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Hymecromone and Its Derivatives as Promising Cytotoxic Agents: A Review

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Abstracts

Cancer is continuing to be a leading cause of death and a major concern for the health-care system. Despite the enormous effort to isolate, design, and synthesize new chemotherapeutic agents, the serious side-effects, mounting tumor-resistance, and poor selectivity are still representing substantial challenges to medicinal chemists. In the past few decades, much focus was placed on investigating the anti-cancerous potential of many nature-derived products. One class of such products is coumarin-based compounds that are characterized by their structural diversity and broad pharmacological properties. Of those, hymecromone, which is commonly known as 7-hydroxy-4-methylcoumarin, and its derived products demonstrated promising results in the management of multi-drug cancer resistance, reduction of adverse effects caused by chemotherapeutic drugs, and development of photo-directed cancer therapy. Additionally, many synthetic hymecromone-derived products were shown to possess a diverse antitumor potential making them effective against different cancer types such as leukemia, prostate, lung, breast, and renal. In this work, we reviewed many recently published scientific papers and analyzed their outcomes to highlight the structural characteristics of the hymecromone-derived products that are important in their potential as antitumor agents. Specification of these characteristics may guide the incoming research toward the design and synthesis of novel chemotherapeutic agents with enhanced properties.

Keywords: Cytotoxicity, Hymecromone, Derivatives, Synthetic coumarins, 7-hydroxy-4-methylcoumarin.

Introduction

Interest has directed in the last decades toward a characteristic family of the natural and synthetic products belonged to the benzo-α-pyrone class named coumarins (1). This interest has based on the broad spectrum of their pharmacological potentials (2) as well as their industrial applications (3,4). Coumarin-based products can be isolated from different natural sources (5) and also synthesized by various chemical reaction phenotypes (6,7). Many of these products exhibited numerous biological effects such as anticancer (8), antimicrobial (9), antioxidant (10), anti-inflammatory (11,12), anti-aggregation (13), and cardio-protective (14) activities. Concerning the antitumor activity, coumarin-derived products can exert this effect by various documented mechanisms (15). This relying on the substitutional pattern of the coumarin core structure (16).

Hymecromone that commonly known as 7-hydroxy-4-methylcoumarin is one of the most interested and evaluated coumarins (17). The chemical backbone of hymecromone, as depicted in Figure 1, has utilized as a pharmacological scaffold to prepare a large number of derived products and subsequently investigate their medicinal activities (18). Among them, the antitumor potential of hymecromone-derived products has been widely investigated by many scientists, and the results of their investigations have been recorded in many scientific papers (19–21). This incites the team-work for reporting this review to highlight the

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characteristic features of hymecromone-derived products that mediate their antitumor activity. Also, this review may facilitate the choice of a proper substitutional pattern by medicinal chemists to optimize such activity of these products.

Figure 1: Chemical backbone of hymecromone.

Bhattacharyya *et al.* have investigated the consequence of utilizing hymecromone for managing the skin tumor-excited in mice. This investigation revealed that hymecromone has a beneficial role in the expression and regulation of many signal-related proteins. Such proteins as Caspase-3, Caspase-9, IL-6, Cytochrome-c, NF-kB Apaf, PCNA, Bax, Akt, Aryl hydrocarbon receptor, Bad, Bcl-2, Bcl-xL, and p53. The authors concluded that this coumarin-derived product down-regulated the pro-apoptotic proteins as well as up-regulated the apoptotic proteins. Based on these findings, this product may offer a new template for designing and synthesizing specific agents for the treatment of this cancer phenotype (22).

Ibrahim *et al.* have recorded the preparation of three hymecromone derivatives complexed with copper. The antitumor potential of these complexes, herein symbolized as **N1**-**N3** (Figure 2), was evaluated against two cancer lines including MCF-7 belonged to the breast cancer, and A549 belonged to the lung cancer. The results exhibited that the products **N1** and **N2** showed a potent activity toward the first cancer line, while **N3** displayed a powerful inhibitory effect on the second cancer line (23).

