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REVIEW ARTICLE

Selective Synthesis and Biological Application of Flavonoids

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Abstract

Secondary metabolites such as alkaloids, polyphenols, and isoprenoids are produced by plants. From these, flavonoids are one of the most naturally found polyphenol organic compounds. Flavonoids have a wide range of biological uses such as anti-diabetic activity and anti-cancer activity as well as antioxidant properties. This review article presents the various chemical synthetic methods of flavonoids. Flavonoids are prepared from chalcones, coumarin, 1,3-diones, eugenol using cyclic oxidation, Wacker oxidation, Suzuki-Miyaura reaction, and Knoevenagel condensation. Flavonoids can be divided into three main classes such as flavones, isoflavonoids and neoflavonoids (4-arylcoumarins). Flavones are successfully synthesized by Baker and Venkatraman synthesis and Claisen-Schmidt condensation method while Isoflavonoids are prepared using deoxybenzoin, Suzuki-reaction, oxidative rearrengement, and chalcone routes. Neoflavonoids are synthesized from coumarin using Suzuki-Miyaura reaction and Knoevenagel condensation system.

Keywords: Flavonoids, Isoflavonoids, Neoflavonoids, Flavone

Abbreviations/Acronyms

Pph3	triphenyl phosphine
DMSO	dimethylsulfoxide
MW	microwave
THF	tetrahydrofuran
MOMCl	chloromethylmethyl ether
DIA	diazine
DMS	di-methyl sulfide
DMF	di-methyl formamide
Tf2	triflic anhydride
P53	tumor protein
G2M	2nd sub-phase of interphase mitosis
DCC	N,N'-dicyclohexyl carbodiimide
DMAP	4-dimethyl aminopyridine

1. Introduction

Secondary metabolites such as alkaloids, polyphenols, and isoprenoids are produced by plants. Some of these compounds have been used as medicines and nutrition (Lee et *al.*, 2015). Many natural compounds taken from plants are considered as starting materials for the development of new drugs (Lee et *al.,* 2015). Flavonoids are one of the most common naturally occurring polyphenol organic compounds which found in plant, fruits, vegetables, and beverages. They also used as pigments and flower coloration (Lumbiny *et al.*, 2013).

Flavonoids have significant effects on human health (Shriniwas*, 2013*). They play important roles in prevention and treatment of serious diseases, such as inflammation, cancer, ulcer, HIV, and cardiovascular disease (Shaikh and Arshia 2010). Moreover, flavonoids are valuable components of cosmetics, food, and pharmaceuticals (Shaikh and Arshia 2010). Additionally, they are known to inhibit nucleic acid synthesis which causes disturbance in membranes to the extent of affecting energy metabolism (Jana *et al.,* 200l). However, their most studied importance is their antioxidant action since they can eliminate reactive oxygen species (Viskupicova *et al.*, 2012; Ahmed and Parveen; 2006).

Flavonoids contain 2,4-diarylbenzopyran or 2,8-dioxabicyclononane skeletons which comprises a large class of natural products with many uses. Flavonoid constitutes one of the most widespread groups of all plant phenolics. Fifty years ago, information on the working mechanisms of flavonoids was scarce. However, it was well known long ago that compounds of plant origin possess a broad spectrum of biological activity (Baviskar, *2015*). In 1930 Szent-Gyorgyi isolated a new substance from oranges and consequently it was classified as vitamin P. Later, it became clear that this compound was actually a flavonoid called rutin[9]. Flavonoids fascinated researchers with the discovery of the French paradox, i.e., the less incidence of cardiovascular disease detected in the Mediterranean population which was caused by red wine consumption and a large amount of saturated fat in the average diet than in other countries (Tapas et al., 2008).

The improvement of the hydrophilic nature and stability of flavonoids can be accomplished by enzymatic chemical or chemo-enzymatic structural modification (Wang *et al.*, 2010). Flavonoids appeared as aglycones, glycosides and methylated derivatives. Specifically, flavonoid aglycones (i.e., flavonoids without attachment of sugar) occur in a variety of structural forms.

All flavonoids encompass fifteen carbon atoms in their basic structures or nucleus: two six-membered rings linked with a three-carbon unit which may or may not be a part of a third ring. For convenience, the rings are labeled as A, B, and C (*Fig. 1*). The unique carbon atoms are based on a numbering system which uses ordinary numbers for the A and C and “primed” numerals shows for B-ring. Primed modified numbering system is not used for chalcones (Wang *et al.*, 2010). The chemical structures of some representative flavonoids are shown below.

