Sys Rev Pharm 2020;11(12):2263-2274
A multifaceted review journal in the field of pharmacy

Antitumor Attributes of 4-Methylumbelliferone-Based Derivatives: A Review

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ABSTRACT

Despite the isolation, design, and synthesis of a high number of compounds for managing cancer, the discovery of green chemotherapeutic agents is still represented a considerable challenge for medicinal chemists. In this concern, researchers concentrated their efforts to explore novel antitumor scaffolds by studying and screening many natural and synthetic derivatives. One of the most important family of compounds is the coumarin-derived products. Many members belong to this family have shown promising antitumor attributes with an acceptable selectivity and safety. 4-Methylumbelliferone, which is ordinarily referred to as 7-hydroxy-4-methylcoumarin, and it's based compounds have revealed encouraging properties to execute the multidrug tumor resistance, frustrate the toxic side effects of chemotherapeutic drugs, and develop the cancer phototherapy. Also, many synthetic 4-methylumbelliferone derivatives have been authenticated to have a notable antitumor attribute versus several cancer phenotypes. In this report, we screened the published data to specify the structural features of 4-methylumbelliferone-based compounds that play a defined role in their antitumor attribute. This may direct the feature studies to design and prepared new 4-methylumbelliferone derivatives with optimal activity and selectivity.

Keywords: Synthetic coumarins, 4-Methylumbelliferone, Antitumor, Cancer cell line, Chemotherapeutic agents.

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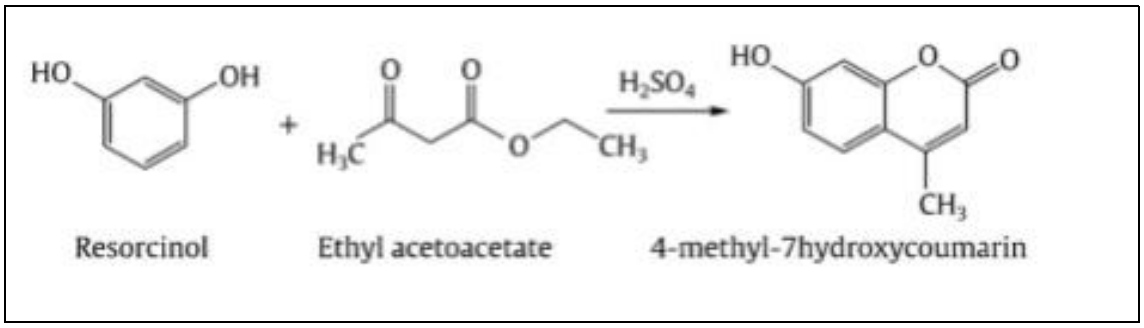
INTRODUCTION

Coumarins are a senior group of oxygen-containing bicyclic compounds that are included in the benzopyrone family of products (1). Many natural, semisynthetic, and synthetic coumarin-derived compounds have been displayed numerous biological attributes (2–11) such as antimicrobial (12,13), antioxidant (14,15), anti-inflammatory (16), anti-Alzheimer (17), anticoagulant (18), cardio-tonic (19), and antitumor activities (20–22). Based on a large number of scientific papers (23), coumarin-based compounds may implement the antitumor attribute on various tumor cell lines via several mechanisms of action (24). This issue depends upon the organization of the different substitutes on the fundamental chemical nucleus of coumarin (25,26).In the laboratory, 4-methylumbelliferone can be synthesized primarily via Pechmann condensation by reacting resorcinol with ethyl acetoacetate, as shown in Scheme 1. The catalyst of this reaction may be homogenous or heterogeneous, and the energy forwarded this transformation maybe came from conventional heating, ultrasound-, or microwave-radiation (27,28).



Scheme 1: Synthesis of 4-methylumbelliferone (7-hydroxy-4-methyl coumarin) by Pechmann condensation reaction.

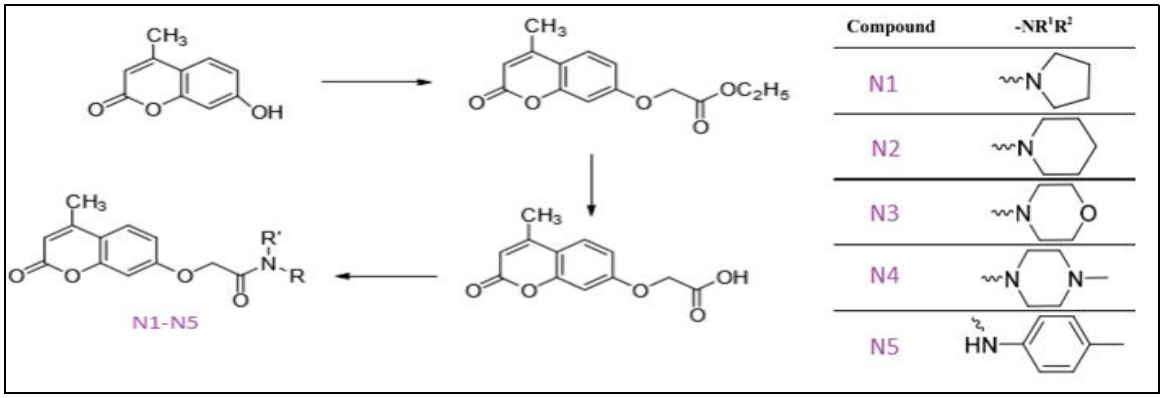
Among several thousands of synthetic coumarins, 4-methylumbelliferone has represented an attractive compound for research (29). This interest is based on much evidence that indicated the significance of its applications in the photo- and chemo-therapy of various cancer types (30). In this concern, it is found that the antitumor property of 4-methylumbelliferone can be improved by the insertion of specific substituents at defined positions. This raises the possibility to utilize this synthetic coumarin as a template to prepare potent and selective coumarin-based chemotherapeutic agents with minimal side effects (3). So, the teamwork reported this review to highlight the antitumor potential of different compounds derived from 4-methylumbelliferone.

Bhattacharyya *et al*. have studied the antitumor attribute of 4-methylumbelliferone against papilloma utilizing the mice as a model. This study indicated that 4-methylumbelliferone possesses an advantageous effect in the translation of several signal-related proteins. The authors concluded that this synthetic coumarin could up-

regulate the proteins that responsible for apoptosis and down-regulate those responsible for the suppression of this vital process. Based on these outcomes, the authors concluded that the chemical backbone of this synthetic compound may offer a new scaffold that can be employed in the design and synthesis of chemotherapeutic agent for treating papilloma-cancer phenotype (31).

