Natural Products as a Source of CNS-Active Agents

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Abstract: Disease and disorders of the central nervous system (CNS) are some of the most common ailments afflicting mankind, and it has been estimated that 32% of the population of the USA suffers from a disorder of the brain once in a lifetime, and 15% of the population over 18 suffer a mental disorder at least monthly. The use of natural products as psychotropic agents to alleviate mental disorders, or to create altered mental states, probably dates back to the dawn of time, when the first trial-and-error experiments by shamans or other experimenters led to the discovery of the effect of certain plant extracts on the mind. It is thus significant that the first alkaloid to be purified from a plant was the psychoactive analgesic morphine.

Although there is extensive literature on the use of plants and plant extracts as hallucinogenic agents, the search for natural products for therapeutic psychotropic purposes is much less well-developed than, for example, the search for anticancer agents. Nevertheless, there are enough examples of the successful search for useful naturally-occurring psychotropic agents to ensure that a continued search is likely to be productive.

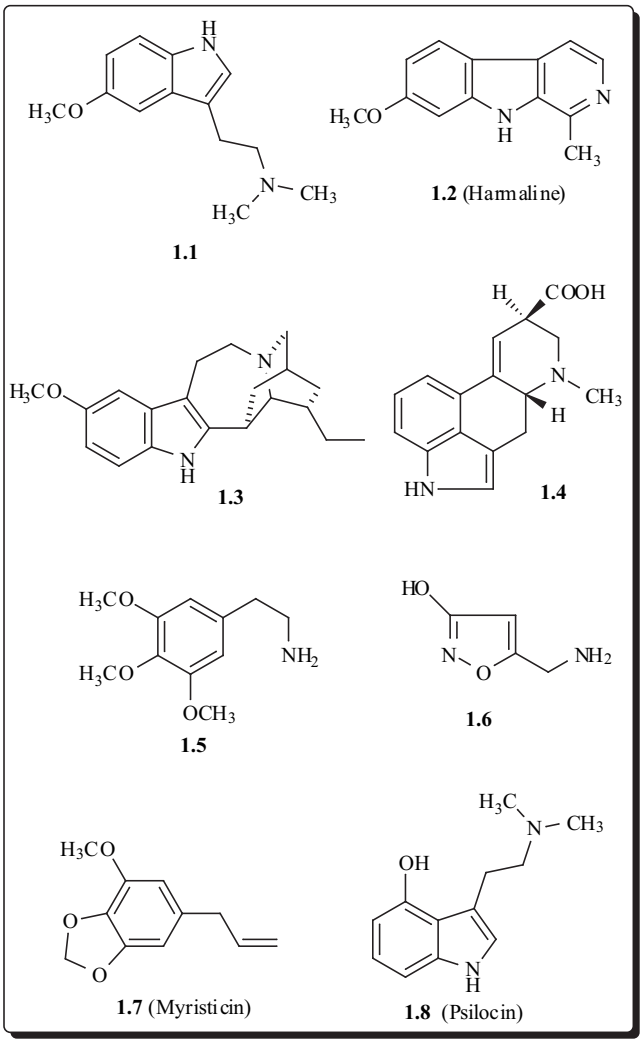
This review will summarize results in the discovery of CNS-active natural products, with an emphasis on compounds that may be useful for therapeutic purposes.

Hallucinogens

The majority of the hallucinogens listed below can be classified as "classic" drugs because their bioactivities have been known for decades (or even centuries), and often the drug's mechanism of action is well understood. Salvinorin A (**1.10**) is perhaps the most interesting of the recent hallucinogen discoveries. This neoclerodane diterpene targets the kappa opioid receptor and may be useful for the treatment of many psychiatric disorders. Ibogaine (**1.4**), on the other hand, is a well-known drug isolated from an African shrub that is receiving renewed interest. The inclusion of 5-methoxy-N,N-dimethyltryptamine (**1.1**) is notable because of its organisim of origin (a Sonoran resert toad), which is one of the rare animal sources of CNS drugs.

Stimulants

Like the hallucinogens, most known CNS stimulants have a long and well-documented history. Lesser known compounds include the helioscopinolides and mangiferin. Helioscopinolides A and D (**2.6**) are two newer diterpenoids from *Euphorbia calyptrata* with an excitatory capability. The xanthone mangiferin (**2.8**) also demonstrated a stimulatory ability through investigations on both frog heart and rat. Nicotine (**2.9**) is one of the best-known natural stimulants, but a recent study has also identified the drug as a potential treatment for Tourette's syndrome as well.



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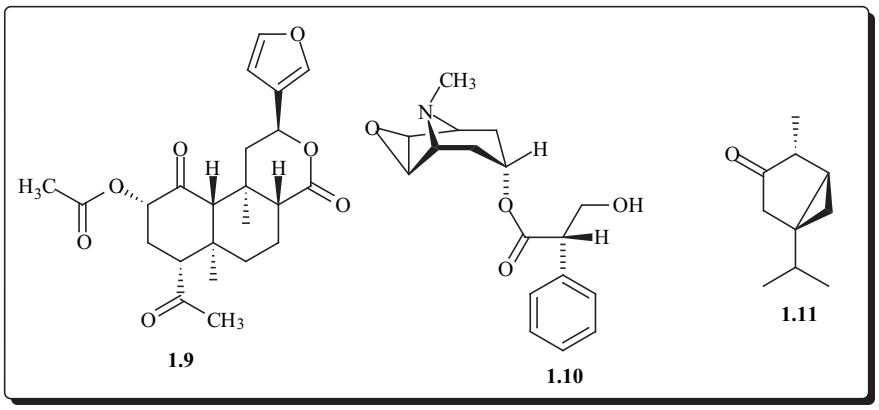


Table 1. Hallucinogens

Compound	Struct.	Organism	Type	Primary mechanism	Other CNS activities	Refs.
5-MeO-DMT	**1.1**	*Bufo alvarius*	A	5-HT_{2A} agonist		[1]
β-carbolines	**1.2**	*Banisteriopsis caapi*	P	5-HT_2 partial agonist	MAO inhibitors	[2-4]
Ibogaine	**1.3**	*Tabernanthe iboga*	P	Unknown	Blocks nicotine-induced DA release	[2,4-6]
Lysergic acid	**1.4**	*Claviceps purpurea*	F	5-HT_2 partial agonist		[2]
Mescaline	**1.5**	*Lophophora williamsi*	P	Monoaminergic	5-HT_{2A} agonist	[2]
Muscimol	**1.6**	*Amanita muscaria*	F	$GABA_A$ agonist		[2]
Myristicin, Elemicin	**1.7**	*Myristica fragrans*	P	Dopaminergic		[2]
Psilocybin, Psilocin	**1.8**	*Psilocybe* spp.	F	5-HT_2 partial agonist		[2,7]
Salvinorin A	**1.9**	*Salvia divinorum*	P	KOR agonist	Anti-Alzheimer's	[8-10]
Scopolamine	**1.10**	*Solanaceae* family	P	mAChR antagonist	REM sleep regulator	[2]
Thujone	**1.11**	*Artemisia absinthium*	P	GABA-gated chloride channel blocker		[11-13]

Abbreviations: 5-HT-serotonin, GABA-γ-aminobutyric acid, KOR- κ-opioid receptor, mAChR-muscarinic acetylcholine receptor, A = animal source, P = plant source, F = fungal source, MA = marine animal

Table 2. Stimulants

Compound	Struct.	Organism	Type	Primary mechanism	Other CNS activities	Refs.
Arecoline, Arecaidine	**2.1**	*Areca cathechu*	P	mAChR agonist		[2]
Caffeine	**2.2**	*Coffea arabica*	P	Adenosine antagonist	Analgesic	[2]
Cathinone	**2.3**	*Catha edulis*	P	DA (or NE) release	Analgesic	[2]
Cocaine	**2.4**	*Erythroxylon coca*	P	Monoamine reuptake blocker	Analgesic	[2]
Ephedrine	**2.5**	*Ephedra sinica*	P	α-,β-adrenoceptor agonist	NE release	[2]
Helioscopinolides A/D	**2.6**	*Euphorbia calyptrata*	P	unknown		[14]
Lobeline	**2.7**	*Lobelia inflata*	P	nAChR agonist		[2]
Mangiferin	**2.8**	*Canscora decussata*	P	unknown	Antidepressant	[15]
Nicotine	**2.9**	*Nicotiana tobacum*	P	nAChR agonist	Tourette's	[2,16]

DA-dopamine, nAChR-nicotinic acetylcholine receptor

Analgesics

The development of new analgesic drugs is an area of high interest. This is evidenced by the many discoveries of novel and interesting bioactive compounds from natural sources. The most significant isolation of the past few decades is epibatidine (**3.4**), from the skin of an Ecuadorian

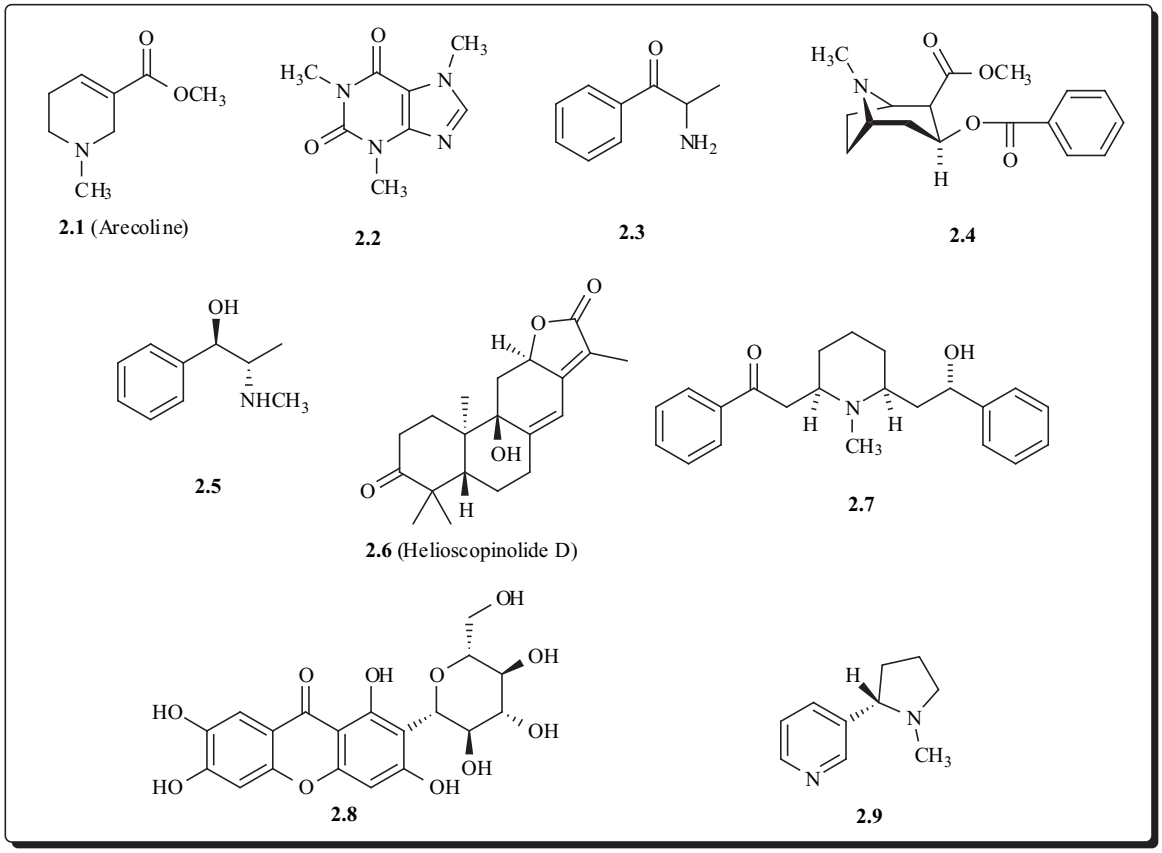


Table 3. Analgesics

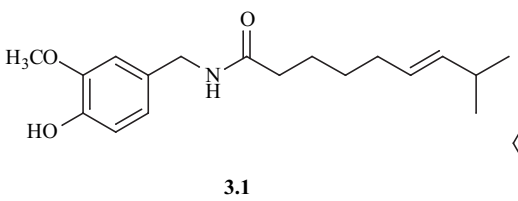
Compound	Struct.	Organism	Type	Primary mechanism	Other CNS activities	Refs.
Capsaicinoids	**3.1**	*Capsicum annum*	P	Vanilloid receptor agonist		[2]
Cinnamyl derivatives	**3.2**	*Cinnamomum cassia*	P	Interleukin-1α regulatory activity	Antipyretic	[17]
Curcurbitacins	**3.3**	*Kageneckia oblonga*	P	unknown	Antipyretic	[18]
Epibatidine	**3.4**	*Epibatadores tricolor*	A	nAChR agonist		[19,20]
Furanoeudesma-1,3-diene, Curzarene	**3.5**	*Commiphora molmol*	P	Central opioid receptor binding		[21,22]
GB1a, GB2a	**3.6**	*Rheedia gardneriana*	P	unknown		[23]
Ginsenoside Rf.	**3.7**	*Panax ginseng*	P	Ca^{2+} channel inhibition		[24]
Kyotorphin	**3.8**	Bovine brain	A	Opioid		[25]
Mitragynine	**3.9**	*Mitragyna speciosa*	P	Opioid receptor agonist	Antitussive	[26-28]
Morphine, Codeine	**3.10**	*Papaver somniferum*	P	MOR agonist	Antitussive	[2]
Parthenolide	**3.11**	*Tanacetum parthenium*	P	Eicosanoid inhibitor		[2]
Pseudopterosins A/E	**3.12**	*Pseudopterogorgia elisabethae*	MA	unknown		[29]
Pericalline, Pericine	**3.13**	*Picralima nitida*	P	Opioid receptor binding		[30]
Salicin	**3.14**	*Salix* spp.	P	Prostaglandin synthesis inhibitor		[2]
Swertiamarin	**3.15**	*Anthocleista* sp.	P	unknown		[31]
Usnic acid, Diffractic acid	**3.16**	*Usnea diffracta*	P	unknown	Antipyretic	[32]

MOR-μ-opioid receptor

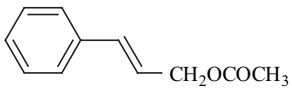
frog. This nicotinic acetylcholine agonist was quickly synthesized by a number of research groups, and it will likely be closely studied in the future. A closer look at the ancient substance myrrh led to the identification of the analgesic compounds furanoeudesma-1,3-diene (**3.5**) and curzarene, two known sesquiterpenes with previously unknown bioactivities. The alkaloid mitragynine (**3.10**) from a Thai herb is also a significant analgesic discovery due to its opioid receptor agonism.

