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NATURAL OCCURRENCE AND SYNTHESIS OF 2′-OXYGENATED FLAVONES, FLAVONOLS, FLAVANONES AND CHALCONES

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Key Word Index—Occurrence of 2′-oxygenated flavonoid; chemical character of 2′-oxygenated flavonoid; ^{13}C NMR.

Abstract—Two hundred and seventy-two flavonoids (flavones, flavonols, flavanones and chalcones) oxygenated at C-2′ (C-2 in the case of chalcones), which have been obtained as natural products and prepared by partial derivation or by total synthesis are surveyed according to their oxygenation patterns. Plausible biosynthetic pathways are suggested for 2′-oxygenated flavonoids, their chemistry and ^{13}C NMR spectra are summarized.

INTRODUCTION

Since the possible oxygenation patterns based on the A ring are 16 in number, and the patterns based on the B ring are 20, the total number of possible hydroxyflavones is 320. This number is doubled to 640 when one adds in the 3-hydroxyflavones of flavonols. Taking into account the fact that any number of the hydroxyl groups present may carry methyl substitution, the total number of flavones now rises to 38 627. Of these, some 20 655 flavones and flavonols may be oxygenated at C-2′. The actual number of naturally occurring flavonoids with 2′-hydroxylation is much fewer than this because biosynthesis is regulated in such a way that some structures are favoured over others.

Due to recent developments in isolation techniques, such as high performance liquid chromatography, and elucidation techniques, such as high resolution ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry, the structure of a flavonoid can now be determined rapidly on a small sample. Flavones and flavonols which are 2′-oxygenated are of interest primarily from the point of view of chemotaxonomy. In this review, the natural occurrences and syntheses of 2′-oxygenated flavone, flavonol, flavanone and those of 2-oxygenated chalcones reported upto the end of 1987 are discussed.

RESULTS

Classification

As mentioned above, there are 16 variants on the oxygenation pattern of the A ring [unsubstituted, 5-(O), 6-(O), 7-(O), 8-(O), 5,6-$(O)_2$, 5,7-$(O)_2$, 5,8-$(O)_2$, 6,7-$(O)_2$, 6,8-$(O)_2$, 7,8-$(O)_2$, 5,6,7-$(O)_3$, 5,6,8-$(O)_3$, 5,7,8-$(O)_3$, 6,7,8-$(O)_3$ and 5,6,7,8-$(O)_4$]. Similarly, there are 20 patterns of variation in B-ring oxygenation (Table 1). Naturally occurring flavones oxygenated in the B-ring at 3′-$(O)_1$, 3′,5′-$(O)_2$, 2′,3′,5′-$(O)_3$, 2′,4′,6′-$(O)_3$, 2′,3′,5′,6′-$(O)_4$, and 2′,3′,4′,5′,6′-$(O)_5$ are rare as are those oxygenated in the A-ring at 6-$(O)_1$, 6,8-$(O)_2$, 5,6,8-$(O)_3$, 6,7,8-$(O)_3$. In this paper, six oxygenated patterns in which 2′-oxygenation is absent that is, 3′-$(O)_1$, 4′-$(O)_1$, 3′,4′-$(O)_2$, 3′,5′-$(O)_2$ and 3′,4′,5′-$(O)_3$ will not be dealt with. From the nomenclatural point of view, the numbering systems, 2′,3′,6′-$(O)_3$ and 2′,3′,4′,6′-$(O)_4$ will be used in preference to the alternatives 2′,5′,6′-$(O)_3$ and 2′,4′,5′,6′-$(O)_4$.

Rearrangement

Demethylation of flavones possessing a methoxy group at C-2′ with hydroxy iodide causes the opening of the C

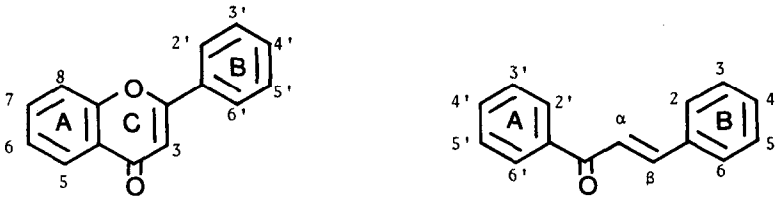

Fig. 1. Numbering systems of flavones (flavonols, flavanols) and chalcones.

Table 1. Possible oxygenation patterns in the B ring moiety of flavonoids

Unsubstituted	:	(1)
Mono-	: 2'-, 3'-, 4'-	(3)
Di-	: 2',3'-, 2',4'-, 2',5'-, 2',6'-, 3',4'-, 3',5'-	(6)
Tri-	: 2',3',4'-, 2',3',5'-, 2',3',6'-, 2',4',5'-, 2',4',6'-, 3',4',5'-	(6)
Tetra	: 2',3',4',5'-, 2',3',4',6',2',3',5',6'-	(3)
Penta-	: 2',3',4',5',6'-	(1)
	total numbers of combinations	(20)

ring and successive recyclization to give rearranged flavones. For example, both 5,8,2'-trimethoxyflavone (**27**) and 2',3',6'-trimethoxyflavone (**155**) give the same compound 5,6,2'-trihydroxyflavone (**10**) on HI demethylation [9]. During the reaction, an intermediate demethylated and ring-opened β-diketone can ring close in three ways (**a**–**c**) as shown in Fig. 2. Dehydrative cyclization by pathway **a** would yield 5,6,2'-trihydroxyflavone (**10**), by pathway **b** 5,8,2'-trihydroxy-(**12**) and by pathway **c** 2',3',6'-trihydroxyflavones (**155**), respectively. In practice, the main product is **10** because it is the most stable of the three possible flavones. The more stable of an isomeric flavone pair is usually that in which the side phenyl nucleus contains the smaller number of hydroxy groups. There are, however, exceptions, for example, cyclization of 2,2',5'-trihydroxydibenzoylmethane, which exists in the more stable form of 2,5,2',β-tetrahydroxychalcone, yields much more 2',5'-dihydroxyflavone (**98**) than 6,2'-dihydroxyflavone. Again, cyclization of 2'-benzyloxy-2-hydroxy-3,4,5,6,6'-pentamethoxydibenzoylmethane (= 2-benzyloxy-2',β-dihydroxy-6,3',4',5',6'-pentamethoxychalcone) with sulphuric acid in acetic acid during the preparation of 5,2'-dihydroxy-6,7,8,6'-tetramethoxyflavone (**132**) (skullcapflavone II) gave two flavones, 2'-hydroxy-5,6,7,8,6'-pentamethoxy-(**133**) and 2'-hydroxy-5,3',4',5',6'-pentamethoxyflavone (**261**) in the ratio 2:1, accompanied by debenzylation [23]. The oxygenation patterns that can be obtained after rearrangement of different B-ring substituted flavones one listed in Table 2.

