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Review Article

Recently Isolated Fawcettimine-Type Alkaloids

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ABSTRACT

Since long back, many Lycopodiaceae or Huperziaceae plants species like *Lycopodium clavatum* L. serratum, *Huperzia serrata, H. carinata, Phlegmariurus squarrosus* and *P. henryi* are being traditionally used in treatment of diseases like Alzheimer's disease and myasthenia gravis. In pursuit of pharmacologically active molecules, here AChE inhibitors present in any of widely used Lycopodiaceae or Huperziaceae plants species, several researchers successfully isolated hundreds of Lycopidium alkaloids, grouped into four classes, one of which is fawcettimine. This review enlisted all fawcettimine alkaloids, isolation and total laboratory synthesis of which have been reported since 2011 (for ex. fawcettimine, lycoflexine, and lycoposerramine B, Lycopoclavamine-A). It can be concluded that, fawcettimine molecule can used as main nucleus which can used as precursor for synthesize new pharmacologically active moieties.

Keywords: Lycopodiaceae, Alkaloids, Fawcettimine, Total synthesis.

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INTRODUCTION

Several club mosses of the family Lycopodiaceae have been used in Chinese Traditional Medicine to treat various illnesses such as strains, contusions swellings, scalds, rheumatic fever, schizophrenia, and myasthenia gravis.[1] Lycopodiaceae plants occupies the wide range of habitats and exhibits a diversity of life forms that include vines, small deciduous semi-aquatics, robust scrambling and clump-forming terrestrials and pendent epiphytes in Himalayan region of China and India, Andean region of South America;[2] also in New Zealand, Australia[3] and Malaysia.[4] Active alkaloids are found in areal part of plants.

Phytochemical analysis proved that lycopodium alkaloids present in club mosses are responsible for different pharmacological activities exhibited by them. So far, more than 300 lycopodium alkaloids have been isolated from different species of club mosses. Lycopodium alkaloids are N-heterocyclic compounds with structural frameworks such as $C_{16}N$, $C_{16}N_2$ and $C_{27}N_3$; based on structure, can be categorised into four major classes: lycopodine, lycodine, fawcettimine and phlegmarine.[5]

In fawcettimine, four rings: A, B, C, and D are attached as given in structure 1a (Figure 1). Fawcettimine exhibit equilibrium between its carbinolamine form (1a) and the keto-amine form (1b). In carbinolamine form, there is one nitrogen present in structure which is common for six-membered C ring and seven-membered A ring while in keto-amine form, single nitrogen is in nine-membered ring of three rings. In fawcettimine analogue, fawcettidine 2, there is no hydroxyl group at C13 and its valency is satisfied by formation of double bond between C13-C14.

Recently isolated fawcettimine alkaloids and cholinesterase inhibitory activity

In last decade, several research groups have isolated and structurally elucidated more than 35 fawcettimine-type of Lycopodium alkaloids from variety of species of *Lycopodium, Huperzia, Phlegmariurus* and *Palhinhaea* (Table 1, Figure 2- 4).

While isolation of fawcettimine alkaloids, they also reported the isolation and characterization of other types of Lycopodium alkaloids like lycodine, lycopodine, serratinine etc; but this review focus only on fawcettimine-type alkaloids, since 2011.

It is note-worthy that, with the few exceptions, almost all of the newly found compounds do not have inhibitory activities on AChE and BuChE, therefore, application of club mosses in AD is due to very few active fawcettimine alkaloids or other lycodine-type lycopodium alkaloids. It was found that, phlegmariurine B (15) and obscurumine L /M (27) inhibited AChE with LC_{50} values of 26.4 and 81.0 µM, respectively, while lycoannotine I (36) inhibited BuChE with LC_{50} value of 40 µM.

Isolation of fawcettimine alkaloids

Several common aspects, mainly pertaining to selection of material and extraction, were found in isolation procedures

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reported by different researchers for isolation of fawcettimine alkaloids. Mostly, air-dried whole plants, sometime only aerial part of plants of Lycopodiaceae or Huperziazeae family were used for initial extraction, mostly with methanol, or in some cases, ethanol. Then alcoholic extract was concentrated *in vacuo* and then, crude extracts was partitioned between ethyl acetate and 3% tartaric acid, in few cases 1% hydrochloric acid. Water-soluble portion of extract was then made alkaline with sodium hydroxide or sodium carbonate or Na_2CO_3 and extracted with dichloromethane or chloroform, giving alkaloidal extract. Significant difference in procedures reported could be observed after this phase of isolation. Alkaloidal extract was then subjected to chromatographic separation using column C-18 reverse phase silica gel or Sephadex LH20 or polyamide as stationary phase eluted with increasing or decreasing gradient of mobile phase CH_2Cl_2/MeOH or MeOH/H_2O; giving several fractions. These fractions were again chromatographed using different combinations of stationary and mobile phases, to obtain single compounds, which were further taken for structural elucidation (Figure 5).

