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REVIEW

*2nd Heterocyclic Update*

# Overview on the recently developed coumarinyl heterocycles as useful therapeutic agents

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**Abstract** The chemical class of benzopyrones consists of a large number of compounds possessing the *benzene ring* fused with the oxygen containing *pyrone ring*. This class is further divided into the *benzo-γ-pyrone* i.e. flavonoids and the *benzo-α-pyrone* i.e. coumarins. Coumarins, the 2*H*-chromen-2-one and its related analogues exhibit a multitude of biological activities. Attempts made in the continuous chemical diversification of this parent nucleus have brought significant alterations in the biological activity among the generated compounds and therefore, this category of benzopyrones has been much exploited in the current medicinal chemistry research. Thus, it was thought worthwhile to present a review on the newly synthesised heterocyclic coumarinyl derivatives with their physicochemical parameters and biological activity, attempted by our co-workers. This review also creates a platform for highlighting approaches and strategies used in the chemical synthesis of coumarinyl compounds along with their biological activity relating to their structure.



*Abbreviations*: MIC, minimum inhibitory concentration; *Log p*, partition coefficient; *Pka*, dissociation constant

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## 1. Introduction

Coumarin and its related analogues are found to occur naturally as secondary metabolites in higher plants (Curir et al., 2007 and Lee, 2004) and also in micro-organisms (Xu et al., 2009). Simple compounds belonging to this chemical class, for instance 7-hydroxy coumarin (Fylaktakidou et al., 2004) and 4-hydroxy coumarin (Jung and Park, 2009) have been used as a backbone to attain chemically and biologically diverse agents. Some of the extensions made on the parent coumarin have generated newer chemical compounds which act against various targets like bacterial DNA *gyrase* (Musicki et al., 2003) and *topoisomerase* (Peng and Marians, 1993), *monoamine oxidase* (Chimenti et al., 2009), *acetylcholinesterase* (Anand et al., 2012), TNF-α (N Noolvi et al., 2011), IL-6 (Upadhyay et al., 2011), ROS pathway (Beillerot et al., 2008), macrophage migration inhibitory factor (MIF) (Orita et al., 2001), *casein kinase* 2 (CK2) (Chilin et al., 2008), *serine protease* (Pochet et al., 1996), *tyrosinase* (Fais et al., 2009), 5α-*reductase* (Fan et al., 2001), 17β-*hydroxysteroid dehydrogenase* type-1, *oxidoreductase*, *cyclooxygenase* and *lipoxygenase* (Geronikaki et al., 2008). In recent years, many structural modifications have been attempted at various positions of the coumarin ring system, Fig. A.1, (Anand et al., 2012; Beillerot et al., 2008 and Chilin et al., 2008) for example, at the **2nd** position (Liu et al., 2006), **3rd** position (Musa et al., 2011; Nikhilet al., 2012 and Sashidhara et al., 2011), **4th** position (Jung and Park, 2009), **5th** position (Noolvi et al., 2011), **6th** position (Starcevic et al., 2011), **7th** position (Manojkumar et al., 2009) and the **8th** position (Eissa et al., 2009). Some of the other modifications include, formation of coumarinyl metal complexes (Kostova and Momekov, 2006), synthesis of thiocoumarin (Kumar et al., 2005 and Reddy et al., 2005) and iminocoumarin analogues (Gorobets et al., 2002). Moreover, the increase in the number of coumarin derivatives synthesised and screened for biological activity has made it essential to study compounds under this chemical class as, such scaffolds possess significant therapeutic potentials. Thus, in this review we focus on some of the modifications attempted on the coumarin ring by our team over a period of time and discuss various synthetic approaches, physicochemical parameters and biological activity studies.

## 2. Synthesis of coumarin analogues

Coumarin and its related derivatives have been well reported to be synthesised via various mechanisms involved in reactions such as Claisen rearrangement (Ghantwal and Samant, 1999), Perkin reaction (Majumder and Majumder, 1993), Pechmann reaction (Upadhyay et al., 2008), Witting reaction (Harayama et al., 1994), Knoevenagel condensation (Shaabani et al., 2009) and Baylis–Hillman Reaction (Musa, 2002). In recent years, attempts have been made to prepare coumarinyl derivatives by other alternative methods such as solid phase synthesis (Liu et al., 2006), microwave irradiation (Kidwai et al., 2004) and ultrasonication (Di Cuollo et al., 1965). Further, the synthesis of coumarin hybrid with resveratrol (Fais et al., 2009) and estrogen (Musa et al., 2009) was among some of the strategies applied to arrive at potential therapeutic agents. In this review, we summarise various approaches used for the synthesis of different conjugated coumarin-heterocyclic ring systems by our team.

### *2.1. Combination of thiazole ring and coumarin nucleus*

Thiazoles have been extensively used in various chemical reactions as a parent, substituent as well as an intermediate

(Siddiqui et al., 2009). This heterocycle has also been reported for the synthesis of various thiazolyl coumarin derivatives (Arshad et al., 2011). The present review highlights the synthesis of various carboxamides and *Schiff's* bases of thiazolyl coumarin. A series of carboxamide derivatives of 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole ***1*** showing analgesic and anti-inflammatory activities were reported (Venugopala and Jayashree, 2003), Fig. A.2, Table B.1. Title compounds ***2–3*** were obtained by treating the parent amine ***1*** with different aromatic acid chlorides in pyridine medium and the acetyl derivative of ***1*** was prepared by treating the same with acetyl chloride. Parent amine ***1*** was prepared by the reaction between 3-bromoacetyl-6-bromocoumarin and thiourea. The former was prepared by bromination of 3-acetyl-6-bromocoumarin in alcohol free chloroform. 3-acetyl-6-bromocoumarin was prepared by mixing appropriate molar quantities of 5-bromosalicyaldehyde and ethylacetoacetate in the presence of piperidine as a catalyst. Further, three series of substituted *Schiff's* bases of aminothiazolyl coumarins were prepared and screened for their analgesic and anti-inflammatory activities, Figs. A.3–5, Table B.1. *Schiff's* bases of aminothiazolyl coumarin ***7–9*** (Jayashree et al., 2004), aminothiazolyl bromocoumarin ***10a–m*** (Venugopala and Jayashree, 2004) and aminothiazolyl chlorocoumarin ***12–14*** (Jayashree et al., 2005a,b), were synthesised by refluxing 2′-amino-4′-(3-coumarinyl) thiazole ***6***, 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole ***1*** and 2′-amino-4′-(6-chloro-3-coumarinyl) thiazole ***11*** with different aldehydes in absolute ethanol as medium, respectively. Parent amines, such as compounds ***6***, ***1*** and ***11*** were prepared by cyclising 3-acetylbromo-6*H*-coumarins ***5***, 3-bromoacetyl-6-bromocoumarin and 3-bromoacetyl-6-chlorocoumarin with thiourea, respectively. Bromination of 3-acetylcoumarin ***4*** (Munshi et al., 2004) in alcohol free chloroform yielded the compound ***5***. 3-acetylcoumarin ***4*** was prepared by mixing appropriate molar quantities of salicylaldehyde and ethylacetoacetate in the presence of piperidine as catalyst. Further, the variation in reaction time with respect to different substituents for formation of compounds belonging to the series ***10a–m*** was also reported (Venugopala and Jayashree, 2004). It was observed that, the order of reactivity of reactants when correlated with the reaction time required for product formation is given as; ***10i*** at lowest (60 min) < ***10b***, ***10f*** and ***10k*** (90 min) < ***10a***, ***10c***, ***10d***, ***10g***, ***10h***, ***10j***, ***10l*** and ***10m*** (120 min) < ***10e*** (150 min).

In addition to this, the synthesis of some of the *Schiff's* bases of aminothiazolyl bromocoumarin ***10a–m*** was also attempted by microwave irradiation on 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole ***1*** with substituted aromatic aldehydes in absolute ethanol at different time intervals (Venugopala and Jayashree, 2008). This method served as an alternative method for enhancing the rate and efficiency of the reaction. Further, comparison of the rate of product formation for all three methods namely, the conventional refluxing method (method A), conventional heating method (method B) and microwave-induced organic reaction enhancement method (MORE, method C) was done. It was found that, products were formed within 65–113 s at 260 W in case of method C when compared with method A and method B, illustrating the efficiency of microwave technique over conventional techniques.

Moreover, synthesis of substituted 2′-arylamino-4′-(3-coumarinyl) thiazoles and 2′-arylamino-4′-(6-bromo-3-coumarinyl) thiazoles, ***17a–u*** was also performed by condensation of 3-bromoacetylcoumarin with thiourea and substituted phenylthioureas (Venugopala et al., 2004), respectively, Fig. A.6, Table B.1. Initially, substituted salicylaldehydes were reacted with ethylacetoacetate in the presence of piperidine, to give 3-acetyl-6-H/bromocoumarins ***5***, ***15***, respectively. These on reaction with bromine in alcohol free chloroform yielded the respective 3-bromoacetyl-6-bromocoumarin ***16***.

### *2.2. Combination of triazole-thiadizine ring and coumarin nucleus*

Triazoles such as 1, 2, 4-triazole have been reported for various pharmacological activities like anti-bacterial (Bhat et al., 2001), anti-viral and anti-fungal (Al-Masoudi et al., 2006). A few triazolyl coumarins have been reported so far along with their biological activities (Shi and Zhou, 2011). Further, some thiaziadinyl coumarins possessing biological activity were also reported (Rao and Reddy, 2009). It was thought worthwhile to bring linkers on the existing coumarin nucleus with other heterocyclic system and in our studies we have tried using triazole-thiadiazinyl ring system, Fig. A.7, Table B.1. A series of novel triazolo-thiadiazinyl bromocoumarin derivatives ***18a–k*** (Jayashree et al., 2005a,b), triazolo-thiadiazinyl chlorocoumarins ***19a–k*** (Jayashree et al., 2006) and triazolo-thiadiazinyl coumarins ***20a–l*** (Jayashree et al., 2007) were prepared and reported. Here, substituted triazole and 3-bromoacetyl-6-bromocoumarin ***16***, 3-bromoacetyl-6-chlorocoumarin and 3-acetylbromo-6*H*-coumarins ***5*** were refluxed with dimethyl formamide in absolute ethanol medium and catalytic pyridine for about 120 min, respectively, to yield title compounds. For the synthesis of 1, 2, 4-triazoles, substituted aromatic acids were converted to their corresponding methyl esters, acid hydrazides, potassium dithiocarbamate salts as intermediates.