Homospecific flavones

Those flavones which will yield the same oxygenation pattern as the original after acid interconversion are called by homospecific flavones (Table 3) [23]. The simplest homospecific flavone in nature is 2'-hydroxy flavone (**1**) and its methyl ether (**2**), which have been isolated from *Primula* and *Pimelea* species. Two other flavones, 5,4',6'-trihydroxy-6,7,2',3'-tetramethoxyflavone (**247**) in *Notholaena aschenborniana* and 5,6'-dihydroxy-6,7,2',3',4'-pentamethoxyflavone (**251**) in *Brickellia veronicaefolia* and *B. chorolepis* were reported as naturally occurring flavones, the oxygenation pattern of which are 5,6,7,2',3',4',6'-$(O)_7$ and are homospecific. Their structures, however, have been revised to 5,2',4'-trihydroxy-3,7,8,5'-tetramethoxy-(**198**) and 5,2'-dihydroxy-3,6,7,4',5'-pentamethoxyflavone (**209**) by re-examination of their spectral data and by comparison with synthetic samples. The only homospecific flavones to have been isolated so far as natural products are **1** and **2**.

Table 2. Oxygenation patterns after interconversions between the A and B rings

B ring	A ring	B ring	A ring
2'	↔ none	2',3',6'	↔ 5,6 or 5,8
2',3'	↔ 8	2',4',5'	↔ 6,7
2',4'	↔ 7	2',4',6'	↔ 5,7
2',5'	↔ 6	2',3',4',5'	↔ 6,7,8
2',6'	↔ 5	2',3',4',6'	↔ 5,6,7 or 5,7,8
2',3',4'	↔ 7,8	2',3',5',6'	↔ 5,6,8
2',3',5'	↔ 6,8	2',3',4',5',6'	↔ 5,6,7,8

Table 3. Homospecific flavones

2'-[O]	6,7,2',4',5-$[O]_5$
5,2',6'-$[O]_3$	6,8,2',3',5'-$[O]_5$
6,2',5'-$[O]_3$	7,8,2',3',4'-$[O]_5$
7,2',4'-$[O]_3$	5,6,7,2',3',4',6'-$[O]_7$
8,2',3'-$[O]_3$	(or 5,7,8,2',3',4',6'-$[O]_7$)
5,6,2',3',6'-$[O]_5$	5,6,8,2',3',5',6'-$[O]_7$
(or 5,8,2',3',6'-$[O]_5$)	6,7,8,2',3',4',5'-$[O]_7$
5,7,2',4',6'-$[O]_5$	5,6,7,8,2',3',4',5',6'-$[O]_9$

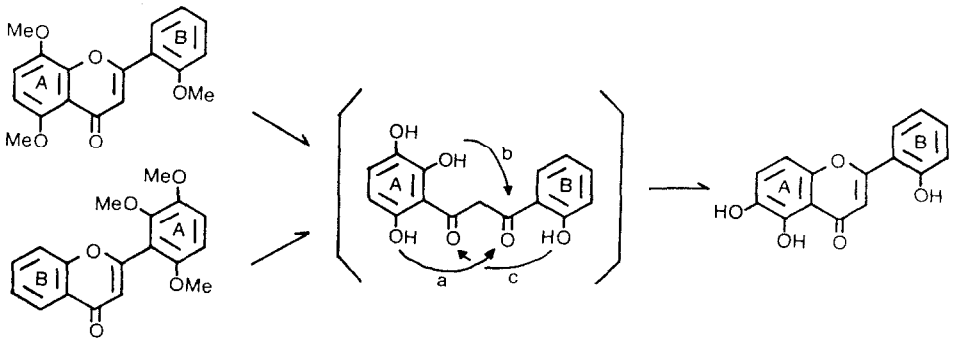

Fig. 2. Rearrangement of *O*-functions during demethylation of flavones with HI.

2'-Monooxygenated flavones

The flavones in *Primula* species (Primulaceae) are known to have unusual oxygenation patterns; flavone itself is present as well as flavonols with 5,6- or 5,8-dioxygenation. Several 2'-oxygenated flavones (**1**, **2**, **4**, **5**, **7** and **12**), which have rather simple patterns, have recently isolated from the farinose exudate of some *Primula* species. Among them, **1** and **2** are homospecific flavone. In addition, two biologically important intermediates [2',β-dihydroxy- and 2,2'-dihydroxychalcone (**264**)] have been isolated from the exudate. 2'-Methoxyflavone (**2**) was also found to be present in *Pimelea simplea* (Thymelaeaceae) in very low amount, as well as flavone.

From the heartwood of *Casimiroa edulis* (Rutaceae), 5,6,2'-trimethoxyflavone (**24**), which also has been recently isolated from the roots of *Sargentia greggi* (Rutaceae), was isolated and the structure was confirmed by

Table 4. 2'-Monooxygenated flavones and flavonols

Substitution pattern*†‡	Compound	mp(°)§	Sources	References
2'/	**1**	250–251	*Primula florindae*	[1]
/2'	**2**	103–104	*Pimelea simplex*	[2]
		97–98	*Primula kewensis*	[3]
		103	synthesis	[4]
3,2'/	**3**	209	synthesis	[5]
5,2'/	**4**	273–274	*Primula florindae*	[1]
8,2'/	**5**	>250 (dec.)	*Primula* spp.	[6]
			synthesis	[6]
3/2'	**6**	215	synthesis	[5]
5/2'	**7**	136–137	*Primula kewensis*	[3]
8/2'	**8**	136	derivative, synthesis	[7]
3,7,2'/	**9**	272–273	synthesis	[5]
5,6,2'/	**10**	278–280	derivative, synthesis	[8]
		274–278 (dec.)	synthesis	[9]
5,7,2'/	**11**	284	*Scutellaria baicalensis*	[10]
		279	synthesis	[11]
			synthesis	[12]
5,8,2'/	**12**	310–312	*Primula florindae*	[13]
		310	synthesis	[9]
3,2'/7	**13**	176–178	synthesis	[5]
5,7/2'	**14**	281–283	*Andrographis echinoides*, derivative	[14]
5,2'/7	**15**	264–265 (dec.)	*Andrographis echinoides* (echinoidinin)	[14]
		262–264 (dec.)	synthesis	[15]
		262–264	*Andrographis wighiana*	[16]
5,2'/7(2'-glc)	**16**	276–278 (dec.)	*Andrographis echinoides*, synthesis	[17]
5,2'/7 @	**17**	201	derivative, synthesis	[18]
5,2'/7(2'-glc) @	**18**	240	*Haplanthus tentaculatus* var. *plumosa* (haplanthin)	[18]
		241	synthesis	[18]
5/6,2'	**19**	153–154	derivative, synthesis	[8]
5/7,2'	**20**	166	derivative	[14]
5/8,2'	**21**	184–185	derivative	[3]
2'/5,7	**22**	282–284 (dec.)	synthesis	[14]
		281–283	synthesis	[17]
2'/5,7 @	**23**	196	synthesis	[5]
/5,6,2'	**24**	124–125	*Casimiroa edulis*	[8]
		124–125	synthesis	[8]
		123–124	*Sargentia greggii*	[19]
		124–125	synthesis	[9]
/5,7,2'	**25**	178	derivative	[14]
/5,7,2' @	**26**	128	synthesis	[5]
/5,8,2'	**27**	200–201	synthesis	[9]
3,5,6,2'/	**28**	241–243	synthesis	[20]
3,5,7,2'/	**29**	*	*Datisca cannabina* (datiscetin)	[21]
		277–278	synthesis	[5]
5,6,7,2'/	**30**	306	synthesis	[21]