Total synthesis of fawcettimine-type alkaloids

Fawcettimine-type *Lycopodium* alkaloids have attracted a vast attention of the researchers in both synthetic and medicinal chemistry discipline due to their captivating structures and vital pharmacological activities, such as acetylcholinesterase inhibition and neural cell protection. A wide variety of approaches have been developed toward their synthesis. This decade started with Yang *et al.* 2011[17] explanation of the endgame of 2010, Ramharter *et al.* used Heathcock-type 6-5-9 tricycle to fawcettimine. Initially, from cyclohexenone, tandem Sakurai reaction followed by oxidation with 2-iodoxybenzoic acid affords first intermediate, which was further alkylated to give second intermediate.[18] Vinyl triflate formation of the less hindered carbonyl and elimination yields terminal alkyne. In next step, alkyne undergoes enyne RCM upon exposure to Grubbs second generation catalyst (Grubbs II) to give Heathcock-type 6-5-9 tricycle, which was Boc protected. Further, Yang *et al.* 2011 oxidised Heathcock-type 6-5-9 tricycle to its ketone derivative which was then cleaved to fawcettimine by the epimerization of the C4 stereo-centre to the thermodynamically favoured diastereomer (Figure 6).[17]

After this, in 2012, Pan and Williams started synthesis of Fawcettimine-type *Lycopodium* alkaloids fawcettimine, lycoflexine, and lycoposerramine B through efficient, unified, and stereo controlled strategy involving Diels–Alder reaction to construct the cis-fused 6,5-carbocycles with one all-carbon quaternary centre and Sharpless asymmetric dihydroxylation (Sharpless AD) of intermediate (Figure 7).[19]

In order to synthesize target alkaloid and also its biologically potent novel derivatives, new strategy has been established, involving proceeding through a common precursor. Huang *et al.* 2018 attempted the synthesis of common precursor, azaspirocycle for the further synthesis of fawcettimine alkaloids. They synthesised azaspirocycle via cascade Wacker-allylation sequence followed by a highly stereo-selective Claisen rearrangement (Figure 8).[20]

Synthesis of Lycopoclavamine-A, Fawcettimine-type alkaloid with a β-methyl group at C-15 and a *trans*-decahydroquinoline ring system at the A/D-ring junction, has been attempted by Zaimoku and Taniguchi in 2014, where they proceeded via Diels–Alder reaction.[21] Recently, Kaneko *et al.* 2019 attempted successful asymmetric synthesis of Lycopoclavamine-A via stereoselective Pauson–Khand Reaction (PKR) and conjugate addition to construct a quaternary C-12. Reaction started with crotonamide, which in many steps including treatment with (S)-Corey–Bakshi–Shibata (CBS) reagent, formed bicyclic enedione. This was compound with Tert-Butyl Diphenyl Silyl (TBDPS) and methoxymethyl acetal (MOM) groups. Then, it was converted to tricyclic compound with only methoxymethyl acetal (MOM) group. Further, both MOM groups were removed and formed compound with two hydroxyl groups, which then converted to (Z)-enone via E1cB-like mechanism. Finally, it was converted to lycopoclavamine-A (Figure 9).[22]

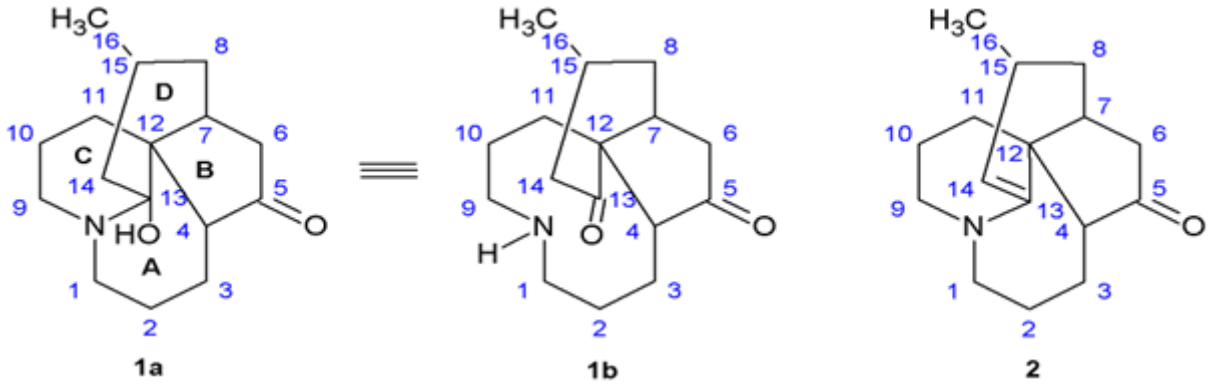

Figure 1: Carbon skeleton of Fawcettimine alkaloid exhibiting carbinolamine form (1a) and the keto-amine form (1b). Another analogue is fawcettidine (2).

