ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Review Article

COUMARIN: A VALID SCAFFOLD IN MEDICINAL CHEMISTRY

Khemchand R. Surana*[1], Sunil K. Mahajan[2], Shital J. Patil[2]

[1]PhD Scholar, Department of Pharmaceutical Chemistry, Mahatma Gandhi Vidyamandir Pharmacy College, Panchavati, Nashik, Maharashtra

[2]Department of Pharmaceutical Chemistry, Mahatma Gandhi Vidyamandir Pharmacy College, Panchavati, Nashik, Maharashtra

*Corresponding author: khemchandsurana411@gmail.com

ABSTRACT

The coumarin scaffold is an important structure in medicinal chemistry because it is found in several naturally occurring molecules which exhibit a variety of biological activities, such as anti-cancer, anti-inflammatory, anti-diabetic, antimicrobial, and antiviral, antifungal. In addition, various synthetic coumarins motifs are present in marketed drugs. They are also involved in the actions of the photosynthesis, control of respiration, plant growth hormones and growth regulators, and also defense against infection. This review will provide an overview of coumarin moieties with medicinal aspects synthesized in the last 15 years and will cover the most potent molecule in each report. In this review, different synthesis methods of coumarin and their derivatives have been covered.

Keywords: Coumarin, Chromane, Synthetic methods of coumarin. Anticancer, Anti-inflammatory, Biological activity.

1. INTRODUCTION

Chromones are a class of naturally occurring compounds that are ever present in nature, chiefly in plants. Chromone is the word derived from the Greek word *chroma*, meaning "color", which identify that number of chromone derivatives can shows a diversity of colors.

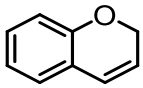


Fig. 1: Structure of chromane ring

Chromones are heterocyclic compounds which contains oxygen with a benzo annelated γ-pyrone ring being chromone (4*H* chromen-4-one, 4*H*-1-benzopyran-4-one) the parent compound. The basic ring of chromane is shown in fig. 1. The chromone ring system is the core structure of many flavonoids, such as flavones and isoflavones [1].

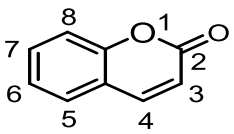


Fig. 2: Structure and atom numbering of coumarin nucleus

Coumarins are an important class of benzopyrones which consist of a benzene ring joined to a pyrone ring. The synthesis of coumarins and their derivatives has entice the significant attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus [2]. The basic structure of coumarin with atom numbering is shown in fig. 2. Coumarins, a part of flavaonoid group of plant secondary metabolite, are a wide class of natural and synthetic compounds that showed versatile pharmacological activity including anti-inflammatory, antioxidant, anti-nociceptive, hepatoprotective, anti-thrombotic, anti-carcinogenic, antimicrobial, antituberculosis, antiviral, antidepressant, antipsychotic, anti-hyperlipidemic and anti-cholinestersase activity [3-6].

Compounds or drug molecules containing coumarins are involved in the actions of the photosynthesis, control of respiration, plant growth hormones and growth regulators, and also defense against infection. Their other important uses are in plant biochemistry and physiology, acting, asenzyme inhibitors, as antioxidants, and precursors of toxic substances. They are also useful in alcoholic beverages, cigarettes, laser dyes perfumes and cosmetics [7, 8].

One of the important application of coumarin derivatives are used as intermediate chemicals in the synthesis of

pharmaceuticals and also agrochemicals, insecticides, food additives, fragrances, and cosmetics [9-13]. Additionally, they are applicable as optical whitening agents, dyes, laser colors, and fluorescent probes for the identification of biologically important chemical species as medicinal stains [14-17]. In the synthetic organic chemistry, the class of coumarin compounds is useful for the synthesis of chromones, coumarones, fluorocoumarins, and 2-acyl resorcinol [18]. However, many important drug molecules have coumarin moieties such as warfarin, calanolide A, 667 coumate, novobiocin, ensaculinalexa 350, hymecromone, and umbelliferone.

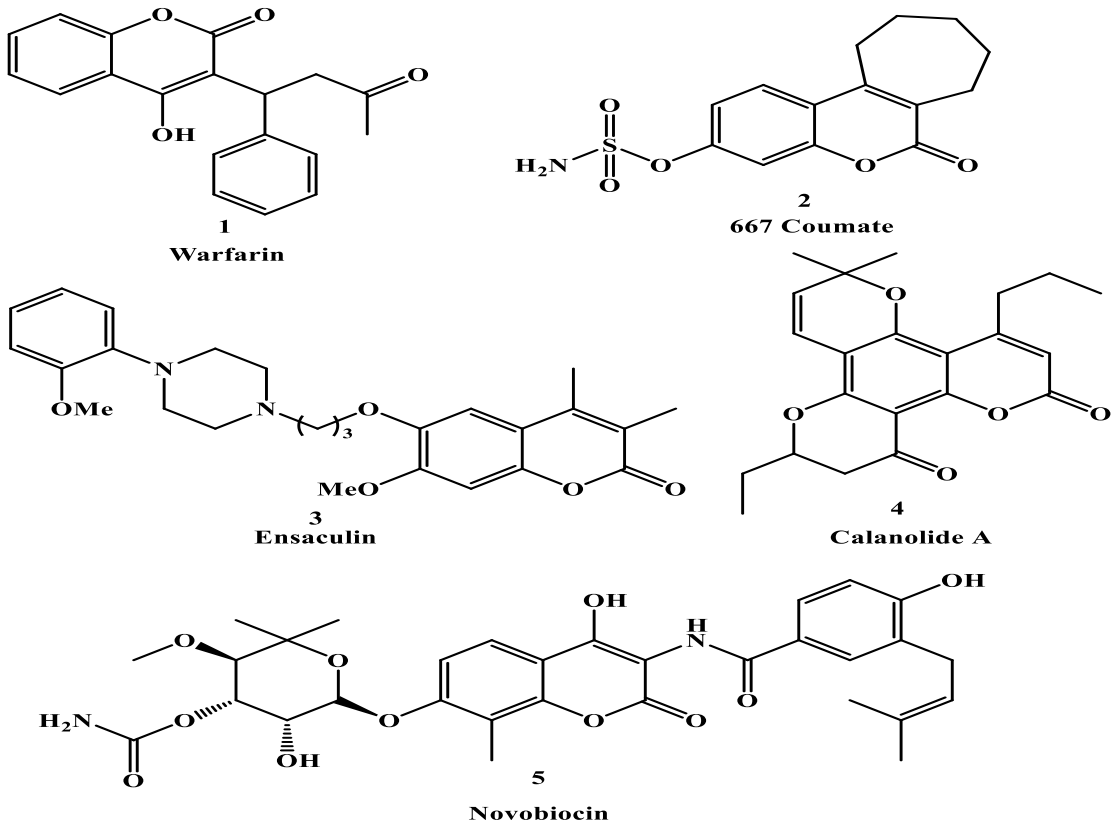


Fig. 3: Drug molecules containing coumarin moiety

First reported method for synthesis of coumarin is via the Perkin reaction in 1868, and number of other coumarin analogs is still synthesized by this method. In the early 1900s, the Knoevenagel reaction emerged as an important synthetic method to synthesize coumarin derivatives with carboxyl group at the 3-position [19, 20]. Many other synthetic methods for coumarins have been reported, including the Pechmann [21], Reformatsky [22], Perkin [23], Kostanecki-Robinson synthesis [24] and Wittig reactions [25]. The general schemes for synthesis of coumarin by various methods are shown in fig. 4. Among these, the Pechmann reaction is the most widely used method, consisting of the condensation of phenols with β-ketoesters in the presence of a variety of reagents, mainly producing 4-substituted coumarins. Sulfuric acid, phosphorus pentoxide, aluminum chloride and trifluoroacetic acid, these are the acid catalyst used in pechmann condensation reaction [26].

More recent research emphasis has been centered on the use of Pd-catalyzed C-C bond formation producing 3- or 4-substituted coumarins. Fujiwara et al. also reported a direct synthesis of coumarins by Pd-catalyzed inter- and intra-molecular hydroarylation of aryl propiolates. Larock et al. reported that Pd catalyzed annulations of internal alkynes by *o*-iodophenols in the presence of CO leads to formation of coumarins. However, the generation of regioisomeric mixtures is unavoidable when unsymmetrical alkynes are employed. Although the synthetic strategies to functionalized coumarins by using other transition-metal-catalyzed reactions have also been reported, most of them depend on the functionalization of a preformed coumarin nucleus [27].

