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Coumarins: Biological activity and SAR studies

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ABSTRACT

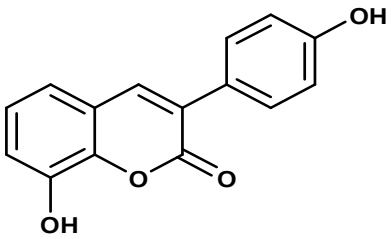
Over the past decades, literature survey revealed that, many naturally occurring and synthetic coumarin derivatives have been discovered and biologically evaluated for a broad range and diverse biological activities. This review provides a systematic summary and insight of the whole range of medicinal chemistry in the current developments of coumarin compounds and some overview on photochemotharpy, linear (psoralen) and angular (angelicin) furocoumarins and structure-activity relationships are also discussed. The perspectives of the future development of coumarin based medicinal chemistry are also presented.

Keywords: Coumarin, furocoumarin, angelicin, biological activity, SAR.

INTRODUCTION

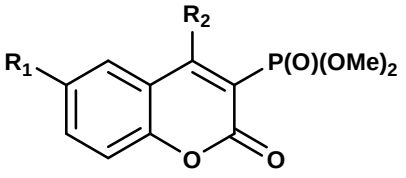
Coumarins are α-benzopyrones which are abundant in plant kingdom, found inessential oils (lavender, cassia, cinnamon) and produced by microorganisms. They are produced by plants as growth regulators and to protect themselves against predator. Coumarin also represents the core structure of several molecules with pharmaceutical importance, such as novobiocin and coumaromycin..Over the years, numerous derivatives of coumarin have been used as anticoagulantagents as they resemble vitamin K structure. They have been used as antimicrobial, antibacterial, antifungal, antioxidant, antitumor, anti-HIV, anti-hypertension, anticoagulant, anticancer, antiviral, anti-inflammatory and analgesic, antidiabetic, antidepressive.

Coumarins
A series of hydroxy-3-arylcoumarins was reported to have antioxidant properties and in particular compound **1**was the most effective antioxidant of the series.[1]



1

Budzisz *et al*[2] investigated the cytotoxic effects and alkylating activity of coumarin derivatives and their phosphonic analogues, compounds **2a-c** were found to possess a very high alkylating activity.



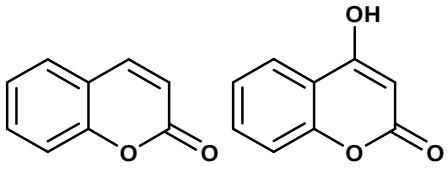
a R_1=CH_3 , R_2=CH_3

b R_1=H , R_2=Ph

c R_1=H , R_2=$(CH_2)_2$Ph

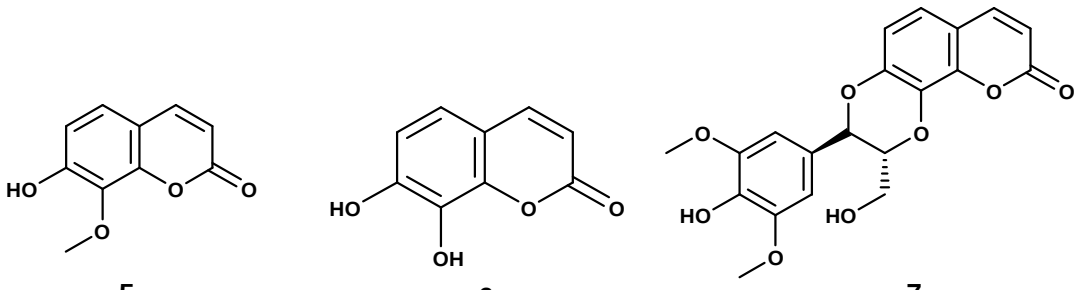
2 a-c

In addition, coumarins are reported to possess anti-inflamoatory activity. Luchini *et al*[3] tested the intestinal anti-inflammatory activity of coumarin **3** and 4-hydroxycoumarin**4** on experimental ulcerative colitis in rats due to its anti-inflammatory activity. The results obtained revealed that the coumarin and 4-hydroxycoumarin at doses of 5, 25 mg/kg, significantly attenuated the colonic damage induced by trinitrobenzenesulphonic acid (TNBS), as evidenced macroscopically, microscopically and biochemically. This effect was related to an improvement in the colonic oxidative status, since coumarin and 4-hydroxycoumarin prevented the glutathione depletion that occurred as a consequence of the colonic inflammation.



