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MOLECULAR DOCKING AND ADMET PREDICTION OF COUMARIN DERIVATIVES AS ACETYLCHOLINESTERASE INHIBITORS

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1. INTRODUCTION

Acetylcholinesterase (AChE) hydrolyses acetylcholine at cholinergic synapses with one of the highest turnover rates of any enzyme, and blocking it remains the most established symptomatic approach to Alzheimer's disease. The cholinergic hypothesis grew out of observations that cholinergic neurons in the basal forebrain degenerate early and that cholinergic deficits track with memory loss [1, 2]. Three inhibitors, donepezil, rivastigmine and galantamine, are still prescribed, although the benefit they give is modest and does not alter

Abstract

Coumarins are among the most frequently studied natural-product scaffolds in the search for new acetylcholinesterase inhibitors, and many reports now pair molecular docking with in silico ADMET screening. This narrative review summarises what published work shows about the enzyme's binding gorge, the way coumarin derivatives are docked and scored, and how absorption, brain penetration and toxicity are predicted. Docking poses often agree with measured inhibition, particularly for compounds that span the catalytic and peripheral sites, but scores correlate only loosely with potency. Prediction tools are useful for triage rather than proof. The article reports no new data; limitations and priorities for validation are discussed.

the course of the disease [3, 4]. That gap between a validated target and a limited clinical return explains why medicinal chemists keep producing new cholinesterase inhibitors, and why computational screening

has become a routine first step.

Coumarins (benzo- α -pyrones) attract attention for several reasons. They occur widely in plants, they are small and synthetically accessible, and the fused lactone ring is planar, which suits the aromatic-rich walls of the AChE gorge. Early reports showed that simple natural coumarins and synthetic 3-aryl derivatives inhibit the enzyme, and that some also act on monoamine oxidase or on amyloid aggregation [5, 6, 7]. Reviews of the scaffold describe a large number of substituted series, with activities ranging from micromolar to low nanomolar [7, 8, 9]. Few of these compounds have progressed beyond cell or rodent work, however, so the field depends heavily on predictions made before synthesis.

This review looks at the computational half of that effort, namely molecular docking against AChE and in silico ADMET prediction, as applied to coumarin derivatives. It is a synthesis of published methods and findings. No docking runs, simulations or assays were performed for this article, and no new numerical results are presented. The emphasis is on how much weight each kind of prediction can bear, which software choices matter, where reported docking scores line up with enzyme assays, and what a reader should check before accepting a claim that a coumarin is a promising lead.

The scale of the problem helps to explain the enthusiasm for early computational filters. Analyses of clinical attrition have repeatedly found that poor pharmacokinetics and unexpected toxicity, rather than lack of potency, removed a large share of candidates in earlier decades, and that better early property screening reduced the pharmacokinetic share of failures [10, 11]. Central nervous system programmes face an additional barrier, because a molecule must cross the blood-brain barrier at useful concentrations. An AChE inhibitor that never reaches the brain is of little use in dementia, however elegant its docking pose may look on the screen.

2. TARGET STRUCTURE AND COUMARIN CHEMISTRY

Existing drugs set the benchmark that any new coumarin must beat. Donepezil, rivastigmine and galantamine produce small average gains on cognitive scales in mild to moderate disease, and systematic reviews describe benefits that are statistically reliable but of uncertain importance to individual patients [3, 4]. Their adverse effects follow from cholinergic excess in the gut and heart: nausea, vomiting, diarrhoea, weight loss and bradycardia. A new inhibitor that is more selective for the brain, or that adds a second useful action, would address a real need, whereas a compound that simply repeats donepezil's profile at lower potency has little to offer. The target profile should be defined before any docking run begins.

The first crystal structure of AChE, from the electric ray *Torpedo californica*, revealed a surprise: the active site sits at the bottom of a narrow gorge about 20 Å deep, lined with aromatic residues [12]. The catalytic triad (Ser200, His440 and Glu327 in the *Torpedo* numbering) lies near the base, while a peripheral anionic site (PAS) surrounds the entrance and is formed in part by Trp279 and Tyr70. Crystal structures of human AChE with ligands followed, and they remain the usual templates for docking [13]. Which structure is chosen matters, because the gorge is flexible and a few side chains, notably Trp286 and Phe338 in the human enzyme, adopt different positions depending on the bound ligand.

