Supporting Information

Discovery, Bioactivities and Biosynthesis of the Spirooxindole Alkaloids

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Content

Figure S1. SOAs from *Mitragyna*/*Uncaria* genus (before 2023)

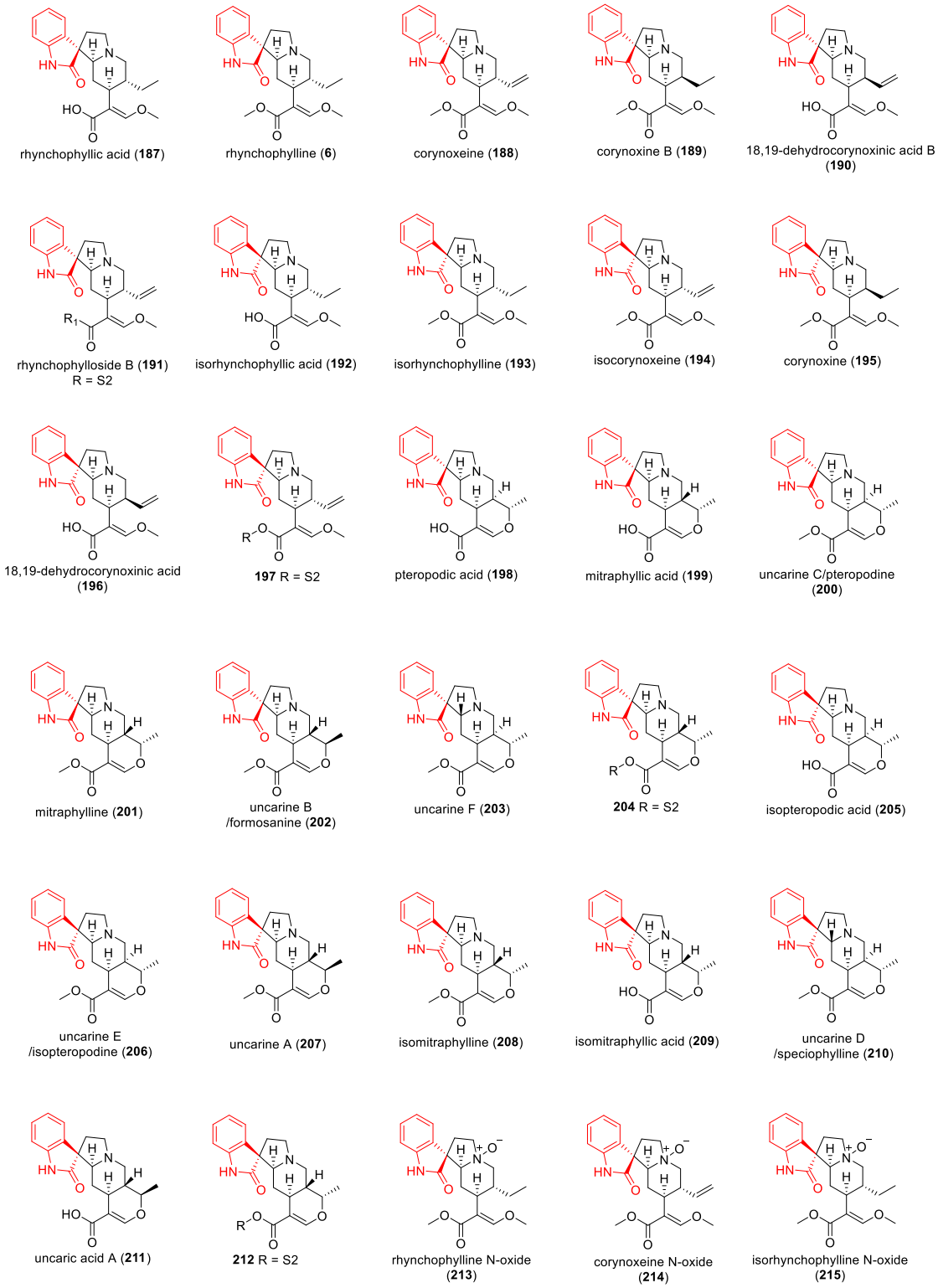


Figure S1. SOAs from *Mitragyna*/*Uncaria* genus (before 2023) (continued)