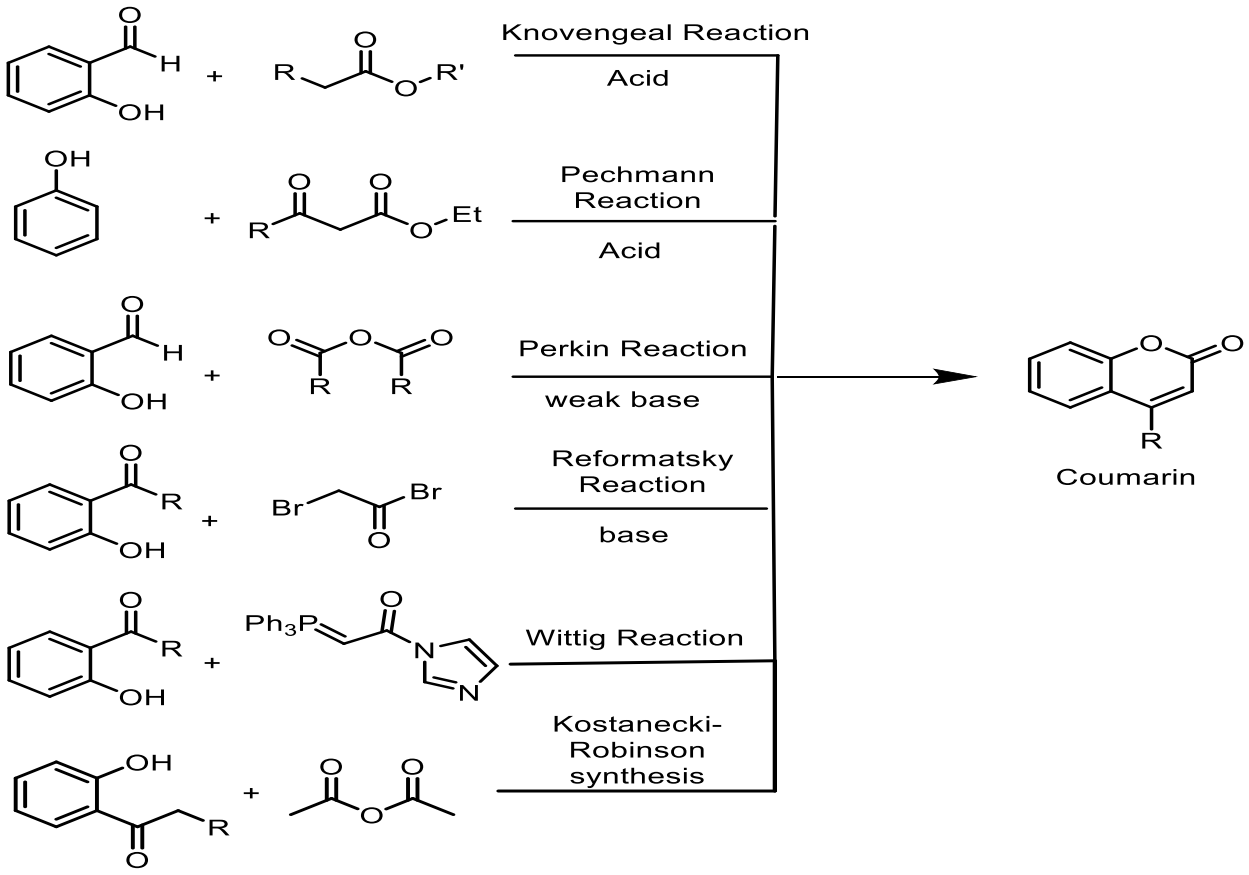


Fig. 4: Various reactions for coumarin synthesis

2. SYNTHETIC METHODS FOR COUMARIN SYNTHESIS

Various strategies for the synthesis of coumarin and its derivatives, including Pechmann, Perkin, Knoevenagel, Claisen-Reformatsky, and Wittig reactions, have been developed by several groups.

2.1. Knoevenagel condensation

The Knoevenagel condensation of 2-hydroxybenzaldehyde is reacted with diethyl malonate in the presence of different catalysts which leads to ethyl coumarin-3-carboxylate (Scheme 1).

Various catalysts were used in this reaction, such as piperidine,18-20 molecular sieves/piperidine catalyst, Magnesium alumino phosphate (MAPO-5) and ion-exchanged MAPO-5, alumina/KSF/K10 montmorillonites, liquid-functionalized SiO2 at 100°C, L-Proline, sodium methoxide, 1-n-butyl-3-methylimidazolium bromide/potassium carbonate, 1-butyl-3-methylimidazolium hydroxide ([bmim]OH), aluminum phosphate-aluminum oxide, zinc chloride, calcined Mg-Al hydrotalcite, N,N-dimethyl (dichlorophosphoryloxy-methylene) ammonium chloride, mixed oxide catalysts obtained from calcined Mg-Al double hydroxides, Mg-Al + Ln (Ln = Dy, Gd) and Li-Al hydrotalcites [3].

The condensation using readily available and bio-degradable choline chloride in water provides an efficient and convenient method, minimizing the problem of highly viscous media without the use of other catalysts or organic solvents (Scheme 2). This method offers marked improvements in terms of simplicity, simple reaction conditions, general applicability, high isolated product yields, and the use of environmentally benign procedures and solvents, which makes it highly suitable for industrial condensation of aromatic aldehydes and active methylene compounds. Choline chloride is of low cost, is non-toxic, and has high water solubility, wide potential window, and environmental compatibility, and it is produced in tonnage scale for chicken feed additive; hence, this method can provide a good alternative for industrial scale. This method also removes the utilization of hazardous organic solvents and toxic catalysts and thus it yields a better and more convenient practical way to existing procedures. It is easy to separate the catalyst and product after completion of the reaction [23].

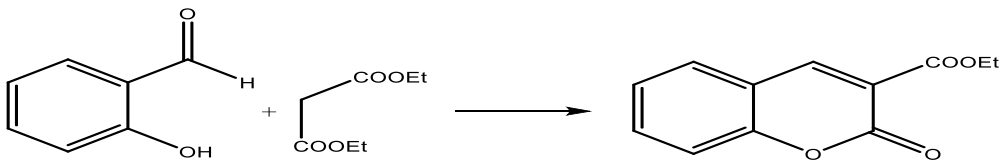
Pechmann Condensation: Condensation of starting material phenol and carboxylic acid or ester containing a β-carbonyl group under acidic conditions which leads to coumarins and their derivatives is called as Pechmann condensation reaction synthesis of coumarins (Scheme 3) [28].

Synthesis of coumarin having several mechanistic steps, which involve esterification/trans-esterification sub-sequentlyattack of the activated carbonyl ortho to the oxygen to leads to the new moiety. Afterwards intermediates undergo dehydration, which involves an aldol condensation. This method was discovered by the German chemist Hans von Pechmann, with simple phenols in presence of harsh conditions, althoughits yield is good.

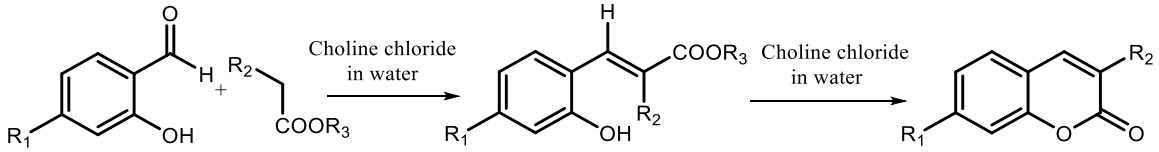
This reaction is carried out with a strong Brønstedt acid such as methane sulfonic acid or a Lewis acid such as $AlCl_3$. The acid catalyses trans-esterification as well as keto-enol tautomerisation [29].

Resorcinol is highly activated phenol, in such conditions the reaction can be carried out under much milder conditions (Scheme 4). This provides a useful route to umbelliferone derivatives:

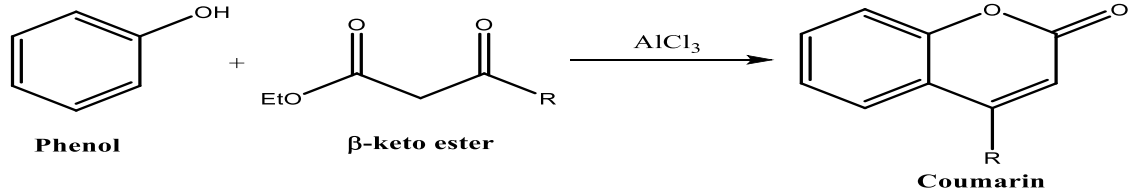
This reaction has extensive scope in the synthesis of coumarin derivatives [30].



