REVIEW ARTICLE

SECOBISBENZYLISOQUINOLINE ALKALOIDS – CHEMISTRY AND PHARMACOLOGY: A REVIEW

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ABSTRACT

Major secobisbenzylisoquinoline alkaloids have been reported from the families Berberidaceae and Annonaceae and to a lesser extent from Menispermaceae, Hernandiaceae, Ranunculaceae, and Atherospermataceae. A critical study on the structures of these alkaloids indicates that secobisbenzylisoquinoline alkaloids could be the first step towards catabolism of bisbenzylisoquinolines but unfortunately, very little pharmacological work has been carried out on secobisbenzylisoquinoline alkaloids. The present review highlights the chemistry and pharmacology of these alkaloids and structures of common secobisbenzylisoquinoline alkaloids isolated from various sources have been reported.

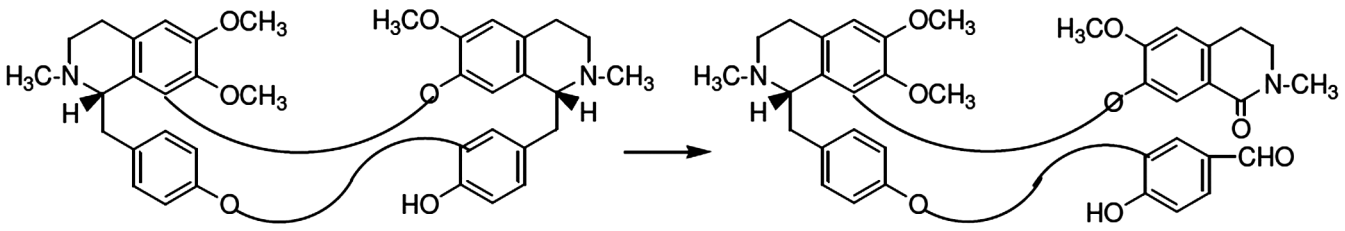
Keywords: Bisbenzylisoquinoline alkaloids, catabolism, isoquinoline-isoquinolone dimers, pharmacology, secobisbenzylisoquinoline alkaloids.

1. INTRODUCTION

Secobisbenzylisoquinoline alkaloids have been found mainly in Berberidaceae and Annonaceae families and to a lesser extent in Menispermaceae, Hernandiaceae, and Ranunculaceae. Isoquinoline alkaloids have diverse structural features and among these the bisbenzylisoquinoline alkaloids comprise the largest group[1-21]. These alkaloids have one, two, or three diaryl ether linkages between the two benzylisoquinoline moieties. However, in a few cases such as secantioquine, antioquine, and secolucidine biphenyl linkages have been found in addition to diaryl ether linkages. Oxidation of one of the benzylisoquinoline cleaves the benzylic bond giving rise to a new group of isoquinoline alkaloid, the 'secobisbenzylisoquinolines'[1-21]. Isolation of several secobisbenzylisoquinoline alkaloids and their sources are given in Table 1.

2. CHEMISTRY

Baluchistanamine (**1**) an alkaloid isolated from *Berberis baluchistanica* was the first alkaloid of its kind reported by Shamma and co-workers in 1974 and placed it in a new group of alkaloids, the isoquinolone–benzylisoquinoline dimer[1]. It appeared to be a cleaved product of a bisbenzylisoquinoline. The structural examination indicated that baluchistanamine must have been derived from in vivo oxidative cleavage of a bisbenzylisoquinoline, oxyacanthine (**2**). In fact, in vitro oxidation of bisbenzylisoquinolines to isoquinolone–benzylisoquinoline dimers have been demonstrated in cases of oxyacanthine (**2**) to baluchistanamine[2]. Later, baluchistanamine was also isolated from *Berberis vulgaris* sub. *australis* along with oxyacanthine.



2. Oxyacanthine **1. Baluchistanamine**

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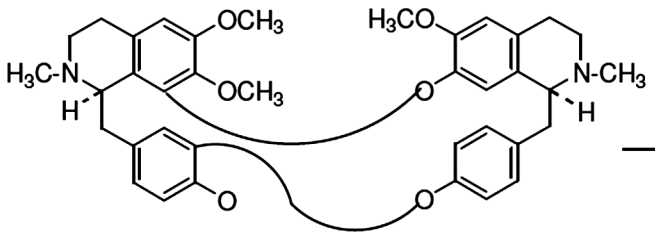
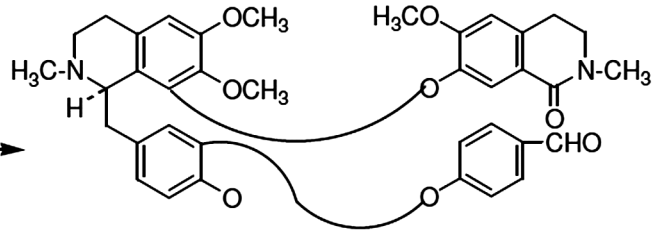
Table 1. Different secobisbenzylisoquinoline alkaloids and their sources

