IJPSR (2014), Volume 5, Issue 9 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 March 2014; received in revised form, 23 April 2014; accepted, 07 June 2014; published 01 September 2014

BIOLOGICALLY POTENTIAL FLAVONES: A SUBGROUP OF FLAVONOIDS

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Keywords:

Flavonoids, Flavones, Flavopiridol, Synthesis, Biological activity

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ABSTRACT: Flavones are an important class of flavonoids having a wide range of biological activities like antioxidant, anti-inflammatory, anti-oestrogenic, antimicrobial, anti-allergic, antioxidant, vascular, antitumor, and cytotoxic activities. First cyclin-dependent kinase inhibitor, flavopiridol, which is a flavone is approved as an orphan drug in Europe for the treatment of relapsed chronic lymphocytic leukemia. So, these structural motifs may show potential activity to wide therapeutic conditions. Thereby synthesis of flavone is an important aspect in medicinal chemistry. This article covers the synthetic strategies available in the literature and their usefulness in terms of yield and reaction condition and the biological activity exerted by the natural and synthetic flavone derivatives and their probable mechanism of action. It is expected that this review may be helpful for medicinal chemist in research regarding flavones with new therapeutic applications.

INTRODUCTION: Flavonoids are ubiquitous and chemically are polyphenolic compounds. Flavonoids constitute a relatively diverse family of aromatic molecules that are derived from Phe and malonyl-coenzyme A (CoA; via the fatty acid pathway). They are categorized according to chemical structure into nine major subgroups: chalcones, flavones, flavanols, flavanones, flavanediols, anthocyanidins, isoflavones, aurones, and tannins **Fig. 1**. [1] They are synthesized exclusively in plants, and many of them possess various biological functions such as acting as floral pigments, signal molecules, and antimicrobial compounds [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(9).3840-48

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(9).3840-48

They occur in the plants as glycosides, meaning that they are bound to sugar molecules. The flavonoids have aroused considerable interest recently because of their potential beneficial effects on human health. They have been reported to have antiviral [3], anti-allergic [4], antiplatelet [5], antioxidant [3, 6,] anti-inflammatory, antitumor [7], and estrogenic [8] activities.

Although, till date more than 5,000 flavonoids have been identified but the implementation of those molecules as potential compounds have been limited only because these compounds exist as a complex mixture of multiple compounds which are difficult to isolate [9]. Naturally available flavones usually belong to benzopyran class, an important secondary metabolite distributed throughout the plant kingdom. Structurally they are made up of two aromatic rings linked to a three carbon chain that forms an oxygenated heterocyclic ring system **Fig. 1**.

Flavones exhibit both hydrophilic as well as lipophilic properties including a wide range of enzyme-modulatory activity. In addition to protecting plants from microbial diseases, flavones have been shown to exhibit several useful biological activities, and these include activity against both metabolic and infective diseases specifically anti-inflammatory, anti-oestrogenic, antimicrobial, anti-allergic, antioxidant, vascular, antitumor and cytotoxic activities. Several reviews have described the interaction of flavonoids and flavones with mammalian cells, including comprehensive articles by Harborne *et al.,* [2] and Verma *et al.* [68] With the ubiquitous molecule flavone, promising target has been reached in treating metabolic complications like diabetes, Alzheimer's disease, atherosclerosis, cancer and also in infectious disease like malaria.

A classic example regarding the importance of flavonoids is the effect of red wine and tea on cardiovascular disease. A recent study estimated that extra daily consumption of three cups of tea approximately reduces the risk of cardiovascular risk by more than ten percent [10]. Epidemiological studies have also shown a relationship between red wine intake and a cardiovascular protective effect. Compounds like flavonols, flavones, and flavanones have been implemented in large community health studies. Most studies show a protective effect for these phytochemicals. Though these molecules have been studied extensively, still they have to be explored to achieve further clinical effects of these flavonoids. Isoflavones have the distinguishing property to bind selectively with estrogen receptors [10]. Animal experiments and epidemiological studies have suggested that isoflavones protect against cardiovascular diseases such as atherosclerosis. They seem to directly improve the health and longevity of blood vessels. Isoflavones have also been found to reduce LDL oxidation through their antioxidant activity.

In the following sections, we will survey the synthetic procedures and biological activity of natural and synthetic flavones, which figure out the usefulness of flavone derivatives.