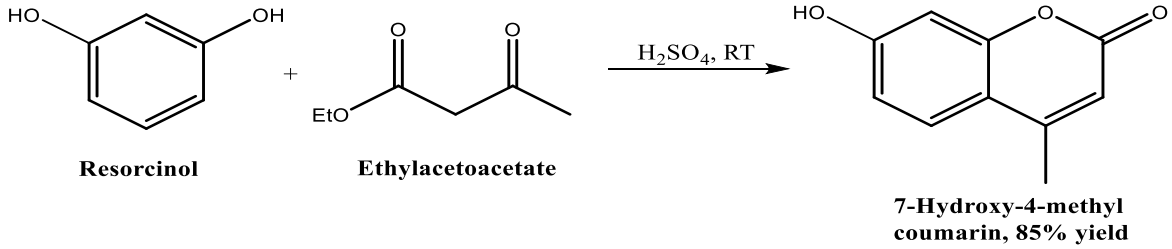
Scheme 1: Reaction of *o*-salicylaldehyde with diethyl malonate



Scheme 2: Synthesis of coumarin via Knoevenagel condensation



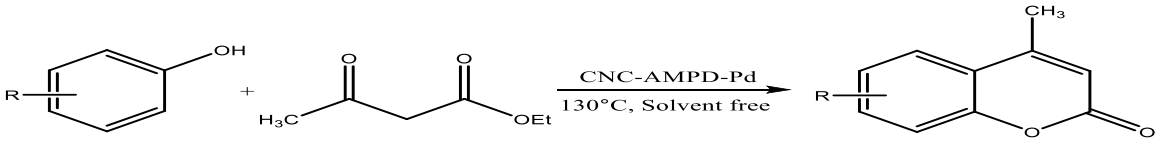
Scheme 3: Synthesis of coumarin via Pechmann condensation reaction



Scheme 4: Synthesis of 7-Hydroxy-4-methyl coumarin in acidic condition via Pechmann condensation

2.2. Solvent-free Pechmann condensation

Mirosanloo et al. developed the Solvent-free Pechmann condensation reaction for synthesis of coumarin derivatives in the presence of cellulose nanocrystal supported palladium nanoparticles (CNC-AMPD-Pd), for which model reactionwas chosen, which is reaction of resorcinol and ethyl acetoacetate (Scheme 5). In order to get the best reaction conditions various solvents and temperatures conditions were taken. 96% of yield was obtained in a solvent-free reaction at 130°C which is considered as the highest yield. Through previous conventional methods of synthesis coumarin derivatives, in which reaction of various phenols and ethyl acetoacetate giving yields from 45 to 97% [31].



Scheme 5: Solvent free Pechmann condensation of coumarin derivatives in the presence of cellulose nanocrystal suported palladium nanoparticles.

2.3. Perkin reaction

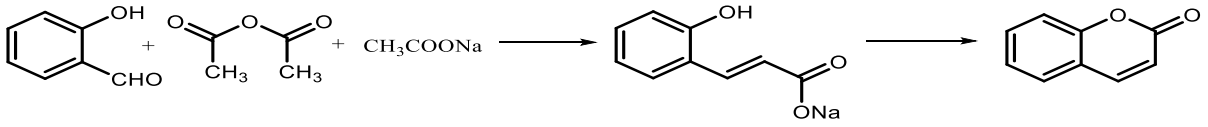
Perkin reaction is the traditionally and the most approachable route for synthesis of coumarin on industrial scale, which reaction between salicylaldehyde and acetic anhydride at 150-200°C for 6-8 h. Acetic acid generated should be removed to keep the reaction at high temperature and the resin generated during the reaction causes an increase in viscosity. Thus, we turned our attention in developing a concise and efficient synthesis of coumarin [32].

The chemical synthesis of coumarin was originally achieved by Perkin. In this reaction as displayed in Scheme 6, the coumarin-based derivative was generated from the heatdependent reaction of acetic anhydride with salicylaldehyde utilizing a basic dry salt like sodium acetate. The reaction intermediate termed ortho-hydroxycinnamic acid is afforded and spontaneously lactonized forming the target product [33].

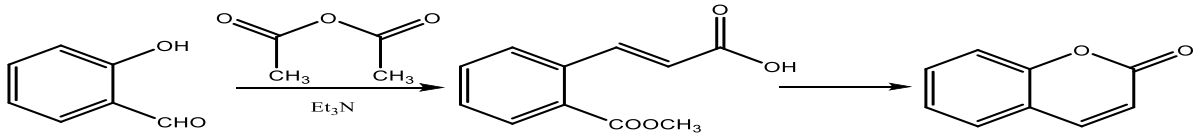
As for many chemical reactions, Perkin synthetic route has several advantages and disadvantages. The most important reported benefit is the improbability for the generation of structural isomer named chromane-based derivative as a side-product. The most significant failure of this reaction is the fakir yield that results from the generation of many side products as a consequence of the applied temperature. However, this failure can be optimized by doubling the molar concentration of the employed anhydride at the expense of the aldehyde. One of the most influential modifications of the Perkin reaction is showed in Scheme 7 and involved the utilization of tertiary amine instead of basic salt as a catalyst for the reaction involves acetic anhydride and salicylaldehyde [34].

2.4. Reformasky Reaction

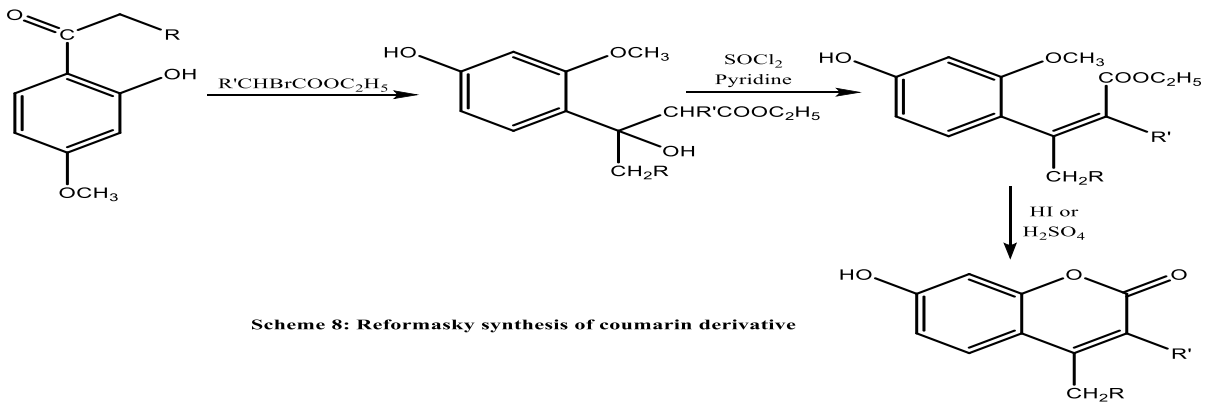
Reformatsky reaction includes a reaction between an activated alkyl halide with a carbonyl compound in the presence of zinc, to form a hydroxy compound, which is converted to β-hydroxy esters. O-Hydroxy aryl/alkyl ketones can be transformed to 3,4-disubstituted coumarins via this reaction (Scheme 8) [35, 36].



Scheme 6: The synthetic pathway of coumarin developed by Perkin.



Scheme 7: The influential modification of Perkin synthetic reaction.



Scheme 8: Reformasky synthesis of coumarin derivative

2.5. Wittig Reaction

The reaction of phosphonium ylide with aryl aldehyde or aryl ketone responded to formation of conjugated alkene, further which results into coumarin-based derivative through oxaphosphetane or betaine reaction inter-mediates (Scheme 9) [37]. On the basis of Witting reaction, many synthetic coumarin based derivatives were synthesized [38]. More ever, there are natural coumarin-based derivatives which are naturally synthesized depending on the basis of this reaction especially those belonged to the prenylated and allylated classes of coumarins [38].

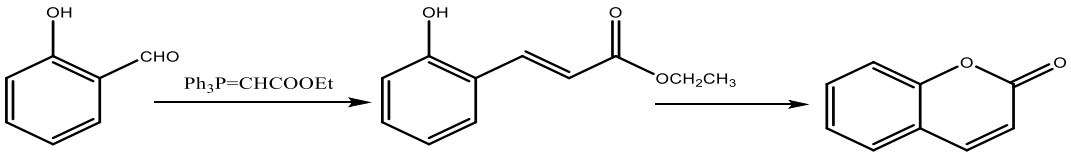
It is documented that the coumarin-based derivatives functionalized at position 4 can be prepared via Witting reaction as shown in Scheme 10. This was carried out by coupling aryl aldehyde or aryl ketone substituted at ortho position with a phenolic hydroxyl group and the stable phosphorene like (carboxymethyl) triphenyl phosphonium bromide ethyl ester [39].

2.6. Claisen rearrangement

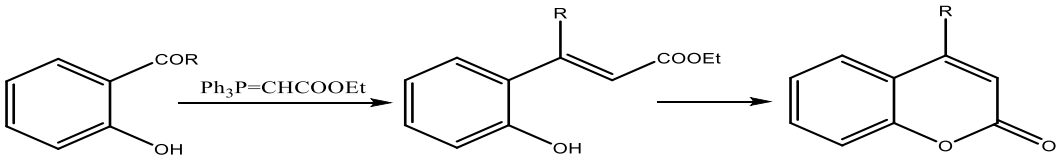
Claisen rearrangement It has been reported that the synthesis of 3,4-dihydro-4- methyl-3-methyle-necou-marin as shown in Scheme 11 can be performed via the Claisen rearrangement by reacting the aryl ether intra-molecularly using a trifluoroacetic acid as a homogenous catalyst [40]. Although this compound has been priorly prepared by others, Drewes and his co-workers have developed a novel synthetic method. This involved the in situ preparation of the intermediate termed chemically as 2-methylene-3-acetoxy alkylbutanoate by acetylating of what is called Baylis-Hillman product. The cyclization of this intermediate was facilitated by trifluoroacetic acid to give 86% yield of the target product in a one-pot technique [41].

