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FULL PAPER

Role of pyridazine analogs as acetylcholinesterase inhibitor: An approach for management of alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disorder causing failure of cognitive aptitude and performance irregularities, resulting in degradation of cerebral and psychological activities. AD is presently a main health trouble and it is the third-major reason of casualty in the developed nations after cardiac and cancer diseases. The physiological pathway of this disorder remains almost unknown. The present curative advances to AD pursue the cholinergic theory. The acetylcholinesterase (AChE) enzyme has an essential role in the therapy of AD. The AChE-inhibitors have been developed into the leading approach for the advance of anti-ADs. Some AChE-inhibitors, like donepezil, tacrine, rivastigmine and ensaculin have shown progress in memory and cognitive actions. However, ensaculin is a coumarin analog that has prevented or lowered the progressive neurodegeneration. Several considerations support that some pyridazine analogs act as AChE and BuAChE inhibitors.

KEYWORDS

Acetyl-cholinesterase; alzheimer's disease; butyryl-cholinesterase; neurodegenerative; pyridazine derivatives.

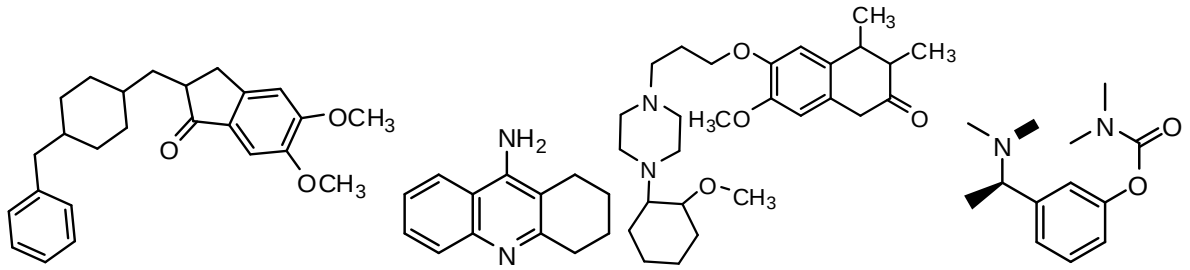
Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder, differentiated by the failure of cognitive capacity and rigorous behavior deformities, which eventually lead to degradation of cerebral and psychological actions [1]. Three key phases can be distinguished in AD [2]. The first phase of amnesia, memory loss, engages early short-term memory loss and also short of significant artlessness. In the second phase of confusion, uncertainty, the patient displays time and liberty confusion, mental uncertainty, and alters in character. The third phase of dementia occupies the totally mental inability and dependence of the patient. While AD itself is not lethal, mental problems related with AD, generally bacterial or viral infections, lead to the patient death [3]. The improvement in life expectancy and the reality that occurrence of AD enhances with age can contribute to handling it [4]. Despite various works, many features of the etiology and physiological paths of the AD remain unclear. The common present drug treatment advances to AD follow the cholinergic theory [5-7].

In recent years, large numbers of pyridazine derivatives have been reported to possess almost all type pharmacological activities viz. analgesic, anti-inflammatory, antipyretics, antiulcer, anticancer, antimicrobial, antifeedant, herbicidal, antiphlogistics, antisecretory, anxiolytics, sedative-hypnotics, antidepressants, tranquilizers, anticonvulsants, immunosuppressant, anti-Alzheimer, GABA antagonists, and some other useful

pharmacological activities. Various pyridazine derivatives are also used as intermediates of drugs and agrochemicals. The cardiovascular activities of pyridazine compounds are very well known such as antiplatelets, antihypertensive, antithrombotics, vasodilators, antiarrhythmics, cardiotonic, β-blockers, and hypocholesterolemic [8-10].

The acetylcholinesterase (AChE) has established extensive awareness as a drug design as anti-AD agent. The AChE inhibitor is a primary strategy for the progress of anti-AD agents [8,9]. Some anti-AChE drugs, like donepezil, rivastigmine, tacrine, and ensaculin have been reported to play a role in enhancing in memory and cognitive activities [10], and were used as anti-AD agent (Figure 1). However, ensaculin is a coumarin analog that stops or slows down the progressive neuro-degeneration. Some pyridazine analogs act as AChE and butyrylcholinesterase (BuAChE) inhibitors. Ensaculin contain benzopyran with a substituted piperazine moiety and used as an anti-AD drug [11,12].



