CHAPTER 1

INTRODUCTION

1.1 Marine natural products and drug development

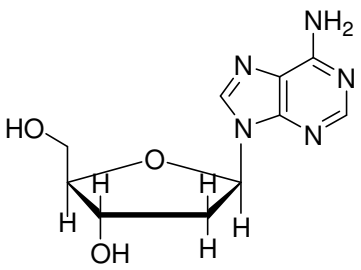
In the area of drug discovery, nature is considered the most attractive source of the therapeutic candidates as the tremendous chemical diversity is found in millions of species of plants, animals and microorganisms. For most of currently used medicines, natural products are starting points for drug discovery and development. As the results, natural products and their derivatives represent more than 50% of all the drugs in clinical use.

Over the past decades, conventional searches for bioactive natural products have relied heavily on terrestrial plants as primary sources. Also, soil-derived microbes were found to be another excellent source of biologically active compounds. However, the continual search for new sources of possible drugs eventually led researchers to look to the ocean. Oceanic marine organisms are of scientific interest for two major reasons. To begin with, marine organisms constitute a major share of the Earth's biological resources. Secondly, marine organisms often possess unique anatomical structures, metabolic pathways, reproductive systems, and sensory and chemical defense mechanisms (Pawlik, 1993), due to the adaptation to a wide range of environmental conditions. The range of marine habitats encompass the frigid cold polar Arctic and Antarctic seas, to the warm and bright shallow waters of the tropics, and to the great pressures of the deep ocean floor. Recent improvements in underwater life-support systems have extensively facilitated the collection of marine organisms from largely unexplored, yet harsh, regions of the oceans. As the results, many bioactive chemicals from the marine organisms have been isolated and characterized over the past 40 years, and some even holds great promise for useful biotechnological application towards a wide range of pharmaceutical compounds, medical research materials, agricultural products, novel energy sources and bioremediation techniques (Faulkner, 2002).

1.1.1 Marine-derived natural products in clinical development

The field of marine natural products has produced a plethora of chemically interesting and important bioactive natural products. During the 1950s, Bergmann's group at

Yale isolated several nucleosides from the Caribbean sponge *Cryptotethya crypta* (family Tethylidea). Two of these, spongothymidine and spongouridine, contained the rare arabinose sugar rather than ribose, which is a quite ubiquitous sugar in nucleosides. This discovery led researchers to synthesize the analogues, ara-A (vidarabine) **(1)**, and ara-C (cytarabine) **(2)**. The two compounds are currently used as antiviral and antileukemic agents, respectively (Guyot, 2000).



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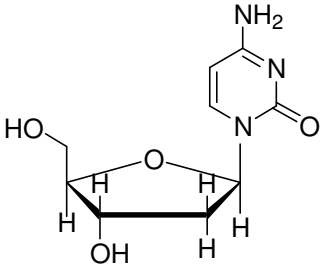

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Since then, the field of marine natural products has grown substantially with numerous natural and synthetically-derived compounds evaluated as clinical drug candidates. Whereas it might be claimed that this is resulted from generous funding by the U.S. National Cancer Institute (NCI), there is also an underlying preponderance of anti-tumor agents produced by marine organisms. Although most have failed due to ineffectiveness or toxicity problems, a fair number of marine derived agents have been passing into clinical trials. Shown in Table 1 are a few selected agents, either as approved drugs or agents currently under clinical investigation.

Table 1 Marine-derived natural products currently approved or in clinical trials (Newman and Cragg, 2004)

Name	**Source**	**Status (disease)**
Ziconotide (Prialt™)	*Conus magus*	Approved (neuropathic pain)
Ecteinascidin 743 (Yondelis™)	*Ecteinascidia turbinata*	Phase III (cancer)
Æ-941(neovastat)	Shark	Phase III (antiasthmatic)
Dehydrodidemnin B (Aplidine™)	*Aplidium albicans*	Phase II (cancer)
Bryostatin 1	*Bugula neritina*	Phase II (cancer)
Soblidotin (TZT-1027)	*Dolabella auricularia*	Phase II (cancer)
Synthatodin (ILX 651)	*Dolabella auricularia*	Phase II (cancer)
Kahalamide F	*Elysia rufescens/Bryopsis* sp.	Phase II (cancer)
HTI-286 (hemiasterlin derivative)	*Cymbastella* sp.	Phase II (cancer)
Squalamine	*Squalus acanthias*	Phase II (cancer)
PM00104 (jorumycin derivative; Zalypsis™)	*Jorunna funebris*	Phase I (cancer)
E7389 (halicondrin B derivative)	*Lissodendoryx* sp.	Phase I (cancer)
ES-285 (spisulosine)	*Spisula polynyma*	Phase I (cancer)
Discodermolide	*Discodermia dissoluta*	Phase I (cancer)
KRN-7000	*Agelas mauritianus*	Phase I (cancer)
GTS-21(anabaseine derivative)	*Paranemertes peregrina*	Phase I (Alzheimer's)
CGX-1160 and CGX-1007	*Conus geographus*	Phase I (pain)

It is not quite surprising to find that most marine-derived drug candidates as seen in Table 1 are anticancer agents, considering that most of the metabolites are in fact produced as toxic agents for chemical defense. However, certain number are otherwise applicable in some other remote diseases, including the analgesic ziconotide and the famous antiaging pseudopterosins. In the remaining section of this review, the use of another group of marine-derived natural products as acetylcholinesterase inhibitors, i.e., promising candidates for the treatment of Alzheimer's disease, is introduced. Such application extends marine natural products research into other disease areas, and suggests its potential as one of the leading branches of research in drug development.

1.2 Alzheimer's disease and cholinesterase inhibitors

1.2.1 Pathophysiology of Alzheimer's disease (AD)

Neuroimaging of the patients with AD or other dementias may reveal atrophy of the brain, such as enlarged ventricles and sulci and narrowed gyri, although these features are not always present. Neuronal loss is the main neuropathologic feature underlying the symptoms of AD. Microscopically, AD is characterized by the presence of amyloid plaques and neurofibrillary tangles. Amyloid plaques contain deposits of β-amyloid, which is a 40- to 42-amino acid peptide derived from amyloid precursor protein. Neurofibrillary tangles are a hyperphosphorylated τ-protein, which forms paired helical filaments. AD is also associated with a loss of cholinergic neurons, which project from the basal forebrain to the cerebral cortex and the hippocampus. The loss of cholinergic neurons is progressive and results in profound memory disturbances (Akhondradeh and Abbasi, 2006).

1.2.2 Cholinergic hypothesis

The first neurotransmitter defect commonly found in AD patients involved acetylcholine (ACh). Because cholinergic function is required for short-term memory function, it has been known that cholinergic deficit in AD patients is also responsible for much of short-term memory deficit. Markers for the cholinergic neurons such as choline acetyltransferase and acetylcholinesterase, which are enzymes responsible for synthesis and degradation of ACh, respectively, decrease in the cortex and hippocampus. The earliest loss of neurons occurs in the nucleus basalis and the entorhinol cortex, where cholinergic neurons are preferentially affected.

One of the most prominent features of AD is a significant deficit in cholinergic transmission in this certain brain area. It was found that concentrations of ACh decrease by nearly 90% in patients with AD in the early illness. The decrease in ACh-dependent neurotransmission is thought to lead to the functional deficits of AD patients (Francis *et al*., 1999; Akhondradeh and Abbasi, 2006).

Clinical drug trials in patients with AD have focused on drugs that augment the levels of ACh in the brain to compensate such losses of cholinergic functions. These drugs include ACh precursors, muscarinic agonists, nicotinic agonists, and cholinesterase inhibitors. The current focus of AD treatment is the use of agents that increase the availability of intrinsic ACh by inhibiting the enzyme acetylcholinesterase (AChE). This may restore the cholinergic functions in the brain and significantly reduce the severity of dementia. As the cognitive dysfunction and other features of AD are mediated by the loss of function at cholinergic synapses in the neocortex and hippocampus, agents that replace the lost cholinergic functions have been suggested to be useful in the management of disease (Hoe *et al*., 2002).

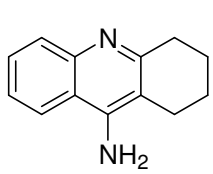
1.2.3 Acetylcholinesterase inhibitors (AChE-I's)

Due to obscure and unknown nature of the disease principle, there are no long-term remedies that are entirely accepted as perfect treatment for AD. Several approaches that are employed by physicians and practitioners include the use of antipsychotic drugs to relieve the symptoms of dementia (Aupperle, 2006). Also, for the patients suffering from mild symptoms of early-stage AD, the use of medicinal plant, *Gingko biloba*, is also acceptable among certain physicians (Eslami *et al*., 2003; Akhondradeh and Abbasi, 2006). However, the best direct approach that targets one of the causes of disease is possibly the use of AChE-I's. Whereas such approach is still controversial for the beneficial effects which normally last no longer than one year, it is still among the best approaches to improve the patients' quality of life (Bullock, 2002; Mukherjee *et al*., 2007).

