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Identifying clinically significant novel drug candidate for highly prevalent Alzheimer's disease

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Pharmacokinetics is very important in target validation and in shifting a lead compound into a drug. It is a cumbersome process in clinical research. A quantitative personation based on computed, pharmacokinetics, physicochemical properties, ILOGP, drug-likeness, medicinal chemistry friendliness, bioavailability radar and BOILED-Egg for all the synthesized, 6 novel compounds have been assessed using Swiss ADME. An effective drug can be produced from the physicochemical properties discussed in this model. The physicochemical properties of all designed Schiff bases of curcumin have been found to be optimal and so, they are perceived to have acceptable oral absorption and adequate permeability. All the monomers obeyed the rule of five by Lipinski and the oral bioavailability is accounted worldwide. The desired set of monomers have been enhanced by effective ADME screening and molecular simulation methods with Microtubule-associated protein tau **(**MAPT) (PDB code: 10636) receptor could represent favourable building blocks as preferable chemotherapeutic factor in resistance to Alzheimers disease.

Keywords: ADME, Lipinski rule, Bioavailability, Curcumin-schiff base, Molecular simulation, Alzheimer's disease

Pharmacokinetics (PK) is to examine the time course of the absorption, distribution, metabolism and excretion (ADME) of a compound, drug or new chemical entity (NCE) after its dispensation to the body[1]. Drug discovery process consists of spotting and personation of new targets. Drug generation requires not only accretion of specific and potent recognition by its pharmacodynamic objective, but also effective delivery to these selected sites[2]. Lipinski states that, an orally vital drug has no more than two violations of the following basis: comparatively $\leq$ 5 hydrogen bond donors (oxygen or nitrogen atoms with more than one hydrogen atoms); less than 10 hydrogen bond acceptors (nitrogen or oxygen atoms); a molecular mass less than 500 daltons (Da); and an octanol--water partition[3] coefficient log P not greater than 5. A quantitative characterization based on computed pharmacokinetics, drug-likeness, physicochemical properties, medicinal chemistry friendliness BOILED-Egg, ILOGP and bioavailability radar for all synthesized 6 novel compounds have been evaluated using Swiss ADME[4]. Apart from these physicochemical properties, the number of rotatable bonds (RBs) in a molecule has also been shown to be important for drug assimilation[5]. Among the aforementioned physicochemical properties, lipophilicity has been accredited as a prime factor for a drug's buoyant passage via clinical development and on to the marketplace.

Curcumin and schiff base novel compounds are of specific passion because they are sparky compounds in the biological field[6-8]. Several chromone analogues have been reported to act as anticancer, anti-HIV, antibacterial, anti-inflammatory agents[9-18] and also act as an efficient agents in the treatment of cystic fibrosis[19,20], kinase inhibitors, etc. However, there has not been examples of polymer synthesis using curcumin as a monomer itself. Herein, we have prepared novel monomers bearing 4-arylidene curcumin units in their main chain. A thorough literature survey reveals that several structural modifications have been made in poly (azomethine) ester's backbone[21]. Among these modifications, the synthesis of polyesters using symmetrical diol monomers consisting of chromone and 4-arylidene curcumin units as backbone has not yet been reported in literature.

Experimental Section

All the chemicals and reagents were of analytical grade and purchased from Alfa Aesar, SRL chemicals, and Sigma Aldrich solvents viz. chloroform (SRL chemicals), methanol and ethanol (Finar Chemicals laboratory) were purified according to standard

procedures. FT-IR spectra of the monomers were recorded using a PerkinElmer FT IR spectrophotometer in the range of 4000-400 cm^{-1}. ^{1}H-NMR spectra of the monomers were recorded on the FT-NMR-400 MHz spectrophotometer (ATR mode) using DMSO-d_6 or CDCl3 as a solvent. The absorption spectra were recorded with the Agilent 8453 UVeVis diode-array spectrophotometer. To screening the ADME properties of the monomers within the Swiss using ADME tool.