Table 4. *Continued*

Substitution pattern*†‡	Compound	mp(°)§	Sources	References
5,7,8,2′/	**31**	323–324	synthesis	[21]
3,5,7/2′	**32**	258–260	synthesis	[22]
3,5,2′/7	**33**	240	synthesis	[5]
5,6,2′/7	**34**	280–283	synthesis	[23]
5,7,2′/6	**35**	270–272	*Scutellaria baicalensis*	[24]
		273	synthesis	[25]
5,7,2′/8	**36**	278 (dec.)	*Scutellaria baicalensis*	[26]
			Scutellaria discolor	[27]
		287–289 (dec.)	synthesis	[25]
3,2′/5,7	**37**	216–217	synthesis	[5]
5,7/8,2′	**38**	231	*Scutellaria virularis*	[28]
			Scutellaria discolor	[27]
5,7/8,2′ (2s) @	**39**	208 (dec.)	*Scutellaria discolor*	[27]
5,2′/6,7	**40**	255	synthesis	[23]
5,2′/6,8	**41**		*Scutellaria baicalensis* (skullcapflavone I) →5,2′/7,8(**42**)	[23, 29, 30]
		251	synthesis	[23]
5,2′/7,8	**42**	263–265	*Scutellaria baicalensis*	[30]
		255–256	synthesis	[23]
		254–255	*Andrographis paniculata*	[31]
		*	*Notholaena neglecta*	[32]
5/3,6,2′	**43**	145.5–146.5	synthesis	[20]
5/3,7,2′	**44**	111–112.5	derivative	[21]
5/6,7,2′	**45**	160–161	synthesis	[20]
5/,7,8,2′	**46**	190–191	*Andrographis paniculata*	[31, 33]
		186–188	synthesis	[30]
		188–189	synthesis	[20]
5/7,8,2′(5-glc)	**47**	126–130	*Andrographis paniculata*	[33]
7/5,8,2′	**48**	249 (dec.)	*Scutellaria discolor*	[34]
7/5,8,2′ (2s) @	**49**	214 (dec.)	*Scutellaria baicalensis*	[27]
2′/5,6,7	**50**	241–245	synthesis	[23]
2′/5,6,8	**51**	239–241	synthesis	[23]
2′/5,7,8	**52**	276–279	synthesis	[23]
/3,5,6,2′	**53**	163–164	synthesis	[20]
/3,5,7,2′	**54**	137–139	synthesis	[22]
/5,6,7,2′	**55**	97–99	synthesis	[20]
		96	synthesis	[16]
/5,2′, (6:7) @	**56**	187–195 (dec.)	as phytoalexin (betagarin)	[35]
/5,7,8,2′	**57**	186–188	synthesis	[20]
		184–186	synthesis	[16]
3,5,2′/7,8 @	**58**	212	*Notholaena neglecta*	[32]
3,5,2′/7,8 @ (2′-acetate)	**59**	*	*Notholaena neglecta*	[32]
5,2′/3,7,8	**60**	208	*Aspergillus candidus* (dechlorochloroflavonin)	[36]
5,2′/3,7,8(3′-Cl)	**61**	217	*Aspergillus candidus* (chloroflavonin)	[36]
5,2′6,7,8	**62**	234–235	*Scutellaria baicalensis*	[24]
		234–236	*Scutellaria tenax* (tenaxin I)	[37]
		228–230	synthesis	[11]
5/3,7,8,2′	**63**	209–211	*Andrographis paniculata*	[38]
/3,5,7,8,2′	**64**	152–154	derivative	[39]

*The numerals before the solidus indicate the positions of hydroxy group, and ones after the positions of methoxy groups, for example; 2′/=2′-hydroxyflavone, /2′=2′-methoxyflavone, 5,2′/7,8=5,2′-dihydroxy-7,8-dimethoxyflavone, respectively.

†@ shows dehydro-derivative, that, is, flavanone, dihydrochalcone, and a conformation of C-2 cited clearly in reference is presented as *S*, *R* or (±).

‡The numerals connected with a colon mean the presence of a methylenedioxy group at the positions.

§An asterisk indicates that mp was not reported.

comparison with the synthetic sample. In addition, two other flavones zapotin and zapotinin were isolated from the plant and their structures were deduced to be 5,6,7,2′-tetramethoxy- (**55**) and 5-hydroxy-6,7,2′-trimethoxyflavone (**45**). The synthetic samples, however, were not identical with the natural products. Furthermore, two other possible synthetic samples, one being the geometric isomer of the A ring, 5,7,8,2′-tetramethoxyflavone (**57**), another was a flavonol related with **24**, i.e. 3,5,6,2′-tetramethoxyflavone (**53**), were compared with the natural flavones, but were found to be different.

Alternative structures were then proposed for zapotin and zapotinin after a ^{1}H NMR spectral investigation, namely 5,6,2′,6′-tetramethoxy- (**21**) and 5-hydroxy-6,2′,6′-trimethoxyflavone (**120**). Another A ring isomer, i.e. 5,8,2′,6′-tetramethoxyflavone was ruled out of the reckoning by means of the Gibbs and the Gossypetone reactions. Furthermore, the unambiguous assignment of all protons of **121** measured in deuterochloroform and trifluoroacetic acid in the NMR spectrum at 100 MHz made the structure clear. Finally the newly proposed structures were proved by synthesis. It took twelve years in all to obtain the correct structures for zapotin and zapotinin.

5,7-Dihydroxy-8-methoxyflavone (wogonin), 5,6,7-trihydroxyflavone (baicalein), 5,6-dihydroxyflavone-7-*O*-glucuronide (baicalin), 5,7-dihydroxy-6-methoxyflavone (oroxylin A), and 5,6,7,4′-tetrahydroxyflavone (scutellarein) are the main flavones of roots of *Scutellaria* species (Labiatae). The characteristic oxygenation patterns of the flavone B ring in these plants are summarized as follows: apart from a few flavones with an unsubstituted B ring (wogonin, baicalein etc) and one flavone with a B ring oxygenated at C-4′ (scutellarein), all flavones in *Scutellaria* species have the B ring moieties oxygenated at C-2′.

From the water soluble extract of the roots of *Scutellaria*, two new flavones, named skullcapflavones I and II were isolated and the structures were proposed to be 5,2′-dihydroxy-6,8-dimethoxy- (**41**) and 5,2′-dihydroxy-6,7,8,6′-tetramethoxyflavone (**132**), respectively. Two features of the structure of skullcapflavone I are unusual: a 5,6,8-trioxygenated A ring, which has not been described before; and an 2′-oxygenated B ring moiety. To confirm the structure, **41** was prepared as well as the isomers, 5,2′-dihydroxy-6,7-dimethoxyflavone (**40**) and 5,2′-dihydroxy- 7,8-dimethoxyflavone (**42**). After comparison with the synthetic specimens, the correct structure for skullcapflavone I was found to be **42**. Following this work on skullcapflavone I, flavones (**36, 38** and **48**) and flavanones (**39** and **49**) with related structures have been reported. The unsubstituted B ring of the flavones in *Scutellaria* species, can be seen to be progressively oxidized from 2′-(O) (ex. **42**) to 2′,3′,6′-(O)$_3$ (**160**) via 2′,3′-(O)$_2$ (**68**), 2′,5′-(O)$_2$ (**110**) and 2′,6′-(O)$_2$ (**118**) as shown in Fig. 3.