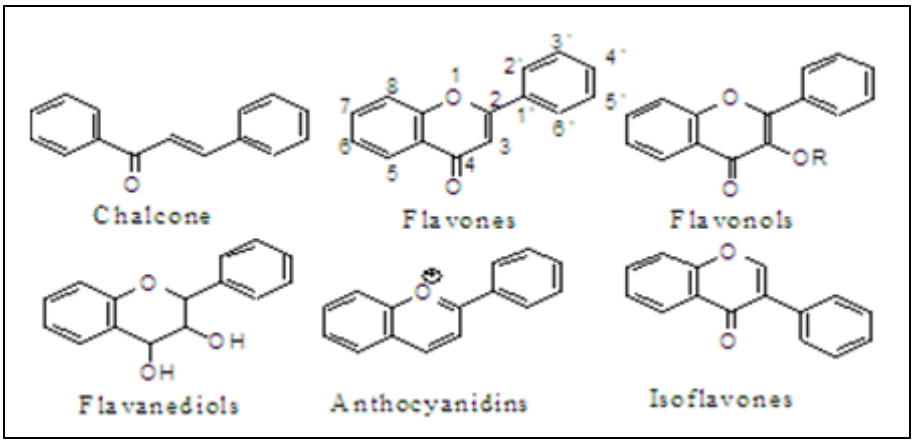
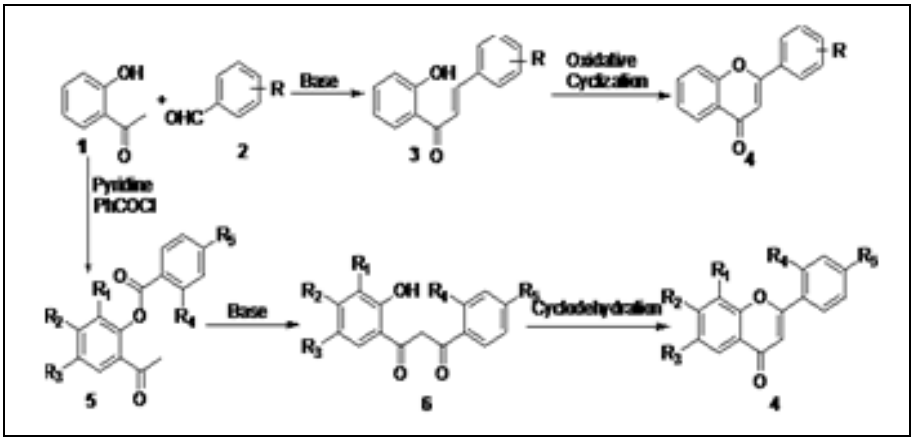