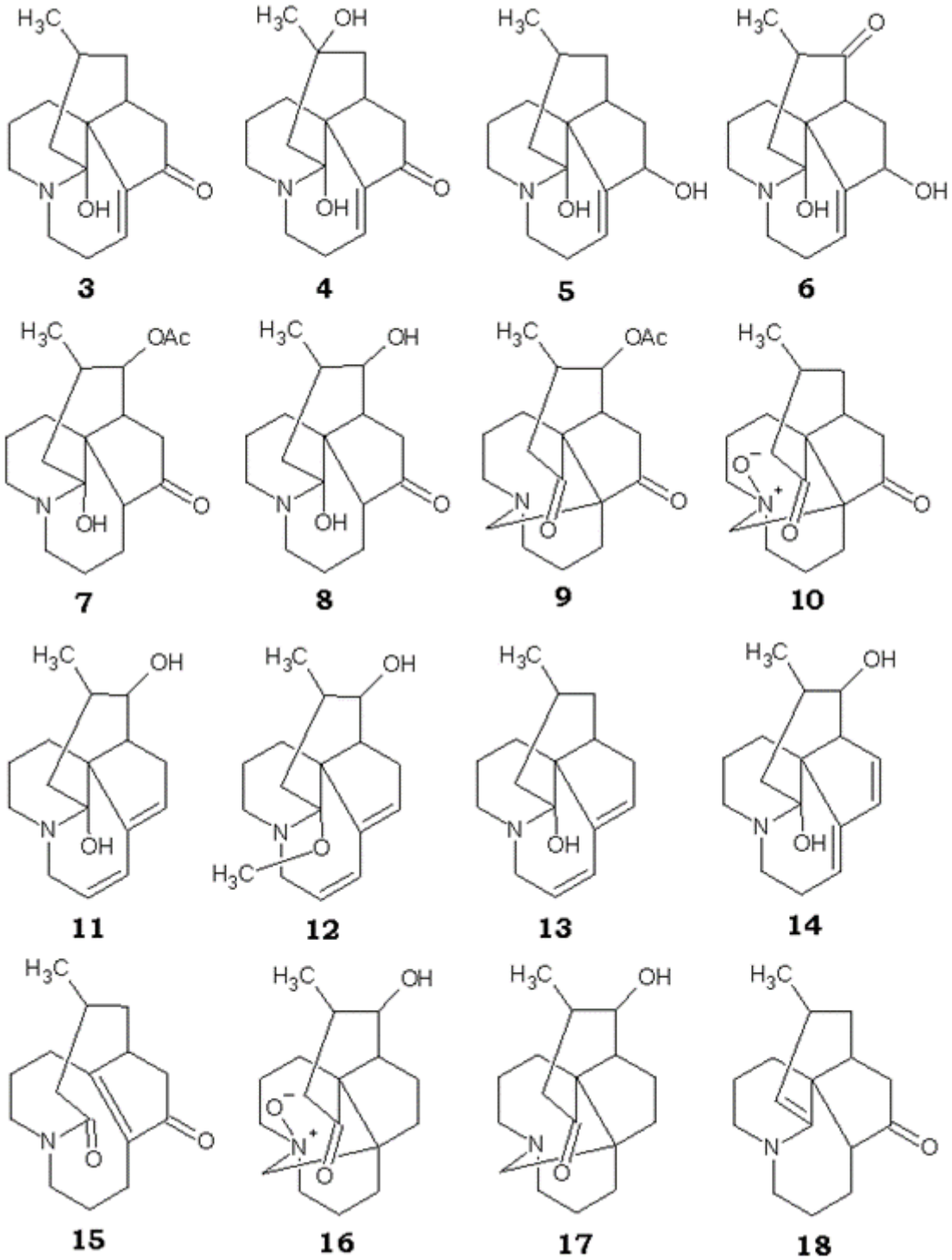

Figure 2: Recently isolated fawcettimine alkaloids (structures 3 to 18).

