Sys Rev Pharm 2020;11(11):438-452
A multifaceted review journal in the field of pharmacy

Biological potentials of Hymecromone-based derivatives: A systematic review

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ABSTRACT

Coumarin-based derivatives occupy a prominent position in many fields related to medicine and industry. This can be attributed to their multilateral biological activities and diversity of chemical features. Among coumarin-based derivatives, hymecromone (7-hydroxy-4-methylcoumarin) has attracted great attention from the medicinal chemists. In addition to its ease preparation, this synthetic coumarin, which is known chemically as 7-hydroxy-4-methyl-2H-chromen-2-one, possesses a phenolic hydroxyl group that considers as one of the most derivatiable functional groups. In the literature, many scientific papers described the synthesis and biological activities of hymecromone-based derivatives. This systematic review focused on the synthesis of these derivatives and description of their biological potentials, especially those related to the antimicrobial, antioxidant, antitumor, antiviral, anti-Alzheimer, anti-inflammatory, and cardio-protective effects. The authors proposed that this review may guide the medicinal chemists to select the proper functional groups and their substitutional positions on hymecromone nucleus for the development of new therapeutic agents.

Keywords: Hymecromone, Antimicrobial, Antioxidant, Anti-inflammatory, antitumor, antiviral, cardio protective.

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INTRODUCTION

Coumarins are a respectable family of oxygen-based heterocycles that have widely used in pharmaceutical (1) and industrial intentions (2). The prototype of this family, coumarin, has historically been isolated via Vogel from Tonka bean, from which the name of coumarin has driven (3). Although the coumarins are sharing a benzo-α-pyrone skeleton, they differ in the presence of substituents and their positions (4). This variation affords a wide range of properties, some of them related to biological activities (5), and the others may be useful for industry (6). Until now, there is a high number of isolated coumarins and those synthesized in the laboratory (7). Most of the investigated natural and synthetic coumarins have exhibited one or more medicinal potentials such as antioxidant (8), anti-diabetic (9), anti-Alzheimer (10), antitumor (11), antimicrobial (12), antiparasitic (13), anti-inflammatory (14), anticonvulsant (15), antipsychotic (16), analgesic (17), anticoagulant (18), and antiviral (19) activities.

Hymecromone, as shown in Figure 1, is one of the most prepared and investigated coumarins. Products with chemical structures based on hymecromone have widely been synthesized (20), and their biological activities attracted great attention (21). This motivated the work team to report the biological potentials of the natural and synthetic coumarins with chemical structures based on hymecromone.

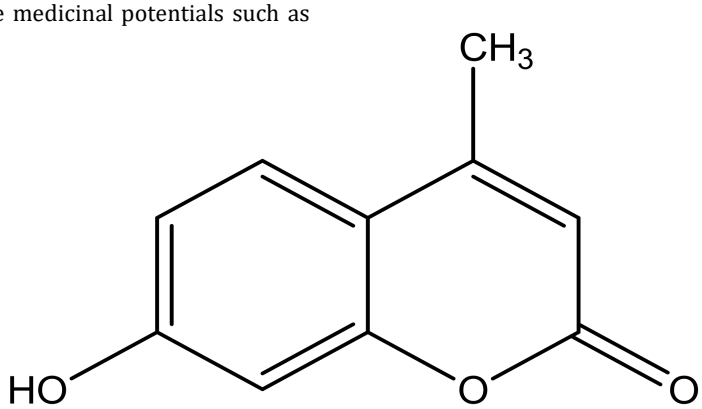


Figure 1: Chemical structure of hymecromone.

Antimicrobial potential

Jogi *et al.* have reported the synthesis and antibacterial activity of six novel coumarin-based azo compounds, herein termed **N1**-**N6**. These products, as shown in Figure 2, were synthesized by using hymecromone as a starting material, and showed a promising antibacterial activity against the test bacteria. Compounds **N1**, **N2**, and **N5** have been found to possess an antibacterial activity similar to those of ampicillin and streptomycin (22).

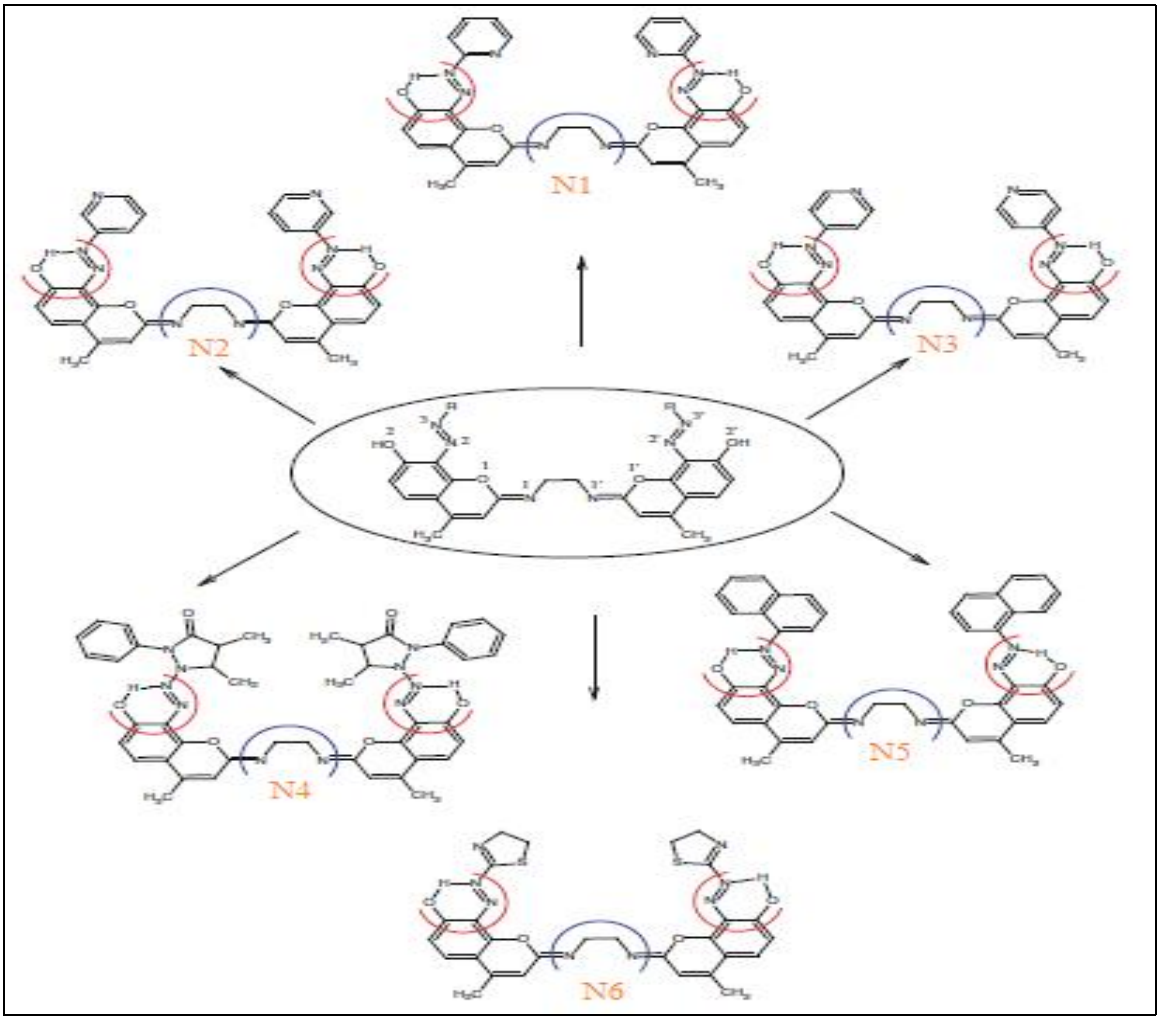
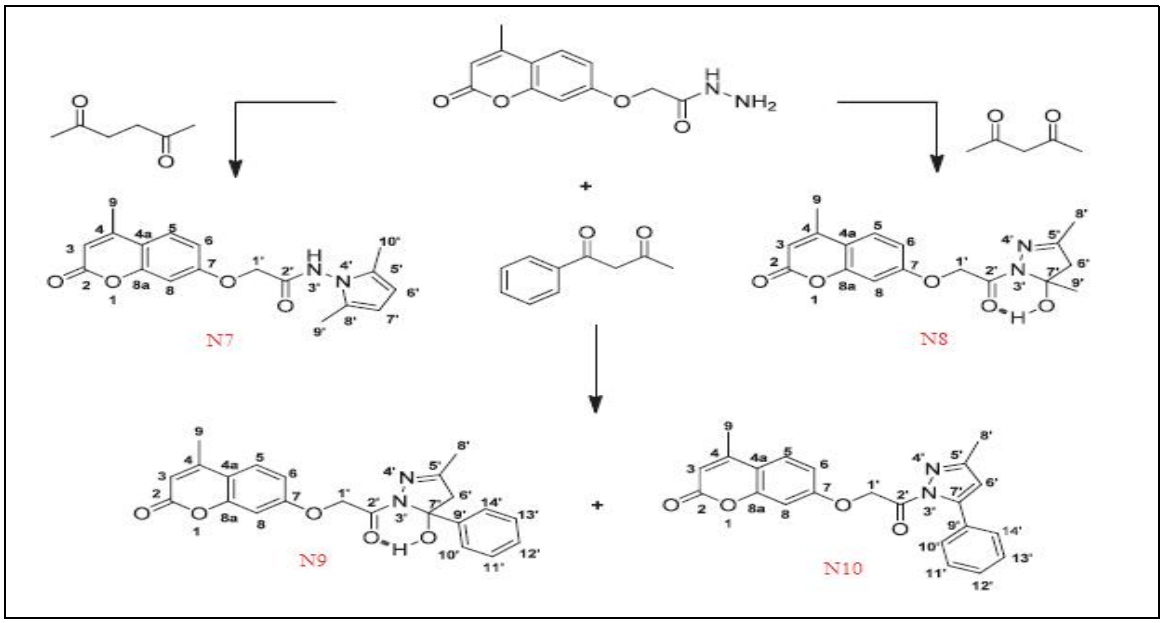