### *2.3. Preparation of coumarinyl chalcones*

Chalcones or 1, 3-diaryl-2-propen-1-ones consist of open-chain flavonoids in which two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl system. Various substituted natural and synthetic chalcones have shown to exhibit significant pharmacological potential (Sahu et al., 2012). In our research, coumarinyl chalcones were prepared and screened for anti-bacterial activity, as shown in Fig. A.8, Table B.1. They were also used as intermediates for further synthesis of other test compounds. Synthesis of coumarinyl chalcones was undertaken by means of both conventional as well as microwave method (Jayashree et al., 2008). Title compounds ***21–22*** were obtained by refluxing as well as by microwave irradiation of substituted 6-*(H/chloro/bromo)* acetylcoumarins and different aromatic aldehydes with ethanol in the presence of piperidine. Different 6-(substituted) acetylcoumarins (Chopra et al., 2006) were synthesised by means of Pechmann reaction, involving the reaction of 5-(substituted) salicylaldehydes with ethylacetoacetate in the presence of piperidine, at freezing temperature for 120–180 min. The application of microwave energy to achieve coumarinyl chalcones significantly reduced the reaction time from 420 min of reflux to 2–3 min of microwave heating along with improved product yield.

On the contrary, preparation of some novel coumarinyl chalcones ***23a–f*** was achieved by reaction between 3-(substi-

tuted) acetylcoumarins with different aromatic aldehydes in the presence of 30% ethanolic sodium hydroxide (Jayashree et al., 2009).

### 2.4. Combination of pyrazoline ring and coumarin nucleus

Substituted pyrazolines have been extensively reviewed for a range of biological activities (Shaaban et al., 2012). Pyrazolinyl coumarins have also been synthesised and reported for their biological activities (Khode et al., 2009). Synthesis of some of the 5-(substituted phenyl)-1-phenyl (2-pyrozoline-3″-yl) substituted coumarins was attempted (Jayashree et al., 2008), as shown in Fig. A.9, Table B.1. The title compounds ***24–25*** were achieved by refluxing different substituted coumarinyl chalcones ***21–22*** with phenyl hydrazine in the presence of piperidine as catalyst in ethanol for about 600 min approximately equivalent to 10 h of conventional heating.

### 2.5. Combination of pyridine ring and quinoline with coumarin nucleus

Pyridine fused coumarins have been synthesised and tested for biological activities such as anti-*cholinesterase* and anti-microbial (Alipour et al., 2012). We reported the synthesis of some of the useful heterocyclic substitutions on coumarin with pyridine and quinoline, Fig. A.10, Table B.1. 3-coumarinoyl pyridinium bromides ***26a–l*** and 3-coumarinoyl quinolinium bromides ***27a–c*** were prepared by 2 h of refluxing followed by reaction at room temperature for 4–5 h in the presence of dry toluene between 3-bromoacetylcoumarins and methyl and ethyl esters of nicotinic acid and isonicotinic acid to give ***26a–l*** and with quinoline to give ***27a–c*** (Porwal et al., 2010). Also, preparation of a series of substituted pyridinyl coumarins ***28a–g*** was reported (Jayashree et al., 2010). Few of the compounds from the synthesised ***26a–l*** series were taken in glacial acetic acid and ammonium acetate and refluxed at 130 °C for 6 h with different chalcones to obtain 7 derivatives of pyridinyl coumarins ***28a–g***.

### 2.6. Other substituted coumarin analogues

Synthesis of novel coumarin analogues such as ***29–32*** was also carried out (Jayashree et al., 2011), as shown in Fig. A.11, Table B.1. Analogues such as ***29a–b***, ***31a–b*** and ***32a–b*** were obtained by benzoylation of coumarins using different acid chlorides in dry pyridine as catalyst. The parent coumarins were obtained by reaction of different substituted resorcinols with redistilled ethylacetoacetate in the presence of concentrated sulphuric acid, initially for 2 h at low temperatures but later maintained at room temperature for 18 h. Carboxamide analogues ***30a–b*** were obtained by reacting amino coumarin with 5-amino salicylic acid. Amino coumarin was prepared by conversion of 6-nitro-3-acetylcoumarin in aqueous ammonia solution by aqueous sodium hydrosulfite, at boiling temperature for 15 min. The former was prepared by treating 5-nitrosalisaldehyde and ethylacetoacetate in absolute alcohol in the presence of catalytic piperidine.

Alternatively, an attempt was made to generate functionally diverse coumarins with the help of microbiology technique, namely biotransformation (Das and Rosazza, 2006). Here, instead of using the conventional synthetic route for obtaining coumarin, it was thought to undertake certain functional group modifications/bioconversions of simple coumarin substrates using micro-organisms. As a result, experiments on the microbial biotransformation of some of the hydroxy and ethoxy substituted coumarins were performed using different bacterial and fungal strains. The microbial biotransformation of hydroxy and ethoxy substituted coumarin substrates under suitable fermentation conditions, led to their successful bioconversion into methoxy and hydroxy substituted coumarin derivatives, respectively (Nigam et al., 2013).

## 3. Biological activity

A wide range of substituted coumarins are reported to possess anti-protozoal (Oketch-Rabah et al., 1997), anti-fungal (Al-Amiery et al., 2012), anti-bacterial (Manojkumar et al., 2009), anti-Parkinsonism (Binda et al., 2007), anti-Alzheimer's (Anand et al., 2012), anti-pyretic, analgesic and anti-inflammatory (Eissa et al., 2009), anti-oxidant (Beillerot et al., 2008), anti-coagulant (Jung and Park, 2009), anti-depressant (Sashidhara et al., 2011), anti-HIV (Kostova et al., 2006), anti-tuberculosis (Upadhyay et al., 2011), anti-viral (Neyts et al., 2009) and anti-cancer activities (Devji et al., 2011). Heterocyclic systems substituted on coumarin at the 3rd position have also shown promising biological activities (Nikhil et al., 2012). Here, work carried out on such systems with their biological applications has been presented.

### 3.1. Analgesic and anti-inflammatory

The analgesic and anti-inflammatory activities of synthesised test compounds were evaluated in *in vivo* models using the acetic acid-induced abdominal constriction method (Collier et al., 1968) and the carrageenan induced rat hind paw oedema method (Kulkarni et al., 1986). Series of carboxamides of 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole ***1–3***, were screened for analgesic and anti-inflammatory activities (Venugopala and Jayashree, 2003). Among all carboxamide derivatives tested, it was found that compounds bearing substitutions at *meta*, *ortho* and *para* positions such as ***2c***, ***2e*** and ***2h*** showed analgesic activity at 41.66% better than that of the standard acetylsalicylic acid at 37.45%. The effect of the *nitro* group on the analgesic activity was more pronounced at *meta* position among all derivatives screened. Whereas, compounds bearing *chloro* and *bromo* substitutions were found to be more effective as analgesics, when substituted at *ortho* and *para* positions in 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole carboxamides. However, overall effect of substitutions clearly suggested the order of increase in analgesic activity with *meta* > *para* > *ortho* position when compared to that of the parent carboxamide ***2a***. Further, test compounds such as ***1*** and ***3*** showed analgesic activity at 6.95% and 26.53%, respectively when compared to their carboxamide analogues ***2a–j*** at 32.36–41.66%. From this study, it was clearly understood that, the substituted aryl carboxamide derivatives of 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole were more potent as analgesics than their counterparts. Alternatively, the anti-inflammatory activity of carboxamide derivatives ***2a–j*** was found to be feeble when compared with the parent compound ***1*** and carboxamide ***3***, showing anti-inflammatory potential at 46.96% and 53.59% respectively against the standard phenylbutazone at 45.30%. However, among the

carboxamides of 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole the anti-inflammatory activity was found to be relatively better for *meta* > *para* > *ortho* substituents. Further, compounds with *bromo* and *chloro* substitutions on the *meta* position such as ***2g*** and ***2j*** showed activity better than the *meta-nitro* derivative ***2c*** and remaining test compounds. It was also found that, the *N*-acetyl derivative of carboxamide ***3*** showed relatively lower analgesic and anti-inflammatory activities when compared with that of other substituted aryl carboxamide derivatives of 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole.

Further, when three series *Schiff's* bases of 2′-amino-4′-(3-coumarinyl) thiazole ***6*** were screened for analgesic and anti-inflammatory activities (Jayashree et al., 2004; Jayashree et al., 2005a,b and Venugopala and Jayashree, 2004), it was found that *chloro* and *bromo* substitutions at the 6th position on the parent aminothiazolyl coumarin ***6*** enhanced the analgesic potential of their *Schiff's* bases when compared with *Schiff's* bases of the parent compound ***6***. The analgesic activity of *Schiff's* bases of 2′-amino-4′-(6-*H*/*chloro*/*bromo*-3-coumarinyl) thiazoles was found to be in the order with 6-*chloro* substituted ***12a–m–14*** > 6-*bromo* substituted ***10a–m*** > 6-*H*/unsubstituted ***7a–j–9***. Further, findings also revealed for the improvement in the analgesic activity of *Schiff's* bases of 2′-amino-4′-(6-substituted-3-coumarinyl) thiazole presumably because of the retention of different substituents at *ortho*, *meta* and *para* positions as compared to the 2′-amino-4′-(6-*H*/unsubstituted-3-coumarinyl) thiazole series. Among the *para* and *meta* di-substituted *Schiff's* bases of aminothiazolyl coumarin, the test compound ***12f***, a di-*methoxy* derivative of the parent 2′-amino-4′-(6-chloro-3-coumarinyl) thiazole ***11*** showed analgesic activity better than test compounds ***10l*** and ***7f***, which were also di-*methoxy* derivatives, but from 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole ***1*** and 2′-amino-4′-(3-coumarinyl) thiazole ***6***, respectively. Further, the test compounds such as ***8–9*** and ***13–14*** were found to show feeble analgesic activity compared to that of the substituted aryl *Schiff's* bases of aminothiazolyl coumarin. The test compound ***12e***, showing more than two-fold activity than that of the standard analgesic, exhibited maximum analgesic activity among the *Schiff's* bases of aminothiazolyl coumarin, thereby highlighting the effect of tri-*methoxy* substitution at *ortho*, *para* and *meta* positions of the aryl group of 2′-amino-4′-(6-chloro-3-coumarinyl) thiazole nucleus. However, the trend observed for the anti-inflammatory activity of the *Schiff's* bases of substituted aminothiazolyl coumarin was paradoxical. Here, the *Schiff's* bases of 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole ***10a–m*** were found to be more active than 6-*chloro* substituted ***12a–m–14*** and 6-*H*/unsubstituted ***7a–j–9*** analogues. Further, all the substituted aryl derivatives of 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole except, the test compound ***10k***, an unsubstituted aryl derivative of the parent, showed anti-inflammatory activity more than that of the standard phenylbutazone. However, the most active anti-inflammatory derivative among all *Schiff's* bases of aminothiazolyl coumarin was found to be the compound ***10b***, an *ortho*, *para, meta* tri-*methoxy* aryl derivative of 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole. The screening of anti-inflammatory and analgesic activities of different series of synthesised *Schiff's* bases of aminothiazolyl coumarin, clearly illustrated that, the substitution made with the tri-*methoxy* group at *ortho*, *meta* and *para* positions of the aryl *Schiff's* bases of 2′-amino-4′-(6-substituted-3-coumarinyl) thiazoles as in case of test compounds ***10b*** and ***12e***, greatly increased the analgesic as well as anti-inflammatory potential of the respective scaffolds. Further, *chloro* and *bromo* substitutions at the 6th position of the 2′-amino-4′-(3-coumarinyl) thiazole, displayed improved analgesic and anti-inflammatory activities over their unsubstituted counterparts. Thus, from variation in response to the analgesic and anti-inflammatory activities of these compounds, it was understood that, the *Schiff's* bases of aminothiazolyl coumarin would interact better with different molecular targets involved in understanding analgesic and anti-inflammatory pathways.