Donepezil gives the classic illustration. In the *Torpedo* complex it spans the whole gorge, with its benzylpiperidine group stacked against Trp84 in the catalytic site and its indanone group interacting with Trp279 at the peripheral site [14]. Dual-site binding of this type explains why compounds designed to contact both sites often reach strong potency, and it also underlies the interest in the peripheral site as a place where AChE promotes amyloid- β assembly [15]. Docking studies of coumarins repeatedly try to reproduce this arrangement, placing the coumarin core at the PAS and a basic amine side chain toward the catalytic region, joined by a linker long enough to span the gorge.

Substitution pattern largely determines how a coumarin behaves. Reports on 3-substituted

and 7-substituted derivatives suggest that a benzyl-amine or phenyl group at position 3 can place an aromatic ring against the gorge wall and a cationic nitrogen near Trp84, as seen with the lead compound AP2238 [6]. Coumarin 106 and related dyes bind in the gorge with the lactone oriented toward the PAS [16]. Natural products such as scopoletin showed activity through virtual screening that was later confirmed in the laboratory, although their potency was weak compared with synthetic hybrids [17]. Linker length, nitrogen basicity and the presence of hydrogen-bond donors on the benzenoid ring appear again and again as variables that influence potency.

Hybrid design has become the dominant strategy. Chemists join a coumarin to a known cholinesterase pharmacophore, such as the benzylpiperidine of donepezil, a tacrine unit or a carbamate group, and test whether the combined molecule keeps both activities [7, 8]. The rationale is easy to follow when looking at the enzyme gorge, because a single ligand is long enough to reach both ends. The practical cost is molecular size. Hybrids tend to carry molecular weights near or above 450 and several rotatable bonds, which makes the later ADMET step harder, and it is common to see a trade-off between strong docking scores and acceptable oral-drug properties.

Alongside AChE, butyrylcholinesterase (BChE) deserves a mention. BChE activity rises in the advancing Alzheimer brain, as AChE falls, and several coumarin series have been reported with balanced or selective BChE inhibition [3, 8]. The BChE gorge is wider because it carries fewer aromatic residues, so ligands that fit poorly in AChE can sometimes be accommodated. For a docking study this means that selectivity claims need a structure of both enzymes and a consistent protocol applied to each. Studies that dock against AChE alone cannot say anything reliable about selectivity, although the abstract of a paper sometimes suggests otherwise.

3. DOCKING METHODOLOGY

A typical coumarin docking study follows a recognisable sequence. The protein structure is downloaded from the Protein Data Bank

[18], water molecules and the co-crystallised ligand are removed, hydrogens are added and charges assigned. Ligands are drawn, energy-minimised and given plausible protonation states. A grid box is placed around the active gorge, usually centred on the position of the original ligand, and a search algorithm generates poses that are ranked by a scoring function. The widely used programs include AutoDock4, AutoDock Vina and Glide [19, 20, 21]. Libraries of purchasable compounds are commonly obtained from the ZINC database [22], whereas synthetic series are usually drawn by hand.

Ligand preparation is easy to underestimate. Coumarins are neutral heterocycles, but the side chains attached to them often contain amines whose protonation state at physiological pH determines whether a cation- π contact with Trp84 can form at all. Programs assign charges and tautomers by default rules, and these rules can differ between packages [19, 20]. Conformer generation also matters, since a flexible linker can adopt many shapes in the gorge. A reasonable report states the pH assumed, the charge model used and the number of conformers or torsions allowed, because a different choice may alter the best pose and its score by more than the difference between two analogues.

Validation by re-docking is the one step that most studies agree on. The co-crystallised inhibitor is extracted, docked back into its own site, and the root-mean-square deviation (RMSD) between the predicted and experimental pose is calculated. A value below about 2 Å is generally taken as acceptable. The test is useful but limited, because it asks the program to solve a problem whose answer is already encoded in the receptor conformation. Comparative assessments of docking programs and scoring functions found that success in pose prediction varied with the target, and that ranking of different ligands by score was considerably less reliable than reproducing a known pose [23, 24].

Defining the search space is another source of variation. Most studies centre a cubic grid of 20 to 25 Å on the gorge, which is large

enough to allow ligands to extend from the base to the entrance but small enough to keep the search efficient. With AutoDock Vina the exhaustiveness setting controls how thoroughly the space is explored, and low values can miss the global optimum for flexible molecules [19]. A box that is too generous lets compounds settle on the protein surface, away from the active site, where they receive respectable scores for no good reason. Checking that top poses lie within the gorge, and not elsewhere on the enzyme, is a simple protection that few papers describe.

