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Review Article

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Research Progress of Chrysin derivatives with potential biological activities

Bhavani Kedika*, Krishna Thotla, Venkatagiri Noole and Krishna Reddy Chepyala

Department of Chemistry, Osmania University, Hyderabad-500007, Telangana, India

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ABSTRACT

Chrysin is a naturally occurring flavonoid, mainly found in honey, propolis and in many plant species. Owing to its multiple pharmacological properties such as antioxidant, anti-inflammatory, anti-allergic, anti-diabetic, anti-estrogenic, antibacterial, neuroprotective activity and antitumor activities, chrysin has become the foremost candidate among flavonoids in recent years. Chrysin derivatives had also seen potential applications in anticancer drug delivery. Due to issues such as bioavailability and absorption associated with Chrysin, its therapeutic benefits remained nascent unlike other flavonoids. To overcome these limitations and to obtain compounds with improved efficacy and developing more active drugs efforts had been made by designing analogs and conjugates of Chrysin. The target of the current review is to articulate the recent progress in research on synthesis and pharmacological activities of Chrysin derivatives. Additional information on the basic chemical reactivity of Chrysin, its bioavailability and toxicity is also presented in this article.

Keywords: Chrysin derivatives, anticancer activity, antimicrobial activity, anticancer drug delivery, carboxylase inhibitors, antihelminthic activity, α-glucosidase inhibitors.

INTRODUCTION

Flavonoids having benzo-γ-pyrone structure are large group of polyphenolic compounds found ubiquitously in plants. Research reports showed that these are secondary metabolites with wide variety of pharmacological activities [1, 2] and their activities depend on the structure. These are hydroxylated phenolic substances synthesized by plants in response to microbial infection. These are categorized according to their molecular structures into flavonols, flavones, flavanones, isoflavone, Catechin, anthocyanidin and chalcones. Among them flavones is the largest subgroup of flavonoids. Flavone basic structural feature includes two benzene rings, A and C rings and B ring (a phenyl) attached to position 2 of the ring. Natural flavones such as Apigenin, luteolin and chrysin were found to possess a broad spectrum of biological profile. [3, 4] The in vivo fate of flavones shows that they are poorly conserved, with most of what is absorbed is destined for rapid excretion.

Chrysin found in several plants, mushroom and honeycomb is extensively studied flavone. It is known to have broad spectrum of biological activities including anticancer, anti-inflammatory, antioxidant, antibacterial, anti-diabetic and anti-HIV [5]. But low solubility and relatively poor absorption in the intestine are the main drawbacks that limit its potential applications. To improve the bioavailability and efficacy of chrysin many efforts had been made by researchers on designing its analogs and conjugates. Several articles and reviews on biological activity of synthetic derivatives of chrysin have been reported earlier [6, 7, 8]. In this article current trends and latest improvements of chrysin use in the biomedical field are summarized.

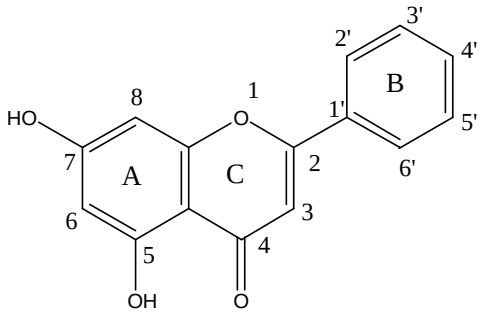


Figure 1. Structure of Chrysin

Occurrence and Chemistry

Chrysin (5,7-dihydroxyflavone or 5,7-dihydroxy-2-phenyl-4Hchromen-4-one) (**Figure 1**) belongs to the flavone class of the ubiquitous 15-carbon skeleton natural polyphenolic compounds collectively called flavonoids. Sources of chrysin includes passion flower (*Passiflora caerulea),* , propolis and honey [9].

Pharmacological acitivites of Chrysin derivatives

The derivatives of chrysin have been reported to show marked change on the function of chrysin.

The multiple biological activities of chrysin (**Figure 2**) with latest improvements in the specified area that had been extensively investigated are summarized in this article.

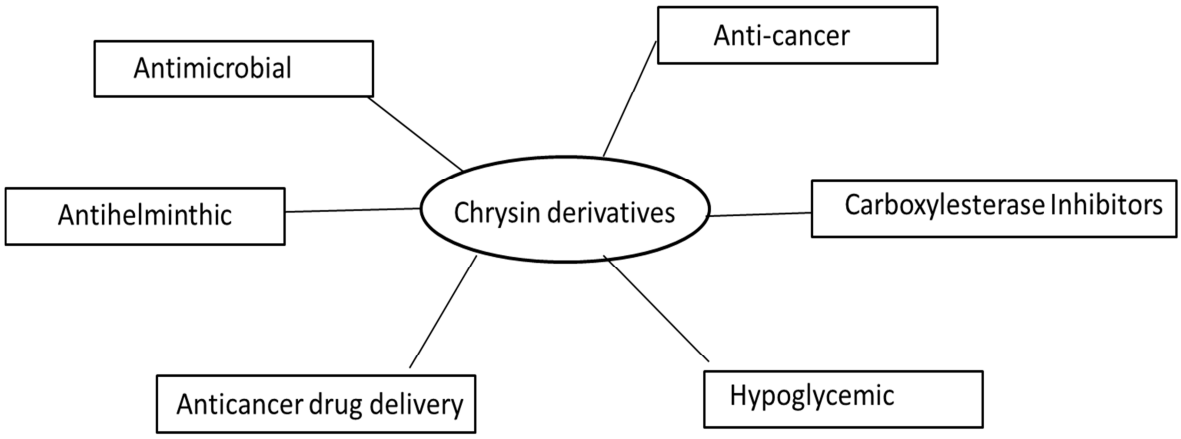
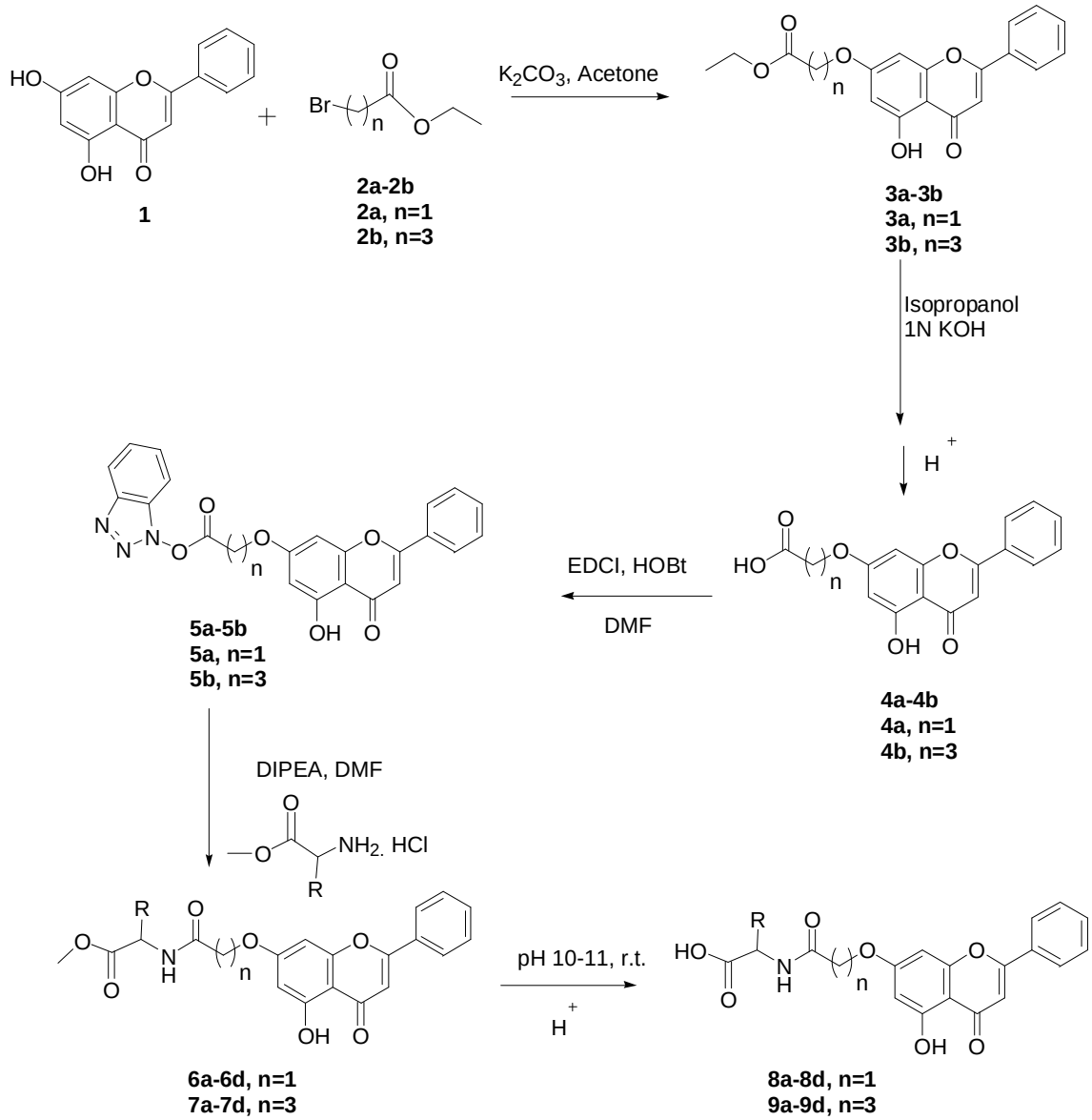