In the quest to develop potential NSAIDs, evaluation of series of substituted 2′-arylamino-4′-(3-coumarinyl) thiazoles and 2′-arylamino-4′-(6-bromo-3-coumarinyl) thiazoles, ***17a–u*** in terms of analgesic and anti-inflammatory activities was done (Venugopala et al., 2004). It was observed that the substitution of the *bromo* group at the 6th position of the 2′-arylamino-4′-(3-coumarinyl) thiazoles did not bring any significant change in their analgesic as well as anti-inflammatory activities as compared to the standard ibuprofen at 74% activity and diclofenac sodium at 72.98% activity. Therefore, it was understood that the substituted aryl amino coumarinyl thiazoles were not effective ligands for these activities. However, from other studies it was found that, the series of their *Schiff's* bases ***12a–m–14***, ***10a–m*** and ***7a–j–9*** had proved to be much better ligands for analgesic and anti-inflammatory activities. Few of the coumarinyl chalcones were also tested for analgesic and anti-inflammatory activities (Jayashree et al., 2009). These compounds were also randomly subjected to anti-oxidant activity using the DPPH radical scavenging method but, none of the compounds exhibited anti-oxidant potential. In contrast, among the different 6-(*chloro*/*bromo*/*H*)-aryl substituted coumarinyl chalcones, test compounds ***21k*** and ***21g*** bearing *chloro* and *bromo* groups on the 6th position of benzopyrone nucleus were not just equally active as analgesics but were also highly active at 92.30% activity as compared to both the standard diclofenac at 74% and 6-*H*/unsubstituted derivatives ***21b*** and ***22a*** at 76–78%. However, randomly selected chalcones screened for anti-inflammatory activity did show activity but, none of the coumarinyl derivatives were nearly active as anti-inflammatory standard ibuprofen at 64.70%. It could be suggested from the screening of coumarinyl chalcones that the halogen substitution at the 6th position of benzopyrone nucleus had a greater influence on the analgesic activity than unsubstituted analogues. It can be understood that these chalcones may be acting through mutually exclusive molecular pathways involved for the three activities.

Screening of few of the 5-((substituted phenyl)-1-phenyl-2-pyrozoline-3″-yl)-6-halogen substituted coumarins for analgesic and anti-inflammatory activities (Jayashree et al., 2008), such as ***24c*** and ***25a*** both at the 6th position unsubstituted derivatives, has shown anti-inflammatory activity comparable to the standard aspirin. Moreover, test compounds such as ***24c***, ***24e***, ***24l*** and ***25a–b*** exhibited potent analgesic activity as compared to the standard aspirin. This scaffold of substituted coumarin consisting of 5-(substituted phenyl)-1-phenyl-2-pyrozoline-3″-yl)-6-halogen could be thereof undertaken for further modifications to arrive at potentially active analgesics and anti-inflammatory agents.

### 3.2. Anti-bacterial activity

The evaluation of anti-bacterial activity of substituted coumarins synthesised was performed *in vitro* by measuring the zone

of inhibition using the agar diffusion method (Di Cuollo et al., 1965) and also by measurement of minimum inhibitory concentration (MIC) (Ericsson et al., 1960), using two fold dilutions in 96-well plate, against some of the gram positive strains like *Bacillus subtilis* and *Staphylococcus aureus* and gram negative strains like *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

*Schiff's* bases of amino thiazolyl bromocoumarins were tested for anti-bacterial activity against *B. subtilis* and *E. coli* (Venugopala and Jayashree, 2008). The MIC of all test compounds showed promising activity and the compound ***10a***, equally active as the standard ampicillin exhibited MIC in the range of 141–147 μg and the compound ***10g*** exhibited weak activity at 280 μg when compared to that of the standard ampicillin at 145 μg and 135 μg against *B.subtilis* and *E. coli*, respectively. *Schiff's* bases of such 2′-amino-4′-(6-bromothiazolyl bromo-3-coumarinyl) thiazole may not be suitable candidates as potent anti-bacterial agents however, there need to be extensive studies on their structural modifications.

On evaluation of anti-bacterial activity of series of substituted triazolo-thiadiazinyl coumarin derivatives when studied against *B. subtilis*, *S. aureus*, *E. coli*, *K. pneumoniae* and *P. aeruginosa* (Jayashree et al., 2005a,b, 2006, 2007), it was found that, compounds ***18i***, ***19i*** and ***20j*** bearing the *pyridinyl* group at *para* position of the substituted phenyl ring on the 5th position, possessed better anti-bacterial activity among all the derivatives of 6-*bromo*/*chloro*/*H* substituted series of compounds ***18a–k***, ***19a–k*** and ***20a–l***, against all bacterial strains as compared to the standard amoxicillin and gentamycin. Alternatively, 2-chlorophenyl derivatives of 6-*bromo*/*chloro*/*H* substituted 3-(5-(substituted phenyl)-1, 2, 4-triazolo-[3, 4-b] [1, 3, 4]-thiadiazin-5-yl)-2H-1-benzopyran-2-ones were among the least active anti-bacterial. However, a clear distinction of the effect of 6-*bromo*/*chloro*/*H* substituted 3-(5-(substituted phenyl)-1, 2, 4-triazolo-[3, 4-b] [1, 3, 4]-thiadiazin-5-yl)-2H-1-benzopyran-2-ones on the anti-bacterial activity could not be established owing to a mixed activity profile for all derivatives.

Further, when anti-bacterial activity of some of the coumarinyl chalcones against *B. subtilis*, *S. aureus*, *E. coli* and *K. pneumoniae* was performed (Jayashree et al., 2009), they were found to be weak to moderately active as anti-bacterial, however, the test compound ***23d***, a di-*methoxy* substituted 6-chlorocoumarinyl chalcone showed activity as compared to the standard streptomycin against all bacterial strains. This scaffold from the coumarinyl chalcone series could be further exploited to enhance and develop potential anti-bacterial agents.

The preliminary screening of certain 3-coumarinoyl pyridinium bromide ***26a–l*** and 3-coumarinoyl quinolium bromide derivatives ***27a–c*** against *B. subtilis*, *S. aureus*, *E. coli* and *P. aeruginosa* (Jayashree et al., 2010; Porwal et al., 2010), showed that these compounds were either inactive or moderately active as anti-bacterial on a few strains. The anti-bacterial sensitivity of series of derivatives of 3-coumarinoyl pyridinium bromide and 3-coumarinoyl quinolium bromide ***26–27*** against various strains was found in order of; *S. aureus* > *B. subtilis* > *E. coli* > *P. aeruginosa* as compared to the standard amoxicillin and gentamycin, which were active against all the strains. Thus, the preliminary screening revealed that such compounds were better anti-bacterial agents against gram positive strains as compared to gram negative organisms. Test compounds such as ***26a***, ***26c***, ***26d*** and ***26i***, bearing 6-*chloro*/*H* on the benzopyrone ring showed better activity against all bacterial strains as compared to the 6-*bromo* analogues and were further selected for determination of MIC at 100 percent growth inhibition. However, test compounds ***26a*** and ***26d*** were found to be equally active as the standard amoxicillin against *E. coli* and gentamycin against *B. subtilis*, respectively. Therefore, it could be inferred that compounds ***26a***, ***26c***, ***26d*** and ***26i*** were not potential enough against all bacterial strains when compared to the standard gentamycin. Also, the quinolium bromide derivatives of coumarin were less active as anti-bacterial when compared to pyridinium bromide derivatives. However, the same compounds did show greater anti-bacterial activity against *E. coli* with MIC better than standard amoxicillin.

Further, some of the substituted pyridinyl coumarins such as ***28b***, ***28d***, ***28f*** and ***28g*** were also evaluated for their anti-bacterial activity. All compounds showed maximum activity against *B. subtilis*, moderate against *E. coli* and minimum against *S. aureus* as compared to standard gentamycin. Test compounds such as ***28b***, ***28f*** and ***28g*** exhibited 100 percent growth inhibition against *B. subtilis* at MIC value same as that of the gentamycin. It was found that, all the four test compounds were highly active against *E. coli* with MIC value better than standard amoxicillin.

### 3.3. Miscellaneous

Evaluation of some of the salicylate derivatives ***29–32*** of coumarins for their anti-diabetic potential was attempted (Jayashree et al., 2011) based on the rationale (Hogale et al., 1987). When test compounds were screened for this activity by *in vitro* non-enzymatic glycosylation of haemoglobin method and by advanced glycation end product inhibition method (Jedsadayanmata, 2005) using quercetin as standard, the results showed that they were poor candidates for anti-diabetic activity.

## 4. Physicochemical parameters

### 4.1. Hydrophobicity

Hydrophobicity is generally parameterised by partition coefficient (*log p*), determined by partitioning of a drug between organic and aqueous phases. For our experiments, this physical constant was determined on some of the synthesised coumarin derivatives by the classical shake flask method (Sangster, 1989), using *n*-octanol/*n*-heptanol and phosphate buffer (*pH* 7.4). Determination of *log p* for the series of compounds such as ***18–20*** was carried out (Jayashree et al., 2005a,b, 2006, 2007). Substitution of halogens at 6th position on the parent compound ***20a*** resulted in an increase in the partition coefficient, which was clearly evident as the corresponding compounds such as ***18a*** and ***19a*** showed *log p* value in the range of 1.27–1.41 as compared to that of the parent compound at 1.18. The results also showed that triazolo thiadiazinyl 6-*bromo* substituted coumarins were more hydrophobic than their 6-*chloro* and 6-*H* counterparts. Substitution of the *hydroxy* group irrespective of its positions in the ring led to a decrease in the lipophilic character of compounds in the case of 6-*chloro*/*bromo*/*H* series. Interestingly, *para-methyl* substituted compounds such as ***18h*** and ***20i*** with the highest partition

coefficient among all did not possess any promising anti-bacterial activity. However, compounds bearing the *pyridinyl* group at *para* position, such as ***18i***, ***19i*** and ***20j***, having optimum lipophilicity with *log p* in the range of 1.04–1.22, showed potent anti-bacterial activity as compared to that of the standard amoxicillin and gentamycin. Also, compounds bearing *ortho*, *para-dichlorophenoxy* group such as ***18k***, ***19k*** and ***20l*** possessed partition coefficient in the range of 1.34–1.47 and were moderately active as anti-bacterial. The compounds with minimum *log p* such as ***18d–e***, ***19d–e*** and ***20e–f*** were least active against bacterial strains. These findings helped in understanding the effect of lipophilicity in terms of *log p* on the anti-bacterial activity of triazolo thiadiazinyl coumarins. Further, compounds with *log p* values above and below the optimum range however, did not show any significant biological activity. From our study it was understood that, to develop a potentially useful anti-bacterial agent using this scaffold, compounds should bear at least an optimum *log p* value as seen in case of *pyridinyl* substituted compounds.