Dopanezil **Tacrine** **Ensaculin** **Rivastigmin**

FIGURE 1 Some acetylcholinesterase (AchE) inhibitors used as anti-alzheimer's drugs (anti-AD)

The anti-Alzheimer activity of pyridazine compounds

Three series of coumarins with phenylpiperazine substitution have been designed as potential anti-AD drugs [13]. Additionally, a large number of pyridazine analogs have interesting biological activities like antibacterial, antiviral, antifungal, analgesic, anti-convulsant, anti-inflammatory, antimalarial, anti-platelets, anti-tuberculosis, anticancer, etc. Some aryl-pyridazines having hetero-cycles, such as furan, pyridine, indole, oxadiazole, triazole, and imidazole, thiadiazole rings have attracted special attention of researchers [14-23]. However, the pharmacological evaluation of pyridazines as AChE and BuAChE inhibitors is an extension of the effort to develop newer and effective anti-AD agents [24,25]. The above mentioned pharmacologically active pyridazines [26, 27] and research efforts [28] to recognize new drugs may be valuable in designing of AChE and BuAChE inhibitors like N'-[(4-aryl) sulphonyl]-2-[4-(aryl)-piperazine]-pyridazin3(*2H*)-one-2-yl-acetohydrazide/propionohydrazides.

The weak, reversible, and competitive AChE-inhibiting action of minaprine (IC_{50}=85 μM on rat striatum AChE, 3-amino-6-phenylpyridazines (**1**) were tested as AChE inhibitor. In relation to minaprine, the main basics for high AChE inhibition are:

(i) existence of a middle pyridazine ring,

(ii) requiring a lipophilic cationic head, and

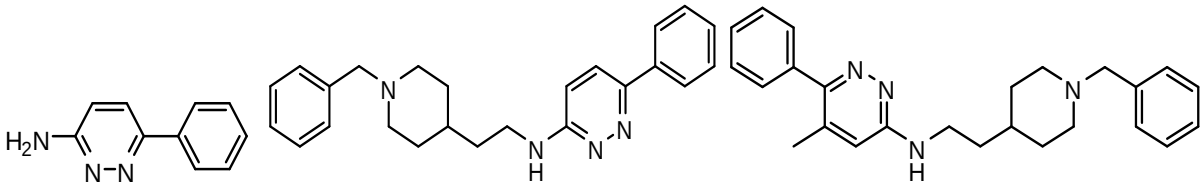
(iii) modification of a 2-5 carbon distance between pyridazine moiety and cationic head.

The 3-[2-(1-benzylpiperidin-4-yl) ethylamino]-6-phenylpyridazine (**2**) showed an IC_{50} of 0.12 μM on AChE and strong anti-AChE inhibitor activity, 5000-time more effective than minaprine. Some pyridazines act as AChE inhibitors. Structural alterations were attained on four dissimilar parts of compound **2** with subsequent remarks.

(i) Introduction of a lipophilic group in the pyridazine moiety at C-5 position is favorable

for the AChE-inhibitory activity and AChE/BuChE selectivity,
(ii) Different substitutes of the C-6 phenyl ring are probable and led to equal or more effective compounds, and
(iii) The isosteric variants of the benzyl-piperidine moiety are critical to the efficiency.

The indeno-pyridazine compound was 12-time more potent inhibitor on AChE compared with compound **2**. Moreover, 3-[2-(1-benzylpiperidin-4-yl)ethylamino]-5-methyl-6-phenylpyridazine (**3**) is 100-times more selective AChE (BuChE/AChE ratio of 24) than tacrine for human [29,30] (Figure 2).



1 **2** **3**

FIGURE 2

The 3-[(β-morpholino ethyl)amino]-4-methyl-6-phenylpyridazine (minaprine) (**4**) is an AChE inhibitor. The 3-Benzidino-6(4-chlorophenyl) pyridazine (BCP) (**5**) and minaprine have a central pyridazine moiety. The actions of BCP on late rectifier potassium ions (K^+) current and transitory outward K^+ ions current in isolated rat hippocampus pyramidal neurons, BCP, inhibited both currents. The BCP potentially inhibits both currents in rat hippocampus pyramidal neurons [31].