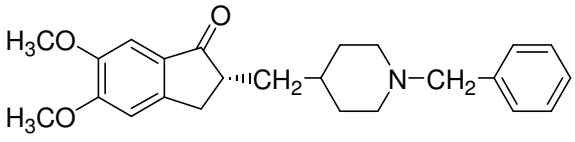
AChE-I's enhance the cholinergic transmission by reducing the enzymatic degradation of ACh. Since cholinergic dysfunction is considered a primary cause of AD, and the degree of cognitive improvement in AD patients are reportedly correlated to central cholinergic

deficiency, elevation of ACh level therefore is thought to be helpful, especially in improving the symptoms of cognitive deficits (Coyle *et al*., 1983; Chemnitius *et al*., 1996).

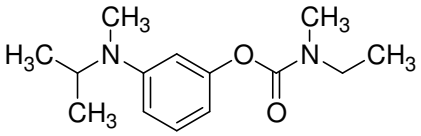
To date, only four AChE-I's have been approved by USA-FDA (Zarotsky *et al.*, 2003). The first drug approved for general clinical use in AD was tacrine. Three new AChE-I's, donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®), are also currently available (Eslami *et al*., 2003). Neither of the four AChE-I's are completly effective, however, especially in the case of severe AD. Furthermore, several side effects have also been reported. In most cases, the adverse effects, mainly gastrointestinal in nature, are mild to moderate, and are reported by 25-46% of patients (Alwahhabi, 2005).



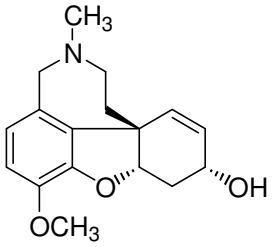
tacrine



donepezil



rivastigmine



galantamine

Figure 1 FDA-approved drugs for AD

As mentioned earlier, even though AChE-I's may provide effective temporary relief of symptoms in some patients, there are currently no cures for AD (Hecker and Snellgrove, 2003). However, with only approach acceptable and fairly efficient for the treatment of such desperate disease, drug research and development are still based primarily on the cholinergic hypothesis that supports the cognition improvement by regulation of the synthesis and release of ACh in the brain.

1.3 Cholinesterase inhibitors derived from natural products

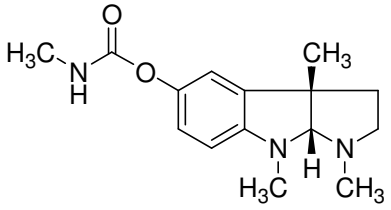
To date, various groups of natural products and their synthetic analogues have been reported to exhibit cholinesterase inhibitory activities to an interesting extent. Among these,

alkaloids constitute a large proportion of enzyme inhibitors. The observation is not surprising considering the fact that for AChE active site, positively charged nitrogens are among the required elements of compounds that can bind to a similar region to that of ACh. Nevertheless, a series of non-nitrogenous compounds, namely terpenoids, have been reported with significant inhibiting potency (Mukherjee *et al*., 2007). The lack of positively-charged moiety among these molecules suggested the possibility of allosteric binding sites, although a thorough investigation regarding such interaction is yet to be explored.

1.3.1 Alkaloids

1.3.1.1 Physostigmine

Physostigmine **(3)** or eserine was isolated from the calabar bean, the seed of *Physostigma venenosum* Balf., in the nineteenth century in studies stimulated by the use of the seeds as an ordeal poison. The early applications of physostigmine were limited to opthalmic preparations and the treatment of myasthenia gravis. However, the realization of its cognitive benefits in both animal models and human subjects led to the development of synthetic analogues bearing the carbamoyl moiety, including neostigmine **(4)** and rivastigmine **(5)**. The latter, as mentioned earlier, has become an approved drug used in patients with early-state AD (Houghton and Howes, 2005).



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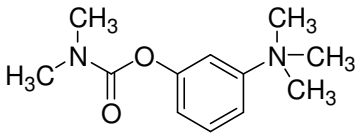

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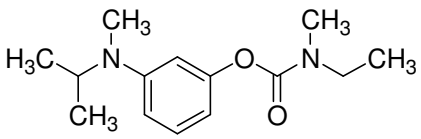

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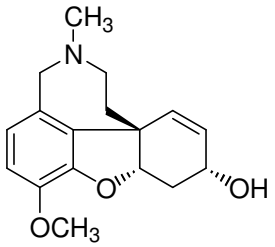
1.3.1.2 Galantamine and related Amaryllidaceous alkaloids

Galantamine **(6)** was found in several members of the Amaryllidaceae such as the Chinese medicinal herb, *Lycoris radiata* Herb. and the European *Galanthus nivalis* L. and

Narcissus spp. Its properties were first exploited in Bulgaria in the mid-twentieth century for the treatment of polio victims, but it only came into prominence as a treatment for AD during the 1990's. Galantamine has been licensed in Europe for AD treatment since 2001. Among several adventages of galantamine over other anti-Alzheimer's drugs include the longer benefit on cognitive functions, which reportedly last for at least 3 years (Eslami *et al*., 2003; Houghton and Howes, 2005).

Other related alkaloids isolated from other Amaryllidaceous species includes crinine **(7)** and its dihydroisoquinoline analogues. Major sources of these alkaloids include plants of the genus *Crinum*. Most of these alkaloids express the AChE inhibiting activity with IC_{50}'s of 213–490 μM (Viegas *et al*., 2005).



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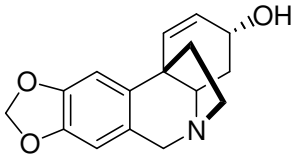

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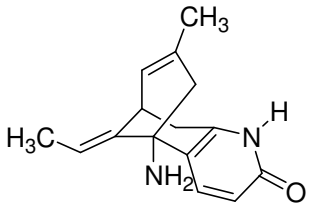
1.3.1.3 Huperzine A and *Lycopodium* alkaloids

Huperzine A **(8)**, isolated from clubmoss *Huperzia serrata* (Thunb. ex Murray) Trevis (syn. *Lycopodium serratum* Thunb.), is a potent, highly specific and reversible inhibitor of AChE (Wang and Tang, 1998). The compound was found to reverse or attenuate cognitive deficits in a broad range of animal models. Clinical trials in China have demonstrated that huperzine A significantly relieves memory deficits in aged subjects, patients with benign senescent forgetfulness, AD and vascular dementia (VD), with minimal peripheral cholinergic side effects (Wang and Tang, 2005).

The discovery of huperzine derivatives from *Huperzia* sp. also led to the investigation in several species of *Lycopodium* mosses, most of which have been long known among Chinese medicinal herbs. Various alkaloids presumably derived from related quinolizidine precursors, such as carinatumins A **(9)** and B **(10)**, were reported to exhibit AChE inhibitory activity in a various extent (Choo *et al*., 2007).



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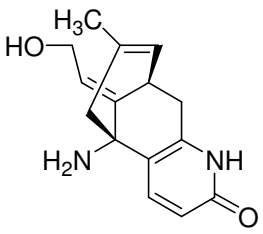

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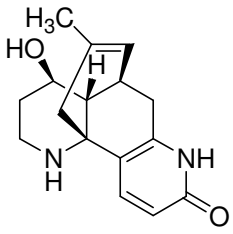

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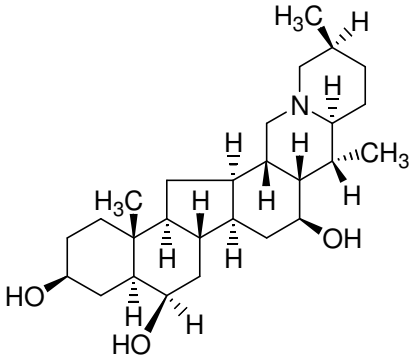
1.3.1.4 Steroidal alkaloids and alkaloids with terpenoid skeletons

Apart from the well-known Solanaceous steroidal alkaloids, some of which were also reported active as AChE inhibitors, most of steroidal alkaloids that showed potent AChE inhibitory activity were isolated from medicinal plants of the family Buxaceae, especially those from the genus *Sarcococca* (Kalauni *et al*., 2002; Choudhary *et al*., 2003; Babar *et al*., 2006). Due to the close relation with the main focus of this thesis, the major review on *Sarcococca* alkaloids and related analogues will be re-addressed in a more elaborated detail in section 1.3.3.

