2. Literature review

Medicinal chemists throughout the world are recognising the importance of multitarget-directed ligands (MTDLs) approach to deal with complex multi-factorial diseases like AD. A variety of new compounds have been designed by the hybrid approach wherein two pharmacophores showing different biological activities on different targets are fused together to form one hybrid structure or molecule which can be called as multi-target-directed ligands (MTDLs). The reported MTDLs for the management of AD are comprised of mainly cholinesterase inhibitors having affinity for dual binding sites (CAS & PAS) as well as some additional potential or property such as metal chelating, anti-oxidant, inhibition of Aβ aggregation, β-site APP cleaving enzyme (BACE-1) and monoamine oxidase-B (MAO-B). Most of these MTDLs have been synthesized by modifying the structure of the existing AChE inhibitors.[1]

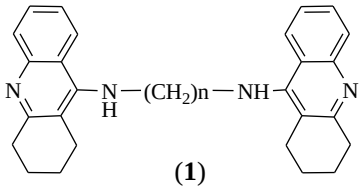
A large number of AChE inhibitors have been reported in the literature. Around 100 molecules faced clinical trials in the last two decades, but out of all of them, only four were successful to reach the market for clinical use.[2] Till date, various multifunctional cholinesterase inhibitors, based on the structures of marketed AChEIs, have been reported either by modifying the core scaffold of these AChEIs or using their active pharmacophores. Some of these most potential multifunctional ChEIs have been discussed in the following sections.

2.1 Tacrine-based multifunctional cholinesterase inhibitors

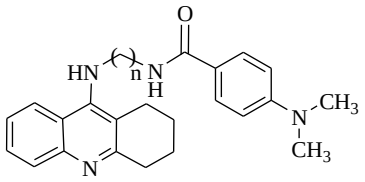
9-Amino-1,2,3,4-tetrahydroacridine (THA) i.e. tacrine, the most potent cholinesterase inhibitor, was the first drug belonging to the class of ChEIs to be used clinically in the year 1993 for the treatment of AD. Unfortunately, it was found that tacrine increased the levels of *serum alanine aminotrasferase* indicating its hepatotoxicity which subsequently led to its withdrawl from the market in the year 2013. In spite of its limited clinical application, tacrine fascinated scientific fraternity to use it as a lead molecule and since then it has widely been utilised to design and develop novel MTDLs.[3]

Pang *et al.* synthesized some tacrine homodimers (**1a-1c**) by linking two tacrine molecules with 7 to 10 methylene units. Surprisingly, these tacrine dimers (**1a-1c**) were found to be 1000 folds more potent than tacrine. Undoubtedly, this work paved the way for further development of the MTDL approach to design novel therapeutics for the treatment of AD.[4]

	n	IC_{50} (nM) mAChE	mBuChE
1a	7	0.40	390
1b	8	0.66	340
1c	9	0.77	190
THA		590	44



(**1**)

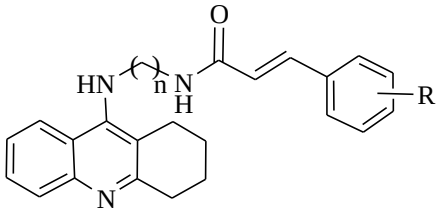


(**2**)

	n
2a	3
2b	2

Bajda *et al.* described synthesis and ChE inhibitory activity of some novel tacrine derivatives. All of these newly synthesized hybrids showed potent *ee*AChE and *eq*BuChE inhibition with IC_{50} values varying from sub-nanomolar to nanomolar. Among the series, compound (**2a**) was found to be the most potent *h*AChE inhibitor with an IC_{50} value of 19 nM while compound (**2b**) exhibited the highest 80.6 and 91.3% inhibition of AChE-induced Aβ-aggregation at 50 and 100 μM concentrations.[5]

Chen *et al.* reported synthesis and ChE inhibitory activity of some tacrine-cinnamic acid hybrids (**3a-3l**) wherein the tacrine was clubbed with substituted cinnamic acids using methylene spacers. All of the synthesized compounds showed promising cholinesterase inhibitory activity. Compounds (**3a-3l**) exhibited potent inhibition of AChE and BuChE *in vitro*.[6, 7]



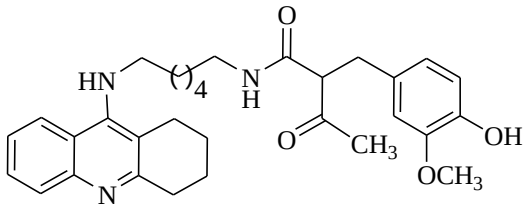
(**3**)

	n	R=	IC_{50} (nM) mAChE[b]	mBuChE[c]
3a	2	3-NO_2	3.8	34.7
3b	2	4-NO_2	6.8	154.3
3c	2	4-Cl-3-NO_2	5.5	64.4
3d	6	3-NO_2	3.6	6.8
3e	6	4-NO_2	2.7	6.5
			10.2[d]	6.3[d]
3f	6	4-Cl-3-NO_2	6.2	11.1
3g	6	3-OH	6.4	25.1
3h	6	4 -Cl	6.9	12.9
			16.5[d]	5.7[d]
3i	6	3-CN	5.1	68.5
3j	6	4-OCH_3	3.7	22.5
			15.3[d]	8.0[d]
3k	6	3,4,5-tri-OCH_3	6.4	3.4
3l	6	4-OH	2.2	43.5
Tacrine			69.8	10.6

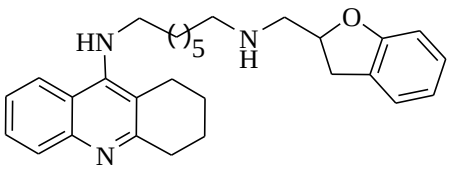
[b]AChE from electric eel, [c]BuChE from horse serum, [d]AChE and BuChE from human.

Liu *et al.*[8] prepared a series of tacrine-curcumin hybrid analogs as multifunctional cholinesterase inhibitors. Among the series, compound (**4**) exhibited the most potent activity

with IC_{50} values of 0.08 μM for AChE and 0.22 μM for BuChE compared to the standard tacrine (AChE, IC_{50}= 0.10 μM and BuChE, IC_{50}= 0.05 μM). In another report, Zha *et al.* described the synthesis and evaluation of ChE inhibitory activity of some novel tacrine-benzofuran hybrid compounds. All the synthesized compounds showed promising activity with an IC_{50} value in submicromolar range except for compound (**5**). Compound (**5**) inhibited *h*AChE (IC_{50} = 0.86 nM) and *h*BuChE (IC_{50} = 2.18 nM) which was found to be the most potent in the series compared to the reference tacrine (*h*AChE, IC_{50} = 424 nM; *h*BuChE, IC_{50} = 45.8 nM). It also displayed 61.3% inhibition of Aβ-aggregation at 10 μM concentration.[9]

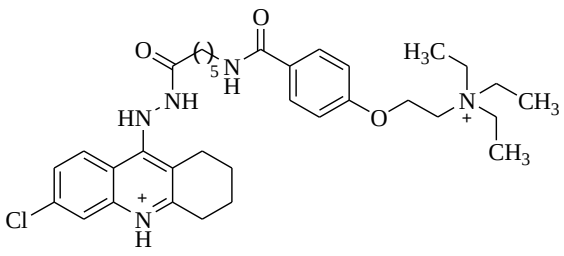


(**4**)

