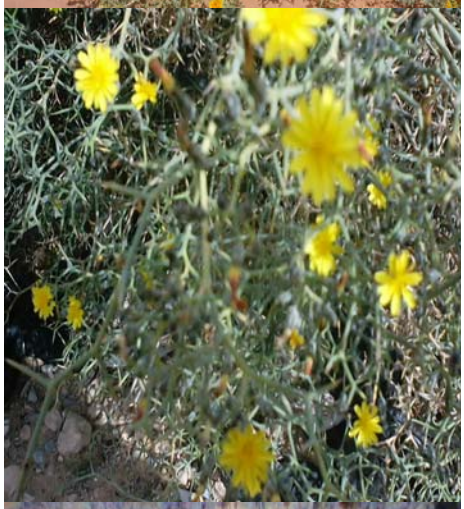
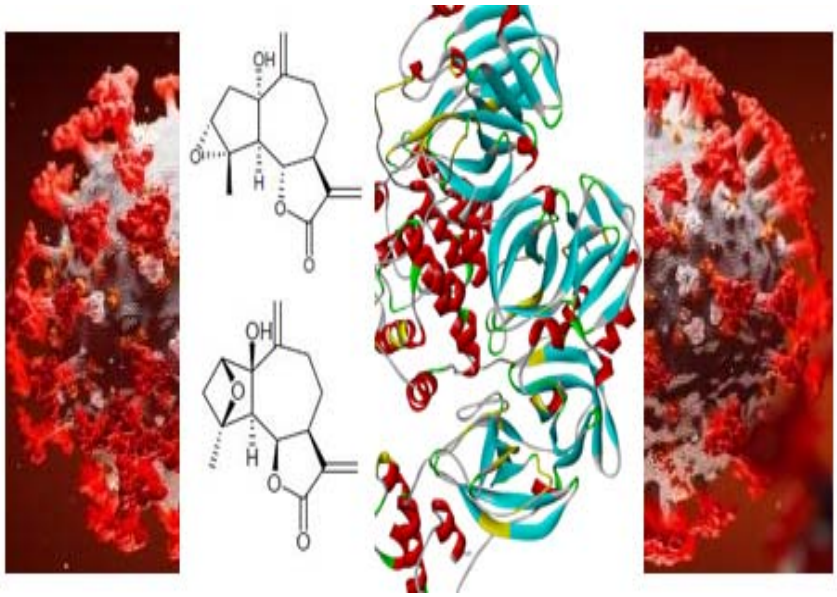
PhytoChem & BioSub Journal

Peer-reviewed research journal on Phytochemistry & Bioactive Substances

ISSN 2170 – 1768 EISSN 2602-5132





PCBS Journal

Volume 15 N° 3 **2021**

ISSN 2170-1768

PhytoChem & BioSub Journal
ISSN 2170 – 1768 EISSN 2602-5132
Peer-reviewed research journal on Phytochemistry & Bioactive Substances
CAS Source Index (CODEN: PBJHB3)

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Phytochemistry & Organic Synthesis Laboratory
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PhytoChem &BioSub Journal Vol. 15(3) 2021
ISSN 2170-1768, EISSN 2602-5132
CAS-CODEN:PBJHB3

PCBS Journal
ISSN 2170-1768

PhytoChem &BioSub Journal

2021
Vol. 15 No. 3

Coumarin containing hybrids and their pharmacological activities

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DOI:10.163.pcbsj/2021.15.-3-292

Abstract. *Coumarin moiety is of great interest to both chemists and biologists as it is present in a wide variety of naturally occurring bioactive compounds. Studies have lent scientific credence to the biological activities of several coumarin derivatives. The broad spectrum of biological activities linked with coumarin includes antibacterial, antimycobacterial, antioxidant, anticancer, antifungal, anti-inflammatory, anticoagulant and antiviral properties. The electron releasing and withdrawing substituent of coumarin affects the pharmacological properties of its resulting derivatives. Thus, identifying key structural features within the coumarin family is vital to the design and development of new analogues with enhanced pharmacological activity due to the variability in the structural complexity of coumarin. This article presents an up-to-date synopsis on the synthesis of coumarin derivatives and their pharmacological properties.*

Key Words: *Coumarin, anticancer, antimicrobial, antioxidant, analgesic, antidiabetic, antiinflammatory*

1. INTRODUCTION

Coumarin (2*H*-chromen-2-one) is a system of heterocyclic rings fused with benzene and 2-pyran. It belongs to the neo-flavonoid family of secondary plant metabolites [1]. Like coumarin, its derivatives are also essential in heterocyclic compounds because of their physical and pharmacological properties[2]. Coumarin derivatives possess many important electro-optical and pharmacological properties such as antioxidant, antiviral, anticancer, antibacterial, antifungal and antitubercular activities[3-5]. Coumarin derivatives may also be used to mark or label lipid droplets in cancer cells and non-cancer cells to demonstrate their biochemical differences [6].

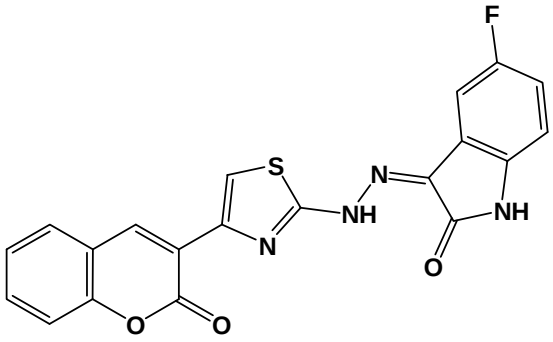
The synthesis of coumarins and their derivatives has attracted the attention of organic and medicinal chemists because several natural products comprise the heterocyclic nucleus [7, 8]. Numerous heterocyclic compounds, especially coumarins, possess vast biological

properties[9] and are highly enhanced by the substituents such as electron-donating and withdrawing groups. Therefore, integrating bioactive molecules into a single molecule by hybrid pharmacophore is a reasonable approach to drug production[10]. Various coumarins have shown anticancer and antimicrobial activities that have been the important reason for their insertion in the hybrid's scaffold. The hybridization of the coumarin nucleus with other molecules results in different molecules of improved biological activity[11]. This review highlights the various research findings of coumarin derivatives as potential therapeutic agents which can be further explored for possibledesign and development into more potent pharmacological moieties.

2. COUMARIN: A UNIQUE SCAFFOLD FOR THE DEVELOPMENT OF POTENTIAL PHARMACOLOGICAL AGENT

2.1 Coumarin scaffold as anticancer agents

Thota *et al*.(2015) synthesized a series of coumarin thiazolederivatives as anticancer agents against molt 4/C_8, CEM, L1210, BEL7402, and HL60 cells.The results showed that these compounds demonstrated cytotoxicity effect ranging from 6.2 to 18µg/mL against CEM, 8.2 to 21 µg/mL against L1210, 09 to 19µg/mL against molt 4/C_8, 8.6 to12 µg/mL against HL60 and 8 to 16 µg/mL against BEL7402, respectively. Compounds **1** and **2** were the most reported active agents against the tested cells [12].



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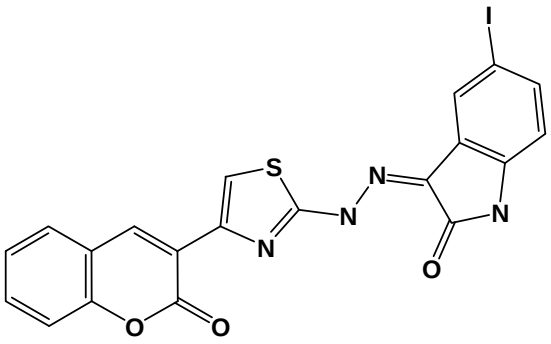
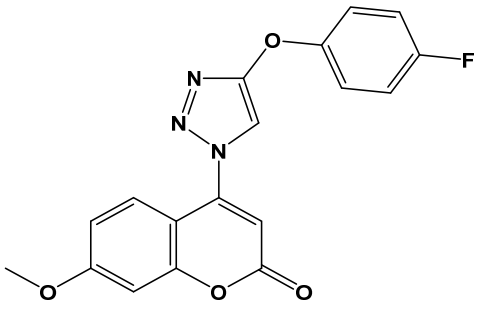


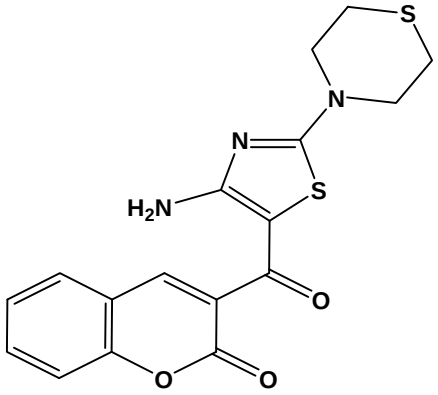
2

Similarly, Zhang *et al*.(2014) synthesized and reported a series of 4-(1, 2, 3-triazol-1-yl) coumarin for its potential anticancer activity against three cancer cell lines, including MCF-7, SW480 and A549. Most of the compounds exhibited remarkable antitumor activity, with compound **3** being the most potent, displaying IC_{50} of 5.89, 1.99 and 0.52 µM against MCF-7, SW480 and A549 cells, respectively. These activities were comparable to doxorubicin control (IC_{50}: 3.51, 2.43, 1.65 µM)[13].



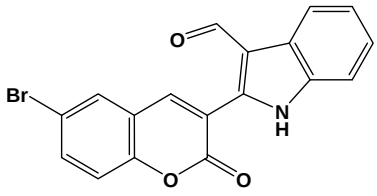
3

In another study, a series of 3-(4-aminothiazole-5-carbonyl)-2*H*-chromen-2-ones containing cyclic amine, cyclic amine substitute, aniline or aniline substitute was synthesized and reported by Ayati *et al*. (2018) for their anticancer potentials. The findings showed that most compounds displayed good cytotoxicity activity against MCF-7, HepG2 and SW400cells. Compound **4** was the most active with IC_{50} values ranging from 7.5 to 16.9 µg/mL[14].



4

Another study involving the synthesis and screening of new indole coumarin hybrids for their anticancer properties against the MCF-7 cancer cell and normal cell line (Vero) was reported by Kamath *et al*. (2015), compounds **5, 6** and **7** were the most active against MCF-7 cells with IC_{50} values of 7.4, 5.5, 13.5 µM, respectively[15].



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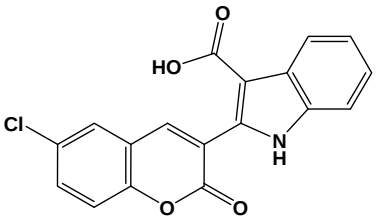

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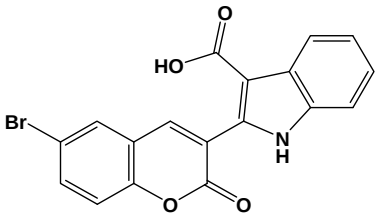
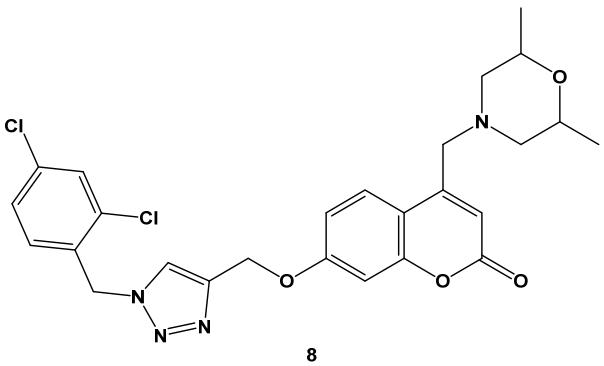


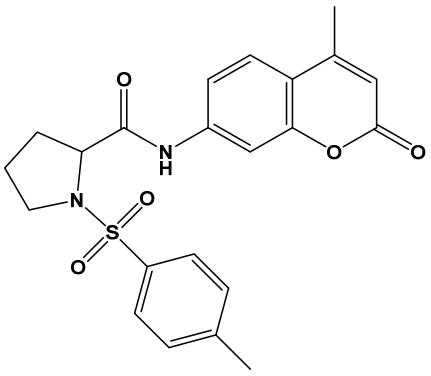
7

Goud *et al*.(2019) synthesized several novel coumarin triazole hybrid morpholines and evaluated their anti-proliferative potential against bone (MG-63), lung (A549), breast (MDA-MB-231), colon (HCT-15) and liver (HepG2) cancer cells. Compound **8** was the most active with an IC_{50} value of 0.80 ± 0.22 µM against MG-63 cells[16].



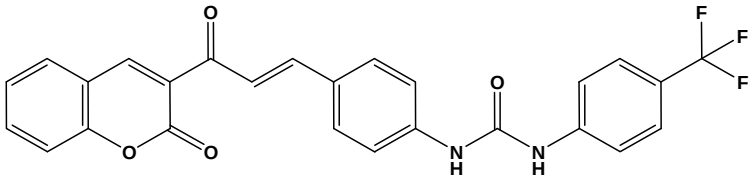
8

In 2019, Durgapa and Soma designed and synthesized coumarin-proline sulphonamide derivatives and evaluated their anticancer activity against cancer cell A549 and MCF7, as well as their antidiabetic potential. Of the compounds evaluated, compound **9** was the most promising with an IC_{50} value of 1.07 µM against MCF7 cells, while others displayed moderate DPP-IV inhibition[17].