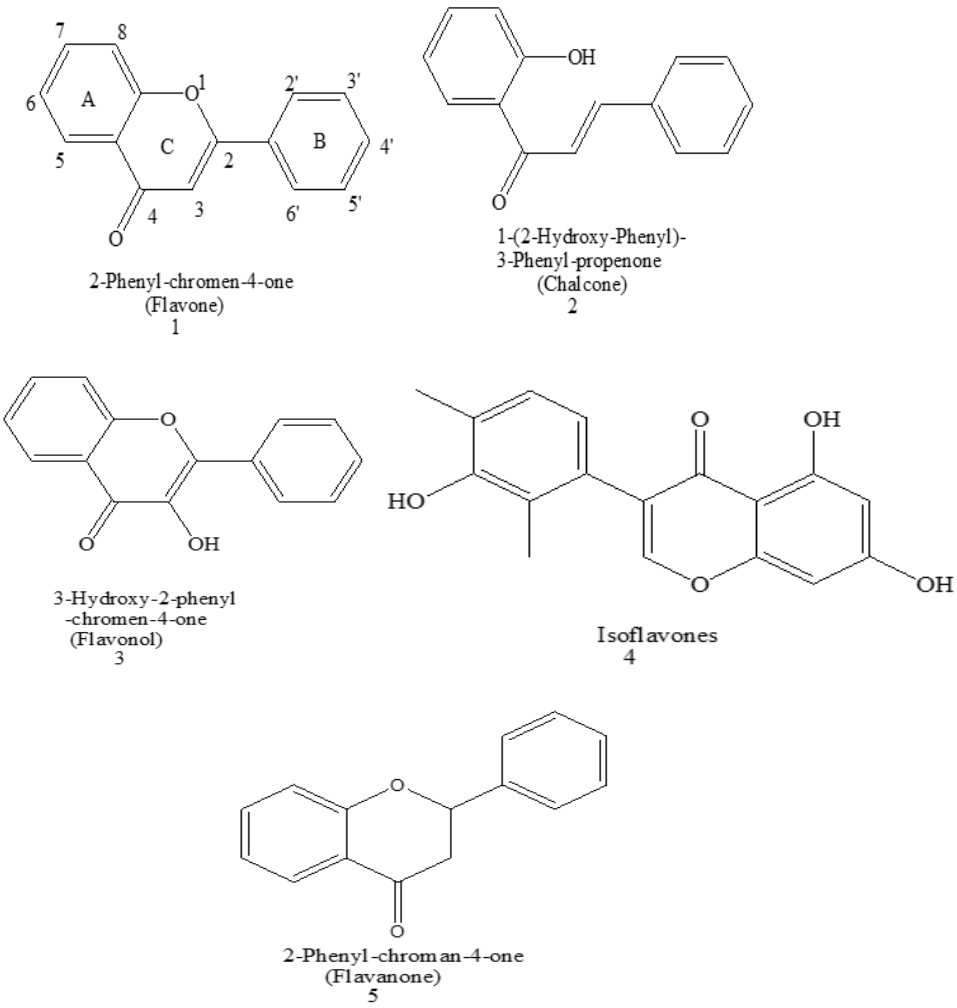


Fig. 1: Chemical Structures of Some Representative Flavonoids

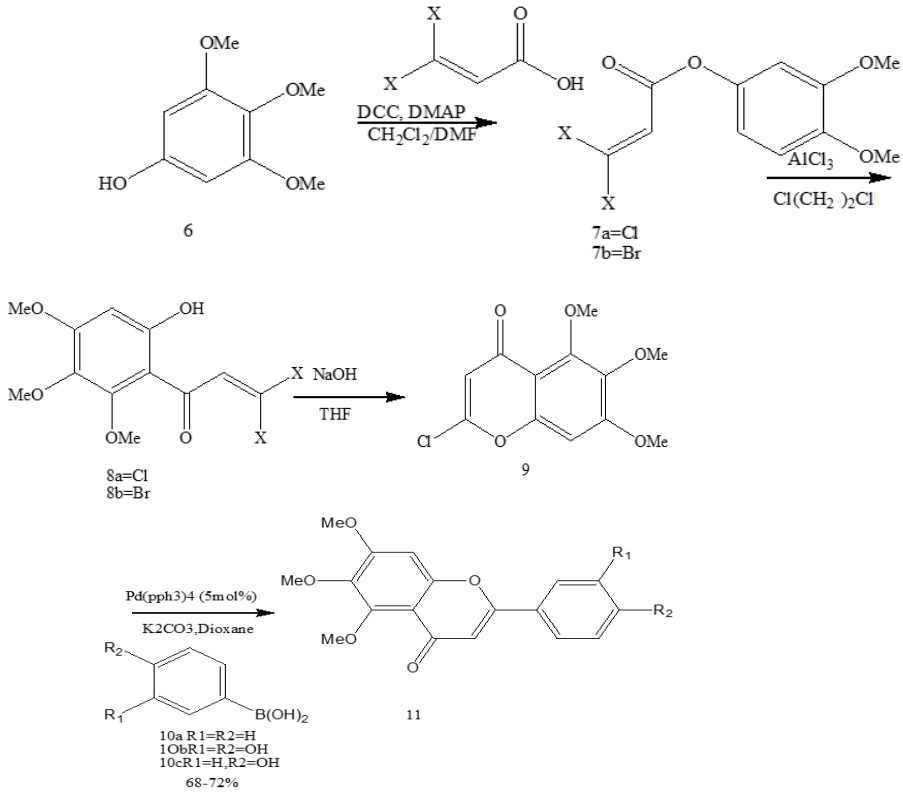
2. The Main Categories and Synthesis of Flavonoids