Antitussives

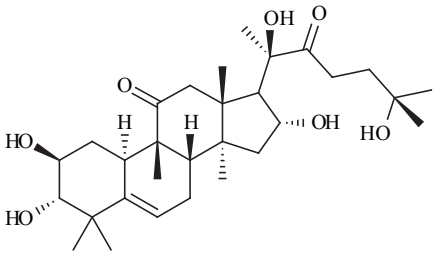
There have been few recent discoveries of stand-alone antitussive drugs, but this type of bioactivity can occasionally be found in other CNS-active compounds. Kardosova and Nosal'ova have discovered glucuronoxylan polysaccharides with significant antitussive activity in a pair of different plants, and these molecules suggest a greater activity in cats than some drugs in clinical use. In Chinese herbal medicine, species of the *Asiasarum* genus have



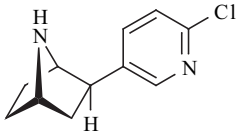
3.1



3.2 (Acetic acid cinnamylester)



3.3 (23,24-dihydrocurcurbitacin F)



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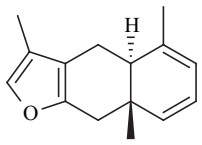
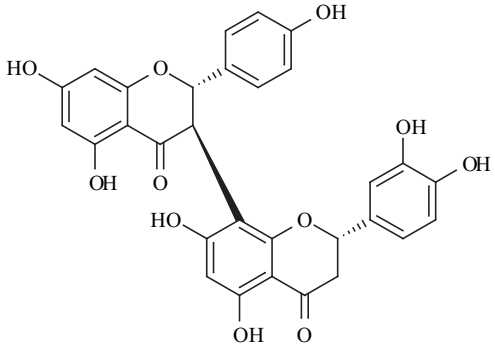
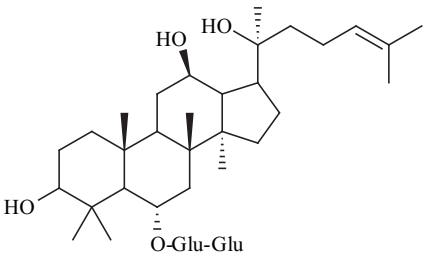


3.5 (Furanoeudesma-1,3-diene)



3.6 (GB2a)



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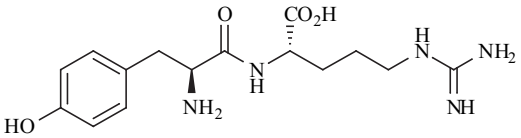

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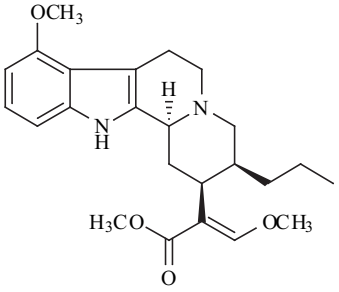

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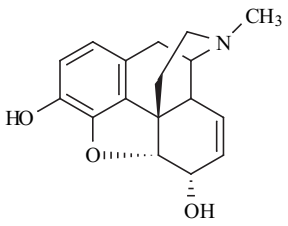


3.10 (Morphine)

traditionally been used as an expectorant and cough suppressant. The discovery of the active principle, higenamine-HCl (**4.2**), has led to a renewed interest in these plants and the larger family from which they derive. Another antitussive discovery rooted in traditional Chinese medicine is the isolation of the novel alkaloid puqiedinone (**4.3**) from *Fritillaria puquiensis*.

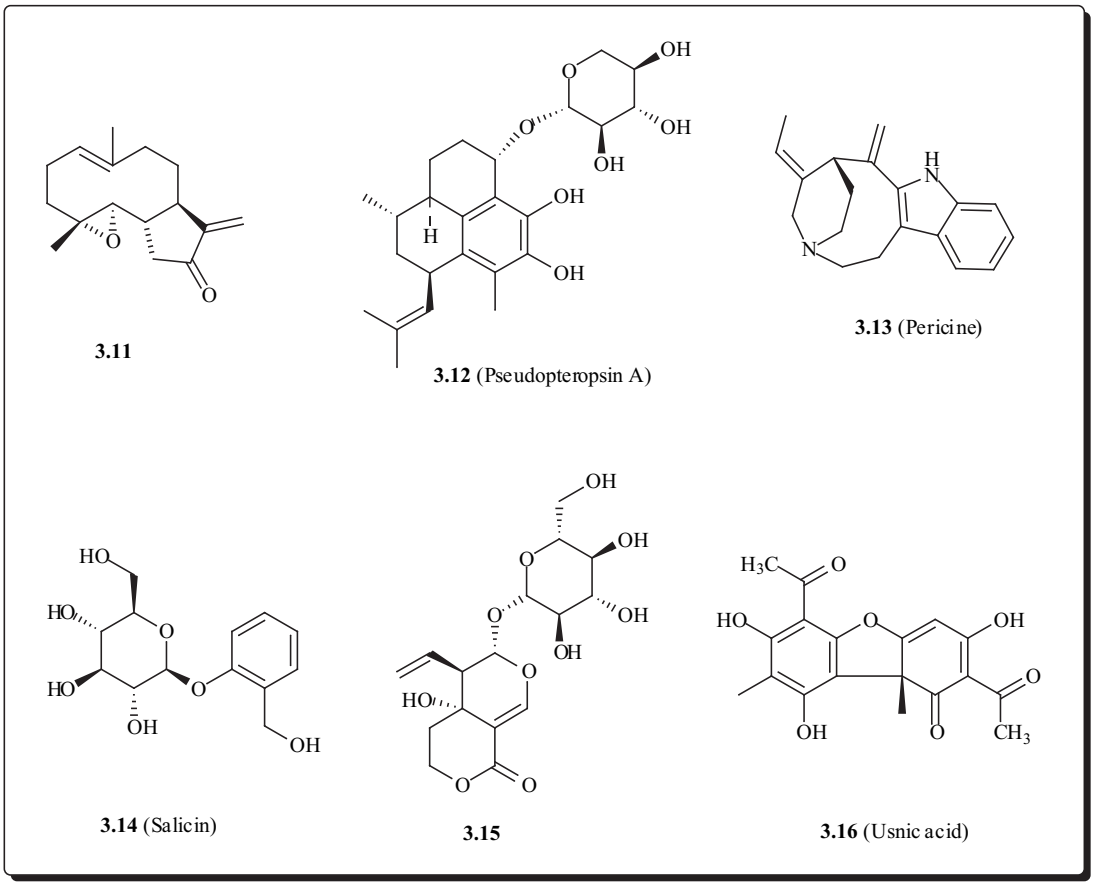
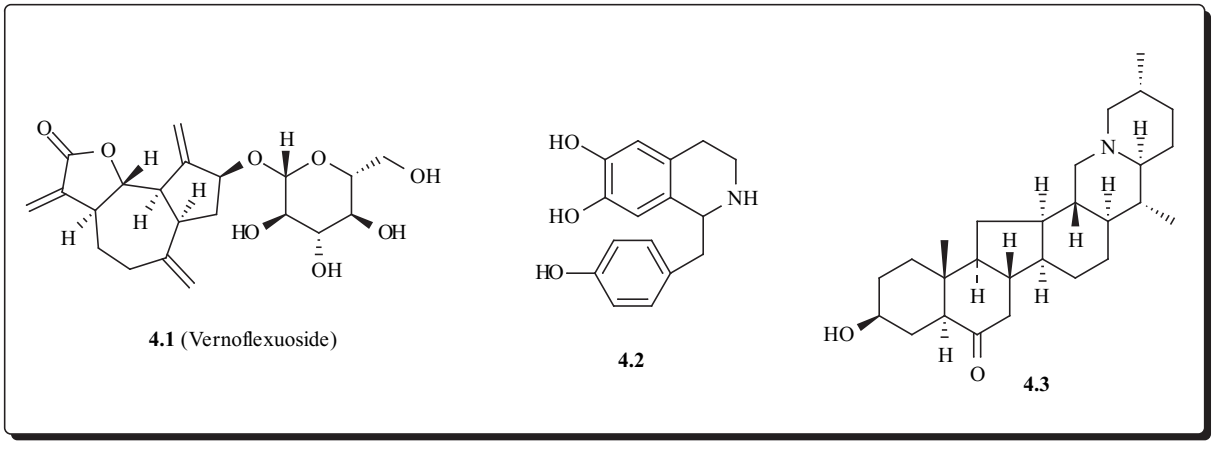


Table 4. Antitussives

Compound	Struct.	Organism	Type	Primary mechanism	Other CNS activities	Refs.
Glucuronoxylans	-	*Rudbekia fulgida*	P	unknown		[33,34]
Guaianolides	**4.1**	*Lactuca virosa*	P	unknown	Analgesic, sedative	[35]
Higenamine-HCl	**4.2**	*Asiasarum heterotropoides*	P	β-adrenergic stimulant		[36]
Puqiedinone	**4.3**	*Fritillaria pugiensis*	P	unknown		[37]



Muscle Relaxants

The most interesting of the recent muscle relaxant discoveries are all products of marine isolation work. Sea sponges have been the source of two terpene classes of compounds with antispasmodic activity. Agelasidines A, B and C (**5.1**) were obtained from *Agelas* sp. and demonstrate smooth muscle contractile inhibition on guinea pig ileum. The same research group also identified a furanosesterterpene, hippospongin (**5.5**), that was present in a different Okinawa sea sponge, but antispasmodic in the same bioassay. Flustramines A and B (**5.4**) are brominated alkaloids discovered in *Flustra foliacea*, a marine bryozoan, that relax both smooth and skeletal muscle.

Sedative-Hypnotics

Over the past few decades, bioassays have suggested the successful identification of a number of sedative-hypnotic drug targets, but only a handful have seen further study. Two of the most promising leads are apigenin and galphimine B. Apigenin (**6.1**) is a rather uninteresting flavonoid from *Matricaria chamomilla* that produces sedative and spasmolytic results. The exact neurotransmission pathway involved *in vivo* is not fully understood, but it is believed that $GABA_A$-benzodiazepine receptors may be involved. A triterpenoid from *Galphimia glauca*, galphimine B (**6.9**), is also showing potential as a sedative with activity on ventral tegmental area neurons in the dopaminergic system.