Figure 2. Different biological activities of Chrysin

Anticancer activity of synthetic chrysin derivatives

The anticancer activity of chrysin has attracted great attention. Chrysin has been found to possess cancer chemopreventive activity through activating notch 1 signaling [10], altering the cell cycle progression [11], inhibiting the histone deacetylase enzymatic activity [12], inducing apoptosis in different malignant tumor cells [13], and inhibiting complexes of cyclins [14]. However, in in vivo studies on humans and animals, the anticancer activity of chrysin has been disappointing mainly due to the low solubility, relative poor absorption in intestinal and the rapid metabolism of glycosylation [15]. Many medicinal chemists have been dedicated to searching for novel chrysin derivatives with high efficacy, low toxicity, and minimum side effects. Anticancer activity of synthetic chrysin derivatives were studied in detail by structural-activity relationships, of which some examples were reviewed earlier. Here in the recent progress in the development of new synthetic chrysin derivatives with anticancer activity were given.

Xiudao et al.,[5] synthesized two series of amino acid derivatives of chrysin via modifying 7(C) OH group with alanine, leucine, isoleucine and phenylalanine by acetyl and butyryl groups. The anti-tumor activities of the synthetic amino acid derivatives of chrysin 6a-7d and 8a-9d (**Scheme 1**) were examined against human gastric carcinoma MGC-803 cells. The results revealed that chrysin coupled with different amino acids displayed moderate to good anti-proliferative activity. Particularly the compound 7c showed the most potent inhibitory activity with an IC_{50} value of 3.78 lmol/L and was comparable with that of Cisplatin (IC_{50}= 4.40 lmol/L). The results can be used further for development of more chrysin based selective and active anti-cancer activity drug candidates.

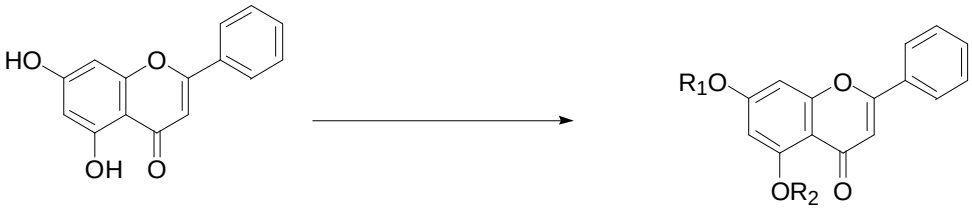


Scheme 1: Synthesis route of chrysin derivatives according to Xiudao et al

In search of potential antitumor agents Zhen-Yuan et al., [16] synthesized a series of 5,7-disubstituted chrysin, 7-monosubstituted chrysin, 5-monosubstituted chrysin derivatives and evaluated their antitumor activity on H22 cells (**Scheme 2**). Among the tested compounds, compound 3 (5,7-diacetyl chrysin) displayed the most potent antitumor activity with IC_{50} value of 141 mM. The results showed that modification of 5- and 7- positions of chrysin would change the activity and the activity depends on the substituents. It was concluded that the small size of hydrophobic substitution at both 5- and 7- positions is a good way of derivatization to increase the chrysin bioactivity.

Recently Bhupendra et al., [17] synthesized a series of chrysin-benzothiazole conjugates using 7-(4-Bromobutoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one, obtained from chrysin with 1,4-dibromobutane, combining with a wide range of 6-substituted 2-aminobenzthiazoles, which had been prepared from the corresponding anilines with potassium thiocyanate (**Scheme 3**). The anticancer activity of the newer analogues were tested against cervical cancer cell line (HeLa and CaSki) and ovarian cancer cell line (SK-OV-3). The authors found that particularly the presence of halogens (6g, 6, 6j-6l) was favourable with IC50 values comparable to the control ascorbic acid. It was observed that length of the aliphatic side sequence linking two different pharmacophores as chrysin and benzothiazole was essential in providing reliable biological profiles. From the structure–activity perspective, characteristics and position of the electron withdrawing and electron donating functional groups on the benzothiazole core may promote the expected anticancer action. One more important observation found by the

authors in this study was, the activity profiles seen for 6a–r against SK-OV-3 was appreciable as compared to parent chrysin. Chrysin has no activity against ovarian cancer cell line SK-OV-3 as noticed in a previous research attempts [18]. This study shows the positive influence of benzothiazole substitution on the activity profiles of chrysin core.



