Synthesis and Biological Evaluation of Some Novel Vicinal Diaryl Substituted Heterocyclic Compounds

A SUMMARY OF THE THESIS
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BY

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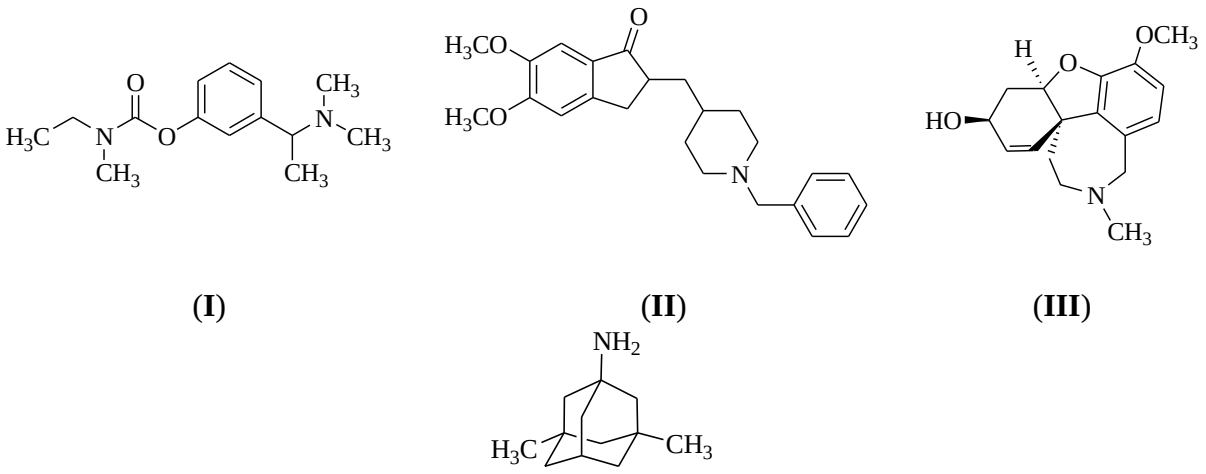
SUMMARY

Alzheimer's disease (AD), one of the major brain diseases, is a complex and progressive neurodegenerative disease which worsens with time. Reports suggest that AD starts 20 years or more prior to appearance of its symptoms, which are generally the small changes in the brain that remain unnoticeable to the affected persons. AD is more prevalent in elderly populations, usually characterized by cognitive impairment with loss of memory, incoherent language and difficulty in learning skills. AD is ranked as the fifth leading cause of death affecting almost 47 million populations worldwide, and the number is still rising and is estimated to grow up to 130 million or more by 2050.

Since the discovery of Alzheimer's disease by a German psychiatrist Dr. Alois Alzheimer in the year 1906, researchers have made great efforts to understand and unravel the pathophysiology of AD. However the exact cause of AD still remains uncertain but various causative factors such as misfolding and aggregation of amyloid-β protein, tau protein hyperphosphorylation, oxidative stress, metal ion dyshomeostasis and deficit of acetylcholine levels have been recognized to play important roles in pathophysiology of the disease.



(I) **(II)** **(III)**

(IV)

Figure 1: Currently marketed drugs for the treatment of AD.

Till date no single drug has been clinically effective to prevent or stop the progress of AD. Currently available drugs in the market for the management of AD (**Figure 1**) include three acetylcholinesterase inhibitors (AChEIs) viz. rivastigmine (**I**), donepezil (**II**) and galantamine (**III**), and one *N*-methyl-*D*-aspartate receptor (NMDAR) antagonist, memantine (**IV**). These AD treatments are mainly effective to treat mild cognitive impairments (MCI)

providing temporary relief from symptoms; however they fail to cure or reverse the progression of AD.

