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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of azomethines derived from cinnamaldehyde and vanillin: in vitro aetylcholinesterase inhibitory, antioxidant and insilico molecular docking studies

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Abstract In the present study, we report the synthesis of azomethines derived from cinnamaldehyde (**C1–C3**) and vanillin (**V1–V3**) using ethanol as a green solvent in the presence of triethyl amine. The synthesized compounds were characterized and investigated for their free radical scavenging activity and anti-Alzheimer properties by DPPH and acetylcholinesterase (AChE) inhibition assays. The anti-Alzheimer properties of the compounds were determined by molecular docking and ADME predictions. Compounds, **C1** and **V1** were found to be potential with IC_{50} values of 0.01 ± 0.09 µM and 0.31 ± 0.03 µM respectively. The antioxidant activity of C1 in terms of DPPH and ABTS was found to be 16.22 ± 0.02 µM and 17.2 ± 0.02 µM, whereas **V1** showed antioxidant activities at 14.07 ± 0.02 µM and 15.06 ± 0.03 µM respectively. In silico studies based on molecular docking and ADME predictions revealed the significance of azomethine derivatives as the potent anti-Alzheimer agents.

Keywords Schiff bases · Cinnamaldehyde · Vanillin · Azomethines DPPH · Molecular docking · Acetylcholine esterase

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Introduction

Alzheimer's disease (AD) is the leading cause of dementia which results in the beginning with impaired memory, particularly among the aged. The etiology of Alzheimer disease is unclear. However, the disease pathogenesis is increasingly associated with oxidative stress (Perumal et al. 2017). Acetylcholinesterase inhibitors (AChEI) with antioxidant activities are considered potential treatments for the AD (Salga et al. 2011; Gwaram et al. 2012; Chigurupati et al. 2016). Several derivates and pharmacophores of vanillin (Elseweidy et al. 2017; Kundu and Mitra 2013; Sridevi et al. 2017) and cinnamaldehyde (Jawale et al. 2016) have shown to inhibit acetylcholinesterase (AChE) enzyme and prevent oxidative stress (Santosh Kumar et al. 2002; King et al. 2007). In particular, azomethines the so-called Schiff base conjugates are one of the most widely used organic compounds (Hameed et al. 2017; Wang

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et al.2017; Zoubi 2013) which are known to exhibit a broad range of biological activities (Tabassum et al. 2013; Fugu et al. 2013; Sridevi 2015; Sridevi et al. 2016). Several Azomethine derivatives were shown to exhibit potential AChEI (Iqbal et al. 2016; Razik et al. 2016) and antioxidant activities (Geronikaki et al. 2004) which could possibly benefit in the treatment of AD. Azomethine derivatives of cinnamaldehyde and vanillin have been extensively studied due to their synthetic flexibility, selectivity and sensitivity (Skoog et al. 1996; Wadher et al. 2009). Given the impending rise in the prevalence of Alzheimer's disease, there is a pressing need for novel anti-Alzheimer's agents. Therefore, the present study was aimed to synthesize and evaluate azomethines derivatives of vanillin and cinnamaldehyde for their antioxidant and AChE inhibitory properties.

Knowing the importance of azomethines derived from cinnamaldehyde and vanillin from various literature sources, in the present study, we attempted to synthesize and characterize the azomethines derivatives of cinnamaldehyde (β-Phenyl acrolein) **C1–C3** and vanillin (4-Hydroxy-3-methoxy benzaldehyde) **V1–V3** using ethanol as solvent. The synthesized compounds were investigated in vitro for their AChE, oxidant inhibitory effect. Further, in silico studies were performed to understand the molecular interactions of these compounds with the AChE enzyme.