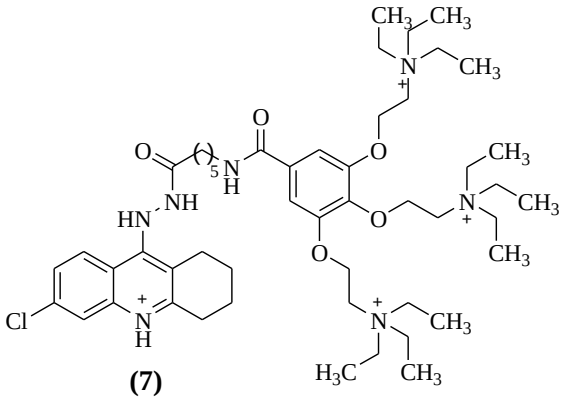


(**5**)

Elsinghorst *et al.* reported a hybrid of gallamine and tacrine. Gallamine is known to be an allosteric modulator of muscarinic M_2 receptors and it also inhibits AChE. Hence the authors thought it logical to combine gallamine and tacrine to produce newer effective dimer hybrids with improved AChE inhibitory activity. Hybrids (**6** and **7**) showed the most potent inhibition of *h*AChE compared to reference gallamine and tacrine. Compound (**6**) inhibited *h*AChE (IC_{50} = 5.44 nM) and *h*BuChE (IC_{50} = 8.55 nM) while compound (**7**) inhibited *h*AChE (IC_{50} = 6.75 nM) and *h*BuChE (IC_{50} = 16.7 nM) compared to standards tacrine (*h*AChE, IC_{50} = 926 nM and *h*BuChE IC_{50} = 10.2 nM) and gallamine (*h*AChE, IC_{50} = 2110 μM and *h*BuChE, IC_{50} = 2390 μM).[10]

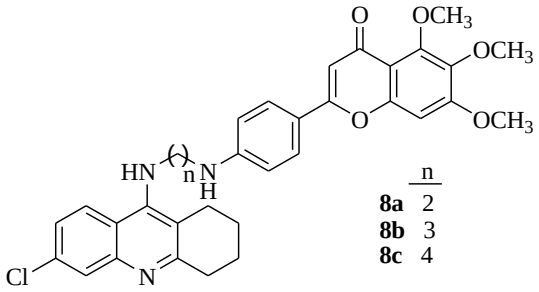


(6)

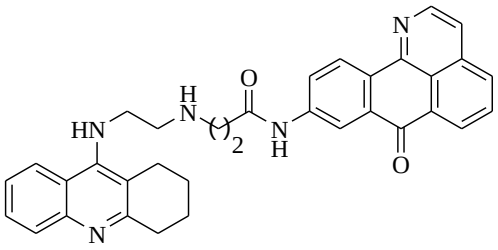


(7)

To exploit the biological potential of scutellarin, Spilovska *et al.* planned to link the 6-chlorotacrine (6-Cl-THA) with scutellarin to offer novel 6-Cl-THA-scutellarin hybrids. Scutellarin is a flavone having a versatile biological profile varying from free radical scavenging, anti-inflammatory, neuroprotective activities and the ability to inhibit aggregation of Aβ-peptide. Unfortunately, it has limited clinical application because of its weak oral absorption, poor solubility and inability to penetrate BBB. Among the series, compounds (**8a-8c**) exhibited the most potent *h*AChE inhibition with IC_{50} values of 1.63, 1.90 and 5.15 nM, respectively compared to the standard 6-Cl-THA (IC_{50} value of 20 nM). Although, all these hybrid compounds were designed as potential antioxidants but unfortunately all of them failed to exhibit anti-oxidant activity.[11]



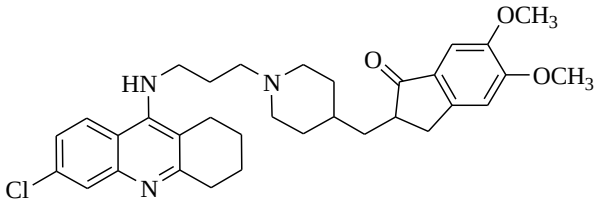
(8)



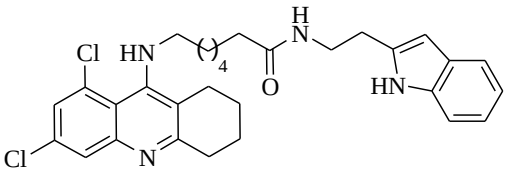
(9)

Tang *et al.* reported some novel tacrine-oxoisoaporphine hybrids wherein 1-azabenzanthrone and tacrine were linked together with methylene spacers containing amines. Hybrid (**9**) showed the most potent AChE inhibitory activity with an IC_{50} value of 3.4 nM compared to tacrine (IC_{50} value of 104 nM). It also exhibited 79.8% inhibition of self-induced and 83.3% inhibition of AChE-induced Aβ aggregation.[12]

Several attempts[13-15] have been reported in the literature wherein either 5,6-dimethoxy-1-indanone or benzylpiperidine moieties of donepezil were hybridized with tacrine or 6-chlorotacrine. Among them all, compound (**10**) showed excellent inhibition of *h*AChE (IC_{50} = 0.27 nM), and also inhibited 46.1% of *h*AChE-induced Aβ aggregation at 100 μM concentration.[15]



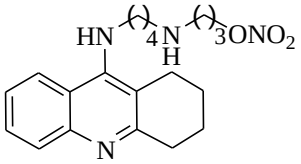
(10)



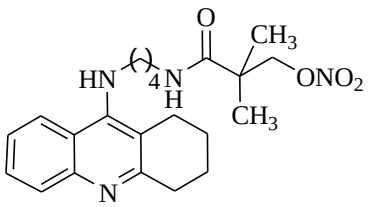
(11)

Rodriguez-Franco *et al.* designed and synthesized some tacrine-melatonin hybrids having potential anti-Alzheimer activity with IC_{50} values varying from sub-nanomolar to picomolar. Compound (**11**) displayed a marked inhibition of AChE (IC_{50} value of 0.008 nM) *in vitro* along with significant reduction in the Aβ-induced apoptosis and amyloid burden, and noticeable improvement in the cognitive functions in *in vivo* experiments.[16]

A series of tacrine-NO donor hybrids have been reported as potential AChE inhibitors by Fang *et al.*[17] wherein the NO donating nitrato moiety and tacrine were clubbed together via alkylenediamine spacers. Among the reported hybrids, compound (**12**) showed the most promising AChE and BuChE inhibitory activity with IC_{50} values of 5.6 nM and 9.9 nM, respectively whereas compound (**13**) was the most potent and selective BuChE inhibitor (AChE,IC_{50} = 226 nM and BuChE, IC_{50} = 7.3 nM). Moreover, compound (**12**) was also found to be safer compared to tacrine in the *in vivo* hepatotoxicity experiments.