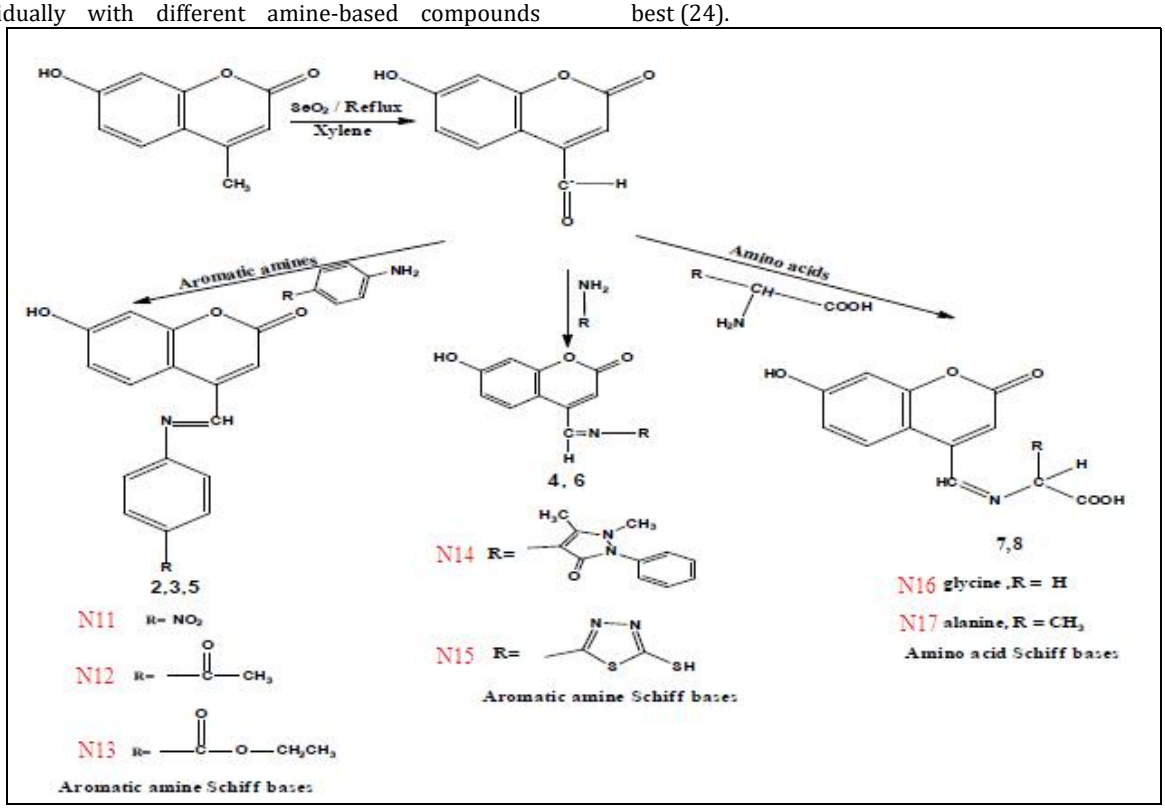
Figure 2: Coumarin-based azo compounds with an antibacterial activity developed by Jogi *et al.*

Zayane *et al.* have reported the synthesis of four novel coumarin esters using hymecromone as a starting material, as shown in Scheme 1. These compounds, herein termed **N7**-**N10**, exhibited a potent antifungal activity versus the test fungi. The authors have concluded that the pyrrole and pyrazole rings may play a significant role in this activity (23).



Scheme 1: The synthetic plan followed by Zayane *et al.* to synthesize four novel coumarin esters.

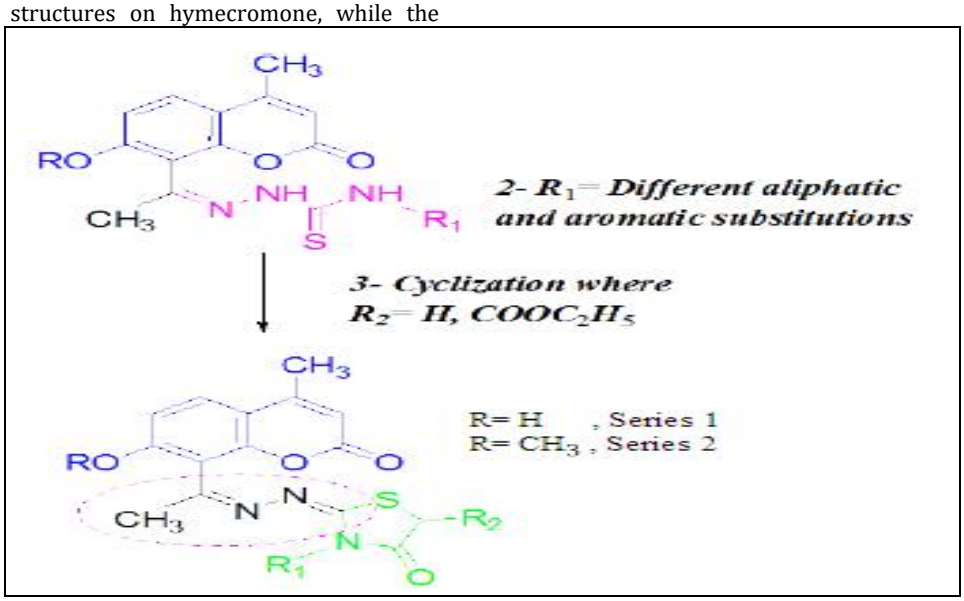
Hussein *et al.* have prepared many new derivatives of hymecromone, as shown in Scheme 2, by oxidizing the carbon atom substituted at position 4. The resulted aldehyde-containing coumarin was condensed individually with different amine-based compounds resulting in the formation of several aromatic- and amino acid-containing Schiff bases, herein termed **N11**-**N17**. These bases revealed a significant antibacterial activity versus the test bacteria, among these bases, **N16** was the best (24).



Scheme 2: Synthetic outline of some Schiff base-containing coumarins reported by Hussein *et al.*

Bansuri *et al.* have tested hymecromone itself as an antibacterial agent versus 10 isolates of *Pseudomonas fluorescens* acquired from the soil of Gujarat state in India. The authors concluded that hymecromone has a potent activity versus 7 isolates and mild activity versus the others (25).