1 **Compound 2-9**

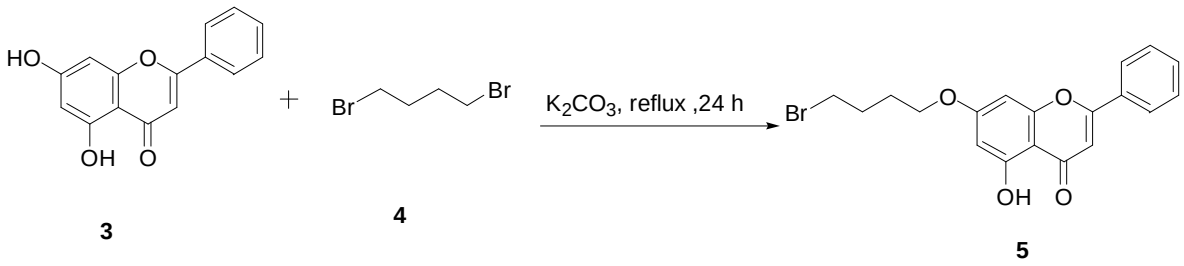
1. Chrysin; **2**.R_1= -$COCH_3$, R_2= H; **3**. R_1=R_2= -$COCH_3$;

4. R_1=R_2= -$CH_2COOCH_2CH_3$; **5**. R_1=R_2= -CH_2COOH;

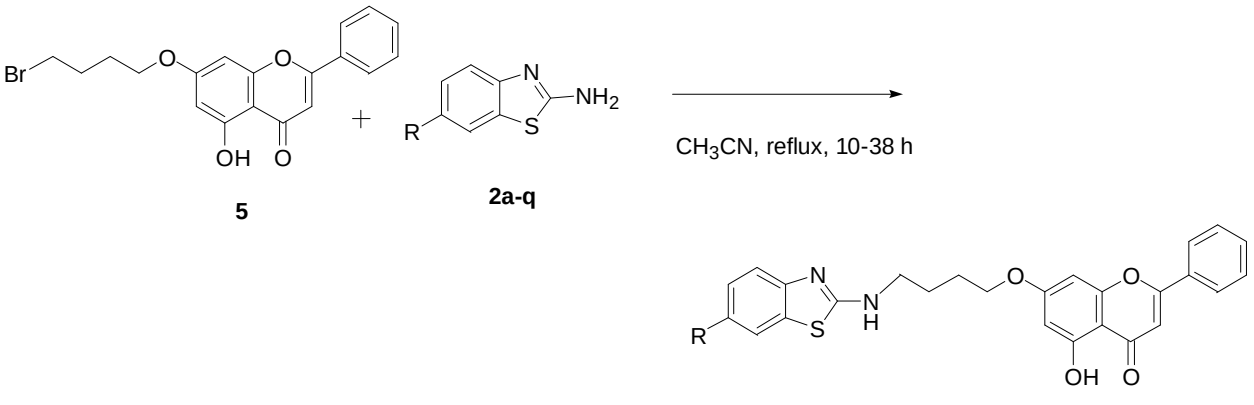
6. R_1= Bz, R_2 = H; **7**. R_1=R_2= Bz; **8**. R_1= Bz,R_2= -$CH_2COOCH_2CH_3$;

9. R_1=H, R_2= -CH_2COOH.

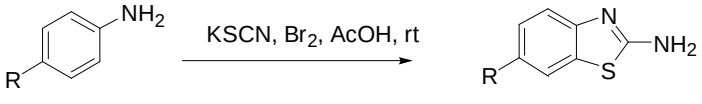
Scheme 2: Synthesis route of chrysin derivatives according to Zhen-Yuan et al



3 **4** **5**



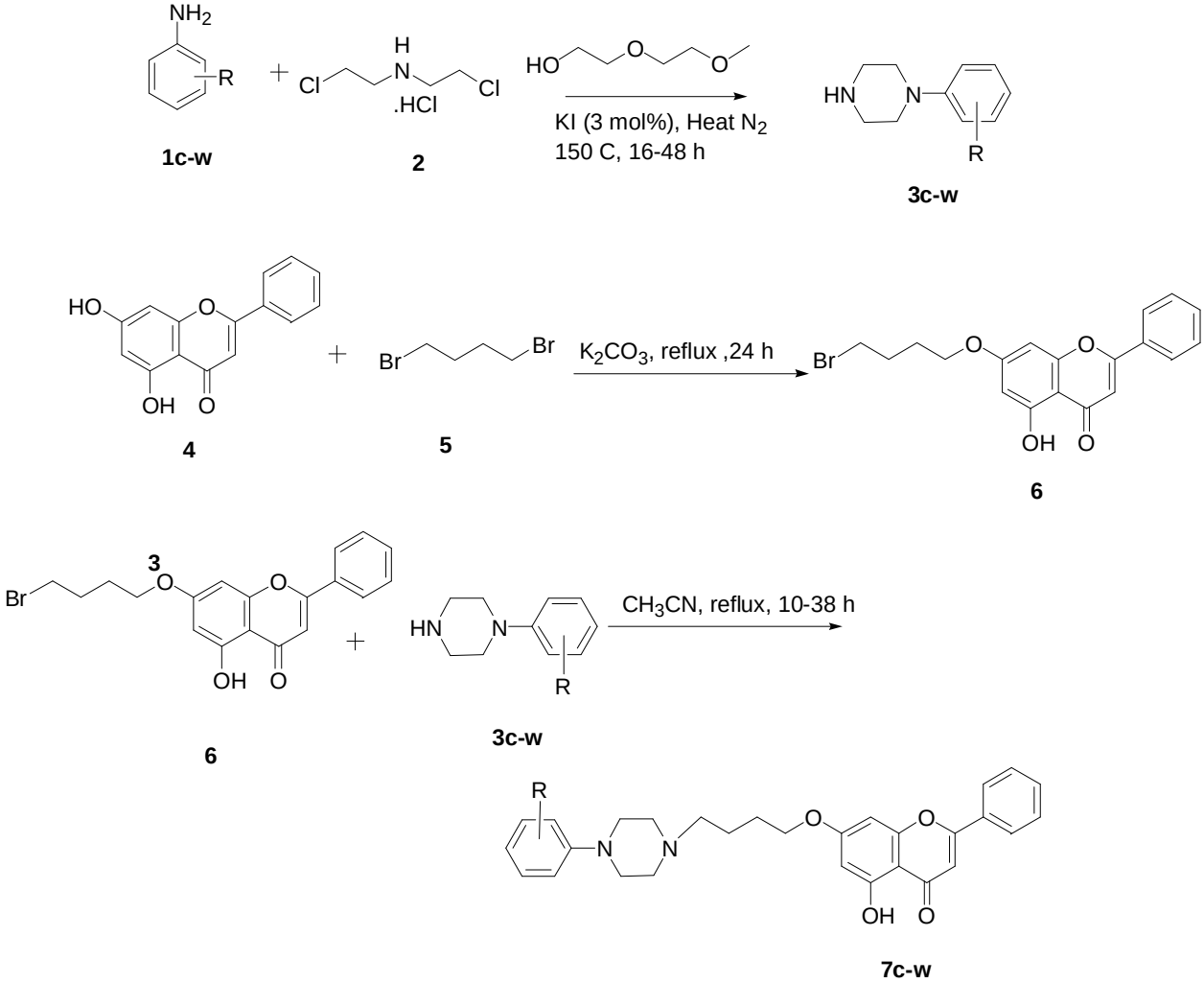
5 **2a-q** **6a-r**



1a-q **2a-q**

Scheme 3: Synthesis route of chrysin derivatives according to Bhupendra et al

Rahul V. et. al [19] produced a new class of chrysin derivatives recently by linking to a variety of substituted piperazines, morpholine and piperidine via a butyl chain and was analyzed for anticancer activity in vitron (**Scheme 4**). The authors found that butyl chain and types of piperazine rings were optimal to furnish constant pharmacological actions as anticancer agents. From the structure-activity point of view, nature and position of the electron withdrawing and electron donating functional groups on the piperazine core may contribute to anticancer action.



