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NSAIDs as potential treatment option for preventing amyloid β toxicity in Alzheimer’s disease: an investigation by docking, molecular dynamics, and DFT studies

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Aggregation of amyloid beta (Aβ) protein considered as one of contributors in development of Alzheimer’s disease (AD). Several investigations have identified the importance of non-steroidal anti-inflammatory drugs (NSAIDs) as Aβ aggregation inhibitors. Here, we have examined the binding interactions of 24 NSAIDs belonging to eight different classes, with Aβ fibrils by exploiting docking and molecular dynamics studies. Minimum energy conformation of the docked NSAIDs were further optimized by density functional theory (DFT) employing Becke’s three-parameter hybrid model, Lee–Yang–Parr (B3LYP) correlation functional method. DFT-based global reactivity descriptors, such as electron affinity, hardness, softness, chemical potential, electronegativity, and electrophilicity index were calculated to inspect the expediency of these descriptors for understanding the reactive nature and sites of the molecules. Few selected NSAID-Aβ fibril complexes were subjected to molecular dynamics simulation to illustrate the stability of these complexes and the most prominent interactions during the simulated trajectory. All of the NSAIDs exhibited potential activity against Aβ fibrils in terms of predicted binding affinity. Sulindac was found to be the most active compound underscoring the contribution of indene methylene substitution, whereas acetaminophen was observed as least active NSAID. General structural requirements for interaction of NSAIDs with Aβ fibril include: aryl/heteroaryl aromatic moiety connected through a linker of 1–2 atoms to a distal aromatic group. Considering these structural requirements and electronic features, new potent agents can be designed and developed as potential Aβ fibril inhibitors for the treatment of AD.

Keywords: amyloid β fibril; molecular docking; density functional theory; NSAIDs; HOMO-LUMO energy; molecular dynamics

1. Introduction
Alzheimer’s disease (AD), named after its inventor Alois Alzheimer, is the most common age-related neurodegenerative disorder characterized by progressive deterioration of memory, cognition, and behavior (Möller & Graeber, 1998). AD represents a major public health concern because an estimated 24 million people worldwide have dementia, the majority of whom are thought to have this disease. As a result of the steady growth of the aging population as well as lack of effective treatment strategies, the prevalence of dementia is expected to further increase in future across all nations (Kumar et al., 2016; Thies & Bleiler, 2013). Amyloid plaques and neurofibrillary tangles are considered as two core pathological hallmarks of AD. According to the amyloid cascade hypothesis, the accumulation of Aβ in the brain is the leading pathological event in AD, which triggers neuronal dysfunction and death (Awasthi, Singh, Pandey, & Dwivedi, 2016). Aβ are small peptides whose aggregates, once accumulated in neuronal cell membranes and dendrites, gradually lead to the development of dementia in AD. There are two types of Aβ peptides namely, Aβ42 and Aβ40, which are produced by sequential proteolytic cleavages of the amyloid precursor protein (APP) by the action of β-secretase and γ-secretases. Aβ42 contains 42 amino acids, whereas peptide of Aβ40 is shorter by two amino acids at the C-terminus (Haass, Hung, & Selkoe, 1991). Both Aβ42 and Aβ40 peptides can exist as monomers inside as well as outside the neuronal cells and can make innumerable types of oligomeric structures such as prefibrils, fibrils and plaques, depending upon the extent of oligomerization (Awasthi et al., 2016). When a number of Aβ peptides are linked together through hydrogen bonds, prefibril of 25–30 Å are formed which is comprised of short β sheets along its width with aligned strands along the length. Accumulation of several prefibrils creates fibrils of 60–80 Å and further aggregation of these fibrils produces plaques.

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which are highly neurotoxic (Masters et al., 1985; Sandberg et al., 2010). Aβ42 is known to oligomerize and aggregate easily as it is more hydrophobic than Aβ40, and the ratio of these two isoforms is influenced by the pattern of cleavage from APP by α, β, and γ secretases (Hardy, 2006; Sandebring, Welander, Winblad, Graff, & Tjernberg, 2013). Tau is a microtubule-associated protein which is major constituent of the neurofibrillary tangles. According to the amyloid cascade hypothesis, changes in tau and consequent neurofibrillary tangle formation are triggered by toxic concentrations of Aβ (Ballard et al., 2011).

