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COUMARINS: AN OVERVIEW OF MEDICINAL CHEMISTRY. POTENTIAL FOR NEW DRUG MOLECULES

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ABSTRACT: Fusion of a pyrone ring with a benzene nucleus gives rise to a class of heterocyclic compounds called Benzopyrones, of which two distinct types are recognized: (1) benzo-α-pyrone commomly called coumarins and (2) benzo-ϒ-pyrone called chromones or flavanoids, latter differing from former only in the position of the carbonyl group in heterocyclic system. Coumarins have attracted considerable attention of medicinal chemists and pharmacologists in recent years as they been demonstrated to bear various pharmacological activities like anti microbial, anti oxidant, anti inflammatory and analgesic, anti cancer, ulcerogenic, anti malarial, antihyperlipidemic, tyrosinase inhibitor, anti convulsant, anti-parkinsonian, antihepatitis, anticoagulant, cholinesterase inhibitor, vasorelaxant. This review focus on therapeutic importance of coumarins along with various methods of synthesis.

INTRODUCTION: Coumarins are cinnamic acid derived phenolic compounds which are found in fungi, bacteria and plants, particularly in edible plants of different botanical families. The name coumarin is derived from `coumarou', which is the vernacular name of Tonka bean (*Dipteryx odorata willd*, Fabaceae), from which coumarin was isolated in 1820 [1].

Coumarin comes under the benzopyrone family of compounds, all of which consist of a benzene ring joined to a pyrone ring [2]. Coumarins can be subdivided into two categories:

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(1) benzo-α-pyrone commonly called as coumarins (2) benzo-ϒ-pyrones called as chromones or flavanoids, differs only in the position of carbonyl group on the heterocyclic system.

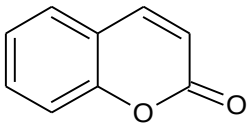


FIG. 1: 2-H CHROMEN-2-ONE COUMARIN

Some important compounds isolated from coumarin are Warfarin, Acenocoumarol, Armillarisin A, Novobiocin, Clorobiocin, Hymecromone etc. coumarin and its derivatives could be synthesized in laboratory by Pechmann reaction, perkin reaction, Reformatsky reaction and Knovenegal reaction. Coumarins have been under extensive studies for their versatile biodynamic activities, for example coumarins with phenolic hydroxyl group have the ability to scavenge reactive oxygen species and thus prevent the formation of 5- HETE and 5- HHT in arachadonic

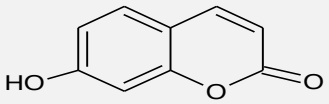
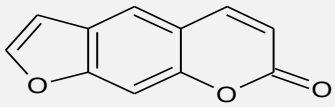
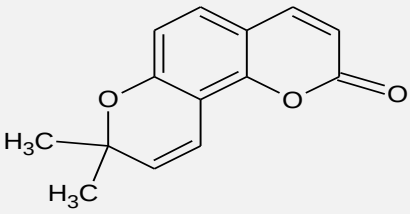
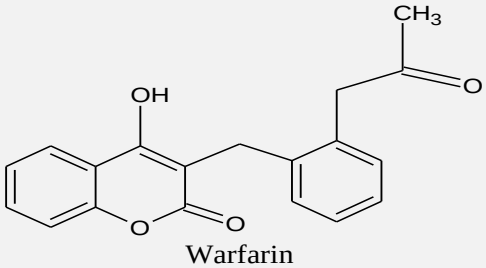
acid pathway of suppression of inflammation. Recent in vivo studies have revealed the role of coumarins in hepatotoxicity and also in depletion of cytochrome P450. Similarly 1-azacoumarins which is part of quinoline alkaloids are known for their diverse biological activity and recently, a 6-functionalized 1-aza coumarins are undergoing human clinical trials as an orally active antitumor drug in view of its farnesyl protein-inhibiting activity in the nanomolar range. Furthermore, several synthetic coumarins with a variety of pharmacophoric groups at C-3, C-4 and C-7 positions have been intensively screened for anti-microbial, anti-HIV, anti-cancer, lipidlowering, anti-oxidant, and anti-coagulation activities. Specifically, coumarin-3-sulfonamides and carboxamides were reported to exhibit selective cytotoxicity against mammalian cancer cell lines.

The C4-substituted aryloxymethyl, arylaminomethyl, and dichloroacetamidomethyl coumarins, along with the corresponding 1-azacoumarins, have been demonstrated to be potential anti-microbial and anti-inflammatory agents. To expand the structural diversity of synthetic courmarins for biological functions, attempts have also been made to attach a chloramphenicol side chain at C-3 position of courmarin. In addition, the bi- and tri-heterocyclic coumarins and 1-azacoumarins with benzofuran, furan and thiazole ring systems along with biocompatible fragments like vanillin have shown remarkable potency as anti-inflammatory agents in animal models.

Photobiological studies on pyridine-fused polycyclic coumarins have highlighted their potential as thymine dimer photosensitisers and the structurally related compounds of both coumarin and carbostyrils have also been found to act via the DNA gyrase pathway in their anti-bacterial activity.

Apart from the above works, the present review focuses on the recent research done on coumarins, which basically incudes the synthesis of therapeutically useful coumarins alongwith the SAR, so as to give an overview of essential structural features required for therapeutic activities. [3]

TABLE 1: CLASSIFICATION OF COUMARINS

Classes	Characteristic Features	Examples
Simple Coumarins	Hydroxylated, Alkylated, Alkoxylated on benzene ring	 4- hydroxycoumarin
Furano Coumarins	5 membered furan ring attached on benzene ring	 Psoralene
Pyranocoumarins	6 membered pyrone ring attached on benzene ring	 Seselin
Pyrone substituted Coumarins	Substitution on pyrone ring	 Warfarin

Occurrence:

Coumarins comprise a very large class of compounds found throughout the plant kingdom [4-6]. They are found at high levels in some essential oils, particularly cinnamon bark oil (7,000 ppm), cassia leaf oil (up to 87,300 ppm) and lavender oil. Coumarin is also found in fruits (e.g. bilberry, cloudberry), green tea and other foods such as chicory [7]. Most coumarins occur in higher plants, with the richest sources being the Rutaceae and Umbelliferae. Although distributed throughout all parts of the plant, the coumarins occur at the highest levels in the fruits, followed by the roots, stems and leaves. Environmental conditions and seasonal changes can influence the occurrence in diverse parts of the plant [8]. Recently six new minor coumarins have been isolated from the fruits and the stem bark of *Calophyllum dispar* (Clusiaceae). The genus *Calophyllum*, which comprises 200 species, is widely distributed in the tropical rain forest where several species are used in folk medicine [9]. Although most of the natural coumarins in existence have been isolated from the higher plants, some members have been discovered in microorganisms.

Some important coumarin members have been isolated from microbial sources e.g. novobiocin and coumermycin from *Streptomyces*, and aflatoxins from *Aspergillus* species [10, 11]. The aflatoxins are a group of highly toxic fungal metabolites and the most commonly occurring member of the group is aflatoxin B1 [8]. Coumarin group antibiotics, such as novobiocin, coumermycin A1 and clorobiocin, are potent inhibitors of DNA gyrase. These antibiotics have been isolated from various *Streptomyces* species and all possess a 3-amino-4-hydroxy-coumarin moiety and a substituted deoxysugar; noviose, as their structural core that is essential for their biological activity.

Synthesis:

1. Perkin reaction: Perkin [12] first synthesized coumarin from salicylaldehyde by heating it with acetic anhydride and anhydrous sodium acetate **(Fig.2)**. This reaction occurs with the formation of an intermediate o-hydroxycinnamic acid derivative which passes spontaneously into the lactone when liberated from its sodium salt

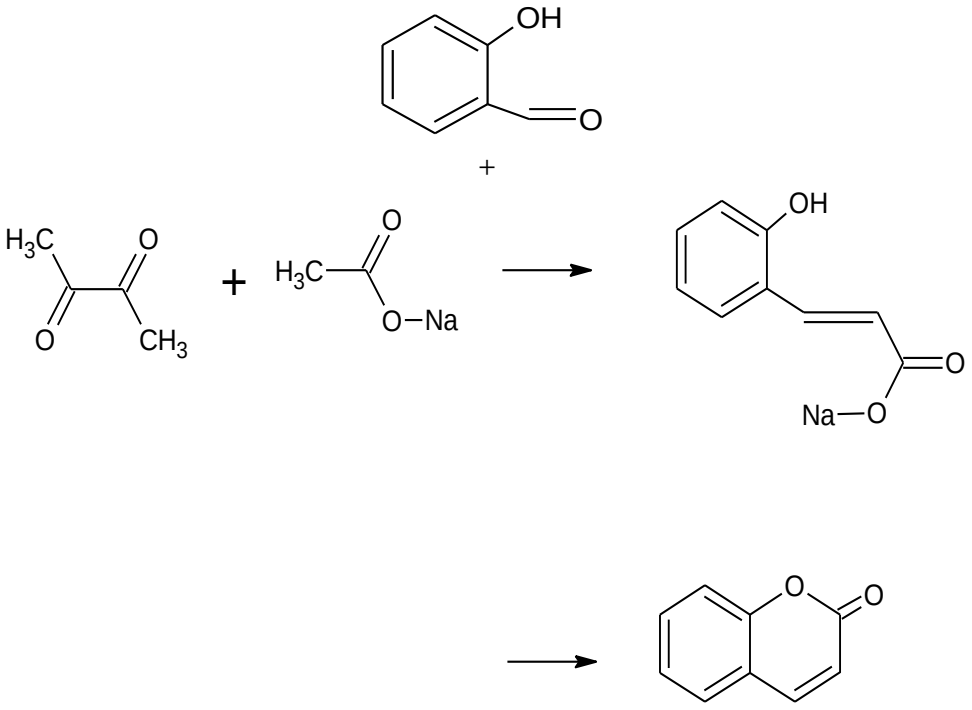


FIG. 2

2. Pechmann reaction: Pechmann [13] found that a coumarin derivative is formed when a mixture of a phenol and malic acid is heated in the presence of concentrated sulfuric acid **(Fig. 3)**. This method has limited applicability. Many substituted phenols do not undergo this reaction; only coumarins unsubstituted in the pyrone ring are obtained.

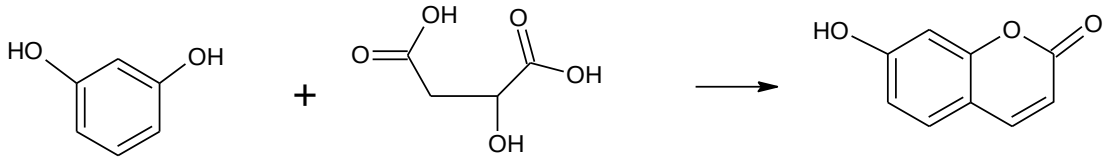


FIG.3

3. Pechmann-Duisberg reaction: Pechmann and Duisberg [14] found that phenols condense with p-ketonic esters in the presence of sulfuric acid, giving coumarin derivatives **(Fig. 4)**.