Pathophysiology of AD

- Cholinergic hypothesis
- Amyloid β-cascade and Tau (τ) hypothesis
- Oxidative stress
- Metal ion dyshomeostasis

Our research group has been actively involved in the designing and development of various therapeutically active compounds and successfully reported some vicinal diaryl heterocyclic systems as anti-Alzheimer agents. Earlier we have disclosed the anti-Alzheimer activity of compounds (**I**) containing vicinal diaryltriazine scaffold (**Figure 2**). Some benzylpiperidine-linked vicinal diarylthiazole derivatives (**II**) as MTDLs for the treatment of AD have also been reported from the lab (**Figure 2**). Based on these previous research works, it was planned to explore the structure of vicinal diaryltriazine fused with the substituted benzylpiperidines to develop a novel series of compounds (**III**) as anti-Alzheimer agents (**Figure 2**).

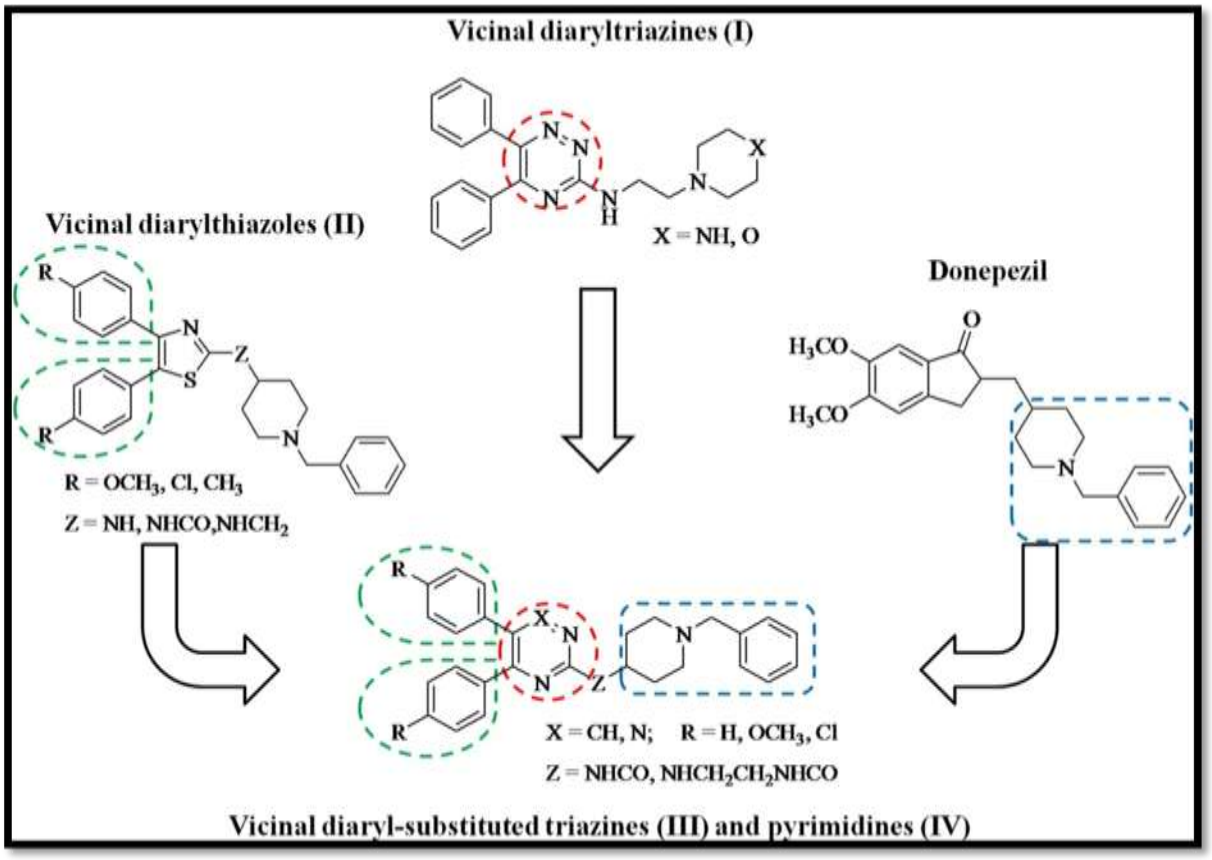


Figure 2: Designing of novel vicinal diaryl-substituted triazines (**III**) and pyrimidines (**IV**).