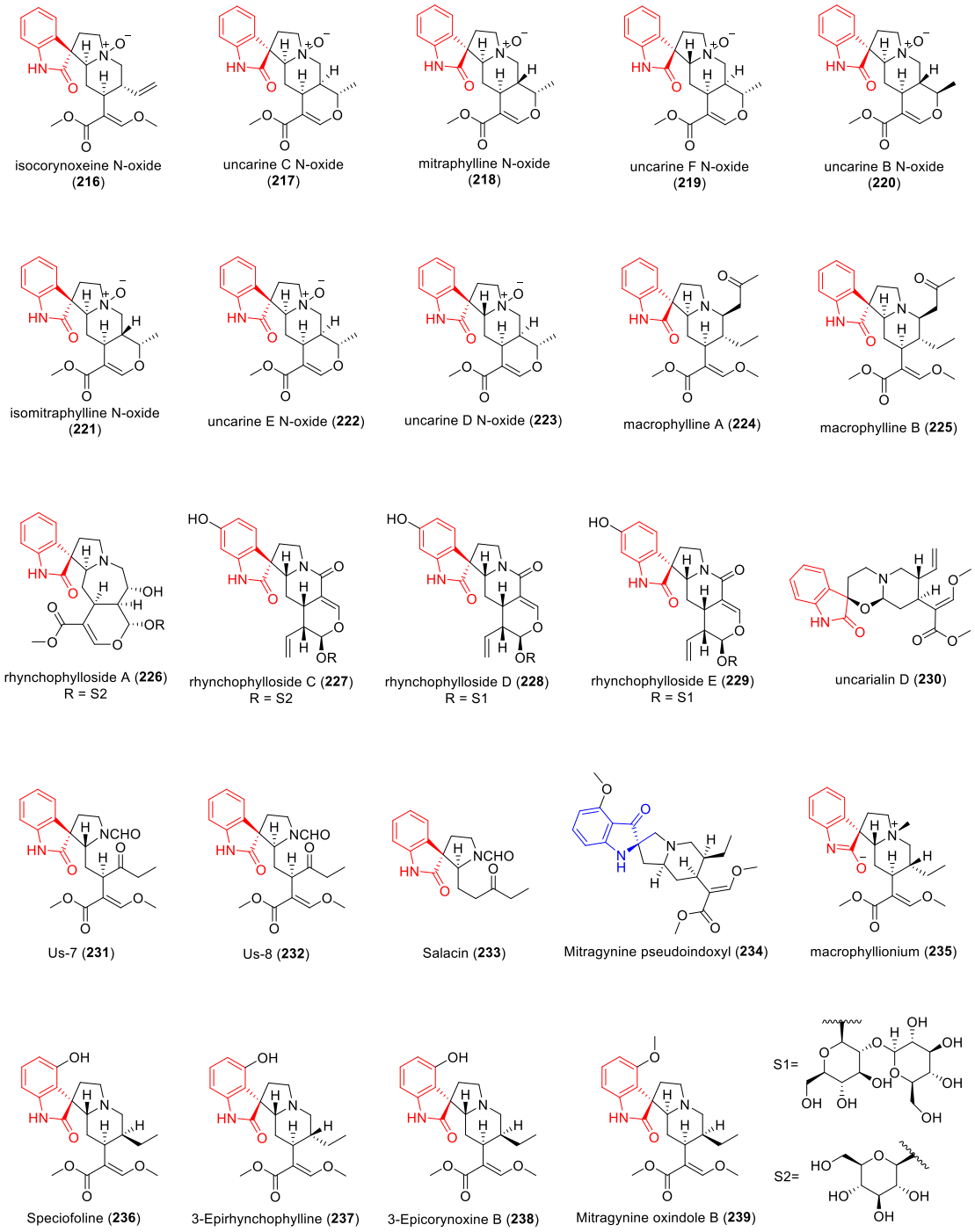


Figure S2. SOAs from *Gelsemium* genus (before 2023)

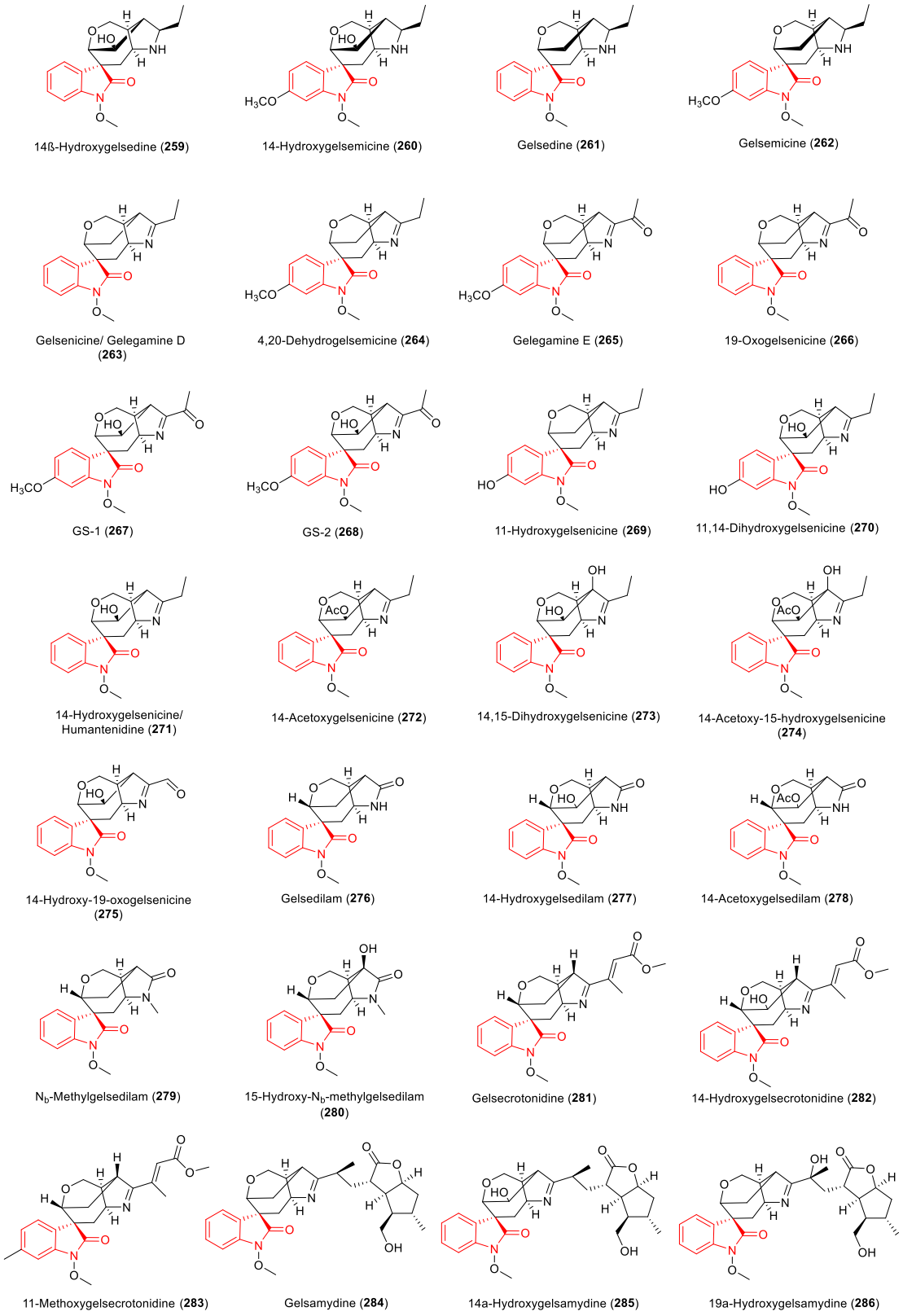


Figure S2. SOAs from *Gelsemium* genus (before 2023) (continued)

