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A closer look at amyloid ligands, and what they tell us about protein aggregates†

Timothy S. Chisholm and Christopher A. Hunter *

The accumulation of amyloid fibrils is characteristic of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease. Detecting these fibrils with fluorescent or radiolabelled ligands is one strategy for diagnosing and better understanding these diseases. A vast number of amyloid-binding ligands have been reported in the literature as a result. To obtain a better understanding of how amyloid ligands bind, we have compiled a database of 3457 experimental dissociation constants for 2076 unique amyloid-binding ligands. These ligands target Aβ, tau, or αSyn fibrils, as well as relevant biological samples including AD brain homogenates. From this database significant variation in the reported dissociation constants of ligands was found, possibly due to differences in the morphology of the fibrils being studied. Ligands were also found to bind to Aβ(1–40) and Aβ(1–42) fibrils with similar affinities, whereas a greater difference was found for binding to Aβ and tau or αSyn fibrils. Next, the binding of ligands to fibrils was shown to be largely limited by the hydrophobic effect. Some Aβ ligands do not fit into this hydrophobicity-limited model, suggesting that polar interactions can play an important role when binding to this target. Finally several binding site models were outlined for amyloid fibrils that describe what ligands target what binding sites. These models provide a foundation for interpreting and designing site-specific binding assays.

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Introduction

Amyloidogenic proteins are an expansive class of polypeptides that self-assemble into fibrillar, highly structured, β-sheet rich aggregates.[1–5] The modern biophysical definition of an amyloid fibril encompasses an unbranched protein fibre with a

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† Electronic supplementary information (ESI) available: Details on database preparation, heatmaps summarising competition binding experiments, and spreadsheet containing the ligand database. See DOI: https://doi.org/10.1039/d3cs00518f

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repeating substructure composed of β-strands aligned perpendicular to the fibre axis, forming an extended cross-β sheet structure. The accumulation and deposition of amyloid fibrils are characteristic hallmarks of a range of neurodegenerative diseases.[6–15] The most common fibrils implicated in these diseases are composed of amyloid-β (Aβ) peptide and tau in Alzheimer's disease (AD), and α-synuclein (αSyn) in Parkinson's disease (PD).

Detailed structural information of amyloid fibrils has been historically challenging to obtain due to the difficulty in obtaining crystalline samples for X-ray studies.[16] More recent applications of cryo-electron microscopy techniques have negated the need for crystalline samples and revealed high-resolution structures for several amyloid fibrils.[17–21] These structures show that the fibrils are typically composed of two protofilaments, each containing an extended β-sheet structure.[1,16,21] Structural investigations of amyloid fibrils have consistently demonstrated a significant degree of polymorphism, where a single amyloid protein can aggregate to form a range of fibril structures.[1,20–26] This polymorphism can arise due to differences in the structures of individual protofilaments, the number of protofilaments, and the arrangement of protofilaments relative to one another. Amyloid structure is therefore not strictly dictated by the primary sequence of the polypeptide, but is instead a complex property that is dependent on environmental conditions during aggregation.[24,25,27–36]

A range of amyloid-binding ligands have been reported for studying and imaging amyloid fibrils.[3,37–46] Amyloid-binding ligands are typically either fluorescent or radiolabelled to allow for binding to be detected and measured. Many fluorescent ligands, such as Thioflavin T (ThT, **1**) and Congo Red (CR, **2**) (Fig. 1), are solvatochromic and exhibit a change in fluorescence properties upon binding to amyloid fibrils. Fluorescent ligands have a range of applications in microscopy, and in identifying or characterising amyloid fibrils. These changes in fluorescence properties can also be used to measure the proportion of bound ligand in binding assays.

Radiolabelled ligands are important for the detection of amyloids *in vivo*. These ligands are designed as radiotracers for positron emission tomography (PET) by incorporating ^{3}H, ^{11}C or ^{18}F (*e.g.* **3**), or for single-photon emission computerized tomography (SPECT) by incorporating ^{125}I (*e.g.* **4**). Binding assays of radiotracers are typically performed by isolating the radioligand–fibril complex by filtration and determining the concentration of this species by measuring radioactivity.[47–49]

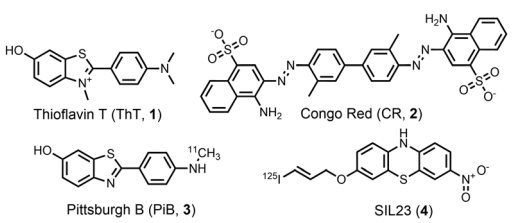

Fig. 1 Examples of amyloid-binding ligands: fluorescent ligands thioflavin T (ThT, **1**) and Congo Red (CR, **2**), and radiolabelled ligands Pittsburgh B (PiB, **3**) and SIL23 (**4**).

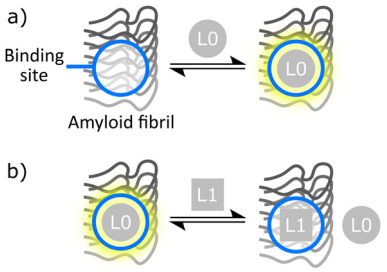

Fig. 2 (a) A saturation binding assay involves addition of a fluorescent or radiolabelled ligand (L0) into a solution of amyloid fibril. Binding of L0 is determined by either monitoring a change in fluorescence, or by isolating the fibril–ligand complex and measuring radioactivity. (b) A competition binding assay involves addition of a competing ligand (L1) into a solution of amyloid fibril bound to a fluorescent or radiolabelled reporting ligand (L0). Binding of L1 is determined by measuring the signal due to displacement of L0.

The field has focused on developing high-affinity ligands that selectively bind to aggregates comprised of a specific protein. High binding affinities are a necessary feature for PET ligands to provide strong signal-to-noise in imaging, and for detecting dilute aggregates in biofluids.[3,41] Selective binding is important as many diseases, such as Alzheimer's disease and Parkinson's disease, are characterised by aggregates comprised of different proteins that are useful to differentiate. Lower-affinity and less-selective ligands, such as ThT, can also be useful as universal markers of amyloids for imaging and biophysical studies.

Fluorescence or radiometric binding assays are frequently employed to measure the dissociation constant (K_d) of amyloid ligands. Two common experiments are saturation binding assays and competition binding assays (Fig. 2). Saturation binding assays involve titrating a ligand directly into a sample of amyloid fibril and measuring the proportion of bound ligand. Competition binding assays involve first binding a reporter ligand (L0 in Fig. 2) that is either fluorescent or radioactive to an amyloid fibril. Then, a second competing ligand (L1 in Fig. 2) is added. The change in signal due to displaced L0 is used to indirectly monitor binding of L1, which means that this experiment can be used to study L1 ligands that are not fluorescent or radioactive.

Although a large number of ligand–amyloid fibril interactions have been reported in the literature, a compilation and review of these data has yet to be performed. Here we present an analysis of literature data on amyloid-binding ligands and use this information to provide some insights into the properties required for ligands to bind to amyloid fibrils and the nature of the ligand binding sites that are present on different types of amyloid fibril.

Database of amyloid ligands

We compiled a database of 3457 measurements of ligand–amyloid fibril interactions from the scientific literature.[50–385] The requirements to be included in this database were (1) a known chemical structure, (2) a structure that does not contain

Table 1 Distribution of fibril type in the database

Fibril or source[a]	Number of data points
Aβ(1–40)	832
Aβ(1–42)	1014
Tau	279
αSyn	459
AD brain homogenates	720
Other	153

[a] Aβ(1–40), Aβ(1–42), tau, and αSyn all refer to the fibrillar species formed *in vitro*.

metals (metalloligands have been thoroughly reviewed elsewhere in the literature[43,386–391]), (3) a K_d or IC_{50} measurement, and (4) a fibril target related to Aβ, tau, or αSyn. Nearly half of the database reports on binding to Aβ fibrils formed *in vitro*, although recent years has seen a shift in focus toward tau and αSyn fibrils formed *in vitro* (Table 1). There is also a significant amount of data on binding to AD brain homogenates. Most of the reported K_d values in the database are in the nanomolar range, with smaller numbers of picomolar or micromolar values (Fig. 3). The database contains 2,076 unique ligands, which are structurally diverse. The most common structural cores are illustrated in Fig. 4.

We will use this database to investigate four questions. First, how reproducible are the K_d measurements reported in the literature? Second, how selective are ligands for different types of fibril? Third, what properties of ligands lead to high affinity binding? And fourth, what can we learn about the nature of the binding sites present on amyloid fibrils?

Variation between reported measurements

Reproducibility underpins the scientific method yet for many amyloid ligands, such as ThT **1**, a wide range of K_d values have been reported. The variability in K_d values in the database was investigated by comparing K_d values for ligands binding to a specific target and measured using the same method: fluorescence saturation assays, radioligand saturation assays, or radioligand competition assays. Only binding measurements corresponding to a one-site model were used, and K_d values measured using competition binding assays were only compared for reporting ligands from the same structural class (Fig. 4). The results for all of the ligand–fibril combinations with three or more K_d measurements are illustrated in Fig. 5, and the structures of the ligands are shown in Fig. 6.

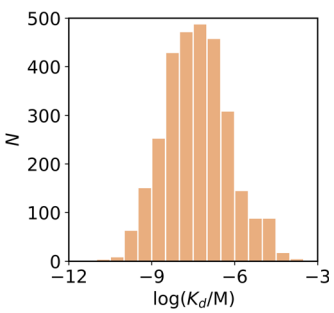

Fig. 3 Frequency distribution of log(K_d/*M*) values in the database plotted as the number of ligands (*N*).

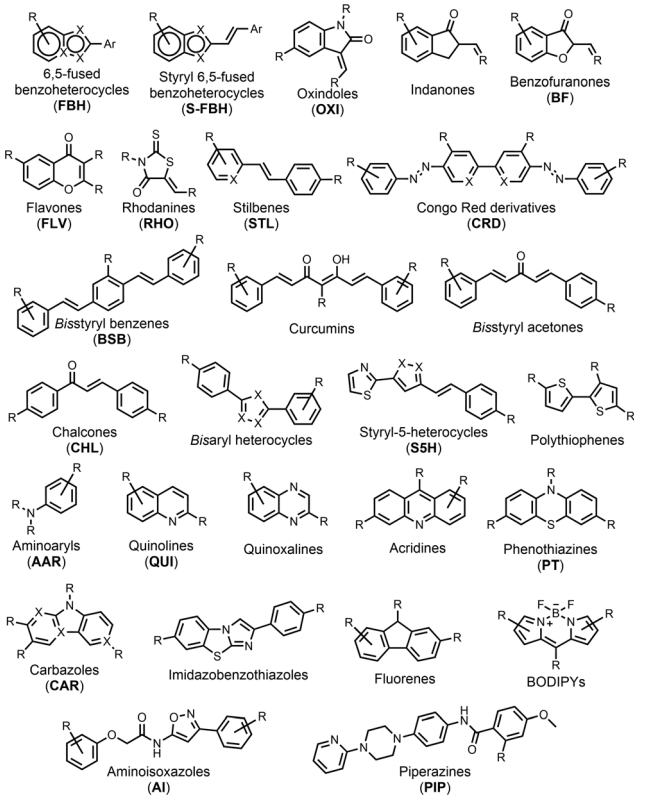

Fig. 4 Common structural classes of ligand in the database.

For some ligands, the measurements of dissociation constant are consistent between different publications. For example, the results for BTA ligands **3**, **5**, **6**, **7**, **8**, **10** (see Fig. 6 for structures) show excellent reproducibility for binding to Aβ(1–40) (Fig. 5(a)), and similarly for **16** binding to αSyn (Fig. 5(d)) and **22** binding to AD brain homogenates (Fig. 5(f)). However, the measured dissociations constants for ligand–fibril combinations can vary by more than an order of magnitude. For example, the dissociation constants measured for **3** binding to Aβ(1–42) range from 0.8–77 nM (Fig. 5(b)), and similar variation is found for **3** and **21** binding to AD brain homogenates (Fig. 5(f)), and for **1** binding to αSyn (Fig. 5(d)).

Where multiple measurements of K_d are reported in a single publication, such as for **22** binding AD brain homogenates, the results are usually relatively consistent. The variability seen in Fig. 5 may therefore come primarily from differences in sample preparation or assay methodology between publications. A main source of variability for amyloid binding is that fibrils composed of the same protein can have different morphologies. Different publications often use different fibril aggregation procedures, or do not describe the aggregation procedure in detail. For measurements using biological fibrils, the method of isolating fibrils from brain homogenates varies and may also influence fibril structure. Different studies may therefore be screening different morphologies. Ideally, fibrils should be characterised using techniques such as transmission electron microscopy (TEM), circular dichroism (CD), or limited

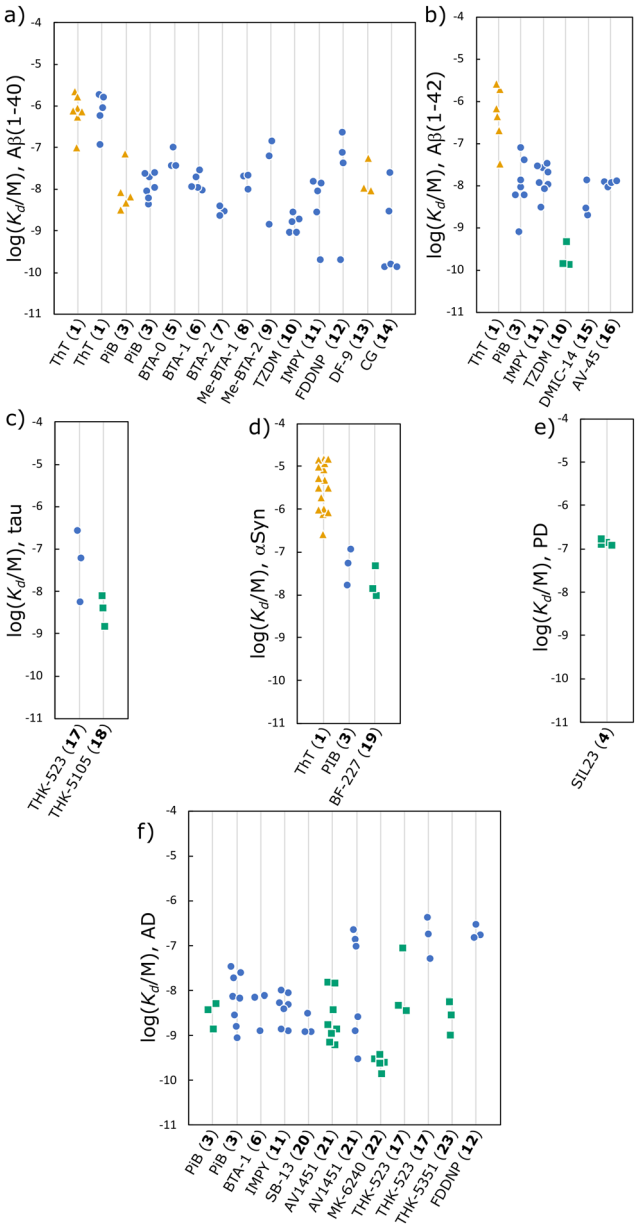

Fig. 5 Variation of log(K_d/M) values for ligand binding to (a) Aβ(1–40), (b) Aβ(1–42), (c) tau, (d) αSyn, (e) PD brain homogenates, and (f) AD brain homogenates. Each datapoint corresponds to a single K_d measurement. Datapoints correspond to fluorescence saturation assays (yellow triangles), radioligand saturation assays (green squares), and radioligand displacement assays (blue circles).

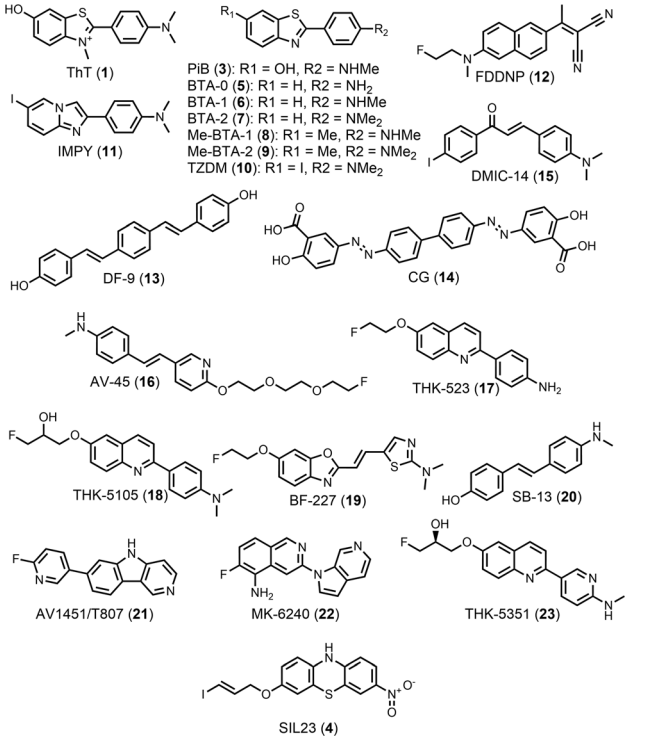

Fig. 6 Structures of ligands listed in Fig. 5 with three or more K_d measurements reported in the literature.

proteolysis, which can reveal differences and similarities in morphology.