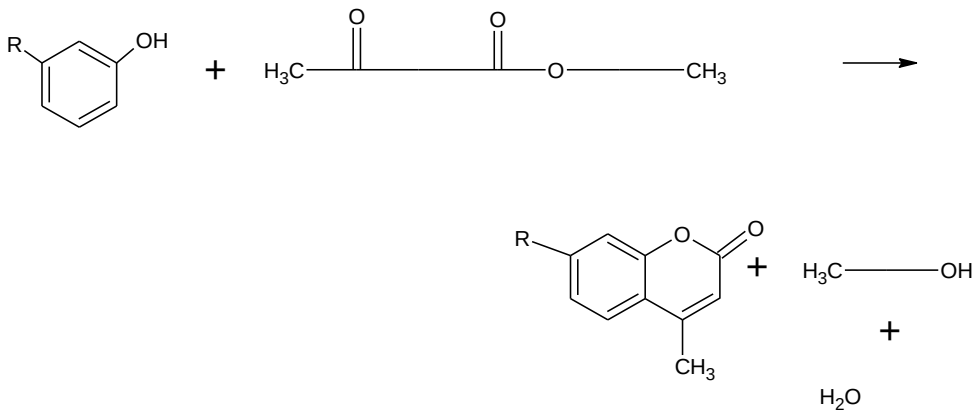
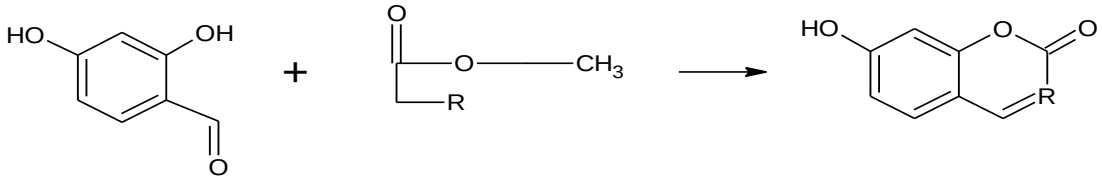


FIG. 4

4. Knoevenagel reaction: Knoevenagel [15] developed a method for the synthesis of coumarin derivatives from o-hydroxyaldehydes by condensation with ethyl malonate, ethyl acetoacetate, ethyl cyanoacetate, etc., in the presence of piperidine, pyridine, and other organic bases **(Fig. 5)**.



(R = $COOC_2H_5$, $COCH_3$)

FIG. 5

5. Solvent free synthesis of Coumarins: Pechmann reaction has been extensively used for the preparation of coumarin and its derivatives from simple starting materials. The present investigation describes an ecofriendly route for the Pechmann synthesis of coumarin derivatives over Al-MCM-41 and its supported catalysts under solvent-free condition [16] **(Fig. 6)**.

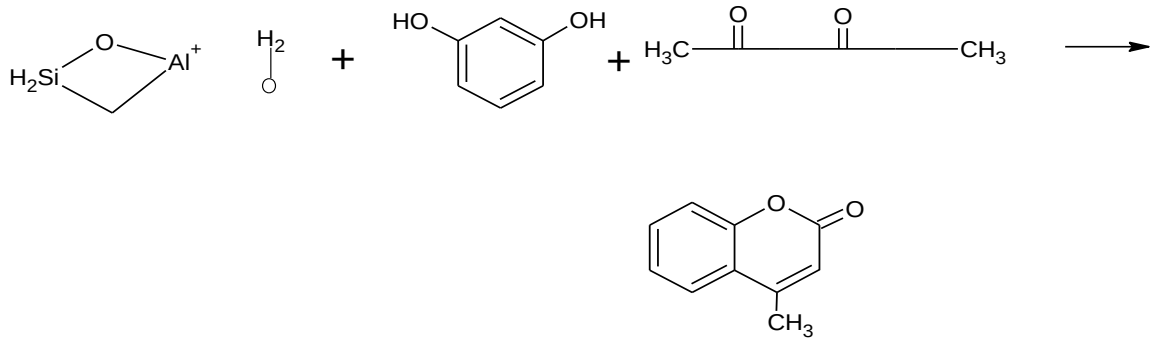


FIG. 6

Pharmacological activities:

Antimicrobial activity:

Coumarin derivatives are having promising antimicrobial activities as per recent literature survey, details of which have been presented as given below:

Rama Ganesh *et al*. synthesized some coumarin derivatives containing thiazolidin-4-one ring [17] and were screened for their antibacterial activity against Gram positive bacteria *Staphylococcus aureus, Bacillus subtilis* and Gram-negative bacteria *Klebsiella pneumonia*, *Escherichia coli* at the concentration of 0.001mol/ml compared with standard drug Ciprofloxacin. Zone of inhibition of highly active compound **(Fig. 7)** was 20 mm against *Staphylococcus aureus* and *Bacillus subtilis*.

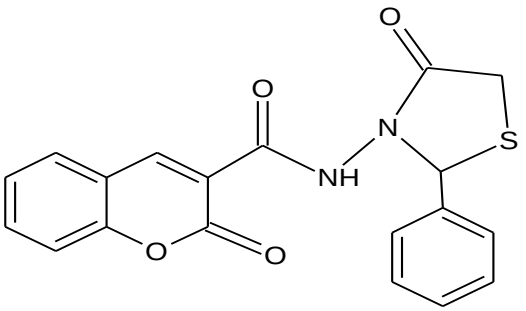


FIG. 7

Purohit *et al*. reported synthesis and biological activities of some substituted 3-(4-hydroxybenzoyl)-1*H* isochromen - 1 - one [18], 2-benzopyran 1*H* - 2 - one, 1 *H*-2 – oxobenzopyran - 3-carboxylic acids and 2-benzofuran-1*H*-one **(Fig. 8)**. All the compounds showed good activity against *Staphylococcus aureus* and *Escherichia coli*.

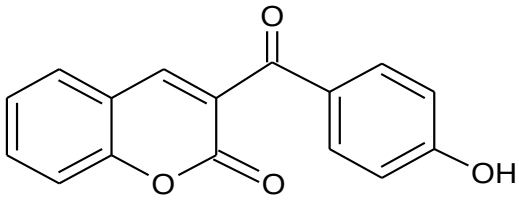


FIG. 8

Brahmbhatt *et al*. synthesized 4-methyl-3-phenyl-6-[4-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl) - 6 - aryl-pyridin-2-yl] coumarin derivatives [19] **(Fig. 9)** and were screened for their antibacterial activity against *Escherichia coli* (Gram negative bacteria), *Bacillus subtillis* (Gram positive bacteria) and anti-fungal activity against *Candida albican* by agar cup diffusion method. DMF was used as blank, Streptomycin was used as anti-bacterial standard and Clotrimazole was used as anti-fungal standard drug at concentration of 1000µg/ml. All the synthesized compounds showed activity against both gram positive and gram negative bacteria but lesser activity compared to standard drug.

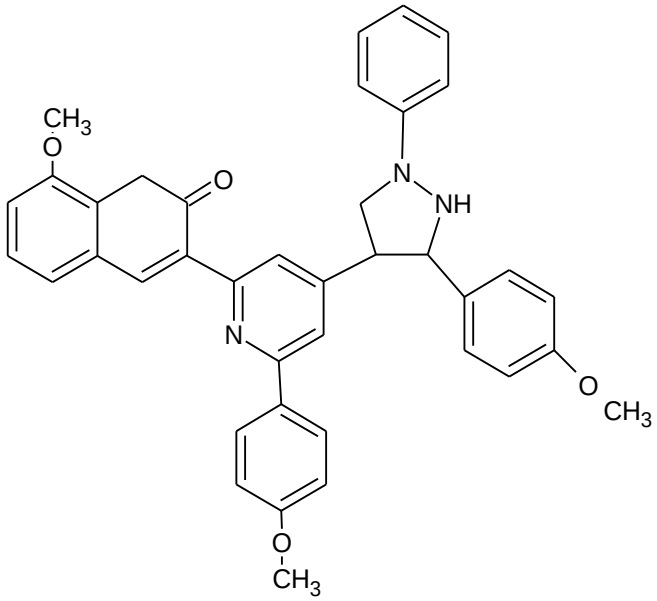


FIG. 9

Patel et al synthesized some 4-aryl-2,6-di(coumarin-3-yl)pyridines by the reaction of 3-coumarinoyl methyl pyridinium salts with1-[2H-1-benzopyran-2-on-3-yl]-3-aryl-prop-2-ene-1-ones in the presence of ammonium acetate and acetic acid under the Krohnke reaction conditions **(Fig. 10)**. All the synthesized compounds were screened for antimicrobial activity.

None of the compounds showed activity against *A. niger*. Eighteen compounds showed moderate activity against gram positive bacteria *B. subtilis*. The result towards this bacteria showed that incorporation of substituents like $–CH_3$ or $–OCH_3$ either in the coumarin nucleus or in the phenyl ring did not affect the antibacterial activity much more and all the compounds have the same activity. Activity of other compounds indicated that the presence of an additional fused benzene ring between the C-5` and C-6` positions inhibited the antibacterial activity towards *E.coli.*

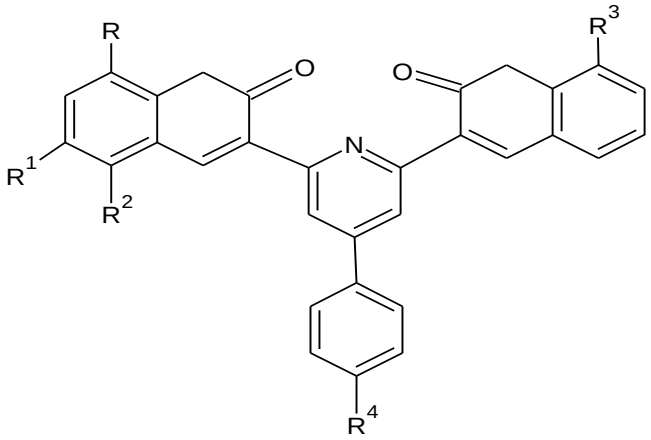


FIG. 10

A new series of coumarin inhibitors of DNA gyrase B bearing a *N*-propargyloxycarbamate at C-3' of various 5',5'-di-alkylnoviose including RU79115 [20] **(figure11)** were synthesised and their antibacterial activities were delineated by Musicki *et al*. *In-vitro*, RU79115 bactericidal activity of compound 11 against *E. faecium* and *S. aureus* was time dependent and similar to that of standard drug vancomycin in the case of *S. Aureus.*

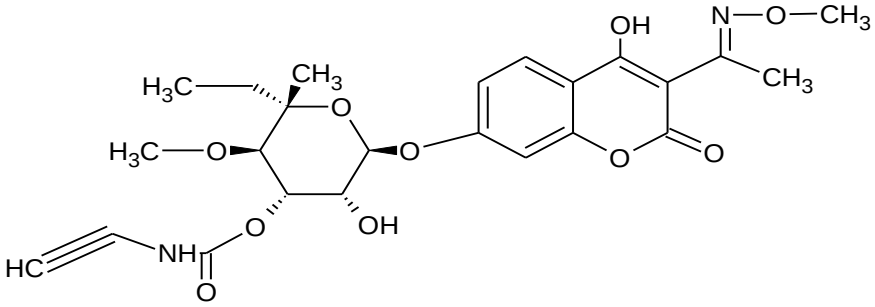


FIG.11

Al-Amiery *et al*. synthesized 4-[(5-mercapto-4-phenyl-4*H*-1,2,4-triazol-3-yl) - methoxy] - 2*H* - chromen-2-one as coumarin derivatives [21] and antifungal activity was determined based on the growth inhibition rates of the mycelia of strains (*Aspergillus niger* and *Candida albicans*) compared to in Potato Dextrose Broth medium (PDB). Appropriate volumes of tested compounds were added to produce concentrations ranging from 10 to 100µg/mL. Two compounds **(Fig. 12)** and **(Fig.13)** showed good activity as antifungals compared to the antifungal ability of fluconazole, which was used as a standard drugs.