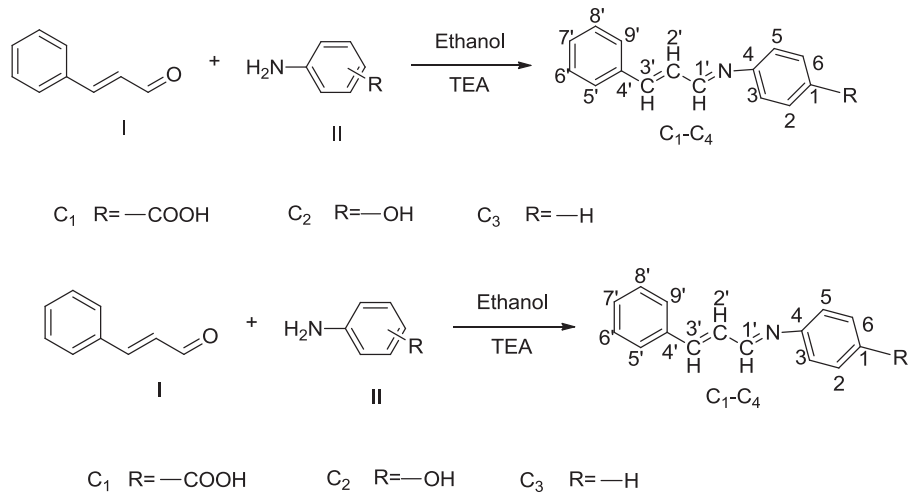
Experimental

General

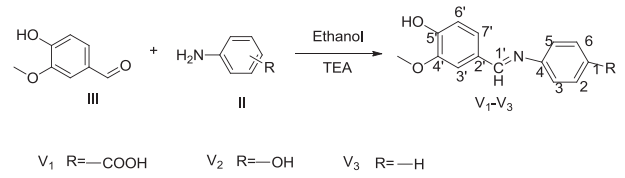
All the solvents and chemicals used were of analytical grade and obtained from Sigma-Aldrich Pvt. Ltd; U.S.A and Merck Pvt. Ltd; U.S.A and were used without further purification. The melting points of the compounds were determined on a Thoshniwal Electric Melting point apparatus and the values were uncorrected. The purity of all the compounds was routinely examined by thin layer chromatography (TLC) on Silica gel-GF 254 (Merck Pvt. Ltd; U.S.A) coated plates. Spots of TLC were identified using iodine chamber. The UV-Visible spectra of the compounds were recorded using double beam Shimadzu UV1800 spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker UX-NMR Instrument at 300 MHz with TMS as an internal standard and $CDCl_3$ as a solvent; and chemical shift values were expressed in δ p.p.m. The Mass spectra were recorded on MASPEC (MSW/9629) and values were expressed as % relative abundance. Elemental analysis of synthesized compounds was carried out using a Perkin Elmer 240 CHN analyzer.

General procedure for synthesis of cinnamaldehyde azomethines (C1–C3)

The solid starting materials, cinnamaldehyde (I), and aromatic amines (II) were finely powdered before use. A mixture of cinnamaldehyde (2.5 mM) and aromatic amines (2.5 mM) were dissolved in 5 mL of ethanol and subjected to trituration at room temperature (Bendale et al. 2011; Kaupp 2009) to give respective cinnamaldehyde azomethines (Scheme 1). The crystalline product formed was collected by filtration, washed with water and recrystallized using aqueous ethanol. The completion of reaction was confirmed by R_f with TLC using benzene:pyridine:ammonia (8:2:1) as solvent system. The spots were identified with the help of Iodine chamber. The crystalline precipitates formed were dried in an oil pump-vacuum to remove the residual solvent and further dried in a desiccator to protect the product from atmospheric moisture. A base catalyst triethyl amine was added during trituration (Sridevi 2015).



Scheme 1 Synthesis of cinnamaldehyde azomethines (**C1–C3**)



Scheme 2 Synthesis of vanillin azomethines (**V1–V3**)

The structures of the synthesized compounds were confirmed by physical and spectral data.

General procedure for synthesis of vanillin azomethines derivatives (V1–V3)

Vanillin azomethine derivates were synthesized similar to the method used for the synthesis of cinnamaldehyde azomethine derivates as described above (Bendale et al. 2011; Kaupp 2009) to give respective vanillin azomethines (Scheme 2). The crystalline product formed was collected by filtration, washed with water and recrystallized using aqueous ethanol. The completion of the reaction was confirmed by R_f with thin layer chromatography (TLC) technique, using benzene: pyridine: ammonia (8:2:1) as the solvent system and the spots were identified with the help of Iodine chamber. The formed crystalline powder was dried in an oil pump to remove the residual solvent and further dried in a desiccator to protect the product from atmospheric moisture. A base catalyst triethyl amine was added during trituration (Sridevi 2015). The structures of the synthesized compounds were confirmed by physical and spectral data.

4-(3-Phenylallylideneamino) benzoic acid (C1)

Yield: 86%; mp: 130–140 °C; R_f (TLC): 0.6; Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.42; H, 5.29; N, 5.52%. Found C, 72.51; H, 5.32; N, 4.88%; ^{1}H-NMR (500.1 MHz, $CDCl_3$-d, δ/p.p.m.): 5.85 (1H, *t*, $J = 9.5$ Hz, H-2'), 6.76 (1H, *d*, $J =$ 12 Hz, H-3'), 7.64–7.92 (9H, *m*, phenyl), 8.41 (1H, *d*, $J =$ 7.8 Hz, H-1'), 11.00 (1H, *s*, COOH); MS (*m/z*, (relative abundance, %): 251 (M^+, 32.6), 174, 130, 121, 102, 77, 53, 51 (BP, 100); UV-Vis (MeOH) (λ_{max}/nm): 307.