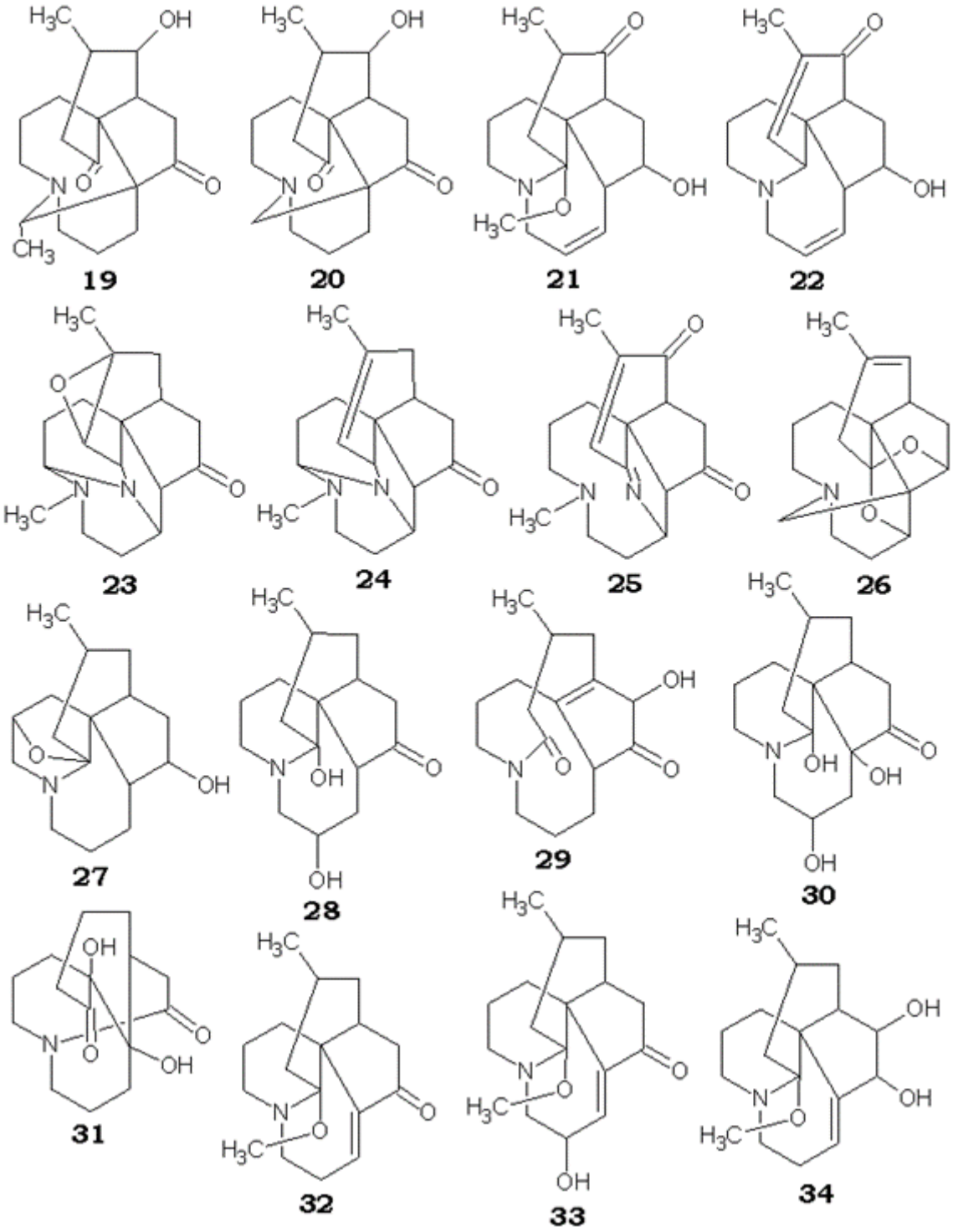

Figure 3: Recently isolated fawcettimine alkaloids (structures 19 to 34).