Synthetic methods

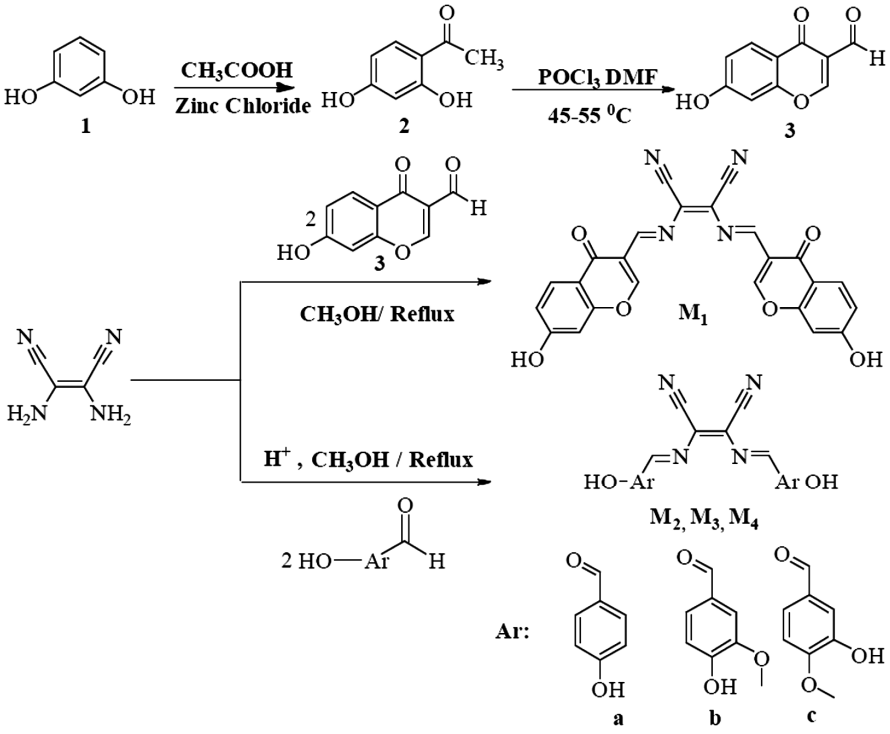
A series of chromone based schiff base diol monomers were synthesized as shown in Scheme 1. In the first step, the compound (1) resorcinol was treated with acetic acid in the presence of zinc chloride to get compound (2). The Vilsmeier-Haack formylation reaction using compound (2), $POCl_3$ and DMF yielded 7-hydroxy-4*H*-chromone-3-carbaldehyde (3) in good yield[22]. Finally, the reaction between compound (3) and diaminomaleonitrile in methanol at reflux condition afforded the chromone based schiff base diol monomer (M_1).

The other Schiff base diol monomers M_2, M_3 & M_4 were prepared using (a) 4-hydroxy benzaldehyde , (b) vanillin and (c) isovanillin, respectively in the place of compound (3) as in the procedure aforementioned.

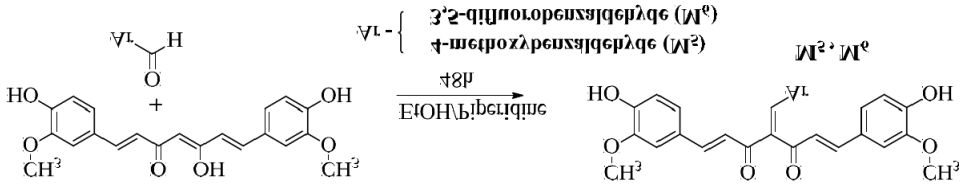
Structurally different curcumin based monomers were synthesized as depicted in Scheme 2. Here, curcumin was made to react with 4-methoxy-benzaldehyde or 3, 5-diflurobenzaldehyde in the presence of piperidine catalyst in the medium of mixture of methanol and chloroform for 48 hours to obtain 4-methoxy arylidene curcumin based diol monomer (M_5) or 3, 5-difluro arylidene based diol monomer (M_6).

