Electronic Supplementary Information (ESI)

Structural Diversity and Chemical Logic Underlying the Assembly of Monoterpene Indole Alkaloids Oligomers

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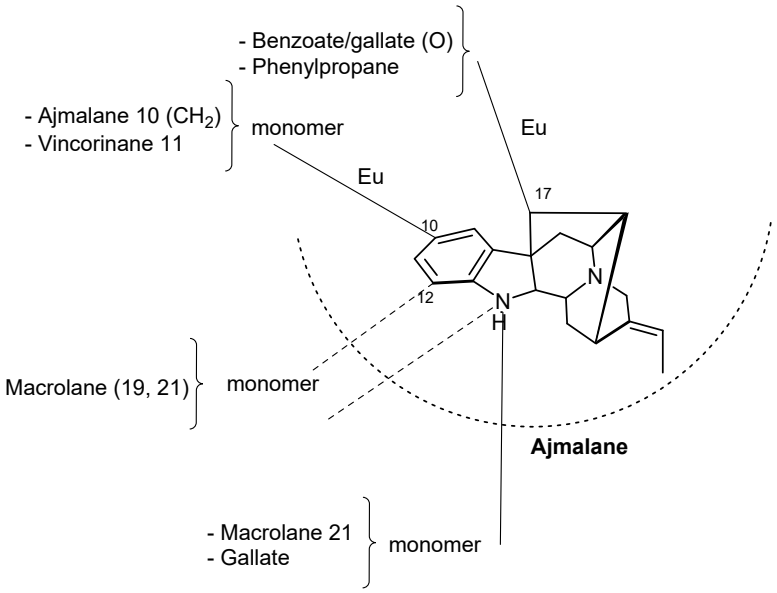
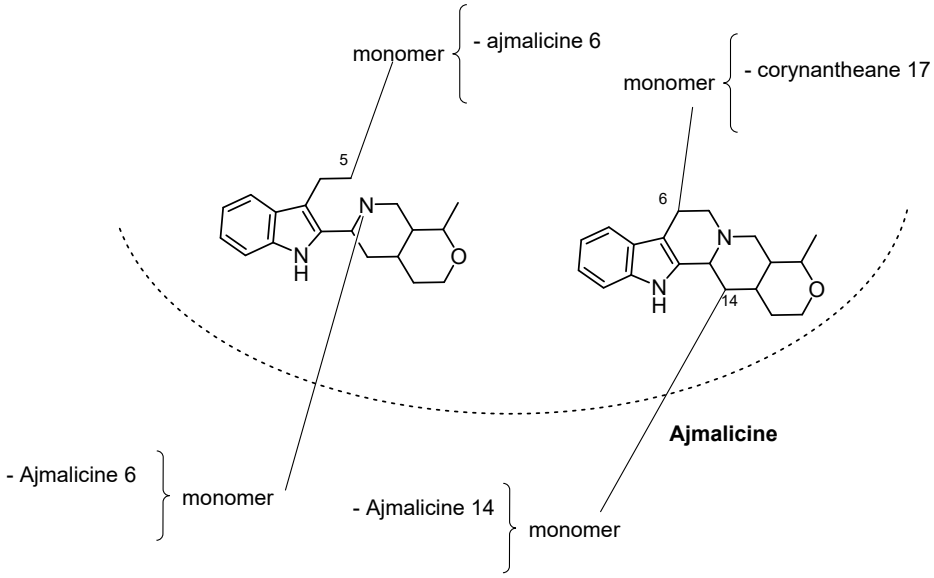
Summary

1 Bridging sites by skeleton

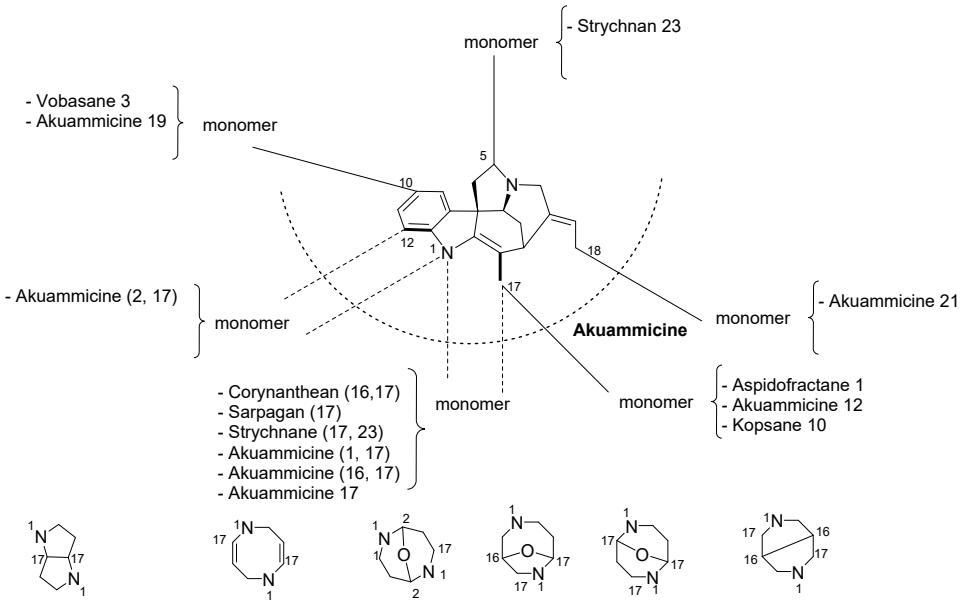
1.1 Ajmalane skeleton reactivity mapping



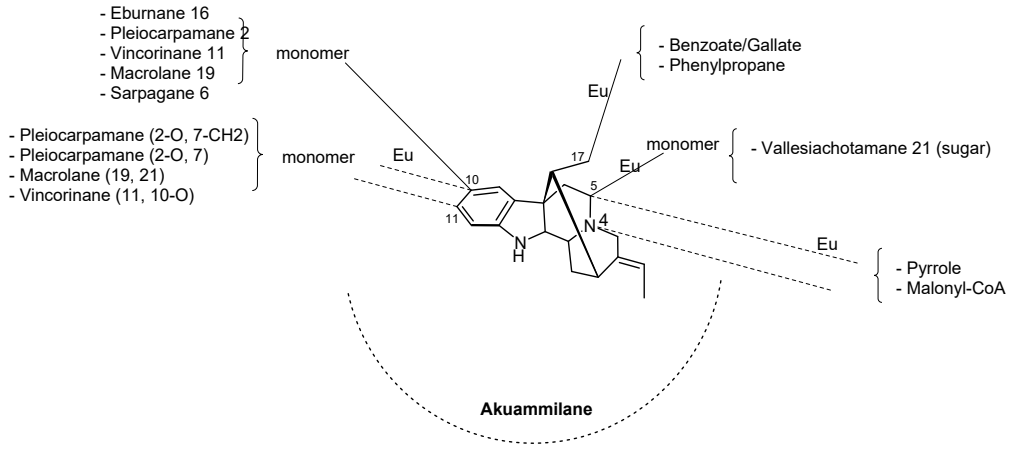
1.2 Ajmalicine skeleton reactivity mapping



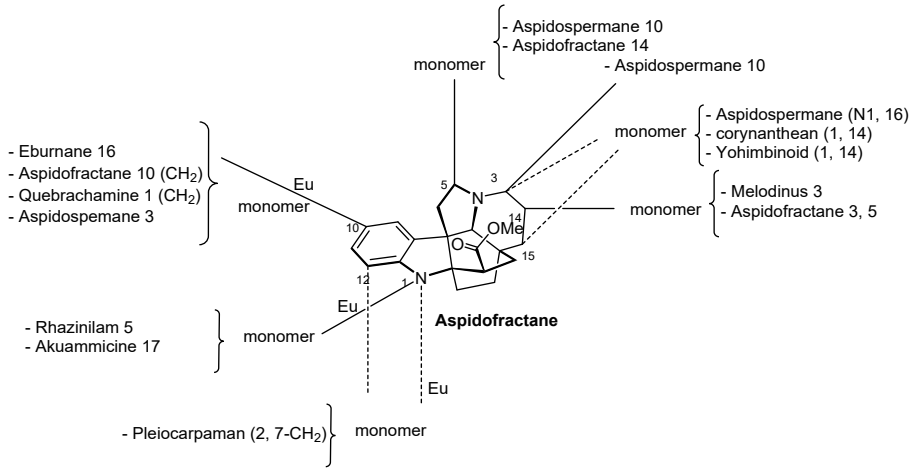
1.3 Akuammicine skeleton reactivity mapping



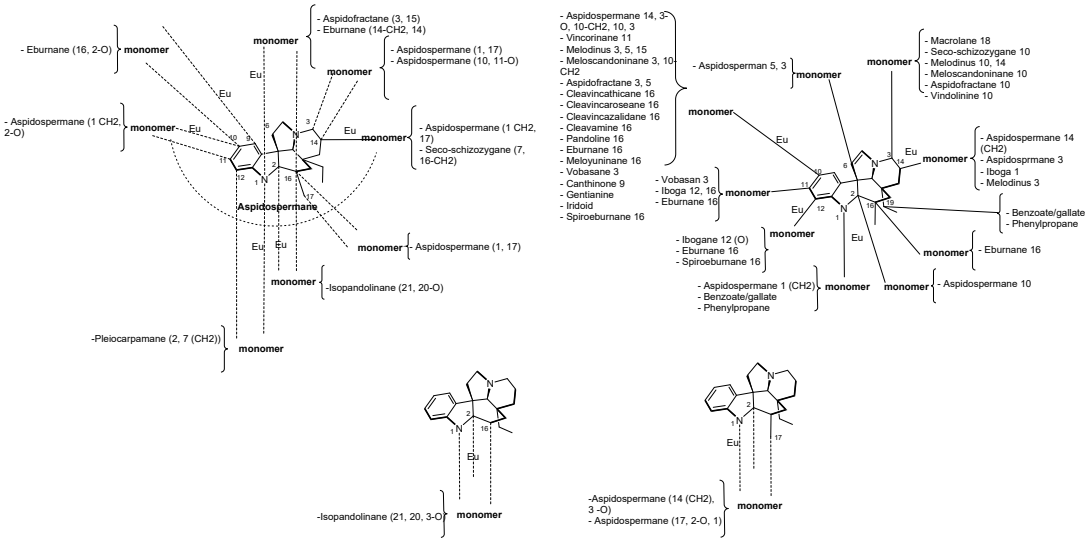
1.4 Akuammilane skeleton reactivity mapping



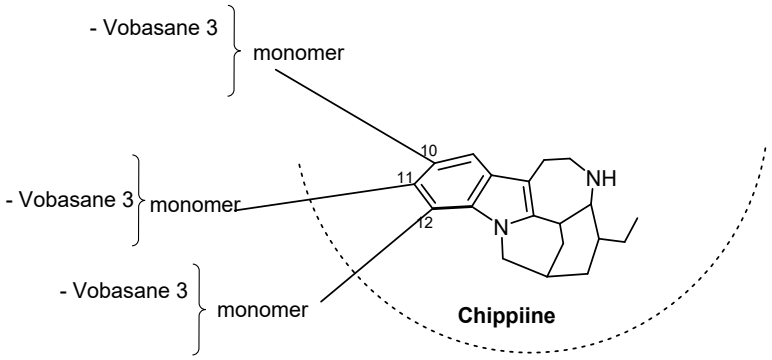
1.5 Aspidofractane skeleton reactivity mapping



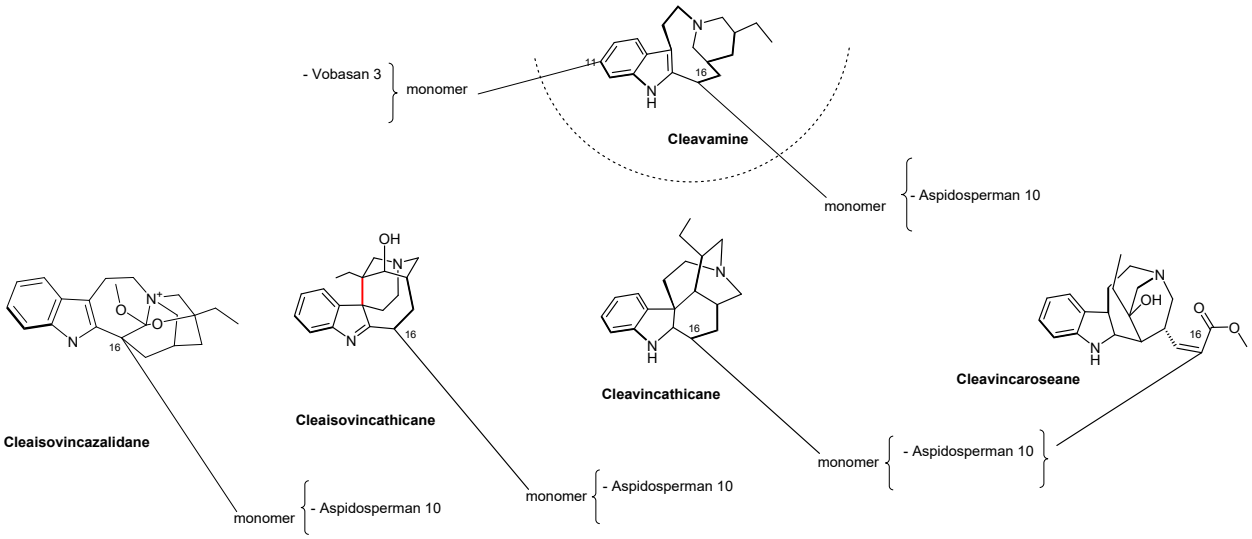
1.6 Aspidospermane skeleton-cotaining based oligomers



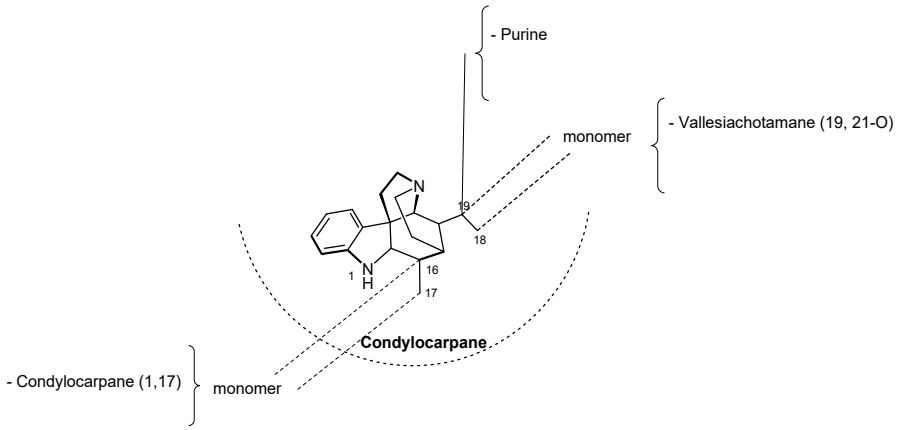
1.7 Chippiine skeleton reactivity mapping



