additionally, some derivatives were potent cytotoxic, with superiority attributed to compounds N133 and N134. The authors made the conclusion that such derivatives of 4-methylumbelliferone may act as good candidates for modulating the resistance of tumors to chemotherapeutic agents with minimal toxicity toward normal cells [39].

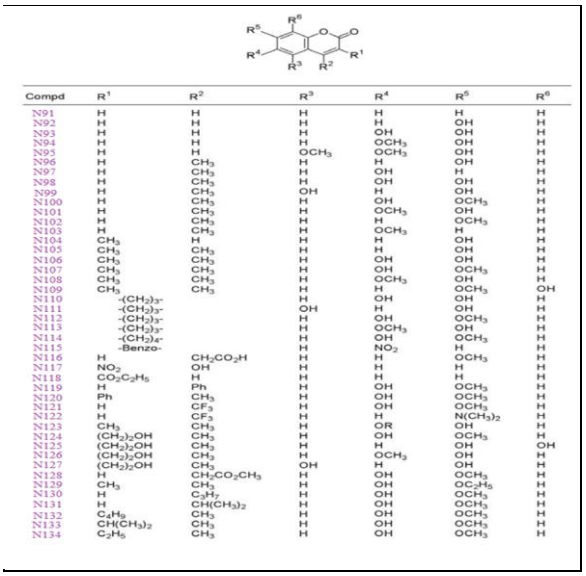


Fig. 5. Chemical structure of the general 4-methylumbelliferone-based compound prepared via Kawase et al. as well as the substituents of its prepared products [39].

The antitumor activity of formerly synthesized derivatives of coumarin including 4-methylumbelliferone (Fig. 6) was tested by Ostrowska et al. The investigation was carried out on five different human cancer cell lines; HCC-2998 (colon), HOP-92 (lung), CCRFCEM and HL-60 (leukemia), and 786-0 (renal). The authors suggested that a reduction in cytotoxic activity may result from a small increase in the lipophilicity of coumarin derivatives. Another suggestion was that the addition of acetyl moiety to O-alkyl derivatives of 4-methylumbelliferone may enhance their antitumor effect. It was recommended that other studies are required to highlight the effect of the lipophilicity on the anticancer attribute of 4-methylumbelliferone-based compounds [40].

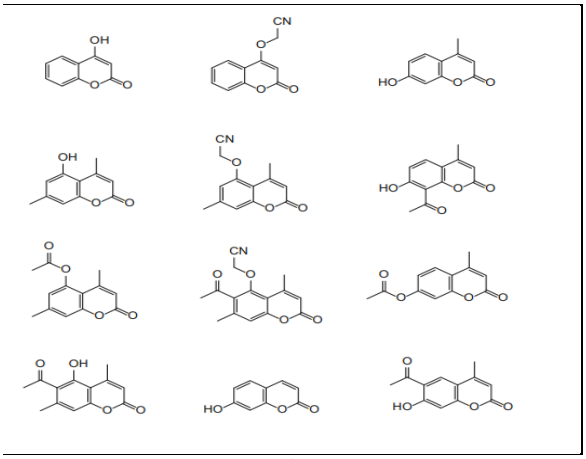
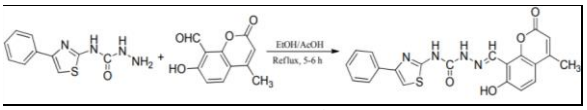


Fig. 6. Chemical structures of the products investigated via Ostrowska et al [40].

Based on the structure of 4-methylumbelliferone, a ligand was prepared by Yernale et al. following the equation shown in Scheme 10. This ligand was then complexed with metals such as Zn+2, Co+2, Cu+2, and Ni+2 producing novel complexes. The antitumor effect of the latter was evaluated against many cancer cell lines, and the results indicated that the complexes N135 and N136 (Fig. 7) had the best cytotoxic effect when compared to the other complexes [41].