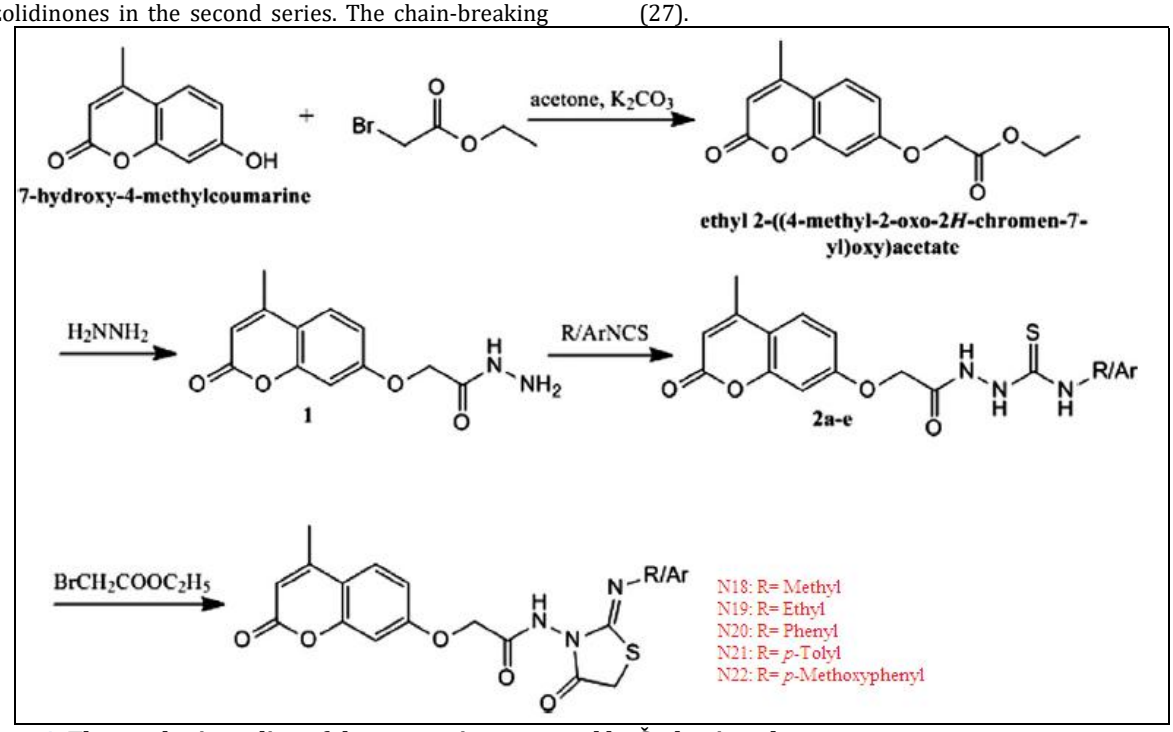
Amin *et al.* have reported the synthesis of two series of thiosemicarbazone-containing coumarins, as shown in Scheme 3. Coumarins of the first series were based in their chemical structures on hymecromone, while the chemical structures of the coumarins belong to the second series have the backbone of 7-methoxy-4-methylcoumarin. The antimicrobial activity of the prepared coumarins has been investigated versus many bacterial and fungal strains. The authors concluded that the coumarins of the first series have better antimicrobial activity versus the test microbes than those of the second series (26).



Scheme 3: The synthetic pathway for the thiosemicarbazone-containing coumarins as reported by Amin *et al.*

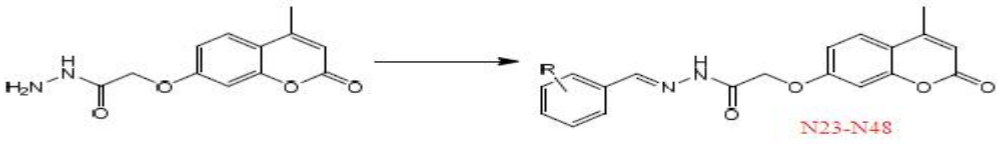
Antioxidant potential

Šarkanj *et al.* have reported the synthesis of two series, as shown in Scheme 4, of new five hybrid coumarins, herein termed **N18**-**N22**, starting from hymecromone. In the first series, hymecromone was hybridized with thiosemicarbazides, while it was hybridized with 4-thiazolidinones in the second series. The chain-breaking capability of these new coumarins was tested versus 2,2-diphenyl-1-picrylhydrazyl (DPPH) and galvinoxyl free radicals. The authors concluded that the hybridized coumarins of the first series showed better antioxidant activity than those of the second one. Also, the best activity was contributed to compounds **N20** and **N21** (27).



Scheme 4: The synthetic outline of the coumarins prepared by Šarkanj *et al.*

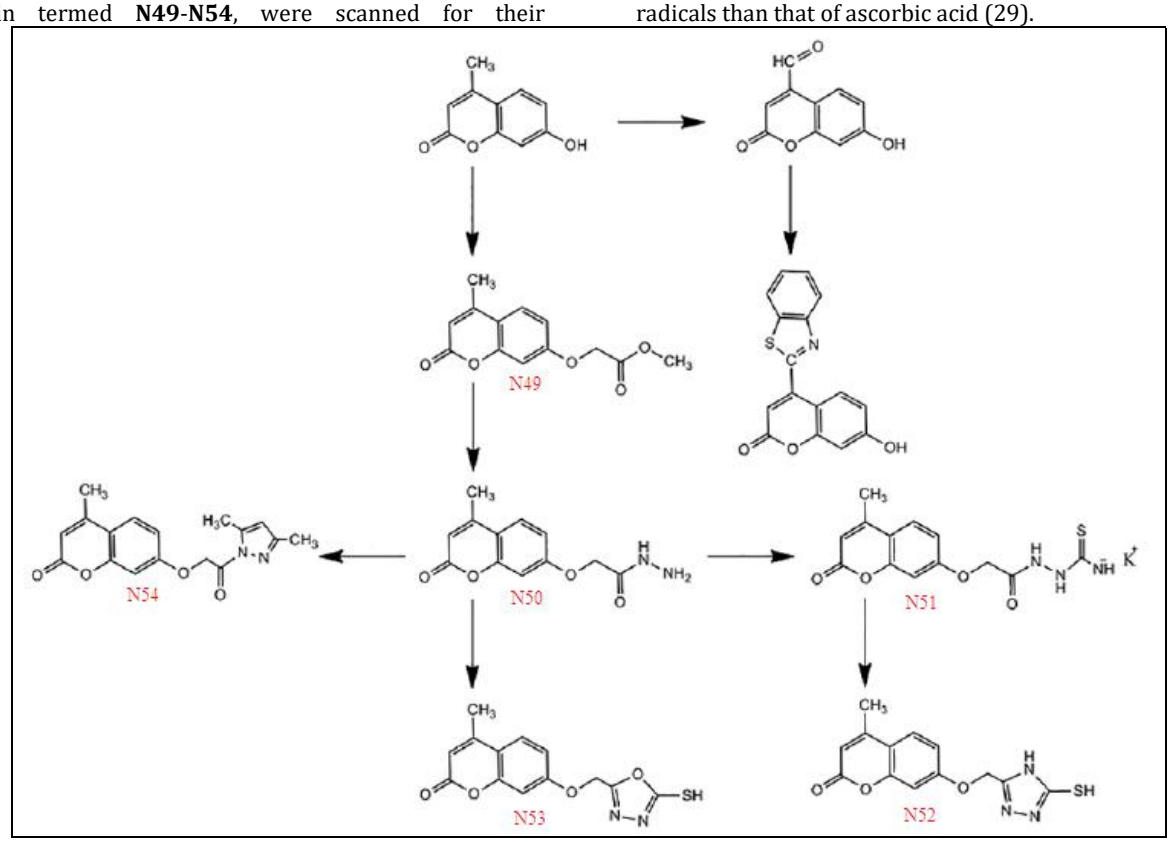
Molnar *et al.* have prepared 26 new coumarinyl-Schiff bases, as shown in Scheme 5, using hymecromone as a building block. These products, herein termed **N23**-**N48**, were examined for their antioxidant potential against galvinoxyl and DPPH free radicals. The authors concluded that coumarin derivatives **N30**-**N34** that possess dihydroxyphenyl moiety in their chemical structures exhibited the best antioxidant activity among the others (28).



	R		R
N23	H	N36	3-phenoxy
N24	2-OH	N37	2-OH-5-NO_2
N25	3-OH	N38	3,4,5-$(OCH_3)_3$
N26	4-OH	N39	2-Cl
N27	2-OCH_3	N40	3-Cl
N28	3-OCH_3	N41	2-Br
N29	4-OCH_3	N42	3-Br
N30	2,3-$(OH)_2$	N43	4-Br
N31	2,4-$(OH)_2$	N44	2-F
N32	2,5-$(OH)_2$	N45	3-F
N33	3,4-$(OH)_2$	N46	4-F
N34	3,5-$(OH)_2$	N47	styryl
N35	3-OCH_3-4-OH	N48	4-$N(CH_3)_2$

Scheme 5: New coumarins prepared by Molnar *et al.*

Al-Amiery *et al.* have synthesized six new hymercromone-based derivatives, as shown in Scheme 6, via a microwave-assisted method. These derivatives, herein termed **N49**-**N54**, were scanned for their antioxidant activity versus hydrogen peroxide radicals. The authors concluded that the new derivatives have higher trapping activity versus hydrogen peroxide radicals than that of ascorbic acid (29).



