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Peptide-to-Small-Molecule Scaffold Exploration with Amino Acid Mapping

Peptides and macrocycles can bind targets beyond the reach of many conventional smaller molecules. Converting that binding insight into a smaller scaffold with room for further development remains a substantial medicinal chemistry challenge. Conventional analogue design usually remains close to the structure that produced the original activity. That is useful for optimisation within a series, but less useful when the series itself has become the constraint.

drug2drugs AI-AAM® (Amino Acid Mapping) begins from a different premise. It maps amino-acid interaction features around an active reference ligand and uses those features to guide exploration of alternative molecular frameworks. The objective is to identify structurally differentiated molecules that may retain selected elements of the reference interaction profile.

A case study on peptide-to-small-molecule conversion using drug2drugs AI-AAM® is presented in this application note. In this published study on PD-L1, a 1,796 Da macrocyclic peptide was translated into a 482 Da small molecule with measurable activity, improved binding efficiency per molecular weight, and substantially greater membrane permeability; structure-based chemical modification then improved potency more than six-fold.

The Scaffold Limitation Problem in Lead Discovery

Analogue design can refine a known chemical series, but it rarely changes the central framework that defines the series' chemical, developability and intellectual-property constraints. This becomes a problem when the scaffold itself contributes to metabolic instability, poor solubility, excessive lipophilicity, difficult synthesis or overlaps with existing patents.

The challenge is greater for cyclic peptides and macrocycles. These ligands can bind difficult protein surfaces with high affinity, yet their size and polarity can restrict membrane permeability and complicate oral delivery. Conventional fingerprint and pharmacophore methods often favour structures that remain close to the starting ligand. Peptide-to-small-molecule conversion requires a search criterion that can retain selected binding-relevant features while allowing the framework to change.

drug2drugs AI-AAM®: *In Silico* Spatial Feature Mapping

drug2drugs AI-AAM® is a ligand-based computational service for scaffold exploration and molecule prioritisation from one active reference structure (Figure 1). The platform maps amino-acid interaction features around the reference ligand, then uses those features to guide generation or selection of alternative molecular frameworks. It delivers computationally prioritised molecules for synthesis and biological testing; experimental validation remains downstream.

AAM is the core descriptor. It records the spatial distribution of interaction features associated with each of the 20 natural amino-acid probe types around a ligand. The resulting four-dimensional map combines amino-acid identity with three-dimensional position. It provides a ligand-side representation of binding-relevant features, rather than a reconstruction of the complete protein binding site.

The atom-based generator designs molecules through sequential atom addition, deletion and bond formation while assessing the evolving structure against the reference AAM profile. Learned adjacent-atom patterns suppress chemically unreasonable local structures.

AAM similarity, diversity selection and project-defined computational filters then refine the generated pool into a focused molecule set.