Pharmacokinetic studies

Six novel monomers were effectively designed and put through a theoretical in-silico ADME prediction using the web tool, Swiss ADME. The 2D structures of the designed monomers which had been converted



Scheme 1 — Synthesis of schiff base diol monomers (M_1–M_4).



Scheme 2 — Synthesis of 4-arylidene curcumin based diol monomers (M_5, M_6).

to canonical SMILES format were used to assess the ADME properties within the Swiss ADME tool. Bioavailability radar plot gives us a graphical insight on drug-likeness decisions based on the bioavailability index.

Molecular docking studies

Molecular docking studies were carried out using the Auto Dock Tools version 1.5.6 and Auto Dock version 4.2.5.1 docking program. The energy predictions were formulated using genetic algorithms. The three-dimensional X-ray structure of microtubule-associated protein tau (MAPT) (PDB code: 10636) was offloaded from protein data bank (http://www.pdb.org) and the anatomy of monomers (M_1 to M_6) was portrayed by CHEMSKETCH and changed into PDB format from mol format with OPENBABEL.

Results and Discussion

Spectral characterization

FT IR spectra of monomers (M1-M4), showed strong absorptions between 1621–1660 cm^{-1} which indicate the presence of CH=N (azomethine) group and the stretching vibrations of pyrone ring carbonyl (C=O) group at 1609 cm^{-1}. The presence of C≡N and OH groups absorption were observed at 2236–2200 cm^{-1} & 3510–3262 cm^{-1}, respectively for schiff based backbone monomers. The FT-IR spectra of structurally different curcumin based monomers (**M5, M6)** the stretching vibrations of C=O groups exhibited at 1627-1624 cm^{-1}. The presence of arylidene CH stretching absorption showed at 962 and 965 cm^{-1}, respectively. Fig 1.

In ^{1}H NMR spectra of compounds M1-M4 (Fig. (2A, 2B, 3A & 3B)), signals that appear among 9.79-9.1 ppm, 10.90-9.77 ppm, and 8.38 ppm indicated the presence of azomethine proton, phenolic OH proton and pyrone ring proton, respectively. The signal at 6.77–8.50 ppm was due to the aromatic ring protons of monomers.

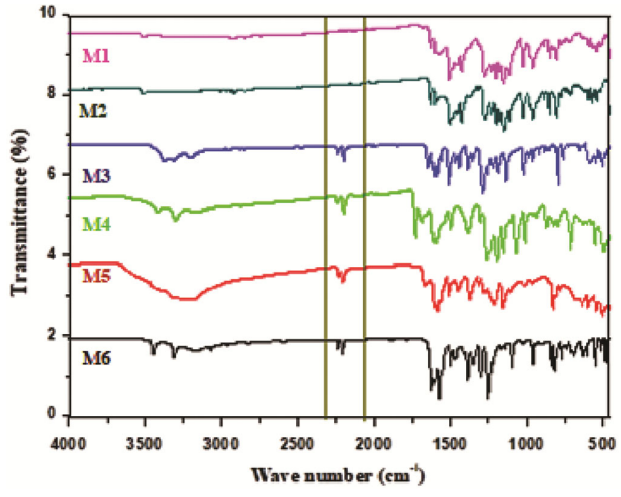


Fig. 1 — FT IR spectrum of schiff base monomers; M1-M4 and curcumin monomers: M5, M6