Although remotely related in core structures, certain nitrogenated terpenoids also coincidentally exhibited cholinesterase-inhibiting activity. The examples include delavine **(11)** and persicanidine **(12)** from the bulbs of plant in genus *Fritillaria*, which show butyrylcholines-terase-inhibiting activity with IC_{50}'s of 1.71 and 4.25 μM, respectively (Atta-ur-Rahman *et al*., 2002a).



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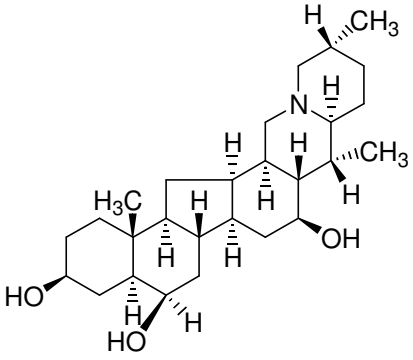

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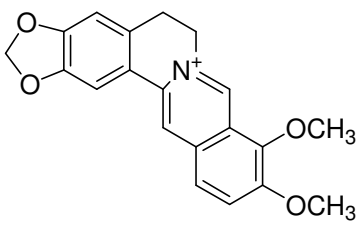
1.3.1.5 Miscellaneous alkaloids

Although it is not an intention of this review to compile all the AChE inhibitors completely, it is worth exemplifying here certain interesting alkaloids that exhibit a cholinesterase

inhibitory activity in an interesting extent. Of particular interest were those with protoberberine and indole moieties. These include berberine **(13),** palmatine **(14),** and protopine **(15)** from *Corydalis speciosa* Maxim., which showed cholinesterase-inhibiting activity with IC_{50}'s of 3.3, 5.8, and 16.1 μM, respectively (Kim *et al*., 2004). For indole alkaloids, the prototypes included rutaecarpine **(16)** and dehydroevodiamine **(17)**, both of which were isolated from *Evodia rutaecarpa* (Juss) Benth. Compound **17** showed AChE-inhibiting activity with IC_{50} of 37.8 μM (Park *et al*., 1996).



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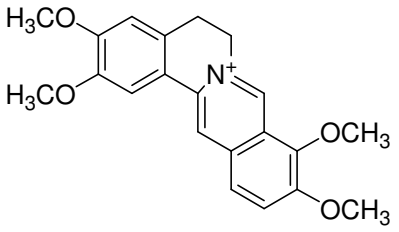

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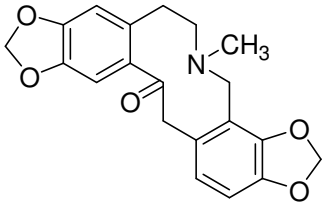

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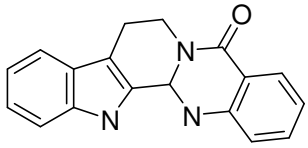

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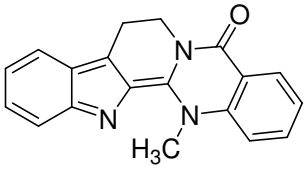

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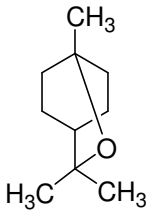
3.2 Terpenoids

As mentioned earlier, despite the extensive studies on the AChE binding sites that suggested a requirement of positively-charged moieties, certain oxygenated and lipophilic terpenoids, i.e., non-positive compounds, were reported highly active in cholinesterase-inhibiting assays. Of particular interest were volatile and small-molecule terpenoids, which were actually good for the memory as recorded in their history.

One such group of plants was the various European species of *Salvia* (family Labiatae). An ethanolic extract and oil of *S. officinalis* L. and *S. lavandulaefolia* Vahl. were investigated for AChE-inhibiting activity. Whereas the isolated single components such as 1,8-cineole **(18)** and α-pinene **(19)**, from the both *Salvia* species, were virtually inactive, the total volatile oils were found active in animal models (Houghton and Howes, 2005).



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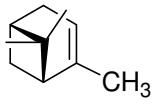

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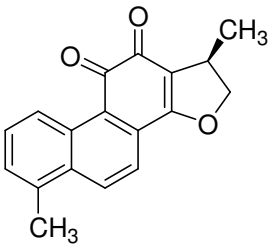
Larger-size terpenoids such as the norditerpenes, dihydrotanshinone **(20)** and cryptotanshinone **(21)** from root of *S. miltiorrhiza* Bunge, were also among AChE-inhibiting terpenes. Compounds **20** and **21** showed high AChE inhibitory activity (IC_{50}'s 1.0 and 7.0 μM, respectively). The plant was also known in Chinese medicines for its calmative effects, and there is evidence showing the neurodegenerative-protecting activity in its root extract (Houghton and Howes, 2005; Viegas *et al*., 2005).



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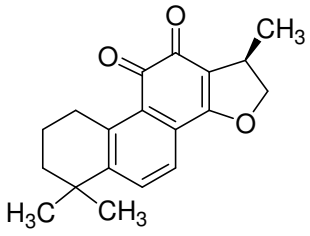

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1.3.3 Buxaceous steroidal alkaloids

The chemical structures of steroidal alkaloids found in natural products exhibit a wide variety both in the core steroid skeletons and nitrogenous substituent groups. However, as mentioned in section 1.3.1.4, most of steroidal alkaloids that were reported active as AChE inhibitors were predominantly isolated from medicinal plants of the family Buxaceae, especially those from the genera *Sarcococca* and *Buxus* (Babar *et al*., 2006). The chemical structures and potency towards the AChE inhibition of Buxaceous steroidal alkaloids and related compounds are shown in Table 2.

Primarily, the core structures of the AChE-inhibiting steroidal alkaloids from Buxaceous plants are based on pregnane-type steroid skeleton, with nitrogenated substituted groups on C-3 and C-20. Although the molecular docking study suggested influence from either

of the nitrogens, the QSAR study indicated the positive effects from C-3 amino or amide nitrogen. Surprisingly, the remote nitrogen on C-20 was found irrelevant to the potency. In addition, the negatively-charged functional groups surrounding rings A and B (other than on C-3 and C-4) posted negative influences on the enzyme-inhibiting activity (Zaheer-ul-Huq *et al*., 2003b; Khalid *et al*., 2004a).

Table 2 Steroidal alkaloids as cholinesterase inhibitors

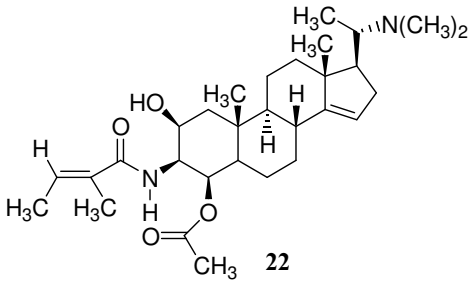
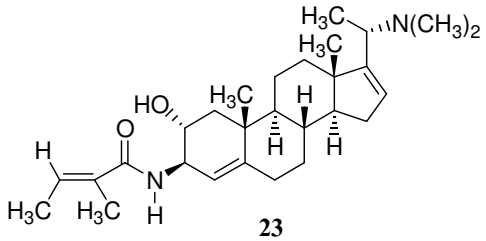
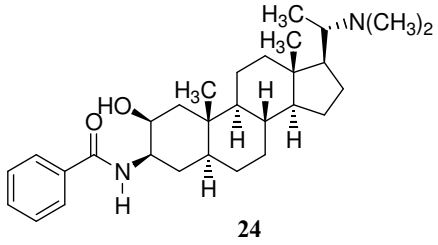
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
salignenamide C **(22)**	 **22**	61.3	38.4	Atta-ur-Rahman *et al.*, 2002b
salignenamide D **(23)**	 **23**	185.2	23.8	Atta-ur-Rahman *et al.*, 2002b
2β-hydroxyepipachysamine D **(24)**	 **24**	78.2	29.0	Atta-ur-Rahman *et al.*, 2002b

