Send Orders for Reprints to reprints@benthamscience.net

Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 2020, *19*, 222-239

REVIEW ARTICLE

Psoralen Derivatives: Recent Advances of Synthetic Strategy and Pharmacological Properties

Joazaizulfazli Jamalis[1,*], Faten Syahira Mohamed Yusof[1], Subhash Chander[2], Roswanira Abd. Wahab[1], Deepak P. Bhagwat[2], Murugesan Sankaranarayanan[3], Faisal Almalki[4] and Taibi Ben Hadda[4,*]

[1]*Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia, 81310 Johor Bahru, Johor, Malaysia;* [2]*School of Pharmacy, Maharaja Agrasen University, Atal Shiksha Kunj, Village Kalujhanda, Solan-174103, Himachal Pradesh, India;* [3]*Medicinal Chemistry Research Laboratory, Department of Pharmacy, Birla Institute of Technology & Science Pilani, Pilani Campus, Pilani-333031, Rajasthan, India;* [4]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Umm Al-Qura University, Makkah Almukkarramah, Saudi Arabia*

ARTICLE HISTORY

Received: February 27, 2019
Revised: April 14, 2019
Accepted: May 02, 2019

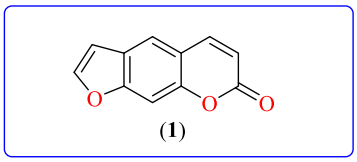
DOI:
10.2174/1871523018666190625170802

Abstract: Psoralen or furocoumarin is a linear three ring heterocyclic compound. Psoralens are planar, tricyclic compounds, consisting of a furan ring fused to a coumarin moiety. Psoralen has been known for a wide spectrum of biological activities, spanning from cytotoxic, photosensitizing, insecticidal, antibacterial to antifungal effect. Thus, several structural changes were introduced to explore the role of specific positions with respect to the biological activity. Convenient approaches utilized for the synthesis of psoralen skeleton can be categorized into two parts: (i) the preparation of the tricyclic ring system from resorcinol, (ii) the exocyclic modification of the intact ring system. Furthermore, although psoralens have been used in diverse ways, we mainly focus in this work on their clinical utility for the treatment of psioraisis, vitiligo and skin-related disorder.

Keywords: Biological activity, chemotherapeutic agents, furan ring, heterocyclic compound, pharmacological properties, psoralen derivatives.

1. INTRODUCTION

Psoralen (**1**) is a naturally occurring compound. Chemically, it possesses the furocoumarin entity which consists of coumarin moiety fused furan ring [1]. The furan may be fused in different ways producing several isomers. Psoralen is the most common isomers that form the core structures of linear furocoumarin (Fig. **1**).



(**1**)

Fig. (1). Structure of psoralen.

Medicinal plants are limitless sources of secondary metabolites. Therefore, these plants have been endowed as important sources of phytomedicines [2]. Psoralen is produced in certain plants like in the fruits and seeds of legumes *Psoraleacoryli folia L*, common figure, celery, parsley and in all citrus fruits. Psoralen based bioactive compounds have wide biomedical application and

*Address correspondence to these authors at the Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia, 81310 Johor Bahru, Johor, Malaysia and Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Umm Al-Qura University, Makkah Almukkarramah, Saudi Arabia; Tel: +0133176356; E-mails: joazaizulfazli@utm.my (JJ); taibi.ben.hadda@gmail.com (TBH)

1875-614X/20 $65.00+.00

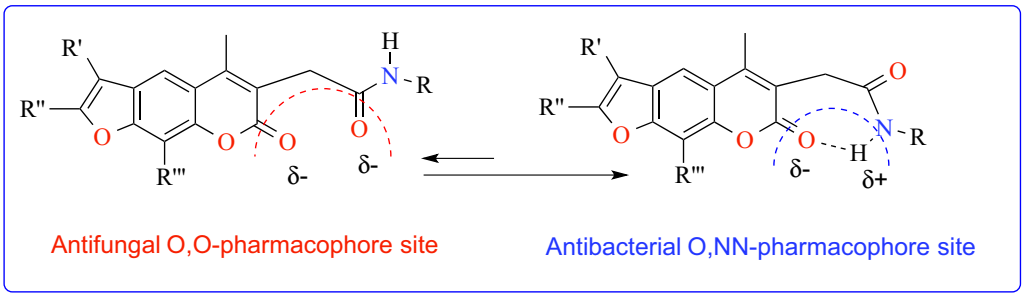


Fig. (2). Point of diversity in the psoralen structure (**1**) according POM Theory.

are used in pharmaceuticals, health, and body-care products [3].

Apart from psoralen (**1**), its several derivatives had been identified and isolated from different plants and their parts. Around, one hundred psoralen derivatives have been reported in the literature of which approximately half are naturally occurring, whereas the rest of these derivatives are synthetically prepared. In order to explore the structural-activity relationship, several structural changes were made at certain points of psoralen structure as shown in Fig. (**2**) [4-21].

Over the past few decades, the incidence of viral infections has increased worldwide. Thus, the search for a safe and effective vaccine is gaining a great importance for better treatments. Hence, one of the challenges facing researchers in bio containment is the treatment. Materials moved from a higher level of bio containment to a lower bio containment level which must be a valid and verified method for agent inactivation [22]. Therefore, psoralen is one of the compounds that have shown to possess a wide spectrum of biological activities spanning from cytotoxic, phytotoxic, photosensitizing, insecticidal, and antibacterial to antifungal effect [23]. With the increasing studies and interest in molecular biology, psoralen has been investigated and modified to enhance its ability for virus inactivation. In this direction, new psoralen derivatives were synthesized and evaluated as a potential new vaccine.

The synthesis and modification of the targeted psoralen compounds and their derivatives were undertaken. A commercial starting material and simple condensation was used to synthesize the psoralen and all of its derivatives. The successful synthesis of the compound could encourage future development of psoralen as a template for modification or derivatization to obtain more potent therapeutic agents.

2. HETEROCYCLIC PSORALEN

Psoralen or furocoumarin (**1**) is a linear three ring heterocyclic compound consisting of a furan ring fused in a coumarin moiety [24]. At around 200-350 nm, psoralens exhibit strong absorption bands, while it shows lower absorbance in a visible region. Psoralen can form intercalation with DNA bases because of their planar aromatic structure and hydrophobic nature.

Psoralen is a class of organic chemical compounds produced by a variety of plants. Psoralen is an important family of compounds of natural or synthetic origin because of their biological and industrial applications. Different classes of heterocyclic compounds can also be fused with the coumarin molecule [25]. The furan ring can be fused in either a 2,3- or 3,2-arrangement, at the c, f, g or h bonds of the coumarin (**8**) as shown in Fig. (**3**). The most common representatives of this class of compounds reported in the literature are psoralen (**1**), pseudopsoralen (**9**), allopsoralens (**10**), pseudoisopsoralen (**11**), isopseudopsoralen (**12**), furo [3,2-c]coumarin (**13**) and angelicins (**14**) [26]. Furocoumarins are currently of great interest for research. Therefore, the study of their reactivity and properties is of a growing interest.

3. METHOD OF PSORALEN SYNTHESIS

In 1934, psoralen has been synthesized and many furocoumarin have been reported, but the yield was poor [27]. Nonetheless, the number of excellent reviews on furocoumarins in the 1980s with regard to their biological effects have become mainly aimed at chemical-biological and clinical-

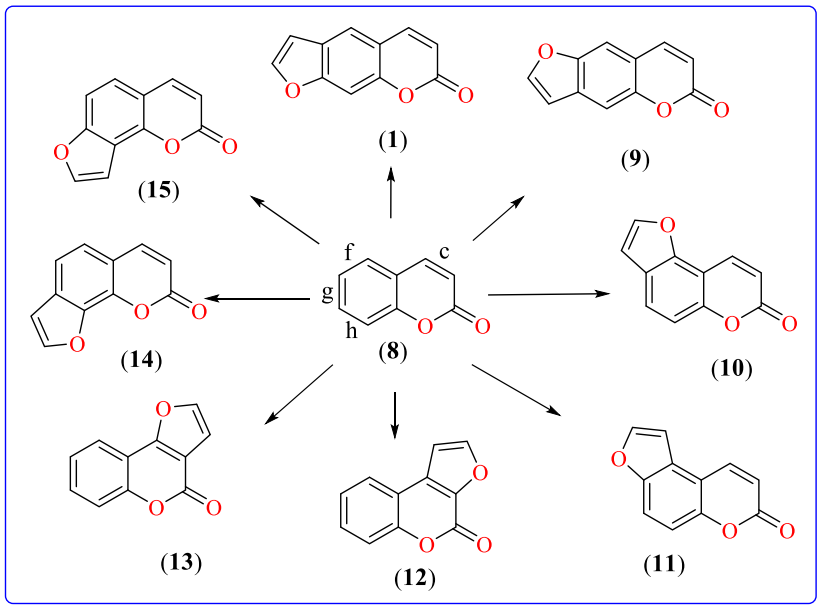


Fig. (3). Possible fusions of the furan ring on the coumarin nucleus.

pharmacological aspects. Therefore, reviews regarding the synthetic procedure as well as the biosynthetic routes and their bioaccumulation in plants have been published. The most common method for the synthesis of psoralen is building a furan ring on coumarin moiety to obtain furocoumarins.

Particular emphasis has been given to more recent methods for the preparation of furocoumarins as well as to older methods that are still commonly used. The methods of synthesis have been arranged into approaches: (A) the formation of the furan ring onto a furocoumarin, (B) the formation of the pyrone ring onto a benzofuran and (C) simultaneous formation of both heterocyclic rings onto a central benzene unit as shown in Fig. (**4**) [28]. In all cases, a brief discussion will highlight the most general and established methods.

4. FORMATION OF FURAN RING ONTO FUROCOUMARIN

The most traditional and widely used method for the preparation of furocoumarins is the formation of furan ring into coumarin. Usually, the starting materials used in this strategy are hydroxycoumarin which can undergo a condensation reaction with furan ring through a number of different routes [29]. There have been a lot of efficient routes to the formation of furan ring onto furocoumarin which is fusion furan on benzene ring or fusion of furan on lactone ring as shown in Fig. (**5**) [30].