Table 5. Muscle Relaxants

Compound	Struct.	Organism	Type	Primary mechanism	Other CNS activities	Refs.
Agelasidine A-C	**5.1**	*Agelas* sp.	MA	Antispasmodic		[38,39]
Coumarins	**5.2**	*Boenninghausenia albiflora*	P	Spasmolytic on guinea pig ileum		[40]
Cyclanoline	**5.3**	*Cyclea insularis*	P	Muscarinic		[41]
Flustramine A and B	**5.4**	*Flustra foliacea*	MA	Smooth and skeletal muscle relaxant		[42,43]
Hippospongin	**5.5**	*Hippospongia* sp.	MA	Antispasmodic		[44]
Pluchine	**5.6**	*Pluchea lanceolata*	P	Smooth muscle relaxant spasmolytic		[45]
Steponine	**5.7**	*Stephania japonica*	P	Muscarinic		[42]

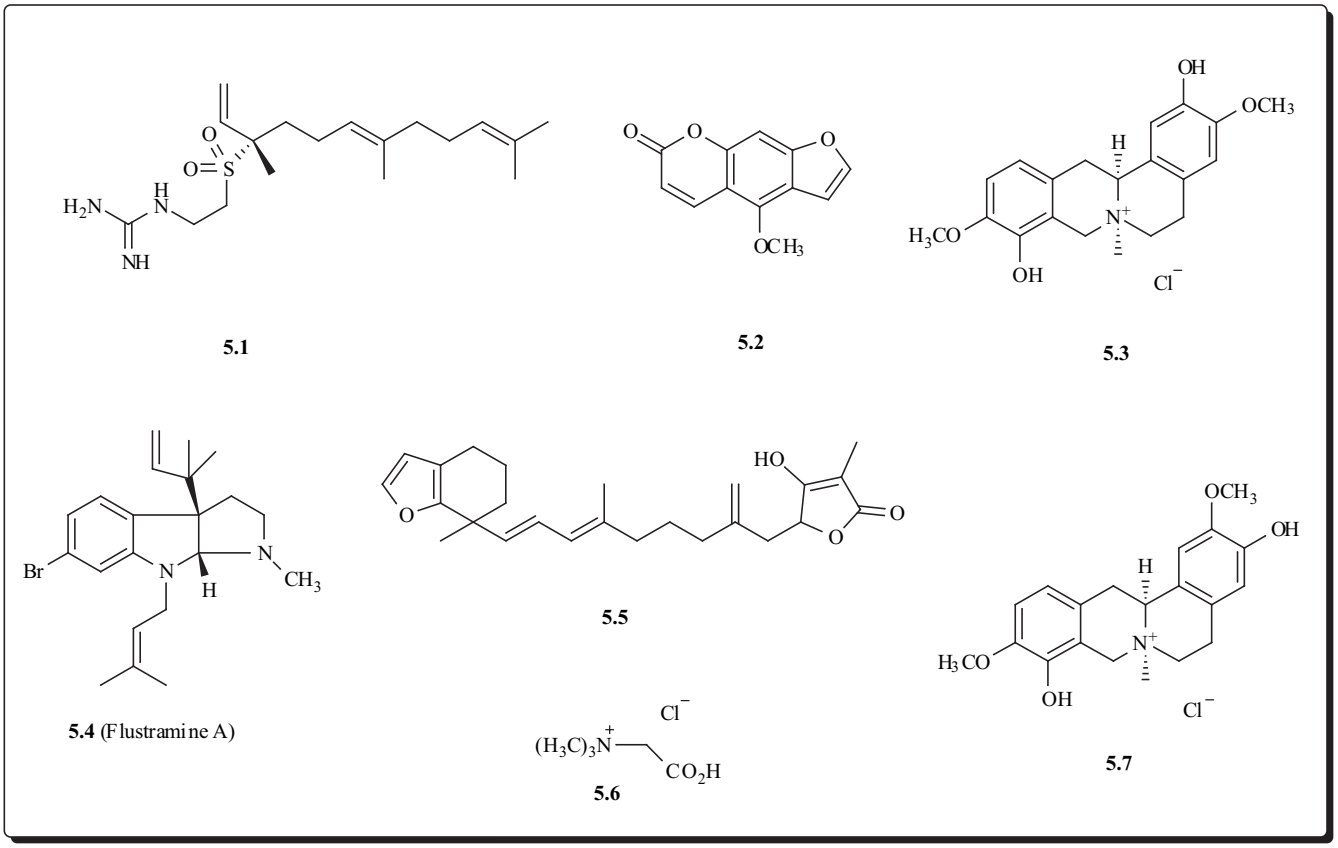
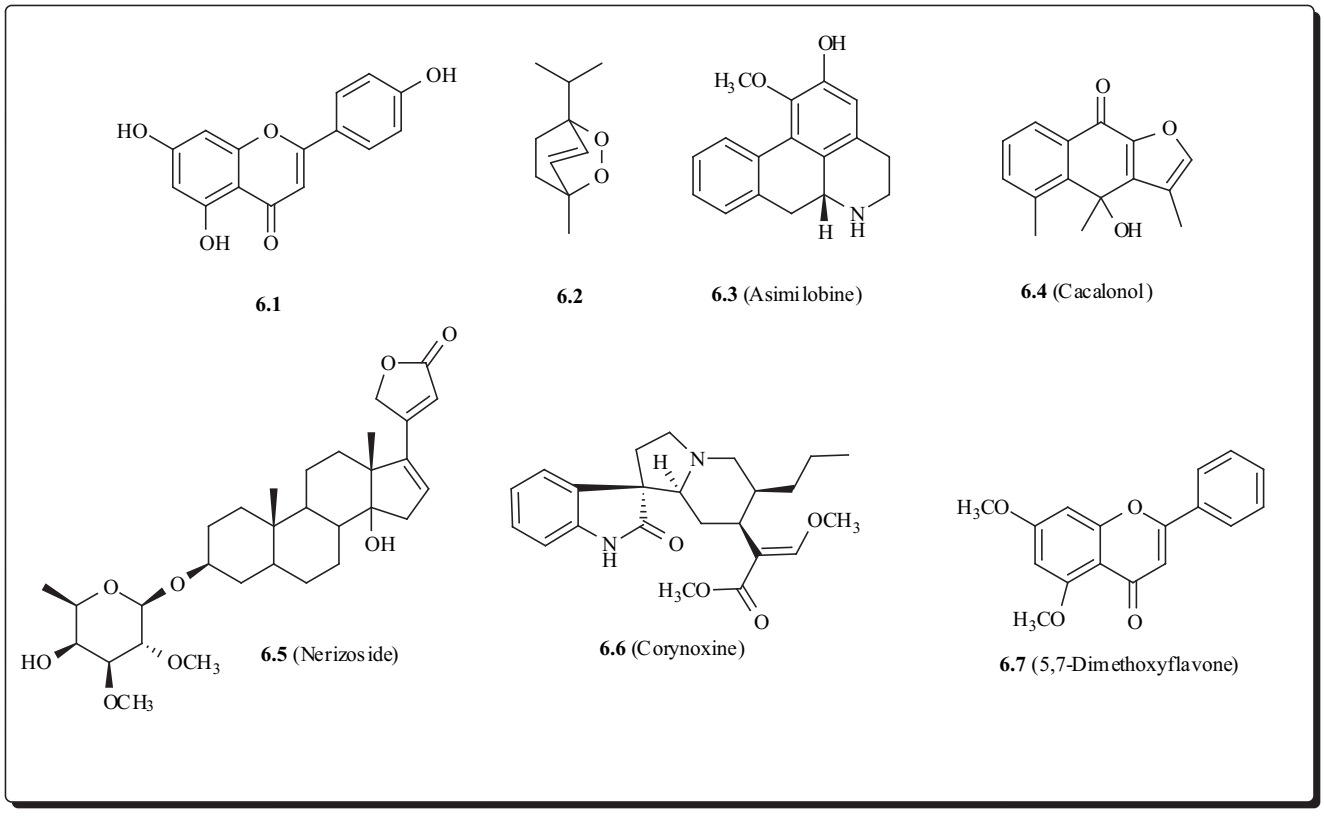
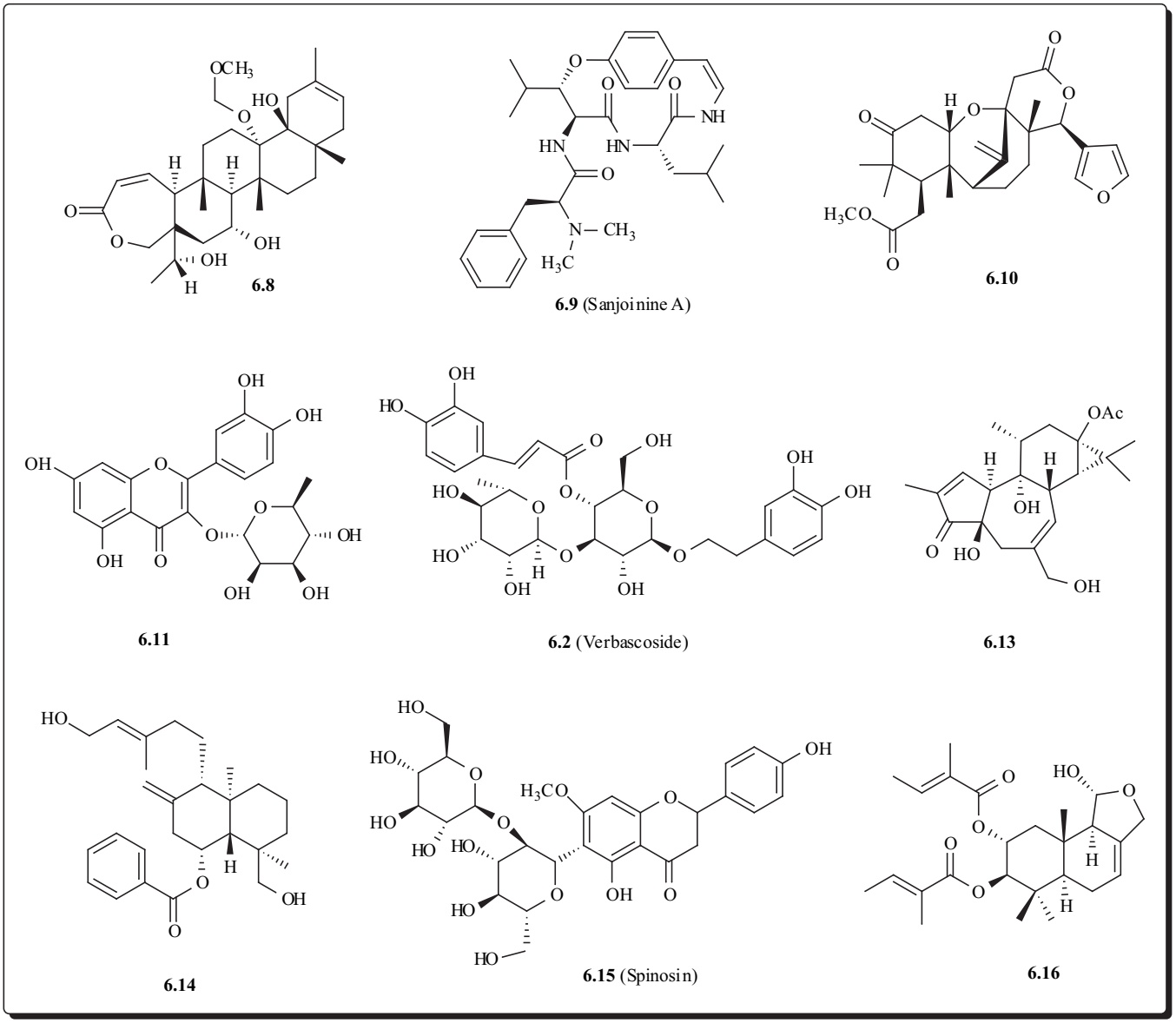


Table 6. Sedative-Hypnotics

Compound	Struct.	Organism	Type	Primary mechanism	Other CNS activities	Refs.
Apigenin	**6.1**	*Matricaria chamomilla*	P	GABA-activated Cl^- current reducer	Spasmolytic	[46]
Ascaridole	**6.2**	*Chenopodium ambrosioides*	P	unknown	Analgesic	[47]
Asimilobine, Annonaine, Nornuciferine	**6.3**	*Annona muricata*	P	5-HT_{1A} agonist	Anti-depressant	[48]
Cacalohastine, Cacalonol	**6.4**	*Culcitium canescens*	P	unknown	Analgesic, antipyretic	[49]
Cardenolides	**6.5**	*Nerium oleander*	P	unknown		[50]
Corynoxine, Rhynchophylline	**6.6**	*Uncaria macrophylla*	P	Prolonged thiopental induced hypnosis	Glutamatergic	[51,52]
Flavonoids	**6.7**	*Leptospermum scoparium*	P	BD-receptor binder		[53,54]
Galphimine B	**6.8**	*Galphimia glauca*	P	Dopaminergic		[55,56]
Jujubosides	**6.9**	*Zizyphus* spp.	P	Ca^{2+}-ATPase inhibitor		[57,58]
Methyl angolensate	**6.10**	*Entandrophragma angolense*	P	unknown	Inhibits 5-HT-induced GI contractions	[59-61]
Quercitrin	**6.11**	*Albizzia julibrissin*	P	Increases phenobarbital sleep time	Antispasmodic	[62]
Phenylpropanoids	**6.12**	*Ballota nigra*	P	Binds to BD, DA, and MOR receptors		[63]
Prostratin	**6.13**	*Euphorbia fischeriana*	P	unknown	Analgesic	[64]
Scoparinol	**6.14**	*Scoparia dulcis*	P	Potentiates phenobarbital-induced sedation	Analgesic, diuretic	[65]
Spinosin, Swertish	**6.15**	*Ziziphus jujuba*	P	unknown		[66]
Stagninol	**6.16**	*Persicaria stagnina*	P	Potentiates phenobarbital-induced sedation	Analgesic, diuretic	[67,68]

BD-benzodiazepine





Antidepressants

Although natural products isolation work has led to few recent antidepressant discoveries, the three compounds listed form a potent trio of possibilities. Beta-amyrin palmitate (**7.1**), from the leaves of *Lobelia inflate*, may be involved in norepinephrine release and noradrenergic activation. Hyperforin (**7.2**) is only one of the many active components in Saint-John's-wort, and is currently under intense investigation as an inhibitor of catechol-O-methyltransferase. Antidepressant-like inhibition effects have also been observed with rosmarinic acid (**7.3**) among mice subjected to fear stress.