Flavonoids are secondary metabolites of plants with polyphenolic structure. The biological use of these compounds greatly vary (Ghasemzadeh and Ghasemzadeh, 2011). Flavonoids can be divided into three main classes: flavone, isoflavonoids and neoflavonoids (4-arylcoumarins). Due to the biological importance of flavonoids mentioned earlier, there was an interest in the development of synthetic procedures that can conveniently give access to these molecules and their derivatives (Selepe and Heerden, 2013). Flavonoids can be synthesized from chalcones, coumarin,

and eugenol using oxidative cyclization, Wacker oxidation, Suzuki-Miyaura reaction, and Knoevenagel condensation (Mamoalosi *et al.,* 2013). In the following sections, the synthesis of the three classes of flavonoids and some of their dimeric analogues are reviewed using diverse reaction methods.

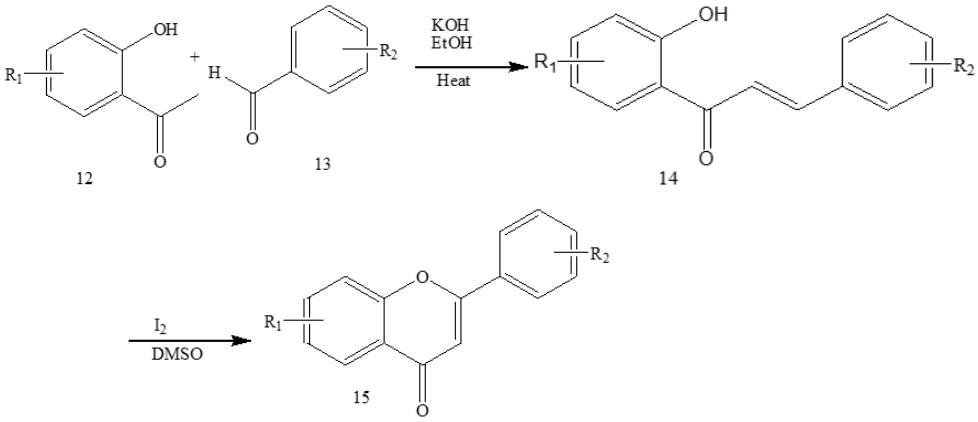
2.1. Flavones

Flavones (1) are one of the sub-groups of flavonoids and found in various plants. They are well known due to their widespread range of biological properties (Viskupicova *et al.*, 2012). Therefore, a number of synthetic methods were developed. In this review, we have tried to cover various synthetic strategies for flavones. The well-known methods used for flavones are Baker--Venkatraman synthesis and Claisen-Schmidt condensation (Kshatriya *et al*, 2013). Furthermore, flavones can be successfully prepared using other methods such as Suzuki-Miyaura reaction, oxidative cyclization, and Wacker oxidation. However, there are no many reports on the synthesis of the flavone nucleus due to the difficulty of accessing the prerequisite precursors for the Suzuki-Miyaura reaction which are the 2-halochromones (Selepe, and Heerden, 2013).



Scheme1: Synthesis of Flavone by Suzuki-Miyaura Reaction

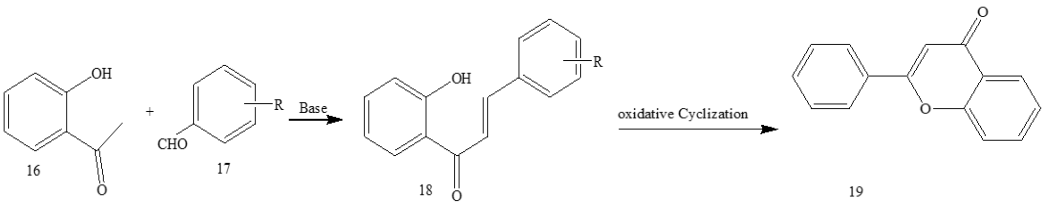
Synthesis of Flavone by Using 2-Hydroxy Acetophenone and Aromatic Aldehyde



R-stands for H or -OH

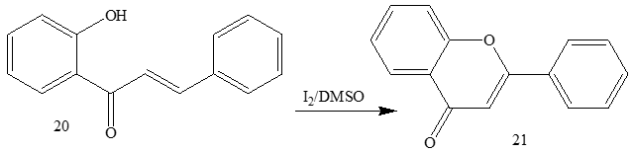
Scheme 2: This Invention Converts 2-Hydroxyaceophenone into Flavones