There are number of research articles appeared in the literature describing the anti-Alzheimer activity of pyrimidine containing heterocyclic compounds. Pyrimidine itself is a bioactive molecules present in various biologically important natural products. Keeping the significant biological potential of pyrimidine and its derivatives in the mind, it was planned to synthesize some novel vicinal diaryl-substituted pyrimidine derivatives (**IV**) as anti-Alzheimer agents (**Figure 2**). To the best of our knowledge, it is for the first time that these novel vicinal diaryl-substituted pyrimidines would be reported as anti-Alzheimer agents.

Besides this, we decided to synthesize some donepezil-triazine hybrids (**V**) wherein the 5,6-dimethoxy-indanone of the donepezil have been linked with the vicinal diaryl-substituted triazines as shown in figure 3. Further, it was planned to evaluate all the synthesized compounds (**III-V**) for their anti-Alzheimer activity.

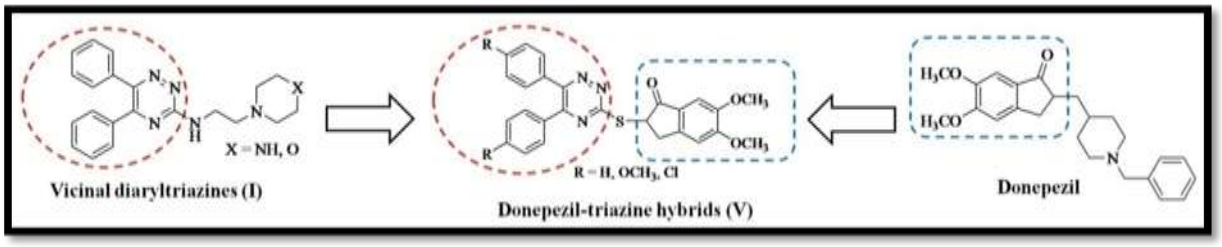


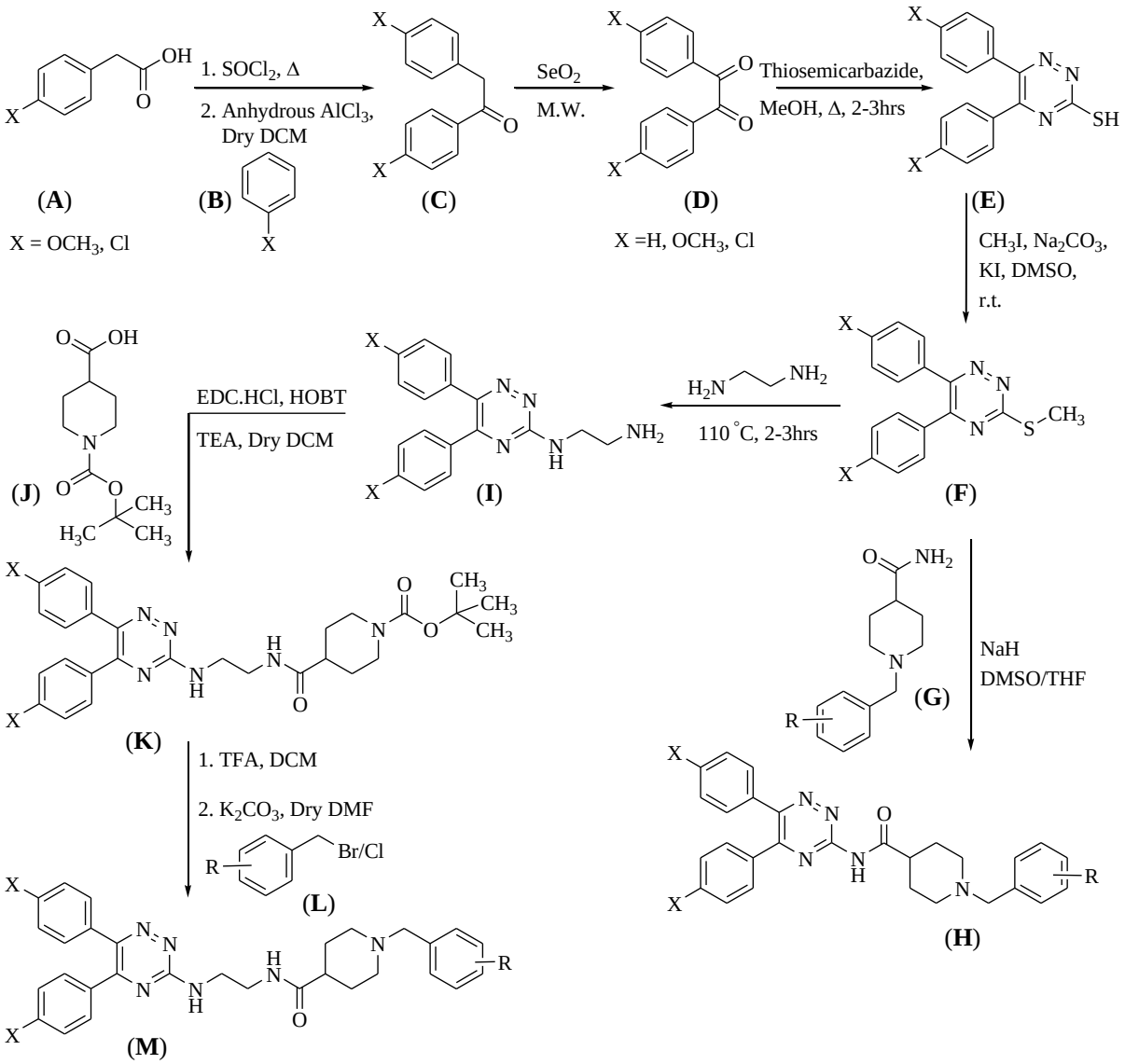
Figure 3: Designing of novel donepezil- triazine hybrids (**V**).