Scoring deserves a more sceptical look. Docking scores are approximations of binding free energy, expressed in kcal/mol, and they omit or simplify entropy, desolvation and receptor flexibility. For AChE, whose gorge is lined with tryptophan and tyrosine residues, scoring functions tend to reward large hydrophobic ligands that make many aromatic contacts. A coumarin hybrid with a higher molecular weight may therefore outscore a smaller and more efficient compound even when measured inhibition shows the opposite. Authors who report ligand efficiency, which divides the score by the number of heavy atoms, give readers a fairer basis for comparison, but such normalisation is still the exception.

Receptor flexibility is a known weakness of rigid-receptor protocols. Several side chains in the AChE gorge move on ligand binding, and the choice between structures bound to donepezil, galantamine or tacrine can change which coumarins appear to fit [13, 14]. Ensemble docking, in which several receptor conformations are used, and induced-fit protocols reduce this problem at greater computational cost. Short molecular dynamics (MD) simulations are increasingly added after docking to check whether the top pose remains stable over tens of nanoseconds [25]. A pose that drifts out of the gorge in simulation is a poor candidate, regardless of how favourable its original score was.

Comparison of docking outcomes with enzyme data relies on the Ellman assay, in which thiocholine released from acetylthiocholine reacts with a chromogenic reagent and the colour change is read at 412 nm [26]. The method is quick, cheap and

widely available, which is the reason that nearly every coumarin paper reports IC_{50} values from it. It is also vulnerable to artefacts. Compounds that absorb near 412 nm, react with the thiol reagent or aggregate in buffer can produce spurious inhibition. Such compounds are sometimes flagged by structural alerts for assay interference [27], and a careful study will report controls that rule them out before comparing assay values with predicted scores.

Software choice is rarely neutral, and the literature offers few head-to-head comparisons on coumarins. Vina is fast and freely available, and it is probably the program behind most of the published coumarin work. Glide is commercial, and it applies a more elaborate empirical scoring scheme with extra precision modes. Reports using more than one program on the same set often find that they agree on the broad binding mode but disagree on the order of the top few compounds. A sensible reading of any single-program result is that it supports a binding hypothesis, while a ranking among close analogues should be treated as provisional until it is checked against assay results.

4. ADMET PREDICTION

Early property screening exists because late failure is expensive. Analyses of clinical attrition from the 1990s showed that poor pharmacokinetics and bioavailability accounted for roughly two-fifths of failures in development, and that this share fell sharply once companies began to measure absorption and metabolism before selecting candidates [10, 11]. Toxicity and lack of efficacy then became the dominant causes. The lesson for academic groups is that computational ADMET screening is not an optional extra tacked onto a docking paper. It is the stage at which many apparently strong inhibitors would have been lost in practice, and so it deserves the same methodological care as the docking itself.

Once docking has shortlisted candidates, ADMET (absorption, distribution, metabolism, excretion and toxicity) prediction is used to decide which are worth synthesising. The first filters are rule-based.

Lipinski's rule of five flags poor oral absorption when a compound has more than five hydrogen-bond donors, more than ten acceptors, a molecular weight above 500 or a calculated logP above 5 [28]. Palm and colleagues showed that polar molecular surface area predicts intestinal absorption of drugs in humans [29], and polar surface area is usually calculated quickly from fragment contributions [30]. Ghose's ranges for lipophilicity and size are also common [31]. These rules were derived for oral drugs in general, not for CNS agents.

Web tools make such calculations routine. SwissADME gives physicochemical descriptors, lipophilicity estimates, gastrointestinal absorption and a set of drug-likeness filters from a SMILES string, while admetSAR and ADMETlab provide regression and classification models for a wider range of endpoints [32, 33]. Simple graphical devices such as the BOILED-Egg plot place compounds in regions of likely gut absorption and likely brain penetration according to lipophilicity and polarity, and knowledge-based property ranges derived from marketed central nervous system drugs give a similar guide for new candidates [34]. Many coumarin papers present this plot as evidence that their compounds cross the blood-brain barrier. It is a quick and sensible screen, but it is a two-parameter model and not a substitute for measured permeability.