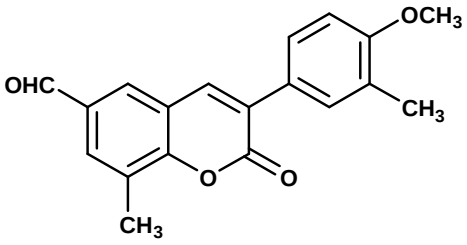
3 **4**

Interestingly, 7-hydroxy-8-methoxycoumarin**5**, daphnetin**6** and daphneticin**7**induced potent inhibition effect on hepatitis C virus protease NS3/4 A, and can be applied as prophylactic against hepatitis C.[4]



5 **6** **7**

Moreover, a series of novel 3-phenylcoumarin derivatives were synthesized and evaluated for antidepressant activity. Remarkably compounds**8** and**9**were reported to possess antidepressant activity at very low dose.[5]



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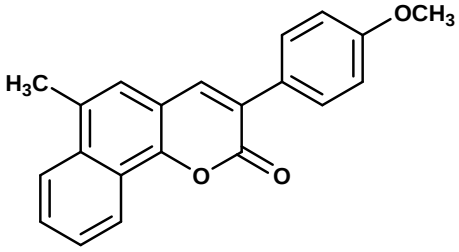
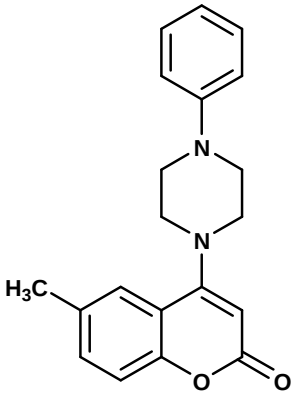


9

In addition, coumarin analogues with phenylpiperazine or benzoylpiperazine functions were synthesized and studied for their potential to treat Alzheimer. Compounds **10** and **11** showed potential activities.[6]



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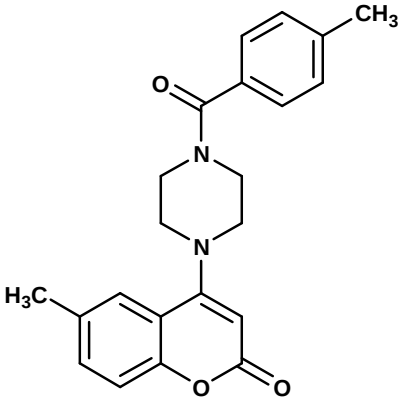
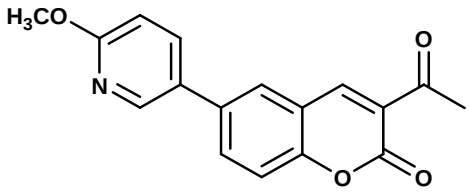


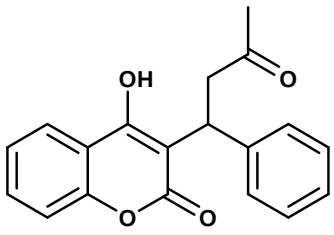
11

A series of coumarin derivatives were evaluated for their antihyper-glycemic activity. Compound **12**emerged as the most potent α-glucosidase inhibitor in present series of compounds.[7]



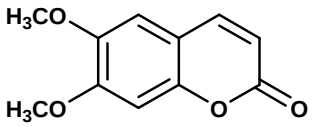
12

Warfarin **13** is the most commonly used oral anticoagulant. It has established efficacy for the prevention of thromboembolic events in patients with chronic atrial fibrillation, prosthetic heart valves, venous thromboembolism, and coronary artery disease. [8,9]



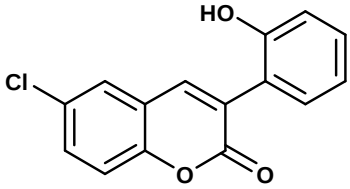
13

Thakur *et al*[10] evaluated the hypotensive activity of dihydroxy-coumarin and its congeners. They found that, the naturally occurring dimethoxycoumarin, Scoparone**14**has maximal activity, more significant than L-α-methyl dopa.