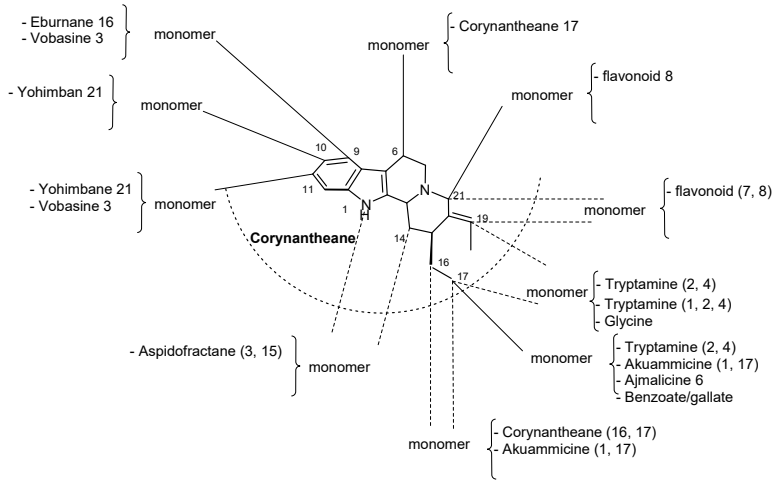
1.8 Cleavamine skeleton and its derivatives reactivity mapping



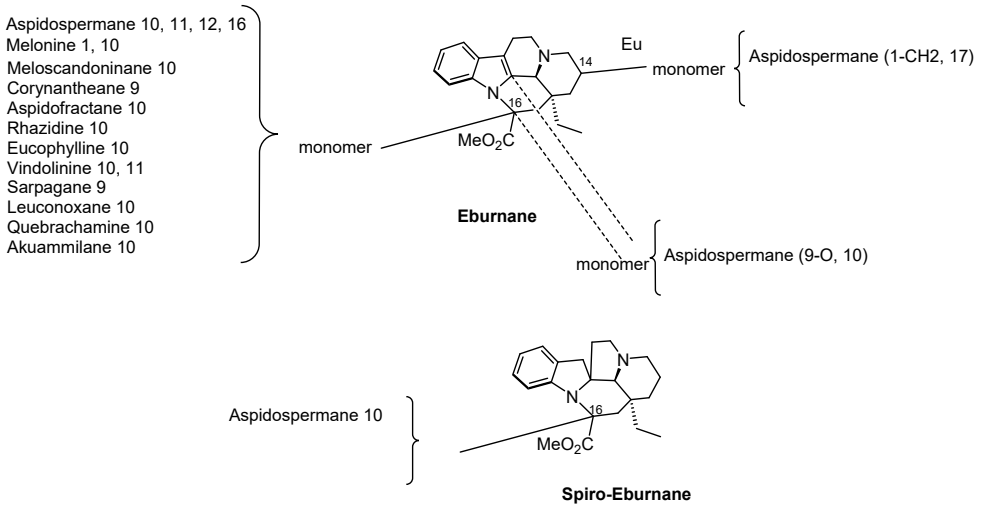
1.9 Condylocarpane skeleton reactivity mapping



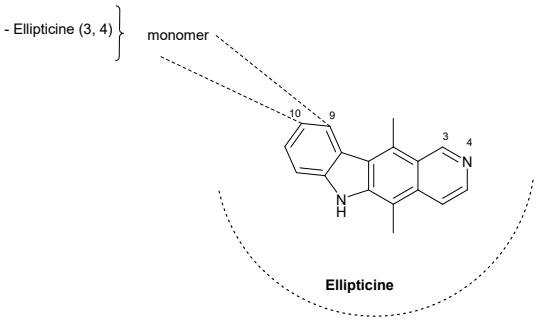
1.10 Corynantheane skeleton reactivity mapping



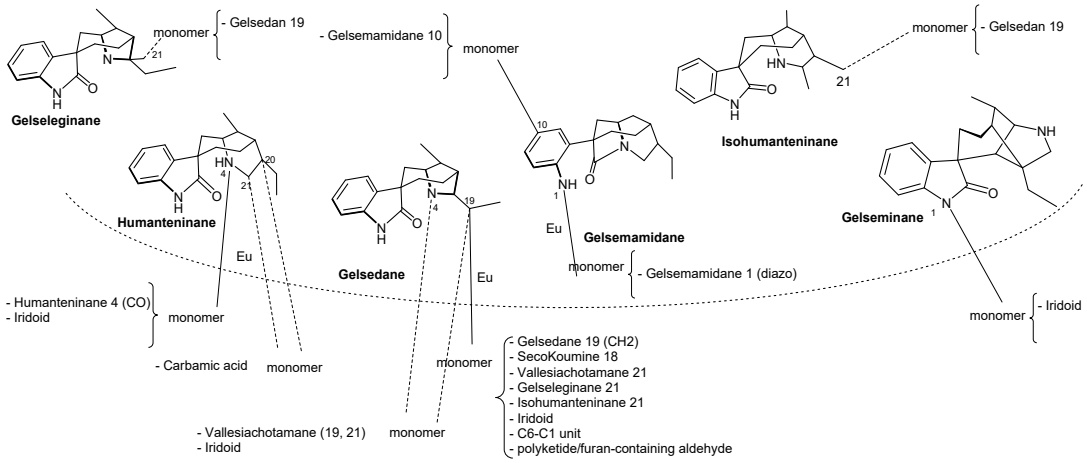
1.11 Eburnane skeleton reactivity mapping



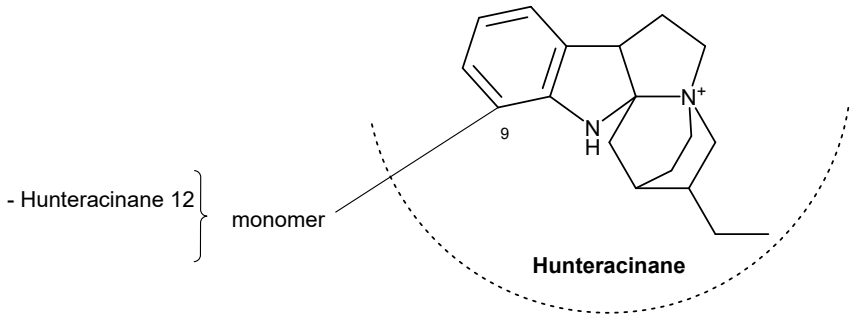
1.12 Ellipticine skeleton reactivity mapping



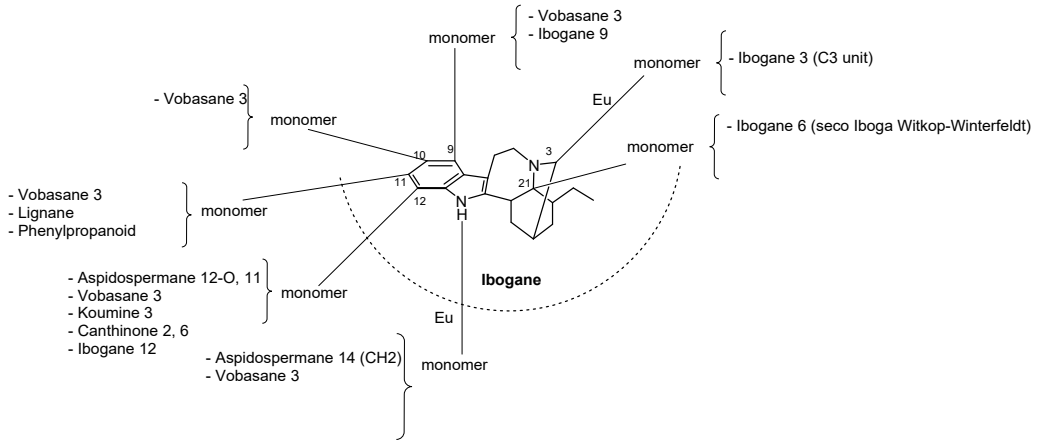
1.13 Gelsemium skeletons reactivity mapping



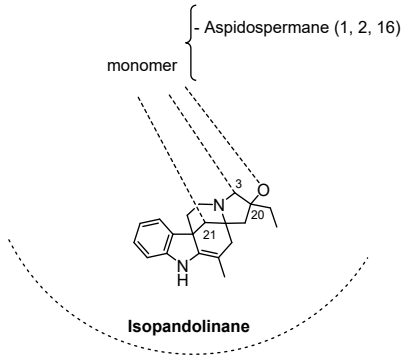
1.14 Hunteracinane skeleton reactivity mapping



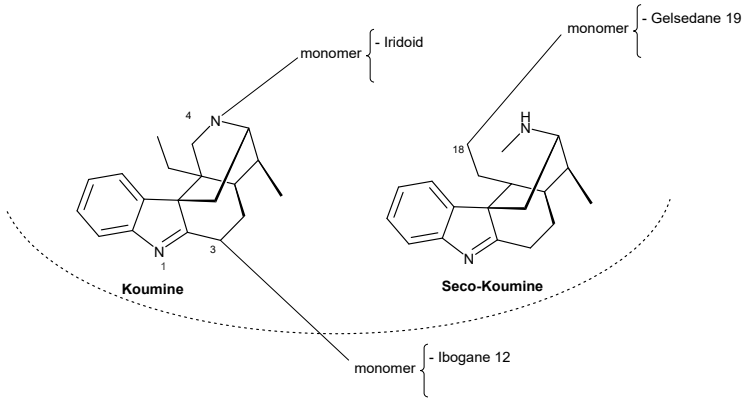
1.15 Ibogane skeleton reactivity mapping



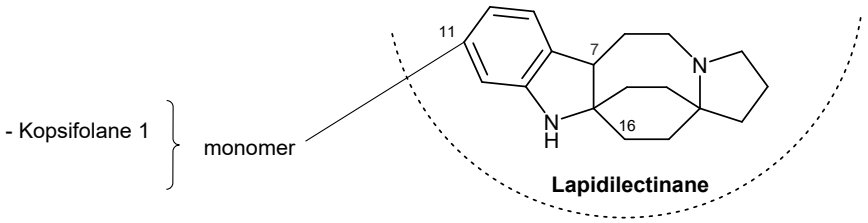
1.16 Isopandolinane skeleton reactivity mapping



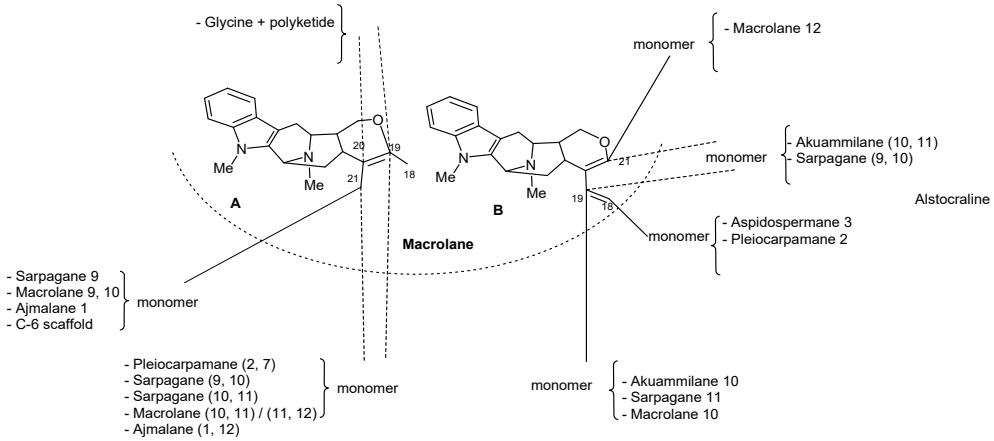
1.17 Koumine skeletons reactivity mapping



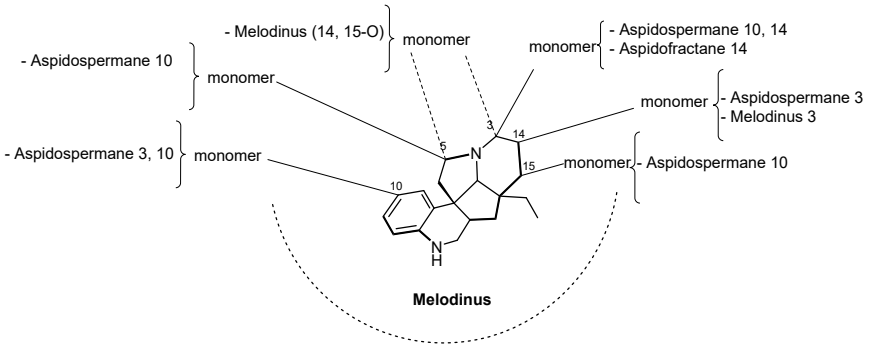
1.18 Lapidilectinane skeleton reactivity mapping



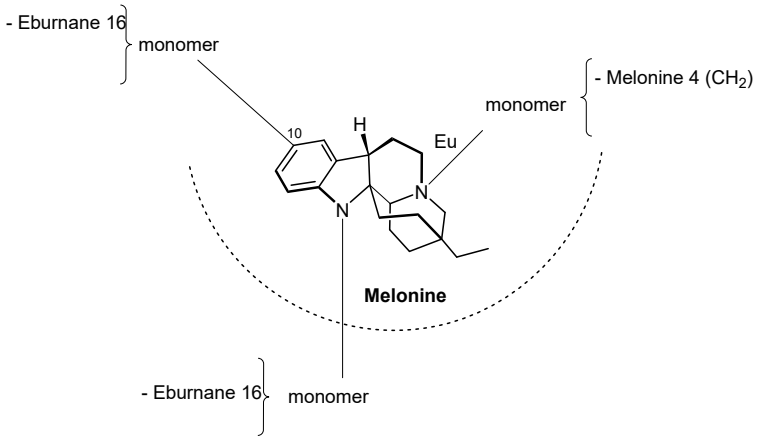
1.19 Macrolane skeletons reactivity mapping



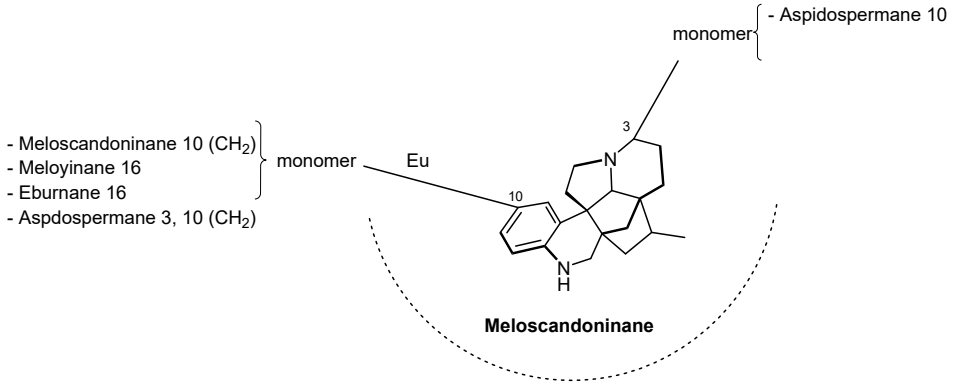
1.20 Melodinus skeleton reactivity mapping