Presently, there is no cure for AD, although few medications are available which can temporarily reduce some symptoms or slow down the progression of the condition in some patients. The treatment options include: acetylcholinesterase (AChE) inhibitors (tacrine, donepezil, rivastigmine, and galantamine) and a non-competitive inhibitor of NMDA receptors, memantine. Although these drugs improve the cognitive functions of AD patients symptomatically, they are incapable to modify the disease progression in the long run (Allain et al., 2003). Moreover, they demonstrate limited clinical benefits over the shorter term for few patients, mild to moderate adverse effects in a minority of patients, and disgusting toxicity over the longer term (Schneider, 2013). Supplements such as vitamin E, coenzyme Q10, coral calcium, ginkgo biloba, and huperzine A are anticipated as alternative treatments but the rationale in clinic practice is yet to be ascertained (Azam, 2010). Therefore, owing to the non-availability of safe and effective remedies for AD, several novel therapeutic strategies are being routinely investigated (Chatterjee & Roy, 2016; Eslami, Hashemianzadeh, Bagherzadeh, & Seyed Sajadi, 2016; Gurung, Aguan, Mitra, & Bhattacharjee, 2017; Palakurti & Vadrevu, 2017).

Non-steroidal anti-inflammatory drugs (NSAIDs) are well known for the treatment of several diseases, such as arthritis, fever, and pain. The pharmacological effects of these drugs are largely ascribed to the inhibition of the cyclooxygenase (COX)-mediated synthesis of prostaglandins (PGs) (Rao & Knaus, 2008). Recent findings have disclosed that, in addition to their traditional uses in arthritis and pain, cancer and neurodegenerative diseases such as AD could also be treated with some NSAIDs (Umar, Steele, Menter, & Hawk, 2016; Wang et al., 2015). AD brain is characterized by chronic inflammatory status owing to activated glial cells and increased expression of inflammatory cytokines, chemokines and reactive oxygen species (Dumont & Beal, 2011). Concomitantly, the process of neuroinflammation can be intensified by protein aggregates (mainly formed by extracellular deposition of amyloid-β-peptide) and intracellular neurofibrillary agglomerates (formed by hyperphosphorylated tau protein filaments) (Lloret, Fuchsberger, Giraldo, & Viña, 2015). The association of AD to inflammation suggests that NSAIDs might be beneficial for the treatment of this devastating disorder and therefore, several pre-clinical as well as epidemiological studies have established a link between their usage and disease prevalence (Deardorff & Grossberg, 2016; Townsend & Praticò, 2005). Furthermore, NSAIDs minimize the risk of AD, delay the onset of dementia, decelerate its progression and reduce the severity of cognitive symptoms (Gilgun-Sherki, Melamed, & Offen, 2006). They are capable of altering the conformation of Aβ peptides exerting anti-aggregation activity and inducing the expression of amyloid-binding proteins, e.g. transferrin, that plays an important role in confiscating Aβ peptides and inhibiting their aggregation (Dinarello, 2010; Gasparini, Rusconi, Xu, del Soldato, & Ongini, 2004). Fibrillar β-amyloid deposits co-localize with numerous chronic inflammatory mediators and can activate the microglia in the brain (McGeer & McGeer, 1995).

In structure-based drug design, high-resolution 3D structures of proteins are used to guide the design of compounds that bind tightly to disease-linked proteins and block their deleterious activity which is recognized as a key strategy for translating basic biomedical research into therapeutic compounds (Tiller & Tessier, 2013). More than 20 years ago, this approach was exploited to produce HIV protease inhibitors, and led to several valued antiviral drugs entering the clinical practice years earlier and at a much lower cost than would have otherwise been possible (Wlodawer & Erickson, 1993). Not restricted to antiviral agents, this approach has been used to generate therapeutic agents for a number of human ailments. Molecular docking is a technique commonly used in structure-based drug design which furnishes an understanding about the intermolecular interaction between the ligand molecule and the amino acids present in the active site of receptor protein. Furthermore, it provides information about the molecular conformation, binding mode, binding energy and affinity of the lipid (Azam, Mohamed, & Alhussen, 2015). Computational approaches have been frequently implemented to inspect the effect of innumerable inhibitors on Aβ and fibrils (Awasthi, Singh, Pandey, & Dwivedi, 2017; Dutta & Mattaparthi, 2017; Lemkul & Bevan, 2012; Ngo & Li, 2012; Verma, Kumar, & Deb Nath, 2016). Recognition of the beneficial role of NSAIDs in AD has fascinated drug design and medicinal chemists to optimize these potential leads for controlling Aβ aggregation (Fortin & Benoit-Biancamano, 2016; Hirohata, Ono, & Yamada, 2008; Pasinetti, 2002). In view of this, the present research aims to investigate the interactions of the various NSAIDs with the Alzheimer’s peptide Aβ fibrils by employing molecular docking and quantum chemical calculations.


