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Review Article

A Systematic Review on Pharmacological Activities of 4-Methylumbelliferon

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ABSTRACT
Umbelliferon, the natural crenelated coumarin distributed in the plants of a piaceae family, has shown various biological activities, especially as a cancer chemo preventive agent. Coumarins have been categorized as a member of family of benzo-pyrone, that consist of pyrone ring united to benzene ring. The benzo-pyrones may be sectioned to alfa type that coumarins belong and the gama type that flavonoids have been major members. Coumarins are chemical entity which has being synthesized in the past few years many forms of its derivatives; the entity provides the principal origin of motivating to numerous chemist to investigate its diverse medical efforts especially with regards to the anticoagulant activity. In present article we review recent 4-Methylumbelliferon, (4-MU) that are synthesized with it pharmacological activities antioxidant, anti-inflammatory, antimicrobial activity, ant hepatitis, hepatoprotective, anticancer, antipyretic and analgesic activity.

Key words: 7-hydroxy-4-mehtyl coumarin, 4-Methylumbelliferon, 4-MU, Antioxidant, Antitumor, Anti-inflammatory, Antimicrobial, Anticoagulant, Anticonvulsant activity.

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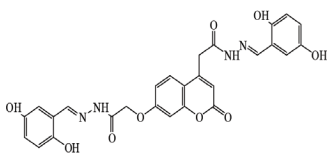
INTRODUCTION

Coumarins were significant oxygen having merge heterocyclic utilized in pharmaceuticals and pigmentations.[1] Coumarins be restricted their category denomination to 'coumarou' the argot name Tonkabean (Dipteryx odorata willd, Fabaceae), from which coumarins there were separated in 1820. Coumarins are the origin of lactones that having benzophenone skeletal structure which were revel extracted from plants and also synthesised in lab.[2] The combination groups as merge components into principle coumarins alter the characteristic of origin coumarin and change it into additional valuable products.[1] Coumarins are plants flavonoids quite spread in nature. Natural coumarins have been used for antidiabetic efficiency,[3] anabolic antioxidant and hepatic protective activities.[4] It was reported that coumarins have various medicinal activities. The effective antibiotics such as Novobiocin, coumaromycin in addition to chartesium were coumarins. Nowadays, the attention on coumarins were refreshed employ to their utilized as fluorescents in enzymes chemomedical determination. Coumarins are recognized natural compounds show a wide range of medicinal activities.[5] Due to coumarins various bioactivities namely, anticoagulants, ant-microbials, anti-biotics, spasmolytic, anthelmintic, diuretic, anti-inflammatory, ant tubercular agents, anti-histamic agents, antidepressant and antimalarial.[6] Chelating capability of coumarins were investigated to propose their employs as chelating factors.[7,8] Concerning to coumarins high fluorescence activity, they were quite utilized as fluorescent probes in biology and medicine.[9] Coumarins have been evaluates in the therapy of human immunodeficiency virus, because of capability of coumarins to inhibit human immunodeficiency virus integrase.[10] *In vitro* impacts of coumarin derivatives on growth of renal carcinoma exhibit that 7-hydroxy-4-methylcoumarin were effective cytotoxic with cytostatic factors. Attention in metal complexes coumarins have arisen from the consideration for new lead coumarins along with the desire to develop the biological profile.[11] In continuation of previous studies on coumarins,[12-34] herein we are reporting a review for such recent derivatives of 4-Methylumbelliferon, 4-MU with pharmacological activities.

PHARMACOLOGICAL ACTIVITIES

Antioxidant Activity

Molnar and Čačić synthesized a series of coumarins (1, 2, 3, and 4) and have been investigated for antioxidant activities. These derivatives contain 3,4-dihydroxyphenyl and 2,5-dihidroxyphenyl ring with these substituents, the compounds was expected to possess antioxidant activities since donation of hydrogen progress to creation of a steady structures, and were published that two groups (hydroxyl) in ortho position are significant for antioxidant activities.[35]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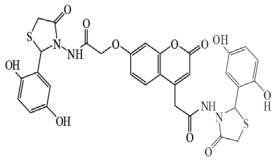
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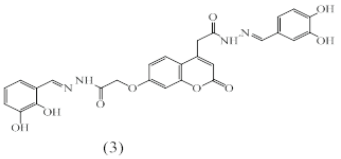
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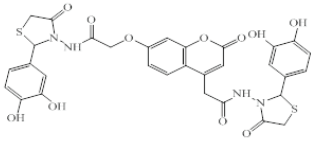
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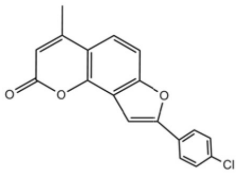
Roussaki, K.*et al*, develop a facial appropriate and high fruitful preparation of a combinatory category of coumarins (5, 6) by reaction of 4-methylumbelliferon with phenacyl bromides fellowed by condensation with poly phosphoric acid. The evaluation of Scavenging activity towards the 2, 2- DiPhenyl-1-Picryl hydrazyl (DPPH) as stable free radical compound has been calculated and were found efficiently .The novel synthesized coumarins showed antioxidant activities.[36]