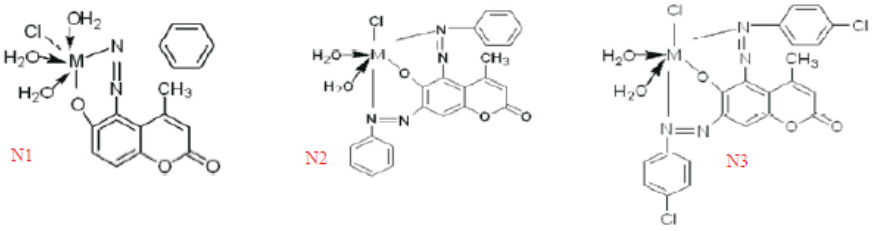

Figure 2: Chemical backbones of the hymecromone derivatives complexed with copper as displayed by Ibrahim *et al.*

Yelchuri *et al.* have recorded the preparation of ten coumarin-derived products by conjugating hymecromone with various benzyl, allyloxy, acrylic acid, fatty acid, and acrylonitrile analogues, as shown in Scheme 1. These hymecromone-derived products, herein symbolized as **N4**-**N13**, have been evaluated as potential antitumor agents against four cancer cell lines. These cell lines included MDA-MB 231 (Human breast cancer), SKOV3 (Ovarian cancer), HepG2 (Hepatocellular carcinoma), and DU145 (Prostate carcinoma). The results exhibited that the synthesized conjugates revealed an encouraging antitumor potential with supremacy effects contributed to products **N4** and **N8** (24).

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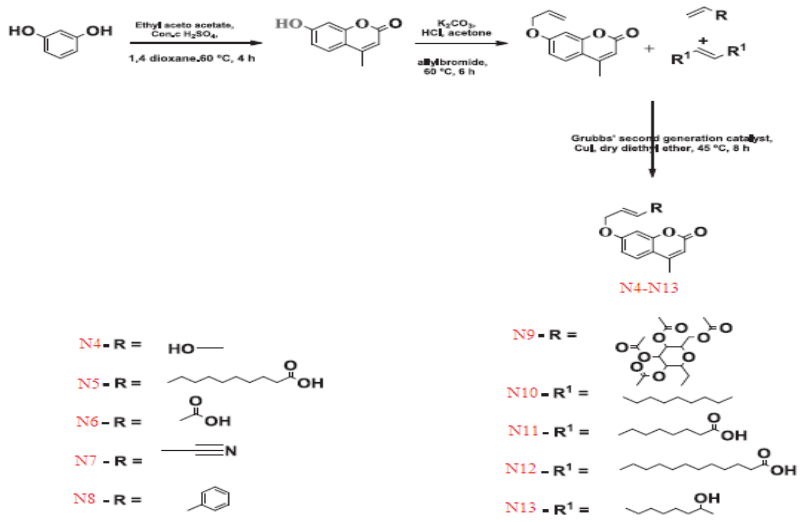
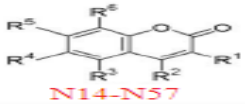


Scheme 1: Synthetic plan of the hymecromone-derived conjugates as reported by Yelchuri *et al.*

Kawase *et al*. have investigated the potential of 44 coumarin-derived products as modulators for cancer-resistance toward cytotoxic drugs. These products, herein symbolized **N14**-**N57** (Figure 3), showed a good selectivity toward tumor cells in comparison with normal ones. Also, products **N56** and **N57** exhibited a powerful anticancer activity. The authors concluded that these coumarin-derived products may account for new modulators of cancer cell-resistance with minimal toxicity against normal cells. In addition, there is a correlation between the chemical structures of these products and their modulating impact, this may contribute to the synthesis of optimal cytotoxic products (25).