4-(3-Phenylallylideneamino) phenol (C2)

Yield: 80%; mp: 120–130 °C; R_f (TLC): 0.7; Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27%. Found C, 80.56; H, 5.78; N, 5.82%; ^{1}HNMR (500.1 MHz, $CDCl_3$-*d*, δ/p.p.m.): 5.4 (1H, *s*, –OH, D_2O exchangeable), 5.72 (1H, *t*, H-2'), 6.59 (1H, *d*, H-3'), 7.4–7.8 (9H, *m*, phenyl), 8.29 (1H, *d*, H-1'); MS (*m/z*, (relative abundance, %)): 223 (M^+, 18.5), 146, 102, 93, 77, 53, 51, (BP, 100); UV-Vis (MeOH) (λ_{max}/nm): 302.

N-(3-Phenylallylidene) benzamine (C3)

Yield: 70%; mp: 98–100 °C; R_f (TLC): 0.5; Anal. Calcd. for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76%. Found C, 86.89; H, 6.28; N, 6.66%; ^{1}H-NMR (500.1 MHz, CDCl3-d, δ/p.p.m.): 5.76 (1H, *t*, H-2'), 6.52 (1H, *d*, H-3'), 7.23–7.60 (10H, *m*, phenyl), 8.24 (1H, *d*, H-1'); MS (*m/z*, (relative abundance, %)): 207 (M^+, 18.9), 130107, 102, 77, 53, 51 (BP, 100); UV-Vis (MeOH) (λ_{max}/nm): 353.

4-(4-Hydroxy-3-methoxybenzylideneamino) benzoic acid (V1)

Yield: 60%; m.p: 156–159 °C; R_f (TLC): 0.56; Anal. Calcd. For $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; O, 23.59; N, 5.16%. Found C, 75.99; H, 4.80; O, 22.59; N, 5.06%; ^{1}H-NMR (500.1 MHz, CDCl3-d, δ/p.p.m.): 3.83 (s, 3H, $-OCH_3$), 6.91 (s, 1H, Ar–H), 7.42–7.54 (m, 4H, Ar-H), 8.21 (s, 2H, Ar-H), 8.67 (s, 1H, –CH=N), 9.83 (s, 1H, Ar-OH), 12.23 (s, 1H, Ar-COOH). MS (*m/z*, (relative abundance, %)): 271 (M^+, 20.0), 271, 150, 124, 122, 77, 51 (BP, 100); UV-Vis (MeOH) (λ_{max}/nm): 286.

4-(4-Hydroxyphenylimino) methyl)-2-methoxyphenol (V2)

Yield: 75%; m.p: 144–147 °C; R_f (TLC): 0.67; Anal. Calcd. For $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; O, 19.73; N, 5.76%. Found C, 68.94; H, 5.29; O, 19.71; N, 5.06%; ^{1}H-NMR (500.1 MHz, CDCl3-d, δ/p.p.m.): 3.83 (s, 3H, $-OCH_3$), 6.85 (m, 3H, Ar-H), 7.45–7.55 (m, 4H, Ar-H), 8.67 (s, 1H, CH=N), 9.43 (s, 1H, Ar-OH), 9.83 (s, 1H, Ar-OH). MS (*m/z*, (relative abundance, %)): 243(M^+, 19.0), 243, 150, 124, 94, 77, 51 (BP, 100); UV-Vis (MeOH) (λ_{max}/nm): 336.

2-Methoxy-4-(phenylimino) methyl) phenol (V3)

Yield: 78%; m.p: 110–114 °C; R_f (TLC): 0.66; Anal. Calcd. For $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; O, 14.08; N, 6.16%. Found C, 73.01; H, 5.31; O, 13.99; N, 6.06%; ^{1}H-NMR (500.1 MHz, CDCl3-d, δ/p.p.m.): 3.83 (s, 3H, $-OCH_3$), 6.92 (m, 2H, Ar-H), 7.41–7.51 (m, 6H, Ar-H), 8.66 (s, 1H, CH=N), 9.83 (s, 1H, Ar-OH). MS (*m/z*, (relative abundance, %)): 227(M^+, 19.5), 150 124, 104, 77, 51 (BP, 100); UV-Vis (MeOH) (λ_{max}/nm): 320.

In vitro acetylcholinesterase and antioxidant assay

The synthesized compounds were subjected to acetylcholinesterase and antioxidant activities by following the previously described methods for DPPH (Sridevi et al. 2011; Molyneux 2004; Chigurupati et al. 2016), ABTS (Re

et al. 1999; Chigurupati et al. 2016) radical scavenging effect and AChE enzyme inhibition (Ellman et al. 1961). The IC_{50} values, concentration required by a compound to inhibit the production of free radicals (DPPH, ABTS) and substrate hydrolysis (AChE) by 50% were calculated (Chigurupati et al. 2016) by a non-linear regression graph plotted between percentage inhibition (x-axis) vs. concentrations (y-axis), using a Graph Pad Prism Software (Version 5).

