Off-target interaction of the amyloid PET imaging tracer PiB with acetylcholinesterase

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Keywords: *in silico* studies; computational analysis; Alzheimer's disease; molecular dynamics; molecular docking; amyloid, tau

Abstract

Pittsburgh compound B (PiB) is a widely used Positron Emission Tomography (PET) tracer for detecting amyloid-β (Aβ) deposits in Alzheimer's disease (AD). While PiB is assumed to bind selectively to Aβ, emerging evidence suggests off-target interactions that may complicate PET signal interpretation. Here, we report that PiB can interact with acetylcholinesterase (AchE), a key enzyme in the cholinergic system. Similarity screening identified the AchE ligand thioflavin T (ThT) as the top structural analog of PiB. Docking studies and molecular dynamics simulations showed that PiB stably binds the peripheral anionic site (PAS) of AchE, with binding energies comparable to ThT and clinically relevant AchE inhibitors. *In vitro* fluorescence-based assays confirmed this interaction and suggest an involvement of the PAS. These findings indicate a stable off-target interaction between PiB and AChE with implications for interpreting PiB-PET signals in AD, particularly in regions with altered AchE expression or under AchE inhibitor therapy.

Positron emission tomography (PET)-based biomarkers are largely employed in research and clinical settings for disease diagnosis and monitoring, patient stratification, or as an efficacy outcome of interventions [1]. In Alzheimer's disease (AD), PET tracers have been developed to quantitatively detect changes in the accumulation of key pathological markers, like cortical amyloid-β (Aβ) deposits, hyperphosphorylated tau (p-tau) protein buildup, and neurodegeneration [2,3]. Alterations in these biomarkers mirror disease progression and are the "gold standard" for diagnosing AD and for the early detection of people at-risk of developing the condition [4,5]. The shift from a clinical- to a biomarker-based definition of AD is also at the basis of the "ATN research framework", a biological definition of the disease (i.e., 'A' – amyloid, 'T′ – tau, and 'N′ – neurodegeneration) aimed at offering a quantifiable and unbiased staging of AD [4]. The approach is relevant since the pathological alterations of AD can occur and are detectable long before the onset of cognitive and behavioral symptoms [6,7]. Early identification of individuals in the very early stages of the condition represents a transformative step for the effective development and targeted implementation of disease-modifying interventions.

Alterations of Aβ levels are widely recognized as one of the earliest molecular changes that can foreshadow the onset of AD pathology, although the specific contribution of Aβ to disease pathogenesis is debated [8,9]. Quantitative assessment of Aβ is either performed in biological fluids like liquor and plasma, where decreases in Aβ abundance reflect the cerebral deposition of the peptide, or by PET-based imaging, where specific radioligands are employed to detect the presence of fibrillar Aβ (fAβ) aggregates in the brain. Several Aβ radiotracers have been developed since the early 2000s with Pittsburgh compound B (^{11}C-PiB), a thioflavin T (ThT) analog, being the first of this class of imaging agents. The short half-life of ^{11}C-PiB led to the development of fluorine-18 derivatives more suitable for clinical applications, like ^{18}F-

flutemetamol or the trans-stilbene-based compounds ^{18}F-florbetapir and ^{18}F-florbetaben. Nevertheless, ^{11}C-PiB is still broadly adopted in clinical research settings.

Although these radioligands are widely employed for the diagnosis of AD and for monitoring target engagement of Aβ-targeting interventions, doubts have been cast on their specificity and sensitivity [10–13]. Previous studies demonstrated that 2-aryl-6-hydroxybenzothiazole-based tracers can effectively bind to off-target molecules, like sulfotransferases, that likely contribute to PET signals unrelated to the overall Aβ load [10,12]. However, it is unclear whether this class of Aβ radioligands has additional off-target effects.

This study aims to investigate PiB binding characteristics at the molecular level and, by employing unbiased *in silico* screening, docking calculations, molecular dynamics (MD) simulations, and *in vitro* assay, we surveyed for potential novel binding partners unrelated to Aβ pathology.

To identify potential off-target partners of Aβ PET tracers, we performed an unbiased screening of biologically relevant molecules that show structural similarity with PiB by employing the SwissSimilarity 2021 Web Tool. Our analysis returned the score of 400 molecules (Fig. 1A and Supplementary chart 1) with ThT being the top-scoring molecule (score 0.996). More importantly, ThT was identified because the molecule is a ligand for acetylcholinesterase (AchE) in the Protein Data Bank (PDB ID: pdb_00002j3q). To test the hypothesis that PiB interacts with AchE, we performed docking studies within the AchE pocket using the crystal structure of the human AchE (PDB ID: pdb_00004ey7). AchE has two binding sites: the catalytic site and the peripheral anionic site (PAS) [14,15]. We focused on the latter, located at the entrance of the catalytic gorge, since it mediates the interaction of AchE with ThT [16–18]. Analysis of docking results shows that PiB has binding energy comparable with that of ThT (8.603 and

8.771 kcal/mol, respectively; Fig. 1B). Binding energy of clinically approved AchE inhibitors (donepezil, galantamine, and rivastigmine) was calculated for comparison (Fig. 1B). Fig. 1C and D show the two- and three-dimensional poses and the interaction of PiB with the amino acid residues in the AchE PAS. PiB forms a π–π-sulfur interaction with residue Phe297 along with several hydrophobic, alkyl, and Van der Waals interactions with residues Trp86, His447, Tyr337, Phe338, Tyr72, Trp286, Phe295, Tyr341, and Tyr124 (Fig. 1C, D).

We further investigated the PiB-AchE complex by performing a 300 ns molecular dynamics (MD) simulation. Analysis of the energy of binding shows that PiB maintains a high and stable binding energy throughout the simulation (Fig. 1E). The stability of the PiB-AchE complex is also supported by the root mean square deviation (RMSD) analysis of the ligand movement after superimposing the molecule on the enzyme structure (Fig. 1F). After a stabilization phase, the ligand remains within the AchE PAS. The compound exhibits only a few modest, sharp fluctuations that return to baseline levels during the simulation (Fig. 1F). We attribute the stability of the complex to the sulfur interaction, along with the dense network of hydrophobic interactions that keep PiB within the AchE PAS.

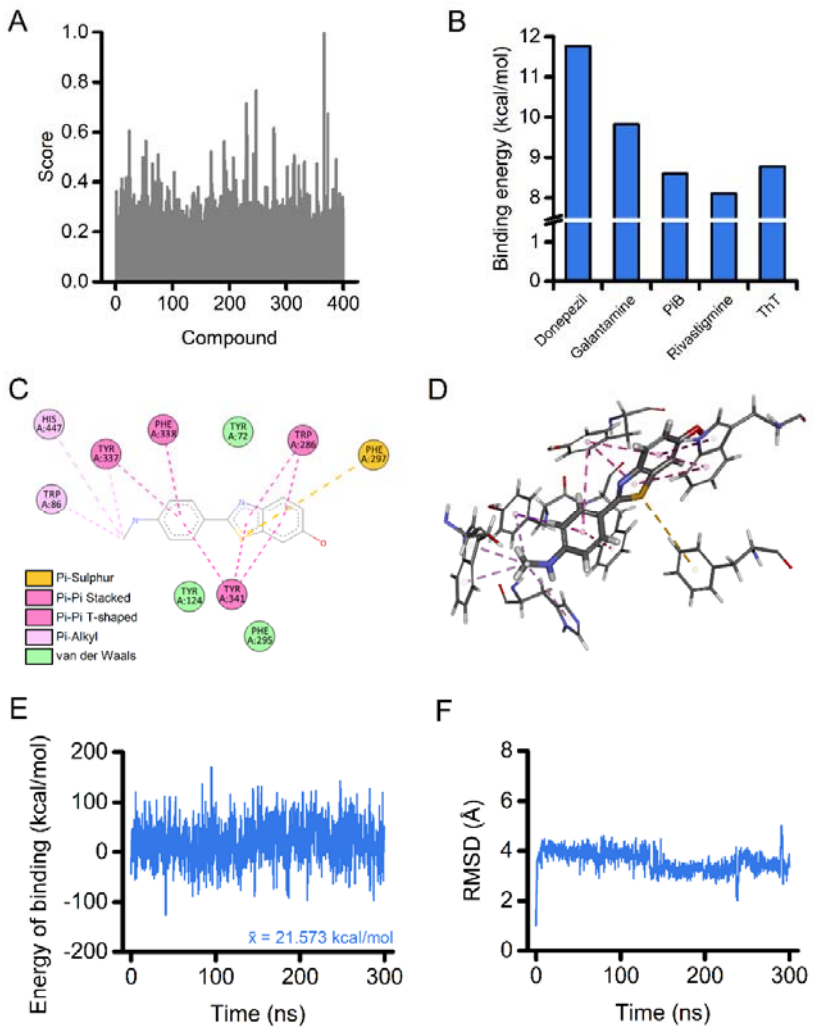

Figure 1. Identification and *in silico* characterization of AchE as a potential target of PiB. (A) The plot illustrates the similarity score of each compound screened with the SwissSimilarity 2021 Web Tool. (B) The histogram depicts the binding energy calculation of the listed ligands after docking on AchE. (C - D) Two-dimensional (C) and three-dimensional (D) docking poses and interactions of PiB in the AchE PAS. The dashed yellow line indicates π–π-sulfur interaction; dashed pink lines indicate π–π-alkyl interactions; magenta lines indicate π–π and T-shaped interactions; green residues show van der Waals interactions. (E - F) Time course of

energy of binding (E) and root mean squared displacement (RMSD; F) for the PiB-AchE complex over a 300 ns MD simulation.

To determine whether PiB forms a stable complex with AchE *in vitro*, we leveraged the intrinsic spectroscopic properties of the compound. The molecule displays an absorbance and an emission maximum at 348 and 432 nm, respectively (Fig. 2A). We measured the fluorescence signal of PiB after incubation with or without AchE from *Electrophorus electricus* (eeAchE), followed by size-exclusion filtration to remove unbound ligand. Samples incubated with eeAchE retained a significantly higher fluorescence signal when compared to the PiB sample alone, indicating PiB binding to the enzyme (Fig. 2B and C). The specificity of this approach was confirmed by performing a similar set of experiments in which PiB was incubated with bovine catalase, an enzyme that shares with eeAchE a tetrameric structure and a similar molecular weight (Fig. 2D and E).

To further evaluate PiB binding to the PAS of eeAChE, we performed propidium iodide (PI) displacement, an assay used for probing the interaction of candidate drugs with the PAS of AchE [19]. The binding of PI to the PAS increases dye fluorescence. Meanwhile its displacement by PAS-interacting compounds leads to signal reduction [20]. In the presence of 20 μM PiB, PI fluorescence was reduced by approximately 15% compared to control conditions (Fig. 2F). Although this difference did not reach statistical significance (P = 0.10), the data suggest a potential trend toward PI displacement. The reduction increased to ≈ 78% in the presence of the high-affinity, PAS-binding AchE inhibitor donepezil (20 μM; Fig. 2F) [14,21].

Together, these findings support the formation of a stable PiB–eeAchE complex *in vitro* and are consistent with the possibility that PiB interacts with the PAS of the enzyme.

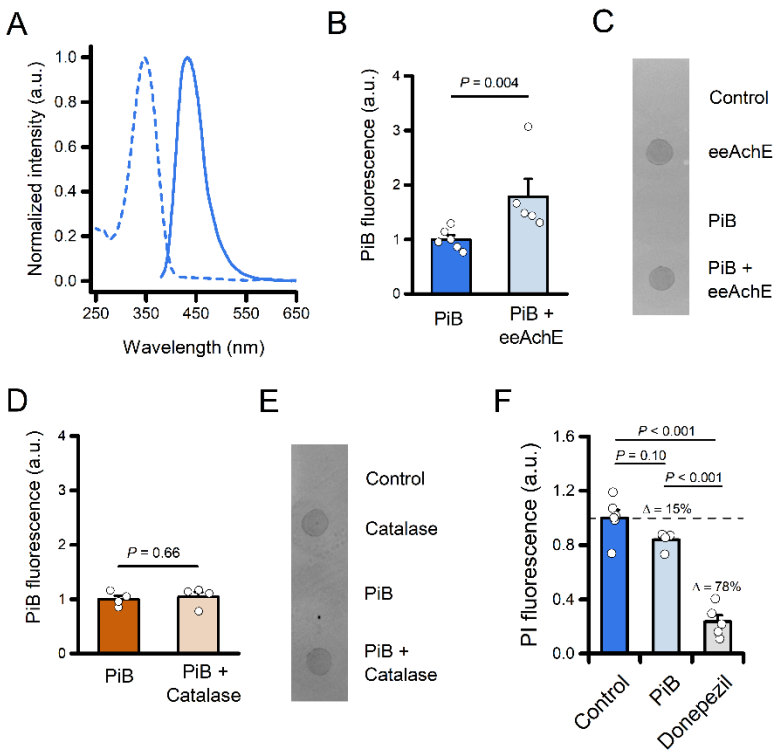

Figure 2. Experimental validation of the formation of the PiB-eeAchE complex. (A) Absorption (dashed line) and emission (solid line) normalized spectra of PiB in KPi buffer (pH 7.4). (B) The bar graph depicts normalized fluorescence of PiB following incubation of the compound with or without eeAchE (2 µg) and size-exclusion filtration (PiB n = 6 and PiB + eeAchE n = 5 independent experiments). (C) Ponceau S staining of the retentate was spotted onto a nitrocellulose membrane to assess protein recovery. (D) The bar graph depicts normalized fluorescence of PiB following incubation of the compound with or without Catalase (2 µg) and size-exclusion filtration (PiB n = 4 and PiB + Catalase n = 4 independent experiments). (E) Ponceau S staining of the retentate was spotted onto a nitrocellulose membrane to assess protein recovery. (F) The bar graph depicts normalized fluorescence of PI following incubation with eeAchE in the presence of vehicle (Control; 0.8% DMSO), PiB (20 µM, 0.8% DMSO), or Donepezil (20 µM, 0.8% DMSO). Note the ≈ 15% signal reduction in the presence of PiB. In B

and D, the comparison of mean values was assessed by the Mann-Whitney U Test. In F, mean values were compared by one-way ANOVA followed by Tukey's post-hoc test.