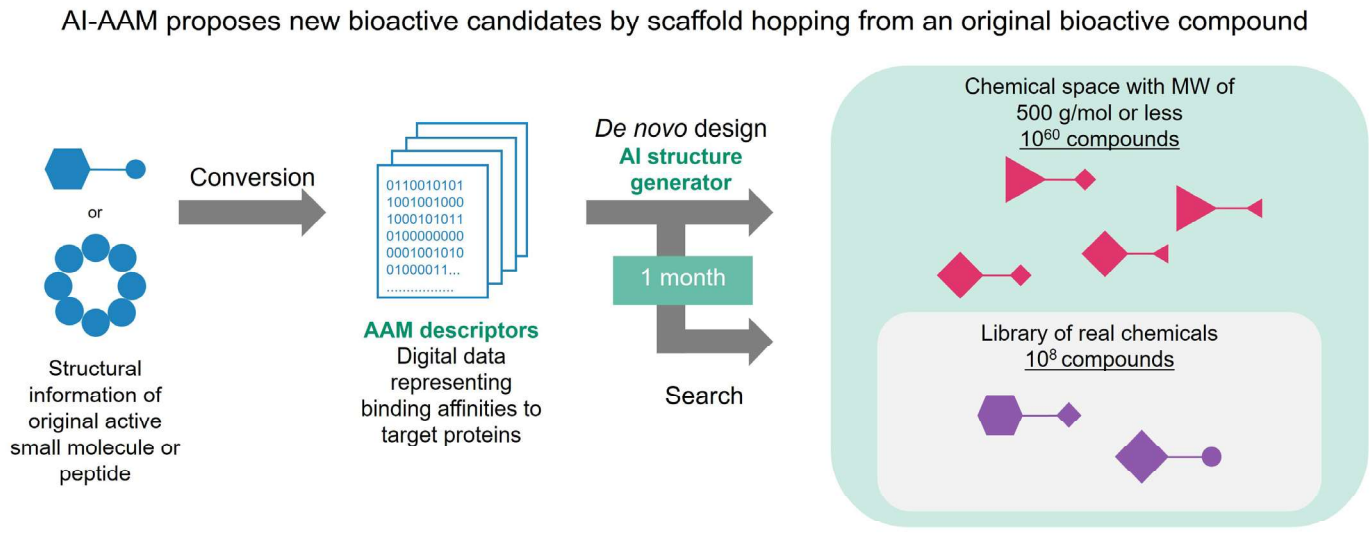


Figure 1. drug2drugs AI-AAM® converts an active reference compound into an AAM interaction profile, then uses that profile to support both library screening and atom-based de novo molecule design

AAM similarity can be evaluated during molecular generation because the comparison operates on ligand-side interaction maps rather than full protein calculations. A complete generation campaign can still require substantial resources: in the PD-L1 study, one run used multiple GPUs over approximately one month. The final output is typically a prioritised set of approximately 100 structures for further review and validation. During the computation phase, the generator also applies learned adjacent-atom patterns to suppress chemically unreasonable local structures, including implausible bond patterns and inappropriate connectivity. Computational indicators related to synthetic accessibility and stability can further refine the set of molecular structures. The workflow expands the search beyond close analogues of the reference scaffold (Figure 2).

AAM similarity compares amino-acid-specific spatial maps after relative alignment. Conventional fingerprint similarity rewards shared molecular connectivity; AAM similarity can rank molecules with unrelated cores when they present related interaction features in similar regions of space. The score is used to prioritise molecules within a defined system. It is not a direct measure of biological activity or a universal predictor of potency (Figure 3).

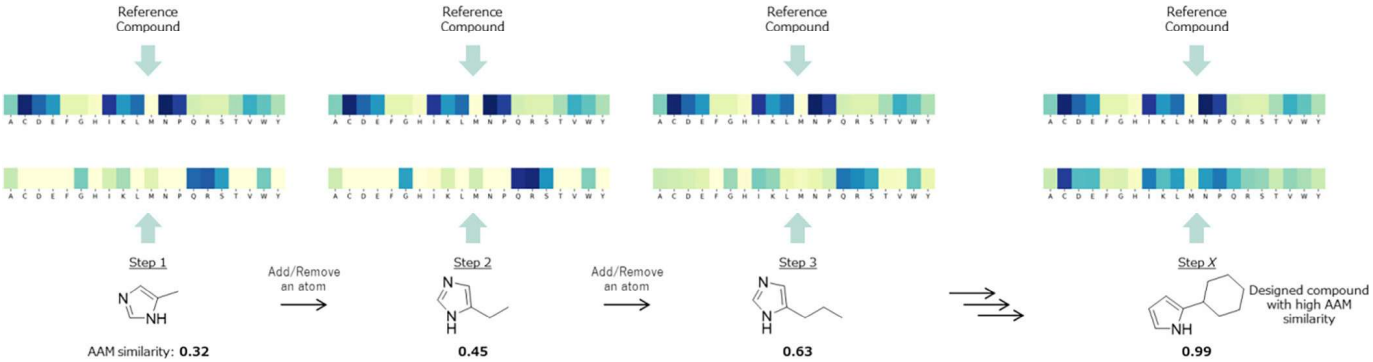
For larger ligands, the calculation can focus on selected regions rather than the complete molecule. This selected residue strategy is important for peptide-to-small-molecule work because it directs the generator towards localised interaction motifs that may be represented within a lower-molecular-weight scaffold.