Synthesis of Flavone by Using Oxidative Cyclization



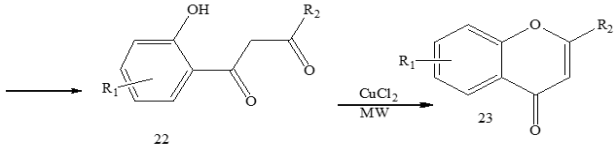
Scheme 3: *Synthesis of Flavone by Oxidative Cyclization*

Synthesis of Flavone From 2-Hydroxy Chalcones



Scheme 4: Synthesis of Flavones from 2'-Hydroxy Chalcones

Microwave Assisted Synthesis of Flavones



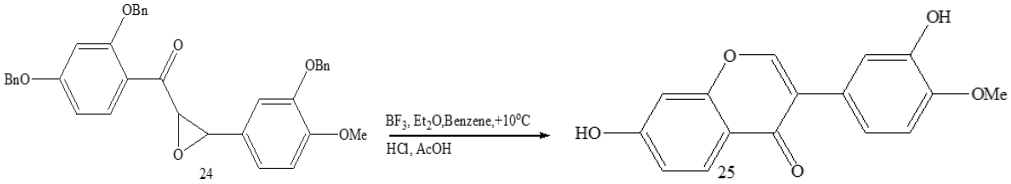
Scheme 5: Microwave Assisted Synthesis of Flavone; Copper Chloride Used as Catalyst

2.2. Isoflavonoids

Isoflavonoids are important sub-group of flavonoids mainly in species of leguminose family (Singh, OM, 2005). Isoflavonoids use for some important biological activities such as the growth inhibitor of cancer, antibacterial, antimicrobial, protein tyrosine kinase, cervical and liver cancer cells (Wang *et al.,* 2010). Although isoflavonoids have a lot of benefits, isolating them from natural products give only very limited amount[18]. The most commonly available substitution pattern of naturally occurring isoflavonoids is alkoxy/hydroxy groups which are located at 7, 5 and 7, and 7 and 8 positions of ring A. Over the years, many synthetic methods have been developed for the synthesis of isoflavonoids (Singh and Muthukrishnan, 2005).

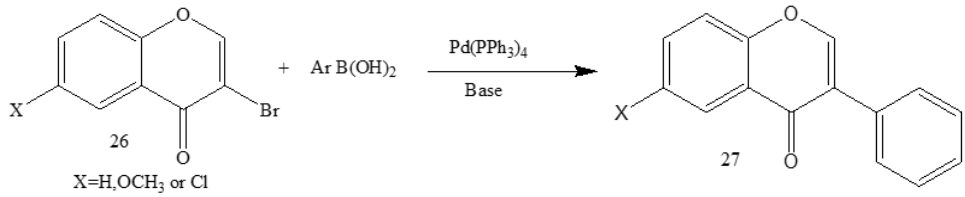
The most widely used methods to synthesize isoflavonoids are deoxybenzoin and chalcone routes. The methods that have been developed more recently are the Wacker-Cook tandem conversion of α-methylene deoxybenzoins into isoflavones and the Cu (I)-mediated cyclization of 3-(2-bromophenyl)-3-oxopropanal (Tsou *et al.*, 2016; Yang, 2016). Regardless of the presentation of many new synthetic approaches, the application of many of them has not been demonstrated in the synthesis of polyhydroxylated isoflavones and isoflavonoids because of other naturally-occurring patterns of substitution. In 1988, Suzuki and co-workers were the first to demonstrate the versatility of the palladium-catalyzed cross-coupling reactions in the synthesis of isoflavones from 3-bromo chromones and aryl boronic acids/esters (Selepe and Heerden, 2013). Some of the synthetic methods for

Synthesis of Isoflavonoids from Epoxidated Chalcone



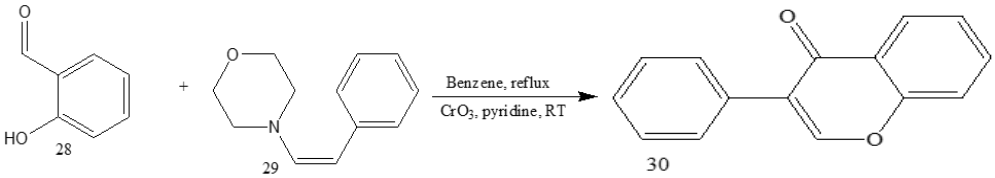
Scheme 6: Conversion of Epoxidated Chalcone to Isoflavonoids