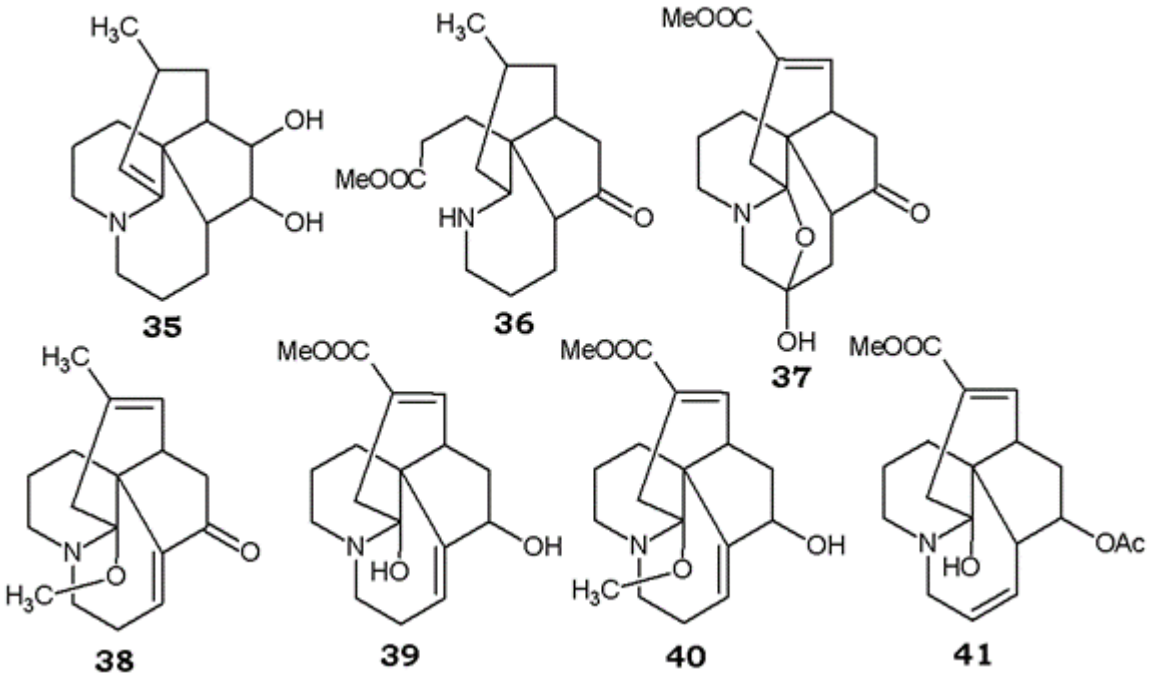

Figure 4: Recently isolated fawcettimine alkaloids (structures 35 to 41).

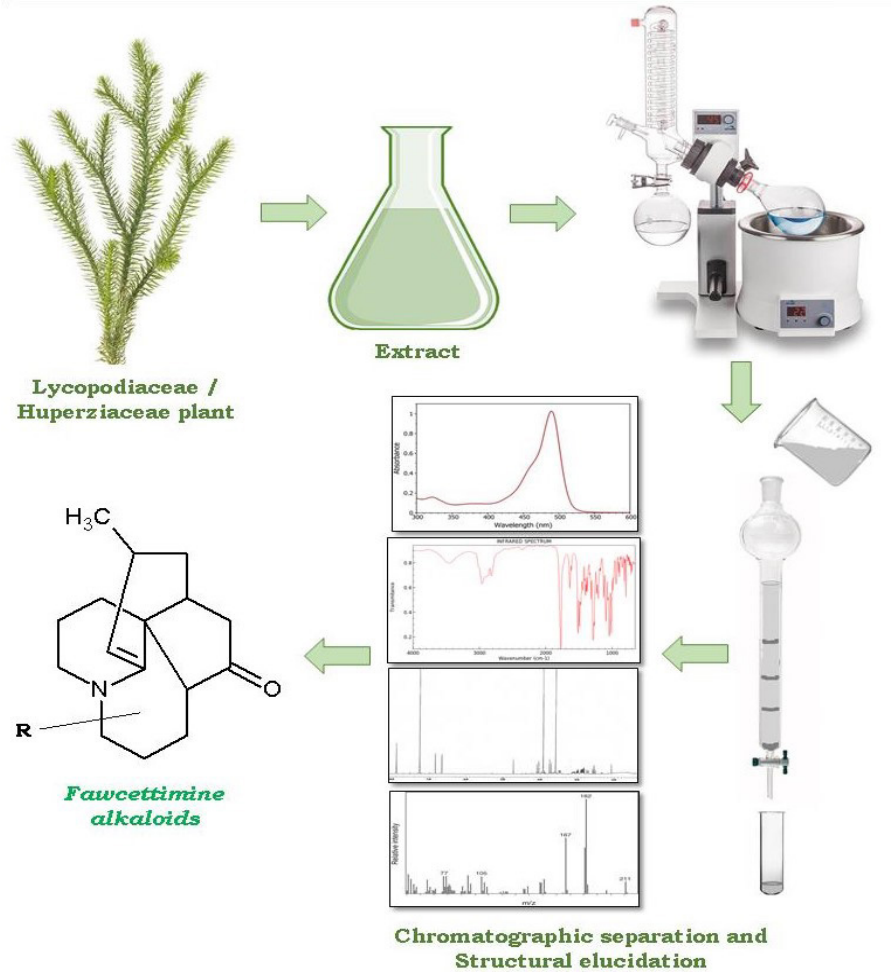

Figure 5: Isolation of fawcettimine alkaloids from Lycopodiaceae/ Huperziaceae plant.