Peer-Reviewed Case Study:
Macrocyclic Peptide to Small Molecule Conversion

To rigorously evaluate the platform, a proof-of-concept study was conducted and published in Bioorganic and Medicinal Chemistry Letters in 2026 (https://doi.org/10.1016/j.bmcl.2026.130655). The study investigated whether the AI-AAM platform could transform a high-molecular-weight macrocyclic peptide targeting the programmed death ligand-1 (PD-L1) interaction surface into an active, membrane-permeable small molecule.

The starting reference molecule was Peptide-71, a macrocyclic peptide inhibitor of the PD-L1 interaction possessing a molecular weight of 1796.12 g/mol and a measured inhibition constant Ki of 0.004 μM (4 nM, PDB ID: 5O45). The Binding Efficiency Index (BEI), defined as -log10(Ki) / (MW/1000), was calculated at 4.7. To identify the critical interaction domain, FMO-based energy decomposition was applied to the PD-L1/Peptide-71 complex model. The total calculated FMO interaction-energy score for Peptide-71 was -90 kcal/mol.

Energy decomposition revealed that binding energy was unevenly distributed across the peptide backbone. Four spatially localised residues, namely 1Phe, 7NMePhe, 10Trp and 11Tyr, accounted for -61 kcal/mol, representing approximately



Note: This design process includes an algorithm to avoid the generation of thermodynamically unstable structures, although this aspect is omitted from the illustration.

Figure 2. Atom-based generation modifies molecular structures iteratively while assessing similarity to the reference AAM profile

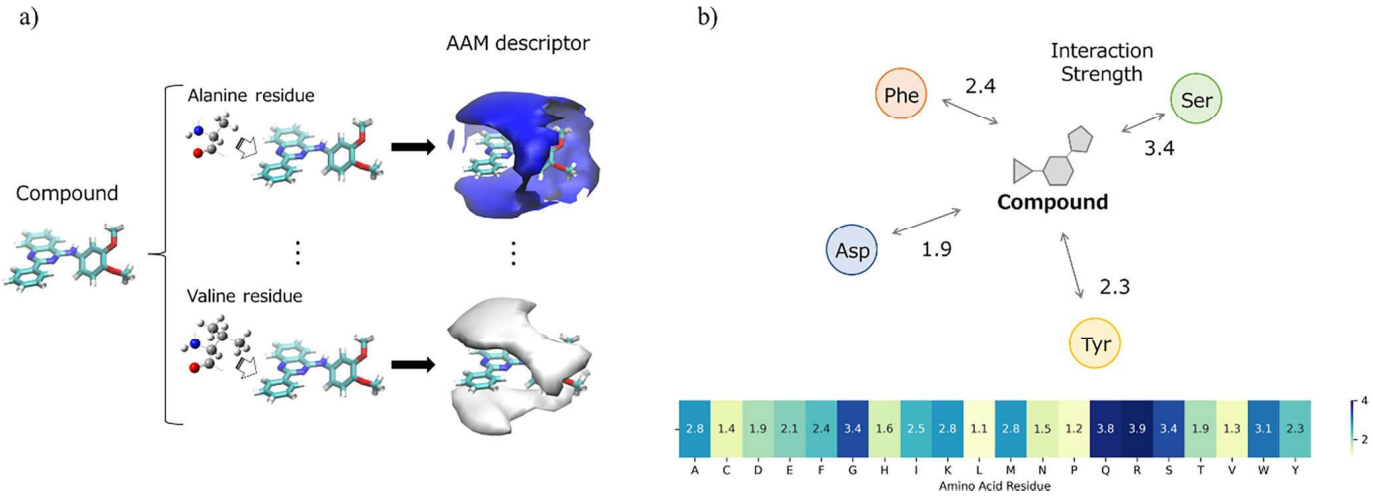


Figure 3. (a) The AAM descriptor maps the spatial interaction profile of each amino-acid residue type around a reference compound. Together, these amino-acid-specific 3D maps form a four-dimensional interaction descriptor. (b) A simplified heatmap view shows the relative interaction profile by amino-acid type