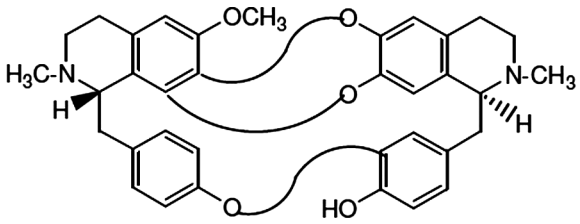
Alkaloid	Biological Source	Family	Reference
Auroramine	*Gyrocarpus americanus* Jacq.	Hernandiaceae	12
Baluchistanamine	*Berberis baluchistanica* Ahrendt	Berberidaceae	1
	Berberis vulgaris sub. *australis*	Berberidaceae	10
Bargustanine	*Berberis vulgaris* L.	Berberidaceae	20
Berkristine	*Berberis vulgaris* L.	Berberidaceae	19
Chenabine	*Berberis lycium*	Berberidaceae	18
Chenabinol	*Berberis vulgaris* L.	Berberidaceae	19
Curacautine	*Berberis buxifolia* Lam	Berberidaceae	9
Dihydrosecocephanthrine	*Stephania sasakii* Hayata	Menispermaceae	5
Gilgitine	*Berberis lycium* Royle	Berberidaceae	3
Jhelumine	*Berberis lycium* Royle	Berberidaceae	18
Karakoramine	*Berberis lycium* Royle	Berberidaceae	13
Maroumine	*Gyrocarpus americanus* Jacq.	Hernandiaceae	12
O-methylpunjabine	*Stephania sasakii* Hayata	Menispermaceae	4
O-methyldeoxyopunjabine	*Mahonia nepalensis* DC	Berberidaceae	5
	Pseudoxandra cuspidata	Annonaceae	6
	Stephania sasakii Hayata	Menispermaceae	4
Pecrassipine A	*Phaeanthus crassipetalus* Becc	Annonaceae	21
Pecrassipine B	*Phaeanthus crassipetalus* Becc	Annonaceae	21
Punjabine	*Berberis lycium* Royle	Berberidaceae	3
Revolutinone	*Thalictrum revolutum* DC	Ranunculaceae	11
Secolucidine	*Pseudoxandra sclecarpa* Maas	Annonaceae	17
Secantioquine	*Pseudoxandra aff. lucida* Fries	Annonaceae	15
Secoobaberine	*Pseudoxandra aff. lucida* Fries	Annonaceae	7
Secocepharanthine	*Stephania sasakii* Hayata	Menispermaceae	5
Secohomoaromoline	*Anisocycla jollyana* (Pierre) Diels	Menispermaceae	6
Secojollyanine	*Anisocycla jollyana* (Pierre) Diels	Menispermaceae	6
Secoisotetrandrine	*Laurelia sempervirens* R. & P.	Atherospermataceae	8
Sindamine	*Berberis lycium* Royle	Berberidaceae	3
Talcamine	*Berberis buxifolia* Lam.	Berberidaceae	9
Tejedine	*Berberis vulgaris* sub. *australis* (Boiss)	Berberidaceae	10
Verfilline	*Berberis vulgaris* L.	Berberidaceae	19
Vietnamine	*P. crassipetalus* Becc	Annonaceae	21



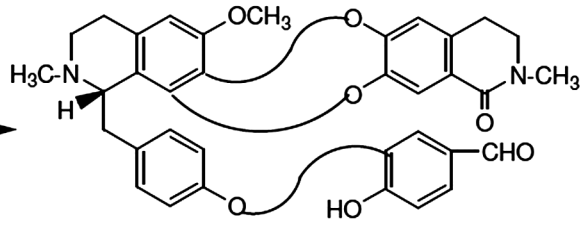
6. Berbamine



3. Sindamine



7. Cocsuline

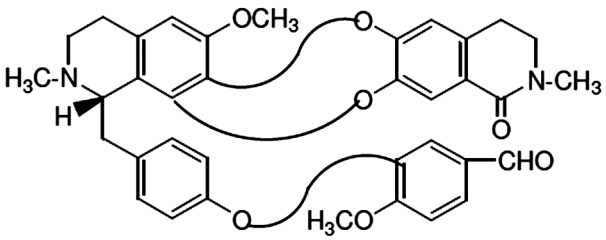


4. Punjabine

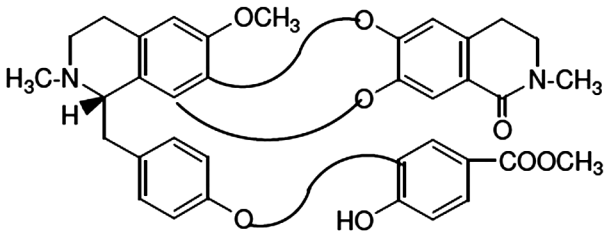
Baluchistanamine and several other secobisbenzylisoquinoline alkaloids have been isolated from different sources (Table 1). Sindamine (**3**), punjabine (**4**), and gilgitine (**5**) have been isolated from *Berberis lycium*[3]. Sindamine (**3**) may have formed from in vivo oxidation of berbamine (**6**) while punjabine (**4**) from cocsuline (**7**).

Aldehyde group of punjabine may have been oxidized to the carboxylic group and subsequently methylated to yield gilgitine (**5**). In case of the secobisbenzylisoquinolines, *O*-methylpunjabine (**8**) and *O*-methyldeoxyopunjabine (**9**) isolated from *Stephania sasakii*[4], methylation of OH group of punjabine would give *O*-methylpunjabine (**8**) while complete reduction of the aldehydic group and methylation of OH would give *O*-methyldeoxyopunjabine (**9**). Isolation of *O*-methylpunjabine has also been reported from *Mahonia nepalensis*[5], and *Pseudoxandra cuspidata*[6].