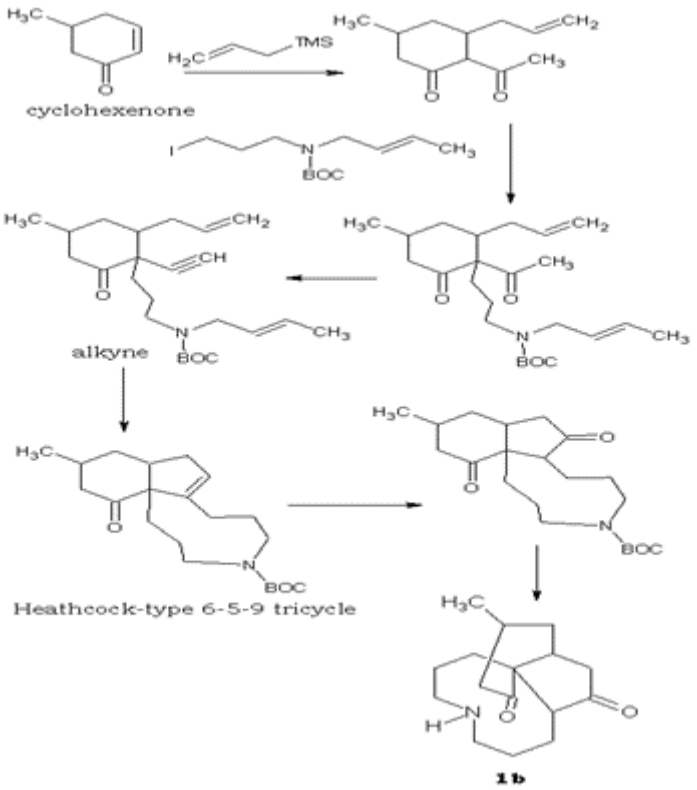

Figure 6: Total synthesis of fawcettimine (Yang *et al*. 2011).

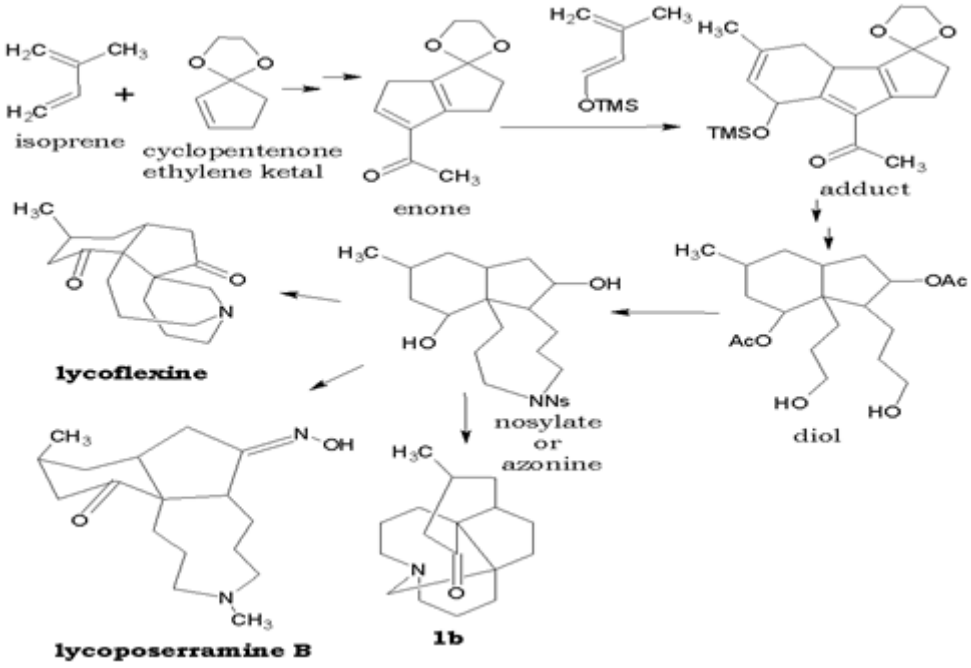

Figure 7: Total synthesis of fawcettimine, lycoposerramine B and lycoflexine (Pan *et al*. 2012).