Several N'-[(4-aryl)sulphonyl]-2-[4-(aryl)-piperazine]-pyridazin-3(*2H*)-one-2-yl-aceto hydrazide/propionohydrazides may be important in designing and developing AChE and BuChE inhibitors. The AChE and BuAChE inhibition of pyridazine analogs was determined *in-vitro* by using galantamine as a reference drug. Some compounds exhibited inhibitory actions close to galantamine at 25, 50, 100, 200µg/mL dos levels. The N'-[(4-aryl)sulphonyl]-2-[4-(aryl)-piperidine/piperazine]-pyridazin-3(*2H*)one-2yl-acetohydrazide/propionohydrazides, which have CF_3 group on para position of phenyl sulfonyl ring, enhanced the anti-AChE action [32]. Some substituted or non-substituted benzalhydrazones of 3-(6-substituted-pyridazin3(*2H*)-on-2-yl) propionohydrazides exhibited AChE and BuChE inhibitor activities. Only (4-chlorophenyl-benzal)hydrazones of 3-(6-(4-fluorophenyl)-pyridazin3(*2H*)-on-2-yl) propionohydrazide exhibited a very good AChE inhibitory action. All other compounds also exhibited significant BuAChE inhibitory action [33]. Some ethyl-6-[(aryl piperazine]-pyridazin-3(*2H*)one-2-ylpropionate and 6-[(arylpiperazine]-pyridazin-3(*2H*)one-2-yl propionohydrazides exhibited AChE and BuAChE inhibitory action. The 6-Substituted-pyridazin-3(*2H*)one-2-yl propionates exhibited significant AChE and BuAChE inhibitory action. The 6-[4-(3-Trifluoromethyl phenyl)-piperazine]-pyridazin-3(*2H*)-one-2-ylpropionate exhibited most active compound AChE and BuAChE inhibitor actions and showed inhibitory action close to the galantamine and did not show any selectivity between the two enzymes [28].

Some 6-substituted-pyridazin-3(*2H*)one-2-propyl-3-(substituted or nonsubstituted benzal) hydrazones showed significant AChE inhibitory action. None of the compounds exhibited BuChE inhibitory action. These compounds exhibited AChE inhibitors with AChE or BuChE selectivity [25]. The 2,6-disubstituted pyridazinone was an AChE inhibitor and displayed high AChE inhibitory action and AChE or BuChE selectivity. The 6-ortho-tolylamino and N-ethyl-N-isopropylacetamide substituted piperidine exhibited peripheral anionic site and catalytic

active site binding activity. Some N'-[(4-aryl)sulfonyl]-2-[4-(arylphenyl)-piperazine]-pyridazin3(*2H*)-on-2-yl aceto-hydrazides showed AChE and BuChE inhibitor activity. Some of N'-[(aryl)sulfonyl]-2-(6-substituted-3(*2H*)-pyridazinone-2-yl)acetohydrazides exhibited inhibitory actions close galantamine at 0.05 mM 0.1 mM and 0.2 mM dose levels. These compounds, possessing CF_3 group on para position of phenyl sulfonyl ring enhanced the anti-AChE action [34,35] (Figure 3).