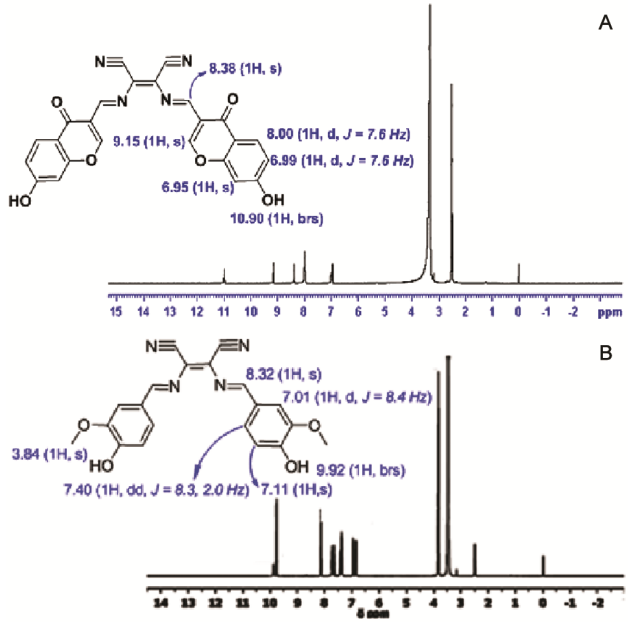


Fig. 2A — ^{1}HNMR Spectra of Schiff base monomer- M1; 2B ^{1}HNMR spectra of schiff base monomer- M3

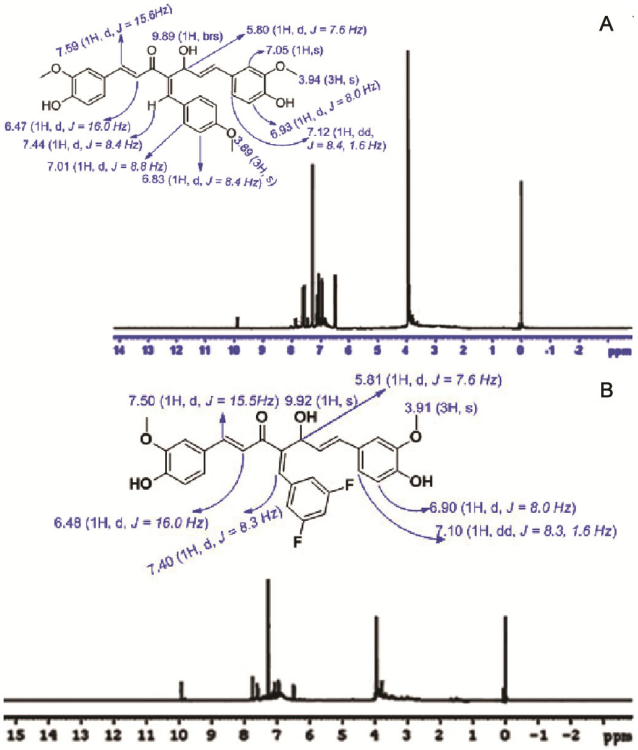


Fig. 3A—^{1}HNMR spectra of 4-arylidine monomer- M5; 3B ^{1}HNMR spectra of 4-arylidine monomer- M6.

The oxymethylene (–OCH_3) protons of M3, M5 and M6 compounds signal appeared in the range at 3.83–3.87 ppm.

Physicochemical properties

The physicochemical assets of a drug have a remarkable effect on the pharmacokinetic and metabolic fate in the body. The results observed from Table 1 convey that all the monomers obey the Lipinski rule of five. All the monomers have less than 10 rotatable bonds and thus satisfied the benchmark for oral bioavailability. The synthesized monomers have log p values ≤ 5 and so, they are predicted to have acceptable oral absorption and good permeability. The lower the permeability lower is the lipophilicity. The reduction in log p increases the compound stability. The synthesized monomers discern to have a high intestinal absorption excluding the monomer **M1** which has low GI absorption and high TPSA, and could pervade quite easily over the intestinal face of the cell membrane. Drugs need to travel through the blood brain barrier (BBB) to reach their goal. It is perceived from the Table 2 that all the monomers do not penetrate into BBB and accordingly do not influence the CNS. From Table 2, it is seen that M6 has the least negative value and thus it is more skin permeant. M1 has more negative log k_p value and least is the skin permeant. From Table 3, it is noticed that there is zero violation to Lipinski for all the monomers from M1 to M6 and the monomer M1 has 1 violation to Veber (TPSA >140) and 1 violation with Egan (TPSA > 131.6). The Abbot bioavailability score depends on the total charge, TPSA and negligence to Lipinski rule explains four classes of monomers with possibilities of 11%, 17%, 56%, 85%. The data from Table 3, shows that the monomers possess bioavailability score (BAS) of 55% and so, they are good oral drug candidate.