2. Computational details

2.1. Docking studies

2.1.1. Preparation of the receptor

Three-dimensional (3D) NMR solution structure of amyloid fibril (PDB Code: 2BEG) was downloaded from the protein data bank. As fibrils are the most ordered and rigid among the different forms of Aβ, the NMR determined structure of 2BEG was selected for this study (Lührs et al., 2005). The structure of amyloid fibril is composed of five chains of β amyloid namely A, B, C, D, and E. Distinct from soluble oligomeric species of Aβ, this pentameric structure can be described as a protofibril or a cross-β subunit (Fan et al., 2015; Shea & Urbanc, 2012). The protein is presented in 10 models, but for docking simulation, we have chosen its first model. In this structure, N-terminal residues 1–16 are structurally disordered and is missing from each peptide monomer. The remaining residues 17–42 are most ordered and were suggested to contribute the stability of the mature fibril. Residues 18–26 and 31–42 form two β-strands, β1 and β2, respectively, connected by a U turn spanning four residues, 27–30 (Lührs et al., 2005). All chains of this protein are intact and used in the docking studies (Ali-Torres, Rimola, Rodríguez-Rodríguez, Rodríguez-Santiago, & Sodupe, 2013; Aloisi et al., 2013; Fan et al., 2015; Ngo & Li, 2013). Polar hydrogen and charges were added using MGLTools 1.5.6.

2.1.2. Preparation of the ligands

Two-dimensional (2D) structures of 24 NSAIDs belonging to diverse chemical classes were retrieved from PubChem database (Figure 1). The structures of the ligands were drawn in ChemDraw Ultra 8.0 and converted to their three-dimensional structures in Chem3D Ultra 8.0, energy minimized by PM3 method using MOPAC and saved as pdb format. The prepared ligands were used as input files for AutoDock 4.2 in the next step.

2.1.3. Docking simulation

As amyloid fibril does not have any particular binding or active site and there is not enough information about any specific activity region, we used blind docking approach in which large search space is created which covers the whole protein, to check all possible binding conformations (Kuang, Murugan, Tu, Nordberg, & Ågren, 2015; Kumar et al., 2016; Singh et al., 2014; Verma et al., 2016).

Lamarckian genetic algorithm methodology implemented in AutoDock 4.2 (Morris et al., 1998) program was employed for molecular docking studies and was run for 100 times for each ligand, which generated 100 possible protein-ligand complexes. The standard docking procedure was adopted for a rigid protein and a flexible ligand. A grid box centered on the protein was defined with a dimension of $126 \times 70 \times 80$ Å in $x$, $y$, and $z$ directions, respectively, which is large enough to encompass the whole protein and also leave enough space for ligands to be docked on the surface (Kumar et al., 2016). A grid spacing of 0.375 Å and a distance-dependent function of the dielectric constant were used for the calculation of the energetic map. The default settings were used for all other parameters. The result of molecular docking between amyloid fibril and NSAIDs is summarized in Table 1.

2.1.4. Analysis and visualization of docking simulation results

Conformations showing best docking energy of each clustered family were analyzed for possible interactions between docked NSAIDs and amyloid fibril complexes. Hydrogen bonding and π interactions were visualized in Biovia Discovery Studio Visualizer 4.5 (Accelrys Software Inc.) and PyMol 1.7.4 (The PyMOL Molecular Graphics System) programs. From the estimated free energy of ligand binding ($ΔG_{b\text{inding}}$ kcal/mol), the inhibition constant ($K_i$) for each ligand has been reported (Table 1).

2.2. Molecular dynamics (MD) simulations

The coordinates of the best docking configurations of selected NSAID-Aβ fibrils complexes were subjected to molecular dynamics simulation using Desmond (Bowers et al., 2006; Desmond Molecular Dynamics System, 2016) to inspect the stability of these complexes. Each complex was immersed in an orthorhombic box with ~3900 water molecules using simple point charge (SPC) solvent model and the optimized potential for liquid simulations (OPLS3) force field (Harder et al., 2016) was employed. A suitable number of Na$^+$ counter-ions were used to neutralize the complexes. Isothermal-isobaric (NPT) ensemble class was used with temperature and pressure adjusted to 300 K and 1.01325 bar, respectively. Simulation time was set to 10 ns for each system and the coordinates were saved for every 4.8 ps. A cut-off radius of 9.0 Å was applied for short-range van der Waals and Coulomb interactions. A Nose–Hoover thermostat (Hoover, 1985) and Martyna–Tobias–Klein (Martyna, Tobias, & Klein, 1994) methods were implemented to maintain the temperature and the pressure of the systems, respectively. The RESPA integrator was used with a time step of 2.0 fs (Tuckerman, Berne, & Martyna, 1992) for the overall simulations. The systems were minimized and equilibrated with the default protocols of the Desmond.
2.3. Density functional theory (DFT) calculations

Minimum energy conformation of the docked NSAIDs were optimized by density functional theory (DFT) employing Becke’s three-parameter hybrid model, Lee–Yang–Parr (B3LYP) correlation functional method at 6–311G (d,p) level, using Gaussian09 software program suite (Frisch et al., 2010). DFT-based global reactivity descriptors, such as electron af- finity, hardness, softness, chemical potential, electronegativity, and electrophilicity index were calculated to inspect the expediency of these descriptors for understanding the reactive nature and sites of the molecules. The minimum energy conformer obtained from molecular docking study in the form of pdb format, served as input structure for the DFT calculations.