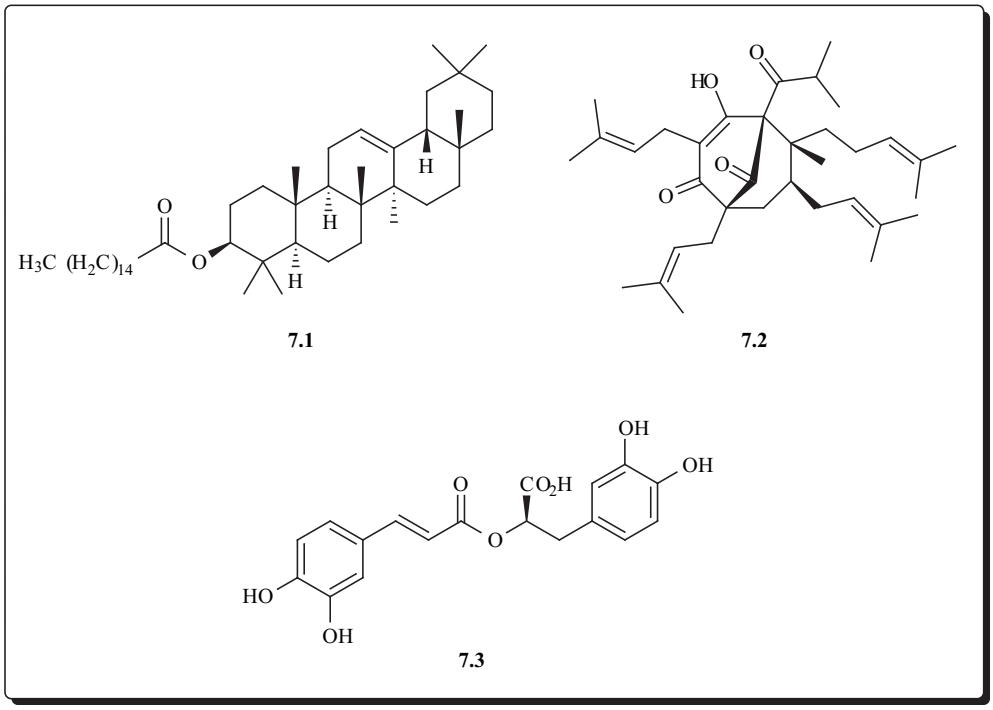
Anxiolytics

On the spectrum of CNS depressant drugs, anxiolytics represent the mildest of inhibitory effects. Kavain (**8.2**) is the most recognizable (and only significant member) of this group of anxiolytics, due to its origin in kava, the well-studied South Pacific plant. Both the ginkgolic acids (**8.1**)

Table 7. Antidepressants

Compound	Struct.	Organism	Type	Primary mechanism	Other CNS activities	References
β-Amyrin palmitate	**7.1**	*Lobelia inflata*	P	Causes NE release		[69]
Hyperforin	**7.2**	*Hypericum perforatum*	P	COMT inhibition		[2,70]
Rosmarinic acid	**7.3**	*Perilla frutescens*	P	unknown		[71]

NE-norepinephrine, COMT-catechol-O-methyltransferase

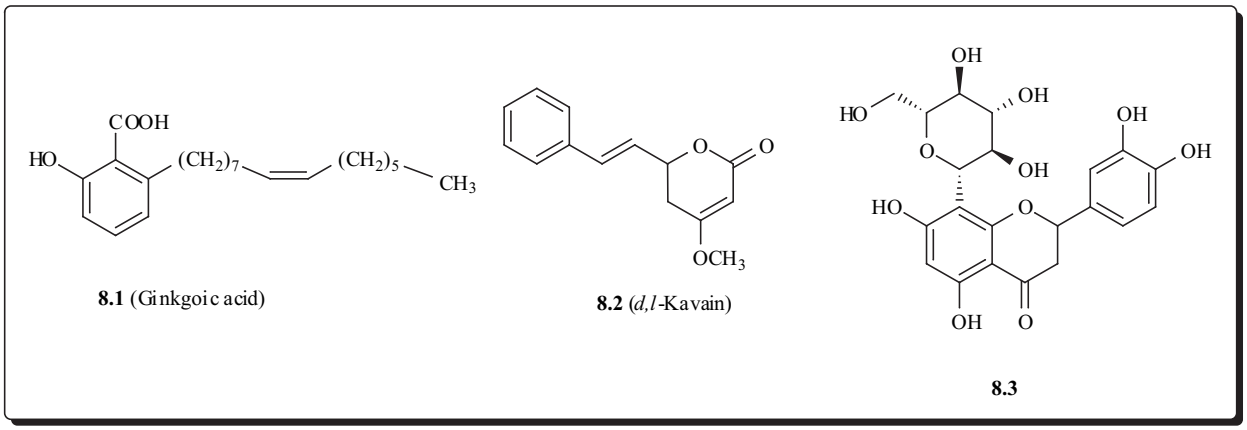


7.1 **7.2**

7.3

Table 8. Anxiolytics

Compound	Struct.	Organism	Type	Primary mechanism	Other CNS activities	Refs.
Ginkgolic acids	**8.1**	*Ginkgo biloba*	P	unknown		[72]
Kavain	**8.2**	*Piper methysticum*	MP	Ca^{2+} channel inhibition	Analgesic, muscle relaxant	[2,73]
Orientin	**8.3**	*Jatropha cilliata*	P	unknown	Anti-conflict	[74]



8.1 (Ginkgoic acid) **8.2** (*d,l*-Kavain)

8.3

and orientin (**8.3**) documentations are isolated associations between structure and activity.

Antipsychotics

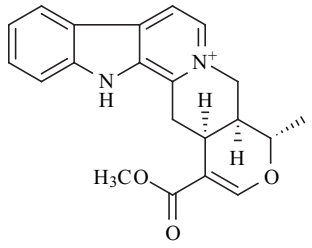
Among the novel discoveries of potential antipsychotic drugs from natural sources are two compounds of high interest. The first is actually a class of amino acid sequences produced by a fungal strain. Ampullosporins A, B, and D (**9.2**) all are purported to have similar, strong neuroleptic activities. The neolignoid mannasantin A (**9.5**) also appears to act as a neuroleptic agent, although its mechanism of action appears to be less common and difficult to identify.

Anti-Alzheimer's Disease Agents

Alzheimer's disease (AD) is a neurodegenerative disorder that afflicts a high percentage of people over the age of 80. The most notable symptoms of AD are memory loss and the formation of plaques and tangles in the brain of the patient. Deficiencies in several neurotransmitters have been observed with AD, but the most important target of interest in AD

Table 9. Antipsychotics/Neuroleptics

Compound	Struct.	Organism	Type	Primary mechanism	Other CNS activities	Refs.
Alstonine	**9.1**	*Alstonia muelleriana*	P	unknown		[75]
Ampullosporins A/B/D	**9.2**	*Sepedonium ampullosporum*	F	unknown	Antipyretic	[76]
Dichotosin, Dichotosinin	**9.3**	*Hoppea dichotoma*	P	Adaptogenic		[77]
Diffutin	**9.4**	*Canscora diffusa*	P	Adaptogenic		[78]
Manassantin A	**9.5**	*Saucurus cernuus*	P	unknown		[79-81]
Skimmianine	**9.6**	*Rutaceae* family	P	unknown	Antispasmodic	[82]

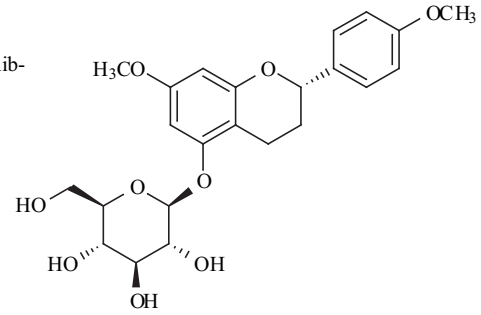


9.1

Ac-L-Trp-L-Ala-Aib-Aib-L-Leu-Aib-L-Gln-Aib-Aib-Aib-L-Gln-L-Leu-Aib-L-Gln-L-Leuol

Ac-L-Trp: *N*-Acetyl-L-tryptophane
Aib: α-aminoisobutyric acid
L-Leuol: L-Leucinol

9.2 (Ampullosporin A)



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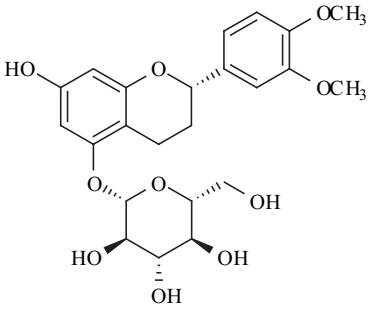

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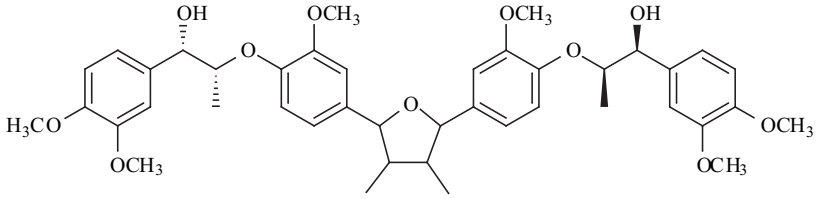

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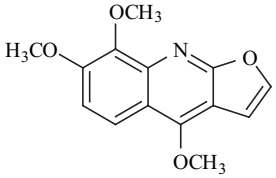


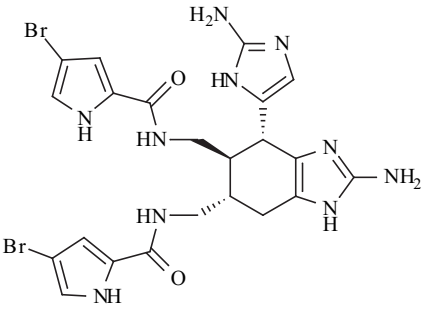
9.6

drug research has been the cholinergic system. These efforts aim to stabilize the levels of acetylcholine (ACh) in the brain by preventing its breakdown or by modulating its activity at the ACh receptor. Currently, there is interest in galanthamine (**10.5**), which is a potent inhibitor of the enzyme acetylcholinesterase (AChE). AchE is part of the system which regulates Ach levels in the brain, and inhibiting this enzyme leads to higher Ach levels and improved cognitive function. Huperzine A (**10.7**) is also a potent AChE inhibitor of current interest. Other areas of anti-Alzheimer research include targeting neurite growth factor (NGF) and neuroprotective agents. NGF has been shown to ease memory loss and prevent cholinergic neuronal loss in rats [102], and sargaquinoic acid (**10.9**) has been shown to promote NGF-mediated neurite outgrowth. With neuroprotective agents, it is hoped that agents like **10.12** can prevent oxidative stress in the brain and therefore prevent AD onset.

Table 10. Anti-Alzheimer's Agents

Compound	Struct.	Organism	Type	Mechanism	Other CNS activities	Refs.
Ageliferine	**10.1**	*Agelas novaecaledoniae*	MA	SRIF and/or VIP inhibitors	Antimuscarinic activity	[83,84]
Arisugacin A	**10.2**	*Penicillium* sp. FO 4259	F	Potent, selective AChE inh.		[85,86]
Corynoline	**10.3**	*Corydalis incisa*	P	Reversible, non- competitive AChE inhibitor		[87-89]
Dehydroevodiamine·HCl	**10.4**	*Evodia rutaecarpa*	P	Noncompetitive AChE inh.,	Blood flow enhancer	[90-92]
Galanthamine	**10.5**	*Narcissus* sp.	P	Specific competitive AChE inhibitor		[93,94]
Hericenones C-G	**10.6.1-2**	*Hericium erinaceus*	P	NGF synthesis promoter		[95-97]
Huperzine A	**10.7**	*Huperzia serrata*	P	AChE inh.		[98]
Neuroprotectins A and B	**10.8.1-2**	*Streptomyces* sp. Q27107	P	Glutamate toxicity protectant	Possibly anti-HIV	[99,100]
Sargaquinoic acid	**10.9**	*Sargassum macrocarpus*	MP	Promoter of NGF-mediated neurite outgrowth		[101,102]
Sceptrin	**10.10**	*Agelas novaecaledoniae*	MA	SRIF and/or VIP inhibitors	Antimuscarinic activity	[84,103,104]
Sitoindosides	**10.11.1-2**	*Withania somnifera*	P	Affect cholinergic system	IX: COX-2 inh.	[105, 106]
TDB	**10.12**	*Symphyocladia latiuscula*	MP	Peroxynitrite scavenging		[107, 108]
Xestospongine B	**10.13**	*Xestospongia* sp.	MA	SRIF and/or VIP inhibitors	Antimuscarinic activity	[84, 109]
Zeatin	**10.14**	*Fiatoua villosa*	P	AChE inhibitor		[110,111]

SRIF-somatotropin release inhibiting factor, VIP-vasoactive intestinal peptide, COX-2 – cyclooxygenase-2



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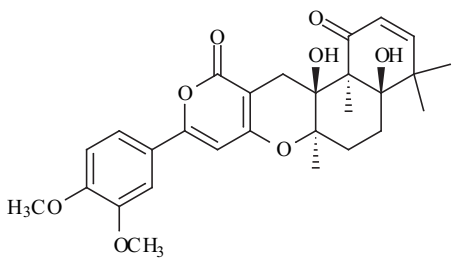