Scheme 10: Schematic synthesis of the ligand as suggested by Yernale et al [41].

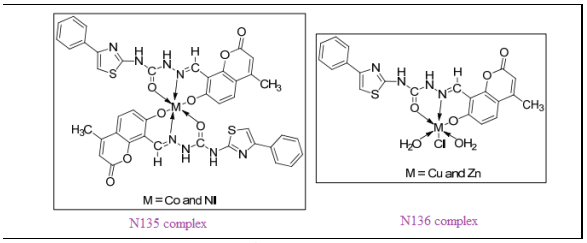


Fig. 7. Chemical structures of the N135 and N136 complexes [41].

The design and synthesis of a series of six novel 1,2,3-triazoles-4-methylumbelliferone conjugates, herein named N137-N142 (Fig. 8) was carried out by Kraljević et al. The authors investigated the cytotoxic activity of these conjugates versus HepG2 (liver cancer) cell line. Compound N138 resulted in the best cytotoxic effect. The proposed mechanism for this activity was based on the inhibitory effect of the compound on the phosphodiesterase group of enzymes inducing cell apoptosis [16].

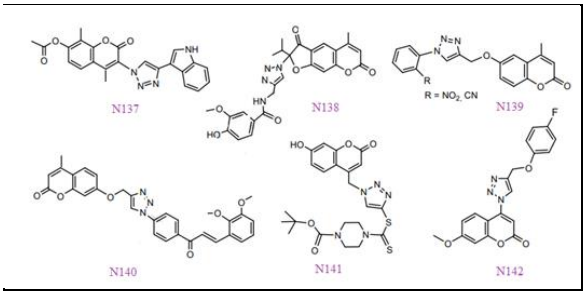


Fig. 8 Chemical structures of the conjugates prepared by Kraljević et al [16].

Finally, Table 1 may summarize the symbol, test cancer cell line (s), the LC_{50} value (s) for each of the investigated 4-methylumbelliferone-derived compounds, which are listed in this brief review.

Table 1: The symbol, test cancer cell line (s), the LC_{50} value (s) for each of the investigated compounds.

Sym.	Test cancer cell line (s)	LC_{50} value (s) μM	Ref.
N1	A549	9.26	[29]
N2	A549	0.66	
N3	A549	0.41	
N3	A549	NA	
N5	A549	0.001	
N6	CFPAC, HeLa	27, 36	[30]
N7	CFPAC, HeLa	207, 57	
N8	CFPAC, HeLa	9, 12	
N9	CFPAC, HeLa	32, 34	
N10	CFPAC, HeLa	10, 22	
N11	CFPAC, HeLa	47,36	
N12	CFPAC, HeLa	8, 12	
N13	CFPAC, HeLa	135,111	
N14	CFPAC, HeLa	76, 78	
N15	CFPAC, HeLa	104, 89	
N16	MCF-7, HeLa	107,46	
N17	MCF-7, HeLa	135, 120.33	[31]
N18	MCF-7, HeLa	34.12, 37.44	
N19	MCF-7, HeLa	9.02, 7.89	
N20	MCF-7, HeLa	20.56, 21.45	
N21	MCF-7, HeLa	83.45, 77.83	
N22	MCF-7, HeLa	15.11, 13.12	
N23	MCF-7, HeLa	45.35, 41.45	
N24	MCF-7, HeLa	24.86, 25.48	
N25	MCF-7, HeLa	8.46, 7.01	
N26	HepG2, SKBR-3, Caco-2	10.56, 15.86, 176.98	[32]
N27	HepG2, SKBR-3, Caco-2	12.48, 21.45, 128.05	
N28	HepG2, SKBR-3, Caco-2	2.11, 8.14, 128.23	
N29	HepG2, SKBR-3, Caco-2	14.87, 22.80, 143.89	
N30	HepG2, SKBR-3, Caco-2	5.23, 7.18, 112.22	
N31	HepG2, SKBR-3, Caco-2	12.89, 21.87, 126.65	
N32	Ehrlich ascites cancer	6.34	[33]
N33	PC-3, MDA-MB-231	68.34, >100	[34]
N34	PC-3, MDA-MB-231	43.30, >100	
N35	PC-3, MDA-MB-231	67.80, >100	
N36	PC-3, MDA-MB-231	41.10, 31.27	
N37	PC-3, MDA-MB-231	78.73, 66.67	
N38	PC-3, MDA-MB-231	24.43, 67.89	
N39	PC-3, MDA-MB-231	47.20, >100	
N40	A549, MCF-7	36.80, >100	
N41	A549, MCF-7	7.5, 1.87	[35]
N42	A549, MCF-7	15, 1.87	
N43	A549, MCF-7	1.45, 30	
N44	HCT-116, KB, MGC-803	62.34, 25.47, 22.42	[36]
N45	HCT-116, KB, MGC-803	35.25, 55.12, 25.48	
N46	HCT-116, KB, MGC-803	31.38, 41.02, 11.19	
N47	HCT-116, KB, MGC-803	31.21, 36.13, 21.09	
N48	HCT-116, KB, MGC-803	27.25, 23.71, 29.75	
N49	HCT-116, KB, MGC-	23.20, 19.33,	