Differences in assay conditions can also influence the measurement of ligand dissociation constants. For radioligand assays, washing steps are used to separate bound and free ligand. Poorly optimised washing steps may remove bound ligand, leading to incorrect quantification of binding.[47,48] For fluorescence competition assays, **1** is commonly used as a reporting ligand. However, **1** is typically sold as an impure mixture with dye content as low as 65%, so purification by recrystallisation is required for quantitative measurements.[392] Additionally **1** typically shows only micromolar affinities for amyloid fibrils, but at concentrations above 4–5 μM in aqueous solution **1** forms micelles and self-fluoresces.[392–394] Accurately measuring the micromolar binding of **1** is therefore challenging, possibly explaining the large variability in K_d values for **1** binding to αSyn. An additional source of error may be the methods used to analyse titration data. Many publications do not describe the procedure used to fit titration data to a binding isotherm, and some use a two-site binding model to fit data without a clear justification or comparison to a one-site model.

The variation of measurements reported within individual studies, *i.e.* the reported error, is illustrated in Fig. 7. The median error in the reported K_d was 15% or 0.35 log units, and only 9% of the reported K_d measurements had an error greater than 1 log unit. In contrast, 42% of the ligands listed in

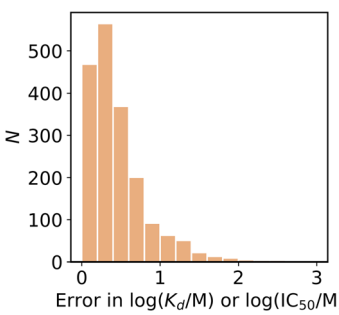

Fig. 7 Frequency distribution of reported errors in binding affinities in the database.

Fig. 5 have K_d measurements with a range of more than 1 log unit. The variations reported within individual studies is therefore less than the variation between studies. To accurately represent this variation it is important that truly independent replicates are performed, and that the meaning of provided error values are stated. It should be clear whether a reported error is, for example, a confidence interval or a standard error.

Steps can therefore be taken to reduce, or better understand, the variability in reported K_d values: the method for fibril aggregation and isolation should be reported in detail; fibrils should be characterised using techniques such as TEM, CD, and limited proteolysis; the method used for the binding assay should be reported in detail; the method used to fit titration data should be reported, as well as justification for the use of isotherms that are more complex than a one-site model. In other words, the variation in K_d values highlighted in Fig. 5 is most likely due to differences in what was actually measured in different reports of the same ligand–fibril interaction.

Ligand selectivity

Amyloid ligands that selectively bind to a specific type of fibril are useful for imaging and diagnostic applications. To evaluate binding selectivity between different fibril targets, ligands in the database with K_d values for two or more types of fibril were identified. As above, only K_d values measured using the same assay method and a one-site binding model were compared, and K_d values measured using competition binding assays were only compared for reporting ligands from the same structural class (see Fig. 4). When multiple K_d values were reported for the same ligand–fibril combination with the same assay method, the average value was used.

If the ligand binding profiles for different types of amyloid fibril are similar, we can assume that the nature of the binding sites that are present are likely to be similar. The root mean square difference (RMSD) in ligand binding affinity as defined by eqn (1) was therefore used for pairwise comparison of different amyloid fibrils.

$$\mathrm{RMSD} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(\log\left(K_{\mathrm{d},i,\mathrm{A}}\right) - \log\left(K_{\mathrm{d},i,\mathrm{B}}\right)\right)} \qquad (1)$$

where n is the number of ligands, and $K_{\mathrm{d},i,\mathrm{A}}$ and $K_{\mathrm{d},i,\mathrm{B}}$ are the dissociation constants for ligand i binding to fibril A and fibril B respectively.

Fig. 8 shows that there is an excellent correlation between the results obtained for ligand binding to Aβ(1–40) and Aβ(1–42) fibrils. The RMSD between the $\log(K_d/M)$ for Aβ(1–40) and the $\log(K_d/M)$ for Aβ(1–42) is 0.46, and most of the datapoints fall very close to the $y = x$ line. This result suggests that the binding sites on Aβ(1–40) and Aβ(1–42) fibrils are structurally similar, so the data for ligands binding to both Aβ fibril isoforms will be combined and collectively referred to as Aβ fibrils. There are two outliers highlighted in red in Fig. 8, and the structures of these ligands are shown in Fig. 9. Thiazine red (ThR, **24**) and curcumin (**25**) show selectivity between the two Aβ isoforms with an affinity

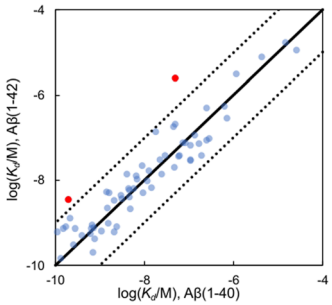

Fig. 8 Comparison of values of K_d measured for ligand binding to Aβ(1–40) and Aβ(1–42) fibrils (65 ligands, RMSD = 0.46 log units). The solid line is $y = x$, and the dotted lines correspond to ± 1 log unit. Red datapoints are outliers that bind to one fibril target at least one order-of-magnitude stronger than the other fibril target. The chemical structures of these outliers are shown in Fig. 9.

for Aβ(1–40) that is more than an order of magnitude higher than for Aβ(1–42).

Fig. 10 compares dissociation constants measured for the same ligand binding to Aβ, αSyn, and tau. The ligand affinities for Aβ and tau fibrils are broadly similar with most datapoints clustered around the $y = x$ line and an overall RMSD of 0.55 log units (Fig. 10(a)). However, when binding of a ligand to either Aβ or tau is compared with the affinity for αSyn fibrils, the correlation is much weaker (RMSD = 0.66 log units for Fig. 10(b), and 0.79 log units for Fig. 10(c)). These results suggest that the ligand binding sites found on Aβ and tau have a high degree of similarity, but αSyn fibrils are quite different, which would make αSyn selective ligands an attractive target.

The structures of the ligands that are outliers in Fig. 10 (highlighted in red) are shown in Fig. 10–12. The ligands in Fig. 11 show selectivity for Aβ over αSyn. Ligands **29** and **30** also show selectivity for Aβ over tau.[54,55] The ligands in Fig. 12 show selectivity for tau over Aβ, although **36** only bound to soluble rather than insoluble tau aggregates.[56] Ligands **33**, **34**, and **35** also show selectivity for tau over αSyn. Fig. 13 shows the ligands that selectivity bind to αSyn fibrils.[54,55,57–61]

Fig. 14 compares the K_d values measured for ligands binding to AD brain homogenates with the K_d values for binding to Aβ and tau fibrils. Relatively small datasets are available, although several selective ligands were identified. The benzoheterocycles flutemetamol (**43**), AZD2184 (**44**), and **45** are all selective for AD brain homogenates. IMSB (**46**) has a greater affinity for Aβ

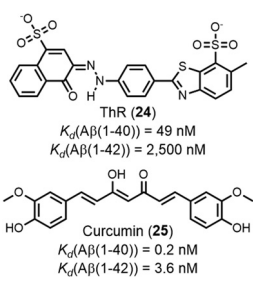

Fig. 9 Structures of ligands that show selectively between Aβ(1–40) fibrils and Aβ(1–42) fibrils, highlighted as red datapoints in in Fig. 8.

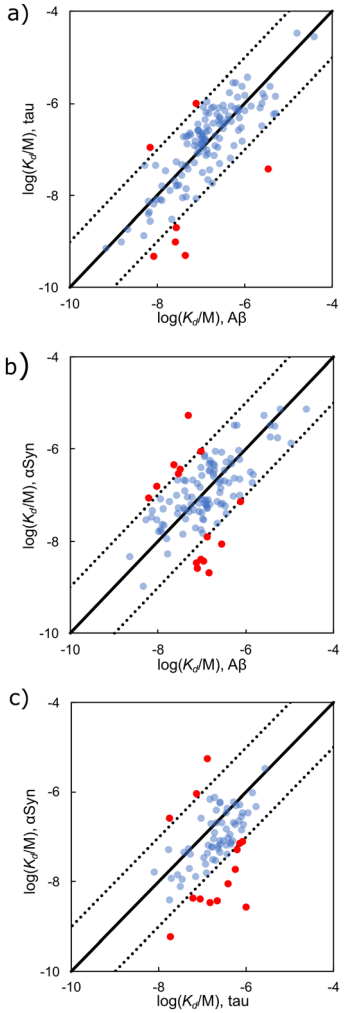

Fig. 10 Comparison of K_d values measured for ligand binding to (a) Aβ and tau fibrils (139 ligands, RMSD = 0.55 log units), (b) Aβ and αSyn fibrils (119 ligands, RMSD = 0.66 log units), and (c) tau and αSyn fibrils (76 ligands, RMSD = 0.79 log units). The solid line is $y = x$, and the dotted lines correspond to ± 1 log unit. Red datapoints bind to one fibril type at least one order-of-magnitude stronger than the other (structures in Fig. 11 and 12).

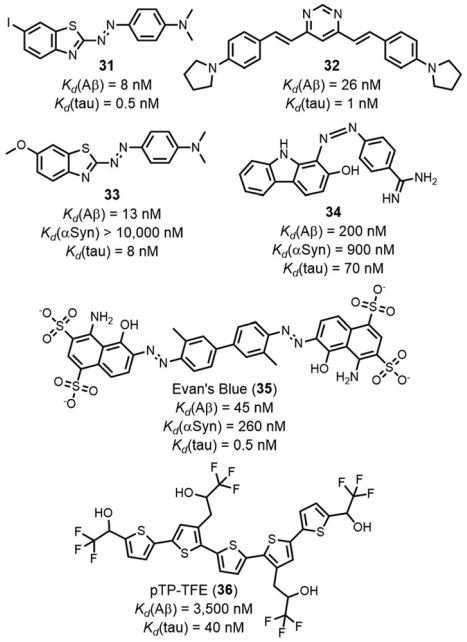

Fig. 12 Structures of ligands that show selective binding for tau fibrils, highlighted as red datapoints in in Fig. 10(a) and (c).

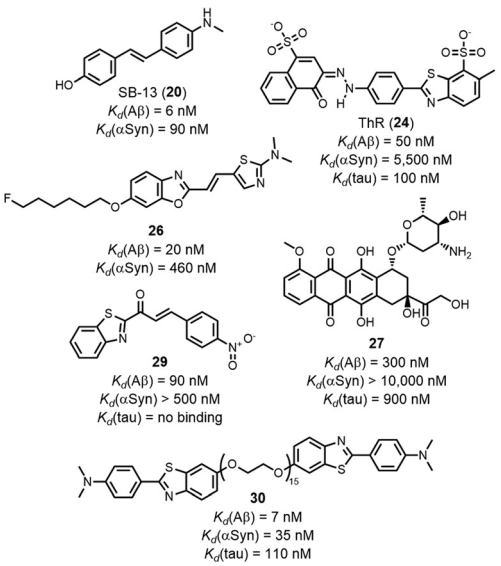

Fig. 11 Structures of ligands that show selective binding for Aβ fibrils, highlighted as red datapoints in in Fig. 10(a) and(b).

fibrils, and a screen of several indanones by Nan *et al.* demonstrated that all had a higher affinity for Aβ fibrils (*e.g.* **47**).[62] Amyloid ligands are often screened against fibrils formed *in vitro* (*e.g.* Aβ or tau fibrils) as a substitute for fibrils formed *in vivo* (*e.g.* AD brain homogenates). Fig. 14 suggests that binding affinities against *in vitro* Aβ and tau fibrils are similar to binding affinities against AD brain homogenates, although a larger dataset would help define the limitations of this comparison. For example, different types of ligands target different binding sites, and some binding sites on *in vitro* fibrils may more closely resemble biological binding sites than others. Additionally, different publications appear to be screening ligands against different fibril morphologies. Some *in vitro* preparations will be more representative of biological fibrils than others. Recently *in vitro* aggregation procedures have been reported that produce fibrils with biological morphologies, which would lead to more biologically relevant binding assays.[28]

Selectivity was also achieved by using different types of binding assays. Honson *et al.* demonstrated that **24** selectively targeted tau (K_d = 200 nM) over Aβ(1–42) (K_d > 2000 nM) fibrils when measured by a fluorescence displacement assay with thioflavin S (ThS, **54**). However, **24** exhibited a similar affinity to both fibrils (K_d = 1000–2500 nM) when measured by a fluorescence saturation assay.[63] This difference in affinity may be due to different assays targeting different binding sites.

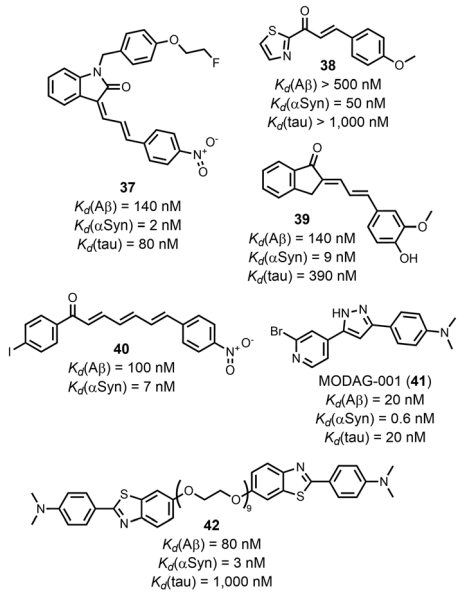

Fig. 13 Structures of ligands that show selective binding for αSyn fibrils, highlighted as red datapoints in in Fig. 10(b) and (c).

Ligand hydrophobicity

The relationship between K_d and various molecular descriptors of the ligands (*e.g.* molecular weight, topological polar surface area, the number of rotatable bonds) was explored. The only descriptor found to have any relationship with K_d was log *P* (see ESI†). Amyloid ligands are thought to bind in hydrophobic grooves on the surface of fibrils,[392] and if the hydrophobic effect is largely responsible for binding, there may be some relationship between the log(K_d/*M*) and the *n*-octanol–water partition coefficient (log *P*) of the ligands. The value of log *P* provides a measure of the free energy change associated with replacing the solvation shell of a ligand dissolved in water with a non-polar environment (Fig. 16(a)), and simple calculations based on chemical structure provide reasonably reliable values of log *P*.[396] In general non-polar groups, such as hydrocarbons, increase the value of log *P*, while polar functional groups, such

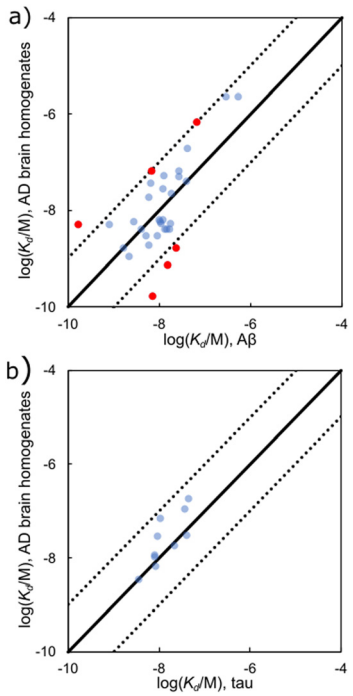

Fig. 14 Comparison of values of K_d measured for ligand binding to (a) Aβ fibrils and AD brain homogenates (32 ligands RMSD = 0.70 log units), and (b) tau fibrils and AD brain homogenates (7 ligands, RMSD = 0.40 log units). The solid line is $y = x$, and the dotted lines correspond to ± 1 log unit. Red datapoints are outliers that bind to one fibril target at least one order-of-magnitude stronger than the other fibril target. The chemical structures of these outliers are shown in Fig. 15.

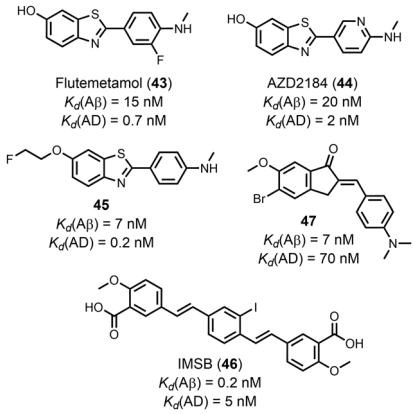

Fig. 15 Structures of ligands that show selectively between Aβ fibrils and AD brain homogenates, highlighted as red datapoints in Fig. 14.

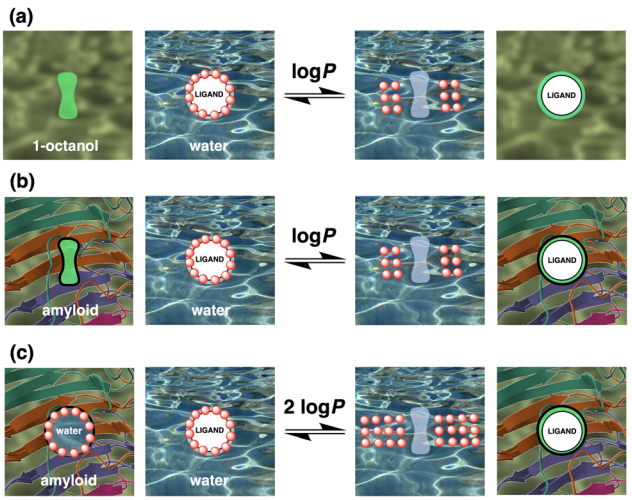

Fig. 16 Relationship between ligand binding affinity and log *P*. (a) Transfer of a ligand from water into 1-octanol involves release of high energy water molecules from the non-polar surface of the ligand (red) into bulk water. (b) Binding of a ligand to a hydrophobic pocket, which is collapsed and not solvated, only requires desolvation of the ligand with release of the same high energy water molecules (red). (c) Binding of a ligand to a hydrophobic pocket, which is open and solvated, requires desolvation of both the ligand and the binding pocket with release of twice as many high energy water molecules (red).

as hydroxyls, are well-solvated by water and decrease the value of log *P*.