FIG. 1: GENERAL STRUCTURE OF FLAVONOIDS

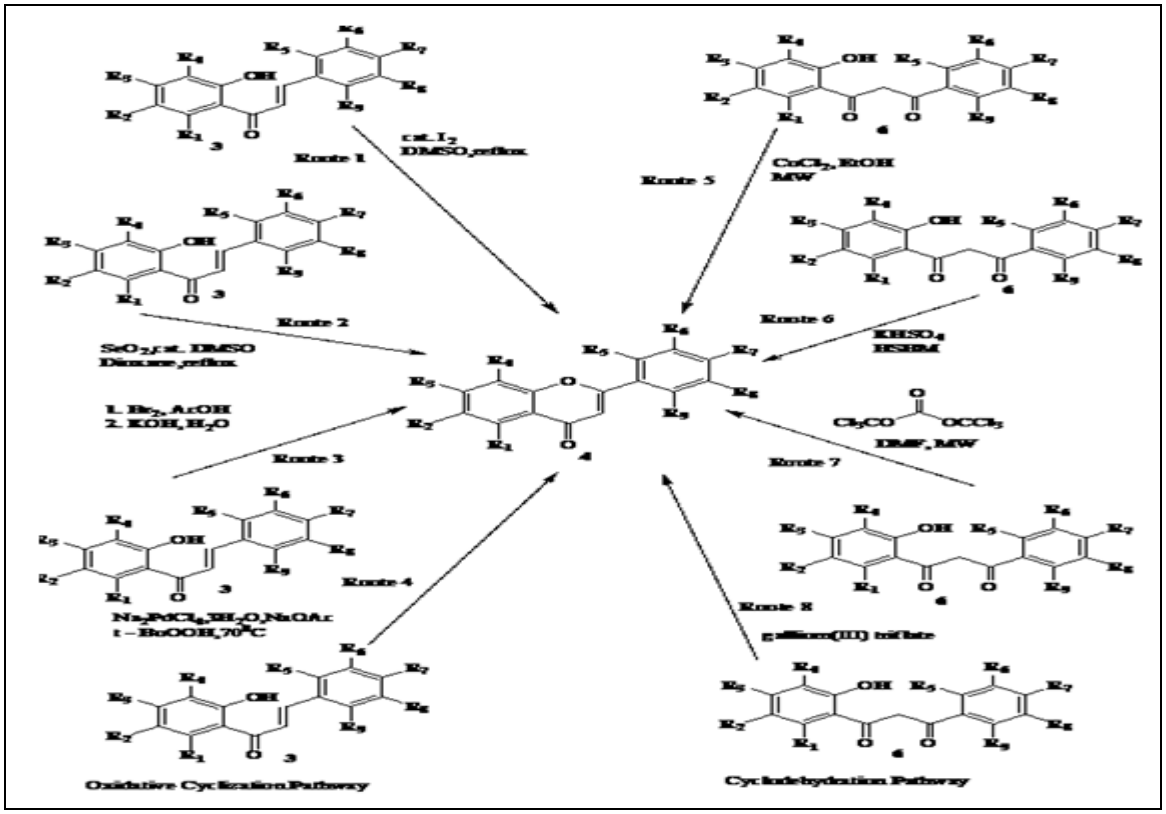


SCHEME 1: GENERAL OUTLINE OF PATHWAYS TO SYNTHESIZE FLAVONES

Synthesis of Flavones: Wide range of biological property of flavones has resulted in intense synthetic efforts towards the synthesis of various flavones. There are several methods reported for the synthesis of flavones. Both flavones and flavonols are structurally very close. Flavonols are known as 3-hydroxyflavones. Many publications in the literature have been illustrating different synthetic strategies of flavones, but a majority of these methods falls into the category of either oxidative cyclization of various substituted 2-hydroxychalcones 3 or cyclodehydration of substituted 1-(2-hydroxyphenyl)-3-phenylpropane -1, 3-dione6 **Scheme 1**.

Oxidative cyclization is usually carried out by preparing 2-hydroxychalcone 3 upon condensation of appropriately substituted 2 - hydroxy acetophenone 1 with various substituted benzaldehydes 2 under basic conditions [11].

There have been several reports of reagent conditions to carry out oxidative cyclization, and the most common of them are summarized in **Scheme 2**. In one of the reported works on the synthesis of flavones, Lokhande et al. reported the cyclization of 2-hydroxychalcone 3 in the presence of the catalytic amount of iodine in dimethyl sulfoxide which yielded flavones 4 (**Scheme 2**, **Route 1**) [12]. This catalytic iodine mediated method has been further explored and modified into a greener method by using iodine adsorbed on neutral alumina [13] and utilizing microwave reactor assisted techniques [14]. Another commonly employed method for the oxidative cyclization involves using selenium dioxide in isoamyl alcohol, which requires prolonged heating to yield flavones 4 [15]. Use of selenium dioxide to mediate reaction has also been improved over the years to make it more benign and greener. The most common improvement of this method is the use of selenium dioxide and traces of dimethyl sulfoxide over silica gel under microwave irradiation to get respective flavones (**Scheme 2**, **Route 2**) [16].



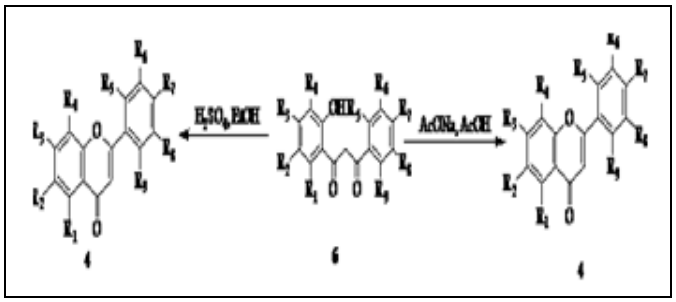
SCHEME 2: PREPARATION OF FLAVONES VIA OXIDATIVE AND CYCLODEHYDRATION PATHWAY

It has been found by addition of bromine across the chalcone double bond followed by base mediated cyclization afforded flavones 4 from 2-hydroxychalcone 3 as shown in **(Scheme 2, Route 3)** [17]. It does not involve the use of high-temperature or toxic reagents like dimethyl sulfoxide making it advantageous. But, the major disadvantage is that the yields for the flavones 4 are

moderate at best due to the formation of aurone **Fig. 1** aside products [18, 19].