For a CNS target the properties required differ from those of an ordinary oral drug. Compounds that reach the brain tend to have lower polar surface area, fewer hydrogen-bond donors and moderate lipophilicity, and a basic centre is acceptable provided it is not too strongly ionised [35]. The multiparameter CNS desirability score developed by Wager and co-workers combines six properties into a single value between zero and six, and marketed CNS drugs cluster at the high end [36]. Applying it to coumarin hybrids is informative, because the larger molecules that dock well often lose points on molecular weight and polar surface area. It remains uncommon in the coumarin literature, despite being easy to calculate.

Distribution to the brain is governed by more than passive permeability. The blood-brain

barrier carries efflux transporters, notably P-glycoprotein, which remove many lipophilic amines before they accumulate, and a compound that looks permeable on the BOILED-Egg plot may still be a substrate [34, 35]. Plasma protein binding adds a further layer, since only the unbound fraction crosses the barrier, and highly lipophilic coumarins bind strongly to albumin. Web tools such as ADMETlab do output predicted P-glycoprotein substrate status, fraction unbound and brain-to-blood partitioning [33], and SwissADME flags substrate status too. Reports that quote all of these values, and not just the single most flattering, give a more balanced picture of the likelihood of CNS exposure.

Metabolism is a particular concern for this scaffold. Coumarin itself is hydroxylated at the 7-position by CYP2A6, and substituted derivatives can be oxidised, demethylated or conjugated, with consequences that depend on substitution [9, 37]. Prediction tools estimate whether a compound is a substrate or an inhibitor of the major cytochrome P450 enzymes, and the output is typically a yes/no flag. Such flags are helpful in spotting drug-interaction risk, which matters in older patients taking several medicines. Computational prediction of metabolism, though, is generally less accurate than prediction of simple physicochemical properties, and experts caution that site-of-metabolism models need to be confirmed with microsomal or hepatocyte experiments [37].

Toxicity endpoints in the web tools include AMES mutagenicity, hERG inhibition, hepatotoxicity and acute oral toxicity in rodents. The predictions are built from training sets of known compounds, and their reliability falls when a query molecule lies far from that chemical space. Some coumarins carry specific concerns. Dicoumarol-type anticoagulants act on vitamin K epoxide reductase, and high exposure to coumarin itself has been linked to liver toxicity in sensitive rodent species [9]. A prediction of low toxicity for a new hybrid is therefore a starting point, not a safety conclusion, and a high-quality paper will say what the model was trained on.

The agreement between different web tools is worth examining. It is common to find that two programs give the same absorption class for a compound but different values for water solubility, plasma protein binding or clearance. Most tools were trained on overlapping public data sets, so concordance does not amount to independent confirmation. Authors sometimes report only the output that looks favourable, and select the tool that gives it. A transparent report would give values from at least two sources, state the version and date, and note where they differ. Reviewers of computational papers can easily request this, though they do so only occasionally.

5. PUBLISHED FINDINGS FOR COUMARIN DERIVATIVES

Taken as a body of work, published docking studies of coumarins report consistent binding themes. The coumarin core is repeatedly placed at the peripheral site, where it forms π - π stacking with Trp279 and sometimes hydrogen bonds with Tyr70 or Tyr121, while a protonatable nitrogen in the side chain forms cation- π contacts with Trp84 deeper in the gorge [6, 7, 8]. These descriptions are compatible with crystal structures of donepezil and with kinetic studies that classify many coumarins as mixed-type inhibitors [6, 14]. A summary of representative studies and what they report is given in table 1, and the grouping of that evidence by approach is shown in fig. 1.

Table 1: Representative published work on coumarin derivatives, docking and ADMET screening for AChE inhibition

Study type approach	Reported finding	Ref.
3-Aryl coumarin with benzylamine chain AP2238 series	Modelled across the gorge; inhibited AChE and AChE-induced amyloid aggregation, mixed-type kinetics.	[6]
Coumarin 106 dye scaffold	Inhibited AChE; docking placed the lactone ring toward the peripheral site.	[16]
Scopoletin and scopolin natural coumarins	Virtual screening predicted activity later confirmed in vitro; potency weaker than synthetic hybrids.	[17]