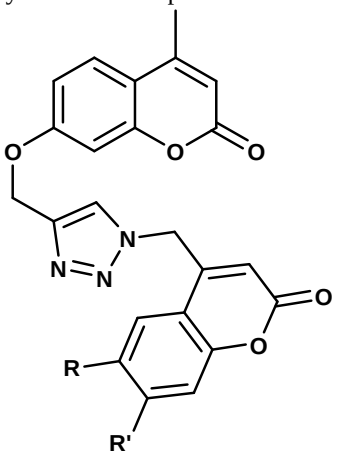
14

Moreover, Quezada *et al*[11] synthesized a new series of 6-chloro-3-[2-hydroxyphenyl]coumarins and evaluated their vasorelaxant activity. Compound **15** had the highest vasorelaxant activity among the synthesized series.



15

A series of bis-chromenyltriazole hybrids**16a-d**were synthesized under click reaction condition. Antimycobaterial screening data reveal that the synthesized compounds showed significant activity.[12]

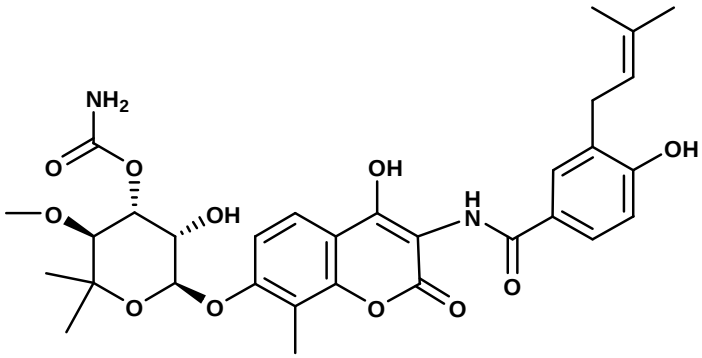


a: R=Cl, R'=H
b: R=H, R'=Cl
c: R=Br, R'=H
d: R=CH_3, R'=H

16 a-d

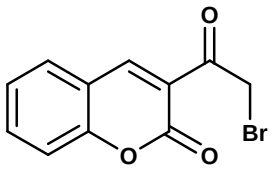
Interestingly, a numerous number of naturally occurring and synthetic coumarin derivatives were discovered and biologically evaluated to possess photosensitizing and antibacterial activities.

In 1956, clinical trials revealed the antimicrobial activity of Novobiocin **17**, which is aminocoumarin produced by a species of Streptomyces.[13]



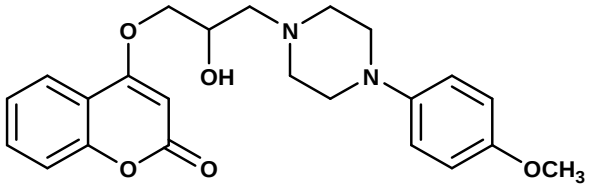
17

However, in 2014, a series of synthesized compounds, particularly CRMN3 **18** showed broad spectrum antibacterial activity [14].



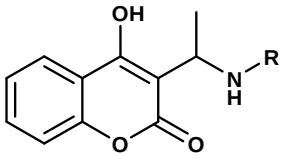
18

A series of coumarin derivatives were evaluated as potential antibacterial agents against Gram positive strains. Compound**19** was found to be the most potent derivative of this series.[15]



19

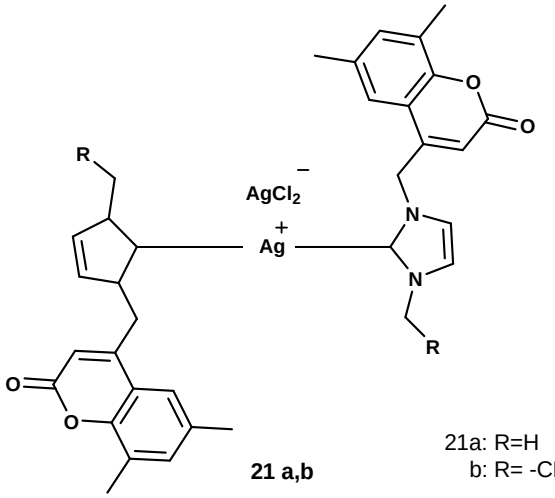
A series of amino derivatives **20a-g** of 4-hydroxycoumarins were synthesised and evaluated for antimicrobial activity against 13 different types of bacteria. Observed data indicated strong antibacterial activity of all tested amino derivatives.[16]