Lorenz *et al.*, demonstrated an interesting and flexible synthesis of flavones 4 using a Wacker-Cook oxidation as the key step. Chalcone 3 starting material was prepared by using a common base mediated condensation of 2-hydroxyacetophenone and benzaldehyde. Though initial attempts using original Wacker conditions resulted in very poor conversions of chalcone to flavones 4. Moreover, Wacker conditions required the use of stoichiometric amounts of palladium. They got a better yield by using excess *tert*-butyl hydroperoxide. This method needed only catalytic amounts of the palladium catalyst and moderately high temperatures, as shown in **(Scheme 2, Route 4).** Several substituted flavones 4 were synthesized in good yields by using these methods [20].

Preparation of flavones 4 and flavonols 15 by cyclodehydration of substituted 1-(2-hydroxyphenyl)-3-phenylpropane-1, 3-dione 6 is shown in **Scheme 3**. The starting material 6 is usually prepared by a Baker-Venkataraman type rearrangement, which involves the base-induced transfer of the ester acyl group in an O-acylated phenol ester **5**, which leads to a 1, 3-diketone 6 as shown in **Scheme 1**. Like oxidative cyclization, the cyclodehydration pathway has also been very extensively used; studies have modified it as shown by the examples in **Scheme 2**.

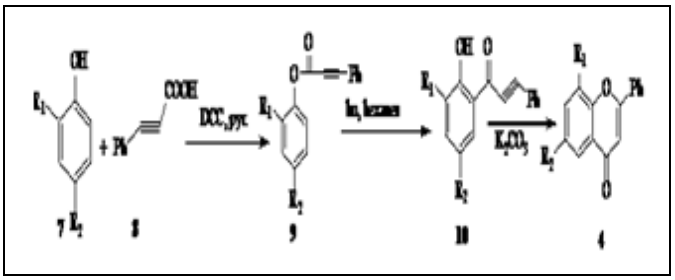


SCHEME 3: PREPARATION OF FLAVONES *VIA* CYCLODEHYDRATION PATHWAY

The usefulness of 1, 3-diketone 6 in the synthesis of flavones 4 was demonstrated by Wilson Baker and an unsubstituted 6 while treated with sodium acetate in acetic acid afforded flavone 4 **Scheme 3** [21]. Mahal *et al.*, successfully attempted the same reaction under acidic conditions shown in **Scheme 3** [22]. Since then, many different acidic and basic conditions have been tried and reported. The use of hydrochloric acid in acetic acid [23], hydrobromic acid in acetic acid [24], para-toluene sulfonic acid in xylene [25] and Lewis acids[26]has been reported to yield flavones from 6.

Some more important cyclodehydration pathways are discussed in Scheme 2. Most of the seroutes use microwave irradiation as a way to make the synthesis more environmental friendly. Kabalka *et al.*, reported a high yielding synthesis of flavones and chromones by using a catalytic amount of cupric chloride in a solution of the appropriate 1,3-diketone 6 in ethanol under microwave conditions shown in **(Scheme 2**, **Route 5)** [27]. A solid-state synthesis of flavones using high-speed ball milling (HSBM) was reported by Zhu *et al*. This route of synthesis was an efficient, mechanically activated solid-state synthesis by using potassium bisulfate as a reagent to achieve the desired product. Distinct advantage of these route is not using strong acids like sulfuric acid, hydrochloric acid or hydrobromic acid for the synthesis. Moreover, this route was the environmentally benign high yielding flexible route and thereby making it an attractive option to other routes **(Scheme 2**, **Route 6**) [28].

Popular Vilsmeier-Haack reaction was utilized for the synthesis of flavones for the first time by Su *et al*. They used Vilsmeier-Haack conditions with bis-(trichloro-methyl) carbonate/N, N-dimethyl-formamide to cyclodehydrate the 1,3-diketone 6 to flavone 4 shown in **(Scheme 2, Route 7)** [29]. Many other research groups have reported the use of various catalysts like gallium(III) triflate [30], indium(III) chloride [31] and ionic liquids [32] to achieve the cyclodehydration step to synthesize flavones efficiently in good yield **(Scheme 2, Route 8)**.