Firstly, the formation of furocoumarin occurs by the fusion on benzene ring using the reaction of hydroxycoumarin with halo ketone in the presence of potassium carbonate and followed by the classical technique reported by MacLeod [31]. Alternatively, to obtain the same product, the modification of this method can be used employing microwaves in the absence of solvent. Then, the cyclization reaction which is performed in the presence of polyphosphoric acid (PPA) is continued. It gives a mixture of cyclization products ortho to the hydroxy group. A basic medium can also be used such as NaOH/EtOH, KOH/MeOH. In the case of coumarin unsubstituted at the benzene ring, it gives an essentially regioselective cyclization in the para position with respect to the phenoxide intermediate Scheme **1**.

One of the examples is the synthesis of 9-methyl-1-phenyl-7H-furo[3,2-f]chromen-7-one (**23**) and 4,9-dimethyl-3-phenyl-7H-furo[2,3-f]chromen-7-one (**26**) as angular furocoumarin derivatives by Williamson reaction of hydroxycoumarin with phenacyl bromide in refluxing acetone in the presence of K_2CO_3 for 4 hours giving the keto ether of coumarin [32]. Then, it is followed by the cyclization of keto ether with polyphosphoric acid which

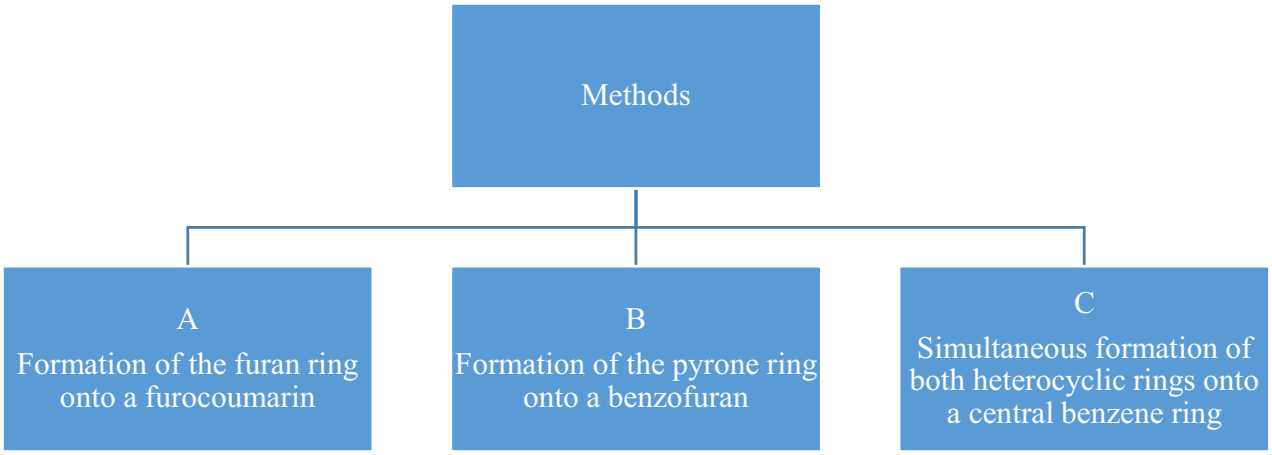


Fig. (4). Methods for the synthesis of furocoumarins.

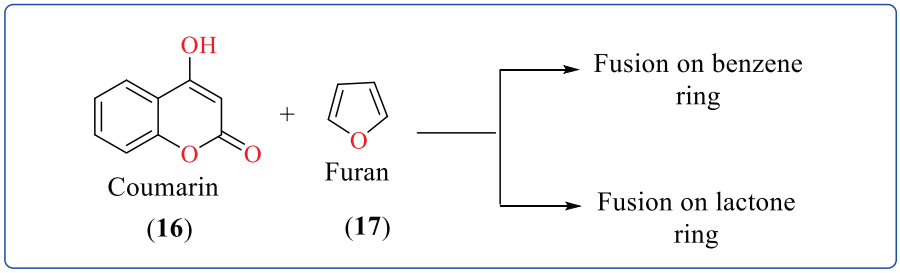
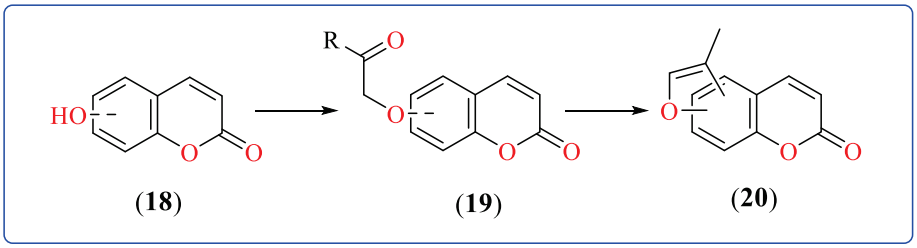
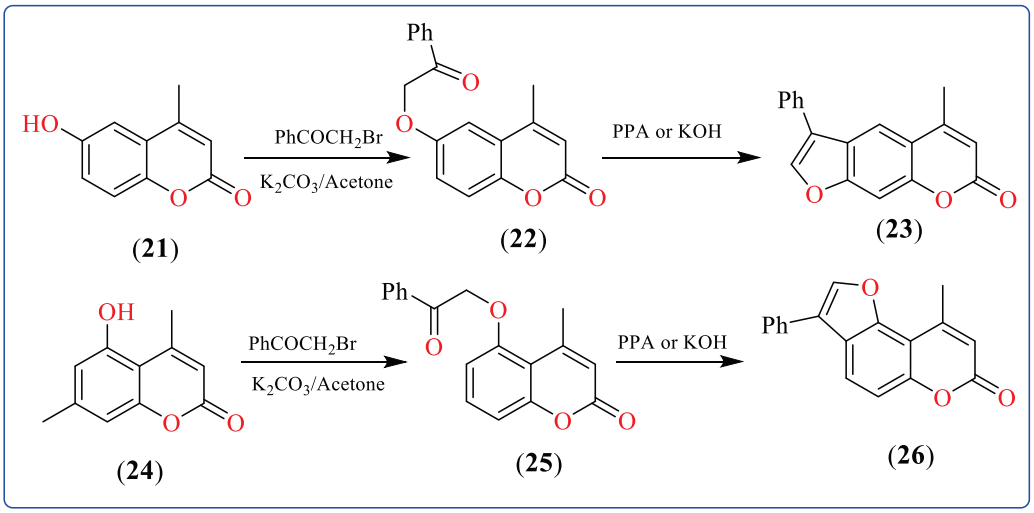


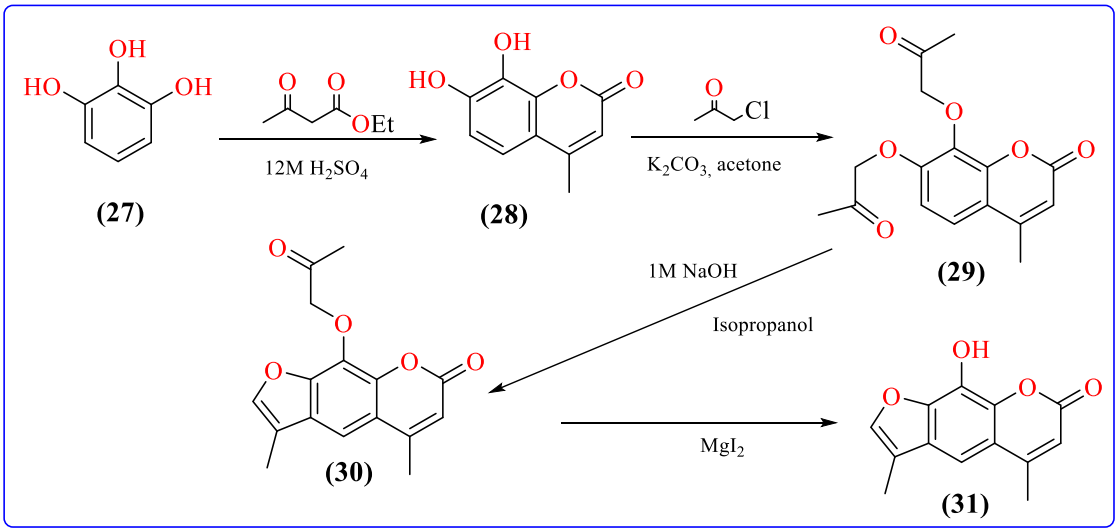
Fig. (5). Representative furo-coumarin core structure [30].



Scheme 1. General route formation of furan onto furocoumarins [28].



Scheme 2. Synthesis of new angular furocoumarin derivatives (**23**) and (**26**) [32].



Scheme 3. Synthesis of 4,4'-dimethylxanthoxol (**31**) [33].

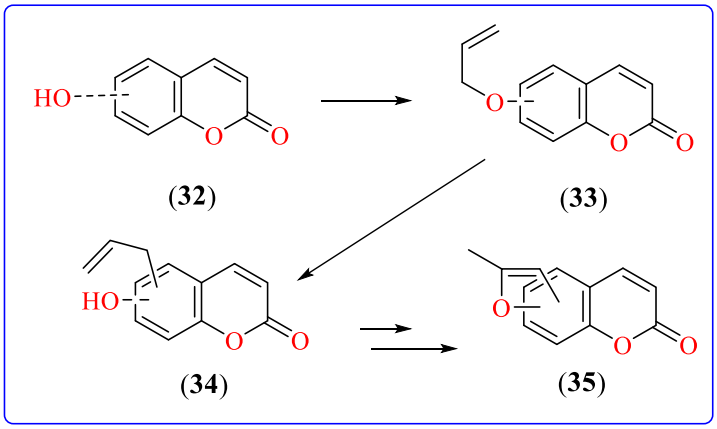
afforded corresponding furocoumarin with high percentage yield of the targeted compound as shown in Scheme **2**.

Another example is the synthesis of target psoralen moiety 4-4'-dimethylxanthotoxol (**31**) [33]. Initially, commercial pyrogallol (**27**) was employyed as a starting material to undergo Pechmann reaction with ethylacetoacetate in the solution of 12 M sulfuric acid. It afforded the desired coumarin derivative (**28**) in 81% yield. Coumarin (**28**) then was etherated with 1-chloroacetone in acetone to give coumarin derivative (**29**) in 24% yield. So, the mixture after the O-dialkylation reaction was used directly into the cyclization reaction of (**29**) without separation. It afforded the desired psoralen derivative (**31**) in one pot with 43% overall yield as shown in Scheme **3**.