20 a-g

7a: R= ph
b: R= *p*-tolyl
c: R= *m*-tolyl
d: R= o-tolyl
e: R= *p*-NO_2-phenyl
f: R= *m*-NO_2-phenyl
g: R= Benzyl

Recently, Karatas*et al*[17] synthesized new coumarin substituted silver(I) N-heterocyclic carbene (NHC) complexes **21a,b** by the interaction of the corresponding imidazolium chlorides and Ag_2O in dichloromethane at room temperature. The antimicrobial activities were tested against gram-positive, gram-negative and fungal strains. Results showed that all the tested compounds inhibited the growth of the all bacteria and fungi strains.



21 a,b

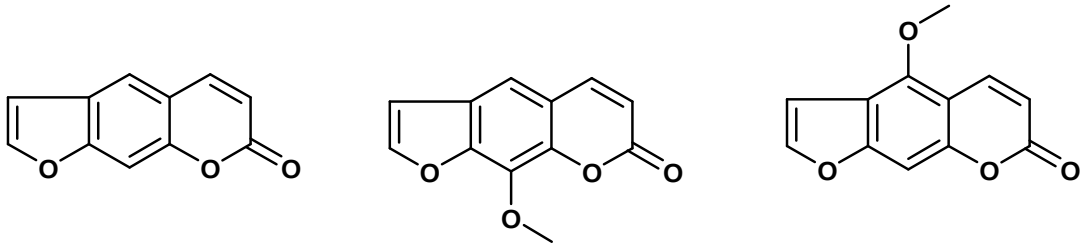
Photochemotherapy

Photochemotherapy, sometimes called Photodynamic therapy (PDT), is a treatment method in which light (nonionizing radiation) of an appropriate wavelength is used to induce a therapeutic response in presence of photosensitizing drug (phtosensitizer).[18]

Light must first be absorbed by photosensitizing agent to produce its effects when administered topically or systemically. After absorption of photons, the chromophore is excited and undergoes a chemical reaction that induces biological responses. At the dose used for photochemotherapy, the combined action of the photosensitizing drug and light give the therapeutic effect.[18]

Photochemotherapy is generally used for treatment of hyperproliferative skin diseases such as psoriasis, mycosis fungoides. In skin diseases, a combination of psoralen and radiation in the interval of UV-A (320-400 nm), is called PUVA [therapy derived from psoralens and UV-A].[18]

The pharmacologic concept of photochemotherapy was elucidated in 1967, although it was used in India and Egypt since 1200 and 2000 B. C., respectively. Photochemotherapy for vitiligo disease was practiced in the ancient world by herbalists, who used boiled extracts of PsoraleaCorylifolia seeds in fruit *Ammi Majus* in Egypt, these plants contain psoralen **22**, xanthotoxin (8-methoxypsoralen or 8-MOP) **23** and bergapten (5-methoxypsoralen or 5-MOP) **24**.[19]

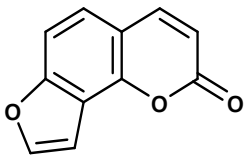


22 **23** **24**

Early, in 1974 the antiproliferative effect of psoralen was attributed to its ability to photoreact with DNA and block its biologic functions and cell division. It was considered that, the light (UV-A) is necessary to photo-activate the psoralen and affect only skin layers (the stratum corneum, the epidermis, and partly the dermis) and decided to treat skin diseases characterized by hyperproliferative conditions, such as psoriasis, with systemic psoralen and UV-A.[19]

Furocoumarins [Furobenzopyrones]

Furocoumarins are an important natural compounds isolated mainly from higher plants. These compounds are derivatives of the linear furocoumarin (psoralen) **22**, or its angular isomers angelicin (isopsoralen) **25** and allopsoralen**26**.[20]



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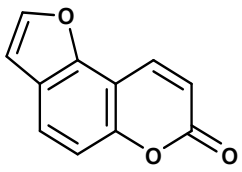
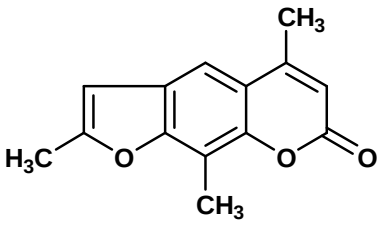