Synthesis of Isoflavonoids by Suzuki-Reaction



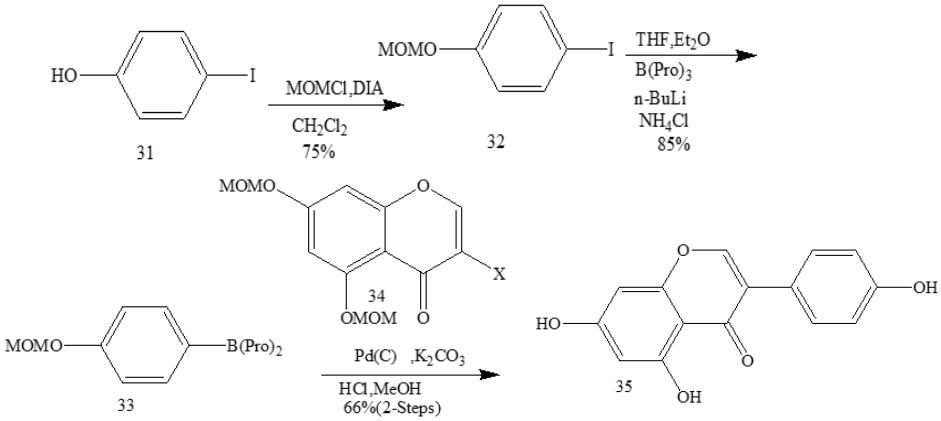
Scheme 7: Synthesis of Isoflavonoids by Suzuki-Reaction Methods

Synthesis of Isoflavonoids from Condensation of Enamine



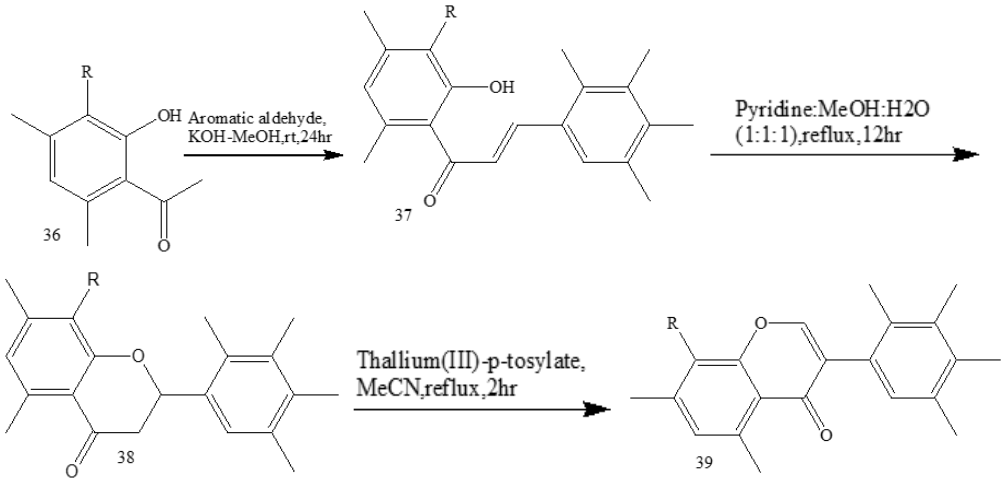
Scheme 8. Isoflavonoids from Epoxidated Chalcone

Synthesis of Isoflavonoids by Using Suzuki-Reaction



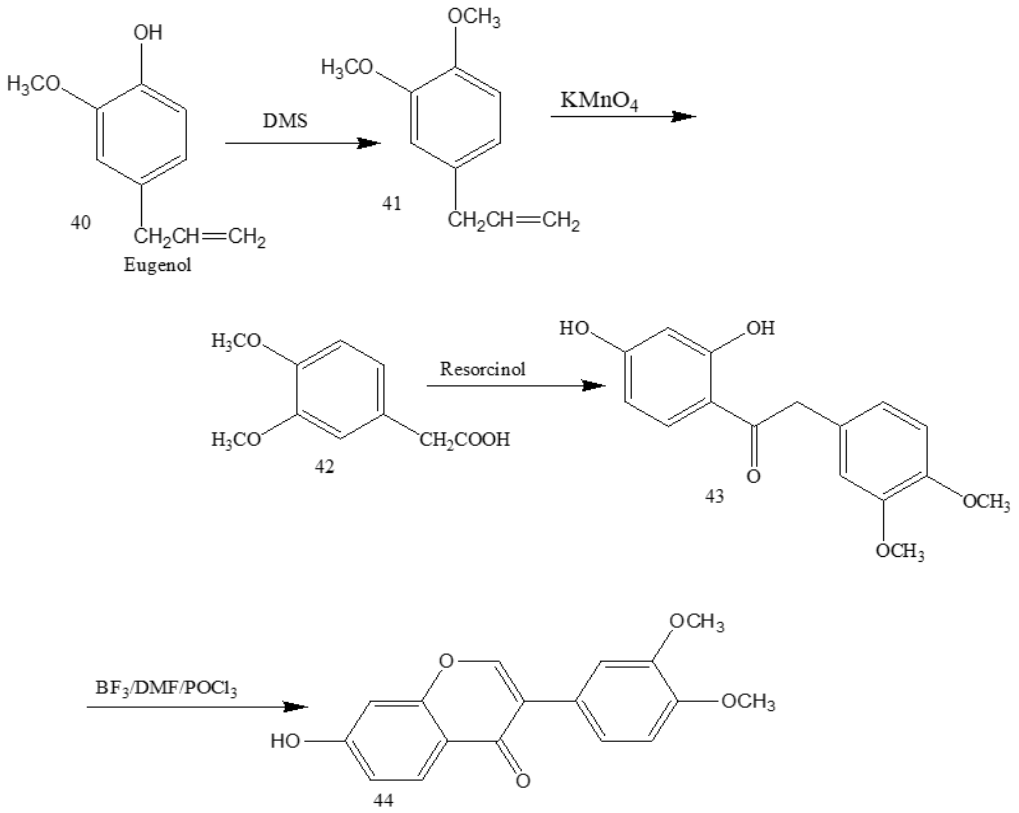
Scheme 9: Synthesis of Isoflavonoids Based on Suzuki- Reaction