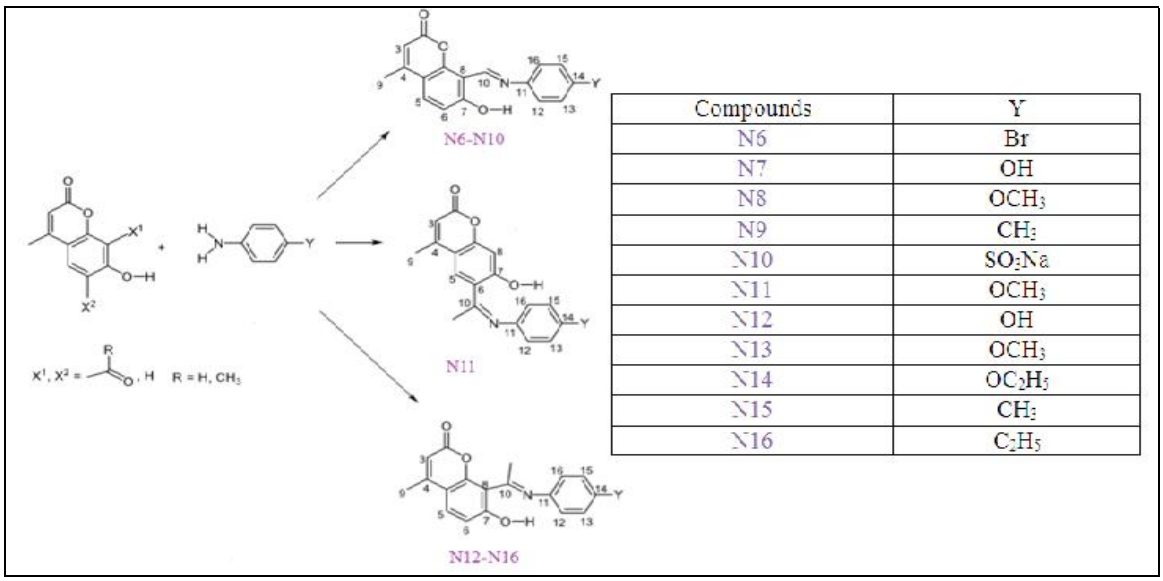
Lokeshwar *et al*. have assessed the attributes of 4-methylumbelliferone as an antitumor agent against prostate cancer cells. The results of this assessment revealed that this synthetic coumarin has good oral bioavailability. Also, it has an encouraging antitumor impact by inhibiting the expression of hyaluronic acid receptors, Hyaluronan synthase 2 (HAS2), and protein kinase B /PKB that also known as Akt kinase (32).

Shah *et al*. have prepared five derivatives of 7-coumarinyl-oxyacetamides, herein called **N1**-**N5**, utilizing 4-methylumbelliferone as a starting compound (Scheme 2). The authors have also investigated the antitumor attribute of the prepared compounds against two cell-lines. The results of this investigation indicated that these synthetic coumarins exhibited a satisfying antitumor attribute against the test line A549 cells (specific line acquired from lung cancer). Besides, compound **N4** showed an exceptional activity against A375 (specific line acquired from melanoma) (33).



Scheme 2: The synthetic project followed by Shah *et al* to prepare 7-coumarinyl-oxyacetamide derivatives.

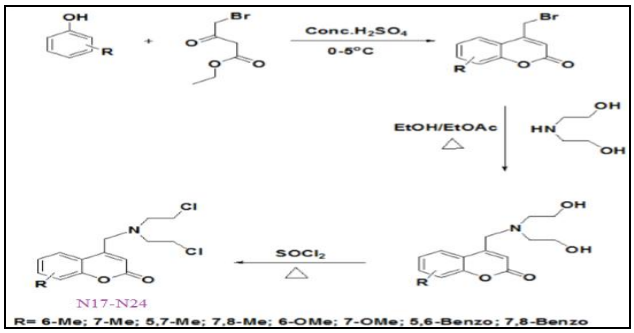
Hejchman *et al.* have recoded the synthesis of eighteen coumarin-Schiff base conjugates, from them, eleven were novel, as shown in Scheme 3. These novel synthetic compounds, herein referred to as **N6**-**N16**, were derived from aldehyde- or ketone-based 4-methylumbelliferone derivatives substituted with 6-acetyl, 8-acetyl, or 8-formyl functional groups. Their antitumor attribute was assessed against two cancer cell lines, which are human pancreatic (CFPAC) and cervical (HeLa) tumors. 4-Methylumbelliferone-based derivatives may confer higher selectivity for cancer cells than normal ones, with the topmost anticancer effect contributed to the compounds **N8** and **N12** (34).



Compounds	Y
N6	Br
N7	OH
N8	OCH_3
N9	CH_3
N10	SO_3Na
N11	OCH_3
N12	OH
N13	OCH_3
N14	OC_2H_5
N15	CH_3
N16	C_2H_5

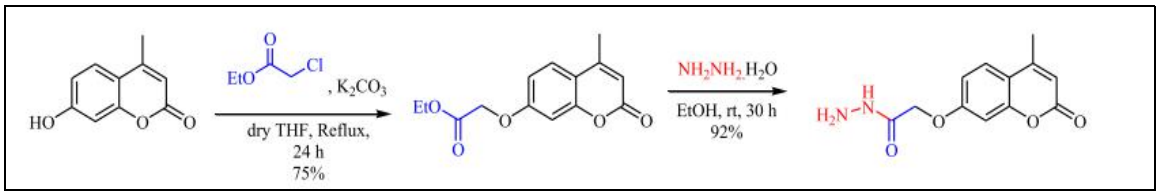
Scheme 3: The synthetic route of the eleven novel Schiff bases prepared by Hejchman *et al.*

MV *et al.* have used 4-bromomethyl coumarin as a starting material for the synthesis of 4-((Bis (2-chloroethyl) amino)) methyl-coumarins, as shown in Scheme 4. These compounds, herein termed **N17**-**N24**, have been evaluated for their cytotoxicity against MCF-7 (breast cancer) and HeLa (cervix cancer) cells. The acquired results revealed that these synthetic 4-alkylcoumarins exhibited an acceptable antitumor property against these two test cell lines, mainly by inducing apoptosis (35).