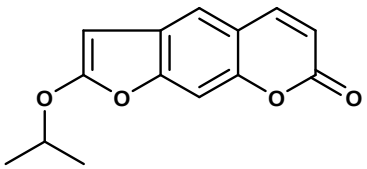
26



27

Furocoumarins such as psoralen**22**, xanthotoxin**23**, bergapten**24** and the synthetic trioxsalen (4,5′,8-trimethylpsoralen or TMP**) 27**are widely used in photochemotherapy for the treatment of some skin diseases (e.g. psoriasis, vitiligo, mycosis, and eczema),[21-24] as well as bacterial[25] and fungal[26] infections. Some derivatives are also used as biological probes to investigate the structure and function of nucleic acid in the field of molecular biology.[27] In addition, psoralen have been used in extracorporeal photochemotherapy to treat cutaneous T-cell lymphoma,[28] human immunodeficiency disease[29] and prevention of organ transplants rejection.[30] Other activities included anti-inflammatory, anticoagulant, antihistaminic, anticonvulsant and antialzehimer.[31,32] psoralen derivatives are also recognized as effective virucidal agents[33,34], especially againist enveloped viruses such as the herpes simplex virus or human immunodeficiency virus type I (HIV-1). [35]

In addition to PUVA and antibacterial activities, further studies showed that some furocoumarins as psoralen **22**, xanthotoxin **23** and 5′-isopropyloxypsoralen **28** possessed tuberculostatic activity, while bergapten**24** and isopimpinellin**29** were found to exert a molluscicidal activity.[36]



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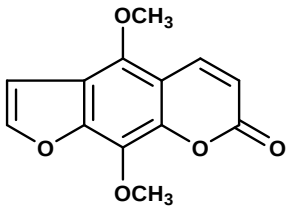
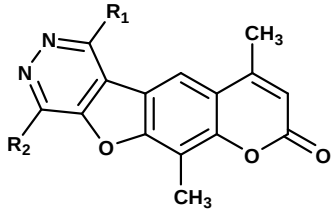


29

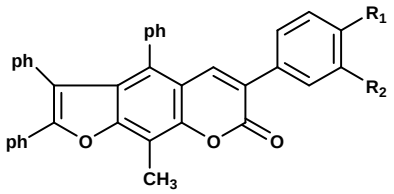
Interestingly, new substituted pyridazinopsoralen derivatives **30a-f**were studied for their photobiological properties. they showed comparable photo-antiproliferative effect and in some cases better than that of xanthotoxin.[37]



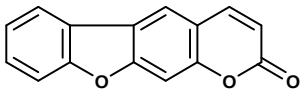
30a-f

a.R_1=R_2=H
b.R_1=$CONH(CH_2)_3N(CH_2CH_3)_2$,$R_2$=H
c.R_1=R_2=$CONH(CH_2)_3N(CH_2CH_3)_2$
d.R_1=R_2=$CONH(CH_2)_3N(CH_3)_2$
e.R_1=R_2=$CONH(CH_2)_2N(CH_2CH_3)_2$
f.R_1=R_2=$CONH(CH_2)_2N(CH_3)_2$

Furocoumarin analogues as 4′,5′-diphenylfurocoumarins **31a,b** were found to possess anti-infertility activity,[38,39] while benzofurocoumarin**32** was well known for its estrogenic [40] and insecticidal activities.[41]

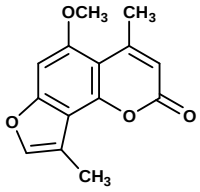


31 a.R_1=R_2= H
b.R_1=R_2= OCH_3



32

In 1998, antiproliferative activity of compounds **33-35** were reported.[42]



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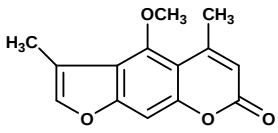

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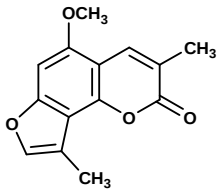
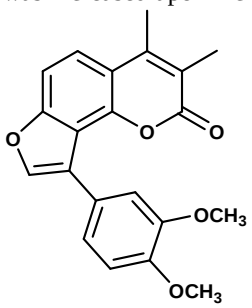