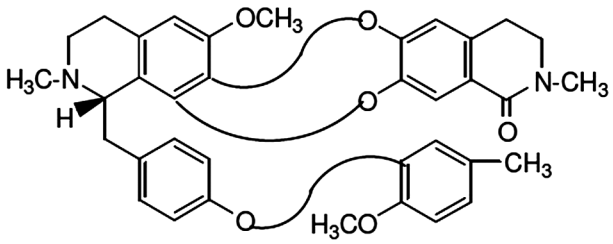
Two secobisbenzylisoquinoline alkaloid secojollyanine (**10**) and seco-homoaromoline (**11**) have also been isolated from *Anisocycla jollyana*[7].



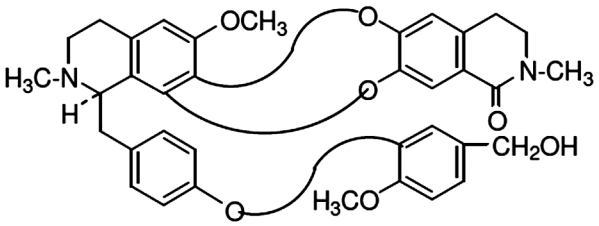
8. O-Methylpunjabine



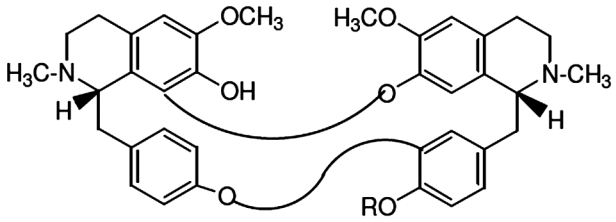
5. Gilgitine



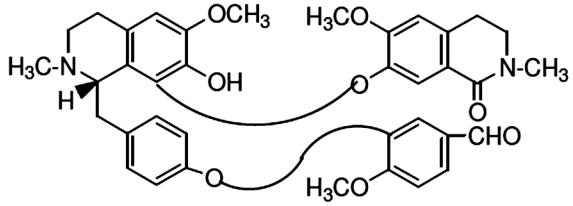
9. O-Methyldeoxopunjabine



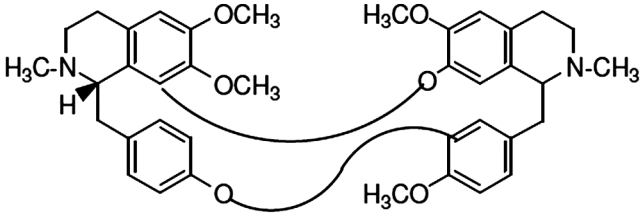
10. Secojollyanine



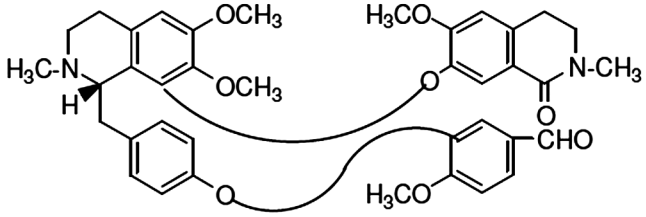
12. Homoaromoline R= CH_3
13. Aromoline R = H



11. Seco-homoaromoline



15. Obaberine

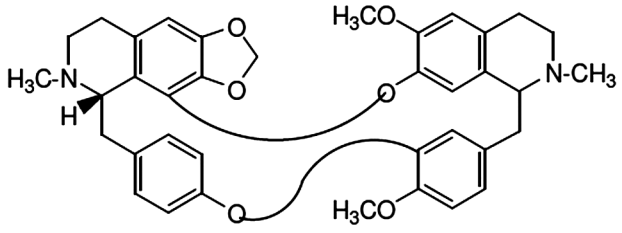


14. Seco-obaberine

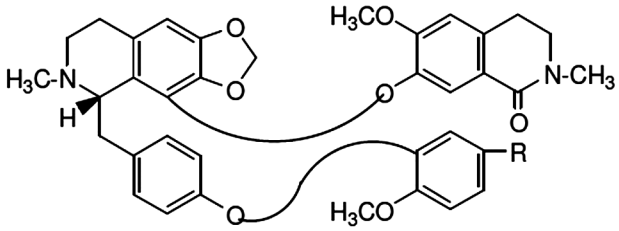
Structural examination indicates that *O*-methylpunjabine (**8**) may have been reduced to yield secojollyanine (**10**), while seco-homoaromoline (**11**) may have been formed from homoaromoline (**12**) or from aromoline (**13**) which is subsequently methylated. Another alkaloid seco-obaberine (**14**) was reported from *Pseudoxandra aff. lucida*[8] which may have been formed as a result of in vivo oxidation of obaberine (**15**) or *O*-methylation of baluchistanamine (**1**).

Another secobisbenzylisoquinoline alkaloids secocepharanthine (**16**) and dihydrosecocephanthrine (**17**) have been isolated from *Stephania sasakii*[4]. In vivo oxidation of cepharanthine (**18**) would give secocepharanthine (**16**), which on reduction would give dihydrosecocephanthrine (**17**).