Compd	R^1	R^2	R^3	R^4	R^5	R^6
1	H	H	H	H	H	H
2	H	H	H	H	OH	H
3	H	H	H	OH	OH	H
4	H	H	H	OCH_3	OH	H
5	H	H	OCH_3	OCH_3	OH	H
6	H	CH_3	H	H	OH	H
7	H	CH_3	H	OH	H	H
8	H	CH_3	H	OH	OH	H
9	H	CH_3	OH	H	OH	H
10	H	CH_3	H	OH	OCH_3	H
11	H	CH_3	H	OCH_3	OH	H
12	H	CH_3	H	H	OCH_3	H
13	H	CH_3	H	OCH_3	H	H
14	CH_3	H	H	H	OH	H
15	CH_3	CH_3	H	H	OH	H
16	CH_3	CH_3	H	OH	OH	H
17	CH_3	CH_3	H	OH	OCH_3	H
18	CH_3	CH_3	H	OCH_3	OH	H
19	CH_3	CH_3	H	H	OCH_3	OH
20	-$(CH_2)_3$-		H	OH	OH	H
21	-$(CH_2)_3$-		OH	H	OH	H
22	-$(CH_2)_3$-		H	OH	OCH_3	H
23	-$(CH_2)_3$-		H	OCH_3	OH	H
24	-$(CH_2)_4$-		H	OH	OCH_3	H
25	-Benzo-		H	NO_2	H	H
26	H	CH_2CO_2H	H	H	OCH_3	H
27	NO_2	OH	H	H	H	H
28	$CO_2C_2H_5$	H	H	H	H	H
29	H	Ph	H	OH	OCH_3	H
30	Ph	CH_3	H	OH	OCH_3	H
31	H	CF_3	H	OH	OCH_3	H
32	H	CF_3	H	H	$N(CH_3)_2$	H
33	CH_3	CH_3	H	OR	OH	H
34	$(CH_2)_2OH$	CH_3	H	OH	OCH_3	H
35	$(CH_2)_2OH$	CH_3	H	H	OH	OH
36	$(CH_2)_2OH$	CH_3	H	OCH_3	OH	H
37	$(CH_2)_2OH$	CH_3	OH	H	OH	H
38	H	$CH_2CO_2CH_3$	H	OH	OCH_3	H
39	CH_3	CH_3	H	OH	OC_2H_5	H
40	H	C_3H_7	H	OH	OCH_3	H
41	H	$CH(CH_3)_2$	H	OH	OCH_3	H
42	C_4H_9	CH_3	H	OH	OCH_3	H
43	$CH(CH_3)_2$	CH_3	H	OH	OCH_3	H
44	C_2H_5	CH_3	H	OH	OCH_3	H

Figure 3: Chemical structures of the coumarin-derived products that prepared by Kawase *et al.* as modulators for cancer-resistance.

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Musa *et al.* have investigated the mechanism of the antitumor potential for nine coumarin-derived products including hymecromone. This evaluation was performed by using crystal violet-dependent assay on two cancer lines, which are MDA-MB-231 (breast cancer) and PC-3 (prostate cancer). These products, herein symbolized as **N58**-**N66** (Figure 4), exhibited a promising effect against the test cancerous lines with a notability attributed to product **N63**. The authors concluded that the antitumor mode of action of the product **N63** involved the loss of mitochondrial membrane potential, arrest of the cell-cycle at phase at G0/G1, enhancement of the generation of the reactive oxygen species, deprivation in the GSH level, and induction of apoptosis by activating the intrinsic pathway (26).

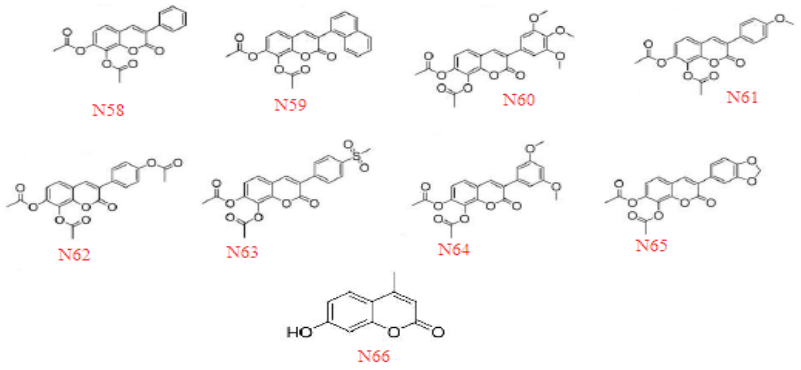
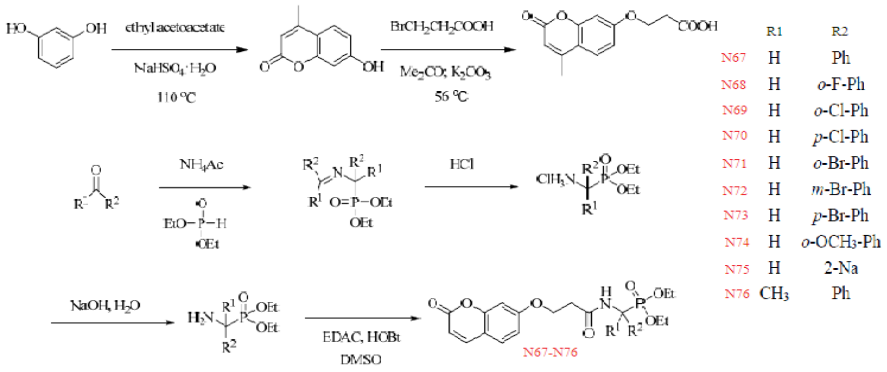