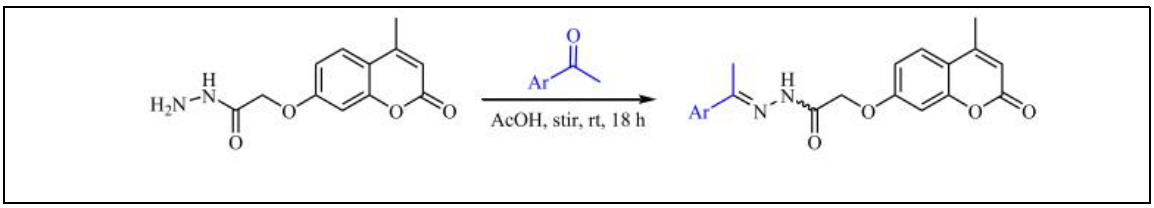


Scheme 4: **Synthetic project of the N17-N24 compounds as proposed by MV *et al.***

Duangdee *et al.* have reported the design and synthesis of 4-methylumbelliferone-hydrazide hybrids, as shown in Schemes 5 and 6. The authors have investigated the antitumor attribute of these hybrids, herein called **N25-N31** (Figure 1), against three common cancer lines acquired from humans including hepatocellular (HepG2), breast (SKBR-3), and colorectal cancer (Caco-2) cancer phenotype. The results revealed that the hybrid named **N28** showed the highest antitumor attribute against HepG2 line cells, while the hybrid named **N30** showed the highest cytotoxic property against SKBR-3-line cells. The researchers concluded that the potent antitumor effect of these hybrids may be contributed to the presence of specific substituents on the para position of the phenyl ring (36).



Scheme 5: **Synthesis of hydrazide component of the hybrids prepared by Duangdee *et al.***



Scheme 6: **Condensation of hydrazide with acetophenone-based derivatives to afford the final hybrids named N25-N31.**

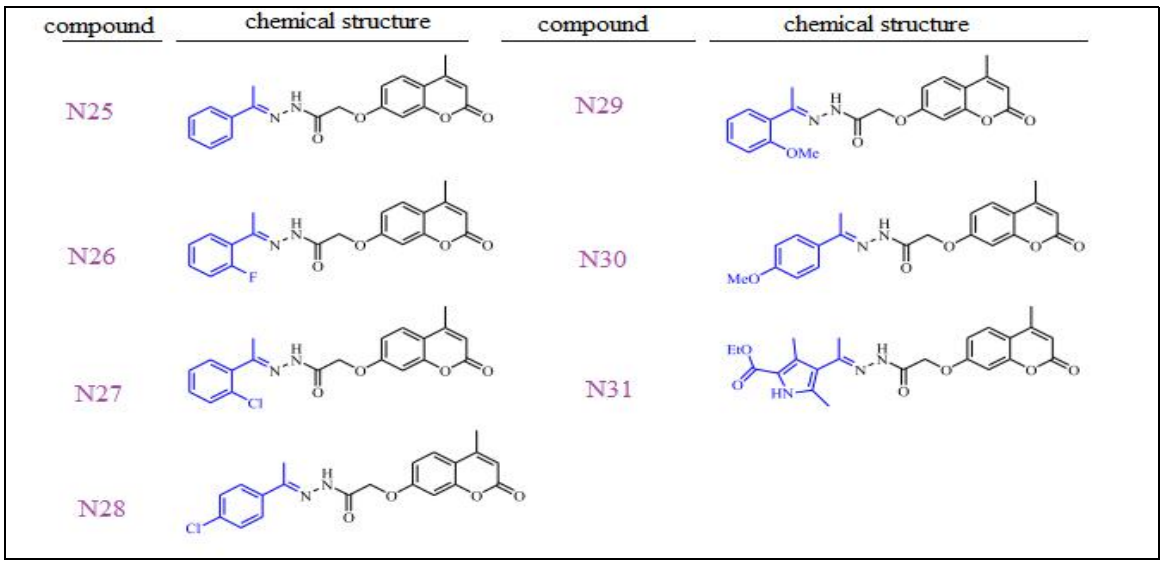


Figure 1: **Chemical structures of 4-methylumbelliferone-based compounds prepared by Duangdee *et al.***

Nofal *et al*. have synthesized a panel of novel 4-methylumbelliferone-based compounds. These synthetic coumarin derivatives have examined for their anticancer property against Ehrlich ascites cancer. Some of these derivatives have shown a cytotoxic effect, with the highest antitumor activity revealed by the compound **N32** with the chemical structure shown in Figure 2 (37).

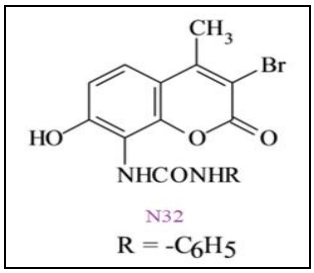


Figure 2: Chemical structure of the 4-methylumbelliferone-based product named N32.

Musa *et al.* have investigated the antitumor attribute of a panel consists of eight coumarin conjugates, herein called **N33**-**N40** (Figure 3). This attribute was examined against two human cancers, which are prostate and breast cell lines. The issues acquired from this examination revealed that the compound named **N38** showed the highest selectivity and antitumor property against prostate carcinoma cell line. The authors concluded that the substitution of the p-methyl sulfonyl phenyl group at carbon 3 of the coumarin backbone may enhance the antitumor attribute of these conjugates (38).