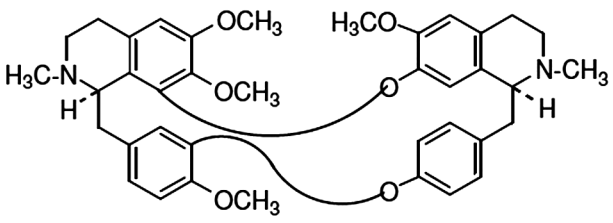
Secoisotetrandrine (**20**), isolated from *Laurelia sempervirens*[9] may have formed by in vivo oxidation of isotetrandrine (**19**).



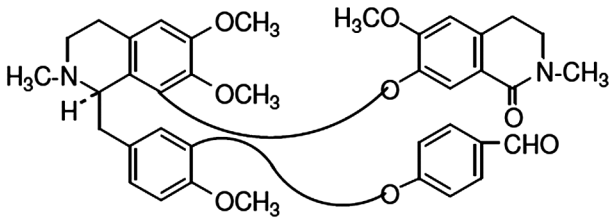
18. Cepharanthine



16. Secocepharanthine R = CHO
17. Dihydrosecocephanthrine R = CH_2OH



19. Isotetrandrine

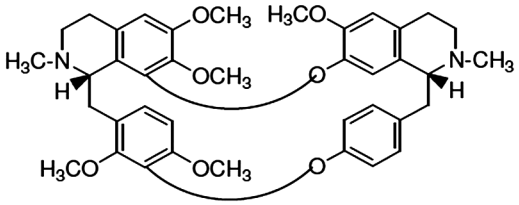


20. Secoisotetrandrine

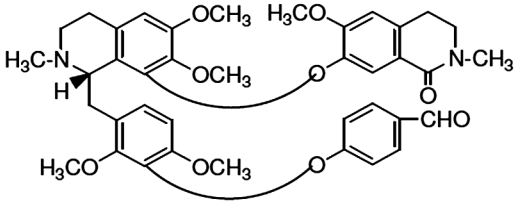
Curacautine (**21A**), another secobisbenzyl-isoquinoline alkaloid isolated from *Berberis buxifolia*[10] may have resulted from in vivo oxidation of a bisbenzylisoquinoline alkaloid such as calafatine (**21**), which on further oxidation and methylation would give talcamine[10] (**22**), an alkaloid also isolated from *Berberis buxifolia*.

Tejedine[11] (**23**) is another secobisbenzylisoquinoline that has been isolated from *Berberis vulgaris* sub. *australis*, which is structurally close to baluchistanamine (**1**), and may have been formed by further oxidation and subsequent methylation of the resulting carboxyl group.

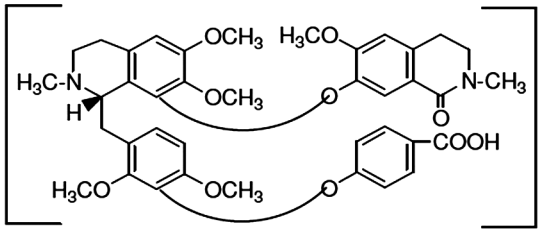
Revolutinone[10] (**24**) is another secobisbenzyl-isoquinoline alkaloid isolated from *Thalictrum revolutum*, which may have resulted from in vivo oxidation of a stereo-isomer of*O*-methyl-isothalicberine (**25**).