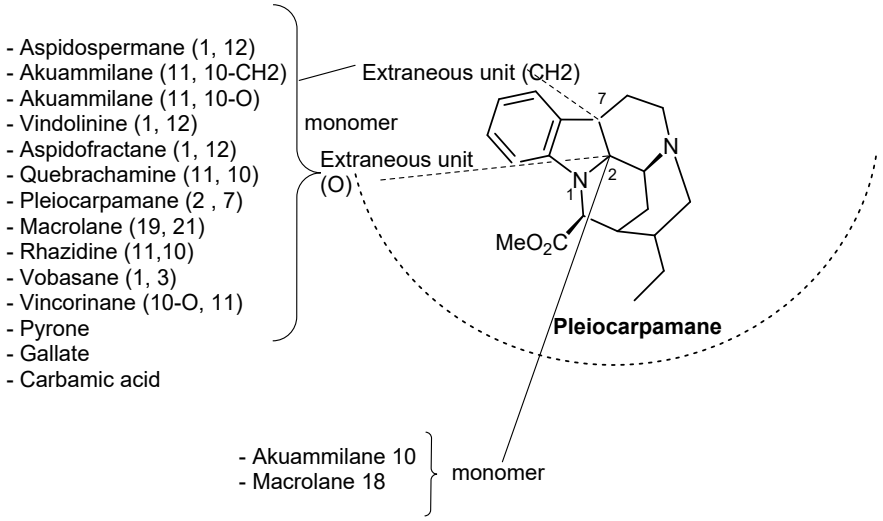
1.21 Melonine skeleton reactivity mapping



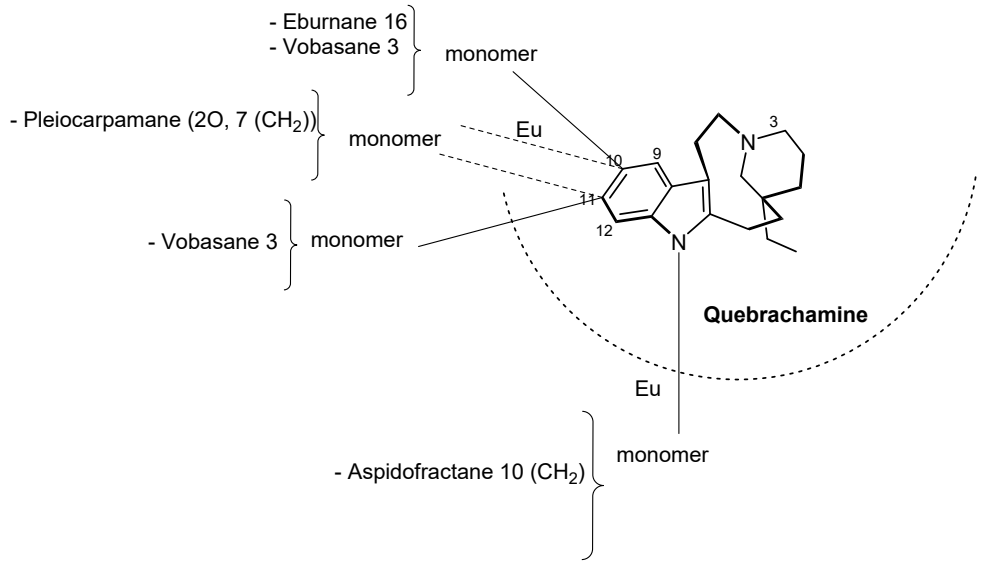
1.22 Meloscandoninane skeleton reactivity mapping



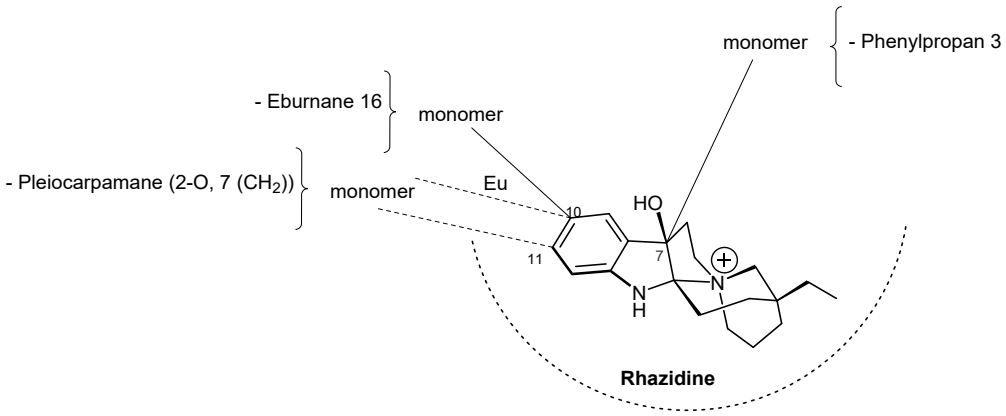
1.23 Pleiocarpamane skeleton reactivity mapping



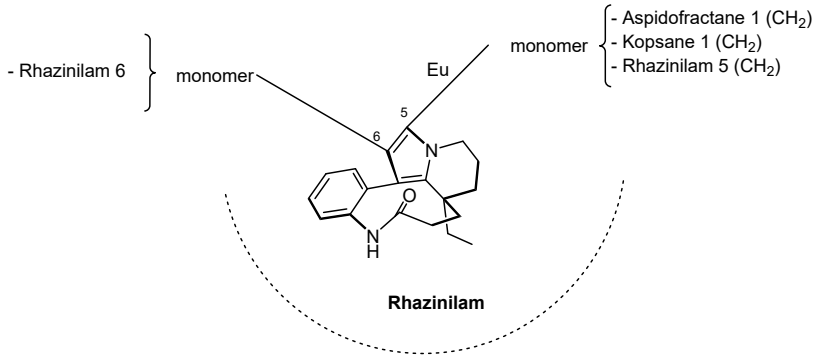
1.24 Quebrachamine skeleton reactivity mapping



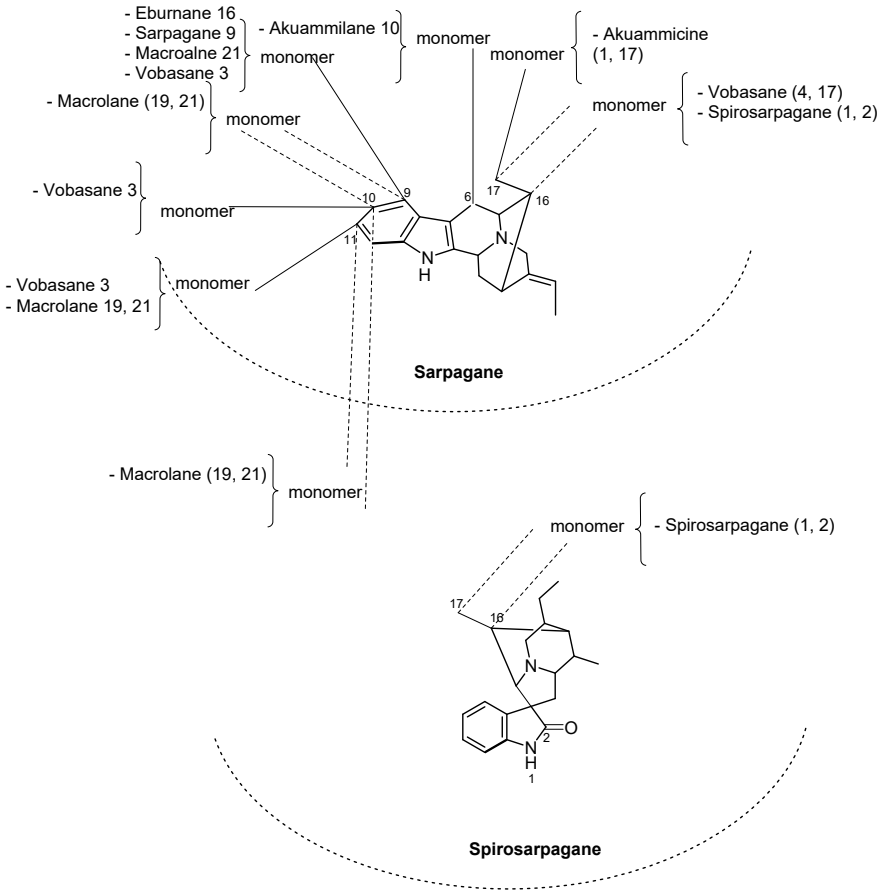
1.25 Rhazidine skeleton reactivity mapping



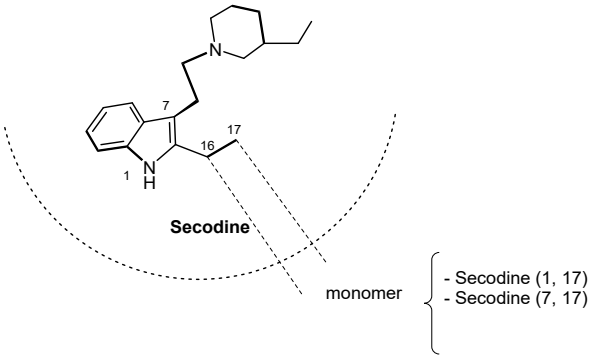
1.26 Rhazinilam skeleton reactivity mapping



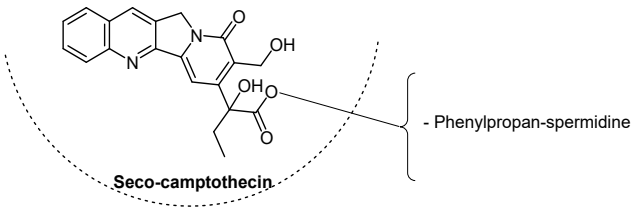
1.27 Sarpagane and spirosarpagnane skeleton reactivity mapping



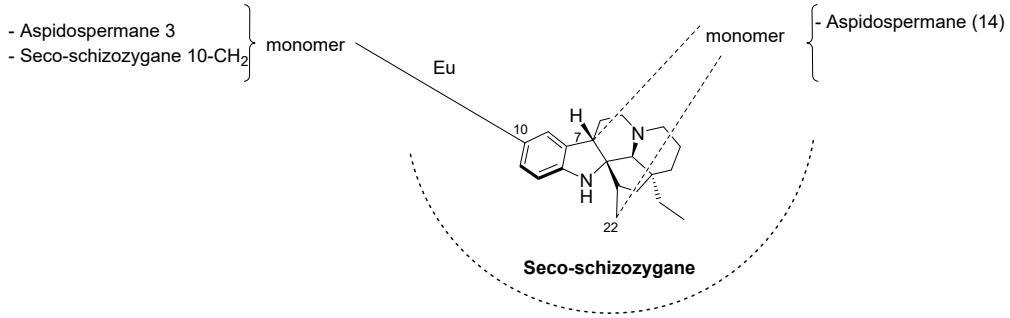
1.28 Secodine skeleton reactivity mapping



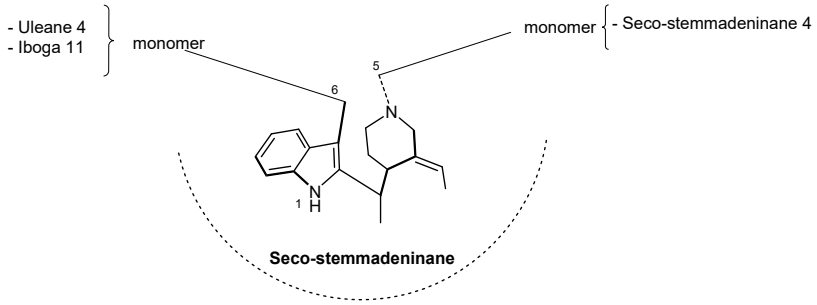
1.29 Seco-camptothecine skeleton reactivity mapping



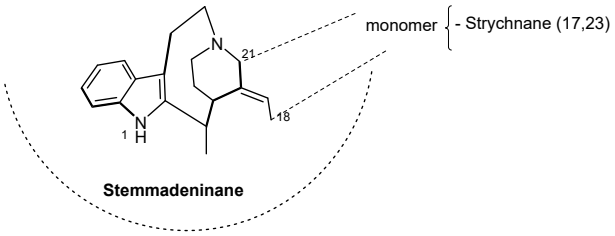
1.30 Seco-schizozygane skeleton reactivity mapping



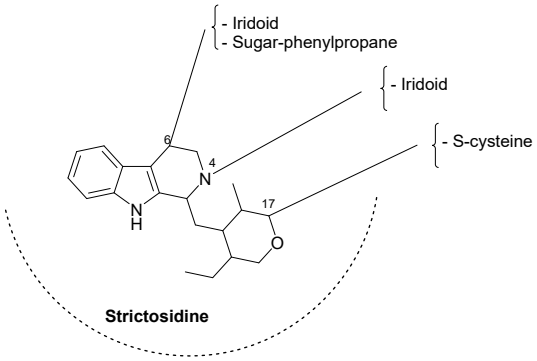
1.31 Seco-stemmadeninane skeleton reactivity mapping



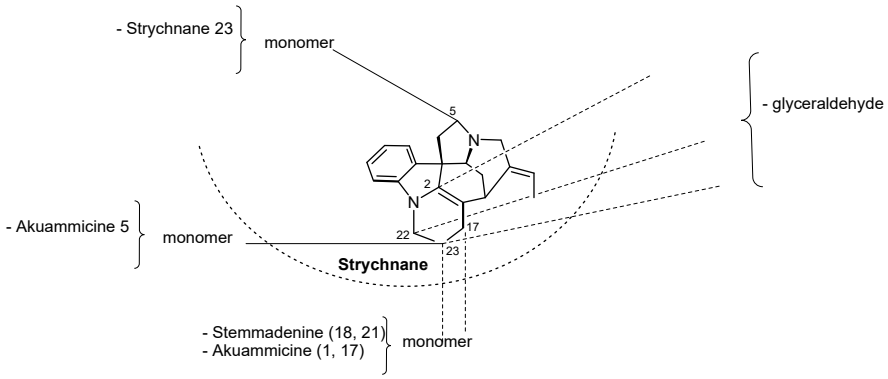
1.32 Stemmadeninane skeleton reactivity mapping