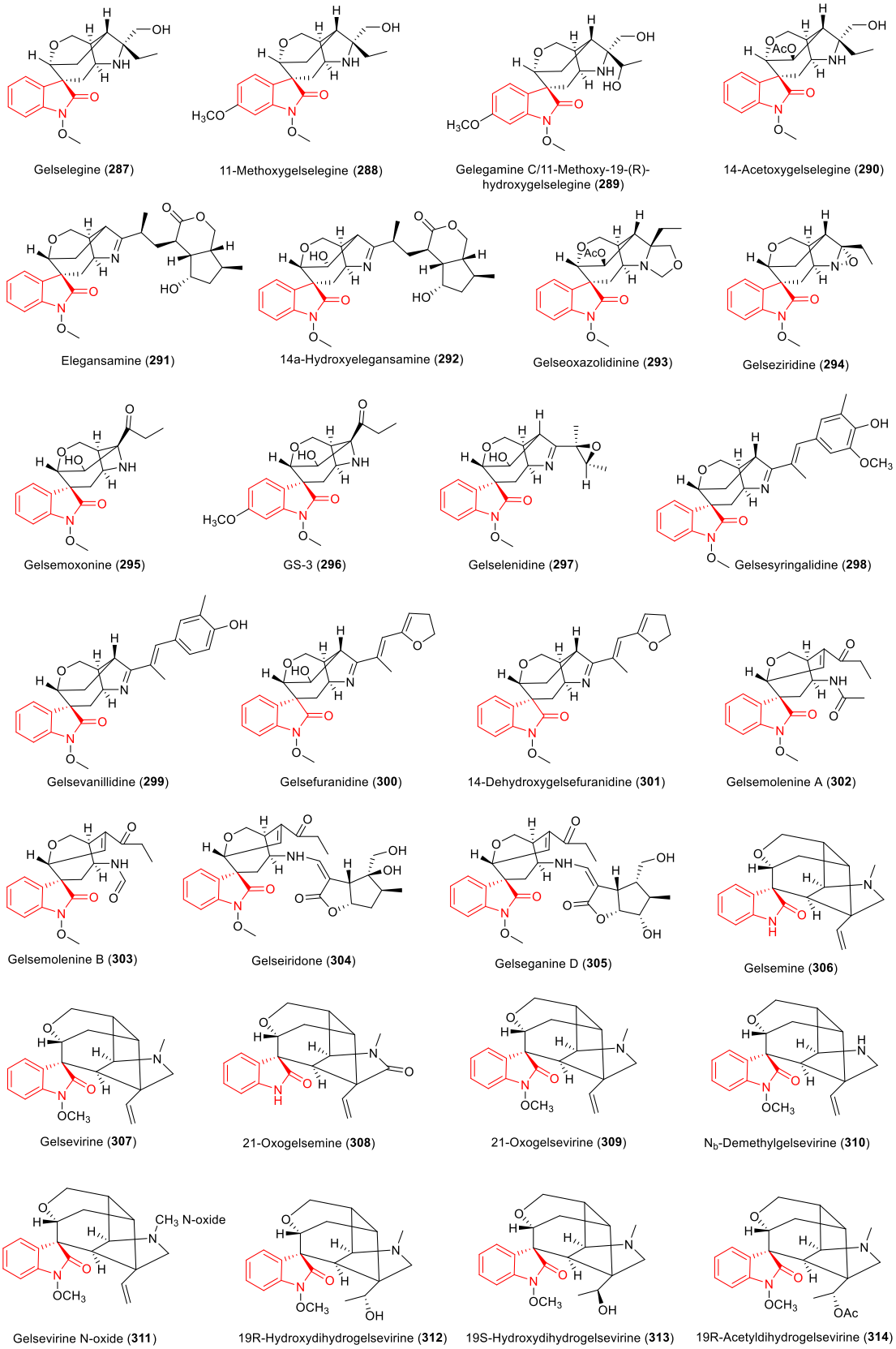
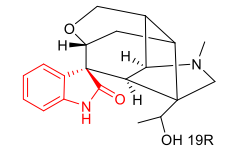
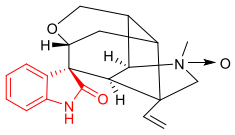
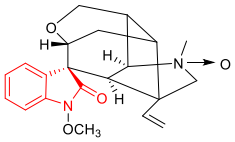
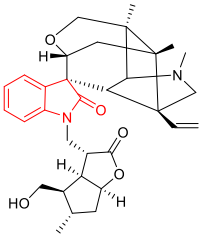


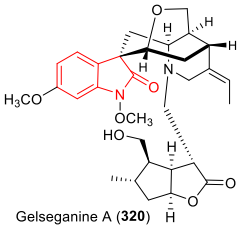
Figure S2. SOAs from *Gelsemium* gnus (before 2023) (continued)

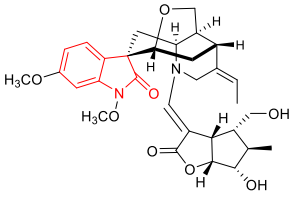

19R-Hydroxydihydrogelsemine (**315**)


4S- Gelsemine N-oxide (**316**)
4R- Gelsemine N-oxide (**317**)


4R-Gelsevirine N4-oxide (**318**)


Gelsebanine (**319**)


Gelseganine A (**320**)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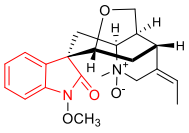
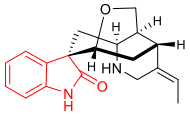
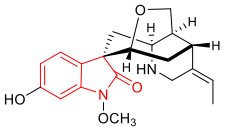

Humantenine N4-oxide (**322**)


N-Desmethoxyrankinidine (**323**)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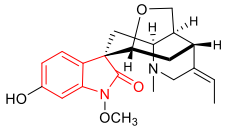
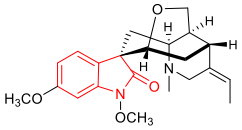

11-Hydroxyhumantenine (**325**)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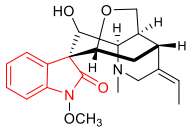
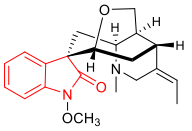

6-Hydroxyhumantenine (**327**)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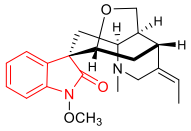
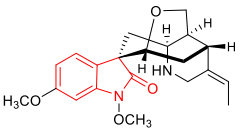
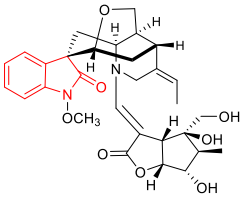

Humantenine (**329**)