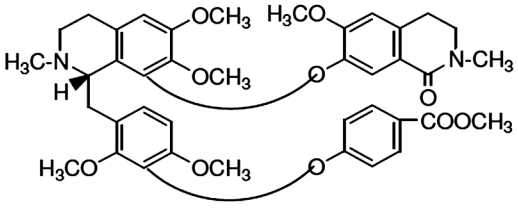


21. Calafatine

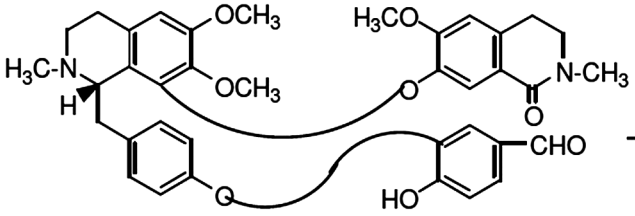


21A. Curacautine

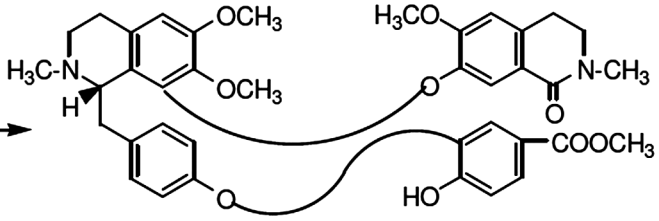




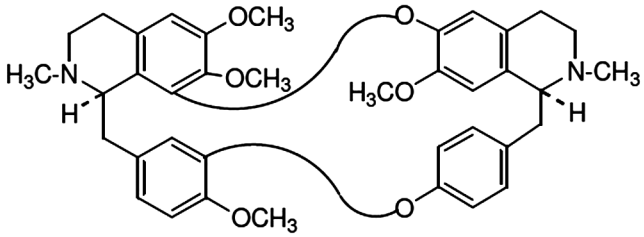
22. Talcamine



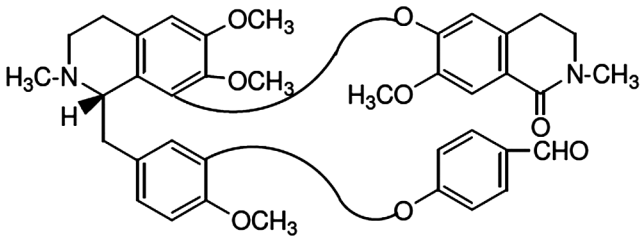
1. Baluchistanamine



23. Tejedine



25. O-Mthylisothalicberine

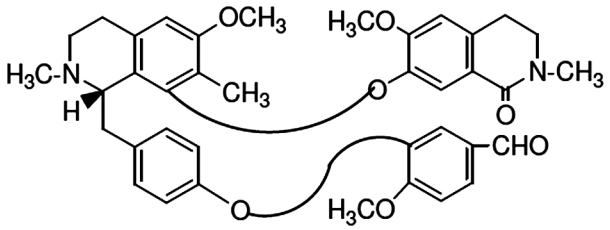


24. Revolutinone

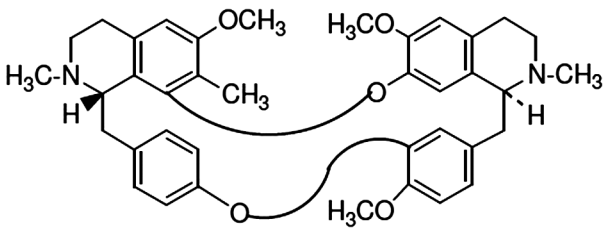
Another two secobisbenzylisoquinoline alkaloids auroramine (**26**) and maroumine (**27**) along with the corresponding bisbenzylisoquinoline gyrolidine (**28**) and gyrocapine (**29**), respectively, have been isolated from *Gyrocarpus americanus*[12] belonging to family Hernandiaceae. It is apparent that gyrolidine (**28)** may have been oxidized to auroramine (**26**) and gyrocapine (**29**) to maroumine (**27**).

Karakoramine[10] (**30**), a secobisbenzylisoquinoline alkaloid isolated from *Berberis lycium* may have resulted from in vivo oxidation, and subsequent reduction of a bisbenzylisoquinoline possessing one diaryl ether linkage such as berbamunine (**31**) also occurring in the same plant[10]. However, in this case, the lactamic part is missing because the precursor alkaloid has only one diaryl ether linkage. Isolation of corypalline[13] (discussed later), the missing lactam, substantiates the hypothesis.

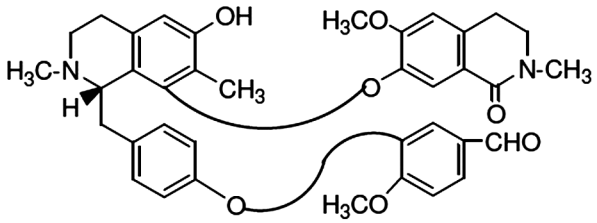
A bisbenzylisoquinoline alkaloid, secantioquine[10] (**33**) with biphenyl linkage along with diaryl ether linkage, has been isolated from *Pseudoxandra aff. lucida*. This may have resulted from bisbenzylisoquinoline alkaloid, antioquine (**34**) obtained from the same plant and also from *Guatteria boliviana*[14].



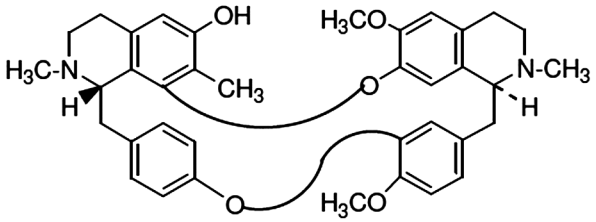
26. Auroramine



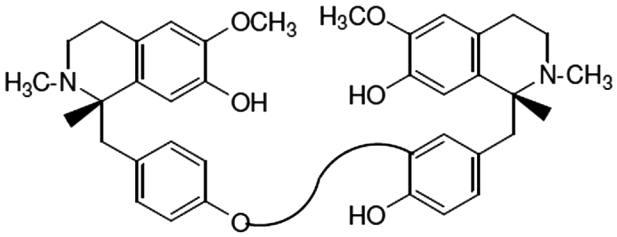
28. Gyrolidine



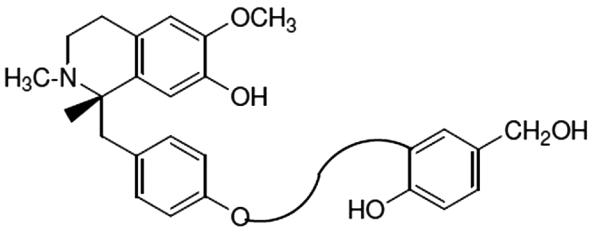
27. Maroumine



29. Gyrocapine



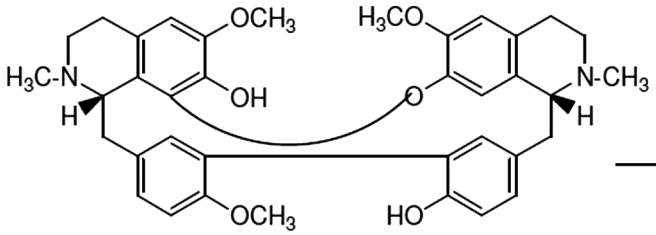
31. Berbamunine



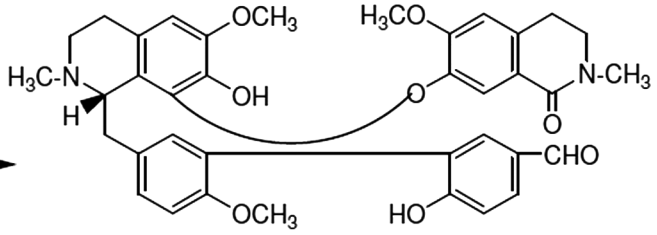
30. Karakoramine

Secolucidine[15] (**35**) is another alkaloid with a biphenyl linkage along with diaryl ether linkage isolated from *Pseudoxandra sclerocarpa*. In this case, the precursor could be cocsuline (**7**) type alkaloid which has two diaryl ether linkages attached to isoquinoline moieties and instead of diaryl ether linkage at the phenyl rings, a diphenyl linkage has been created.