Fig. 17 compares the values of K_d measured for ligands binding to AD brain homogenates, Aβ fibrils, tau fibrils, and αSyn fibrils with the corresponding values of log *P*. Although there is no direct correlation between the two parameters, high affinity ligands tend to have a log *P* value of 3 or more. There appears to be a sharp cut-off in Fig. 17(a), indicated by the red line, suggesting that there is a lower limit on the value of K_d that can be achieved for a given value of log *P*. Many hydrophobic ligands lie to the right of this line and exhibit lower binding affinities, but there are some polar ligands that lie to the left of the line and exhibit a higher binding affinity. The slope of this red line is −2, corresponding to where the $\log(K_d/M)$ of a ligand is proportional to twice the log *P* of the ligand.

A slope of −2 would be expected for idealised ligand binding that is based entirely on the hydrophobic effect. If a ligand was completely desolvated on binding into a completely non-polar pocket on the surface of a fibril, then the binding affinity would be directly related to log *P*, if the binding pocket on the fibril did not require any desolvation (Fig. 16(b)). However, ligand binding involves not only desolvation of the ligand, it also requires desolvation of the binding pocket. If the binding pocket was perfectly complementary to the ligand, then the molecular surface that would be desolvated on the fibril would be the same as the surface of the ligand. The contribution due to desolvation of both the ligand and the binding pocket would therefore be twice the value of log *P* for the ligand (Fig. 16(c)).

Ligands that are not perfectly complementary to the binding site or are not fully encapsulated inside the pocket on the surface of the fibril will have lower affinities because they fail to maximise the hydrophobic interactions that are possible. Fig. 17(a) shows that increasing the hydrophobicity of the ligand does not necessarily improve affinity, because hydrophobicity can be added in regions that do not contact the binding site. For example, there are ligands with log *P* values ranging from 2 to 8 that all achieve the same $\log(K_d/M)$ of −8.

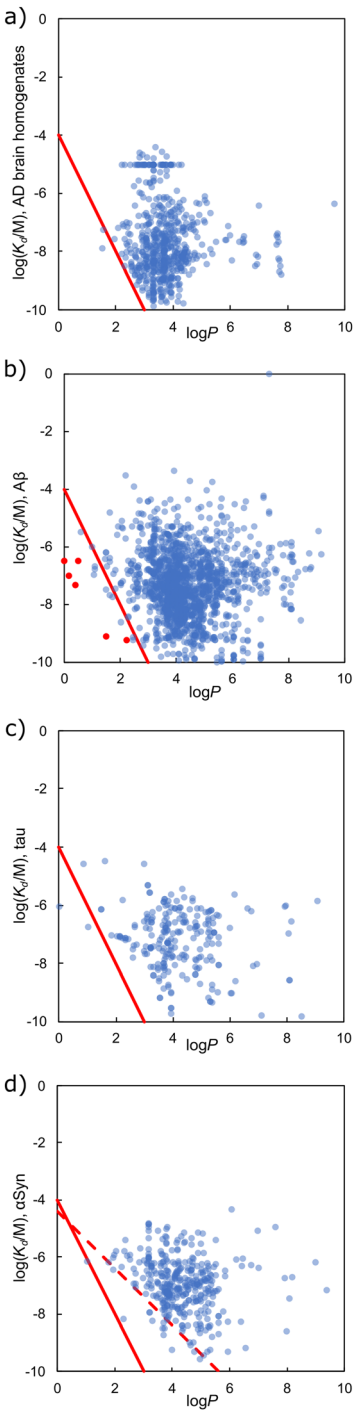

Fig. 17 Comparison of ligand log *P* values[395] with values of $\log(K_d/M)$ measured for binding to (a) AD brain homogenates, (b) Aβ fibrils, (c) tau fibrils, and (d) αSyn fibrils. The slope of the solid red lines is −2, and the slope of the dotted red line is −1. Examples of outliers with a binding affinity greater than that predicted by the solid red line are highlighted in red. The chemical structures of these outliers are shown in Fig. 18.

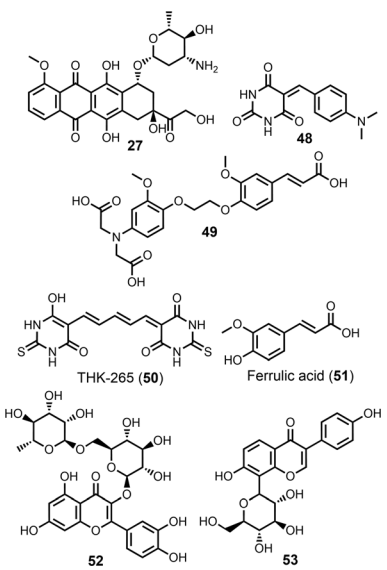

Fig. 18 Structures of polar Aβ ligands with high binding affinities, highlighted as red datapoints in Fig. 17(b).

However, there are no ligands with a log *P* value less than 2 that achieve a log(K_d/M) of −8.

Although there is more scatter in the Aβ data shown in Fig. 17(b), a similar cut-off appears to apply to these measurements. There are two differences between Fig. 17(a) and (b). Firstly, the cut-off for the majority of the datapoints in Fig. 17(b) appears to be displaced to the right by about one log *P* unit compared with the red cut-off line. Notably, when binding of the same ligand to AD brain homogenates and Aβ fibrils was compared, significant differences were not observed (Fig. 14(a)). However, Fig. 14 considered only a subset of ligands that were screened against both targets, whereas the data shown in Fig. 17 is for all ligands in the database. The other notable difference between Fig. 17(a) and (b) is that a small number of ligands lie to the left of the cut-off line and have higher affinities for Aβ fibrils than the hydrophobic effect alone would allow (red datapoints in Fig. 17(b)). Polar interactions with some of the functional groups on these more polar ligands (Fig. 18) may play an important role in binding. Ligands that make binding site-specific polar interactions are particularly attractive lead compounds for the development of ligands with increased fibril selectivity. Alternatively, polar groups like the sugars in **27**, **51** and **52** may sit outside the binding pocket and have a minimal impact on binding, whilst significantly decreasing log *P* of the ligand.

Fewer datapoints are available for ligand binding to tau and αSyn fibrils. The relationship between K_d and log *P* for tau fibrils is similar to that observed for AD brain homogenates and Aβ fibrils. For αSyn fibrils, the datapoints are significantly displaced to the right of the cut-off line (Fig. 17(d)). For ligands with similar hydrophobicities, binding affinities for αSyn fibrils were generally lower than observed for the other fibrils. This result suggests that there may be some fundamental difference in the structure of the binding sites present on αSyn fibrils, which is consistent with the differences in ligand binding affinities highlighted in Fig. 10. For example, if the αSyn binding pocket were partially collapsed in the absence of ligand, then the hydrophobic contribution to binding would be substantially reduced. In the limit where no desolvation of the binding pocket was required, because it was fully collapsed and opened only to accommodate a ligand, then the maximum log(K_d/*M*) of a ligand would become proportional to twice the log *P* of the ligand. The red dotted line in Fig. 17(b) shows this situation and provides a rather good description of an alternative cut-off line for the αSyn data. Of course, it is also possible that only relatively weak αSyn ligands have been discovered to date.

Binding site heterogeneity

Competition binding assays are a useful tool for identifying different binding sites on amyloid fibrils. Typically, a competing ligand is titrated into a solution of fibril bound to a reporting ligand that produces either a fluorescent or radioactive signal (Fig. 2). Binding of the competing ligand (L1) is observed by monitoring changes in the signal produced by the reporting ligand (L0). Using this assay format, ligands that target the same or different binding sites can be identified. Several publications have used this approach and show that some ligands independently bind to amyloid fibrils but do not compete with one another, indicating the presence of different types of binding sites.[64–67,397] Similarly, if the dissociation constant measured for a competing ligand changes as a function of the reporter ligand, then the presence of multiple binding sites with different ligand affinities can be inferred.

A small number of binding site models have previously been proposed for amyloid fibrils based on competition binding assays and a range of analytical and computational techniques.[65–67,397–406] Lockhart *et al.*, Ye *et al.*, and LeVine all reported Aβ(1–40) binding site models and include multiple ThT **1** binding sites, a separate high-affinity FBH site, and a site accessible to both ThT **1** and CRD.[66,67,401] Ye *et al.* also proposed that CRD and FBH share a binding site, which other studies do not show.[67] Hsieh *et al.* proposed a binding site model for αSyn fibrils with three sites, denoted site 2, site 9, and site 3/13.[65] S5H were shown to bind to site 2, with a weaker affinity for site 9, while PIP were shown to bind to site 9, with a weaker affinity for site 2. OXI and PHT targeted site 3/13. Cai *et al.* identified that FBH, QUI, and CAR all have separate high-affinity binding sites in AD brain homogenates.[397] However, all of these binding sites consider a relatively small subset of amyloid binding ligands and do not consider other data from the literature.

Here, data from different competition binding assays is collated to propose binding site models for each of these fibril types. The ligands in the database were first grouped by structural class (Fig. 4), as ligands with a shared structural core are assumed to target the same subset of fibril binding sites. Structural class BSB was found to consistently target the same binding sites as CRD, and so these ligands are treated as a single CRD class in the analysis that follows. Key reporter ligands commonly used in competition assays are shown in Fig. 19.

Heatmaps were used to summarise competition binding experiments for each fibril type. Fig. 20 shows the heatmap for Aβ(1–40) fibrils (see ESI† for other fibrils). Green tiles are used to show that the ligand class on the *y*-axis displaces the ligand class on the *x*-axis. Red tiles are used to show that no

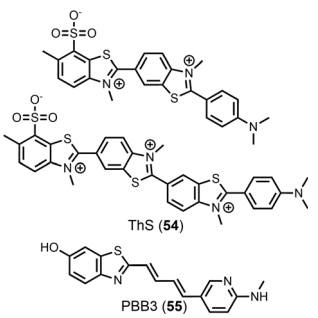

Fig. 19 Structures of additional ligands commonly used in competition assays. ThS **54** is used as a mixture of compounds, with the two most abundant components shown.

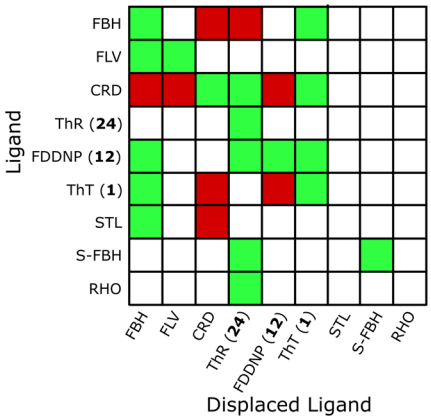

Fig. 20 Heatmap summarising competition binding experiments for Aβ(1–40) fibrils. A green tile indicates that a ligand or structural class on the *y*-axis displaced a ligand or structural class on the *x*-axis. A red tile indicates that no displacement was observed, and a white tile indicates that there is no data available.

displacement was observed, and white tiles indicate experiments that have not been carried out. The data in the heatmap can be used to construct the simplest binding site model that satisfies the competition binding assay data for each fibril.

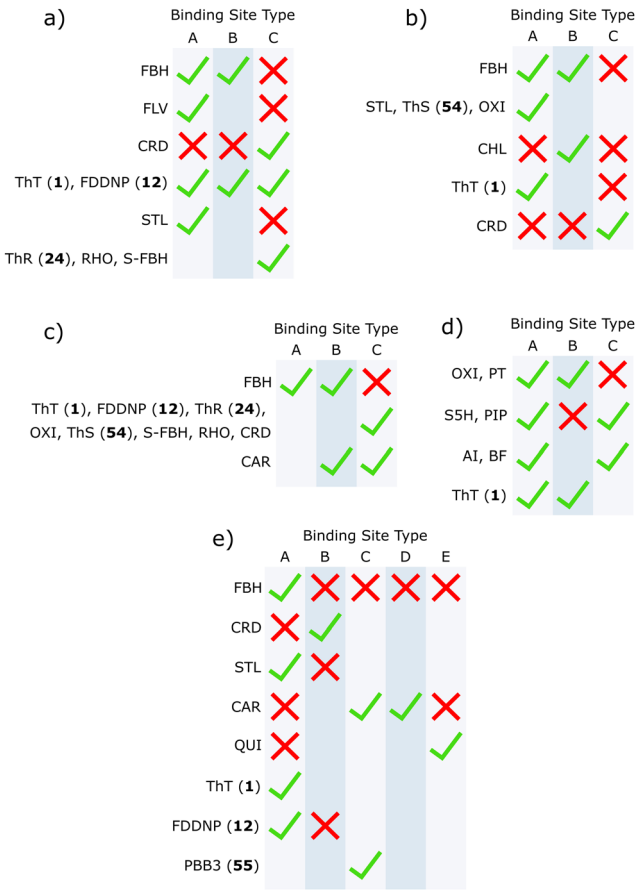

Fig. 21 Binding site model for (a) Aβ(1–40) fibrils, (b) Aβ(1–42) fibrils, (c) tau fibrils, (d) αSyn fibrils, and (e) AD brain homogenates. Ticks and crosses indicate whether a ligand or structural class does or does not bind to a site.

Analysis of the data in Fig. 20 requires three different binding sites. For example, FBH bind to Aβ(1–40) fibrils with a high affinity at a site we define as site A. Ligands FLV, STL, ThT and FDDNP displace FBH and therefore also bind to site A. Several reports suggest that FBH targets a second site on Aβ(1–40) fibrils that is also shared with ThT, which we define as site B. Ligand CRD is not displaced by either FBH or ThT, which means that there is a third site, which we define as site C. Some reports suggest that ThT and CRD share a binding site,[66,260] so ThT may also bind to site C. This assignment is supported by reports that show that ThT completely displaces FBH, but FBH partially displaces ThT.[66] However, it is also worth noting that other reports find no competition between ThT and CRD.[166,325] The three binding site model shown in Fig. 21(a) accounts for all of the competition experiments shown in the heatmap in Fig. 20. A similar analysis was carried out for Aβ(1–42), tau, αSyn, and AD brain homogenates to give the binding site models summarised in Fig. 21 (see ESI† for details).

Using the results from reported competition binding assays we have constructed models of the binding sites present on different types of amyloid fibrils. Each site bound a different combination of ligands, and many ligands were shown to bind to multiple sites. While different binding studies may employ morphologically distinct fibrils, these models were supported by data from multiple sources. Some inconsistencies were observed between publications, such as the orthogonal binding of ThT **1** and CRD to Aβ(1–40) fibrils. These inconsistencies may suggest that certain binding sites are particularly sensitive to fibril morphology and could therefore inform the development of morphology-selective ligands. These binding site models also allow specific binding sites to be targeted by designing competition assays using specific combinations of ligands.

Conclusions

In summary we have compiled a comprehensive database of amyloid-binding ligands, comprising a total of 3457 experimental dissociation constants for 2076 unique compounds. This represents the largest reported database of ligands that bind amyloid fibrils involved in neurodegenerative diseases. Our hope is that this database will be used to guide ligand development and to improve our understanding of how ligands interact with amyloid fibrils.

The reproducibility of binding measurements in this database was then investigated. Many examples of ligands with binding constants spanning more than an order of magnitude were found. This variability may be a result of ligands being assayed against different fibril morphologies, which must be considered when comparing binding studies.

Ligands were then shown to bind to Aβ(1–40) and Aβ(1–42) fibrils with similar affinities, whereas a greater difference was found for binding to Aβ or tau and αSyn fibrils. This result may be due to αSyn fibrils possessing the most unique binding sites, or due to the larger number of studies developing αSyn-

selective ligands. Ligands were then found to bind AD brain homogenates similarly to Aβ and tau fibrils that were formed *in vitro*, although more work is needed to confidently determine how representative these *in vitro* fibrils are of biological fibrils for binding studies.

The binding of ligands to fibril binding sites was then found to be limited by the hydrophobic effect. Near complete desolvation of both the ligand and binding site is observed for high-affinity ligands binding to AD brain homogenates. For Aβ fibrils, some ligands did not fit into this hydrophobicity-limited model suggesting that polar interactions can contribute to binding this target. For αSyn fibrils, relatively little desolvation of the binding site was required for binding to occur.

Finally, binding site models were constructed for Aβ(1–40), Aβ(1–42), tau, and αSyn fibrils, and AD brain homogenates. Three to five binding sites were found for each fibril, and the ligands that target each site were identified. This result provides a framework for interpreting the results of binding assays, and for designing new site-specific assays.