Molecular docking and ADME study

In order to predict the binding modes of synthesized cinnamaldehyde and vanillin azomethines, docking studies were carried out on the crystal structure of AChE (PDB ID: 1EVE) (Kryger et al. 1999). Prior to docking studies, the crystal structure of the AChE enzyme was prepared by using protein preparation wizard. The crystal structure was retrieved from the protein data bank (PDB), and the structure was optimized by removing the water molecules, hetero atoms and co-factors. Hydrogen, missing atoms, bonds, and charges were computed through Macromodel module (Maestro 2015). The synthesized cinnamaldehyde and vanillin azomethines used for docking were ligand prepared and optimized using built and LigPrep module implemented in Schrodinger Maestro. Preparation of ligands includes generating various tautomers, assigning bond orders, ring conformations, and stereo chemistries. All the conformations generated were minimized using OPLS2005 force field prior to docking study. Further, a receptor grid was generated around the AChE enzyme active site by choosing centroid of AChE enzyme complex ligand (Aricept). Grid box size was set to 20 Å radius, using the receptor grid generation implemented in Glide (Maestro 2015). Docking calculations were accomplished using Glide (Maestro 2015) as well as by following the method suggested by M. Taha et al. (2016). Docking calculations were performed using Standard Precision (SP) mode and Extra Precision (XP) mode. The Glide docking score was used to determine the best-docked structure from the output. The interactions of these docked complexes were further analyzed and imaged using PyMOL (Augustyniak et al. 2010). Besides, Qikprop prediction of ADME properties was carried out for all the eight indolopyrazoline derivatives (QikProp 2012).

Results and discussion

Chemistry

Azomethines of cinnamaldehyde (**C1–C3**) and vanillin (**V1–V3**) were prepared successfully using a synthetic

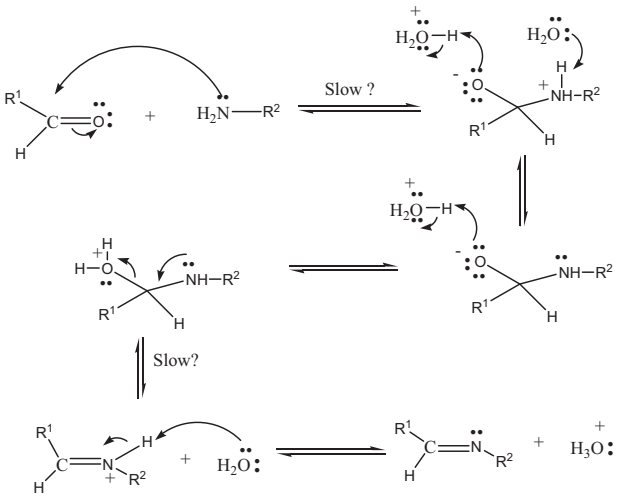


Fig. 1 Mechanism of azomethine formation

method in the ambience of a basic catalyst, triethylamine and the procedure was found to be time-saving and environment friendly as compared to the conventional synthetic procedure (Schemes 1 and 2). The mechanism involved in the formation of azomethines from aldehyde and aromatic amines is illustrated in Fig. 1. The solidified crude products were recrystallized from aqueous ethanol and the azomethines were obtained in high yields. The purities of the compounds were checked by the R_f value of TLC and melting points. Physical data and spectral data further confirmed the structures and purity of the synthesized compounds. The percentage yield was found to be in a range of 70–86% and 60–78% for cinnamaldehyde and vanillin azomethines, respectively. The λ_{max} for the cinnamaldehyde and vanillin azomethines was in the range of 300–440 nm and 280–340 nm respectively. The formation of cinnamaldehyde azomethines was confirmed by the presence of triplet between 5.7 and 5.8 ppm, in ^{1}H NMR spectra. On the other hand, the formation of vanillin azomethines was confirmed by the presence of singlet between 8.6 and 8.7 ppm in ^{1}H NMR spectra. All other aliphatic and aromatic protons were observed within the expected regions. The structure of compounds was further confirmed by their characteristic mass fragment spectra. The mass fragment pattern of compound **C1** displayed parent ion peak at 251, base peak at 51, and different fragment peaks at 174, 130, 121, 102, 77, and 53 (Fig. 2). Similarly, all other azomethines were characterized. This part confirmed the synthesis of a series of six azomethines.