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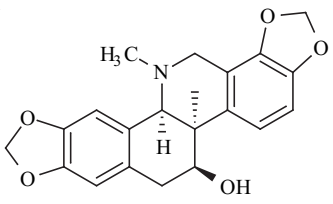

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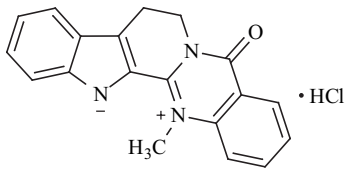

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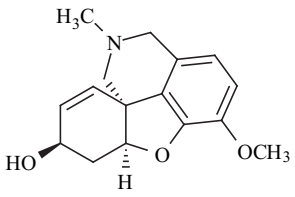

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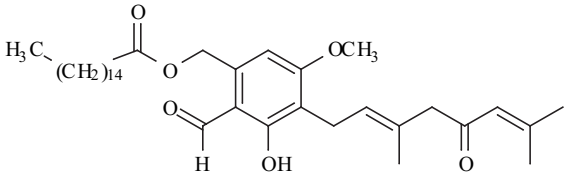
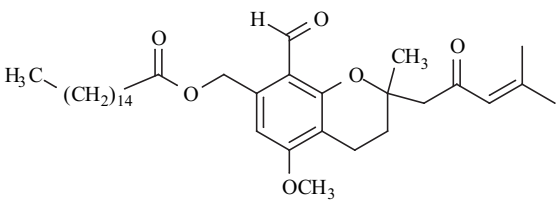
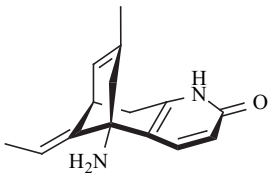


10.6.1 (Hericenone C)



10.6.2 (Hericenone F)



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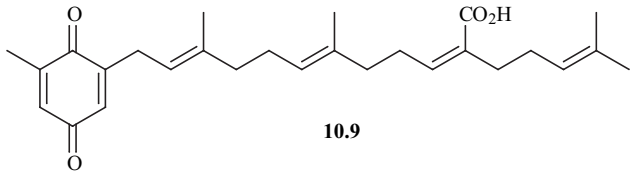

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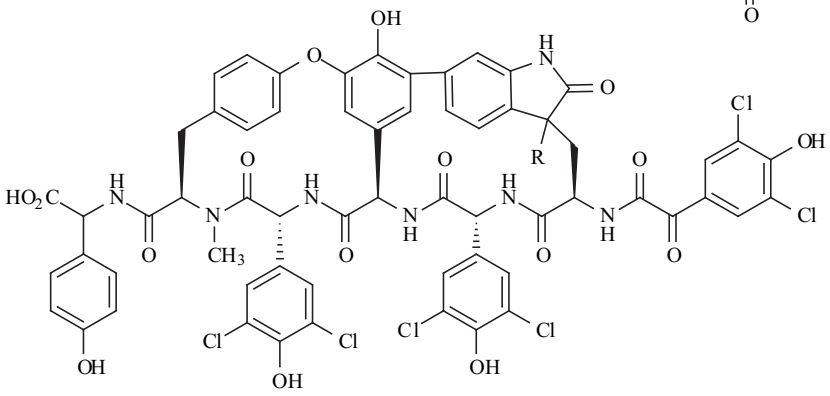
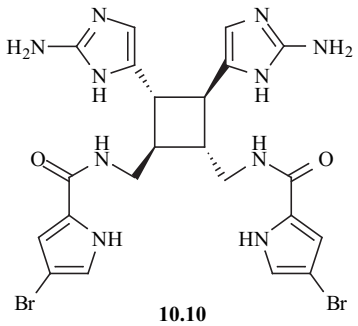


10.8.1 R = H Neuroprotectin A
10.8.2 R = OH Neuroprotectin B



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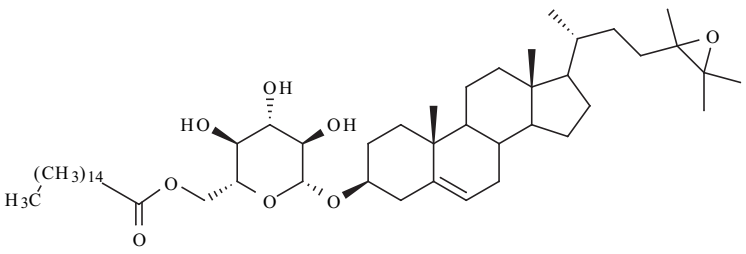
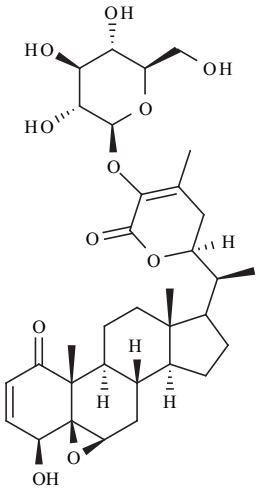
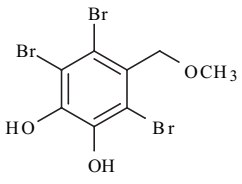


10.11.1 Sitoindoside VIII



10.11.2 sitoindoside IX



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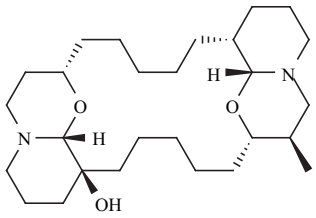

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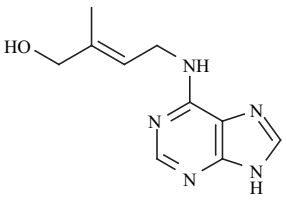


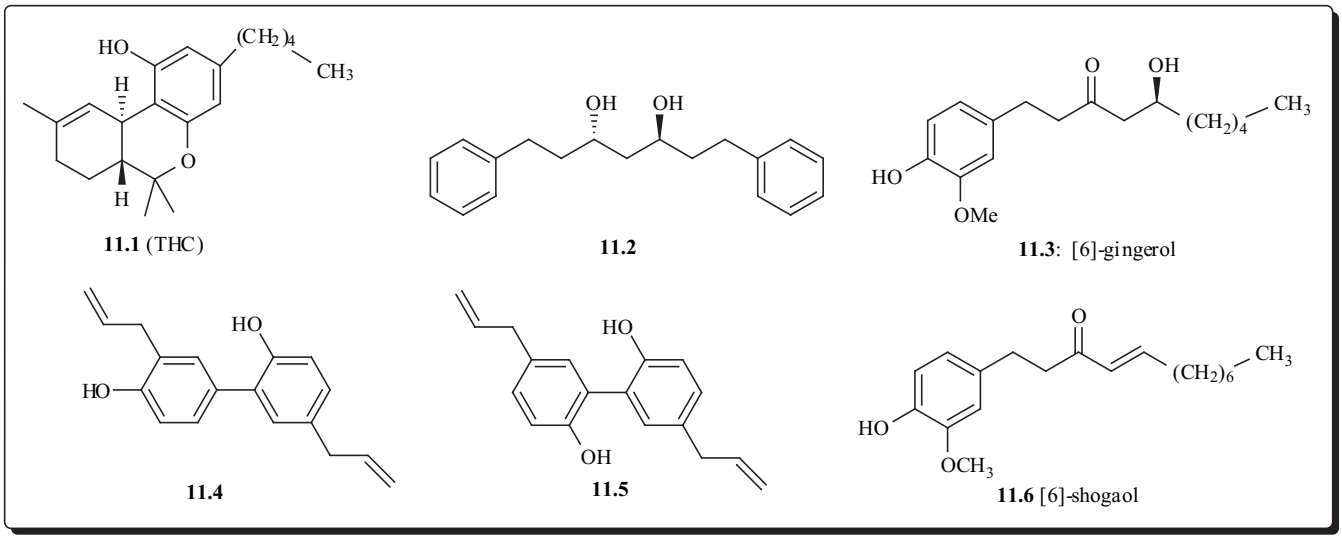
10.14

Antiemetic Agents

Antiemetic agents are of interest in part because of the emesis side effect accompanying some kinds of cancer chemotherapies. The most effective antiemetic agents have been either corticosteroids or serotonin (5-HT) antagonists. Some examples of serotonin antagonists are found in Table **19**. The cannabinoids, represented by THC (**11.1**), have generated enormous interest for their antiemetic activity, but also controversy due to their source.

Table 11. Antiemetic Agents

Compound	Struct.	Organism	Type	Mechanism	Other CNS activities	Refs.
Cannabinoids	**11.1**	*Cannabis* sp.	P	Antiemetic activity		[112, 113]
Diaryl heptanoids	**11.2**	*Alpinia officinarum*	P	Antiemetic activity in chicks		[114, 115]
Gingerols	**11.3**	*Zingiber officinale*	P	Antiemetic activity in chicks		[116,117]
Honokiol	**11.4**	*Zingiber officinale*	P	Antiemetic activity in chicks	Anxiolytic	[116,118]
Magnolol	**11.5**	*Magnolia obovata*	P	Antiemetic activity in chicks	Anxiolytic; inhibits 5-HT release in rat hypothalamus	[116,119]
Shogaols	**11.6**	*Zingiber officinale*	P	Antiemetic activity in chicks		[116,117]



11.1 (THC) **11.2** **11.3**: [6]-gingerol

11.4 **11.5** **11.6** [6]-shogaol

Anticonvulsants and Antiepileptic Agents

There appear to be many causes for epilepsy [120], but epileptic seizures are characterized by simultaneous firing of cortical neurons. Therapeutic use of antiepileptic drugs has focused on lowering Na^+, K^+, or Ca^{2+} flux in neurons, inhibiting glutamate (Glu) neurotransmission, or promoting γ-aminobutyric acid (GABA) activity at Cl^- channels. The *Aconitum* alkaloids, represented by the toxic compound aconitine (**12.1**), have been shown to block Na^+ channels in rat brain [121]. The *Aconitum* alkaloids have also been

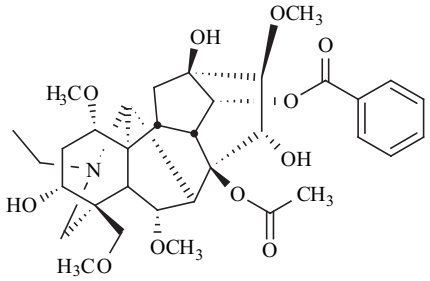
Table 12. Anticonvulsant and Antiepileptic Agents

Compound	Struct.	Organism	Type	Mechanism	Other CNS activities	Refs.
Aconitum alkaloids	**12.1**	*Aconitum* sp.	P	Inhibition of Na^+ channels in brain		[121-126]
Brazilin	**12.2**	*Caesalpinia sappan*	P	GABA degradation inhibitor	DNA strand scission	[127-129]
Chrysin	**12.3**	*Passiflora coerulea*	P	Prevents seizures in mice		[130, 131]
Farnesylacetone epoxide	**12.4**	*Cystophora moniliformis*	MP	Prevents seizures in mice		[132]
Gastrodin	**12.5**	*Gastrodia elata*	P	GABA degradation inhibitor		[133, 134]
Goodyerin	**12.6**	*Goodyeara schlechtendaliana*	P	unknown		[135, 136]
4-hydroxy benzaldehyde	**12.7**	*Gastrodia elata*	P	GABA oxidation inhibitor	GABA modulator	[137]
Otophyllosides A and B	**12.8**	*Cynachum otophyllum*	P	prevents seizures in rats		[138]
Palmitone	**12.9**	*Annona diversifolia*	P	Diminishes rat seizures		[139]
Peptide C119	**12.10**	*Centruroides limpidus*	A	Na^+ permeability inhibitor	neurodepressant	[140]
Pimprinine	**12.11**	*Streptomyces* sp. CDRIL-312	B	prevents seizures in mice		[141, 142]
Sappanchalcone	**12.12**	*Caesalpinia sappan*	P	GABA degradation inhibitor		[127]

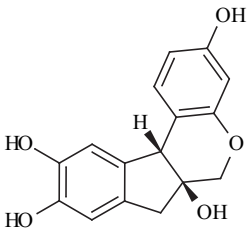
traditionally used as analgesics in Chinese traditional medicine. The GABA modulator 4-hydroxybenzaldehyde (**12.7**) was also shown to inhibit GABA oxidation. Brazilin (**12.2**) is of interest for its inhibition of GABA degradation, as well as its possible antitumor activity [129].