To understand the pattern of lipophilic character of coumarinyl pyrazolines, few of the test compounds such as ***24a***, ***24e***, ***24j***, ***25a*** and ***25b*** were randomly selected (Jayashree et al., 2008). Presence of an electronegative atom at the 6th position of coumarin moiety in such studies greatly influenced *log p* value. However, the average range of *log p* for *bromo/chloro* and unsubstituted derivatives was found to be 0.08, 0.02 and 0.03, respectively. The increase in the lipophilicity of coumarinyl pyrazolines was found to be in the order of: *bromo* > *chloro* ⩾ unsubstituted compounds. A similar pattern was also observed for compounds such as ***25a*** and ***25b***. Further, to clearly understand the effect of various substituted coumarinyl pyrazolines on the partition coefficient, some more related studies may be required in future. Further, the partition coefficient of substituted pyridinyl and quinolium coumarin derivatives was also studied (Jayashree et al., 2010). The *log p* value of substituted pyridinyl coumarins varied with the position of substituents on the pyridine ring. Compounds such as ***26a–c***, bearing the *para-ethoxy carbonyl* group were less lipophilic than their corresponding *meta* analogues ***26d–f***. Alternatively, other derivatives bearing the *para-methoxy* group, for example ***26g–i*** possessed higher partition coefficient as compared to their corresponding *meta* derivatives ***26j–l***. Further, in case of quinolium bromide salts of coumarin, compounds ***27b–c*** bearing halogen in form of the *chloro/bromo*