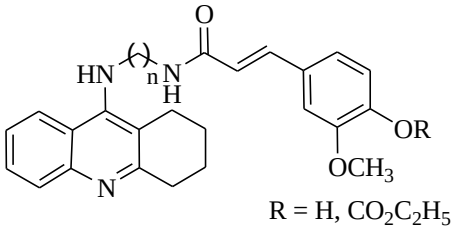


(12)



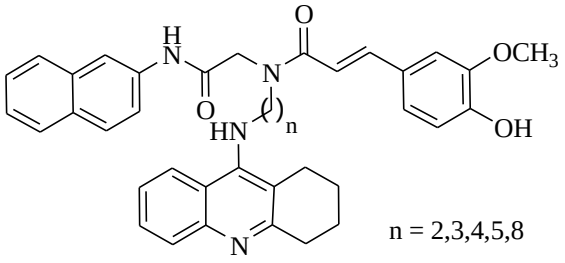
(13)

A number of research articles appeared in the literature describing the AChE inhibitory activity of some tacrine-ferulic acid hybrids (**14** and **15**)[18-21] and tacrine-coumarin hybrids (**16-18**).[22-25] These hybrids were found to possess antioxidant and neuroprotective properties also.



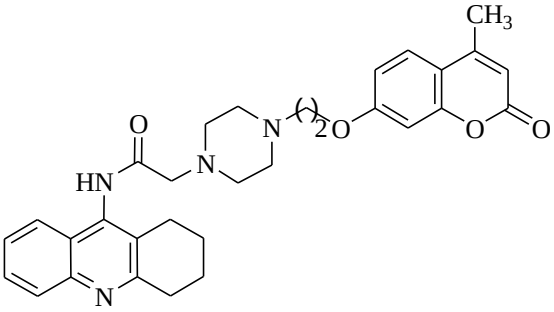
R = H, $CO_2C_2H_5$
n = 2,3,4,5,6,8

(14)

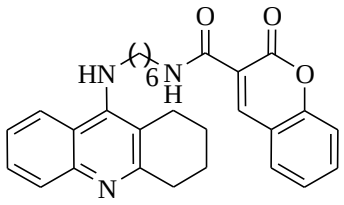


n = 2,3,4,5,8

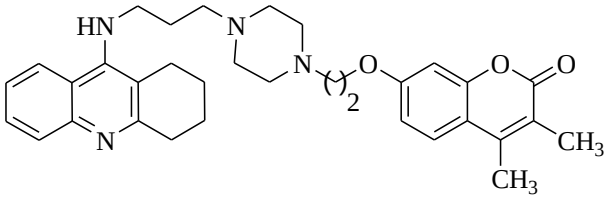
(15)



(16)

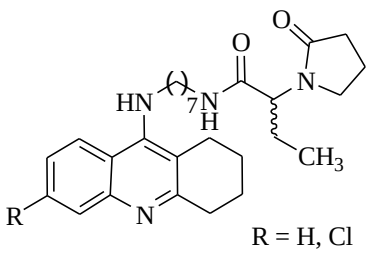


(17)



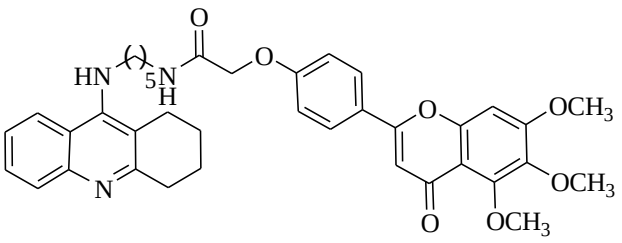
(18)

Levetiracetam, an anti-epileptic drug was linked to tacrine to offer novel levetiracetam-tacrine hybrids (**19**) as AChE inhibitors.[26] In another report[27], synthesis of tacrine-trimethoxyflavone hybrid (**20**) was described having potential AChE inhibitory and anti-oxidant activities along with the ability to inhibit self-induced Aβ-aggregation. A tacrine-quinone hybrid (**21**) comprising of a tacrine molecule and a 5-hydroxy-1,4-naphthoquinone has also been reported with prominent AChE and self-induced Aβ-aggregation inhibitory activities.

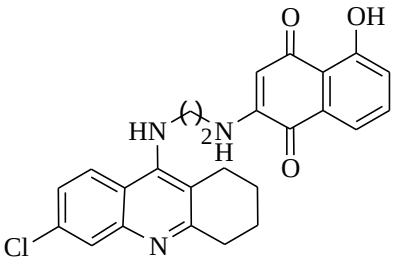


R = H, Cl

(19)

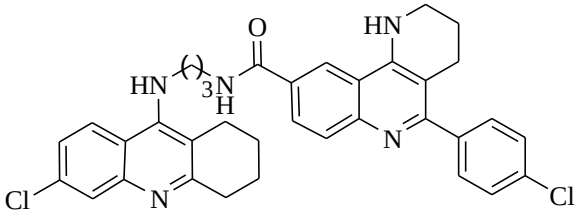


(20)



(21)

Di Petro *et al.* designed and synthesized novel 1,2,3,4-tetrahydrobenzo[*h*][1,6] naphthyridine-6-chlorotacrine hybrid (**22**) as multifunctional AChE inhibitor. Compound (**22**) exhibited the most potent and selective AChE inhibitory activity with IC_{50} values of 0.006 nM for *h*AChE and 120 nM for *h*BuChE along with 52.5% inhibition of Aβ-aggregation and 40.7% inhibition of tau protein aggregation both at 10 μM concentration.[101] Hui *et al.* synthesized tacrine-phenothiazine hybrid (**23**) and evaluated it for *r*AChE and tau phosphorylation inhibitory activities. Compound (**23**) inhibited *r*AChE with an IC_{50} value of 89 nM and tau phosphorylation (39.5%).[28]



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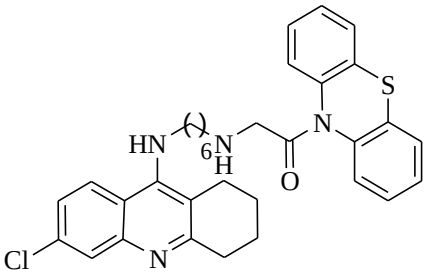
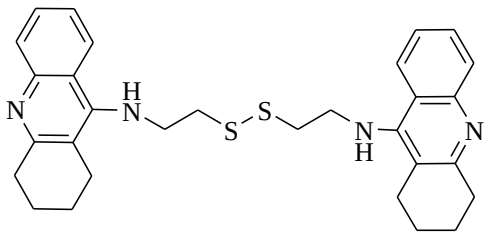


(23)

Tacrine dimer (**24**) was reported by Minarini *et al.* wherein two tacrine molecules were linked through cystamine. Interestingly, this hybrid (**24**) showed excellent inhibition of *h*AChE (IC_{50} = 5.04 nM) and *h*BuChE (IC_{50} = 5.66 nM). It also inhibited self-induced (52.6%) and AChE-induced (24.2%) Aβ-aggregation effectively.[29]

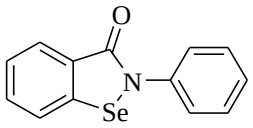


(24)