Scheme 4: Synthesis route of chrysin derivatives according to Rahul et al

Hong-zhuan et. al .,[20] synthesized novel chrin-organotin (Chry-Sn) compound with enhanced anticancer activities by the reaction of chrysin and triphenyltin chloride. The results suggested that Chry-Sn possessed enhanced anticancer effects compared to chrysin on the proliferation of MCF-7, A549 and HeLa human cancer cell lines.

Inês L. et.al.,[21] synthesized selenium-containing chrysin (SeChry) by microwave-based methodology. When tested in a panel of cancer cell lines selenium-derivatives revealed consistently to be more cytotoxic with mean IC_{50} values 18- and 3- fold lower than those observed for chrysin and cisplatin respectively.

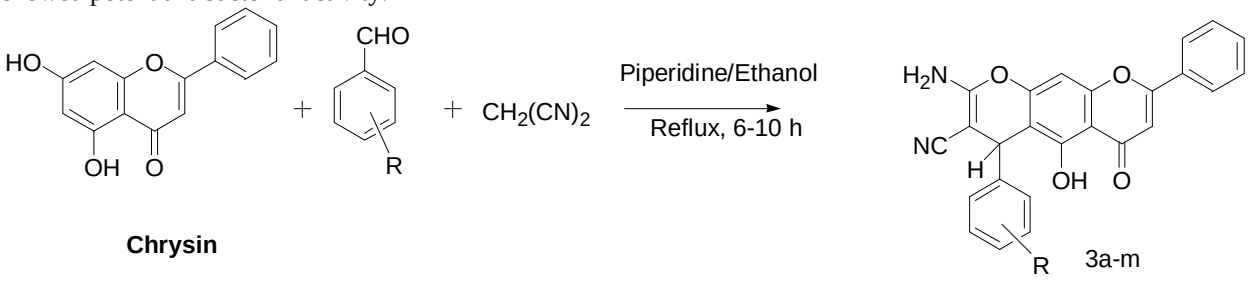
Chrysin derivatives with antimicrobial activity

Although several classes of antibacterial agents are presently available, resistance in pathogenic bacterial to these drugs has led to the constant need for new types of antibacterial agents and thus had become a very important task. Therefore, in recent years the research has been focused toward development of new antibacterial agents. Many flavonoids were reported as effective antimicrobials [22, 23]. Even though the mechanism of action is still unclear, chrysin derivatives had proven to be effective in exhibiting antimicrobial activity [24, 25].

Ramesh et. al, [26] synthesized a series of novel 2-amino 3-cyano 4-aryl pyrano[2,3H]chrysin derivatives (3a–m) by one-pot three-component reaction of aromatic aldehydes, malononitrile and chrysin (**Scheme 5**). All the newly synthesized compounds were evaluated for their in vitro antimicrobial activity (antibacterial and antifungal). Among the tested compounds, the authors found that compounds 3a, 3g, 3h, 3j and 3k showed potent antibacterial activity

compared to ciprofloxacin and the compounds 3a, 3g, 3h, 3i and 3k showed excellent antifungal activity compared to itrazole.

The results indicated that the compounds 3a, 3g, 3h and 3k containing phenyl, 4-methyl, 3-flouro 4-methyl and 4,4-dimethylamino phenyl group, respectively, at tenth position displayed potent antimicrobial activity, which are further supported by their docking studies. The compound 3j containing 4-methoxy phenyl group at tenth position also showed potent antibacterial activity. The compound 3i containing 4-hydroxy phenyl group at tenth position also showed potent antibacterial activity.

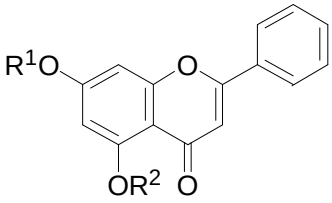


Chrysin

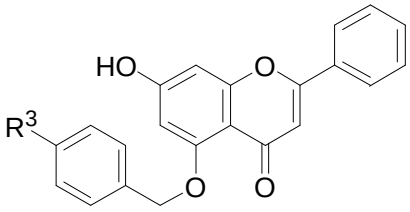
3a: R=H
3b: R=2-Cl
3c: R=4-Cl
3d: R=4-Br
3e: R=3-NO_2
3f: R= 4-NO_2
3g: R= 3-F, 4-CH_3
3h: R=4-CH_3
3i: R=4-OH
3j: R=4-OCH_3
3k: R=4-$N(CH_3)_2$
3l: R=3-OH, 4-OCH_3
3m: R= 3-OC_2H_5, 4-OH

Scheme 5: Synthesis route of chrysin derivatives according to Ramesh et al

Chrysin was recently shown to potently inhibit enterovirus71 (EV71) by suppressing viral 3C protease ($3C_{pro}$) activity. In a study carried out by Jae-Hyoung. et. al., [27] (**Scheme 6**) with an intuition to find weather chrysin can also shows antiviral activity against coxsackievirus B3 (CVB3), which belongs to the same genus (Enterovirus) as EV71 found that chrysin showed antiviral activity against CVB3 at 10 mM, but exhibited mild cellular toxicity at 50 mM. This prompted the authors to synsthesize derivatives of chrysin to increase the antiviral activity and reduce its cytotoxicity. Among four 4-substituted benzyl derivatives derived from C(5) benzyl-protected derivatives 7, 9-11 had significant antiviral activity and showed the most potent activity against CVB3 with low cytotoxicity in vero cells. The authors also found that among 4-substituted benzyl derivatives, 9 exhibited the highest activity against CVB3 *in vivo*.



Chrysin derivatives



Chrysin derivatives

2: R^1= Bn , R^2=H
3: R^1= Bn , R^2=Bn
4: R^1= Me , R^2=Me
5: R^1= Me , R^2=H
6: R^1= H , R^2=Me