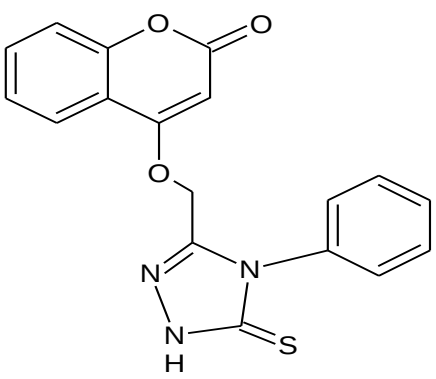


FIG. 12

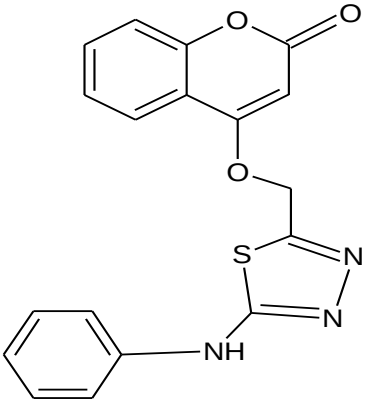


FIG.13

4-Heteroaryl-coumarin-3-carbaldehydes [22] **(Fig. 14)** were synthesized by Govori *et al*. and antimicrobial properties of these new coumarins were investigated and results were submitted for their activities against *Staphylococcus aureus, Escherichia coli*, *Hafnia alvei*, *Pseudomonas aeruginosa* and *Enterobacter cloacae*. The Agar disc diffusion technique measured the diameters of the inhibition zone around discs which were previously wetted with *N, N*-DMF solution of compounds at concentrations of 1, 3 and 5 mg/mL. One compound, 14 was more active against *Staphylococcus aureus, E.coli and Enterobacter cloaco* and not active as antimicrobial agent against *Hafnia alvei* and *Pseudomonas aeruginosa.*

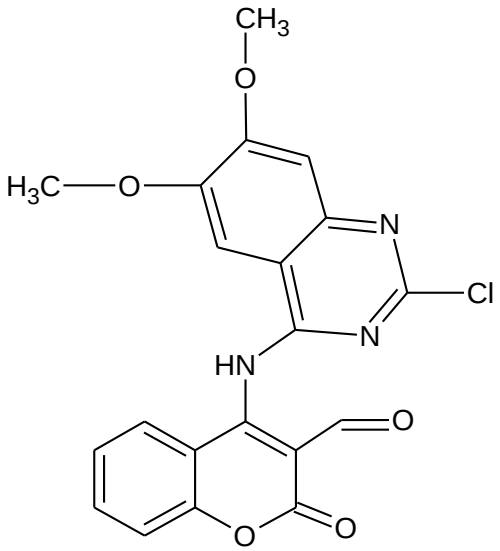


FIG.14

Some novel 4-substituted coumarins [23] were synthesized by Mashelkar *et al*. (**Fig. 15, Fig. 16)** and subjected to *in-vitro* screening against gram-positive *Staphylococcus aureus* and gram-negative *Salmonella typhi* using tube dilution technique. Ampicillin (MIC=0.01µg/mL against gram positive *S. aureus*) and trimethoprim (MIC=1µg/mL against gram-negative *S. typhi*) were used as standard drugs. Two compounds showed significant antibacterial activity at concentration levels of 10 to 200µg/mL against *S. aureus* and *S. typhi*.

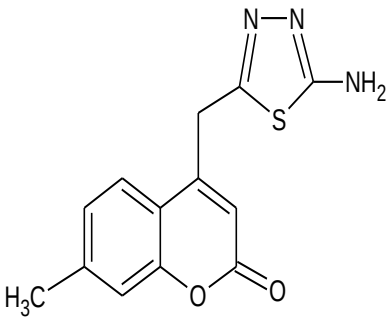


FIG.15

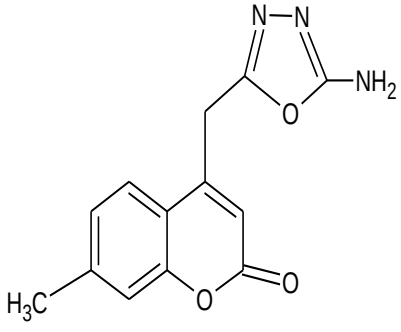


FIG. 16

Novel 4-hydroxy-chromene-2-one derivatives [24] were synthesized by Mladenovic *et al*. and screened for their antibacterial activity against Gram-positive bacteria *Staphylococcus aureus, Bacillus subtili* and Gram-negative bacteria *Klebsiella pneumonia*, *Escherichia coli* and their antifungal activity against *M. mucedo, C. albicans.* Streptomycin was used as standard anti-bacterial drug and ketoconazole was used as standard anti-fungal drug. One compound, **(Fig. 17)** had activity equal to that of standard drug ketoconazole (31.25 µg/mL) against *M. Mucedo.*

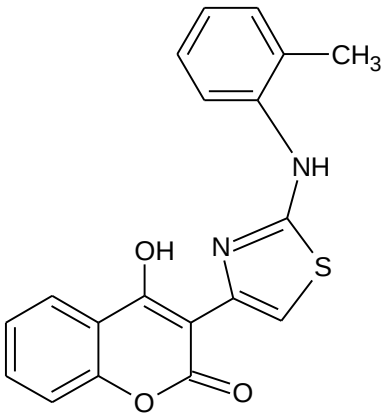


FIG.17

Acyl coumarins, 4-hydroxy-, and 7-hydroxycoumarins and coumaric amide dimmers [25] were synthesized by Lin *et al*. and were tested against stains of *Bacillus subtilis* (BCRC 10029), *Staphylococcus aureus* (BCRC 11863), *Escherichia coli* (BCRC 11758), and *Pseudomonas aeruginosa* (BCRC 11733) and Penicillin G potassium salt (CAS 113-98-4, USP grade) was used as a reference drug. One compound, **(Fig. 18)** was the most potent compound out of the tested compounds against *B. subtilis* with MIC value of 8µg/mL

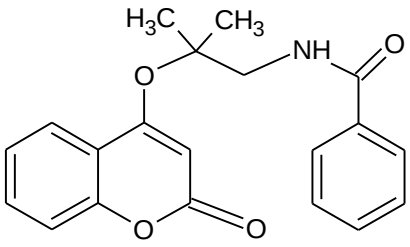
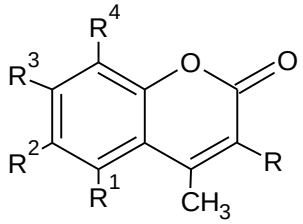


FIG.18

Antiinflammatory and analgesic activity:

Parmar V et al synthesized 4-methyl coumarin derivatives 7,8-dihydroxy-3-ethoxycarbonyl methyl -4-methylcoumarin (DHEMC) and 7,8-diacetoxy-3 - ethoxycarbonylmethyl - 4 - methylcoumarin (DAEMC) **(Fig. 19)** by using Pechman condensation of pyrogallol with ethyl acetoacetate [26] by introduction of an ethoxycarbonylmethyl group at C-3 position. DAEMC was obtained by acetylation of DHEMC. Both were examined on the inflammatory process induced by lipopolysaccharide (LPS) in activated primary rat microglial cultures by Anna Rita Togna et al [27]. LPS induced production of nitric oxide and other pro inflammatory mediators such as prostaglandins PGE_2 and thromboxane were inhibited in the presence of 100µM of DHEMC and DAEMC. Their experimentation showed that 4-methyl coumarin derivatives can modulate inflammatory pathways in microglial cells, probably by acting at the protein expression level.



	R	R^1	R^2	R^3	R^4
DHEMC	$CH_2COOCH_2CH_3$	-H	-H	-OH	-OH
DAEMC	$CH_2COOCH_2CH_3$	-H	-H	$-OOCH_3$	$-OOCH_3$

FIG. 19

Kullampalayam Krishnasamy Sivakumar et al synthesized [28] some mannich base of 5-methyl-[(2-oxo-2H-chromen-3-yl) carbonyl]-2,4-dihydro-3H-pyrazol-3-one **(Fig. 20)** by using conventional and non conventional (microwave) techniques. Ethyl 2-oxo-2H-chromene-3-carboxylate was prepared by cyclization of salicylaldehyde with diethylmalonate in presence of catalytic amount of piperidine. Reaction of this ester compound with hydrazine hydrate in ethanol formed 2-oxo-2H-chromene-3-carbohydrazide.

The key intermediate was prepared by cyclization of compound with ethyl acetoacetate in presence of glacial acetic acid. The key intermediate pyrazolone considered as a cyclic amide and hydrogen atom attached to C4 atom should be appreciably labile to participate in the Mannich condensation.

Therefore, the condensation of pyrazolone with formaldehyde (60%) and various aromatic primary amines resulted in the formation the corresponding Mannich base derivatives. Antiinflammatory activity was evaluated by carageenan induced paw oedema in albino rats. Each compound was dosed orally (at 0.03mmol/kg), 1h prior to induction of inflammation by carageenan injection. Anti-inflammatory activity was expressed as percentage inhibition of oedema. All compounds were

evaluated for analgesic activity by applying the acetic acid induced writhing test in mice using indomethacin as the standard drug. Percentage protection was calculated. Compounds containing sulfonic group at para- or meta- position showed better anti-inflammatory activity compared to indomethacin. All the synthesized compounds demonstrated significant reduction in oedema after 6th h compared to 4th h.

This difference in activity between 4th h and 6th h can be attributed to the bioavailability and pharmacokinetic parameters of the drug. The candidate molecules might get ionized after 4 h, which enhances the drug absorption and distribution thereby increasing the bioavailability (Cmax). Among the titled pyrazolones, possessing electron withdrawing substituents at 4th position in the Mannich base phenyl ring the highest anti inflammatory activity was obtained **(Fig. 21)** with substituent having lowest lipophilicity, lowest electron withdrawing power and highest polarizability.

The presence of p-chloro substituent favoured anti-inflammatory activity at 6th h has highest lipophilicity. On the other hand, introduction of disubstituent or bulky groups resulted in drastic decrease anti-inflammatory activity. Presence of hetero atom in the phenyl ring decreased anti-inflammatory activity. The analgesic activity data showed that compounds having 4-chloro group in the phenyl ring at 4th position in the Mannich base pyrazoline nucleus possess highest percentage of protection (103.78%), greater than the standard drug indomethacin.