2.2 Donepezil-based multifunctional cholinesterase inhibitors

Donepezil, one of the marketed drugs for AD treatment, inhibits AChE effectively interacting with both the active sites of the enzyme. Owing to this dual-binding mode of donepezil, many researchers worldwide modified and explored the structure of donepezil to obtain various donepezil-based MTDLs as multifunctional cholinesterase inhibitors.[30]

Luo *et al.* described the synthesis and biological evaluation of some MTDLs for the treatment of AD. In their efforts to develop a novel series of MTDLs, the authors combined structural pharmacophores of donepezil and ebselen (**25**), an antioxidant. Among the series, compound (**26**) was found to be the most potent inhibitor of AChE (IC_{50} value of 42 nM for *ee*AChE and 97 nM for *h*AChE) and AChE-induced Aβ aggregation (21.4%).[31]



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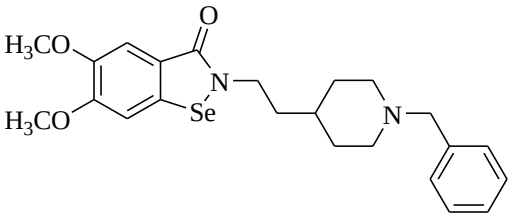
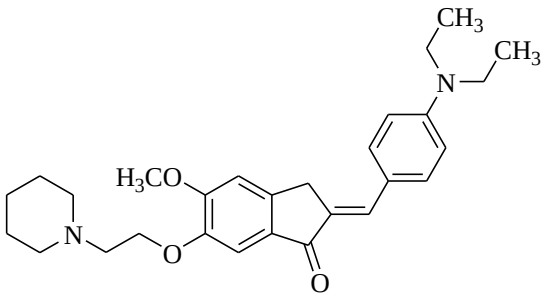


(26)

In another report, Huang *et al.* disclosed a series of some indanone derivatives as anti-AD agents wherein compounds (**27** and **28**) were observed to inhibit *ee*AChE with IC_{50} values of 14.8 nM and 18.6 nM, respectively. Both of these compounds (**27** and **28**) also showed 85.5% and 83.8% inhibition of self-induced $A\beta_{1-42}$ aggregation, respectively.[32]



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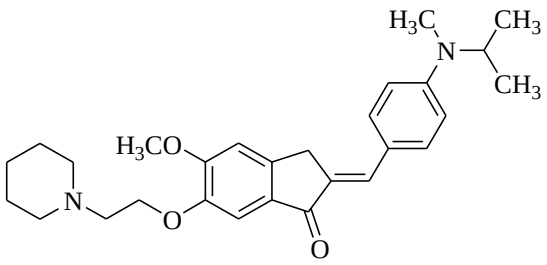
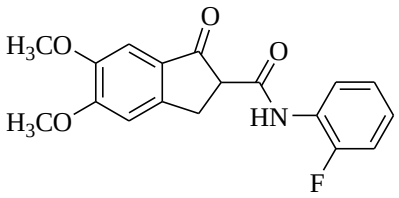


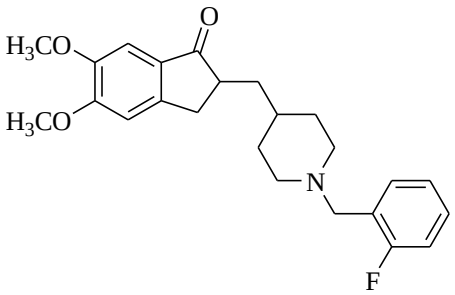
(28)

A series of substituted carboxamide analogs of donepezil have been reported by Yerdelen *et al*. as anti-Alzheimer Agents. Compound (**29**) was found to be the most potent showing the highest AChE inhibition with an IC_{50} value of 80 nM (*ee*AChE) and about 55% inhibition of self-induced $A\beta_{1-42}$ aggregation. It also showed promising antioxidant characteristics.[33]



(29)

Wang *et al.* synthesized some donepezil derivatives having substituted phenyl and heteroaryl rings. Various substituents (CH_3, Cl, F, CF_3 and NO_2) at different positions (2^{nd}, 3^{rd} and 4^{th}) of the phenyl ring of donepezil have been employed to improve the AChE inhibitory activity of donepezil. Biological screening of these compounds revealed that compounds with fluoro substituent at 2^{nd} and 3^{rd} positions of the phenyl ring offered more potent AChE inhibitory activity and higher selectivity towards AChE compared to BuChE. Compound (**30**) showed inhibition of both *h*AChE with an IC_{50} value of 32 nM and *ee*AChE with an IC_{50} value of 43 nM. Further, the metal chelating property was introduced into the compounds in addition to AChE inhibition by replacing the phenyl ring with the pyridyl ring. Compound (**31**) exhibited the most potent AChE inhibitory activity in the series with an IC_{50} value of 73 nM (*h*AChE) and 85 nM (*ee*AChE) comparable to the standard, donepezil having IC_{50} value of 48 nM (*h*AChE) and 51 nM (*ee*AChE). It has also displayed moderate potency to inhibit 18.5% of self-induced, 46.3% of Cu^{2+}-induced and 72.4% of AChE-induced $A\beta_{1-42}$ aggregation.[34]



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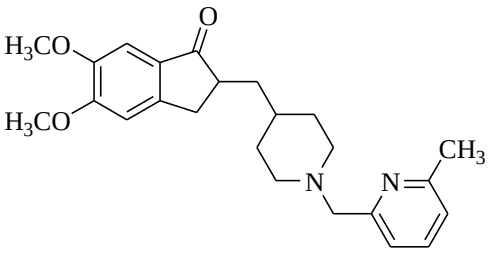
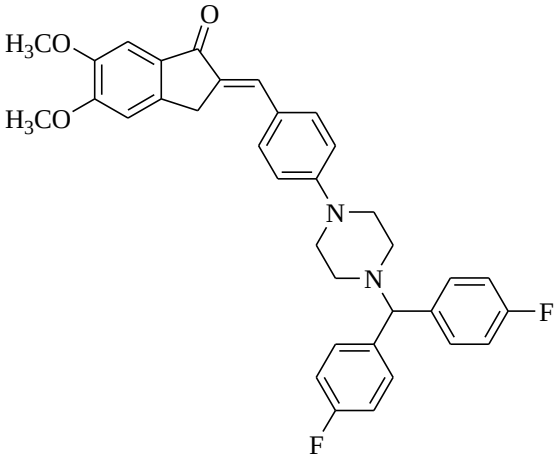
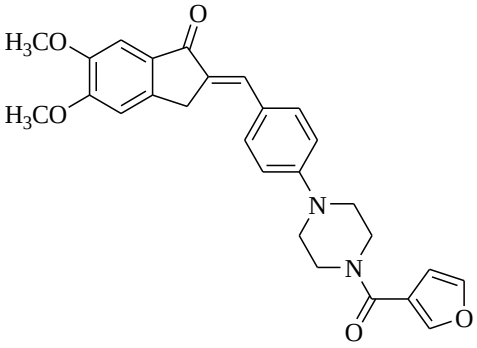


(31)