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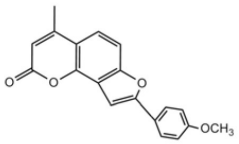

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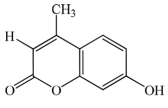
Ravi S. *et al*, synthesized three derivatives 4-methylumbelliferon (7), 4-methylbenzocoumarin compound (8), 6,4-dimethylcoumarin (9). The antioxidant investigations have been done by utilizing of phosphomolybdenum technique, exhibit that the investigated coumarins have excellent antioxidant activities. The anti-oxidant activities of coumarins could be attributed to donating of electron nature of the substituted groups such as –OH, -CH_3, C_6H_5 on coumarins scaffold, which reduce radicals in addition to prevents cell damage.[37]



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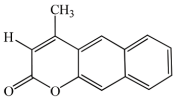

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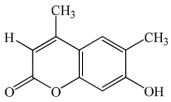

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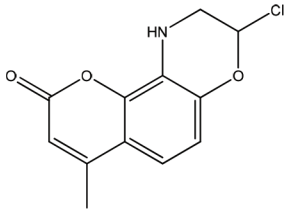
Antimicrobial activity

New coumarins have been prepared by Sahoo *et al*. and anti-microbial activities were examined vs, *Staphylococcus aureus* as Gram positive bacteria and *Escherichia coli* as Gram negative bacteria. The novel synthesized coumarin (10) has excellent anti-microbial activity comparing with amoxicillin as standard drug and that could be regarding to aromatic chlorine on coumarin moiety. The other synthesized coumarins were showed good activities at low and high concentrations.[38]



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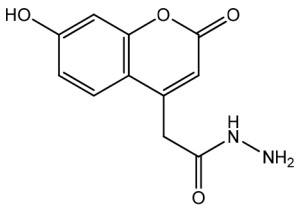
4-Umbelliferonacetohydrazide (11) has been synthesised by Cacic *et al*. and it has a high anti-bacterial activities against *the* Gram positive *Staphyloccocus pneumoniae* and was less activites against other microbes namely *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Bacillus cereus* and *Salmonela panama* comparing with the standard drug.[39]



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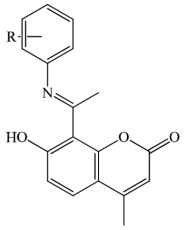
4-Methyl-8-(1-(phenylimino)ethyl)umbelliferon (12) was prepared by Balaji, PN *et al* , 4-methyl-8-acetylumbelliferon and aniline (with various groups) have been refluxed in ethanol with few acetic acid drops. The 4-Methyl-8-(1-(phenylimino)ethyl)umbelliferon (12) and its derivatives were examined for anti-microbial activities and the obtained results were comparing with ampicillin or Fluconazole as standard drugs were showed motive characteristics.[40]



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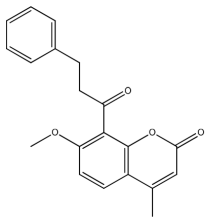
R= H ,ortho-NH_2 ,para-COOH, para-NO_2, para-F,para-OH

Cacic, T *et al*, synthesized 8-(3-phenylpropanoyl)herniarin (13) with 8-(5-phenylisoxazol-3-yl)herniarin (14) and examined for antibacteria activities against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus Bacillus subtilis* in addition to *Aspergillus niger*, *Aspergillus flavus* and *candida albicans* as fungi and were utilized standard drugs namely ciprofloxacin and fluconazole. Synthesized coumarins (13 and 14) displayed motivating inhibition zones against selected bacteria and fungi.[39]



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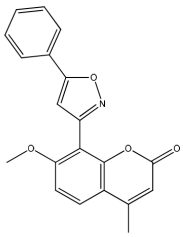