Author contributions

The manuscript was written through contributions of all authors.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 J. Greenwald and R. Riek, *Structure*, 2010, **18**, 1244–1260.
2 Z. L. Almeida and R. M. M. Brito, *Molecules*, 2020, **25**, 1195.
3 C. A. Mathis, B. J. Lopresti, M. D. Ikonomovic and W. E. Klunk, *Semin. Nucl. Med.*, 2017, **47**, 553–575.
4 J. Vaquer-Alicea and M. I. Diamond, *Annu. Rev. Biochem.*, 2019, **88**, 785–810.
5 P. C. Ke, R. Zhou, L. C. Serpell, R. Riek, T. P. J. Knowles, H. A. Lashuel, E. Gazit, I. W. Hamley, T. P. Davis, M. Fändrich, D. E. Otzen, M. R. Chapman, C. M. Dobson, D. S. Eisenberg and R. Mezzenga, *Chem. Soc. Rev.*, 2020, **49**, 5473–5509.
6 F. Chiti and C. M. Dobson, *Annu. Rev. Biochem.*, 2017, **86**, 27–68.
7 F. U. Hartl, *Annu. Rev. Biochem.*, 2017, **86**, 21–26.
8 P. Sweeney, H. Park, M. Baumann, J. Dunlop, J. Frydman, R. Kopito, A. McCampbell, G. Leblanc, A. Venkateswaran, A. Nurmi and R. Hodgson, *Transl. Neurodegener.*, 2017, **6**, 6.
9 A. Alzheimer, *Neurol. Cent.*, 1906, **23**, 1129–1136.
10 A. Alzheimer, *Allg. Z. Psychiatr. Psych.-Gerichtl. Med.*, 1907, **64**, 146–148.
11 G. R. Lafora, *Trab. Lab. Invest. Biol. Univers. Madr.*, 1913, **11**, 29–42.
12 G. R. Lafora, *Trab. Lab. Invest. Biol. Univers. Madr.*, 1913, **11**, 43–54.
13 F. H. Lewy, in *Handbuch der Neurologie, Dritter Band, Spezielle Neurologie I*, ed. M. Lewandowsky, Julius Springer, Berlin, 1912, pp.920–933.
14 C. Trétiakoff, *Contribution a l'etude l'anatomie pathologique du locus Niger de soemmering: avec quelques déductions relatives à la pathogénie des troubles du tonus musculaire et de la maladie de Parkinson*, Jouve, 1919.
15 M. G. Spillantini, M. L. Schmidt, V. M.-Y. Lee, J. Q. Trojanowski, R. Jakes and M. Goedert, *Nature*, 1997, **388**, 839–840.
16 R. N. Rambaran and L. C. Serpell, *Prion*, 2008, **2**, 112–117.
17 M. Sunde, L. C. Serpell, M. Bartlam, P. E. Fraser, M. B. Pepys and C. C. F. Blake, *J. Mol. Biol.*, 1997, **273**, 729–739.
18 B. C. Creekmore, Y. W. Chang and E. B. Lee, *J. Neuropathol. Exp. Neurol.*, 2021, **80**, 514–529.
19 M. G. Iadanza, M. P. Jackson, E. W. Hewitt, N. A. Ranson and S. E. Radford, *Nat. Rev. Mol. Cell Biol.*, 2018, **19**, 755–773.
20 D. Li and C. Liu, *Nat. Rev. Neurosci.*, 2022, **23**, 523–534.
21 M. Fändrich, M. Schmidt and N. Grigorieff, *Trends Biochem. Sci.*, 2011, **36**, 338–345.
22 B. H. Toyama and J. S. Weissman, *Annu. Rev. Biochem.*, 2011, **80**, 557–585.
23 A. K. Paravastu, R. D. Leapman, W. M. Yau and R. Tycko, *Proc. Natl. Acad. Sci. U. S. A.*, 2008, **105**, 18349–18354.
24 M. Y. Suvorina, O. M. Selivanova, E. I. Grigorashvili, A. D. Nikulin, V. V. Marchenkov, A. K. Surin and O. V. Galzitskaya, *J. Alzheimer's Dis.*, 2015, **47**, 583–593.
25 M. Fändrich, J. Meinhardt and N. Grigorieff, *Prion*, 2009, **3**, 89–93.
26 J. P. Colletier, A. Laganowsky, M. Landau, M. Zhao, A. B. Soriaga, L. Goldschmidt, D. Flot, D. Cascio, M. R. Sawaya and D. Eisenberg, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 16938–16943.
27 W. Hoyer, T. Antony, D. Cherny, G. Heim, T. M. Jovin and V. Subramaniam, *J. Mol. Biol.*, 2002, **322**, 383–393.
28 S. Lövestam, F. A. Koh, B. van Knippenberg, A. Kotecha, A. G. Murzin, M. Goedert and S. H. W. Scheres, *eLife*, 2022, **11**, e76494.
29 V. H. Finder, I. Vodopivec, R. M. Nitsch and R. Glockshuber, *J. Mol. Biol.*, 2010, **396**, 9–18.
30 T. Härd, *J. Phys. Chem. Lett.*, 2014, **5**, 607–614.
31 P. I. Kitov, J. M. Sadowska, G. Mulvey, G. D. Armstrong, H. Ling, N. S. Pannu, R. J. Read and D. R. Bundle, *Nature*, 2000, **403**, 669–672.
32 G. Bhak, J. Lee, T. H. Kim, S. Lee, D. Lee and S. R. Paik, *Biochem. J.*, 2014, **464**, 259–269.
33 A. T. Petkova, R. D. Leapman, Z. Guo, W. M. Yau, M. P. Mattson and R. Tycko, *Science*, 2005, **307**, 262–265.

34 L. Bousset, A. Alik, A. Arteni, A. Böckmann, B. H. Meier and R. Melki, *Methods Mol. Biol.*, 2023, **2551**, 345–355.
35 R. Guerrero-Ferreira, N. M. I. Taylor, A. A. Arteni, P. Kumari, D. Mona, P. Ringler, M. Britschgi, M. E. Lauer, A. Makky, J. Verasdock, R. Riek, R. Melki, B. H. Meier, A. Böckmann, L. Bousset and H. Stahlberg, *eLife*, 2019, **8**, e48907.
36 P. Ragonis-Bachar and M. Landau, *Curr. Opin. Struct. Biol.*, 2021, **68**, 184–193.
37 C. A. Mathis, N. S. Mason, B. J. Lopresti and W. E. Klunk, *Semin. Nucl. Med.*, 2012, **42**, 423–432.
38 N. S. Mason, C. A. Mathis and W. E. Klunk, *J. Labelled Compd. Radiopharm.*, 2013, **56**, 89–95.
39 A. Leuzy, K. Chiotis, L. Lemoine, P. G. Gillberg, O. Almkvist, E. Rodriguez-Vieitez and A. Nordberg, *Mol. Psychiatry*, 2019, **24**, 1112–1134.
40 L. Saint-Aubert, L. Lemoine, K. Chiotis, A. Leuzy, E. Rodriguez-Vieitez and A. Nordberg, *Mol. Neurodegener.*, 2017, **12**, 19.
41 A. Kallinen and M. Kassiou, *Nucl. Med. Biol.*, 2022, **114–115**, 115–127.
42 D. Willbold, B. Strodel, G. F. Schröder, W. Hoyer and H. Heise, *Chem. Rev.*, 2021, **121**, 8285–8307.
43 A. Aliyan, N. P. Cook and A. A. Martí, *Chem. Rev.*, 2019, **119**, 11819–11856.
44 A. Kaur, E. J. New and M. Sunde, *ACS Sens.*, 2020, **5**, 2268–2282.
45 F. Tang, K. Wang, X. Liu, X. Zhang, W. Zhou, Z. Mu, T. Zhang, W. Shu, Y. Liu and H. Xiao, *Chem. – Eur. J.*, 2023, **29**, e202300592.
46 D. Su, W. Diao, J. Li, L. Pan, X. Zhang, X. Wu and W. Mao, *ACS Chem. Neurosci.*, 2022, **13**, 540–551.
47 J. J. Maguire, R. E. Kuc and A. P. Davenport, *Methods Mol. Biol.*, 2012, **897**, 31–77.
48 A. P. Davenport and F. D. Russell, *Current Directions in Radiopharmaceutical Research and Development*, Springer, Netherlands, 1996, pp.169–179.
49 D. B. Bylund and M. L. Toews, *Am. J. Physiol. Lung Cell. Mol. Physiol.*, 1993, **265**, L421–L519.
50 Y. Wang, W. E. Klunk, M. L. Debnath, G. F. Huang, D. P. Holt, L. Shao and C. A. Mathis, *J. Mol. Neurosci.*, 2004, **24**, 55–62.
51 J. Kang and K. Han, *Bull Korean Chem. Soc.*, 2001, **22**, 1065.
52 L. Lemoine, P.-G. Gillberg, M. Svedberg, V. Stepanov, Z. Jia, J. Huang, S. Nag, H. Tian, B. Ghetti, N. Okamura, M. Higuchi, C. Halldin and A. Nordberg, *Alzheimer's Res. Ther.*, 2017, **9**, 96.
53 A. Manook, B. H. Yousefi, A. Willuweit, S. Platzer, S. Reder, A. Voss, M. Huisman, M. Settles, F. Neff, J. Velden, M. Schoor, H. von der Kammer, H. J. Wester, M. Schwaiger, G. Henriksen and A. Drzezga, *PLoS One*, 2012, **7**, e31310.
54 C. J. Hsieh, K. Xu, I. Lee, T. J. A. Graham, Z. Tu, D. Dhavale, P. Kotzbauer and R. H. Mach, *ACS Omega*, 2018, **3**, 4486–4493.
55 E. Sanna, M. Rodrigues, S. G. Fagan, T. S. Chisholm, K. Kulenkampff, D. Klenerman, M. G. Spillantini, F. I. Aigbirhio and C. A. Hunter, *Chem. Sci.*, 2021, **12**, 8892–8899.
56 Y. Zhao, O. Tietz, W.-L. L. Kuan, A. K. Haji-Dheere, S. Thompson, B. Vallin, E. Ronchi, G. Tóth, D. Klenerman and F. I. Aigbirhio, *Chem. Sci.*, 2020, **11**, 4773–4778.
57 W. Chu, D. Zhou, V. Gaba, J. Liu, S. Li, X. Peng, J. Xu, D. Dhavale, D. P. Bagchi, A. D'Avignon, N. B. Shakerdge, B. J. Bacskai, Z. Tu, P. T. Kotzbauer and R. H. Mach, *J. Med. Chem.*, 2015, **58**, 6002–6017.
58 X. Sun, P. Admane, Z. A. Starosolski, J. L. Eriksen, A. V. Annapragada and E. A. Tanifum, *ChemMedChem*, 2022, **17**, e202100611.
59 S. Kaide, H. Watanabe, S. Iikuni, M. Hasegawa, K. Itoh and M. Ono, *ACS Chem. Neurosci.*, 2021, **13**, 16–26.
60 S. Kaide, H. Watanabe, S. Iikuni, M. Hasegawa and M. Ono, *ACS Chem. Neurosci.*, 2022, **13**, 2982–2990.
61 L. Kuebler, S. Buss, A. Leonov, S. Ryazanov, F. Schmidt, A. Maurer, D. Weckbecker, A. M. Landau, T. P. Lillethorup, D. Bleher, R. S. Saw, B. J. Pichler, C. Griesinger, A. Giese and K. Herfert, *Eur. J. Nucl. Med. Mol. Imaging*, 2021, **48**, 1759–1772.
62 D. D. Nan, C. S. Gan, C. W. Wang, J. P. Qiao, X. M. Wang and J. N. Zhou, *Eur. J. Med. Chem.*, 2016, **124**, 117–128.
63 N. S. Honson, R. L. Johnson, W. Huang, J. Inglese, C. P. Austin and J. Kuret, *Neurobiol. Dis.*, 2007, **28**, 251–260.
64 Z. P. Zhuang, M. P. Kung, C. Hou, D. M. Skovronsky, T. L. Gur, K. Plössl, J. Q. Trojanowski, V. M. Y. Lee and H. F. Kung, *J. Med. Chem.*, 2001, **44**, 1905–1914.
65 C. J. Hsieh, J. J. Ferrie, K. Xu, I. Lee, T. J. A. Graham, Z. Tu, J. Yu, D. Dhavale, P. Kotzbauer, E. J. Petersson and R. H. Mach, *ACS Chem. Neurosci.*, 2018, **9**, 2521–2527.
66 A. Lockhart, L. Ye, D. B. Judd, A. T. Merrittu, P. N. Lowe, J. L. Morgenstern, G. Hong, A. D. Gee and J. Brown, *J. Biol. Chem.*, 2005, **280**, 7677–7684.
67 L. Ye, J. L. Morgenstern, A. D. Gee, G. Hong, J. Brown and A. Lockhart, *J. Biol. Chem.*, 2005, **280**, 23599–23604.
68 E. D. Agdeppa, V. Kepe, J. Liu, G. W. Small, S. C. Huang, A. Petrič, N. Satyamurthy and J. R. Barrio, *Mol. Imaging Biol.*, 2003, **5**, 404–417.
69 T. Akasaka, H. Watanabe, S. Kaide, S. Iikuni, M. Hasegawa and M. Ono, *Bioorg. Med. Chem. Lett.*, 2022, **64**, 128679.
70 D. Alagille, H. Dacosta, R. M. Baldwin and G. D. Tamagnan, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2966–2968.
71 J. An, P. Verwilst, H. Aziz, J. Shin, S. Lim, I. Kim, Y. K. Kim and J. S. Kim, *Bioact. Mater.*, 2022, **13**, 239–248.
72 U. R. Anumala, J. Gu, F. Lo Monte, T. Kramer, R. Heyny-Von Haußen, J. Hölzer, V. Goetschy-Meyer, C. Schön, G. Mall, I. Hilger, C. Czech, J. Herms and B. Schmidt, *Bioorg. Med. Chem.*, 2013, **21**, 5139–5144.
73 D. P. Bagchi, L. Yu, J. S. Perlmutter, J. Xu, R. H. Mach, Z. Tu and P. T. Kotzbauer, *PLoS One*, 2013, **8**, e55031.
74 H. Benzeid, E. Mothes, E. M. Essassi, P. Faller and G. Pratviel, *C. R. Chim.*, 2012, **15**, 79–85.
75 J. Bian, Y.-Q. Liu, J. He, X. Lin, C.-Y. Qiu, W.-B. Yu, Y. Shen, Z.-Y. Zhu, D.-Y. Ye, J. Wang and Y. Chu, *Eur. J. Med. Chem.*, 2021, **226**, 113887.