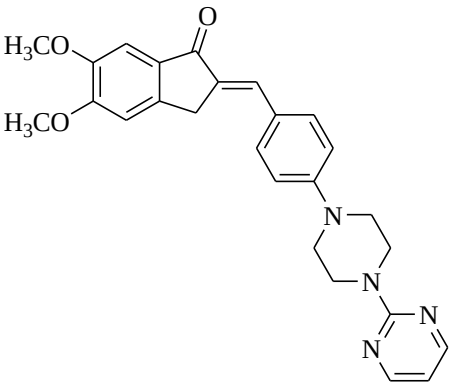
Mishra *et al.* designed and synthesized some substituted benzylidene derivatives of donepezil as MTDLs for AD therapy. Amongst the series, compounds (**32-34**) showed excellent AChE inhibitory activity against *ee*AChE with IC_{50} values of 45 nM, 34 nM and 25 nM, respectively. Additionally, the most active compound (**34**) displayed prominent (81%) inhibition of self-induced $A\beta_{1-42}$ aggregation.[35]



(32)

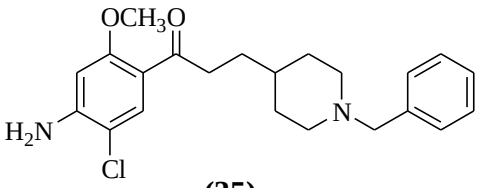


(33)



(34)

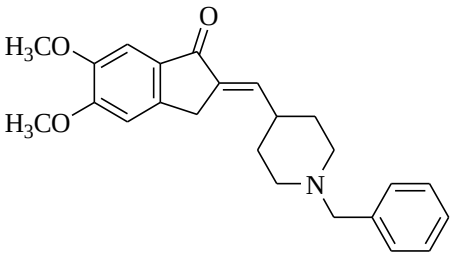
Rochais *et al.* reported some donecopride analogs as MTDLs for the treatment of AD. All the compounds of the series showed promising ChE inhibitory activity with IC_{50} values in nanomolar range. Compound (**35**) displayed the most potent and selective AChE inhibition in the series with an IC_{50} value of 8.5 nM which was equipotent to the reference donepezil (IC_{50} value of 6 nM).[36]



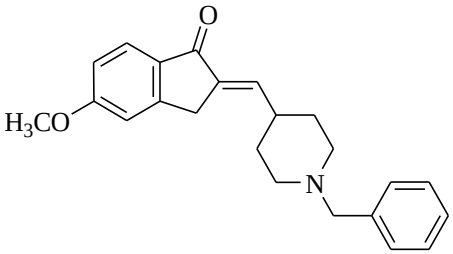
(35)

An attempt has been made by Costanzo *et al.* to offer rigidity to the donepezil structure by substituting the stereocenter present between the indanone and benzylpiperidine moieties with the double bond. Actually it was assumed that rigidity in the structures of these newly designed donepezil analogs would lead to improved dual inhibitory activity on AChE and BACE1. Out of fifteen reported compounds, two compounds (**36** and **37**) showed the

most potent and highly selective AChE inhbiton with IC_{50} values of 58 and 43 nM respectively along with the effective BACE1 inhibitory activity.[37]

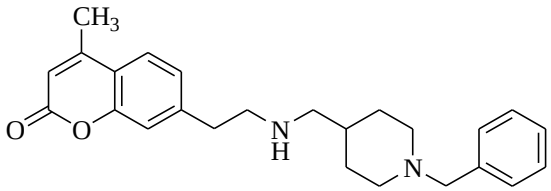


(36)



(37)

A series of novel donepezil-coumarin hybrids have been reported by Kong *et al.* wherein the *N*-benzylpiperidine moiety of the donepezil was linked with coumarin. Among the series, hybrid (**38**) possessed the most potent AChE inhibitory activity with an IC_{50} value of 67 nM for *h*AChE and 3.45 μM for *h*BuChE.[38] Similar type of hybrids involving coumarin and donepezil have also been reported by Asadipour *et al.* as potent AChE inhibitors. Among all of the synthesized hybrids, compound (**39**) was found to be the most potent and highly selective *ee*AChE inhibitor with an IC_{50} value of 0.3 nM which was 46-times more potent than the standard donepezil (*ee*AChE, IC_{50} = 14 nM).[39] In another report, Dias *et al.* synthesized some donepezil-feruloyl hybrids as MTDLs for the treatment of AD. Compound (**40**) showed the most potent and selective *ee*AChE inhibotry activity with an IC_{50} value of 0.46 μM.[40]



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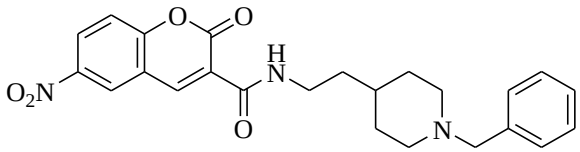

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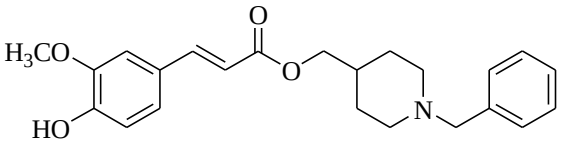
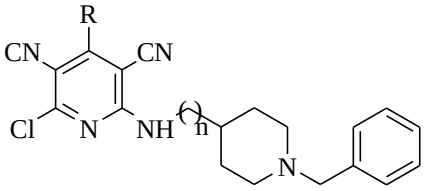


(40)

Samadi *et al.* reported synthesis and AChE inhibitory activity of some pyridonepezil analogs i.e. pyridine-donepezil hybrids. All the synthesized compounds exhibited good to moderate potential to inhibit AChE but compounds (**41a-41c**) were outstanding as they

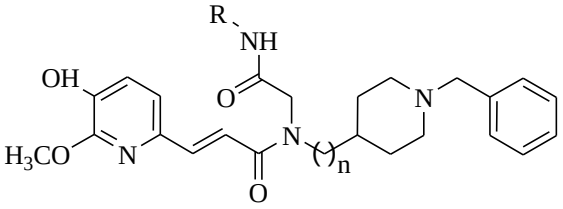
inhibited *h*AChE selectively with IC_{50} values of 31, 54 and 13 nM, respectively. Particularly, compound (**41c**) was highly selective *h*AChE inhibitor, equipotent to the standard donepezil (*h*AChE, IC_{50}=10 nM).[41]



	n	R=
41a	4	Ph
41b	3	H
41c	4	H

(41)

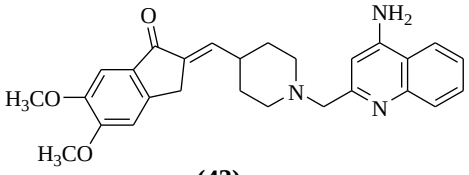
	n	R=
42a	3	2-Cl-6-CH_3-Ph
42b	3	5-OCH_3-indol-3-yl
42c	2	5-OCH_3-indol-3-yl



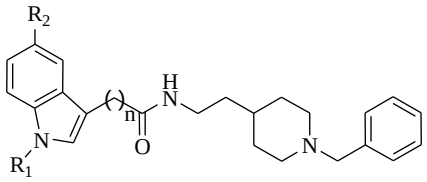
(42)