In vitro acetylcholinesterase enzyme and antioxidant assay

All the synthesized compounds showed better IC_{50} values in both AChE and antioxidant assays. In the AChE enzyme

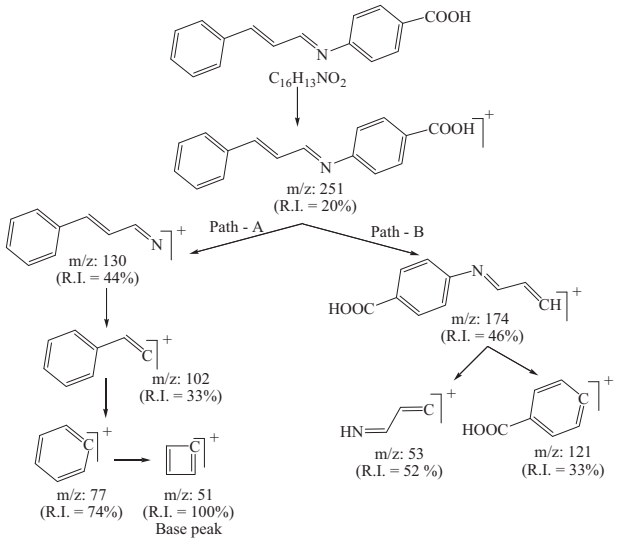


Fig. 2 Mass fragmentation pattern of **C1**

inhibition assay study, **C1** (0.01 ± 0.09 μM) and **V1** (0.31 ± 0.03 μM) showed better IC_{50} values as compared to other derivatives (Table 1).

The IC_{50} value of **C1** was comparable with the positive control Donepezil (0.01 ± 0.40 μM). Based on DPPH and ABTS antioxidant assays both **C1** (16.22 ± 0.02 μM and 17.2 ± 0.02 μM) and **V1** (14.07 ± 0.02 μM and 15.06 ± 0.03 μM) showed promising antioxidant activities as compared to other derivatives (Fig. 3 and Fig. 4). The antioxidant activities of **C3** and **V3** were comparable with the IC_{50} values obtained for ascorbic acid in DPPH (15.73 ± 0.01 μM) and ABTS (16.79 ± 0.01 μM) assays.

Docked binding mode analysis of azomethines

Docking results were analyzed based on the glide SP scores obtained from GLIDE (Grid-based ligand docking with energetics) docking (Friesner et al. 2004). In each case, the binding mode was analyzed for the interaction between a specific compound and AChE. In-depth analysis of the interaction pattern for the active compounds **C1–C3** and **V1–V3** is described in the following section. The binding modes of compounds **C1–C3** and **V1–V3** in comparison with donepezil is shown in Figs. 5a and 6a. The binding modes of cinnamaldehyde and vanillin azomethines are different from the binding mode of donepezil. The binding of donepezil to AChE only establishes the hydrophobic interaction. However, hydrogen bonding, stable π–π stacking and cation–π interaction in addition to hydrophobic interactions were observed in cinnamaldehyde and azomethines. Therefore, we report there is a high potency in the activity profile of these series. Overall, the presence of these additional interactions improves the activity of the acetyl cholinesterase inhibitor.

The probable binding mode of **C1** is shown in Fig. 5b. The oxygen of benzoic acid moiety forms hydrogen bond with side chain oxygen of Glu199 and the main chain NH of Gly118 respectively. While, the benzene ring of **C1** forms stable π–π stacking with the imidazole ring NH of His440 and the same group forms cation–π interaction with the side chain rings of Tyr334. Additionally, the marked hydrophobic interactions between the benzene rings Phe290, Ile287, Phe288, and Phe331 and Tyr121 is noteworthy.

Figure 5c represents the binding mode of compound **C2**. The benzoic acid group oxygens form hydrogen bond with the side chain oxygen of Glu199. While the benzene ring forms stable π–π stacking with the imidazole ring of His440 and the indole ring of Trp84, respectively, the amine forms cation–π interaction with Trp84 and Phe330. Moreover, there is a hydrophobic interaction between the benzene ring of **C2** with Phe290, Tyr334, Phe331, and Tyr121. The phenol ring compound **C2** forms a hydrophobic interaction with Ile444. In compound **C3** (Fig. 5d), one of the benzene rings forms π–π stacking with a phenyl ring of Phe330, and there is a cation–π interaction between the NH group and the phenyl ring of Tyr334. In addition, **C3** also forms a hydrophobic interaction with Phe331, Ty334, Phe290, and Phe288. With respect to **V1**, the binding orientation clearly shows that the benzoic acid oxygens form hydrogen bond with the side chain oxygen of Glu199 and main chain NH of Gly118 respectively. Similarly the benzene ring of the benzoic acid moiety forms stable π–π stacking with the imidazole ring of His440 and Phe331, respectively. Interestingly, the phenol ring of the Tyr334 forms π–π stacking with the methoxyphenol group and cation–π interaction between NH groups of **V1**, respectively. In addition, the formation of hydrophobic interactions by methoxyphenol group with Phe288, Phe290, and Tyr121 is also palpable (Fig. 6b).