3. Results and discussion

3.1. Validation of docking protocol

Method validation is an important requirement for any research protocol and hence docking methods should be validated to check the suitability of the employed procedure. Since the crystal structure of amyloid β fibril used in current study is devoid of any co-crystallized ligand (PDB code: 2BEG), we have used crystal structure of ovine COX-1 complexed with ibuprofen (PDB code: 1EQG) to check the accuracy and suitability of AutoDock 4.2 as an appropriate docking tool. For this, the native co-crystallized ligand (Ibuprofen; 2-(4-isobutylphenyl) propionic acid) was re-docked within the inhibitor binding cavity of COX-1. The docked position was compared to the crystal structure position by recording RMSD value.

Figure 1. Chemical structures of the NSAIDs used in present study.
of 1.00 Å. It can be noted that if the best-docked conformation of a ligand resembles the bound native ligand in the experimental crystal structure, the used scoring function is said to be successful (Ahmed et al., 2016; Azam, Amer, Abulifa, & Elzwawi, 2014; Azam, Prasad, & Thangavel, 2012a, 2012b; Hussain, Azam, Ahamed, Ravichandiran, & Alkskas, 2016; Shushni, Azam, & Lindequist, 2013). However, as per the method of validation cited in the literature, the successful scoring function is the one in which the RMSD of the best docked conformation is \( \leq 2.0 \) Å from the experimental one (Wang, Lu, & Wang, 2003). Therefore, the docking protocol of AutoDock 4.2 employed in present study is reliable and can be used to study the drug-receptor interactions (Figure 2).

### 3.2. Docking study of NSAIDs with amyloid β protofibrils

Inhibition of Aβ aggregation represents a viable therapeutic approach in AD (Hayden & Teplow, 2013). A wide range of studies have demonstrated that NSAIDs as well as their derivatives could inhibit β-amyloid fibril formation (Daniels et al., 2016; Hirohata, Ono, Naiki, & Yamada, 2005; Malkki, 2016; Yan et al., 2003). Initially, investigators targeted mainly Aβ40 protein for developing drugs that could inhibit fibril formation. However, it was recognized later that amyloid fibrils are formed through oligomeric Aβ assembly intermediates, which are more toxic than the polymeric fibrils. In addition, the Aβ42 protein passes through a different oligomeric process than Aβ40 proteins, in which protofibril-type oligomers are formed. Consequently, because of superior-amyloidogenic character, Aβ42 is considered as more neurotoxic than Aβ40 (Lesné et al., 2006; Walsh et al., 2005). So, nowadays, the drug

Table 1. Results obtained after docking of NSAIDs with Aβ fibril (PDB code: 2BEG).

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>Drugs</th>
<th>( \Delta G_b )</th>
<th>( K_i^b )</th>
<th>H-bonds</th>
<th>π-interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipyretic (analgesic)</strong></td>
<td>Acetaminophen</td>
<td>−7.45</td>
<td>3.43</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Aryl and hetero-aryl acetic acids</td>
<td>Bromfenac</td>
<td>−12.09</td>
<td>1.38</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Diclofenac</td>
<td>−10.63</td>
<td>16.26</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Etodolac</td>
<td>−11.10</td>
<td>7.25</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Indomethacin</td>
<td>−11.69</td>
<td>2.7</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Nabumetone</td>
<td>−9.79</td>
<td>66.5</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Sulindac</td>
<td>−12.44</td>
<td>0.76</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Tolmetin</td>
<td>−10.92</td>
<td>9.96</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Aryl and hetero-aryl propionic acids</td>
<td>Fenoprofen</td>
<td>−10.49</td>
<td>20.62</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Flurbiprofen</td>
<td>−10.47</td>
<td>21.18</td>
<td>1</td>
<td>4</td>
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<tr>
<td></td>
<td>Ibuprofen</td>
<td>−9.23</td>
<td>172.21</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Ketoprofen</td>
<td>−11.08</td>
<td>7.6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Ketorolac</td>
<td>−10.36</td>
<td>25.67</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Naproxen</td>
<td>−10.46</td>
<td>21.37</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Oxaprozin</td>
<td>−12.04</td>
<td>1.51</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Suprofen</td>
<td>−10.85</td>
<td>11.07</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>N-arylanthranilic acids (Fenamic acids)</td>
<td>Meclofenamic acid</td>
<td>−10.66</td>
<td>1528</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Mefenamic acid</td>
<td>−10.81</td>
<td>11.98</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Selective COX-2 inhibitor</td>
<td>Celecoxib</td>
<td>−11.91</td>
<td>1.88</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Oxicams</td>
<td>Meloxicam</td>
<td>−12.24</td>
<td>1.06</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Piroxicam</td>
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<td>1.85</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Salicylates</td>
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<td>375.92</td>
<td>2</td>
<td>1</td>
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<tr>
<td></td>
<td>Diflunisal</td>
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<td>29.26</td>
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<td>4</td>
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<tr>
<td>Sulfonanilide</td>
<td>Nimesulide</td>
<td>−11.58</td>
<td>3.24</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

\( ^a \)Gibbs free energy of binding (kcal/mol).