Previously, a comparable advancement for the synthesis of 3-methylenecoumarin has been documented. This synthesis involved the Claisen rearrangement of the reaction-intermediate chemically termed as α-aryloxy methyl acrylate ester in the presence of Lewis acid as shown in Scheme 12. The dimer may be afforded in a tiny amount in this reaction as a by-product and usually results from the high reactivity of the double bond of the aforementioned intermediate [42].

In an attempt to clobber the obstacles linked to the synthesis of coumarin-based derivatives via Pechmann reaction, a novel modification of the Claisen rearrangement has been reported. This modification as shown in Scheme 13 involved the utilization of aryl ethers conjugated via their oxygen with the double or triple bond [43]. This modification was applied in case of failure of the formation of a coumarin based derivative by ordinary Pechmann reaction. Considering its reaction mechanism, this modification proceeded through the transformation of the reactant to form an intermediate chemically termed as alkoxychroman, which is subsequently oxidized to coumarin-based derivative [44].

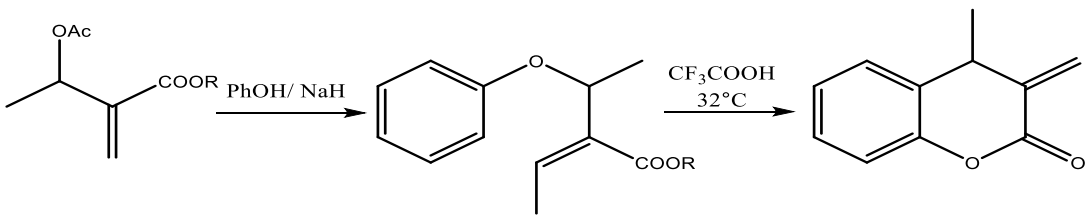


Scheme 9: Synthesis of coumarins by wittig reaction

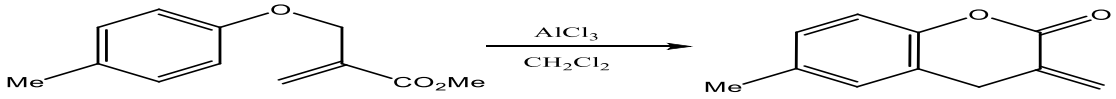


R= Me, H

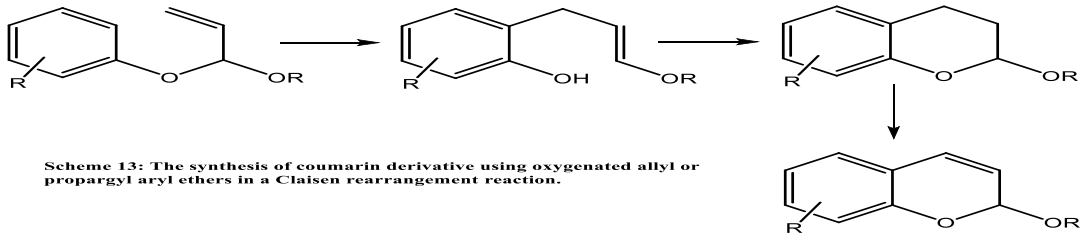
Scheme 10: Synthetic route of coumarins as reported by Hepwarh et al



Scheme 11: Synthesis of 3, 4-dihydro-4-methyl-3-methylene coumarin by claisen reaction



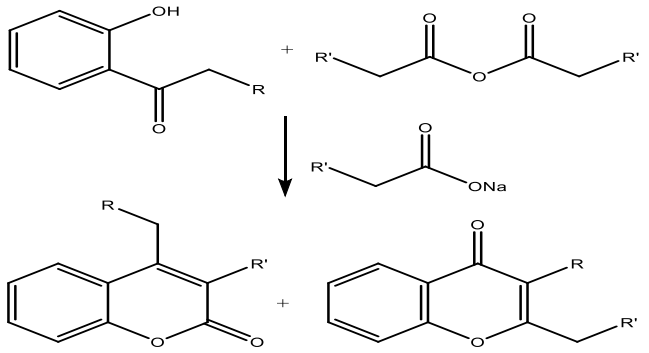
Scheme 12: The Lewis acid-catalyzed synthesis of 3-methylenecoumarin using a Claisen rearrangement



Scheme 13: The synthesis of coumarin derivative using oxygenated allyl or propargyl aryl ethers in a Claisen rearrangement reaction.

2.7. Kostanecki-Robinson synthesis

Kostanecki-Robinson synthesis of coumarins proceeds from o-hydroxy aryl alkyl ketones, acid anhydride and the sodium salt of an acid, by the formation of the 3, 4 carbon-carbon bonds via the ester enolate (Scheme 14). When the reaction proceeds via ketone enolate, chromones (4H-1-benzopyran-4-ones) 1 can be the major products [36, 45].



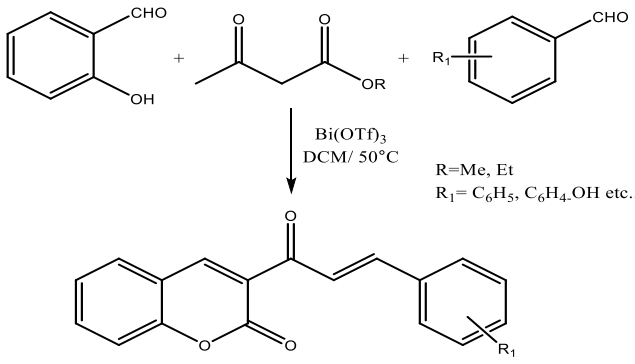
Scheme 14: Kostanecki-Robinson synthesis of coumarins

2.8. One pot reaction

One-pot three-component reactions were performed between salicylaldehyde, α-ketoester and various aromatic aldehydes (Scheme 15) [46, 47]. Several reactions were performed in order to optimize reaction conditions changing catalyst ($FeCl_3 \cdot 6H_2O$, $Fe(OTf)_3$, $ZnBr_2$, $Zn(OTf)_2$, $MgCl_2$, $Mg(OTf)_2$, $CuCl_2$, $Cu(OTf)_2$ and $Bi(OTf)_3$) and solvent (MeOH, N, N-dimethyl formamide, toluene, MeCN and DCM). The highest yield of 96% was obtained in presence of Bi $(OTf)_3$ in DCM at 50°C. Coumarin- chalcone compounds were obtained in excellent yields (88-96%).

2.9. Microwave-helped synthesis

In comparison with the conventional methods of heating, microwave irradiation has revealed many benefits such as the potential inner heating that results in a marked reduction in the time required for the reaction to be finished, in addition to being an ecologically benign source of energy [48]. Also, the use of microwaves to evoke the chemical reactions may reveal a high % yield due to the dropping in the possibilities of the unwanted side reactions. Accordingly, this type of heating can be considered as a part of the global trend toward the application of green chemistry [49]. It has been reported the utilization of a microwave-helped Pechmann reaction can offer an efficient technique to synthesize coumarin-based derivatives in a fast, simple, economically working method. For instance, the synthesis of 4,7-dimethylcoumarin as shown in Scheme 16 from the condensation of m-cresol and ethyl acetoacetate utilizing sulphuric acid as a homogenous acid catalyst [50, 51].

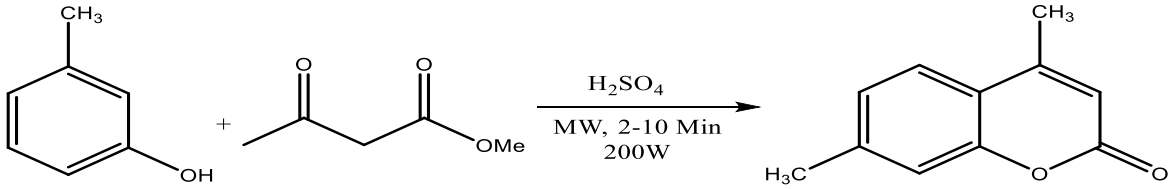


Scheme 15: Synthesis of Coumarin-chalcon compounds in multicomponants reaction

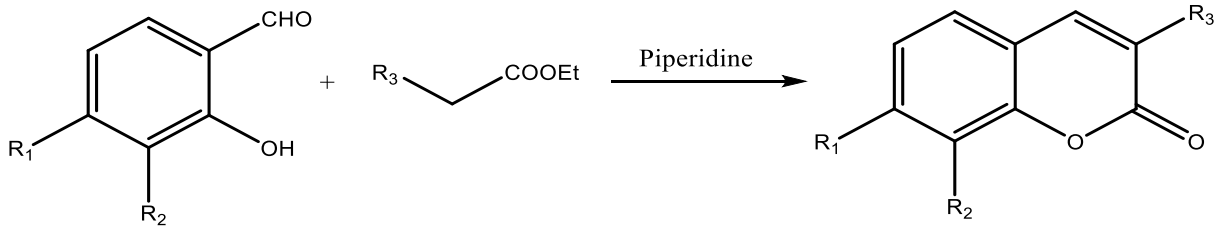
It has been shown that the utilization of microwave irradiation as a source of energy may rise the possibility of getting up the ideal % yield. For instance, the microwave helped synthesis of trisubstituted coumarin-based derivatives as shown in Scheme 17 by reacting different carboxylic ester- and salicylaldehyde-based derivatives. This condensation is usually performed in a solvent-free environment and catalyzed by an organic base [52].