Synthesis of Isoflavonoids by Oxidative Rearrangements of Respective Flavanones Using Thallium(III)-*P*-Tosylate.



Scheme 10: Synthesis of Isoflavonoids by Oxidative Rearrangement Method

Synthesis of Isoflavonoids from Eugenol



Scheme 11: Synthesis of 7-Hydroxy-3', 4'-Dimethoxy Isoflavonoid (Isoflavone) from Eugenol

2.3. Neoflavonoids

Neoflavonoids are one of the sub-group of flavonoids derived from 4-phenyl coumarin. Some of these posses pharmacological properties such as bactericide, insecticide, and molluscide (Bezerraa *et al.*, 1997). Neoflavonoids are structurally and biogenetically related to the flavonoids and isoflavonoids. The chemical structure of neoflavonoids is shown below.

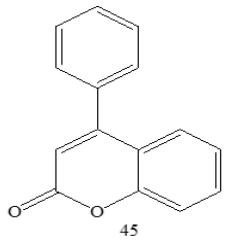
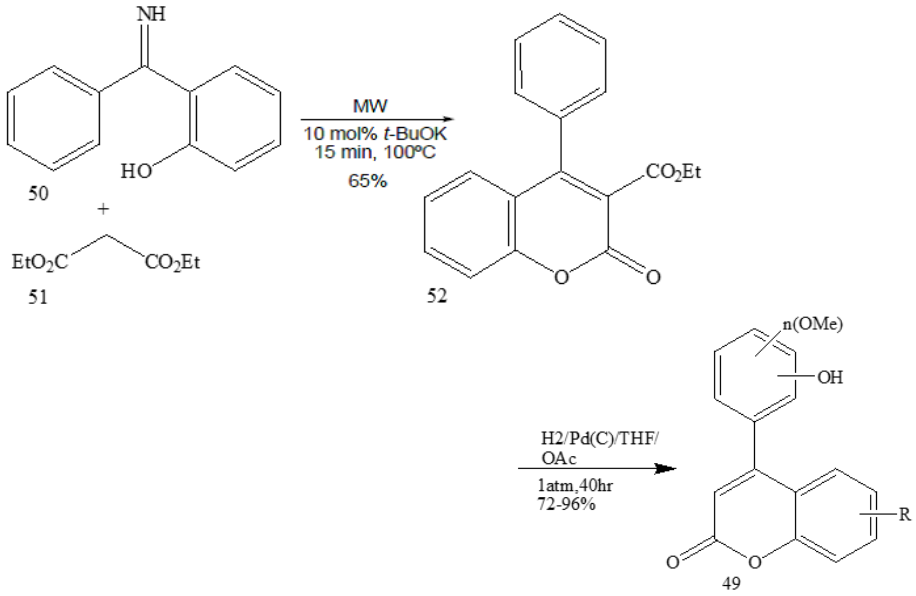


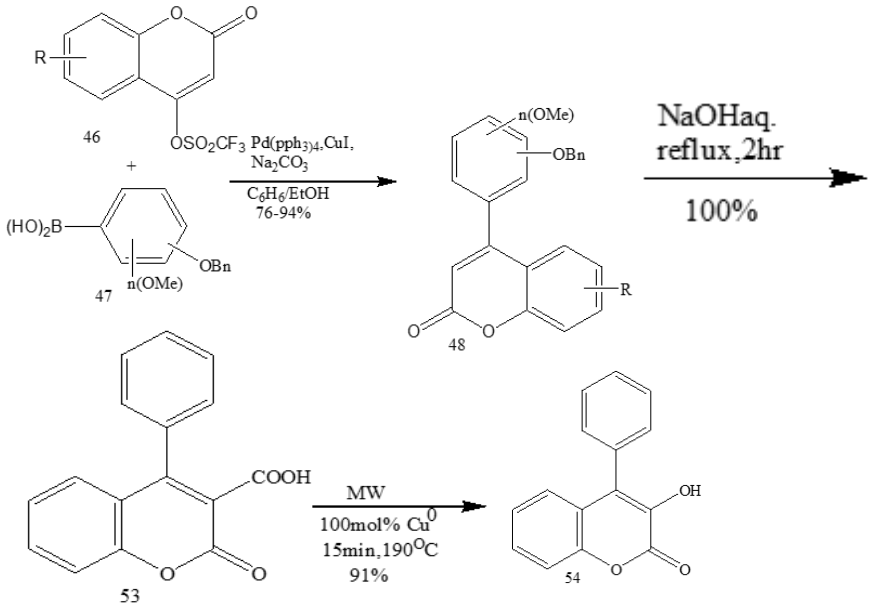
Fig. 2: *Basic Chemical Structures of Neoflavonoids*