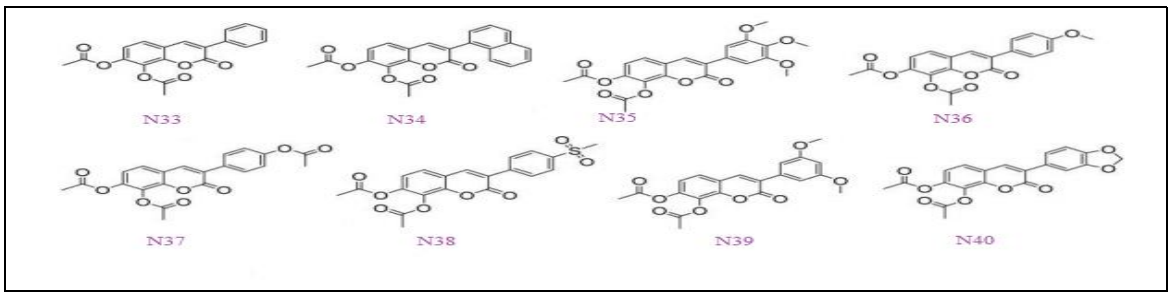
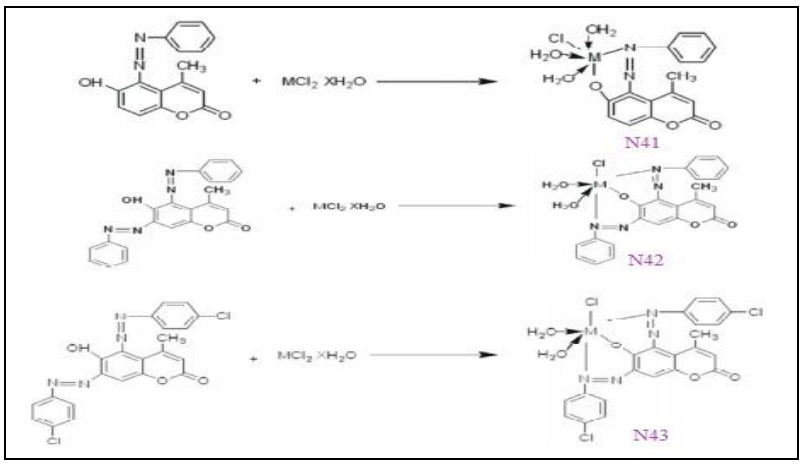


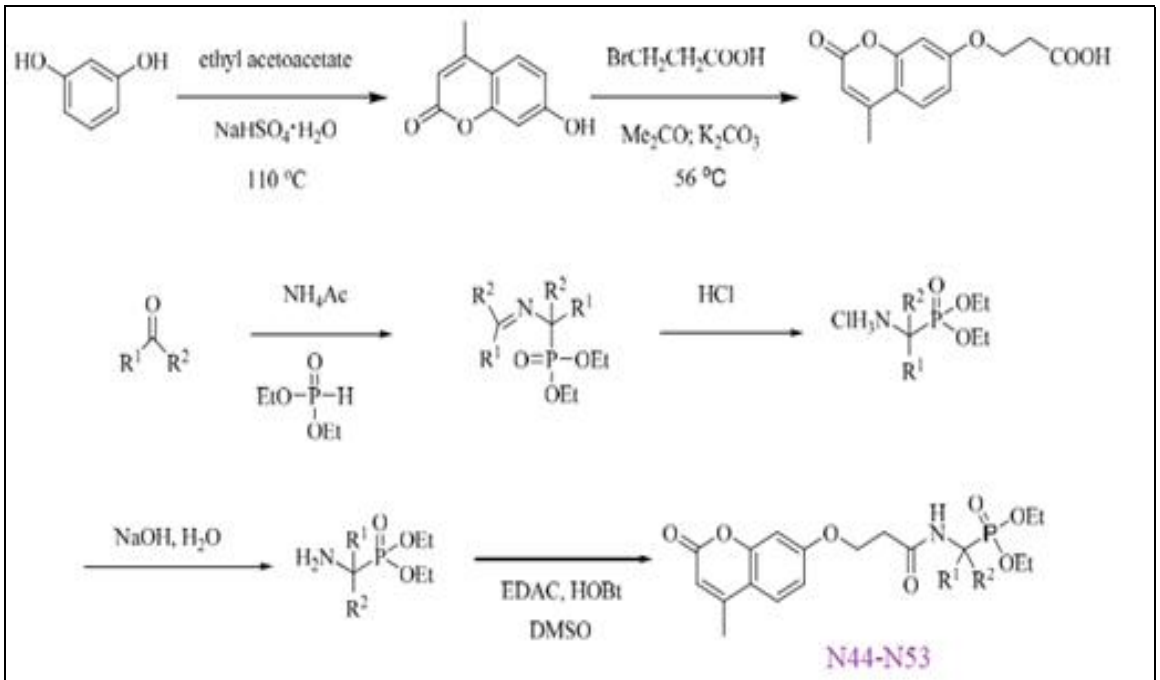
Figure 3: Chemical structures of 7,8-Diacetoxy-3-aryl coumarin conjugates prepared by Musa *et al.*

Ibrahim *et al*. have recorded the synthesis of three new complexes result from the interaction between copper and coumarin derivatives, as depicted in Scheme 7. These three novel complexes, herein called **N41**-**N43**, have examined as antitumor agents versus two cancer cell lines named A549 (lung cancer) and MCF-7 (breast cancer). The researchers revealed that **N41** and **N42** complexes showed the potent anticancer property against the breast cancer cell lines, while the complex named **N43** has the highest anticancer attribute versus the lung cancer cell line. The author concluded that the presence of the coumarin backbone in the same plane with the copper metal is favorable for the tested activity. Also, the electron transfer characteristic of the utilized coumarins is another important contribution (39).