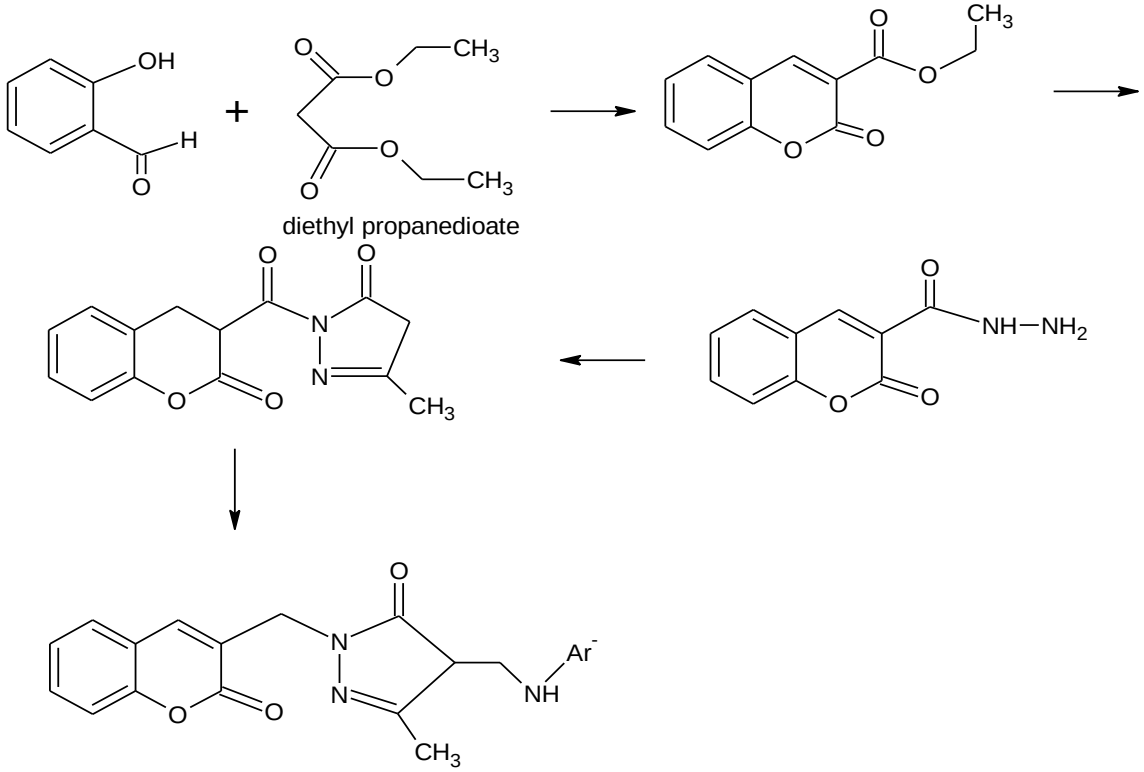


FIG.20

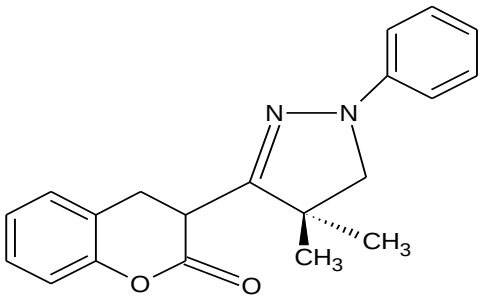


FIG. 21

Khode et al synthesized [29] a novel series of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl – 2 - pyrazolines **(Fig.22)** by reacting various substituted 3-aryl-1-(3-coumarinyl)propan-1-ones with phenyl hydrazine in the presence of hot pyridine. Structures of all newly synthesized compounds were characterized on the basis of elemental analysis and spectral data (IR, 1 H NMR and ^{13}C NMR). The title compounds were screened for *in vivo* anti inflammatory and analgesic activites at a dose of 200 mg/kg b.w. Among the twelve prepared compounds, compounds having 4-Cl-C_6H_4, 2,4-$(Cl_2)C_6H_3$, 3-OMe-C_6H_3 and 4-F-C_6H_4 exhibited significant anti inflammatory activity in model of acute inflammation such as carageenan-induced rat paw oedema while compounds having 4-Cl-C_6H_4 and 2,4-(Cl_2)-C_6H_3 showed considerable activity in model of chronic inflammation such as adjuvant induced arthritis and were compared with diclofenac (13,5mg/kg b.w.) as a standard drug. These compounds were also found to have analgesic activity in acetic acid induced writhing model.

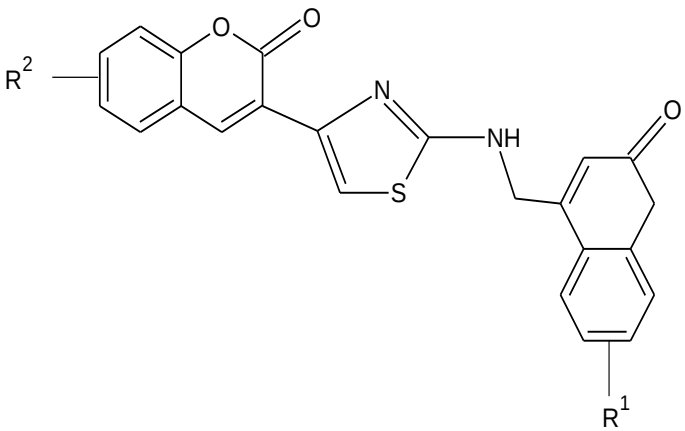
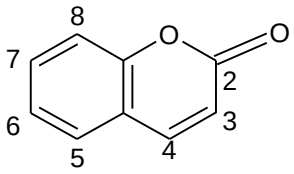


FIG.22

Bylov et al synthesized [30] a series of N-aryl substituted 2-imino-2H-1-benzopyran-3-carboxamide and 2-oxo-2H-1-benzopyran-3-carboxamide and evaluated them for anti inflammatory in carageenan induced rat paw oedema and in acetic acid peritonitis test in albino rats. The results were found to be comparable with piroxicam taken as reference drug. In the consideration of the efficacy of the compounds in these assays, 2-imino/oxo-2H-1-benzopyran-3-carboxamides were further studied at graded doses for their acute toxicities (ALD_{50}) in albino mice and were found to be essentially non toxic at highest dose test.

Antioxidant activity:



Coumarin Derivatives	C4	C6	C7	C8
Scopoletin (6-methoxy hydroxycoumarin)	-	-OCH_3	-OH	-
Scoparone (6,7-dimethoxy coumarin)	-	-OCH_3	-OCH_3	-
Fraxetin (7,8-dihydroxy-6-methoxycoumarin)	-	-OCH_3	-OH	-OH
4methylumbelliferone (4methyl-7-hydroxy coumarin)	-CH_3	-	-OH	-
Escullin (6,7-dihydroxy-6-O-glucosylcoumarin)	-	-OGlu	-OH	-
Daphnetin (7,8-dihydroxy-coumarin)	-	-	-OH	-OH

FIG.23

Aline Witaicenis et al evaluated antioxidant activity [31] of some plant derived coumarins (scopoletin, scoparone, fraxetin, 4-methyl-umbeliferone, esculin and daphnetin) **(Fig.23)** to verify if potential intestinal anti inflammatory activity was related to anti oxidant activity. Two *in vitro* assays were used to test the antioxidant activity of the coumarin derivatives: the lipid peroxidation in rat brain membranes and DPPH assays.

The lipid peroxidation assay in rat brain membranes was performed and the free radical scavenging activity of the coumarin derivatives was estimated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical reagent, adapted to a 96-well microplate. The data were obtained in triplicate and used to determine the effective concentration (EC50) of each coumarin derivative necessary for scavenging 50% of the DPPH. This study showed that coumarin derivatives are potential agents for treating intestinal inflammatory diseases and that the consumption of foods rich in coumarin derivatives, particularly daphnetin, esculin and scoparone, could be used in complementary

strategies to prevent and treat intestinal inflammatory diseases. All coumarin derivatives showed antioxidant activity in the DPPH assay, while daphnetin and fraxetin also showed antioxidant activity by inhibiting lipid peroxidation. Coumarins, except 4-methyl-umbeliferone, also showed antioxidant activity through the counteraction of glutathione levels or through the inhibition of myeloperoxidase activity.

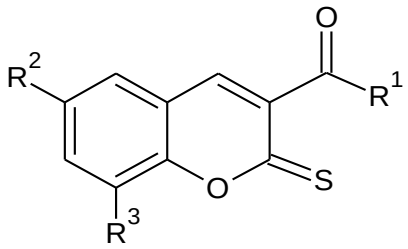


FIG. 24

Singh Om et al developed [32] a facile, convenient and high yielding synthesis of combinatorial library of 3- alkanoyl/aroyl/heteroaroyl-2H-chromene-2-thiones **(Fig. 23)** by condensation of easily accessible β-oxodithioesters and salicylaldehyde/ substituted 2-hydroxybenzaldehyde ander solvent free conditions. The assessment of radical scavenging activity of the compounds towards the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) was measured and these compounds were found to scavenge DPPH radicals efficiently. The newly synthesized compounds exhibited profound antioxidant activity. Five selected compounds were able to protect curcumin from the attack of suphur free radical generated by radiolysis of glutathione (GSH).

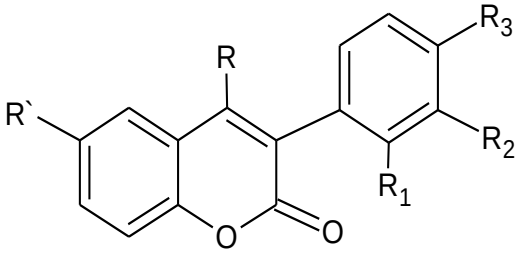


FIG.24

Roussaki et al synthesized [33] a series of coumarin analogues bearing a substituted phenyl ring on position 3 via a novel methodology through an intermolecular condensation reaction of 2-hydroxyacetophenone and 2-hydroxybenzaldehyde with imidazoylphenylacetic acid active intermediate. *In vitro* antioxidant activity of synthesized derivatives was evaluated using two different antioxidant assays (radical scavenging ability of DPPH stable free radicals and inhibition of lipid peroxidation induced by thermal free radical AAPH). Ability of compounds, (**Fig. 24)** to inhibit soybean lipoxygenase was also determined as an indication of potential anti inflammatory activity.

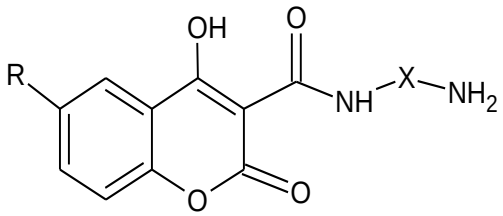


FIG. 25

Melagraki G. et al synthesized [34] a series of novel coumarin-3-carboxamides and their hybrids with the alpha lipoic acid (**Fig. 25)**. Compounds were evaluated for their *in vitro* antioxidant activity and *in vivo* anti inflammatory activity. These compounds were found to possess mentioned activities and on the basis of results, structure activity relationship was developed in order to define the structural features required for activity.