7: R^3= H
8: R^3= OMe ,
9: R^3= F
10: R^3= Cl
11: R^3= Br

Scheme 6: Chrysin derivatives studied by Jae-Hyoung et al

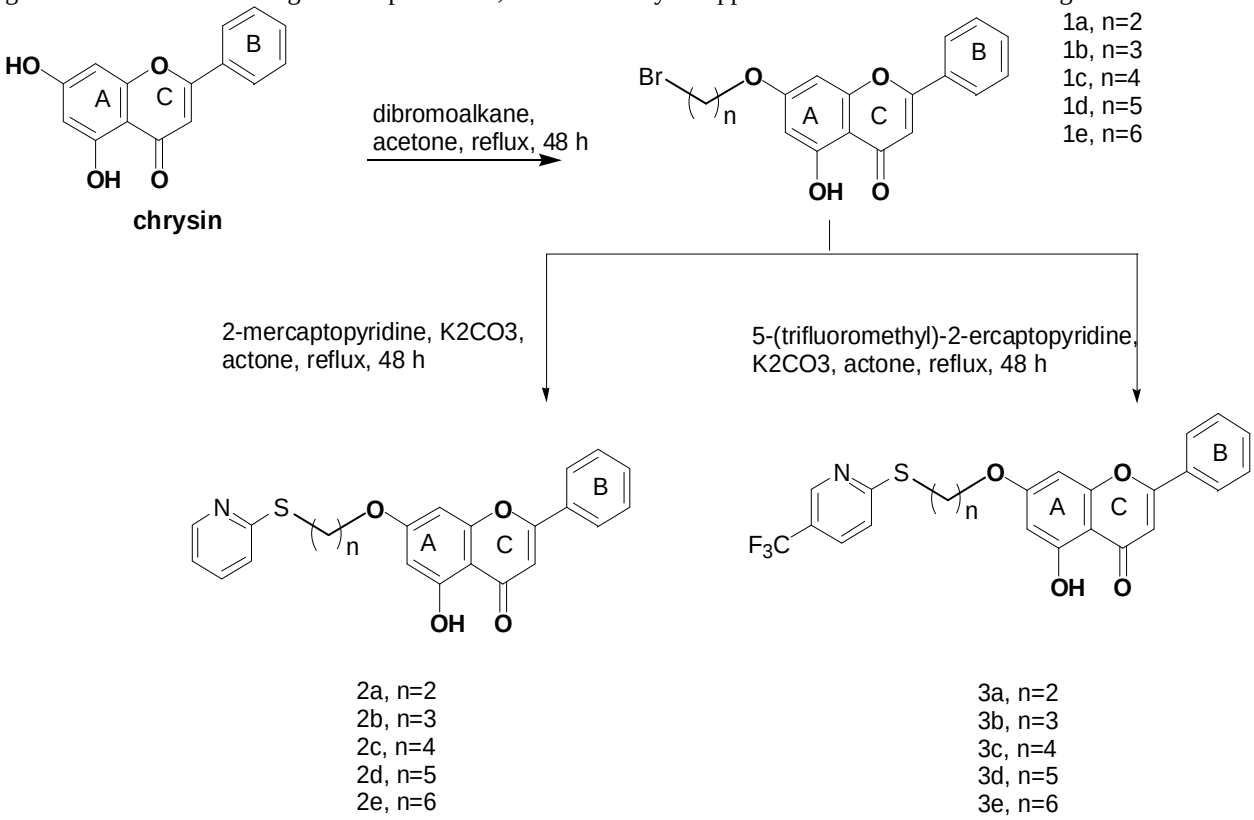
Chrysin derivatives with antihelminthic activity

Recently Alejandro et. al.,[28] synthesized new derivatives of chrysin containing 2- mercaptopyridine (2a-2e) or 5-(trifluormethyl)-2-mercaptopyridine (3a-3e) moieties as shown in (**Scheme 7**). The bromo-derivatives of Chrysin

(1a-1e) were prepared as previously described [29,30]. The reaction between the bromoderivatives and 2-mercaptopyridine or 5-(trifluormethyl)-2-mercaptopyridine lead to the formation of final compounds.

Due to previous studies of flavonoids having been shown to effect development of the nematode Caenorhabditis elegans , for example , apigenin derivatives inhibit larval growth of this species of nematode and these observations have providing meaningful structural insights in the search for new anthelminthic drugs [31,32] the authors tested the newly synthesized derivatives on growth assays of this worm. The results show that the new derivatives of chrysin (2a-2e and 3a-3e) did not effect on the number of eggs that hatched during the assay. Significant observation found by the authors was that the worms that were exposed to 2e, 3b and 3c developed slowly and showed delayed larval development compared to other compounds.

Nematodes possess a plethora of GABA receptors expressed in neurons and muscle cells (32) that are involved in neural transmission and flavonoids were known to effect the neural transmission mediated by ionotropic GABA receptors. Authors described these receptors may be the molecular target of their compounds. Considering, the larval growth inhibition in C. elegans compounds 2e, 3b and 3c may be applied as new anthelminthic drugs.

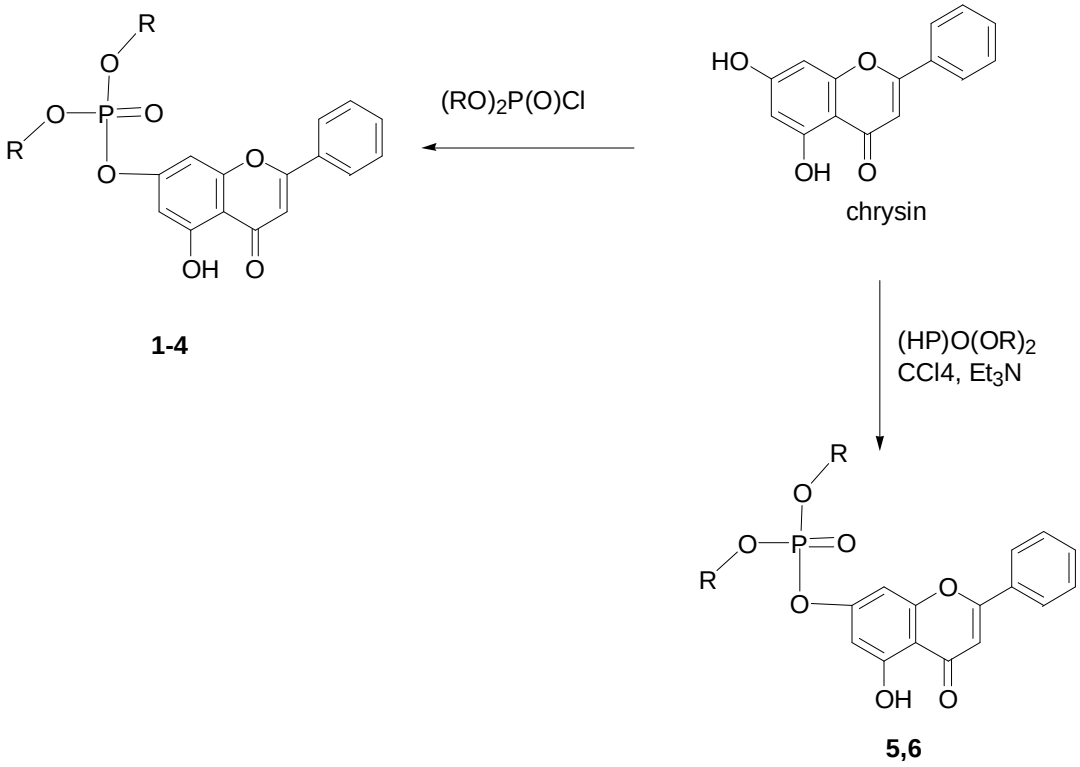


Scheme 7: Synthesis route of chrysin derivatives according to Alejandro et al

Chrysin derivatives as carboxylesterase inhibitors

Discovery of new selective and efficient carboxylesterase inhibitors may significantly revolutionize drug discovery. Earlier work showed the inhibitory activity of flavonoids towards three serine esterases. Abzianidze, et.al., [33] recently carried out a structure-activity study on the chrysin derivatives aiming to establish the correlation between the increase of hydrophobicity of the substituents at the phosphate group and the activity as well as selectivity of the final compounds. Chrysin was selected as the starting flavonoid due to high inhibitory activity and selectivity of its diethyl phosphorylated derivative [34].