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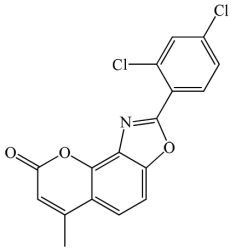
Sahoo *et al* were prepared new coumarin derivatives and study the antibacterial vs *Stophylococcus aureus* as Gram positive bacteria, and *Escherichia coli* as Gram negative bacteria through cup plate technique. Amoxicillin was utilized as standard drug. The results exhibit motiving zone of inhibition ($P<0.001$) comparing with the standard. 2-(2,4-Dichlorophenyl)-6-methyl-8H-chromeno[8,7-d]oxazol-8-one (15) and 3-chloro-7-methylchromeno[7,8-b][1,4]oxazine-2,9(1H,3H)-dione (16) have the highest efficiencies that could be because of chloro atoms coumarin moitiy.[38]



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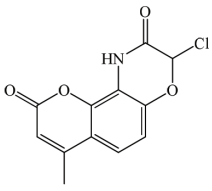

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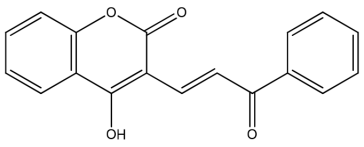
(E)-4-hydroxy-3-(3-oxo-3-phenylprop-1-en-1-yl)-2H-chromen-2-one (17) was prepared through nucleophilic addition reaction of 3-acetyl-4-hydroxy-2H-chromen-2-one aromatic aldehyde. The antimicrobial activity of the (E)-4-hydroxy-3-(3-oxo-3-phenylprop-1-en-1-yl)-2H-chromen-2-one has been done *Pseudomonas aeruginosa*, *Echerichia coli*, *Salmonella typhimurium, Bordatella bronchiseptica*, *Bacillus subtilis* and *Staphyloccocusaureus*.(E)-4-hydroxy-3-(3-oxo-3-phenylprop-1-en-1-yl)-2H-chromen-2-one displayed good inhibition zones at low and high concentrations.[41]

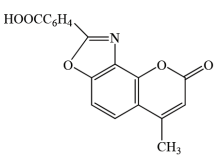


(17)

R=2-OH, 5Br, 4-CH_3, 4-OCH_3, 4-OH, 4-Br, 4-Cl, 2-F, 2-NO_2

Anti-inflammatory activity

Swayam *et al*, synthesized a series of coumarin and the anti-inflammatory activity has been evaluated by using Carrageenan- induced rat paw oedema method, the synthesized compounds (18, 19and 20) showing significantly inhibition (P<0.001) of carrageenan induction. The results of the evaluation have been viewed by taking Ibuprofen as the standard drug; the compound (20) showed maximum anti-inflammatory effect due to the presence of chlorine at 3 positions and the compound 18, 19 carrying methyl groups at 6 positions respectively, showed moderate activity.[42]



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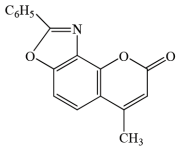

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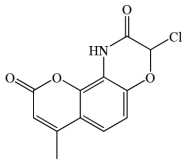
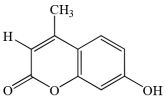


(20)

Ashok. *et al*, synthesized three derivatives of (7-hydroxy, 4-methyl Chromen-2-one) compound (21), (4-methyl benzo Chromen-2-one) compound (22) and (6, 4-dimethyl Chromen-2-one) compound (23), anti-inflammatory activity of three derivatives showed highly significant activity when compared to that of standard Diclofenac sodium. The presence of -OH, - CH_3, - C_6H_5 groups on benzo-pyrone ring system are responsible for this activity.[43]



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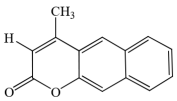

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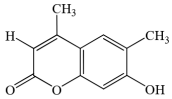
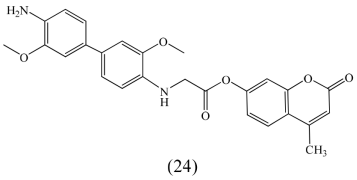


(23)

Rao and Reddy synthesized new compounds (24, 25, 26, and 27) and screened for their anti-inflammatory activity using carrageenan induced paw oedema method. Among the synthesized compounds (24) possesses good anti-inflammatory when compared to that of other synthesized compounds and (25, 26, 27) showed moderate anti-inflammatory activity.[44]



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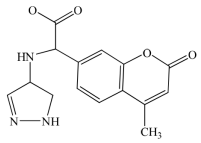