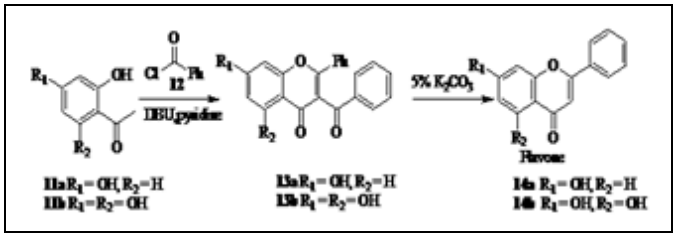


SCHEME 4: SYNTHESIS OF FLAVONE

Another procedure for the synthesis of flavones is detailed above in **Scheme 4**. This approaches to synthesize flavones involving the coupling of

substituted phenol 7 with substituted acetylene 8 in presence of DCC (N,N'-Dicyclohexylcarbodiimide) and pyridine to synthesize aryl propynoate 9 which, on irradiation, undergoes Photo-Fries rearrangement to give *o*-hydroxyarylethynyl ketone 10. This ketone 10 can then be cyclized to the corresponding flavone 4 in 10-25% overall yield reported by Mc Garry *et al.* [33]

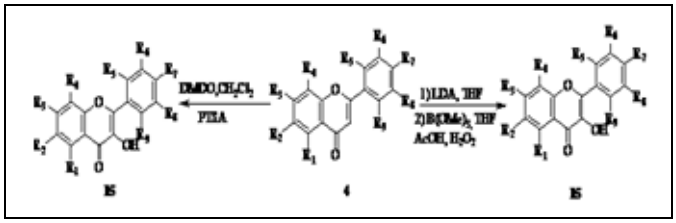
Ganguly's Synthesis of Flavone: Over years, several groups have investigated and improved upon the experimental conditions of Baker-Venkataraman reaction amongst which the work of Ganguly *et al.* [34] By modifying Baker-Venkataraman reaction, a novel class of 3-acylflavones, which is the precursors to flavones have been synthesized.



SCHEME 5: GANGULY'S SYNTHESIS OF FLAVONE

In their procedure, compounds such as 2´, 4´-dihydroxyacetophenone 11a and 2´, 4´, 6´-trihydroxyacetophenone 11b were heated with acyl chloride 12 in the presence of 1, 8-diazabicyclo [5.4.0] undec-7-ene (DBU) and pyridine to obtain 3-acyl flavones 13a and 13b. On heating under reflux with an aqueous solution of 5% potassium carbonate, compound 13a and 13b yielded 14a and 14b, respectively, as shown in **Scheme 5**.

Synthesis of 3-hydroxy flavones: Flavones 4 are usually converted to 3-hydroxy flavones 15 by either of the methods shown in **Scheme 6**. In a method demonstrated by Karim *et al.*, the 3-position of flavones are lithiated by LDA, and then the 3-lithioflavone is reacted with methyl borate followed by hydrogen peroxide to give flavonols 15 in good yields [35].



SCHEME 6: SYNTHESIS OF 3-HYDROXY FLAVONES

Another method to carry out the conversion is to oxidize the flavone 4 with dimethyl dioxirane (DMDO), followed by the treatment with a catalytic amount of *para*-toluene sulfonic acid (PTSA) to give the 3-hydroxy flavones in decent yields reported by Horie *et al.* [36]

Biological Aspects of Flavones: Some of the important natural and synthetic flavones of pharmacological importance are shown in **Fig. 2** & **3**. Apigenin 16 acts as a monoamine transporter activator, one of the few chemicals demonstrated to possess this property [37]. At high concentrations, chrysin 17 is reported to be an aromatase inhibitor *in-vitro* [38]. Some epidemiological studies have found a positive association between the consumption of foods containing kaempferol 18 and a reduced risk of developing several disorders such as cancer and cardiovascular diseases. Numerous preclinical studies have shown kaempferol, and some glycosides of kaempferol 19 have a wide range of pharmacological activities, including antioxidant, anti-inflammatory, anti-microbial, anticancer, cardioprotective, neuro-protective, antidiabetic, antiosteoporotic, estrogenic /antiestrogenic, anxiolytic, analgesic, and antiallergic activities [39]. *In-vitro* studies suggest that luteolin has anti-inflammatory activity [40, 41] and that it acts as a monoamine transporter activator [42], a phosphodiesterase inhibitor [43], and an interleukin-6 inhibitor [40].