In this study, we provide computational and experimental evidence that the amyloid PET tracer PiB can bind AchE, suggesting a previously unrecognized off-target interaction. Our findings extend prior observations that ThT-based compounds may interact with non-amyloid targets and raise important questions on the specificity of PiB and related PET tracers used in AD research and diagnostics [16].

Our *in silico* similarity screening identified ThT – a known AchE ligand – as the compound most structurally related to PiB among biologically relevant molecules in the PDB, pointing to a potential interaction between PiB and AchE. We further tested this hypothesis using molecular docking and MD simulations. Docking results showed that PiB binds the PAS of AchE with binding energy comparable to ThT and within the range of clinically relevant AchE inhibitors. PiB establishes π–sulfur and hydrophobic interactions with residues located in the PAS and near the gorge of the active site, like Phe297, Trp286, Tyr337, and His447. These residues were found to be key for the interaction with AchE-targeting drugs [14]. MD simulations further confirmed the persistence of these interactions, indicating a stable and energetically favorable complex.

We validated the computational predictions with a binding assay that exploits the intrinsic fluorescence properties of PiB, supporting the formation of a stable PiB–AchE complex *in vitro* and suggesting that the interaction occurs at the PAS of the enzyme. It is important to notice that a more thorough investigation of the interaction between PiB and AchE was hampered by both the physicochemical properties of PiB and the sensitivity of AchE to PiB-compatible solvents. We found that in conditions suitable for the AchE enzymatic assay, PiB began to precipitate at

concentrations above 25 μM (Supplementary Fig. 1B). The use of alternative solvents or surfactants was unsuccessful (unpublished observations). Moreover, higher concentrations of DMSO were shown to substantially impair AchE activity [22]. In a further attempt to directly examine PiB-PAS interaction, we also tested an *in vitro* competition assay in the presence of donepezil [14,21]. However, preliminary control experiments showed a substantial spectral overlap between PiB and donepezil (Supplementary Fig. 1B), making fluorescence-based comparisons difficult to interpret and prone to bias. While these technical constraints limit our ability to perform orthogonal or competitive binding assays, they do not undermine the core observation that PiB interacts with AchE, as suggested in our fluorescence-based filtration assay and PI displacement.

The identification of AChE as a potential off-target of PiB has several implications. First, it imposes the need to carefully interpret PET signals in brain regions where AchE is abundantly expressed, particularly in early-stage or atypical AD presentations, where amyloid deposition may not be the unique contributor to the tracer uptake. Second, given that AchE expression and activity can change in the aging brain and neurodegenerative conditions beyond AD [23,24], the off-target binding of PiB to AchE could contribute to false positives or elevated baseline signals in specific populations. Third, the PiB signal could be influenced by the use of AchE inhibitors that act by binding the PAS of the enzyme, leading to false negative results. Moreover, the high lipophilicity of PiB could also explain the elevated retention of the tracer in lipid-enriched white matter regions [25,26].

Our findings align with previous reports of off-target binding for other radiotracers used in AD, for whom interactions with enzymes like monoamine oxidases and sulfotransferases have

been reported [10,11,27]. In addition, our similarity virtual screening does not rule out the existence of additional PiB binding partners.

To our knowledge, this is the first study to indicate an interaction between PiB and AchE at both the computational and experimental levels. While the functional consequences of this binding remain to be explored, such interactions may alter AchE activity or affect PiB signals *in vivo*. Further studies using radiolabeled PiB and AchE inhibitors *in vivo* are warranted to confirm whether this interaction occurs under pathophysiological conditions and contributes to PET signals.

In conclusion, these results underscore the importance of integrative approaches combining computational modeling with biochemical validation to uncover and assess the biological relevance of such interactions.

Materials and methods

Reagents and chemicals

PiB was purchased from TargetMol. eeAchE, catalase from bovine liver and all the other chemicals were from Sigma-Aldrich.

Library screening

Similarity screening for the PiB amyloid PET tracer was performed with the SwissSimilarity 2021 Web Tool (http://www.swisssimilarity.ch/ [28,29]) on August 3, 2024. The search was limited to ligands present in the Protein Data Bank (LigandExpo; 19500 compounds) using a consensus

2D/3D screening using a score based on both FP2 Tanimoto coefficient and Electroshape-5D Manhattan distance [28]. Screening scores and SMILES notations were downloaded for further analysis.

Molecular modeling

All the molecules investigated in this study were downloaded as three-dimensional conformer .sdf files from PubChem [30]. The Energy Minimization Experiment function, using YASARA AutoSMILES for automatic force field parameter assignment, was used to optimize the 3D structure before docking.

Docking calculations were performed using VINA default docking parameters as implemented in the YASARA suite, as previously described [31]. Briefly, the crystal structure of the target protein was downloaded from the PDB (PDB ID: pdb_00004ey7), a cell encompassing all atoms extending 5 Å from the surface of the structure of the ligand was generated, and the crystallized ligand was removed. Global ligand docking was performed using VINA using the default parameters and further refined with VINA Local Search [32].

The molecular dynamics simulations of the acetylcholinesterase complexes were run with the same YASARA suite [33] by employing the macro *md_runfast*. A cuboid periodic simulation cell extending 20 Å from the protein surface was set and filled with water (density: 0.997 g/mL). The setup included an optimization of the hydrogen bonding network [34] to increase the solute stability, and a pKa prediction to fine-tune the protonation states of protein residues at pH 7.4 [35]. NaCl ions were added at a physiological concentration of 0.9%. After steepest descent and simulated annealing minimizations to remove clashes, the simulation was run for 300 nanoseconds using the AMBER14 force field [36] for the solute, GAFF2 [37] and AM1BCC [38] for

ligands and TIP3P for water. The cutoff was 8 Å for Van der Waals forces [39], no cutoff was applied to electrostatic forces (using the Particle Mesh Ewald algorithm) [40]. The equations of motions were integrated with a multiple timestep of 2.5 fs for bonded interactions and 5.0 fs for non-bonded interactions at a temperature of 298K and a pressure of 1 atm (NPT ensemble) using algorithms described previously [41]. MD conformations were recorded every 250 ps. The energies of binding and the MD trajectory have been calculated using the *md_analyzebindenergy* macro implemented in the YASARA suite employing the MM/PBSA method as previously described [42]. Ligand movement RMSD was calculated with the YASARA *md_analyze* function after superposing on the receptor.

PiB spectra

A 20 µM PiB (0.8 % DMSO final concentration) solution was prepared in a 100 mM potassium phosphate buffer solution (KPi, pH 7.4). Absorbance spectrum was measured by employing a PerkinElmer Lambda 35 spectrophotometer (Range: 200 – 900 nm; slit: 2nm; resolution: 1 nm; speed: 240 nm/min). Fluorescence emission spectrum was measured with a BioTek Synergy H1 plate reader (Ex λ: 350 nm; Em range: 380 – 700 nm; resolution: 1 nm; gain: 60 a.u.).

Turbidity assay

The turbidity assay was performed as previously described [43]. In brief, the absorbance of increasing concentrations of PiB (1.56 µM to 1600 µM) was measured at 405 nm using a PerkinElmer SPECTRAmax 190 microplate reader. Absorbance readings from the buffer alone

(KPi containing 0.8% DMSO) served as reference. The purpose of the assay was to determine the highest PiB concentration that does not result in precipitation of the compound.

Fluorescence-based interaction assay

A fluorescence-based binding assay was performed to assess the potential interaction between PiB and eeAchE. PiB (25 µM final concentration; dissolved in 100mM KPi, 0.1 % DMSO) was incubated *in vitro* either in the presence or absence of 2 µg of eeAchE in a total volume of 50 µL. Incubations were carried out for 5 hours at 30 °C under gentle agitation (1100 rpm). Following incubation, each mixture was filtered using Amicon Ultra-0.5 centrifugal filters with a 30 kDa molecular weight cutoff (Millipore), centrifuged at 14,000 × g for 10 minutes at room temperature to separate unbound PiB from AchE-bound PiB. The retentate, containing eeAchE and any bound PiB, was recovered and transferred to a black walled 96-well plate for fluorescence measurement. Fluorescence was measured using a BioTek Synergy H1 plate reader with excitation at 350 nm and emission at 440 nm. The retentate was subsequently spotted onto a nitrocellulose membrane, stained with Ponceau S, and imaged to assess protein recovery.

Propidium iodide displacement assay

To evaluate the interaction between PiB and the PAS of eeAchE, we employed a PI displacement assay. A total of 25 U of eeAchE were incubated overnight with PI (1 µM), either alone or in the presence of PiB (20 µM, 0.8% DMSO). A parallel experiment using donepezil (20 µM, 0.8% DMSO) served as a positive control. PI fluorescence was measured using a BioTek Synergy H1 plate reader with excitation at 535 nm and emission at 630 nm.

Background fluorescence from PI alone was subtracted from all readings. Data were then normalized as $F_x/F_{vehicle}$, where F_x represents the PI fluorescence for each condition, and $F_{vehicle}$ is the PI fluorescence in the presence of eeAchE and 0.8% DMSO.

Statistical analysis

Microsoft Excel (Microsoft) and OriginPro (OriginLab) were employed for statistical analysis and data plotting. Data in Fig. 2 are represented as mean ± 1 standard error of the mean (s.e.m.); data points represent individual experiments. Exact P values are reported for each relevant comparison. The number of replicates and the statistical test used are provided in the figure legends.

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Author Contributions

Conceptualization, AG; methodology, AG, RF, LM, MB, CDM, SDP, and GF; formal analysis, AG and GF; investigation, AG, RF, and GF; writing original draft, AG; supervision, AG, GF, and SLS; funding acquisition, AG. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding Sources

AG is supported by the European Union - Next Generation EU, Mission 4 Component 1, CUP: D53D23019280001.

Acknowledgments

AI-assisted technology (ChatGPT 4o) has been used in the writing process to improve the readability and language of the manuscript.

Abbreviations

Aβ, amyloid-β; AchE, Acetylcholinesterase; AD, Alzheimer's disease; DMSO, dimethyl sulfoxide; eeAchE, *electrophorus electricus* Acetylcholinesterase; KPi, Potassium phosphate buffer; PAS, Peripheral Anionic Site; PDB, Protein Data Bank; PET, Positron Emission Tomography (PET); PI, Propidium iodide; PiB, Pittsburgh compound B; RMSD, root mean square displacement; ThT, thioflavin T.

References

(1) Nasrallah, I.; Dubroff, J. An Overview of PET Neuroimaging. *Semin. Nucl. Med.* **2013**, *43* (6), 449–461. https://doi.org/10.1053/j.semnuclmed.2013.06.003.

(2) Burkett, B. J.; Babcock, J. C.; Lowe, V. J.; Graff-Radford, J.; Subramaniam, R. M.; Johnson, D. R. PET Imaging of Dementia: Update 2022. *Clin. Nucl. Med.* **2022**, *47* (9), 763–773. https://doi.org/10.1097/RLU.0000000000004251.

(3) Wang, J.; Jin, C.; Zhou, J.; Zhou, R.; Tian, M.; Lee, H. J.; Zhang, H. PET Molecular Imaging for Pathophysiological Visualization in Alzheimer's Disease. *Eur. J. Nucl. Med. Mol. Imaging* **2023**, *50* (3), 765–783. https://doi.org/10.1007/s00259-022-05999-z.