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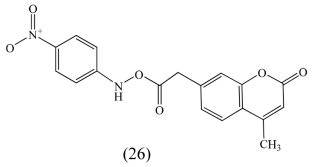

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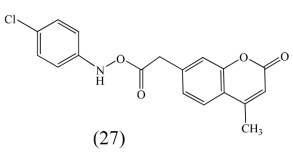
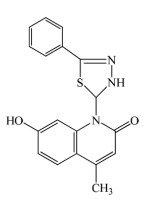


(27)

Anticonvulsant activity

Demena *et al*, prepared several compounds and were tested for anticonvulsant activity utilizing pentylenetetrazole induced seizure (PTZ), maximal electroshock seizure (MES) and Neurotoxicity tests at 5, 27 $mgkg^{-1}$ dose levels. The compounds (28-35) exhibited significant anticonvulsant activity at $27mgkg^{-1}$ dose level comparable to the standard drug-phenytoin.[45] After 60 min and 120 min interval compound (29, 32) and 34 quinolin-2(1H)-one derivative showed maximum anticonvulsant activity. Compound (28, 30, 31, 33, and 34) and 35 quinolin-2(1H)-one derivative exhibited better activity, with duration of hind limb extensor.[45]



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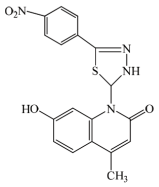

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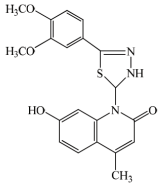

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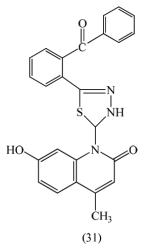

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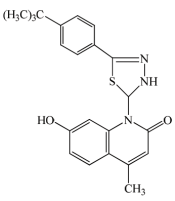

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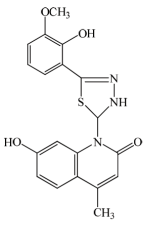

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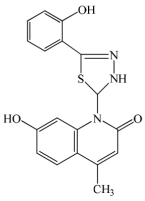

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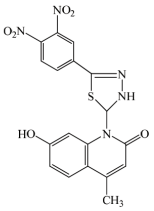

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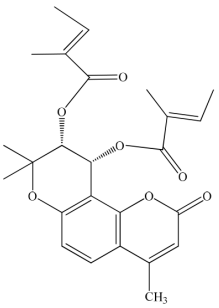
Antitumor activity

Srivastava and Sen synthesized (2E,2'E)-(9R,10R)-4,8,8-trimethyl-2-oxo-2,8,9,10-tetrahydropyrano[2,3-f]chromene-9,10-diyl bis(2-methylbut-2-enoate) (36) and (2Z,2'Z)-(9R,10R)-4,8,8-trimethyl-2-oxo-2,8,9,10-tetrahydropyrano[2,3-f]chromene-9,10-diyl bis(but-2-enoate) (37) have abilities to inhibit human cancer cell HEPG-2.[46]



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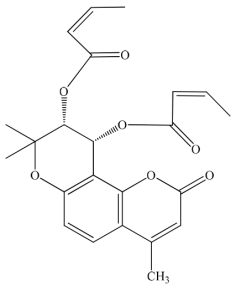
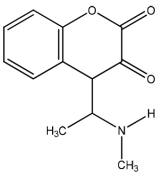


(37)

The cytotoxic impacts and alkylating efficiencies of synthesized coumarins 4-(1-(methylamino)ethyl)chroman-2,3-dione (**38**), 2-methoxy-4-(1-(methylamino)ethyl)-2H-benzo[e][1,2]oxaphosphinin-3(4H)-one 2-oxide (**39**) and [dimethyl (4-methyl-2-oxo-2H-chromen-3-yl)phosphonate (**40**) on the leukemia cell lines namely HL-60 and NALM-6. The synthesized coumarins have toxic impact on NALM-6 cells than to HL-60 cells.[47]



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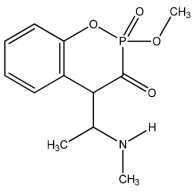
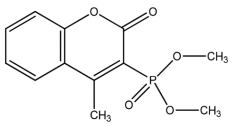


(39)

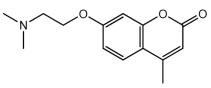


(40)