Scheme 6: The outline for the synthesis of new hycromone-based derivatives as depicted by Al-Amiery *et al.*

Šeršeň and Lácová have investigated the antioxidant activity of 19 previously prepared coumarins including hymecromone versus DPPH, hydroxyl, and superoxide free radicals. The authors concluded that the antioxidant activity of these coumarins versus the test free radicals was related to the number of the substituted phenolic hydroxyl groups and their positions on the benzene component of the coumarin skeleton. Accordingly, the derivatives without this type of functional group showed very poor activity. Furthermore, the highest antioxidant potential was attributed to the coumarins substituted on positions 7 and 8 with phenolic hydroxyl groups (30).

Tyagi *et al.* have synthesized 14 hymecromone-based derivatives, herein termed **N53**-**N66**. Their influences on the NADPH-dependent hepatic microsomal lipid peroxidation and the antiradical activity versus DPPH were investigated. This study aimed to highlight some issues concerning the structure-activity relationship (SAR) of these derivatives that have the chemical structures shown in Figure 3. The authors concluded that the presence of a carboxylic acid group reduces the antioxidant activity of the hydroxycoumarins, primarily due to the hydrogen bonding (31).

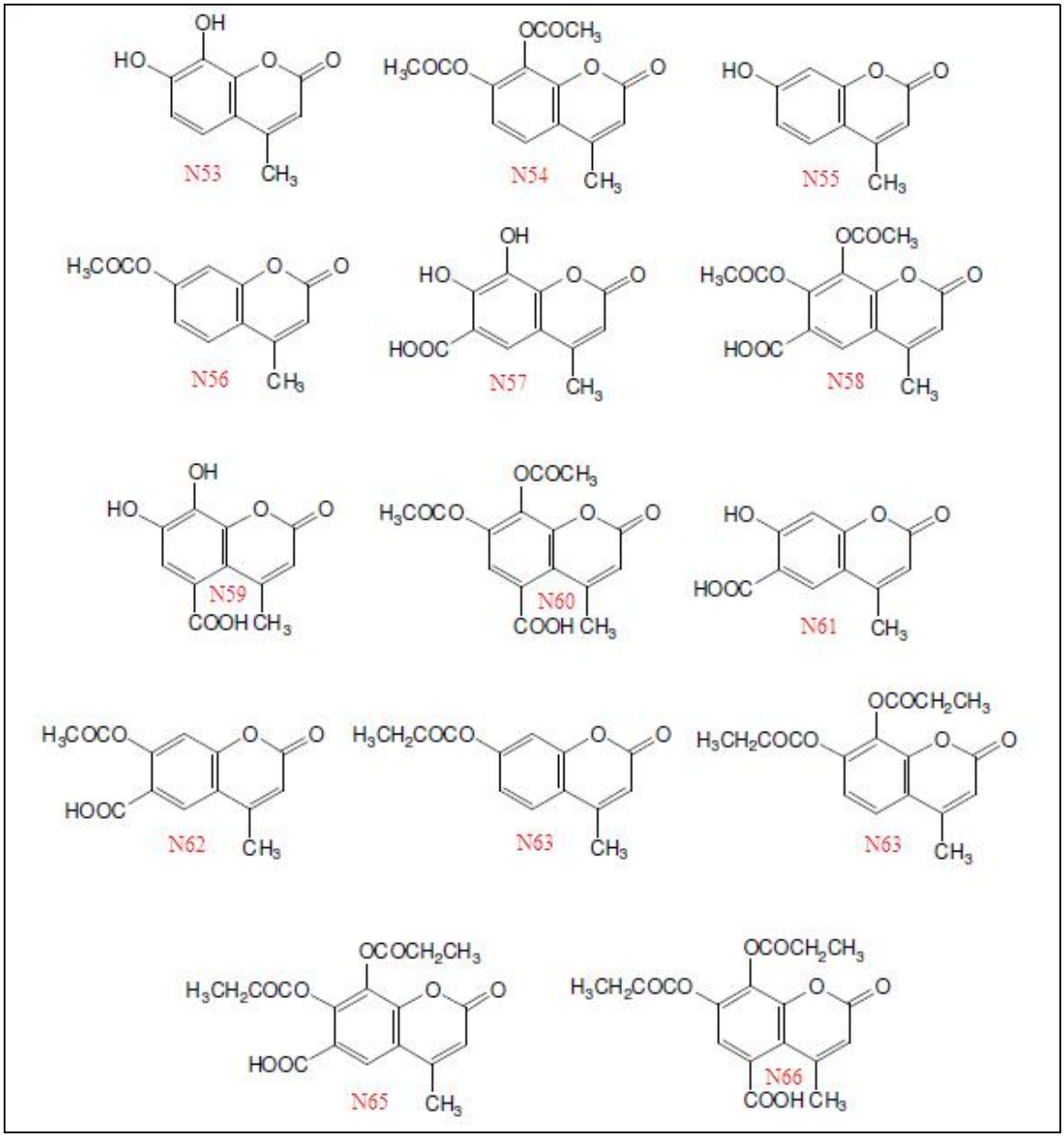
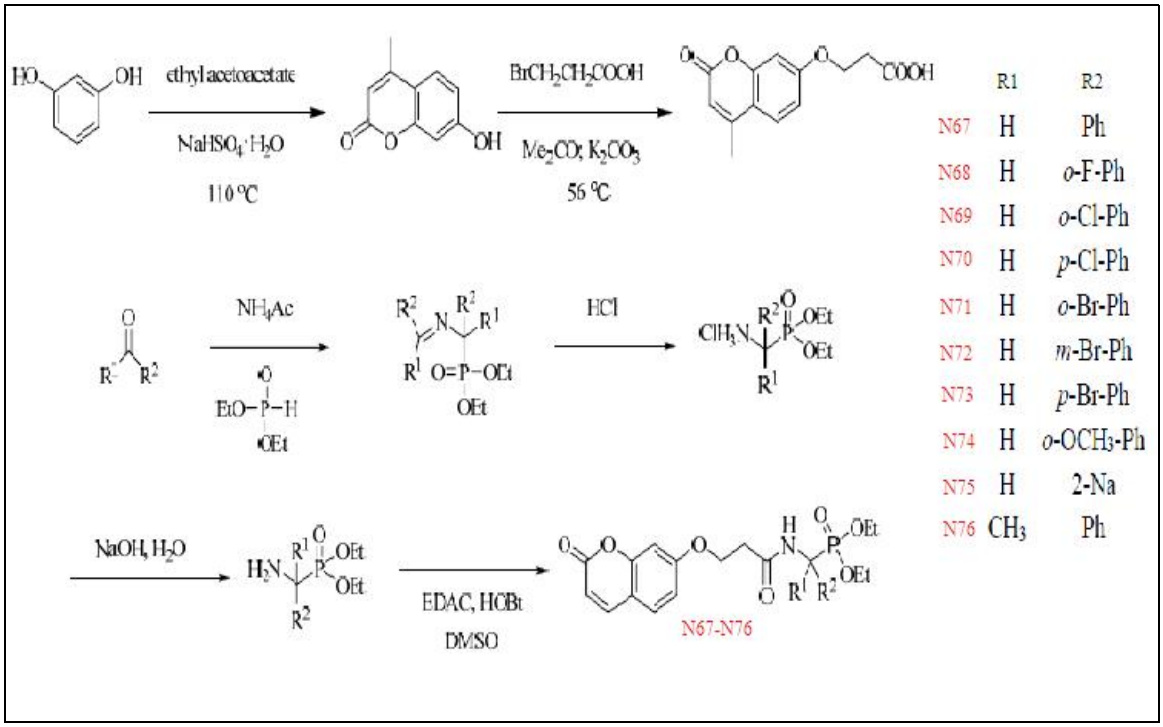


Figure 3: The chemical structures of the hymecromone-based derivatives that investigated by Tyagi *et al*.