Synthesis of Neoflavonoids by Using Suzuki-Miyaura Reaction



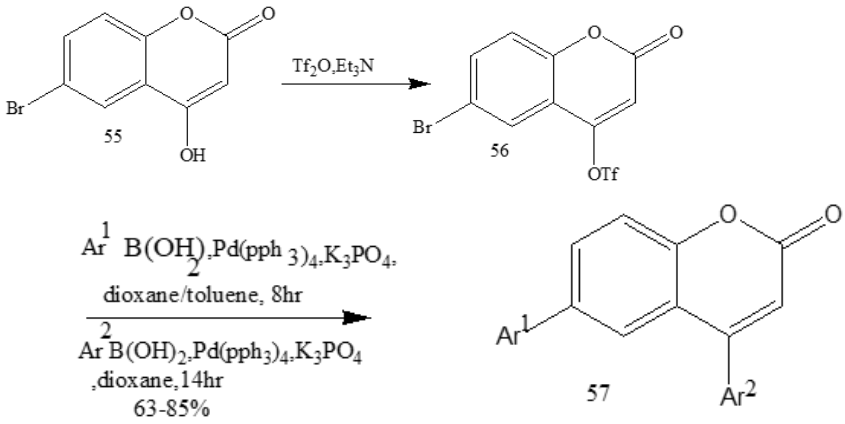
Scheme 12: Synthesis of Hydroxylated Neoflavonoids

Synthesis of Neoflavonoids from 2-Hydroxybenzophenoneimine and Diethylmalonate by Microwave Assisted Knoevenagel Condensation



Scheme 13: Synthesis of Neoflavonoids by Using Knoevenagel Condensation Method

Synthesis of Neoflavonoids from Coumarin



57	Ar^1	Ar^2
a	4-$MeOC_6H_4$	4-ClC_6H_4
b	4-$MeOC_6H_4$	3-ClC_6H_4
c	3,4-$Me_2C_6H_3$	4-$MeOC_6H_4$
d	4-ClC_6H_4	4-$MeOC_6H_4$
e	4-ClC_6H_4	3-FC_6H_4

Scheme 14: One-pot synthesis of 6-aryl Neoflavonoids from Coumarin

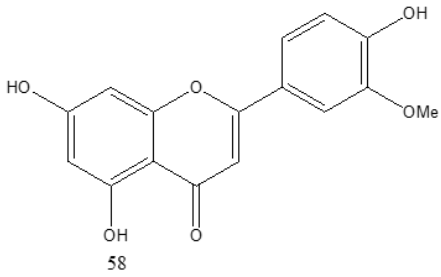
3. Application of Flavonoids

Flavonoids are presented in higher concentration in big plants and contribute to the flower and fruit color. They give mostly red, yellow, blue and violet color to plant organs (Wen-Hsin *et al.*, 2003). Chemically, they are phenolic compounds and most of them have flavone nucleus with two side aromatic rings (Santos and Koffas, 2011). Due to their frequent occurrence, complex diversity and manifold functions, flavonoids have attracted researchers (Forkman and Martens, 2001).

Flavonoids have several biological benefits (anti-inflammatory, anti-oxidant, anti-viral, anti-bacterial, anti-obesity, and anti-ulcer) that are useful for the treatment of several human pathologies (Marisa, 2014). Despite these broad ranges of pharmaceutical versatility, their availability is currently limited in inefficiency amount in both their chemical synthesis and extraction from natural plant sources. As a result, the development of strains and processes for the microbial production of flavonoids has emerged recently as an interesting and commercially attractive challenge for metabolic engineering (Marisa, 2014).

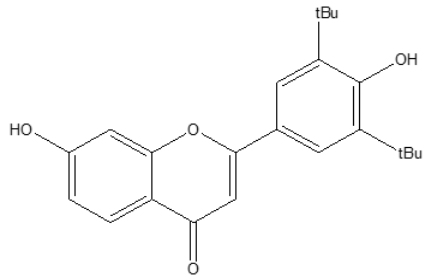
Some of the biological activities and corresponding flavonoids are described below.