(4) Jack, C. R.; Bennett, D. A.; Blennow, K.; Carrillo, M. C.; Feldman, H. H.; Frisoni, G. B.; Hampel, H.; Jagust, W. J.; Johnson, K. A.; Knopman, D. S.; Petersen, R. C.; Scheltens, P.; Sperling, R. A.; Dubois, B. A/T/N: An Unbiased Descriptive Classification Scheme for Alzheimer Disease Biomarkers. *Neurology* **2016**, *87* (5), 539–547. https://doi.org/10.1212/WNL.0000000000002923.

(5) Rabinovici, G. D.; Knopman, D. S.; Arbizu, J.; Benzinger, T. L. S.; Donohoe, K. J.; Hansson, O.; Herscovitch, P.; Kuo, P. H.; Lingler, J. H.; Minoshima, S.; Murray, M. E.; Price, J. C.; Salloway, S. P.; Weber, C. J.; Carrillo, M. C.; Johnson, K. A. Updated Appropriate Use Criteria for Amyloid and Tau PET: A Report from the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging Workgroup. *J. Nucl. Med.* **2025**. https://doi.org/10.2967/jnumed.124.268756.

(6) Aisen, P. S.; Cummings, J.; Jack, C. R.; Morris, J. C.; Sperling, R.; Frölich, L.; Jones, R. W.; Dowsett, S. A.; Matthews, B. R.; Raskin, J.; Scheltens, P.; Dubois, B. On the Path to 2025: Understanding the Alzheimer's Disease Continuum. *Alzheimers Res. Ther.* **2017**, *9* (1), 60. https://doi.org/10.1186/s13195-017-0283-5.

(7) Frisoni, G. B.; Altomare, D.; Thal, D. R.; Ribaldi, F.; van der Kant, R.; Ossenkoppele, R.; Blennow, K.; Cummings, J.; van Duijn, C.; Nilsson, P. M.; Dietrich, P.-Y.; Scheltens, P.; Dubois, B. The Probabilistic Model of Alzheimer Disease: The Amyloid Hypothesis Revised. *Nat. Rev. Neurosci.* **2022**, *23* (1), 53–66. https://doi.org/10.1038/s41583-021-00533-w.

(8) Kepp, K. P.; Robakis, N. K.; Høilund-Carlsen, P. F.; Sensi, S. L.; Vissel, B. The Amyloid Cascade Hypothesis: An Updated Critical Review. *Brain* **2023**, awad159. https://doi.org/10.1093/brain/awad159.

(9) Granzotto, A.; Sensi, S. L. Once upon a Time, the Amyloid Cascade Hypothesis. *Ageing Res. Rev.* **2024**, *93*, 102161. https://doi.org/10.1016/j.arr.2023.102161.

(10) Cole, G. B.; Keum, G.; Liu, J.; Small, G. W.; Satyamurthy, N.; Kepe, V.; Barrio, J. R. Specific Estrogen Sulfotransferase (SULT1E1) Substrates and Molecular Imaging Probe Candidates. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107* (14), 6222–6227. https://doi.org/10.1073/pnas.0914904107.

(11) Surmak, A. J.; Wong, K.-P.; Cole, G. B.; Hirata, K.; Aabedi, A. A.; Mirfendereski, O.; Mirfendereski, P.; Yu, A. S.; Huang, S.-C.; Ringman, J. M.; Liebeskind, D. S.; Barrio, J. R. Probing Estrogen Sulfotransferase-Mediated Inflammation with [11C]-PiB in the Living Human Brain. *J. Alzheimers Dis. JAD* **2020**, *73* (3), 1023–1033. https://doi.org/10.3233/JAD-190559.

(12) Høilund-Carlsen, P. F.; Alavi, A.; Castellani, R. J.; Neve, R. L.; Perry, G.; Revheim, M.-E.; Barrio, J. R. Alzheimer's Amyloid Hypothesis and Antibody Therapy: Melting Glaciers? *Int. J. Mol. Sci.* **2024**, *25* (7), 3892. https://doi.org/10.3390/ijms25073892.

(13) Høilund-Carlsen, P. F.; Alavi, A.; Barrio, J. R. PET/CT/MRI in Clinical Trials of Alzheimer's Disease. *J. Alzheimer's Dis.* **2024**, *101* (s1), S579–S601. https://doi.org/10.3233/JAD-240206.

(14) Cheung, J.; Rudolph, M. J.; Burshteyn, F.; Cassidy, M. S.; Gary, E. N.; Love, J.; Franklin, M. C.; Height, J. J. Structures of Human Acetylcholinesterase in Complex with

Pharmacologically Important Ligands. *J. Med. Chem.* **2012**, *55* (22), 10282–10286. https://doi.org/10.1021/jm300871x.

(15) Dvir, H.; Silman, I.; Harel, M.; Rosenberry, T. L.; Sussman, J. L. Acetylcholinesterase: From 3D Structure to Function. *Chem. Biol. Interact.* **2010**, *187* (1–3), 10–22. https://doi.org/10.1016/j.cbi.2010.01.042.

(16) Auletta, J. T.; Johnson, J. L.; Rosenberry, T. L. Molecular Basis of Inhibition of Substrate Hydrolysis by a Ligand Bound to the Peripheral Site of Acetylcholinesterase. *Chem. Biol. Interact.* **2010**, *187* (1–3), 135–141. https://doi.org/10.1016/j.cbi.2010.05.009.

(17) Harel, M.; Sonoda, L. K.; Silman, I.; Sussman, J. L.; Rosenberry, T. L. Crystal Structure of Thioflavin T Bound to the Peripheral Site of Torpedo Californica Acetylcholinesterase Reveals How Thioflavin T Acts as a Sensitive Fluorescent Reporter of Ligand Binding to the Acylation Site. *J. Am. Chem. Soc.* **2008**, *130* (25), 7856–7861. https://doi.org/10.1021/ja7109822.

(18) Sulatskaya, A. I.; Rychkov, G. N.; Sulatsky, M. I.; Rodina, N. P.; Kuznetsova, I. M.; Turoverov, K. K. Thioflavin T Interaction with Acetylcholinesterase: New Evidence of 1:1 Binding Stoichiometry Obtained with Samples Prepared by Equilibrium Microdialysis. *ACS Chem. Neurosci.* **2018**, *9* (7), 1793–1801. https://doi.org/10.1021/acschemneuro.8b00111.

(19) Alarcón-Enos, J.; Muñoz-Núñez ,Evelyn; Gutiérrez ,Margarita; Quiroz-Carreño ,Soledad; Pastene-Navarrete ,Edgar; and Céspedes Acuña, C. Dyhidro-β-Agarofurans Natural and Synthetic as Acetylcholinesterase and COX Inhibitors: Interaction with the Peripheral Anionic

Site (AChE-PAS), and Anti-Inflammatory Potentials. *J. Enzyme Inhib. Med. Chem.* **2022**, *37* (1), 1845–1856. https://doi.org/10.1080/14756366.2022.2091554.

(20) Singh, Y. P.; Shankar, G.; Jahan, S.; Singh, G.; Kumar, N.; Barik, A.; Upadhyay, P.; Singh, L.; Kamble, K.; Singh, G. K.; Tiwari, S.; Garg, P.; Gupta, S.; Modi, G. Further SAR Studies on Natural Template Based Neuroprotective Molecules for the Treatment of Alzheimer's Disease. *Bioorg. Med. Chem.* **2021**, *46*, 116385. https://doi.org/10.1016/j.bmc.2021.116385.

(21) Sugimoto, H.; Yamanishi, Y.; Iimura, Y.; Kawakami, Y. Donepezil Hydrochloride (E2020) and Other Acetylcholinesterase Inhibitors. *Curr. Med. Chem.* **2000**, *7* (3), 303–339. https://doi.org/10.2174/0929867003375191.

(22) David, B.; Schneider, P.; Schäfer, P.; Pietruszka, J.; Gohlke, H. Discovery of New Acetylcholinesterase Inhibitors for Alzheimer's Disease: Virtual Screening and in Vitro Characterisation. *J. Enzyme Inhib. Med. Chem.* **2021**, *36* (1), 491–496. https://doi.org/10.1080/14756366.2021.1876685.

(23) García-Ayllón, M.-S.; Small, D. H.; Avila, J.; Saez-Valero, J. Revisiting the Role of Acetylcholinesterase in Alzheimer's Disease: Cross-Talk with P-Tau and β-Amyloid. *Front. Mol. Neurosci.* **2011**, *4*. https://doi.org/10.3389/fnmol.2011.00022.

(24) Campanari, M.-L.; Navarrete, F.; Ginsberg, S. D.; Manzanares, J.; Sáez-Valero, J.; García-Ayllón, M.-S. Increased Expression of Readthrough Acetylcholinesterase Variants in the Brains of Alzheimer's Disease Patients. *J. Alzheimer's Dis.* **2016**, *53* (3), 831–841. https://doi.org/10.3233/JAD-160220.

(25) Glodzik, L.; Rusinek, H.; Li, J.; Zhou, C.; Tsui, W.; Mosconi, L.; Li, Y.; Osorio, R.; Williams, S.; Randall, C.; Spector, N.; McHugh, P.; Murray, J.; Pirraglia, E.; Vallabhajolusa, S.; de Leon, M. Reduced Retention of Pittsburgh Compound B in White Matter Lesions. *Eur. J. Nucl. Med. Mol. Imaging* **2015**, *42* (1), 97–102. https://doi.org/10.1007/s00259-014-2897-1.

(26) Klunk, W. E.; Engler, H.; Nordberg, A.; Wang, Y.; Blomqvist, G.; Holt, D. P.; Bergstr??m, M.; Savitcheva, I.; Huang, G. F.; Estrada, S.; Aus??n, B.; Debnath, M. L.; Barletta, J.; Price, J. C.; Sandell, J.; Lopresti, B. J.; Wall, A.; Koivisto, P.; Antoni, G.; Mathis, C. A.; L??ngstr??m, B. Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B. *Ann. Neurol.* **2004**, *55* (3), 306–319. https://doi.org/10.1002/ana.20009.

(27) Murugan, N. A.; Chiotis, K.; Rodriguez-Vieitez, E.; Lemoine, L.; Ågren, H.; Nordberg, A. Cross-Interaction of Tau PET Tracers with Monoamine Oxidase B: Evidence from in Silico Modelling and in Vivo Imaging. *Eur. J. Nucl. Med. Mol. Imaging* **2019**, *46* (6), 1369–1382. https://doi.org/10.1007/s00259-019-04305-8.

(28) Zoete, V.; Daina, A.; Bovigny, C.; Michielin, O. SwissSimilarity: A Web Tool for Low to Ultra High Throughput Ligand-Based Virtual Screening. *J. Chem. Inf. Model.* **2016**, *56* (8), 1399–1404. https://doi.org/10.1021/acs.jcim.6b00174.

(29) Bragina, M. E.; Daina, A.; Perez, M. A. S.; Michielin, O.; Zoete, V. The SwissSimilarity 2021 Web Tool: Novel Chemical Libraries and Additional Methods for an Enhanced Ligand-Based Virtual Screening Experience. *Int. J. Mol. Sci.* **2022**, *23* (2), 811. https://doi.org/10.3390/ijms23020811.

(30) Kim, S.; Chen, J.; Cheng, T.; Gindulyte, A.; He, J.; He, S.; Li, Q.; Shoemaker, B. A.; Thiessen, P. A.; Yu, B.; Zaslavsky, L.; Zhang, J.; Bolton, E. E. PubChem 2023 Update. *Nucleic Acids Res.* **2023**, *51* (D1), D1373–D1380. https://doi.org/10.1093/nar/gkac956.

(31) Floresta, G.; Granzotto, A.; Patamia, V.; Arillotta, D.; Papanti, G. D.; Guirguis, A.; Corkery, J. M.; Martinotti, G.; Sensi, S. L.; Schifano, F. Xylazine as an Emerging New Psychoactive Substance; Focuses on Both 5-HT7 and κ-Opioid Receptors' Molecular Interactions and Isosteric Replacement. *Arch. Pharm. (Weinheim)* **2025**, *358* (3), e2500041. https://doi.org/10.1002/ardp.202500041.

(32) Trott, O.; Olson, A. J. AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization and Multithreading. *J. Comput. Chem.* **2010**, *31* (2), 455. https://doi.org/10.1002/jcc.21334.

(33) Krieger, E.; Vriend, G. YASARA View - Molecular Graphics for All Devices - from Smartphones to Workstations. *Bioinforma. Oxf. Engl.* **2014**, *30* (20), 2981–2982. https://doi.org/10.1093/bioinformatics/btu426.

(34) Krieger, E.; Dunbrack, R. L.; Hooft, R. W. W.; Krieger, B. Assignment of Protonation States in Proteins and Ligands: Combining pKa Prediction with Hydrogen Bonding Network Optimization. *Methods Mol. Biol. Clifton NJ* **2012**, *819*, 405–421. https://doi.org/10.1007/978-1-61779-465-0_25.