Antitumor potential

Bhattacharyya *et al.* have studied the influence of hymecromone on the skin tumor-stimulated in mice. This study involved monitoring the impact of this coumarin on the expressions of many signal proteins including Caspase-9, Caspase-3, Cytochrome-c, IL-6, NF-kB Apaf, Bax, Bad, Bcl-xL, Bcl-2, Akt, PCNA, p53, and Aryl hydrocarbon receptor. The outcomes revealed that hymecromone has a positive modulation impact on the regulation of the aforementioned proteins, in such a way, by up-regulating the apoptotic proteins and down-regulating of pro-apoptotic proteins. Based on these outcomes, the authors concluded that this synthetic coumarin may represent a promise antitumor agent for the treatment of skin cancer (32).

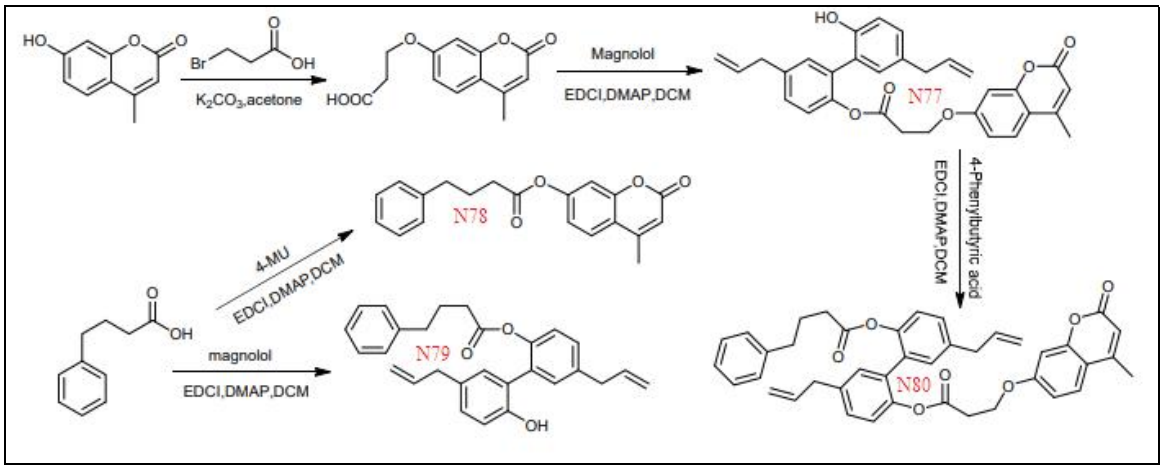
Li *et al.* have synthesized a series of 10 novel coumarinyl-α-aminophosphonates, as shown in Scheme 7. The antitumor activity of these compounds was tested versus three human cancer cell lines including lung adenocarcinoma (MGC-803), nasopharyngeal carcinoma (human KB), and colorectal (HCT-116). The outcomes revealed that the new compounds, herein termed **N67-N76,** have an improved activity in comparison with hymecromone, and compound **N76** was the best (33).



Scheme 7: Synthetic outline of novel coumarinyl-α-aminophosphonates that prepared by Li *et al.*

Benitez *et al.* have demonstrated that the concurrent intake of hymecromone with sorafenib potentiated the effect of this angiogenesis inhibitor to suppress capillary formation (76%), motility/invasion (65%), and proliferation (95%) in renal cell carcinoma. Also, this combination may induce apoptosis in the cells of this cancer phenotype eightfold that sorafenib alone. The principle disadvantage of this combination is the inhibition of hyaluronic acid synthesis that can be reversed by the addition of hyaluronic acid to the proposed therapeutic schedule (34), (35).

Tao *et al.* have reported the design and synthesis of four multifunctional molecules, as shown in Scheme 8. The chemical structures of these molecules were based on hymecromone, phenylbutyric acid, and magnolol. The antitumor activity of these products was investigated *in vitro* versus A549, A431, MCF-7, and HepG2 cell lines. The outcomes revealed that compound **N80** has a better effect than those of its precursors. Also, this compound offered other benefits as the long-term influence, and the ease of *in vivo* monitoring because of its fluorescent property. The authors concluded that this compound may represent a good template for designing and synthesizing more active derivatives of magnolol (36).



Scheme 8: Synthetic outline of the phenylbutyric acid-magnolol-coumarin conjugates N77-N80.

Nikalje *et al.* have reported the synthesis of piperazinyl-prop1-en-2-yloxy-coumarins derivatives based on the chemical structure of hymecromone. The cytotoxic activity of these conjugates, herein termed **N81** and **N82** (Figure 4), against MCF-7, HeLa, and NCI-H226 has been investigated. The outcomes showed that compound **N81** exhibited a strong inhibitory effect versus HeLa and MCF-7 in comparison with adriamycin as a reference and moderate inhibition activity versus NCI-H226 (37).

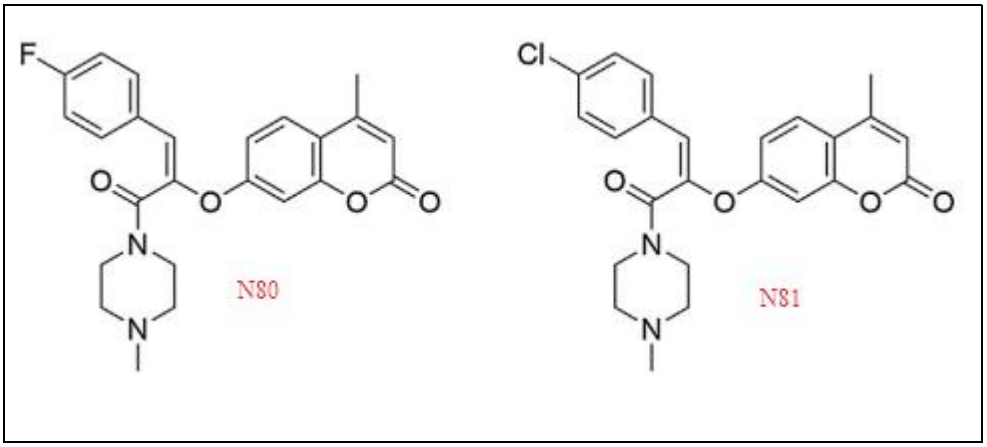
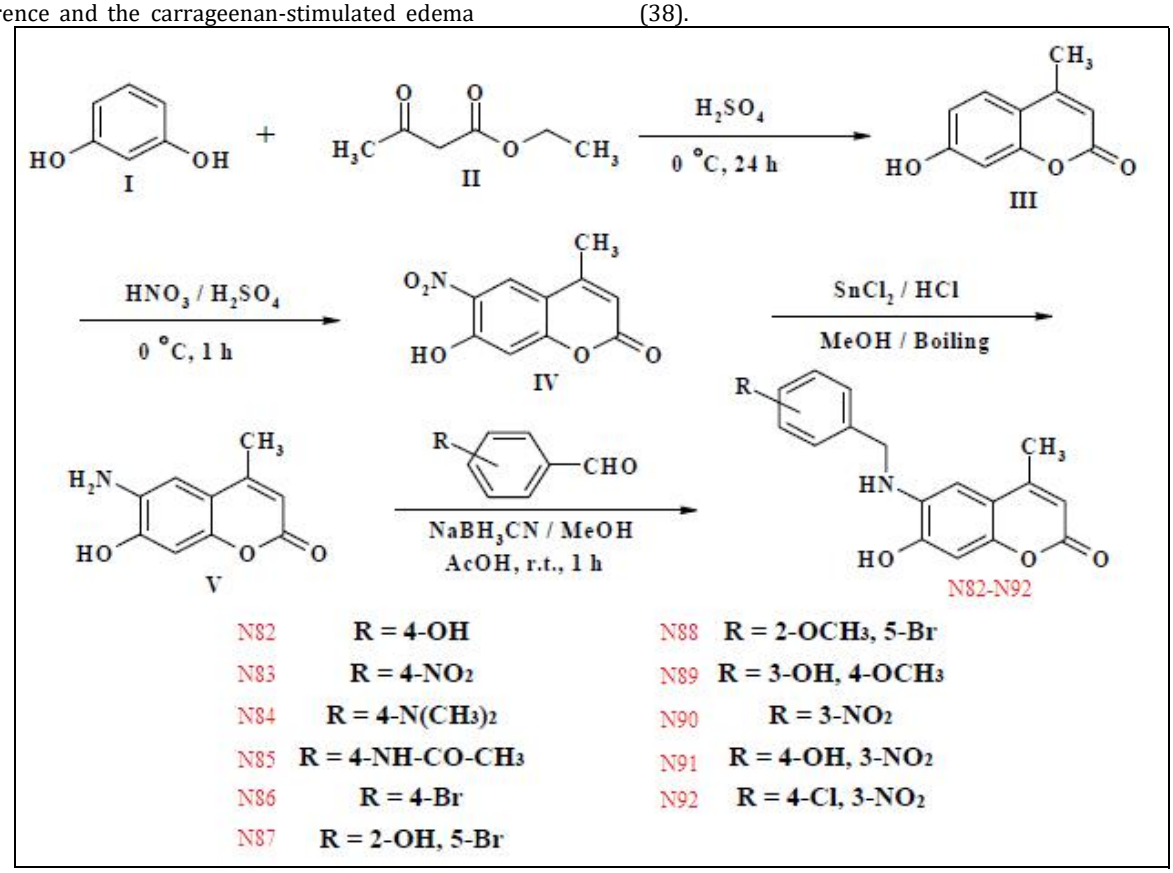


Figure 4: Chemical structures of the coumarinyl conjugates prepared by Nikalje *et al*.