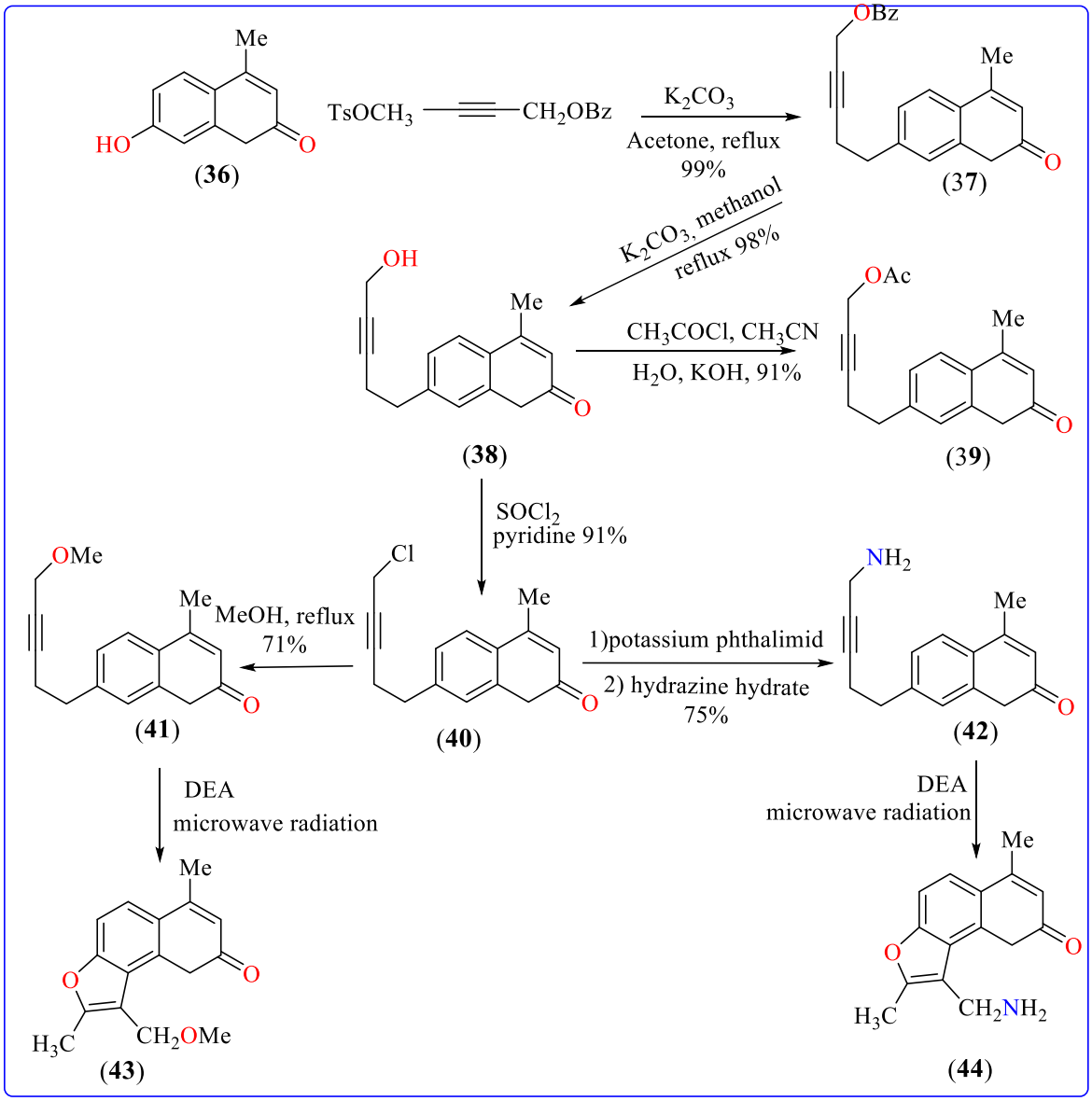
However, one limitation associated with this method is that it only allows the synthesis of 4'-subsitituted furocoumarins. Appropriate formyloxycoumarin is needed as starting material if the synthesis of analogs does not contain a substituent which will prior undergo a cyclization reaction. Besides that, furocoumarins can also be synthesized in a manner analogous to the biosynthetic route where the starting hydroxycoumarin converted into the corresponding allylic ethers. The latter undergoes Claisen rearrangement followed by cyclization to generate the furan ring as shown in Scheme **4**. Allyl group was introduced through the classical reaction of hydroxycoumarin with allylic halide in the presence of potassium carbonate. Lately, the coupling of the hydroxycoumarin with allylic alcohols under Mitsunobo conditions has been used to avoid allyl rearrangement prior to the formation of the ether. The condition of Claisen rearrangement is usually carried out by heating the reagents under reflux in *N*,*N*-diethylaniline (DEA) or *N*,*N*-dimethylaniline (DMA) or, more recently, *N*-ethylformamide (NEF) or *N*-methylformamide (NMF). The solvent is advantageous that it is miscible with water and thus it is easier to be removed. The allyhdroxycoumarin subsequently cyclize in acidic medium (usually sulfuric acid) and then dehydrogenated with Pd or dichlorodicyanobenzoquinone (DDQ). In some cases, allylhydroxycoumarins can be oxidatively cyclized with $PdCl_2$ to give directly the furocoumarin in good yield [28].

The approach reported for the synthesis of 4'-(amino and methoxy)-methyl-4,5'-dimethylangelicins (**43**, **44**) involved an efficient and rapid synthesis *via* Claisen rearrangement of 4-methyl-7-[4-(hydroxy, chloro, amino, acetoxy and methoxy)-but-2-ynyloxy]-coumarins (**41**, **42**) respectively under microwave irradiation as shown in Scheme **5** [34].

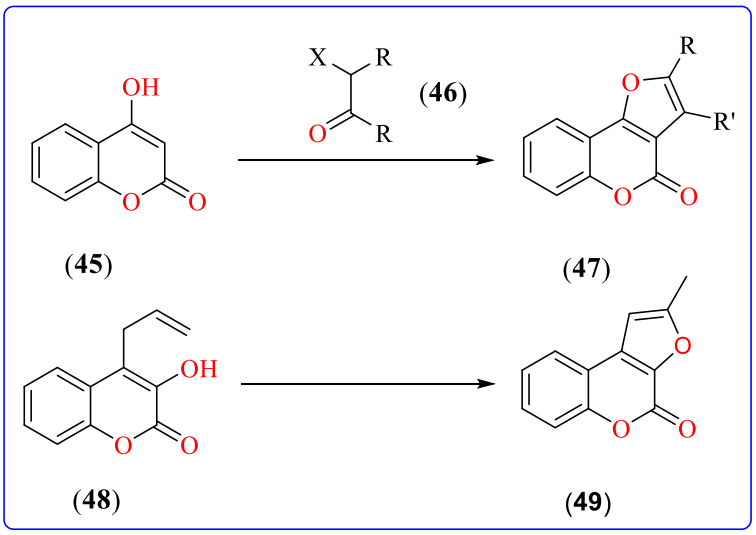
The advantages of this new method are the operational simplicity, the good yields in short reaction times, and the easy work-up employed procedures. However, another liability of the referred approaches is the lack of regioselectivity in the rearrangement which generally gives a mixture of linear and angular furocoumarins.



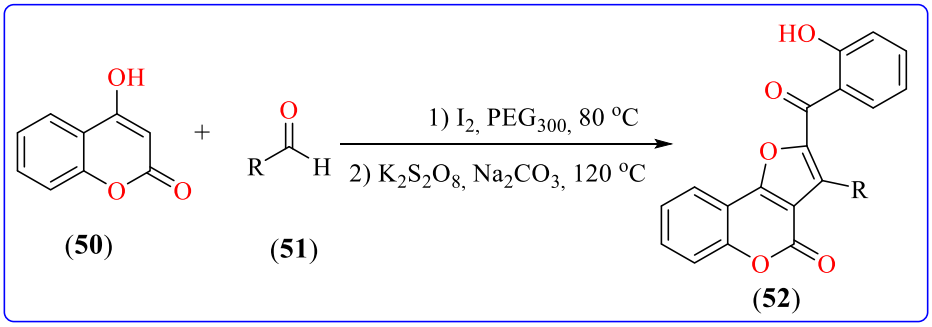
Scheme 4. General route formation of furan onto furocoumarins (**35**) [28].



Scheme 5. (4'-(amino and methoxy)-methyl-4,5'-dimethylangelicins (**43**, **44**) synthesized *via* Claisen rearrangement of 4-methyl-7-[4-(amino and methoxy)-but-2-ynyloxy]-coumarins (**41**, **42**) under microwave irradiation [34].



Scheme 6. Furo[3,2-c]coumarin (**47**) and furo[3,2-c]coumarins (**49**) [28].



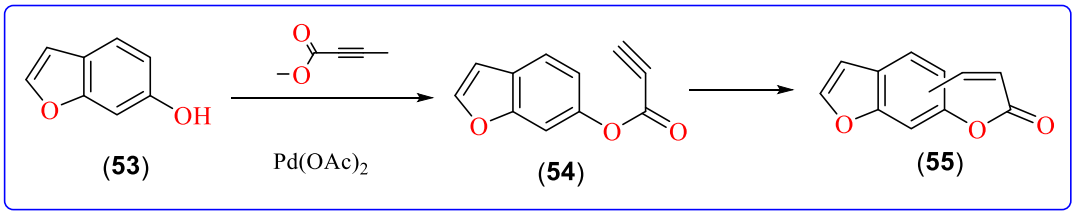
Scheme 7. Synthesis of furocoumarins (**52**) by a one-pot oxidative pseudo three-component condensation [35].