35

Some new furobenzopyrones were synthesized and evaluated for their antimicrobial and photochemotherapeutic activity previously in our laboratory. Compounds **36** and **37** exhibited antimicrobial activity higher than that of xanthotoxin, while compounds **38** and **39** exhibited better photosensitizing activity than xanthotoxin. In addition, photosensitizing activity was increased upon increasing time of radiation and concentration of substance.[43,44]



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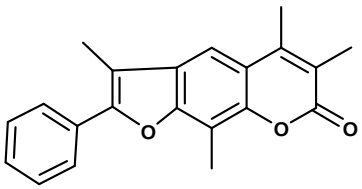

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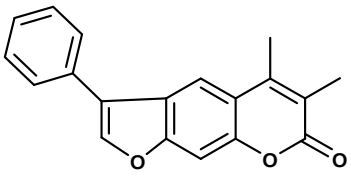

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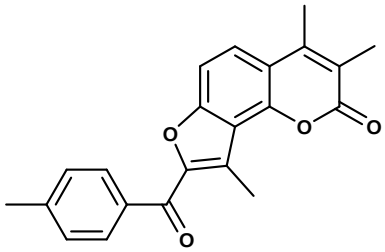
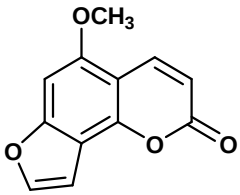


39

Angular furocoumarins (angelicin)

Angelicin, 5*H*-furo[2,3-h]-1-benzopyran-5-one **25** is an angular furocoumarin which is the parent compound of naturally occurring derivatives. It was first isolated from roots of *Angelica archangelica* L. in 1934 by Spath and Pesta.[45] Subsequently, 8-methoxyangelicin **40**, 9-methoxyangelicin **41** and 8,9-dimethoxyangelicin **42**derivatives were also isolated from natural sources.



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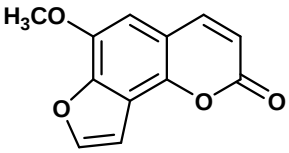

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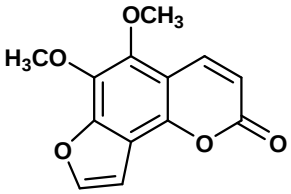
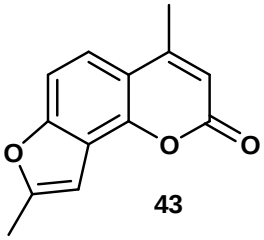


42

Angelicin and its derivatives were studied by Musajo and coworkers[46,47] and Pathak and Fitzpatrick [48].

Musajo and Rodighiero[49] in 1962 reported poor photosensitizing activity of angelicin. On the other hand Pathak and Fitzpatrick [50] found that 4,5'-dimthylangelicin, DMA**43** lacked skin-phototoxicity.

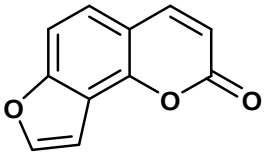


43

Later on, in 1972 Musajo andRodighiero[51] discovered that furocoumarins are able to photobind selectively with DNA. They found that angelicin**25** has a puzzling behavior, despite its lack of skin phototoxicity, exhibited appreciable DNA photobinding even lower than that of other psoralens.

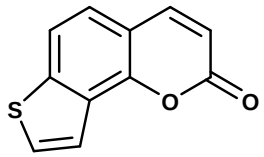
In the meantime Dall' Acqua*et al* [52] demonstrated a study led to a furocoumarins classification as:
(a) Bifunctional furocoumarins: those able to form interstrand crosslinks in the photoreaction with DNA,
(b) Monofunctionalfurocoumarins: those able to form only monoadducts in the photoreaction with DNA.

Cho *et al*[53] has reported that angelicin**25**, the parent angular furocoumarin isolated from natural plants is able to inhibit lytic replication of both murine and human gamma herpes viruses during the early stage of de novo infection. Angelicin treatment down-regulates expression of viral gene transcripts as well as genome replication, leading to reduction of plaque formation.