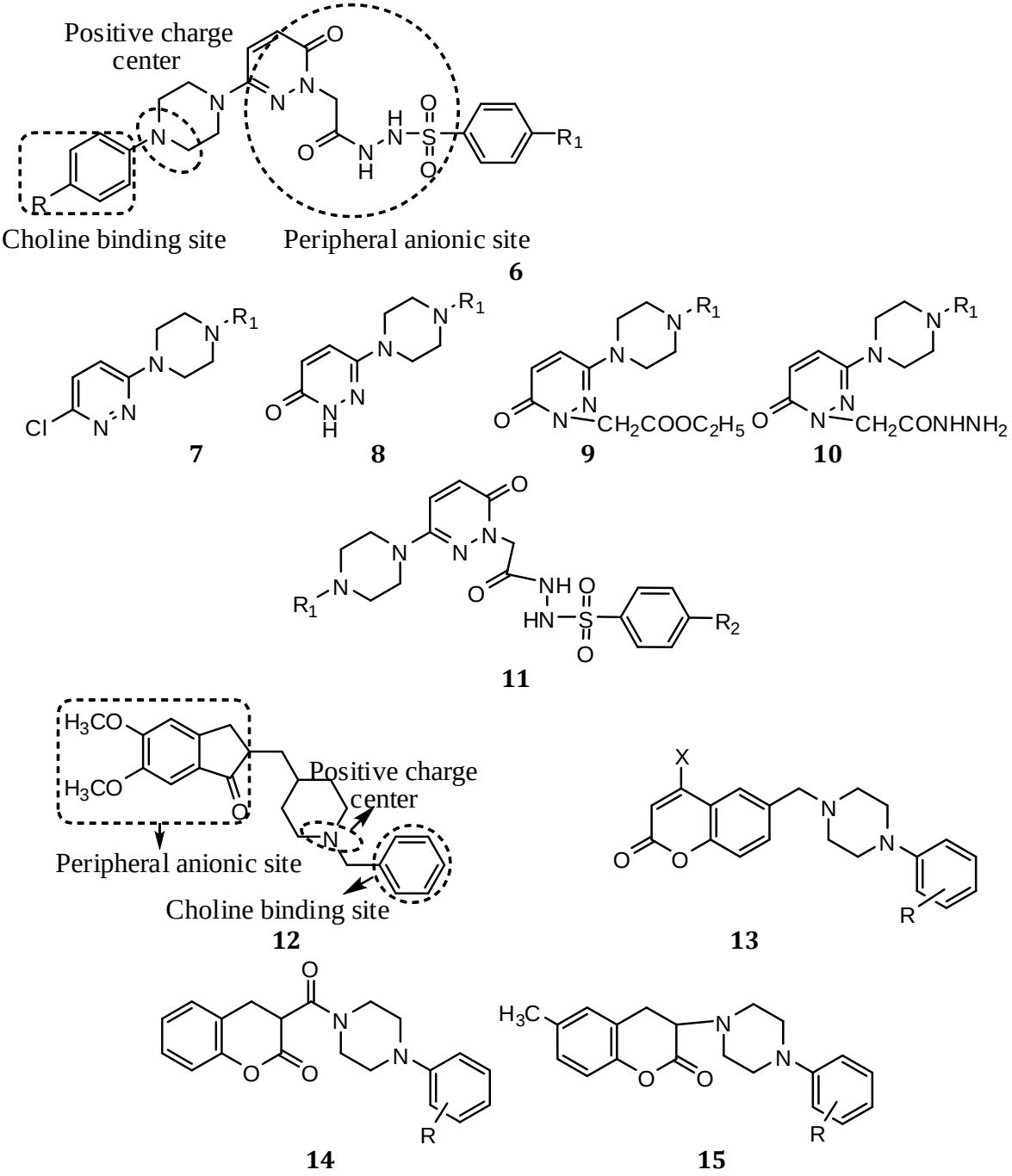


FIGURE 3

Some N'-[(aryl)sulfonyl]-2-(6-substituted-pyridazin3(*2H*)-one-2-yl)aceto-hydrazides exhibited AChE Inhibitor activity and were explained by three reasons: (**1**) the coumarin ring, *2H*-chromen-2-one, included in ensaculin with cognitive activities, a well-suited with

high anti-AChE activity and act as peripheral anionic site; (2) the nitrogen atom from the phenyl piperazine groups act as active AChE inhibitor, which is related with the catalytic center of AChE. The AChE or galantamine and AChE or donepezil are complexes; and **(3)** the phenyl ring connecting with the piperazine ring act as the choline-binding site. The N'-[(4-aryl)sulfonyl]-2-[4-(aryl)-piperazine]-pyridazin3(2H)-one-2-yl-acetohydrazides might offer structural necessities for AChEI and BuChEI actions [33,34] (Figure 4).