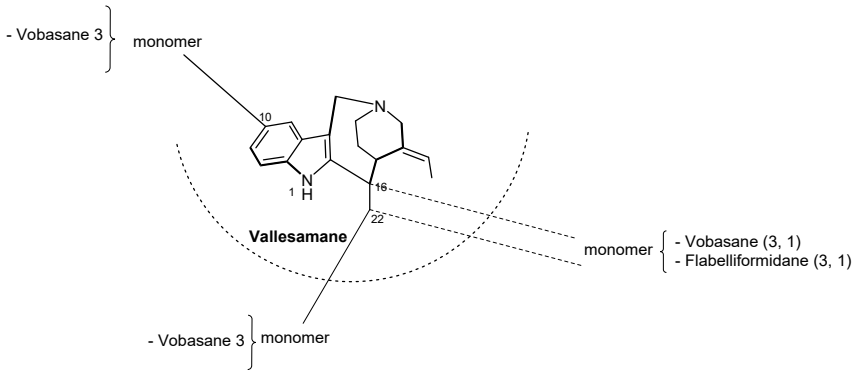
1.33 Strictosidine skeleton reactivity mapping



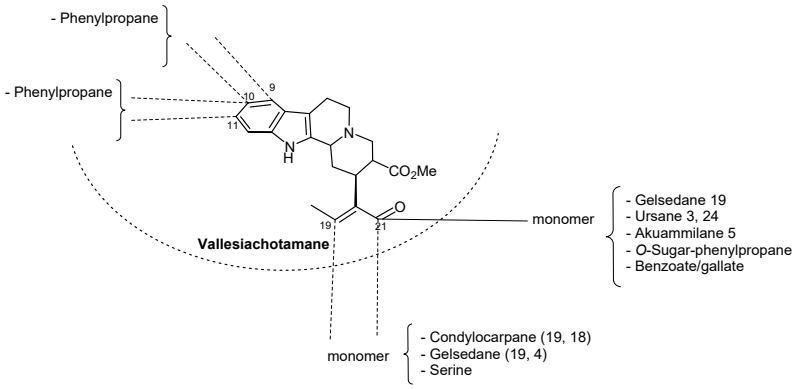
1.34 Strychnane skeleton reactivity mapping



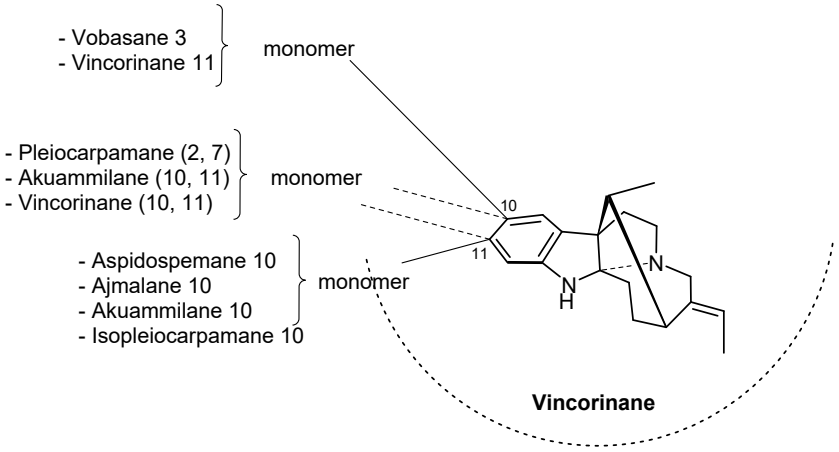
1.35 Vallesamane skeleton reactivity mapping



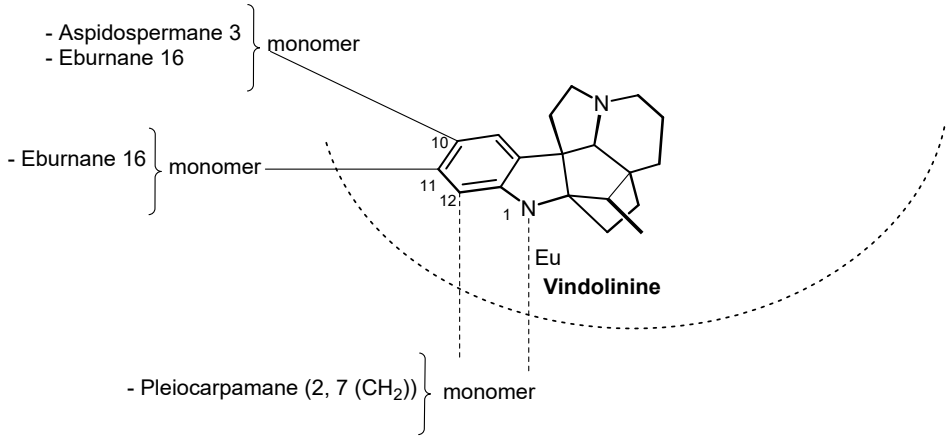
1.36 Vallesiachotamane skeleton reactivity mapping



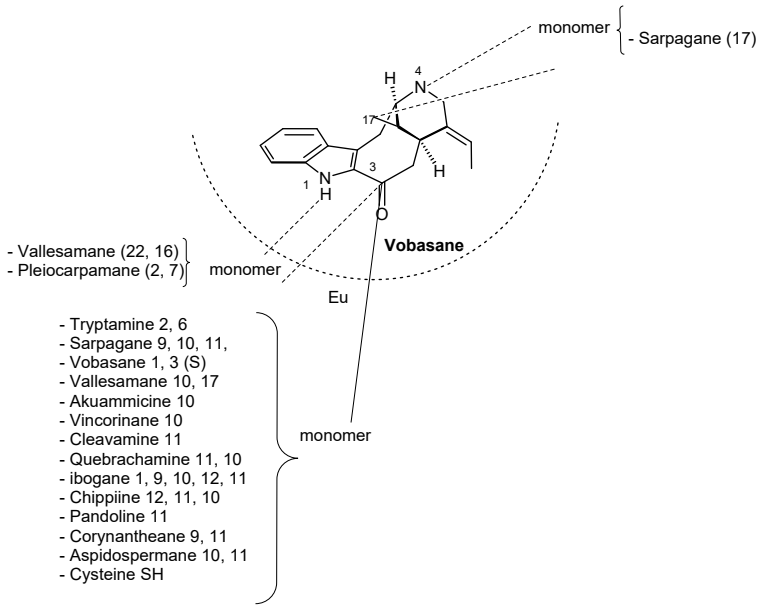
1.37 Vincorinane skeleton reactivity mapping



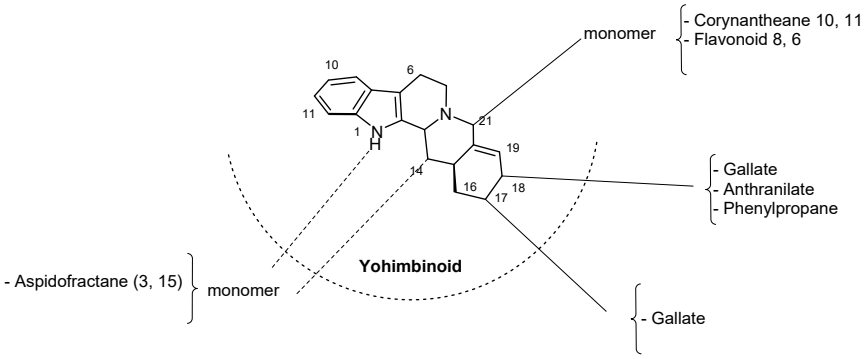
1.38 Vindolinine skeleton reactivity mapping



1.39 Vobasane skeleton reactivity mapping



1.40 Yohimbinoid skeleton reactivity mapping



2 MIA oligomers classified according to their assembly logic

Tethering mode	Reactivity	Oligomers
3.1.1. Electrophilic aromatic substitution		
1	Electrophilic aromatic substitution onto formaldehyde	raureflexine, kopoffine C, melotenuine A pleiokomenines A-B, methylenebismehranine, vindolicine, melomorsine I, meloyine II-III, 10,10'-methylenebis[norvallesamidine], taberdisine F
1	Electrophilic aromatic substitution quinone methide	conoliferine, isoconoliferine, conomicidines A-B, isoconomicidines A-B,
1	Electrophilic aromatic substitution via conjugate addition 1,6	tabernaemontabovine, tabernaemontavine, accedinisine, demethylaccedinisine, accedinine, bisnaecarpamines A-B, pseudovobparicine, coryzeylamine, deformylcoryzeylamine, voacalgine F, vobatensine E, voacamidine, 3'oxotabernaelegantine B, tabernaelegantine B,(3'*R*)-tabernaelegantinal B, conodiparine A, ervahanine B, N-demethylervahanine B, 3'-hydroxy-N4-demethylervahanine B, ervahaimine B, ervahainamidine B, polyneurine P, conoduramine, 19,20-epoxyconoduramine, 3'(R)-hydroxyconoduramine, 3'(S)-hydroxyconoduramine, 3' (R/S)-hydroxy-N(4)-demethylervahanines B, 11' -demethylconoduramine, 19' (R)-hydroxyconoduramine, 19' (S)-hydroxyconoduramine, gabunamine (N-demethylconoduramine), 3 (R/S)-hydroxytabernaelegantine B, conodiparine C conodirinine A, tabernaelegantinine D, tabernaelegantine D, (3'*R*)-hydroxytabernaelegantine D, ervachinines C-D, tabernaricatine C, tabernaricatine E, tabernaelegantinine B, taberdivarines C- D, 3'-(2-oxopropyl)-ervahanine B, 3'-oxotabernaelegantine D, taburnaemine D taburnaemine H, taberyunines H-I, taberine D, tabernaricatines A-B, tabernaricatine D, 3'-oxotabernaelegantine A, 3'-(R/S)-hydroxytabernaelegantine A, tabernaelegantine C, 3'-*S*-hydroxytabernaelegantine C, 3-R/S-methoxytabernaelegantine C, tabernaelegantinine A, 3-(2-oxopropyl)conodurine, tabernaelegantine A, 19' R-tabernaelegantine A, conodiparine B, conodurine, gabunine, 19'(*S*)-hydroxyconodurine, conodurinine, ervahanine C, 3' (R/S)-hydroxyconodurine, 3' (R/S)-hydroxy-16-decarbomethoxyconodurine, 19' (R)-hydroxyconodurine, conodiparines D-F, conodutarines A-B, cononitarines A-B, conodirinine B, tabernaelegantinine C, tabernaelegantinal A, (3' R)-tabernaelegantinal E, tabercorines A-C, tabernaecorymbosine A, 17-acetyltabernaecorymbosine A, tabercorymine B, taburnaemines A-C, taburnaemines E-G, taberines A-C, (19'S)-hydroxytabernaelegantine A, (19'S)-hydroxytabernaelegantine C, 3'-oxotabernaelegantine C, 3'-oxoconodurine, 3'S-hydroxy, ervahanine A, 19'(*S*)-hydroxyervahanine A, 3'-(2-oxopropyl)ervahanine A, 3'-hydroxy-N4-demethylervahanine A, ervahaimine A, ervahainamidine A, 16'-decarbomethoxyvoacamine, 16'-decarbomethoxyvoacaminepseudoindoxyl, 16'-decarbomethoxy-20-epidihydrovoacamine, 16'-decarbomethoxy-19,20-dihydrovoacamine, Voacamine (20alphaH/20betaH), voacamine A, 3' (R/S)-hydroxyvoacamine, 3' (R/S)-hydroxytabernamine, N4-demethyltabernamine, 3' (R/S)-hydroxy-N(4)-demethyltabernamine, 3' (R/S)-hydroxy-N(4)-demethylervahanines A, voacorine, epivoacorine, 19,20-dihydro-20(S)-tabernamine, conodusarine, ervachinines A -B,

		ervatensine B, 19,20-dehydrotabernamine, 19,20-dihydroervahanine A, 3'-hydroxyvoacamine, voacamine Nb-oxide, N-demethylvoacamine, 10'-demethoxy-19,20-dihydrovobatensine D, taberdivarine E, vobatensines A-D, vobatensine F, tabernamine, 19'(R/S)-hydroxytabernamine, tabernadimines A-B, ervadivaricatines A-B, 3'-(2-oxopropyl)-19,20-dihydrotabernamine, capuvosine, N-demethylcapuvosine, dehydroxycapuvosine, taberdivarines A-B, bistabercarpamines A-B, tabercarpamines A-B, capuvosidine, 1'-2'-dihydrocapuvosidine, tabercorymine A, hunterizeylines A-E, vobatricine, ceridimine, demethylceridimine, hunteriatryptamine, pyrrovobasine
1	Polonovski-Potier fragmentation + Electrophilic aromatic substitution via conjugate addition 1,6	vinblastine, vincristine, leurocolumbine, anhydrovinblastine, leurosinone, vinblastine Nb'-oxide, isoleurosine (20'-deoxyvinblastine, vincovaline), leurosidine (vinrosidine ou 20'-epivinblastine), leurosidine Nb'-oxide, 20'-deoxyleurosidine, isoleurosine N4'-oxide (20'-deoxyvinblastine N4'-oxide), leurosine (=vinleurosine), pleurosine, catharine, vinamidine (syn catharinine), (3*R*)-hydroxyvinamidine, vincovalinine, catharanthamine, vinformide, 17-deacetoxyvinamidine, 17-deacetoxyleurosine, 17-deacetoxyvinblastine, 17-deacetoxyvinblastine N'b-oxide, 20'-deoxyvinblastine N'b-oxide, 21'-hydroxyleurosine, 21'-oxoleurosine, vincadioline, N-demethylvinblastine (N-deformylvincristine), vincovalicine, cycloleurosine, 14',15'-didehydrocyclovinblastine, cyclovinblastines A-B, 17-deacetoxycyclovinblastine,roseadine, vincathicine, isovincathicine, vincazalidine A
1	Electrophilic aromatic substitution onto iminium	tabernaebovine, peduncularidine, pedunculine/conofoline, melosuavines A-H, melofusinines C-H, taberyunines D-F, taberdivarine B, taberdivarine H, axidimins A-D, scandomelonine, episcandomelonine, scandomeline, episcandomeline, melokhanines L-M, scandomelidine, plumocraline, suadimin J, pleiomutine, norpleiomutine, kopsoffine, kopsoffinol, demethylnorpleiomutine, insulopinine, tenuicausine, demethyltenuicausine, strempeliopidine, melodinine J, mekongenines A-F, melofusine A, melotenuines B-C, bousigonine H, bousigonines C-D, bisleuconothine A, melodinine V, celastromelidine, bisnicalaterines B-D, leucophyllinines A-B, melaxillarinine, leucophyllidine, melodinines H-I, melodinhenines A-B, leuconoline, melodinines Y1-Y2, bousigonine A, bousigonine G, umbellamine/hunterine, bisleuconothines C-D, angustifonines A-B, criophylline, 14'-hydroxycriophylline, 14'-sulfocriophylline, uncaramine, callophyllines A-B, callophyline, taberdisines D-E, melofusinines A-B, gentiacraline, bonafousine, isobonafousine, uncariagambiriines A-C, epicatechocorynantheines A-B
1	Electrophilic aromatic substitution onto α,β-unsaturated carbonyle and α,β-unsaturated iminium	leucoridine D, lumusidines A-D, panganensines X-Y, arbolodinine C, suadimin I, alstomacrophylline, angusticraline, angustilongine A, angustilongines C-K, perhentisines A-C, perhentidines A-C, vincarubine, undulatine, macralstonine, *O*-methylmacralstonine, des-N1a-methylanhydromacralstonine, perhentinine, taberdisines A-B, alstomaphylines A-C, F-I, vindogentianine
1	Electrophilic aromatic substitution onto oxygenated functionality, onto epoxide and dehydration	undulatine, deformoundulatine, tabernaemontine L, melokhanine K