Compounds **1–4** were synthesized via reaction of chrysin with chlorophosphates in anhydrous pyridine. Derivatives **5** and **6** were prepared via the known method [35] using phosphites as the phosphorylating agents (**Scheme 8**).The authors tested all the prepared compounds 1-6 in vitro for the inhibitory activity towards carboxylesterase isolated from pig liver and against human acetylcholinesterase. Experimental results shows that increased hydrophobicity of the substituents at the phosphate group caused an increase in selectivity of the final chrysin derivatives towards carboxylesterase.



R=Me (**1**), Et (**2**), iPr (**3**), Ph (**4**), Bu (**5**), 2,2,2-CF_3CH_2 (**6**)

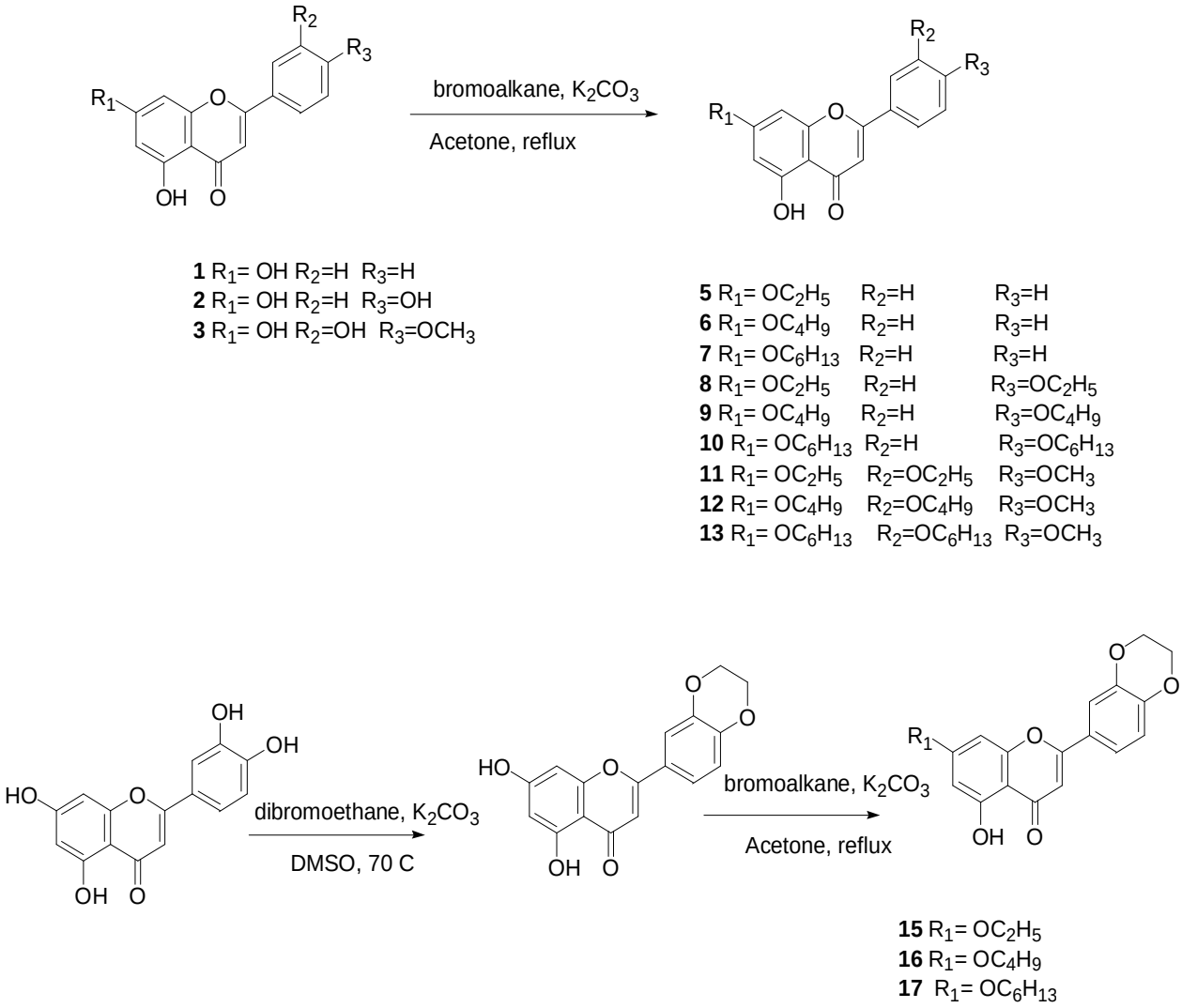
Scheme 8: Synthesis route of chrysin derivatives according to Abzianidze et al

α-glucosidase Inhibitors

Type II diabetes mellitus is more prevalent in developed countries is characterized by reduced insulin sensitivity and impaired insulin secretion. Type II diabetes mellitus can be effectively treated by a-glucosidase inhibitors, which have the ability to delay and reduce postprandial blood glucose spike. [36, 37, 38] α-Glucosidase is involved in carbohydrate metabolism and has a crucial function in diabetes, viral infection, and cancer. α-Glucosidase has diverse bioactivities and is considered an attractive drug target. At present, a number of α-glucosidase inhibitors have been discovered and studied. Anti-diabetic agents that are used in clinical practice, such as acarbose , voglibose, and miglitol, competitively inhibit α -glucosidase in the brush border of the small intestine, which consequently delay the hydrolysis of carbohydrates and alleviate postprandial hypergly-cemia. However, the continuous administration of these agents may cause several adverse effects, such as diarrhea, abdominal discomfort, flatulence, and hepatotoxicity. Therefore, developing novel α -glucosidase inhibitors lacking these liabilities is necessary given the therapeutic challenge of type II diabetes mellitus [39.40]. Flavonoids, such as baicalein, luteolin, kaempferol, apigenin, and chrysin, have the ability to inhibit α -glucosidase activity [33,34].

Recently Ning et. al., [41] synthesized a series of alkylated flavonoids such as chrysin, diosmetin, apigenin and luteolin and studied their α-glucosidase inhibitory activity (**Scheme 9**). The flavonoid derivatives were synthesized from the corresponding naturally occurring flavonoids and their yeast α-glucosidase inhibitory activity were evaluated.

The α -glucosidase inhibitory activity of these compounds was evaluated. The glucosidase inhibitory activity of all derivatives was higher compared with that of the reference drug, acarbose and 1- deoxynojirimycin These compounds showed a higher inhibitory ability compared with their precursors except the luteolin derivatives. In general, the inhibitory activity of the synthetic derivatives was enhanced with long alkyl chains at positions 3', 4' and 7 of the flavonoid.