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

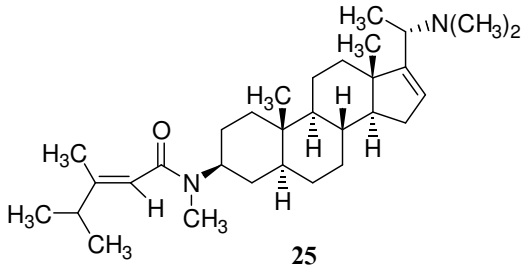
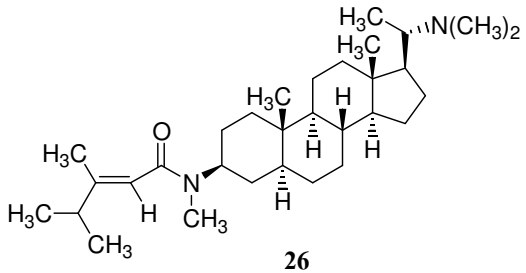
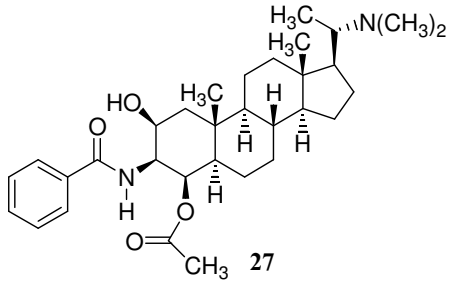
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
salignenamide E **(25)**	 **25**	6.2	3.7	Atta-ur-Rahman *et al.*, 2002b
salignenamide F **(26)**	 **26**	6.4	4.1	Atta-ur-Rahman *et al.*, 2002b
axillarine C **(27)**	 **27**	227.9	18.0	Atta-ur-Rahman *et al.*, 2002b

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

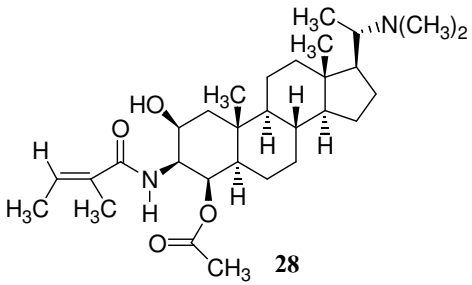
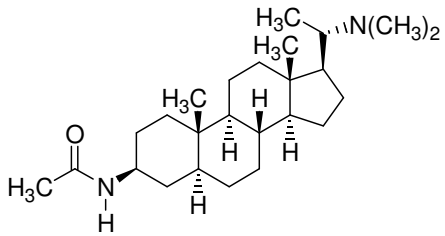
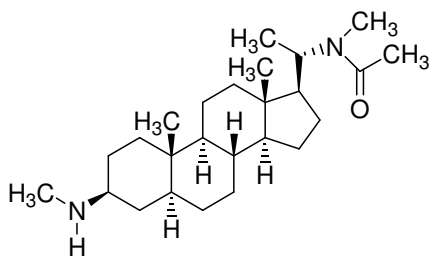
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
axillarine F **(28)**	 **28**	182.4	18.2	Atta-ur-Rahman *et al.*, 2002b
sarcorine **(29)**	 **29**	70.0	10.3	Atta-ur-Rahman *et al.*, 2002b
3-*N*-demethylsarcodine **(30)**	 **30**	204.2	16.6	Atta-ur-Rahman *et al.*, 2002b

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

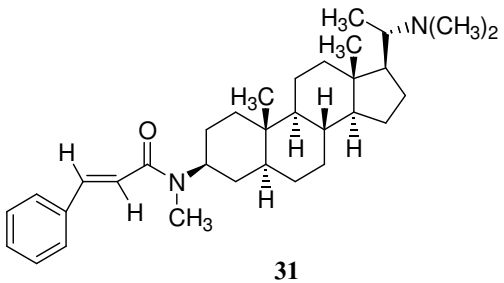
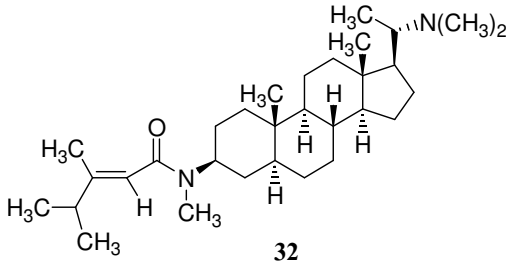
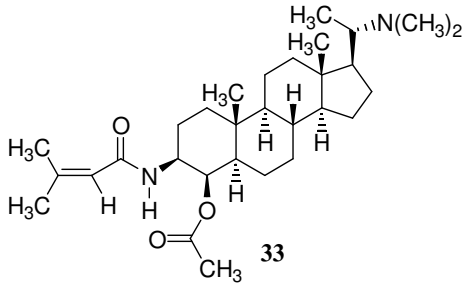
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
saligcinnamide **(31)**	 **31**	20.0	4.8	Atta-ur-Rahman *et al.*, 2002b
salignenamide A **(32)**	 **32**	50.6	4.6	Atta-ur-Rahman *et al.*, 2002b
vaganine A **(33)**	 **33**	8.6	2.3	Atta-ur-Rahman *et al.*, 2002b

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

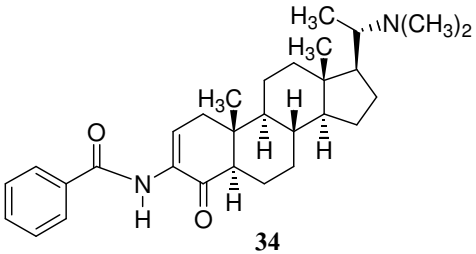
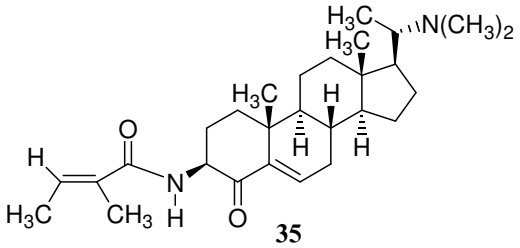
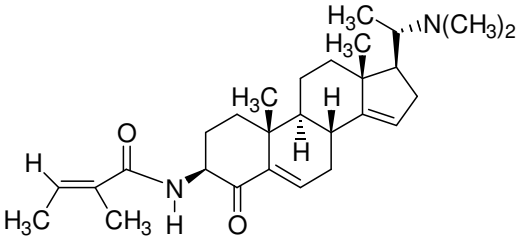
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
axillaridine A **(34)**	 **34**	5.2	2.5	Atta-ur-Rahman *et al.*, 2002b
sarsalignone **(35)**	 **35**	7.0	2.2	Atta-ur-Rahman *et al.*, 2002b
sarsalignenone **(36)**	 **36**	5.8	4.3	Atta-ur-Rahman *et al.*, 2002b

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

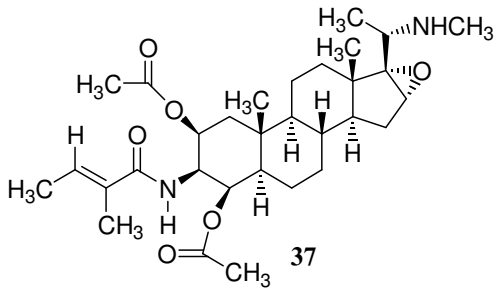
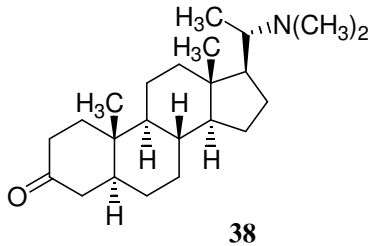
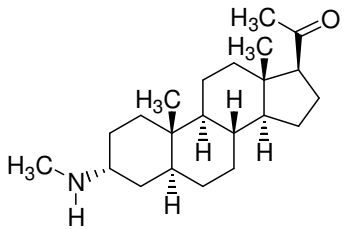
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
epoxynepapakistamine-A **(37)**	 **37**	>200.0	77.4	Kalauni *et al*., 2002
funtumafrine **(38)**	 **38**	45.8	6.6	Kalauni *et al*., 2002
N-methylfuntumine **(39)**	 **39**	97.6	12.7	Kalauni *et al*., 2002

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

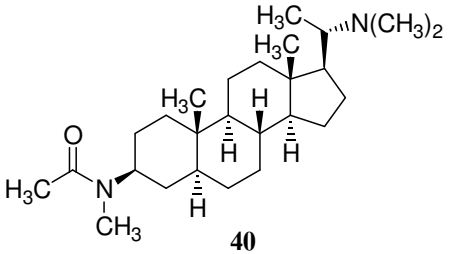
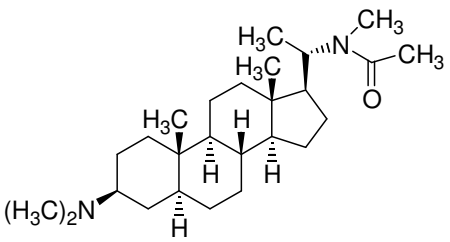
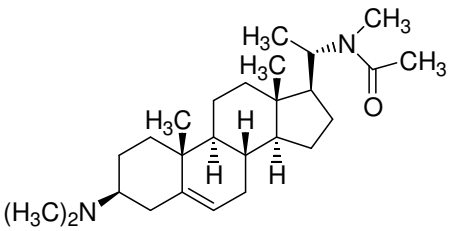
Name	Structure	IC_{50} (μM)		Reference
		AChE	**BChE**	
isosarcodine **(40)**	 **40**	10.3	1.9	Khalid *et al*.,2004b
sarcodine **(41)**	 **41**	49.8	18.3	Khalid *et al*.,2004b
sarcocine **(42)**	 **42**	20.0	3.9	Khalid *et al*.,2004b