(35) Krieger, E.; Nielsen, J. E.; Spronk, C. A. E. M.; Vriend, G. Fast Empirical pKa Prediction by Ewald Summation. *J. Mol. Graph. Model.* **2006**, *25* (4), 481–486. https://doi.org/10.1016/j.jmgm.2006.02.009.

(36) Maier, J. A.; Martinez, C.; Kasavajhala, K.; Wickstrom, L.; Hauser, K. E.; Simmerling, C. ff14SB: Improving the Accuracy of Protein Side Chain and Backbone Parameters from ff99SB. *J. Chem. Theory Comput.* **2015**, *11* (8), 3696–3713. https://doi.org/10.1021/acs.jctc.5b00255.

(37) Wang, J.; Wolf, R. M.; Caldwell, J. W.; Kollman, P. A.; Case, D. A. Development and Testing of a General Amber Force Field. *J. Comput. Chem.* **2004**, *25* (9), 1157–1174. https://doi.org/10.1002/jcc.20035.

(38) Jakalian, A.; Jack, D. B.; Bayly, C. I. Fast, Efficient Generation of High-Quality Atomic Charges. AM1-BCC Model: II. Parameterization and Validation. *J. Comput. Chem.* **2002**, *23* (16), 1623–1641. https://doi.org/10.1002/jcc.10128.

(39) Hornak, V.; Abel, R.; Okur, A.; Strockbine, B.; Roitberg, A.; Simmerling, C. Comparison of Multiple Amber Force Fields and Development of Improved Protein Backbone Parameters. *Proteins* **2006**, *65* (3), 712–725. https://doi.org/10.1002/prot.21123.

(40) Essmann, U.; Perera, L.; Berkowitz, M. L.; Darden, T.; Lee, H.; Pedersen, L. G. A Smooth Particle Mesh Ewald Method. *J. Chem. Phys.* **1995**, *103* (19), 8577–8593. https://doi.org/10.1063/1.470117.

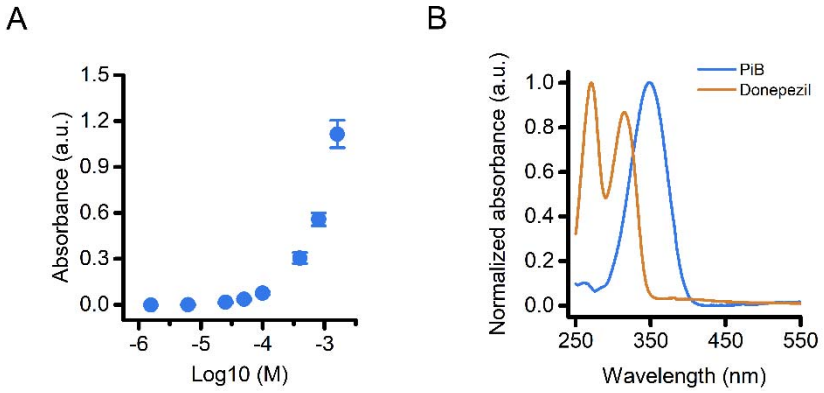
(41) Krieger, E.; Vriend, G. New Ways to Boost Molecular Dynamics Simulations. *J. Comput. Chem.* **2015**, *36* (13), 996–1007. https://doi.org/10.1002/jcc.23899.

(42) Floresta, G.; Patamia, V.; Mazzeo, P. P.; Lombardo, G. M.; Pistarà, V.; Bacchi, A.; Rescifina, A.; Punzo, F. Structural, Morphological, and Modeling Studies of *N*-(Benzoyloxy)Benzamide as a Specific Inhibitor of Type II Inosine Monophosphate

Dehydrogenase. *J. Mol. Struct.* **2024**, *1303*, 137588. https://doi.org/10.1016/j.molstruc.2024.137588.

(43) Granzotto, A.; Bolognin, S.; Scancar, J.; Milacic, R.; Zatta, P. Beta-Amyloid Toxicity Increases with Hydrophobicity in the Presence of Metal Ions. *Monatshefte Chem.* **2011**, *142* (4), 421–430. https://doi.org/DOI 10.1007/s00706-011-0470-1.

Supplementary Information



Supplementary Figure 1. Limited PiB solubility and spectral properties of PiB and donepezil complicate fluorescence- and enzymatic-based assays. (A) The scatter plot depicts absorbance of PiB measured across increasing concentrations (1.56 – 1600 µM) and reveals precipitation above 25 µM, limiting its use in assays requiring higher concentrations. (B) Normalized absorbance spectra of PiB (blue) and donepezil (orange) highlight substantial spectral overlap which complicates interpretation of fluorescence-based competition assays involving both compounds. Data are representative of at least two independent experiments. a.u., arbitrary units.

Supplementary chart 1

Ligand PDB ID	Similarity Score	SMILES
TFL	0.996	CN(C)C1=CC=C(C=C1)C1=[N+](C)C2=CC=C(O)C=C2S1
GK1	0.767	CC1=CC=C(O)C=C1NC1=CC=NC2=CC(=CC=C12)C1=CSC(C=O)=N1
EVW	0.715	NC1=NC2=CC=C(C=C2S1)C(=O)NC(C1=CC=CC=C1)C1=CC=CC=C1
UUL	0.672	OC1=CC=C(NC2=NC(=CS2)C2=CC=C(Cl)C=C2)C=C1
JMT	0.616	OC1=CC=C2NC=C(CN3CCN(CC3)C3=NC4=CC=CC=C4S3)C2=C1
09H	0.606	O=C(NC1=CC=CC=C1N1CCNCC1)C1=CSC(=N1)C1=CC=C2OCCC2=C1
JMW	0.594	OC1=CC=C2NC=C(CN3CCN(CC3)C3=NC4=CC(Cl)=CC=C4S3)C2=C1
EWK	0.585	NC1=NC2=CC=C(SCC3=CC=C(C=C3)C(=O)NCC3=CC=CC=C3)C=C2S1
EWT	0.574	NC1=NC2=CC=C(C=C2S1)C(=O)NCC1=CC(Cl)=C(Cl)C=C1
2WJ	0.565	CC(=O)NC1=NC2=CC=C(C=C2S1)C1=CC=CN=C1
AQE	0.563	C1CC[C@@]2(CCCN(C2)C2=C3C(NC=C3C3=NC=CS3)=NC=C2)NC1
94U	0.522	CCN(CC)C1=CC=C(NC(=O)C2=CC3=C(N2)N=CS3)C=C1
G4A	0.514	CN1\\C(OC2=CC=CC=C12)=C\\C1=[N+](CCCS(O)(=O)=O)C2=CC=CC=C2S1
3TI	0.51	OC1=CC=C(C=C1)\\N=C\\C1=C2C=CC=CC2=CC=C1O
N0E	0.505	OC1=CC=C(NC(=O)CCC2=CC=CC=C2)C=C1

2JR	0.5	C1CCN(C1)C1(CCCCC1)C1=CN=C(S1)C1=CC=C2NC=CC2=C1
EV8	0.498	COC(=O)C1CCN(CC1)C(=O)C1=CC=C(CNC(=O)C2=CC=C3N=C(N)SC3=C2)C=C1
CP9	0.497	CC1=NC2=CN=CC=C2N1C1=CC=C(CN2C(=O)SC3=CC=CC=C23)C=C1
X1H	0.492	COC1=CC=C(C=C1)C(=O)C1=C(SC2=CC(O)=CC=C12)C1=CC=C(O)C=C1
B4K	0.484	CC(=O)NC1=C2C=CC(=NC2=NN1)C1=CC=C(O)C(O)=C1
P2X	0.48	CC(C)N1N=C(C2=CC3=CC(O)=CC=C3N2)C2=C(N)N=CN=C12
RU5	0.475	NC(=O)C1=CC=C2NC(=NC2=C1)C1=CC=C(OC2=CC=C(Cl)C=C2)C=C1
3F4	0.474	OC1=CC=C(C=C1)C1=NC(=O)C2=CC=CC=C2N1
MKY	0.472	CCOC(=O)CN1\\C(SC2=CC(O)=CC=C12)=N\\C(N)=N
OFI	0.471	CCCC(=O)NC1=NNC2=CC(=CC=C12)C1=CC=C(O)C=C1
NU3	0.466	NC(=O)C1=C2N=C(NC2=CC=C1)C1=CC=C(O)C=C1
LNJ	0.462	COC1=CC=C(CC2=CC=C(C=C2)C2=CSC(N)=N2)C=C1
C2J	0.442	OC1=CC=C(C=C1)C1=CC=C2C(NN=C2NC(=O)C2CC2)=C1
57X	0.44	CCCN1C2=NNC(C3=CN=C(S3)C3=CC=CN=C3)=C2C=CC1=O
972	0.419	CC(C)COC1=CC=CC(C2=NC3=CC(C(N)=N)=C(Cl)C=C3N2)=C1O
JV5	0.418	CC1=CC=CC=C1OCC(=O)NC1=CC2=NNN=C2C=C1
917	0.417	CC(=O)NC[C@H]1CN(C(=O)O1)C1=CC=C(C=C1)C1=CN=CS1
2RE	0.416	OC1=CC=C(C=C1)C1=NC(=C(N1)C1=CC=NC=C1)C1=CC=C(F)C=C1
0HD	0.416	O=C(NCCC1=CC=CC=C1)NC1=CC2=CNN=C2C=C1

656	0.413	CC(C)COC1=CC=CC(C2=NC3=CC(=CC=C3N2)C(N)=N)=C1O
3U6	0.411	NC1=NN=C(S1)C1=CC=C2NC=C(C2=C1)C1=NC(NC2CCCC2)=CC=C1
D58	0.408	C[C@H]1NCCC[C@@H]1NC1=C2C=C(SC2=C(C=N1)C(N)=O)C1=CC=CC=C1
EK7	0.404	CN(C)C1=C2C(CCC3=C2N=C(NC2=CC=CC(O)=C2)N=C3)=C(S1)C#N
3TX	0.4	OC1=CC=C(C=C1)N1C=C(N=N1)C1=NC2=CC=CC=C2C=C1
3J7	0.4	CC(C)(N)CNC1=C2C=CN=CC2=NC(=N1)C1=CC2=CNN=C2C=C1
41Z	0.394	CC1=NC2=C(C=CC=C2C(NCC2=C(C)C=CC=C2C)=C1)C(N)=O
97K	0.393	O=C1N=C(NC2=CC=CC=C12)C1=CC2=CNN=C2C=C1
I0D	0.379	CN1CCC2=C(C1)C=CC=C2NC1=C(Cl)C(=O)N(C)N=C1
79X	0.379	COC1=CC2=C(C=C1OC)C1=CC3=CC(O)=CC=C3N1C2=O
4GM	0.379	NC(=O)C1=CC=C(NCC2=CC=CC=C2O)N=C1
IOK	0.377	C[C@H](CCC1=CC=C(O)C=C1)NC(=O)CC1=C(NC2=CC=CC=C12)C1=CC=CC=C1
3T9	0.376	COC1=CC(=CC=C1O)C1=NC2=NNC(=C2C=C1)C1=CC=CC=C1
655	0.374	NC(=N)C1=CC=C2NC(=NC2=C1)C1=C(O)C(OC2CCCC2)=CC=C1
WTF	0.373	CCS(=O)(=O)C1=CC=CC=C1C(=O)N1CCN(C[C@@H]1C)C1=NC2=CC=C(F)C=C2S1
WAM	0.37	COC1=CC(\\C=C\\C2=[N+](C)C3=CC=CC=C3C(=C2)C(N)=O)=CC=C1O
C70	0.368	NC(=O)C1=C2SC(=CC2=C(N[C@H]2CCCNC2)N=N1)C1=CC=C(Cl)C=C1
NUW	0.367	CNC(=O)C1=CC=C2N(CC3CCN(CC3)C(C)=O)C(=NC2=C1)C1=CC(C)=C(O)C(C)=C1
4KK	0.365	COC1=CC=CC(CC(=O)NC2=NC(=CS2)C2=CC=NC=C2)=C1