Myricetin 21 has antioxidant properties. *In-vitro* research suggests that myricetin in high concentrations can modify LDL cholesterol. A study has shown the correlation of high myricetin consumption with lowered rates of prostate cancer [44]. Quercetin 22 and myricetin 3-O-beta-D-galactopyranoside inhibit HIV-1 reverse transcriptase, all with IC_{50} values of 60 μM [45]. Quercetin is an effective bronchodilator and helps reduce the release of histamine and other allergic or inflammatory chemicals in the body [46]. Quercetin has demonstrated significant anti-inflammatory activity because of direct inhibition of several initial processes of inflammation [47]. Serum IgE levels are highly elevated in eczema patients, and virtually all eczema patients are positive for allergy testing. Excessive histamine release can be minimized by the use of antioxidants. Quercetin has been shown to be effective in reducing IgE

levels in rodent models [48]. Quercetin may have properties of a calcineurin inhibitor, similar to cyclosporin A and tacrolimus, according to one laboratory study by Lei *et al.* [49] It has also been shown that quercetin reduces blood pressure in hypertensive [50] and obese subjects in whom LDL cholesterol levels were also reduced by quercetin [51]. Quercetin may be effective in the treatment of fibromyalgia because of its potential anti-inflammatory or mast cell inhibitory properties shown in laboratory studies [52]. *In-vitro* studies showed quercetin and resveratrol combined inhibited the production of fat cells [53] and vascular smooth muscle cell proliferation [54].

Rutin 23 shows anti-inflammatory activity in some animal and *in-vitro* models [55, 56]. Rutin inhibits aldose reductase activity reported by Reddy *et al.* [57] Aldose reductase is an enzyme normally present in the eye and elsewhere in the body. It helps to change glucose into the sugar alcohol sorbitol. Furthermore, it has been shown to inhibit the vascular endothelial growth factor in subtoxic concentrations, so acts as an inhibitor of angiogenesis in *in-vitro* conditions. This finding may have potential relevance for the control of some cancers [58].