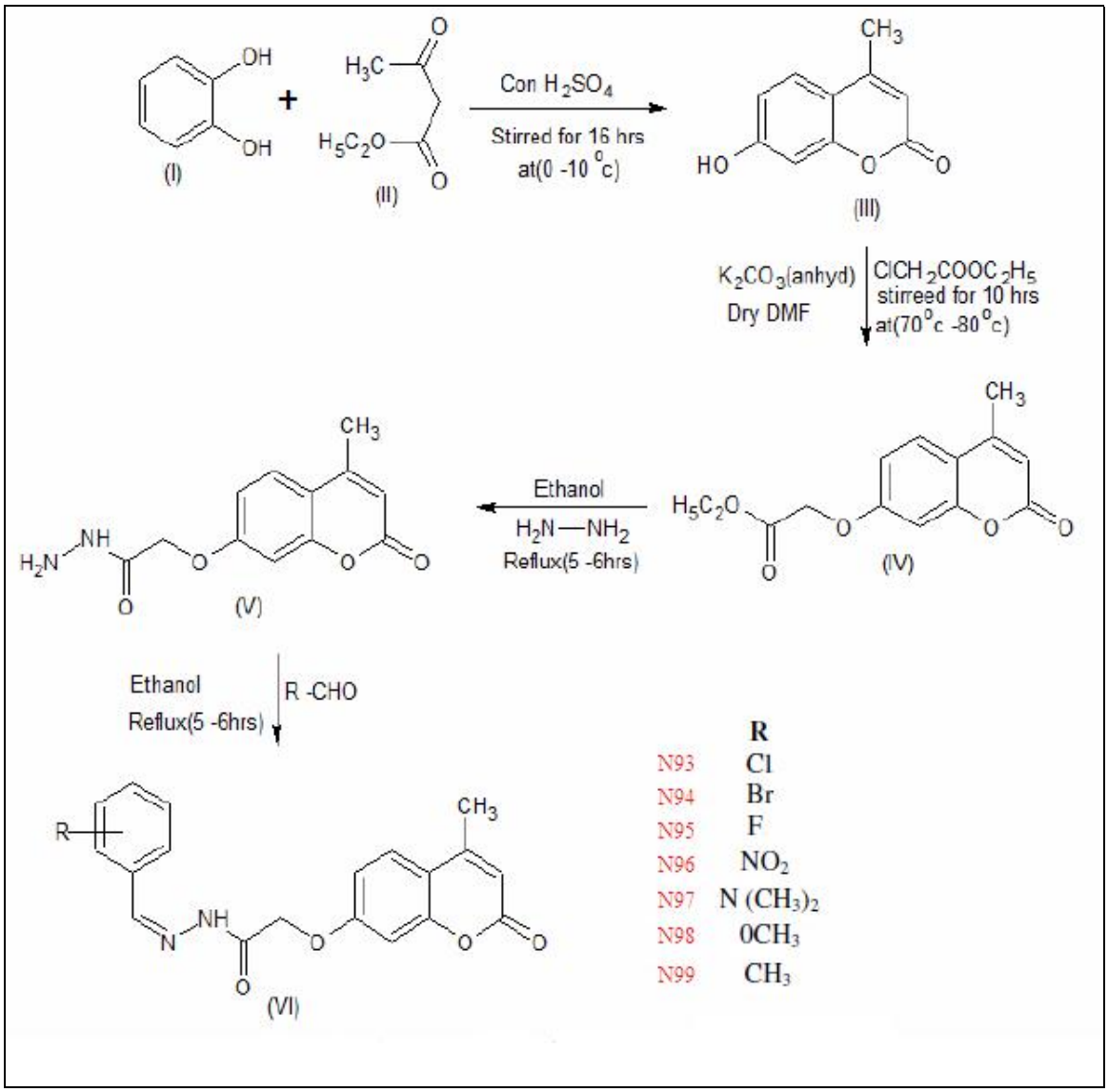
Anti-inflammatory potential

El-Haggar and Al-Wabli have reported the synthesis of 11 hymecromone-based derivatives, as shown in Scheme 9. The anti-inflammatory potential of these derivatives, herein termed **N82**-**N92**, was examined using indomethacin as a reference and the carrageenan-stimulated edema method. The outcomes revealed that the derivatives **N83**, **N84**, **N85**, and **N90** surpassed the effect of the reference in the first hour of treatment. Also, the derivatives **N85** and **N89** exhibited a higher minimizing impact on edema than the reference after 3 hours of administration (38).



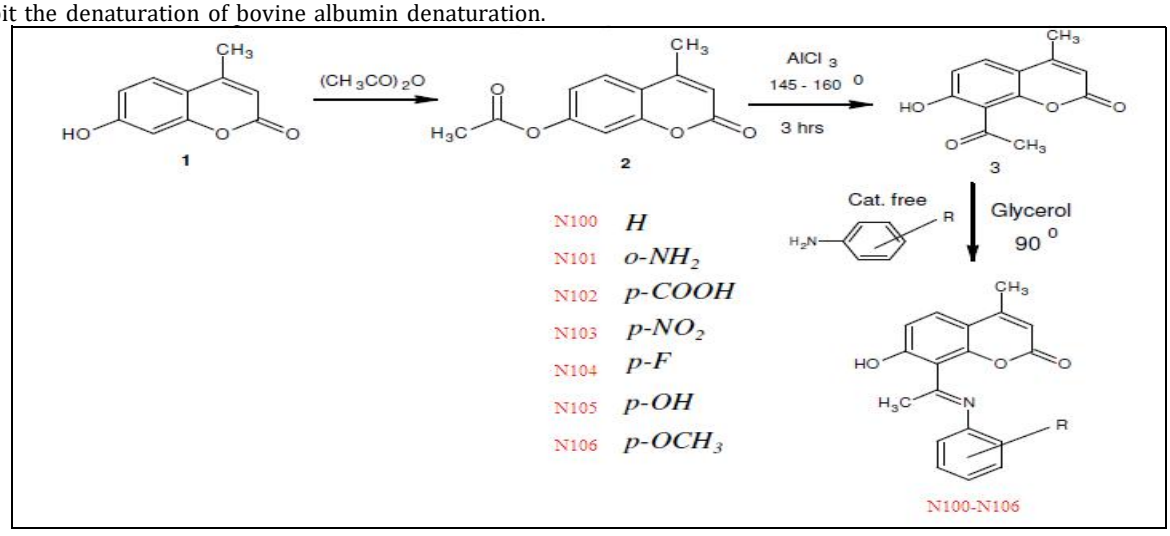
Scheme 9: Synthetic outline of the hymecromone-based derivatives prepared by El-Haggar and Al-Wabli.

Kardile *et al.* have reported the synthesis of seven hymecromone-based derivatives, as shown in Scheme 10. These derivatives, herein termed **N93**-**N99**, were scanned for their anti-inflammatory impact using ibuprofen as a reference and the carrageenan-stimulated edema method. The outcomes revealed that in comparison with the reference, derivatives **N95**, **N97**, and **N99** exhibited the highest anti-inflammatory impact, while the other derivatives showed the lowest impact (39).



Scheme 10: Synthetic outline of the hymecromone-based derivatives as proposed by Kardile *et al.*

Balaji *et al.* have synthesized seven hymecromone-based derivatives, as shown in Scheme 11. The anti-inflammatory impact of these derivatives, herein termed **N100**-**N106**, was determined by following their ability to inhibit the denaturation of bovine albumin denaturation. The outcomes revealed that only four derivatives exhibited a prominent anti-inflammatory effect, and their order of decreasing activity is **N105**, **N100**, **N106**, and **N103** (40).