Scheme 7: Synthesis of copper-coumarin complexes as depicted by Ibrahim *et al.*

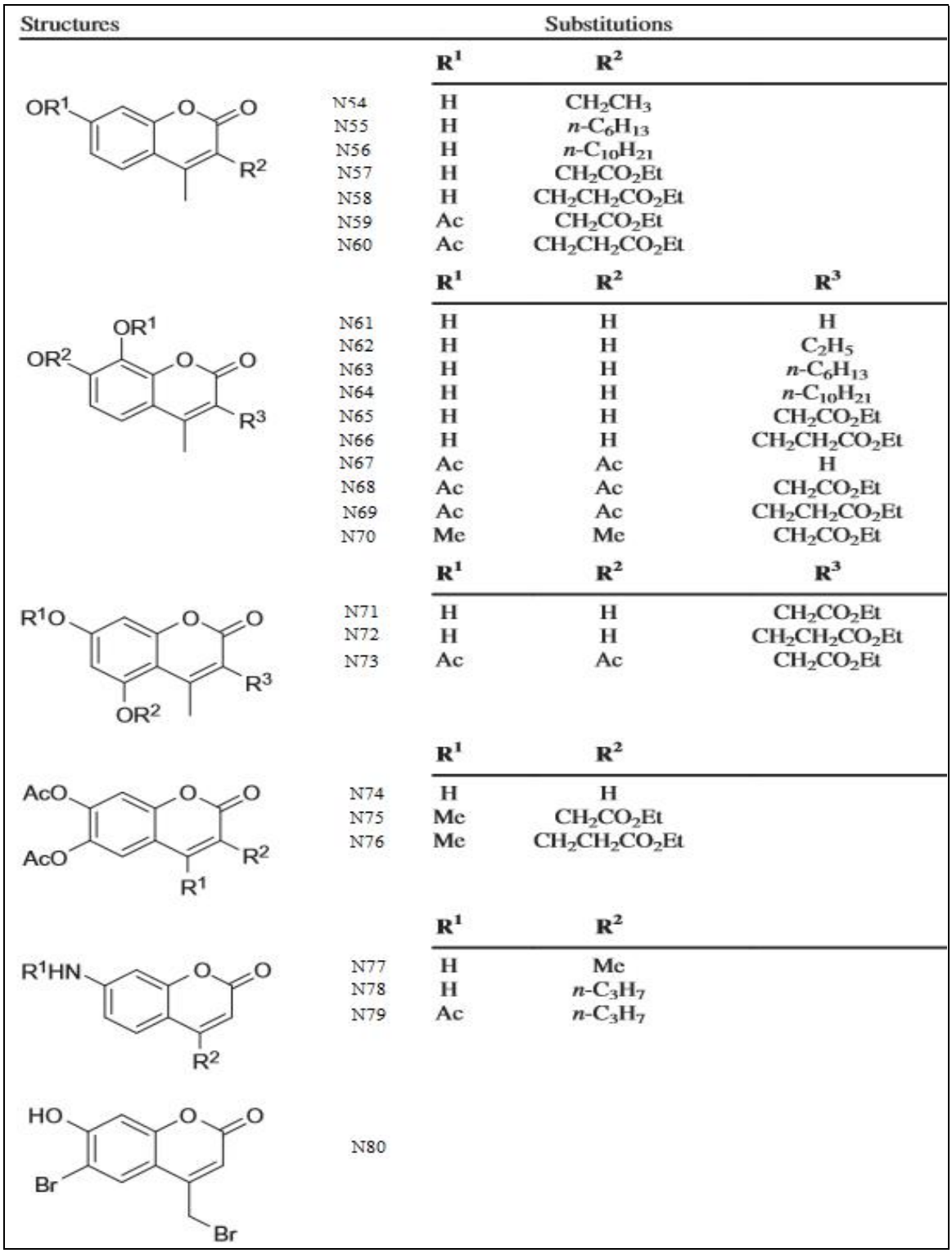
Li *et al.* have synthesized a panel of ten new 4-methylumbelliferone-derived α-amino phosphonates, as shown in Scheme 8. The cytotoxic attribute of these conjugates, herein called **N44**-**N53**, has examined against three human cancer cell lines, which are HCT-116 (colorectal carcinoma), KB (nasopharyngeal carcinoma), and MGC-803(lung adenocarcinoma) cell lines. The reported that revealed that these compounds have a higher anticancer property in comparison with the parent compound, 4-methylumbelliferone. Besides, a compound named **N53** exhibited the best antitumor activity that results from the induction of apoptosis (40).



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 of compounds N44-N53 from 4-methylumbelliferone as proposed by Li *et al.*

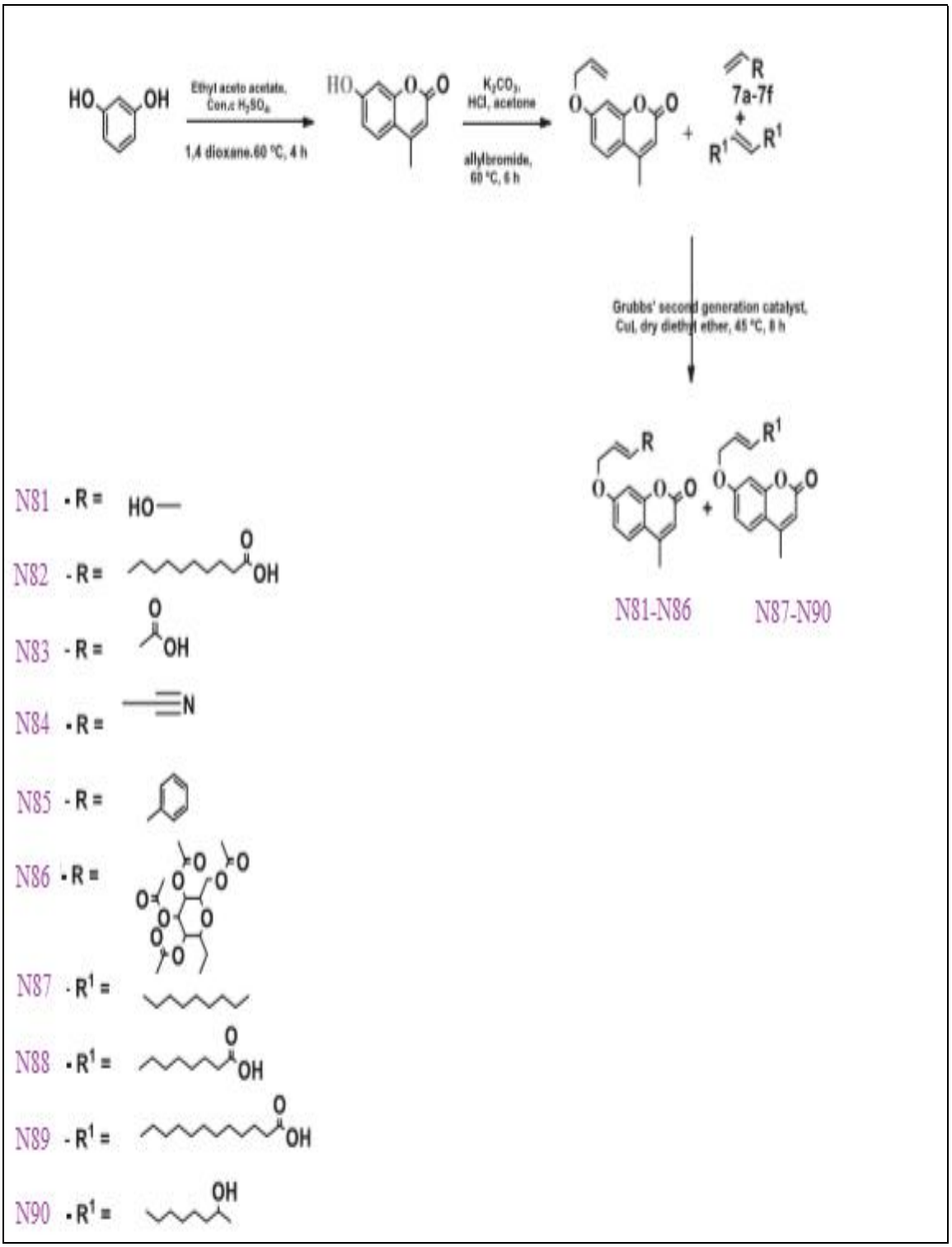
Miri *et al.* have recorded the preparation of many 4-alkylcoumarin derivatives and evaluated their cytotoxic attribute against three cancer cell lines named K562 (chronic myelogenous leukemia), LS180 (colorectal cancer), and MCF-7 (breast cancer). The examined compounds (Figure 4), herein called **N54-N80**, including 4-methylumbelliferone have revealed an acceptable antitumor activity with notability contributed to those having the highest lipophilic character. The authors concluded that the presence of a long alkyl chain at carbon number 3 of the coumarin backbone may improve the antitumor effect mainly because of the better penetration to the target cells (41).