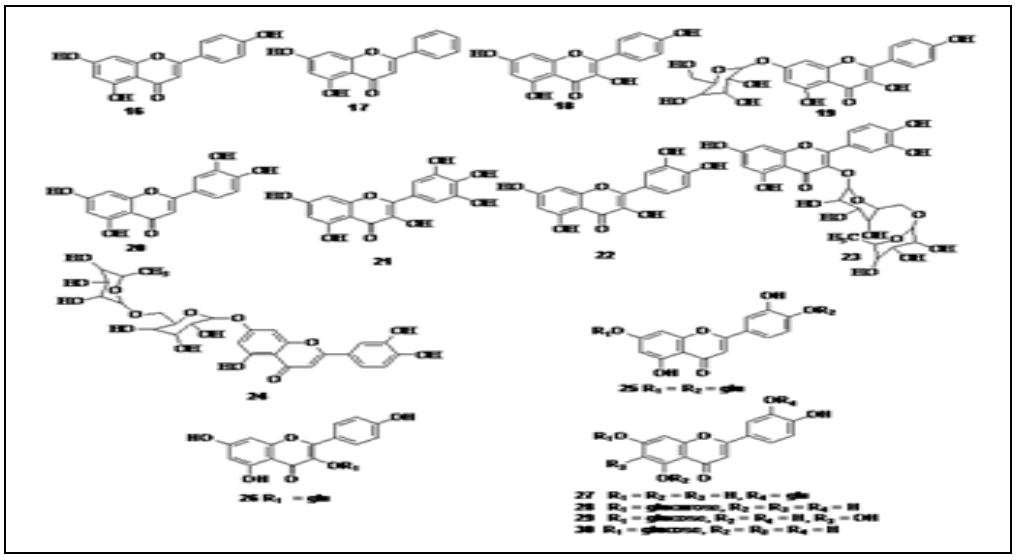


FIG. 2: SOME FLAVONES OF PHARMACOLOGICAL IMPORTANCE

The chemical constituent studies on *Phlomis Nissolii* have yielded luteolin 20 or 5, 7, 3´, 4´-tetrahydroxyflavone as well as luteolin-7-rutinoside 24 [59]. Luteolin 20, luteolin-4´, 7-di-*O*-glucoside 25 and kaempherol-3-*O*-glucoside 26 were isolated from *Helichrysum compactum* which has been used as a folk medicine for at least 2000 years against gall bladder disorders in the form of medicinal teas [60]. Few polyphenols from *Salvia officinalis* namely luteolin-3'-*O*-glucuronide, luteolin 7-*O*-glucuronide 27, 6-hydroxyluteolin 7-*O*-glucoside 28, luteolin-7-*O*-glucoside 29 and apigenin-6,8-di-*C*-glucoside 30 were isolated byLu *et al.* [61] The antioxidant activities of these compounds have been studied and the results obtained showed that those with a catechol B-ring (luteolin glycoside) were more active than compound 28 as the presence of the *o*-dihydroxybenzene (catechol) in the B-ring is important to enhance radical-scavenging activities. Rohitukine **Fig. 3** has been found to possess anti-inflammatory and immunomodulatory activities [62].

Rohitukine was later modified into flavopiridol **Fig. 3**, an anti cancer agent presently in clinical trials [63, 64]. It is the first cyclin-dependent kinase inhibitor designated as an orphan drug in Europe. It is also known as Alvocidib. If it is licensed, it would be the first cyclin-dependent kinase inhibitor and may offer an additional option for patients who generally have a poor prognosis in the treatment of chronic lymphocytic leukemia [65-67]. The various biological activities exhibited by the flavones are dependent on the nature and position of the substituents on the flavone skeleton. The flavones exhibit great diversity in their biological activities due to their unique ability to modulate various enzyme systems [68].

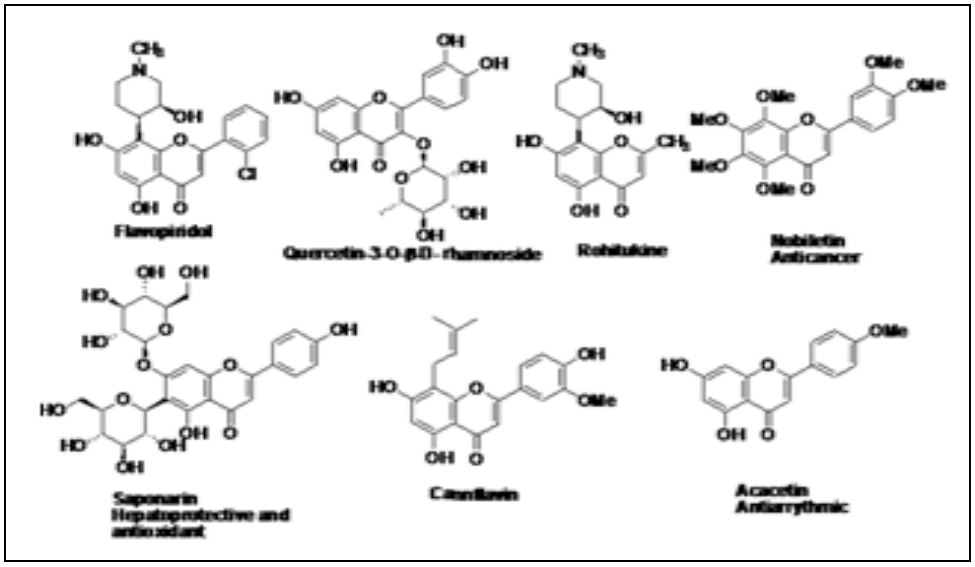


FIG. 3: SOME FLAVONES OF PHARMACOLOGICAL IMPORTANCE

CONCLUSION: Wide range of biological activity of flavones confirms that these derivatives are important to anchor in the field of modern medicinal chemistry. Therefore synthetic strategies discussed above may be useful to develop greener synthetic methods with benign and environmentally friendly reaction conditions to afford respective flavones with better yields. Though flavopiridol like molecule is proved to be an important anticancer agent, more research effort is to be implemented to generate further efficient and promising lead molecules to diversify this molecule into the drug pipeline and amplify its activity in various therapeutic complications. So, it is expected that above review upon flavones, and its derivatives may be helpful for medicinal chemist.

ACKNOWLEDGEMENT: The authors are grateful to the Department of Pharmacy, Tripura University (A Central University).

CONFLICT OF INTEREST: Nil

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How to cite this article:
Das M, Manna K, Banik U, Ghosh PS and Sarkar P: Biologically potential flavones: a subgroup of flavonoids. Int J Pharm Sci & Res 2014; 5(9): 3840-48. doi: 10.13040/IJPSR.0975-8232.5(9).3840-48.