Stanchev S et al synthesized [35] four 4-hydroxycoumarin derivatives, ethyl 2-[(4-hydroxy-2-oxo-2Hchromen-3-yl)(4-hydroxyphenyl)methyl]-3-oxobutanoate, 4-[1- (4-hydroxy-2 – oxo - 2H-chromen-3-yl)-2-(ethoxycarbonyl) – 3 - oxobutyl] benzoic acid, ethyl-2-[(4-hydroxy-2-oxo-2H-chromen - 3 - yl) (3-nitrophenyl) methyl] - 3-oxobutanoate and ethyl-2-[(3,4,5-trimethoxy phenyl) - (4-hydroxy-2 – oxo - 2H-chromen-3-yl) methyl]-3-oxobutanoate.

These compounds were tested for *in vitro* antioxidant activity in hypochlorous system. The assay was based on the luminal-dependent chemiluminescence of free radicals, which decreased in the presence of 4-hydroxycoumarin derivative. Ethyl-2-[(4-hydroxy-2-oxo-2H-chromen-3-yl) (4- hydroxyphenyl) -methyl]-3-oxobutanoate expressed the best scavenger activity at the highest concentration (10–4molL $^{-1}$)

Ulcerogenic activity:

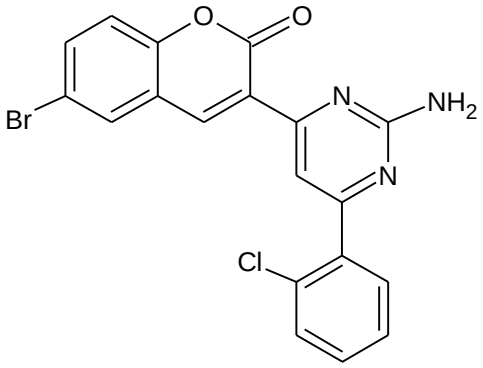


FIG.26

Gupta JK et al. synthesized a novel series of 3-(2-amino-6- pyrimidin-4-yl)-6-bromo-2Hchromen-2-one [36] **(Fig. 26)**. The synthesized compounds were tested for in-vivo analgesic activity at a dose of 20mgkg–1 body weight. Among them, compounds having o-chloro, m-chloro and m-bromophenyl exhibited significant analgesic activity and compounds having 2,4-dichloro and 2,6-dichloro phenyl exhibited highly significant activity comparable with standard drug Diclofenac sodium. Compounds having o-chloro phenyl, 2,4-dichloro and 2,6-dichloro phenyl were further screened for acute-ulcerogenic activity. Among them, compound having 2,6-dichloro phenyl was found to be most promising analgesic agent devoid of ulcerogenic effects [37].

Anticonvulsant activity:

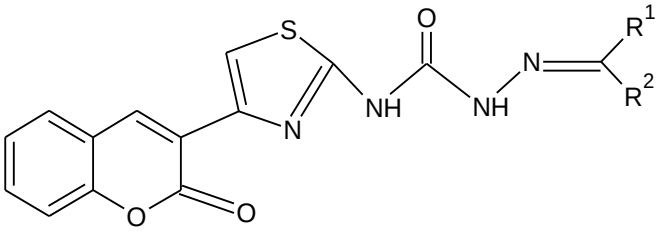


FIG. 27

Siddiqui N et al. prepared several heteroaryl semicarbazones [38] **(Fig. 27)** and compounds were tested for anticonvulsant activity utilizing pentylenetetrazole induced seizure (PTZ), maximal electroshock seizure (MES) and Neurotoxicity tests at 30, 100 and 300mgkg–1 dose levels. Three compounds having 3,4-Cl.C_6H_3, 2-OCH_3.C_6H_4 and 4-Br.C_6H_4 exhibited significant anticonvulsant activity at 30mgkg–1 dose level comparable to the standard drug-phenytoin.

Anticancer activity:

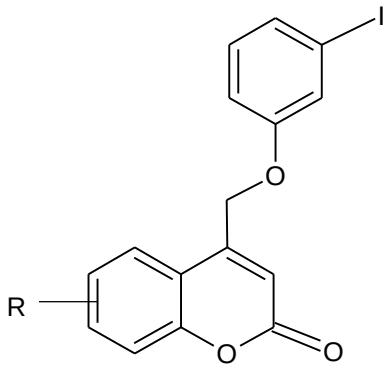


FIG. 28

Mahantesha Basanagouda et al synthesized [39] a series of new iodinated 4aryloxymethyl coumarins have been obtained from reactin of various 4-bromomethylcoumarins with 2-iodophenol, 3-iodophenol and 4-iodophenol **(Fig. 28)** respectively. All the compounds were screened for anticancer activity against two cancer cell lines (MDA-MB human adenocarcinoma mammary gland A-549 human lung carcinoma) The SAR results indicate that nine compounds are potent, among these having chlorine are most effective.

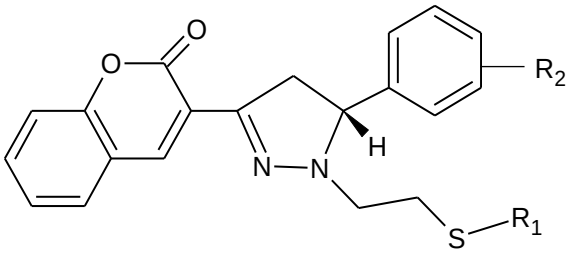


FIG.29

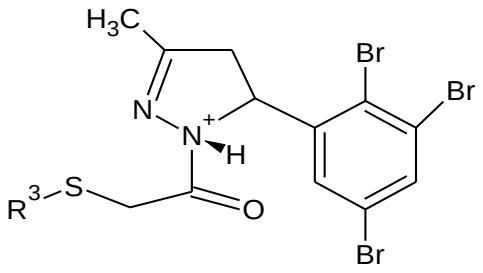


FIG. 30

Xian-Qin Wu et al synthesized [40] a series of novel 1-(3-substituted-5-phenyl-4,5-dihydropyrazol-1-yl)- 2-thion-ethanone derivatives as potential telomerase inhibitors. The bioassay demonstrated

that compounds (R)-3-(1-(2-(butylthio)acetyl)-5-(2-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-2H-chromen-2-one, (R)-3-(1-(2-(butylthio) acetyl)-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-2H-chromen-2-one, (R)-3-(1-(2-(pyrimidin-2-ylthio)acetyl)-5-(4-(trifluoromethyl) phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-2Hchromen-2-one, (R)-1-(5-(3,5-dibromo-2-hydroxyphenyl)-3-methyl-4,5-dihydropyrazol-1-yl)- 2 - (propylthio) ethanone, (R) – methyl 2 - (2-(5-(3,5-dibromo-2-hydroxyphenyl)-3-methyl-4,5-dihydropyrazol-1-yl)-2-oxoethylthio)acetate **(Fig. 29, 30)** occupied high antiproliferative activity against SGC-7901, MGC-803, Bcap-37 and HEPG-2 cell lines. By a modified TRAP assay, some title compounds were tested against telomerase, and compound showed the most potent inhibitory activity with IC50 value at 0.92_0.09 mM.

The mechanism of antitumor action indicated that title compounds could suppress cell proliferation through inducing cell cycle arrest in G0/G1 phase.

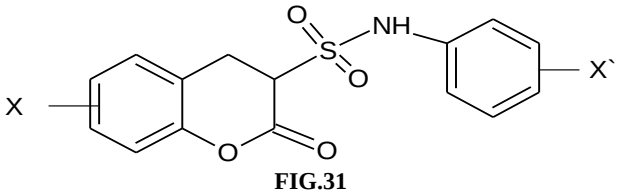


FIG.31

Reddy NS et al. synthesized coumarin 3-(N-aryl) sulphonamides [41] **(Fig. 31)**. The effect of all the compounds on the growth of human tumor cells in culture was evaluated using androgen receptor negative prostate (DU145), colorectal (DLD-1), non-small cell lung carcinoma (H157), estrogen receptor negative breast (BT20), and chronic myeloid leukemia (K562) cell lines. The dose response of each cell line was established by determining the number of viable cells after 96 hours of continuous treatment against five different concentrations (1-100 μM range) of each compound. The activation of JNK1 by these compounds as shown in immune complex kinase assay, clearly showed that they activate JNK pathway either by interacting with JNK1 or with one of the upstream kinases in this pathway [42].

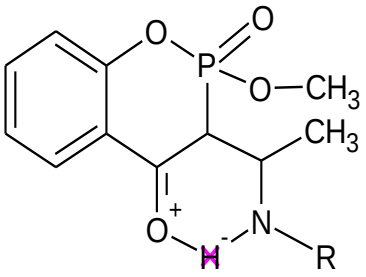


FIG.32

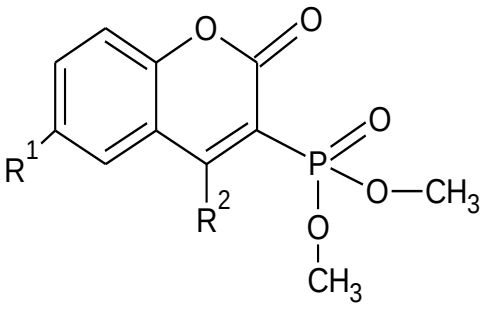


FIG.33

Budzisz E et al. determined the cytotoxic effects and alkylating activity of a series of 3- [1-(alkylamino)-ethylidene]-chroman-2,4-dione, 2-methoxy - 3 - [1- (alkylamino) - ethylidene - 2, 3 - dihydro -2,4-dioxo-2λ5- benzo[e][1,2] oxaphosphinane **(Fig. 32)** [43] and [2-oxo-4-phenyl(alkyl)-2Hchromen-3-yl]-phosphonic acids dimethyl ester **(Fig.33)** [44] on the two leukemia cell lines HL-60 and NALM-6. These compounds were highly toxic to NALM-6 cells than to HL-60 cells. IC50 data are about nine times lower for the NALM-6 than for the HL-60 cell lines. Their cytotoxic effect increased with an increase of the hydrophobic parameters in the region of the substituents at the 2-, 3- and 4-positions of the benzopyrone skeleton of these compounds [45].