Acetylcholine Targeting Agents

Acetylcholine is found in all parts of the human body and is an important neurotransmitter for the control of autonomic processes, including heart rate regulation, smooth muscle contraction, and blood vessel dilation [143]. There



12.1 (aconitine)



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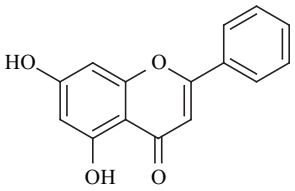

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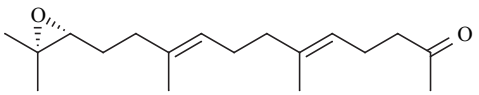

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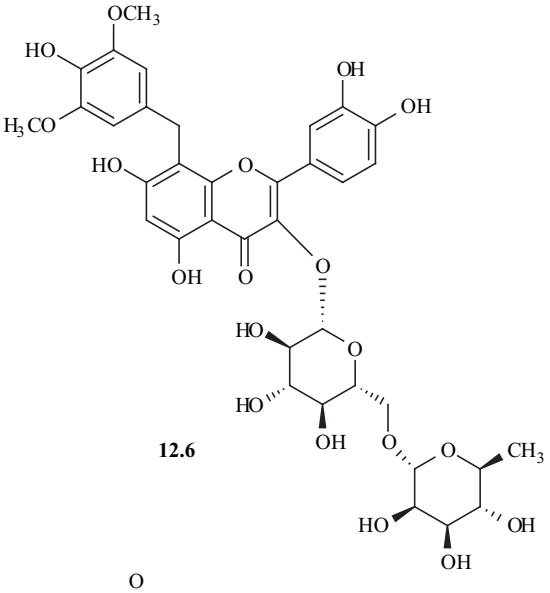

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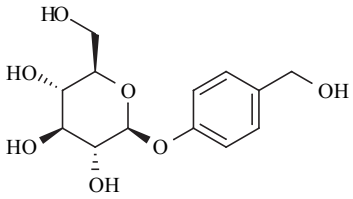

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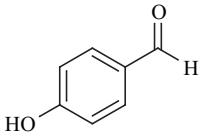

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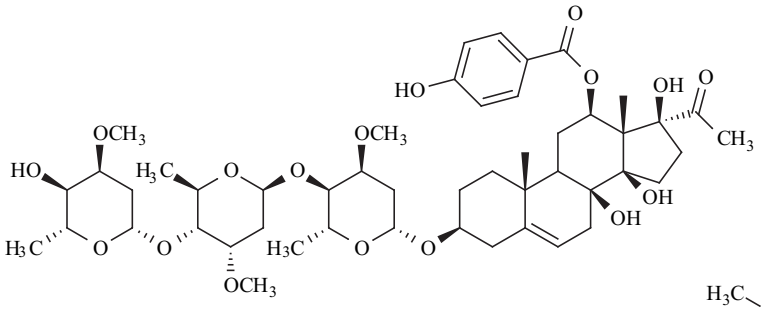
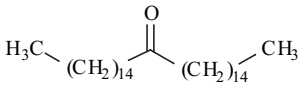


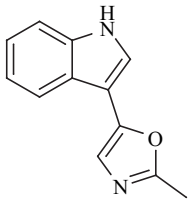
12.8 (Otophylloside A)



12.9

L-Glu-L-Asp-Gly-L-Tyr-L-Leu-L-Phe-L-Asp-L-Lys-L-Arg-L-Lys-L-Arg-L-Cys-L-Thr-L-Leu-L-Ala-L-Cys-L-Ile-L-Asp-L-Lys-L-Thr-Gly-L-Asp-L-Lys-L-Asn-L-Cys-L-Asp-L-Arg-L-Asn-L-Cys-L-Lys-L-Lys-L-Glu-Gly-Gly-L-Ser-L-Phe-Gly-L-His-L-Cys-L-Ser-L-Tyr-L-Ser-L-Ala-L-Cys-L-Trp-L-Cys-L-Lys-Gly-L-Lys-L-Pro-Gly-L-Ser-L-Thr-L-Pro-L-Ile-L-Ser-L-Arg-L-Thr-L-Pro-Gly-L-Lys-L-Thr-L-Cys

12.10



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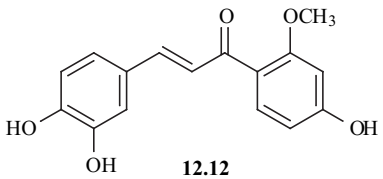
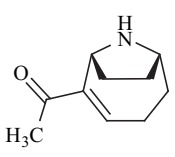


12.12

are two major types of ACh receptors, muscarinic (mAChR) and nicotinic receptors (nAChR). Nicotinic receptors are found most abundantly in the peripheral nervous system (PNS), while muscarinic receptors are much more prevalent in the CNS. As mentioned earlier, much of the work in AD drugs has focused on compounds which interact with the cholinergic system. Another disorder involving ACh is Huntington's chorea, which is a hereditary disease marked

Table 13. Acetylcholine Targeting Agents

Compound	Struct.	Organism	Type	Mechanism	Other CNS activities	Refs.
(+)-Anatoxin	**13.1**	*Anabaena flos-aquae*	B	nAChR agonist		[146-149]
Cantleyine	**13.2**	*Strychnos trinervis*	P	Ca^{2+} channel blocker, nonspecific muscle relaxant		[150-152]
(+)-Cavidine	**13.3**	*Corydalis meifolia*	P	Reduces ACh-induced contractions		[153, 154]
α-Conotoxin MII	**13.4**	*Conus magus*	MA	Targets α3β2 nAChR		[155]
ω-Conotoxin	**13.5**	*Conus geographus*	MA	Ca^{2+} channel blocker, prevents ACh release		[156-158]
Corlumine	**13.6**	*Corydalis meifolia*	P	Reduces ACh-induced contractions		[151,159, 160]
Crambescidin 816	**13.7**	*Crambe crambe*	MA	Reversible Ca^{2+} blocker, spasmolytic	Antiviral, cytotoxic	[161,162]
Cycleanine	**13.8**	*Synclisia scabrida*	P	Induces rat uterine contractions, unaffected by atropine	sedative	[163]
Cyclostellettamines A-F	**13.9**	*Stelletta maxima*	MA	mAChR antagonists		[164]
Dehydrocavidine	**13.10**	*Corydalis meifolia*	P	Reduces ACh-induced contractions		[151]
Dibromosceptrin	**13.11**	*Agelas* sp.	MA	mAChR antagonist		[165, 166]
3-Epioleanolic acid	**13.12**	*Ekebergia capensis*	P	Induces guinea pig uterine contractions, at a cholinergic receptor		[167, 168]
Liriodenine	**13.13**	*Liriodendron tulipifera*	P	Selective M_3 mAChR antagonist		[169, 170]
Methyllycaconitine	**13.14**	*Delphinium biternatum*	P	Specific bungarotoin-sensitive nAChR antagonist		[171-173]
Neosurugatoxin	**13.15**	Bacterium living in *Babylonia japonica*	MB	Specific nAChR antagonist		[174-176]
Oroidin	**13.16**	*Agelas* sp.	MA	mAChR antagonist		[163,177, 178]
Protopine	**13.17**	*Corydalis meifolia*	P	Reduces ACh-induced contractions		[151]
Quercetin glycosides	**13.18**	*Psidium guajava*	P	Interaction with Ca^{2+}-mediated actions		[179,180]
Yenhusomine	**13.19**	*Corydalis meifolia*	P	Reduces ACh-induced contractions		[151,181]



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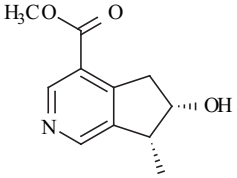

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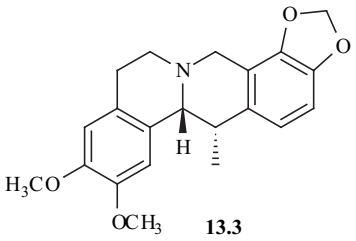


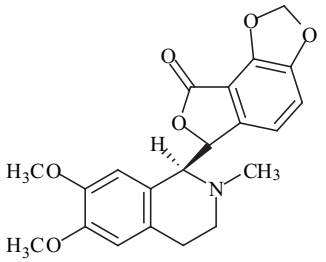
13.3

Gly-L-Cys-L-Cys-L-Ser-L-Asn-L-Pro-
L-Val-L-Cys-L-His-L-Leu-L-α-Glu-
L-His-L-Ser-L-Asn-L-Leu-L-Cys
(2→8),(3→16)-bis(disulfide)

13.4

L-Cys-L-Lys-L-Ser-(4-hydroxy-L-Pro)-Gly-L-Ser-L-Ser-L-Cys-L-Ser-(4-hydroxy-L-Pro)-L-Thr-L-Ser-L-Tyr-L-Asp-L-Cys-L-Arg-L-Ser-L-Cys-L-Asp-(4-hydroxy-L-Pro)-L-Tyr-L-Thr-L-Lys-L-Arg-L-Cys-L-Tyr

13.5



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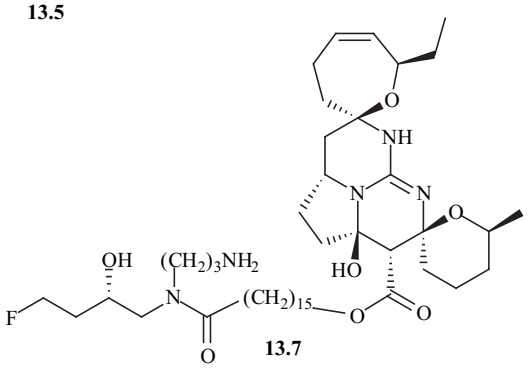
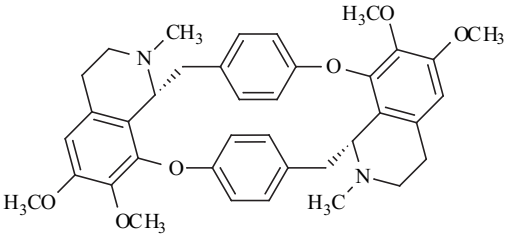


13.7

by the loss of cholinergic neurons in the *striatum nigra* [144]. Table **13** includes several compounds which interact with ACh receptors. One of the major problems with targeting cholinergic receptors is crossing the blood-brain barrier (BBB). It has been observed that anticholinergic compounds that are able to cross the BBB do not show strong CNS effects [145]

Adenosine Targeting Agents

Adenosine is a neuromodulator with specific receptors in the human body, and adenosine receptors are associated with receptors for the other neurotransmitters listed in this review. Adenosine has neuroprotective effects in the brain and is also important in controlling sleep and regulating arousal [182]. Caffeine (**2.2**), which has stimulant activity, is an adenosine



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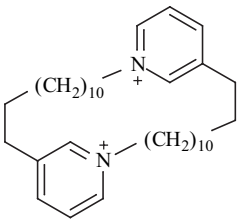
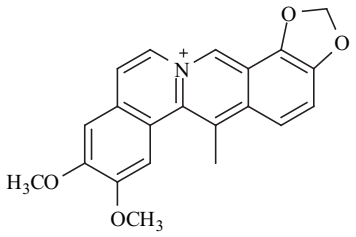


13.9 (Cyclostellettamine A)



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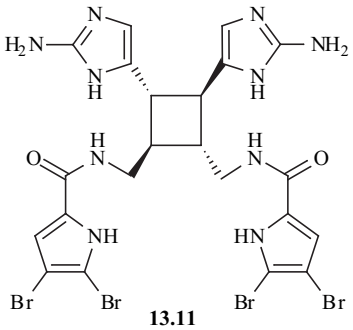

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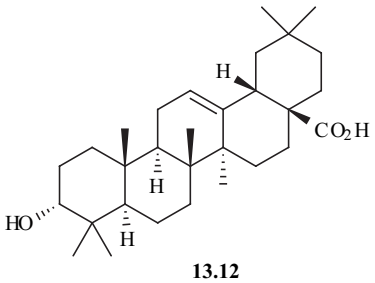

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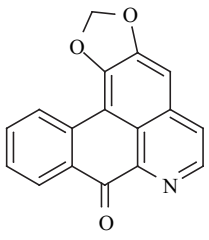
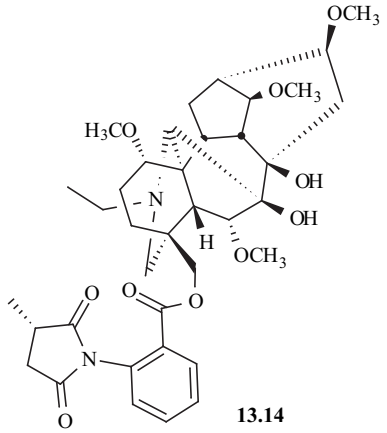