824	0.365	OC1=CC2=C(NC3=C2C2=C(C(=O)NC2=O)C(=C3)C2=CC=CC=C2)C=C1
950	0.364	CC(C)COC1=CC=CC(C2=NC3=CC(F)=C(C=C3N2)C(N)=N)=C1O
879	0.364	NC1=NC(CN2C(=CC=C2C2=CC=CC=C2Cl)C2=CC=C(OC3=CN=CN=C3)C=C2)=CC=C1
133	0.364	CC(C)COC1=C(O)C(=CC=C1)C1=NC2=CC(F)=C(C=C2N1)C(N)=N
G4E	0.362	CC1=CC=CC(NC2=NNC(=N2)C2=CC=C(OC3=CC=NC=C3)C=C2)=C1C
CJH	0.361	CCOC1=CC=CC(=C1)C1=CC=C(NC(=O)C(C#N)C(C)=O)C=C1
6QJ	0.356	CC1=CC(=CC=C1O)C1=CC=CC(=N1)C(=O)C1=CC=C(F)C(O)=C1
9ET	0.354	CC(=O)OC[C@]1(C)OC2=C(C=C1)C1=C(C=C2C)C2=C(N1)C=C(O)C=C2
YVQ	0.353	N1C=C(C=N1)C1=CN2C(C=N1)=NC=C2C1=CNC2=CC=CC=C12
Q4A	0.352	COC1=CC2=NC(=NC(NC3CCN(CC4=CC=CC=C4)CC3)=C2C=C1OC)N1CCCN(C)CC1
0VN	0.35	CC(C)(C)C1=CC=C(NC2=NC3=CC(=CC=C3N2)C#N)C=C1
QP8	0.347	CC(C)(C)OC(=O)N1CCN(CC1)C1=CC(=NN=C1N)C1=CC=CC=C1O
859	0.347	NC(=O)C1=CC=CC=C1NC1=CC=NC(NC2=CC=CC(O)=C2)=N1
6W3	0.346	CN1C(=CC2=C1C=CS2)C(=O)NC1=CC=CC=C1COC1=CC=C(OC2CCN(C)CC2)C=C1
C72	0.345	NC(=O)C1=C2SC(=CC2=C(N[C@H]2CCCNC2)N=C1)C1=CC=C(Cl)C=C1
28C	0.345	CC1=NN2C=NN=C2C(NCCC2=CC=C(O)C=C2)=C1
U81	0.343	BrC1=CC2=C(OCC[C@H]2NCCCNC2=CC(=O)C3=C(N2)C=CS3)C(Br)=C1
A3F	0.343	COC1=CC(=CC(OC)=C1OC)C1=CC(=CN=C1N)C1=CC=CC(O)=C1
6H2	0.343	OC1=CC=C(C=C1O)C1=CN2C=CC=CC2=N1

2YX	0.341	NC1=NC(=O)C2=CC3=C(NC(NCCC4=CC=C(C=C4)C#N)=N3)C=C2N1
ZZF	0.34	CC1=CC=C(OC2=CC=NC(NC3=CC=C(C=C3)S(N)(=O)=O)=C2)C(C)=N1
MCV	0.338	COC1=CC=C(OC)C(CCC2=CSC3=NC(N)=NC(N)=C23)=C1
8UN	0.338	C[C@@H](C1CCCCC1)N1C2=CC=C(C=C2N=C1C1=CC2=C(OCO2)C=C1Br)C(=O)NC1=CC=C(C=C1)C#N
PKJ	0.337	CC1=CC=C(C=C1)C1=CSC2=NN=C(SCC(=O)NC3=CC=C4OCOC4=C3)N12
O1Q	0.332	CC1=CC=CC(=C1)N1N=CC=C1C1=CC(Cl)=C2N=NN(C2=C1)C1=CC2=NNC=C2C=C1
D62	0.332	COC1=CC=C(C=C1OC)C1=NN(C2CCN(CC2)C2=C3C=CSC3=NC(N)=N2)C(=O)[C@@H]2CC=CC[C@H]12
CK6	0.332	CNC1=NC(C)=C(S1)C1=CC=NC(NC2=CC=C(O)C=C2)=N1
826	0.332	OC1=CC=C(CN2C3=C(CCN(C3)C(=O)C3=CC=C(O)C=C3)C3=CC=CC=C23)C=C1
KTQ	0.331	COC1=CC=C(CCNC2=C(N=C3C=CC=CN23)C2=CC=C(C=C2)[N+]([O-])=O)C=C1
8HZ	0.331	CC1=CC=C(NC2=C(N=C3N2C=CC=C3C)C2=CC=C(O)C=C2)C=C1
5ES	0.33	OC1=CC=C(C=C1)C(=CC1=CC(NC2=CC=C(F)C=C2)=CC=C1)C1=CC=C(O)C=C1
5C4	0.33	CC(=C(C1=CC=C(O)C=C1)C1=CC=C(O)C=C1)C1=CC=CC(NC2=CC=CC=C2)=C1
0N5	0.33	COC1=CC2=C(NC3=CC=C(NC(=O)C4=CC=CC=C4)C=C3)N=CN=C2C=C1O
70M	0.326	OC1=C(C=C2C(CCCCN3CCN(CC3)C3=CC=C(C=C3)C#N)=CNC2=C1)C#N
LUO	0.325	COC1=CC=C(NC(=O)[C@H](C)NC2=NC(=O)C3=C(N2)N(N=C3)C2=CC=CC=C2C)C=C1
K0Q	0.325	OC1=CC=CN(CC(=O)NCCC2=CNC3=CC=CC=C23)C1=O
9JX	0.325	ClC1=CC=CC=C1C1=CC=CC(=C1)N1C[C@@H](CC1=O)N1CCN(CC1)C(=O)C1=NC=CS1
4G3	0.324	NC(=O)C1=CC=C(NCC2=CC(O)=CC=C2)N=C1

D4Q	0.323	NC(=O)C1=C2SC(=CC2=C(N[C@H]2CCCNC2)N=C1)C1=CC(F)=CC=C1
RY8	0.322	CC1=NC(=CS1)C1=CC=C(C=C1)C(=O)NC1=C(C)C(C)=CC(=C1)S(N)(=O)=O
1DY	0.322	COC1=CC=CC=C1NC(=O)C1=CC=C(NC(=O)CCC2=NC(=O)C3=CC=CC=C3N2)C=C1
JGZ	0.321	CC1=CC(=CC(C)=C1OC1=CC=NC(NC2CCN(CC2)C2=CC=C(C=C2)S(N)(=O)=O)=N1)C#N
9HP	0.32	OC1=CC=C(C=C1)C1=CC2=C(C=CC3=C2C=NC=C3)N=C1
O1S	0.319	CC1=NNC=C1C1=CC2=C(S1)C(=O)N=C(CN1CCCC1)N2
GUK	0.319	CC(C)NC1=CC(Cl)=NN2C(=CN=C12)C1=CC2=CNN=C2C=C1
F1Y	0.318	CCCC1=C(NC2=CC=C(C=C2)C(=O)NO)N2C=CC=CC2=N1
F45	0.317	OC1=CC=C(C=C1O)C1=NC(=CC=C1)C(=O)C1=CC=C(F)C(O)=C1
EL2	0.317	CNC(=O)C1=CC=C2N([C@@H]3CCC[C@@H](C3)NC(=O)C3=CC=C(Br)S3)C(=NC2=C1)C1=CC=CC=N1
AAI	0.317	CCCN1CCC(CC1)C1=NC2=C(C=CC=C2N1)C(N)=O
CR3	0.316	NC(=N)C1=CC=C2NC(=CC2=C1)C1=C(O)C(OC2CCCC2)=CC=C1
0JA	0.316	FC1=CC=C(OC2=CC=C3N=C(NC(=O)C4CC4)SC3=N2)C=C1NC(=O)C1=C(Cl)C(=CC=C1)C1(CC1)C#N
3DX	0.315	CN1CCN(CC1)C1=CC=C(C=C1)C1=CC2=C(NC3=C2C=C(N=C3)C#N)N=C1
AI3	0.313	COC1=CC2=CN=C3C(CC4=C3C=C3OCOC3=C4)=C2C=C1OC
1NS	0.313	CS(=O)(=O)NCCC1CCN(CC1)C1=C2SC(=CC2=NC=N1)C(N)=O
Q4M	0.312	COC1=CC=C2NC(=CC2=C1)C(=O)N1C[C@@H](CCl)C2=C3C=CNC3=CC=C12
ALH	0.312	CCCCC1=C(NC2=NC=CN=C12)C1=CC=C(O)C=C1
K1H	0.311	COC(=O)N1CCN(CC1)C1CCC(CC1)NC1=C2C=C(C=CC2=NC=N1)C#N

E2J	0.311	CC1=C(CCN2CCC(CC2)=C(C2=CC=C(F)C=C2)C2=CC=C(F)C=C2)C(=O)N2C=CSC2=N1
O97	0.31	NC(=O)C1=CC2=C(C=CC=C2S1)C1=CC=C(S1)C(=O)NC1CC1
KTG	0.31	OC1=CC=C(CCCNC2=CC=CC3=C2C(=O)NC3=O)C=C1
4HN	0.31	CCOC1=CC=CC=C1C1=CC=C(C=C1)C1=C(C#N)C(=O)C2=CN=CC=C2N1
2WH	0.31	CCCN1C=NC(CCNC(=O)NC2=NC3=CC=C(C=C3S2)C2=CC(OC)=CN=C2)=C1
9Y2	0.309	CC(C)(C)CC(=O)NC1=C(F)C=C(C=C1F)C(=O)NC1=NC=CS1
7FW	0.308	CN(CC1=CC2=NC=CN=C2C=C1)C(=O)C1=CC=C(C=C1)N(CC1=CC=CC=C1)C(=O)C1=CC=C(O)C=C1O
H49	0.307	N=C(NC1=CC=CC(CNC[C@@H]2CCCN2)=C1)C1=CC=CS1
7IP	0.306	COC1=CC=CC(=C1)C1=CC=CC(CCC2=CC=CC(N)=N2)=C1
3X7	0.306	N#CC1=CC2=C(NC3=C2C=C(C=N3)C2=CC=C(CN3CCCCC3)C=C2)C=N1
15X	0.305	COC1=CC=C(CC2=CC=C(NC(N)=O)C=C2)C(F)=C1C1=CC=CC(=C1)N(=O)=O
UPX	0.304	C\\C(=N/NC1=NC=CN1)C1=CC=C(NC(=O)C2=CC3=CC=CC(=C3N2)[N+]([O-])=O)C=C1
LKG	0.304	OC1=CC=C(CC2=NN=C3C=CC(=NN23)C2=CC=CC=C2)C=C1
S79	0.303	NC1=NC(=O)C2=CC3=C(NC(NCC4=C5C=CC=CC5=CC=C4)=N3)C=C2N1
KA5	0.303	COC1=CC=C(OC)C(CNC2=C(Cl)C3=C(N)N=C(N)N=C3C=C2)=C1
5XQ	0.303	COC1=CC=CC=C1NC1=NC(=CS1)C1=C(C)N=C(NC(C)=O)S1
625	0.303	NC1=NC(CN2C(=CC=C2C2=CC=CC=C2Cl)C2=CC=C(OCCCC#N)C=C2)=CC=C1
N55	0.302	OC1=CC=C(C=C1Cl)C1=CC=C(C=C1)[C@@H](C=C)N1C=CN=C1
FZ9	0.302	C1CC(=CCN1C1=NC=NC2=NNC=C12)C1=CNC2=CC=CC=C12

2YO	0.302	O=C1N=CNC2=CC3=C(C=C12)N=C(NCCN1CCCCC1)N3
N58	0.301	CN1N=C(C=C1NC(=O)NC1=CC=C(SC2=CC=NC=C2)C=C1)C(C)(C)C
EYF	0.301	COC1=CC=CC(CN2C=CC3=CC(=CN=C23)C(=O)NO)=C1
2YM	0.301	NC1=NC(=O)C2=CC3=C(NC(NCCN4CCCCC4)=N3)C=C2N1
4L7	0.3	BrC1=CC=C(S1)C(=O)[C@H]1CNC[C@@H]1C1=CC=C2C(=O)N=CNC2=C1
926	0.3	CN1C=CN=C1SC1=CC=CC(=C1)C1=CC=CC(=O)N1
Y6V	0.299	O=C(N(CC1=CC=CS1)C1CC1)C1=CC=C2NC(=O)COC2=C1
IEO	0.299	NC(=O)C1=C2NC=C(C#N)C2=C(OC2CCNCC2)C=C1
HZY	0.299	COC1=CC(C[N+]2=CC=C3C=C(OS(N)(=O)=O)C=CC3=C2)=CC(OC)=C1OC
H2K	0.297	ClC1=CC(NC(=O)NC2=CN=C(C=N2)C#N)=C(O[C@@H]2CCNC2)C=C1
8E6	0.297	NC(=O)C1=C2N=C(NC2=CC(F)=C1)C1=CC2=C(CCNC2)S1
37R	0.297	NC(=O)CCCCC1=C(O)C=C2OC3=C(NC2=C1)C=CC(O)=C3
2YV	0.297	NC1=NC(=O)C2=CC3=C(NC(NCCC4=CC=CC=C4)=N3)C=C2N1
1RQ	0.296	OC1=CC=C2N=C(N(C2=C1)C1=CC=NC(N[C@@H]2CCCN(C2)C(=O)C2CC2)=N1)C1=CC2=CC=CC=C2C=C1
07Q	0.295	COC1=CC(=CC=C1)[C@@H](C)NC(=O)NC1=NC(=CS1)C1=CC=NC=C1
ZZW	0.294	ONC(=O)C1=CC2=C(C=N1)N(CC1=CC=C(F)C=C1)C1=C2C=CC=C1
DLN	0.294	CC(C)N1N=C(C#CC2=CC=CC(O)=C2)C2=C(N)N=CN=C12
9N2	0.294	OC1=CC(=CC=C1F)C(=O)C1=NC2=CC(=CC=C2C=C1)C#N
3KC	0.294	OC1=CC=C(C(Cl)=C1)C1=NC2=C(C=CC=C2)C2=CC=NC3=C2C1=CN3