Figure 4: Chemical backbones of the coumarin-derived products investigated for their antitumor activity by Musa *et al.*

Li *et al.* have prepared a panel of ten new coumarinyl-α-aminophosphonate products, as displayed in Scheme 2. The anticancer effect of these products was investigated against three human cancerous lines, which were KB (human nasopharyngeal carcinoma), MGC-803 (lung adenocarcinoma), and HCT-116 (colorectal). The results indicated that these novel products, herein symbolized **N67**-**N76,** have a better antitumor activity than that of hymecromone, and among these products, **N76** showed the best effect (27).



Scheme 2: Synthetic plan of new coumarinyl-α-aminophosphonate products which synthesized by Li *et al.*

Tao *et al.* have recorded the preparation of 4 multi-functional products, as displayed in Scheme 3. The chemical backbones of these products have derived from three units named phenyl butyric acid, hymecromone, and magnolol. The anticancer potential of these molecules was examined against four cancerous lines including MCF-7, A549, HepG2, and A431. The results exhibited that the product **N80** has a better effect in comparison with those of its precursors. Besides, this product presented other advantages such as the long duration of effect, and the possibility of *in vivo* monitoring owing to its fluorescent characteristic. The authors concluded that the product **N80** offered a promising scaffold to design and synthesize more potent derivatives related to magnolol (28).

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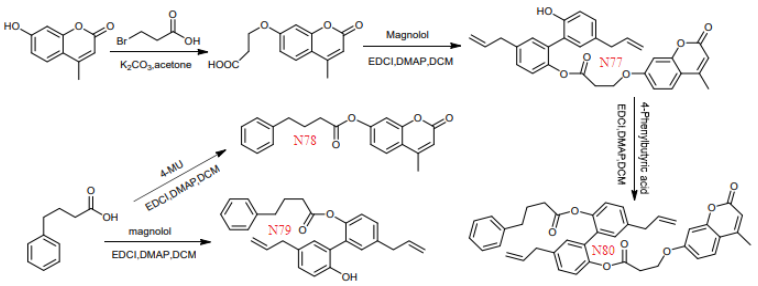

Scheme 3: Synthetic plan of the phenyl butyric acid-coumarin-magnolol derivatives named N77-N80.

Nikalje *et al*. have recorded the preparation of piperazinyl-coumarin conjugates using the chemical core of hymecromone as a building unit. The cytotoxicity of these hybridized molecules, herein symbolized as **N81** and **N82** (Figure 5), versus three cancerous lines including MCF-7, HeLa, and NCI-H226 has been tested. The results indicated that the product **N81** has a powerful inhibitory potential versus MCF-7 and HeLa compared with adriamycin as a standard cytotoxic drug and moderate inhibitory potential against NCI-H226 (29).

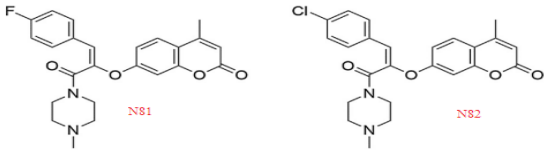

Figure 5: Chemical backbones of the piperazinyl-coumarin conjugates synthesized via Nikalje *et al*.

Benitez *et al.* have reported that the synchronous administration of hymecromone with sorafenib enhanced the anti-angiogenesis potential of the last agent resulting in the reduction of capillary generation, proliferation, and invasion of renal carcinoma cells. Besides, this incorporation may enhance apoptosis in this type of cancerous cells 8-fold than that of sorafenib alone. The main advantage arisen from such incorporation is the reduction of hyaluronic acid (HA) synthesis. This may opposite by adding HA to the proposed schedule of therapy (30,31).