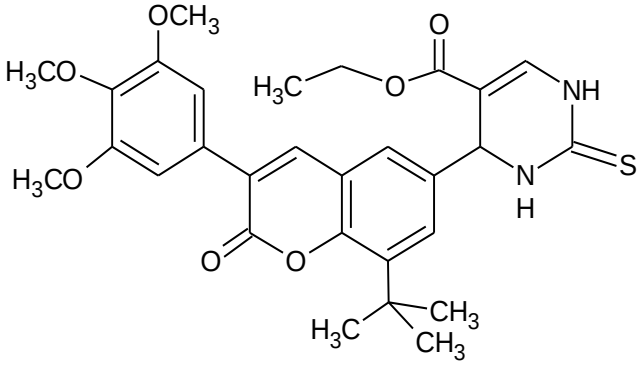


FIG.34

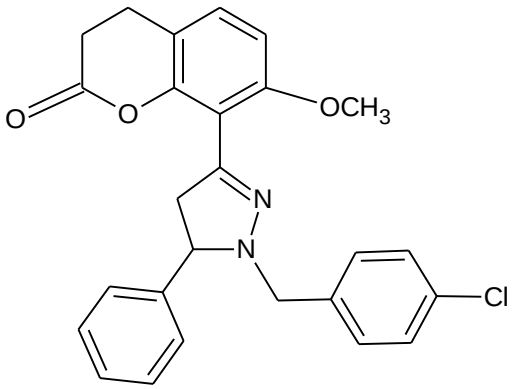


FIG. 35

Sashidhara et al. have reported coumarin–monastrol hybrids as potential anti breast tumor specific agents, which selectively induce apoptosis in primary and metastatic breast cancer cell Lines [46]. SAR studies have shown that increase in number of methoxy groups on phenyl ring present at 3-position of coumarin increases the activity whereas tert-butyl group at 4-position of coumarin is critical for activity. Compound (34) significantly inhibited the proliferation of MCF-7 breast cancer cell lines (IC50 value of 2.4 mM), T47D (IC50 value of 3.1 mM) and MDA-MB-231 (IC50 value of 3.9 mM) at all concentrations in a time dependant manner. It was found compound (**Fig. 34)** and **(Fig. 35)** were equipotent to tamoxifen but less active in comparison to epirubicin.

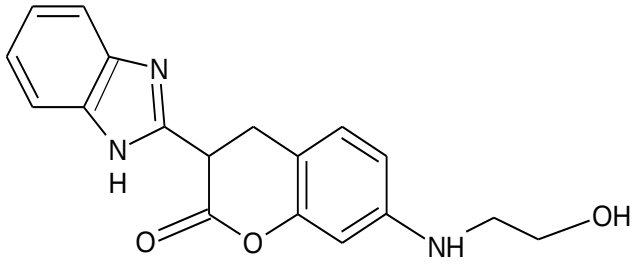


FIG.36

Amin et al. have developed various coumarin–pyrazoline hybrids and evaluated against different cancer cell lines [47]. The maximum anticancer activity is exhibited against gastric cancer cell lines with IC50 values ranging from 10 lM to 2.8 mM. Wide range of the aromatic groups are tolerated at 5-position of pyrazoline. In general strong electron withdrawing groups on phenyl ring at 5-position increases the activity. Compound **(Fig.36)** is the most active hybrid with IC50 value of 10 lM.

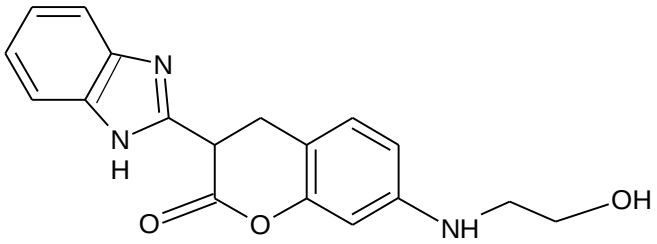


FIG. 37

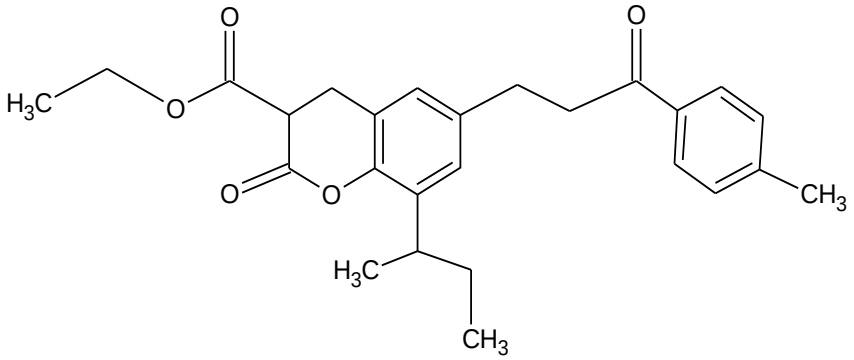


FIG.38

Benzimidazole nucleus is an important heterocyclic core that provides large artillery of compounds having wide spectrum of pharmacological activities [48]. Conjugation of this nucleus with coumarin has generated benzimidazole–coumarin hybrids, which are screened for in vitro antitumor activity on

different cell lines. The representative compound (**Fig. 37)** at a concentration of 10 lM causes more than 50% inhibition of most of the cell lines, with higher selectivity against leukemic cancer cell lines [49]. Hybridization of variedly substituted coumarins with different chalcones has yielded a series of molecules exemplified by compound **(Fig. 38)**, which exhibit good anticancer activities (IC50 value of 3.59–8.12 lM) [50]. SAR study has revealed that a substituent at 3-position of coumarin plays a pivotal role in incurring anticancer activity. Esteric groups incur/ increase the activity significantly better than ketones. On the other hand, an electron withdrawing group such as chloro at para position of chalcone diminishes the selectivity for cancer cell lines. Compound 38 is the most promising member from the series which shows around 30-fold more selectivity towards cervical carcinoma cell lines (C33A) over normal fibroblast cell line (NIH3T3).

Antihyperlipidemic activity:

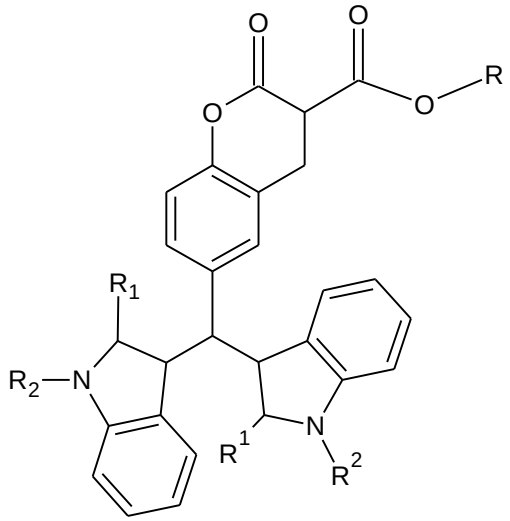


FIG. 39

Sashidhara KV et al. synthesized a series of novel coumarin bisindole heterocycles [51] **(Fig. 39)** and these compounds were evaluated for antihyperlipidemic activity in hyperlipidemic hamster model. In these compounds, as far as coumarin pharmacophore is considered, it revealed that the substitution at position 3 play a pivotal role and the presence of ethyl ester over methyl is preferred for pronounced activity. On the other hand, cursory look at the lower indole pharmacophore highlighted that the unsubstituted indoles have good activity profile compared to substituted indoles. Among twelve compounds tested, one compound having R = C_2H_5 and R1 = R2 = -H showed potent activity and was found to decrease the plasma triglyceride levels (TG) by 55%, total cholesterol (TC) by 20%, accompanied by an increase in HDL-C/TC ratio by 42% in hyperlipidemic rats to a greater degree than some of the reference statins.

Acetylcholine esterase inhibitor activity:

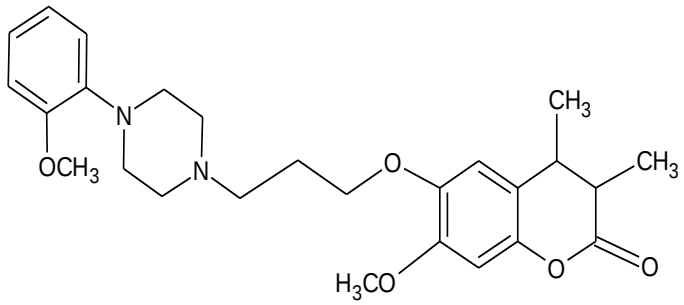


FIG. 40: ENSACULIN

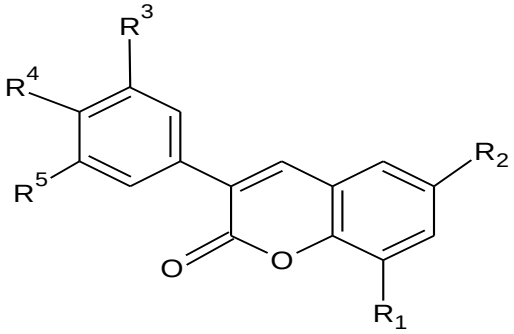
A series of coumarin alkylamines matching the structural determinants of donepezil as acetylcholinesterase inhibitors (AchEIs) are currently the drugs of choice, although only symptomatic and palliative, for the treatment of Alzeimer's disease. For fairly good inhibition of AChE with high selectivity, 6,7-Dimethoxycoumarin derivatives carrying a protonatable benzylamino group, linked to position 3 by suitable linkers mustbe present. The inhibitory potency was strongly influenced by the length and shape of the spacer and by the methoxy substituents on the coumarin scaffold. Alzheimer's disease (AD) is a progressive, chronic, neurodegenerative disorder that is characterized by a loss of memory and cognition, severe behavioral abnormalities and ultimately death.

It is the fourth leading cause of death in Western countries. As general health care improves and the proportion of the elderly increases, the number of AD patients is anticipated to increase dramatically. The loss of basal forebrain cholinergic cells results in sharp reduction in acetylcholine (ACh), which is believed to play an important role in the cognitive impairment associated with AD. On this basis, the cholinergic hypothesis has become the leading strategy for the development of anti-AD agents.

Several anti- AChE agent such as ensaculin have shown to induce a modest improvement in memory and cognitive functions. Recent study showed that AChE could also play a key role in accelerating amyloid β plaques deposition. It is likely that AChE interacts with amyloid β fibres and promotes amyloid fibril formation through a pool of amino acids located in proximity of the peripheral anionic binding site (PAS) of the enzyme. Moreover, it has been shown that molecules are able to interact either exclusively with PAS or with both catalytic and peripheral binding site, which can prevent the pro-aggregation of AChE toward amyloid β fibres. Compounds showing peripheral and dual binding with AChE are intriguing and could represent a new type of therapeutic agents through the prevention of amyloid β aggregation.

Monoamine oxidase inhibitor activity/ Antiparkinsonism Activity:

Monoamine oxidase (MAO) inhibitors have been proved to be the most important drugs for the clinical management of depression and Alzheimer disease. Many studies have demonstrated potent MAO inhibitory activities of synthetic as well as natural coumarins. Coumarins linked with dihydrofuranyl have been studied for this activity.