Humantenirine (**330**)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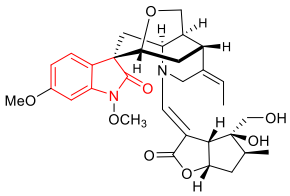
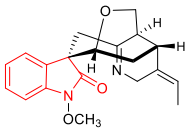
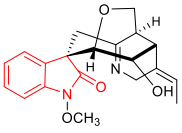
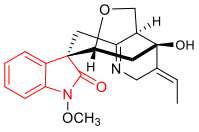
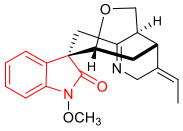
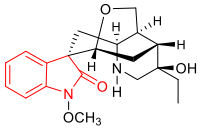

Humanteniridine (**332**)

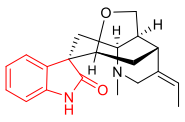

4,5-Dehydrorankinidine (**333**)

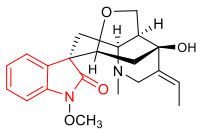

14-Hydroxyrankinidine (**334**)

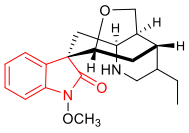

15-Hydroxyrankinidine (**335**)

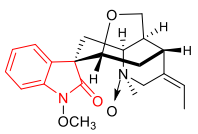

Rankinidine (**336**)

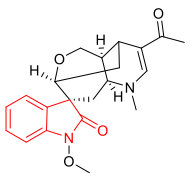

20-Hydroxydihydrorankinidine (**337**)


N-Desmethoxyhumantenine (**338**)


15-Hydroxyhumantenine (**339**)


19,20-Dihydrorankinidine (**340**)


(4R)-Humantenine N_4-oxide (**341**)


Humantenoxenine (**342**)

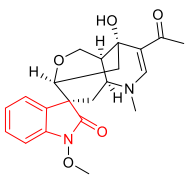
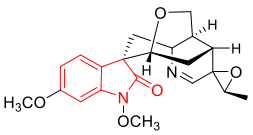
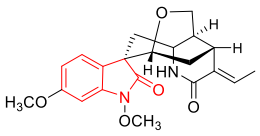

15-Hydroxyhumantenoxenine (**343**)

Figure S2. SOAs from *Gelsemium* genus (before 2023) (continued)



Gelegamine A (**344**)



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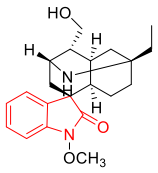

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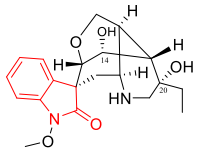
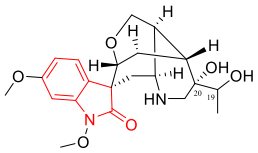
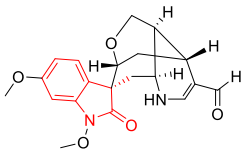


14ß,20a-dihydroxydihydrorankinidine (**347**)



11-methoxy-19,20a-dihydroxydihydrorankinidin (**348**)



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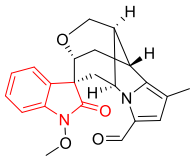

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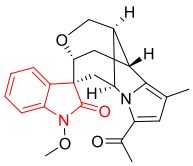

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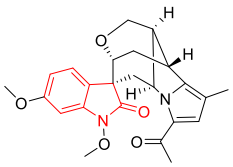

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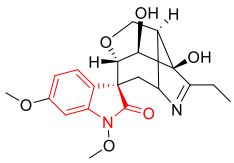
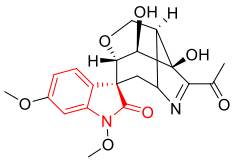


11-methoxy-14,15-dihydroxyhumantenmine (**353**)



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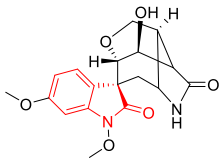

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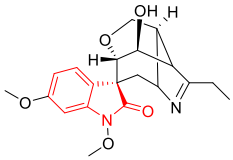
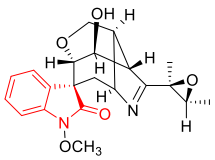
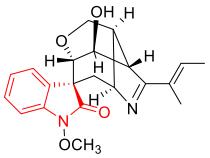


11-methoxy-14-hydroxyhumantenmine (**356**)



14b-hydroxygelselenidine (**357**)



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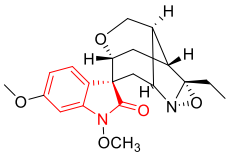

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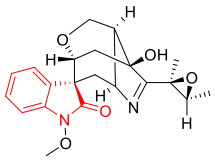
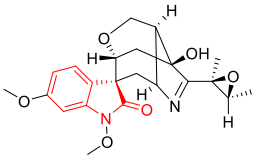


gelseleganin A (**360**)



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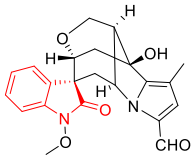

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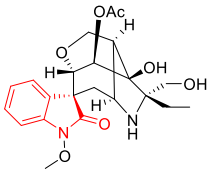

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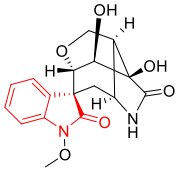

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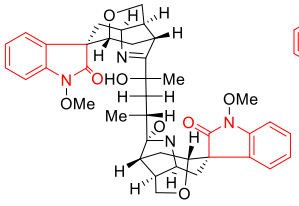
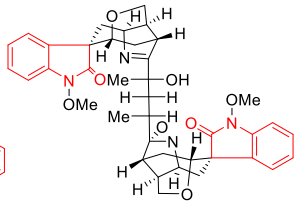
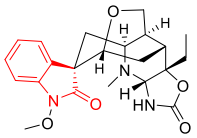


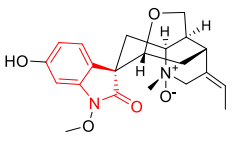
geleganimine A (**365**)



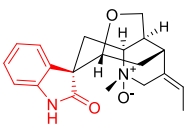
geleganimine B (**366**)



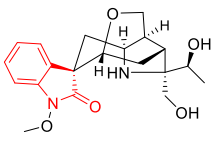
gelstriamine A (**367**)



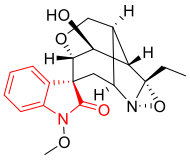
11-hydroxyhumantenine N_4-oxide (**368**)