Benchekroun *et al.* disclosed a novel series of some donepezil-ferulic acid hybrids (DFAH) as potential anti-Alzheimer agents. Interestingly, most of the synthesized DFAHs exhibited prominent AChE inhibitory activity with IC_{50} values in nanomolar range along with potent antioxidant activity. Among the series, compounds (**42a**; IC_{50} = 29.3 nM and **42b**; IC_{50} = 75 nM) having propylene spacer were the most potent and selective AChE inhibitors whereas compound (**42c**) having ethylene spacer was the most potent and selective BuChE inhibitor (AChE: inactive; BuChE, IC_{50} = 10.39 nM). From the biological screening results, it was concluded that increasing the length of the spacer improved selectivity of DFAHs for AChE.[42]

Chierrito *et al.* hybridized donepezil with quinoline to offer novel quinolinyl donepezil hybrid compounds as AChE inhibitors. Unfortunately, among the series, only one compound (**43**) exhibited potent inhibition of *h*AChE and *h*BuChE with IC_{50} values of 14 nM and 3.69 μM respectively.[43] In their next report, the authors described the synthesis of some novel indolylppiperidines and the evaluation for ChE inhibitory activity. All the reported compounds showed potent and selective BuChE inhibitory activity. Compounds (**44a-44d**) were found to be the most potent BuChE inhibitors with IC_{50} values of 0.87, 0.25, 0.68 and 0.89 nM respectively.[44]



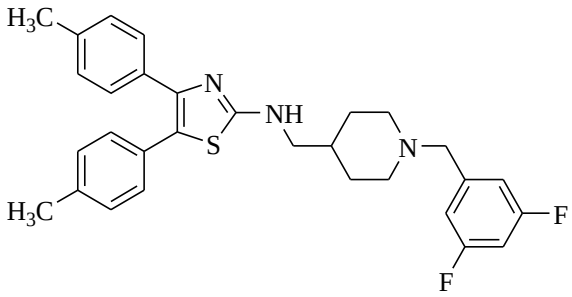
(43)



	n	R_1	R_2
44a	1	H	H
44b	1	CH_3	H
44c	1	H	Br
44d	2	H	H

(44)

Based on their previous research work[45], Shidore *et al*. designed and synthesized some novel benzylpiperidine-linked vicinal diarylthiazole derivatives as promising AChE inhibitors. Compound (**45**) displayed potent AChE inhibition with IC_{50} value of 0.30 μM for *h*AChE and it also demonstrated good *in vivo* protection of neuronal cells.[46]

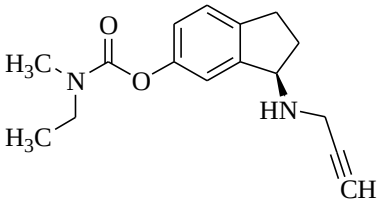


45

2.3 Rivastigmine-based multifunctional cholinesterase inhibitors

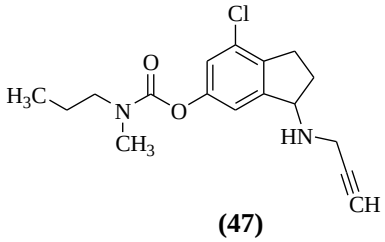
Rivastigmine is another drug belonging to the class of AChE inhibitors approved in the year 2000 for clinical use for the treatment of AD. It is a pseudo-irreversible ChEI with lower selectivity towards AChE compared to donepezil but it inhibits BuChE as well. Initially rivastigmine was formulated in the capsular form but unfortunately it was associated with adverse effects including nausea, diarrhoea, anorexia, and vomiting. To reduce such GI side effects, rivastigmine was then reformulated in the year 2007 in the form of transdermal patch. Rivastigmine is used to treat mild to moderate AD and dementia in Parkinson's disease also. A number of rivastigmine-based cholinesterase inhibitors having the active pharmacophore i.e. carbamate group of rivastigmine, have been reported in the literature.[47, 48]

A novel hybrid molecule, ladostigil (**46**) was synthesized by introducing the carbamate group of rivastigmine at the C_6-position of the rasagiline, a selective MAO-B inhibitor. Ladostigil (**46**) showed potent MAO inhibitory activity along with 100-fold more selectivity for *r*BuChE over *r*AChE. Overall, this new rivastigmine-rasagiline hybrid (**46**) was found to be a useful therapeutic having effective ChE and MAO inhibitory potential for the treatment of AD.[49]

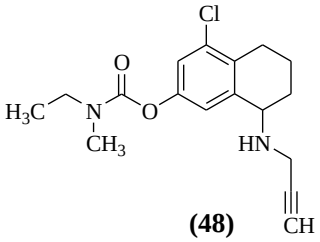


Ladostigil **(46)**

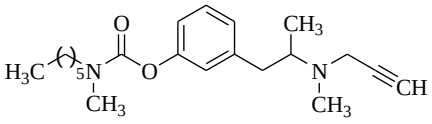
In another report[50], Sterling *et al.* designed and synthesized some novel *N*-propargylaminoindans and *N*-propargylphenethylamines substituted with carbamoyl group. In fact, these derivatives were prepared as rivastigmine-rasagiline/selegiline hybrids (**47**-**49**) possessing potent ChE and MAO inhibitory activity. Interestingly, all these hybrids (**47**-**49**) exhibited potent AChE inhibition with IC_{50} values of 43.9, 52.4 and 3.06 nM respectively.



(47)

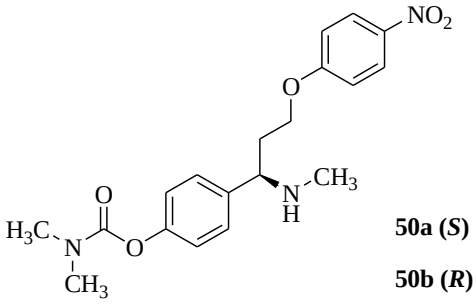


(48)



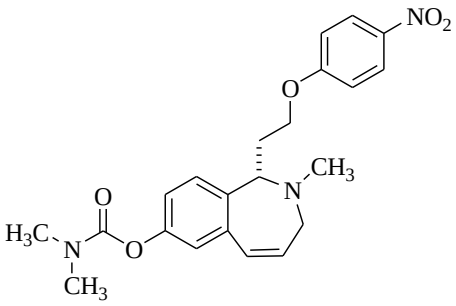
(49)

To target other neurotransmitter systems like SERT along with ChE, Kongen *et al.* developed some novel rivastigmine-fluoxetine hybrid compounds by incorporating carbamate moiety of rivastigmine on the phenyl ring of fluoxetine. Among the series, compounds (**50** and **51**) were found to exhibit the most potent AChE and SERT inhibitory activities.[51, 52]



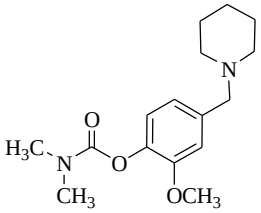
(50)

	IC_{50} (nM)	
	AChE	SERT
50a (*S*)	101	42
50b (*R*)	14	6

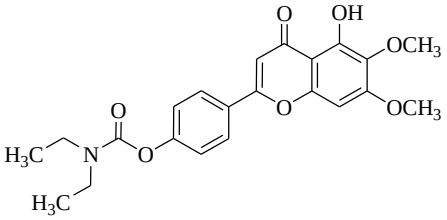


(51)

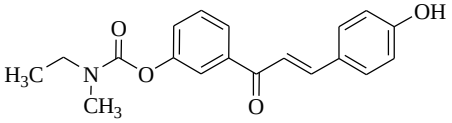
Several new rivastigmine hybrids such as rivastigmine-curcumin (**52**)[53]/scutellarin (**53**)[54]/chalcone (**54**)[55] have been described having good to moderate ChE inhibitory activity.