76 B. Blass, *ACS Med. Chem. Lett.*, 2014, **5**, 619–620.
77 S. Sanabria Bohórquez, J. Marik, A. Ogasawara, J. N. Tinianow, H. S. Gill, O. Barret, G. Tamagnan, D. Alagille, G. Ayalon, P. Manser, T. Bengtsson, M. Ward, S.-P. Williams, G. A. Kerchner, J. P. Seibyl, K. Marek and R. M. Weimer, *Eur. J. Nucl. Med. Mol. Imaging*, 2019, **46**, 2077–2089.
78 A. Boländer, D. Kieser, C. Voss, S. Bauer, C. Schön, S. Burgold, T. Bittner, J. Hölzer, R. Heyny-Von Haußen, G. Mall, V. Goetschy, C. Czech, H. Knust, R. Berger, J. Herms, I. Hilger and B. Schmidt, *J. Med. Chem.*, 2012, **55**, 9170–9180.
79 E. Boukherrouba, C. Larosa, K.-A. Nguyen, J. Caburet, L. Lunven, H. Bonnet, A. Fortuné, A. Boumendjel, B. Boucherle, S. Chierici and M. Peuchmaur, *Eur. J. Med. Chem.*, 2022, **231**, 114139.
80 S. R. Byeon, Y. J. Jin, S. J. Lim, J. H. Lee, K. H. Yoo, K. J. Shin, S. J. Oh and D. J. Kim, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4022–4025.
81 L. Cai, F. T. Chin, V. W. Pike, H. Toyama, J. S. Liow, S. S. Zoghbi, K. Modell, E. Briard, H. U. Shetty, K. Sinclair, S. Donohue, D. Tipre, M. P. Kung, C. Dagostin, D. A. Widdowson, M. Green, W. Gao, M. M. Herman, M. Ichise and R. B. Innis, *J. Med. Chem.*, 2004, **47**, 2208–2218.
82 L. Cai, J. Cuevas, S. Temme, M. M. Herman, C. Dagostin, D. A. Widdowson, R. B. Innis and V. W. Pike, *J. Med. Chem.*, 2007, **50**, 4746–4758.
83 L. Cai, B. Qu, B. T. Hurtle, S. Dadiboyena, R. Diaz-Arrastia and V. W. Pike, *ACS Chem. Neurosci.*, 2016, **7**, 897–911.
84 M. S. Celej, E. A. Jares-Erijman and T. M. Jovin, *Biophys. J.*, 2008, **94**, 4867–4879.
85 R. Chandra, M. P. Kung and H. F. Kung, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1350–1352.
86 R. Chandra, S. Oya, M. P. Kung, C. Hou, L. W. Jin and H. F. Kung, *J. Med. Chem.*, 2007, **50**, 2415–2423.
87 Y. S. Chang, J. M. Jeong, Y. S. Lee, H. W. Kim, R. B. Ganesha, Y. J. Kim, D. S. Lee, J. K. Chung and M. C. Lee, *Nucl. Med. Biol.*, 2006, **33**, 811–820.
88 W. M. Chang, M. Dakanali, C. C. Capule, C. J. Sigurdson, J. Yang and E. A. Theodorakis, *ACS Chem. Neurosci.*, 2011, **2**, 249–255.
89 C. J. Chen, K. Bando, H. Ashino, K. Taguchi, H. Shiraishi, O. Fujimoto, C. Kitamura, S. Matsushima, M. Fujinaga, M. R. Zhang, H. Kasahara, T. Minamizawa, C. Jiang, M. Ono, M. Higuchi, T. Suhara, K. Yamada and B. Ji, *Bioorg. Med. Chem.*, 2014, **22**, 4189–4197.
90 C. J. Chen, K. Bando, H. Ashino, K. Taguchi, H. Shiraishi, K. Shima, O. Fujimoto, C. Kitamura, S. Matsushima, K. Uchida, Y. Nakahara, H. Kasahara, T. Minamizawa, C. Jiang, M. R. Zhang, M. Ono, M. Tokunaga, T. Suhara, M. Higuchi, K. Yamada and B. Ji, *J. Nucl. Med.*, 2015, **56**, 120–126.
91 Y. F. Chen, J. Bian, P. Zhang, L. L. Bu, Y. Shen, W. B. Yu, X. H. Lu, X. Lin, D. Y. Ye, J. Wang and Y. Chu, *Bioorg. Med. Chem.*, 2020, **28**, 115358.
92 Y. Chen, Q. Ouyang, Y. Li, Q. Zeng, B. Dai, Y. Liang, B. Chen, H. Tan and M. Cui, *Eur. J. Med. Chem.*, 2022, **227**, 113968.
93 X. Chen, Y. Li, J. Kang, T. Ye, Z. Yang, Z. Liu, Q. Liu, Y. Zhao, G. Liu and J. Pan, *J. Lumin.*, 2023, **256**, 119661.
94 Y. Cheng, M. Ono, H. Kimura, S. Kagawa, R. Nishii, H. Kawashima and H. Saji, *ACS Med. Chem. Lett.*, 2010, **1**, 321–325.
95 Y. Cheng, M. Ono, H. Kimura, S. Kagawa, R. Nishii and H. Saji, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6141–6144.
96 Y. Cheng, B. Zhu, Y. Deng and Z. Zhang, *Anal. Chem.*, 2015, **87**, 4781–4787.
97 Y. Cheng, B. Y. Zhu, X. Li, G. B. Li, S. Y. Yang and Z. R. Zhang, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 4472–4476.
98 S. Chia, Z. Faidon Brotzakis, R. I. Horne, A. Possenti, B. Mannini, R. Cataldi, M. Nowinska, R. Staats, S. Linse, T. P. J. Knowles, J. Habchi and M. Vendruscolo, *Mol. Pharmaceutics*, 2023, **20**, 183–193.
99 D. T. Chien, S. Bahri, A. K. Szardenings, J. C. Walsh, F. Mu, M.-Y. Su, W. R. Shankle, A. Elizarov and H. C. Kolb, *J. Alzheimer's Dis.*, 2013, **34**, 457–468.
100 S. R. Choi, G. Golding, Z. Zhuang, W. Zhang, N. Lim, F. Hefti, T. E. Benedum, M. R. Kilbourn, D. Skovronskyhank and H. F. Kung, *J. Nucl. Med.*, 2009, **50**, 1887–1894.
101 J. W. Choi, Y. H. Ju, Y. H. Ju, Y. Choi, Y. Choi, S. J. Hyeon, C. G. Gadhe, J. H. Park, M. S. Kim, S. Baek, Y. Kim, K. D. Park, K. D. Park, A. N. Pae, A. N. Pae, H. Ryu, H. Ryu, C. J. Lee, C. J. Lee, B. R. Cho, B. R. Cho and B. R. Cho, *ACS Chem. Neurosci.*, 2020, **11**, 1801–1810.
102 R. Chongzhao, X. Xiaoyin, S. B. Raymond, B. J. Ferrara, K. Neal, B. J. Bacskai, Z. Medarova and A. Moore, *J. Am. Chem. Soc.*, 2009, **131**, 15257–15261.
103 S. C. Young, J. L. Soo, J. O. Seung, H. M. Dae, J. K. Dong, C. G. Cho and H. Y. Kyung, *Bull. Korean Chem. Soc.*, 2008, **29**, 1765–1768.
104 A. Cornejo, J. Caballero, M. Simirgiotis, V. Torres, L. Sánchez, N. Díaz, M. Guimaraes, M. Hernández, C. Areche, S. Alfaro, L. Caballero and F. Melo, *J. Enzyme Inhib. Med. Chem.*, 2021, **36**, 154–162.
105 M. C. Cui, Z. J. Li, R. K. Tang and B. L. Liu, *Bioorg. Med. Chem.*, 2010, **18**, 2777–2784.
106 M. Cui, M. Ono, H. Kimura, B. Liu and H. Saji, *Bioorg. Med. Chem.*, 2011, **19**, 4148–4153.
107 M. Cui, M. Ono, H. Kimura, B. Liu and H. Saji, *J. Med. Chem.*, 2011, **54**, 2225–2240.
108 M. Cui, M. Ono, H. Kimura, B. L. Liu and H. Saji, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 980–982.
109 M. Cui, M. Ono, H. Kimura, H. Kawashima, B. L. Liu and H. Saji, *Nucl. Med. Biol.*, 2011, **38**, 313–320.
110 M. Cui, M. Ono, H. Kimura, B. Liu and H. Saji, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 4193–4196.
111 M. Cui, M. Ono, H. Kimura, M. Ueda, Y. Nakamoto, K. Togashi, Y. Okamoto, M. Ihara, R. Takahashi, B. Liu and H. Saji, *J. Med. Chem.*, 2012, **55**, 9136–9145.
112 M. Cui, X. Wang, P. Yu, J. Zhang, Z. Li, X. Zhang, Y. Yang, M. Ono, H. Jia, H. Saji and B. Liu, *J. Med. Chem.*, 2012, **55**, 9283–9296.

113 M. Cui, M. Ono, H. Watanabe, H. Kimura, B. Liu and H. Saji, *J. Am. Chem. Soc.*, 2014, **136**, 3388–3394.
114 Y. Dai, T. Fang, Y. Xu, T. Jiang and J. Qiao, *Chem. Biol. Drug Des.*, 2022, 1–12.
115 P. Dao, F. Ye, Y. Liu, Z. Y. Du, K. Zhang, C. Z. Dong, B. Meunier and H. Chen, *ACS Chem. Neurosci.*, 2017, **8**, 798–806.
116 L. Declercq, S. Celen, J. Lecina, M. Ahamed, T. Tousseyn, D. Moechars, J. Alcazar, M. Ariza, K. Fierens, A. Bottelbergs, J. Mariën, R. Vandenberghe, I. J. Andres, K. Van Laere, A. Verbruggen and G. Bormans, *Mol. Imaging*, 2016, **15**, 1–15.
117 L. Declercq, F. Rombouts, M. Koole, K. Fierens, J. Mariën, X. Langlois, J. I. Andrés, M. Schmidt, G. MacDonald, D. Moechars, W. Vanduffel, T. Tousseyn, R. Vandenberghe, K. Van Laere, A. Verbruggen and G. Bormans, *J. Nucl. Med.*, 2017, **58**, 975–981.
118 A. A. Deeg, A. M. Reiner, F. Schmidt, F. Schueder, S. Ryazanov, V. C. Ruf, K. Giller, S. Becker, A. Leonov, C. Griesinger, A. Giese and W. Zinth, *Biochim. Biophys. Acta, Gen. Subj.*, 2015, **1850**, 1884–1890.
119 X. H. Duan, J. P. Qiao, Y. Yang, M. C. Cui, J. N. Zhou and B. L. Liu, *Bioorg. Med. Chem.*, 2010, **18**, 1337–1343.
120 M. V. Fawaz, A. F. Brooks, M. E. Rodnick, G. M. Carpenter, X. Shao, T. J. Desmond, P. Sherman, C. A. Quesada, B. G. Hockley, M. R. Kilbourn, R. L. Albin, K. A. Frey and P. J. H. Scott, *ACS Chem. Neurosci.*, 2014, **5**, 718–730.
121 J. J. Ferrie, Z. Lengyel-Zhand, B. Janssen, M. G. Lougee, S. Giannakoulias, C.-J. Hsieh, V. V. Pagar, C.-C. Weng, H. Xu, T. J. A. Graham, V. M.-Y. Lee, R. H. Mach and E. J. Petersson, *Chem. Sci.*, 2020, **11**, 12746–12754.
122 D. P. Flaherty, S. M. Walsh, T. Kiyota, Y. Dong, T. Ikezu and J. L. Vennerstrom, *J. Med. Chem.*, 2007, **50**, 4986–4992.
123 D. P. Flaherty, T. Kiyota, Y. Dong, T. Ikezu and J. L. Vennerstrom, *J. Med. Chem.*, 2010, **53**, 7992–7999.
124 M. T. Fodero-Tavoletti, D. P. Smith, C. A. Mclean, P. A. Adlard, K. J. Barnham, L. E. Foster, L. Leone, K. Perez, M. Cortés, J. G. Culvenor, Q.-X. Li, K. M. Laughton, C. C. Rowe, C. L. Masters, R. Cappai and V. L. Villemagne, *J. Neurosci.*, 2007, **27**, 10365–10371.
125 M. T. Fodero-Tavoletti, R. S. Mulligan, N. Okamura, S. Furumoto, C. C. Rowe, Y. Kudo, C. L. Masters, R. Cappai, K. Yanai and V. L. Villemagne, *Eur. J. Pharmacol.*, 2009, **617**, 54–58.
126 M. T. Fodero-Tavoletti, N. Okamura, S. Furumoto, R. S. Mulligan, A. R. Connor, C. A. Mclean, D. Cao, A. Rigopoulos, G. A. Cartwright, G. O'keefe, S. Gong, P. A. Adlard, K. J. Barnham, C. C. Rowe, C. L. Masters, Y. Kudo, R. Cappai, K. Yanai and V. L. Villemagne, *Brain*, 2011, **134**, 1089–1100.
127 H. Fu, L. Yu, M. Cui, J. Zhang, X. Zhang, Z. Li, X. Wang, J. Jia, Y. Yang, P. Yu, H. Jia and B. Liu, *Bioorg. Med. Chem.*, 2013, **21**, 3708–3714.
128 H. Fu, M. Cui, P. Tu, Z. Pan and B. Liu, *Chem. Commun.*, 2014, **50**, 11875–11878.
129 H. Fu, M. Cui, L. Zhao, P. Tu, K. Zhou, J. Dai and B. Liu, *J. Med. Chem.*, 2015, **58**, 6972–6983.
130 H. Fu, P. Tu, L. Zhao, J. Dai, B. Liu and M. Cui, *Anal. Chem.*, 2016, **88**, 1944–1950.
131 W. Fu, C. Yan, Z. Guo, J. Zhang, H. Zhang, H. Tian and W. H. Zhu, *J. Am. Chem. Soc.*, 2019, **141**, 3171–3177.
132 T. Fuchigami, N. Kobashi, M. Haratake, M. Kawasaki and M. Nakayama, *Eur. J. Med. Chem.*, 2013, **60**, 469–478.
133 T. Fuchigami, Y. Yamashita, M. Haratake, M. Ono, S. Yoshida and M. Nakayama, *Bioorg. Med. Chem.*, 2014, **22**, 2622–2628.
134 T. Fuchigami, A. Ogawa, Y. Yamashita, M. Haratake, H. Watanabe, M. Ono, M. Kawasaki, S. Yoshida and M. Nakayama, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 3363–3367.
135 S. Furumoto, N. Okamura, K. Furukawa, M. Tashiro, Y. Ishikawa, K. Sugi, N. Tomita, M. Waragai, R. Harada, T. Tago, R. Iwata, K. Yanai, H. Arai and Y. Kudo, *Mol. Imaging Biol.*, 2013, **15**, 497–506.
136 C. Gan, L. Zhou, Z. Zhao and H. Wang, *Med. Chem. Res.*, 2013, **22**, 4069–4074.
137 C. Gan, Z. Zhao, D. D. Nan, B. Yin and J. Hu, *Eur. J. Med. Chem.*, 2014, **76**, 125–131.
138 C. Gan, J. Hu, D. D. Nan, S. Wang and H. Li, *Future Med. Chem.*, 2017, **9**, 1587–1596.
139 J. Gu, U. R. Anumala, F. Lo Monte, T. Kramer, R. Heyny Von Haußen, J. Hölzer, V. Goetschy-Meyer, G. Mall, I. Hilger, C. Czech and B. Schmidt, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 7667–7671.
140 J. Gu, U. R. Anumala, R. Heyny-von Haußen, J. Hölzer, V. Goetschy-Meyer, G. Mall, I. Hilger, C. Czech and B. Schmidt, *ChemMedChem*, 2013, **8**, 891–897.
141 H. Han, C. G. Cho and P. T. Lansbury, *J. Am. Chem. Soc.*, 1996, **118**, 4506.
142 R. Harada, N. Okamura, S. Furumoto, T. Tago, M. Maruyama, M. Higuchi, T. Yoshikawa, H. Arai, R. Iwata, Y. Kudo and K. Yanai, *Eur. J. Nucl. Med. Mol. Imaging*, 2013, **40**, 125–132.
143 R. Harada, N. Okamura, S. Furumoto, T. Yoshikawa, H. Arai, K. Yanai and Y. Kudo, *Mol. Imaging Biol.*, 2014, **16**, 19–27.
144 S. T. Harrison, J. Mulhearn, S. E. Wolkenberg, P. J. Miller, S. S. O'Malley, Z. Zeng, D. L. Williams, E. D. Hostetler, S. Sanabria-Bohórquez, L. Gammage, H. Fan, C. Sur, J. C. Culberson, R. J. Hargreaves, J. J. Cook, G. D. Hartman and J. C. Barrow, *ACS Med. Chem. Lett.*, 2011, **2**, 498–502.
145 S. H. Hausner, D. Alagille, A. O. Koren, L. Amici, J. K. Staley, K. P. Cosgrove, R. M. Baldwin and G. D. Tamagnan, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 543–545.
146 M. Hintersteiner, A. Enz, P. Frey, A. L. Jaton, W. Kinzy, R. Kneuer, U. Neumann, M. Rudin, M. Staufenbiel, M. Stoeckli, K. H. Wiederhold and H. U. Gremlich, *Nat. Biotechnol.*, 2005, **49**, 2725–2730.
147 N. Okamura, R. Harada, A. Ishiki, A. Kikuchi, T. Nakamura and Y. Kudo, *Clin. Transl. Imaging*, 2018, **6**, 305–316.
148 N. S. Honson, R. L. Johnson, W. Huang, J. Inglese, C. P. Austin and J. Kuret, *Neurobiol. Dis.*, 2007, **28**, 251–260.

149 E. D. Hostetler, A. M. Walji, Z. Zeng, P. Miller, I. Bennacef, C. Salinas, B. Connolly, L. Gantert, H. Haley, M. Holahan, M. Purcell, K. Riffel, T. G. Lohith, P. Coleman, A. Soriano, A. Ogawa, S. Xu, X. Zhang, E. Joshi, J. Della Rocca, D. Hesk, D. J. Schenk and J. L. Evelhoch, *J. Nucl. Med.*, 2016, **57**, 1599–1606.

150 S. S. Hou, J. Yang, J. H. Lee, Y. Kwon, M. Calvo-Rodriguez, K. Bao, S. Ahn, S. Kashiwagi, A. T. N. Kumar, B. J. Bacskai and H. S. Choi, *Nat. Biomed. Eng.*, 2023, **7**, 270–280.

151 L. Ji, X. Zhou, R. Liu, L. Wang, Y. Hu, J. Gu, Z. Li, C. Li, T. Huang and Y. Yu, *Sens. Actuators, B*, 2023, **380**, 133415.

152 J. Jia, J. Song, J. Dai, B. Liu and M. Cui, *ACS Chem. Neurosci.*, 2016, **7**, 1275–1282.

153 A. E. Johnson, F. Jeppsson, J. Sandell, D. Wensbo, J. A. M. Neelissen, A. Juréus, P. Ström, H. Norman, L. Farde and S. P. S. Svensson, *J. Neurochem.*, 2009, **108**, 1177–1186.

154 L. Josephson, N. Stratman, Y. Liu, F. Qian, S. H. Liang, N. Vasdev and S. Patel, *Mol. Imaging*, 2018, **17**, 1–6.

155 A. Juréus, B. M. Swahn, J. Sandell, F. Jeppsson, A. E. Johnson, P. Johnström, J. A. M. Neelissen, D. Sunnemark, L. Farde and S. P. S. Svensson, *J. Neurochem.*, 2010, **114**, 784–794.

156 S. Kaide, M. Ono, H. Watanabe, Y. Shimizu, Y. Nakamoto, K. Togashi, A. Yamaguchi, H. Hanaoka and H. Saji, *Bioorg. Med. Chem.*, 2018, **26**, 3352–3358.

157 S. Kaide, H. Watanabe, Y. Shimizu, S. Iikuni, Y. Nakamoto, M. Hasegawa, K. Itoh and M. Ono, *ACS Chem. Neurosci.*, 2020, **11**, 4254–4261.

158 D. Kim, H. Moon, S. H. Baik, S. Singha, Y. W. Jun, T. Wang, K. H. Kim, B. S. Park, J. Jung, I. Mook-Jung and K. H. Ahn, *J. Am. Chem. Soc.*, 2015, **137**, 6781–6789.

159 W. E. Klunk, M. L. Debnath and J. W. Pettegrew, *Neurobiol. Aging*, 1994, **15**, 691–698.

160 W. E. Klunk, M. L. Debnath and J. W. Pettegrew, *Neurobiol. Aging*, 1995, **16**, 541–548.

161 W. E. Klunk, Y. Wang, G. Feng Huang, M. L. Debnath, D. P. Holt and C. A. Mathis, *Life Sci.*, 2001, **69**, 1471–1484.

162 W. E. Klunk, B. J. Bacskai, C. A. Mathis, S. T. Kajdasz, M. E. McLellan, M. P. Frosch, M. L. Debnath, D. P. Holt, Y. Wang and B. T. Hyman, *J. Neuropathol. Exp. Neurol.*, 2002, **61**, 797–805.

163 W. E. Klunk, Y. Wang, G. Feng Huang, M. L. Debnath, D. P. Holt, L. Shao, R. L. Hamilton, M. D. Ikonomovic, S. T. DeKosky and C. A. Mathis, *J. Neurosci.*, 2003, **23**, 2086–2092.

164 H. Kroth, F. Oden, J. Molette, H. Schieferstein, F. Capotosti, A. Mueller, M. Berndt, H. Schmitt-Willich, V. Darmency, E. Gabellieri, C. Boudou, T. Juergens, Y. Varisco, E. Vokali, D. T. Hickman, G. Tamagnan, A. Pfeifer, L. Dinkelborg, A. Muhs and A. Stephens, *Eur. J. Nucl. Med. Mol. Imaging*, 2019, **46**, 2178–2189.