N-Desmethoxyhumantenine N_4-oxide (**369**)



19-hydroxygelselegine (**370**)



14-hydroxygelseziridine (**371**)

Figure S2. SOAs from *Gelsemium* genus (before 2023) (continued)

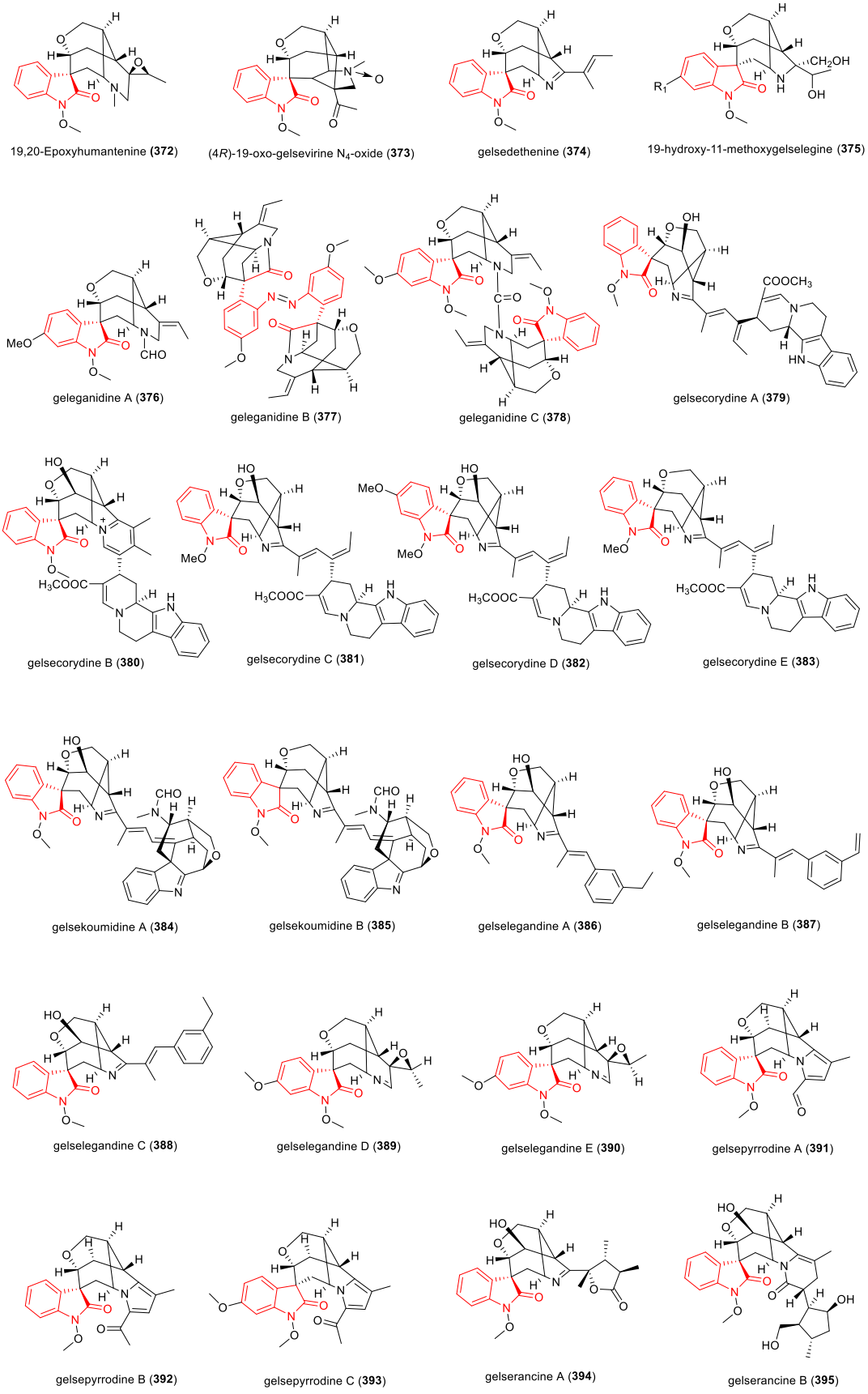
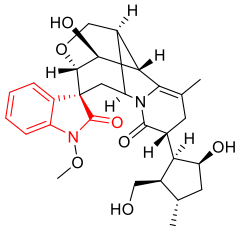
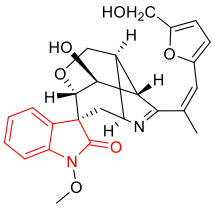


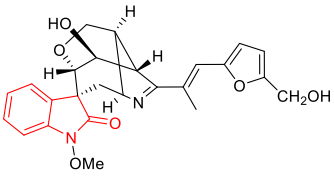
Figure S2. SOAs from *Gelsemium* genus (before 2023) (continued)



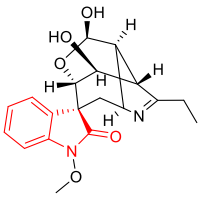
gelserancine C (**396**)



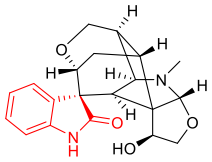
gelserancine D (**397**)



gelserancine E (**398**)