N61	0.293	CN1N=C(C=C1NC(=O)NC1=CC=C(OC2=CC=NC=C2)C=C1)C(C)(C)C
EWV	0.293	COC1=CC2=C(C=C1OC)C1=CC3=CC=C4OCOC4=C3C=[N+]1CC2
770	0.293	ClC1=CC=CC=C1C1=CC2=C(C3=C(N2)C=CC(NC=O)=C3)C2=C1C(=O)NC2=O
QK0	0.292	CC(=O)NC1=NC2=CC=C(C=C2S1)C1=CC(NS(=O)(=O)C2=CC=C(F)C=C2)=C(Cl)N=C1
8TK	0.292	C[C@H](NC1=C(C#N)C(N)=NC=N1)C1=C(C(=O)N2C(C)=CSC2=C1)C1=CC=CC=C1
0WP	0.292	COC1=C2C=C(NC(=O)C3=C(F)C(NC(=O)C4=CC(=CC=C4)C(C)(C)C#N)=CC=C3F)C=NC2=NN1
P8Z	0.291	CN1CCN(CC1)C1=CC=CC=C1CNC1=C(C)C(=O)N(C)N=C1
JVT	0.291	CN1CCN(CC1)C1=CC=C(NC(=O)C2=NNC3=CC=CC=C23)C=C1
DTM	0.291	COC1=CC(CN(C)C2=CC3=C(N)N=C(N)N=C3N=C2)=CC(OC)=C1OC
9MK	0.291	CC1=CC2=CC=C(N=C2C=C1)C(=O)C1=CC=C(F)C(O)=C1
8PV	0.291	O=C(NCC1=CC=CC=C1)C1=CC=CC(NCC2=NN=C(N2)C2=CC=NC=C2)=C1
VXS	0.289	OC1=CC=CC=C1CCCNC1=CC=CC2=C1C(=O)NC2=O
MEY	0.289	OC1=CC(O)=C(Cl)C=C1N1C(=O)NC2=CC(CNS(=O)(=O)C3=C4C=CC=CC4=CC=C3)=CC=C12
6GE	0.289	CC1=CC=C(O)C=C1NC1=CC=NC2=CC=C(C=C12)S(C)(=O)=O
5DG	0.289	CC(=C(C1=CC=C(O)C=C1)C1=CC=C(O)C=C1)C1=CC=CC(NC2=CC=C(F)C=C2)=C1
N9W	0.288	CN1CCC2=C(C1)C1=CC=CC=C1N2CC1=CC=C(C=C1)C(=O)NO
JCW	0.288	NC(=O)C1=CC(=NC=C1)C1=CC(=CN=C1F)[C@H]1C[C@@H]2CC[C@H]1N2
7DZ	0.288	CC(C)CCN1[C@@H](C)C(=O)N(C)C2=CN=C(NC3=CC(F)=C(O)C(F)=C3)N=C12
FJU	0.287	CCC1=CC(NC(=O)C2=CC3=CC=CC(O)=C3OC2=N)=CC=C1

64N	0.287	CCC(=O)NC1=CC(Cl)=C(OC2=CC=C(O)C(=C2)C2=CC=C(C=C2)C(N)=O)C(Cl)=C1
MDY	0.286	COC1=CC=CC=C1C1=CC=C(NC(=O)C(C#N)C(C)=O)C(Cl)=C1
5GD	0.286	COC1=CC(OC)=C2C(=O)N=C(NC2=C1)C1=CC(C)=C(OCCN2CCCC2)C(C)=C1
58W	0.285	OC1=CC(O)=C(Cl)C=C1NC(=O)C1(CCC1)C1=CC=CC=C1
2KL	0.285	CCNC(=O)C1=CC2=C(N=C(N)N=C2S1)C1=CC(OCCN2CCCC2)=C(Cl)C=C1Cl
LXX	0.284	N1C=C2C=C(C=NC2=N1)C1=CC2=C(C=CN=C2C=C1)C1=CC=NC=C1
L26	0.284	CCC1=C(NC(C)=C1C(C)=O)C(=O)NC1=CC=CC(OCC(N)=O)=C1
5NW	0.284	COC1=CC(=CC=C1NC1=NC2=C(NCC(C)(C)C)N=CC=C2C=N1)C1=CN(C)N=C1
4Q3	0.284	CC(C)N1N=C(NC(C)=O)C=C1C1=CC=C(N(C)C(=O)C2=C(F)C=CC=C2Cl)C(=C1)N1C[C@@H]2C[C@@H]2C1
17V	0.284	CC(C)N1N=CN=C1C1=CC2=C(S1)C1=CC=C(C=C1OCC2)C(N)=O
75X	0.283	CC1=C(C=CC=C1O)C1=NC2=NC(N)=NC(OCC3CCCCC3)=C2N1
GQW	0.282	ONC(=O)C1=CC=C(Cl)C(NC(=O)C2=C3SC=CC3=CC=C2)=C1
4H7	0.282	CN1CCN(CC1)C1=CC=CC=C1CNC1=CC=C(C=N1)C(N)=O
GXK	0.281	ClC1=NN2C(=CN=C2C(NCC2CC2)=C1)C1=CC2=CNN=C2C=C1
G6J	0.281	CCCN1[C@H](C)C(=O)N(CCC)C2=CN=C(NC3=CC(F)=C(O)C(F)=C3)N=C12
0CV	0.281	COC1=CC2=C(N3CCNCC3)C3=C(C)NN=C3N=C2C(C)=C1
J2V	0.28	COC1=CC=C(C=N1)C1=C(NC2=CC=CN=C12)C1=CC=NC(NC(C)=O)=C1
G6T	0.28	NC1=NC(OCC2CCCCC2)=C2NC(=NC2=N1)C1=CC(=CC=C1)S(N)(=O)=O
5CC	0.279	CCC(=C(C1=CC=C(O)C=C1)C1=CC=C(O)C=C1)C1=CC=CC(NC2=CC=CC=C2)=C1

43A	0.278	COC1=CC(=CC=C1O)C1=CC=C2C(NC(=O)C2=CC2=CC=CN2)=C1
41E	0.278	COC1=CC(NC(=O)CCC2CCN(CC2)C(=O)C2=CC=C(S2)C(C)=O)=CC=C1
SV8	0.277	O=C1NCC2=C1NC=C2C1=CN=C2NC=C(CC3=CC=CC=C3)C2=C1
DUL	0.277	CCSC1=CC=CC(=C1)C1=CC=C(S1)C(N)=O
V5G	0.276	NC1=NC(CCC2=CC(OCC3=CC=C4C=CC(N)=NC4=C3)=CC=C2)=CC=C1
HVU	0.276	CN1CCC(CC1)C1=CNC2=CC=C(O)C=C12
4P9	0.276	OC1=CC=C(\\C=N\\NC2=CC=C(Cl)C=C2)C(O)=C1O
43H	0.276	OB(O)C1=CN(C=C(O)C1=O)C1=CC=CC(=C1)C1=CC=CC=C1
8C1	0.275	CC(C)OC1=CC2=C(O[C@@H]3CCCNC3)C=CN=C2C=C1C(N)=O
43R	0.275	COC1=CN=CC(=C1)N1CCC2=C(C1)SC(NC(C)=O)=N2
0NV	0.275	C(N1CCC(CC1)N1C=NC2=C1C1=C(NC=C1)N=C2)C1=CC=CC=C1
99S	0.274	COC(=O)C1=CC=C(S1)C1=CC(=CC(=C1)C#N)[C@]1(C(C)C)C2=C(C)NN=C2OC(N)=C1C#N
584	0.274	CC(C)CCN1[C@H](C)C(=O)N(C)C2=CN=C(NC3=CC(F)=C(O)C(F)=C3)N=C12
KT4	0.273	OC1=CC=C(CCCNC2=CC=CC3=C2C(=O)NC3=O)C(O)=C1
GQB	0.273	Nc1[nH]c2ccc(CNC(=O)C3=CC4=CC=CC=C4N3)cc2s1
E5M	0.273	C[C@@H]1N(C)C2=NC(NC3=CC(F)=C(O)C(F)=C3)=NC=C2N(C)C1=O
COQ	0.273	COC1=CC(OC)=CC(CN(C)C2=CC3=C(N)N=C(N)N=C3N=C2)=C1
NVV	0.272	IC1=CC=CC(=C1)C(=O)[C@H]1CNC[C@@H]1C1=CC=C2C(=O)N=CNC2=C1
R8E	0.271	NC1=NC2=NNC(COC3=CC(OC4=CC(=CC(Cl)=C4)C#N)=C(Cl)C=C3)=C2C=C1

JZH	0.271	OC1=CC=C(C=C1)[C@H]1C2=CNC3=NC=CC(=C23)C2=CC=CC=C2NC1=O
8Q7	0.271	COC1=CC=C(CN2C3=C(C4=C(CN(CC4)C(=O)[C@@H]4CC4(F)F)S3)C3=NC=NN3C2=O)C=C1
5JN	0.271	CC1=CC(NC(=O)CC2=CC=C(OC(C)(C)C(=O)OCCO[N+]([O-])=O)C=C2)=CC(C)=C1
4FX	0.271	COC1=CC=CC=C1CNC1=CC=C(C=N1)C(N)=O
NUM	0.27	OC1=CC=C(CCNC(=O)C2=CC=CC=N2)C=C1
E78	0.27	C[C@@H](C1CC1)N1CC2=C(C1=O)C(C)=CC(=C2)C1=C(C)N=C(NC(C)=O)S1
35O	0.27	COC1=CC=C(NC(=O)[C@@H](C)NC2=NC(=O)C3=C(N2)N(N=C3)C2CCCC2)C=C1
JEW	0.268	NC1=NNC(=C1)C1=CC=C2C=CN(CC3=CC=CC=C3C#N)C2=C1
5O1	0.267	COC1=CC(=CC=C1NC1=NC2=C(NC3CCCCC3)N=CC=C2C=N1)C1=CN(C)N=C1
3ND	0.267	ClC1=CC=C(C=C1)[C@@H]1CNC[C@H]1C(=O)NC1=C(Cl)C=C2C(=O)NC=CC2=C1
3DC	0.267	N(C1=CC=NC=C1)C1=NC=NN2C=C(C=C12)C1=CNN=C1
30J	0.267	C[C@@H]1CN(CCN1C1=CC=C(C=N1)C#N)C1=C2C=C(Cl)C=CC2=C(CC2=CC=CC=C2)N=N1
16L	0.267	CC1=CC(\\C=C\\C2=CC=CC(NC(=O)C=C)=C2)=CC(C)=C1O
9F4	0.266	ONC(=O)[C@@H]1[C@@H]([C@H]1C1=CC=C(C=C1)C1=NC=C(F)C=N1)C1=CC=CC=C1
3XK	0.266	CC(=O)NC1=CC=CC(=C1)C1=CC2=C(NC3=C2C=C(N=C3)C#N)N=C1
S1W	0.265	CN(C)C1=CC=CC(OC2=CN=C(NC3=CC=CC(O)=C3)N=C2)=C1
CO4	0.265	COC1=CC(=CC(OC)=C1OC)N(C)CC1=C(C)C2=C(N)N=C(N)N=C2N=C1
666	0.265	C[C@@H]1CC(=O)NN=C1C1=CC=C(NC2=C(CC3=CC=CC(I)=C3)C(=O)CCC2)C=C1
ZSO	0.264	FC1=CC=C(C=C1)[C@@H]1CCNC[C@H]1COC1=CC2=CNN=C2C=C1