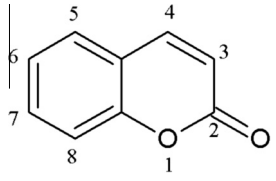


**Figure A.1** Parent nucleus of coumarin.

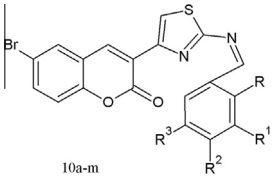


**Figure A.4** Synthesised amino bromocoumarin-thiazole *Schiff's* bases.

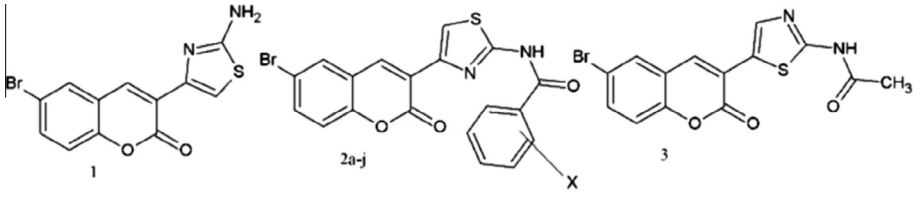


**Figure A.2** Synthesised coumarin-thiazole carboxamide derivatives.

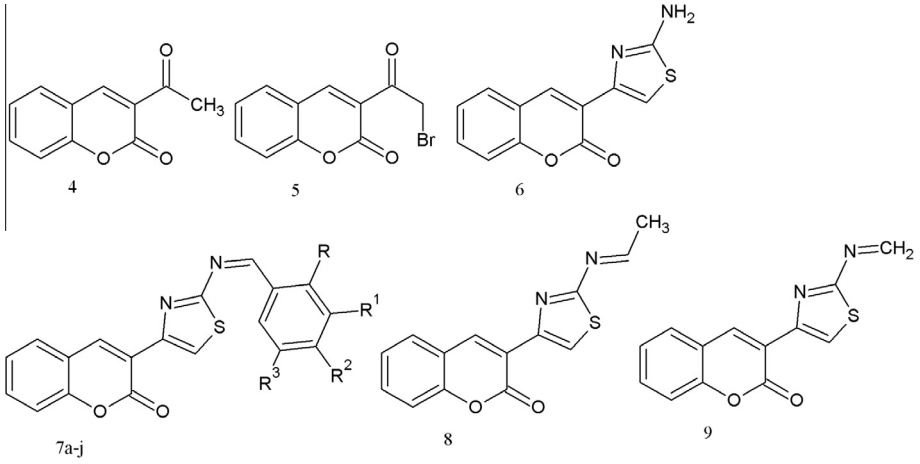


**Figure A.3** Synthesised amino coumarin-thiazole *Schiff's* bases.

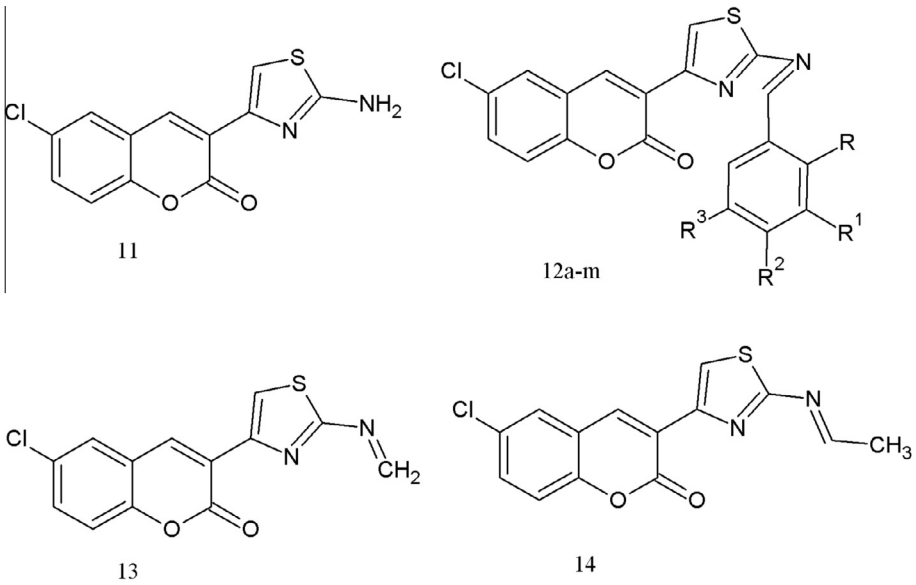


**Figure A.5** Synthesised amino chlorocoumarin-thiazole *Schiff's* bases.

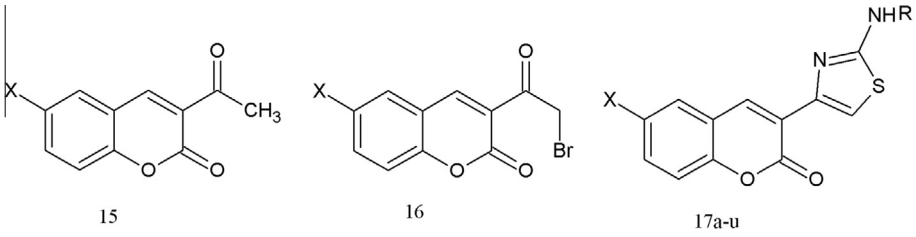


**Figure A.6** Synthesised arylamino-bromocoumarin-thiazole derivatives.

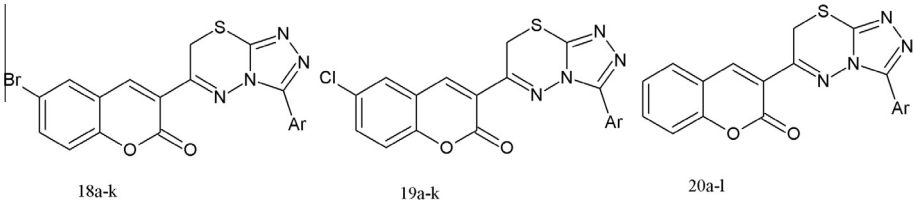


**Figure A.7** Synthesised triazolo-thiadiazinyl coumarin derivatives.

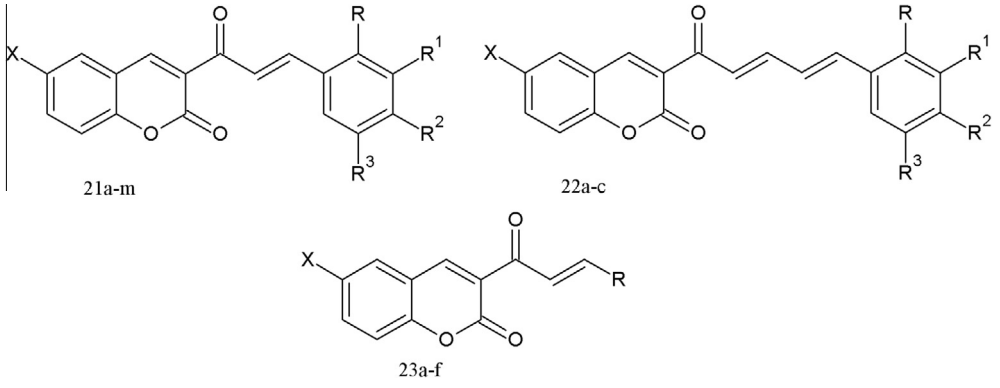


**Figure A.8** Synthesised coumarinyl chalcones derivatives.

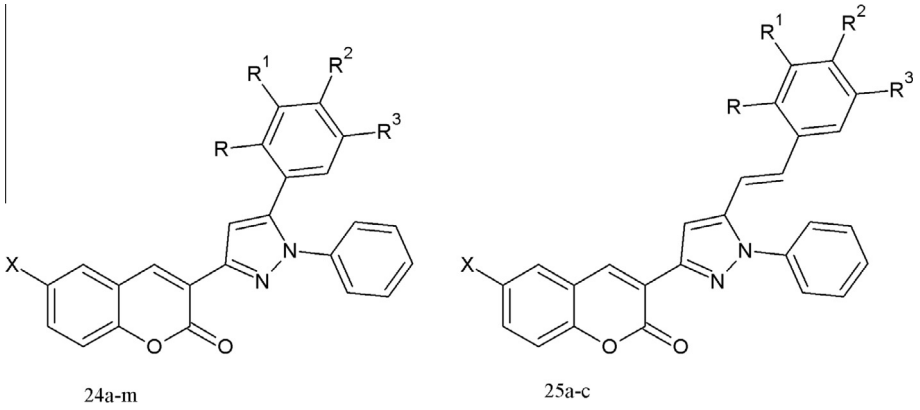


**Figure A.9** Synthesised pyrazoline-coumarin derivatives.

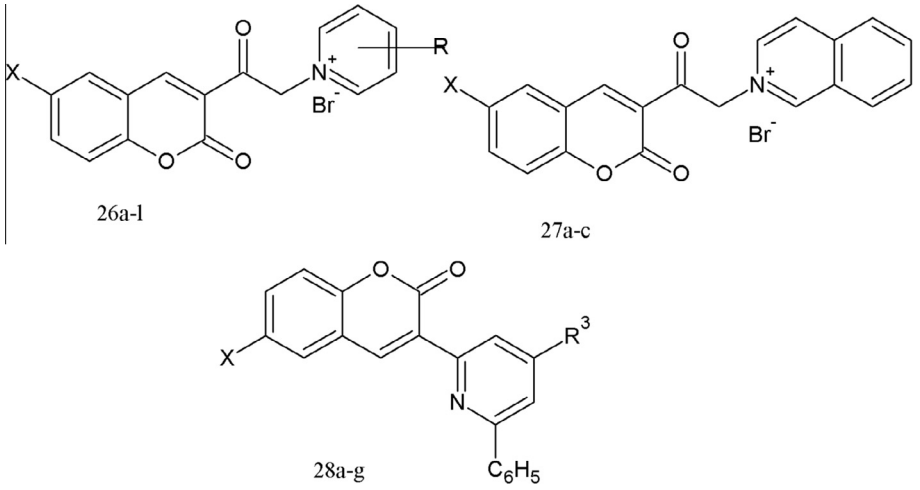


**Figure A.10** Synthesised pyridine/quinoline-coumarin derivatives.

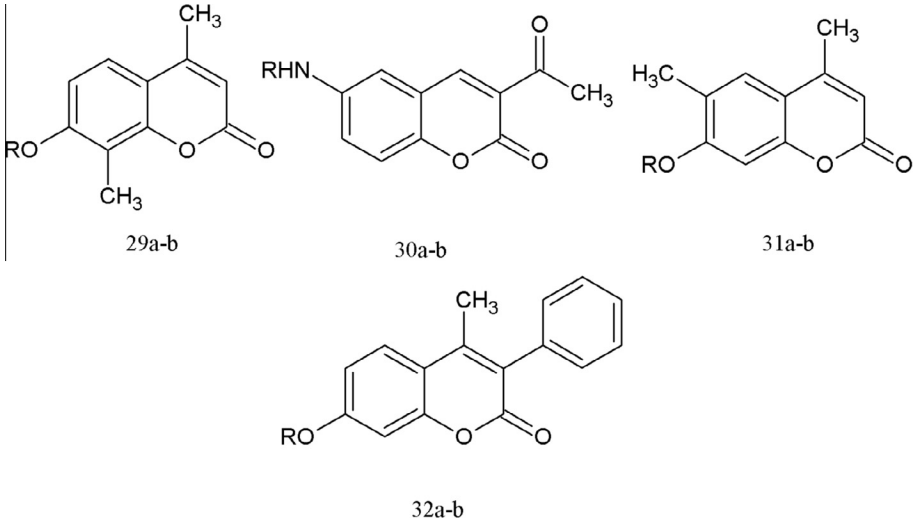


**Figure A.11** Few other novel coumarin derivatives which were synthesised.

**Table B.1** Various coumarin derivatives synthesised and their physicochemical characteristics.

| Code | X | R | $R^1$ | $R^2$ | $R^3$ | Ar | Yield (%) | Melting point (°C) |
|---|---|---|---|---|---|---|---|---|
| 1 | - | - | - | - | - | - | 81 | 211 |
| 2a | H | - | - | - | - | - | 82 | 240 |
| 2b | p-$NO_2$ | - | - | - | - | - | 74 | 263 |
| 2c | m-$NO_2$ | - | - | - | - | - | 75 | 250 |
| 2d | o-$NO_2$ | - | - | - | - | - | 69 | 180 |
| 2e | o-Cl | - | - | - | - | - | 76 | 220 |
| 2f | p-Cl | - | - | - | - | - | 78 | 285 |
| 2g | m-Br | - | - | - | - | - | 63 | 275 |
| 2h | p-Br | - | - | - | - | - | 59 | 266 |
| 2i | o-Br | - | - | - | - | - | 61 | 218 |
| 2j | m-Cl | - | - | - | - | - | 72 | 266 |
| 3 | - | - | - | - | - | - | 77 | 265 |
| 4 | - | - | - | - | - | - | 96 | 120 |
| 5 | - | - | - | - | - | - | 76 | 162 |
| 6 | - | - | - | - | - | - | 70 | 220 |
| 7a | - | H | $OCH_3$ | OH | H | - | 55 | 200 |
| 7b | - | $NO_2$ | H | H | H | - | 53 | 262 |
| 7c | - | H | $NO_2$ | H | H | - | 50 | 195 |
| 7d | - | H | H | $N(CH_3)_2$ | H | - | 40 | 240 |
| 7e | - | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | - | 42 | 185 |
| 7f | - | H | $OCH_3$ | $OCH_3$ | H | - | 45 | 265 |
| 7g | - | OH | H | H | H | - | 50 | 193 |
| 7h | - | $CH_3$ | H | H | H | - | 52 | 280 |
| 7i | - | H | H | Cl | H | - | 55 | 284 |
| 7j | - | OH | H | H | Br | - | 50 | 260 |
| 8 | - | - | - | - | - | - | 58 | 146 |
| 9 | - | - | - | - | - | - | 56 | 187 |
| 10a | - | H | H | Cl | H | - | 62 | 255 |
| 10b | - | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | - | 71 | 234 |
| 10c | - | $NO_2$ | H | H | H | - | 58 | 243 |
| 10d | - | H | $NO_2$ | H | H | - | 60 | 256 |
| 10e | - | H | $OCH_3$ | OH | H | - | 66 | 235 |
| 10f | - | OH | H | H | Br | - | 66 | 276 |
| 10g | - | H | H | $N(CH_3)_2$ | H | - | 69 | 180 |
| 10h | - | $CH_3$ | H | H | H | - | 64 | 218 |
| 10i | - | OH | H | H | H | - | 68 | 224 |
| 10j | - | $OCH_3$ | H | H | H | - | 62 | 150 |
| 10k | - | H | H | H | H | - | 78 | 225 |
| 10l | - | H | $OCH_3$ | $OCH_3$ | H | - | 67 | 214 |
| 10m | - | H | H | $NO_2$ | H | - | 64 | 264 |
| 11 | - | - | - | - | - | - | 88 | 235 |
| 12a | - | H | H | Cl | H | - | 59 | 291 |
| 12b | - | H | H | H | H | - | 73 | 251 |
| 12c | - | OH | H | H | H | - | 62 | 289 |
| 12d | - | H | H | $NO_2$ | H | - | 68 | 282 |
| 12e | - | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | - | 69 | 221 |
| 12f | - | H | $OCH_3$ | $OCH_3$ | H | - | 68 | 217 |
| 12g | - | H | $OCH_3$ | H | H | - | 66 | 276 |
| 12h | - | $OCH_3$ | H | H | H | - | 70 | 204 |
| 12i | - | H | H | $N(CH_3)_2$ | H | - | 78 | 218 |
| 12j | - | $NO_2$ | H | H | H | - | 65 | 262 |
| 12k | - | H | $NO_2$ | H | H | - | 67 | 289 |
| 12l | - | H | Cl | H | H | - | 63 | 231 |
| 12m | - | Cl | H | H | H | - | 67 | 247 |
| 13 | - | - | - | - | - | - | 67 | 218 |
| 14 | - | - | - | - | - | - | 61 | 211 |
| 15 | Br | - | - | - | - | - | 94 | 220 |
| 16 | Br | - | - | - | - | - | 80 | 205 |
| 17a | H | H | - | - | - | - | 78 | 223 |
| 17b | H | $C_6H_5$ | - | - | - | - | 77 | 204 |