2.10. Ultrasound-helped synthesis

The utilization of ultrasound radiation has been grown for organic chemistry in the last three decades. This may be attributed to the efficiency and ease of monitoring this type of energy. In the literature, it seems to find a huge number of scientific papers utilized this type of energy to facilitate many synthetic pathways [53, 54]. Although most of these reactions were carried out by utilizing organic solvents, there are many attempts to replace these organic solvents with water. These attempts were evoked by the desirable properties of water such as the availability, cheapness, safety, and ecologically friended compound. For instance, the ultrasound-helped synthesis of tetra substituted coumarin-3- carboxylic acid derivatives performed in an aqueous medium as shown in Scheme 18 [55, 56].



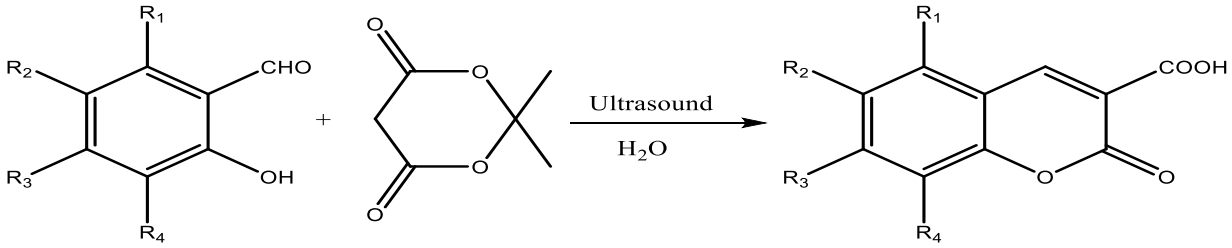
Scheme 16: Synthesis of 4, 7-dimethylcoumarin via microwave-helped pechmann reaction



R_1= H, Et_2N R_3= COOEt, COMe, CN, p-$C_6H_4NO_2$

R_2= H, OMe

Scheme 17: Mircowave helped synthesis of coumarins



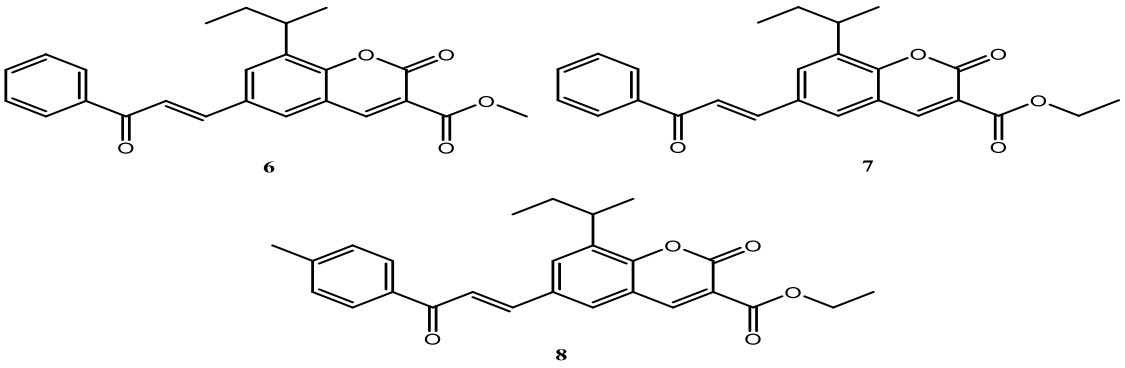
Scheme 18: Ultrasound helped synthesis of tetrasubstituted coumarin-3-carboxylic acid derivative

3. BIOLOGICAL ACTIVITY OF COUMARIN

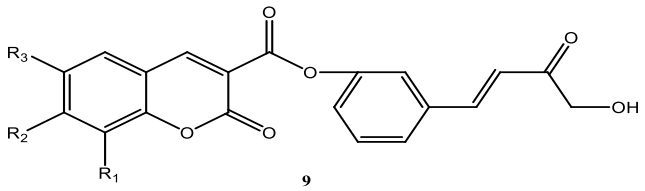
3.1. Anticancer Activity

K. V. Shashidhara and co-workers synthesized and evaluated a number of coumarin-chalcone hybrids for their in vitro cytotoxicity against a group of 4 human cancer cell lines and normal fibroblasts (NIH3T3). Out of 21 Molecules screened, three (6, 7 and 8) molecules showed IC_{50} range from 3.59 to 8.12 lM. The most promising molecule **8** showed around 30-fold more selectivity towards C33A (cervical carcinoma) cells over normal fibroblast NIH3T3 cells with an IC50 value of 3.59 lM [57].

Zhiyu guan and co-workers synthesized a series of novel coumarin-based N-hydroxy cinnamamide derivatives as histone deacetylase (HDAC) inhibitors. Most of the synthesized molecules exhibit potent HDAC inhibitory activity and significant antiproliferative activity against human cancer cell lines MCF-7, HepG2, HeLa and HCT-116. Out of that, molecule **9** showed the most potent HDAC inhibition, especially against HDAC1 with IC_{50} value of 0.19 μM, which was better than that of SAHA (IC_{50} = 0.23 μM). It also exhibit the strongest anti-proliferative activity towards HeLa cells and more than 25-fold selectivity for HDAC1 compared with HDAC6. In addition, compound **9**c ould inhibit colony formation, upregulate the acetylation level of histone H3, and induce apoptosis and cell cycle arrest at G2/M phase in HeLa cells. Taken together, these results highlighted that compound **9** might be a promising HDAC inhibitor for cancer therapy [58].

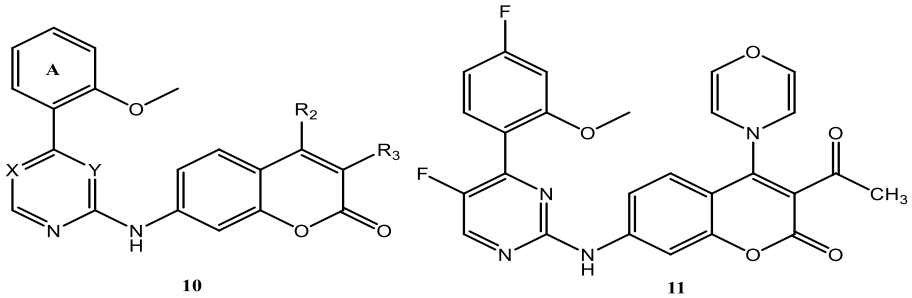


6 7 8



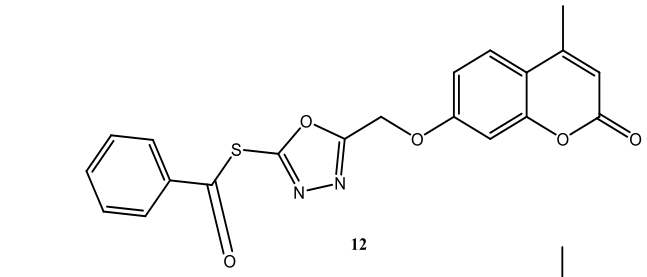
9

Specific inhibition of CDK9 is considered a promising way for development of effective anticancer medicine [59]. Yadong Chen and co-workers discovered a coumarin derivative **10** as a target molecule with selective inhibition against CDK9. Then, a series of derivatives of 7-(pyrimidin-2-yl amino)-2H-chromen-2-one and 7-(pyrimidin-4-ylamino)-2Hchromen-2-one were designed, synthesized and evaluated as anti-tumour agents. This effort of authors led to the generation of a highly promising potent and selective CDK9 inhibitor **11**, which beneficially inhibited CDK9 with an IC50 value of 2 nM and presented 160- to 978-fold selectivity versus CDK1/2/3/4/5/6 (cell cycle CDKs) and over 3250-fold selectivity versus CDK7/8/19 (transcriptional CDKs). Further profiles of kinase selectivity exhibit that **11** most selectively inhibit CDK9 among 372 kinases. Analysis of the binding mode illustrated that the 3-acetyl-4-morpholino-2H-chromen-2-one moiety occupied the flexible hinge/aD region of CDK9 which shows the steric hindrance in other CDKs, and this may account for its remarkable selectivity. Furthermore, **11** illustrated impressive anti-proliferative activity in a panel of tumour cell lines, including leukaemia, pancreatic cancer, gastric cancer, melanoma, liver cancer, breast cancer, colon cancer and non-small-cell lung cancer. The moderate metabolic stability in liver microsomes and low hERG inhibition illustrated acceptable drug-like properties. In vivo, **11** exhibited a moderate pharmacokinetic profile, and it significantly induced tumour growth inhibition in a dose dependent manner in an MV4-11 (AML) mice xenograft model without causing mortality or an obvious loss of body weight. The study of cellular mode of action suggests **11** down regulated Mcl-1 and c-Myc by dose-dependently inhibiting the CDK9-mediated phos-phorylation of RNAPII [60].