Subsequently, two hydrogen bonds were observed in **V2**, one between the hydroxyl group of the phenol and backbone oxygen of Ser286 and the other between the hydroxyl group of the methoxyphenol moiety and the side chain carboxy oxygen of Asp72. In addition, the methoxyphenol moiety also forms π–π stacking with a Phenyl ring of Phe334. Besides this, the presence of hydrophobic interactions of residues Leu282, Ile287, Phe288 with the phenol ring of **V2** and interaction of methoxyphenol moiety of **V2** with Tyr70, Tyr121, and Phe330 as shown in Fig. 6c. Regarding the binding mode of **V3**, the methoxyphenol group's methoxy oxygen forms hydrogen bonds with the backbone oxygen of Gly118 and similarly the amine forms hydrogen bond with the oxygen of Tyr121. Also, the phenyl ring forms a hydrophobic interaction with Tyr334, Phe331, and Phe290. Furthermore, the methoxyphenol ring forms a hydrophobic interaction with His440 and Tyr121 (Fig. 6d).

Table 1 IC_{50} values of azomethines of cinnamaldehyde (**C1–C3**) and vanillin (**V1–V3**)

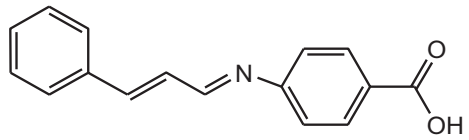
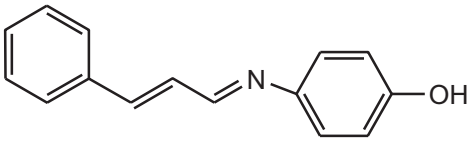
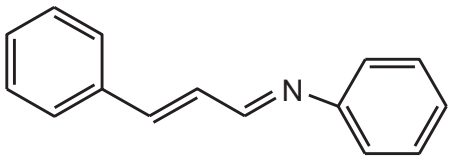
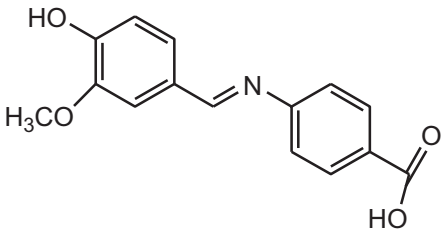
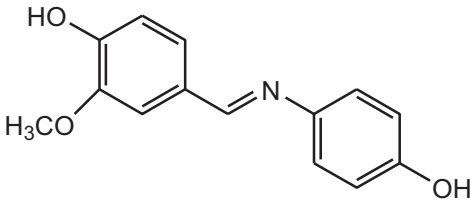
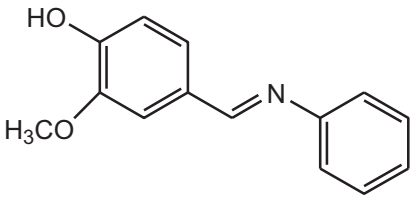
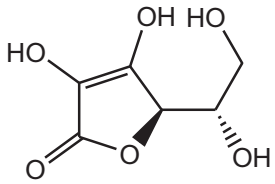
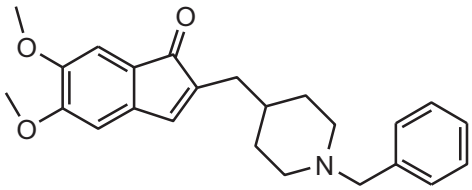
Compound code	Chemical structure	IC_{50} (μM ± SEM[a])		
		DPPH	ABTS	AChE
C1		16.22 ± 0.02	17.2 ± 0.02	0.01 ± 0.09
C2		25.18 ± 0.04	28.86 ± 0.01	0.11 ± 0.04
C3		35.47 ± 0.01	50.97 ± 0.04	2.88 ± 0.03
V1		14.07 ± 0.02	15.06 ± 0.03	0.31 ± 0.03
V2		22.29 ± 0.02	21.9 ± 0.03	1.10 ± 0.01
V3		34.8 ± 0.02	32.24 ± 0.03	3.22 ± 0.07

Table 1 continued

Compound code	Chemical structure	IC_{50} (μM ± SEM[a])		
		DPPH	ABTS	AChE
Ascorbic acid		15.73 ± 0.01	16.79 ± 0.01	–
Donepezil		–	–	0.01 ± 0.40

[a] Standard error of mean using Graph Pad prism 5 ($n = 3$)