**Table B.1** (*continued*)

| Code | X | R | R1 | R2 | R3 | Ar | Yield (%) | Melting point (°C) |
|---|---|---|---|---|---|---|---|---|
| 17c | H | o-$ClC_6H_4$ | - | - | - | - | 67 | 282 |
| 17d | H | m-$ClC_6H_4$ | - | - | - | - | 66 | 248 |
| 17e | H | p-$ClC_6H_4$ | - | - | - | - | 76 | 225 |
| 17f | H | o-$CH_3C_6H_4$ | - | - | - | - | 58 | 248 |
| 17g | H | m-$CH_3C_6H_4$ | - | - | - | - | 72 | 215 |
| 17h | H | p-$CH_3C_6H_4$ | - | - | - | - | 75 | 233 |
| 17i | H | p-$BrC_6H_4$ | - | - | - | - | 65 | 229 |
| 17j | H | p-$FC_6H_4$ | - | - | - | - | 64 | 222 |
| 17k | Br | H | - | - | - | - | 81 | 211 |
| 17l | Br | $C_6H_5$ | - | - | - | - | 76 | 180 |
| 17m | Br | o-$ClC_6H_4$ | - | - | - | - | 59 | 198 |
| 17n | Br | m-$ClC_6H_4$ | - | - | - | - | 58 | 285 |
| 17o | Br | p-$ClC_6H_4$ | - | - | - | - | 77 | 190 |
| 17p | Br | o-$CH_3C_6H_4$ | - | - | - | - | 65 | 265 |
| 17q | Br | m-$CH_3C_6H_4$ | - | - | - | - | 69 | 234 |
| 17r | Br | p-$CH_3C_6H_4$ | - | - | - | - | 72 | 194 |
| 17s | Br | p-$BrC_6H_4$ | - | - | - | - | 63 | 280 |
| 17t | Br | p-$FC_6H_4$ | - | - | - | - | 68 | 282 |
| 17u | Br | p-$NO_2C_6H_4$ | - | - | - | - | 64 | 190 |
| 18a | - | - | - | - | - | $C_6H_4$ | 65 | 252 |
| 18b | - | - | - | - | - | m-$BrC_6H_4$ | 66 | 242 |
| 18c | - | - | - | - | - | p-$BrC_6H_4$ | 69 | 246 |
| 18d | - | - | - | - | - | o-OH—$C_6H_4$ | 68 | >294 |
| 18e | - | - | - | - | - | p-OH—$C_6H_4$ | 72 | >294 |
| 18f | - | - | - | - | - | o-$ClC_6H_4$ | 70 | 272 |
| 18g | - | - | - | - | - | p-$ClC_6H_4$ | 70 | 276 |
| 18h | - | - | - | - | - | p-$CH_3$—$C_6H_4$ | 66 | 242 |
| 18i | - | - | - | - | - | p-Pyridyl | 65 | 250 |
| 18j | - | - | - | - | - | p-Chlorophenoxy | 67 | 222 |
| 18k | - | - | - | - | - | o,p-Dichlorophenoxy | 71 | 240 |
| 19a | - | - | - | - | - | $C_6H_4$ | 62 | 224 |
| 19b | - | - | - | - | - | m-$BrC_6H_4$ | 65 | 230 |
| 19c | - | - | - | - | - | p-$BrC_6H_4$ | 61 | 280 |
| 19d | - | - | - | - | - | m-OH—$C_6H_4$ | 60 | >294 |
| 19e | - | - | - | - | - | p-OH—$C_6H_4$ | 68 | >294 |
| 19f | - | - | - | - | - | o-$ClC_6H_4$ | 72 | 264 |
| 19g | - | - | - | - | - | p-$ClC_6H_4$ | 70 | 270 |
| 19h | - | - | - | - | - | p-CH3—$C_6H_4$ | 66 | 230 |
| 19i | - | - | - | - | - | p-pyridyl | 65 | 232 |
| 19j | - | - | - | - | - | p-chlorophenoxy | 67 | 210 |
| 19k | - | - | - | - | - | o,p-dichlorophenoxy | 71 | 220 |
| 20a | - | - | - | - | - | —$C_6H_4$ | 62 | 218 |
| 20b | - | - | - | - | - | —$CH_2$—$C_6H_4$ | 65 | 196 |
| 20c | - | - | - | - | - | m-$BrC_6H_3$ | 65 | 208 |
| 20d | - | - | - | - | - | p-$BrC_6H_3$ | 67 | 274 |
| 20e | - | - | - | - | - | o-OH—$C_6H_4$ | 68 | >294 |
| 20f | - | - | - | - | - | p-OH—$C_6H_4$ | 66 | >294 |
| 20g | - | - | - | - | - | o-$ClC_6H_4$ | 70 | 240 |
| 20h | - | - | - | - | - | p-$ClC_6H_4$ | 70 | 276 |
| 20i | - | - | - | - | - | p-$CH_3$—$C_6H_4$ | 66 | 230 |
| 20j | - | - | - | - | - | p-pyridyl | 65 | 230 |
| 20k | - | - | - | - | - | p-chlorophenoxy | 62 | 196 |
| 20l | - | - | - | - | - | o,p-dichlorophenoxy | 71 | 212 |
| 21a | H | H | H | $N(CH_3)_2$ | H | - | 42 | – |
| 21b | H | Cl | H | H | H | - | 36 | 282 |
| 21c | H | H | H | $OCH_3$ | H | - | 36 | 213 |
| 21d | H | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | - | 45 | – |
| 21e | Br | H | H | $N(CH_3)_2$ | H | - | 35 | – |
| 21f | Br | Cl | H | H | H | - | 40 | 218 |
| 21g | Br | H | H | H | H | - | 38 | 218 |
| 21h | Br | OH | H | H | Br | - | 37 | – |

(*continued on next page*)

**Table B.1** (*continued*)

| Code | X | R | R1 | R2 | R3 | Ar | Yield (%) | Melting point (°C) |
|---|---|---|---|---|---|---|---|---|
| 21i | Br | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | - | 41 | – |
| 21j | Cl | H | H | $N(CH_3)_2$ | H | - | 37 | – |
| 21k | Cl | Cl | H | H | H | - | 35 | 217 |
| 21l | Cl | H | H | $OCH_3$ | H | - | 43 | – |
| 21m | Cl | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | - | 42 | – |
| 22a | H | H | H | H | H | - | 35 | 164 |
| 22b | Br | H | H | H | H | - | 34 | – |
| 22c | Cl | H | H | H | H | - | 36 | – |
| 23a | H | $C_6H_5$ | - | - | - | - | – | 262 |
| 23b | H | m-$CH_3C_6H_4$ | - | - | - | - | – | 240 |
| 23c | H | p-$CH_3C_6H_4$ | - | - | - | - | – | 222 |
| 23d | Cl | m, p-$(OCH_3)_2C_6H_3$ | - | - | - | - | – | 242 |
| 23e | Br | CH═CH─$C_6H_3$─[$(OCH_3)_2$ m,p] | - | - | - | - | – | 212 |
| 23f | Br | CH═CH─$C_6H_4$ (p-$OCH_3$) | - | - | - | - | – | 247 |
| 24a | H | H | H | $N(CH_3)_2$ | H | - | 43 | 160 |
| 24b | H | Cl | H | H | H | - | 38 | 155 |
| 24c | H | H | H | $OCH_3$ | H | - | 40 | 198 |
| 24d | H | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | - | 35 | 184 |
| 24e | Br | H | H | $N(CH_3)_2$ | H | - | 45 | 162 |
| 24f | Br | Cl | H | H | H | - | 45 | 160 |
| 24g | Br | H | H | H | H | - | 45 | 162 |
| 24h | Br | H | H | H | Br | - | 42 | 172 |
| 24i | Br | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | - | 40 | 180 |
| 24j | Cl | H | H | $N(CH_3)_2$ | H | - | 40 | 180 |
| 24k | Cl | Cl | H | H | H | - | 45 | 160 |
| 24l | Cl | H | H | $OCH_3$ | H | - | 50 | 165 |
| 24m | Cl | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | - | 50 | 135 |
| 25a | H | H | H | H | H | - | 42 | 174 |
| 25b | Br | H | H | H | H | - | 40 | 164 |
| 25c | Cl | H | H | H | H | - | 44 | 167 |
| 26a | H | p-$COOC_2H_5$ | - | - | - | - | 85 | 210 |
| 26b | Br | p-$COOC_2H_5$ | - | - | - | - | 75 | 228 |
| 26c | Cl | p-$COOC_2H_5$ | - | - | - | - | 78 | 220 |
| 26d | H | m-$COOC_2H_5$ | - | - | - | - | 75 | 224 |
| 26e | Br | m-$COOC_2H_5$ | - | - | - | - | 79 | 225 |
| 26f | Cl | m-$COOC_2H_5$ | - | - | - | - | 82 | 226 |
| 26g | H | p-$COOCH_3$ | - | - | - | - | 83 | 200 |
| 26h | Br | p-$COOCH_3$ | - | - | - | - | 78 | 208 |
| 26i | Cl | p-$COOCH_3$ | - | - | - | - | 82 | 218 |
| 26j | H | m-$COOCH_3$ | - | - | - | - | 79 | 218 |
| 26k | Br | m-$COOCH_3$ | - | - | - | - | 83 | 221 |
| 26l | Cl | m-$COOCH_3$ | - | - | - | - | 76 | 227 |
| 27a | H | - | - | - | - | - | 79 | 230 |
| 27b | Br | - | - | - | - | - | 76 | 219 |
| 27c | Cl | - | - | - | - | - | 75 | 220 |
| 28a | H | - | - | - | $C_6H_5$ | - | 62 | 188 |
| 28b | Br | - | - | - | $C_6H_5$ | - | 62.5 | 190 |
| 28c | Cl | - | - | - | $C_6H_5$ | - | 72.3 | 191 |
| 28d | H | - | - | - | $C_6H_4$─(2′-Cl) | - | 65 | 191 |
| 28e | Br | - | - | - | $C_6H_4$─(2′-Cl) | - | 55 | 191 |
| 28f | Cl | - | - | - | $C_6H_4$─(2′-Cl) | - | 73 | 200 |
| 28g | H | - | H | H | Furfuryl | - | 56.5 | 189 |
| 29a | - | ─OOC─$C_6H_4$ | - | - | - | - | 88 | 210 |
| 29b | - | ─OOC─$C_6H_3$─5Cl,2OH | - | - | - | - | 86 | 238 |
| 30a | - | - | - | - | - | - | 56 | 220 |
| 30b | - | ─OC─$C_6H_3$─5$NH_2$,2OH | - | - | - | - | 78 | > 300 |
| 31a | - | ─OOC─$C_6H_4$ | - | - | - | - | 91 | 224 |
| 31b | - | ─OOC─$C_6H_3$─5Cl,2OH | - | - | - | - | 79 | 256 |
| 32a | - | ─OOC─$C_6H_4$ | - | - | - | - | 84 | 238 |
| 32b | - | ─OOC─$C_6H_3$─5Cl,2OH | - | - | - | - | 71 | 246 |

–, not found.

group at the 6th position of the coumarin nucleus exhibited higher *log p* as compared to the unsubstituted derivative ***27a***. The presence of the *chloro* substituted phenyl group at the 4th position in the pyridine ring of the derivatives like ***28d–f***, led to an increase in the *log p* value of the corresponding 4th position unsubstituted derivatives ***28a–c***. However, when the biological activity was correlated with partition coefficient of these derivatives, it was found that the derivative ***26e*** with highest *log p* was inactive against all bacterial strains tested. On the other hand, it was noted that most of derivatives with quinolium bromide salts of coumarins with optimum *log p* range of 1.10–1.41, were moderately active as anti-bacterial.

From the results, it could be understood that substitution of electronegative atom in form of halogens such as the *chloro*/*bromo* group at the 6th position of the coumarin nucleus leads to an increase in the partition coefficient of the parent/unsubstituted compound. It was also realised that, compounds possessing an optimum balance of lipophilic and hydrophilic characters were biologically active when compared to the standards.

### *4.2. Other parameters*

We wanted to understand the effect of substituents on few other important physicochemical properties such as determination of dissociation constant in terms of *pKa* value. The dissociation constant of both acidic and basic drug is governed by *pKa*. The lower the *pKa* of an acidic drug, the stronger will be the acid. Whereas, the higher the p*Ka* of a basic drug, the stronger will be the base. To have better understanding, one such study was performed (Jayashree et al., 2010) where, estimation of *pKa* of the substituted pyridinyl coumarin derivatives was done. It was observed that compounds, including the bromide salts ***26–28***, were in the range of 6–6.5, showing moderate to weak basic character. Such compounds would get ionised in the acidic *pH* as in case of gastric *pH*, but they remain relatively unionised at intestinal *pH*, thereby showing better absorption from the intestine. It was also observed that substitution of different groups on the coumarin nucleus did not bring any noticeable change in their dissociation constant value. However, there is a need for further investigation to determine *pKa* of other substituted coumarins.