A new flavone echinoidin isolated from *Andrographis echinoides* (Acanthaceae) was shown to be 5,2′-dihydroxy-7-methoxyflavone (**15**) by spectral analysis, and this was confirmed by degradation and synthesis. Later, another new glycoside from the plant named echinoidin was isolated and determined to be echinoidinin 2′-*O*-glucoside (**16**). On the other hand, two new flavones were isolated from the same genus; one was 5,3′-dihydroxy-7,8,2′-trimethoxyflavone (**73**) named wightin, isolated from the leaves of *A. wightiana*, another was 5-hydroxy-7,8,2′,3′,4′-pentamethoxyflavone (**140**) named serpyllin from *A. serpyllifolis*. Both flavones were methylated and compared with the synthetic samples of 5,7,8,2′,3′-pentamethoxyflavone (**77**) and 5,6,7,2′,3′,4′-hexamethoxy- (**141**) or 5,7,8,2′,3′,4′-hexamethoxyflavone (**142**) and the proposed structures were confirmed. The B ring moiety of the flavones in *Andrographis* species appears to undergo stepwise oxidation from 2′-(O) to 2′,3′-(O)$_2$ and finally to 2′,3′,4′-(O)$_3$ as represented by the isolation of echinoidinin (**15**), wightin (**73**) and serpyllin (**140**). These oxidative patterns are summarized in Fig. 4. Recently 5-hydroxy-7,8,2′-trimethoxyflavone (**46**) and 5,2′-dihydroxy-7,8-dimethoxyflavone (**42**) have been isolated from differentiating tissue cultures, of *A. paniculata*, while 5-hydroxy-3,7,8,2′-tetramethoxyflavone (**63**) has been obtained from the roots.

Notholeana species (Gymnogrammoideae) contain 2′-oxygenated flavones like **42** and its flavonol derivative **58**. The oxygenation patterns of the B ring of the fern flavonoids are different from those of *Andrographis* species as shown in Fig. 4.

2′,3′-, 2′,4′-, 2′,5′- *and* 2′,6′-*Dioxygenated flavones*

From whole plants of *Pimelea decora* (Thymelaeaceae), 6,2′,3′-trimethoxyflavone (**67**) was isolated along with

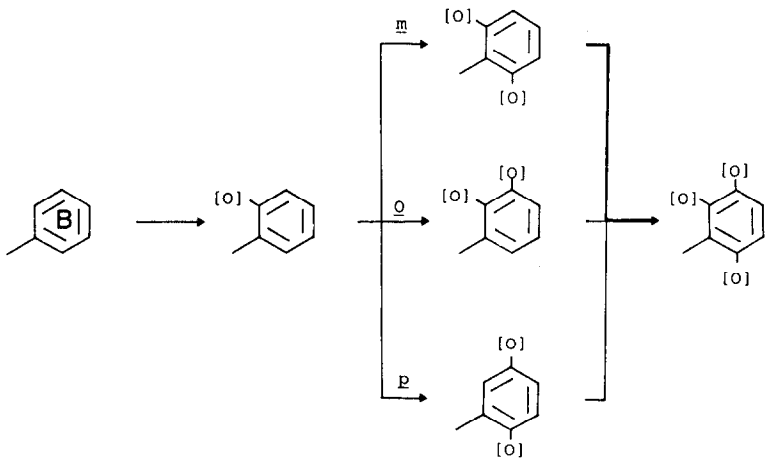

Fig. 3. Biosynthetic oxidation in the B ring moiety of flavonoids in *Scutellaria* species.

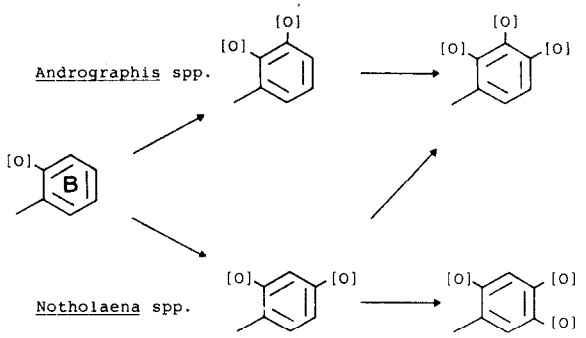

Fig. 4. Biosynthetic oxidation in the B ring moiety of flavonoids in *Andrographis* and *Notholaena* species.

other flavones in a very low yield (0.00093%). The structure has an unusual oxygenation pattern in the B ring as well as in the A ring. Recently glycosides of the 2',3'-dioxygenated flavone (**72** and **75**) were reported in the roots of *Andrographis paniculata*.

2',4'-Dioxygenated flavones (**79, 80** and **85**) are mainly concentrated in Moraceae (*Morus* and *Artocarpus*), and they sometimes also contain isopropyl substituents. In rare instances, 2',4'-dioxygenated flavones have been found in *Prunus* (Rosaceae), *Terminalia* (Combretaceae) and *Chrysosplenium* (Saxifragaceae). Another related flavone, originally formulated as 5,2',4'-trihydroxy-6,8-dimethoxyflavone (**89**) rehderianin I, from *Scutellaria rehderiana*, was shown to be 5,2',4'-trihydroxy-7,8-dimethoxyflavone (**110**), by comparison with synthetic samples of **88–90, 109** and **110**. The other natural source

Table 5. 2',3'-, 2',4'-, 2',5'-and 2',6'-Dioxygenated flavones and flavonols

2',3'/	**65**	246 (dec.)	synthesis	[39]
		197–198	synthesis	[40]
/2',3'	**66**	80–83	synthesis	[41]
/6,2',3'	**67**	116–117	*Pimelea decora*	[2]
5,7,2',3'/	**68**	>360	*Scutellaria baicalensis*	[26]
		327 (dec.)	synthesis	[11]
/5,6,2',3'	**69**	149–150	synthesis	[42]
5,7,8,2',3'/	**70**			[43]
5,2',3'/7,8	**71**	297–299	derivative	[33]
5,2',3',/7,8(3'-glc)	**72**	230	*Andrographis paniculata* (andrographidine B)	[33]
5,3'/7,8,2'	**73**	188–189	*Andrographis wightiana* (wightin)	[44, 45]
		187–189	synthesis	[15, 43]
5/7,8,2',3'	**74**	156, 150–152	derivative	[33, 44]
			Andrographis paniculata	[46]
5/7,8,2',3' (5-glc)	**75**	181–184	*Andrographis paniculata* (andrographidine D)	[33]
3'/5,7,8,2'	**76**	237–239	synthesis	[15]
/5,7,8,2',3'	**77**	190–191	derivative, synthesis	[39, 43, 44]
/2',4'	**78**	93–94	synthesis	[41]
5,7,2',4'/	**79**	330 (dec.)	*Artocarpus integrifolia* (norartocarpetin)	[47]
		334–336	synthesis	[9]
5,2',4'/7 @	**80**		*Artocarpus integrifolia* (artocarpetin)	[48, 49]
5,2',4'/7	**81**		(artocarpanone)	[48, 49]
7/5,2',4' @	**82**	200–207	*Prunus cerasus* (cersinone)	[51]
		200–201	synthesis	[52]
/5,7,2',4'	**83**	179–180	synthesis	[9]
			synthesis	[53]
/5,7,2',4' @	**84**	170	*Terminalia arjuna* (arjunone)	[54]
3,5,7,2',4'/	**85**	289–290	*Morus tinctoria* (morin)	[55]
3,5,7,2',4'/@	**86**		(dihydromorin)	[50]
2'/3,5,7,4'	**87**	246–248	synthesis	[56]
5,2',4'/6,7	**88**	264–266	synthesis	[57]
5,2',4'/6,8	**89**		*Scutellaria rehderiana* (rehderianin I)→5,2',5'/7,8	[58] (**110**)
		249–250	synthesis	[57]
5,2',4'/7,8	**90**	288 (dec.)	synthesis	[57]
5,4'/3,6,7,2'	**91**	191–193	*Chrysosplenium pseudo-faurieri* (chrysosplin)	[59]
5,4'/3,7,8,2'	**92**	*	*Notholaena affinis*	[60]
5/3,7,8,2',4'	**93**	*	*Notholaena affinis*	[60]