\( ^b \)Docking predicted inhibition constant in nM.

\( ^c \)Value given in \( \mu \)M.

Figure 2. The validation of accuracy and performance of AutoDock 4.2. The native and docked ibuprofen is shown as stick in blue and cherry red color, respectively, within the active site of COX-1 exhibiting RMSD of 1.0 Å (PDB code: IEQG).
discovery programs for AD are mainly focused on how to inhibit oligomer formation using Aβ42 as the target (Li, Liu, Lam, Jin, & Duan, 2011). Therefore, we have used NMR-based 3D structure of amyloid β fibril (PDB code: 2BEG) as a suitable target for testing affinity of NSAIDs.

Molecular docking analysis was employed to illustrate the molecular mechanisms/interactions by which NSAIDs can inhibit Aβ1-42 aggregation. After the validation of the docking method, a data-set of 24 compounds, composed of eight different classes of selective and non-selective COX inhibitors was docked into NMR structure of amyloid β protofibrils/fibrils (PDB code: 2BEG). All docked compounds were ranked according to their binding energy and calculated inhibition constant. The most stable conformation of the NSAIDs–Aβ complex was determined as the lowest energy complex with the largest population using the integrated clustering method in Autodock (Morris, Goodsell, Huey, & Olson, 1996; Morris et al., 1998). Conformation having minimum energy obtained from 100 docking runs was visualized in Biovia Discovery Studio and PyMol programs to demonstrate ligand-receptor interactions. The results in terms of binding free energy, predicted inhibition constant, number of hydrophobic as well as hydrophilic interaction are presented in Table 1.

All of the docked NSAIDs belong to aryl/hetero-aryl acetic acid, aryl/hetero-aryl propionic acid, N-arylanthranilic acid (fenamic acid), selective COX-2 inhibitor, oxicam, salicylates, sulfonamide, and antipyretic analgesic classes (Figure 1). All of the in silico tested compounds have shown variable affinities with Aβ fibril occupying same binding region of the receptor (Figure 3). Most active compounds belonging to each class can be ranked as: sulindac > meloxicam > oxaprozin > celecoxib > nimesulide > mefenamic acid > diflunisal > acetaminophen.

Based on experimental findings, role of naproxen and ibuprofen has been highly appreciated in controlling Aβ aggregation (Cole & Frautschy, 2010). Both of these compounds falls under aryl/hetero-aryl propionic acid class of NSAIDs. However, according to our docking results, potency of this class of compounds can be assembled as: oxaprozin > ketoprofen > suprofen > feno-profen > flurbiprofen > naproxen > ketorolac > ibuprofen (Figure 4). Several in vitro experimental studies have confirmed that naproxen and ibuprofen reduce the number of Aβ fibrils upon coincubation with fresh Aβ monomers and destabilize but do not depolymerize Aβ fibrils (Agdeppa et al., 2003; Hirohata et al., 2005). It is evident that these NSAIDs interfere with Aβ fibril elongation (Hirohata et al., 2005). These experiments have also revealed that naproxen has a stronger binding affinity than ibuprofen (Agdeppa et al., 2003), but it has a weaker antiaggregation effect (Hirohata et al., 2005). Likewise, our results also identified naproxen as better agent than ibuprofen in terms of affinity with Aβ fibril. In line with this, chronic prophylactic intake of naproxen moderately reduced the risk of AD in epidemiological studies (Imbimbo, 2009; Vlad, Miller, Kowall, & Felson, 2008). Moreover, naproxen has been shown to reduce the AD risk by 67% in a large-scale clinical trial (Cole & Frautschy, 2010). However, it has also been noticed that naproxen fails to exert any therapeutic effect in pre-existing AD cases (Gasparini, Ongini, & Wenk, 2004). For example, preventive effect of naproxen was established against AD-related alternations in brain microglia in mice models, but failed to reverse existing AD conditions (Varvel et al., 2009).