(52)



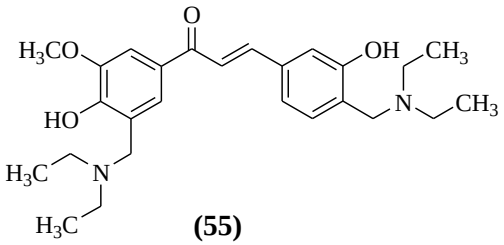
(53)



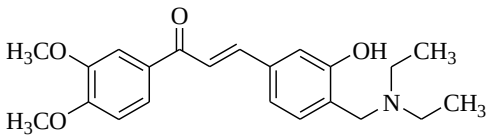
(54)

2.4 Miscellaneous cholinesterase inhibitors

Numerous heterocyclic and fused heterocyclic compounds have also been reported in the literature having potential cholinesterase inhibitory activity. Zhang *et al.*[56] reported some chalcone Mannich base analogs as MTDLs possessing potential AChE inhibitory activity. Among the series, compound (**55**) showed the most potent AChE inhibition with an IC_{50} value of 70 nM while compound (**56**) with moderate *ee*AChE inhibition (IC_{50} value of 0.44 μM) exhibited 55% inhibition of self-induced Aβ-aggregation at 25 μM along with moderate chelating and antioxidant properties.

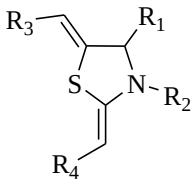


(55)



(56)

Shehzadi *et al.*[57] developed some novel thiazolidin-2-imines as potent AChE inhibitors. The authors reported one-pot four-component strategy to synthesize the final compounds and evaluated them for AChE inhibitory activity. Compounds (**57a-57d**) were found to be the most potent AChE inhibitors in the series.

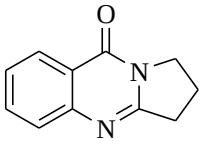


(57)

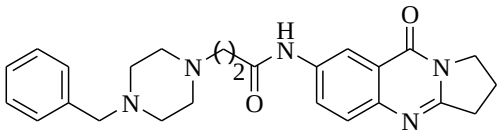
	R_1	R_2	R_3	R_4	AChE IC_{50} (nM)
57a	Ph	Ph	Ph	Ph	9.9
57b	*t*-Bu	*n*-Pr	3-CH_3-Ph	Ph	7.5
57c	*t*-Bu	*n*-Pr	Ph	3-CH_3-Ph	2.3
57d	*t*-Bu	*n*-Pr	Ph	2-Naph	2.9

Deoxyvasicinone (**58**), an alkaloid from natural sources, is a quinazoline-pyrrolidine containing fused-heterocyclic compound. Du *et al.* reported some deoxyvasicinone derivatives, among which compound (**59**) was found to be the most potent multifunctional

AChE inhibitor. It inhibited *h*AChE, BACE1 and $A\beta_{1-42}$ effectively with IC_{50} values of 3.29 nM, 0.129 μM and 9.26 μM respectively.[58] A number of research articles appeared in the literature describing potent AChE inhibitory activity of deoxyvasicinone derivatives (**60-62**).[59-61]



Deoxyvasicinone **(58)**



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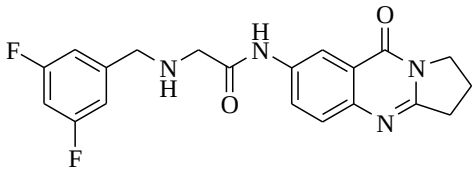
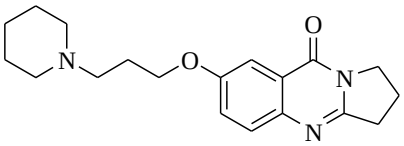


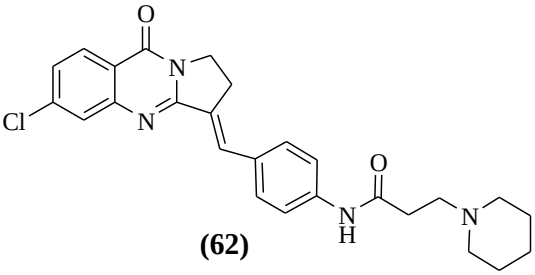
(60)

*h*AChE, IC_{50} = 7.6 nM



(61)

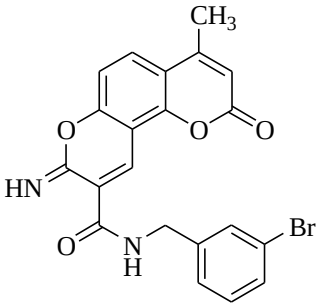
*h*AChE, IC_{50} = 33.9 nM



(62)

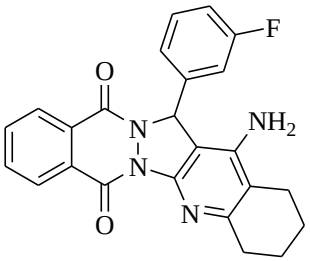
*ee*AChE, IC_{50} = 23 nM

A number of fused heterocyclic compounds (**63-66**) have been reported to possess potent inhibitory activity against AChE. Some of these most potent AChE inhibitors have been listed here.[62-65]



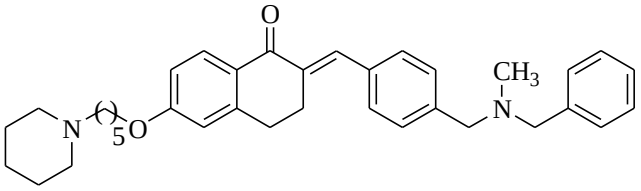
(63)

*ee*AChE, IC_{50} = 3 nM



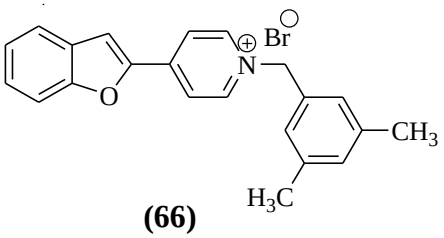
(64)

*ee*AChE, IC_{50} = 23 nM



(65)

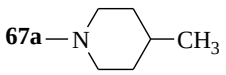
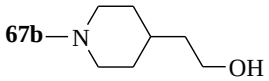
*h*AChE, IC_{50} = 52 nM

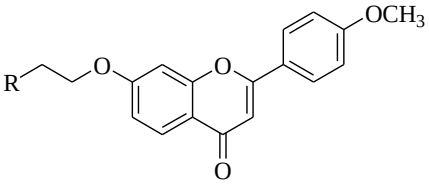


(66)

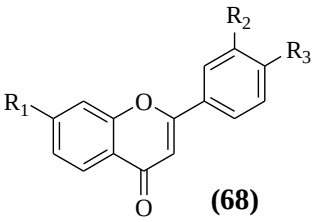
*ee*AChE, IC_{50} = 4.1 nM

Some 4-chromone derivatives (**67** and **68**) reported by Singh *et al.*[66] and coumarin derivative (**69**) reported by Montanari *et al.*[67] exhibited potent and selective AChE inhibition.