165 Y. Kudo, N. Okamura, S. Furumoto, M. Tashiro, K. Furukawa, M. Maruyama, M. Itoh, R. Iwata, K. Yanai and H. Arai, *J. Nucl. Med.*, 2007, **48**, 553–561.

166 H. F. Kung, C. W. Lee, Z. P. Zhuang, M. P. Kung, C. Hou and K. Plössl, *J. Am. Chem. Soc.*, 2001, **123**, 12740–12741.

167 M. P. Kung, C. Hou, Z. P. Zhuang, D. M. Skovronsky, B. Zhang, T. L. Gur, J. Q. Trojanowski, V. M. Y. Lee and H. F. Kung, *J. Mol. Neurosci.*, 2002, **19**, 7–10.

168 M. P. Kung, C. Hou, Z. P. Zhuang, B. Zhang, D. Skovronsky, J. Q. Trojanowski, V. M. Y. Lee and H. F. Kung, *Brain Res.*, 2002, **956**, 202–210.

169 M. P. Kung, Z. P. Zhuang, C. Hou, L. W. Jin and H. F. Kung, *J. Mol. Neurosci.*, 2003, **20**, 249–253.

170 M. P. Kung, C. Hou, Z. P. Zhuang, D. Skovronsky and H. F. Kung, *Brain Res.*, 2004, **1025**, 98–105.

171 C. W. Lee, Z. P. Zhuang, M. P. Kung, K. Plössl, D. Skovronsky, T. Gur, C. Hou, J. Q. Trojanowski, V. M. Y. Lee and H. F. Kung, *J. Med. Chem.*, 2001, **44**, 2270–2275.

172 C. W. Lee, M. P. Kung, C. Hou and H. F. Kung, *Nucl. Med. Biol.*, 2003, **30**, 573–580.

173 J. H. Lee, S. R. Byeon, Y. S. Kim, S. J. Lim, S. J. Oh, D. H. Moon, K. H. Yoo, B. Y. Chung and D. J. Kim, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5701–5704.

174 B. C. Lee, J. S. Kim, B. S. Kim, J. Y. Son, S. K. Hong, H. S. Park, B. S. Moon, J. H. Jung, J. M. Jeong and S. E. Kim, *Bioorg. Med. Chem.*, 2011, **19**, 2980–2990.

175 I. Lee, J. Yang, J. H. Lee and Y. S. Choe, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5765–5769.

176 L. Lemoine, L. Saint-Aubert, A. Marutle, G. Antoni, J. P. Eriksson, B. Ghetti, N. Okamura, I. Nennesmo, P. G. Gillberg, A. Nordberg, G. Gillberg and A. Nordberg, *Acta Neuropathol. Commun.*, 2015, **3**, 40.

177 Z. Lengyel-Zhand, J. J. Ferrie, B. Janssen, C. J. Hsieh, T. Graham, K. Y. Xu, C. M. Haney, V. M. Y. Lee, J. Q. Trojanowski, E. J. Petersson and R. H. Mach, *Chem. Commun.*, 2020, **56**, 3567–3570.

178 C. Wai, T. Leung, F. Guo, Y. Hong, E. Zhao, R. Tsz, K. Kwok, N. Lik, C. Leung, S. Chen, N. N. Vaikath, O. Mukhtar El-Agnaf, Y. Tang, W.-P. Gai and B. Z. Tang, *Chem. Commun.*, 2015, **51**, 1869.

179 Z. Li, M. Cui, J. Zhang, J. Dai, X. Zhang, P. Chen, H. Jia and B. Liu, *Eur. J. Med. Chem.*, 2014, **84**, 628–638.

180 Y. Li, D. Xu, S.-L. Ho, H.-W. Li, R. Yang and M. S. Wong, *Biomaterials*, 2016, **94**, 84–92.

181 Z. Li, X. Zhang, X. Zhang, M. Cui, J. Lu, X. Pan and X. Zhang, *J. Med. Chem.*, 2016, **59**, 10577–10585.

182 Y. Li, J. Yang, H. Liu, J. Yang, L. Du, H. Feng, Y. Tian, J. Cao and C. Ran, *Chem. Sci.*, 2017, **8**, 7710–7717.

183 Y. Li, D. Xu, A. Sun, S. L. Ho, C. Y. Poon, H. N. Chan, O. T. W. Ng, K. K. L. Yung, H. Yan, H. W. Li and M. S. Wong, *Chem. Sci.*, 2017, **8**, 8279–8284.

184 Y. Li, C. Chen, D. Xu, C. Y. Poon, S. L. Ho, R. Zheng, Q. Liu, G. Song, H. W. Li and M. S. Wong, *ACS Omega*, 2018, **3**, 6812–6819.

185 K. Liu, T. L. Guo, J. Chojnacki, H. G. Lee, X. Wang, S. L. Siedlak, W. Rao, X. Zhu and S. Zhang, *ACS Chem. Neurosci.*, 2012, **3**, 141–146.

186 X.-Y. Liu, X.-J. Wang, L. Shi, Y.-H. Liu, L. Wang, K. Li, Q. Bu, X.-B. Cen and X.-Q. Yu, *Anal. Chem.*, 2022, **94**, 7665–7673.

187 T. Liu, Y. Li, Y. Wang, X.-X. Yan, J. Dai and M. Cui, *Eur. J. Med. Chem.*, 2023, **246**, 114991.
188 C. Lois, I. Gonzalez, K. A. Johnson and J. C. Price, *Brain Imaging Behav.*, 2019, **13**, 333–344.
189 G. Lv, B. Cui, H. Lan, Y. Wen, A. Sun and T. Yi, *Chem. Commun.*, 2015, **51**, 125–128.
190 P. Lv, C. L. Xia, N. Wang, Z. Q. Liu, Z. S. Huang and S. L. Huang, *Bioorg. Med. Chem.*, 2018, **26**, 4693–4705.
191 R. Mallesh, J. Khan, K. Pradhan, R. Roy, N. R. Jana, P. Jaisankar and S. Ghosh, *ACS Chem. Neurosci.*, 2022, **13**, 2503–2516.
192 M. Maruyama, H. Shimada, T. Suhara, H. Shinotoh, B. Ji, J. Maeda, M. R. Zhang, J. Q. Trojanowski, V. M. Y. Lee, M. Ono, K. Masamoto, H. Takano, N. Sahara, N. Iwata, N. Okamura, S. Furumoto, Y. Kudo, Q. Chang, T. C. Saido, A. Takashima, J. Lewis, M. K. Jang, I. Aoki, H. Ito and M. Higuchi, *Neuron*, 2013, **79**, 1094–1108.
193 C. A. Mathis, B. J. Bacskai, S. T. Kajdasz, M. E. McLellan, M. P. Frosch, B. T. Hyman, D. P. Holt, Y. Wang, G. F. Huang, M. L. Debnath and W. E. Klunk, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 295–298.
194 C. A. Mathis, Y. Wang, D. P. Holt, G. F. Huang, M. L. Debnath and W. E. Klunk, *J. Med. Chem.*, 2003, **46**, 2740.
195 K. Matsumura, M. Ono, S. Hayashi, H. Kimura, Y. Okamoto, M. Ihara, R. Takahashi, H. Mori and H. Saji, *MedChemComm*, 2011, **2**, 596–600.
196 K. Matsumura, M. Ono, H. Kimura, M. Ueda, Y. Nakamoto, K. Togashi, Y. Okamoto, M. Ihara, R. Takahashi and H. Saji, *ACS Med. Chem. Lett.*, 2012, **3**, 58–62.
197 K. Matsumura, M. Ono, M. Yoshimura, H. Kimura, H. Watanabe, Y. Okamoto, M. Ihara, R. Takahashi and H. Saji, *Bioorg. Med. Chem.*, 2013, **21**, 3356–3362.
198 A. Maurer, A. Leonov, S. Ryazanov, K. Herfert, L. Kuebler, S. Buss, F. Schmidt, D. Weckbecker, R. Linder, D. Bender, A. Giese, B. J. Pichler and C. Griesinger, *ChemMedChem*, 2020, **15**, 411–415.
199 Y. Maya, M. Ono, H. Watanabe, M. Haratake, H. Saji and M. Nakayama, *Bioconjugate Chem.*, 2009, **20**, 95–101.
200 J. Miao, M. Miao, Y. Jiang, M. Zhao, Q. Li, Y. Zhang, Y. An, K. Pu and Q. Miao, *Angew. Chem., Int. Ed.*, 2023, **62**, e202216351.
201 P. Miranda-Azpiazu, M. Svedberg, M. Higuchi, M. Ono, Z. Jia, D. Sunnemark, C. S. Elmore, M. Schou and A. Varrone, *Brain Res.*, 2020, **1749**, 147131.
202 G. Ribeiro Morais, H. Vicente Miranda, I. C. Santos, I. Santos, T. F. Outeiro and A. Paulo, *Bioorg. Med. Chem.*, 2011, **19**, 7698–7710.
203 R. J. A. Nabuurs, V. V. Kapoerchan, A. Metaxas, S. De Jongh, M. De Backer, M. M. Welling, W. Jiskoot, A. D. Windhorst, H. S. Overkleeft, M. A. Van Buchem, M. Overhand and L. Van Der Weerd, *Bioorg. Med. Chem.*, 2014, **22**, 2469–2481.
204 K. Nakagawa, H. Watanabe, S. Kaide and M. Ono, *ACS Med. Chem. Lett.*, 2022, **13**, 1598–1605.
205 R. Narlawar, M. Pickhardt, S. Leuchtenberger, K. Baumann, S. Krause, T. Dyrks, S. Weggen, E. Mandelkow and B. Schmidt, *ChemMedChem*, 2008, **3**, 165–172.
206 L.-M. Needham, J. Weber, J. A. Varela, J. W. B. Fyfe, D. T. Do, C. K. Xu, L. Tutton, R. Cliffe, B. Keenlyside, D. Klenerman, C. M. Dobson, C. A. Hunter, K. H. Müller, K. O'Holleran, S. E. Bohndiek, T. N. Snaddon and S. F. Lee, *Chem. Sci.*, 2020, **11**, 4578–4583.
207 E. E. Nesterov, J. Skoch, B. T. Hyman, W. E. Klunk, B. J. Bacskai and T. M. Swager, *Angew. Chem., Int. Ed.*, 2005, **44**, 5452–5456.
208 B. Neumaier, S. Deisenhofer, C. Sommer, C. Solbach, S. N. Reske and F. Mottaghy, *Appl. Radiat. Isot.*, 2010, **68**, 1066–1072.
209 N. Okamura, T. Suemoto, H. Shimadzu, M. Suzuki, T. Shiomitsu, H. Akatsu, T. Yamamoto, M. Staufenbiel, K. Yanai, H. Arai, H. Sasaki, Y. Kudo and T. Sawada, *J. Neurosci.*, 2004, **24**, 2535–2541.
210 N. Okamura, T. Suemoto, S. Furumoto, M. Suzuki, H. Shimadzu, H. Akatsu, T. Yamamoto, H. Fujiwara, M. Nemoto, M. Maruyama, H. Arai, K. Yanai, T. Sawada and Y. Kudo, *J. Neurosci.*, 2005, **25**, 10857–10862.
211 N. Okamura, M. Mori, S. Furumoto, T. Yoshikawa, R. Harada, S. Ito, Y. Fujikawa, H. Arai, K. Yanai and Y. Kudo, *J. Alzheimer's Dis.*, 2011, **23**, 37–48.
212 N. Okamura, S. Furumoto, R. Harada, T. Tago, T. Yoshikawa, M. Fodero-Tavoletti, R. S. Mulligan, V. L. Villemagne, H. Akatsu, T. Yamamoto, H. Arai, R. Iwata, K. Yanai and Y. Kudo, *J. Nucl. Med.*, 2013, **54**, 1420–1427.
213 M. Ono, M.-P. Kung, C. Hou and H. F. Kung, *Nucl. Med. Biol.*, 2002, **29**, 633–642.
214 M. Ono, A. Wilson, J. Nobrega, D. Westaway, P. Verhoeff, Z. P. Zhuang, M. P. Kung and H. F. Kung, *Nucl. Med. Biol.*, 2003, **30**, 565–571.
215 M. Ono, M. Haratake, M. Nakayama, Y. Kaneko, K. Kawabata, H. Mori, M. P. Kung and H. F. Kung, *Nucl. Med. Biol.*, 2005, **32**, 329–335.
216 M. Ono, N. Yoshida, K. Ishibashi, M. Haratake, Y. Arano, H. Mori and M. Nakayama, *J. Med. Chem.*, 2005, **48**, 7253–7260.
217 M. Ono, H. Kawashima, A. Nonaka, T. Kawai, M. Haratake, H. Mori, M. P. Kung, H. F. Kung, H. Saji and M. Nakayama, *J. Med. Chem.*, 2006, **49**, 2725–2730.
218 M. Ono, Y. Maya, M. Haratake, K. Ito, H. Mori and M. Nakayama, *Biochem. Biophys. Res. Commun.*, 2007, **361**, 116–121.
219 M. Ono, M. Hori, M. Haratake, T. Tomiyama, H. Mori and M. Nakayama, *Bioorg. Med. Chem.*, 2007, **15**, 6388–6396.
220 M. Ono, Y. Maya, M. Haratake and M. Nakayama, *Bioorg. Med. Chem.*, 2007, **15**, 444–450.
221 M. Ono, M. Haratake, H. Mori and M. Nakayama, *Bioorg. Med. Chem.*, 2007, **15**, 6802–6809.
222 M. Ono, M. Haratake, H. Saji and M. Nakayama, *Bioorg. Med. Chem.*, 2008, **16**, 6867–6872.
223 M. Ono, R. Watanabe, H. Kawashima, Y. Cheng, H. Kimura, H. Watanabe, M. Haratake, H. Saji and M. Nakayama, *J. Med. Chem.*, 2009, **52**, 6394–6401.