	803	12.23	
N50	HCT-116, KB, MGC-803	19.46, 96.50, 91.30	
N51	HCT-116, KB, MGC-803	16.30, 23.45, 14.34	
N52	HCT-116, KB, MGC-803	32.45, 39.47, 17.05	
N53	K562, LS180, MCF-7	6.12, 0.12, 4.24	
N54	K562, LS180, MCF-7	12.48, 21.45, 128.05	[37]
N55	K562, LS180, MCF-7	10.11, 8.14, 128.23	
N56	K562, LS180, MCF-7	14.87, 22.80, 143.89	
N57	K562, LS180, MCF-7	11.23, 7.18, 112.22	
N58	K562, LS180, MCF-7	12.89, 21.87, 126.65	
N59	K562, LS180, MCF-7	67.34, 45.47, 23.16	
N60	K562, LS180, MCF-7	34.27, 65.12, 21.28	
N61	K562, LS180, MCF-7	32.38, 45.02, 18.49	
N62	K562, LS180, MCF-7	30.27, 36.23, 26.09	
N63	K562, LS180, MCF-7	24.25, 23.01, 23.45	
N64	K562, LS180, MCF-7	21.20, 19.34, 18.23	
N65	K562, LS180, MCF-7	16.46, 26.56, 11.34	
N66	K562, LS180, MCF-7	15.36, 21.47, 14.10	
N67	K562, LS180, MCF-7	31.45, 29.48, 19.05	
N68	K562, LS180, MCF-7	78.12, 61.12, 58.24	
N69	K562, LS180, MCF-7	67.34, 45.47, 23.46	
N70	K562, LS180, MCF-7	34.27, 65.12, 21.48	
N71	K562, LS180, MCF-7	32.38, 45.02, 18.43	
N72	K562, LS180, MCF-7	40.27, 36.23, 26.07	
N73	K562, LS180, MCF-7	24.25, 23.01, 29.45	
N74	K562, LS180, MCF-7	21.20, 19.34, 18.23	
N75	K562, LS180, MCF-7	17.46, 26.56, 11.34	
N76	K562, LS180, MCF-7	15.36, 21.47, 14.10	
N77	K562, LS180, MCF-7	12.45, 29.48, 19.05	
N78	K562, LS180, MCF-7	23.12, 61.12, 23.24	
N79	K562, LS180, MCF-7	67.34, 45.47, 23.46	
N80	MDA-MB 231, DU145, SKOV3, HepG2	34.27, 65.12, 21.48	
N81	MDA-MB 231, DU145, SKOV3, HepG2	25.2, 13.6, 18.2, 17.7	[38]
N82	MDA-MB 231, DU145, SKOV3, HepG2	46.5, 44.4, 39.5, 31.6	
N83	MDA-MB 231, DU145, SKOV3, HepG2	56.5, 54.5, 59.5, 51.26	
N84	MDA-MB 231, DU145, SKOV3, HepG2	32.8, 44.5, 39.5, 36.6	
N85	MDA-MB 231, DU145, SKOV3, HepG2	12.9, 13.2, 12.5, 10.6	
N86	MDA-MB 231, DU145, SKOV3, HepG2	14.9, 13.8, 12.8, 12.6	
N87	MDA-MB 231, DU145, SKOV3, HepG2	82.9, 89.2, 85.1, 80.5	
N88	MDA-MB 231, DU145, SKOV3, HepG2	78.2, 85.2, 77.7, 79.8	
N89	MDA-MB 231, DU145, SKOV3, HepG2	75.8, 82.1, 77.1, 80.1	
N90	MDA-MB 231, DU145, SKOV3, HepG2	19.0, 17.3.5, 22.6, 18.3	
N91	HCS-2	75	[39]
N92	HCS-2	>200	
N93	HCS-2	>200	
N94	HCS-2	100	
N95	HCS-2	154	
N96	HCS-2	150	
N97	HCS-2	96	