3.1. Anti-Oxidant Activity



58

Chrysoeriol



59

7,4'-dihydroxy,3'5'-ditertiary butyl flavone

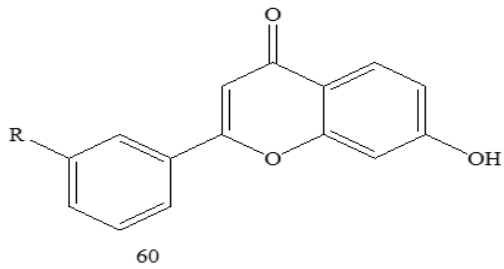
Fig. 3: Flavonoid Skeleton with an Anti-Oxidant Activity

As we know, free radicals are highly reactive species that react with plasma membrane to give carbon free radical which generates peroxy radicals. In this manner, one free radical can damage large number of lipid molecules via chain reaction (Swarnlata et *al.*, 2007). Our body produces defensive forces or mechanisms against free radicals in different ways. Many enzymes and proteins are generated to react against free radicals (Swarnlata et *al.*, 2007). For example, superoxide enzyme dismutase, catalase, copper and iron transport proteins as well as lipid and water-soluble antioxidant. If the numbers of free radicals are greater than defensive mechanism of body, then above-mentioned diseases start to attack. Antioxidant prevents superoxide ion formation which leads to inhibition of oxidation initiation. Also trace metal ions (copper and iron) forms chelate with antioxidants & stops oxidation process (Selepe and Heerden, 2013).

3.2. Anti-Diabetic Activity

Flavonoids, especially flavone skeleton have been reported to possess anti-diabetic activity. It is reported that flavone skeleton brings about the regeneration of pancreatic islets and probably increases insulin release in strptozotocin-induced diabetic rates (Swarnlata et *al.*, 2007). Similarly. in another study, Hif and Howell reported that flavone skeleton stimulates insulin release and enhanced Ca^{2+} uptake from isolated islets cell which suggested a place for flavonoids in non-insulin-dependent diabetes (Tapas *et al*., 2008).

3.3. Anti-Cancer Activity



60

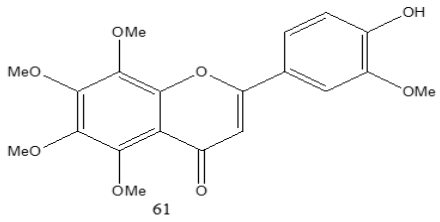
7-hydroxy flavone/7,,3'-dihydroxy flavone

R-Stands for H or - OH

Figure 4. Some Flavonoid Skeleton with Anti-Diabetic Activity

Flavonoids in our food plays important role for the prevention of cancer. Flavonoids react against cancer in various mechanisms like cell cycle arrest, tyrosine kinase inhibition, inhibition of

heat shock proteins (Selepe and Heerden, 2013). Estrogenic binding inhibits expression of Rasprotein and down regulation of mutant proteins p53. Mutation in protein p53 is common cause of cancer in human beings (Swarnlata et *al.*, 2007). The protein expression was inhibited at G2M phase of cell cycle. In human breast cancer cell lines, flavones work better by inhibiting expression of this protein (Swarnlata et *al.*, 2007).



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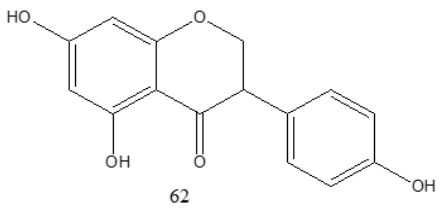
5,6,7,8,3'-pentamethoxy,4'-hydroxy flavone



62

Genestein

Figure 5: Flavonoid Skeleton with Anti-Cancer Activity

Additionally, flavonoids are used for different biological functions such as: anti-microbial activity, anti-protozoan activity, anti-platelet and anti-thrombotic activity, and neuroprotective effects (Lumbiny et *al.*, 2013; Asif, (2013).

Conclusion

Flavonoids are one of the most heterocyclic organic compounds extracted from plants. They are presented as aglycones, glycosides and methylated derivatives. All flavonoids contain fifteen carbon atoms (C6-C3-C6) in their basic structure. Depending on the position of the linkage of the aromatic ring to the benzopyran (chroman) moiety, flavonoids can be categorized in to three main groups. These are: Flavone, Isoflavonoids and Neoflavonoids. Flavonoids can be synthesized in different ways such as Suzuki-Miyaura reaction, cyclic oxidation, Wacker-oxidation, Knoevenegel condensation, and from 1,3-dione and coumarin. Flavonoids possess biochemical properties that are valuable for the treatment of several human pathologies such as anti-oxidant activity, anti-cancer activity, anti-inflammatory activity, anti-diabetic activity, anti-microbial activity, anti-HIV activity, anti-viral activity, neuroprotective activity, anti -protozoan activity, anti-platelet and anti-thrombotic activity.

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