Table 5. *Continued*

5,2′,4′/3,6,7,8	**94**	*	*Notholaena affinis*	[60]
5,2′/3,6,7,8,4′	**95**	*	*Notholaena affinis*	[60]
5,4′/3,6,7,8,2′	**96**	*	*Notholaena affinis*	[60]
5/3,6,7,8,2′,4′	**97**	*	*Notholaena affinis*	[60]
2′,5′/	**98**	*	*Primula* spp.	[7]
		173–175	synthesis	[7]
2′,5′/(5′-acetate)	**99**	221–222	*Primula pulverulenta*	[7]
/2′,5′	**100**	108–110	synthesis	[41]
5;2′,5′/	**101**		*Primula* spp.	[61]
		270 (dec.)	synthesis	[61]
5,7,2′,5′/ (2s) @	**102**	195 (dec.)	*Inula cappa*	[62]
5,7,2′/5′ @	**103**	155–160	derivative	[62]
5/7,2′,5′ @	**104**	122–124	derivative	[62]
3,5,7,2′/5′ (2R, 3R) @	**105**	98–100	*Inula cappa*	[62]
3,5,7,2′/5′	**106**	200	derivative	[62]
3,5,2′,/7,5′ @	**107**	158	derivative	[62]
3,5,2′/7,5′	**108**	205	*Inula cappa*	[62]
5,2′,5′/6,7	**109**	267–269 (dec.)	synthesis	[57]
5,2′,5′/7,8	**110**	264–267	*Scutellaria rehderiana*	[58]
		265	synthesis	[57]
3,5/7,2′,5′ @	**111**	115	derivative	[62]
5/3,7,2′,5′	**112**	140–145	derivative	[62]
/3,5,7,2′,5′	**113**	142	derivative	[62]
5,2′,5′/6,7,8	**114**	268 (dec.)	*Scutellaria baicalensis*	[10]
		264 (dec.)	synthesis	[11]
/2′,6′	**115**	147–148	synthesis	[42]
5,7,2′,6′/	**116**	>360	*Scutellaria baicalensis*	[63]
		>300	synthesis	[64]
			Argemone mexicana →5,7,3′,4′/	[65, 66]
5,7,2′,6′/ (2s) @	**117**	240 (dec.)	*Scutellaria baicalensis*	[67]
		246	synthesis	[11]
5,7,2′/6′	**118**	256–257 (dec.)	*Scutellaria baicalensis*	[26]
		253–256 (dec.)	synthesis	[64]
7,2′,6′/5 (2s) @	**119**	211 (dec.)	*Scutellaria baicalensis*	[26]
5/6,2′,6′	**120**	224–225	*Casimiroa edulis* (zapotinin)	[68]
/5,6,2′,6′	**121**	150–151	*Casimiroa edulis* (zapotin)	[68, 69, 70]
		149–150	synthesis	[71]
		144–145	*Sargentia greggii*	[72]
3,5,7,2′,6′/	**122**	293 (dec.)	*Scutellaria baicalensis*	[26]
		294–297	*Scutellaria viscidula* (viscidulin I)	[73]
3,5,7,2′,6′/(2R, 3R) @	**123**	221–225 (dec.)	*Scutellaria baicalensis*	[67]
5,7,2′/8,6′	**124**	266	*Scutellaria baicalensis*	[10]
		249 (dec.)	*Scutellaria discolor*	[34]
		263–265	synthesis	[64]
5,2′,6′/7,8	**125**	292–293	*Scutellaria viscidula*	[73]
		286 (dec.)	*Scutellaria baicalensis*	[26]
		282–285	synthesis	[64]
5,7/8,2′,6′	**126**	206 (dec.)	*Scutellaria discolor*	[34]
5,2′/6,7,6′(±) @	**127**	221 (dec.)	*Scutellaria discolor*	[27]
5,2′/7,8,6′	**128**	257–259	*Scutellaria rivularis* (rivularin)	[74]
		250–253	synthesis	[64]
5,2′/7,8,6′(±) @	**129**	202 (dec.)	*Scutellaria discolor*	[27]
5/7,8,2′,6′	**130**	199 (dec.)	*Scutellaria discolor*	[34]
5,6,2′/7,8,6′	**131**	223–226	synthesis	[23]
5,2′/6,7,8,6′	**132**	180–181	*Scutellaria baicalensis* (skullcapflavone II)	[29]
		170–171	synthesis	[23]
2′/5,6,7,8,6′	**133**	175–177	synthesis	[23]

producing 2',4'-dioxygenated flavones is *Notholaena affinis* (Gymnogrammoideae). The flavones are usually found in farinose exudates of this fern.

2',5'-Dioxygenated flavones have been reported from three plant genera: *Primula* (Primulaceae), *Scutellaria* (Labiatae) and *Inula* (Compositae). From the biosynthetic viewpoint, it is likely that such flavones will be found in further genera of the Compositae, especially since 2',5'-dioxygenated flavones could be considered as intermediates to the more stable 2',4',5'-trioxygenated compounds.

2',6'-Dioxygenated flavones have mainly been isolated from *Scutellaria* species. Once 5,7,2',6'-tetrahydroxyflavone (**116**) was reported as the constituent of the seeds of *Argemone mexicana* (Papaveraceae) but re-examination of the material, revealed that the 'compound' was a mixture of luteolin and eriodictyol. The above findings led to the following comment on methods of structural elucidation for flavonoids: "The present results indicate the danger of relying too heavily on spectral data for structural assignments in flavonoid series. In this case, chromatographic comparison with known makers would have immediately revealed the identity of the *Argemone* flavone. Additionally, the incorrectness of the analysis would have been apparent if a comparison with a synthetic sample had been attempted. The use of either chemical degradation or chemical synthesis would seem to be an essential prerequisite before reporting the presence in plant of "novel flavonoid aglycone" [66]. The structure of 5,7,2',6'-tetrahydroxyflavone from *Scutellaria baicalensis* was indeed confirmed by synthesis. The structures of all flavonoids, except the flavanones (**119**, **123**, **127** and **129**), in the genus were confirmed by respective syntheses.