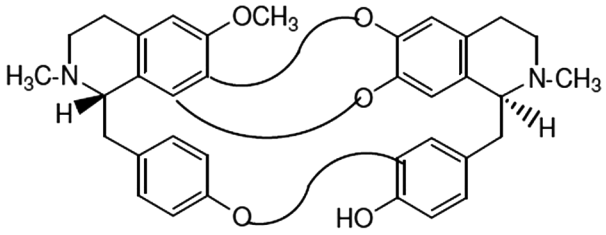
Three secobisbenzylisoquinoline alkaloids, chenabine (**36**), jhelumine (**37**), and chenabinol methyl ether (**38**) isolated from *Berberis lyceum*[16]. Another three secobisbenzylisoquinoline alkaloids; berkristine (**39**), verfilline (**40**), and chenabinol (**41**) have been reported from *Berberis vulgaris*[17] where the cleaved moiety is isoquinoline instead of isoquinolone. In these alkaloids, the carbonyl group of lactam is supposed to have been reduced to form simple tetrahydro-isoquinoline. Chenabinol (**41**) may have been formed by the reduction of chenabine (**36**), which is subsequently methylated to yield chenabinol methyl ether (**38**)[17].



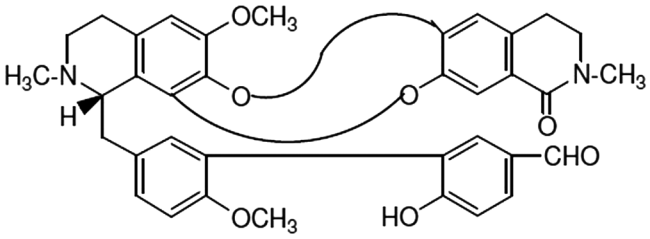
34. Antioquine



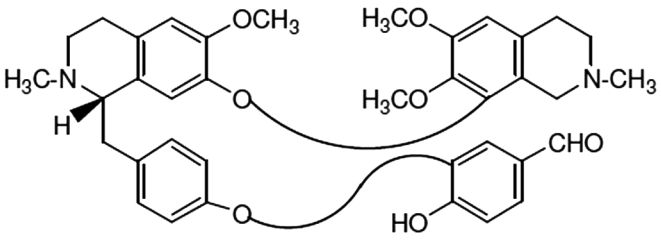
33. Secantioquine



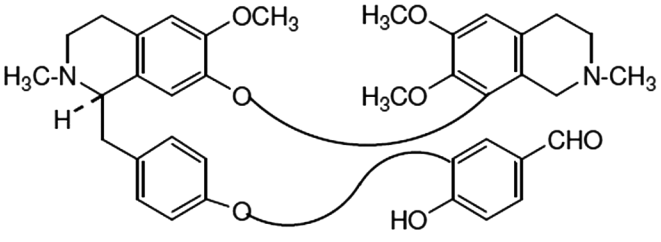
7. Cocsuline



35. Secolucidine



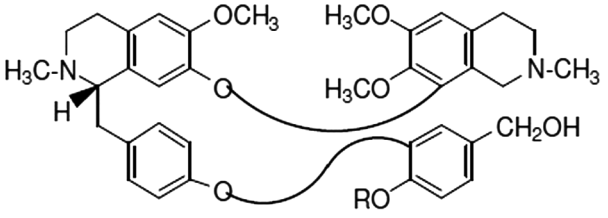
36. Chenabine



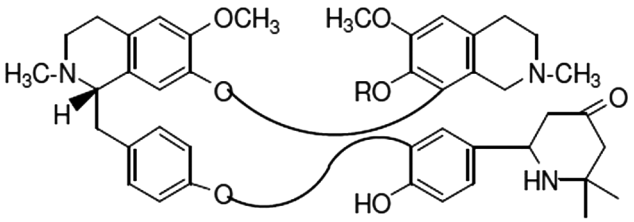
37. Jhelumine

All lactamic secobisbenzylisoquinoline alkaloids, baluchistanamine (**1**), sindamine (**3**), punjabine (**4**), gilgitine (**5**), *O*-methylpunjabine (**8**), *O*-methyldeoxopunjabine (**9**), secojollyanine (**10**), seco-homoaromoline (**11**), seco-obaberine (**14**), secocepharanthine (**16**), dihydroseco-cephanthrine (**17**), secoisotetrandrine (**19**), curacautine (**21A**), talcamine (**22**), tejedine (**23**), revolutinone (**24**), auroramine (**26**), maroumine (**27**), karakoramine (**30**), secantioquine (**33**), and secolucidine (**35**) have one common feature that in vivo oxidation has occurred at the less sterically hindered benzylic site, i.e., at that site of the molecule in which C–8 is unsubstituted. In case of chenabine (**36**), jhelumine (**37**), chenabinol methyl ether (**38**), berkristine (**39**), and verfilline (**40**), cleavage has occurred at the more hindered and less reactive benzylic site. An alternative biogenetic route has been suggested which involves the phenolic oxidative coupling of the aldehyde analog of karakoramine with the simple isoquinoline, corypalline (**42**)[10,13]. If this biogenetic route holds true chenabine and jhelumine, would become the first example of isoquinoline–benzylisoquinoline dimer. However, this hypothesis may not