LTQ	0.264	CC1=CC(=CC=C1N1CCN(CC1)S(=O)(=O)N1CSC[C@@H]1C(=O)NO)C#N
9ST	0.264	CN1C[C@@H](C[C@@H](C1)C1=CC=CC=C1)NC1=C(Br)C(=O)N(C)N=C1
5B2	0.264	NC1=NNC2=CC=C(C=C12)C1=CC=CC=C1
15F	0.264	ClC(Cl)(Cl)C(=N)OCC1=CC=[N+](CC2=CC=CC=C2)C=C1
YDJ	0.263	NC(=O)NC1=C(SC(=C1)C1=CC(F)=CC=C1)C(=O)N[C@H]1CCCNC1
RKZ	0.263	C[C@H](CN1C(C)=NC2=CC=C(N=C12)C1=CC(N)=NC(N)=C1)OC1=CC=CC=C1
6JU	0.263	ONC(=O)CN1C=C(CC2=CC=CC=C2)C2=CC(Br)=CC=C12
5H2	0.263	COC(=O)NC1=CC=C2C3=C(CCOC2=C1)C=C(S3)C1=NN=CN1C1=CC=CC=C1Cl
3FR	0.263	C[C@H](NC1=NC=C2C(C)=NN(C2=C1)C1=CC(=CC(Cl)=C1)C1=CC=CC=C1C(N)=O)C1=CC=CC=C1
304	0.263	CC[C@@H](C)NC1=NC=C(S1)C(=O)NC1=CC(=CC=C1C)C(=O)NC
92Q	0.262	CC1=CC=CC(Cl)=C1NC(=O)C1=CN=C(NC2=CC=CC(=C2)C(=O)N[C@H]2CCNC2)S1
ZVZ	0.261	CNC(=O)COC1=CC=C(C(CN2CCN(CC2)C2=CC=CC=N2)=C1)C1=CC=C(C=C1)C#N
BER	0.261	COC1=C(OC)C2=C[N+]3=C(C=C2C=C1)C1=C(CC3)C=C2OCOC2=C1
3GN	0.261	C[C@]1(CCCN1)C1=NC2=C(C=CC=C2N1)C(N)=O
S8B	0.26	CC(C)NC(=O)C1=CC=C(C=N1)C#CC1=CC=NC=C1
RT3	0.26	CC1=CC=C2N(CCCC2=C1)C(=O)SCC(=O)NC1=CC=C(C=C1Cl)S(N)(=O)=O
GQ5	0.26	C[C@H]1CCCN1CC1=NC2=CC(NC(=O)C3=CC=C4N(C)N=CC4=C3)=CC=C2N1
3L0	0.26	C[C@H]1N2C(COC3=CC(C4=CC=CC=C4)=C(C=C23)N(C)C2(C)CN(C)C2)=NNC1=O
3E1	0.26	CC(=O)NC1=CC=C(O)C(=C1)C1=CC(NC(C)=O)=CC=C1O

18A	0.26	CCC(=O)NC1=CC=C(\\C=C\\C2=CC(C)=C(O)C(C)=C2)C=C1
M94	0.258	CNCCC1=CC=CC(OCC2=CC3=NC(N)=CC=C3C=C2)=C1
5B4	0.258	CN1C=C(C=N1)C1=CC(OC2=CC(F)=C(NC(=O)C3(CC3)C(=O)NC3=CC=C(F)C=C3)C=C2F)=CC=N1
1NR	0.258	CC(C)(C)C(=O)NCCC1CCN(CC1)C1=C2SC(=CC2=NC=N1)C(N)=O
A27	0.257	CCCC(=O)NC1=NNC2=CC(C3=CC=C(O)C=C3)=C(C=C12)C1=CC=CC=C1
BAI	0.256	NC(=N)C1=CC=C2NC(CC3=NC4=CC=CC=C4N3)=NC2=C1
5H5	0.256	CC(C)N1N=CN=C1C1=CN2CCOC3=CC(O[C@@H](C)C(N)=O)=CC=C3C2=N1
LKQ	0.255	COC1=NN(C)C=C1NC1=NC=C(C)C(=N1)C1=CNC2=C(NC(=O)C3=CC=CN=C3C)C=CC=C12
7DQ	0.255	CC(C)C1=CC=C(CC(=O)N2CCN(CC2)C2=CC=C(N=N2)C#N)C=C1
R69	0.254	CN(C)C1=CC=C(O)C(=C1)C(=O)C1=CC=C(C=C1)C(=O)N[C@@H]1CCCNC[C@H]1NC(=O)C1=CC=NC=C1
JA1	0.254	CCCCCCC1=CC=C(OC2=CC=C(C=C2)[N+]([O-])=O)C(O)=C1
EMW	0.254	COC1=CC=C(NC(=O)N2CCN([C@@H](C)C2)C2=C3C=NN(C)C3=NC(N)=N2)C(C)=C1
ABZ	0.254	NC1=NC(NC2=CC=C(C=C2)C#N)=NC(CC2=C3C=CNC3=CC=C2Cl)=N1
9LP	0.254	OS(=O)(=O)OC1CCC(CC1)NC(=O)[C@H](C1CCCCC1)N1C2=CC(F)=C(F)C=C2N=C1C1=CC=C(Cl)C=C1
KT1	0.253	COC1=CC(O)=CC=C1CCCNC1=CC=CC2=C1C(=O)NC2=O
68M	0.253	C[C@H](CC1=CC2=CC(=CC=C2N=C1N)C1=NC=CC=C1C)C(=O)NCCC(C)(C)C
58G	0.253	NC(=O)C1=CC=C(N[C@@H]2CC[C@@H](C2)C2=CC=CC=C2)N=C1
50B	0.253	COC1=C(OC)C2=C[N+]3=C(C(CCCC(C4=CC=CC=C4)C4=CC=CC=C4)=C2C=C1)C1=CC2=C(OCO2)C=C1CC3
SK6	0.252	CC1=CC(CCC2=CC(=CC(NCCC3=CC=CC=N3)=C2)C#N)=NC(N)=C1

4G4	0.252	CN(C)C1=CC=CC=C1CNC1=CC=C(C=N1)C(N)=O
Z7H	0.251	COC1=CC=C(OC2=C(Cl)C=C(NC(=O)CC3=CC=CN=C3)C=C2Cl)C=C1C(C)C
U1T	0.251	CC1=C2C=C(NC(=O)C2=CC=C1)C1=CC=C(CN2CCCC2)C=C1
MXI	0.251	COC1=CC2=CC=C(C=C2C=C1)C1=C(NC(=N1)C(C)(C)C)C1=CC=NC(N)=C1
CTI	0.251	COC1=C(OC)C2=C(C=C1)C1=C(C3=C(C=C1)C=C1OCOC1=C3)[N+](C)=C2
78P	0.251	C[C@@]1(CCCN1)C1=NC2=C(C=CC=C2N1)C(N)=O
3FV	0.251	ClC1=CN(N=C1C(=O)NC1=CNN=C1C1=CC=CC=N1)C1CCNCC1
WXV	0.25	CNC(=O)C1=NN(C)C2=C1C=CC1=C2N=C(NC2CCN(CC2)S(C)(=O)=O)N=C1
NVS	0.25	COC1=CC=C(C=C1)N1CC2=CC=C(O)C=C2OC1=O
EX7	0.25	OC1=C2N=C(CCC3=CC(Cl)=CC=C3)NC2=CC=C1
43G	0.25	OC1=CN(C=CC1=O)C1=CC(=CC=C1)C1=CC=CC=C1
JC8	0.249	NC(=O)C1=CN=C(C=C1)C1=CC(=CN=C1F)[C@H]1C[C@@H]2CC[C@H]1N2
E89	0.249	COC1=CC=C(CCC2=C3NC=NC3=CC3=C2NC(N)=NC3=O)C=C1
C51	0.249	C[C@H](C1CCC(CC1)C1=CC=NC2=CC=CC=C12)C(=O)NC1=CC=C(C=C1)C#N
RKK	0.248	CCCCN1C(CCCC)=NC2=CC=C(N=C12)C1=CC(N)=NC(N)=C1
9ME	0.248	OC1=CC(=CC=C1F)C(=O)C1=NC2=CC=CC=C2C=C1
6GH	0.248	NC1=NC(=CC(=N1)C1=CSC=C1)N(CC1=CC=CC=N1)CC1=CC=CC=N1
924	0.248	NC1=C2C(SC=C2C2=CC3=C(C=C2)N(CC3)C(=O)CC2=CC=CC=C2)=CC=N1
H5G	0.247	OC1=CC=CC(CC(=O)NC2=CC=CC(Cl)=C2)=C1

52D	0.247	O=C(C1=CC=NC=C1)C1=CC=C(OCCN2CCCC2)C=C1
19Z	0.247	NC(=O)C1=CC(=CC=C1NCC1=CC=C(O)C=C1)[N+]([O-])=O
QV5	0.246	CC(C)OC1=CC(=CC=C1C1=C(NC2=CC(F)=C(Cl)C=C12)C(N)=O)N1CCNCC1
H0M	0.246	OC1=CC(CC(=O)NC2=CC=CC=N2)=CC=C1
D90	0.246	CN1CCC2=C(C1)SC(=N2)C(=O)NC1=CC=CC=C1NC(=O)C1=CC2=CC(Cl)=CC=C2N1
6WW	0.246	CN([C@H]1CC[C@H]2[C@@H]3CCC4=CC(O)=CC=C4[C@H]3CC[C@]12C)C1=CC=CC=C1
6BU	0.246	O=C(NC1=NNC2=CC(=CC=C12)C1=CC(NS(=O)(=O)C2CC2)=CC=C1)C1CC1
2HV	0.246	CC(=O)NC1=NC(=CS1)C(=O)NC1=CC=CC=C1N1CCCCC1
9HJ	0.244	CCCN(C)C1=NC2=CC(OC)=C(OC)C=C2C(NC2CCN(C)CC2)=N1
8ZZ	0.244	CC1=CC=CC(Cl)=C1NC(=O)C1=CN=C(NC2=CC=CC(=C2)C(=O)N[C@@H]2CCNC[C@H]2F)S1
8ZH	0.244	CC1=CC=CC(Cl)=C1NC(=O)C1=CN=C(NC2=CC=CC(=C2)C(=O)NC2CCNCC2)S1
65O	0.244	CC1=C(SC2=CC=CC3=CC=CC=C23)SC2=NC(N)=NC(N)=C12
2UQ	0.244	N=CC1=NC=C(C=N1)C(=O)NCC1=CC=CC=C1
VXV	0.243	OC1=CC(Cl)=CC(CCCNC2=CC=CC3=C2C(=O)NC3=O)=C1
FAZ	0.243	CN(C(=O)C1=CC2=C(S1)C1=CC=C(NC(C)=O)C=C1OCC2)C1=CC=CC=C1Cl
C4Q	0.243	C(N1CCNCCNCCNCC1)C1=C2C=CC=CC2=NC=C1
45R	0.243	COC1=CC(=CC=C1C(=O)NC1=CC=C2CCNCCC2=C1)C1=CNN=C1
Z68	0.242	NC1=C(SC(NC2CCCCC2)=N1)C(=O)C1=CC(=CC=C1)[N+]([O-])=O
QPC	0.242	CC(C)(C)CNC(=O)CC1=CC=C(NC2=C(C=NC(=N2)C2=CC=CC=C2)C(N)=O)C=C1

JHT	0.242	CN(C)C1=CC=CC(CNCC2=CC3=NC(N)=CC=C3C=C2)=C1
9P1	0.242	CN(C)C1=CC=C(CNCC2=CC3=NC(N)=CC=C3C=C2)C=C1
76B	0.242	CC1=CC(=CC=N1)C1=NN=C(CCNC(=O)C2=CC(=CC(O)=C2O)C2=CC=C(F)C=C2)N1
7U6	0.241	NC(=O)C1=C2N=C(NC2=CC=C1)C(=O)N1CCNCC1
5UO	0.241	ClC1=CC=C(C=C1)C1CCN(CCC2=CN(N=C2)C2=C3NC=NC(=O)C3=CC=N2)CC1
516	0.241	CN[C@@H](C)C(=O)N[C@@H](C1CCCCC1)C(=O)N1CCC[C@H]1C1=NC(=CS1)C1=CC=CC2=CC=CC=C12
W4G	0.24	O=C1N(CC2=CC=CC=C2)C=NC2=CC(=CC=C12)C1=CNN=C1
T61	0.24	ONC(=O)C1=CC=C(Cl)C(NC(=O)C2=CC=CC=C2)=C1
IDK	0.24	O=C(NC1=NNC2=CC(=CC=C12)C1=CC(NS(=O)(=O)CC2CC2)=CC=C1)C1CC1
8CG	0.24	CC[C@H]1[C@@H](COC2=C3C=C(OC)C(=CC3=CC=N2)C(N)=O)NC(=O)[C@H]1F
RFM	0.239	O=C(CN1N=NC2=CC=CC=C12)N(CC1=CSC=C1)C1=CC=C(NC(=O)C2=CC=CC=C2)C=C1
O1H	0.239	ClC1=C2N=NN(C2=CC(=C1)C1=CC=NN1CC1=CC=C(C=C1)C#N)C1=CC2=NNC=C2C=C1
KZQ	0.239	CC1=C([C@@H](NC(=O)N1)C1=CC=C(F)C=C1)C(=O)NC1=CC2=CNN=C2C=C1
426	0.239	NC(=N)C1=CC2=CC=C(C=C2C=C1)C(=O)NC1=CC=CC(OC2CCCC2)=C1
VUG	0.238	CC1=CC=CC(=C1)C1CCC(CC1)N1CCN(CC1)C1=CC=CN=C1
4G0	0.238	CN(C)C1=CC=CC(CNC2=CC=C(C=N2)C(N)=O)=C1
VXM	0.237	OC1=CC=C(F)C=C1CNC1=CC=CC2=C1C(=O)NC2=O
QWI	0.237	C1C[C@H](CC2(CCN(CC2)C2=C3NC=NC3=NC=N2)N1)C1=CC=CC=C1
IXF	0.237	CC(C)C1=CC=C(C=C1)N(C)C1=CC2=C(N)N=C(N)N=C2N=C1