2',3',4'-, 2',3',5'-, 2',3',6'-, 2',4',5'- *and* 2',4',6'-*Trioxygenated flavones*

Five naturally occurring flavones with a 2',3',4'-trioxygenated B ring have been isolated from the three

Table 6. 2',3',4'-, 2',3',5'-, and 2',3',6',-Trioxygenated flavones and flavonols

/2',3',4'	**134**	90–91	synthesis	[41]
3,5,7,2',3'/4'	**135**	272–273	synthesis	[57]
3,5,7,3'/2',4'	**136**		*Scutellaria rehderiana* (viscidulin III)→5,7,3',6'/8,2'	[58] (**160**)
		216–218	synthesis	[57]
5,2',3'/3,7,4'	**137**	154–156	*Apuleia leiocarpa*	[75]
5,4'/7,8,2',3'	**138**	236–237	derivative	[33]
5,4'/7,8,2',3'(5-glc)	**139**	135–140	*Andrographis paniculata*	[33]
5/7,8,2',3',4'	**140**	170	*Andrographis serpyllifolia* (serpyllin)	[75]
/5,6,7,2',3',4'	**141**	141–143	synthesis	[76]
/5,7,8,2',3',4'	**142**	180–182	derivative, synthesis	[76]
5,6,2',3'/3,7,4'	**143**	193–195	*Apuleia leiocarpa* (apuleisin)	[75]
5,8/3,7,2',3',4' (8-acetate)	**144**	183–185	*Notholaena aschenborniana*	[77]
5/3,6,7,2',3',4'	**145**	136–138	derivative	[75]
/3,5,6,7,2',3',4'	**146**	186–188	derivative	[75]
/2',3',5'	**147**	112–113	synthesis	[78]
/6,8,2',3',5'	**148**	167–169	synthesis	[78]
5,2'/6,7,3',5'	**149**	>260	synthesis	[79]
5,5'/6,7,2',3'	**150**		*Gardenia cramerii*	[80]
			Gardenia fosbergii →5,3'/6,7,4',5'	[80]
		261	synthesis	[79]
5/6,7,2',3',5'	**151**	181–183	synthesis	[79]
2'/5,6,7,3',5'	**152**	232–234	synthesis	[79]
5'/5,6,7,2',3'	**153**	231–233	synthesis	[79]
/5,6,7,2',3',5'	**154**	140–142	synthesis	[79]
2',3',6'/	**155**	>340	synthesis	[9]
/2',3',6'	**156**	158–159	synthesis	[9]
5,7,2',3'/8,6'	**157**	272–274 (dec.)	synthesis	[81]
5,7,2',6'/8,3'	**158**	163–164 (dec.)	synthesis	[81]
5,7,3',6'/6,2'	**159**	212–213	synthesis	[81]
5,7,3',6'/8,2'	**160**	255	*Scutellaria baicalensis*	[10]
		250 (dec.)	*Scutellaria baicalensis*	[81]
		262–264	*Scutellaria rehderiana*	[83]
		252–254	synthesis	[81]
/5,7,8,2',3',6'	**161**	174–176	derivative	[82]
5,7,2',4',5'/	**162**	*	*Isoetis delilei, Isoetis durieui*	[84]
		305–307	synthesis	[85]

Table 7. 2′,4′,5′- and 2′,4′,6′-Trioxygenated flavones and flavonols

5,7/2′,4′,5′	**163**	295–305 (dec.)	synthesis	[84]
3,5,7,2′,4′,5′/	**164**	>350 (dec.)	synthesis	[86]
3,5,7,2′,5′/4′	**165**	280–284	synthesis	[86]
5,7,2′,4′/6,5′	**166**	291–294 (dec.)	*Artemisia ludoviciana* var. *ludoviciana*	[87]
		285 (dec.)	synthesis	[85]
5,7,2′,5′/8,4′	**167**	*	*Gutierrezia microcarphala*	[88]
5,7,4′,5′/3,2′	**168**	*	*Gymnospeuma glutinosum*	[89]
5,6,4′/7,2′,5′	**169**		*Artemisia capillaris* (isocapillin) not identitive	[85, 90]
		246	synthesis	[85]
5,7,2′/6,4′,5′	**170**	285–287	synthesis	[85]
5,7,4′/6,2′,5′	**171**	241–242	synthesis	[85]
5,2′,4′/6,7,5	**172**	272–274	*Artemisia capillaris*	[91]
		287–290 (dec.)	synthesis	[85]
5,2′,5′/3,7,4′	**173**	229–230	*Distemonanthus benthamianus* (oxyayanin A)	[82]
		225–227	synthesis	[93]
		225–226	derivative	[94]
		225–227	*Apuleia leiocarpa*	[75]
5,2′,5′/3,7,4′(2′-glc)	**174**	274–275	*Chrysosplenium grayanum* (chrysosplenaside A)	[94]
5,2′,5′/6,7,4′	**175**	285 (dec.)	synthesis	[85]
5,7/3,2′,4′,5′	**176**	264–265	synthesis	[92]
5,7/6,2′,4′,5′	**177**	213–214	*Chukrasia tabularis* (tabularin)	[95]
		210–211	synthesis	[96]
		208–209	synthesis	[85]
5,2′/3,7,4′,5′	**178**	190–192	derivative	[97]
5,2′/3,7,4′,5′(2′-glc)	**179**	242–243	*Chrysosplenium grayanum* (chrysosplenoside E)	[97]
2′,5′/3,5,7,4′	**180**	258–260	*Apuleia leiocarpa* (5-*O*-methyloxyayanin A)	[75]
5/3,7,2′,4′,5′	**181**	149–150	derivative, synthesis	[92]
5/6,7,2′,4′,5′	**182**	199–203	*Ageratum houstonianum* (agehoustin G)	[98]
		193	synthesis	[85]
7/5,6,2′,4′,5′	**183**	220–222	synthesis	[96]
/3,5,7,2′,4′,5′	**184**	193–195	derivative, synthesis	[92]
		189–191	derivative	[75]
		195–196	derivative	[94]
		198	derivative	[86]
/5,6,7,2′,4′,5′	**185**	180–182	synthesis	[96]
		184	derivative	[95]
		180–181	synthesis	[85]
5,6,2′,5′/3,7,4′	**186**	250–260	derivative	[75]
5,7,2′,4′/3,8,5′	**187**	*	*Gutierrezia microcephala*	[88]
5,7,2′,5′/3,6,4′	**188**	*	*Gutierrezia gradis*	[99]
5,7,2′,4′/3,6,5′	**189**	*	*Gutierrezia gradis*	[99]
5,7,2′,5′/6,8,4′	**190**	*	*Gutierrezia microcephala*	[88]
5,7,4′,5′/3,6,2′	**191**	*	*Gymnosperuma glutinosa*	[89]
3,5,4′/6,7,2′,5′	**192**	203–205	synthesis	[100]
3,5,2′/6,7,4′,5′	**193**	191–193	synthesis	[100]
3,2′,4′/5,6,7,5′	**194**	208–210	synthesis	[100]
3,2′,5′/5,6,7,4′	**195**	199–201	synthesis	[100]
5,7,2′/3,6,4′,5′	**196**	*	*Gutierrezia microcephala*	[88, 101]
5,7,2′/3,8,4′,5′	**197**	*	*Gutierrezia microcephala*	[101]
5,2′,4′/3,7,8,5′	**198**	199–200	*Notholaena aschenborniana* (NAS-3)	[77,102,103]
		188–189	synthesis	[42, 103]
5,2′,4′/3,6,7,3′	**199**	157–158	synthesis	[42]
5,2′,4′/6,7,8,5′	**200**	258–260	*Ageratum corymbosum* (agecorynin D)	[104]
		258–260	synthesis	[85]