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

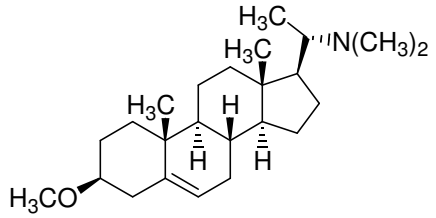
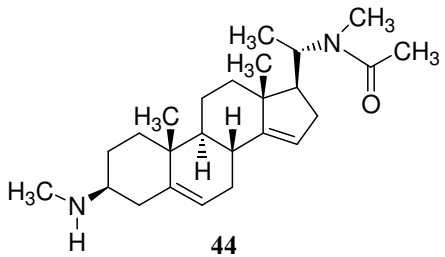
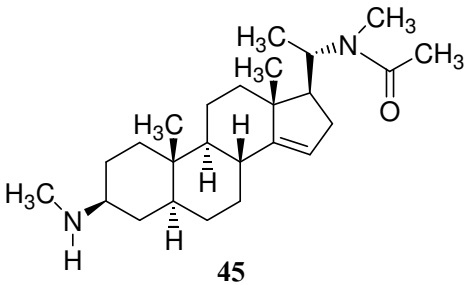
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
alkaloid-C **(43)**	 **43**	42.2	22.1	Khalid *et al*.,2004b
5,14-dehydro-3-*N*-demethylsaracodine **(44)**	 **44**	>200.0	25.0	Atta-ur-Rahman *et al.*, 2004a
14-dehydro-3-*N*-demethylsaracodine **(45)**	 **45**	183.1	10.1	Atta-ur-Rahman *et al.*, 2004a

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

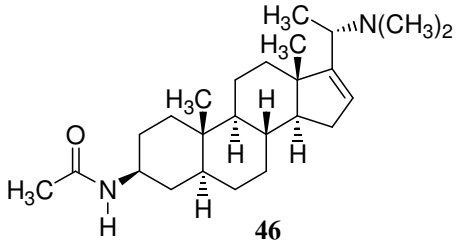
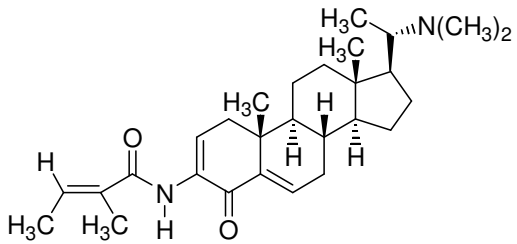
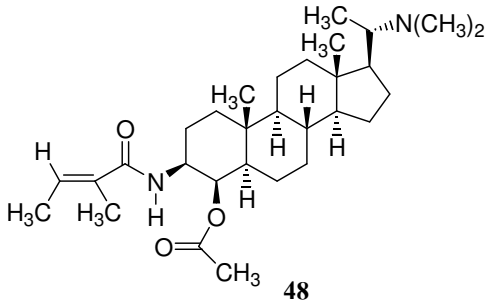
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
16-dehydrosarcorine **(46)**	 **46**	12.5	4.0	Atta-ur-Rahman *et al.*, 2004a
2,3-dehydrosarsalignone **(47)**	 **47**	7.0	32.2	Atta-ur-Rahman *et al.*, 2004a
sarcovagenine-C **(48)**	 **48**	187.8	1.5	Atta-ur-Rahman *et al.*, 2004a

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

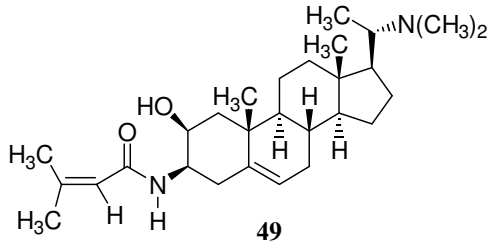
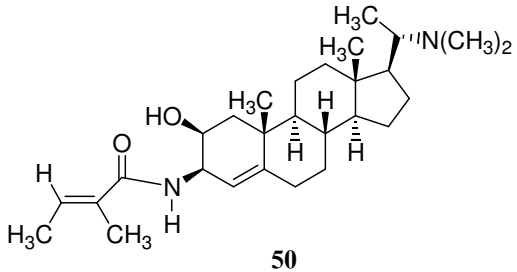
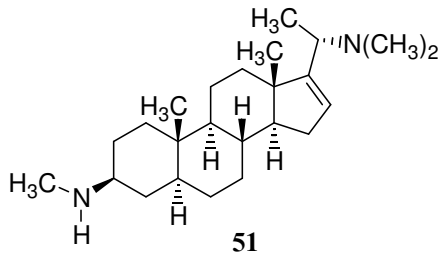
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
salignarine-C **(49)**	 **49**	19.7	1.3	Atta-ur-Rahman *et al.*, 2004a
2-hydroxysalignarine-E **(50)**	 **50**	16.0	6.9	Atta-ur-Rahman *et al.*, 2004b
5,6-dihydrosarconidine **(51)**	 **51**	20.3	1.9	Atta-ur-Rahman *et al.*, 2004b

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

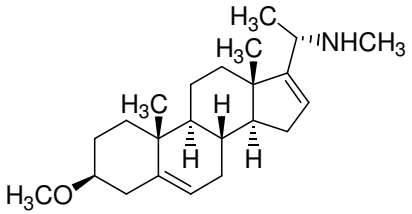
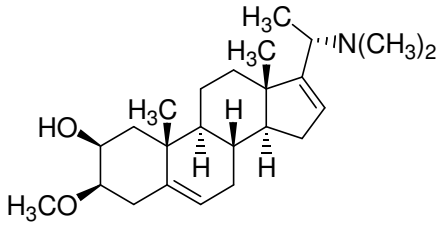
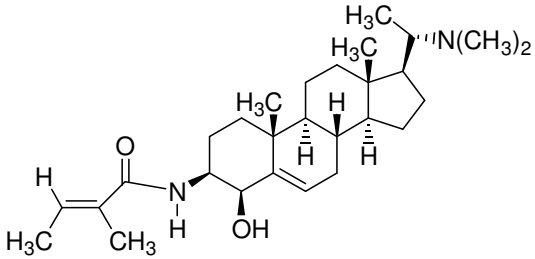
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
salignamine **(52)**	 **52**	249.0	25.7	Atta-ur-Rahman *et al.*, 2004bb
2-hydroxysalignamine **(53)**	 **53**	82.5	21.0	Atta-ur-Rahman *et al.*, 2004b
salignarine-F **(54)**	 **54**	30.2	1.9	Atta-ur-Rahman *et al.*, 2004b

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

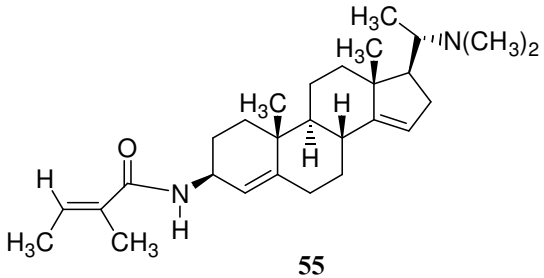
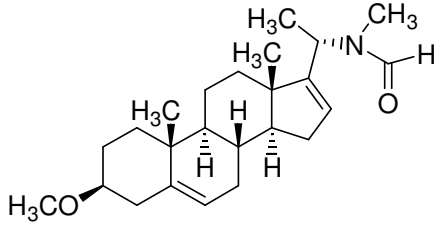
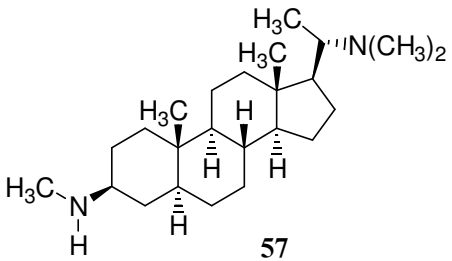
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
salonine-C **(55)**	 **55**	7.8	32.2	Atta-ur-Rahman *et al.*, 2004b
N-[formyl (methyl)amino] salonine-B **(56)**	 **56**	48.6	10.5	Atta-ur-Rahman *et al.*, 2004b
dictyophlebine **(57)**	 **57**	6.2	3.7	Atta-ur-Rahman *et al.*, 2004b