Fibril extension most probably occurs at the tip of the protofilaments (Luhrs et al., 2005). So, an incoming Aβ monomer could initially bind by means of the adjoining hydrophobic stretch of residues 17–21. The last added Aβ monomer has been reported to be stabilized permanently only by the addition of the next monomer, which suggests a sequence-selective, cooperative mechanism of Aβ fibril extension that follows first-order kinetics (Hayden & Teplow, 2013). In line with this, apparent unidirectional Aβ1–40 fibril growth with a constant slow rate was observed experimentally (Ban et al., 2004). Therefore, this mechanism provides a rationale for the activity of Aβ peptide analog inhibitors comprising the Aβ peptide segment of residues 17–21 (Bieler & Soto, 2004; Gordon, Sciarretta, & Meredith, 2001). These inhibitors presumably bind to the hydrophobic stretch of residues 17–21, and hence, block this site and avert incoming Aβ molecules from extending the fibril (Lemkul & Bevan, 2012). Similarly, in the present study, all of the docked NSAIDs occupied this hydrophobic area belonging to residues 17–21, and hence, might be capable of blocking this site to prevent incoming Aβ molecules from extending the fibril (Figure 3). In addition,
Various experimental and other simulations result also found that the N-terminal is the primary aggregation interface in Aβ fibril growth (Hou et al., 2004; Melquiond, Dong, Mousseau, & Derreumaux, 2008). Consequently, aggregation can be prevented by deleting the residues 14–23 from the Aβ sequence (Tjernberg et al., 1999). Other study with a different implicit solvent model also found the N-terminal to be the primary aggregation interface (Takeda & Klimov, 2008).
Sulindac emerged as the best ligand among the docked NSAIDs (Figure 5), possessing highest probability of inhibiting the aggregation of the Aβ1–42 amyloid peptide. The lowest binding energy of the sulindac–Aβ system was noted as -12.44 kcal/mol of run 83 and having 26 populations in cluster (maximum number). Recently, sulindac sulfide was shown to deplete the pool of toxic oligomers by enhancing the rate of fibril formation in vitro through formation of colloidal particles which catalyze the formation of fibrils (Prade et al., 2016). It was reported that sulindac sulfide-induced aggregates are structurally homogeneous where C-terminal part of the peptide adopts β-sheet structure, but the N-terminus is disordered and sulindac sulfide co-localizes with the Aβ peptide in the aggregate (Prade et al., 2016). A number of studies suggest that three distinct regions of the Aβ monomer, the central hydrophobic core composed of Leu-17 – Ala-21, a turn region formed from Val-24 – Asn-27, and the second hydrophobic region consisting of Gly-29 – Met-35, play important roles in the aggregation process (Nguyen & Derreumaux, 2014). Experimentally, it has been found that sulindac sulfide intercalates specifically between the two β-strands formed in mature Aβ fibrils (Prade et al., 2015). However, direct binding to Aβ monomers (Richter et al., 2010; Yesuvadian, Krishnamoorthy, Ramamoorthy, & Bhunia, 2010) oligomers (Fu et al., 2014) and fibrils [Yesuvadian et al., 2010] has been reported, whereas other reports refute a direct interaction (Barrett, Sanders, Kaufman, Michelsen, & Jordan, 2011).

Ligplot diagram presented in Figure 6 confirms that sulindac inserts specifically between the two β-strands of Aβ fibrils. Leu-17, Val-18 and Phe-19 residues of central hydrophobic core participate in van der Waals interactions with docked sulindac. However, Gly-37 and Val-39 of chain E contribute hydrophobic interaction in terms of hydrogen bonds. Moreover, sulindac sulfide binds to the transmembrane sequence of APP (Botev et al., 2011; Kukar et al., 2008) and this has been reported as an additional mechanism for lowering Aβ1–42 levels (Richter et al., 2010).

Structure-activity relationship based on the docking predicted activity is presented in Figure 7. Most of the compounds belonging to aryl and hetero-aryl acetic acids exhibited appreciable affinity for Aβ fibrils in silico. Sulindac, the highest active drug among the tested NSAIDs, also belongs to this chemical class. Meloxicam and piroxicam of oxicam class achieved second and fifth rank, respectively, bear benzothiazine ring system. More specifically, the SAR can be described as follows: (1) aryl or hetero-aryl ring system of most potent compounds are substituted with Sulfoxide and Sulfone functional groups, e.g. sulindac, meloxicam, piroxicam, nimesulide, and celecoxib; (2) most common hetero-aryl ring includes benzothiazine, indole, pyrrole, pyrazole, oxazole, and thiophene; (3) compounds lacking linker group as well as distal aromatic moiety are very poor performers, e.g. aspirin, acetaminophen and ibuprofen; (4) replacement of linker group and distal aromatic moiety with indene methylene group gave most potent compound, e.g. sulindac; (5) compounds lacking linker and distal aromatic groups and having naphthalene as aryl ring system demonstrated very poor activity, e.g. nabumetone and naproxen; (6) carboxylic group is most commonly substituted in distal aromatic moiety, but is not an absolute requirement; (7) potent compounds possess these linker groups: –O–, –NH–, –CO–, –CH=, and –CONH–, etc.