Table 7. *Continued*

5,2',5'/3,6,7,4'	**201**	228–230	*Apuleia leiocarpa* (5-*O*-demethylapulein)	[75]
	202	220–222	synthesis	[100]
5,2',5'/3,7,8,4'	**203**	203–205	synthesis	[100]
5,2',5'/6,7,8,4'	**204**	*	*Gutierrezia microcephala*	[88]
3,5/6,7,2',4',5'	**205**	159	synthesis	[105]
3,2'/5,6,7,4',5'	**206**	208–210	synthesis	[105]
3,4'/5,6,7,2',5'	**207**	166–167	synthesis	[105]
5,6/3,7,2',4',5'	**208**	142–145	*Distemonanthus benthaminus*	[106]
5,2'/3,6,7,4',5'	**209**	*	*Gutirrezia microcephala*	[101]
		197	*Brickellia veronicaefolia* (brickellin)	[107, 108]
		188–189	synthesis	[105]
5,2'/6,7,8,4',5'	**210**	237–238	*Ageratum houstonianum* (agehoustin F)	[98]
5,4'/3,6,7,2',5'	**211**	175	synthesis	[105]
2',4'/3,5,6,7,5'	**212**	166–167	synthesis	[105]
2',5'/3,5,6,7,4'	**213**		*Apuleia leiocarpa*	[109]
		211–213	*Apuleia leiocarpa* (apulein)	[75]
		196–198	synthesis	[105]
3/5,6,7,2',4',5'	**214**	189–191	synthesis	[105]
5/6,7,8,2',4',5'	**215**	140–143	*Ageratum houstonianum* (agehoustin E)	[98]
/3,5,6,7,2',4',5'	**216**	159–160	derivative	[75]
		157–159	derivative	[106]
/5,6,7,8,2',4',5'	**217**	158–160	*Ageratum corymbosum* (agecorynin D)	[104]
			synthesis	[85]
5,7,2',4'/3,6,8,5'	**218**	*	*Gutierrezia microcephala*	[101]
5,7,2',5'/3,6,8,4'	**219**	*	*Gutierrezia microcephala*	[101]
		*	*Gutierrezia gradis*	
5,7,4',5'/3,6,8,2'	**220**	*	*Gymnosperuma glutinosum*	[89]
3,7,2'/5,6,8,4',5'	**221**	174–175	synthesis	[110]
3,7,4'/5,6,8,2',5'	**222**	201–202	synthesis	[110]
3,7,5'/5,6,8,2',4'	**223**	205	synthesis	[110]
5,7,2'/3,6,8,4',5'	**224**	*	*Gutierrezia microcephala*	[88, 101]
		184–185	synthesis	[110]
5,7,4'/3,6,8,2',5'	**225**	182–183	synthesis	[110]
		*	*Gymnosperum glutinosum*	[89]
5,7,5'/3,6,8,2',4'	**226**	*	*Gutierrezia microcephala*	[101]
		145–150	synthesis	[110]
5,4',5'/3,6,7,8,2'	**227**	*	*Gymnosperuma glutinosum*	[89]
5,7/3,6,8,2',4',5'	**228**	*	*Gymnosperuma glutinosum*	[89]
5,2'/3,6,7,8,4',5'	**229**	*	*Gutierrezia microcephala*	[88, 101]
/3,5,6,7,8,2',4',5'	**230**	132–133	*Pogostemon purpurascens* (purpurascetin)	[111]
/2',4',6'	**231**	153–155	synthesis	[41]
7,2',4',6'/	**232**	303–304 (dec.)	synthesis	[9]
/7,2',4',6'	**233**	197	synthesis	[9]

genera *Andrographis*, *Apuleia* and *Notholeana*. The structure of viscidulin III from *Scutellaira rehderiana*, which was first thought to be 3,5,7,3'-tetrahydroxy-2',4'-dimethoxyflavone (**136**), has since been revised to 5,7,3',6'-tetrahydroxy-8,2'-dimethoxyflavone (**160**), following synthetic comparisons.

At the present time, flavones with the 2',3',5'-trioxygenated B-ring have not been found as natural products. Once 5,5'-dihydroxy-6,7,2',3'-tetramethoxyflavone (**150**) was reported as a constituent of the bud exudate of *Gardenia ramerii* and *G. fosbergii* (Rubiaceae). But the spectral properties of a synthetic sample showed that it was quite different from the natural product. The structure has been revised to 5,3'-dihydroxy-6,7,4',5'-tetramethoxyflavone, from spectral and biosynthetic considerations.

5,7,3',6'-Tetrahydroxy-8,2'-dimethoxyflavone (**16**) is the only known naturally occurring flavone with a 2',3',6'-trioxygenated B ring. The flavone was isolated from *Scutellaria baicalensis* and its structure was elucidated by two different Japanese research groups and confirmed by comparison with synthetic materials (**157**–**160**).

A 2',4',5'-trioxygenated pattern is the most common among the flavones with a trioxygenated B ring, and is widespread in nature: in Pteridophyta (*Isoetes*, *Nothoalaena*); and in Spermatophyta, Saxifragaceae (*Chrysosplenium*), Leguminosae (*Apulea*, *Distemonathus*), Meliaceae (*Chukrasia*), Labiatae (*Pogostemon*), Compositae (*Ageratum*, *Artemisia*, *Brickellia*, *Gutierrezia*, *Gymnosperma*).

2',3',4',5'-, 2',3',4',6'-, 2',3',5',6'-Tetraoxygenated and 2',3',4',5',6'-pentaoxygenated flavones

Agehoustins A-D are highly oxygenated flavones with both a 2',3',4',5'-tetraoxygenated B ring and a 5,6,7,8-

Table 8. 2',3',4',5'-, 2',3',4',6'-, 2',3',5',6'-Tetraoxygenated and 2',3',4',5',6'-pentaoxygenated flavones and flavonols

5,3'/6,7,2',4',5'	**234**	228	*Psiadia arabica* (psiadiarabin)	[112]
5/6,7,2',3',4',5'@	**235**	151–152	derivative	[113]
/5,6,7,2',3',4',5' @	**236**	122–123	*Polygonum nepalense*	[113]
/5,6,7,2',3',4',5'	**237**	85–86	*Ageratum houstonianum* (agehousin B)	[114]
		98–99	synthesis	[115]
/5,7,8,2',3',4',5'	**238**	159–161	synthesis	[115]
5,3'/6,7,8,2',4',5'	**239**	168–169	*Ageratum houstonianum* (agehoustin D)	[116]
3'/5,6,7,8,2',4',5'	**240**	145–146	*Ageratum houstonianum* (agehoustin C)	[116]
/5,6,7,8,2',3',4',5'	**241**	116–117	*Ageratum houstonianum* (agehoustin A)	[113]
		114–115	synthesis	[115]
/5,6,2',3',4',6'	**242**	126–127	*Sargentia gregii*	[19]
		124–125	synthesis	[19]
5,2',4'/6,7,3',6'	**243**	241	synthesis	[100, 117]
5,2',4'/7,8,3',6'	**244**	220 (dec.)	synthesis	[100, 117]
5,2',6'/6,7,3',4'	**245**	239 (dec.)	synthesis	[100, 117]
5,3',6'/6,7,2',4'	**246**	232–233	synthesis	[100, 117]
5,4',6'/6,7,2',3'	**247**	281	synthesis	[100, 117]
5,2'/6,7,3',4',6'	**248**	187–188	synthesis	[105, 118]
5,3'/6,7,2',4',6'	**249**	198–199	synthesis	[105, 118]
5,4'/6,7,2',3',6'	**250**	193–194	synthesis	[105]
5,6'/6,7,2',3',4'	**251**	177–178	synthesis	[105, 118]
4',6'/5,6,7,2',3'	**252**	222–224 (dec.)	synthesis	[117]
/5,6,7,2',3',4',6'	**253**	149–151	synthesis	[115]
/5,7,8,2',3',4',6'	**254**	166–167	synthesis	[115]
/5,6,7,8,2',3',4',6'	**255**	113–114	synthesis	[115]
/2',3',5',6'	**256**	132–133	synthesis	[41]
/5,6,7,2',3',5',6'	**257**	149–150	synthesis	[115]
/5,7,8,2',3',5',6'	**258**	173–174	synthesis	[115]
/5,6,7,8,2',3',5',6'	**259**	118–120	synthesis	[115]
/2',3',4',5',6'	**260**	97–98	synthesis	[41]
2'/5,3',4',5',6'	**261**	148–151	synthesis	[23]
/5,2',3',4',5',6'	**262**	oil	synthesis	[23]
/5,6,7,8,2',3',4',5',6'	**263**	115–116	synthesis	[41]