9

Kurt *et al*. (2020) recently synthesized and assessed a series of coumarin chalcone derivatives containing urea moiety against H4IIE and HepG2 cells for their anticancer activity. The results revealed that most of the compounds showed excellent antitumor activity against the tested cells. Compounds **10** and **11** elicited the most significant effect against H4IIE and HepG2 cells with IC_{50} values of 1.62 and 2.326 µM, respectively[18].



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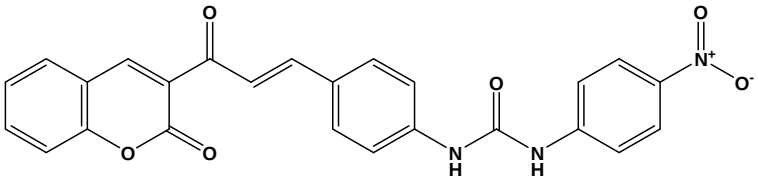
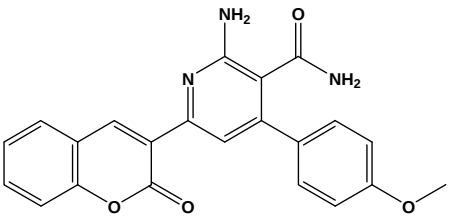


11

A series of coumarin pyridine/fused pyridine hybrids were designed, synthesized and accessed by Fayed *et al*. (2019) for their anticancer activities against MCF-7, HCT-116, HepG and A549 cells. The results demonstrated that compounds **12**, **13** and **14** were the most active, with IC_{50} values ranging from 1.1 to 2.4 µM against MCF-7 cells[19].



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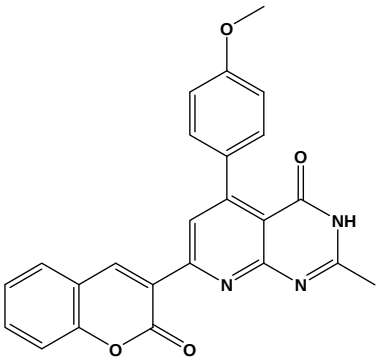

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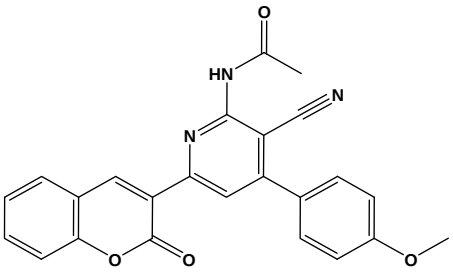
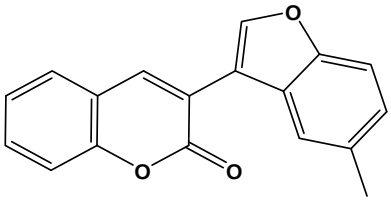


14

Chougala *et al*. (2015) synthesized a series of 3-(3-benzofuranyl)-coumarin derivatives for their anticancer potential against the HeLa cell. The results showed that compounds **15**, **16** and **17** demonstrated anticancer activity against HeLa cells with IC_{50} values of 20 and 25 µg/mL, respectively[20].



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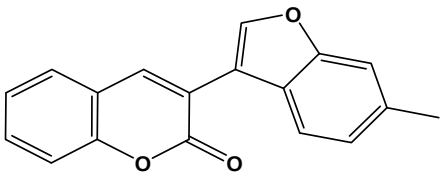

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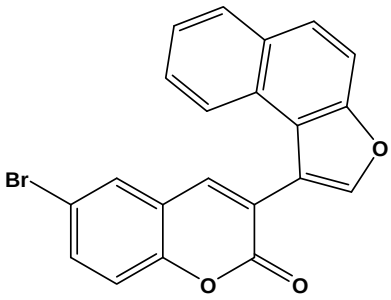
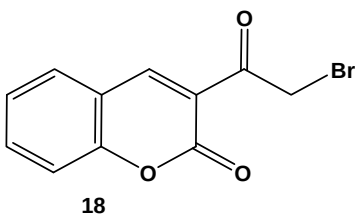


17

Kasumbwe *et al*. (2017) synthesized a series of mono/di- halogenated coumarins derivatives as anticancer agents against MCF-7(Human breast cancer cell line) and UACC-62 (Human melanoma cell lines) cells. The results revealed that compounds **18**, **19**, **20** and **21** strongly suppressed cell proliferation of MCF-7 and UACC-62 cells. Compounds **19** and **20** were the most active against UACC-62 cancer cells with IC_{50}values of 7.28±0.03 and 1.77±0.01, respectively [21].



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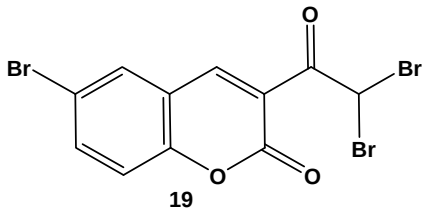

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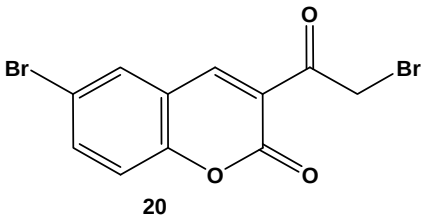

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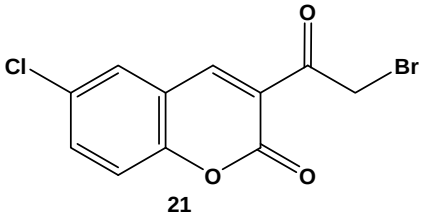
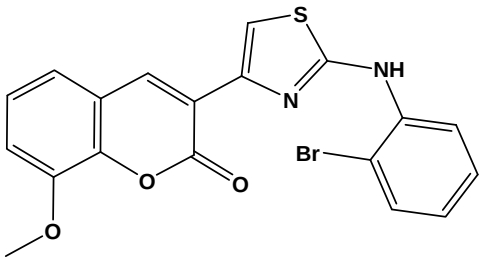


21

2.2 Coumarin scaffold as antimicrobial agents

A series of thiazole-containing coumarin derivatives were synthesized and screened by Osman *et al*.(2018) as antibacterial agents against two Gram-positive (*S. pneumonia and S. aureus*) and three Gram-negative bacteria (*E. coli, E. aerogenes and S. typhi*). Among the synthesized compounds, the results revealed compounds **22** and **23** were the most promising with a MIC value of 73 µM against all tested bacteria[10].



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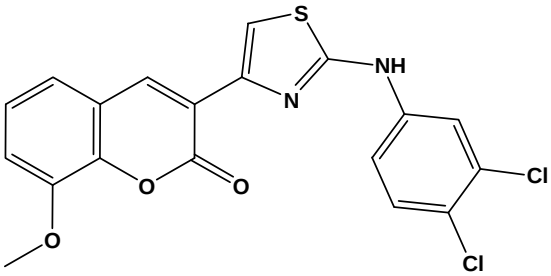
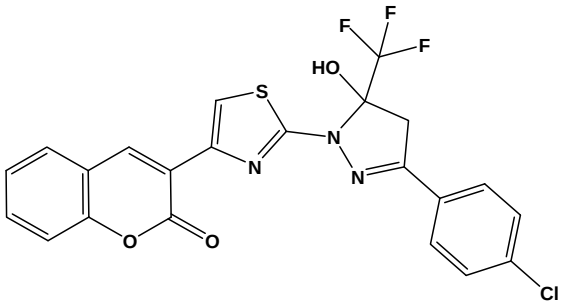


23

Aggarwal *et al*.(2013) synthesized and screened new series of 2-(5-hydroxy-5-trifluoromethyl-4-5 dihydropyrazol-1-yl)-4-(coumarin-3-yl) thiazoles for their antibacterial activity against *S. aureus, B. subtilis, S. Epidermidis,K. aerogenes, E. coli, P. mirabilis,* and *P. aerinosa*. The results demonstrated that all tested compounds showed moderate to good antibacterial activity. Compounds **24** and **25** were the most effective against *E.coli* and *P. mirabilis* with MIC values of 2 and 4 µg/mL, respectively[22].



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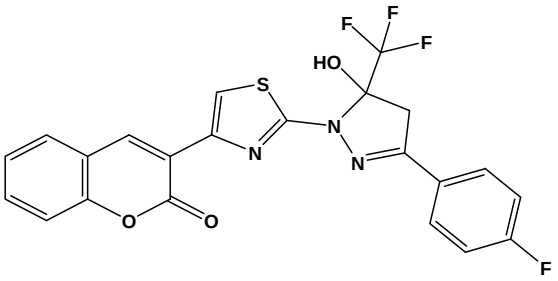
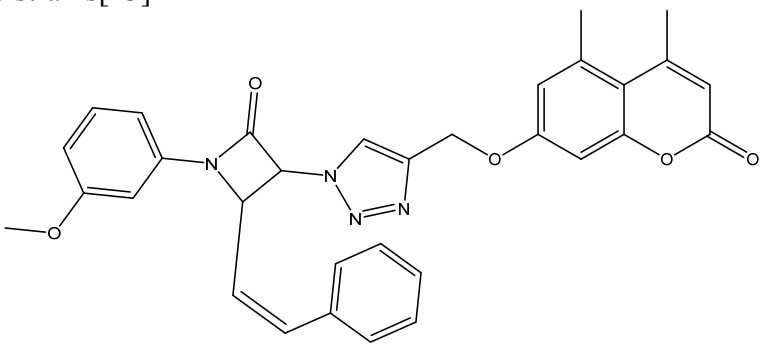


25

A new series of coumarin-tagged β- lactam triazole hybrid was synthesized and tested by Dhawan *et al*.(2019) for their antimicrobial activity against *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Escherichia coli, Acinetobacter baumannii,* and two fungal including *Candida albicans* and *Cryptococcus neoformans*. The results showed that compounds **26** and **27** had shown moderate antimicrobial activity against *Pseudomonas aeruginosa* and *Candida albicans* strains[23]



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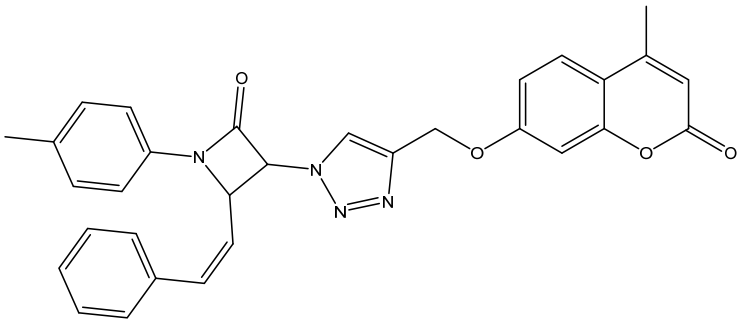
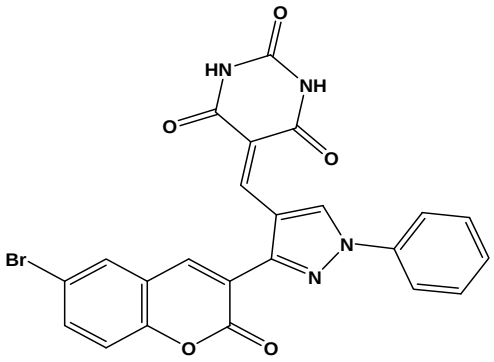


27

Laxmi *et al*.(2013) synthesized a series of coumarin pyrazole pyrimidine 2, 4, 6(*1H, 3H, 5H*)triones and thioxopyrimidine 4, 6(*1H, 5H*)diones for their antibacterial and antifungal activity against *bacillus subtilis, Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, and* fungi, *Aspergillus niger*. The results showed that these compounds were moderately active against the microorganisms used. Compounds **28** and **29** demonstrated good antifungal activity with 14 and 7 mm inhibition zone, respectively, against *Aspergillus niger*[24].



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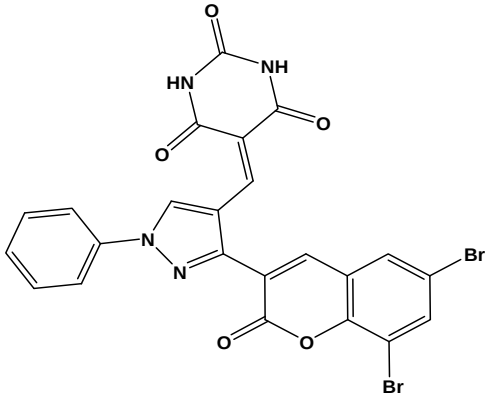
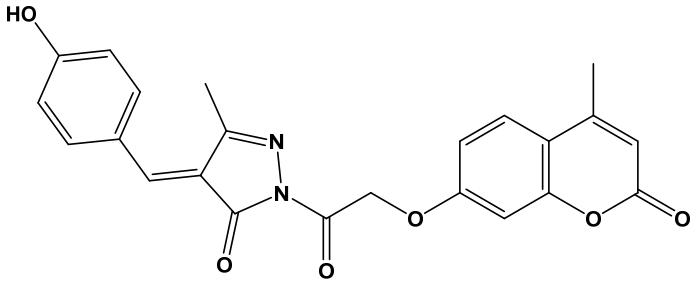


29

In another study, a series of oxadiazole and pyrazole derivatives were designed and synthesized by Mahesh *et al*. (2016) as possible antimicrobial agents against *Staphylococcus aureus, Escherichia coli,* and *Aspergillus niger*. Among all tested derivatives, compounds **30** and **31** were more active against all microorganisms with a MIC value of 75 µg / mL[25].