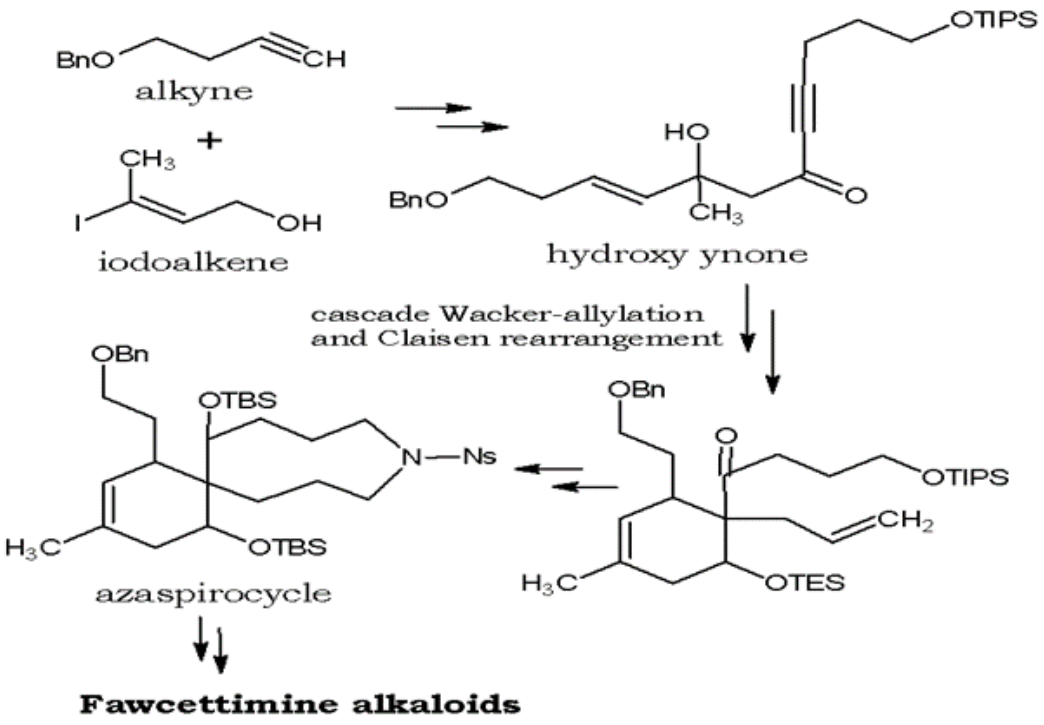

Figure 8: Total synthesis of fawcettimine alkaloids via azaspirocycle (Huang *et al*. 2018).