Another approach involves the construction of furan ring at lactone ring. The 3,4-bond of the coumarin can be achieved by the similar reaction of hydroxycoumarin (**45**) with compound (**46**). The difference is only the furo[2,3-c]coumarin skeleton. It forms the corresponding 3-hydroxycoumarin and the furo[3,2-c]coumarins from 4-hydroxycoumarin as shown in Scheme **6**. Mechanistically, 4-hydroxycoumarin behaves as 1,3-dicarbonyl systems and allows them to undergo oxidative cycloaddition reaction with alkene (vinyl ether or vinyl thioethers) in the presence of Ag_2CO_3 and Celite (Fetixon's reagent).

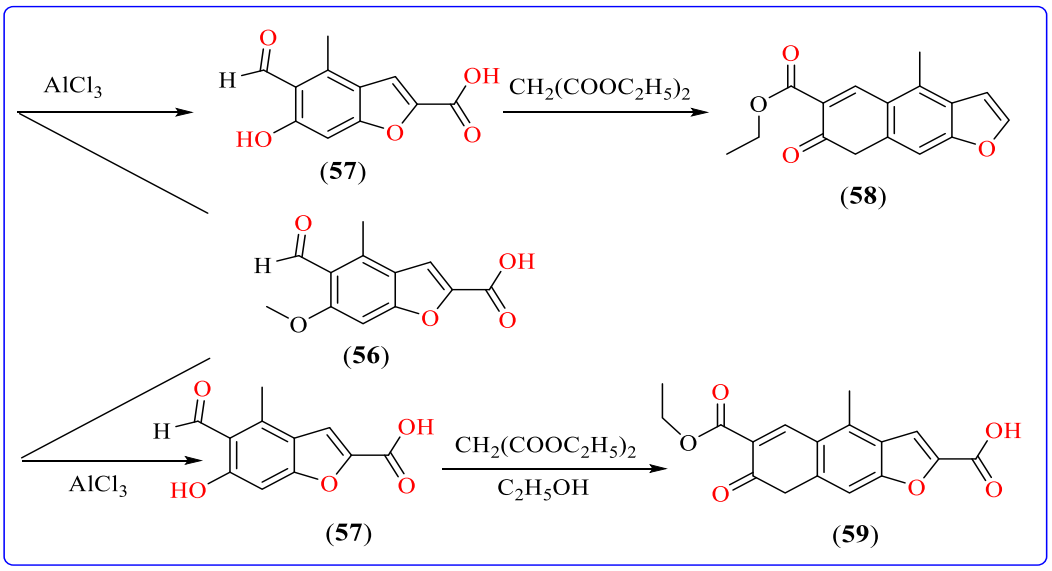
The efficient and straightforward synthesis of functionalized furo[3,2-c]coumarin by this method was recently reported. The condensation of 2 equivalent of 4-hydroxycoumarin and aldehydes under one-pot oxidative pseudo three-component condensation, followed by the formation of furocoumarin ring [35]. The Scheme **7** showed 4-hydroxycoumarin (**50**) treated with benzaldehydes (**51**) in the presence of iodine to generate the corresponding biscoumarin under optimum condition and this crude was reacted with potassium persulfate and sodium carbonate. It has been proven under this condition that the corresponding furocoumarin was obtained without a significant loss of yield in comparison other methods [35].

5. FORMATION OF PYRONE RING ONTO A BENZOFURAN

Another general method for the synthesis of furocoumarin (**55**) is the formation of pyrone ring onto benzofuran (**53**). Mostly, the starting material of substituted benzofuran (**53**) moiety has been employed for the formation of pyrone ring onto a benzofuran. Recently, a new method has been introduced for the synthesis of furocoumarin with a good yield by starting from acetylenic ester of 6-hydroxybenzofurans. In this reaction, the compounds undergo an intramolecular arylation reaction which involves the triple bond in the presence



Scheme 8. Formation of pyrone ring onto a benzofuran [36].



Scheme 9. Synthesis of 3-carbethoxypsoralens (**58**) and 3,5'-dicarbethoxy-8-methylpsoralen (**59**) [37].

of palladium acetate at room temperature as shown in Scheme **8** [36].

A report has been published recently on the syntheses of psoralen (**1**) and angelicins (**14**) which generally starts from the performance of suitably substituted coumarin or benzofuran derivatives to obtain the monofunctional DNA-binding compound psoralen derivatives with a bulky group at one of their photoactivable sites, or at both. Scheme **9** showed the synthesis of 3-carbethoxy psoralen (**58**) and 3,5'-dicarbethoxy-8-methylpsoralen (**59**) which was then prepared from the substituted benzofuran [37].

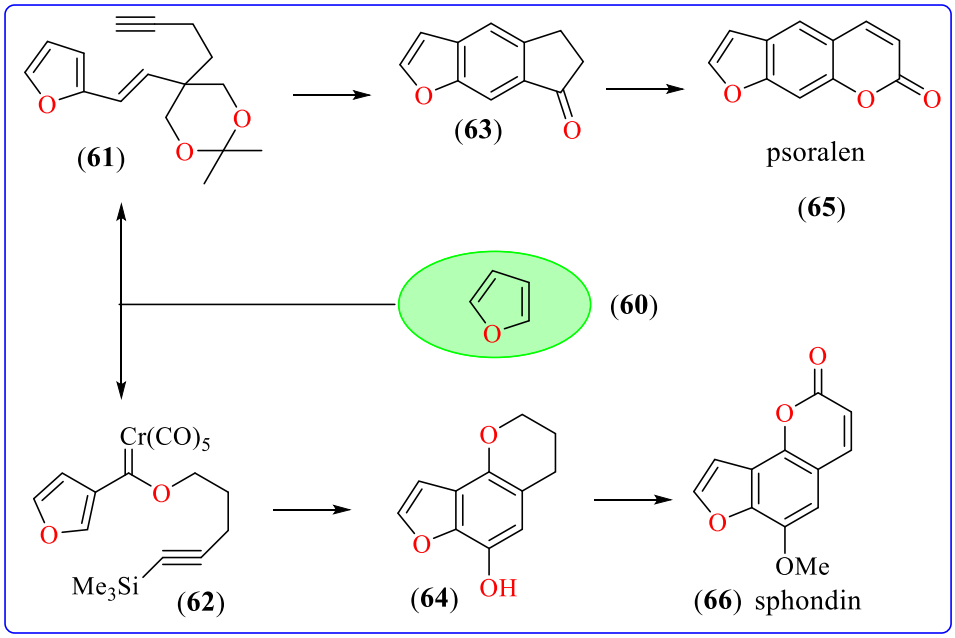
6. SIMULTANEOUS FORMATION OF BOTH HETEROCYCLIC RINGS

The third approach for the construction of furocoumarin is from suitably substituted central benzene nucleus by simultaneous formation of the two oxygen-containing rings in a single step. One example is shown in Scheme **10**.

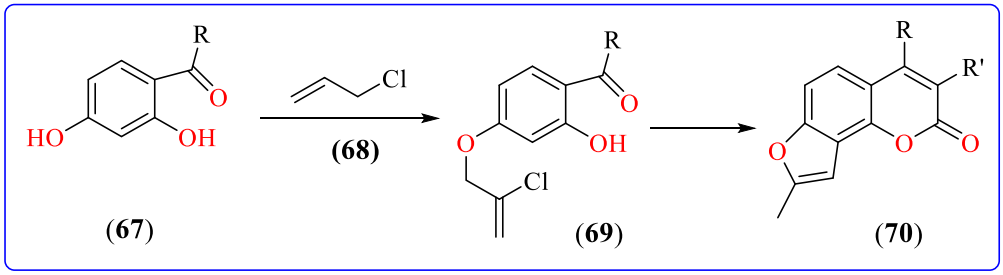
Another example is the synthesis of 2,4-dihydroxybenzaldehyde (**70**) by using 2,3-chloropropene (**68**) and the corresponding allylic ether (**69**). After Claisen rearrangement (**61**, **62**) of this intermediate, a one-pot tandem Wittig reaction and cyclization was performed which gives angelicins shown in Scheme **11**. However, the final product was obtained in low yield.

7. PSORALEN FROM NATURAL RESOURCES

Furocoumarin is widely dispersed in nature as secondary metabolites in a variety of plant species, especially of genus Umbellifera and Rutacea [28]. Since 1812, several coumarin have been isolated and many of them have appeared lately. At present, over one hundred psoralen derivatives exist in the chemical literature, of which approximately half are naturally occurring and the remaining are synthetically prepared [24]. However, such compounds have been the topic of the debate because the specific roles of these compounds are not well



Scheme 10. Example of general simultaneous formation of both heterocyclic rings (**65**, **66**) [28].



Scheme 11. Synthesis of 2,4-dihydroxybenzaldehyde (**70**) [38].

understood. The majority of natural furocoumarins are linear (psoralens) or angular derivatives (angelicins) because they can exist either in the free or glycosylated form [2]. Position 4' and 5' in furan ring is saturated in many cases of the double bond. Murray *et al*. have written an excellent book that provides a comprehensive overview of naturally occurring coumarins which includes a tabulated summary of all botanical sources of coumarins.

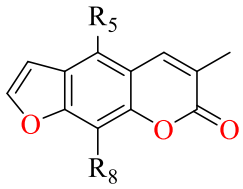
The present work is not intended to be a comprehensive review for the whole field, but our only concern is the simple structure of novel furocoumarin which is not associated with other ring systems as compared to the last 15 years [28]. Thus, focusing on psoralen compound, some of the sources of these compounds are presented in Table **1** which shows 5 and 8 substituted psoralens.

8. METHOD OF PSORALEN DERIVATIVES SYNTHESIS BEARING AMIDE MOIETY

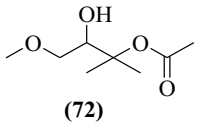
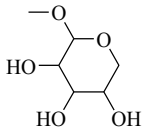
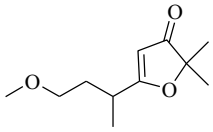
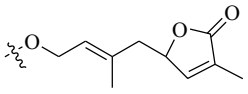
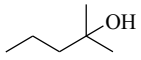
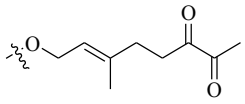
Four points of structural diversity have been considered in psoralen structure: (i) the furan substituents; (ii) the presence/absence of a methyl in the central benzene ring (iii) the length of the spacer between the psoralen nucleus and the amide function; (iv) the nature of the amide moiety. In particular, with respect to the four points of diversity, we are focusing the amide moiety which required terminal carboxylic function that probably interacted with positively charged amino acids.