3.3. MD simulation of NSAID-Aβ fibril complexes

The stability of the docked NSAIDs in the Aβ fibrils was validated by performing MD simulations of the best docked configurations of few promising ligands (ketoprofen, meloxicam, nimesulide and sulindac) using Desmond (Desmond Molecular Dynamics System, 2016). To come within reach of the real physiological situation, MD simulations were performed in water and the system was neutralized with Na+ counter ions, maintaining the salt concentration at 0.15 M. The values of RMSD (Maiorov & Crippen, 1994) with respect to the time evolution are frequently exploited to inspect whether or not a simulated system attains stability. A plot of protein-ligand RMSD with the time progression is presented in Figure 8. RMSD values of protein depicted on left Y-axis is based on all backbone Ca atoms relative to the corresponding starting structures of all trajectories for the simulated NSAID-Aβ fibrils system. RMSD values of ligand shown on right Y-axis indicates how stable the ligand is with respect to the protein and its binding pocket. The plot, ‘Fit lig Prot’ (ligand fitting on protein) shows the RMSD of a ligand when the protein-ligand complex is first aligned on the protein backbone of the reference and then the RMSD of the ligand heavy atoms is measured. In all cases, the RMSD values increased quickly during the first 2–5 ns and then reach plateaus, which imply that the simulated systems achieve stability.

In addition, the plot of root-mean-square fluctuations (RMSF) in the orientation of side chain of each residue and backbone of the protein in the MD trajectory were also calculated and presented in Figure 9. RMSF for most of the residues of all the simulated complexes were within 4.0 Å, but fluctuation for few residues exceeded 4.8 Å in sulindac and meloxicam, and 5.6 Å in case of ketoprofen. The lower atomic fluctuation for residues
and its backbone atoms is due to small conformational changes during the simulation.

Per-residue interaction analysis can be classified into four types: hydrogen-bond, hydrophobic interactions, ionic bonds and water bridges. At the end of the simulation, each system was independently examined based on the average value of the interaction occupancies of the binding site residues. The results in the form of stacked bar plots which were normalized over the course of the trajectory are presented in Figure 10. In the case of sulindac-bound system, approximately 100% of the simulation time C:Leu-17 was involved in the hydrogen bonding with the ligand whereas E:Gly-38 and E:Val-39 were observed to maintain this interaction for less than 10% of the simulation time. Hydrophobic interaction was contributed predominantly by D:Phe-19 and
B:Leu-17, maintaining the contact for nearly 60% of the simulation time. However, it was interesting to note that C:Leu-17 participates in hydrogen bond, hydrophobic interaction as well as water bridges in case of ketoprofen, nimesulide, and meloxicam-bound systems. Bar plot of this amino acid in ketoprofen has shown 120% of the simulation time demonstrating an aggregate of all types of contacts. Contribution of E:Gly-38 was well appreciated in meloxicam-bound system for hydrogen bond and water bridges for more than 80% of the simulation time. In nimesulide-bound system, most pronounced interaction was exhibited by C:Leu-17 in terms of hydrogen bond, hydrophobic, and water bridges for approximately 80% of the simulation time.

3.4. Quantum chemical computations

Energies of the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) are very popular quantum chemical descriptors which describe the reactivity, shape, and binding properties of a complete molecule as well as of molecular fragments and substituents. Concept of HOMO and LUMO has been successfully implemented in explaining the biological activity and molecular properties of the drug molecules (Azam, El-gnidi, & Alkskas, 2010; Latosińska, Latosińska, Maurin, Orzeszko, & Kazimierczuk, 2014). Furthermore, these orbitals play a major role in governing many chemical reactions and are also responsible for the formation of many charge-transfer complexes (Franke, 1984; Ośmilowski, Halkiewicz, Radecki, & Kaliszan, 1985; Zhou & Parr, 1990).

In the present study, minimum energy conformation of docked NSAIDs were further optimized by density functional theory (DFT) employing Becke’s three-parameter hybrid model, Lee–Yang–Parr (B3LYP) correlation functional method (Becke, 1988; Lee, Yang, & Parr, 1988). HOMO is considered as an electron donor, because it is the outer orbital containing electrons. Hence, ionization potential is directly related to the energy of the HOMO. While on the other hand, LUMO can accept electrons and therefore, the LUMO energy is directly related to electron affinity (Fukui, 1982). The delocalization of electrons between HOMO and LUMO is the most important factor in determining the easiness of a chemical reaction. So, they are regarded as the principal orbitals which help in determining the way molecule interacts with other species; for example, drug-receptor interaction (Miertus & Tomasi, 1982). The gap between HOMO and LUMO energies has been used as a simple indicator of kinetic stability. A large HOMO-LUMO gap implies high kinetic stability resulting in low chemical reactivity (Aihara, 1999).
Figure 8. The Root Mean Square Deviations (RMSD) of backbone atoms relative to the starting complexes during 10 ns MD simulation of (a) ketoprofen, (b) meloxicam, (c) nimesulide, and (d) sulindac. Each plot shows the RMSD of protein on left Y-axis whereas ligand RMSD is presented on right Y-axis.
Figure 9. The Root Mean Square Fluctuation (RMSF) of complexes during 10 ns MD simulation of (a) ketoprofen, (b) meloxicam, (c) nimesulide, and (d) sulindac.