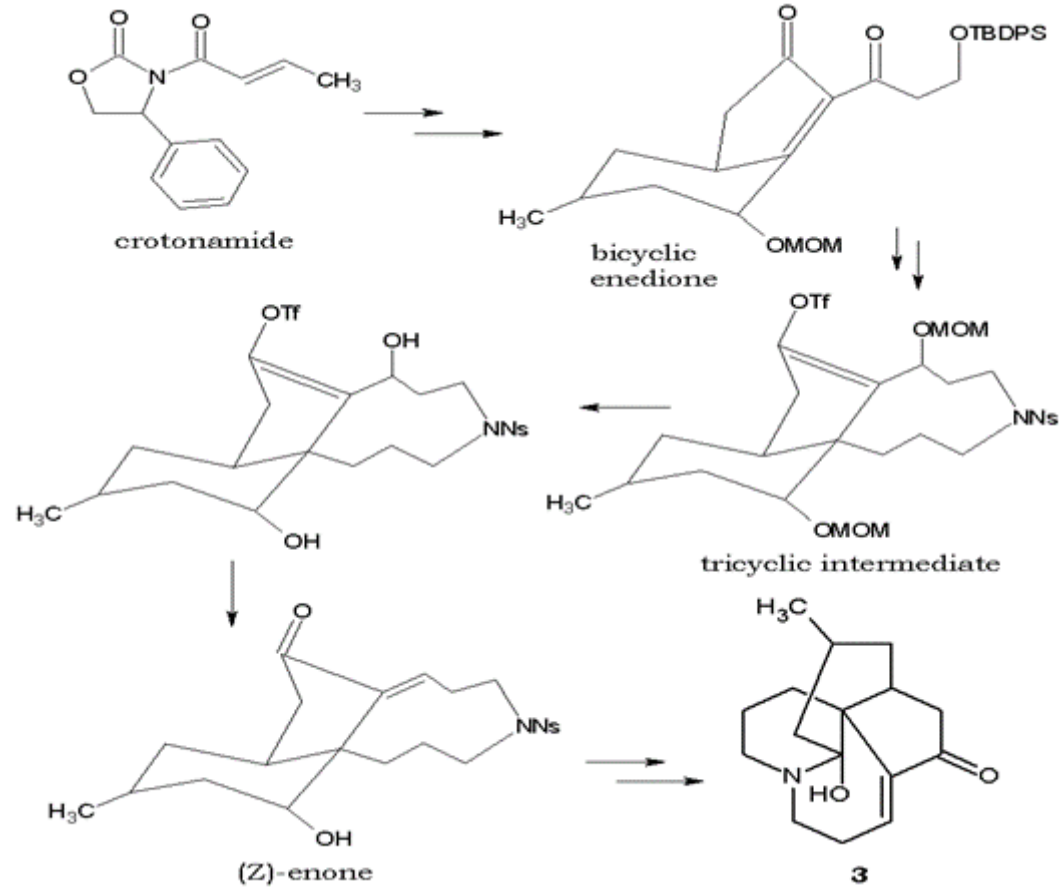

Figure 9: Total synthesis of Lycopoclavamine-A (Kaneko *et al*. 2019).

Table 1: Recently isolated fawcettimine alkaloids.

Alkaloid	Plant species	References
Lycopoclavamine-A (3)	*Lycopodium clavatum*	6
Lycopoclavamine-B (4)		
Dihydrolycopoclavamine-A (5)	*Lycopodium serratum*	
Lycoposquarrosamine-A (6)	*Lycopodium squarrosum*	
Acetylaposerratinine (7)		
8-hydroxyfawcettimine (8)		
Acetyllycoposerramine-U (9)		
Lycoflexine N-oxide (10)		
Huperserine A (11)	*Huperzia serrata*	7
Huperserine B (12)		
Huperserine C (13)		
Huperserine D (14)		
Fawcettimine (1)	*Huperzia carinata* and *Huperzia squarrosa*	8
Phlegmariurine B (15)		
Lycoflexine N-oxide (10)		
Lycoposerramine U N-oxide (16)		
8-epilycoposerramine U (17)	*Phlegmariurus squarrosus*	9
Fawcettidine (18)		
8b-hydroxy-17a-methyl-lycoflexine (19)	*Phlegmariurus squarrosus*	10
8b-hydroxylycoflexine (20)		
5-epi-13-methoxy lycoposquarrosamine A (21)		
15-epi-8-hydroxy lycoposerramine Q (22)		
Obscurumine H (23)	*Lycopodium obscurum*	11
Obscurumine I (24)		
Obscurumine J (25)		
Obscurumine K (26)		
Obscurumine L /M (27)		
Obscurumine N (28)		
6α-hydroxyphlegmariurine A (29)	*Phlegmariurus henryi*	12
2S,4R-dihydroxyfawcettimine (30)		
Lycoclavatumide (31)	*Lycopodium clavatum*	13
palhicerine A (32)	*Palhinhaea cernua*	14
palhicerine B (33)		
palhicerine C (34)		
palhicerine D (35)		
Lycoannotine I (36)	*Lycopodium annotinum*	15
Lycogladine A (37)	*Lycopodium complanatum* var. *glaucum* Ching	16
Lycogladine B (38)		
Lycogladine C (39)		
Lycogladine D (40)		
Lycogladine E (41)		

CONCLUSION AND FUTURE PROSPECTS

Fawcettimine is one of the types of Lycopodium alkaloids. Number of alkaloids isolated (those from fawcettimine class) indicates that it is a prominent group of alkaloids, so far isolated from Lycopodiaceae or Huperziaceae plants. Only few of them have been found active as AChE inhibitor and thereby use in treatment of related diseases, unlike lycopodine-type alkaloids. But, based on results of molecular docking studies of leads active as AChE inhibitor, new analogues or derivatives of already existing fawcettimine alkaloids with necessary functional groups could be attempted for total synthesis and further evaluated for AChE inhibition. Reviewing the synthetic approaches explored for fawcettimine alkaloids, it is clear that synthesis can be started with various small and simple molecules; however, further it includes several critical and complex steps. Protective groups and catalysts also play very important role.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AChE: Acetyl choline esterase; **BuChE:** Butyryl choline esterase; **PKR:** Pauson–Khand reaction; **CBS:** (S)-Corey–Bakshi–Shibata reagent; **TBDPS:** Tert-butyl diphenyl silyl; **MOM:** Methoxymethyl acetal.

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