R =	IC_{50} (nM) *r*AChE
67a 	6.33
67b 	7.56

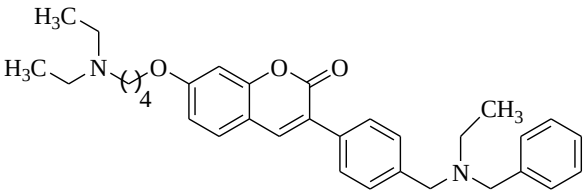


(67)



(68)

	R_1	R_2	R_3	IC_{50} (nM) *r*AChE
68a	H	NO_2	H	8.2
69b	OH	H	F	8.0

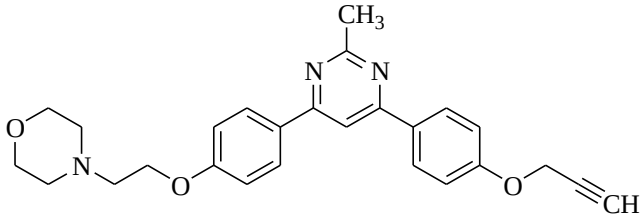


(69)

*h*AChE, IC_{50} = 12.9 nM

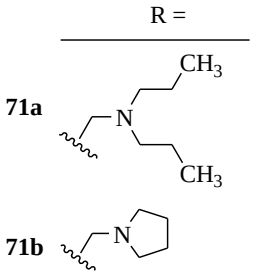
Pyrimidine is a bioactive molecule present in various natural biologically important compounds such as nucleotides and alloxan. It has also been considered as one of the most important components or building blocks to synthesize numerous biologically active synthetic medicinal compounds or derivatives like barbiturates, zidovudine and trimethoprim, to name a few.[68]

Kumar *et al.* reported some pyrimidine-based heterocyclic compounds having dual AChE and MAO inhibitory activities. Compound (**70**) showed the most potent ACh*E* inhibition with an IC_{50} value of 9.54 nM.[69]



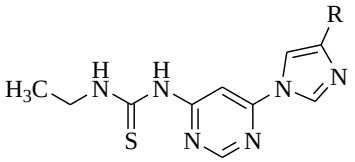
(70)

Researchers from East China University of Science and Technology, China have been actively involved in the search of new potential pyrimidine derivatives for the treatment of AD.[70-72] In the year 2016, the authors' reported a novel series of pyrimidinylthiourea derivatives as multifunctional anti-Alzheimer agents. Among the series, compounds (**71a** and **71b**) showed good inhibition of AChE with IC_{50} values of 0.204 μM and 67 nM respectively, and a selectivity of >196 and >597 respectively for AChE *over* BuChE. Moreover, these compounds also exhibited metal chelating and antioxidant properties, and inhibited metal-induced Aβ-aggregation effectively.[70]

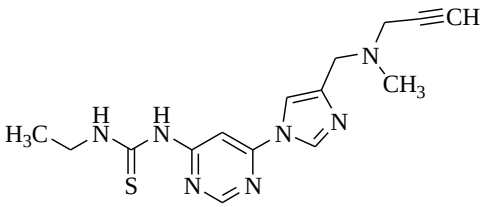


71a

71b



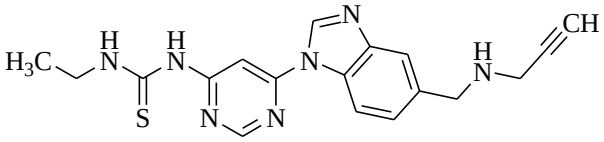
(71)



(72)

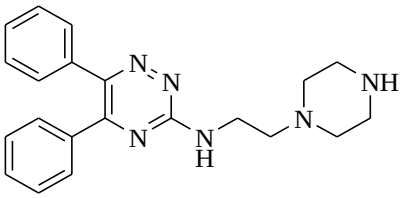
In the next report, the authors disclosed AChE and MAO inhibitory activity of imidazole substituted pyrimidinylthiourea derivatives. With an aim to integrate the MAO inhibitory potential to the final compounds, propargyl amine component of selegiline, a selective MAO-B inhibitor, was incorporated into the structure of the previously reported pyrimidinylthiourea derivatives (**71**). Interestingly, compound (**72**) showed potent and selective inhibition of AChE (IC_{50} value of 0.324 μM, SI > 123 *vs* BuChE) and MAO-B (IC_{50} value of 1.427 μM, SI > 35 *vs* MAO-A).[71]

Further to improve AChE/MAO-B inhibitory activities and blood-brain barrier (BBB) permeability of the previously disclosed compound (**72**), the authors planned to increase the lipophilicity of the compounds by introducing benzene ring to imidazole. Interestingly, compound (**73**) was found to be the most potent AChE (IC_{50} = 32 nM) and MAO-B (IC_{50} value of 2.117 μM) inhibitor along with enhanced BBB permeability.[72]

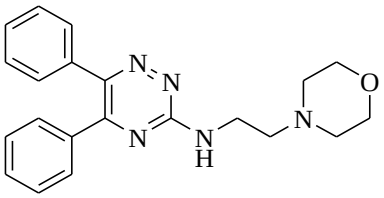


(73)

Our research group at The Maharaja Sayajirao University of Baroda reported vicinal diaryltriazines as potent MTDLs for AD. Compounds (**74** and **75**) showed good AChE inhibitory activity and prevented Aβ aggregation.[45]

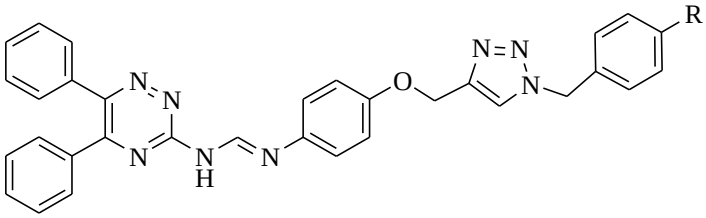


74



75

Yazdani *et al.* demonstrated BACE1 inhibitory potential of some novel vicinal diaryl-substituted triazine derivatives for the treatment of AD. Amongst all the reported derivatives, compounds (**76a** and **76b**) exhibited prominent BACE1 inhibitory activity with IC_{50} values of 8.55 and 11.42 μM. Moreover, compound (**76b**) also displayed metal chelating and good antioxidant properties in addition to moderate neuroprotection against Aβ peptide toxicity.[73]



R =	
76a	Cl
76b	NO_2

(76)

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