3.1.2. Radical coupling		
1	Radical coupling	11-[10-(11-methoxyvincamajinyl)]-vincorine, 11-[10- (11-methoxy-17-*epi*-vincamajinyl)]-vincorine, 11-[10-(11-methoxyvincamedinyl)]-vincorine, flexicorine, cabufiline, deoxycabufiline, rausutrine, rausutranine, vingramine, methylvingramine, ceylanine, peceylanine, 10,10'-bis[*N*-acetyl-11,12-dihydroxyaspidospermidine], dispegatrine, geleganamide, rausutrine, rausutranine geleganidine B (N=N bond), 11-demethoxygelsemazonamide (N=N bond), obovatine, 12,12'-Bis[11-hydroxycoronaridine]-12, pendulifloramine, blumeanine, tetrastachyne (ether bond), 14-dehydrotetrastachyne (ether bond), tetrastachynine, 14-dehydrotetrastachynine, bousangustine C, cimilophytine, cimiciduphytine, norisohaplophytine, haplocidiphytine, haplophytine, crooksiine, cimiciphytine, norcimiciphytine
3.1.3. Enamine reactivity		
1	Enamine nucleophilic attack onto quinone methide	inaequalisines A-B
1	Enamine nucleophilic attack onto aldehyde (or ketone)	serpentinine, 20'-episerpentinine, 16'-demethoxy-*epi*-serpentinine, alstonine-6-ethylpropionate (presumed dimer catabolite), moandaensine, moandaensines B-C, gelsekoumidines A-B, gelsecorydine A, gelsecorydines C-E, gelsekoumidine A, alstorupine A (ketone), gelseginedines A-B, neonaucleosides B-C (+ oxidation and lactonization for neonaucleoside C), hirsutaside D, gelsevanillidine, gelsesyringalidine, gelselegandines A-C, gelsefuranidine, 14-deoxygelsefuranidine, gelserancines D-E
1	Enamine nucleophilic attack onto formaldehyde	kopoffines A-B (dienamine), bousangustines A-B (dienamine), geleganimine A (+ epoxidation and enamine reactivity), geleganimine B
1	Enamine nucleophilic attack onto iminium	panganensines R-S (dienamine), gabonine, arbolodinine A, melosine A, paucivenine
1	Enamine nucleophilic attack onto α,β-unsaturated carbonyle	gelsamydine, 14*α*-hydroxygelsamydine, 19α-hydroxygelsamydine, elegansamine, 14-hydroxyelegansamine, eleganine A, gelsegansymines A-B
1	Trienamine nucleophilic attack via 1,6 addition	vobparicine, 19,20-dihydrovobparicine, vobparicine N_4-oxide
3.1.4. (Hetero)nucleophilic coupling		
1	Heteronucleophilic coupling following Ring-closure driven nucleophilic attack into formaldehyde +/- double bond regeneration via ring reopening	voacinol, voacandimine C, biscarpamontamine A

1	$\Delta^{14,15}$ hydration-driven nucleophilic attack into iminium (or ring closure driven)	voafrines A and B, 3-hydroxy-14'-(3α"-tabersonyl)voafrine B, voacafrines A-G, 3-oxovoafrine B, melosine B, melosine H, melosuavine I, melodinusines A and B, tabernaemontines A-K, bis-19β-hydroxyvenalstonidine, sungucine, isosungucine, 18-hydroxysungucine, 18-hydroxyisosungucine, Melodinusines B, Tabernaemontines A-K, Sungucine, isosungucine, 18-hydroxysungucine, 18-hydroxyisosungucine, strychnogucine A (ring-closure driven), strychnogucine B, strychnogucine C (ring-closure driven) , suadimins A-B, suadimins D-G, H, nitaphylline
1	Heteronucleophilic attack (onto aldehydic or alcohol carbon)	neonaucleoside A (= bahienoside A), bousigonines E-F, mappiodoside I (*S*-triggered)
1	heteronucleophilic attack into iminium	kisantine (*O*-triggered), celastromeline (*N*-triggered),
1	Nucleophilic attack of dienol ether onto iminium	macrocarpamine, 10-methoxymacrocarpamine, 10-methoxymacrocarpamine $N_{4'}$-oxide, angustilongine L, pandicine, alstomaphyline J.
1	Heteronucleophilic coupling onto formaldehyde	melofusine I, *N*b, *N*b'-methylenebismeloninium, geleganidine C
1	Heteronucleophilic attack via conjugate addition 1,6	hazuntamine, vobasonidine, bisnicalaterine A, theionbrunonines A-C (S-triggered), pagisulfine, hemitheion
1	Nucleophilic attack onto iminium (X2) (triggered by acetone as an extraneous unit)	tabercrassine A, 3,3'-(oxopropyl)dicoronaridine
1	Heteronucleophilic attack onto α,β-unsaturated ketone or α,β-unsaturated iminium	angustiphylline (after Polonovski-Potier fragmentation), arbolodinine B, alstomacroline, alsmaphylines B-C, scholaphylline, alstomaphylines D-E, rankiniridine, humanteniridine, gelseiridone, gelseganines A-D, gelsebanine
1	Esterification with C6-C1, C6-C3 units, anthranilate derivatives	19-epi-(+)-echitoveniline, echitoveniline, 11-methoxyechitoveniline, echitoserpidine, echitoserpine, maireines A-B, ajmalimine, *O*-benzoylvincamajine, vincamajine-17-*O*-veratrate, vincamajine-17-*O*-veratrate N_4-oxide, *O*-(4-Hydroxy-3,5-dimethoxybenzoyl)vincamajine, *O*-(3,4,5-trimethoxybenzoyl)vincamajine, *O*-(3,4,5-trimethoxybenzoyl)vincamajine N_4-oxide, (3,4,5-trimethoxybenzoyl)quebrachidine, 10-Hydroxy-O^{17}-(3,4,5-trimethoxybenzoyl)vincamajine, rauvomitine, norrauvomitine, 3,4,5-trimethoxybenzoylseredamine, 3,4,5-Trimethoxycinnamoylvincamajine, 10-hydroxy-O^{17}-(3,4,5-trimethoxycinnamoyl)vincamajine, 10-methoxy-O^{17}-(3,4,5-trimethoxycinnamoyl)vincamajine, alstiphyllanines B-F, *O*-(3,4,5-Trimethoxybenzoyl)burnamine, alstiyunnanenine B, 10-methoxy-N_a-methylburnamine 17-*O*-benzoate, 10-Methoxy-N_a-methylburnamine 17-*O*-veratrate, rauvoyunine C, 10,11-dimethoxy-1-methyldeacetylpicraline benzoate, *O*-(3,4,5-trimethoxybenzoyl)-(*Z*)-burnamine, lanciferine, 10-hydroxylanciferine, 10-methoxylanciferine, raugustine, isoraunescine, alstorupine B, alstomairine E, reserpine, renoxydine, pseudoreserpine, 3-isoreserpine, 16,17-diepipseudoreserpine, 3,4-dimethoxybenzoylreserpic acid methyl ester, veneserpine, deserpidine, deserpideine, raujemidine, raunescine, alstomairines F-G, anthraserpine, dimethoxyanthraserpine, pseudoanthraserpine, desanthraserpidine, dimethoxydesanthraserpidine, rescinnamine, rescidine, rescinnamidine, 3-epirescinnamine, rhyncophine, rubescine, 6'-trans-feruloyllyaloside, 6'-trans-sinapoyllyaloside, ophiorrhiside C, mappiodoside J, 21-*O*-

		Syringoyl-(3*S*,4*S*,15*S*,20*R*)-antirhine N_4-oxide-4′-O-β-D-glucopyranoside, 21-*O*-syringoylantirhine, 21-*O*-syringoyl-(3*S*,4*S*,15*S*,20*R*)-antirhine 4′-*O*-β-D-glucopyranoside, 21-*O*-syringoylantirhine 4′-*O*-[6′′-*O*-syringoyl]-β-D-glucopyranoside, 21-*O*-syringoylantirhine 4′-*O*-[(E)-6′′-*O*-sinapoyl]-β-D-glucopyranoside, 21-*O*-syringoylantirhine 4′-*O*-[6′′-*O*-feruloyl]-β-D-glucopyranoside, foetidins I-II
1	Amidification	*N*-benzoylcylindrocarine, *N*-benzoyldemethoxycylindrocarine, *N*-benzoyl-19-hydroxycylindrocarine, *N*-cinnamoyldemethoxycylindrocarine, cylindrocarpine, *N*-dihydrocinnamoyl-19-hydroxycylindrocarpine, *N*-cinnamoyl-19-hydroxycylindrocarpine, alstiphyllanines I-O
3.2.1. Doubly tethered oligomers resulting from an electrophilic aromatic substitution associated to an heteronucleophilic attack		
2	Electrophilic aromatic substitution (onto quinone methide) + lactonization	kanluaengosides C-D
2	Electrophilic aromatic substitution α,β-unsaturated carbonyle + hemiketalization + ketalization	angustilongines G-H, lumutinines A-E, macralstonidine
2	Electrophilic aromatic substitution α,β-unsaturated carbonyle + hemiacetalization + acetalization	Alstocraline, foliacraline, angustilongine B, macrospegatrine,
2	Electrophilic aromatic substitution via conjugate addition 1,6 + heteronucleophilic attack on addition 1,6	divaricamine A, ervadivamine A
2	Electrophilic aromatic substitution (onto iminium 3,4) + heteronucleophilic annulation (onto epoxide)	Conophylline, conophyllidine, conophyllinine, conofolidine, polyervinine, conolodinines A-D, melodinine K, 19-hydroxymelodinine K, taberyunines A-C, Taberdivarine A, Taberdivarine B, taberdivarines C-G, taberdisine C
2	Electrophilic aromatic substitution (onto iminium 1,16) + heteronucleophilic annulation	bisleuconothine B
2	Electrophilic aromatic substitution (10-formylation) + enamine nucleophilic attack OR Heteronucleophilic attack + heteronucleophilic annulation	goniomedines A-B, goniomedine A *N*-oxide, goniomedinone, hunzeylanines A-E, melomorsine (electrophilic aromatic substitution + Heteronucleophilic attack + heteronucleophilic annulation)
3.2.2. Doubly tethered oligomers resulting from two electrophilic aromatic substitution		
2	Double electrophilic aromatic substitutions onto iminiums	bousigonine B, vincarostine A
3.2.3. *N*-mediated heteronucleophilic attack doubly tethered oligomers		
2	Heteronucleophilic attack (1-formamide) + enamine nucleophilic attack + electrophilic aromatic substitution	pycnanthinine, huncaniterines A-B, 16-epipleiomutinine, N_4-chloromethylpleiomutinine, pycnanthine, pleiomutinine, 19′-epipleiomutinine, contortarine A
2	(Heteronucleophilic attack) Aza-Michael 1,4 + hemiketalization + electrophilic aromatic substitution	alstonisidine, alsmaphyline A
2	Heteronucleophilic attack Aza-Michael 1,4 + electrophilic aromatic substitution	bisleucocurine A
2	Stepwise Aza-Michael	leucoridines A-C, leucoridine A *N*-oxide, leucofoline, hazuntiphyllidine (DMSO-d_6), anhydrohazuntiphyllidine
2	Mannich-type reactivity + enamine reactivity + dehydration	gelsechizine A
2	Mannich-type reactivity + Aza-Michael addition	gelsechizine B

2	Double Mannich-type reactivity (double hemiaminalization) + double dehydration	toxiferine I (C-toxiferine I, Toxiferine V or Toxiferine XI), *C*-alkaloid H, Caracurine VI (bisnor-C-alkaloid H, 18-hydroxynordihydrotoxiferine or dinor-C-alkaloid H), bisnor-*C*-alkaloid H *N*-oxide, bisnor-*C*-alkaloid H di-*N*-oxide, 18,18'-dideoxytoxiferine I (C-deoxytoxiferine, C-alkaloid K or C-dihydrotoxiferine I), bisnordihydrotoxiferine (4,4'-dimethyl-18,18'-dideoxytoxiferine I), bisnordihydrotoxiferine *N*-oxide, bisnordihydrotoxiferine di-*N*-oxide, gardovatine
2	Double Mannich-type reactivity (double hemiaminalization) + dehydrative cyclizations (side)	caracurine V, caracurine V mono-oxide, caracurine V di-oxide
2	Mannich-type reactivity + dehydrative cyclization OR aldolization	longicaudatine, longicaudatine F, longicaudatine Y, 3',4',5',6'-tetrahydrolongicaudatine Y, longicaudatine Z, dihydrolongicaudatine, dihydrolongicaudatine Y, 3-hydroxylongicaudatine Y, longicaudatine N_4-oxide, guianensine, guiaflavine, guiachrysine, 5',6'-dehydroguiachrysine, 5',6'-dehydroguiaflavine, strychnochrysine, demethoxyguiaflavine, N_b-methyllongicaudatine, strychnoflavine, afrocurarine
2	Aza-Michael 1,4 + heteronucleophilic annulation	strellidimine
2	Aza-Michael 1,4 + aldolization	strychnobaillonine
2	Hemiaminalization (+ heteronucleophilic annulation)	geissospermine, 3',4',5',6'-tetrahydrogeissospermine, geissolosimine, divaricine, strychnobiline, isostrychnobiline, 12'-hydroxystrychnobiline, 16,17-dehydroisostrychnobiline, 12'-hydroxyisostrychnobiline, ligustrinine, gardmultine, 18-demethoxygardmultine
2	Pictet-Spengler + heteronucleophilic attack (heminalization) + dehydration	usambarine, usambarensine, 10-hydroxyusambarine, N_b-methyl-10-hydroxyusambarine, N_b-methyl-11-hydroxyusambarine, 10'-hydroxyusambarensine, 4',17-dihydro-17α-tchibangensine, 4',17-dihydro-17β-tchibangensine, 10'-hydroxy-4',17-dihydro-17α-tchibangensine, N_b-oxide-usambarensine, N_b-methylusambarensine, 3',4'-dihydrousambarensine *N*$_b$-oxide (=5',6'-dihydrousambarensine *N*-oxide), N_b-Methyl-3',4'-dihydrousambarensine (= N_b-methyltchibangensine), N_2'-methyl-3',4'-dihydrousambarensine (=N_2'-methyltchibangensine), 19,20(β)-dihydro-usambarensine, N_b'-carbomethoxy-17*R*-tetrahydrousambarensine, N_b'-carboethoxy-17*R*-tetrahydrousambarensine, 4',5',6',17-tetrahydro-17*R*-usambarensine *N*-oxide, tchibangensine (3',4'-dihydro-usambarensine = 3',4'-Dihydrousambarensine = 5',6'-dihydrousambarensine), ramiflorines A-B, 6',10-dihydroxy,1'*S*,2',3',4'-tetrahydro-usamabrensine = 10,10'-dihydroxytetrahydrousambarensine, N_2'-Me-usambarensine = 10,10'-dihydroxy-N_4'-methyltetrahydrousambarensine, 10-hydroxy-10'-methoxytetrahydrousambarensine, 10-hydroxy-10'-methoxy-N_4'-methyltetrahydrousambarensine, 10,10'-dimethoxytetrahydrousambarensine, 10,10'-dimethoxy-N_4'-methyltetrahydrousambarensine, 1',2',3',4'-tetrahydro-6'-hydroxy-10-methoxy-N_2'-methylusambarensine (= 10'-Hydroxy-10-methoxy-N_4'-methyl-17,4',5',6'-tetrahydrousambarensine), buchtienine, cinchophylline, isocinchophylline, 17-epicinchophyllamine, 3-epiconchophyllamine, 17,4',5',6'-tetradehydro-3α-