The proposed compounds were synthesized using synthetic schemes as depicted in **general schemes 1-3**.

Using **general scheme-1**, two different series of vicinal diaryl-substituted triazines *viz. N*-(5,6-diaryl-1,2,4-triazin-3-yl)-1-benzylpiperidine-4-carboxamides (**H**) and *N*-(2-(5,6-diaryl-1,2,4-triazin-3-ylamino)ethyl)-1-benzylpiperidine-4-carboxamides (**M**) were prepared.

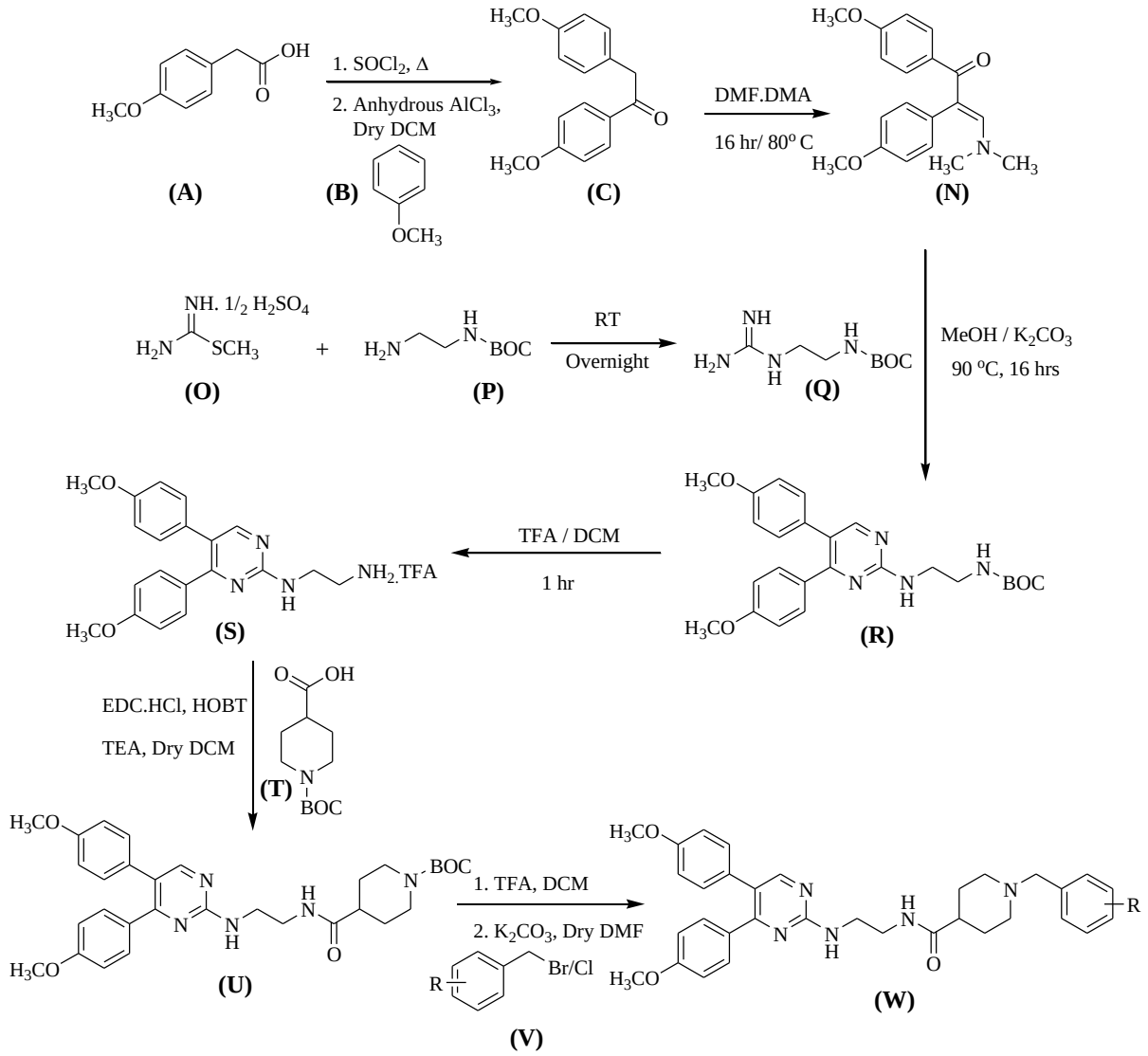
In the first step, the acid chlorides were prepared from substituted phenylacetic acids (**A**) using thionyl chloride. Subsequently, Friedel-Crafts acylation using substituted benzenes (**B**) and the acid chlorides produced 1,2-diarylethanones (**C**). Further oxidation of **C** was carried out using selenium dioxide to get 1,2-diarylethan-1,2-diones (**D**) which on refluxing with thiosemicarbazide undergo cyclization to give 5,6-diaryl-1,2,4-triazine-3-thiols (**E**). In the next step, the thiols (**E)** were methylated by methyl iodide under basic conditions to obtain 3-(methylthio)-5,6-diphenyl-1,2,4-triazines (**F**). Finally, the 