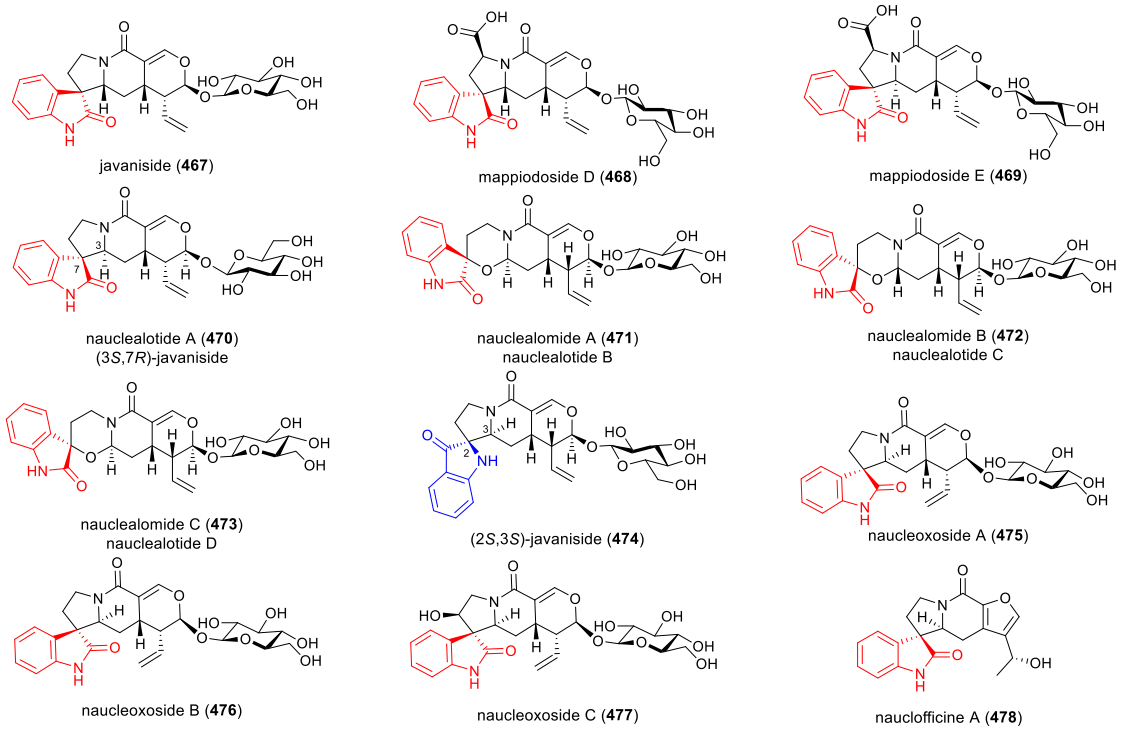


gelsevietmine A (**399**)



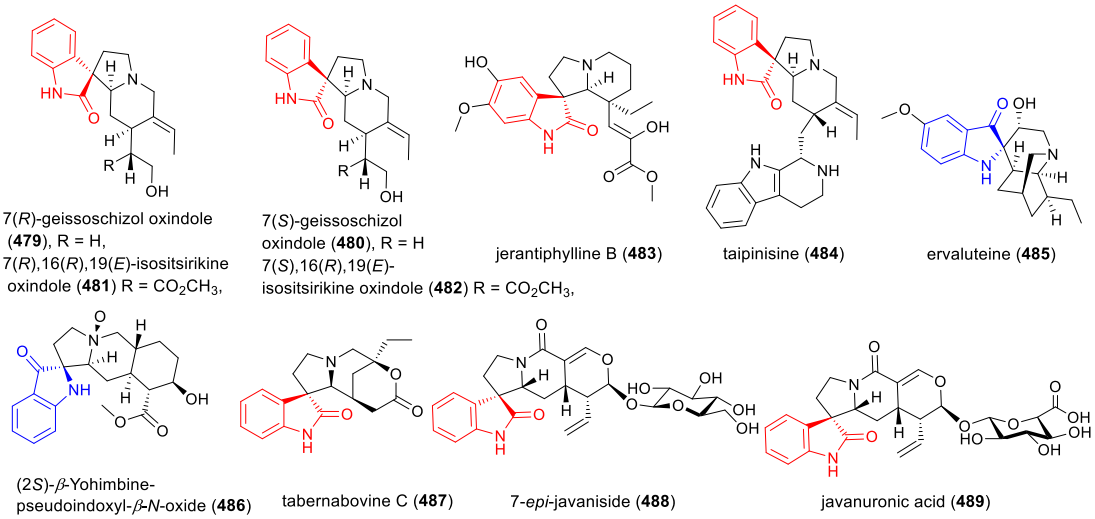
gelsevietmine C (**400**)

Figure S3. SOAs from *Alangium*, *Mappiodoside* and *Nauclea*



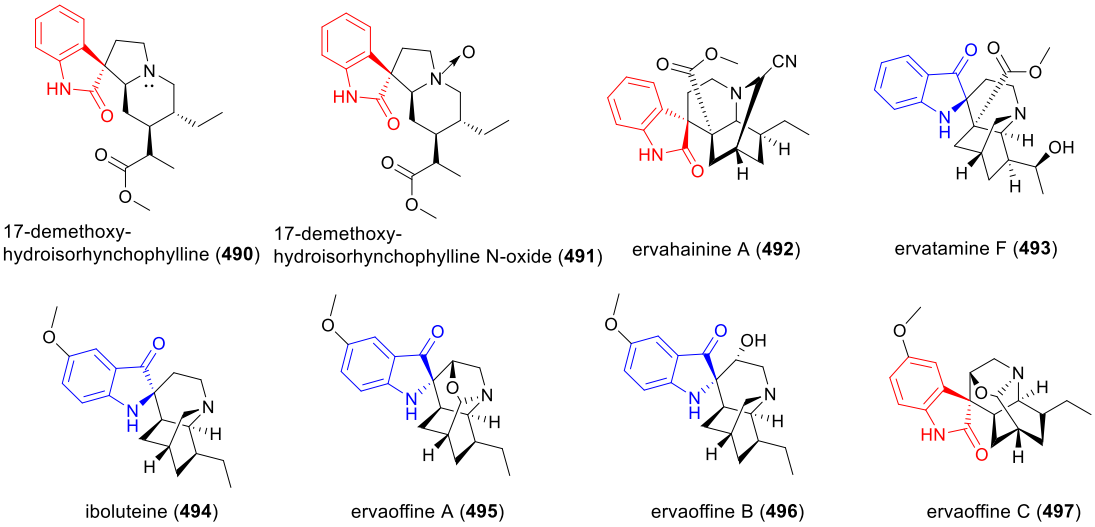
The genus *Alangium*, belonging to the Alangiaceae family, has traditionally been used as folk medicine to treat rheumatism.[1] The genus *Mappianthus* (Icacinaceae family) consists of three species which are distributed in subtropical and tropical regions.[2] The genus *Nauclea* (Rubiaceae) is widely used as the traditional Chinese medicine. Although these genera are distinct, the SOAs they produced exhibit similar skeletal structures. In 2004, Ma and Hecht isolated F 2-oxoindole alkaloid javaniside (**467**) rom *A. javanicum*.[3, 4] Mappiodosides D (**468**) and E (**469**) were isolated from the stems of *M. iodoides*, with **468** was closely related to **467** except for the existence of a carboxyl group at C-5.[2] Nauclealotide A (**470**), also named (3S,7R)-javaniside, was isolated from *N. officinalis*.[5, 6] Nauclealomide A (**471**) was isolated in 2015, possessing a rare tetrahydro-2H-1,3-oxazine ring.[5] Nauclealomides B (**472**) and C (**473**) were also isolated from *N. officinalis,* and their planar structures were identical to that of **471**.[7] In 2022, (2*S*,3*S*)-javaniside (**474**) was isolated from the stems of *N. officinalis*,[8] and naucleoxoside A-C (**475-477**) were identified in rat plasma after oral administration of total alkaloids extracted from *N. officinalis*.[9] In 2025, naucloffícine A (**478**) possessing a monoterpenoid 2-oxindole core structure, a spiro B/C moiety, and a furan E ring, was isolated from *N. officinalis*.[10]