be tenable due to the fact that talcamine (**22**) may have formed by oxidation and subsequent methylation of the carboxyl group of the alkaloid curacutine that has cleaved at the less hindered site. Therefore, it is likely that both simple isoquinoline–benzylisoquinoline dimers and isoquinolone–benzylisoquinoline dimers have been formed by oxidation at the benzylic site of the bisbenzylisoquinoline and may be placed in the secobisbenzylisoquinoline group of alkaloids. Moreover, isolation of bargustanine (**43**), a dimer from *Berberis vulgaris*[18] in which the pendant phenyl ring attached to the benzylisoquinoline moiety is missing and therefore, points towards the hypothesis of the formation of an isoquinoline–benzylisoquinoline dimer where the lactam part is reduced.

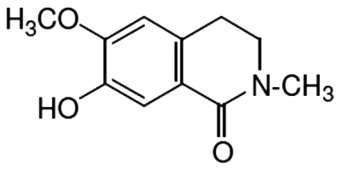
The alkaloids (+)-pecrassipine A (**44**), (+)-pecrassipine B (**45**)[19], and vietnamine (**46**)[20] have been isolated from *Phaeanthus crassipetalu* (Annonaceae) where the pendant phenyl ring is attached to benzylisoquinoline. The lost isoquinolone may be corypalline or its analogue. Isolation of these alkaloids which contain a pendant phenyl ring similar to that of karakoramine (**30**) indicate that these must have been formed by catabolism of bisbenzylisoquinolines.



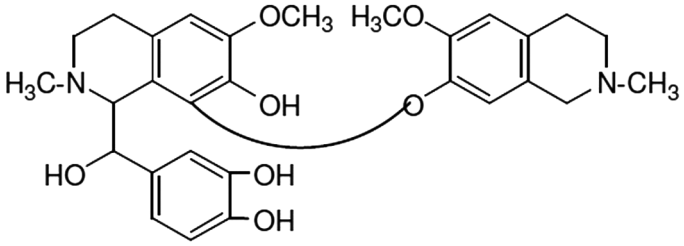
41. Chenabinol R = H
38. Chenabinol methyl ether R= CH_3



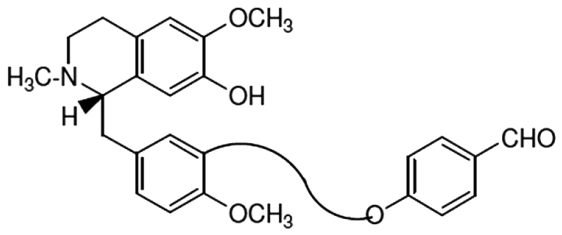
39. Berkristine R = CH_3
40. Verfilline R =H



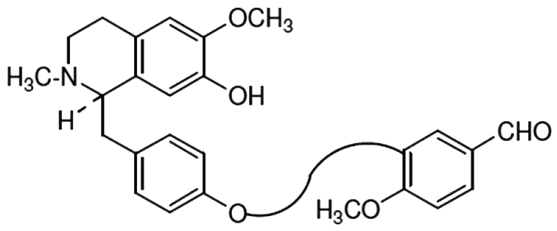
42. Corypalline



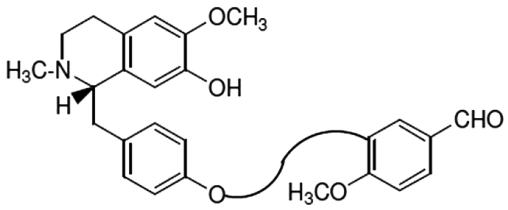
43. Bargustanine



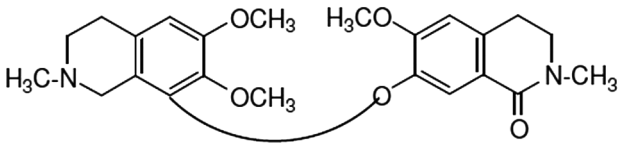
44. Pecrassipine A



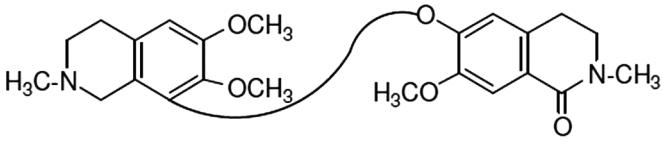
45. Pecrassipine B



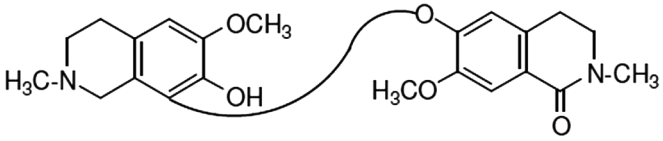
46. Vietnamine



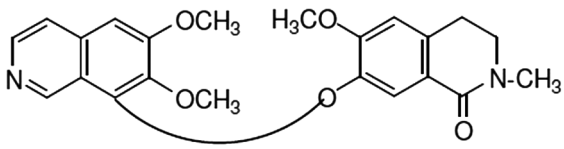
47. Berbidine



48. Turconidine



49. Turcberine



50. Berbanine

Isolation of four isoquinoline-isoquinole dimers, berbidine[21] (**47**) from *Berberis brandisiana*, turconidine[22] (**48**), and turcberine[23] (**49**) from *Berberis turcomanica* and berbanine[24] (**50**) from *Berberis vulgaris* have been reported. In all the above cases, it has been observed that oxidation has occurred on the less hindered side to give a lactam while the more hindered side gives an isoquinoline.