One of the examples is when (7-oxo-7*H*- furo[3,2-g][1]benzopyran-6-yl)acetic or propionic acids (**78**) were synthesized according to previously reported methods, but the method was slightly modified to take advantage of MAOS (microwave assisted organic synthesis), as described for

Table 1. The 5- and/or 8-substituted psoralens (71) [28].

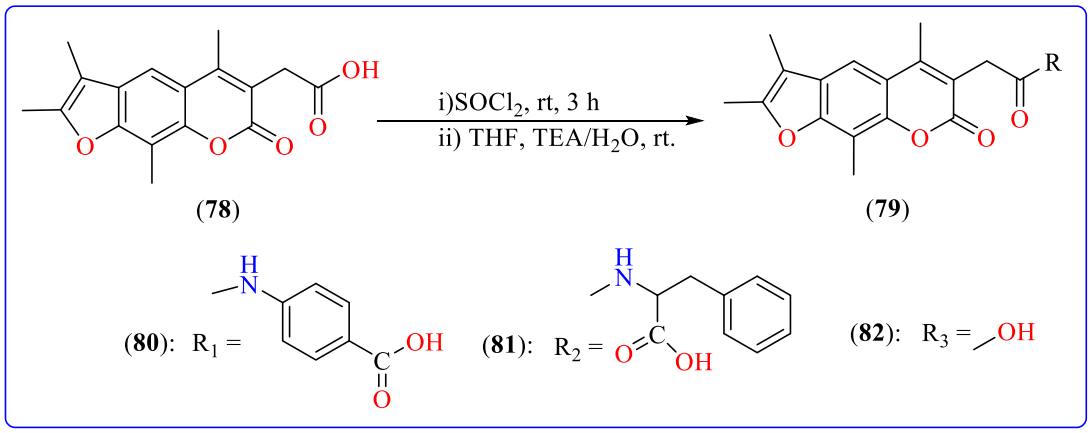


(71)

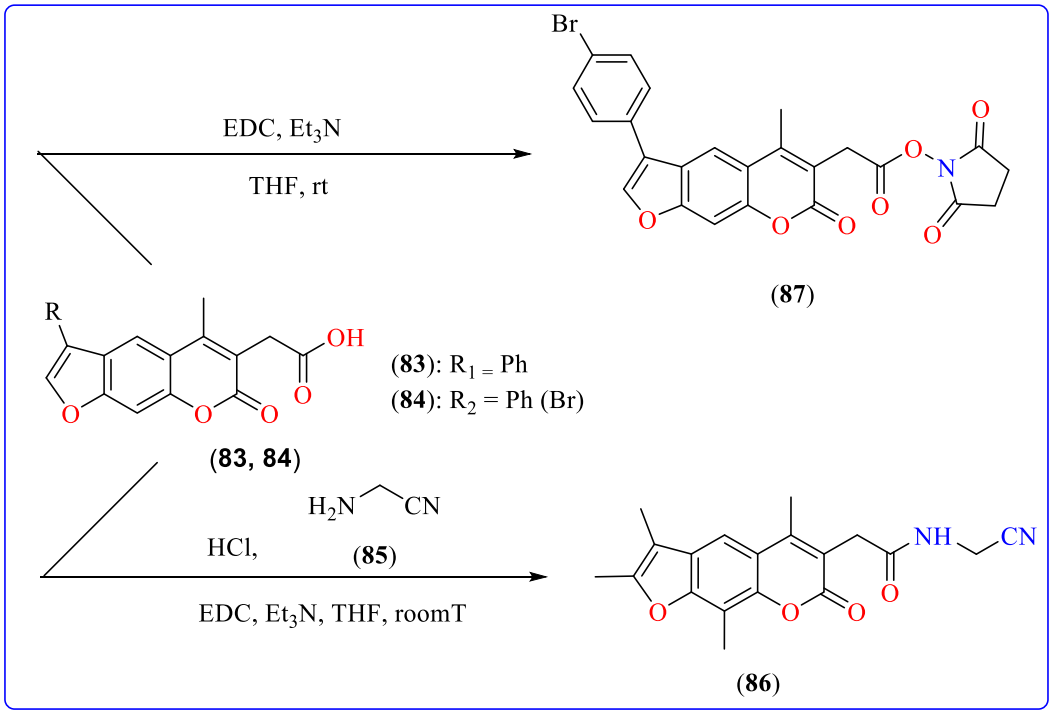
Compound	R5	R8	Sources
5-[3-(Acetyloxy)-2 hydroxy-3-methylbutoxy]psoralen	 **(72)**	H	*Peucedanum ostruthium*
8-(β-LArabinopyranosyloxy)psoralen	H	 **(73)**	*Aegle marmelos*
Dorstenin	 **(74)**	H	*Dorstenia contrajerva, Dorstenia bahiensis*
5-Formylxanthotoxol	CHO	OH	*Cnidium monnieri*
Fernolin	OCH_3	 **(75)**	*Feronia limonia*
5-(3-Hydroxy-3methylbutyl)-8-methoxy-psoralen	 **(76)**	OCH_3	*Elsholtzia densa*
Lansiumarin	H	 **(77)**	*Clausena lansium*

compound (**7**) [23]. Acid derivatives were activated as acyl chlorides and then reacted with the opportune amines or amino acids (**80**-**82**) to give the desired amides (**79**) as shown in Scheme **12**.

Besides that, the invention relates to novel inhibitors of the chymotrypsin-like activity of the immunoproteasome with general formula structure (**6**) where the substituents are clearly defined in the form of pure enantiomers, mixture of enantiomers, in the form of diastereoisomers, mixture of diastreomers, and their pharmaceutically acceptable salts, hydrates or solvates. The invention relates to the use of the described compounds for the treatment of diseases where the immunoproteasome activity is increased. For example, the synthesis of *N*-(cynomethyl)amides (**85**) uses the starting compound carboxyalkylpsoralen (**83**) and (**85**) reacts with *N*-methylamineacetonitrile hydrochloride (**84**) in THF and Et_3N under argon atmosphere as shown in Scheme **13**. Purification was done by crystallization or column chromatography.



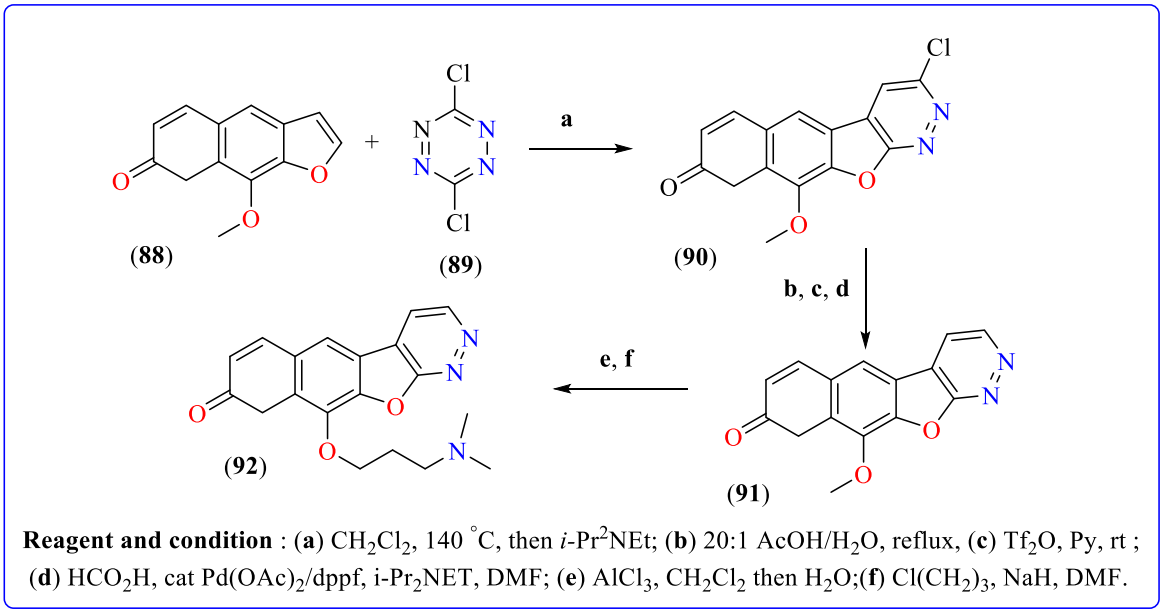
Scheme 12. Synthesis of psoralen derivatives by (7-oxo-7*H*- furo[3,2-g][1]benzopyran-6-yl) acetic or propionic acids (**78**) [23].



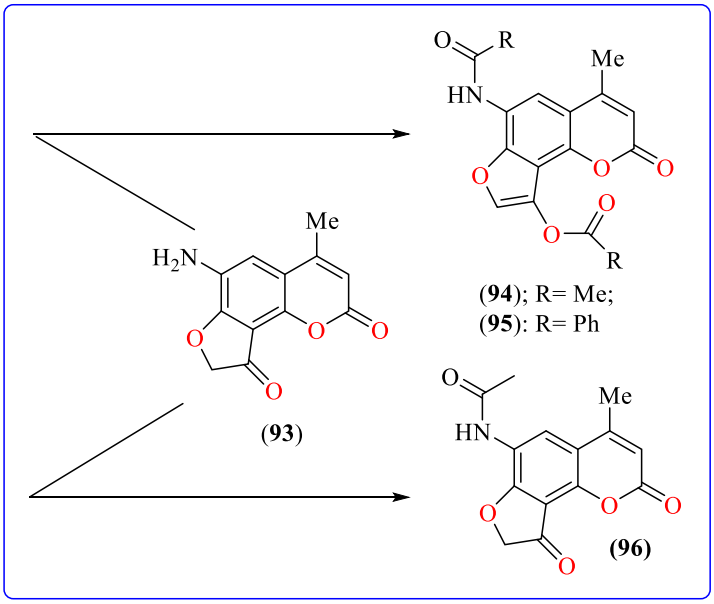
Scheme 13. Synthesis of *N*-(cynomethyl)-2-(5-methyl-7-oxo-3-phenyl-7*H*-furo[3,2-*g*]chromen-6-yl)acetamide (**86**) and 2,5-dioxopyrolidin-1-yl 2(3-(4-bromophenyl)-5-methyl-7-oxo-7*H*-furo[3,2-gchromen-6-yl)acetate (**87**).