	R_1	R_2	R_3	R_4	R_5
a	H	H	OCH_3	H	OCH_3
b	H	CH_3	H	H	OCH_3
c	Br	CH_3	H	OCH_3	H

FIG.41

Matos et al. have explored the potential of variedly substituted 3-phenylcoumarins (coumarin–resveratrol hybrids) **(Fig. 41)** to inhibit MAO [52-54]. All compounds from the series showed high selectivity for MAO-B isoenzyme with very low IC50 values. Initial reports suggested compound (a) (3,5-dimethoxyphenyl derivative) to be the most potent. Increase in number of methoxy groups decreased the activity. Subsequent studies have revealed that 50-methoxy Analog (b) exhibits an extraordinary low IC50 value of 802.6 pM against MAO-B. Further, a bromine at 8-position of coumarin nucleus (c) enhanced the MAO-B inhibitory property than at 2-position of phenyl ring (15 times loss of the activity)

Anti Coagulant (Anti Platelet Aggregation) Activity:

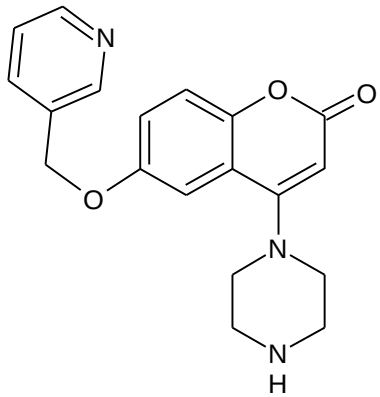


FIG. 42

In vitro evaluation of coumarin-linked piperazine moiety for inhibitory activity on human platelet aggregation induced in platelet-rich plasma by adenosine diphosphate (ADP), collagen or the calcium ionophore. These compounds **(Fig. 42)** show notably high activity towards all the platelet aggregation inducers used, and the most active one, 8-methyl-4-(1-piperazinyl)-7-(3- pyridylmethoxy) coumarin, proved to be a potent in vitro antiplatelet agent. The screening of this compound can be carried out by conducting test in which human blood from healthy volunteers was added to a130 mM trisodium citrate aqueous solution, then centrifuged to give platelet-rich plasma (PRP) which was diluted with platelet-poor plasma (PPP) and preincubated at 37°C with drug solution before the addition of the platelet aggregation agent. PRP aggregation was induced by inducers mentioned.

The compound 8-methyl-4-(1-piperazinyl)-7-(3 pyridylmethoxy)-coumarin proved to be a potent in vitro inhibitor of human platelet aggregation

towards all the platelet aggregation inducers used, suggesting proper heteroarylmethoxy groups as novel useful 7-alkoxy substituents.

Antimalarial activity:

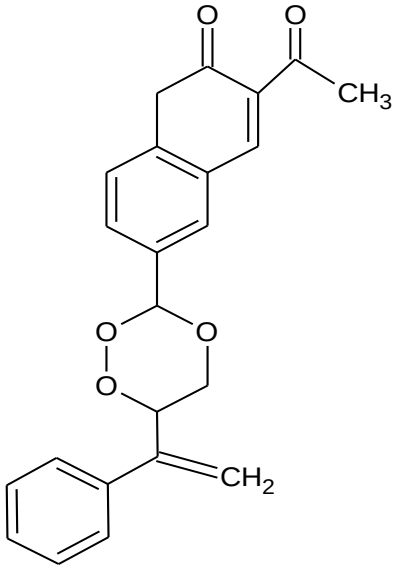


FIG.43

The main reason for recent dramatic increase in deaths as a result of malaria is attributed to the spread of *Plasmodium falciparum* strains resistant to the mainstay antimalarial chloroquine. To overcome the challenges of multi-drug resistance in this plasmodial species, many approaches are currently being adopted. These follow optimization of treatment with available drugs including combination therapy, developing analogs of the existing drugs and evaluation of drug resistance reversers such as chemo sensitizers as well as exploring new chemotherapeutic targets.

Recently the concept of hybrid antimalarials has attracted much attention for tackling the alarming problem of drug resistance, as these molecules often act on multiple therapeutic targets because of the presence of two different, covalently fused pharmacophores. Some hybrid molecules like trioxaquine and ferroquine are under clinical trials as hybrid antimalarial agents. This concept has been exploited to develop a new series of coumarin-linked trioxane **(Fig. 43)** hybrids by using new methodology. These hybrids have been evaluated for their antimalarial activity against a sensitive strain of *P. falciparum* and some of which exhibited the moderate activity.

Antihepatitis activity:

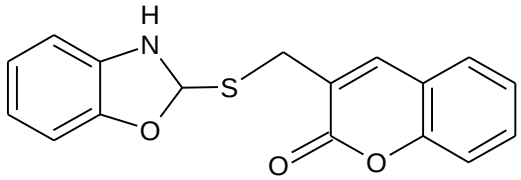


FIG. 44

Inhibitory activity against hepatitis virus RNA polymerase can be shown by coumarin-linked benzoxazole-5-carboxylic acids. Recently, it has been found that the benzoxazole **(Fig. 44)** moiety conjugated with a coumarin moiety with a methylene thio linker exhibited potent inhibitory effects on hepatitis virus. The thio methylene (-SCH2-) linker has been used to connect a heterobicycle with various aromatic rings by synthetic methods to form hybrid compounds for antiviral bioassays. The coumarin can be linked with heterobicycles like benzimidazole, imidazopyridine, purine, benzoxazole, and benzothiazole to evaluate the activity [55].

TNF-α inhibitory activity:

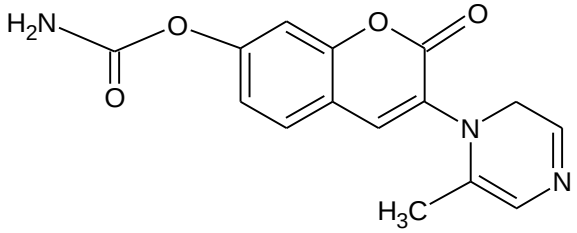


FIG. 45

Tumor necrosis factor α (TNF- α) is a pro-inflammatory cytokine secreted by a variety of cells, including monocytes and macrophages, in response to many inflammatory stimuli or external cellular stress. It is a key cytokine in the inflammation cascade, causing the production and/or release of other cytokines and agents. A coumarin-linked with piperidinylmethyl dimethyl-carbamic acid 3- benzyl-4-methyl-2-oxo-2H-chromen-7-yl ester has been found to be a moderate inhibitor of TNF-α. Representative compounds **(Fig. 45)** that possess excellent in vitro TNF- α inhibitory activity were tested in vivo by subcutaneous (SC) administration. TNF-a inhibitory activity was assessed by *in vivo* inhibition of serum TNF-production in the rats [56].

Base-1 Inhibitory Activity:

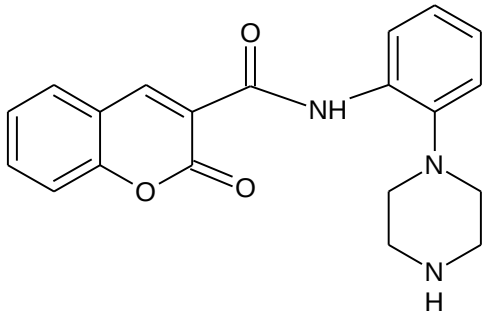


FIG. 46

Alzheimer's disease (AD) is the biggest unmet medical need in neurology, with >12 million AD sufferers worldwide. Actually the 'amyloid cascade hypothesis' claims that amyloid b-42 (Ab42), a proteolytic derivative of the large transmembrane protein, plays an early and crucial role in all cases of AD. Ab42 forms aggregates that are thought to Two key enzymes β-secretase (BASE-1 and 2) and γ-secretase have been identified as ideal targets for therapeutic intervention. Coumarin-linked with substituted phenyl-piperazine **(Fig. 46)** have good β- secretase inhibitory activity like new nonpeptidomimetic derivatives which incorporate in their structure various heterocyclic moieties: coumarin, quinoline or chromene. These moieties have been linked through an amide bond to form phenyl-piperazine scaffold which have shown modified BASE inhibitory properties [57].

Casein Kinase-2 Inhibitory Activity:

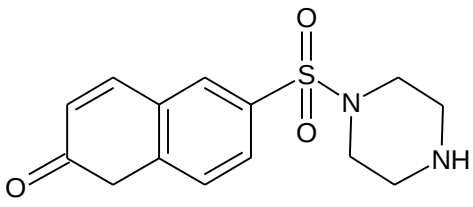


FIG. 47

Casein kinase-2 (CK2) is probably the most pleiotropic protein kinase known, with more than 300 protein substrates already recognized, a feature which might, at least partly, account for its lack of strict control over catalytic activity. Its two catalytic subunits are in fact constitutively active either with or without the regulatory-subunits, which appear to play a role in targeting and substrate recruiting, rather than controlling catalytic activity. Although constitutively active CK2 is ubiquitous, essential, and implicated in a wide variety of important cell functions, evidence has been accumulating that its catalytic subunits may behave as oncogenes, consistent with the observation that they display an anti-apoptotic effect in prostate cancer cell lines.

The most promising inhibitor, coumarin linked piperazine **(Fig. 47)** has been also crystallized in complex with CK2, and the experimental binding mode has been used to derive a linear interaction energy (LIE) model. In the last few years, intensive screening program has been performed, using both conventional and *in silico* approaches, with the aim of discovering novel potent and selective CK2 inhibitors [58].

Cytochrome P - 450 Enzyme Inhibitory Activity:

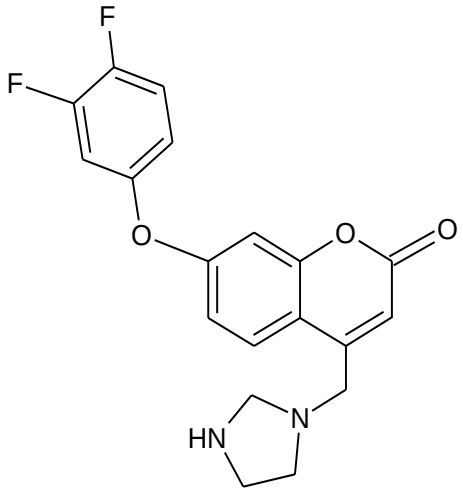


FIG. 48

Cytochrome P450 (CYP) is a large family of hemoproteins present in most forms of life (plants, bacteria, and mammals). They are concerned with metabolism in vital processes and many of them with the ability to activate carcinogens have been implicated as risk factors for cancers Coumarin-linked imidazoles **(Fig. 48)** have been proved to be most promising compounds as CYP450 inhibitors. It (48) has been shown to display stronger CYP19 inhibitory activity (IC50 = 47 nM) than the standard drug fadrozole (IC50=52 nM) with excellent selectivity over CYP11B1 and CYP11B2 [59].