Scheme 11: Synthetic outline of the hymecromone-based derivatives as proposed by Balaji *et al.*

Naik *et al.* have reported the synthesis of 13 hymecromone-based derivatives. The anti-inflammatory impact of the obtained derivatives, herein termed **N107**-**N119** (Figure 5), was screened by a protein denaturation technique, and their QSAR (quantitative structure-activity relationship) was also studied. The outcomes revealed that these derivatives have a remarkable anti-inflammatory effect. Also, the authors concluded that various substitutions on the aromatic ring have a minor impact on this type of activity (41).

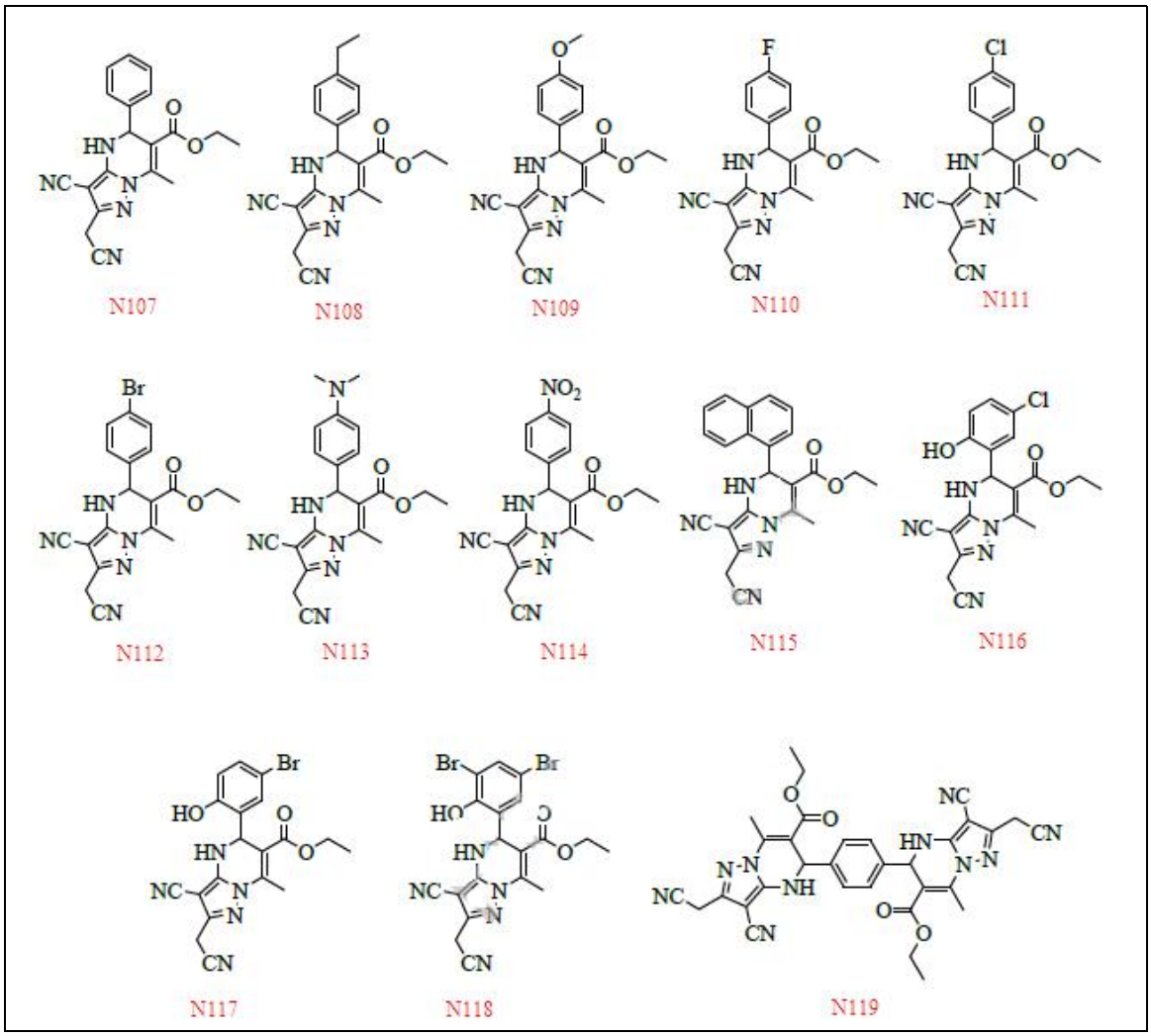


Figure 5: Chemical structures of hymecromone-based derivatives as depicted by Naik *et al.*

Lim *et al.* have studied the impact of hymecromone on the chronic dermatological disease named atopic dermatitis. The results revealed that the daily intake of hymecromone for one month results in the significant reduction of spleen size, weight, ear thickness, serum IgG2a, IgG1, IgE, IL-4, and TNF-α. Also, it has resulted in the reduction of the production of pro-inflammatory cytokines and chemokines. Accordingly, the author concluded that hymecromone may represent a potential candidate for the treatment of this inflammatory disease (42).

Antiviral potential

Bishnoi *et al.* have reported the synthesis of five hymecromone-based derivatives, herein termed **N120**-**N124** (Figure 6), and their antiviral activity was tested versus RNA virus named Japanese encephalitis virus. The results revealed that compounds **N120** and **N123** have showed an excellent antiviral activity with an inhibition percent of 100. Compounds **N121** and **N124** have showed a good inhibition percent of about 75. Only compound **N122** has showed a poor activity that may be attributed to having weak interactions with the target (43).

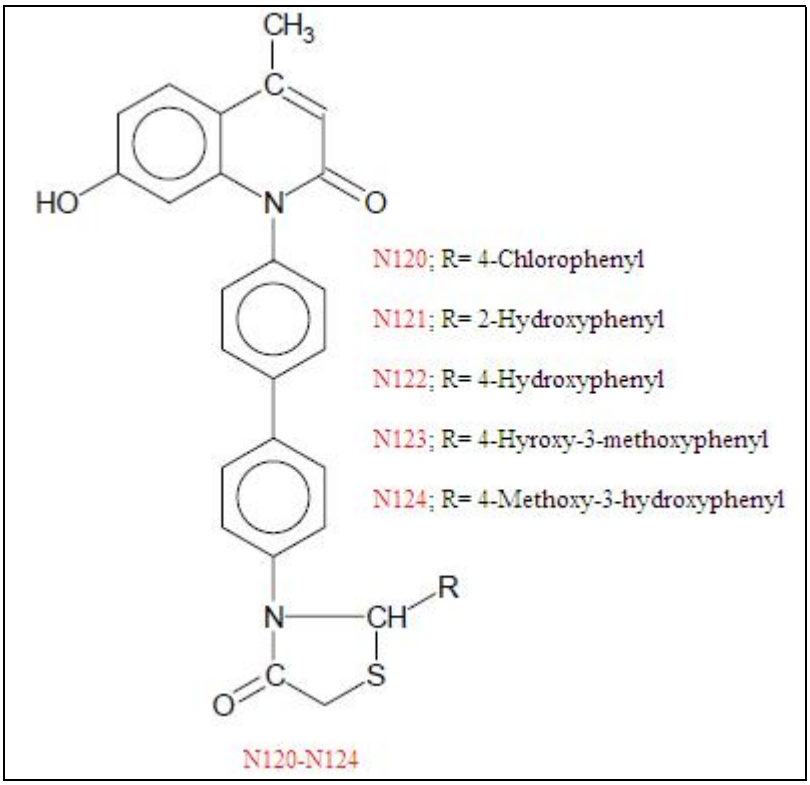
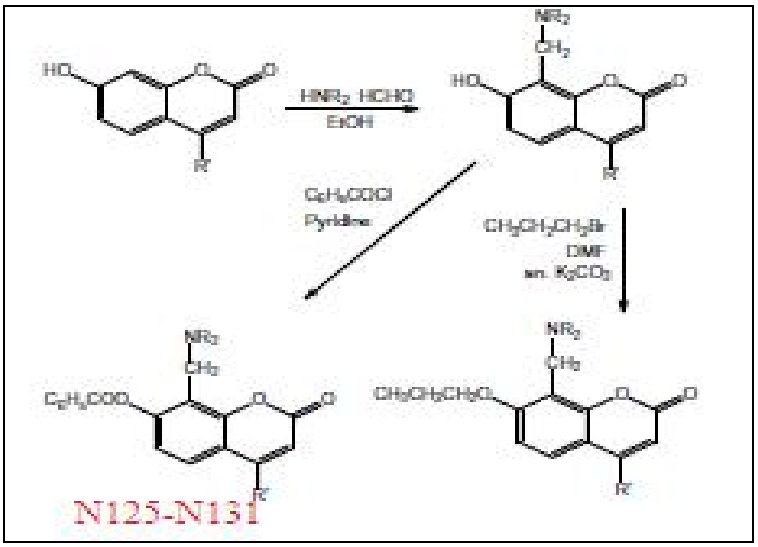