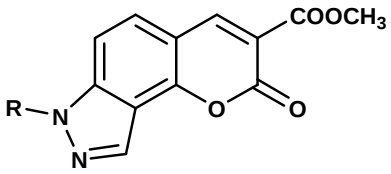
25

A series of angelicinheteroanalogues, in which the furan was replaced by thiophene was synthesized and evaluated for their antiproliferative activity. The new thioangelicin**44**showed higher antiproliferative activity than that of angelicin.[54]



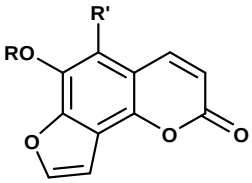
44

Interest in developing furocoumarinisosters is still considered. Pyrazolocoumarins were designated in which 1-substituted pyrazole moiety replace the furan ring in angelicin nucleus. Compound **45a** showed good anti-inflammatory and antipyretic properties while compound **45b** showed significant local anaesthetic activity.[54]



(**45**a) R= CH_3
(**45**b) R= C_6H_5

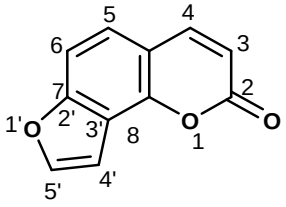
In addition, the antifugalactivity of a number of angular furocoumarin derivatives **46a-c** were investigated. It was found that the free 6-OH is essential for antifungal activity. [55]



46a: R= H R'= H
46b: R= H R'= $PhCH_2$
46c: R= Me R'= OMe

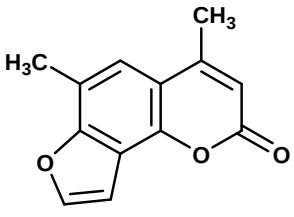
Structure activity relationship

1- SAR studies of angular furocoumarins have shown that introduction of one or two methyl groups at positions 5 or 4,5′ respectively in the angelicin molecule **25** led to increase in complex formation with DNA compared with parent angelicins. This was attributed to the increase in hydrophobicity and photobinding capacity towards DNA.[56] On the other hand, these methyl angelicins did not provoke any skin phototoxicity but showed much lower mutagenic effect than psoralen, as they were proved to react monofunctionally with DNA.[57]



25

2- Presence of methyl group in position 6 of angelicin markedly enhanced the DNA photobinding in comparison with the parent angelicin. The role ofthe position of the methyl substituent in terms of DNA photobinding has the following order 4′ > 6 > 5 > 5′> 4.[58]Introduction of a second methyl group in the 4 or 4′-position to 6-methyl angelicin as in compounds **47** and **48** respectively led to further increase of the photobinding to DNA.[58]In addition, introduction of a third methyl group to 6-methyl angelicin led to the most promising compound 4,6,4'-trimethylangelicin **49**.[59]



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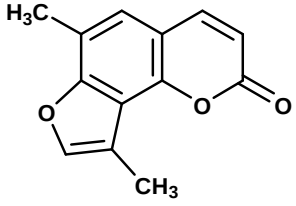

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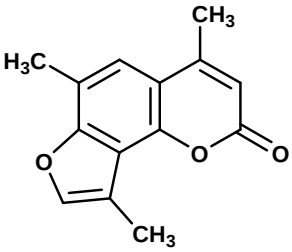
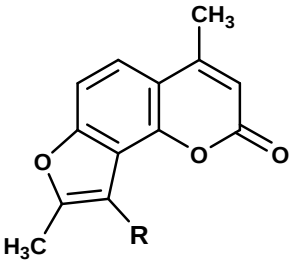


49

3- In continuing research to modify the lipophilic character of 4,5'-dimethylangelicin , hydroxymethyl**50a**, methoxymethyl**50b**, and aminomethyl**50c** groups were introduced to 4' position. When a hydroxymethyl group is

introduced into the 4' position **50a**, the affinity in the dark for DNA complex formation is only slightly lowered. On the other hand, when a methoxymethyl group is introduced into the same position **50b**, the extent of complexation is markedly decreased. Finally, compound **50c**demonstrates a very low photobinding capacity, even lower than that of reference angelicin. The new derivatives lack skin phototoxicity.[60]

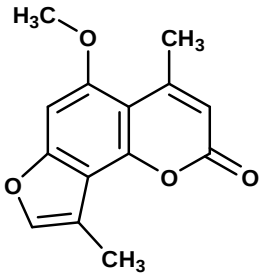


50a: R= CH_2OH
50b: R= CH_2OCH_3
50c: R= CH_2NH_2
50d: R= CH_2NH_2.HCl

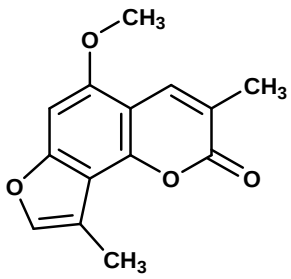
50 (a-d)