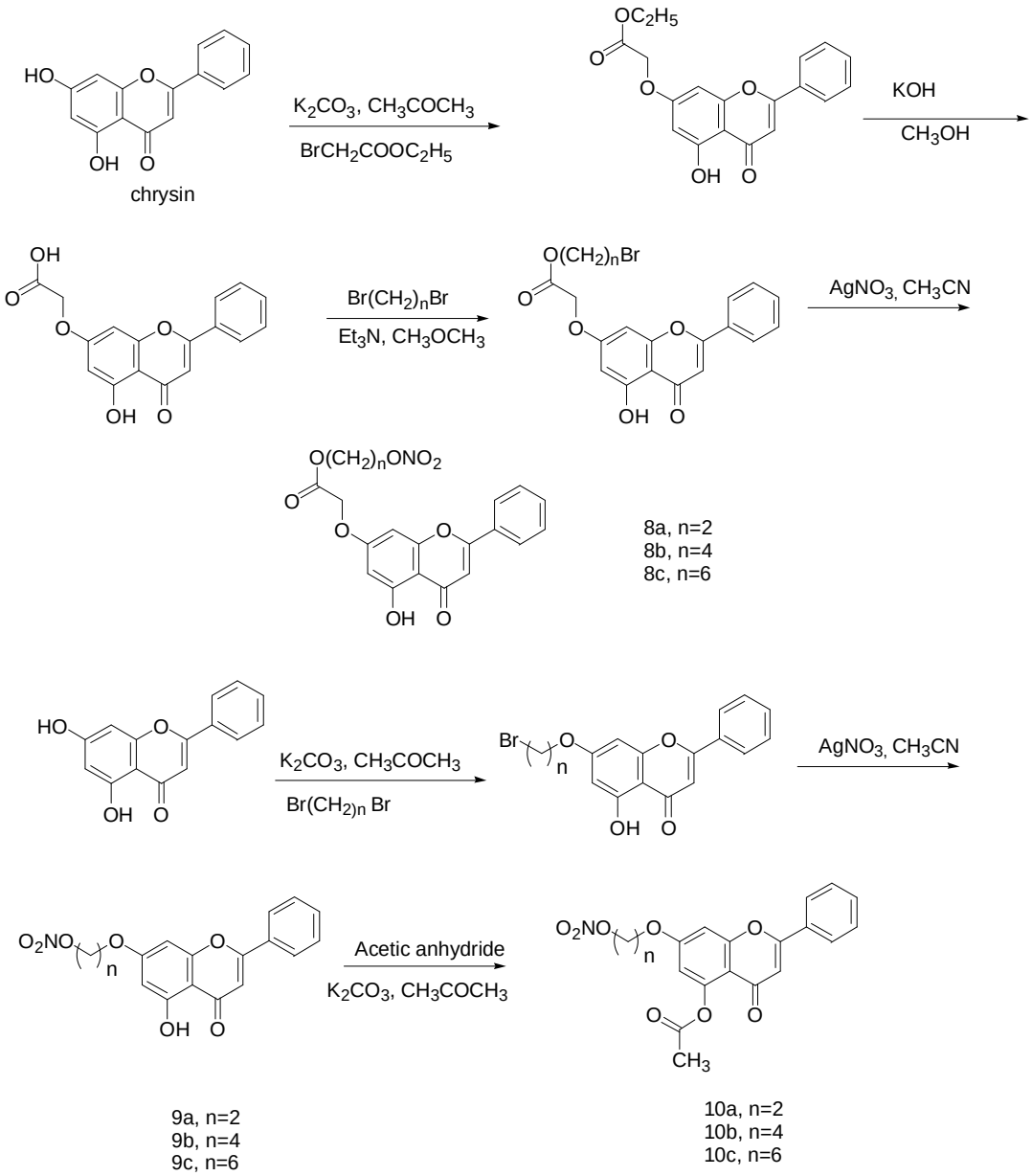
1 R_1= OH R_2=H R_3=H
2 R_1= OH R_2=H R_3=OH
3 R_1= OH R_2=OH R_3=OCH_3

5 R_1= OC_2H_5 R_2=H R_3=H
6 R_1= OC_4H_9 R_2=H R_3=H
7 R_1= OC_6H_{13} R_2=H R_3=H
8 R_1= OC_2H_5 R_2=H R_3=OC_2H_5
9 R_1= OC_4H_9 R_2=H R_3=OC_4H_9
10 R_1= OC_6H_{13} R_2=H R_3=OC_6H_{13}
11 R_1= OC_2H_5 R_2=OC_2H_5 R_3=OCH_3
12 R_1= OC_4H_9 R_2=OC_4H_9 R_3=OCH_3
13 R_1= OC_6H_{13} R_2=OC_6H_{13} R_3=OCH_3

15 R_1= OC_2H_5
16 R_1= OC_4H_9
17 R_1= OC_6H_{13}

Scheme 9: Synthesis route of chrysin derivatives according to Ning et al

Based on earlier studies of Hakamata et al.[42] showing that catechin derivatives showed potent antioxidant activity and α -glucosidase inhibitory activity with alkyl side chains of various lengths, and Shin et al. [43] showing that a series of alkyl or acetyl derivatives of chrysin have hypoglycemic effects. Qi-Qin, et. al.,[44] attempted to obtain novel AGIs by optimizing the hydrophilicity of apigenin and chrysin via addition of alkyl chains of various lengths (**Scheme 10**). In this study NO donors (organic nitrates) were coupled to the active hydroxyl groups of apigenin and chrysin using a series of ether or ester chains of varying lengths to produce compounds capable of supplying adequate amounts of NO and inhibiting α-glucosidase activity. Five series of apigenin and chrysin nitric oxide (NO) donating derivatives were synthesized and evaluated for their AG inhibitory activity and NO releasing capacity in vitro. Among the tested compounds expect 9a-9c, twelve compounds showed remarkable inhibit activity against α-glucosidase with potency better than of acarbose and 1-deoxynojirimycin. Sturcture activity relationship studies indicated that 5-OH, hydrophobic coupling and carbonyl groups of the coupling chain could enhance the inhibitory activity.