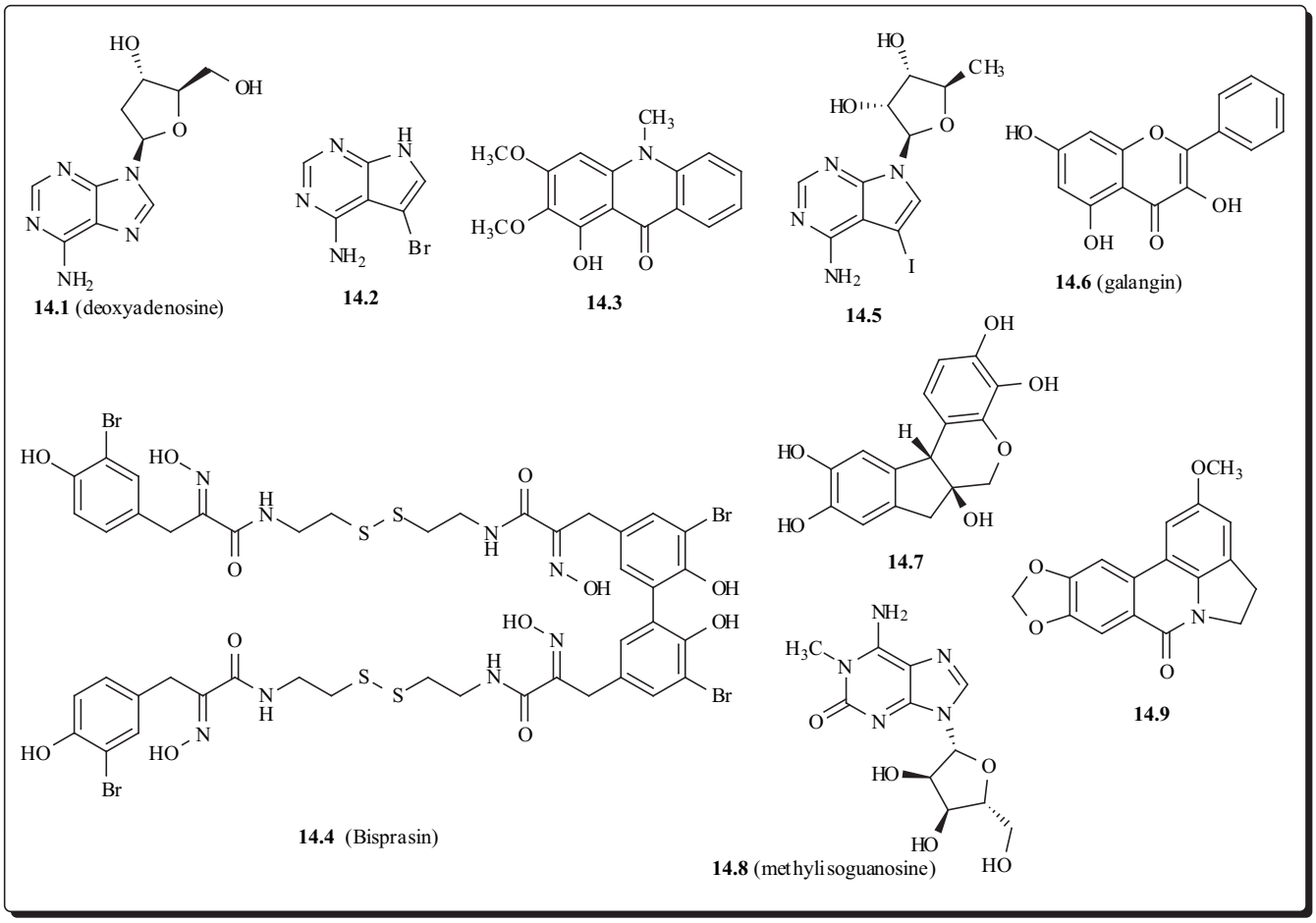
13.13



13.14

Table 14. Adenosine Targeting Agents

Compound	Struct.	Organism	Type	Mechanism	Other CNS activities	Refs.
Adenosine analogs	**14.1**	(various organisms)	-	A_2 adenosine receptor agonist		[184, 185]
4-Amino-5-bromopyrrolo[2,3-d]pyrimidine	**14.2**	*Echinodictyum* sp.	MA	Adenosine uptake inhibitor		[186-188]
Arborinine	**14.3**	(various organisms)	-	Selective A_1 receptor binder		[189]
Bromotyrosine disulfides	**14.4**	*Aplysinella rhax*	MA	Binds to rat brain adenosine receptors		[190-193]
5'-Deoxy-5-iodotubercidin	**14.5**	*Hypnea valentiae*	MP	Adenosine uptake inhibitor		[183,185, 194]
Flavanoids	**14.6**	(various organisms)	-	Selective A_1, A_{2a}, or A_3 receptor binding		[195,196]
Hematoxylin	**14.7**			Selective A_1 receptor binding		[186]
Isoguanosine derivatives	**14.8**	(various organisms)	-	Adenosine receptor binding		[197-200]
Oxogalanthine lactam	**14.9**	(various organisms)	-	Selective A_1 receptor binding		[186,201]



antagonist [183]. Many of the compounds in Table 14 are structurally very similar to adenosine.

Dopamine Targeting Agents

Dopamine is an important neurotransmitter in the human brain, as well as in other parts of the body. The receptors are subdivided into five groups, $D_1 - D_5$. The main center of dopaminergic neurotransmission is in the *striatum nigra* (SN), the area of the brain where muscle control is regulated [202]. Parkinson's disease is caused by the breakdown of the SN, which destroys dopamine neurotransmission and causes the classic Parkinsonian symptoms. There has been much interest in studying monoamine oxidase inhibitors, which are believed to be part of the mechanism for the destruction

of the SN [203]. Dopamine agonists can also cause emesis by acting in the chemoreceptor trigger zone in the brain [204]. Table **15** shows several natural products which have been shown to have activity at dopamine receptors. From the Chinese plant *Phoebe chekiangensis*, 5-hydroxyindoline (**15.1**) has better dopamine receptor selectivity for D_4 than the clinically used dopamine blocker clozapine.

GABA Targeting Agents

GABA is the major inhibitory neurotransmitter in the human body. As mentioned previously, GABA receptors are potential therapeutic targets for epilepsy, as well as depression. Muscimol (**1.7**) is a $GABA_A$ receptor agonist. There has been relatively little recent work on finding compounds targeting GABA for therapeutic use. The avermectins, represented by avermectin A_{1a} (**16.1**), are

Table 15. Dopamine Targeting Agents

Compound	Struct.	Organism	Type	Mechanism	Other CNS activities	Refs.
5-Hydroxyindoline	**15.1**	*Phoebe chekiangensis*	P	D_4 DA agonist		[205,206]
Hypericin	**15.2**	*Hypericum perforatum*	P	D_3 and D_4 binder	Inhibits β_1-adrenoceptor binding	[207]
Polygalasaponins	**15.3**	*Polygala tennifolia*	P	DA and 5-HT antagonists	Possible antipsychotics	[208,209]
Pycnocomolides	**15.4**	*Pycnocoma cornuta*	P	DA inhibitor		[210, 211]
SCH 71450	**15.5**	*Phoebe chekiangensis*	P	D_4 DA antagonist		[202]

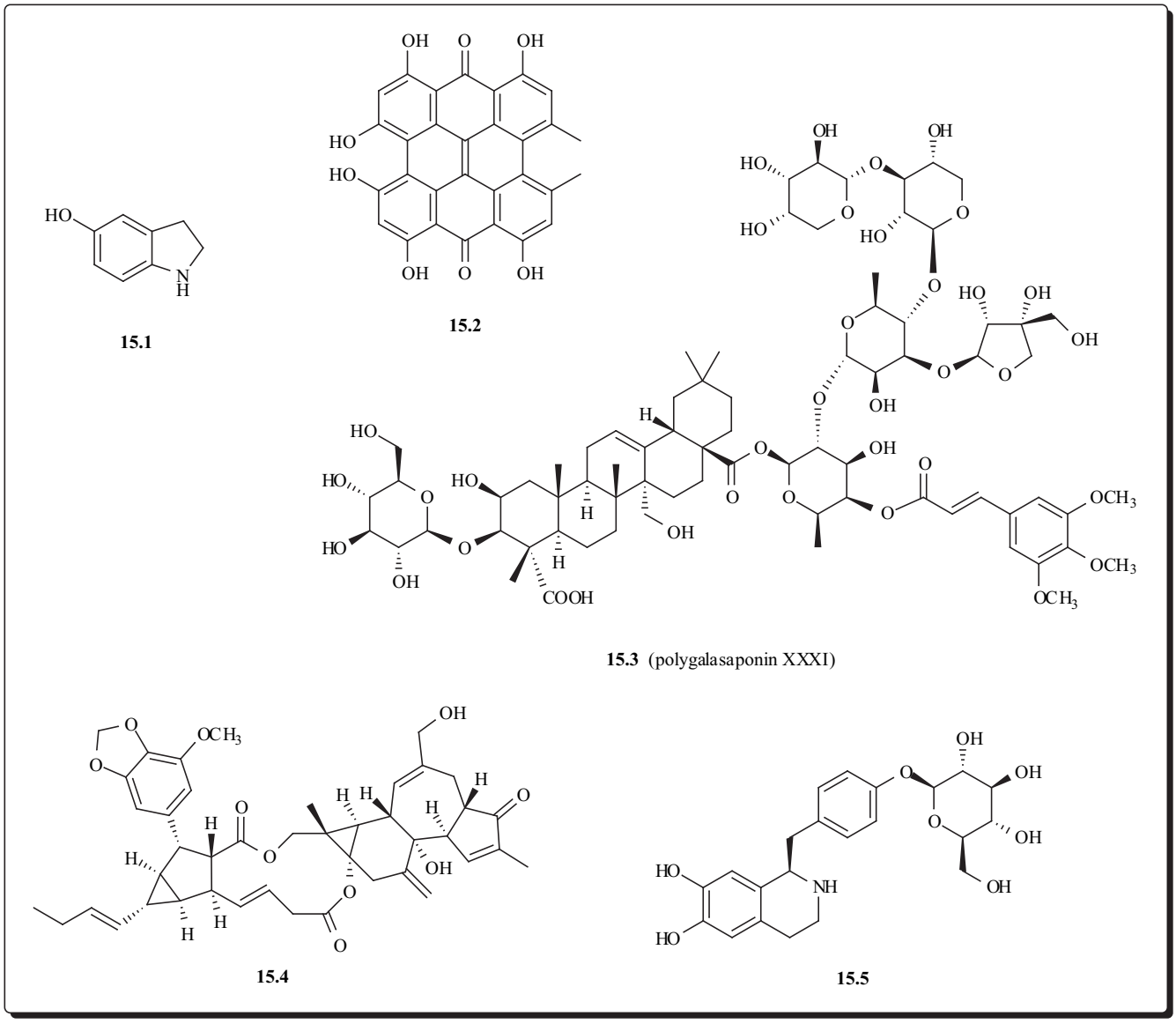
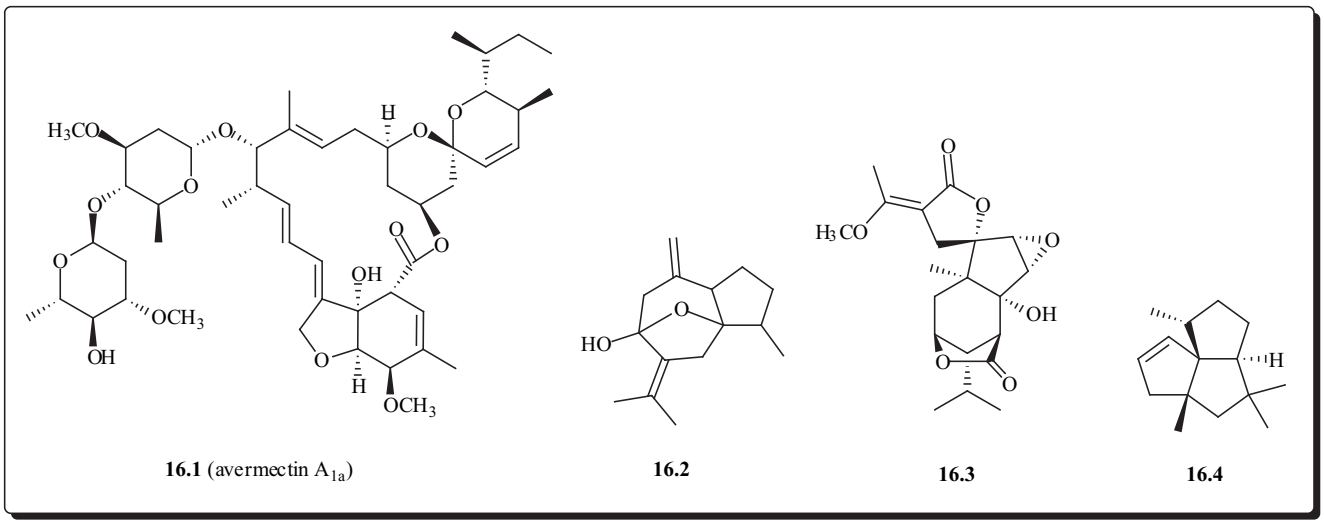


Table 16. GABA Targeting Agents

Compound	Struct.	Organism	Type	Mechanism	Other CNS activities	Refs.
Avermectins	**16.1**	*Streptomyces avermitilis*	B	GABA modulator	Anthelmintic	[212-214]
Isocurcumenol	**16.2**	*Cyperus rotundus*	P	BD receptor agonist allosteric modulator		[215-217]
Picrodendrin-Q	**16.3**	*Picrodendron baccatum*	P	GABA antagonist	insect antifeedant	[218,219]
Silphinene	**16.4**	*Senecia palmensis*	P	GABA antagonist	Insect antifeedant; antifungal activity	[220,221]



16.1 (avermectin A_{1a}) **16.2** **16.3** **16.4**

principally known as antiparasitic agents, but some avermectins have shown GABA modulating activity.