Study type approach	Reported finding	Ref.
Coumarin-based dual inhibitors AChE and MAO	Single scaffold reported to act on both enzymes, supporting multi-target design.	[5, 7]
AutoDock4 and Vina docking programs	Widely used and free; reproduce known poses but rank close analogues unreliably.	[19, 20, 23, 24]
Glide commercial docking	Empirical scoring with extra-precision mode; good pose accuracy in published tests.	[21, 24]
SwissADME and egg plot web tools	Rapid physicochemical and permeation screening; brain-penetration estimate; CNS property ranges.	[30, 34]
admetSAR and ADMETlab web tools	Broad models for metabolism and toxicity; reliability depends on chemical space of training data.	[32, 33]
CNS desirability scoring multiparameter	Combines six properties; large hybrids often lose points on size and polarity.	[35, 36]
Ellman assay enzyme test	Standard colorimetric check of predicted inhibitors; open to optical and aggregation artefacts.	[26, 27]
Re-docking and MD pose checks	RMSD under about 2 Å and stable simulations raise confidence in poses.	[23, 25]

The relationship between docking score and measured inhibition has been examined less often than the headline claims suggest. When congeneric series are tested, correlation coefficients between predicted binding energy and pIC_{50} are often modest, and sometimes absent. This is unsurprising, since a small difference in the assay can reflect a difference of only a few tenths of a kcal/mol, which lies well within the error of the scoring function [23, 24]. The more defensible use of docking is qualitative: does the compound adopt a sensible pose, make contact with the residues known to matter, and avoid steric clashes? Ranking is a secondary benefit.

Structure-activity patterns reported across series are broadly consistent. Substitution at position 7 of the coumarin ring, often with an alkoxy linker that carries an amine, repeatedly gives the most potent compounds, because it

directs the basic group toward the catalytic region [7, 8]. Substitution at position 3 or 4 with an aryl group strengthens contact with the peripheral site, while methoxy or hydroxy groups on the benzenoid ring add hydrogen-bond opportunities. Bulky groups close to the lactone carbonyl tend to reduce activity. Because many reviews draw on the same limited number of series, these generalisations rest on fewer independent data sets than their frequency of repetition would suggest [9].

Several reports describe a good match between predicted and measured behaviour. In the AP2238 work, the 3-aryl-coumarin with a benzylmethylamine side chain was modelled in the gorge and later shown to inhibit both AChE and AChE-induced amyloid aggregation, in line with the proposed contact at the peripheral site [6]. The virtual screening of natural products that identified scopolin and scopoletin predicted activity before it was confirmed in an enzyme assay, so the computational step contributed to the discovery rather than just describing it afterwards [17]. These prospective successes carry more weight than retrospective fits to existing data.

There are also cautionary examples. Studies of coumarin derivatives with extended hydrophobic substituents have found docking scores that look excellent while enzyme inhibition is weak, an outcome that tends to arise when the ligand is poorly soluble or aggregates in the assay buffer. Others report predicted activity for compounds that were then shown to act on a different enzyme. Alerts for assay-interfering substructures help here, because some coumarin motifs, such as catechol-substituted or highly conjugated derivatives, can trigger them [27]. The existence of these cases is a reminder that docking identifies compounds that could bind, and the assay decides whether they do.

A further pattern concerns the pairing of docking with ADMET output. Reports often claim that a lead is both strongly bound and drug-like. When the property data are read closely, the compounds with the best scores are frequently the heaviest and most lipophilic, and they are the ones most likely to breach one or more of the rules mentioned

earlier [28, 29, 36]. The compromise is usually a mid-sized coumarin with a short linker and a single basic centre. This pattern matches what is known from successful cholinesterase inhibitors: donepezil itself has a molecular weight below 400 and good brain exposure, and it was not the product of maximising any one score [3, 14].

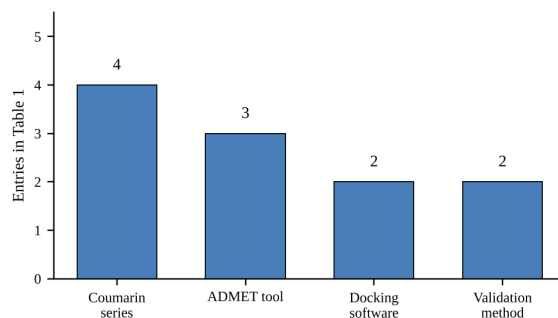


Fig. 1: Number of entries in table 1 by approach

Reproducibility is the final consideration in this section. A docking study can be repeated by others only if the structure identifier, grid dimensions, protonation protocol, software version and scoring settings are given. Many papers state a few of these and omit the rest. Those that deposit input files and coordinates in a repository are still rare. Without them a reader cannot tell whether a reported score of, say, -10 kcal/mol is robust or the result of one fortunate grid placement. Journals could do much to improve the position by requiring a short methods checklist, and several now do, though practice is uneven.