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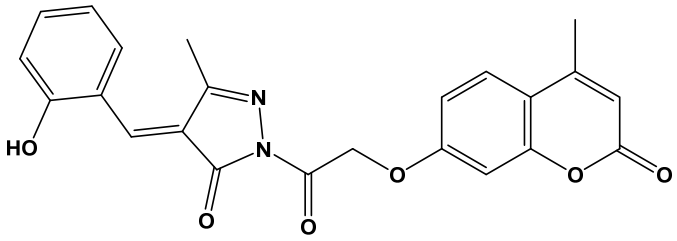
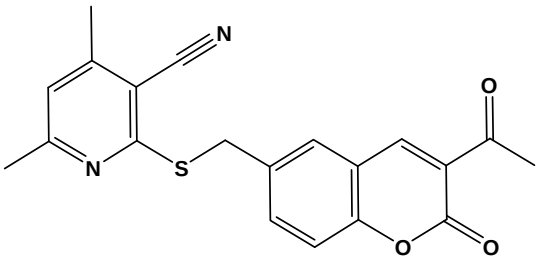


31

Sanad *et al*.(2020) synthesized and evaluated a series of nicotinonitrile coumarin hybrids for their antibacterial activity against *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Streptococcus mutans*. The results showed that compounds **32** and **33** were the most promising among the synthesized compounds, with MIC values ranging from 1.9 to 7.8 and 3.9 to 15.6 µg/mL, respectively, against the tested bacterial strain [26].



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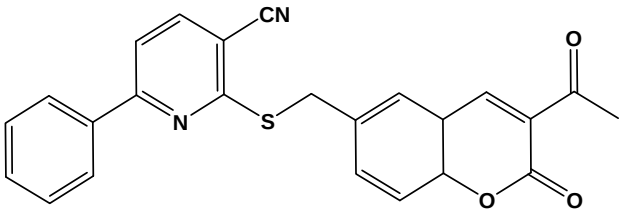
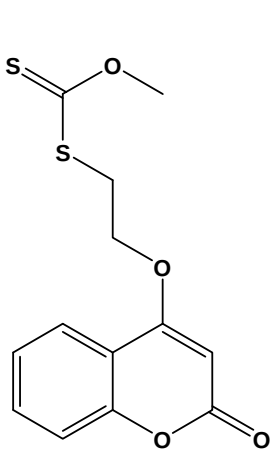
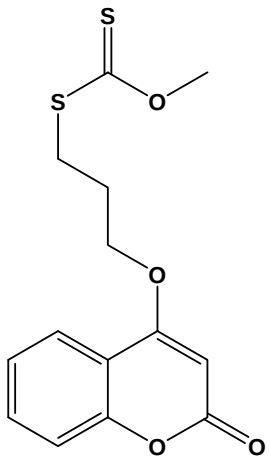


33

Mangasuli *et al*. (2018) synthesized and assessed the antifungal efficacy of carbonodithioate derivatives of coumarin against *Aspergillus flavus, Trichoderma harzianum, Penicillium chrysogenum,* and *Candida albicans*. The results demonstrated that compound **34** was the most potent against *Aspergillus flavus* and *Trichoderma harzianum*, with a MIC value of 0.25µg/mL. In contrast, compound **35** exhibited excellent antifungal activity against *Aspergillus flavus and Trichoderma harzianum* with a MIC value of 0.5 µg/mL[27].

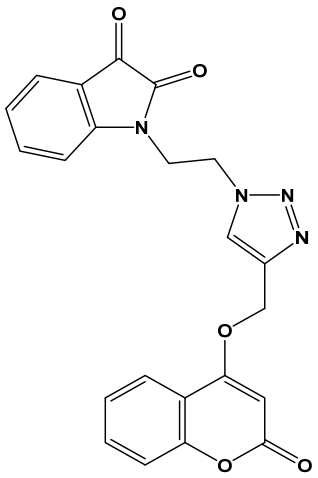


34

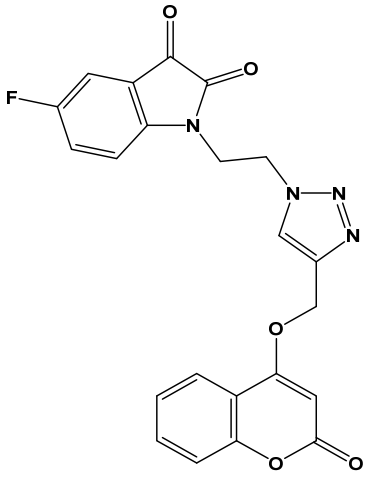


35

Bhaga *et al*.(2019) synthesized novel indolinedione coumarin hybrids and investigated their antimicrobial activity against *Escherichia coli, Salmonella enteric, Staphylococcus aureus* and fungi*, Candida albicans, Alternaria mali, Penicillium sp*., and *Fusarium oxysporum*. The results revealed that compounds **36** and **37** showed the best growth inhibitory activity with 30 and 312 µg/mL MIC values against *Penicillium sp.* and *S. aureus,* respectively[3].

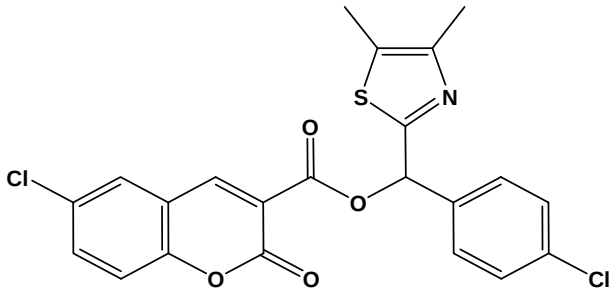


36



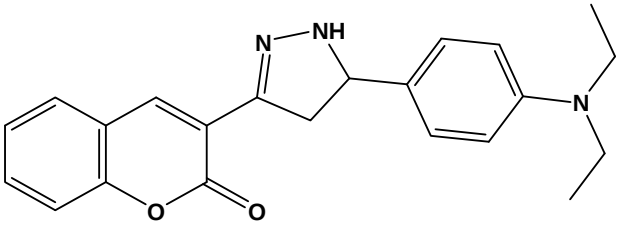
37

Liu *et al*.(2020) synthesized and evaluated a series of thiazolyl esters of coumarin derivatives as an antibacterial agent against *Staphylococcus aureus, Listeria monocytogenes, Escherichia coli* and *Salmonella typhi*. Compound **38** was the most active among all synthesized analogues with MICs values of 0.05, 0.05, 8, and 0.05 µg / mL, respectively[28].



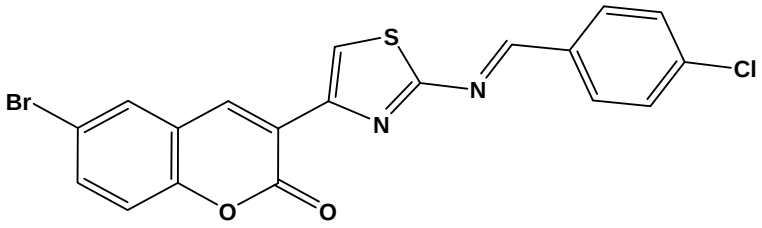
38

Ajani *et al*. (2019) synthesised a series 3-(5-(substituted-phenyl)-4, 5-dihydro-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one and assessed their antibacterial activity. The results revealed that compound **39** emerged as the most potent antibacterial activity with MICs values of 3.91±0.22µg/mL against *Staphylococcus aureus* and *Enterococcus faecalis* and 15.63±0.94 µg/mL against *K. Pneumonia* and *P. Vulgaris*[29].



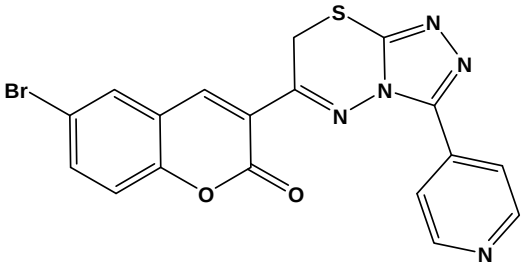
39

Venugopala *et al*. (2008) synthesized a series of Schiff bases of amino thiazolyl bromocoumarin for antibacterial activity against *Bacillus subtilis*and *E. coli.* The results demonstrated that compound **40** was the most active with MICs values of 147 and 141 µg/ml against *Bacillus subtilis* and *Escherichia coli,* respectively [30].

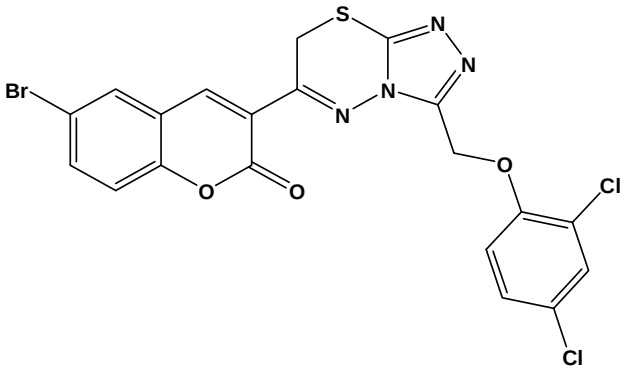


40

Jayashree *et al*. (2005) synthesized new triazole thiadiazinylbromocoumarin derivatives for antibacterial activity against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*. The results showed that compounds **41** and **42** were the most potent with a zone of inhibition ranging between 27 to 34 mm and 36 to 40 mm, respectively, against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia* and *Pseudomonas aeruginosa*[31].

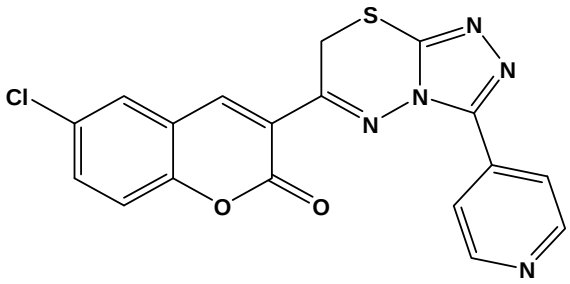


41



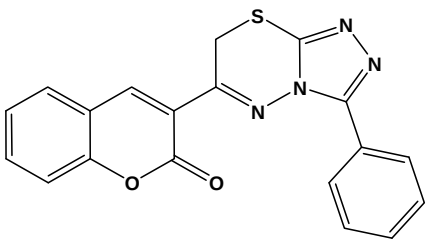
42

Jayashree *et al*.(2006) synthesized and assessed a series of triazolo thiadiazinylchlorocoumarin derivatives for their antibacterial activity against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia* and *Pseudomonas aeruginosa*. Among the synthesized analogues, compound **43** was the most active against the tested bacteria, with a zone of inhibition ranging from 38 to 42 mm compared to the standard drug amoxicillin (36 to 39 mm)[32].

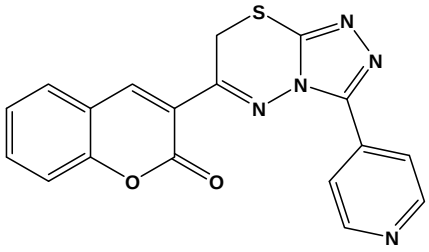


43

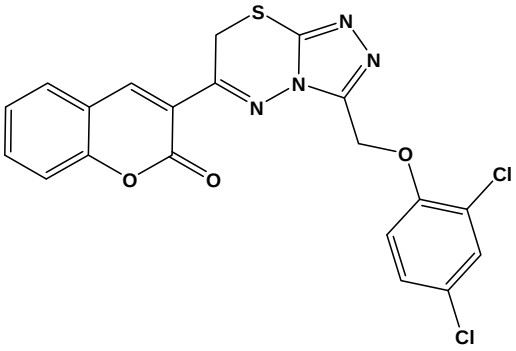
A series of triazole derivatives of coumarins was designed, synthesized by Jayashree *et al*. (2007) and assessed their antibacterial activity against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia* and *Pseudomonas aeruginosa.* Compounds **44**, **45** and **46** have shown good antibacterial activity with a zone of inhibition ranging between 31 to 38 mm, 40 to 43 mm and 18 to 36 mm, respectively, against the tested bacterial strain[33].