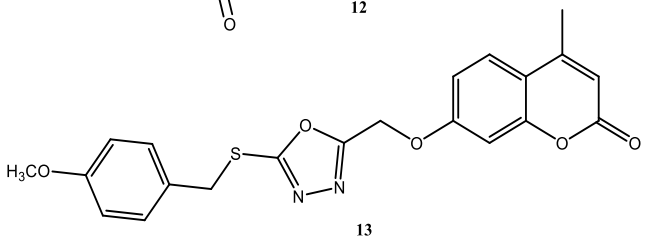


10 11

M. Alvala and co-workers developed novel heterocyclic hybrids as potent anticancer agents synthesized a series of coumarin-1, 3, 4-oxadiazole hybrids and evaluated for their inhibitory activity against the four physiologically relevant human carbonic anhydrase (hCA, EC 4.2.1.1) isoforms CA I, CA II, CA IX and CA XII. The CA inhibition answersdistinctlyspecify that the coumarin-1, 3, 4-oxadiazole derivatives showed selective inhibition of the tumor associated isoforms, CA IX and CA XII over CA I and II isoforms. Out of that **12** molecule, shown significant inhibition in lower micromolar potency against hCA XII, with a Ki of 0.16 µM and molecule **13**, exhibited significant inhibition in lower micromolar potency against hCA IX, with a Ki of 2.34 µM respectively [61, 62].



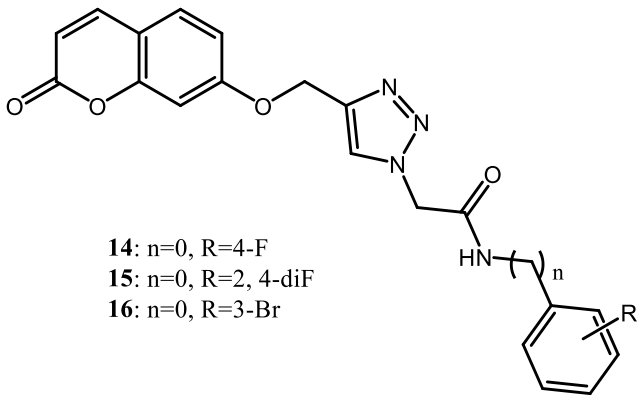
12



13

3.2. Inhibitors of metabolic enzymes

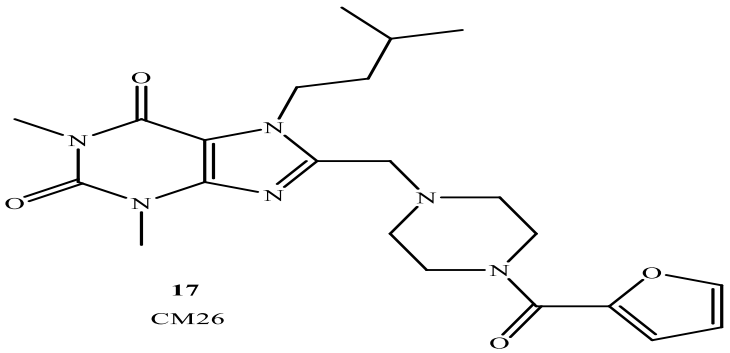
Parham Taslimi and co-workers synthesized a series of novel coumarin-1, 2, 3-triazole-acetamide hybrids was examine against some metabolic enzymes including α-glycosidase human carbonic anhydrase I (hCA I), and hCA II, α-amylase (α-Amy), (α-Gly), acetylcholine-sterase (AChE), butyrylcholinesterase (BChE). All of the compounds have showed a significant sub-nanomolar inhibition against all metabolic enzymes, especially compound **14** for cytosolic hCA I and II isoenzymes, **15** for both cholinergic enzymes and α-amylase enzyme, and **16** for α-glycosidase enzyme. Different moieties of the compounds are of crucial importance for the inhibition for indicated enzyme receptors. Novel coumarin–1,2,3-triazole-acetamide could modulate different pathways involved in disease progression [63].



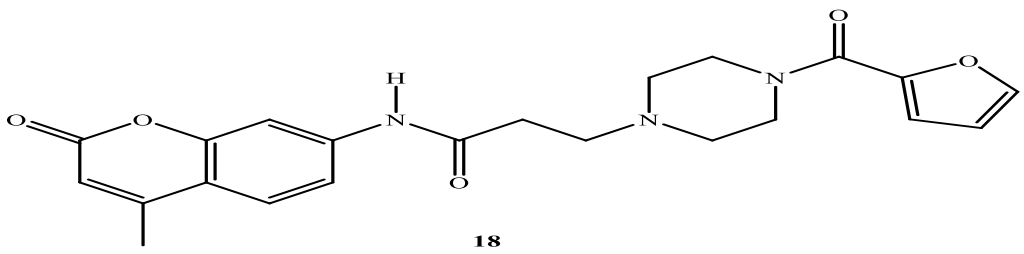
14: n=0, R=4-F
15: n=0, R=2, 4-diF
16: n=0, R=3-Br

3.3. Anti-diabetic Activity

Li Liu and co-workers synthesized and evaluated a series of coumarin-based ALDH1A1 inhibitors. Several of them showed potent inhibitory activity against ALDH1A1 and high selectivity over other ALDH isozymes (ALDH1A2, ALDH1A3, ALDH2 and ALDH3A1). The optimized compound **18** showed potent ALDH1A1 inhibitory activity and excellent selectivity against other ALDH isozymes, together with markedly improved PK characters comparing to compound **17** (CM26). Compound **18** can effectively alleviate palmitic acid-induced impairment of glucose consumption in HepG2 cells. Compound **18** provided an excellent lead compounds for optimization towards the development as a promising candidate for the treatment of obesity and diabetes. hALDH1A1 % inhibition at 10 μM of Compound **17** (CM26) and **18** was 75.22 ± 5.28 and 61.82 ± 7.97 respectively. hALDH1A1 IC50 ± SD [μM] of Compound **17** (CM26) and **18** was1.21±0.18, **18**=3.87±0.48respectively [64].

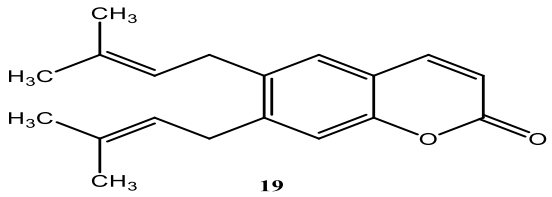


17
CM26



18

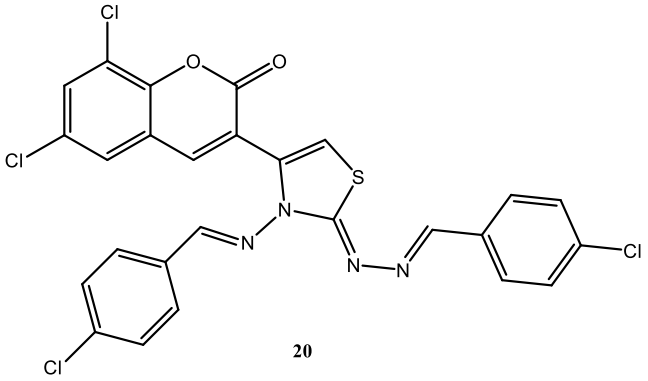
Constitutive androstane receptor (CAR, NR1I3), a member of the super family of nuclear receptors, is a xenobiotic receptor responsible for the regulation of drug metabolism as well as the pathological involvement of various diseases such as cancer, diabetes, inflammatory disease, metabolic disease and liver disease, suggesting a potential target for drug discovery [65]. CAR activation has already been associated with amelioration of various diseases such as diabetes. However, clinical CAR agonists are still lacking, therefore, a safe and effective CAR activator would be an interesting alternative option for these diseases. In this study, sixty coumarin derivatives either synthesized or purified from Yin Chen were screened for CAR activation activity. Among all the compounds, **19** is the most effective for CAR activation and were selected for further studies. Modification on the 6 position is generally more beneficial than at other positions. Electron-withdrawn groups are detrimental to the activity. Mechanism of action studies showed that CAR activation of **19** might be through the inhibition of EGFR signaling and upregulated PP2Ac methylation. In vivo OGTT, scoparone can lower blood sugar and fructosamine levels without insulinotropic effects. In addition, a preliminary pharmacokinetic study also indicated the desired scoparone blood concentration can be achieved. This study established also a screening system providing a rapid method for CAR activator discovery and development and provided scientific evidence for the effects of coumarins on CAR activation [66].