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

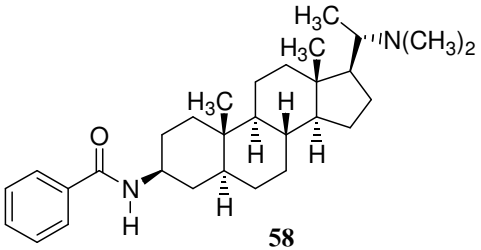
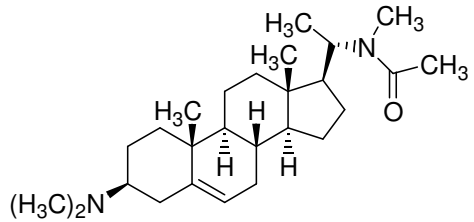
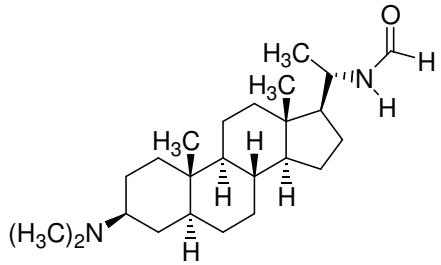
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
epipachysamine-D **(58)**	 **58**	28.9	2.8	Atta-ur-Rahman *et al.*, 2004b
saracosine **(59)**	 **59**	20.0	3.9	Atta-ur-Rahman *et al.*, 2004b
iso-*N*-formylchonemorphine **(60)**	 **60**	6.4	4.1	Atta-ur-Rahman *et al.*, 2004b

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

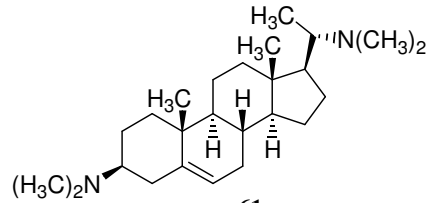
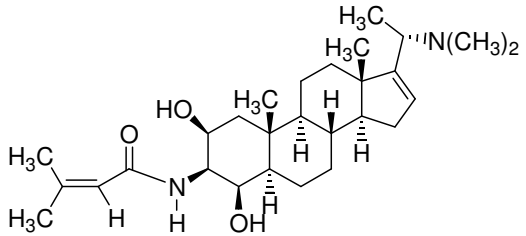
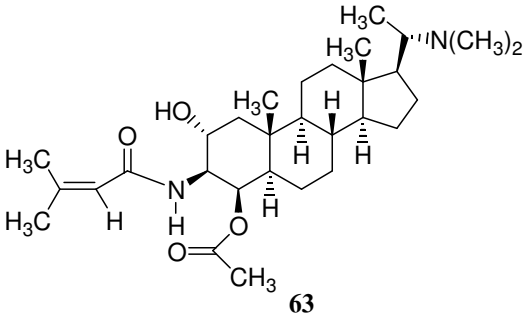
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
sarcodinine **(61)**	 **61**	40.0	12.5	Atta-ur-Rahman *et al.*, 2004b
hookerianamide A **(62)**	 **62**	82.7	200.0	Choudhary *et al*., 2004
hookerianamide B **(63)**	 **63**	26.4	0.8	Choudhary *et al*., 2004

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

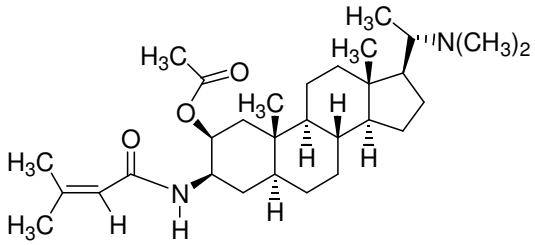
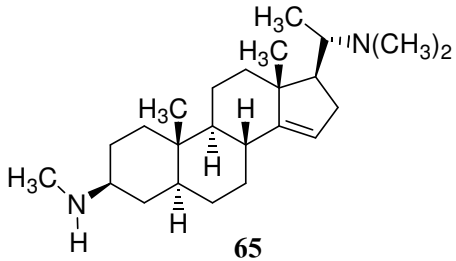
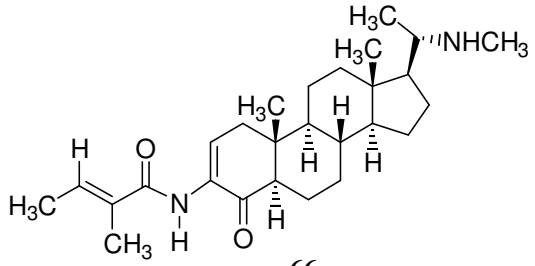
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
hookerianamide C **(64)**	 **64**	23.2	0.6	Choudhary *et al*., 2004
hookerianamine A **(65)**	 **65**	18.9	0.9	Choudhary *et al*., 2004
phulchowkiamide A **(66)**	 **66**	0.5	0.4	Choudhary *et al*., 2004

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

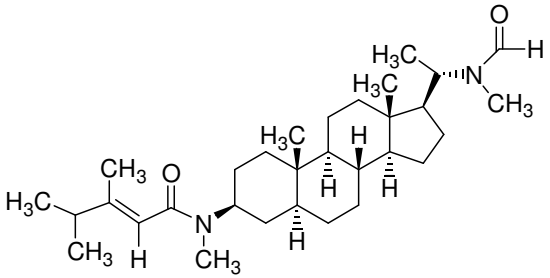
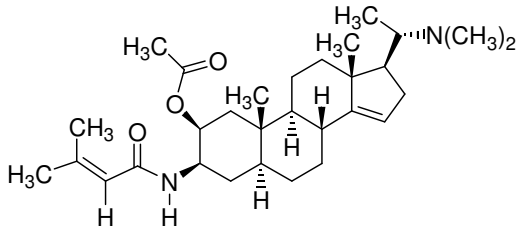
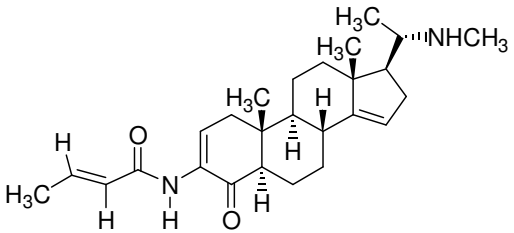
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
hookerianamide-D **(67)**	 **67**	59.0	100.2	Choudhary *et al*., 2005
hookerianamide-E **(68)**	 **68**	15.9	6.0	Choudhary *et al*., 2005
hookerianamide-F **(69)**	 **69**	1.6	7.2	Choudhary *et al*., 2005

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

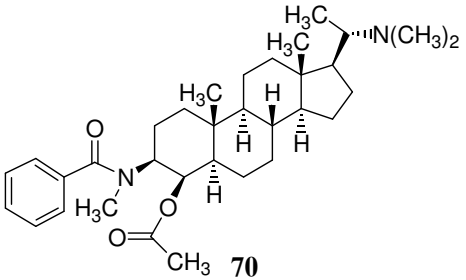
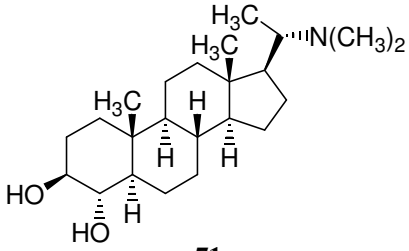
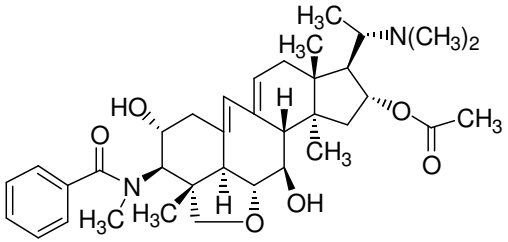
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
hookerianamide-G **(70)**	 **70**	11.4	1.5	Choudhary *et al*., 2005
terminaline **(71)**	 **71**	113.1	0.6	Choudhary *et al*., 2005
6-*O*-buxafurandiene **(72)**	 **72**	17.0	-	Babar *et al*., 2006

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

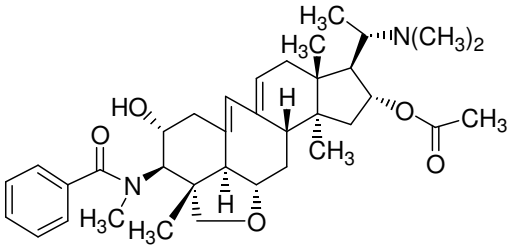
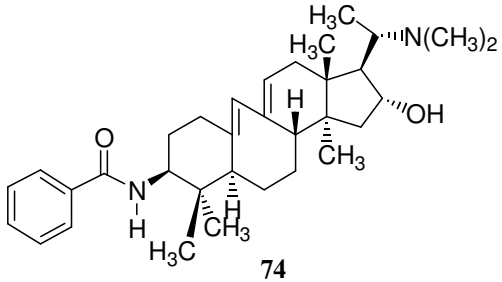
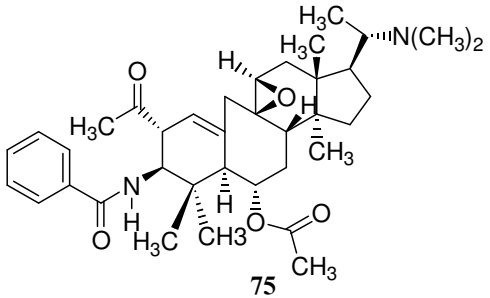
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
7-deoxy-6-*O*-buxafurandiene **(73)**	 **73**	13.0	-	Babar *et al*., 2006
benzoylbuxidienine **(74)**	 **74**	35.0	-	Babar *et al*., 2006
buxapapillnine **(75)**	 **75**	80.0	-	Babar *et al*., 2006

Table 2 Steroidal alkaloids as cholinesterase inhibitors (cont.)