N98	HCS-2	>200	
N99	HCS-2	>200	
N100	HCS-2	>200	
N101	HCS-2	38	
N102	HCS-2	52	
N103	HCS-2	75	
N104	HCS-2	>200	
N105	HCS-2	48	
N106	HCS-2	78	
N107	HCS-2	67	
N108	HCS-2	34	
N109	HCS-2	66	
N110	HCS-2	85	
N111	HCS-2	97	
N112	HCS-2	98	
N113	HCS-2	78	
N114	HCS-2	70	
N115	HCS-2	71	
N116	HCS-2	61	
N117	HCS-2	>200	
N118	HCS-2	100	
N119	HCS-2	54	
N120	HCS-2	75	
N121	HCS-2	92	
N122	HCS-2	>200	
N123	HCS-2	>200	
N124	HCS-2	>200	
N125	HCS-2	108	
N126	HCS-2	89	
N127	HCS-2	79	
N128	HCS-2	121	
N129	HCS-2	>200	
N130	HCS-2	100	
N131	HCS-2	157	
N132	HCS-2	124	
N133	HCS-2	14	
N134	HCS-2	11	
N135	DU145, SKOV3, K562, LS180, MCF-7	9.34, 12.47, 22.05, 17.32, 22.38	[41]
N136	DU145, SKOV3, K562, LS180, MCF-7	10.86, 11.69, 20.19, 18.06,	

		18.79	
N137	HepG2	13.56	[16]
N138	HepG2	8.59	
N139	HepG2	12.67	
N140	HepG2	18.45	
N141	HepG2	17.54	
N142	HepG2	14.76	

2. Conclusions

The characteristic pharmacological attributes of natural-coumarins have been intensified the interest of medicinal chemists in designing, synthesizing, and investigating the various bioactivities of the coumarin-derived compounds. Among these bioactivities and compounds, the cytotoxic activity of 4-methylumbelliferone-derived products has magnetized plentiful research works. By analyzing the data gathered from these works, the authors highlighted the structural traits that are important to extend and improve the cytotoxic effect of these products. These structural traits involved linking carbon-3 with alicyclic- secondary amine via a shortened carbon chain, representing the coumarin backbone at carbon-5 with a small/strong electron-releasing group, and conjugating the carbon-8 with a long hydrophobic group. This report concluded that the masterful application of these traits in the design and synthesis of novel 4-methylumbelliferone-derived products could result in the discovery of effective cytotoxic agents with green lateral hints.

3. Conflicts of interest

There are no conflicts to declare.

4. Formatting of funding sources

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5. References

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