7O3	0.237	OC1=CC=C(Cl)C(NC2=C3C=CC(NC(=O)CCl)=CC3=NC=N2)=C1
TWP	0.236	ONC(=O)C1=CC=C(CN2C=CC3=CC=CC=C23)C=C1
PRD	0.236	COC1=CC=C(OC)C(CN(C)C2=CC3=C(N)N=C(N)N=C3N=C2)=C1
DEH	0.236	COC1=CC=C2C=C3N(CCC4=C3C=C(O)C(OC)=C4)C=C2C1=[OH+]
8QE	0.236	CC(C)(C)NC1=C(C#N)C(N)=CC(NC2=CC=C(C=C2)C(N)=O)=N1
TMU	0.235	COC1=CC=C(CNC(=O)NC2=NC=C(S2)[N+]([O-])=O)C=C1
M8G	0.235	ONC(=O)\\C=C\\C1=CC=CC=C1NC(=O)C1=CC=CC=C1OC1=CC=CC=C1
K8M	0.235	FC1=CC(=CC(=C1)C1=CC=NC=C1)C(=O)N1C[C@@H](CC(F)(F)C1)C(=O)NC1=CC=C(Cl)C=C1
5UL	0.235	ClC1=CC=C(CC2CCN(CCC3=CN(N=C3)C3=C4NC=NC(=O)C4=CC=N3)CC2)C=C1
XU2	0.234	O=C(NC1=CC=C(NC2=CC=NC3=C2C2=C(C=CC=C2)C(=O)N3)C=C1)C1=CC=CC=C1
X5M	0.234	CCN(CC)C1=CC=C(C=C1[N](O)=O)C1=NNC(=O)C[C@H]1C
WDY	0.234	O=C(NC1=CC=CC(=C1)C1=NNC=C1)C1=CC=CC2=CNN=C12
TJH	0.234	OC1=CC=CC2=C1C(=O)C=C(NCCNC1=C3C=CC(Cl)=CC3=NC3=C1CCCC3)C2=O
HJM	0.234	CC[C@H]1C[C@@H]2C[C@@H]3[C@H]1N(C2)CCC1=C3NC2=CC=C(OC)C=C12
5Q2	0.234	CN1CCN(CC1)C1=CC=C(NC(=O)C2=C(NCCC3=CC=C(Cl)C=C3)C=CNC2=O)C=C1
16X	0.234	CC1=C(SC(N)=N1)C1=CC=NC(NC2=CC=CC(=C2)N2OO2)=N1
0P8	0.234	COC1=C(CNCCCNC2=CC(=O)C3=CC=CC=C3N2)C=C(Br)C=C1Br
S9H	0.233	COC1=CC=C(NC2=NC=CC(=N2)C2=CC=C3NC(=O)CCCC3=C2)C=C1
279	0.233	CCNC(=O)C1=CN2N=CN=C(NC3=CC(=CC=C3C)C(=O)NOC)C2=C1C

Q26	0.232	CCOC1=CC=C(C=C1C1=CC2=NC(N)=NC(N)=C2C=C1)C1=CC=CC(NS(C)(=O)=O)=C1
KSY	0.232	OC1=CC=CC(CCCNC2=CC=CC3=C2C(=O)NC3=O)=C1
E1D	0.232	C[C@H]1N(C)C2=NC(NC3=CC(F)=C(O)C(F)=C3)=NC=C2N(C)C1=O
9S1	0.232	NC1=CC=C2NC(=CC2=N1)C1C=NN(C1=O)C1=CC(CNC(=O)NC2=CC=CC=C2)=CC=C1
QRX	0.231	CCCN1C(CNC2=CC=CC(=C2)C(=O)NCC2=C(F)C=CC=C2F)=NN=C1C1=CC=NC=N1
LKT	0.231	ClC1=CC=CC(N2CC[C@@H](C2)[C@H](CC#N)N2C=C(C=N2)C2=C3C=CNC3=NC=N2)=C1C#N
LD2	0.231	O=C1COC2=CC=C(C=C2N1)C(\\CC1=CC=CC=C1)=N\\N1CN=NC1=S
K4A	0.231	CCN1N=CC(=C1C)C1=NC2=C(N=CN=C2N1C)N1CCC(CC1)N1C(=O)NC2=NC=CC=C12
KTM	0.23	OC1=CC=CC=C1CNC1=CC=CC2=C1C(=O)NC2=O
GVK	0.23	ClC1=CC=C(C=C1)C1(CCNCC1)C1=CC=C(C=C1)C1=C2N=CNC2=NC=N1
FH3	0.23	CN1C=C(C(C)=N1)C1=NC2=NC=C(Cl)C(N3CC[C@@H](CNC(C)=O)C3)=C2N1
7KZ	0.23	CCCCCCNC1=NC2=CC(OC)=C(OC)C=C2C(NC2CCN(C)CC2)=N1
65C	0.23	CC1=CNC(=N1)C1=CN=C(NCCNC2=CC=C(C=N2)C#N)N=C1C1=CC=C(Cl)C=C1Cl
4YU	0.23	COC(=O)C=CCNC(=O)C1=C(C)N(C)C2=CC=C(OC)C=C12
W45	0.229	SCC(=O)NCCCCCN1C=CC2=CC(Cl)=C(Cl)C=C12
328	0.228	COC1=CC=NC(NC2CCN(CC2)C(=O)C2=CC=C(C=C2)C#N)=C1
SM6	0.227	CCOC(=O)C1=C(NC2=CC3=CCC(NO)=C3C=C2)C2=CC=NC=C2S1
JCE	0.227	NC1=NNC(=C1)C1=CC=C2C=CN(CC3=CC=CC=N3)C2=C1
4TV	0.227	CN1C=C(C=N1)C1=CC=C(C=C1)C1=CN=CC(Cl)=C1N1CCC2(CCNC2=O)CC1

T27	0.226	CC1=CC(\\C=C\\C#N)=CC(C)=C1NC1=CC=NC(NC2=CC=C(C=C2)C#N)=N1
JDQ	0.226	NC1=NNC(=C1)C1=CC=C2C=CN(CC3=CC=CC=C3)C2=C1
81F	0.226	CC1=CC=CC(=C1)C1CCC(CC1)N1CCN(CC1)C1=CC(Br)=CN=C1
5TD	0.226	O=C(CCC1CCN(CC1)C1=CC=C(C=C1)C#N)N1CCCC1
56Y	0.226	CCC1=C(NC(C)=C1C(C)=O)C(=O)N(C)CC1=CC=CC(=C1)C(N)=O
C9J	0.225	CN1C=CC2=CC=C(N=C2C1=O)C1=CN(N=N1)C1=CC=C(O)C(F)=C1
6WV	0.225	C[C@]12CC[C@H]3[C@@H](CCC4=CC(O)=CC=C34)[C@@H]1CC[C@@H]2NC1=CC=CC=C1
YKC	0.224	O=C(N[C@@H]1C2=CC=CC=C2C2=C(C=CC=C12)C1=NC2=CC=NC=C2N1)C1=CC=NC=C1
VM4	0.224	C[C@@H](SC1=NC2=C(C=NN2C)C(=O)N1C1=CC=CC=C1)C1=CC=CC(O)=C1
L74	0.224	ClC1=CC=C(C=C1)N1CCN(CC2=CNC3=NC=CC=C23)CC1
H6K	0.224	O=C(NC1=NNC(=C1)C1=CC=CC=C1)NC1=CN=C(C=N1)C#N
EKT	0.224	CC(C)CCN1C2=C(C=NC(NC3=CC(F)=C(O)C(F)=C3)=N2)N(C)C(=O)C1(C)C
EDH	0.224	CCCN1C(NC(=O)C2=CC=CC(=C2)C(N)=O)=NC2=CC=CC=C12
C73	0.224	NC(=O)NC1=C(C=C(S1)C1=CC=C(Cl)C=C1)C(=O)N[C@H]1CCCNC1
WR2	0.223	CNC(=O)[C@@H](NC(=O)[C@H](CC(C)C)[C@H](CNC(=O)C1=NC=CS1)C(=O)NO)C(C)(C)C
RK8	0.223	C[C@@H](CN1C(C)=NC2=CC=C(N=C12)C1=CC(N)=NC(N)=C1)OC1=CC=CC(Br)=N1
QKQ	0.223	COC1=CC=C(C=C1)C1=CN=CC2=CC=C(N=C12)C(=O)NCCCN1C=CN=C1
7Z0	0.223	COC1=NNC2=NC=C(C=C12)C#CC1=C(F)C=CC(NS(=O)(=O)C2=CC=CC(Br)=C2)=C1F
64O	0.223	CCC(=O)NC1=CC(Cl)=C(OC2=CC=C(O)C(=C2)C2=CC=C(NC(N)=O)C=C2)C(Cl)=C1

172	0.223	NC1=NC2=CC(O)=CC=C2N1
7AH	0.222	FC1=CC=C(CC(=O)NC2=CC=C3NC=C(C4CCNCC4)C3=C2)C=C1
6GM	0.222	NC1=NC(=CC(=N1)C1=CC=C(O)C=C1)N(CC1=CC=CC=N1)CC1=CC=CC=N1
1WQ	0.222	C[C@@H]1OC2=CC=C(CN3CCC(=CC3)C3=CC=C(Cl)C=C3)C=C2NC1=O
0MH	0.222	COC1=CC=CC=C1C1=NOC(C)=C1C(=O)N1CCN(CC1)C1=CC(NC(=O)C2=CC=CS2)=C(C=C1Cl)[N+]([O-])=O
A42	0.221	COC1=CC(OC)=C(Cl)C=C1NC(=O)NC1=CN=C(C=N1)C#N
5EZ	0.221	ClC1=C(OC[C@@H]2CCNC2)C=C2C=CNC(=O)C2=C1
NT5	0.22	C[C@@H]1CC[C@@H](COC2=CC=C(F)C=N2)CN1C(=O)C1=CC(C)=CC=C1C1=NC=CC=N1
K9Y	0.22	CC1=CC=C(C=C1)N1N=C(C=C1NC(=O)NC1=CC=C(C=C1)N1C=NC2=C(N)N=CN=C12)C(C)(C)C
JDS	0.22	O\\N=C/C1=NC(CCCCNC2=C3C=C(Cl)C=CC3=NC3=C2CCCC3)=CC=C1O
HWQ	0.22	CN(CCC#N)C1=C2SC=CC2=NC(=N1)N(C)C1CCNCC1
D5Z	0.22	COC1=CC=C(C=C1OC)C1=NN(C2CCN(CC2)C2=C3C=CC=CC3=NC(N)=N2)C(=O)[C@@H]2CC=CC[C@H]12
3MW	0.22	NC1=CC=C(C=C1)C(=O)N[C@@H](C(=O)NO)C1=CC=C(C=C1)N1C=CC=N1
WYE	0.219	CN1C=C(\\C=C2/OC3=CC(O)=CC(O)=C3C2=O)C2=C(C=CN=C12)N1CCN(C)CC1
SCQ	0.219	BrC1=C2C=C(C=C(NCC3=CN=CN=C3)N2N=C1)C1=CC=CC=C1
QXQ	0.219	CCC(CC)(C=O)C(=O)NC1=CC=CC(CN2CCC3=CC4=C(OCO4)C=C3C2)=C1
NTI	0.219	CC(=O)OC1=CC=CC=C1C(=O)NC1=NC=C(S1)[N+]([O-])=O
NJD	0.219	COC1=NC(NCCC2=CNC3=CC=CC=C23)=NC(NC2=CC3=CNN=C3C=C2)=N1
LTJ	0.219	C\\C=C\\C(=O)N[C@H]1CCCN(C1)C1=C2C(C)=C(C)NC2=C(C=C1F)C(N)=O

C9G	0.219	CN1C=CC2=CC=C(N=C2C1=O)C1=CN(N=N1)C1=CC=C(O)C=C1
5G3	0.219	OC1=CC=C(C=C1)C(=N/C1=CC=CC=C1Cl)\\C1=CC=C(O)C=C1O
5G4	0.218	CC1=CC=CC=C1\\N=C(/C1=CC=C(O)C=C1)C1=CC=C(O)C=C1O
30M	0.218	CC(=O)NCCCCN1C2=C(C3=CC=CC=C13)C(=O)NCC2
G9G	0.217	CN1CCN(CC1)C1=NC2=C(NC(=O)C3=C2C=CC=C3)C=C1