Cons. LogP – Consensus LogP, L- Lipinski, V- Veber, E- Egan, BAS- Bioavailability Score. SA– Synthetic Accessibility

Boiled egg representation

The brain or intestinal estimate D penetration method (BOILED-Egg) is the intuitive technique to appraise the passive gastrointestinal absorption (HIA) and brain penetration (BBB) apropus WLOGP-versus-TPSA. The white region (yolk) of the egg showed high possibility of submissive absorption by the gastrointestinal tract and the yellow region (yolk) was of high likeness towards brain penetration. The monomers 1b, 1c, 1d, 2a and 2b lie in white region

Table 1 — Physicochemical properties.

Monomers	MW	#Rotatable bonds	TPSA	ESOL Class	iLOGP
M1	452.38	4	173.18	Moderately soluble	2.72
M2	316.31	4	112.76	Soluble	2.15
M3	376.37	6	131.22	Soluble	2.71
M4	376.37	6	131.22	Soluble	2.71
M5	486.51	10	102.29	Moderately soluble	4.2
M6	492.47	9	93.06	Poorly soluble	3.47

Table 2 — Permeability effect of the compound.

Monomers	GI absorption	BBB permeant	iLOGP	log Kp (cm/s)
M1	Low	No	2.72	-7.7
M2	High	No	2.15	-6.63
M3	High	No	2.71	-7.04
M4	High	No	2.71	-7.04
M5	High	No	4.2	-5.5
M6	High	No	3.47	-5.38

Table 3 — Drug likeness and medicinal chemistry properties.

Molecules	Lipophilicity					Druglikeness				Medicinal chemistry			
						No. of violations			BAS	#ALERTS		Lead likeness	SA
	iLOGP	XLOGP3	WLOGP	MLOGP	Cons logP	L	V	E		Pains	Brenk		
M1	2.72	1.91	3.11	-1.96	2.03	0	1	1	0.55	0	2	1	3.86
M2	2.15	2.25	2.89	0.18	2.16	0	0	0	0.55	0	2	0	3.05
M3	2.71	2.19	2.91	-0.41	2.18	0	0	0	0.55	0	2	1	3.32
M4	2.4	2.19	2.91	-0.41	2.12	0	0	0	0.55	0	2	1	3.32
M5	4.2	5.3	4.75	2.31	4.46	0	0	0	0.55	0	3	3	3.6
M6	3.47	5.53	5.86	3.38	4.95	0	0	0	0.55	0	3	3	3.48

and 1a was out of range of the plot (Fig. 4). Monomer M1 was not absorbed and not influenced by brain (outside the Egg), monomers M2, M3, M4, M5 and M6 were well-absorbed but not accessing the brain (in the white). In this connection, if the monomer was speculated as brain-permeant (in the yolk) was not directed to active efflux.

Bioavailability radar

Bioavailability radar plot gave us graphical insight on drug-likeness decisions based on the bioavailability index (Fig. 5).