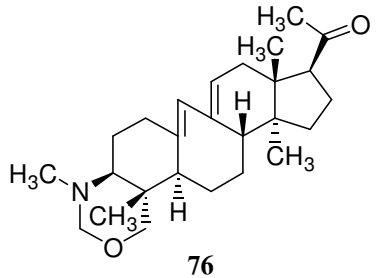
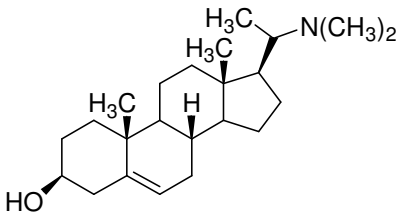
Name	Structure	IC_{50} (μM)		Reference
		AChE	BChE	
buxaquamarine **(76)**	 **76**	76.0	-	Babar *et al*., 2006
irehine **(77)**	 **77**	100.0	-	Babar *et al*., 2006

Table 3 Compounds isolated from sponges of the genus *Corticium*

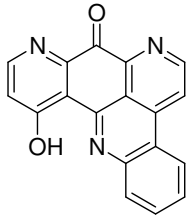
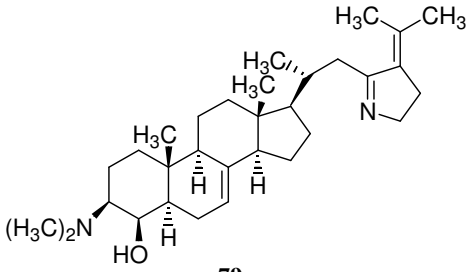
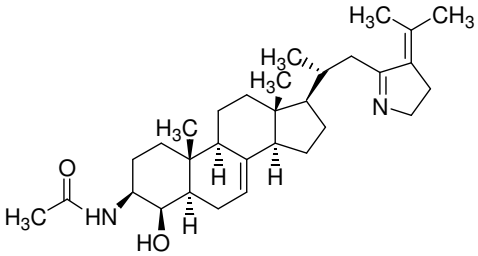
Name	Structure	Activities	Reference
meridine **(78)**	 **78**	antifungal (*Candida albicans*; MIC 0.2 μg/mL and *Cryptococcus neoformans*; MIC 0.8 μg/mL)	McCarthy *et al*., 1992
lokysterolamine A **(79)**	 **79**	cytotoxicity (P- 388, IC_{50} 0.5 μg/mL; A-549, IC_{50} 0.5 μg/mL; HT-29, IC_{50} 1.0 μg/mL; MEL-28, IC_{50} 5 μg/mL); antimicrobial (*B. subtilis*, 19 mm; 50 μg/disc); antifungal (*C. albicans*, 11 mm; 50 μg/disc)	Jurek *et al*., 1994
lokysterolamine B **(80)**	 **80**	cytotoxicity (P- 388, IC_{50} 1.0 μg/mL; A-549, IC_{50} 0.5 μg/mL; HT-29, IC_{50} 1.0 μg/mL; MEL-28, IC_{50} >2 μg/mL); antimicrobial (*B. subtilis*, 8 mm; 50 μg/disc)	Jurek *et al*., 1994

Table 3 Compounds isolated from sponges of the genus *Corticium* (cont.)

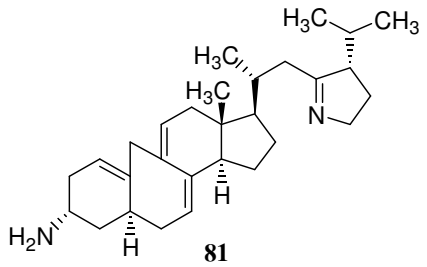
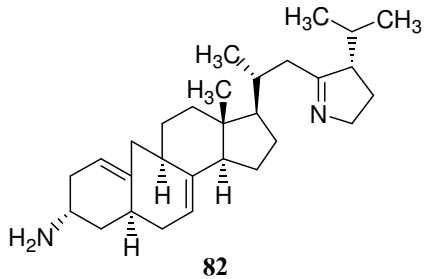
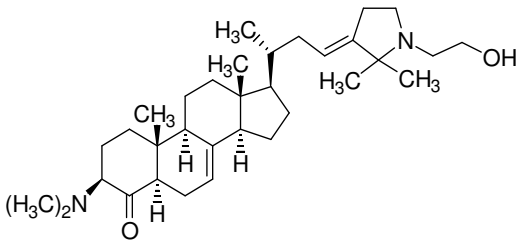
Name	Structure	Activities	Reference
3α-amino-23, 29-imino-β (9a)-homo-19-nor-5α-stigmasta-1(10),7,9,(11), 23(*N*)-tetraene **(81)**	 **81**	no reported activity available	De Marino *et al.*, 1998
3α-amino-23,29-imino-β (9a)-homo-19-nor-5α-stigmasta-1(10),7,23,(11), 23(*N*)-triene **(82)**	 **82**	no reported activity available	De Marino *et al.*, 1998
plakinamine C **(83)**	 **83**	anti-HIV (inhibit *syncytia* formation after HIV infection of MT_4 cell line at 0.1μg/mL)	De Marino *et al.*, 1999

Table 3 Compounds isolated from sponges of the genus *Corticium* (cont.)

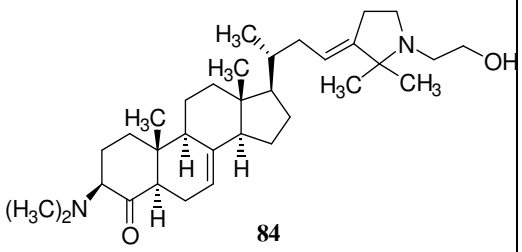
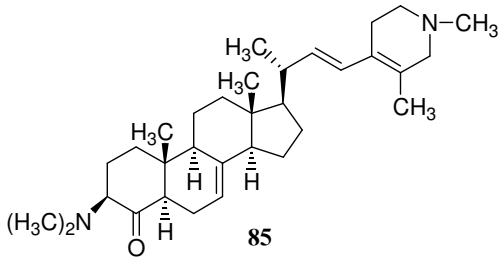
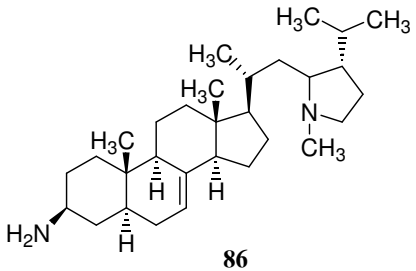
Name	Structure	Activities	Reference
plakinamine D **(84)**	 **84**	cytotoxicity (NSCLC-N6, IC_{50} 3.3 μg/mL)	De Marino *et al.*, 1999
N, *N*- dimethyl-4-oxo-3-*epi*-plakinamine B **(85)**	 **85**	cytotoxicity (NSCLC-N6, IC_{50} 3.6 μg/mL)	De Marino *et al.*, 1999
25,26-dihydro-plakinamine A **(86)**	 **86**	anti-HIV activity (inhibit *syncytia* formation after HIV infection of MT_4 cell line at 0.05 μg/mL); cytotoxicity (NSCLC-N6, IC_{50} 5.7 μg/mL)	De Marino *et al.*, 1999

Table 3 Compounds isolated from sponges of the genus *Corticium* (cont.)