224 M. Ono, R. Watanabe, H. Kawashima, T. Kawai, H. Watanabe, M. Haratake, H. Saji and M. Nakayama, *Bioorg. Med. Chem.*, 2009, **17**, 2069–2076.
225 M. Ono, S. Hayashi, H. Kimura, H. Kawashima, M. Nakayama and H. Saji, *Bioorg. Med. Chem.*, 2009, **17**, 7002–7007.
226 M. Ono, M. Ishikawa, H. Kimura, S. Hayashi, K. Matsumura, H. Watanabe, Y. Shimizu, Y. Cheng, M. Cui, H. Kawashima and H. Saji, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3885–3888.
227 M. Ono, S. Hayashi, K. Matsumura, H. Kimura, Y. Okamoto, M. Ihara, R. Takahashi, H. Mori and H. Saji, *ACS Chem. Neurosci.*, 2011, **2**, 269–275.
228 M. Ono, Y. Cheng, H. Kimura, M. Cui, S. Kagawa, R. Nishii and H. Saji, *J. Med. Chem.*, 2011, **54**, 2971–2979.
229 M. Ono, H. Watanabe, H. Kimura and H. Saji, *ACS Chem. Neurosci.*, 2012, **3**, 319–324.
230 M. Ono, Y. Cheng, H. Kimura, H. Watanabe, K. Matsumura, M. Yoshimura, S. Iikuni, Y. Okamoto, M. Ihara, R. Takahashi and H. Saji, *PLoS One*, 2013, **8**, e74104.
231 M. Ono, Y. Doi, H. Watanabe, M. Ihara, A. Ozaki and H. Saji, *RSC Adv.*, 2016, **6**, 44305–44312.
232 M. Ono, N. Sahara, K. Kumata, B. Ji, R. Ni, S. Koga, D. W. Dickson, J. Q. Trojanowski, V. M.-Y. Lee, M. Yoshida, I. Hozumi, Y. Yoshiyama, J. C. Van Swieten, A. Nordberg, T. Suhara, M.-R. Zhang and M. Higuchi, *Brain J. Neurol.*, 2017, **140**, 764–780.
233 Y. D. Park, J. H. Park, M. G. Hur, S. W. Kim, J. J. Min, S. H. Park, Y. J. Yoo, Y. J. Yoon and S. D. Yang, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4106–4110.
234 K.-S. Park, Y. Seo, M. K. Kim, K. Kim, Y. K. Kim, H. Choo and Y. Chong, *Org. Biomol. Chem.*, 2015, **13**, 11194.
235 Y. Dae Park, J.-J. Kim, S. Lee, C.-H. Park, H.-W. Bai and S. S. Lee, *J. Anal. Methods Chem.*, 2018, **2018**, 1651989.
236 A. Petrič, S. A. Johnson, H. V. Pham, Y. Li, S. Cěh, A. Golobič, E. D. Agdeppa, G. Timbol, J. Liu, G. Keum, N. Satyamurthy, V. Kepe, K. N. Houk and J. R. Barrio, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**, 16492–16497.
237 J. P. Qiao, C. S. Gan, C. W. Wang, J. F. Ge, D. D. Nan, J. Pan and J. N. Zhou, *ChemBioChem*, 2012, **13**, 1652–1662.
238 L. Qin, J. Vastl and J. Gao, *Mol. BioSyst.*, 2010, **6**, 1791–1795.
239 W. Qu, M. P. Kung, C. Hou, T. E. Benedum and H. F. Kung, *J. Med. Chem.*, 2007, **50**, 2157–2165.
240 W. Qu, M. P. Kung, C. Hou, S. Oya and H. F. Kung, *J. Med. Chem.*, 2007, **50**, 3380–3387.
241 W. Qu, M. P. Kung, C. Hou, L. W. Jin and H. F. Kung, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3581–3584.
242 W. Qu, S. R. Choi, C. Hou, Z. Zhuang, S. Oya, W. Zhang, M. P. Kung, R. Manchandra, D. M. Skovronsky and H. F. Kung, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4823–4827.
243 K. Rajasekhar, N. Narayanaswamy, N. A. Murugan, G. Kuang, H. Ågren and T. Govindaraju, *Sci. Rep.*, 2016, **6**, 23668.
244 K. Rajasekhar, N. Narayanaswamy, N. A. Murugan, K. Viccaro, H. G. Lee, K. Shah and T. Govindaraju, *Biosens. Bioelectron.*, 2017, **98**, 54–61.
245 L. Rejc, L. Šmid, V. Kepe, Č. Podlipnik, A. Golobič, M. Bresjanac, J. R. Barrio, A. Petrič and J. Košmrlj, *J. Med. Chem.*, 2017, **60**, 8741–8757.
246 W. Ren, J. Zhang, C. Peng, H. Xiang, J. Chen, C. Peng, W. Zhu, R. Huang, H. Zhang and Y. Hu, *Bioconjugate Chem.*, 2018, **29**, 3459–3466.
247 L. E. Rojo, J. Alzate-Morales, I. N. Saavedra, P. Davies and R. B. MacCioni, *J. Alzheimer's Dis.*, 2010, **19**, 573–589.
248 E. K. Ryu, Y. S. Choe, K. H. Lee, Y. Choi and B. T. Kim, *J. Med. Chem.*, 2006, **49**, 6111–6119.
249 P. M. Seidler, D. R. Boyer, M. R. Sawaya, P. Ge, W. S. Shin, M. A. DeTure, D. W. Dickson, L. Jiang and D. S. Eisenberg, *Nat. Commun.*, 2022, **13**, 5451.
250 N. Seneca, L. Cai, J.-S. Liow, S. Zoghbi, R. Gladding, J. Little, P. Aisen, J. Hong, V. Pike and R. Innis, *Curr. Radiopharm.*, 2010, **2**, 129–136.
251 Y. Seo, K. S. Park, T. Ha, M. K. Kim, Y. J. Hwang, J. Lee, H. Ryu, H. Choo and Y. Chong, *ACS Chem. Neurosci.*, 2016, **7**, 1474–1481.
252 K. Serdons, C. Terwinghe, P. Vermaelen, K. Van Laere, H. Kung, L. Mortelmans, G. Bormans and A. Verbruggen, *J. Med. Chem.*, 2009, **52**, 1428–1437.
253 K. Serdons, T. Verduyckt, D. Vanderghinste, J. Cleynhens, P. Borghgraef, P. Vermaelen, C. Terwinghe, F. Van Leuven, K. Van Laere, H. Kung, G. Bormans and A. Verbruggen, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 602–605.
254 K. Serdons, K. Van Laere, P. Janssen, H. F. Kung, G. Bormans and A. Verbruggen, *J. Med. Chem.*, 2009, **52**, 7090–7102.
255 K. Serdons, T. Verduyckt, D. Vanderghinste, P. Borghgraef, J. Cleynhens, F. Van Leuven, H. Kung, G. Bormans and A. Verbruggen, *Eur. J. Med. Chem.*, 2009, **44**, 1415–1426.
256 X. Shao, G. M. Carpenter, T. J. Desmond, P. Sherman, C. A. Quesada, M. Fawaz, A. F. Brooks, M. R. Kilbourn, R. L. Albin, K. A. Frey and P. J. H. Scott, *ACS Med. Chem. Lett.*, 2012, **3**, 936–941.
257 S. K. Sonawane, H. Chidambaram, D. Boral, N. V. Gorantla, A. A. Balmik, A. Dangi, S. Ramasamy, U. K. Marelli and S. Chinnathambi, *Sci. Rep.*, 2020, **10**, 12579.
258 F. Sozmen, S. Kolemen, H.-O. Kumada, M. Ono, H. Saji and E. U. Akkaya, *RSC Adv.*, 2014, **4**, 51032–51037.
259 K. A. Stephenson, R. Chandra, Z.-P. Zhuang, C. Hou, S. Oya, M.-P. Kung and H. F. Kung, *Bioconjugate Chem.*, 2007, **18**, 238–246.
260 T. Suemoto, N. Okamura, T. Shiomitsu, M. Suzuki, H. Shimadzu, H. Akatsu, T. Yamamoto, Y. Kudo and T. Sawada, *Neurosci. Res.*, 2004, **48**, 65–74.
261 G. S. M. Sundaram, D. D. Dhavale, J. L. Prior, P. Yan, J. Cirrito, N. P. Rath, R. Laforest, N. J. Cairns, J. M. Lee, P. T. Kotzbauer and V. Sharma, *Sci. Rep.*, 2016, **6**, 35636.
262 J. Sutharsan, M. Dakanali, C. Capule, M. Haidekker, J. Yang and E. Theodorakis, *ChemMedChem*, 2010, **5**, 56–60.
263 B. M. Swahn, D. Wensbo, J. Sandell, D. Sohn, C. Slivo, D. Pyring, J. Malmström, E. Arzel, M. Vallin, M. Bergh, F. Jeppsson, A. E. Johnson, A. Juréus, J. Neelissen and S. Svensson, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1976–1980.

264 B. M. Swahn, J. Sandell, D. Pyring, M. Bergh, F. Jeppsson, A. Juréus, J. Neelissen, P. Johnström, M. Schou and S. Svensson, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4332–4337.
265 T. Tago, S. Furumoto, N. Okamura, R. Harada, H. Adachi, Y. Ishikawa, K. Yanai, R. Iwata and Y. Kudo, *J. Nucl. Med.*, 2016, **57**, 608–614.
266 R. Tao, N. Wang, T. Shen, Y. Tan, Y. Ren, W. Wei, M. Liao, D. Tan, C. Tang, N. Xu, H. Wang, X. Liu and X. Li, *Theranostics*, 2022, **12**, 2549–2559.
267 P. W. Thompson, L. Ye, J. L. Morgenstern, L. Sue, T. G. Beach, D. J. Judd, N. J. Shipley, V. Libri and A. Lockhart, *J. Neurochem.*, 2009, **109**, 623–630.
268 Y. Tu, K. Chai, J. Wu, Y. Hu, S. Shi, D. Yang and T. Yao, *Sens. Actuators, B*, 2023, **380**, 133406.
269 N. Vasdev, P. Cao, E. M. Van Oosten, A. A. Wilson, S. Houle, G. Hao, X. Sun, N. Slavine, M. Alhasan, P. P. Antich, F. J. Bonte and P. Kulkarni, *MedChemComm*, 2012, **3**, 1228–1230.
270 M. Verdurand, E. Levigoureux, W. Zeinyeh, L. Berthier, M. Mendjel-Herda, F. Cadarossanesaib, C. Bouillot, T. Iecker, R. Terreux, S. Lancelot, F. Chauveau, T. Billard and L. Zimmer, *Mol. Pharmaceutics*, 2018, **15**, 3153–3166.
271 C. Vermeiren, P. Motte, D. Viot, G. Mairet-Coello, J.-P. Courade, M. Citron, J. Mercier, J. Hannestad and M. Gillard, *Mov. Disord*, 2018, **33**, 273–281.
272 K. D. Volkova, V. B. Kovalska, A. O. Balanda, M. Y. Losytskyy, A. G. Golub, R. J. Vermeij, V. Subramaniam, O. I. Tolmachev and S. M. Yarmoluk, *Bioorg. Med. Chem.*, 2008, **16**, 1452–1459.
273 Y. Wang, C. A. Mathis, G. F. Huang, D. P. Holt, M. L. Debnath and W. E. Klunk, *J. Labelled Compd. Radiopharm.*, 2002, **45**, 647–664.
274 Y. Wang, W. E. Klunk, G. F. Huang, M. L. Debnath, D. P. Holt and C. A. Mathis, *J. Mol. Neurosci.*, 2002, **19**, 11–16.
275 H. Watanabe, M. Ono, R. Ikeoka, M. Haratake, H. Saji and M. Nakayama, *Bioorg. Med. Chem.*, 2009, **17**, 6402–6406.
276 H. Watanabe, M. Ono, M. Haratake, N. Kobashi, H. Saji and M. Nakayama, *Bioorg. Med. Chem.*, 2010, **18**, 4740–4746.
277 H. Watanabe, M. Ono, H. Kimura, S. Kagawa, R. Nishii, T. Fuchigami, M. Haratake, M. Nakayama and H. Saji, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 6519–6522.
278 H. Watanabe, M. Ono, H. Kimura, K. Matsumura, M. Yoshimura, Y. Okamoto, M. Ihara, R. Takahashi and H. Saji, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5700–5703.
279 H. Watanabe, M. Ono, K. Matsumura, M. Yoshimura, H. Kimura and H. Saji, *Mol. Imaging*, 2013, **12**, 338–347.
280 H. Watanabe, M. Ono, H. Kimura, K. Matsumura, M. Yoshimura, S. Iikuni, Y. Okamoto, M. Ihara, R. Takahashi and H. Saji, *MedChemComm*, 2014, **5**, 82–85.
281 H. Watanabe, M. Ono and H. Saji, *Chem. Commun.*, 2015, **51**, 17124–17127.
282 H. Watanabe, M. Ono, S. Iikuni, H. Kimura, Y. Okamoto, M. Ihara and H. Saji, *RSC Adv.*, 2015, **5**, 1009–1015.
283 H. Watanabe, T. Ariyoshi, A. Ozaki, M. Ihara, M. Ono and H. Saji, *Bioorg. Med. Chem.*, 2017, **25**, 6398–6403.
284 H. Watanabe, M. Ono, T. Ariyoshi, R. Katayanagi and H. Saji, *ACS Chem. Neurosci.*, 2017, **8**, 1656–1662.
285 H. Wongso, M. Ono, T. Yamasaki, K. Kumata, M. Higuchi, M.-R. Zhang, M. J. Fulham, A. Katsifis and P. A. Keller, *RSC Med. Chem.*, 2023, **14**, 858.
286 M. C. Wren, T. Lashley, E. Årstad and K. Sander, *Acta Neuropathol. Commun.*, 2018, **6**, 34.
287 C. Wu, J. Wei, K. Gao and Y. Wang, *Bioorg. Med. Chem.*, 2007, **15**, 2789–2796.
288 C.-F. Xia, J. Arteaga, G. Chen, U. Gangadharmath, L. F. Gomez, D. Kasi, C. Lam, Q. Liang, C. Liu, V. P. Mocharla, F. Mu, A. Sinha, H. Su, A. K. Szardenings, J. C. Walsh, E. Wang, C. Yu, W. Zhang, T. Zhao and H. C. Kolb, *Alzheimers Dement.*, 2013, **9**, 666–676.
289 T. Xie, Y. Li, C. Tian, C. Yuan, B. Dai, S. Wang, K. Zhou, J. Liu, H. Tan, Y. Liang, J. Dai, B. Chen and M. Cui, *J. Med. Chem.*, 2022, **65**, 14527–14538.
290 J. W. Yan, J. Y. Zhu, K. X. Zhou, J. S. Wang, H. Y. Tan, Z. Y. Xu, S. B. Chen, Y. T. Lu, M. C. Cui and L. Zhang, *Chem. Commun.*, 2017, **53**, 9910–9913.
291 Y. Yang, L. Zhu, X. Chen and H. Zhang, *J. Mol. Graphics Modell.*, 2010, **29**, 538–545.
292 Y. Yang, X. H. Duan, J. Y. Deng, B. Jin, H. M. Jia and B. L. Liu, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5594–5597.
293 W. Yang, Y. Wong, O. T. W. Ng, L.-P. Bai, D. W. J. Kwong, Y. Ke, Z.-H. Jiang, H.-W. Li, K. K. L. Yung and M. S. Wong, *Angew. Chem., Int. Ed.*, 2012, **51**, 1804–1810.
294 Y. Yang, H.-M. Jia and B.-L. Liu, *Molecules*, 2012, **17**, 4252–4265.
295 Y. Yang, M. Cui, X. Zhang, J. Dai, Z. Zhang, C. Lin, Y. Guo and B. Liu, *J. Med. Chem.*, 2014, **57**, 6030–6042.
296 Y. Yang, H. Fu, M. Cui, C. Peng, Z. Liang, J. Dai, Z. Zhang, C. Lin and B. Liu, *Eur. J. Med. Chem.*, 2015, **104**, 86–96.
297 Y. Yang, X. Zhang, M. Cui, J. Zhang, Z. Guo, Y. Li, X. Zhang, J. Dai and B. Liu, *Sci. Rep.*, 2015, **5**, 12084.
298 J. Yang, B. Zhu, W. Yin, Z. Han, C. Zheng, P. Wang and C. Ran, *Chem. Sci.*, 2020, **11**, 5238–5245.
299 L. Ye, J. L. Morgenstern, J. R. Lamb and A. Lockhart, *Biochem. Biophys. Res. Commun.*, 2006, **347**, 669–677.
300 L. Ye, A. Velasco, G. Fraser, T. G. Beach, L. Sue, T. Osredkar, V. Libri, M. G. Spillantini, M. Goedert and A. Lockhart, *J. Neurochem.*, 2008, **105**, 1428–1437.
301 M. Yoshimura, M. Ono, K. Matsumura, H. Watanabe, H. Kimura, M. Cui, Y. Nakamoto, K. Togashi, Y. Okamoto, M. Ihara, R. Takahashi and H. Saji, *ACS Med. Chem. Lett.*, 2013, **4**, 596–600.
302 B. H. Yousefi, A. Manook, A. Drzezga, B. V. Reutern, M. Schwaiger, H. J. Wester and G. Henriksen, *J. Med. Chem.*, 2011, **54**, 949–956.
303 L. Yu, J. Cui, P. K. Padakanti, L. Engel, D. P. Bagchi, P. T. Kotzbauer and Z. Tu, *Bioorg. Med. Chem.*, 2012, **20**, 4625–4634.
304 P. Yu, M. Cui, X. Wang, X. Zhang, Z. Li, Y. Yang, J. Jia, J. Zhang, M. Ono, H. Saji, H. Jia and B. Liu, *Eur. J. Med. Chem.*, 2012, **57**, 51–58.
305 X. Yue, D. D. Dhavale, J. Li, Z. Luo, J. Liu, H. Yang, R. H. Mach, P. T. Kotzbauer and Z. Tu, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 1011–1019.