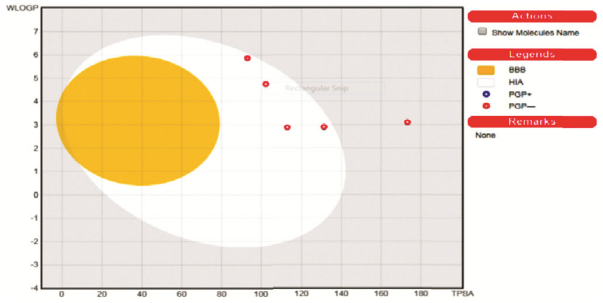


Fig. 4 — BOILED-Egg depiction of curcumin and schiff base diol monomers.

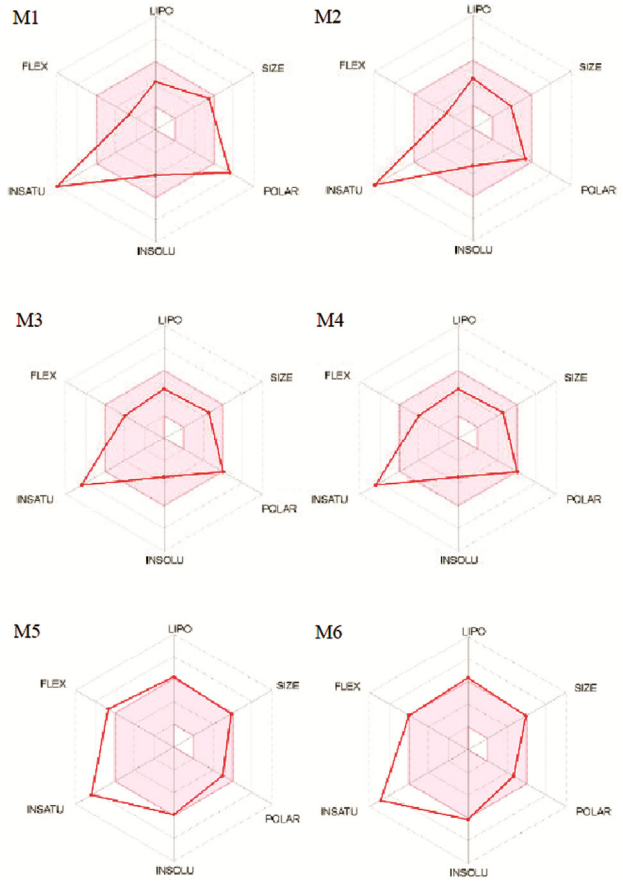


Fig. 5 — Bioavailability radar.

The pink coloured area is the acceptable physiochemical room for oral bioaccessibility and the radar has to drop entirely in the pink zone and is observed to be drug-like[23]. The optimal range of each of the property in the pink area: LIPO (Lipophilicity): -0.7 < XLOGP 3 < +5.0; SIZE: 150g/mol < MW < 500 g/mol; POLAR (polarity):20Å2< TPSA < 130Å2; INSOLU (Insolubility): 0 < Log S (ESOL) < 6; INSATU (Insaturation): 0.25 <Fraction of Csp3 < 1; FLEX (Flexibility): 0 < Num. rotatable bonds < 9.

Molecular docking studies of monomers

The docking outcomes are shown in Table 4. All the monomers have been deeply coherent into the active site of the receptor (Fig. 6). The monomers M2, M3, M5, & M6 are possessed higher binding energy and observe to have lesser affinity for binding with protein targeted and accordingly showed weak inhibition effect on the organism. The ligand molecules and the receptor have lower relative binding energy, so more effective is the binding affinity. The results accomplished from molecular docking studies spotlight that the interaction between the curcumin and schiff base diol monomers and the protein target is vanquished by strong hydrogen bonding, hydrophobic forces and π- interactions. The molecular docking pattern thus, proposes the following monomers M1 and M4 among the 6 monomers as the most propitious to bind with MAPT receptor with powerful binding affinity.