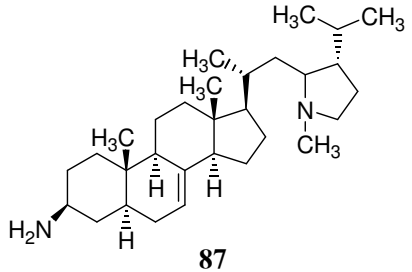
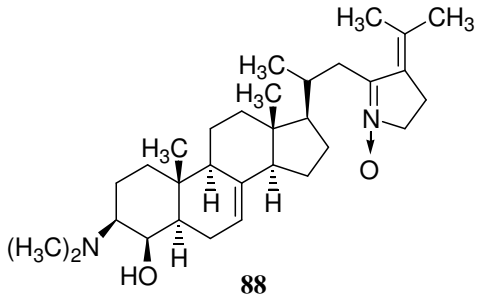
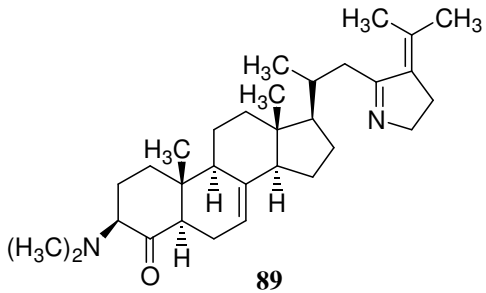
Name	Structure	Activities	Reference
23-(*N*-methyl)-plakinamine **A (87)**	 **87**	anti-HIV activity (inhibit *syncytia* formation after HIV infection of MT_4 cell line at 0.1 μg/mL); cytotoxicity (NSCLC-N6, IC_{50} 4.9 μg/mL)	De Marino *et al.*, 1999
plakinamine E **(88)**	 **88**	cytotoxicity (K562, IC_{50} 0.2 μg/mL); antifungal (*C. albicans*, 12 mm; 25 μg/disc); DNA- and RNA- cleaving activities at 10 μg/20mL	Lee *et al*., 2001
plakinamine F **(89)**	 **89**	cytotoxicity (K562, IC_{50} 1.3 μg/mL); antifungal (*C. albicans*, 8 mm; 25 μg/disc)	Lee *et al*., 2001

Table 3 Compounds isolated from sponges of the genus *Corticium* (cont.)

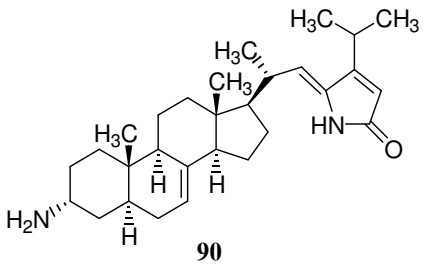
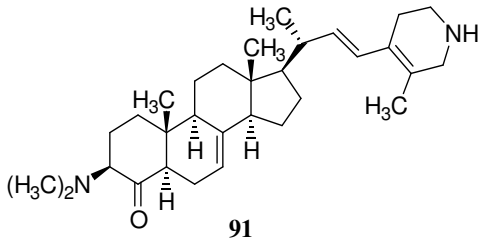
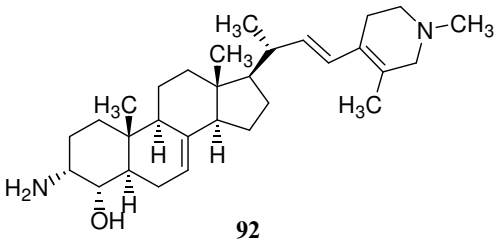
Name	Structure	Activities	Reference
plakinamine G **(90)**	 **90**	cytotoxicity (C6, IC_{50} 6.8 µg/mL)	Borbone *et al*., 2002
plakinamine H **(91)**	 **91**	cytotoxicity (C6, IC_{50} 9.0 µg/mL; RAW 264, IC_{50} 61.0 µg/mL)	Borbone *et al*., 2002
4α-hydroxydemethyl-plakinamine B **(92)**	 **92**	cytotoxicity (C6, IC_{50} 26.1 µg/mL; RAW 264, IC_{50} 16.2 µg/mL)	Borbone *et al*., 2002

Table 3 Compounds isolated from sponges of the genus *Corticium* (cont.)

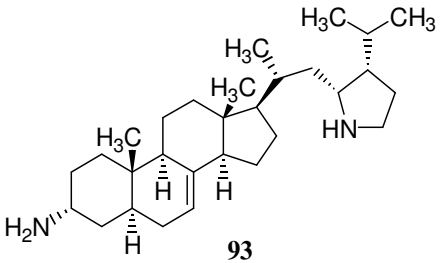
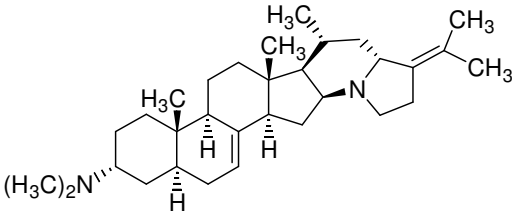
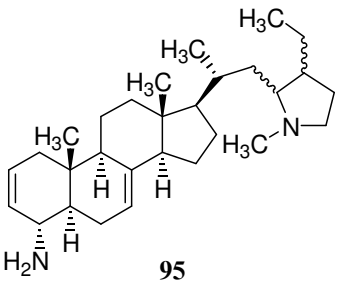
Name	Structure	Activities	Reference
tetrahydroplakinamine A **(93)**	 **93**	cytotoxicity (C6, IC_{50} 1.4 μg/mL)	Borbone *et al*., 2002
plakinamine I **(94)**	 **94**	cytotoxicity (HCT-116, IC_{50} 10.6 μM)	Ridley and Faulkner, 2003
plakinamine J **(95)**	 **95**	cytotoxicity (HCT-116, IC_{50} 6.1 μM)	Ridley and Faulkner, 2003

Table 3 Compounds isolated from sponges of the genus *Corticium* (cont.)

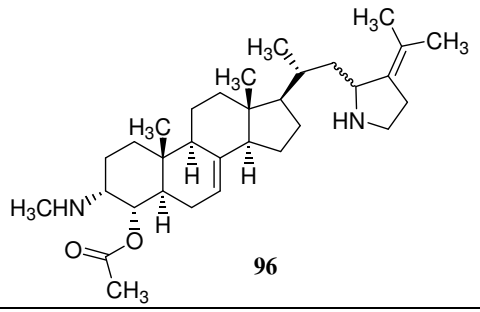
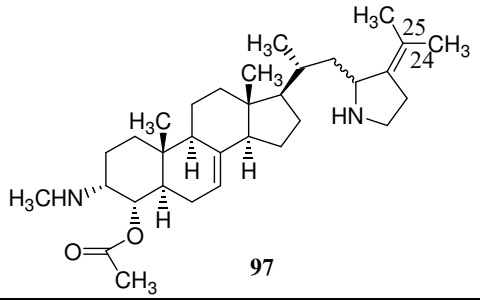
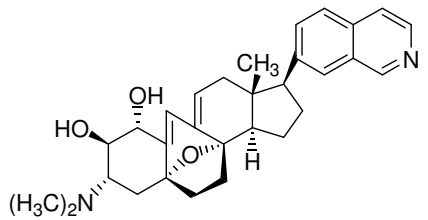
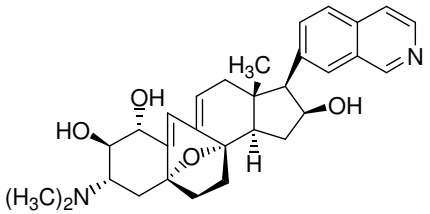
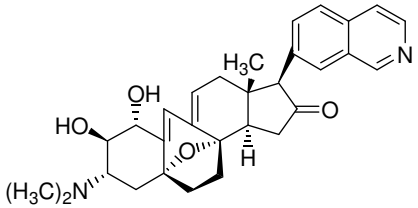
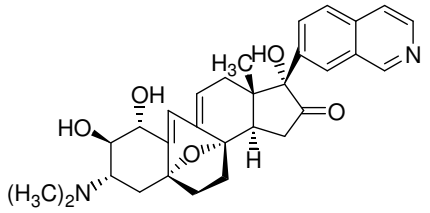
Name	Structure	Activities	Reference
plakinamine K **(96)**	 **96**	cytotoxicity (HCT-116, IC_{50} 1.4 μM)	Ridley and Faulkner, 2003
24,25-dihydroplakinamine K **(97)**	 **97**	cytotoxicity (HCT-116, IC_{50} 1.4 μM)	Ridley and Faulkner, 2003
cortistatin A **(98)**	 **98**	anti-proliferative activity (HUVECs, IC_{50} 0.0018 μM)	Aoki *et al*., 2006

Table 3 Compounds isolated from sponges of the genus *Corticium* (cont.)

Name	Structure	Activities	Reference
cortistatin B **(99)**	 **99**	anti-proliferative activity (HUVECs, IC_{50} 1.1 μM)	Aoki *et al*., 2006
cortistatin C **(100)**	 **100**	anti-proliferative activity (HUVECs, IC_{50} 0.019 μM)	Aoki *et al*., 2006
cortistatin D **(101)**	 **101**	anti-proliferative activity (HUVECs, IC_{50} 0.15 μM)	Aoki *et al*., 2006