44



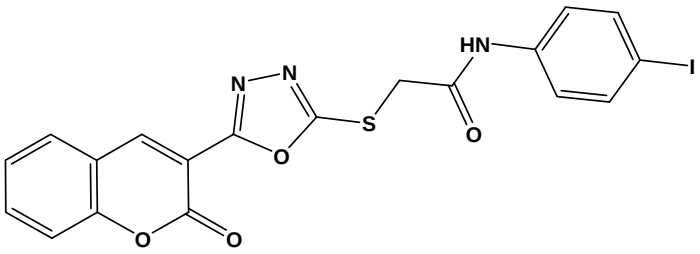
45



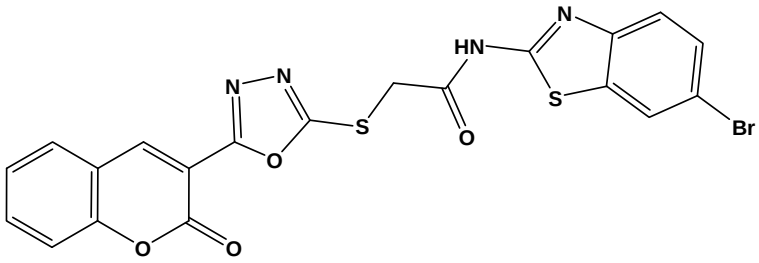
46

2.3 Coumarin scaffold as antitubercular agents

Patel *et al*.(2013) designed and synthesized a series of coumarin-based 1, 3, 4-oxadiazol-2ylthio-*N*-phenyl/benzothiazolyl acetamides and assessed their *in-vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv. The results showed that compounds **47** and **48** were the most promising antimycobacterial with a MIC value of 12.51 µg/mL, comparable to the reference drug pyrazinamide (6.25 l µg /mL)[34].

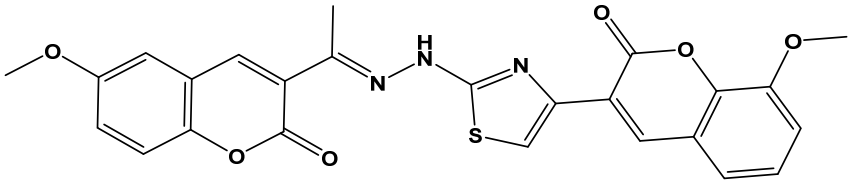


47

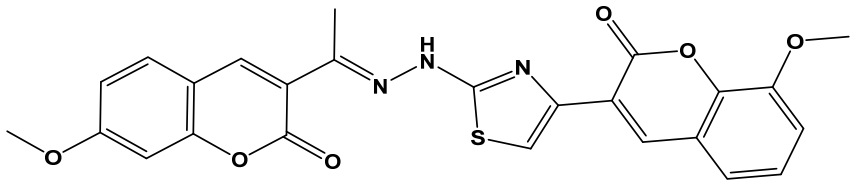


48

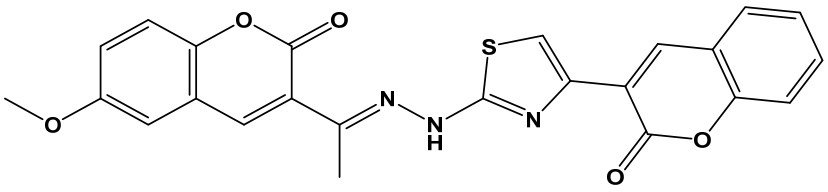
In another study, Yusufzai *et al.*(2017) synthesized a series of hydrazinyl thiazolyl coumarin derivatives for their *in-vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (ATCC 25618). The results revealed that compounds **49, 50, 51, 52** and **53** were the most potent antitubercular agents with a MIC value of 50 µg / mL[35].



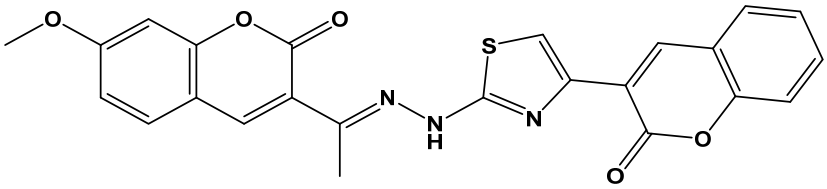
49



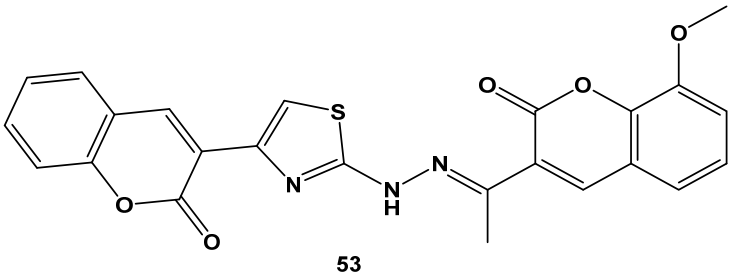
50



51

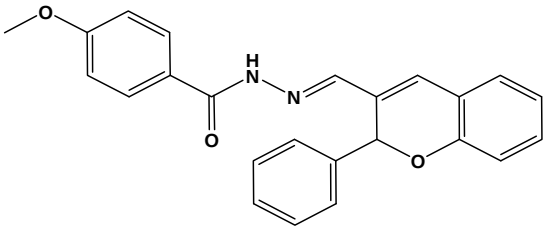


52

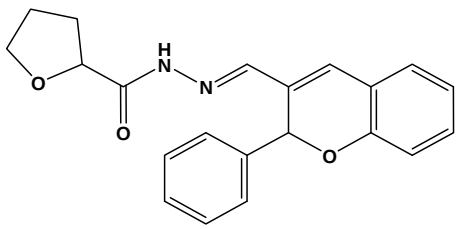


53

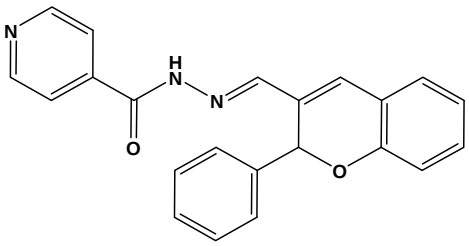
Furthermore, a series of novel hydrazide hydrazone derivatives with 2*H*-chromene and coumarin scaffold was synthesized by Angelova *et al*.(2016) for their antimycobacterial activity against H37Rv strains of *Mycobacterium tuberculosis*. Isoniazid and ethambutol were used as reference drugs. Compounds **54, 55** and **56** were the most active with MIC values of 0.13, 0.15 and 0.17 µM, respectively, against H37Rv strains of *Mycobacterium tuberculosis*[36].



54

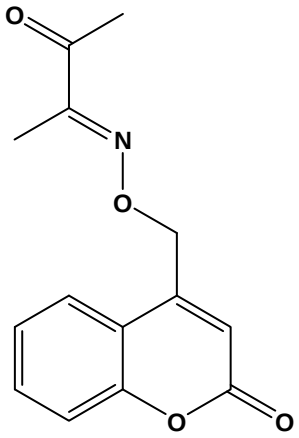


55



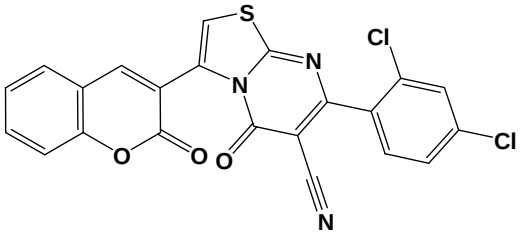
56

Reddy *et al*.(2018) synthesized and evaluated a series of novel coumarin- oxime ethers antimycobacterial activity against H37Rv strains of *Mycobacterium tuberculosis*. The results demonstrated that compound **57** was the most active with a MIC value of 0.04 µg/L, as compared to the positive control, Isoniazid (0.02 µg m/L)[37].

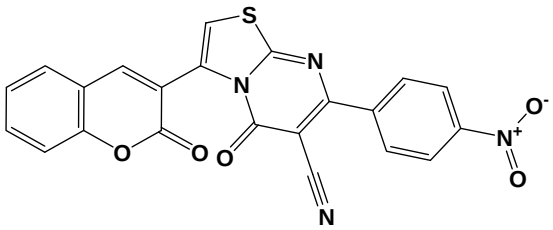


57

A series of hybrid coumarin analogues were synthesized and assessedby Hassan *et al*.(2019) for their antimycobacterial activity against the H37Rv TB strain. Among the newly synthesized compounds, the results showed that compounds **58** and **59** exhibited excellent antitubercular activity with a MIC value of 12.5 µM[38].

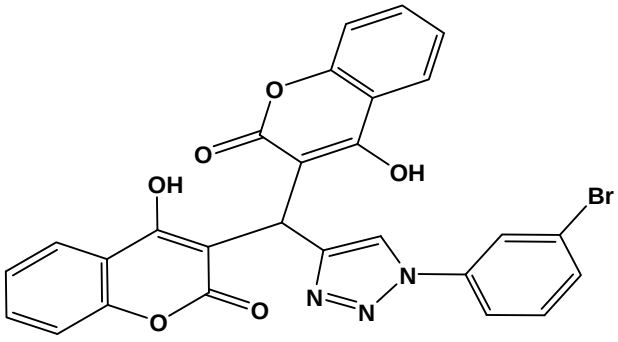


58



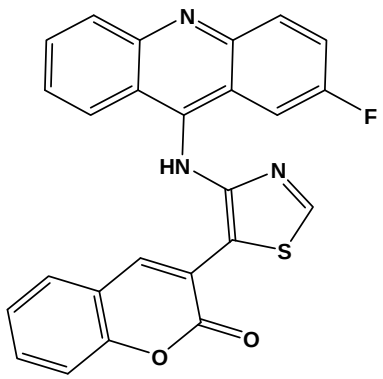
59

Danne *et al*.(2018) synthesized and evaluated a series of triazole-biscoumarin conjugates as a possible antimycobacterial agent against active and dormant Mtb H37Rv. The results demonstrated that compound **60** displayed excellent antitubercular activity against latent Mtb H37Rv, with a MIC value of 1.44 µg/mL [39].

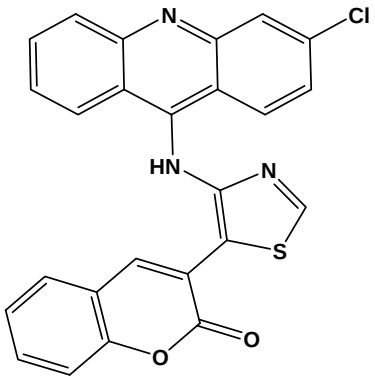


60

A series of polycyclic acridin-(9-yl-amino) thiazol-5-yl)-2*H*-chromen-2-one derivatives was synthesized by Mane *et al*.(2020) for their antimycobacterial efficacy against H37Rv MTB. Among the synthesized derivatives, compounds **61** and **62** showed excellent antimycobacterial activity with MICs values of 0.78 and 1.56 µg/mL, respectively[40].



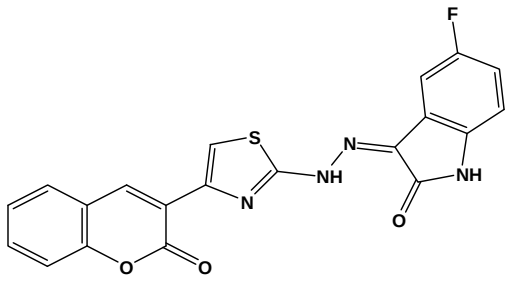
61



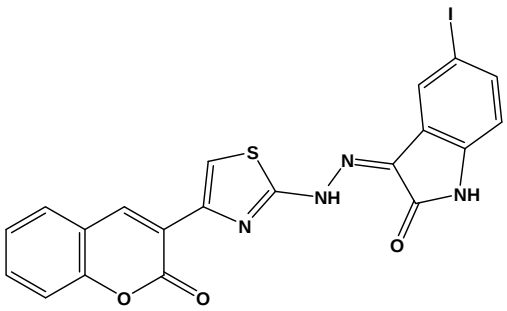
62

2.4 Coumarin scaffold as antioxidants

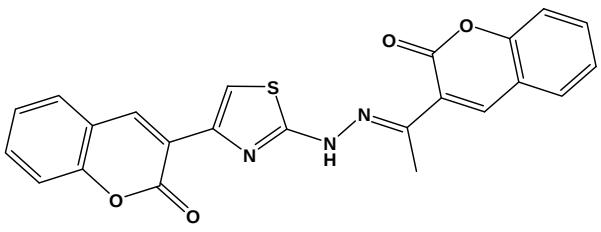
In a study conducted by Thota *et al*.(2014), a series of coumarin thiazole derivatives were synthesizedand assessed for their antioxidant activity using the DPPH scavenging method. The results showed that these compounds showed moderate to high scavenging capacity as compared to the standard drug. Compounds **63**, **64** and **65** were the most active with IC_{50} values of 11.04±0.18, 11.28±0.06 and 12.16±0.28 µg/mL, respectively[12].