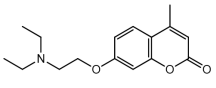
R= CH_3, CH_2CH_2OH, $CH_2C_6H_5$

Antipsychotic activity

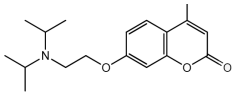
Synthesis 7-(2-(dimethylamino)ethoxy)-4-methyl-2H-chromen-2-one (41) 7-(2-(diethylamino)ethoxy)-4-methyl-2H-chromen-2-one (42), 7-(2-(diisopropylamino)ethoxy)-4-methyl-2H-chromen-2-one (43), 7-(2-(dibutylamino)ethoxy)-4-methyl-2H-chromen-2-one (44), 7-(2-(dipropylamino)ethoxy)-4-methyl-2H-chromen-2-one (45) and 7-(2-(diphenylamino)ethoxy)-4-methyl-2H-chromen-2-one (46) through the reaction of 7-(2-chloroethoxy)-4-methyl-2H-chromen-2-one with Dialkylamine (Saini, Bajaj *et al.* 2016). All synthesized coumarins exhibit inhibition impacts of apomorphine and 5-HTP induced behavior confirming that synthesized coumarins have both dopamine and 5-HT receptor blocking activity.[48]



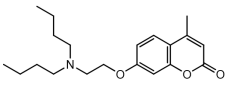
(41)



(42)



(43)



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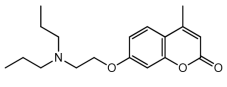

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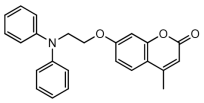
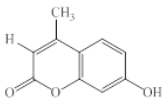


(46)

Anticoagulant Activity

Ashok, L.*et al*, synthesized three derivatives of (7-hydroxy, 4-methyl Chromen-2-one) compound 47, (4-methyl benzo Chromen-2-one) compound 48 and (6, 4-dimethyl Chromen-2-one) compound 49, anticoagulant activity of all the derivatives had remarkable anti- coagulant activity than the control solution.[43] The results of anticoagulant activity show all of the synthesized compounds exhibited good anti- coagulant activity.[43]



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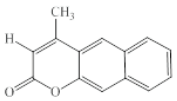
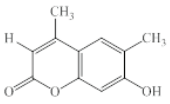


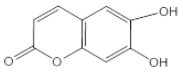
(48)



(49)

Antihepatitis Activity

Zhang. S *et al*, extracted and identified of three coumarin derivatives from the plants (Zhang, Sun *et al.* 2010), utilizing deferent chromatographic techniques and interpretation of spectroscopically results as compared with literatures and found as anti-HCV activities and characterizing the responsible bio-active constituents of the antihepatitis ethnomedicinal plant.[49]



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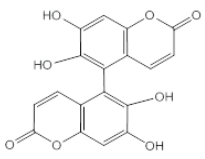
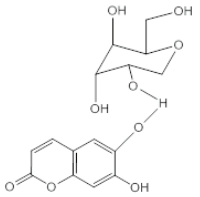


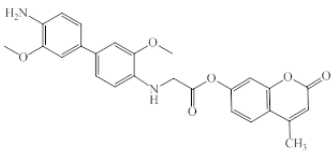
(51)



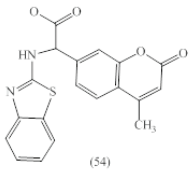
(52)

Analgesic Activity

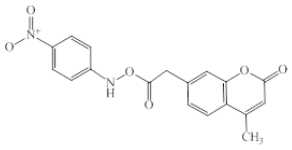
Synthesized new compounds and investigated for their analgesic activities using ethanoic acid induced writhing technique in mice. Among the prepared coumarins (53) possesses an excellent analgesic activity when compared to that of other synthesized compounds and compounds (54, 55, 56) showed moderate analgesic activity.[50]



(53)



(54)



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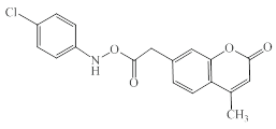

(56)

CONCLUSION

In this survey we studied various derivatives of 7-hydroxy-4-methyl coumarin which were synthesized by different methods. It may be concluding that umbelliferon with other rings, have synergistic impacts of biological activities. Deferent rings combined with umbelliferon produce different impacts and potencies.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATION USED

4-MU: 4-Methylumbelliferon; **DPPH:** 2, 2- DiPhenyl-1-Picryl hydrazyl; **–OH:** Hydroxyl; **-CH3:** Methyl; **C6H5:** Phenyl; **PTZ:** Pentylenetetrazole induced seizure; **MES:** Maximal electroshock seizure; **HEPG-2:** Human liver cancer cell line; **HL-60:** Human promyelocytic leukemia cells; **5-HT receptor:** 5-hydroxytryptamine receptors.

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