19

3.4. Antibacterial Activity

R. R. Vedula and co-workers developed a robust microwave irradiatedgreen synthetic protocol for the synthesis of new coumarin based thiazoles. All the compounds were screened for their *in vitro* antibacterial activity and the results revealed that the compound **20** exhibited remarkable activity *against S. aureus*. Furthermore, it was established from docking studies that interactions with Arg 138 (or) Lys 36 in coumarin based thiazoles might play a pivotal role in binding of inhibitors to topoisomerase [67-69].



20

3.5. Anti-inflammatory Activity

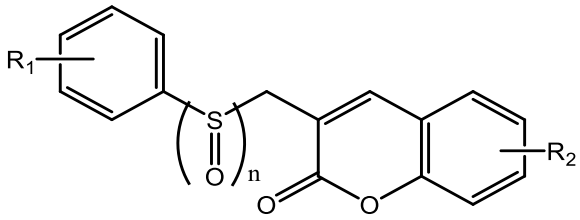
Lin Wang and co-workers synthesized a total of twelve coumarin derivatives linked substituted benzyl sulfone/sulfoxide moieties at C-3 position. The anti-inflammatory effects of these molecules were examined *in vitro* and *in vivo*, including the inhibition of TNF-α production induced by LPS in RAW 264.7 macrophages, cyclooxygenase inhibition study and xylene-induced ear swelling in mice. Conclusion of the in vitro evaluation gives information about that most of the molecules could repress the release of TNF-α and showed favorable inhibitory activity against COX-1 at the concentration of 10 μM. Moreover, **24** and **26** exhibited the highest inhibitory potency on COX-2. In addition, at the dose of 20 mg/kg, the active molecules **21, 22, 23, 24, 25** and **26** could obviously repress ear swelling *in vivo*. Principally, molecule **26** exhibit satisfactory inhibitory activity like indomethacin at the dose of 10 mg/kg [70].

3.6. Antifungal Activity

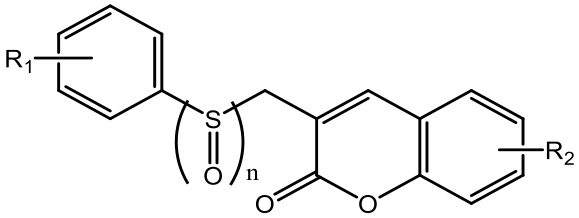
Maoping chu and co-workers investigated the exact mechanism by which coumarin (1,2-benzopyrone) **27** works against this fungus using Annexin V-FITC/PI double staining, TUNEL assay, and DAPI staining, and found that it induced a series of apoptotic features, including phosphatidylserine (PS) externalization, DNA fragmentation, and nuclear condensation.

Moreover, it also induced cytochrome c release from the mitochondria to the cytoplasm and metacaspase activation. Further study revealed that intracellular reactive oxygen species (ROS) levels were increased and mitochondrial functions, such as mitochondrial membrane potential and mitochondrial morphology, were altered after treatment with coumarin. Cytosolic and mitochondrial Ca^{2+} levels were also found to be elevated. However, pretreatment with ruthenium red (RR), a known mitochondrial Ca^{2+} channel inhibitor,

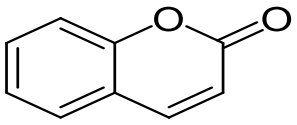
attenuated coumarin-mediated DNA fragmentation and metacaspase activity, indicating that the coumarin-induced *C. albicans* apoptosis is associated with mitochondrial Ca^{2+} influx. Finally, coumarin was found to be low-toxic and effective in prolonging the survival of *C. albicans*-infected mice. This study highlights the antifungal activity and mechanism of coumarin against *C. albicans* and provides a potential treatment strategy for *C. albicans* infection [71-73].



21: R_1 = 4-Br, R_2 = 6-OCH_3, n = 2
22: R_1 = 4-Br, R_2 = 6-OCH_3, n = 1
23: R_1 = 4-Br, R_2 = 5,7-$(OCH_3)_2$, n = 2
24: R_1 = 3-OCH_3, R_2 = 6-Br, n = 1



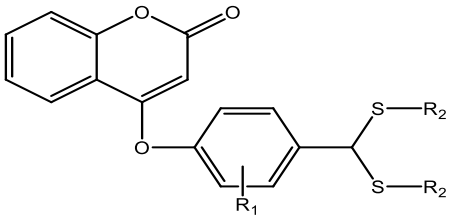
25: R_1 = 3-OCH_3, R_2 = 5,7-$(OCH_3)_2$, n = 2
26: R_1 = 3-OCH_3, R_2 = 6-Br



27

3.7. Antiviral Activity

Baoan Song and co-workers synthesized a series of coumarin derivatives containing dithioacetal moieties and evaluated for their anti-TMV activities. The results of the biological activity assay exhibit that the targeted molecule shown good curative, protective, and inactivation activities. In particular, **28, 29,** and **30** molecules showed excellent anti-TMV inactivation activity with EC50 values of 68.4, 54.2, and 65.3 mg/L, respectively. SAR conclusion of this conclude that the addition of unbranched aliphatic groups (Et, n-Pr, and n-butyl) into the molecule increases its anti-TMV activity. With respect to the title compound, it has good anti-TMV inactivation activity, and compound **29** exhibited a good binding ability toward TMV CP through molecular docking analysis. The results of MST experiments showed that compound **29** has a strong binding ability with TMV CP, which is consistent with the results of molecular docking experiments. The TEM results showed that the morphology of the TMV particles was severely disrupted and ruptured in the presence of compound **29**. These findings indicate that compound **29** has a strong binding ability toward TMV and can disrupt its structure and cause its rupture, thereby inactivating the virus and inhibiting the infection of plants. The results of the current study provide reliable support for the use of the dithioacetal-containing coumarin structure as a potential lead compound for anti-TMV virus agents [74, 75].



28: R_1=OCH_3, R_2=Et
29: R_1=H, R_2=Et
30: R_1=H, R_2=n-Butyl

4. CONCLUSION

The plethora of biological and pharmaceutical applications of naturally occurring as well as synthetic coumarins has prompted researchers to explore methodologies for the development of this class of compounds and to evaluate their pharmacological activities. In this review, coumarin has been highlighted as a unique scaffold in medicinal chemistry. In particular, the review covers only synthetic methods of coumarin and their derivatives of coumarins; Based on the substitution pattern on the coumarin moiety, the pharmacological activity of these molecules vary. Although coumarin showed potential in various biological activities, such as anticancer, anti-inflammatory, antibacterial, anti-diabetic, etc., most work has been performed on the derivatization of whole coumarin moiety. Further here number of methods for synthesis of coumarin have been discussed such as Pechmann condensation reaction, knovengeal reaction, Reformatsky reaction, Perkin reaction etc., It should be noted that various biological active and potent molecule have been reportedwith diverse substitutions; however, their biological activity, which we believe can lead to

various new drug candidates, is lacking. This review may stimulate researchers to use coumarin scaffolds and further carry out diverse functionalizations to develop new structural motifs in drug design and medicinal chemistry.