Antiviral Activity:

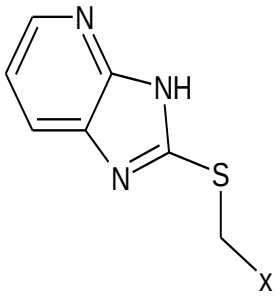


FIG.49

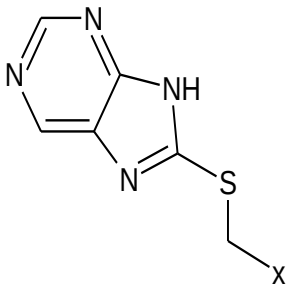


FIG.50

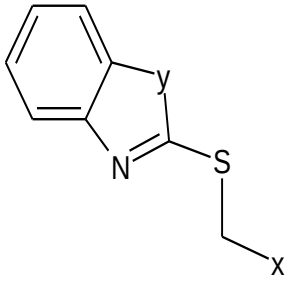


FIG. 51

Y = O, S

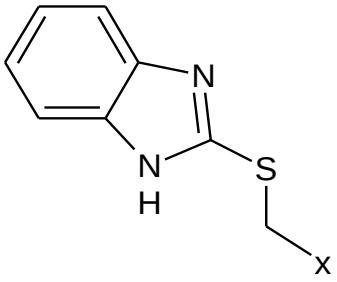


FIG.52

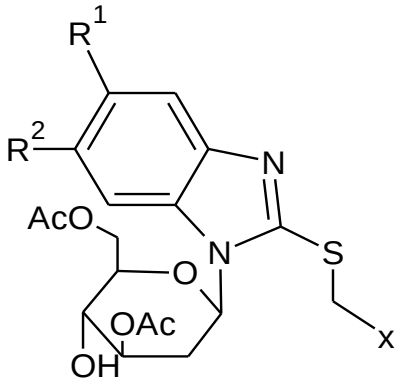


FIG.53

Viral and Human immunodeficiency viral (HIV) infections have no complete and effective remedy, and hence are posing the greatest threats to human health. The classical treatment involves use of drugs that have serious side effects. Owing to the urgent need for new drugs, compounds having multiple functional scaffolds are synthesized [60]. Heteronuclei such as imidazopyridine **(Fig. 49)**, purine **(Fig. 50)**, benzoxazole **(Fig. 51)**, benzothiazole **(Fig. 52)** and benzimidazole **(Fig. 53)** and its nucleoside have been linked to the coumarin nucleus via methylenethio linker, and evaluated for antiviral activity on HUH 5–2 cells.

SAR study suggested that while coumarin is an essential scaffold for the activity, the potency decreased in the order of purine conjugates (figure 50, EC50 values of 2.0 lM), imidazopyridine conjugates (figure 49, EC50 values of 6.8 lM) and benzoxazole conjugates (**Fig. 51**, EC50 values of 12 lM). Further, presence of a bromo or methoxy substituent on coumarin nucleus increases the activity of the conjugates. Incorporation of an arene moiety on benzimidazole does not improve the activity whereas peracetyl 2-deoxyb- D-glucose increases the Hepatitis C virus (HCV) inhibition by 8.2-fold compared to unsubstituted benzimidazole conjugates [61].

A recent study by Tsay et al. reports that direct hinging of benzimidazole nucleus with coumarin **(Fig. 54-56)** affords better antiviral profile (IC50 value of 3.0 lM) in comparison to compounds **52** (IC50 value of 10 lM). It is attributed to methylenethio linker in 52, which discourages intra-molecular H-bond between benzimidazole and coumarin. Compounds 54-60 exhibited potent anti-HCV activity with IC50 values of 3.0, 5.5 and 20 lM, respectively. SAR studies have revealed that attachment of methyl group(s) to benzimidazole **(Fig. 54, 55)** lead to remarkable increase in the activity. Appendage of methyl, bromo or methoxy substituent on coumarin nucleus reduces cytotoxicity and anti-HCV activity whereas fusion of benzene ring (8) increases the activity. Incorporation of b-D-ribofuranose [40] also leads to potent compounds [62].

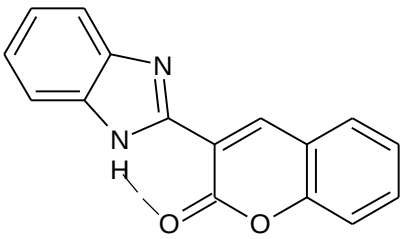


FIG. 54

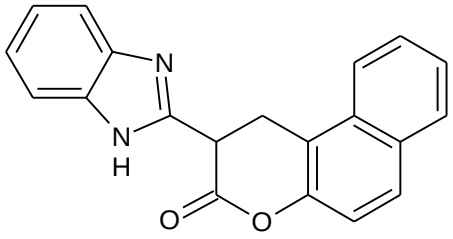


FIG. 55

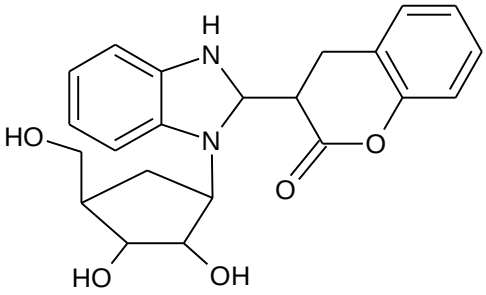


FIG.56

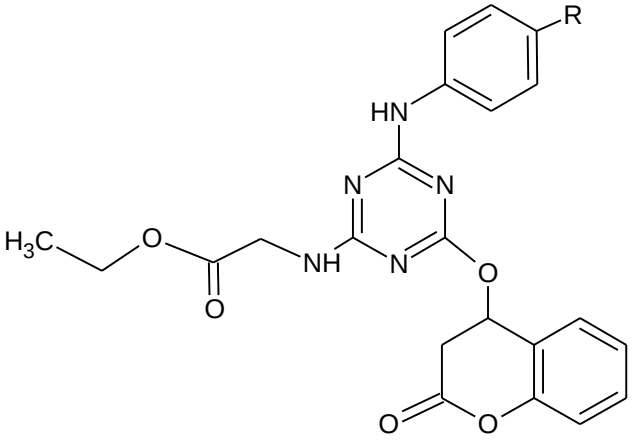


FIG. 57 R – CH_3
FIG. 58 R – Cl
FIG.59 R – Br

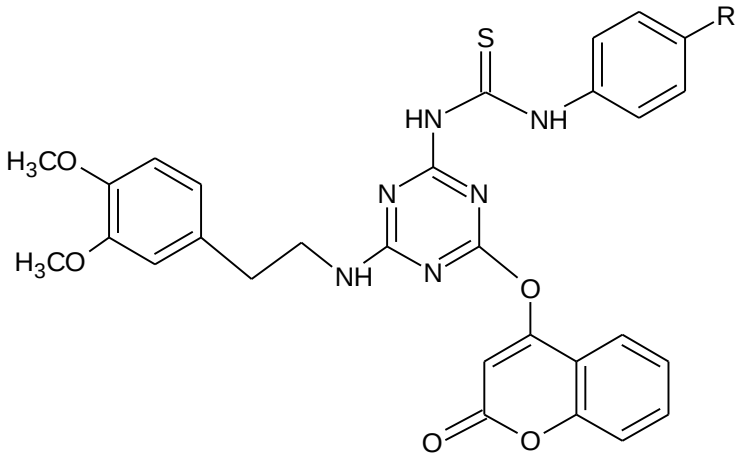


FIG. 60 R – CH_3
FIG.61 R – OC_2H_5

A series of coumarin–triazine hybrids, reported as novel non-nucleoside reverse transcriptase inhibitors (NNRTIs), has been explored against different strains of HIV, that is HIV-1 (III-B), HIV-2 (ROD), and double RT mutant HIV-1 (K103N and Y181C). Compound 41 is the most potent with IC50 value of 1 lg/ml against all strains whereas compounds **58-61** display selective activity against HIV-1[63]. Coumarin–chalcone hybrids are inactive against both HIV-1 and HIV-2 strains [64].

Tyrosinase inhibitory activity:

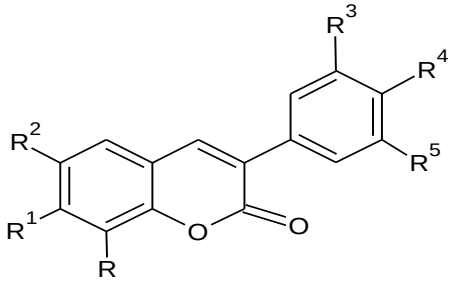


FIG. 62

Fais A. e al resynthesized coumarin- resveratrol hybrids by a traditional Perkin reaction carried out in refluxing dimethylsulfoxide (DMSO) between o-hydroxybenzaldehyde (or their methoxy substituted derivatives) and the corresponding aryl acetic acids, using dicyclohexylcarbodiimide (DCC) as dehydrating agent to investigate the structure activity relationship. Tyrosinase activity assays were performed with L-DOPA as substrate with slight modifications and activity of mushroom tyrosinase was determined by sectrophotometric technique. IC_{50} values of these compounds were measured. The result showed that these compounds (figure 62) exhibited tyrosinase inhibitory activity. 3-(3',4',5'-trihydroxyphenyl - 6, 8 - dihydroxy coumarin was found to be the most potent compound (0.27mM) more than umbelliferone (0.42mM) used as a reference compound. The kinetic studies revealed that these compounds non-competitive tyrosine kinase inhibition and the number and the position of free hydroxyl groups play an important role in determining the activity.

Antifungal activity:

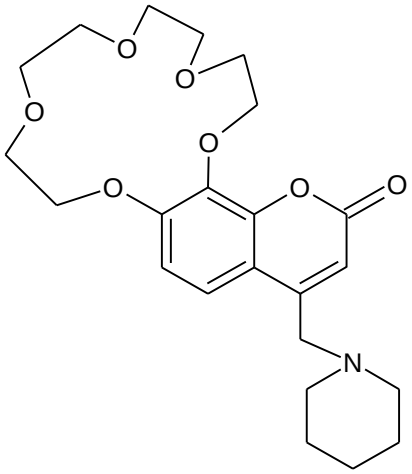


FIG. 63

Macrocyclic molecules have attracted much attention because of their potential use in a variety of chemical processes, complexation ability, selective complexing agents for metal ions, and photo-induced electron transfer since its discovery by Pedersen. 4- aminomethyl coumarin crown ether derivatives **(Fig.63)** have been studied for their antifungal activity. The complexation selectivity of coumarin fused crown ethers has often been explained in terms of the size-fit concept which states that crown ether forms a more stable complex with the cation which is more suitable in size for the crown ether cavity [65].

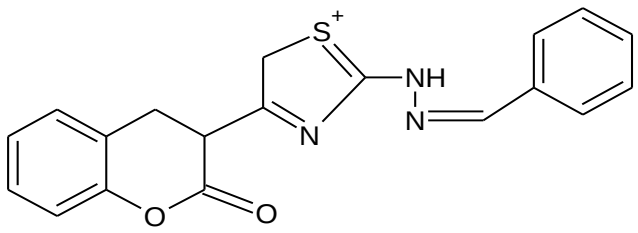


FIG. 64

Also, antifungal activity of coumarins fused with thiazoles **(Fig. 64)** has been assessed against a fungal strain of *Candida albicans*. The minimum inhibition concentration (MIC) of the compounds was determined by broth micro-dilution method [66].

CONCLUSION: In present review we focused on different derivatives of coumarin which were synthesized by various methods and their activities were studied. It can be concluded that coumarin ring is fused with other rings, a synergistic effect of both the rings in their biological activities were obtained, such compounds were exploited in development of various important molecule which provides scaffolds for drug development.

ACKNOWLEDGEMENT: We are grateful to the director, Dr. Dharam Pal Pathak, Mrs Rubina Bhutani and Mrs. Garima Kapoor for the valuable discussion and suggestions.

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