		cinchophyllamine (tetradehydroisocinchophyllamine), dehydroisocinchophyllamine, 18,19-dihydro-3β,17β-cinchophyllamine, strychnopentamine, isostrychnopentamine A, ochrolifuanines A-F, 18-dehydroochrolifuanine A, 18-dehydroochrolifuanine E, 18-dehydroochrolifuanine F, nigritanine (=18,19-dihydrousambarine), 18,19-dihydrousambaridine Vi, 10-methoxy,18,19-didehydro-ochrolifuanine B, 18,19-dihydrousambaridine Br., usambaridine Br., strychnofoline, isostrychnofoline, barterine, 10-hydroxybarterine, taipinisine, strychnophylline, isostrychnophylline, chrysopentamine
2	Carbamoylation + heteronucleophilic attack onto iminium	gelstriamine A
3.2.4. *C*- and *O*-mediated nucleophilic attack generating doubly tethered oligomers		
2	$\Delta^{14,15}$ hydration-driven nucleophilic attack into iminium heteronucleophilic annulation into other iminium= doubly tethered	suadimin C
1	Aldolization	voacalgine D (+ hemiketalization), voacalgine E (+ Oxa-Michael 1,4)
2	Ring-closure driven Michael addition + heteronucleophilic annulation (into iminium 3,4)	voacandimine A
2	Ring-closure driven nucleophilic attack into formamide + double bond regeneration via ring reopening + ring closure driven double bond nucleophilic attack onto methylester carbonyl	vobtusine, biscarpamontamine B (3'-hydroxy-18-oxovobtusine, 3'-hydroxyvobtusine lactone), vobtusine lactone (10-oxovobtusine), 12-demethylvobtusine, 3'-hydroxyvobtusine, globospiramine, deoxyvobtusine lactone (2-deoxy-18-oxovobtusine), deoxyvobtusine (goziline), 3'-oxovobtusine (vobtusine lactame), N-oxide-3'-oxovobtusine, 2-deoxy-3'-oxovobtusine (2-deoxyvobtusine lactame), voafolidine, 2-deoxyvoafolidine (voafoline), 14'epimervoafolidine (isovoafolidine), 14'epimer, 2-deoxyvoafolidine (isovoafoline), owerrine (anhydrodihydroamataine), quimbeline, voacandimine B, tabernaesines A-J, vobtusamine
2	Aldolization + dehydration + allylic oxidation + hemiketalization	strychnofuranine
2	Aldolization + Mannich + aldolization	gelsepyrrodines A-C
2	Aldolization + Mannich	alstopirocine
2	Aldolization + hydration + hemiaminalization	19,20-(*E*)-alstoscholarine, 19,20-(*Z*)-alstoscholarine
2	Aldolization + tandem hemiketalization	macrodasines A-H, voacalgine C
2	Mannich-type heteronucleophilic attack (x2) + dehydrative etherification	alstoscholarinine A
2	Ring-closure driven Michael addition + rearrangement aspidospermane=>vallesamidine + enamine nucleophilic attack (onto indoleninium system)	callichiline
2	Ketalization	alstoniasidines A-B, latifolianine A
2	Enolization-driven nucleophilic attack (monomer rearrangement) + aminalization + Mannich-type heteronucleophilic attack	alstoscholarisine K
3.2.5. Doubly tethered oligomers generated through an enamine reactivity		

2	Enamine nucleophilic attack onto onto α,β-unsaturated ketone (Michael acceptor) + translactamization	gelserancines B-C
2	Enamine reactivity + Heteronucleophilic annulation onto iminium	rupestrisines A-B, meloyine I
2	Enamine reactivity + Imine formation (mannich)	gelsecorydine B
2	Enamine nucleophilic attack (Michael addition) + hemiketalization + heteronucleophilic annulation	villalstonine, villalstonine N_4'-oxide, 10-methoxyvillalstonine, 10-methoxyvillalstonine N_4'-oxide, villalstonidines A-F, alstomaphyline K
2	Enamine nucleophilic attack (conjugate addition 1,6) + heteronucleophilic annulation	hunterizeyline F
2	Enamine nucleophilic attack (Michael addition (1,4) + heteronucleophilic annulation	voacalgine A, pleiomaltinine
2	Enamine nucleophilic attack (Michael addition (1,4) + heteronucleophilic annulation + Enamine nucleophilic attack (Michael addition (1,6) + heteronucleophilic annulation	bipleiophylline
2	Enamine reactivity + Heteronucleophilic-driven addition 1,6 by exomethylene	monogagaine, flabelliparicine
2	Enamine nucleophilic attack + Enolate-driven epoxide opening + lactonization	gelserancine A, gelseleganin C
2	Enamine nucleophilic attack (O+) + heteronucleophilic attack on carbamate + heteronucleophilic annulation	pleiomalicine
2	Enamine nucleophilic attack onto aldehyde + heteronucleophilic attack on ketone	trirosaline
2	Enamine nucleophilic attack onto iminium + heteronucleophilic annulation	ervafolidene, 3-epiervafolidene, ervafolidine, 3-epiervafolidine, 19'-*R*-hydroxyervafolidine, 19'-S-hydroxy-3-epiervafolidine
3.2.6. Cycloaddition and radical coupling-generated doubly tethered oligomers		
2	Cycloaddition + Aza-conjugate addition 1,6 OR hetero-Diels Alder	Presecamine, dihydropresecamine, tetrahydropresecamine, secamine, dihydrosecamine, decarbomethoxytetrahydrosecamine, tetrahydrosecamine, 16-demethoxycarbonyltetrahydrosecamine, didemethoxycarbonyltetrahydrosecamine, 16-hydroxy-16-demethoxycarbonyltetrahydrosecamine, 16-hydroxytetrahydrosecamine, kopsiyunnanine M, kopsiyunnanine A
2	Orhto oxygenated radical coupling + dehydrative etherification	peceyline, pelankine, ceylanicine
2	Radical oxidative coupling + intramolecular iminium trapping	pleiocorine, N-demethylpleiocorine, pleiocraline
3.3. Oligomers with a mixed tethering mode		
Mixed tethering		voatriafricanines A/B, alasmontamine A, strychnohexamine,
3.4. Triply-tethered oligomers		
3	Double Mannich-type reactivity (double hemiaminalization) + dehydrative etherification	matopensine, matopensine *N*-oxide, 16-methoxyisomatopensine, 16-ethoxyisomatopensine, 18-hydroxymatopensine, 18,18'-dihydroxymatopensine
3	Double Mannich-type reactivity (double hemiaminalization) + unilateral	divarine

	dehydration/epoxidation + hemiaminal OH-driven epoxide ring opening	
3	Double Mannich-type reactivity (double hemiaminalization) + enamine-driven C-2 dioxygenation + enamine-driven O_2 elimination + heteronucleophilic attack-driven iminium trapping	*C*-Alkaloid D, bisnor-*C*-alkaloid D, caracurine II, toxiferine IX, dolichocurine
3	Double Mannich-type reactivity (double hemiaminalization) + double indoleninium generation + unilateral C-2 hydroxylation + heteronucleophilic attack-driven iminium trapping	*C*-Curarine, bisnor *C*-Curarine, *C*-Alkaloid G, *C*-Alkaloid E
3	Double Mannich-type reactivity (double hemiaminalization) + putative photochemical-generated C-C bond	calebassine, *C*-alkaloid F, *C*-alkaloid A
3 (2)	Pictet-Spengler + Mannich	janussines A-B, , oxojanussine (doubly-tethered deoxygenation product)
3	Mannich + heteronucleophilic annulation + Winterfeldt rearrangement (Bischler-Napieralski-type)	roxburghines A-E, roxburghine X,
3	Enamine nucleophilic attack (onto iminium 3,4) + heteronucleophilic annulation (iminium trapping) + heteronucleophilic annulation	ervafoline, 19'-hydroxyervafoline, ervafolene, 19'-hydroxyervafolene
3	Double aza michael + heteronucleophilic annulation	Hazuntiphylline
3	Ring-closure driven nucleophilic attack into formamide + double bond regeneration via ring reopening + ring closure driven double bond nucleophilic attack onto methylester carbonyl + heteronucleophilic annulation	Subsessiline (grandifoline ou amataine), 18-oxoamataine (subsessiline lactone), folicangine
3	(Heteronucleophilic attack) Aza-Michael 1,4 + enamine Michael addition + heteronucleophilic annulation onto iminium	hazuntiphyllidine (C_6D_6)
3	Aldolization + 2 heteronucleophilic annulation	melohenine A

*Color code: no highlight = MIA/MIA or MIA/MIA/MIA or MIA/MIA/MIA, blue = MIA/tryptamine pseudodimer, green = MIA/monoterpene pseudodimer, yellow = MIA + phenylpropanoid (*sensu lato*, including lignan-derived dimers and C6-C1 derivatives) or gallate (*sensu lato*) or anthranilate, gray = MIA + other biosynthetic adduct.

3 The puzzling case of tenuiphylline

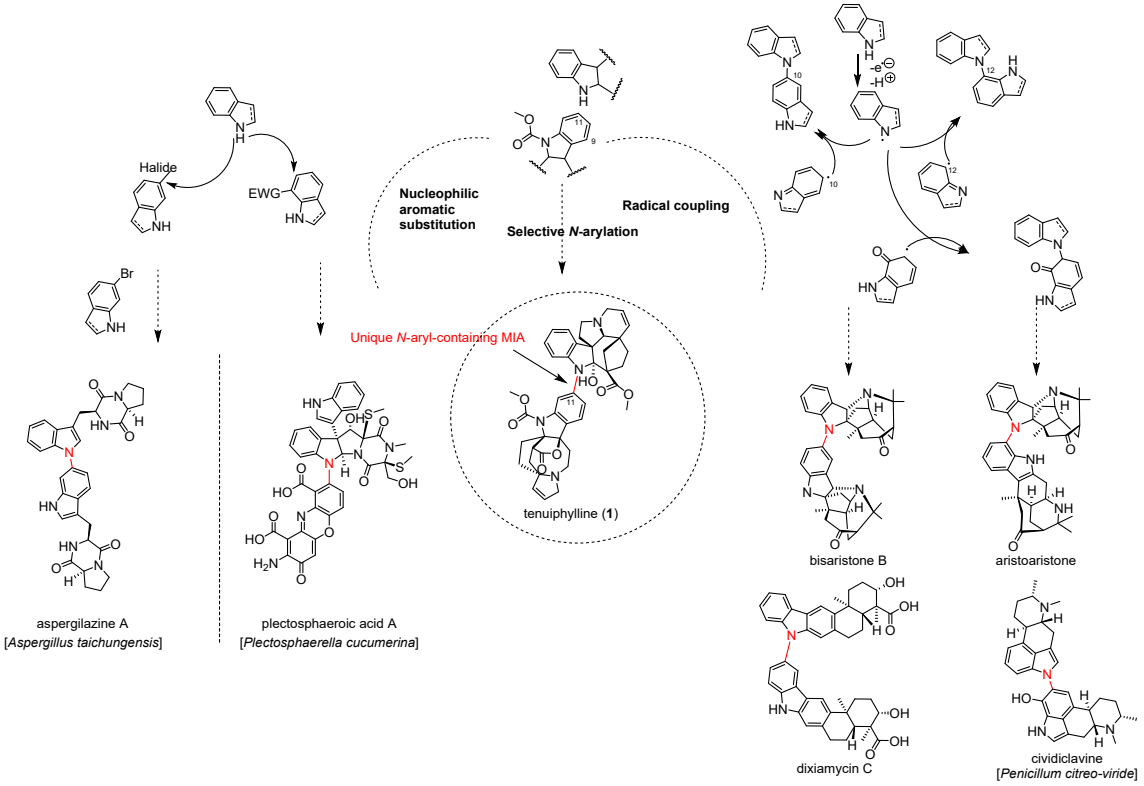


Fig. S1. The puzzling case of tenuiphylline intermonomeric assembly mode: comparison with some natural products revealing a C-aryl-N bonding

During this endeavour towards the classification of the MIA oligomer chemical space, only one molecule, tenuiphylline[1] (Fig. 1) could not be deciphered in terms of chemical logic assembly. For this reason, it has not been added in the table above. Remarkably, tenuiphylline (**1**) features a unique *N*-aryl bond among the MIA oligomer chemical space. Although this linkage (*i.e. N*-Aryl) is not forbidden from a biosynthetic perspective[2], it requires specific structural features to follow either a radical coupling or a nucleophilic aromatic substitution.

Concerning radical coupling-mediated *N*-aryl bonding, a radical can appear at the nitrogen atom of the indoline ring or on the oxygen atom of a phenol group either by deprotonation and single-electron transfer or by abstraction of a hydrogen radical. The generated radical will give rise to a possible set of regiodivergent products with N-C linkages at *ortho* or *para* positions (see the examples of bisaristone B, aristoaristone, dixiamycin C and cividiclavine).[3] Notably, Hertweck *et al.* were able to explain the biosynthesis of *N,N*-coupled indolosesquiterpene dimers dixiamycines[4] following the identification of a single bacterial flavoenzyme.