3-(methylthio)-5,6-diphenyl-1,2,4-triazines (**F**) were treated with 1-substituted benzylpiperidine-4-carboxamides (**G**) in the presence of sodium hydride-DMSO at room temperature to obtain the desired *N*-(5,6-diaryl-1,2,4-triazin-3-yl)-1-benzylpiperidine-4-carboxamides (**H**).

3-(Methylthio)-5,6-diaryl-1,2,4-triazines (**F**) on refluxing with ethylenediamine at 110 ^{o}C for 2-3 hrs gave *N*-(2-aminoethyl)-5,6-diaryl-1,2,4-triazin-3-amines (**I**) which in the next step were treated with 1-(*t*.butyloxycarbonyl)piperidine-4-carboxylic acid (**J**) in presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) and hydroxy benzotriazole (HOBt) under basic condition to prepare *t*.butyl 4-(2-(5,6-diaryl-1,2,4-triazin-3-ylamino)ethylcarbamoyl)piperidine-1-carboxylates (**K**). In the last step, the carbamates (**K)** were deprotected using trifluoroacetic acid (TFA) and refluxed with substituted benzyl bromides (**L**) to obtain the final desired products *N*-(2-(5,6-diaryl-1,2,4-triazin-3-ylamino) ethyl)-1-substituted benzyl piperidine-4-carboxamides (**M**).