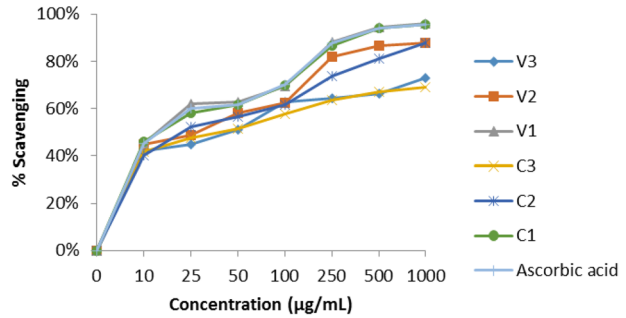


Fig. 3 DPPH radical cation scavenging assay results of azomethines

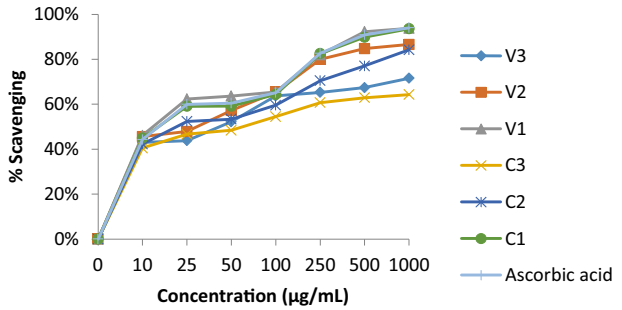


Fig. 4 ABTS radical cation scavenging assay results of azomethines

ADME prediction of cinnamaldehyde and vanillin azomethines

Drug kinetics and exposure of drug to tissues largely influence the pharmacological activity and the performance of a drug, which is eventually determined by its ADME properties. Almost twelve physically significant descriptors and pharmacologically relevant properties of cinnamaldehyde and vanillin benzaldehyde azomethines were predicted and analyzed (Supplementary Material, Table S1). Aqueous solubility (QPlogS) of organic compounds shows a key impact on many ADME associated properties like uptake, distribution, transport and bioavailability. The solubility values of cinnamaldehyde and vanillin azomethines were within the range (Lipinski et al. 2001). Additionally, the predicted values for the blood–brain barrier penetration of all the compounds were found to be in the optimum penetration range (−2–+2 scale) and consequently were measured as active compounds on the CNS. Finally, the Lipinski's rule of five and Qikprop rule of three were all within the range for the cinnamaldehyde and vanillin azomethines and thus making them as promising drug candidates.

Conclusion

Both docking studies and the inhibition assay of cinnamaldehyde and vanillin azomethines unveiled their competence to bind the AChE that induces strong inhibition. Prediction of ADME properties using Qikprop indicates that the compounds are CNS active and fulfilled the Lipinski's