63

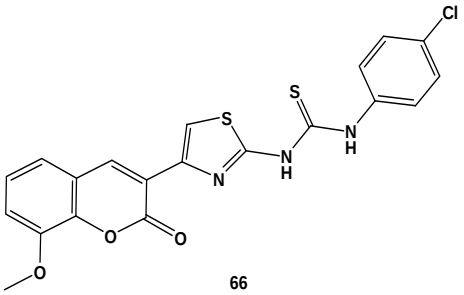


64

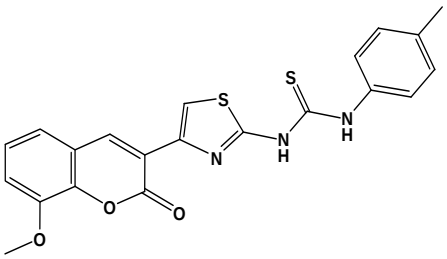


65

Kurt *et al*. (2015) designed and synthesized a series of urea/thiourea substituted coumarinyl thiazole derivatives as antioxidant agents. The results indicated that the most active compounds, **66**, **67**, **68**, **69** and **70**, exhibited high scavenging capacitywith IC_{50} values of 1.64, 1.82, 2.69, 3.31 and 5.49 µM, respectively[41].



66



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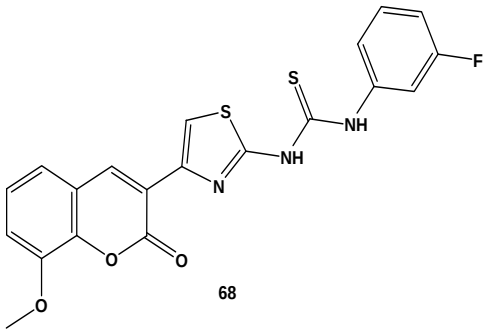
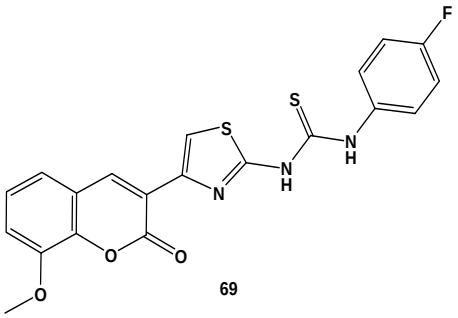


68



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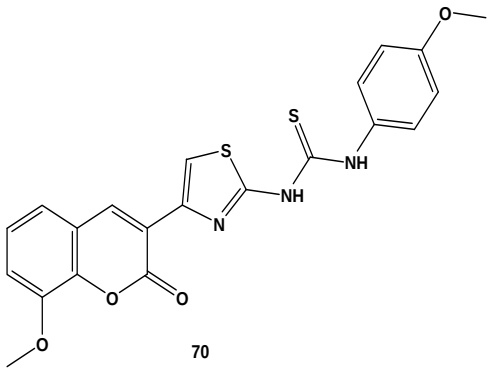
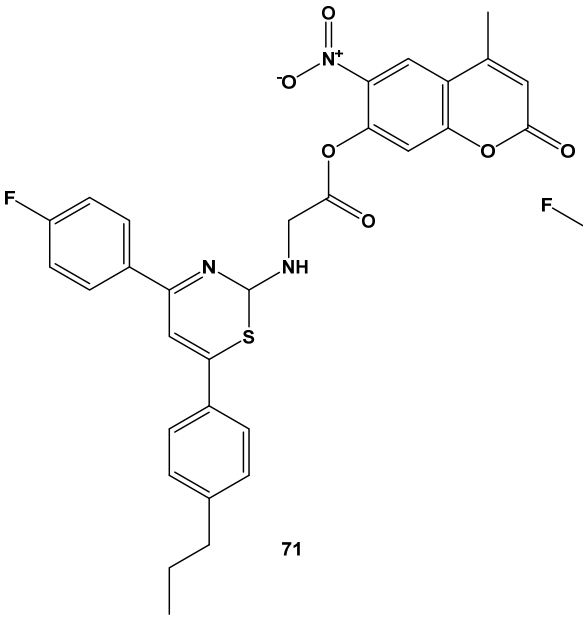
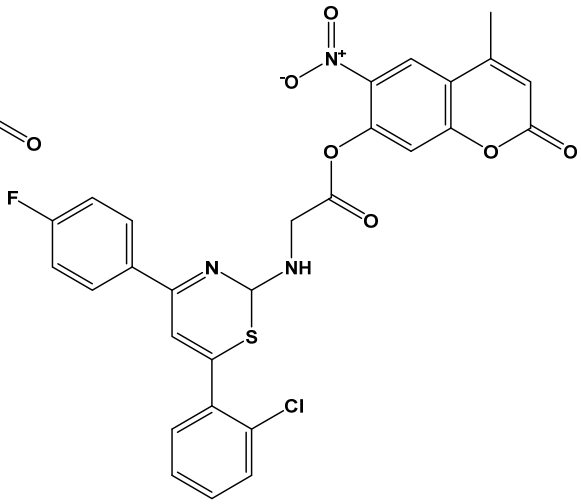


70

A series of coumarin nucleus clubbed with thiazine scaffolds was designed, synthesized and evaluated for their antioxidant activity using DPPH and ABTS bioassay by Chauhan *et al*. (2018). The results revealed that compounds **71** and **72** were the most active with IC_{50} values of 33.99±03 and 35.35±0.47µg/mL in DPPH and ABTS bioassay, respectively[42].

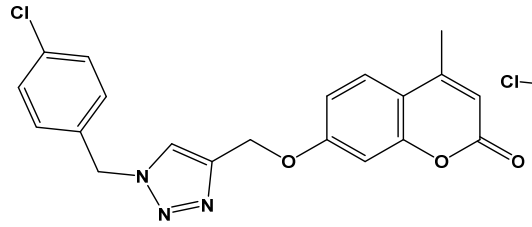


71

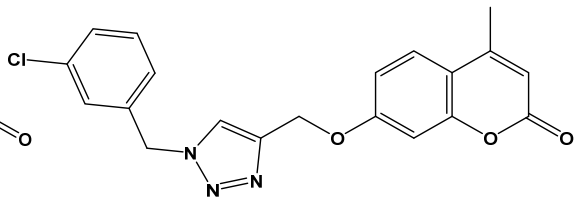


72

Shaikh *et al*.(2016) synthesized a series of coumarin-based 1, 2, 3 triazoles and evaluated their antioxidant activity. The results showed that compounds **73** and **74** having chloro-substituent on phenyl ring demonstrated potent antioxidant capacitywith IC_{50} values of 12.48 and 16.30 µg/mL, respectively[43].

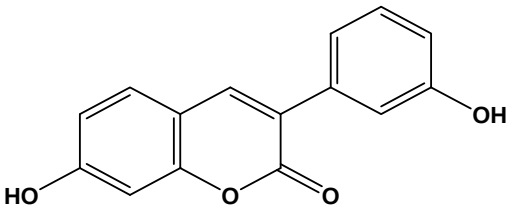


73



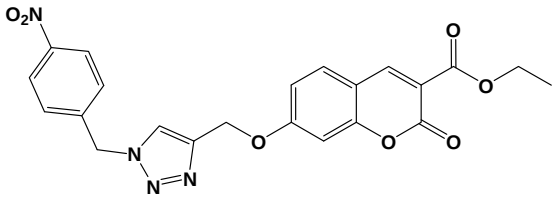
74

In another study, Matos *et al*.(2015) synthesized a series of hydroxylated 3-phenylcoumarin and assessed their antioxidant efficacy. The results showed that compound **75** was the most active in the four assays performed (ORAC-FL=11.8, the capacity of scavenging hydroxyl radicals=54%, TROLOX index=2.33, and AI_{30} index=0.18)[44].

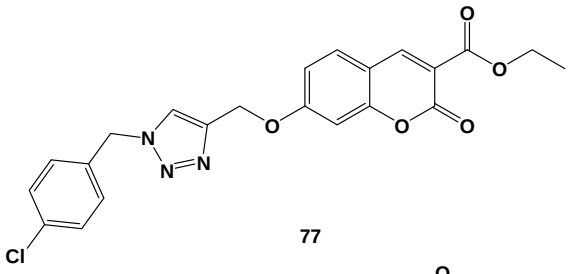


75

Shaikh *et al*. (2016) synthesized a series of 1, 2, 3 triazole incorporated coumarin derivatives as possible antioxidant agents. The results showed that all synthesized compounds exhibited high to moderate antioxidant capacity compared to the standard drug butylated hydroxytoluene (BHT). Compounds **76, 77, 78** and **79** were the most potent with IC_{50} values of 15.20, 16, 15.99, and 15.29 µg/mL, respectively[45].



76



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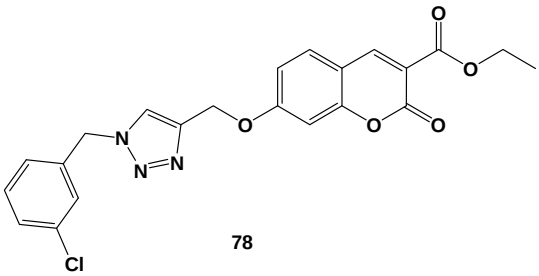

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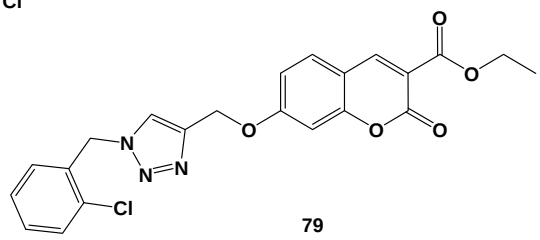
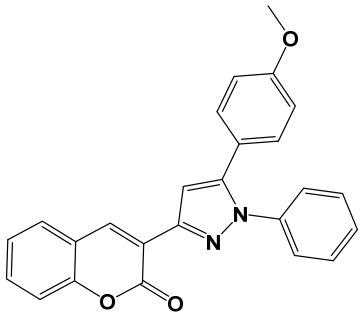


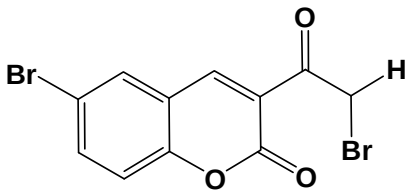
79

Jayashree *et al*. (2008) synthesized a series of 5 ((substituted and unsubstituted phenyl)-1-phenyl-2pyrazoline-3-yl)-6-chloro and evaluated their antioxidant activity. The results showed that compound **80** was a potential candidate for scavenging radical oxygen[46].



80

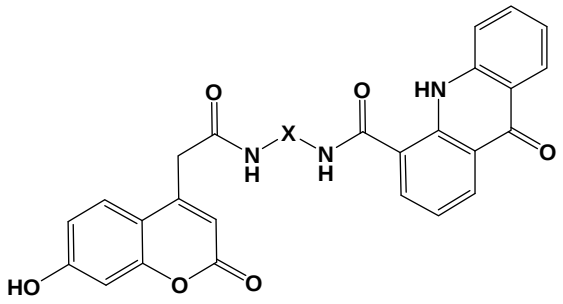
Kasumbwe *et al*. (2014) synthesized a series of mono/dihalogenated coumarins for their antioxidant activity. The results showed that compound **81** was the most promising, with a percentage scavenging capacity of 85%[47].



81

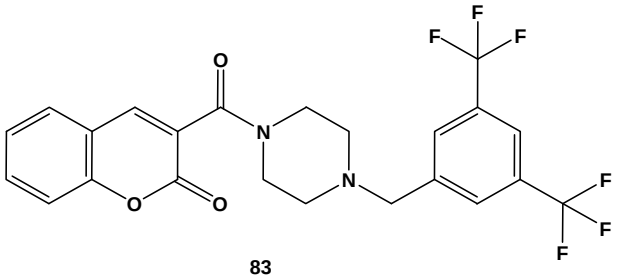
2.5 Coumarin scaffold as acetylcholinesterase inhibitors

Hamulakova *et al*.(2017) synthesized a series of acridine coumarin hybrids and evaluated their inhibitory capacity on acetylcholinesterase and butyryl-cholinesterase. These compounds have shown excellent inhibitory capacity against human acetylcholinesterase. The results revealed that compound **82** showed the highest inhibitory capacity for acetylcholinesterase, with an IC_{50} value of 5.85 µM[48].



82

In another study, a series of coumarinpiperazine hybrids were designed and synthesized by Zhang and Jiang. (2018) for their anti-cholinesterase capacity. The results revealed that compounds **83** and **84** were the most potent human acetyl-cholinesterase inhibitorswith IC_{50} values of 2.42 and 9.89 µM, respectively[49].