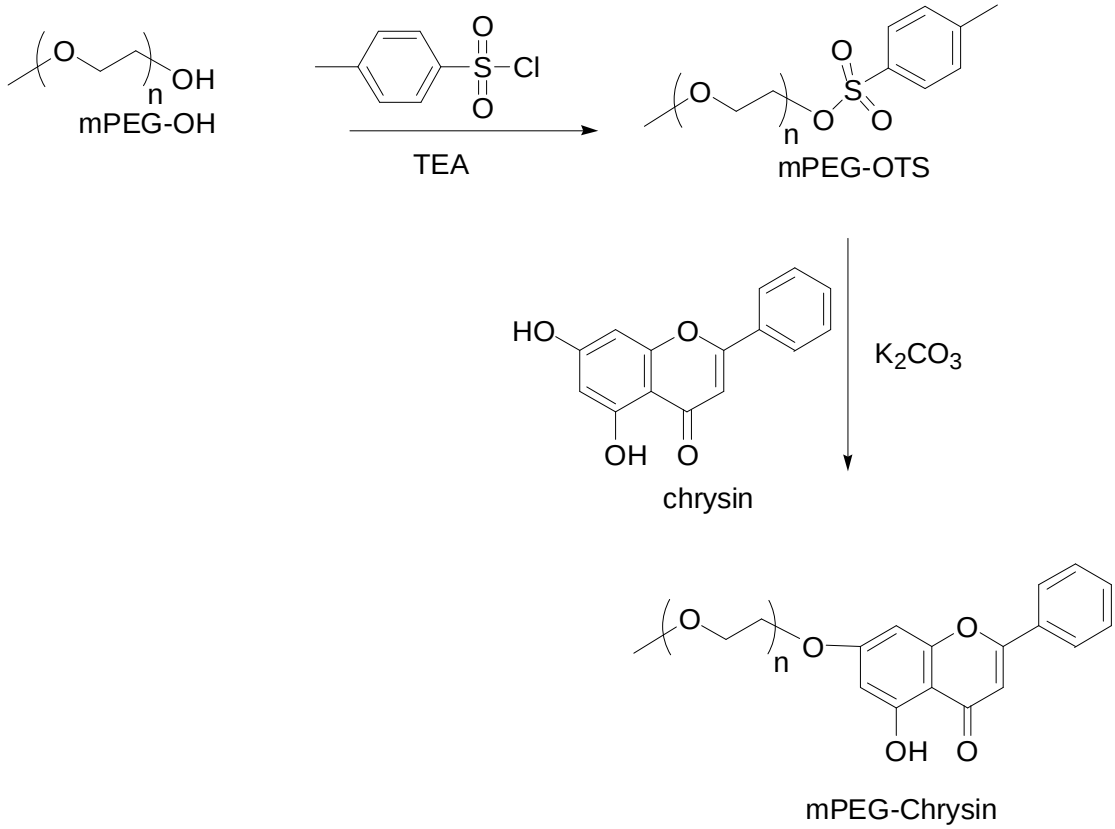


Scheme 10: Synthesis route of chrysin derivatives according to Qi-Qin et al

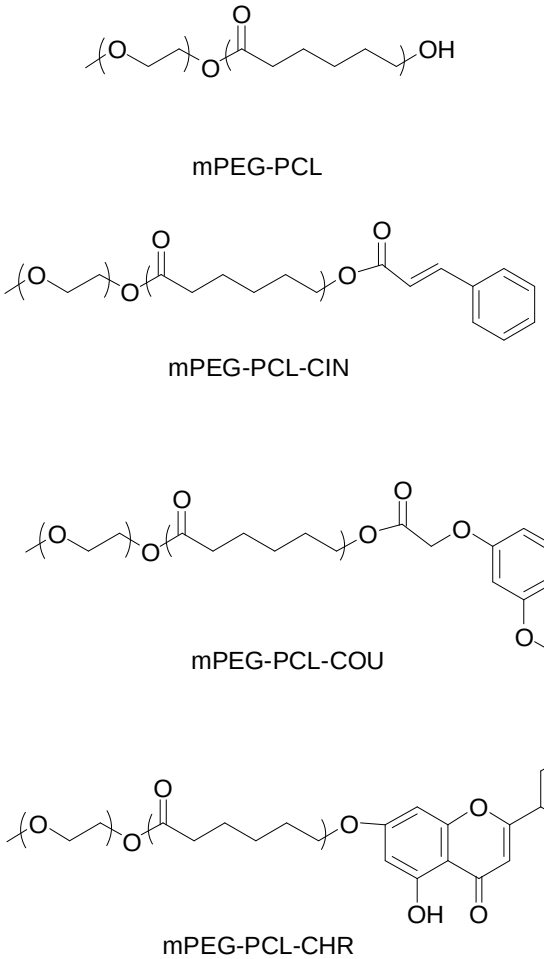
Chrysin derivatives in anticancer drug delivery

In the past decades, drug delivery using nanoparticles self-assembled from polymeric amphiphiles as carriers have become one of the most exciting technique in drug delivery research. While high drug loading content was one of the important factor to achieve efficient anticancer drug delivery, many strategies such as variation of hydrophobic architectures, crosslinking, π-π stacking and conjugation have been tried to enhance drug loading content [45,46].

Chrysin which is composed of three π-π conjugated rings, will provide strong interaction to most anti-tumor drugs with π-π conjugated structures such as Doxorubicin via both hydrophobic and π-π interaction. mPEG-Chrysin conjugate was synthesized by Hui et al., and was self-assembled into nanoparticles [47] (**Scheme 11**). These nanoparticles when loaded with Doxorubicin were found to induce the apoptosis in HepG2 cells. It was found that mPEG-1000 chrysin nanoparticles were more efficient when compared to mPEG-2000 chrysin nanoparticles in inducing apoptosis. This new strategy in fabricating polymeric nanoparticle lead to development of efficient vectors in the field of drug delivery.



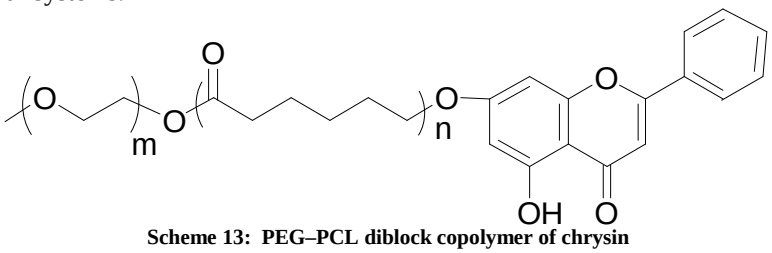
Scheme 11: Synthesis route of chrysin derivatives according to Hui et al



Scheme 12: Synthetic chrysin derivatives according to Yan et al

Chrsin modified (mPEG-PCL) micelles were prepared by Yan et al., by immobilizing chrysin on the terminal group of methoxy poly(ethylene glycol)-poly(ε-caprolactone) (mPEG-PCL) micelles (**Scheme 12**) and these micelles were used for drug (Doxorubicin) delivery [48]. The mentioned results suggested that when compared with other π-conjugated moieties of cinnamic acid, 7-carboxymethoxy coumarin on the terminal group of PCL block, chrysin modified micelles exhibited the higher values in drug loading content and encapsulation efficiency . The authors explained these due to greater π-π stacking interaction between chrysin and the drug DOX. Under both in vitro and in vivo conditions the IC_{50} values of drug loaded modified micelles were much lower compared to drug loaded unmodified (mPEG-PCL) micelles. The results suggested mPEG-PCL-CHR micelle would be a promising carrier for efficient anticancer drug delivery both in vitro and in vivo.

Effect of chain length on drug delivery of chrysin modified mPEG-PCL micelles was studied by Yan et al. [49]. Four PEG–PCL diblocks copolymers of chrysin (mPEG2k–PCL2k–CHS, mPEG2k–PCL5k–CHS,mPEG5k–PCL2k–CHS and mPEG5k–PCL5k–CHS) (**Scheme 13**) were synthesized and tested for in vitro anticancer activity of drug loaded micelles were evaluated using doxorubicin. Based on the results of cellular uptake and IC_{50} values the mPEG2k-PCL5k-CHS micelles were found to be superior in exhibiting in vitro anticancer activity compared with other three micellar systems.



Scheme 13: PEG–PCL diblock copolymer of chrysin

CONCLUSION

In short, the latest improvements in the field of synthetic chrysin derivatives which are of biomedical importance have been summarized. Studies suggested that the use of various chrysin derivatives have left a landmark in the field of search for new antimicrobial, alpha glucosidase inhibitors, drug delivery vehicles and anticancer agents. Its potential has been supported by the reports described in this article. Structure function relationship of chrysin derivatives is epitome of major biological activities. Based on the results and reports, it is suggested that the future trends must aim at developing efficient drug delivery vehicles using synthetic chrysin derivatives. Further achievements will provide newer insights and will certainly lead to a new era of chrysin based pharmaceutical agents.

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