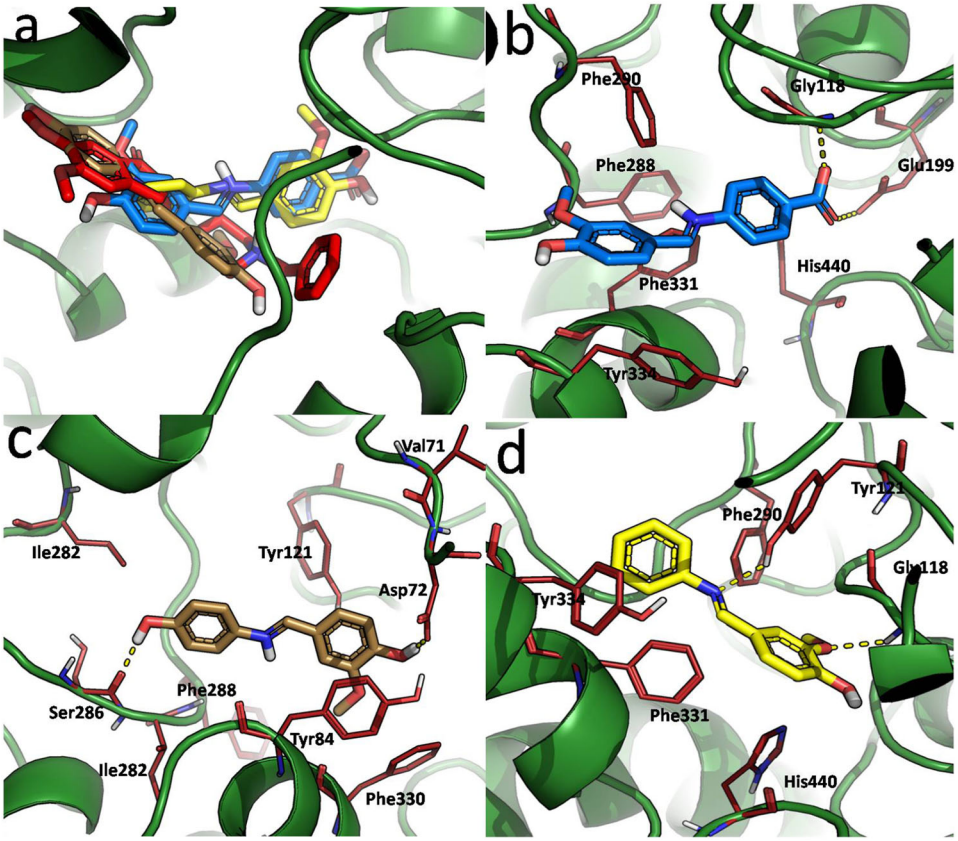


Fig. 5 Graphical illustration of predicted binding modes of cinnamaldehyde azomethines. (**a**) Binding modes of comparison of donepezil with the cinnamaldehyde azomethines, (**b**) compound **C1** in blue, (**c**) compound **C2** in brown, and (**d**) compound **C3** in yellow. Compounds are represented in sticks. The key residues are represented in wireframe with labels and yellow dashed lines represent hydrogen bond interactions

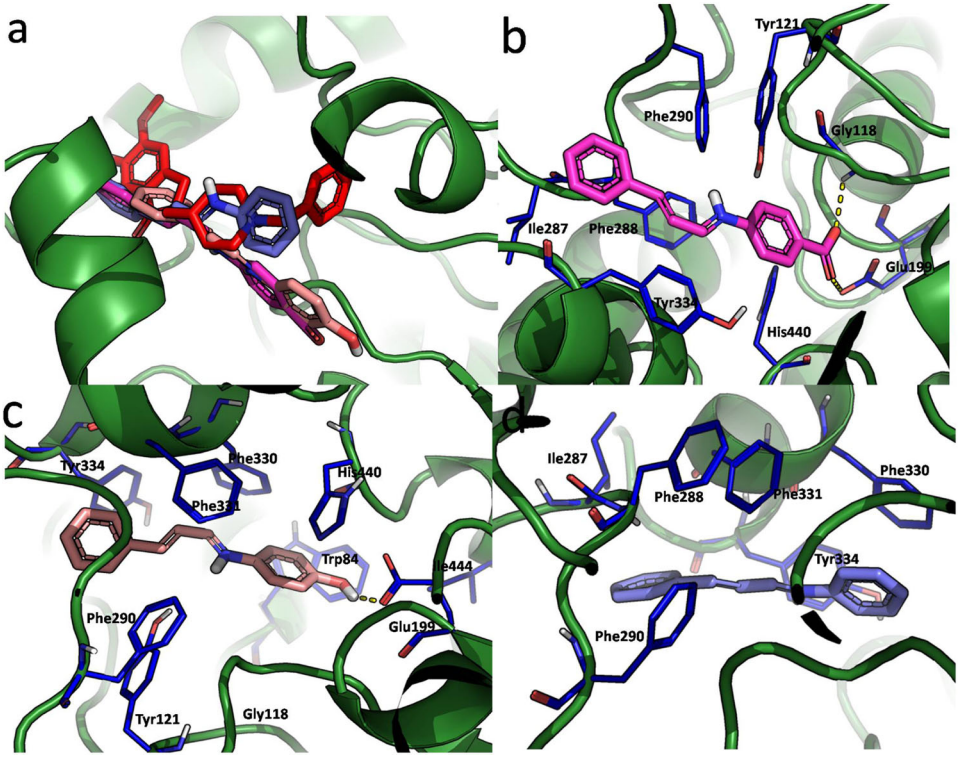


Fig. 6 (**a**) Comparison of the binding mode of Donepezil with the vanillin azomethines, (**b**) magenta color represents the binding mode of **V1**,(**c**) salmon color represents the binding mode of **V2**, and (**d**) slate color represents the binding mode of **V3**. Key interacting residues are shown in line, compounds as sticks and the dashed yellows line represents hydrogen bonds

rule of five. In the case of cinnamaldehyde derivatives (Compounds **C1**, **C2**, and **C3**), the predicted CNS activity was in agreeable range −1, 0, and 1 respectively (refer Supplementary Table S1). Similarly, CNS activities of vanillin azomethines were −2, 0, and 0 for **V1**, **V2**, and **V3**, respectively. Therefore, it is clear that these two classes of compounds can be utilized as a good series to inhibit Aetylcholinesterase. The possible docked binding mode of the azomethine derivatives reveal that the combination of both electron withdrawing group and hydrophobic moieties at the terminal end of the azomethine derivatives is responsible for the activity, which in-turn reflects in the activity profile as revealed in our study. Hence, these azomethine derivatives could be proposed as a potent class of compounds for the AD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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