In addition, the synthesis of a new pyridazino [4,3-h]psoralen and the biological activity evaluation was reported. Compound (**92**) was prepared from commercially available 8-MOP as shown in Scheme **14**. Pyridazinopsoralen (**89**) was obtained in an excellent 98% yield from 8-MOP and 3,6-dichlorotetrazine, in a Diels-Alder reaction, followed by intramolecular cyclization. This procedure was successfully used in a 2-g scale and then crystallized with high purity from the reaction mixture. The hydrolysis of compound (**90**) to the corresponding pyridazinone, followed by triflate preparation and palladium catalyzed hydrogenolysis under transfer conditions, afforded compound (**91**) in about 65% yield over three steps. Demethylation of compound (**88**), using $AlCl_3/CH_2Cl_2$ at room temperature, followed by alkylation under Williamson conditions, with 3 chloro-*N,N*-dimethylpropylamine hydrochloride, afforded the target compound (**92**) in 40% yield over two steps.

Apart from the above, reports are available in which 6-aminocoumarin-9-one (**93**) is readily acetylated with acetic anhydride, forming 6-acetamidocoumarin-9-one (**95**) [38]. However, if pyridine



Scheme 14. Synthesis of pyridazinopsoralen derivative (**92**).



Scheme 15. Synthesis of 6-aminocoumarin-9-one (**93**) derivatives [38].

is used as catalyst, amine (**96**) is acetylated both at the amino group and with simultaneous stabilization of the corresponding enolic form. While, 6-acetamido-9-acetoxy-4-methylangelicin (**94**) was obtained in this way as shown in Scheme **15** and the benzoylation of compound (**93**) by benzoyl chloride is similar and leads to 6-benzamido-9-benzoyloxy-4-methylangelicin (**95**).

In conclusion, similar to the synthesis of psoralen, their derivatives can also be synthesized using a variety of methods and conditions depending on the needs.

9. BIOLOGICAL ACTIVITIES

The name psoralen, which refers to linear furo [3,2-g]coumarins is a reference to the main pharmacological application of these compounds. At the same time psoralen is a compound of interest due to its application in molecular biology and nucleic acid chemistry. In addition, numerous other bioactivities have been attributed to furocoumarins which is the focus of many pharmacological screenings although their mutagenic potential was recognized many years ago [39]. Thus, the photochemistry of furocoumarins has been deeply studied.

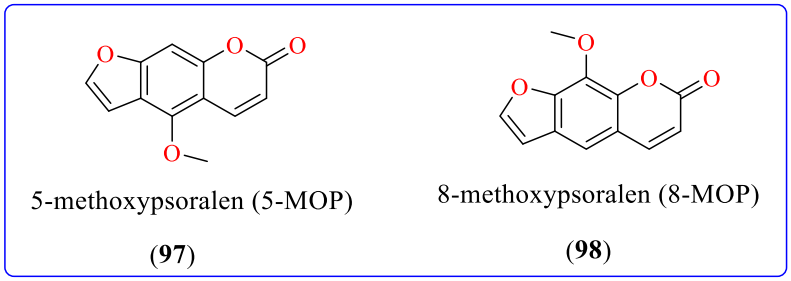


Fig. (6). Structure of 5-methoxypsoralen (5-MOP) (**97**) and 8-methoxypsoralen (8-MOP) (**98**) [41].

10. CHEMOTHERAPEUTIC AGENTS STUDY

Psoralen has been detected as photo chemotherapeutic agents for the treatment of skin diseases (PUVA therapy) for a long time [40]. US Food and Drug Administration (FDA) has also approved psoralen (P) + ultraviolet light (UVA) radiation, PUVA for clinical and pharmaceutical application, PUVA slows down skin proliferation [39]. However, some undesirable side effect are generally associated with PUVA like erythema genotoxicity, phototoxicity, and a possible risk of skin cancer [32]. Therefore, to enhance the photo binding properties and to reduce side effects, structural modifications of psoralen have been attempted in a wide range of furocoumarins [41]. 5-methoxypsoralen (5-MOP) (**80**) and 8-methoxypsoralen (8-MOP) (**81**) are psoralens which are frequently used in PUVA therapy for the treatment of a variety of epidermal proliferative diseases (Fig. **6**). Their biological application for the treatment of different hyper proliferative skin complaints including vitiligo, psoriasis and atopic dermatitis properties are mainly attributed to the ability to bind covalently to nucleic acids.

PUVA bath therapy with long wave UV radiation has been explored for the treatment because PUVA therapy increases the incidence of squamous cell carcinoma. Once it is activated by UVA light, the cycloaddition of psoralen with pyrimidine bases of nucleic acids forming stable cycloadducts and this mechanism has been found efficient in the treatment because the mutations are found at crosslink-able sites. Poor skin deposition, weak percutaneous permeability of psoralen and adverse effects of severe burning, blisters, pigmentation associated with conventional topical psoralen vehicles hinder the therapeutic efficacy and safety of topical PUVA [40].

11. ANTI-CANCER STUDY

Psoralens have also been suggested as potential treatments for several types of cancer [23]. Several furocoumarins have been used to mark DNA in biochemical studies. This area provides a driving force in the study of the mechanism of carcinogenicity. The results of the antimutagenic activity induced by other carcinogens and their strong antitumor promoter activity make them effective materials for cancer prevention. Psoralen derivatives have been synthesized and evaluated as inhibitors of NF-Kb/DNA interaction to investigate the structural determinants which required inhibiting this interaction. Thus, by targeting NF-kb new therapeutic agents, anticancer and/or antiflammatory compounds have been found. Therefore, among NF-kb inhibitors, several psoralen derivatives (**79**) have been found and have been proved as interesting leads for the development of pharmaceutical strategies against the inflammatory phenotype of cystic fibrosis (CF) as they exhibited high efficiency in inhibiting NF-kb/DNA interactions.

In addition, following the result which reported benzopsoralens as potent photochemotherapeuticagents, we also report the anti- proliferative evaluation of nitrogenatedisoster upon and without UVA irradiation. The evaluated pyridazinopsoralen showed a higher photochemotherapeutic activity with respect to the well-known drug 8-MOP and a significant cytotoxicity also in the dark. These results enhance the interest in tetracyclic psoralen derivative skeleton as new anticancer agents. Both the pyridazine ring and the protonable sidechain can account for the significant shift of the psoralen derivatives. These derivatives lead to a dark antiproliferative activity and actually indicate the possibility to modulate the photo-dependent

and independent cellular effect by modifying suitably the intercalative arrangement of the tetracyclic psoralen skeleton.

12. ANTI-VIRAL STUDIES

Investigation into the properties of psoralens led to the realization that this group of compounds may act as anti-viral agents while preserving the structures needed for antigenic activity and nucleic acids for molecular or genomic analysis. Psoralens are small, photoreactive compounds that freely penetrate phospholipid bilayers and intercalate between nucleic acid pyrimidine residues, causing cross-linking and inactivation *via* the inhibition of replication when exposed to UV-A radiation. Psoralens do not appear to interact with proteins and the inactivation of viruses with psoralen may leave immunogenic surface epitopes intact. The photocrosslinking property of psoralens has been exploited to inactivate viral pathogens prior to organ transplantation and to inactivate viruses for potential vaccines. Neither exposure to psoralens alone nor exposure to long-wave UV light alone was sufficient to inactivate DNA or RNA viruses, and incubation with psoralens in the absence of UV light did not cause observable cell death.

Previously, dengue virus was used as a representative positive single-stranded RNA (ssRNA (+)) genome virus and it demonstrated the inactivation of the virus with the psoralen compound 4'-aminomethyl-trioxsalen (AMT) (**99**) as shown in Fig. (**7**). The inactivated dengue virus retained the ability to bind to a panel of five monoclonal antibodies specific for Dengue-2 (DENV-2) envelope protein and elicited a T-cell response in vaccinated mice similar to live, non-inactivated virus.

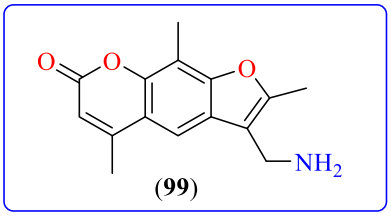


Fig. (7). 4'-Aminomethyl-trioxsalen (AMT) (**99**).

Besides that, psoralen also photochemically responds with DNA by the formation of covalent adducts with pyrimidine bases because their natural products and their main chromosphere is a furocoumarin. They are good against herpes virus and human immunodeficiency virus HIV-1 [22]. Nowadays, and in the previous decade, many new potential therapeutic agent applications for linear furocoumarins were revealed. For instance, some psoralen derivatives were found to induce elytroid differentiation in different cellular models or were characterized as HIV-1 integrase inhibitors. Several psoralen derivatives were able to inhibit NF-kB/DNA interactions. The substituents in the furan ring were found to be responsible for the identification of candidates with inflammatory activity as shown in Fig. (**8**).

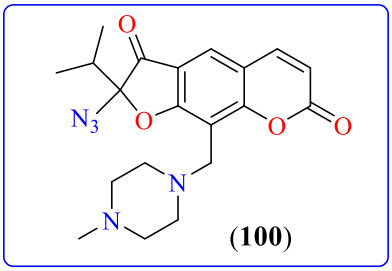


Fig. (8). Targeted psoralen derivatives (**100**) [22].

13. OTHER BIOACTIVITY STUDIES

Abnormal rhythms of the heart which causes the heart to pump less effectively is called arrhytmias. Antiarrhythmic drugs manage arrhythmias through the regulation of the cardiac action potential duration. The development of the lesioned tissue specific antiarrhythamic drugs is one of the ways to reduce this proarrhythmic effect [42]. Scientific reports published in 2006 revealed that the furocoumarin derivative psoralen (7H-furo[3,2-g][1]benzopyran-7- one) blocked a human Kvl.5 potassium channel (hKvl.5) and has a potential antiarrhythmic effect. In the same study, ten psoralen derivatives were synthesized and examined for their blocking effects on hKv1.5 stably expressed in LtK cells [42]. The results on newly synthesized psoralen derivatives revealed that three derivatives (e,i,k) exhibited channel-blocking effect (Fig. **9**).