## 5. Conclusion

In this review, an earnest attempt has been made to consolidate and highlight important research findings in the area of coumarin for last nearly one decade. Emphasis has been made in particular, on the synthetic routes undertaken for arriving at substituted coumarinyl derivatives that have influenced their pharmacological activities. Additionally, some of the important physicochemical parameters fixed for the coumarinyl derivatives are also being furnished. Earlier work on coumarins was mostly related to their isolation, characterisation and exploiting their biological activities from the natural sources, until recently attempts were made in the area of synthetic coumarins useful as potentially biologically active compounds. This review therefore, will provide a better insight to researchers on the potential biologically useful substituted coumarinyl derivatives as intermediates for achieving coumarin analogues with high therapeutic value. Furthermore, it will help in understanding the effect of various substituents on the biological as well as the physicochemical characteristics of such coumarinyl compounds.

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## Appendix A.

### *A.1. List of Figures*

## Appendix B.

### *A.2. List of Tables*

## References

Al-Amiery, A.A., Kadhum, A.A.H., Mohamad, A.B., 2012. Antifungal activities of new coumarins. Molecules 17, 5713–5723.

Alipour, M., Khoobi, M., Foroumadi, A., Nadri, H., Moradi, A., Sakhteman, A., Ghandi, M., Shafiee, A., 2012. Novel coumarin derivatives bearing *N*-benzyl pyridinium moiety: potent and dual binding site acetylcholinesterase inhibitors. Bioorg. Med. Chem. 20, 7214–7222.

Al-Masoudi, I.A., Al-Soud, Y.A., Al-Salihi, N.J., Al-Masoudi, N.A., 2006. 1, 2, 4-Triazoles: synthetic approaches and pharmacological importance (Review). Chem. Heterocycl. Compd. 42, 1377–1403.

Anand, P., Singh, B., Singh, N., 2012. A review on coumarins as acetylcholinesterase inhibitors for Alzheimer's disease. Bioorg. Med. Chem. 20, 1175–1180.

Arshad, A., Osman, H., Bagley, M.C., Lam, C.K., Mohamad, S., Zahariluddin, A.S.M., 2011. Synthesis and antimicrobial properties of some new thiazolyl coumarin derivatives. Eur. J. Med. Chem. 46, 3788–3794.

Beillerot, A., Dominguez, J.C.R., Kirsch, G., Bagrel, D., 2008. Synthesis and protective effects of coumarin derivatives against oxidative stress induced by doxorubicin. Bioorg. Med. Chem. Lett. 18, 1102–1105.

Bhat, A.R., Bhat, G.V., Shenoy, G.G., 2001. Synthesis and in-vitro antimicrobial activity of new 1, 2, 4-triazoles. J. Pharm. Pharmacol. 53, 267–272.

Binda, C., Wang, J., Pisani, L., Caccia, C., Carotti, A., Salvati, P., Edmondson, D.E., Mattevi, A., 2007. Structures of human monoamine oxidase B complexes with selective noncovalent inhibitors: safinamide and coumarin analogs. J. Med. Chem. 50, 5848–5852.

Chilin, A., Battistutta, R., Bortolato, A., Cozza, G., Zanatta, S., Poletto, G., Mazzorana, M., Zagotto, G., Uriarte, E., Guiotto, A., 2008. Coumarin as attractive casein kinase 2 (CK2) inhibitor scaffold: an integrate approach to elucidate the putative binding motif and explain structure activity relationships. J. Med. Chem. 51, 752–759.

Chimenti, F., Secci, D., Bolasco, A., Chimenti, P., Bizzarri, B., Granese, A., Carradori, S., Yanez, M., Orallo, F., Ortuso, F., 2009. Synthesis, molecular modeling, and selective inhibitory activity against human monoamine oxidases of 3-carboxamido-7-substituted coumarins. J. Med. Chem. 52, 1935–1942.

Chopra, D., Venugopal, K.N., Jayashree, B.S., Row, T.N.G., 2006. 3-Acetyl-6-chloro-2H-chromen-2-one. Acta Crystallogr. C, o2310–o2312.

Collier, H.O.J., Dinneen, L.C., Johnson, C.A., Schneider, C., 1968. The abdominal constriction response and its suppression by analgesic drugs in the mouse. Br. J. Pharmacol. Chemother. 32, 295–310.

Curir, P., Galeotti, F., Dolci, M., Barile, E., Lanzotti, V., 2007. Pavietin, a coumarin from *Aesculus pavia* with antifungal activity. J. Nat. Prod. 70, 1668–1671.

Das, S., Rosazza, J.P.N., 2006. Microbial and enzymatic transformations of flavonoids. J. Nat. Prod. 69, 499–508.

Devji, T., Reddy, C., Woo, C., Awale, S., Kadota, S., Carrico-Moniz, D., 2011. Pancreatic anticancer activity of a novel geranylgeranylated coumarin derivative. Bioorg. Med. Chem. Lett. 21, 5770–5773.

Di Cuollo, C.J., Guarini, J.R., Pagano, J.F., 1965. Automation of large plate agar microbiological diffusion assays. Ann. N. Y. Acad. Sci. 130, 672–679.

Eissa, A.A.M., Farag, N.A.H., Soliman, G.A.H., 2009. Synthesis, biological evaluation and docking studies of novel benzopyranone congeners for their expected activity as anti-inflammatory, analgesic and antipyretic agents. Bioorg. Med. Chem. 17, 5059–5070.

Ericsson, B.H., Tunevall, G., Wickman, K., 1960. The paper disc method for determination of bacterial sensitivity to antibiotics: relationship between the diameter of the zone of inhibition and the minimum inhibitory concentration. Scand. J. Clin. Lab. Invest. 12, 414–422.

Fais, A., Corda, M., Era, B., Fadda, M.B., Matos, M.J., Santana, L., Picciau, C., Podda, G., Delogu, G., 2009. Tyrosinase inhibitor activity of coumarin-resveratrol hybrids. Molecules 14, 2514–2520.

Fan, G.-J., Mar, W., Park, M.K., Wook Choi, E., Kim, K., Kim, S., 2001. A novel class of inhibitors for steroid 5α-reductase: synthesis and evaluation of umbelliferone derivatives. Bioorg. Med. Chem. Lett. 11, 2361–2363.

Fylaktakidou, K.C., Hadjipavlou-Litina, D.J., Litinas, K.E., Nicolaides, D.N., 2004. Natural and synthetic coumarin derivatives with anti-inflammatory/antioxidant activities. Curr. Pharm. Des. 10, 3813–3833.

Geronikaki, A.A., Lagunin, A.A., Hadjipavlou-Litina, D.I., Eleftheriou, P.T., Filimonov, D.A., Poroikov, V.V., Alam, I., Saxena, A.K., 2008. Computer-aided discovery of anti-inflammatory thiazolidinones with dual cyclooxygenase/lipoxygenase inhibition. J. Med. Chem. 51, 1601–1609.

Ghantwal, S.R., Samant, S.D., 1999. Claisen rearrangement of 3-bromo-3, 6-dibromo-3, 8-dibromo-and 8-iodo/aminomethyl/acetyl-7-allyloxy-4-methylcoumarins. Indian J. Chem. Sect. B 38 (B), 1242–1247.

Gorobets, N.Y., Borisov, A.V., Silin, A.V., Nikitchenko, V.M., Kovalenko, S.N., 2002. Reactions of 3-(4-Aryl-2-thiazolyl)-and 3-(2-Benzothiazolyl)-2-iminocoumarins with *N*-nucleophiles. Chem. Heterocycl. Compd. 38, 1389–1396.

Harayama, T., Nakatsuka, K., Nishioka, H., Murakami, K., Hayashida, N., Ishii, H., 1994. Convenient synthesis of a simple coumarin from salicylaldehyde and Wittig reagent II: synthesis of bromo- and methoxycarbonylcoumarins. Chem. Pharm. Bull. 42, 2170–2173.

Hogale, M.B., Pawar, B.N., Nikam, B.P., 1987. Synthesis and biological activity of some new flavones. J. Indian Chem. Soc. 64, 486–487.

Jayashree, B.S., Abhishek, K., Pai, A., 2011. Synthesis, characterization and anti-diabetic evaluation of novel coumarin analogues. Pharmacol. Online 3, 1061–1076.

Jayashree, B.S., Anuradha, D., Venugopala, K.N., 2005a. Synthesis and characterization of Schiff bases of 2′-amino-4′-(6-chloro-3-coumarinyl)-thiazole as potential NSAIDs. Asian J. Chem. 17, 2093–2097.

Jayashree, B.S., Arora, S., Nayak, Y., 2008. Antioxidant analgesic and anti-inflammatory activities of some selected heteroaryl substituted coumarins. Pharmacologyonline 2, 404–410.

Jayashree, B.S., Jerald, J., Venugopala, K.N., 2004. Synthesis and characterization of schiff bases of 2′-amino-4′-(3-coumarinyl) thiazole as potential NSAIDs. Orient. J. Chem. 20, 123–126.

Jayashree, B.S., Porwal, B., Nayak, Y., Vijay Kumar, D., 2010. Antibacterial activity of newly synthesised pyridinyl coumarin derivatives. Pharmacologyonline 1, 190–199.

Jayashree, B.S., Sahu, A.R., Srinivasa Murthy, M., Venugopala, K.N., 2005b. Synthesis, determination of partition coefficient and antimicrobial activity of triazolo thiadiazinyl bromocoumarin derivatives. Mater. Sci. Res. India 3, 187–190.

\Jayashree, B.S., Sahu, A.R., Murthy, M.S., Venugopala, K.N., 2006. Synthesis, characterization and determination of partition coefficient of some triazolo thiadiazinyl chlorocoumarin derivatives for their antimicrobial activity. J. Saudi Chem. Soc. 10, 103–108.

Jayashree, B.S., Sahu, A.R., Murthy, M.S., Venugopala, K.N., 2007. Synthesis, characterization and determination of partition coefficient of some triazole derivatives of coumarins for their antimicrobial activity. Asian J. Chem. 19, 73–78.

Jayashree, B.S., Yusuf, S., Kumar, D.V., 2009. Synthesis of some coumarinyl chalcones of pharmacological interest. Asian J. Chem. 21, 5918–5922.

Jedsadayanmata, A., 2005. In vitro antiglycation activity of arbutin. Naresuan Univ. J. 13, 35–41.

Jung, J.C., Park, O.S., 2009. Synthetic approaches and biological activities of 4-hydroxycoumarin derivatives. Molecules 14, 4790–4803.

Khode, S., Maddi, V., Aragade, P., Palkar, M., Ronad, P.K., Mamledesai, S., Thippeswamy, A.H.M., Satyanarayana, D., 2009. Synthesis and pharmacological evaluation of a novel series of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines as novel anti-inflammatory and analgesic agents. Eur. J. Med. Chem. 44, 1682–1688.