Ostrowska *et al.* have recorded the synthesis of 11 coumarin-derived products, herein symbolized as **N83-N93** (Figure 6), by using a microwave-accelerated technique. The antitumor activity of these products was assayed versus two cancerous line cells named DU145 and B16F10. The results indicated that these products showed an encouraging cytotoxicity against the test cell lines, and this effect was dependent on the molecular lipophilic character (32).

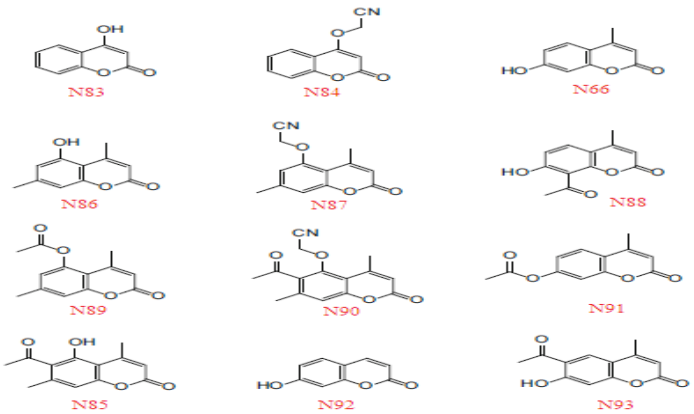

Figure 6: Chemical structures of coumarin-derived products investigated by Ostrowska *et al.* as antitumor agents.

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Goel *et al*. have reported the synthesis of a series consists of 11 conjugates, herein symbolized as **N94-N104** (Figure 7). These products were prepared by coupling two active moieties including hymecromone and midazo[1,2-α]pyrazine. Their anticancer activity was evaluated versus 60 cancerous lines, which are belonged to the following cancer phenotypes: Leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast. The results exhibited that the prepared conjugates have a broad antitumor activity versus the test cancerous lines, and there is a significant correlation between this potential and the lipophilicity of the tested products (33).

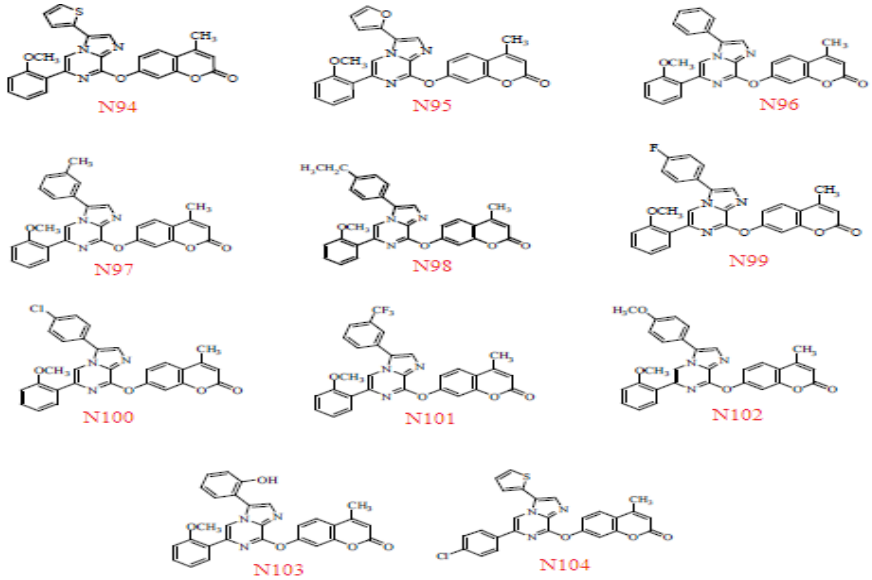

Figure 7: Chemical backbones of hymecromone-midazo[1,2-α]pyrazine conjugates prepared by Goel *et al.*

Conclusion

The various bioactivities and wide distribution of natural coumarin-based compounds have excited the researchers to synthesize many related products and investigate their biopotentials. Concerning the anticancer activity, there are plentiful reports which studied the structural characteristic features of hymecromone-based products as agents for fighting different cancer types. This review, after analyzing a high number of related scientific papers, concluded that the hymecromone could represent a potential template to construct new based agents with a better bioactivity and selectivity. The most important structural features of the hymecromone template that can be used to improve its antitumor potential include the presence of a small electron-donating group at position 5, long carbon-chain at position 8, and secondary amine linked by a short carbon-chain to position 3.

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