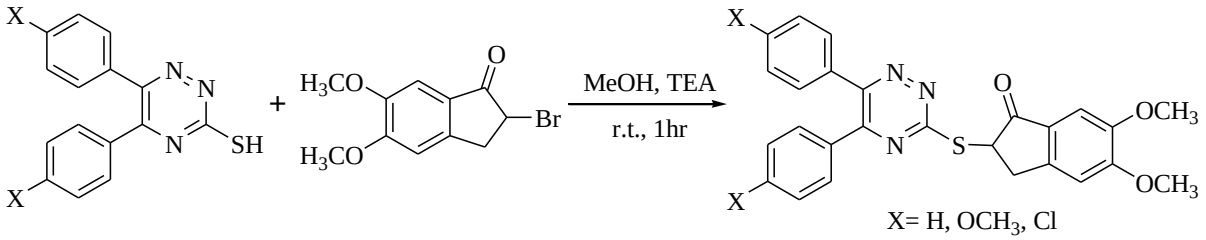
General Scheme 1

General scheme-2 was adopted to synthesize vicinal diaryl-substituted pyrimidine derivatives (**W**) wherein the intermediate (**C**) was treated with *N*,*N*-dimethylformamide dimethylacetal (DMF.DMA) to get 3-(dimethylamino)-1,2-diarylprop-2-en-1-one (**N**). Cyclization of **N** using *t*.butyl 2-guanidinoethylcarbamate (**Q**) offered *t*.butyl 2-(4,5-diaryl pyrimidin-2-ylamino)ethylcarbamate (**R**) which on deprotection and subsequent acid-amine coupling reaction yielded *t*.butyl 4-(2-(4,5-diarylpyrimidin-2-ylamino)ethylcarbamoyl) piperidine-1-carboxylate (**U**). In the final step, (**U**) was deprotected using TFA and refluxed with substituted benzyl bromides (**V**) to afford the final *N*-(2-(4,5-diarylpyrimidin-2-ylamino) ethyl)-1-substituted benzyl-4-carboxamides (**W**).



General Scheme 2

In **general scheme-3**, 5,6-diaryl-1,2,4-triazine-3-thiols (**E**) were hybridized with 2-bromo-5,6-dimethoxyindan-2-one (**X**) to produce vicinal diaryltriazine-donepezil hybrids (**Y**).



(E) **(X)** **(Y)**

General Scheme 3

Conclusion

With an aim to extend our ongoing research work on development of novel therapeutics for the treatment of Alzheimer's disease, a series of novel vicinal diaryltriazine and pyrimidine derivatives have been designed in which vicinal diaryltriazine/pyrimidine scaffold was combined with substituted benzylpiperidine, the active pharmacophore of donepezil through ethylene diamine linker. All the proposed compounds were synthesized successfully with good yields using two general schemes 1 and 2 involving 8-9 synthetic steps. It was envisaged that the newly synthesized vicinal diaryltriazines/pyrimidines would be potential anti-Alzheimer's agents as the interaction of vicinal diaryltriazine with PAS of AChE enzyme has already been disclosed, in which the benzyl piperidine side chain binds to the CAS of the AChE enzyme. Presence of nitrogen containing heterocycles such as triazine and pyrimidine could be helpful in controlling the basicity of the resulting compounds which would be crucial for the BBB permeation.

Using general scheme-3, an attempt has been made to prepare novel donepezil hybrid molecules wherein the vicinal diaryltriazine scaffold has been clubbed with the 5,6-dimethoxyindan-1-one of donepezil. We hope that these new vicinal diaryltriazine-donepezil hybrids would be effective to treat Alzheimer's disease.

All the proposed compounds have been confirmed for their structures by IR, ^{1}H-NMR and mass analysis and submitted for the biological evaluation to determine their potential as anti-Alzheimer agents.