Figure S4. SOAs from *Tabernaemontana*



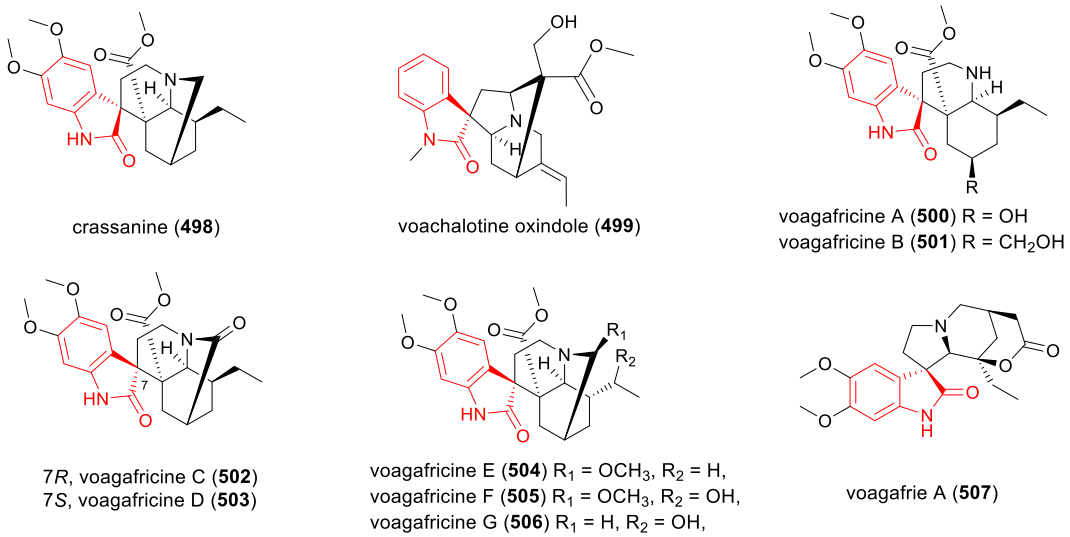
The genus of *Tabernaemontana* (Apocynaceae) is a prolific source of the monoterpene indole alkaloids, known to produce a variety of skeletal types, including secotabersonine alkaloids, bisvobtusine-type alkaloids, and bis-vobasinyl-ibogan indole alkaloids.[11] In 2009, Kam's group isolated four tetracyclic oxindole alkaloids from the Malayan *T. corymbose*, including 7(*R*)- and 7(*S*)-geissoschizol oxindole (**479** and **480**), 7(*R*),16(*R*)- and 7(*S*),16(*R*)-19(*E*)-isositsirikine oxindole (**481** and **482**).[12] In the same year, they also discovered jerantiphylline B (**483**).[13] Later, in 2014, they isolated the bisindole alkaloid taipinsine (**484**) and proposed the oxindole half of this heterodimer was a tetracyclic corynanthean oxindole with an ethylidene side chain, while the other partner, derived from tryptamine, was a tetrahydro-*β*-carboline.[14] In 2015, Kam and co-workers isolated ervaluteine (**485**), a 6-hydroxy derivative of ibogaine pseudoindoxyl.[15] (2*S*)-*β*-Yohimbine-pseudoindoxyl-*β*-*N*-oxide (**486**), an oxidation products of *β*-yohimbine, was isolated from the leaves of *T. corymbosa*.[16] In 2019, tabernabovine C (**487**) was isolated from the leaves of *T. bovina*, and exhibited a bridged ring.[17] In 2023, avaniside derivatives 7-*epi*-javaniside (**488**) and javanuronic (**489**) were isolated from the methanolic leaf extract of *T. peduncularis*.[18]

Figure S5. SOAs from *Ervatamia*



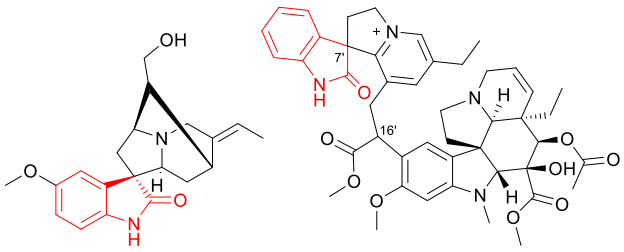
Apart from the genera *Alstonia* and *Tabernaemontana*, the genus *Ervatamia* is also belonging to the Apocynaceae family, and many of which have long been used in Traditional Chinese Medicine.[19] In 1999, 17-demethoxy-hydroisorhynchophylline (**490**) and 17-demethoxy-hydroisorhynchophylline *N*-oxide (**491**) were isolated from *E. yunnanensis* by Liu and co-workers.[19] In 2013, ervahainine A (**492**), a new cyano-substituted oxindole alkaloid, was isolated from *E. hainanensis*. The structure was confirmed by X-ray diffraction analysis.[20] In 2015, ervatamine F (**493**) was isolated from *E. hainanensis* by Gao and co-workers, and was 19-hydroxycoronaridine pseudoindoxy.[21] Additionally, Iboluteine (**494**) and ervaoffines A-C (**495-497**), new iboga-type derivatives, were isolated from the twigs and leaves of *E. officinalis*.[22]