3. PHARMACOLOGY

Berberine, a ubiquitous isoquinoline alkaloid is found in the genus *Berberis*, which has been used in various traditional systems of medicine worldwide for their efficacious medicinal properties. Researches on cardiovascular, hepato-protective, antimicrobial, and anti-cancerous activities have been carried out with positive results. Most of the pharmacological studies have been carried out on berberine[25-49]. Bisbenzylisoquinoline alkaloids are the major group of alkaloids found in all Berberis species. Next to berberine, researches are being conducted on the biological activity of bisbenzylisoquinolines. In recent years, the bisbenzylisoquinoline alkaloids were found to have wide biological activities including antioxidant, cardiovascular effects such as antihypertensive and antiarrhythmic actions[50-52], reversing the multidrug resistance (MDR) effect of human carcinomas[53,54], anti-HIV activity[55], and as anti-tuberculosis agents toward multidrug-resistant *Mycobacterium tuberculosis*[56]. 7-*O*-demethylisothalicberine, a bisbenzylisoquinoline alkaloid isolated from *Berberis chitensis* caused a

significant reduction of mean arterial pressure in normotensive anaesthetized rats[57].

Tetrandrine, dauricine, daurisoline, and neferine are bisbenzylisoquinoline alkaloid and have shown cardiovascular pharmacological effects and the mechanism of actions of these compounds was reviewed[58]. The antihypertensive effects of tetrandrine have been demonstrated in experimental hypertensive animals and patients. A study has shown that in addition to its calcium antagonistic effect, tetrandrine interacted with M receptors. It has also been shown that the antiarrhythmic effect of daurisoline is more potent than that of dauricine[58].

The monoeric benzylisoquinolines and aporphines have been reported to possess antitumor activity. However, the comparative study shows that dimers which are macrocylic rings are necessarily required for such activity[59]. Berbamine, a bisbenzylisoquinoline alkaloid from *Berberis amurensis* has shown to induce selective cell death of both Gleevec-sensitive and -resistant Ph+CML cells[60].

The antimalarial activity of some bisbenzylisoquinoline alkaloids was studied using in vitro culture of both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*. The combination of chloroquine and tetrandrine gave a 44 fold potentiation of malarial killing. The bisbenzylisoquinoline alkaloids fangchinoline, hernandezine, pycnamine, berbamine and isotetrandrine had similar antimalarial activity as tetrandrine against the sensitive strain of *Plasmodium falciparum*. Hernandezine, isotetrandrine, berbamine, fangchinoline, and methoxyadiantifoline had similar antimalarial activity as tetrandrine against a strain of chloroquine-resistant falciparum malaria[61]. Antimalarial activity of bisbenzylisoquinoline alkaloids has also been reported by et al.[62]. Isoliensinine, a natural phenolic bis-benzyltetrahydroisoquinoline alkaloid has received considerable attention for its potential biological effects such as antioxidant and anti-HIV activities[63]. Bisbenzylisoquinoline alkaloids are used in traditional medicine as antiparasitic and are recognized for their strong activity against *Leishmania donovani, Leishmania braziliensis*, and *Leishmania amazonensis*[64]. It has been observed that the oxidation state and the type of substitution on the nitrogen atoms are crucial for the activity as well as the alkaloids with methylated nitrogen is more active than unsubstituted aromatic nitrogen atoms, resulting in loss of leishmanial activity[65]. Cepharanthine, a bisbenzylisoquinoline alkaloid from *Stephania epigaea*, has exhibited cytotoxicity[66] against all cancer cell lines except ECA109.

Although a considerable amount of research on the biological activity of bisbenzylisoquinolines has been carried out, a few of which has been enumerated above, very little work on the biological activity of secobisbenzylisoquinolines have been carried out. The alkaloids chenabinol, berkristine, and verfilline were tested for their inhibition activity of human cholinesterases and prolyl oligopeptidase[17]. Chenabinol (**41**) was found to inhibit human butyrylcholinesterase with an IC_{50} value of 44.8 ± 5.4 μM. Pecrassipine A (**44**) and pecrassipine B (**45**) have shown to inhibit vasocontraction on rat aorta[19]. Secobisbenzylisoquinoline is minor alkaloid and is isolated in small amounts. The bisbenzylisoquinoline alkaloids which are isolated relatively in larger quantities can be conveniently converted into secobisbenzylisoquinoline for undertaking studies on their pharmacological and biological activities.

4. CONCLUSION

From the foregoing discussions, it is proposed that oxidation of the bisbenzylisoquinoline alkaloids on the more hindered side initially provides an iminium salt as part of ring B, which is then reduced to a tertiary amine. The isoquinoline-isoquinolone dimers may be considered as catabolic products of bisbenzylisoquinolines. Thus the formation of secobisbenzylisoquinoline alkaloids may be considered as the first step towards catabolism of bisbenzylisoquinolines.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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