Regarding nucleophilic aromatic substitution, it can occur when strong electron-withdrawing groups are *ortho* or *para*-disposed to the linking site as in the case of plectosphaeroic acid A.[5] Interestingly, during the total synthesis of this molecule, Overman *et al.*[6] used a copper-mediated *N*-arylation of an halogenated form of cinnabarinic acid to install the challenging N-C bond. An alternative scenario for nucleophilic aromatic substitution can rely on an *N*-arylation mechanism with the presence of aryl halides. In this regard, the case of aspergilazine A[7] has attracted our attention because it contains an *N*-aryl bonding on a yet non compatible radical position. Moreover, it does not feature any strong electron-withdrawing groups at the *ortho* neither *para* position to the linking site. Arguably, the assembly of aspergilazine A should follow aryl halide-mediated nucleophilic aromatic substitution. Interestingly, Sperry *et al.*[8] ascertained the structure of aspergilazine A through its total synthesis and used a palladium-catalyzed *N*-arylation in the presence of bromobrevianamide F to forge selectively the N-C bond at the desired position. Due to the similarity between aspergilazine A and tenuiphylline in terms of *N*-arylation substitution pattern, it is tempting to suggest that tenuiphylline (**1**) assembly process could obey to an aryl halide-mediated nucleophilic aromatic substitution. Although aryl halides are widespread in the marine ecosystem (aspergilazine A has been isolated from a marine source) to the best of our knowledge, no natural aryl halide-containing MIA has been described to

date. The unprecedented nature of this C-N bond in the vast ensemble of MIA oligomers appeals for further spectroscopic evidence before speculating on the possible biosynthetic mechanisms by which this bond was established.

4 Summarized figures for MIA oligmerization chemical logic.

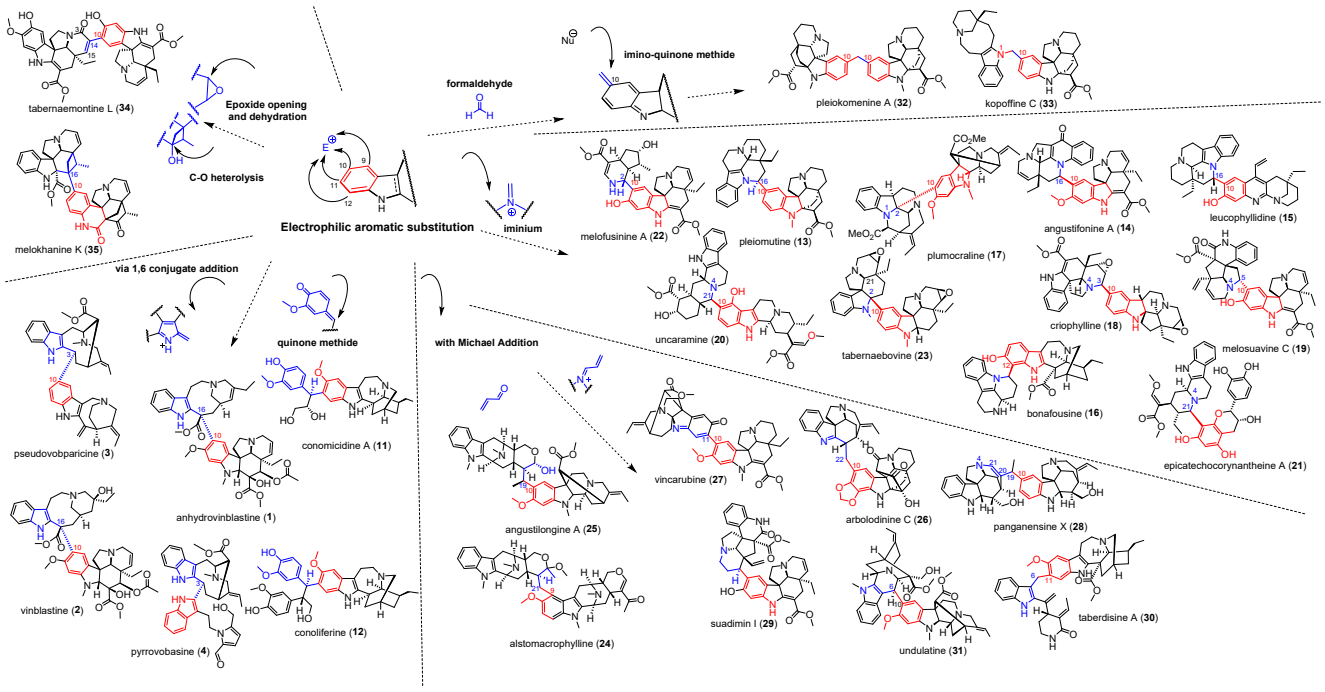


Fig. S2 Singly tethered oligomers resulting from an electrophilic aromatic substitution reactivity (see S2 for a comprehensive listing, red- and blue-colored moieties refer to nucleophilic and electrophilic sites, respectively)

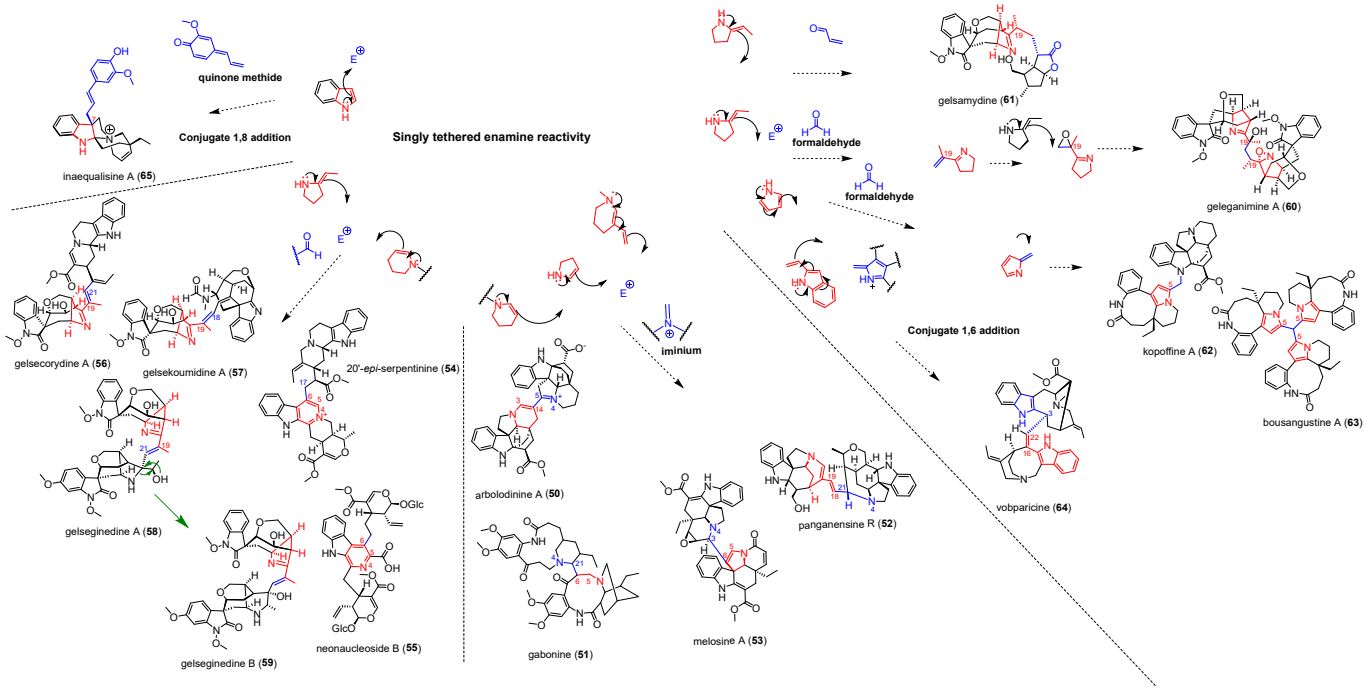


Fig. S3 Singly tethered oligomers resulting from an enamine reactivity (see S2 for a comprehensive listing, red and blue colored moieties refer to nucleophilic and electrophilic sites, respectively)

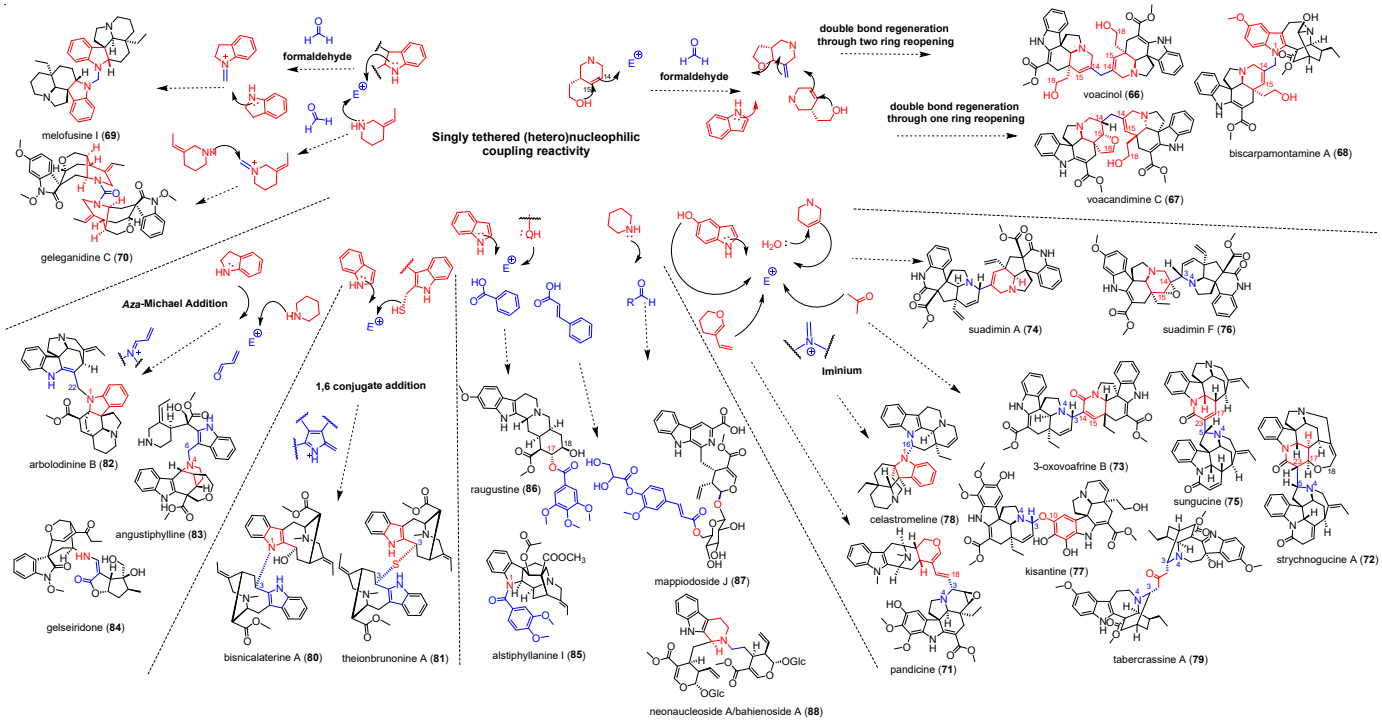


Fig. S4 Singly tethered oligomers resulting from an (hetero)nucleophilic coupling reactivity (see S2 for a comprehensive listing, red and blue colored moieties refer to nucleophilic and electrophilic sites, respectively)

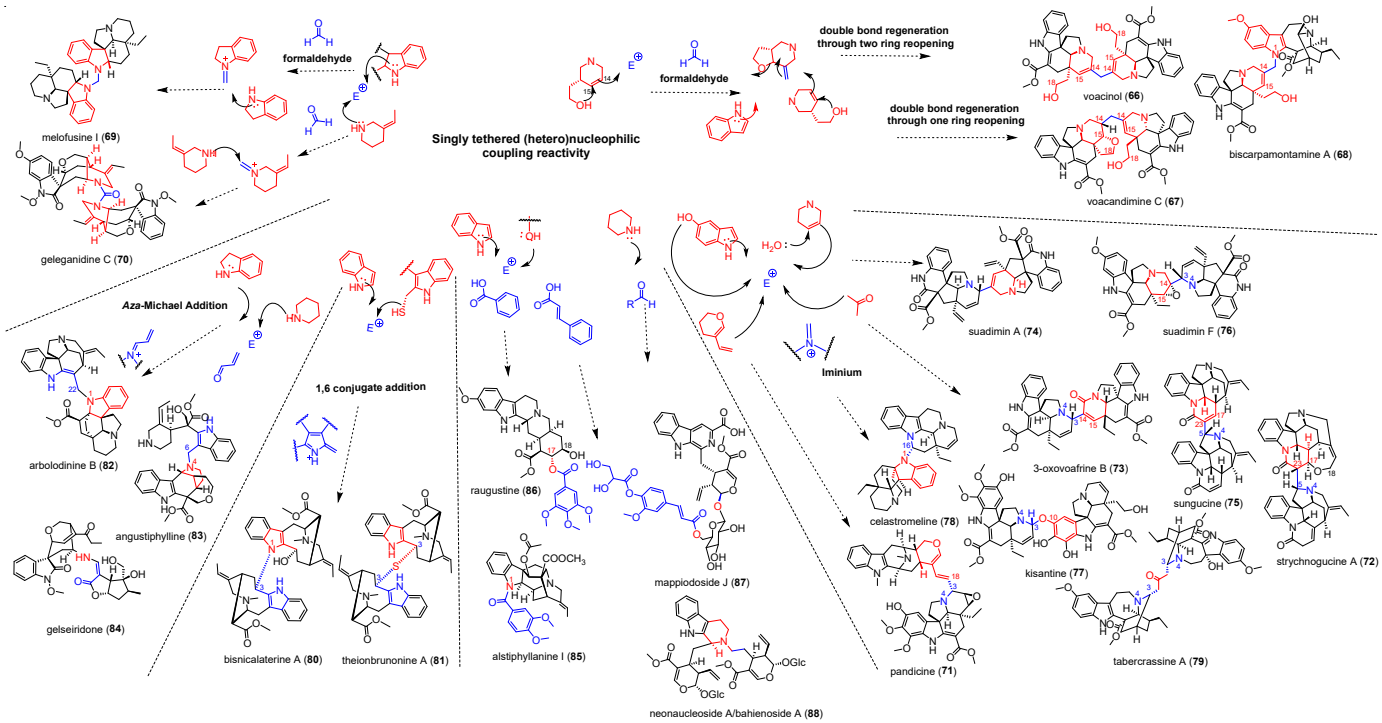


Fig. S5 Singly tethered oligomers resulting from an (hetero)nucleophilic coupling reactivity (see S2 for a comprehensive listing, red and blue colored moieties refer to nucleophilic and electrophilic sites, respectively).