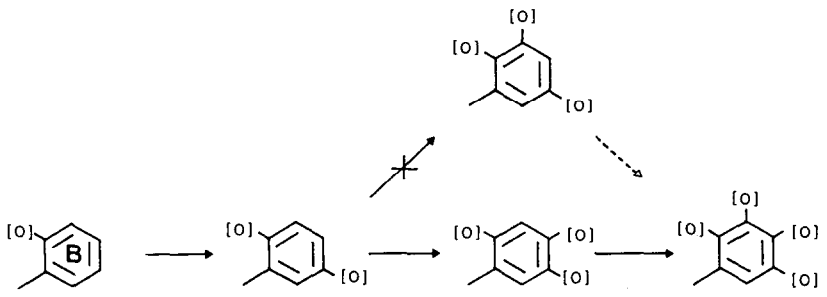

Fig. 5. Possible oxidative pathway in the B ring moiety of flavonoids in the Compositae.

Table 9. 2-Oxygenated chalcones

2,2′/	**264**	143–144	*Primula* spp.	[61]
4,4′/2	**265**	209.5–212 (dec.)	*Glycyrrhiza echinata* (echinatin) tissue culture	[119]
3,4,4′/2	**266**	195–197	*Glycyrrhiza glabra* (licochalcone B)	[120]
2,6,2′,4′/6′	**267**	165 (dec.)	*Scutellaria baicalensis*	[26]
2′,4′/2,4,6′	**268**	157–159	*Prunus cerasus* (cerasin)	[51]
		157–159	synthesis	[52]
2′,4′/2,3′,6′	**269**	134 (dec.)	*Scutellaria discolor*	[27]
2′/2,4,4′,6′	**270**	152–153	*Prunus cerasus* (cerasidin)	[51]
		152–153	synthesis	[51]
		152–153	*Terminalia aujuna*	[54]
		154 155	synthesis	[54]
/2,4,β(3′:4′)@	**271**	92–94	*Millettia hemleyana*	[121]
2′/2,4,5,4′,6′	**272**	184–186	*Derris robusta* (rubone)	[122]

Table 10. ^{13}C NMR chemical shifts in the ring B moieties of flavones

	1′	2′	3′	4′	5′	6′	OMe
none	131.5	126.0	128.8	131.3	128.8	126.0	—
2′	120.0	157.4	111.2	132.4	125.5	128.7	55.6
3′	132.2	111.4	159.5	117.3	129.9	118.3	55.1
4′	123.0	127.7	114.3	161.8	114.3	127.7	55.1
2′,3′	111.2	147.1	153.0	111.2	120.5	116.0	60.2, 55.9
2′,4′	109.9	159.1	98.7	160.9	105.8	129.7	55.5, 55.1
2′,5′	120.2	151.6	114.0	118.3	152.9	111.5	56.1, 55.4
2′,6′	110.4	157.7	104.1	132.3	104.1	157.7	55.8
3′,4′	123.0	109.5	148.9	151.6	111.9	119.4	55.9, 55.2
3′,5′	132.6	104.0	160.4	103.1	160.4	104.0	55.0
2′,3′,4′	108.0	152.0	141.9	155.6	108.0	118.0	60.9, 60.2, 55.8
2′,3′,5′	125.1	140.8	155.4	102.9	153.4	103.6	60.3, 55.8
2′,3′,6′	115.1	150.7	111.4	120.1	142.7	146.3	60.6, 55.7
2′,4′,5′	108.6	152.7	103.0	153.9	143.0	111.3	56.5, 55.7
2′,4′,6′	103.7	158.6	91.0	162.7	91.0	158.6	55.7, 55.0
3′,4′,5′	126.0	104.1	152.9	140.8	152.9	104.1	59.4, 56.1
2′,3′,4′,5′	119.8	147.4	145.8	149.5	147.8	106.1	61.3, 56.2
2′,3′,4′,6′	109.1	154.1	136.2	155.8	92.4	152.9	61.8, 61.0, 56.1
2′,3′,5′,6′	102.2	139.7	148.5	112.9	148.5	139.7	60.7, 56.4
2′,3′,4′,5′,6′	116.2	142.5	148.6	149.4	146.8	142.5	61.1, 60.6

All spectra were measured in $CDCl_3$ as methyl ethers.

tetraoxygenated A ring and their structures were confirmed by respective syntheses. When attention is directed to the B-ring oxygenation patterns found in the Compositae [2′,5′-$(O)_2$: *Inula*; 2′,4′,5′-$(O)_3$: *Gutierrezia*; and 2′,3′,4′,5′-$(O)_4$: *Ageratum* and *Psiadia*], a possible biosynthetic pathway is apparent (Fig. 5). Another 2′,3′,4′,5′-tetraoxygenated flavone has been isolated from the aerial parts of *Psiadia arabica* (Compositae) together with 5,3′-dihydroxy-6,7,2′,4′,5′-pentamethoxyflavone, the structure of which was confirmed by X-ray analysis.

The only natural flavone with a 2′,3′,4′,6′-tetraoxygenated ring B moiety was reported as a constituent of *Sargentia gregii* (Rutaceae). The synthetic products (**243–255**) were all prepared in order to study and confirm the structure of NAS-3 (**198**) and brickellin (**209**). 2′,3′,5′,6′-Tetraoxygenated and 2′,3′,4′,5′,6′-pentaoxygenated flavones have not as yet been found in nature. 5,6,7,8,2′,3′,4′,5′,6′-Nonamethoxyflavone (**263**), the most highly oxygenated flavone, was synthesized in order to observe the behaviour of chemical shifts of skeletal and methoxyl carbons in ^{13}C NMR spectroscopy [41].

Miscellaneous

Some chalcones oxygenated at C-2 (chalcone numbering system) have been reported as natural products, mainly from Leguminosae as shown in Table 9.

Carbon shifts of 20 variants based on the B ring as methyl ethers are listed in Table 10 [41, 78]. All spectra were measured on the methyl ethers.

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