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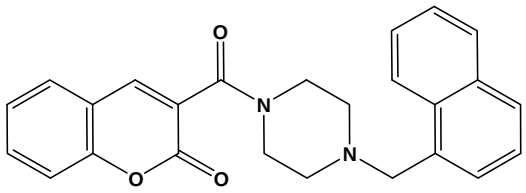
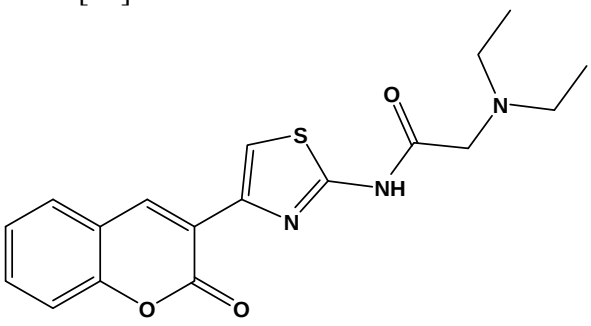


84

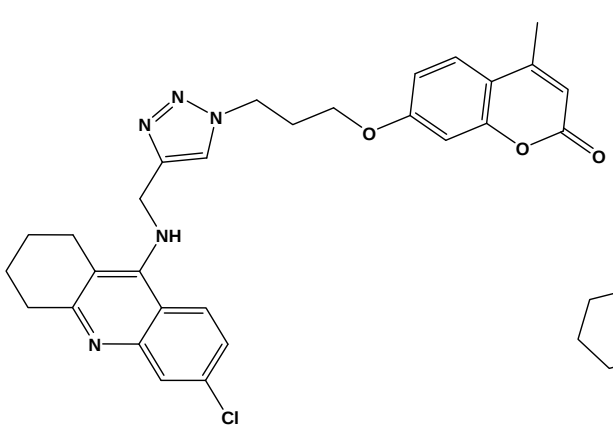
Sonme *et al*.(2017) synthesized a series of coumarinylthiazole derivatives with the acetamide moiety as a linker between the alkyl chains and/or the heterocyclic nucleus for their acetylcholinesterase (AChE) inhibitors capacity in vivo. The results showed that compound **85** was the most potent AChE inhibitor with an IC_{50} value of 43 nM and an index of the selectivity of 4151.16 over BuChE. AChE inhibition kinetic analysis showed that compound **85** was a mixed-type inhibitor[50].



85

Najafi *et al*.(2019) synthesized a series of 1, 2, 3-triazole-linked tacrine-coumarin derivatives for their potent dual binding site cholinesterase inhibitors (ChEIs) to treat Alzheimer's disease. Among the synthesized analogues, compound **86** was the most effective anti-acetylcholinesterase (AChE) derivative with an IC_{50} value of 27 nM; compound **87** demonstrated the best anti- butyrylcholinesterase (BChE) activity with an IC_{50} value of 6 nM[51].

Xie *et al*. (2015) synthesized a series of novel tacrine-coumarin derivatives and screened them against Alzheimer's disease as multi-target agents. The results showed that most compounds displayed strong inhibitory activity against AChE and BuChE and selective MAO-B inhibition. Compound **88** demonstrated excellent inhibitory capacity for AChE (IC_{50} values for electrophorus electricus acetylcholinesterase of 33.63 nM and 16.11 nM for human acetylcholinesterase), butyrylcholinesterase (BuChE) (IC_{50} values of 80.72 nM for *eq*BuChE and 112.72 nM for hBuChE), and the highest inhibitory activity against human monoamine oxidase B (IC_{50} value of 0.24 μM)[52].



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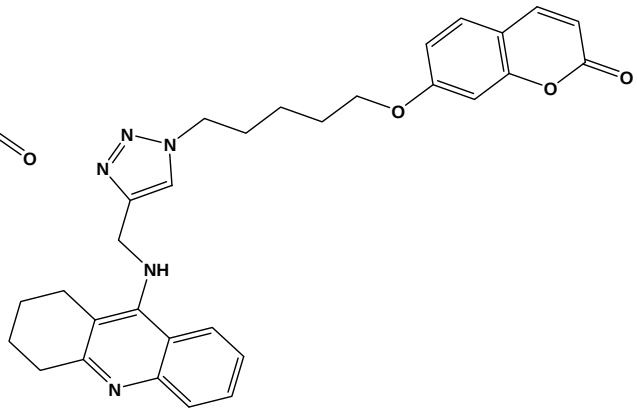

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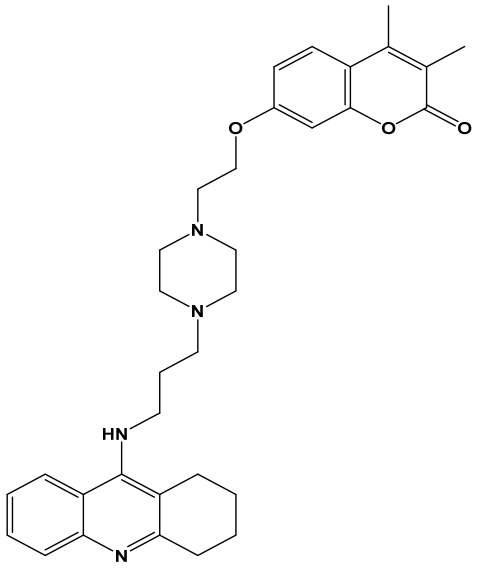


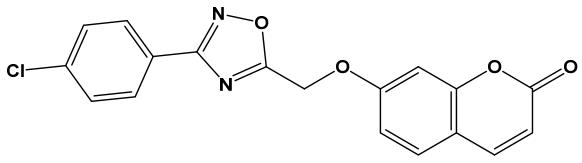
88

2.6 Coumarin scaffold as anticonvulsant agents

New hybrids of coumarin of 1, 2, 3-oxadiazoles were designed synthesized by Khanaposhtani *et al*.(2019) as anticonvulsant agents. Pentylenetetrazole (PTZ) and maximum

electroshock (MES) induced seizures were used to determine the *in-vivo* anticonvulsant activity of the synthesized compounds. The results indicated that these compounds were more effective against MES; Compounds **89**, **90** and **91** were the most active in the MES model[53].

Angelova *et al*. (2017) synthesized a series of aroylhydrazonesof 2*H*- chromen and coumarin carbaldehydes and tested their efficacy as anticonvulsants. In the Maximum Electroshock test, compounds **92** showed the highest protection. Compound **93** was the most active in the maximum electroshock test, whereas compound **94** was the most active in the 6-Hz test[54].



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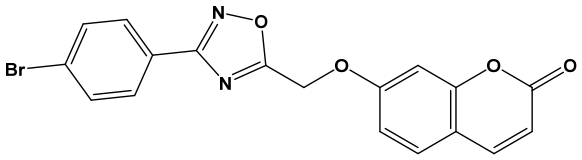

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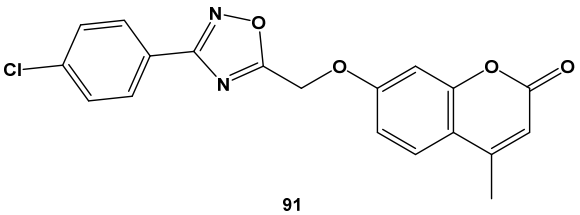

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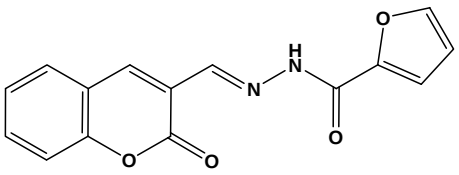

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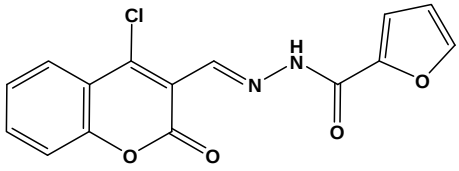

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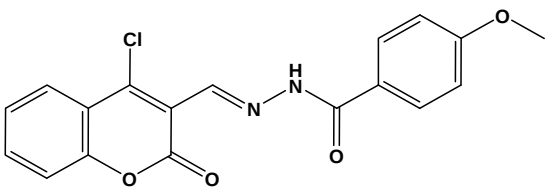
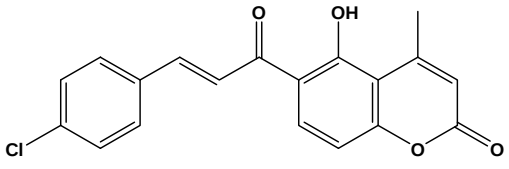


94

2.7 Coumarin scaffold as anti-HIV agents

Srivastav *et al*.(2018) designed and synthesized a series of 6-acetylcoumarin derivatives and evaluated their antiretroviral activity in the C8166 T-cell line infected with HxBru-Gluc strain of human immunodeficiency virus-1. The results revealed that compounds

95, **96** and **97** showed potent inhibitory efficacy against human immunodeficiency virus infection with IC_{50} values of 4.7, 4.5, and 0.35 μM, respectively[55].



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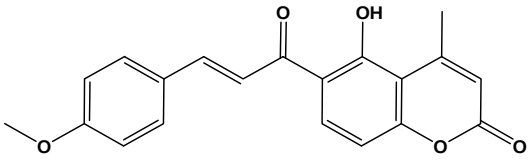

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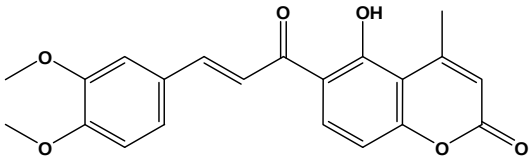
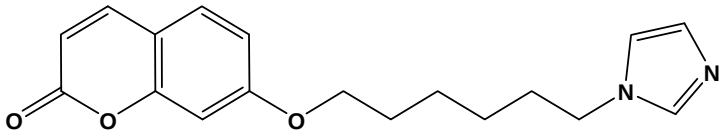


97

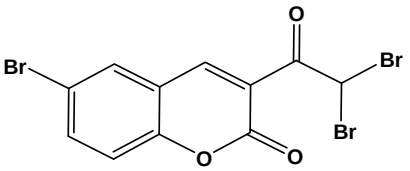
Hu *et al*.(2019) synthesized and evaluated a series of coumarin derivatives for their antiviral activity by comparing the half-maximum inhibitory concentrations (IC_{50}) of the synthesized compounds tested in *Epithelioma Papulosum* Cyprini (EPC) cells infected with IHNV; compound **98** was selected for further validation studies with an IC_{50} of 2.53 μM at 72 h against IHNV glycoprotein. Additional experiments revealed that compound **98** could inhibit apoptosis and morphological damage induced by IHNNV[56].



98

2.8 Coumarin scaffold as anti-mosquito agents

Venugopala *et al*.(2014) synthesized a series of 3-mono acetyl, 6- halogenated coumarins analogues and evaluated their larvicidal activity against an *Anopheles arabiensis*. The results showed that compounds **99, 100, 101** and **102** exhibited close to 100% larvae mortality within 24 hours of exposure[57].



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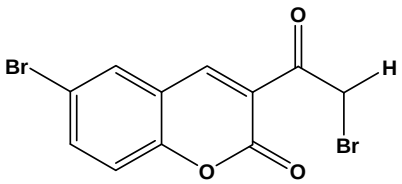

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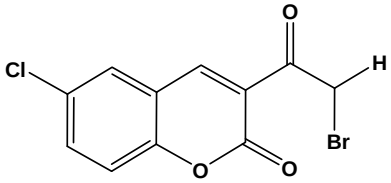

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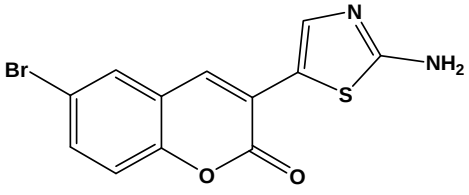
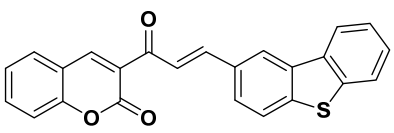


102

Another study by Shao *et al*.(2018) designed and synthesized a series of coumarin-dibenzothiophene or -carbazole derivatives as a larvicidal agent against fourth instars larvae of *Aedes aegypti*. These compounds demonstrated moderate to high larvicidal mortality. Two coumarin-linked dibenzothiophene hybrids **103**, **104** and six coumarin-linked carbazole hybrids **105, 106**, **107**, **108**, **109** and **110** showed potent toxicity (88.53 to 100.00%)[58].