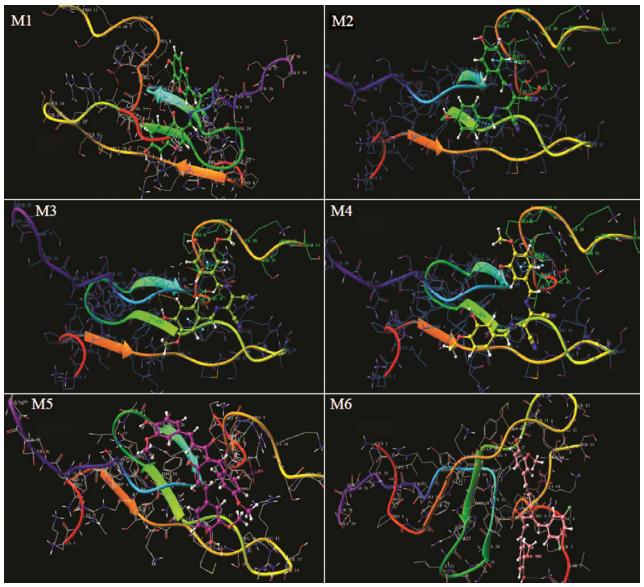


Fig. 6 — Molecular simulations of monomersM1, M2, M3, M4, 5, M6 with the receptor MAPT.

Table 4 — Molecular docking parameters of monomers (M1-M6) with MAPT.

Complexes	Docking score kcal.mol^{-1}	Active sites with a mode of interaction		
		H-bond	π-π stacking	Hydrophobic contacts (Cutoff at 5Å)
M_1	-4.078	ARG A:6 SER B:27	--	PRO 8, ALA 26, VAL 4, VAL 5, SER 27, THR 24, SER 3,
M_2	-2.996	GLU B:30	TRP B:29 TYR B:18	PRO 8, PRO 9, VAL 17, TRP 29, PRO 12, TYR 18, MET 10, TYR 19.
M_3	-2.968	--	TYR B:18 TRP B:29	TYR 19, MET 10, TYR 18, TRP 29, PRO 9, PRO 12, PRO 8, VAL 17,.
M_4	-3.181	TRP B:29 GLU B:30	TRP B:29	PRO 9, PRO 8, TRP 29, VAL 17, MET 10, TYR 18, TYR 19,
M_5	-1.865	TRP B:29 TYR B:18	--	TRP 6, PRO 32, PRO 8, TRP 29, PRO 9, VAL 7, TYR 18, PRO 12,
M_6	-2.994	LYS A:1 ARG B:9 MET B:10	--	VAL 17, MET 10, VAL 4, ALA 26, VAL 5, PHE 20, VAL 2,

Conclusion

Synthesized 6 novel functional monomers of schiff base and curcumin have been exposed to *in-silico* computation of ADME properties using Swiss ADME tool. The complete sets of monomers have moderate water solubility and consequently have good oral absorption and bioavailability. The gastro-intestinal absorption observed for the monomers are high and there is no effect of toxicity at CNS level, owing to non-permeation across the blood-brain barrier. The log P rates of all designed schiff base and curcumin monomers are optimal and consequently have good permeability and oral absorption. The docking results accomplish that the monomers display fine interaction deep inside the receptor sites and revealed bonding and non-bonding interactions with the active residues of the MAPT receptor. Based on the structure, relationship activity of the monomers M1 and M4 shows higher docking score. It reveals that the electron withdrawing pyrone ring in the moiety enhances the reactivity of monomer M1, whereas the methylene substitution which the reactivity of monomer M4. The schiff base monomers M1 and M4 show tough binding affinity to the MAPT and can act as a powerful inhibitor against the organism. The desired set of monomers has been enhanced by effective ADME screening and molecular simulation methods can represent favourable building blocks as better chemotherapeutic factor in resistance to Alzheimer's disease. These studies however help the medicinal chemists to focus on this drug discovery towards the detection of antimycobacterial drugs with upraised repressive potencies.

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