Figure S6. SOAs from *Voacanga*



The genus *Voacanga* also belongs to Apocynaceae family. In 1968, crassanine (**498**) was first isolated from *T. crassa.*[23] In 2024, Qin et al isolated **498** from *V. Africana* and suggested that it could serve as a chemotaxonomic markers to distinguish this genus from other plant species in the family.[24] In 1969, voachalotine oxindole (**499**) was isolated from *V. chalotiana* by Braekman and co-workers.[25] In 2023, Qin et al isolated seven rare SOAs, voagafricines A-G (**500**–**506**), from the stem barks of *V. africana*. These compounds feature a unique 6/5 indoleone ring system conjugated with a 3,4′-decahydroquinoline spiral ring, derived from a secoquinolhiddin core.[26] In 2025, Ding et al. isolated voagafricine A (**507**) from V. africana, which possessed a unique 6/5/5/6/6 spiral ring with an indolone-fused 9-oxo-3aza-tricyclo[6,3,1,03,7]-12-alkane-10-carbonyllactone.[27]

Figure S7. SOAs from *Catharanthus*

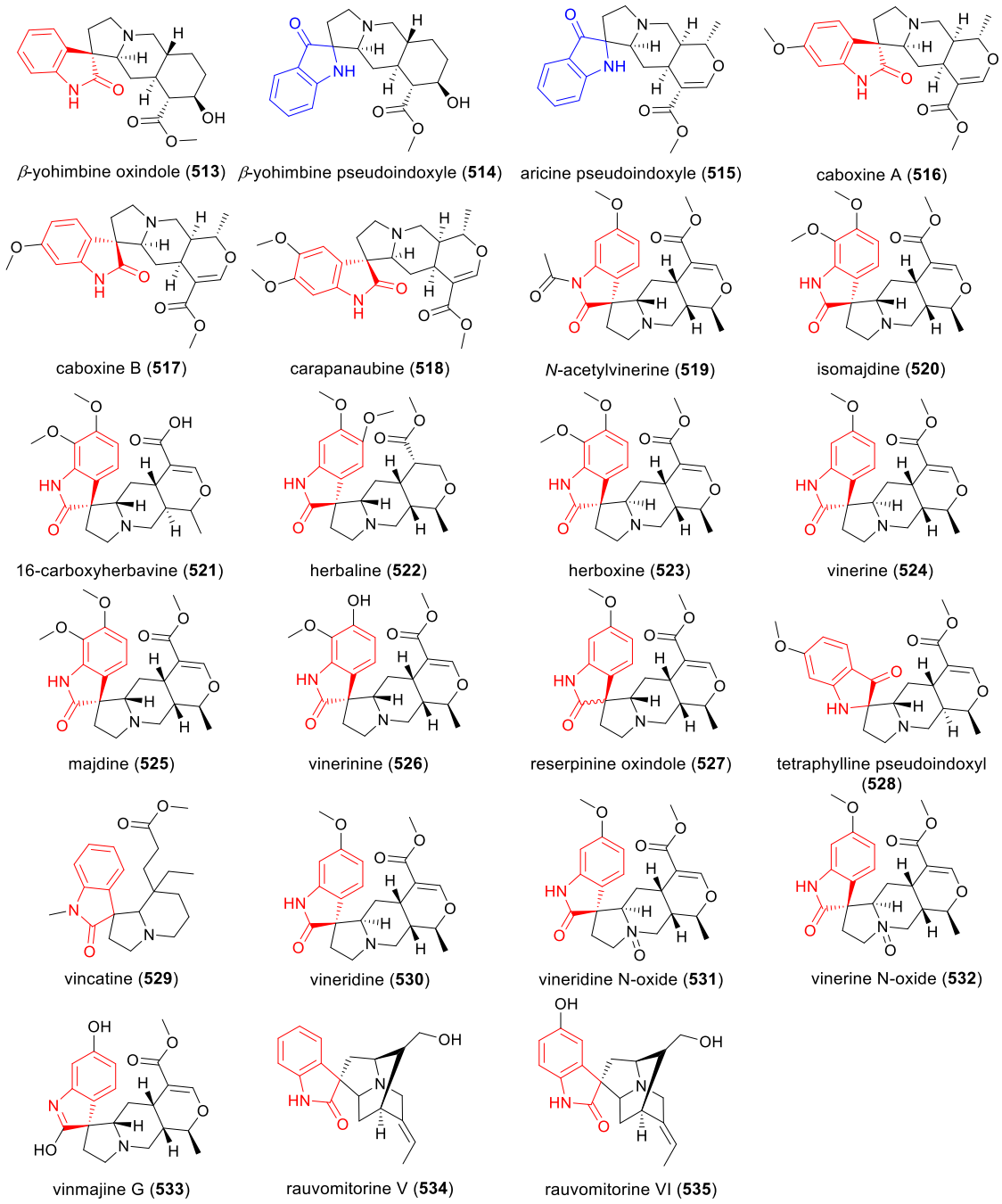


catharanosine A (**508**)

	C-7'	C-16'
cathagine A (**509**)	*R*	*R*
cathagine B (**510**)	*R*	*S*
cathagine C (**511**)	*S*	*R*
cathagine D (**512**)	*S*	*S*

SOAs have been rarely reported in the *Catharanthus* genus until now. In 2021, catharanosine A (**508**) was isolated from the twigs and leaves of *C. roseus,*.[28] In 2025, cathagine A-D (**509-512**) consisting of an aspidosperma and the fused tetracyclic 3-spirooxindole derived from an iboga type skeleton were isolated from the whole plant of *C. roseus* by Hirasawa et al[29]

Figure S8. SOAs from *Aspidosperma*, *Vinca* and *Rauvolfia*



The SOAs from genera *Aspidosperm, Vinca, and Rauvolfia* share nearly identical core structures. In 1983, *β*-yohimbine oxindole (**513**), ß-yohimbine pseudoindoxyle (**514**), and aricine pseudoindoxyle (**515**) were isolated from the seeds of *A. oblongum,*.[30] the absolute configuration of the spiro center in **514** and **515** remain uncertain. In 2011, caboxine A (**516**) and B (**517**), carapanaubine (**518**) were isolated from *A. rigidum* and

A. schultesii.[31] SOAs **516-518** were also isolated from *Vinca* and *Rauvolfia* genera.[32, 33] Besides, compounds **519-535** (Figure S3) were isolated from these genera as documented in the reviews by Vrabec et al[32] and Sunil et al[33].

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