Besides that, *Psoralea corylifolia L.* has been used traditionally as medicine in China and was

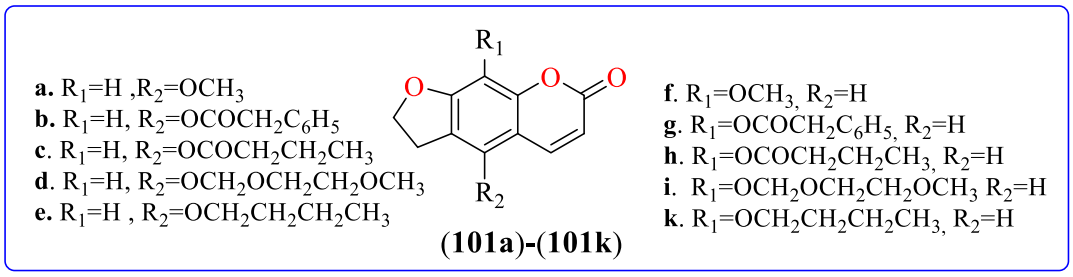


Fig. (9). Chemical structure of psoralen derivatives (**101a-101k**) [42].

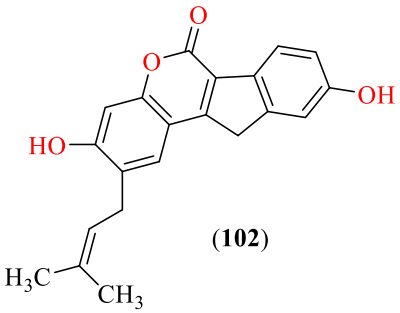


Fig. (10). Psoralidin structure (**102**) [43].

recommended for the treatment of stomachic, deobstruent, anthelmintic, diuretic, and certain skin diseases. Few reports addressed the antioxidant activity of *P. corylifolia L* which was found to have strong antioxidant effects. One of the examples is psoralidin (**102**) in which lactone phenolic structure was found to be fused with aromatic rings. There is an alkyl group at the *ortho* position of the phenolic hydroxyl group and a furan ring at the para-position and an ether bonded oxygen at the meta-position of the hydroxyl group. There is a furan ring fused with ring. These factors make the free radical stable after the functional hydroxyl group donates H-atoms to active free radicals and becomes the most active antioxidant among the compounds in the study as shown in Fig. (**10**) [43].

CONCLUSION

As it is indicated above, Psoralens or Furocoumarins are bearing a furan ring fused to a coumarin moiety. It is well shown that Psoralen derivatives posses an important spectrum of biological activities (cytotoxic, photosensitizing, insecticidal, antibacterial and antifungal effect). Interestingly, various structural changes were introduced to explore the role of specific positions with respect to the biological activity. This nice chemistry leads to the synthesis of the tricyclic ring system from resorcinol and the exocyclic modification of the intact ring system. Furthermore, although psoralens have been used in diverse ways, we mainly focus in this work on their clinical utility for the treatment of psioraisis, vitiligo and skin-related disorder. Another supplementary bioinformatic/doking POM (Petra/Osiris/Molinspiration) study should be engaged in goal to identify their specific pharmacophore sites in goal to get insight on the mechanism of action to understand their pharmacological properties.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

The authors wish to thank the Ministry of Higher Education (MOHE) Malaysia for funding this research under the Research University Grant (RUP) with vote no 18H37. Identifier: 10.13039/501100003093.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Ji, L.; Lu, D.; Cao, J.; Zheng, L.; Peng, Y.; Zheng, J. Psoralen, a mechanism-based inactivator of CYP2B6. *Chem. Biol. Interact.,* **2015**, *240*, 346-352. http://dx.doi.org/10.1016/j.cbi.2015.08.020 PMID: 26335194

[2] Mohammadparast, B.; Rustaiee, A.R.; Rasouli, M.; Zardari, S.; Agrawal, V. *In vitro* enhancement of pso-

ralen as an important anticancer compound in *Psoralea corylifolia* through precursor feeding. *Pharm. Biol.,* **2015**, *53*(5), 735-738.
http://dx.doi.org/10.3109/13880209.2014.942786
PMID: 25331001

[3] Siva, G.; Sivakumar, S.; Prem Kumar, G.; Vigneswaran, M.; Vinoth, S.; Muthamil Selvan, A.; Jayabalan, N. Optimization of elicitation condition with jasmonic acid, characterization and antimicrobial activity of psoralen from direct regenerated plants of *Psoralea corylifolia* L. *Biocatal. Agric. Biotechnol.,* **2015**, *4*, 624-631.
http://dx.doi.org/10.1016/j.bcab.2015.10.012

[4] Marzaro, G.; Guiotto, A.; Borgatti, M.; Finotti, A.; Gambari, R.; Breveglieri, G.; Chilin, A. Psoralen derivatives as inhibitors of NF-κB/DNA interaction: synthesis, molecular modeling, 3D-QSAR, and biological evaluation. *J. Med. Chem.,* **2013**, *56*(5), 1830-1842.
http://dx.doi.org/10.1021/jm3009647
PMID: 23414143

[5] Ben Hadda, T.; Khardli, F.A.; Mimouni, M.; Daoudi, M.; Kerbal, A.; Salgado-Zamora, H.; Gandhare, H.; Parvez, N.A. Impact of geometric parameters, charge and lipophilicity on bioactivity of armed quinoxaline, benzothiaole and benzothiazine: POM analyses of antibacterial and antifungal activity. *Sulfur Silicon Relat. Elem.,* **2014**, *189*(6), 753-761.
http://dx.doi.org/10.1080/10426507.2013.855763

[6] Ben Hadda, T.; Srivastava, S.; Das, B.; Salgado-Zamora, H.; Shaheen, U.; Bader, A.; Naseer, M.M. POM analyses of antimicrobial activity of some 2,3-armed 4,5,6,7-tetrahydro-1-benzothiophenes: favourable and unfavourable physicochemical parameters in design of antibacterial and mycolytic agents. *Med. Chem. Res.,* **2014**, *23*(2), 995-1003.
http://dx.doi.org/10.1007/s00044-013-0707-0

[7] Ben Hadda, T.; Ahmad, M.; Sultana, S.; Shaheen, U.; Bader, A.; Srivastava, S.; Das, B.; Salgado-Zamora, H. POM analyses for antimicrobial evaluation of thienopyrimidinones derivatives: A rapid method for drug design. *Res. Chem. Intermed.,* **2014**, *23*(1), 16-24.

[8] Ben Hadda, T.; Fergoug, T.; Warad, I. POM theoretical calculations and experimental verification of antibacterial potential of 5-hydroxy-4-(substituted-amino)-2(5H)-furanones. *Res. Chem. Intermed.,* **2013**, *39*(5), 1963-1971.
http://dx.doi.org/10.1007/s11164-012-0729-0

[9] Jarrahpour, A.; Fathi, J.; Mimouni, M.; Ben Hadda, T.; Sheikh, J.; Chohan, A.H.; Parvez, A. Petra, osiris and molinspiration (POM) together as a successful support in drug design: antibacterial activity and biopharmaceutical characterization of some azo schiff bases. *Med. Chem. Res.,* **2012**, *21*(8), 1984-1990.
http://dx.doi.org/10.1007/s00044-011-9723-0

[10] Juneja, H.; Panchbhai, D.; Sheikh, J.; Ingle, V.; Ben Hadda, T. Synthesis, antibacterial screening and POM analyses of novel bis-isoxazolyl/pyrazoyl-1,3-diols. *Med. Chem. Res.,* **2014**, *23*(3), 1537-1547.
http://dx.doi.org/10.1007/s00044-013-0755-5

[11] Lahsasni, S.; Ben Hadda, T.; Masand, V.; Pathan, N.B.; Parvez, A.; Warad, I.; Shaheen, U.; Bader, A.; Aljofan, M. POM analyses of Raltegravir derivatives: A new reflection enlightening the mechanism of HIV-integrase inhibition. *Res. Chem. Intermed.,* **2015**, *41*(8), 5121-5136.
http://dx.doi.org/10.1007/s11164-014-1616-7

[12] Mabkhot, Y.N.; Arfan, M.; Zgou, H.; Genc, Z.K.; Genc, M.; Rauf, A.; Bawazeer, S.; Ben Hadda, T. How to improve antifungal bioactivity: POM and DFT study of some chiral amides derivatives of diacetyl-L-tartaric acid and amines. *Res. Chem. Intermed.,* **2016**, *42*(12), 8055-8068.
http://dx.doi.org/10.1007/s11164-016-2578-8

[13] Mabkhot, Y.N.; Alatibi, F.; El-Sayed, N.N.E.; Al-Showiman, S.; Kheder, N.A.; Wadood, A.; Rauf, A.; Bawazeer, S.; Hadda, T.B. Antimicrobial activity of some novel armed thiophene derivatives and petra/osiris/molinspiration (POM) analyses. *Molecules,* **2016**, *21*(2), 222-238.
http://dx.doi.org/10.3390/molecules21020222 PMID: 26901173

[14] Mabkhot, Y.N.; Aldawsari, F.D.; Al-Showiman, S.S.; Barakat, A.; Hadda, T.B.; Mubarak, M.S.; Naz, S.; Ul-Haq, Z.; Rauf, A. Synthesis, bioactivity, molecular docking and POM analyses of novel substituted thieno[2,3-b]thiophenes and related congeners. *Molecules,* **2015**, *20*(2), 1824-1841.
http://dx.doi.org/10.3390/molecules20021824 PMID: 25621424

[15] Mabkhot, Y.N.; Barakat, A.; Yousuf, S.; Choudhary, M.I.; Frey, W.; Ben Hadda, T.; Mubarak, M.S. Substituted thieno[2,3-b]thiophenes and related congeners: Synthesis, β-glucuronidase inhibition activity, crystal structure, and POM analyses. *Bioorg. Med. Chem.,* **2014**, *22*(23), 6715-6725.
http://dx.doi.org/10.1016/j.bmc.2014.08.014 PMID: 25245672