Structures		Substitutions		
		R^1	R^2	
	N54	H	CH_2CH_3	
	N55	H	n-C_6H_{13}	
	N56	H	n-$C_{10}H_{21}$	
	N57	H	CH_2CO_2Et	
	N58	H	$CH_2CH_2CO_2Et$	
	N59	Ac	CH_2CO_2Et	
	N60	Ac	$CH_2CH_2CO_2Et$	
		R^1	R^2	R^3
	N61	H	H	H
	N62	H	H	C_2H_5
	N63	H	H	n-C_6H_{13}
	N64	H	H	n-$C_{10}H_{21}$
	N65	H	H	CH_2CO_2Et
	N66	H	H	$CH_2CH_2CO_2Et$
	N67	Ac	Ac	H
	N68	Ac	Ac	CH_2CO_2Et
	N69	Ac	Ac	$CH_2CH_2CO_2Et$
	N70	Me	Me	CH_2CO_2Et
		R^1	R^2	R^3
	N71	H	H	CH_2CO_2Et
	N72	H	H	$CH_2CH_2CO_2Et$
	N73	Ac	Ac	CH_2CO_2Et
		R^1	R^2	
	N74	H	H	
	N75	Me	CH_2CO_2Et	
	N76	Me	$CH_2CH_2CO_2Et$	
		R^1	R^2	
	N77	H	Me	
	N78	H	n-C_3H_7	
	N79	Ac	n-C_3H_7	
	N80			

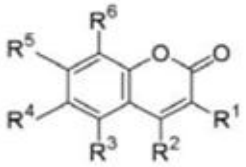
Figure 4: Chemical structures of 4-methylumbelliferone-based derivatives as displayed by Miri *et al.*

Yelchuri *et al.* have recorded the synthesis of ten new 4-methylumbelliferone-derived compounds, herein called **N81**-**N90** as displayed in Scheme 9, by condensing 4-methylumbelliferone with various molecules such as acrylic acid, acrylo-nitrile, benzyl, allyloxy, and others. These new derivatives have investigated for their antitumor attribute against four cancer cell lines named MDA-MB 231 (human breast), DU145 (prostate), SKOV3 (ovarian), HepG2 (hepatic). The researchers assumed that the compounds with nitrile, glycosidic, and hydroxyl substituents have revealed good cytotoxic attributes versus the test cancer lines and may be regarded as a probable scaffold for designing better chemotherapeutic agents (42).



Scheme 9: **Synthetic route of the N81-N90 compounds as proposed by Yelchuri *et al.***

Kawase *et al*. have examined forty-four 4-methylumbelliferone-based compounds, herein called **N91**-**N134** (Figure 5), for their multidrug resistance inversion effect and cytotoxic attribute. The results indicated that fourteen compounds have shown this inversion effect, and compound **N124** has the highest impact that was comparable to that of verapamil. Also, some of these derivatives exhibited a potent cytotoxic attribute, with superiority contributed to compounds **N133** and **N134**. The researchers concluded that the synthesized 4-methylumbelliferone-based compounds may act as good candidates for modulating the tumor multidrug resistance with minimal toxicity toward normal cells (43).



Compd	R^1	R^2	R^3	R^4	R^5	R^6
N91	H	H	H	H	H	H
N92	H	H	H	H	OH	H
N93	H	H	H	OH	OH	H
N94	H	H	H	OCH_3	OH	H
N95	H	H	OCH_3	OCH_3	OH	H
N96	H	CH_3	H	H	OH	H
N97	H	CH_3	H	OH	H	H
N98	H	CH_3	H	OH	OH	H
N99	H	CH_3	OH	H	OH	H
N100	H	CH_3	H	OH	OCH_3	H
N101	H	CH_3	H	OCH_3	OH	H
N102	H	CH_3	H	H	OCH_3	H
N103	H	CH_3	H	OCH_3	H	H
N104	CH_3	H	H	H	OH	H
N105	CH_3	CH_3	H	H	OH	H
N106	CH_3	CH_3	H	OH	OH	H
N107	CH_3	CH_3	H	OH	OCH_3	H
N108	CH_3	CH_3	H	OCH_3	OH	H
N109	CH_3	CH_3	H	H	OCH_3	OH
N110	$-(CH_2)_3-$		H	OH	OH	H
N111	$-(CH_2)_3-$		OH	H	OH	H
N112	$-(CH_2)_3-$		H	OH	OCH_3	H
N113	$-(CH_2)_3-$		H	OCH_3	OH	H
N114	$-(CH_2)_4-$		H	OH	OCH_3	H
N115	-Benzo-		H	NO_2	H	H
N116	H	CH_2CO_2H	H	H	OCH_3	H
N117	NO_2	OH	H	H	H	H
N118	$CO_2C_2H_5$	H	H	H	H	H
N119	H	Ph	H	OH	OCH_3	H
N120	Ph	CH_3	H	OH	OCH_3	H
N121	H	CF_3	H	OH	OCH_3	H
N122	H	CF_3	H	H	$N(CH_3)_2$	H
N123	CH_3	CH_3	H	OR	OH	H
N124	$(CH_2)_2OH$	CH_3	H	OH	OCH_3	H
N125	$(CH_2)_2OH$	CH_3	H	H	OH	OH
N126	$(CH_2)_2OH$	CH_3	H	OCH_3	OH	H
N127	$(CH_2)_2OH$	CH_3	OH	H	OH	H
N128	H	$CH_2CO_2CH_3$	H	OH	OCH_3	H
N129	CH_3	CH_3	H	OH	OC_2H_5	H
N130	H	C_3H_7	H	OH	OCH_3	H
N131	H	$CH(CH_3)_2$	H	OH	OCH_3	H
N132	C_4H_9	CH_3	H	OH	OCH_3	H
N133	$CH(CH_3)_2$	CH_3	H	OH	OCH_3	H
N134	C_2H_5	CH_3	H	OH	OCH_3	H