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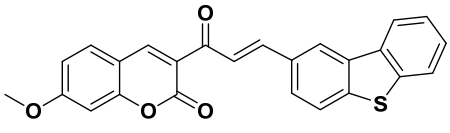

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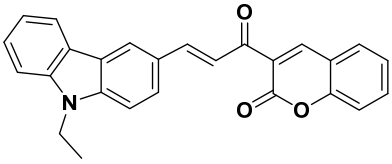

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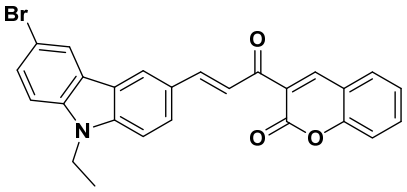

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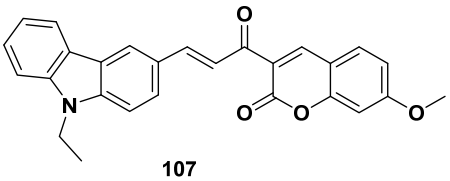

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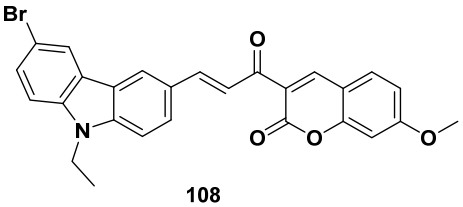

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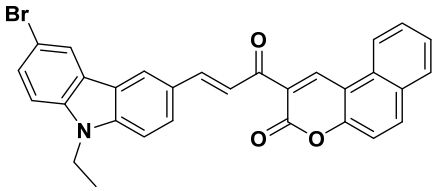

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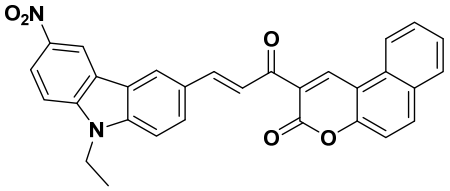
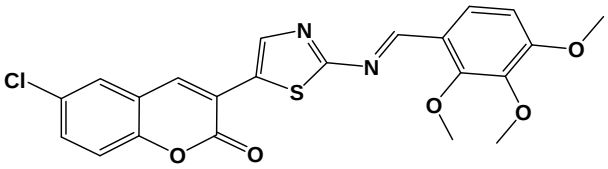


110

2.9 Coumarin scaffold as an analgesic and anti-inflammatory agents

A series of Schiff bases of 2-amino-4-(6-chloro-3-coumarinyl) thiazole as potent NSAIDs were designed and synthesized by Jayashree *et al*. (2005). The results revealed that compounds **111**, **112**, **113**, **114**, **115**, **116** and **117** were the most active; their analgesic activity was more significant than the reference drug, aspirin. The anti-inflammatory results have shown that compounds **113** and **118** were almost as potent as the reference drug ibuprofen[59].



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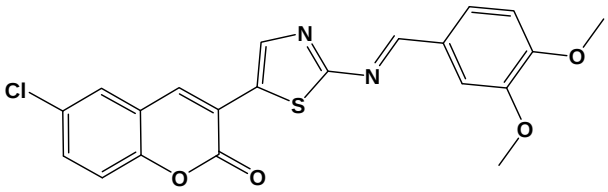

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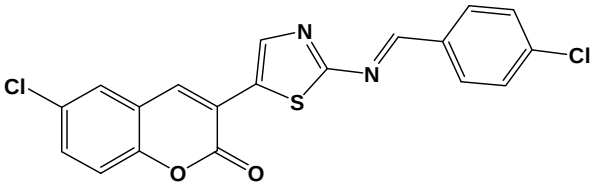

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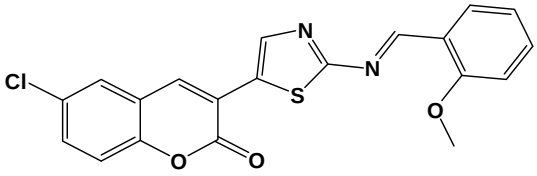

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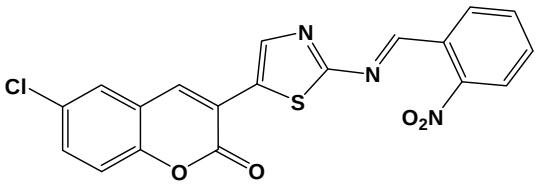

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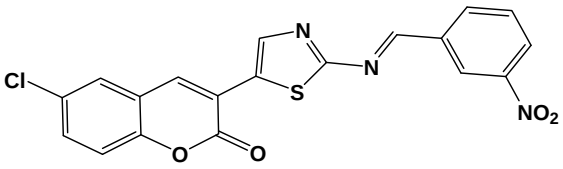

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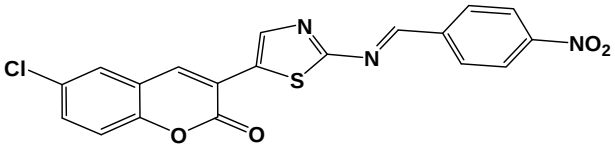

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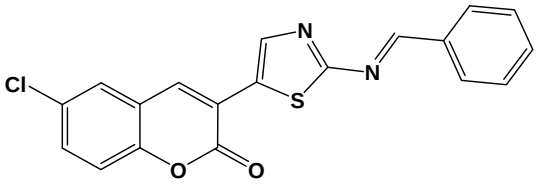
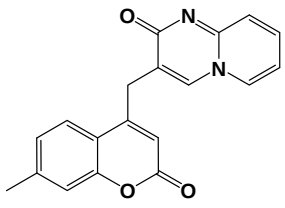


118

Madar *et al*.(2018) synthesized a series of coumarins with pyrido (1, 2-a)pyrimidinone as anti-inflammatory agents against matrix metalloproteinase's (MMPs) family such as MMP-2 and MMP-9. The results revealed that compounds **119** and **120** were highly active against MMP-2, showing 90% inhibition and 95% inhibition of tetracycline, compounds **121**, **122**, **123** and **124** display inhibitions of 85, 88, 89 and 87%, respectively. Compounds **125** and **126** demonstrate 82% and 75% inhibition against MMP-2, respectively[60].



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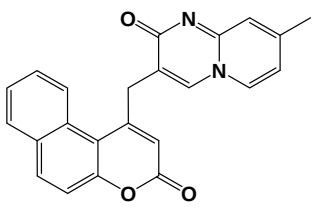

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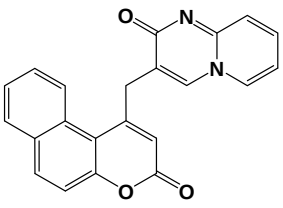

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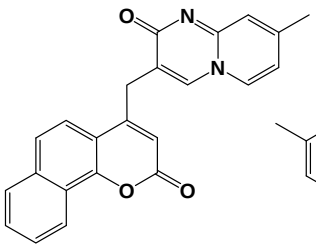

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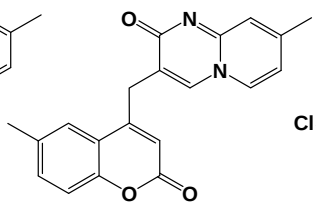

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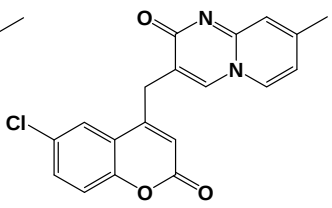

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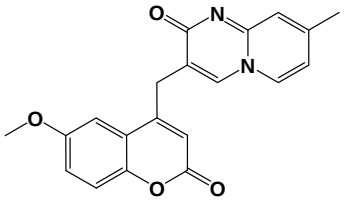

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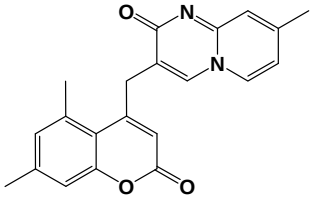
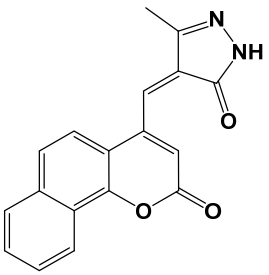
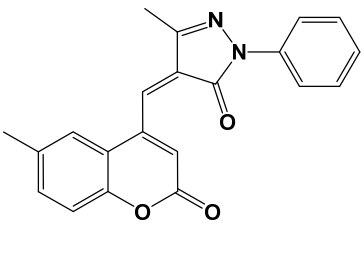


126

Kulkarni *et al*.(2018) developed a series of coumarin-pyrazolone derivatives and assessed their anti-inflammatory activity using the protein denaturation method. The results showed that these compounds were excellent anti-inflammatory agents; among them, compounds**127** and **128** displayed good anti-inflammatory activity[61].



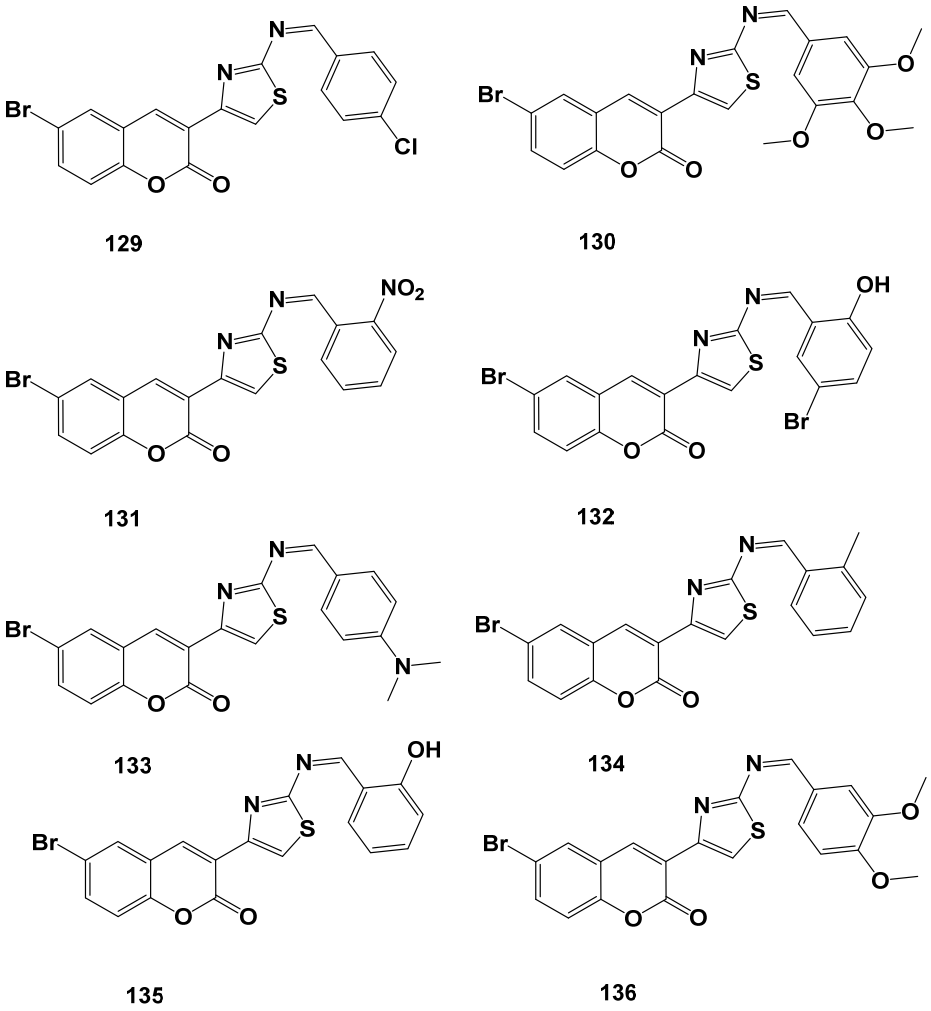
127



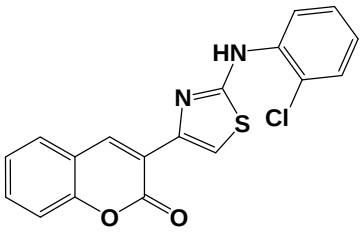
128

Venugopala and Jayashree, (2004) synthesized a series of Schiff bases of amino thiazolylbromo coumarin for their analgesic and anti-inflammatory activity by acetic acid-induced abdominal constriction method in mice using acetylsalicylic acid as standard and carrageenan-induced rat hind paw oedema method respectively using phenylbutazone as

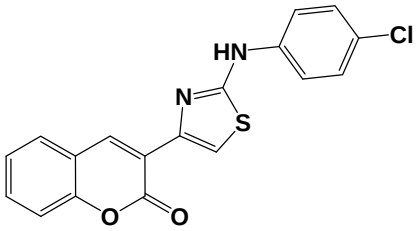
standard. The results revealed that compounds **129, 130, 131, 132, 133, 134, 135** and **136** showed excellent anti-inflammatory activity compared to standard phenylbutazone. The analgesic results demonstrated that compounds **129, 132, 133** and **136** possess higher activity than aspirin[62].



In another study, Venugopala *et al*.(2004) synthesized a series of substituted 2-arylamino coumarinylthiazoles as potent NSAIDs by acetic acid-induced abdominal constriction acetylsalicylic acid as standard and carrageenan-induced rat hind paw oedema method respectively using ibuprofen as standard. The results showed that compound **137, 138, 139, 140** and **141** demonstrated good analgesic activity (68.56, 60.37, 71.69, 66367, and 64.15%, respectively) compared with the standard diclofenac sodium (72.98%). Compounds **142**, **143**, **144**, **145** and **141** showed anti-inflammatory activity of 56.80, 52.06, 59.86, 52.14 and 54.20%, respectively, compared to that of ibuprofen as standard (74.00%)[63].