[16] Mahajan, D.T.; Masand, V.H.; Patil, K.N.; Ben Hadda, T.; Jawarkar, R.D.; Thakur, S.D.; Rastija, V. CoMSIA and POM analyses of anti-malarial activity of synthetic prodiginines. *Bioorg. Med. Chem. Lett.,* **2012**, *22*(14), 4827-4835.
http://dx.doi.org/10.1016/j.bmcl.2012.05.115 PMID: 22732694

[17] Rauf, A.; Uddin, G.; Siddiqui, B.S.; Khan, H.; Ur-Rehman, M.; Warad, I.; Ben Hadda, T.; Patel, S. POM analysis of phytotoxic agents from *Pistacia integerrima* Stewart. *Curr. Bioact. Compd.,* **2015**, *11*, 231-238.
http://dx.doi.org/10.2174/1573407211666151012191902

[18] Sajid, Z.; Ahmad, M.; Aslam, S.; Ashfaq, U.A.; Zahoor, A.F.; Saddique, F.A.; Parvez, M.; Hameed, A.; Sultan, S.; Zgou, H.; Ben Hadda, T. Novel armed pyrazolobenzothiazine derivatives: Synthesis, x-ray crystal structure and POM analyses of biological activity against drug resistant clinical isolate of *Staphy-*

lococcus aureus. *Pharm. Chem. J.,* **2016**, *50*(3), 172-180.
http://dx.doi.org/10.1007/s11094-016-1417-y

[19] Tighadouini, S.; Radi, S.; Sirajuddin, M.; Akkurt, M.; Ozdemir, N.; Ahmad, M.; Mabkhot, Y.N.; Ben Hadda, T. *In vitro* antifungal, anticancer activities and POM analyses of a novel bioactive schiff base, 4-{[(E)-furan-2-ylmethylidene]amino}phenol: Synthesis, characterization and crystal structure. *J. Chem. Soc. Pak.,* **2016**, *38*(1), 253-259.

[20] Youssoufi, M.H.; Ben Hadda, T.; Warad, I.; Naseer, M.M.; Mabkhot, Y.N.; Bader, A. POM analyses of anti-kinase activity of thirteen peptide alkaloids extracted from Zizyphus species. *Med. Chem. Res.,* **2015**, *24*(1), 267-274.
http://dx.doi.org/10.1007/s00044-014-1117-7

[21] Youssoufi, M.H.; Sahu, P.K.; Agarwal, D.D.; Ahmad, M.; Messali, M.; Lahsasni, S.; Ben Hadda, T. POM analyses of antimicrobial activity of 4H-pyrimido[2,1-b]benzothiazole, pyrazole, and benzylidene derivatives of curcumin. *Med. Chem. Res.,* **2014**, *24*(6), 2381-2392.
http://dx.doi.org/10.1007/s00044-014-1297-1

[22] Schneider, K.; Wronka-Edwards, L.; Leggett-Embrey, M.; Walker, E.; Sun, P.; Ondov, B.; Wyman, T.H.; Rosovitz, M.J.; Bohn, S.S.; Burans, J.; Kochel, T. Psoralen inactivation of viruses: A process for the safe manipulation of viral antigen and nucleic acid. *Viruses,* **2015**, *7*(11), 5875-5888.
http://dx.doi.org/10.3390/v7112912 PMID: 26569291

[23] Francisco, C.S.; Rodrigues, L.R.; Cerqueira, N.M.F.S.A.; Oliveira-Campos, A.M.F.; Rodrigues, L.M.; Esteves, A.P. Synthesis of novel psoralen analogues and their *in vitro* antitumor activity. *Bioorg. Med. Chem.,* **2013**, *21*(17), 5047-5053.
http://dx.doi.org/10.1016/j.bmc.2013.06.049 PMID: 23886808

[24] Parsons, B.J. Psoralen photochemistry. *Photochem. Photobiol.,* **1980**, *32*(6), 813-821.
http://dx.doi.org/10.1111/j.1751-1097.1980.tb04061.x PMID: 7005917

[25] Kontogiorgis, C.A.; Hadjipavlou-Litina, D.J. Synthesis and antiinflammatory activity of coumarin derivatives. *J. Med. Chem.,* **2005**, *48*(20), 6400-6408.
http://dx.doi.org/10.1021/jm0580149
PMID: 16190766

[26] Yadav, G.D.; Ajgaonkar, N.P.; Varma, A. Preparation of highly superacidic sulfated zirconia *via* combustion synthesis and its application in pechmann condensation of resorcinol with ethyl acetoacetate. *J. Catal.,* **2012**, *292*, 99-110.
http://dx.doi.org/10.1016/j.jcat.2012.05.004

[27] Chattopadhyay, A.; Mamdapur, V.R.; Chadha, M.S. A convenient synthesis of psoralen. *Indian J. Chem.,* **1983**, *22*, 1221-1223.

[28] Santana, L.; Uriarte, E.; Roleira, F.; Milhazes, N.; Borges, F. Furocoumarins in medicinal chemistry. Synthesis, natural occurrence and biological activity. *Curr. Med. Chem.,* **2004**, *11*(24), 3239-3261.
http://dx.doi.org/10.2174/0929867043363721 PMID: 15579011

[29] Bourgaud, F.; Hehn, A.; Larbat, R.; Doerper, S.; Gontier, E.; Kellner, S.; Matern, U. Biosynthesis of coumarins in plants: a major pathway still to be unravelled for cytochrome P450 enzymes. *Phytochem. Rev.,* **2006**, *5*, 293-308.
http://dx.doi.org/10.1007/s11101-006-9040-2

[30] Lee, J.S. Recent advances in the synthesis of 2-pyrones. *Mar. Drugs,* **2015**, *13*(3), 1581-1620.
http://dx.doi.org/10.3390/md13031581
PMID: 25806468

[31] Nagorichna, I.V.; Dubovik, I.P.; Garazd, M.M.; Khilya, V.P. Modified coumarins. 10. Synthesis of substituted 2-(7-Oxofuro[3,2-g]chromen-6-yl)acetic acids. *Chem. Nat. Compd*., **2003**, *39*, 253-261.
https://doi.org/10.1023/A:1025466317733

[32] Hashem, S.E.N. Synthesis and photooxygenation of angular furocoumarins: isopsedopsoralen and allopsoralen. *Res. Chem. Intermed.,* **2015**, *41*, 1591-1600.
http://dx.doi.org/10.1007/s11164-013-1295-9

[33] Chen, C.Y.; Sun, J.G.; Liu, F.Y.; Fung, K.P.; Wu, P.; Huang, Z.Z. Synthesis and biological evaluation of glycosylated psoralen derivatives. *Tetrahedron,* **2012**, *68*, 2598-2606.
http://dx.doi.org/10.1016/j.tet.2012.01.090

[34] Valizadeh, H.; Shockravi, A. Microwave-assisted claisen rearrangement. Application to the synthesis of angelicin derivatives. *J. Heterocycl. Chem.,* **2006**, *43*, 1-3.
http://dx.doi.org/10.1002/jhet.5570430336

[35] Zareai, Z.; Khoobi, M.; Ramazani, A.; Foroumadi, A.; Souldozi, A. Synthesis of functionalized furo[3,2-c]coumarins *via* a one-pot oxidative pseudo three-component reaction in poly (ethylene glycol). *Tetrahedron Lett.,* **2012**, *68*, 6721-6726.
http://dx.doi.org/10.1016/j.tet.2012.05.112

[36] Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. New method for preparation of coumarins and quinolinones *via* Pd-catalyzed intramolecular hydroarylation of C-C triple bonds. *J. Org. Chem.,* **2000**, *65*(22), 7516-7522.
http://dx.doi.org/10.1021/jo000861q
PMID: 11076610

[37] Bisagni, E. Synthesis of psoralens and analogues. *J. Photochem. Photobiol. B,* **1992**, *14*(1-2), 23-46.
http://dx.doi.org/10.1016/1011-1344(92)85081-5
PMID: 1432382

[38] Traven, V.F.; Sakharuk, I.I.; Kravchenko, D.V.; Ivashchenko, A.V. Synthon in the synthesis of 6-subsitituted angelicin. *Chem. Heterocycl. Compd.,* **2001**, *37*(3), 312-322.
http://dx.doi.org/10.1023/A:1017546730492

[39] Larbat, R.; Hehn, A.; Hans, J.; Schneider, S.; Jugdé, H.; Schneider, B.; Matern, U.; Bourgaud, F. Isolation and functional characterization of CYP71AJ4 encoding for the first P450 monooxygenase of angular furanocoumarin biosynthesis. *J. Biol. Chem.,* **2009**, *284*(8), 4776-4785.

http://dx.doi.org/10.1074/jbc.M807351200
PMID: 19098286

[40] Holmes, O.W. The evolution of photochemotherapy with psoralens U-VA (PUVA). *J. Org. Chem.,* **2000**, *14*, 3-22.

[41] Ropp, S.; Guy, J.; Berl, V.; Bischoff, P.; Lepoittevin, J.P. Synthesis and photocytotoxic activity of new alpha-methylene-gamma-butyrolactone-psoralen heterodimers. *Bioorg. Med. Chem.,* **2004**, *12*(13), 3619-3625.
http://dx.doi.org/10.1016/j.bmc.2004.04.019
PMID: 15186846

[42] Eun, J.S.; Kim, K.S.; Kim, H.N.; Park, S.A.; Ma, T.Z.; Lee, K.A.; Kim, D.K.; Kim, H.K.; Kim, I.S.; Jung, Y.H.; Zee, O.P.; Yoo, D.J.; Kwak, Y.G. Synthesis of psoralen derivatives and their blocking effect of hKv1.5 channel. *Arch. Pharm. Res.,* **2007**, *30*(2), 155-160.
http://dx.doi.org/10.1007/BF02977688
PMID: 17366735

[43] Guo, J.; Weng, X.; Wu, H.; Li, Q.; Bi, K. Antioxidants from a Chinese medicinal herb -*Psoralea corylifolia* L. *Food Chem.,* **2005**, *91*, 287-292.
http://dx.doi.org/10.1016/j.foodchem.2004.04.029