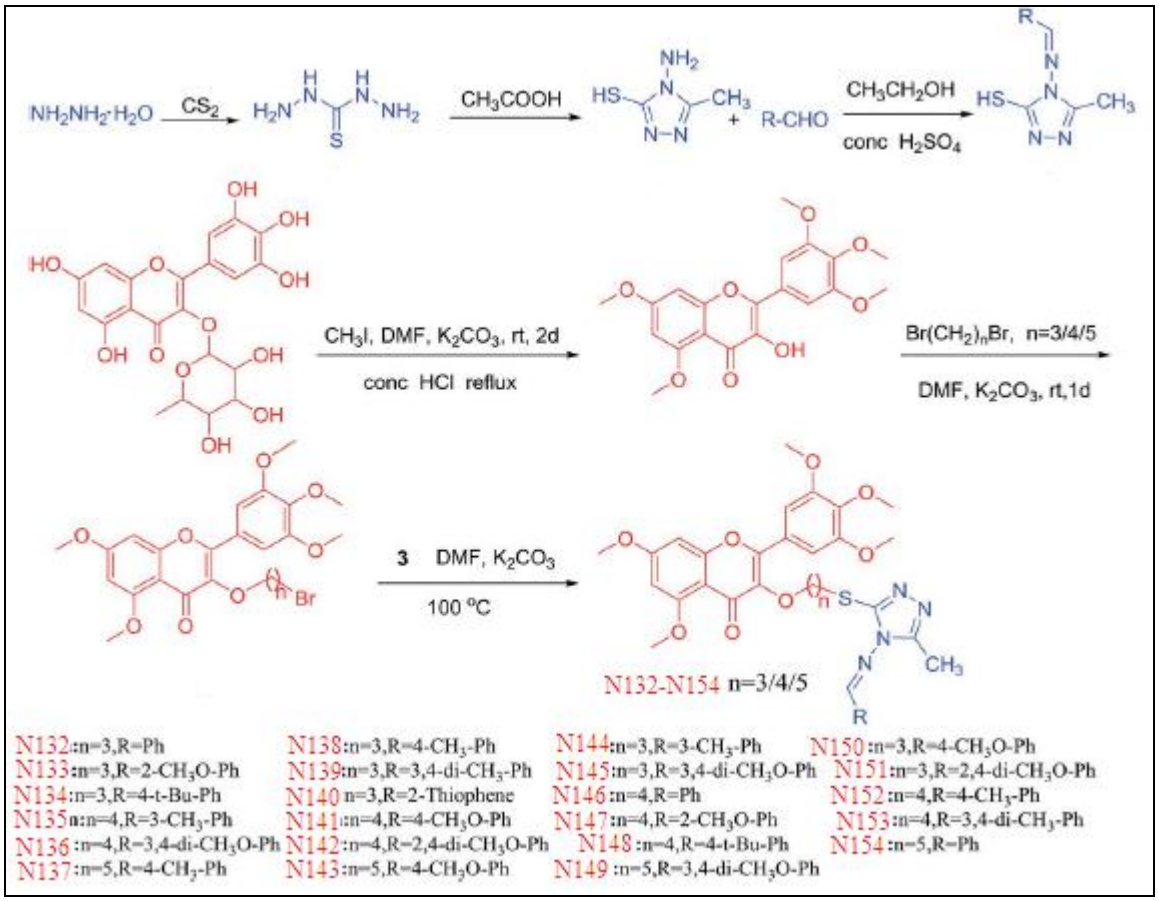
Figure 6: Chemical structures of hymecromone-based derivatives as depicted by Bishnoi *et al.*

Mazzei *et al.* have reported the synthesis of seven coumarinyl-Schiff bases, as shown in Scheme 12. The antiviral activity of these conjugates, herein termed **N125-N131**, was directed toward two phenotypes of the Hepatitis C virus, which are BVDV, YFV. The results revealed that the synthesized conjugates have an encouraging antiviral activity versus the test phenotypes with a superior effect contributed to compound **N130** (44).



Scheme 12: Synthetic outline of hymecromone-based derivatives as proposed by Mazzei *et al.*

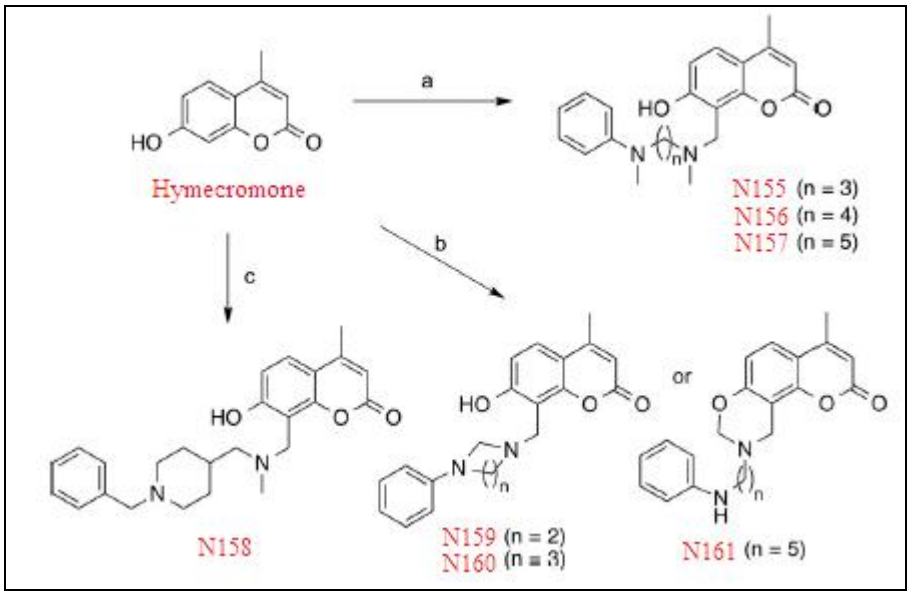
Chen *et al.* have reported the design and synthesis of 23 new myricetin derivatives hybridized with a Schiff-base of 1,2,4-triazole, as shown in Scheme 13. The antiviral activity of these hybridized molecules, herein termed **N132-N154**, was tested versus tobacco mosaic virus. These compounds revealed an excellent activity with the superior effect attributed to **N146**. The docking study showed that this compound has a better interactions with the viral protein named TMV-CP (PDB code: 1EI7) than the other synthesized products (45).



Scheme 13: Synthetic outline of myricetin-hybridized derivatives as proposed by Chen *et al.*

Anti-Alzheimer's disease

Dominguez *et al.* have reported the design and synthesis of seven multi-target therapeutic agents, as shown in Scheme 14, for the treatment of Alzheimer's disease. These agents with chemical structures based on hymecromone showed good affinity for BChE, AChE, and precluded Abamyloid aggregation. Also, the activity of these agents, herein termed **N155-N161**, may similar to that of 9,10-anthraquinone affording the good candidate as a therapeutic agent for the treatment of Alzheimer's disease (46).



Scheme 14: Synthetic pathway of multi-target therapeutic agents prepared by Dominguez *et al.*

Cardio-protective potential

Sharma *et al.* have documented the cardio-protective impact of hymecromone on the isoproterenol-stimulated

myocardial infarction in rats. This report revealed that hymecromone has a radical-trapping activity and an encouraging cardio-protective effect. The authors concluded that the pre-treatment with hymecromone may represent a developing novel strategy for preventing and treating the cardiotoxicity results from the effects of the elevated level of adrenalin (47).

CONCLUSION

Based on the chemical characteristics of various hymecromone-based derivatives, which have been reported as bioactive compounds, this review concluded that the hymecromone may exemplify a promising pharmaceutical scaffold for the construction of therapeutic agents with an improved effect. This can be satisfied by the convenient choice of the substituents and their positions on the hymecromone skeleton.

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