***Conflicts of Interest*:**
There are no conflicts to declare.

5. REFERENCES

1. Gaspar A, Matos MJ, Garrido J, Uriarte E, Borges F. *Chemical reviews*, 2014; **114(9)**:4960-4692.
2. Emami S, Dadashpour S. *European Journal of Medicinal Chemistry*, 2015; **102**:611-630.
3. Abdel-Wahab BF, Mohamed HA, Farhat AA. *Organic Communications*, 2014; **7(1)**:1.
4. Gummudavelly S, Ranganath Y, Bhasker S, Rajkumar N. *Asian Journal of Research in Chemistry*, 2009; **2(1)**:46-48.
5. Balasubramanian A, Ramalingam K, Radhakrishanan R, John R, Arafath YN. *Research Journal of Pharmacy and Technology*, 2019; **12(6)**:2804-2808.
6. Arora P, Ranawat MS, Arora N. *Research Journal of Pharmacy and Technology*, 2012; **5(7)**: 968-972.
7. De SK, Gibbs RA. *Synthesis*, 2005; **2005(08)**:1231-1233.
8. Hussien FA, Keshe M, Alzobar K, Merza J, Karam A. *Int. Lett. Chem. Phys. Astron.*, 2016; **69**:66-73.
9. Egan D, O'kennedy R, Moran E, Cox D, Prosser E, Thornes RD. *Drug metabolism reviews*, 1990; **22(5)**:503-529.
10. Kontogiorgis C, Detsi A, Hadjipavlou-Litina D. *Expert opinion on therapeutic patents,* 2012; **22(4)**:437-454.
11. Hussain MI, Qamar Abbas S, Reigosa MJ. *Planta Daninha*, 2018; **36**:1-12.
12. Narayanaswamy VK, Gleiser RM, Kasumbwe K, Aldhubiab BE, Attimarad MV, Odhav B. *The Scientific World Journal*, 2014; **2014**:1-6.
13. Frosch PJ, Johansen JD, Menne T, Pirker C, Rastogi SC, Andersen KE, et al. *Contact dermatitis*, 2002; **47(5)**:279-287.
14. Kadam MM, Patil DS, Sekar N. *Journal of Molecular Liquids*, 2019; **276**:385-398.
15. Traven VF, Cheptsov DA, Dolotov SM, Ivanov IV. *Dyes and Pigments*, 2018; **158**:104-113.
16. Li J, Zhang CF, Yang SH, Yang WC, Yang GF. *Analytical chemistry*, 2014; **86(6)**:3037-3042.
17. Wang C, Wu C, Zhu J, Miller RH, Wang Y. *Journal of medicinal chemistry*, 2011; **54(7)**:2331-2340.
18. Sethna SM, Shah NM. *Chemical Reviews*, 1945; **36(1)**:1-62.
19. Bigi F, Quarantelli C, *Current Organic Synthesis*, 2012; **9(1)**:31-39.
20. Bigi F, Chesini L, Maggi R, Sartori G. *The Journal of organic chemistry*, 1999; **64(3)**:1033-1035.
21. Smitha G, Sanjeeva Reddy C. *Synthetic communications*, 2004; **34(21)**:3997-4003.
22. Araki S, Ito H, Katsumura N, Butsugan Y. *Journal of organometallic chemistry*, 1989; **369(3)**:291-296.
23. Phadtare SB, Shankarling GS. *Environmental chemistry letters*, 2012; **10(4)**:363-368.
24. Hwang IT, Lee SA, Hwang JS, Lee KI. *Molecules*, 2011; **16(8)**:6313-6321.
25. Hassanabadi A. *Journal of Chemical Research*, 2013; **37(6)**:340-341.
26. Kim S, Kang D, Lee CH, Lee PH. *The Journal of organic chemistry*, 2012; **77(15)**:6530-6537.
27. Wang H, Liu X, Feng X, Huang Z, Shi D. *Green chemistry*, 2013; **15(12)**:3307-3311.
28. Tyndall S, Wong KF, VanAlstine-Parris MA. *The Journal of organic chemistry*, 2015; **80(18)**:8951-8953.
29. Alheety KA, Jamel NM, Ahmed BJ. *Journal of Pharmaceutical Sciences and Research*, 2019; **11(9)**:3344-3347.
30. Pawar V, Chavan SV, Yamgar RS, Atram RG, Thorat BR, Bisht S, Sawant SS. *Asian Journal of Research in Chemistry*, 2011; **4(8)**:1238-1242.
31. Mirosanloo A, Zareyee D, Khalilzadeh MA. *Applied Organometallic Chemistry*, 2018; **32(12)**:4546.
32. Kumar KA, Renuka N, Pavithra G, Kumar GV. *J Chem Pharm Res.,* 2015; **7(9)**:67-81.
33. Lončarić M, Gašo-Sokač D, Jokić S, Molnar M. *Biomolecules*, 2020; **10(1)**:151.
34. Jadhav NH, Sakate SS, Rasal NK, Shinde DR, Pawar RA. *ACS omega*, 2019; **4(5)**:8522-8527.
35. Chandrasekharam M, Bhat L, Ila H, Junjappa H. *Tetrahedron letters*, 1993; **34(40)**: 6439-6442.
36. Dittmer DC, Li Q, Avilov DV. *The Journal of organic chemistry*, 2005; **70(12)**:4682-4686.
37. Cerqueira NM, Oliveira-Campos AM, Coelho PJ, de Carvalho LH, Samat A, Guglielmetti R. *Helvetica chimica acta*, 2002; **85(2)**:442-450.
38. Borges F, Roleira F, Milhazes N, Santana L, Uriarte E. *Current medicinal chemistry*, 2005; **12(8)**:887-916.

39. Krachko T, Lyaskovskyy V, Lutz M, Lammertsma K, Slootweg JC. *Zeitschrift für anorganische und allgemeine Chemie*, 2017; **643(14)**:916-921.
40. Drewes SE, Emslie ND, Karodia N, Loizou G. *Synthetic Communications*, 1990; **20(10)**:1437-1443.
41. Howard BE, Woerpel KA. *Organic letters*, 2007; **9(22)**:4651-4653.
42. Sunitha K, Balasubramanian KK, Rajagopalan K. *Tetrahedron letters*, 1984; **25(29)**:3125-3126.
43. Dalpozzo R, Bartoli G, Sambri L, Melchiorre P. *Chemical reviews*, 2010; **110(6)**:3501-3551.
44. Jung JW, Kim NJ, Yun H, Han YT. *Molecules*, 2018; **23(10)**:2417.
45. Waldvogel SR. *Synthesis*, 2010; **2010(05)**:892.
46. Ali MA. *Chinese Journal of Catalysis*, 2015; **36(7)**:1124-1130.
47. Mashelkar UC, Pandey VJ, Mashelkar BU. *Asian Journal of Research in Chemistry*, 2013; **6(11)**:1007-1010.
48. Bouasla S, Amaro-Gahete J, Esquivel D, López MI, Jiménez-Sanchidrián C, Teguiche M, Romero-Salguero FJ. *Molecules*, 2017; **22(12)**:2072.
49. Elavarasan S, Bhakiaraj D, Elavarasan T, Gopalakrishnan M. *Journal of chemistry*, 2013; **2013**:1-4.
50. Monga Paramjeet K, Sharma D, Dubey A. *ChemInform*, 2012; **43(26)**:1-4.
51. Jainab NH, Sivachidambaram P, Yuvaraju J, Beyatricks KJ, Raj B. *Asian Journal of Research in Chemistry*, 2014; **7(2)**:176-181.
52. Bogdał D. *Journal of Chemical Research, Synopses*, 1998; **1(8)**:468-469.
53. Li JT, Han JF, Yang JH, Li TS. *Ultrasonics Sonochemistry*, 2003; **10(3)**:119-122.
54. Jin H, Xiang L, Wen F, Tao K, Liu Q, Hou T. *Ultrasonics sonochemistry*, 2008; **15(5)**:681-683.
55. Bigi F, Maggi R, Sartori G. *Green chemistry*, **2000; 2(4)**:140-148.
56. Du JL, Li LJ, Zhang DH. *E-Journal of Chemistry*, 2006; **3(1)**:1-4.
57. Sashidhara KV, Kumar A, Kumar M, Sarkar J, Sinha S. *Bioorganic & medicinal chemistry letters*, 2010; **20(24)**:7205-7211.
58. Ding J, Liu J, Zhang Z, Guo J, Cheng M, Wan Y, et al. *Bioorganic Chemistry*, 2020; **101**:104023.
59. Sammons SL, Topping DL, Blackwell KL. *Current cancer drug targets*, 2017; **17(7)**:637-649.
60. Xu J, Li H, Wang X, Huang J, Li S, Liu C, et al. *European Journal of Medicinal Chemistry*, 2020; **200**:112424.
61. Narella SG, Shaik MG, Mohammed A, Alvala M, Angeli A, Supuran CT. *Bioorganic chemistry*, 2019; **87**:765-772.
62. Momin KI, Suryawanshi VB, Bondge AS, Dawale JK. *Asian Journal of Research in Chemistry*, 2018; **11(2)**:453-458.
63. Sepehri N, Mohammadi-Khanaposhtani M, Asemanipoor N, Hosseini S, Biglar M, Larijani B, et al. *Archiv der Pharmazie*, 2020; **353(10)**:20001-20009.
64. Liang D, Fan Y, Yang Z, Zhang Z, Liu M, Liu L, et al. *European journal of medicinal chemistry*, 2020; **187**:1119-1123.
65. Banerjee M, Robbins D, Chen T. *Drug discovery today*, 2015; **20(5)**:618-628.
66. Juang SH, Hsieh MT, Hsu PL, Chen JL, Liu HK, Liang FP, et al. *Molecules*, 2021; **26(1)**:164.
67. Mamidala S, Peddi SR, Aravilli RK, Jilloju PC, Manga V, Vedula RR. *Journal of Molecular Structure*, 2021; **1225**:129114.
68. Soman SS, Thaker TH, Baloni RD. *Asian Journal of Research in Chemistry*, 2011; **4(1)**:132-136.
69. Kumbhar D, Patil R, Patil D, Patravale A, Chandam D, Jadhav S, et al. *Asian Journal of Research in Chemistry*, 2015; **8(8)**:511-520.
70. Wang T, Peng T, Wen X, Wang G, Liu S, Sun Y, et al. *Chemical and Pharmaceutical Bulletin*, 2020; **68**:c19-01085.
71. Xu K, Wang JL, Chu MP, Jia C. *Journal de mycologie medicale*, 2019; **29(1)**:28-34.
72. Kumar A, Shetty P, Amrutha CL, Vaz DR, Baby A. *Research Journal of Pharmacy and Technology*. 2016; **9(5)**:545-548.
73. Mahapatra DK, Talele SG, Haghi AK, *CRC Press*, 2020; **1**:173.
74. Zhao L, Zhang J, Liu T, Mou H, Wei C, Hu D, Song B. *Journal of agricultural and food chemistry*, 2019; **68(4)**:975-981.
75. Ahire ED, Sonawane VN, Surana KR. *Pharm Reson.*, COVID-19 Special Issue 2020; **2020:**24-29.