Glutamic Acid Targeting Agents

Glutamic acid (Glu) is an excitatory neurotransmitter found in the brain, spinal cord, and in Müller cells from the eye [224]. Glu is a major excitatory neurotransmitter and is involved in most types of normal brain activity such as memory and cognition [222]. There are three classes of Glu receptors: NMDA, AMPA, and kainate receptors. Excessive activation of NMDA receptors results in Ca^{2+} into neurons and cell death. A stroke can cause excess Glu release that leads to neuronal death. From a therapeutic standpoint, targeting the neurotoxicity of Glu is of interest. The rhynchophylline derivatives, typified by rhynchophylline (**17.5**), are NMDA antagonists, and are components plants which have been used medicinally as antiepileptic and antipyretic agents.

Norepinephrine Targeting Agents

Norepinephrine (NE) is a neurotransmitter that is present both in the CNS and PNS. In the PNS, it is responsible for autonomic control of the heart, blood vessels, and glands in the body. In the CNS, the importance of NE has been harder to characterize. NE seems to be critical in affecting arousal and attention. NE levels are also important in coping with outside stimuli. Ephedrine (**2.5**) acts non-selectively at α-adrenoceptors. Historically, the development of selective α-adrenoceptor blockers has been a disappointment [235]. Most of the compounds listed in Table **18** are active at α-adrenoceptors.

Table 17. Glutamic Acid Targeting Agents

Compound	Struct.	Organism	Type	Mechanism	Other CNS activities	Refs.
Conotoxin G V	**17.1**	Conus geographus	MA	Competitive NMDA antagonist		[223-225]
Dysiherbaine	**17.2**	*Dysidea herbacea*	MA	Selective kainate receptor agonist		[226-228]
Fangchinoline	**17.3**	*Cyclea peltata*	P	Protects against Glu toxicity		[229]
Linalool	**17.4**	(various organisms)	P	Putative glutamine release inhibitor	anticonvulsant	[230]
Rhynchophylline deriv.	**17.5**	*Uncaria macrophylla*	P	Non-competitive NMDA antagonist		[231,232]
Stizolobic acid	**17.6**	*Stizolobium hassjoo*	P	Competitive quisqualate antagonist		[233,234]

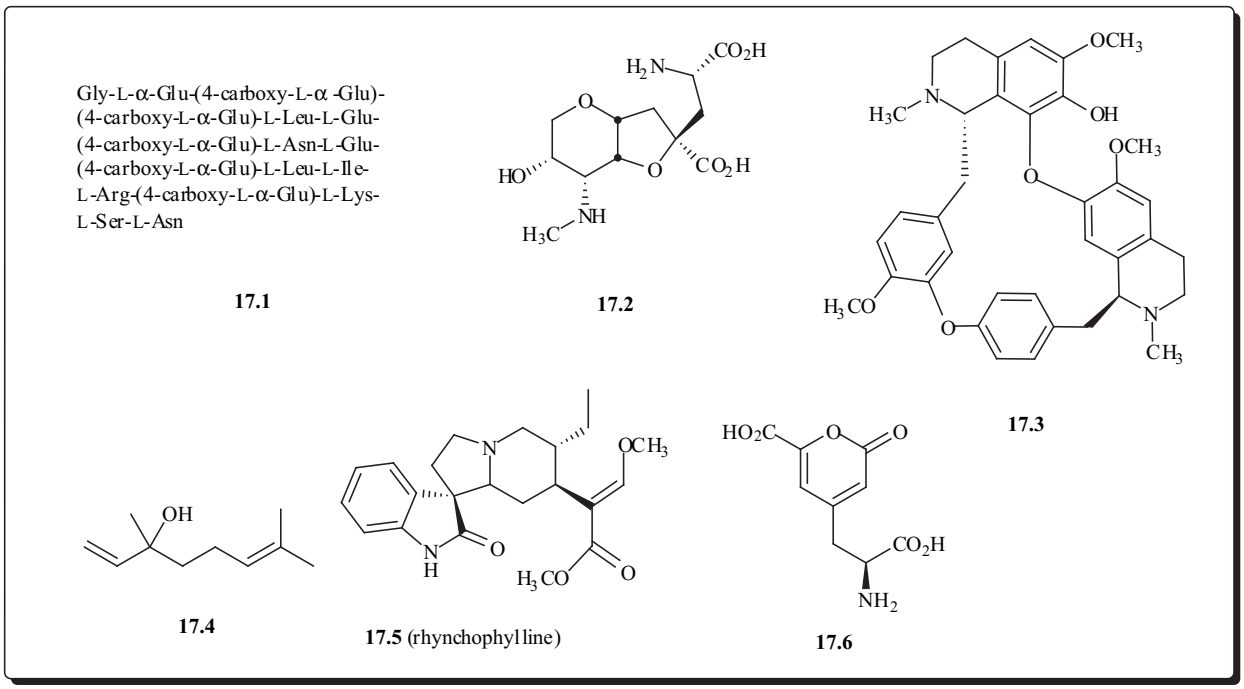
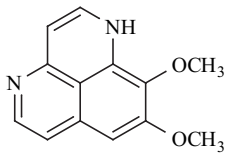


Table 18. Norepinephrine Targeting Agents

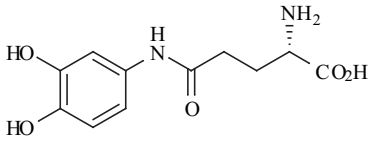
Compound	Struct.	Organism	Type	Mechanism	Other CNS activities	Refs.
Aaptamine	**18.1**	*Aaptos aaptos*	MA	competitive antagonist of α-adrenoceptors		[236-238]
Agaridoxin	**18.2**	*Agaricus bisporus*	P	Selective α_1-adrenoceptor blocker		[239,240]
Brucine	**18.3**	*Strychnos* sp.	P	Allosteric M1 receptor modulator, α_1-adrenoceptor blocker		[241,242]
Cinnamophilin	**18.4**	*Cinnamomum philippinense*	P	Selective α_2-adrenoceptor antagonist		[243]
Crychine	**18.5**	*Cryptocarya chinesis*	P	NE antagonist	Muscle relaxant	[244-246]
Cryptolepine	**18.6**	*Crypolepus* sp.	P	Presypnatic α-adrenoceptor blocker		[247,248]
Dicentrine	**18.7**	*Lindera megaphylla*	P	α_1-adrenoceptor blocker	Possible antihypertensive	[249]
(-)-Discretamine	**18.8**	*Fissistigma glaucescens*	P	α_1-adrenoceptor blocker		[250,251]
Hymenin	**18.9**	*Hymeniacidon* sp.	MA	Selective, competitive antagonist of α-adrenoceptor		[252,253]
Norathyriol	**18.10**	*Magnifera indica*	P	NE inhibitor	Muscle relaxant	[254-256]
Ocoteine	**18.11**	*Cassytha filiformis*	P	α_1-adrenoceptor blocker	High dose: 5-HT blocker	[257-259]
Polygodial	**18.12**	*Drymis winteri*	P	NE antagonist	Muscle relaxant	[260,261]
Scopoletin	**18.13**	*Brunfelsia hopeana*	P	Inhibits NE-mediated Ca^{2+} release		[262,263]
Xanthorrhizol	**18.14**	*Iostephane heterophylla*	P	NE antagonist	Aortic relaxant	[264-266]

Serotonin Targeting Agents

Serotonin (5-HT) is a neurotransmitter that is also found throughout the body and has both central and peripheral effects. There are fourteen receptor types, which are grouped into eight families, 5-HT_1 - 5-HT_8. In the brain, 5-HT has a role in regulating mood, sleep, and appetite, among many other functions [267]. The lysergic acid derivatives (**1.5**) are agonists at 5-HT_{1A} and 5-$HT_{2A/2X}$ receptors. 5-HT_{1A} agonists are possible therapeutic agents for anxiety [143], and they might be helpful in treating schizophrenia. 5-HT_{2X} antagonists are also of interest for treating anxiety [271].



18.1



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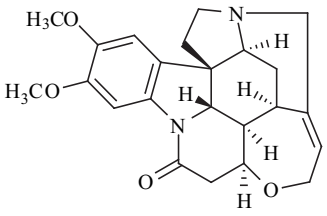

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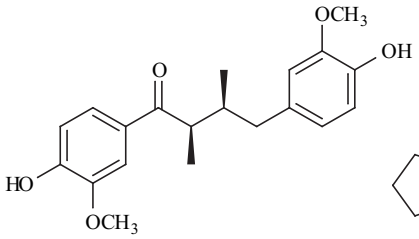

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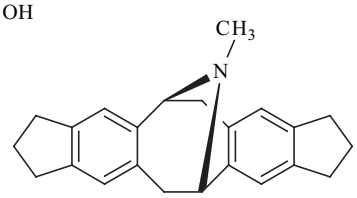

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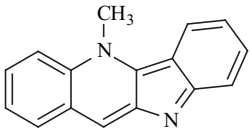

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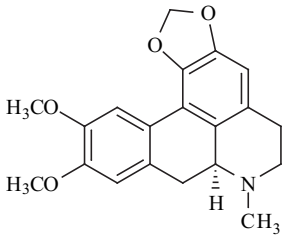

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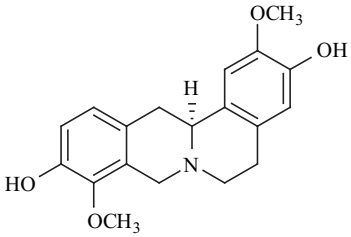

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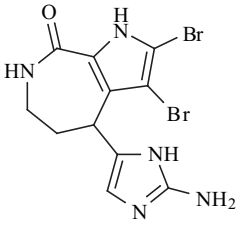

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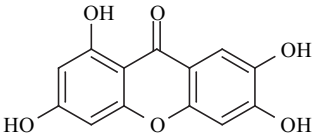

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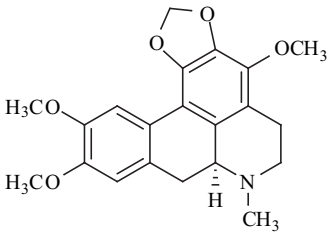

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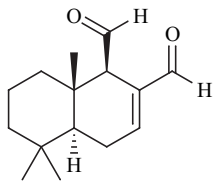

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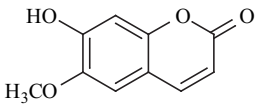

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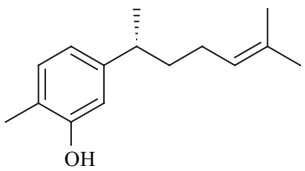
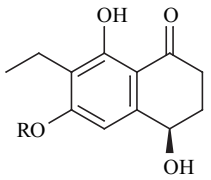


18.14

Table 19. Serotonin Targeting Agents

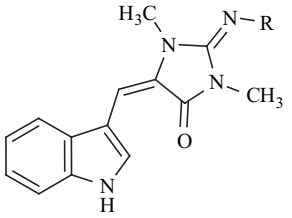
Compound	Struct.	Organism	Type	Mechanism	Other CNS activities	Refs.
Asparvenone deriv.	**19.1**	*Aspergillus parvulus*	P	5-HT_{2C} antagonists		[268,269]
σ-Conotoxin GVIIIA	**19.2**	*Conus* sp.	MA	Selective 5-HT_3 receptor inhibitor		[270]
N-3'-Ethylaplysinopsin	**19.3**	*Smenospongia aurea*	MA	Strong 5-HT_{2C} receptor binder		[271]
Hymenidin	**19.4**	*Hymeniacidon* sp.	M	Potent 5-HT antagonist		[272,273]
Lirinidine	**19.5**	*Nelumbo nucifera*	P	5-HT antagonist		[274]
N-3' Methylaplysinopsin	**19.6**	*Aplysinopsis reticulata*	MA	5-HT reuptake inhibitor	MAO-A inhibitor	[275,276]
Nantenine	**19.7**	*Nandina domestica*	P	5-HT_{2A} receptor blockers		[277-279]



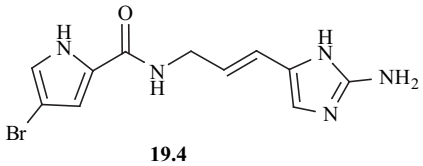
19.1 (Asparvenone)

Gly-L-Cys-L-Thr-L-Arg-L-Thr-L-Cys-Gly-Gly-[(4*R*)-4-hydroxy-L-Pro]-L-Lys-L-Cys-L-Thr-Gly-L-Thr-L-Cys-L-Thr-L-Cys-L-Thr-L-Asn-L-Ser-L-Ser-L-Lys-L-Cys-Gly-L-Cys-L-Arg-L-Tyr-L-Asn-L-Val-L-His-L-Pro-L-Ser-Gly-(6-bromo-L-Trp)-Gly-L-Cys-Gly-L-Cys-L-Ala-L-Cys-L-Ser

19.2



19.3 R = CH_3 *N*-3' Ethylaplysinopsin
19.6 R = CH_3 *N*-3' Methylaplysinopsin



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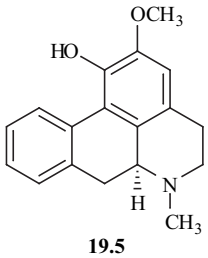

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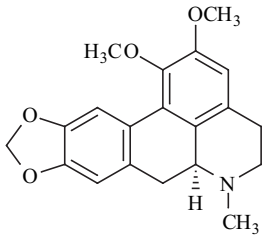

19.7

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