306 N. Yue, H. Fu, Y. Chen, X. Gao, J. Dai and M. Cui, *Eur. J. Med. Chem.*, 2022, **243**, 114715.
307 F. Zeng, J. A. Southerland, R. J. Voll, J. R. Votaw, L. Williams, B. J. Ciliax, A. I. Levey and M. M. Goodman, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3015–3018.
308 Q. Zeng, Y. Chen, Y. Yan, R. Wan, Y. Li, H. Fu, Y. Liu, S. Liu, X.-X. Yan and M. Cui, *Anal. Chem.*, 2022, **94**, 15261–15269.
309 Z. Zha, S. R. Choi, K. Ploessl, B. P. Lieberman, W. Qu, F. Hefti, M. Mintun, D. Skovronsky and H. F. Kung, *J. Med. Chem.*, 2011, **54**, 8085–8098.
310 W. Zhang, S. Oya, M. P. Kung, C. Hou, D. L. Maier and H. F. Kung, *J. Med. Chem.*, 2005, **48**, 5980–5988.
311 W. Zhang, S. Oya, M. P. Kung, C. Hou, D. L. Maier and H. F. Kung, *Nucl. Med. Biol.*, 2005, **32**, 799–809.
312 W. Zhang, M. P. Kung, S. Oya, C. Hou and H. F. Kung, *Nucl. Med. Biol.*, 2007, **34**, 89–97.
313 X. Zhang, Y. Tian, C. Zhang, X. Tian, A. W. Ross, R. D. Moir, H. Sun, R. E. Tanzi, A. Moore and C. Ran, *Proc. Natl. Acad. Sci. U. S. A.*, 2015, **112**, 9734–9739.
314 J. Zhang, A. Sandberg, X. Wu, S. Nyströ, M. Lindgren, P. Konradsson and P. Hammarströ, *ACS Omega*, 2017, **2**, 4693–4704.
315 J. Zhang, J. Wang, A. Sandberg, X. Wu, S. Nyström, H. LeVine, P. Konradsson, P. Hammarström, B. Durbeej and M. Lindgren, *ChemPhysChem*, 2018, **19**, 3001–3009.
316 J. Zhang, A. Sandberg, A. Konsmo, X. Wu, S. Nyström, K. P. R. Nilsson, P. Konradsson, H. LeVine, M. Lindgren and P. Hammarström, *Chem. – Eur. J.*, 2018, **24**, 7210–7216.
317 J. Zhang, A. Konsmo, A. Sandberg, X. Wu, S. Nyströ, U. Obermü, B. M. Wegenast-Braun, P. Konradsson, M. Lindgren and P. Hammarströ, *J. Med. Chem.*, 2019, **62**, 2038–2048.
318 W. Zhang, J. Arteaga, D. K. Cashion, G. Chen, U. Gangadharmath, L. F. Gomez, D. Kasi, C. Lam, Q. Liang, C. Liu, V. P. Mocharla, F. Mu, A. Sinha, A. Katrin Szardenings, E. Wang, J. C. Walsh, C. Xia, C. Yu, T. Zhao and H. C. Kolb, *J. Alzheimer's Dis.*, 2012, **31**, 601–612.
319 W. Zhen, H. Han, M. Anguiano, C. A. Lemere, C. G. Cho and P. T. Lansbury, *J. Med. Chem.*, 1999, **42**, 2805–2815.
320 M. Q. Zheng, D. Z. Yin, J. P. Qiao, L. Zhang and Y. X. Wang, *J. Fluorine Chem.*, 2008, **129**, 210–216.
321 K. Zhou, H. Fu, L. Feng, M. Cui, J. Dai and B. Liu, *Chem. Commun.*, 2015, **51**, 11665–11668.
322 K. Zhou, H. Bai, L. Feng, J. Dai and M. Cui, *Anal. Chem.*, 2017, **89**, 9432–9437.
323 K. Zhou, Y. Li, Y. Peng, X. Cui, J. Dai and M. Cui, *Anal. Chem.*, 2018, **90**, 8576–8582.
324 Z. P. Zhuang, M. P. Kung, C. Hou, K. Plössl, D. Skovronsky, T. L. Gur, J. Q. Trojanowski, V. M. Y. Lee and H. F. Kung, *Nucl. Med. Biol.*, 2001, **28**, 887–894.
325 Z.-P. Zhuang, M.-P. Kung, C. Hou, C.-W. Lee, J. Q. Trojanowski, V. M.-Y. Lee and H. F. Kung, *J. Labelled Compd. Radiopharm.*, 2001, **44**, S29–S32.
326 Z. P. Zhuang, M. P. Kung, A. Wilson, C. W. Lee, K. Plössl, C. Hou, D. M. Holtzman and H. F. Kung, *J. Med. Chem.*, 2003, **46**, 237–243.
327 Z. P. Zhuang, M. P. Kung and H. F. Kung, *J. Med. Chem.*, 2006, **49**, 2841–2844.
328 T. S. Chisholm, M. Mackey and C. A. Hunter, *J. Am. Chem. Soc.*, 2023, **145**, 15936–15950.
329 S.-P. Wey, C.-C. Weng, K.-J. Lin, C.-H. Yao, T.-C. Yen, H. F. Kung, D. Skovronsky and M.-P. Kung, *Nucl. Med. Biol.*, 2009, **36**, 411–417.
330 Y. Wang, C. A. Mathis, G.-F. Huang, M. L. Debnath, D. P. Holt, L. Shao and W. E. Klunk, *J. Mol. Neurosci.*, 2003, **20**, 255–260.
331 N. Okamura, T. Suemoto, T. Shiomitsu, M. Suzuki, H. Shimadzu, H. Akatsu, T. Yamamoto, H. Arai, H. Sasaki, K. Yanai, M. Staufenbiel, Y. Kudo and T. Sawada, *J. Mol. Neurosci.*, 2004, **24**, 247–255.
332 Y. Wang, T. T. Huynh, N. Bandara, H.-J. Cho, B. E. Rogers and L. M. Mirica, *Dalton Trans.*, 2022, **51**, 1216–1224.
333 L. Sun, A. K. Sharma, B.-H. Han and L. M. Mirica, *ACS Chem. Neurosci.*, 2020, **11**, 2741–2752.
334 L. Sun, H.-J. Cho, S. Sen, A. S. Arango, T. T. Huynh, Y. Huang, N. Bandara, B. E. Rogers, E. Tajkhorshid and L. M. Mirica, *J. Am. Chem. Soc.*, 2021, **143**, 10462–10476.
335 Z. Yu, W. Guo, S. Patel, H.-J. Cho, L. Sun and L. M. Mirica, *Chem. Sci.*, 2022, **13**, 12818–12830.
336 M. Rana, A. Pareek, S. Bhardwaj, G. Arya, S. Nimesh, H. Arya, T. K. Bhatt, S. Yaragorla and A. K. Sharma, *RSC Adv.*, 2020, **10**, 28827–28837.
337 K. Terpstra, Y. Wang, T. T. Huynh, N. Bandara, H.-J. Cho, B. E. Rogers and L. M. Mirica, *Inorg. Chem.*, 2022, **61**, 20326–20336.
338 H. F. Kung, S. R. Choi, W. Qu, W. Zhang and D. Skovronsky, *J. Med. Chem.*, 2010, **53**, 933–941.
339 N. Bandara, A. K. Sharma, S. Krieger, J. W. Schultz, B. H. Han, B. E. Rogers and L. M. Mirica, *J. Am. Chem. Soc.*, 2017, **139**, 12550–12558.
340 Y. Huang, H.-J. Cho, N. Bandara, L. Sun, D. Tran, B. E. Rogers and L. M. Mirica, *Chem. Sci.*, 2020, **11**, 7789–7799.
341 A. K. Sharma, J. Kim, J. T. Prior, N. J. Hawco, N. P. Rath, J. Kim and L. M. Mirica, *Inorg. Chem.*, 2014, **53**, 11367–11376.
342 R. Leuma Yona, S. Mazères, P. Faller and E. Gras, *ChemMedChem*, 2008, **3**, 63–66.
343 C. Rodríguez-Rodríguez, M. A. Telpoukhovskaia, J. Alí-Torres, L. Rodríguez-Santiago, Y. Manso, G. A. Bailey, J. Hidalgo, M. Sodupe and C. Orvig, *Metallomics*, 2015, **7**, 83–92.
344 N. Pravin, R. Kumar, S. Tripathi, P. Kumar, G. M. Mohite, A. Navalkar, R. Panigrahi, N. Singh, L. G. Gadhe, S. Manchanda, M. Shimozawa, P. Nilsson, J. Johansson, A. Kumar, S. K. Maji and M. Shanmugam, *J. Neurochem.*, 2021, **156**, 1003–1019.
345 A. S. DeToma, J. Krishnamoorthy, Y. Nam, H. J. Lee, J. R. Brender, A. Kochi, D. Lee, V. Onnis, C. Congiu, S. Manfredini, S. Vertuani, G. Balboni, A. Ramamoorthy and M. H. Lim, *Chem. Sci.*, 2014, **5**, 4851–4862.
346 K. Cisek, J. R. Jensen, N. S. Honson, K. N. Schafer, G. L. Cooper and J. Kuret, *Biophys. Chem.*, 2012, **170**, 25–33.

347 Q. Li, J. Min, Y.-H. Ahn, J. Namm, E. M. Kim, R. Lui, H. Y. Kim, Y. Ji, H. Wu, T. Wisniewski and Y.-T. Chang, *ChemBioChem*, 2007, **8**, 1679–1687.
348 S. J. Jung, Y. D. Park, J. H. Park, S. D. Yang, M. G. Hur and K. H. Yu, *Med. Chem. Res.*, 2013, **22**, 4263–4268.
349 M. A. Telpoukhovskaia, C. Rodríguez-Rodríguez, J. F. Cawthray, L. E. Scott, B. D. G. Page, J. Alí-Torres, M. Sodupe, G. A. Bailey, B. O. Patrick and C. Orvig, *Metallomics*, 2014, **6**, 249–262.
350 H. Fu, C. Peng, Z. Liang, J. Dai, B. Liu and M. Cui, *Chem. Commun.*, 2016, **52**, 12745–12748.
351 H. Fu, P. Tu, L. Zhao, J. Dai, B. Liu and M. Cui, *Anal. Chem.*, 2016, **88**, 1944–1950.
352 M.-L. Pan, M. T. Mukherjee, H. H. Patel, B. Patel, C. C. Constantinescu, M. R. Mirbolooki, C. Liang and J. Mukherjee, *Synapse*, 2016, **70**, 163–176.
353 E. Hellström-Lindahl, P. Westermark, G. Antoni and S. Estrada, *Amyloid*, 2014, **21**, 21–27.
354 E. Fisher, Y. Zhao, R. Richardson, M. Janik, A. K. Buell, F. I. Aigbirhio and G. Tóth, *ACS Chem. Neurosci.*, 2017, **8**, 2088–2095.
355 N. Gour, V. Kshtriya, S. Gupta, B. Koshti, R. Singh, D. Patel and K. B. Joshi, *ACS Appl. Bio Mater.*, 2019, **2**, 4442–4455.
356 S. Rivera-Marrero, L. Fernández-Maza, S. León-Chaviano, M. Sablón-Carrazana, A. Bencomo-Martínez, A. Perera-Pintado, A. Prats-Capote, F. Zoppolo, I. Kreimerman, T. Pardo, L. Reyes, M. Balcerzyk, G. Dubed-Bandomo, D. Mercerón-Martínez, L. A. Espinosa-Rodríguez, H. Engler, E. Savio and C. Rodríguez-Tanty, *Curr. Radiopharm.*, 2019, **12**, 58–71.
357 M. Xu, R. Li, X. Li, G. Lv, S. Li, A. Sun, Y. Zhou and T. Yi, *J. Mater. Chem. B*, 2019, **7**, 5535–5540.
358 H.-L. Yang, S.-Q. Fang, Y.-W. Tang, C. Wang, H. Luo, L.-L. Qu, J.-H. Zhao, C.-J. Shi, F.-C. Yin, X.-B. Wang and L.-Y. Kong, *Eur. J. Med. Chem.*, 2019, **179**, 736–743.
359 J. Zhu, L. Zhou, Y. Li, S. Chen, J. Yan and L. Zhang, *Anal. Chim. Acta*, 2017, **961**, 112–118.
360 G. S. M. Sundaram, K. Garai, N. P. Rath, P. Yan, J. R. Cirrito, N. J. Cairns, J.-M. Lee and V. Sharma, *Org. Lett.*, 2014, **16**, 3640–3643.
361 P. Dao, F. Ye, Z. Y. Du, Q. Chen, K. Zhang, C. Z. Dong, B. Meunier and H. Chen, *Dyes Pigm.*, 2017, **147**, 130–140.
362 G. Lv, Y. Xu, J. Yang, W. Li, C. Li and A. Sun, *Analyst*, 2020, **145**, 6579–6585.
363 N. R. Marzano, K. M. Wray, C. L. Johnston, B. P. Paudel, Y. Hong, A. van Oijen and H. Ecroyd, *ACS Chem. Neurosci.*, 2020, **11**, 4191–4202.
364 H. Sun, H. Leng, J. Liu, G. Roy, J. Yan and L. Zhang, *Sens. Actuators, B*, 2020, **305**, 127509.
365 H. Tan, Y. Qiu, H. Sun, J. Yan and L. Zhang, *Chem. Commun.*, 2019, **55**, 2688–2691.
366 J. Yan, J. Zhu, K. Zhou, J. Wang, H. Tan, Z. Xu, S. Chen, Y. Lu, M. Cui and L. Zhang, *Chem. Commun.*, 2017, **53**, 9910–9913.
367 Y. Wang, Y. Qiu, A. Sun, Y. Xiong, H. Tan, Y. Shi, P. Yu, G. Roy, L. Zhang and J. Yan, *Anal. Chim. Acta*, 2020, **1133**, 109–118.
368 S. Rivera-Marrero, A. Bencomo-Martínez, E. Orta Salazar, M. Sablón-Carrazana, L. García-Pupo, F. Zoppolo, F. Arredondo, R. Dapueto, M. Daniela Santi, I. Kreimerman, T. Pardo, L. Reyes, L. Galán, S. León-Chaviano, L. A. Espinosa-Rodríguez, R. Menéndez-Soto del Valle, E. Savio, S. Díaz Cintra and C. Rodríguez-Tanty, *Bioorg. Med. Chem.*, 2020, **28**, 115700.
369 P. Gaur, M. Galkin, A. Kurochka, S. Ghosh, D. A. Yushchenko and V. V. Shvadchak, *ACS Chem. Neurosci.*, 2021, **12**, 1293–1298.
370 H. Kaur, M. R. Felix, C. Liang and J. Mukherjee, *Bioorg. Med. Chem. Lett.*, 2021, **46**, 128164.
371 J. Wu, C. Shao, X. Ye, X. Di, D. Li, H. Zhao, B. Zhang, G. Chen, H.-K. Liu and Y. Qian, *ACS Sens.*, 2021, **6**, 863–870.
372 J. An, P. Verwilst, H. Aziz, J. Shin, S. Lim, I. Kim, Y. K. Kim and J. S. Kim, *Bioact. Mater.*, 2022, **13**, 239–248.
373 D. Fang, X. Wen, Y. Wang, Y. Sun, R. An, Y. Zhou, D. Ye and H. Liu, *Theranostics*, 2022, **12**, 3178–3195.
374 Y. Guo, H. Leng, Q. Chen, J. Su, W. Shi, C. Xia, L. Zhang and J. Yan, *Sens. Actuators, B*, 2022, **372**, 132648.
375 R. Mallesh, J. Khan, K. Pradhan, R. Roy, N. R. Jana, P. Jaisankar and S. Ghosh, *ACS Chem. Neurosci.*, 2022, **13**, 2503–2516.
376 Y. Wang, D. Mei, X. Zhang, D.-H. Qu and J. Mei, *Sci. China: Chem.*, 2022, **65**, 339–352.
377 H. Tan, K. Zhou, J. Yan, H. Sun, M. Pistolozzi, M. Cui and L. Zhang, *Sens. Actuators, B*, 2019, **298**, 126903.
378 I. Kocsis, E. Sanna and C. A. Hunter, *Org. Lett.*, 2021, **23**, 647–650.
379 L. Esposito, M. C. Yadon, J. Cummings, F. M. Hudson, T. Lake, F. F. Hefti, G. Golding, S.-R. Choi, X. Li, A. D. Snow, H. Qubai and C. Judy, WO2012118935A1, 2012.
380 W. E. Klunk, C. A. Mathis and Y. Wang, *US Pat.*, US10137210B2, 2018.
381 Y. Kudo, S. Furumoto and N. Okamura, WO2012057312A1, 2011.
382 I. Tooyama, H. Taguchi, S. Morikawa, M. Urushitani, D. Yanagisawa, T. Nagae, N. Shirai, K. Hirao, M. Kato, H.Kimura and T. Okada, WO2010098502A1, 2010.
383 W. Abbas, E. Hostetler, T. Greshock, J. Li, K. P. Moore, I. Bennacef, J. Mulheam, H. Selnick, K. Yang and J. Fu, WO2015188368A1, 2015.
384 B. W. Caprathe, J. L. Gilmore, S. J. Hays, J. C. Jaen and H. Levine III, *US Pat.*, US6001331A, 1999.
385 H. F. Kung, M.-P. Kung and Z.-P. Zhuang, *US Pat.*, US7807135B2, 2010.
386 H. F. Kung, personal communication.
387 D. J. Hayne, S. Lim and P. S. Donnelly, *Chem. Soc. Rev.*, 2014, **43**, 6701–6715.
388 K. Chen and M. Cui, *MedChemComm*, 2017, **8**, 1393–1407.
389 J.-F. Morfin, S. Lacerda, C. F. G. C. Geraldes and É. Tóth, *Sens. Diagn.*, 2022, **1**, 627–647.
390 S. Lacerda, J.-F. Morfin, C. F. G. C. Geraldes and É. Tóth, *Dalton Trans.*, 2017, **46**, 14461–14474.
391 O. Krasnovskaya, D. Spector, A. Zlobin, K. Pavlov, P. Gorelkin, A. Erofeev, E. Beloglazkina and A. Majouga, *Int. J. Mol. Sci.*, 2020, **21**, 9190.

392 M. Groenning, *J. Chem. Biol.*, 2010, **3**, 1–18.
393 R. Khurana, C. Coleman, C. Ionescu-Zanetti, S. A. Carter, V. Krishna, R. K. Grover, R. Roy and S. Singh, *J. Struct. Biol.*, 2005, **151**, 229–238.
394 C. Xue, T. Y. Lin, D. Chang and Z. Guo, *R. Soc. Open Sci.*, 2017, **4**, 160696.
395 E. D. Agdeppa, V. Kepe, J. Liu, S. Flores-Torres, N. Satyamurthy, A. Petric, G. M. Cole, G. W. Small, S. C. Huang and J. R. Barrio, *J. Neurosci.*, 2001, **21**, RC189–RC189.
396 S. A. Wildman and G. M. Crippen, *J. Chem. Inf. Comput. Sci.*, 1999, **39**, 868–873.
397 L. Cai, B. Qu, B. T. Hurtle, S. Dadiboyena, R. Diaz-Arrastia and V. W. Pike, *ACS Chem. Neurosci.*, 2016, **7**, 897–911.
398 N. A. Murugan, A. Nordberg and H. Ågren, *ACS Chem. Neurosci.*, 2021, **12**, 2437–2447.
399 N. A. Murugan, A. Nordberg and H. Ågren, *ACS Chem. Neurosci.*, 2018, **9**, 1757–1767.
400 N. A. Murugan, C. Halldin, A. Nordberg, B. Långström and H. Ågren, *J. Phys. Chem. Lett.*, 2016, **7**, 3313–3321.
401 H. Levine, *Amyloid*, 2005, **12**, 5–14.
402 S. K. Mishra, Y. Yamaguchi, M. Higuchi and N. Sahara, *Int. J. Mol. Sci.*, 2020, **22**, 349.
403 R. Ni, P. G. Gillberg, A. Bergfors, A. Marutle and A. Nordberg, *Brain*, 2013, **136**, 2217–2227.
404 A. Sidhu, J. Vaneyck, C. Blum, I. Segers-Nolten and V. Subramaniam, *Amyloid*, 2018, **25**, 189–196.
405 E. Smith and I. Collins, *Future Med. Chem.*, 2015, **7**, 159–183.
406 P. Duan, K. J. Chen, G. Wijegunawardena, A. J. Dregni, H. K. Wang, H. Wu and M. Hong, *J. Am. Chem. Soc.*, 2022, **144**, 1416–1430.