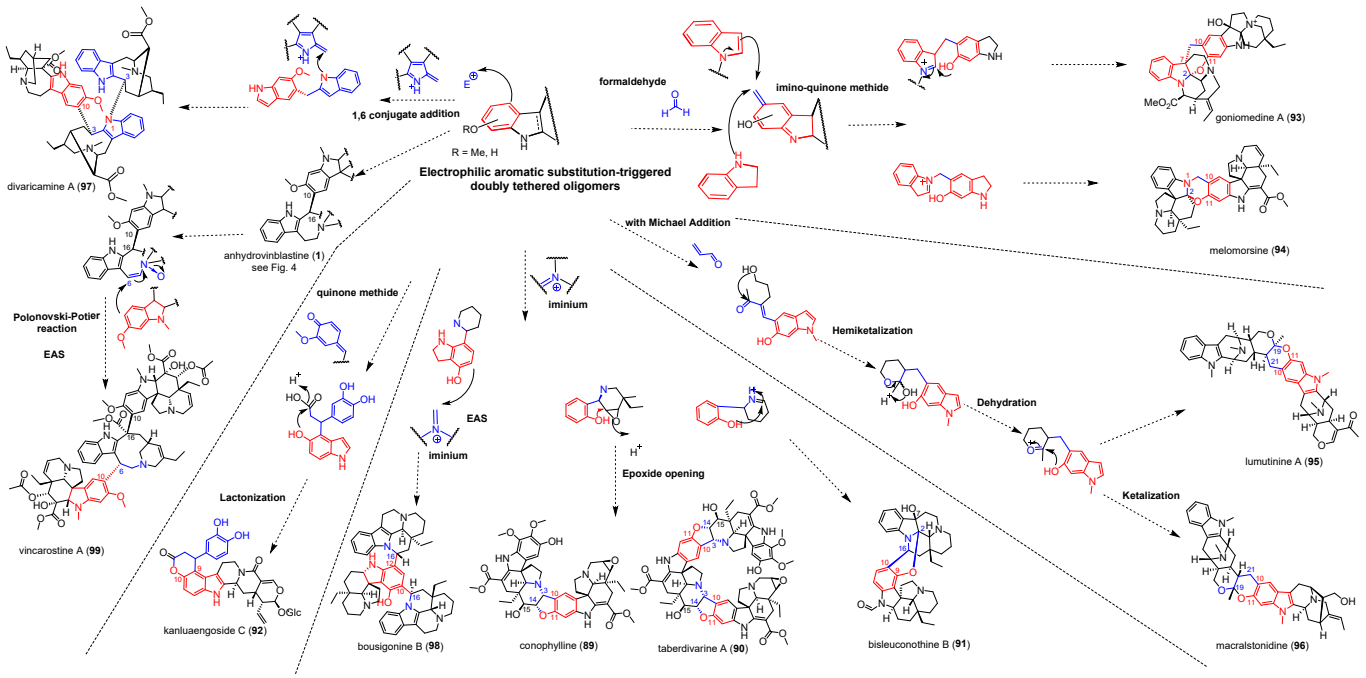


Fig. S6 Doubly tethered oligomers resulting from an electrophilic aromatic substitution and an heteronucleophilic attack (see S2 for a comprehensive listing, red and blue colored moieties refer to nucleophilic and electrophilic sites, respectively)

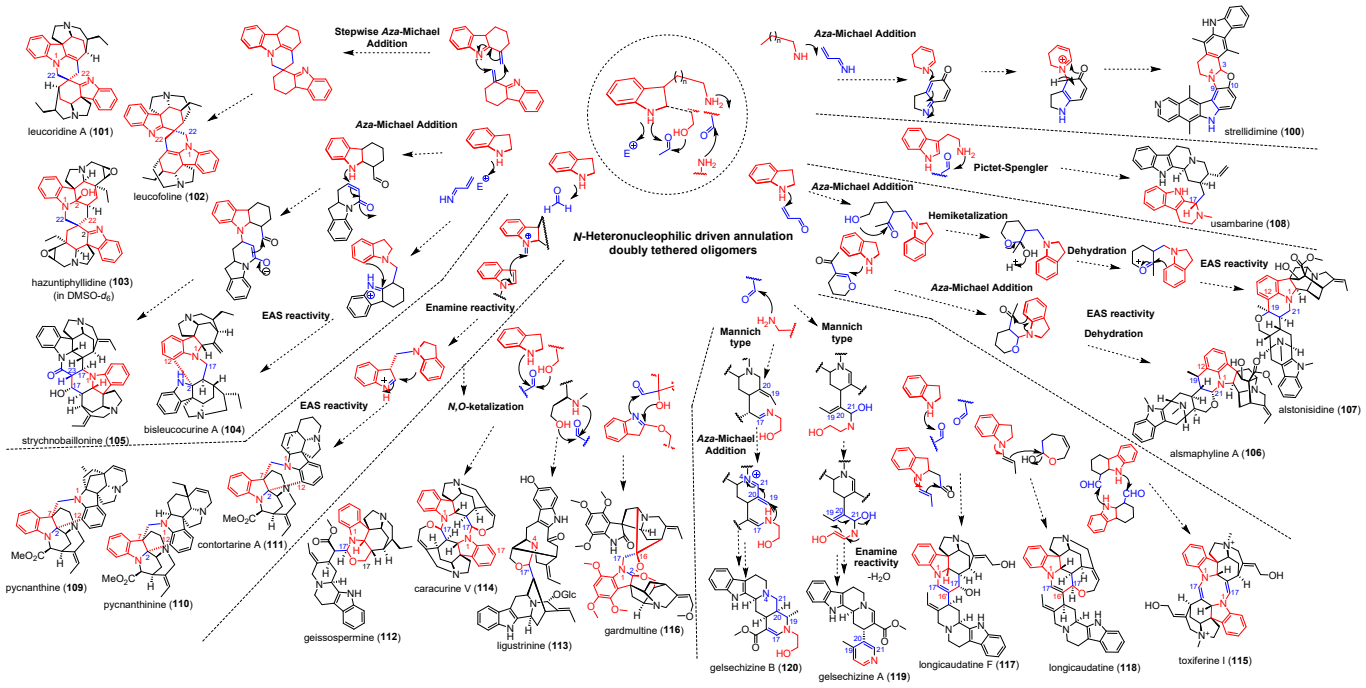


Fig. S7 Doubly tethered oligomers resulting from *N*-mediated nucleophilic attack (see S2 for a comprehensive listing, red and blue colored moieties refer to nucleophilic and electrophilic sites, respectively).

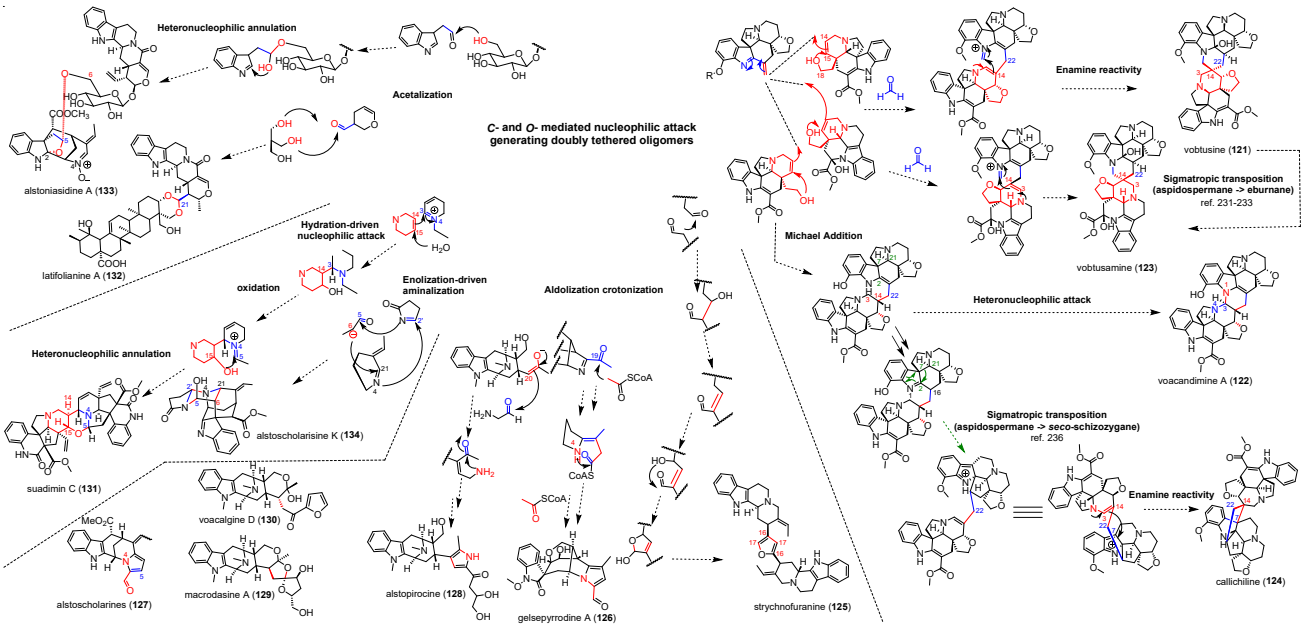


Fig. S8 Doubly tethered oligomers resulting from *C*- and *O*- mediated nucleophilic attack (see S2 for a comprehensive listing, red and blue colored moieties refer to nucleophilic and electrophilic sites, respectively)

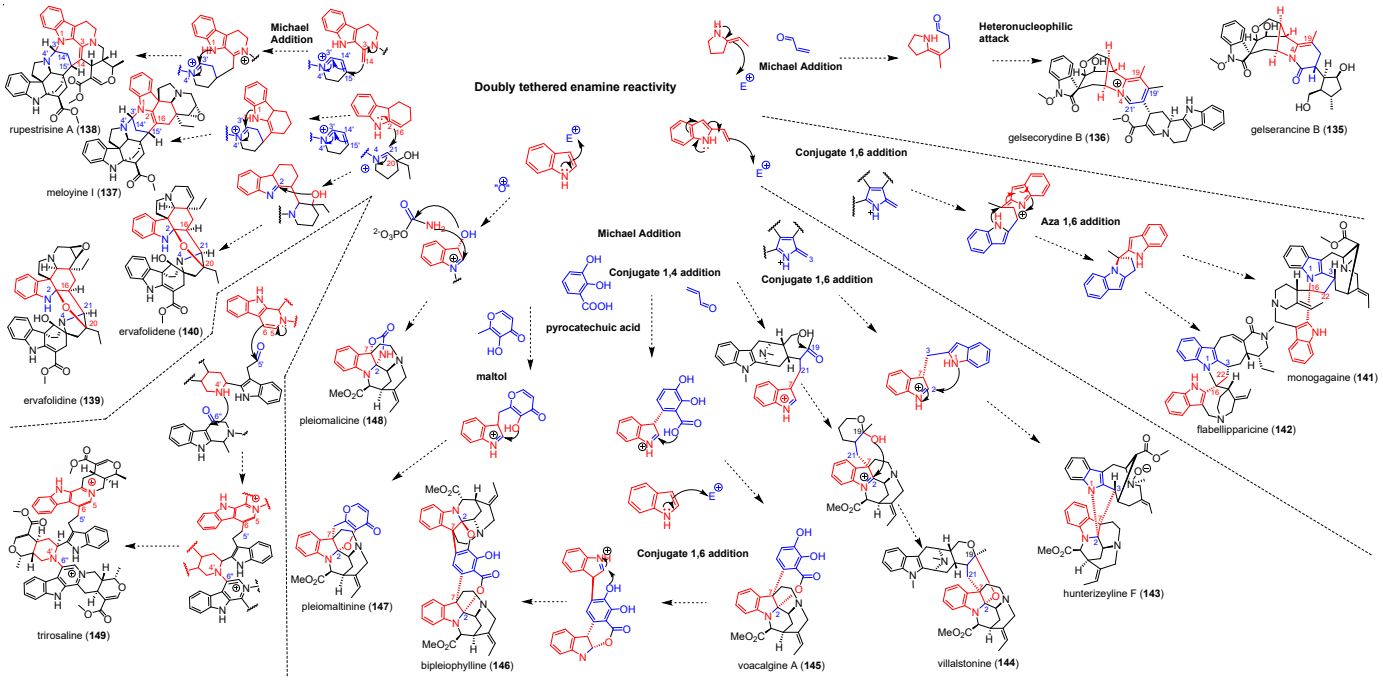


Fig. S9 Doubly tethered oligomers resulting from an enamine reactivity (see S2 for a comprehensive listing, red- and blue-colored moieties refer to nucleophilic and electrophilic sites, respectively).

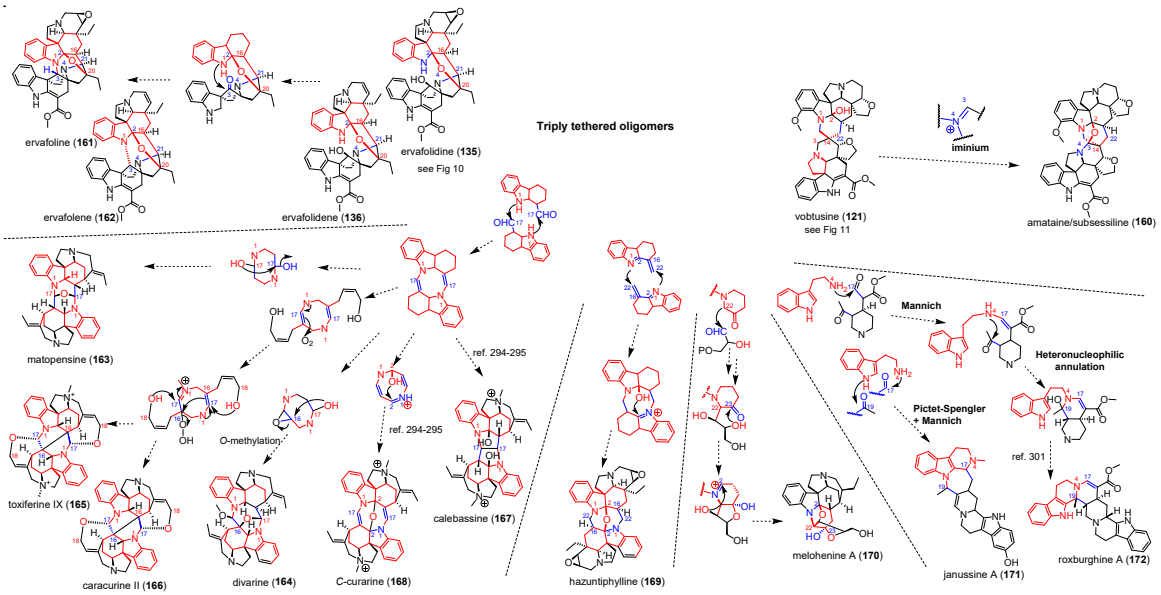


Fig. S10 Triply tethered oligomers (see S2 for a comprehensive listing, red and blue colored moieties refer to nucleophilic and electrophilic sites, respectively)

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