137



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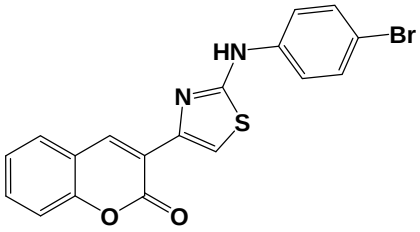

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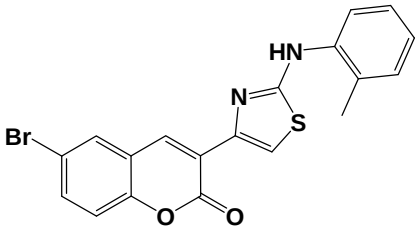

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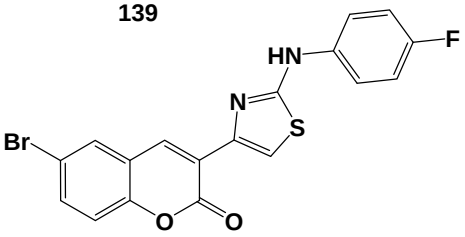

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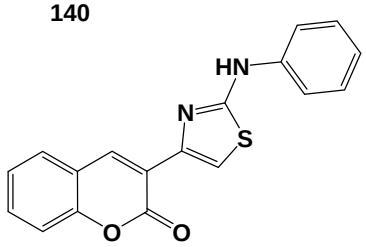

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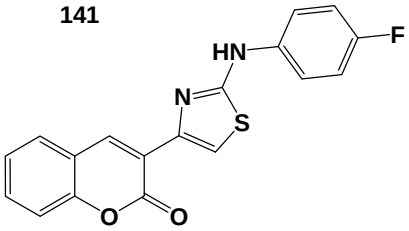

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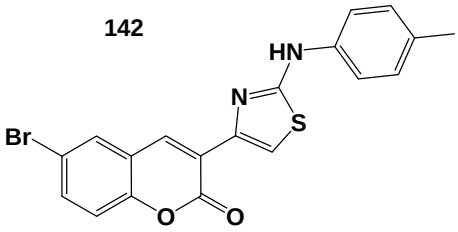

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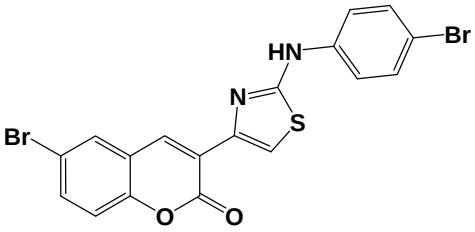
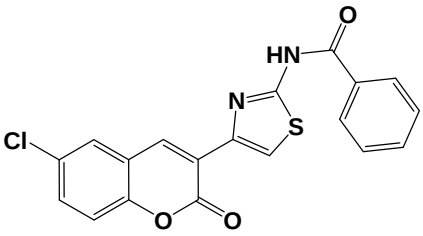


145

Jayashree *et al*.(2006) synthesized a series of carboxamides of 2-amino-4-(6-chloro-3-coumarinyl) thiazole as potential NSAIDs by acetic acid-induced abdominal constriction method using acetylsalicylic acid as standard and carrageenan-induced rat hind paw oedema method respectively using ibuprofen as standard. The results showed that compounds **146**, **147, 148, 149, 150** and **151** showed significant analgesic activity of 46.50, 43.70, 43.70, 46.80, 40.30, and 39.60%, respectively, compared to the standard (31.03%). The anti-inflammatory results revealed that compounds **152, 153, 154, 155** and **156** showed anti-inflammatory activity at 46.23, 45.42, 43.01, 43.01 and 24.73% respectively[64].



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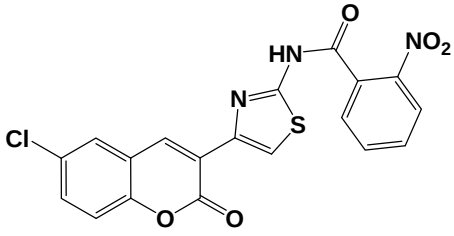

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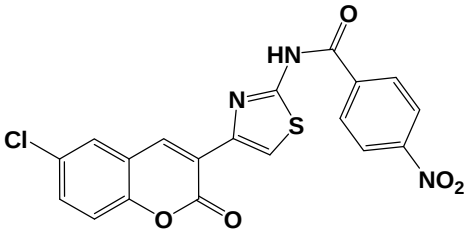

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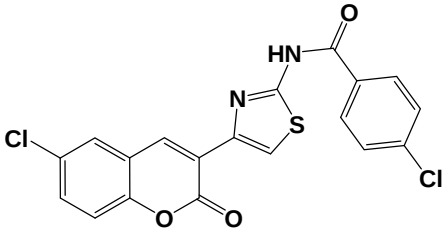

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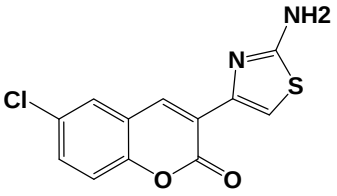

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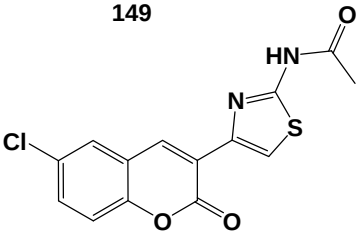

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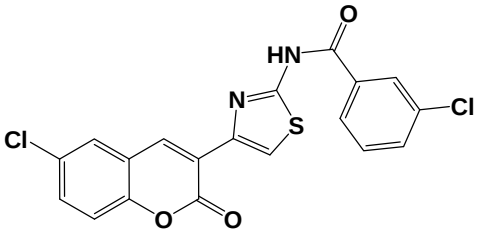

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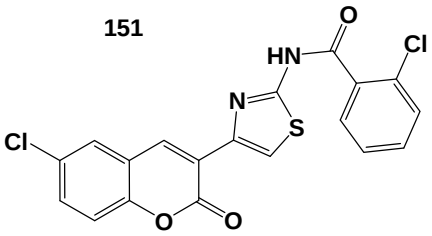

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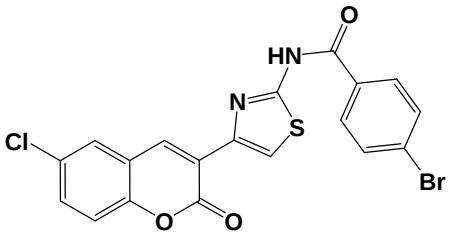
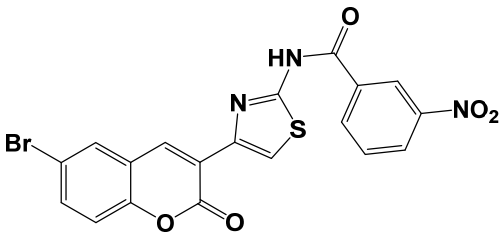


154

Venugopala and Jayashree (2003) synthesized a series of carboxamides of 2-amino-4-(6-bromo-3-coumarinyl) thiazole as an analgesic and anti-inflammatory agent. The results obtained revealed that **155**, **156**, **157**, **158** and **159** had shown significant analgesic activity at 41.66, 41.66, 40.29, 41.66 and 40.29%, respectively, compared to that of standard drug acetylsalicylic acid (37.45%). Compounds **160** and **161** have shown significant anti-inflammatory activity at 46.96 and 53.59%, respectively, compared to the standard drug phenylbutazone(45.30%)[65].



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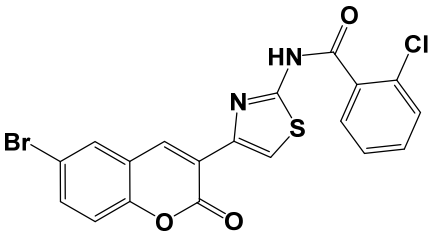

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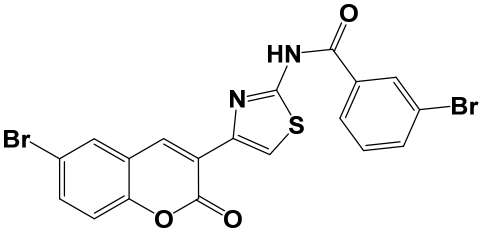

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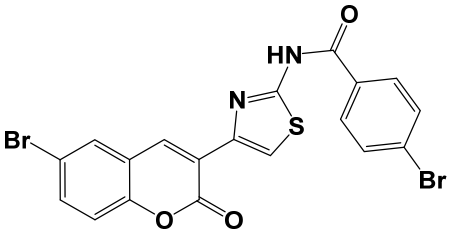

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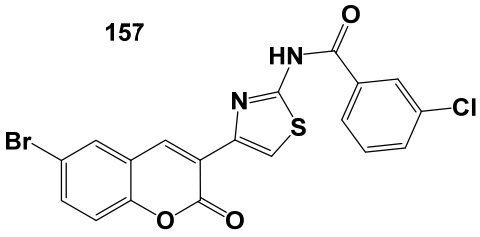

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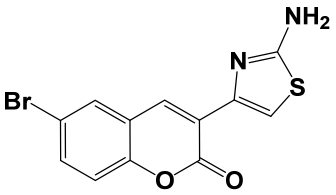

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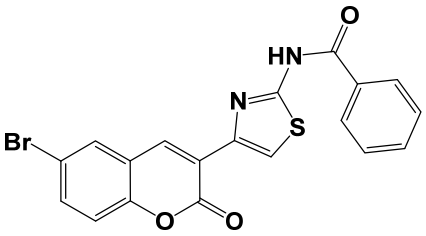
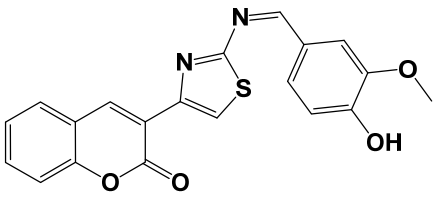


161

Jayashree *et al*. (2004) designed, synthesized and evaluated a series of Schiff bases of 2-amino-4-(3-coumarinyl) thiazole as potential NSAIDs using acetylsalicylic acid as standard and carrageenan-induced rat hind paw oedema method using diclofenac sodium as standard. The results showed that compounds **162, 163** and **164** showedanti-inflammatory activity at 38.00%, while compounds **165**, **166**, **167** displayed moderate activity at 37% compared to standard (44%) [66].



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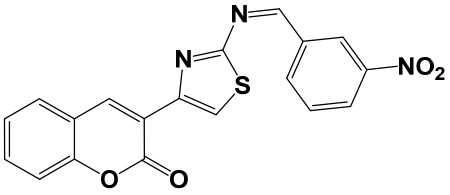

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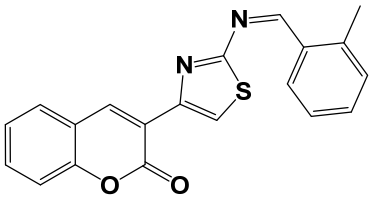

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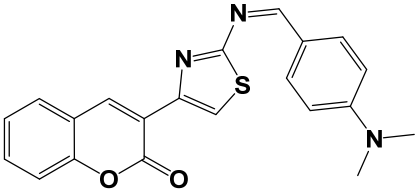

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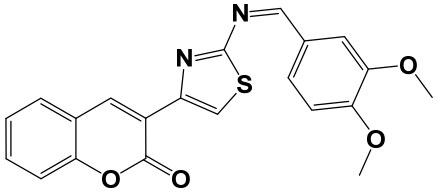

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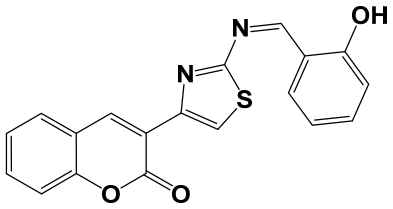
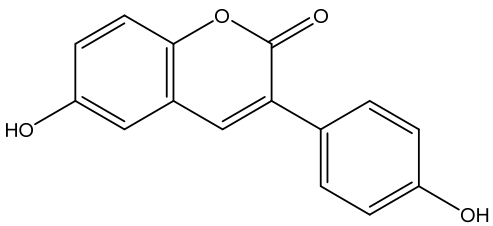


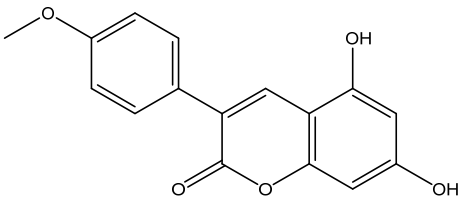
167

2.10 Coumarin scaffold as anantidiabetic agent

Hu *et al*.(2018) synthesized the 3-arylcoumarin derivatives as potential antidiabetic agents. The findings revealed that the effect of **168** and **169** target compounds was equipotent to that of the glibenclamide used as a reference drug *in-vivo*. More importantly, the target compound **169** offered a potential concept of drug design to develop therapeutic or preventive agents for diabetes and its complications[67].



168



169

3. CONCLUSION

Following the information provided in this review, it could be concluded that coumarin derivatives are flexible scaffolds with considerable therapeutic potential against several diseases such as cancer, microbial (bacterial, viral, mycobacterial) infections, diabetes, convulsion and oxidative stress-linked degenerative disorders. Their flexibility could

continuously be harnessed to discover, design, and develop novel moieties with enhanced therapeutic activities that could improve human health and overall well-being.

ACKNOWLEDGMENT
The authors would like to thank the Durban University of Technology for its support.

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ISSN 2170 - 1768 EISSN 2602-5132

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