Figure 10. Per-residues analysis of the representative NSAIDs, (a) ketoprofen, (b) meloxicam, (c) nimesulide, and (d) sulindac in complex with Aβ-fibril (2BEG). The analysis was based throughout the 10-ns MD simulations. Hydrogen bond, hydrophobic, and water bridge interactions are illustrated by green, purple, and blue lines, respectively.
Investigating mechanism of molecular interaction between NSAIDs and amyloid β fibrils by molecular modeling studies

Using HOMO and LUMO orbital energies, global chemical reactivity descriptors of compounds such as hardness (\(\eta\)), chemical potential (\(\mu\)), softness (\(S\)), electronegativity (\(\chi\)), and electrophilicity index (\(\omega\)) have been calculated as reported previously (Parr, Szentpály, & Liu, 1999; Pearson, 1988) and results are presented in Table 2. Koopmans’ theorem (Koopmans, 1934) states that the ionization potential (\(I\)) and electron affinity (\(A\)) can be expressed through HOMO and LUMO orbital energies as: 

\[ I = -E_{\text{HOMO}} \]

\[ A = -E_{\text{LUMO}} \]

\[ \mu = \frac{E_{\text{LUMO}} - E_{\text{HOMO}}}{2} \]

\[ \eta = \frac{E_{\text{LUMO}} - E_{\text{HOMO}}}{2} \]

According to chemical hardness, large HOMO–LUMO energy gap denotes a hard molecule and small HOMO–LUMO gap signifies a soft molecule. In other words, a molecule with smaller HOMO–LUMO gap is more reactive. The softness is defined as the reciprocal of hardness and hence, the reactivity of a molecule increases with the increase in softness: 

\[ S = \frac{1}{\eta} \]

Parr et al. (1999) have defined electrophilicity index as: 

\[ \omega = \frac{\mu^2}{\eta} \]

which defines a quantitative classification of global electrophilic nature of a compound. They proposed \(\omega\) as a measure of energy lowering due to maximal electron flow between donor and acceptor. The applicability of \(\omega\) has been verified in explaining the toxicity of various pollutants in terms of their reactivity and site selectivity (Parthasarathi, Padmanabhan, Subramanian, Maiti, & Chattaraj, 2003).

The visualization of HOMO and LUMO of few potential compounds is displayed in Figure 11 which reflects the localization of frontier molecular orbitals in representative drug molecules. The positive and negative phases of molecular orbitals are represented in red and green color, respectively. The HOMO of the most potent NSAID, sulindac, is localized on distal aromatic moiety and indene methylene groups, whereas the LUMO is mainly focused on indene moiety having fluoro group as substituent. It was interesting to observe that neither HOMO nor LUMO was located on the acetic acid moiety which means that this group is having least role in the binding with the receptor. HOMO of the least active NSAID, acetaminophen, is mainly centered on aromatic moiety including amide linkage, whereas LUMO is dispersed on phenyl ring only.

Table 2. Results of quantum chemical calculations of NSAIDs by Gaussian program.

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<th>S. No</th>
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<th>Dipole moment (Debye)</th>
<th>LUMO (eV)</th>
<th>HOMO (eV)</th>
<th>Hardness (eV)</th>
<th>Softness (eV)</th>
<th>Chemical potential (eV)</th>
<th>Electronegativity (eV)</th>
<th>Electrophilicity index (eV)</th>
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Figure 11. Visualization of frontier molecular orbitals of (a) acetaminophen, (b) ketoprofen, (c) meloxicam, (d) nimesulide, and (e) sulindac.
4. Conclusion

Based on current molecular modeling studies, we hypothesize that NSAIDs bind to Aβ peptide leading to the blockage of hydrophobic site (residues 17–21) which might prevent incoming Aβ molecules from extending the fibril. Results of MD simulation of selected NSAID-Aβ fibrils system in terms of RMSD, RMSF and per-residue interaction analyses authenticate the stability of the studied complexes throughout the simulated trajectories. General structural requirements for interaction of NSAIDs with Aβ fibril include: aryl/heteroaryl aromatic moiety connected through a linker of 1-2 atoms to a distal aromatic group. Findings of the DFT-based global reactivity descriptors, such as electron affinity, hardness, softness, chemical potential, electronegativity, and electrophilicity index can be exploited to investigate the rationale of drug-receptor interactions of the studied NSAIDs. Considering present revelations, new potent agents can be designed and developed as potential Aβ fibril inhibitors for the treatment of AD.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Investigating mechanism of molecular interaction between NSAIDs and amyloid β fibrils by molecular modeling studies