Figure 5: General chemical structure and the substituents of the synthesized 4-methylumbelliferone-based compounds which prepared and examined by Kawase *et al.*

Ostrowska *et al.* have investigated the antitumor potential of many previously prepared coumarin derivatives including 4-methylumbelliferone (Figure 6). This investigation was performed by utilizing five different human cancer cell lines, which are HCC-2998 (colon), HOP-92 (lung), CCRFCEM and HL-60 (leukemia), and 786-0 (renal). The authors suggested that a small increase in the lipophilicity of these coumarins might decrease their cytotoxic attributes. Also, the addition of acetyl moiety to O-alkyl derivatives of 4-methylumbelliferone may improve their cytotoxicity. This will guide other studies to highlight the impact of the lipophilicity on the anticancer attribute of 4-methylumbelliferone-based compounds (44).

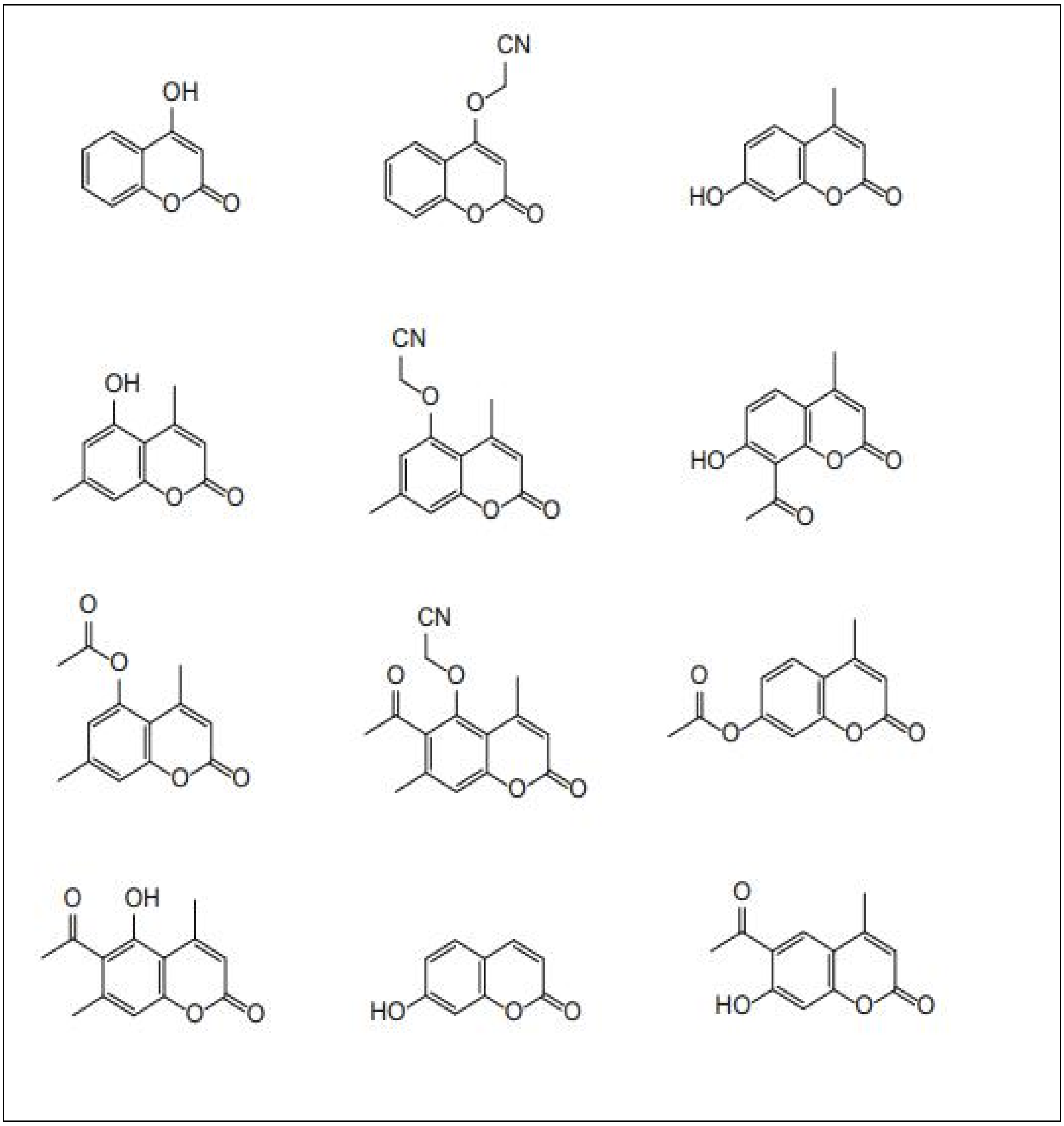
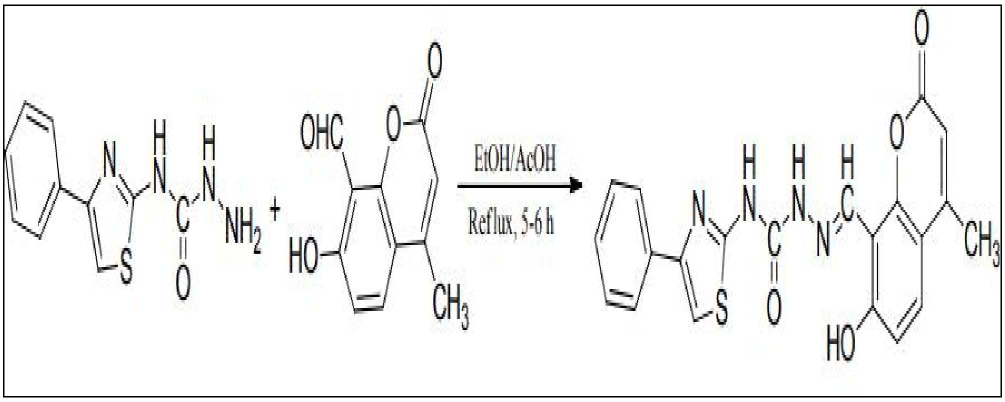


Figure 6: **Chemical structures of coumarin-derivatives studied by Ostrowska *et al.***

Yernale *et al.* have synthesized many novel complexes utilizing a ligand prepared according to the equation listed in Scheme 10. This ligand, which is based in its structure on 4-methylumbelliferone, was complexed with various metals such as Zn^{+2}, Co^{+2}, Cu^{+2}, and Ni^{+2}. These complexes were evaluated for their antitumor attribute versus many cancer cell lines, and the results indicated that the complexes **N135** and **N136** (Figure 7) showed the highest antitumor impact in comparison with the other prepared complexes (45).