Kidwai, M., Rastogi, S., Mohan, R., 2004. A novel route to new bis (benzopyrano) fused dihydropyridines using dry media. Bull. Korean Chem. Soc. 25, 119–121.

Kostova, I., Momekov, G., 2006. New zirconium (IV) complexes of coumarins with cytotoxic activity. Eur. J. Med. Chem. 41, 717–726.

Kostova, I., Raleva, S., Genova, P., Argirova, R., 2006. Structure-activity relationships of synthetic coumarins as HIV-1 inhibitors. Bioinorg. Chem. Appl. 2006, 1–9.

Kulkarni, S.K., Mehta, A.K., Kunchandy, J., 1986. Anti-inflammatory actions of clonidine, guanfacine and B-HT 920 against various inflammagen-induced acute paw oedema in rats. Arch. Int. Pharmacodyn. Ther. 279, 324–334.

Kumar, S., Singh, B.K., Kalra, N., Kumar, V., Kumar, A., Prasad, A.K., Raj, H.G., Parmar, V.S., Ghosh, B., 2005. Novel thiocoumarins as inhibitors of TNF-α induced ICAM-1 expression on human umbilical vein endothelial cells (HUVECs) and microsomal lipid peroxidation. Bioorg. Med. Chem. 13, 1605–1613.

Lee, K.H., 2004. Current developments in the discovery and design of new drug candidates from plant natural product leads. J. Nat. Prod. 67, 273–283.

Liu, Y., Mills, A.D., Kurth, M.J., 2006. Solid phase synthesis of 3-(5-arylpyridin-2-yl)-4-hydroxycoumarins. Tetrahedron Lett. 47, 1985–1988.

Majumder, P.L., Majumder, S., 1993. Further evidence for the mechanism of formation of coumarin by Perkin reaction from salicylaldehyde and a novel synthesis of 1, 1-diphenyl-2(2′-hydroxyphenyl) ethene from O-α, α-diphenylacetylsalicylaldehyde with Et3N. Eur. J. Med. Chem. 28, 572–578.

Manojkumar, P., Ravi, T.K., Gopalakrishnan, S., 2009. Antioxidant and antibacterial studies of arylazopyrazoles and aryl-hydrazonopyrazolones containing coumarin moiety. Eur. J. Med. Chem. 44, 4690–4694.

Munshi, P., Venugopala, K.N., Jayashree, B.S., Guru Row, T.N., 2004. Concomitant polymorphism in 3-acetylcoumarin: role of weak C—H≡O and C—H≡π interactions. Cryst. Growth Des. 4, 1105–1107.

Musa, M.A., 2002. Application of the Baylis-Hillman reaction in the synthesis of coumarin derivatives (Ph.D. thesis). Department of Chemistry, Rhodes University, Grahamstown, p. 218.

Musa, M.A., Badisa, V.L.D., Latinwo, L.M., Cooperwood, J., Sinclair, A., Abdullah, A., 2011. Cytotoxic activity of new acetoxycoumarin derivatives in cancer cell lines. Anticancer Res. 31, 2017–2022.

Musa, M.A., Khan, M.O.F., Cooperwood, J.S., 2009. Synthesis and antiproliferative activity of coumarin-estrogen conjugates against breast cancer cell lines. Lett. Drug Des. Discov. 6, 133.

Musicki, B., Periers, A.M., Piombo, L., Laurin, P., Klich, M., Dupuis-Hamelin, C., Lassaigne, P., Bonnefoy, A., 2003. Noviose mimics of the coumarin inhibitors of gyrase B. Tetrahedron Lett. 44, 9259–9262.

Noolvi, M.N., Patel, H.M., Kaur, T., 2011. A QSAR analysis of coumarin derivatives as TNF-inhibitor-A rational approach to anticancer drug design. Lett. Drug. Des. Discov. 8, 868–876.

Neyts, J., Clercq, E.D., Singha, R., Chang, Y.H., Das, A.R., Chakraborty, S.K., Hong, S.C., Tsay, S.C., Hsu, M.H., Hwu, J.R., 2009. Structure activity relationship of new anti-hepatitis C virus agents: heterobicycle coumarin conjugates. J. Med. Chem. 52, 1486–1490.

Nigam, S., Rao, J.V., Jayashree, B.S., 2013. Microbial biotransformation-A novel approach for modification on coumarin substrates. Indian J. Biotechnol. 12, 379–385.

Nikhil, B., Shikha, B., Anil, P., Prakash, N.B., 2012. Diverse pharmacological activities of 3-substituted coumarins: a review. Int. Res. J. Pharm. 3, 24–29.

Oketch-Rabah, H.A., Lemmich, E., Dossaji, S.F., Theander, T.G., Olsen, C.E., Cornett, C., Kharazmi, A., Christensen, S.B., 1997. Two new antiprotozoal 5-methylcoumarins from *Vernonia brachycalyx*. J. Nat. Prod. 60, 458–461.

Orita, M., Yamamoto, S., Katayama, N., Aoki, M., Takayama, K., Yamagiwa, Y., Seki, N., Suzuki, H., Kurihara, H., Sakashita, H., 2001. Coumarin and chromen-4-one analogues as tautomerase inhibitors of macrophage migration inhibitory factor: discovery and X-ray crystallography. J. Med. Chem. 44, 540–547.

Peng, H., Marians, K.J., 1993. *Escherichia coli* topoisomerase IV. Purification, characterization, subunit structure, and subunit interactions. J. Biol. Chem. 268, 24481–24490.

Pochet, L., Doucet, C., Schynts, M., Thierry, N., Boggetto, N., Pirotte, B., Jiang, K.Y., Masereel, B., De Tullio, P., Delarge, J., 1996. Esters and amides of 6-(chloromethyl)-2-oxo-2 H-1-benzopyran-3-carboxylic acid as inhibitors of α-chymotrypsin: significance of the "aromatic" nature of the novel ester-type coumarin for strong inhibitory activity. J. Med. Chem. 39, 2579–2585.

Porwal, B., Jayashree, B.S., Attimarad, M., 2010. Synthesis of some new 3-coumarinoyl pyridinium and quinolinium bromides for their antimicrobial activity. J. Basic Clin. Pharm. 1, 29–32.

Rao, V.R., Reddy, K.M., 2009. A facile one-step synthesis of new types of 8-thiazolyl and 8-thiadiazinyl coumarins. Phosphorus Sulfur Silicon Relat. Elem. 184, 743–752.

Reddy, P.V.K., Kumar, P.N., Chandramouli, G.V.P., 2005. Synthesis and antimicrobial activity of 6, 6′-arylidene-bis-[5-hydroxy-9-methyl-2, 3-diaryl thieno[3, 2-g-]thiocoumarins]. J. Heterocycl. Chem. 42, 283–286.

Sahu, N.K., Balbhadra, S.S., Choudhary, J., Kohli, V.D., 2012. Exploring pharmacological significance of chalcone scaffold: a review. Curr. Med. Chem. 19, 209–225.

Sangster, J., 1989. Octanol-water partition coefficients of simple organic compounds. J. Phys. Chem. Ref. Data 18, 1111–1227.

Sashidhara, K.V., Kumar, A., Chatterjee, M., Rao, K.B., Singh, S., Verma, A.K., Palit, G., 2011. Discovery and synthesis of novel 3-phenylcoumarin derivatives as antidepressant agents. Bioorg. Med. Chem. Lett. 21, 1937–1941.

Shaaban, M.R., Mayhoub, A.S., Farag, A.M., 2012. Recent advances in the therapeutic applications of pyrazolines. Expert Opin. Ther. Pat. 22, 253–291.

Shaabani, A., Ghadari, R., Rahmati, A., Rezayan, A.H., 2009. Coumarin synthesis via Knoevenagel condensation reaction in 1, 1, 3, 3-N, N, N′, N′-tetramethylguanidinium trifluoroacetate ionic liquid. J. Iran. Chem. Soc. 6, 710–714.

Shi, Y., Zhou, C.H., 2011. Synthesis and evaluation of a class of new coumarin triazole derivatives as potential antimicrobial agents. Bioorg. Med. Chem. Lett. 21, 956–960.

Siddiqui, N., Arshad, M.F., Ahsan, W., Alam, M.S., 2009. Thiazoles: a valuable insight into the recent advances and biological activities. Int. J. Pharm. Sci. Drug Res. 1, 136–143.

Starcevic, S., Brozic, P., Turk, S., Cesar, J., Lanisnik Rizner, T., Gobec, S., 2011. Synthesis and biological evaluation of (6-and 7-phenyl) coumarin derivatives as selective nonsteroidal inhibitors of 17β-hydroxysteroid dehydrogenase type 1. J. Med. Chem. 54, 248–261.

Upadhyay, K., Bavishi, A., Thakrar, S., Radadiya, A., Vala, H., Parekh, S., Bhavsar, D., Savant, M., Parmar, M., Adlakha, P., 2011. Synthesis and biological evaluation of 4-styrylcoumarin derivatives as inhibitors of TNF-α and IL-6 with anti-tubercular activity. Bioorg. Med. Chem. Lett. 21, 2547–2549.

Upadhyay, K.K., Mishra, R.K., Kumar, A., 2008. A convenient synthesis of some coumarin derivatives using $SnCl_2.2H_2O$ as catalyst. Catal. Lett. 121, 118–120.

Venugopala, K.N., Jayashree, B.S., 2003. Synthesis and characterization of carboxamides of 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole for their analgesic and antiinflammatory activity. Indian J. Heterocycl. Chem. 12, 307–310.

Venugopala, K.N., Jayashree, B.S., 2004. Synthesis and characterization of schiff bases of aminothiazolyl bromocoumarin for their analgesic and antiinflammatory activity. Asian J. Chem. 16, 407–411.

Venugopala, K.N., Jayashree, B.S., 2008. Microwave-induced synthesis of schiff bases of aminothiazolyl bromocoumarins as antibacterials. Indian J. Pharm. Sci. 70, 88–91.

Venugopala, K.N., Jayashree, B.S., Attimarad, M., 2004. Synthesis and evaluation of some substituted 2-arylamino coumarinyl thiazoles as potential NSAIDs. Asian J. Chem. 16, 872–876.

Xu, J., Kjer, J., Sendker, J., Wray, V., Guan, H., Edrada, R., Muller, W.E.G., Bayer, M., Lin, W., Wu, J., Proksch, P., 2009. Cytosporones, coumarins, and an alkaloid from the endophytic fungus *Pestalotiopsis* sp. isolated from the Chinese mangrove plant *Rhizophora mucronata*. Bioorg. Med. Chem. 17, 7362–7367.