6. LIMITATIONS AND FUTURE DIRECTIONS

The principal limitation of the evidence is that most of it is computational and retrospective. Docking and ADMET tools are inexpensive, so many series are published with predictions alone or with a single assay, and independent replication is unusual. Publication bias is probable, since negative docking results are seldom reported. The training sets behind web ADMET models are mostly drug-like synthetic molecules, and natural-product-like coumarins may fall outside their applicability domain [33, 37]. Consequently, a reader should treat a favourable *in silico* profile as a reason to test the compound, and nothing more.

Comparing potencies between laboratories is also hazardous. Enzyme source varies, with many early studies using electric eel AChE and later ones using recombinant human enzyme, and the two differ in sensitivity to some inhibitors [13, 26]. Substrate concentration, pre-incubation time, buffer pH and the reference compound all alter an apparent IC_{50} . Docking papers frequently place their own assay values beside literature values for other coumarins measured under other conditions and draw conclusions from the ranking. Careful authors include donepezil or galantamine as an internal standard in each run, so that results can be expressed relative to a drug whose behaviour is well documented [7].

Priorities for better practice are fairly clear. Protocols should include re-docking validation, a decoy or known-active test that shows the program can separate binders from non-binders, and some form of flexibility handling or MD check [23, 25]. Selectivity claims need parallel docking against BChE and a counter-screen. For brain penetration, a CNS-specific score and, ideally, a parallel artificial membrane permeability assay should supplement the web output [35, 36]. Studies might also move beyond potency to consider residence time, interaction with amyloid and tau pathology, and metabolic stability, since these are the properties that separate laboratory curiosities from compounds worth taking forward.

The clinical context is shifting as well. Pipeline surveys show that most late-stage Alzheimer programmes now target amyloid, tau or neuroinflammation, with cholinesterase inhibitors mainly used as the comparator or as one arm of a multi-target design [38]. This favours coumarins that act at more than one target, for instance AChE together with monoamine oxidase or amyloid aggregation, provided each activity is genuinely demonstrated [5, 6]. Computational work that treats multi-target binding with the same rigour applied to AChE alone, including separate validated protocols for each protein, would add the most. Until then, a docking score is a hypothesis and should be described as one.

7. CONCLUSION

The published evidence supports a cautious but positive view of coumarins as a source of AChE inhibitors. Docking consistently places the planar lactone core at the peripheral site and, in better designed hybrids, an amine-bearing side chain close to the catalytic site, matching what crystal structures of donepezil would lead one to expect [6, 12, 14]. Prospective examples show that the method can help find real inhibitors [17]. At the same time, scoring functions rank close analogues poorly, and agreement between score and potency is weaker than many abstracts imply [23, 24]. Taken at face value, many of the best-scoring compounds would need further optimisation before they could be considered as candidates. Hybrid molecules in particular show how potency and drug-likeness pull in different directions.

ADMET prediction contributes a sensible filter but not a verdict. Rule-based and web-tool outputs flag obvious problems, yet brain penetration, metabolism and toxicity all need laboratory confirmation, and the largest hybrids often fail the very criteria that matter in a CNS drug [28, 36, 37]. Better validated protocols, transparent reporting of software and versions, and early experimental follow-up would raise the value of this literature considerably. Coumarins remain worth pursuing, particularly where multi-target activity can be demonstrated, but computational promise should be reported as promise only [38]. That discipline protects readers from over-interpreting early results. Researchers who report their methods fully, share input files and test a few prioritised compounds in assays soon after docking will leave a more durable record than those who publish long lists of scores alone [23].

8. ABBREVIATIONS

AChE-Acetylcholinesterase,
 BChE-Butyrylcholinesterase,
 ADMET-Absorption, distribution, metabolism, excretion and toxicity, PAS-Peripheral anionic site, RMSD-Root-mean-square deviation, MD-Molecular dynamics, CNS-Central nervous system, CYP-Cytochrome P450, IC_{50} -Half-maximal inhibitory concentration, SMILES-Simplified molecular-input line-entry system, MAO-Monoamine oxidase

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

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