Scheme 10: **Synthesis of 4-methylumbelliferone-based ligand as depicted by Yernale *et al.***

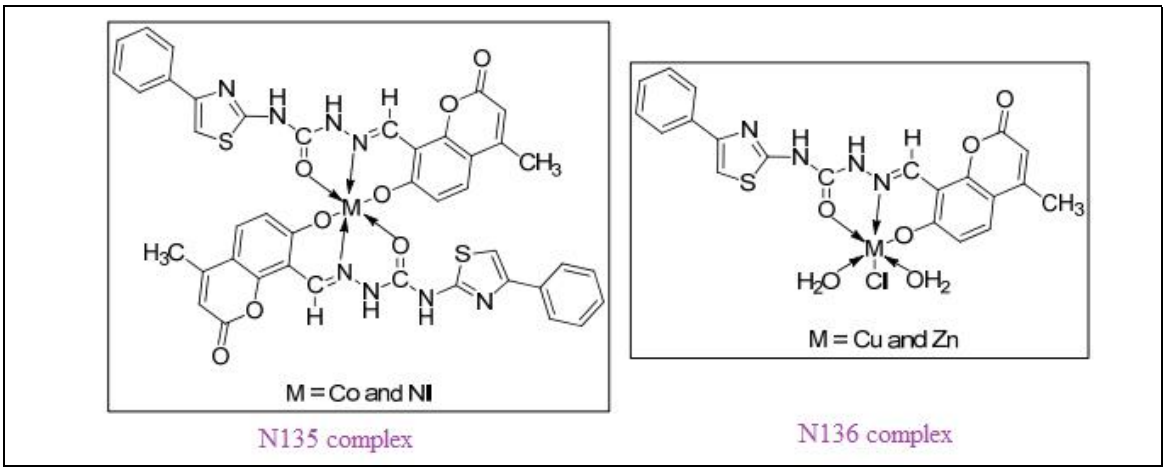


Figure 7: Proposed chemical structures of the complexes named N135, N136.

Kraljević *et al*. have designed and prepared a panel of six novel 1,2,3-triazoles-4-methylumbelliferone conjugates, herein called **N137**-**N142** (Figure 8). The researchers have investigated the cytotoxic attribute of these conjugates versus the liver cancer cell line named HepG2. The results demonstrated that compound **N138** exhibited the highest antitumor attribute. This activity is based on the ability of this compound to inhibit the phosphodiesterase group of enzymes and induce cell apoptosis (16).

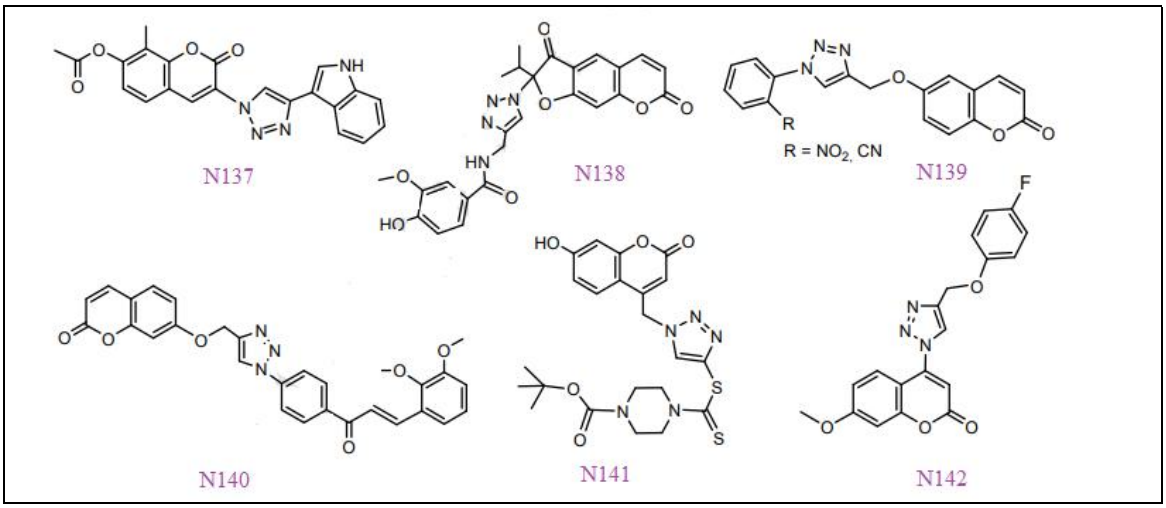


Figure 8: Chemical structures of 1,2,3-triazoles–4-methylumbelliferone conjugates that prepared by Kraljević *et al.* as novel antitumor compounds.

CONCLUSION

The diverse medicinal properties of natural coumarins have directed the interest of medicinal chemists toward the design, synthesis, and exploration of the bioactivity of new coumarin-derived compounds. 4-Methylumbelliferone is one of the most surveyed synthetic coumarins, and the literature is wealthy with scientific papers dealing with the synthesis and antitumor attribute of 4-methylumbelliferone-based derivatives. Analysis of the outcomes acquired from these papers enabled the authors of this review to highlight some characteristic features, which are important for the antitumor attribute of the 4-methylumbelliferone-based derivatives. These structural merits include substituting the carbon number 5 of the coumarin nucleus with a strong and/or small electron-donating group, linking the carbon 8 with the lipophilic group, and coupling carbon 3 with alicyclic secondary amine through a short alkyl bridge. This review concluded that the skillful utilization of these merits for designing and synthesizing new 4-methylumbelliferone-based derivatives will afford compounds with a potent antitumor potential.

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