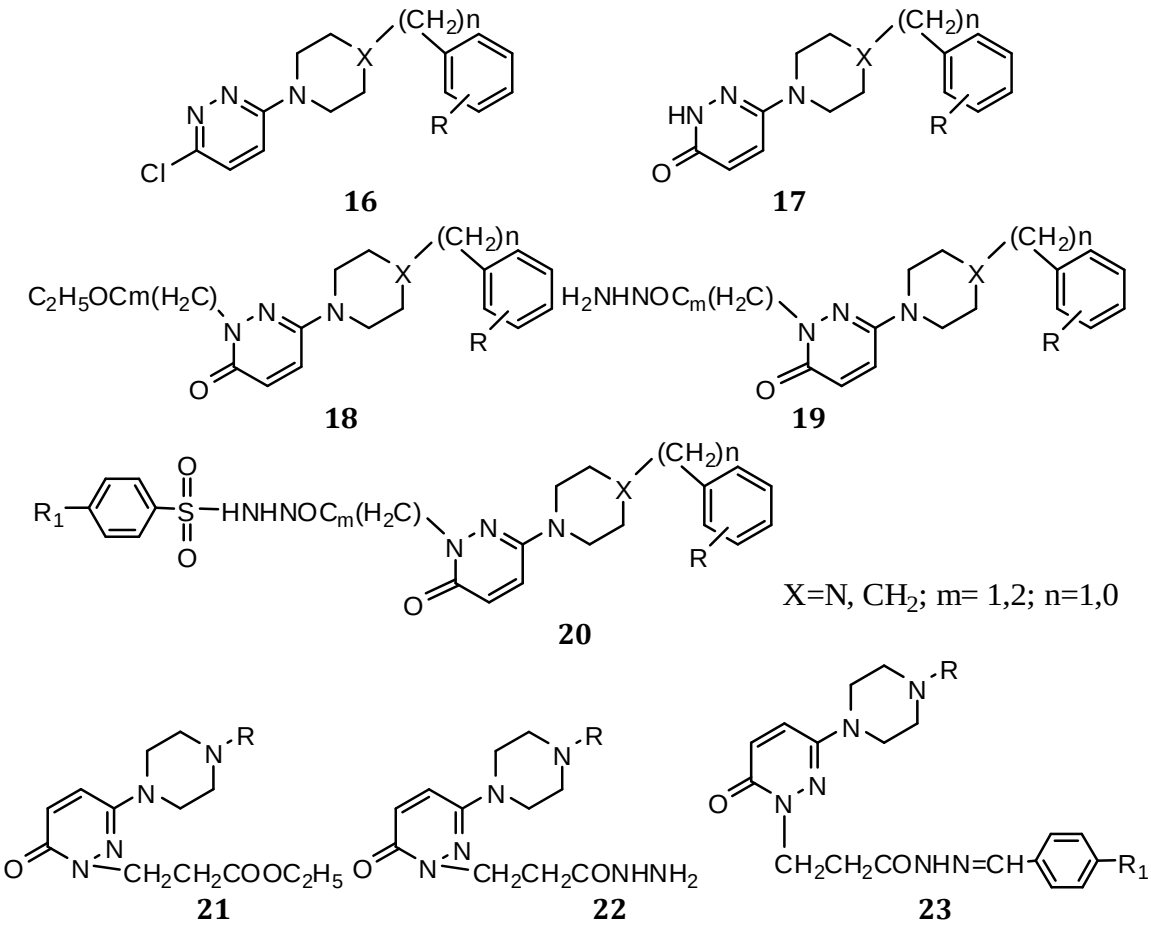


FIGURE 4

The N'-[(4-aryl)sulphonyl]-2-[4-(aryl)-piperidine/piperazine]-pyridazin3(*2H*)-one-2-yl-acetohydrazide/propiono hydrazides, which have CF_3 group on para position of phenyl sulfonyl ring enhanced the anti-AChE action. AChE inhibitory actions of these compounds were superior to the galantamine. Also, some compounds showed a better inhibitory action than galantamine against BuChE at 200µg/mL dose level. The BuChE role in AD makes this compound with a balanced AChE or BuChE inhibition and an essential for further progress. The rest of the N'-[(4-aryl)sulphonyl]-2-[4-(aryl)-piperidine/piperazine]-pyridazin3(*2H*)-one-2-yl acetohydrazide/propiono-hydrazides showed moderate inhibitory action against AChE or BAChE. Some (substituted or nonsubstituted benzal)hydrazones of 3-(6-substituted-pyridazin-3(*2H*)-on-2-yl)propionohydrazides are essential for AChE-I and BuAChE-I actions [32-34]. The N'-[(4-aryl)sulphonyl]-2-[4-(aryl)-piperazine]-3(*2H*)-pyridazinone-2-yl-acetohydrazide/propiono-hydrazide as novel drugs may be useful in the design of AChE and BuAChE inhibitors [35-38].

Conclusion

The structural feature of pyridazine compounds allowed the design of various pharmacologically effective molecules with varied activities. Pyridazinone derivatives have drawn considerable attention related to the research of new organic compounds with physiologically active [39-48]. Some molecules bearing pyridazine moieties have been reported as anti-Alzheimer drugs. Pyridazinone analogs have attracted the attention of researchers because of their easy preparation and functionalization on different positions of the ring, which makes them effective organic molecules for the development of a novel drug with improvement activity in the future, including some with anti-Alzheimer activity.

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Conflict of interest

The authors declare no conflicts of interest.

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