However, introduction of a cationic group in 4' position of 4,5'-dimethylangelicin, as for the hydrochloride of 4'-(aminomethyl)-4,5'-dimethylangelicin **50d**, strongly increases the binding parameters of the complex formed with DNA.[60]

4- In addition, 4,4′-dimethyl-5-methoxyangelicin **51** and 3,4′-dimethyl-5-methoxyangelicin **52** showed better antiproliferative activity with low skinphototoxicity for compound **51**.[61]

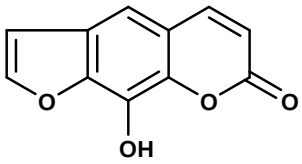


51

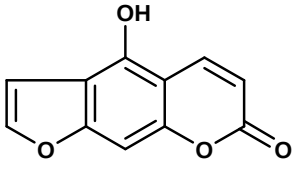


52

5- Early in 1960, it was reported that compounds with free phenolic group as xanthotoxol (8-hydroxypsoralen) **53** and bergaptol (5-hydroxypsoralen) **54** were inactive, while their methylated derivatives xanthotoxin**23** and bergapten**24** respectively were photo-dynamically active.[62]

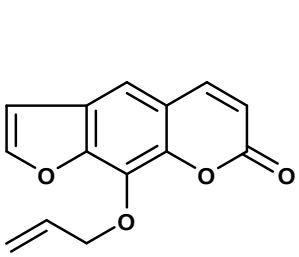


53



54

6- Introduction of acetoxy or benzoyloxy substituents at the 8-position in psoralen resulted in marked loss of the photodynamic activity which is markedly reduced or eliminated upon blocking the 5 and 8-positions. On contrary, they found that psoralen derivatives, 8-(2-propenyloxy) **55** was very active, while 8-methoxy-5-(2-propenyl) **56** or 8-methoxy-5-(3,3-dimethyl-2-propenyl)psoralen **57** were weakly active.[63]



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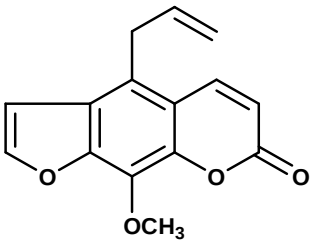

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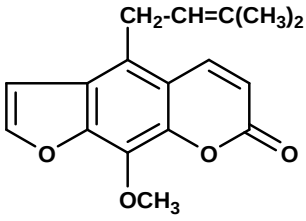
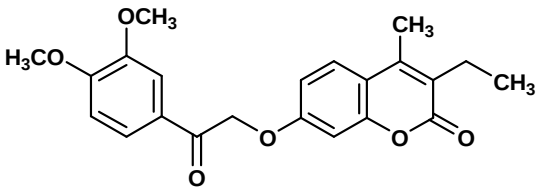


57

7- Concerning antimicrobial activity, presence of 3,4-dimethoxyphenyl substituent at C7 of coumarin **58** or C3 of angelicin**59**, enhance their antimicrobial activity. This was attributed to possible hydrogen bonding with aminoacid residues in the active site of DNA gyrase enzyme.[43]



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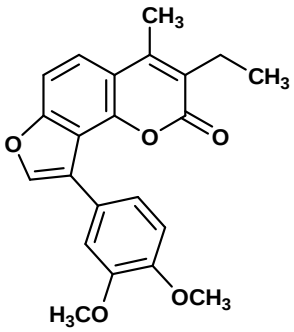

59

CONCLUSION

Summary for all the above mentioned, coumarin compounds have been extensively investigated in medicinal chemistry. They have clearly exhibited overwhelming potential applications not only as anticoagulant, anticancer, antioxidant, antibacterial, antifungal, antiviral, anti-inflammatory and analgesic, antidiabetes, and other bioactive agents, but also as potential photochemotherapeutic agents. More and more coumarin-based chemical drugs with better curative effects, strong pharmacological, less side effects and toxicities for biologically important species will be successfully developed and enter in clinical use, which will undoubtedly make remarkable contributions to protect the human health.

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