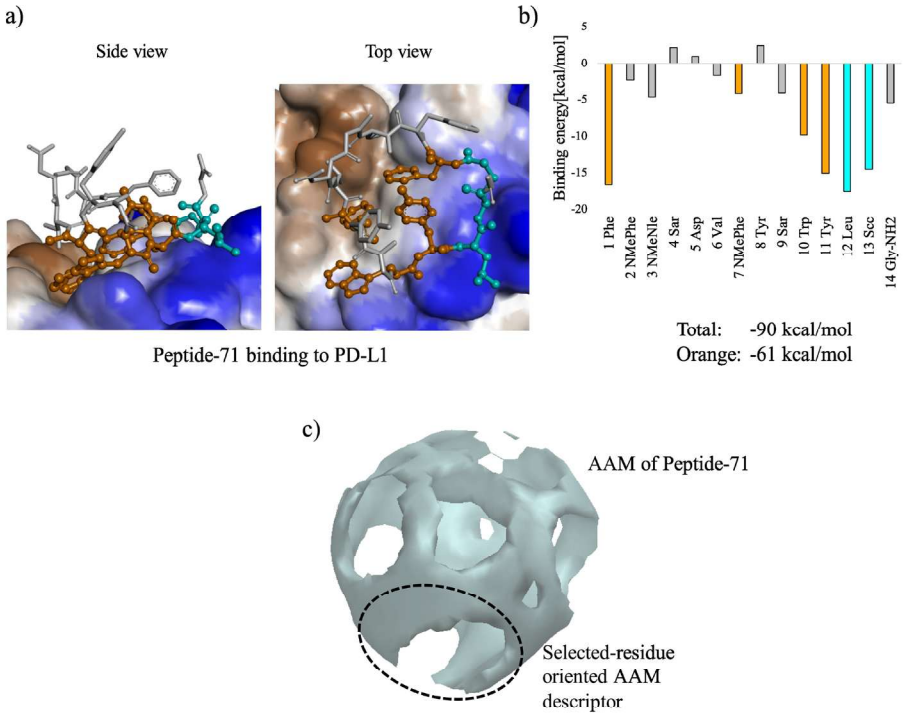


Figure 4. (a) Peptide-71 in the PD-L1 binding site. (b) FMO-derived residue interaction-energy contributions. (c) Selected-residue AAM descriptor derived from the localised peptide region chosen for small-molecule translation

68 per cent of the total interaction energy score. These four residues form a consolidated hydrophobic binding motif within a localised pocket on PD-L1. Other high-contribution residues, such as 12Leu and 13Scc, contacted exposed hydrophilic surface regions and were excluded from feature mapping to enable maximum molecular weight compression (Figure 4).

A selected-residue oriented AAM descriptor was generated specifically for the region encompassing 1Phe, 7NMePhe, 10Trp and 11Tyr. The atom-based generative engine then sampled potential small-molecule space, producing 78,765 unique molecules. The resulting AAM similarity scores had a median value of 0.54, with 95th and 99th percentile thresholds of 0.64 and 0.67, respectively.

FF-ATC-001 had the highest AAM similarity in the generation run, with a score of 0.73 and a molecular weight of 481.51 Da. It inhibited PD-L1 with a reported Ki of 39 μM, compared with 0.004 μM for Peptide-71. The approximately four-log reduction in potency illustrates the difficulty of compressing the peptide's interaction pattern into a 482 Da scaffold. FF-ATC-001 nevertheless retained measurable activity, achieved a BEI of 9.2 versus 4.7 for Peptide-71, and provided a structurally differentiated starting point for optimisation (Table 1).

Complex modelling of FF-ATC-001 aligned within the PD-L1 pocket yielded a calculated FMO interaction-energy score of -50 kcal/mol, closely matching the -61 kcal/mol baseline of the four targeted peptide residues. The compound also avoided the biphenyl-centred chemotype common among reported PD-L1 inhibitors, providing a distinct starting point for further optimisation. When benchmarked against the known small-molecule PD-L1 inhibitor BMS-202 (MW = 419.52 g/mol, BEI = 17.8), FF-ATC-001 (MW=481.51 g/mol) represents a structurally distinct, non-biphenyl starting point derived directly from peptide feature translation. Crucially, in assay models measuring passive diffusion, FF-ATC-001 demonstrated an approximate 100-fold increase in cell membrane permeability compared to Peptide-71.

Where protein structural information is available, AI-AAM-generated structures can provide starting points for subsequent structure-based optimisation. Because FF-ATC-001 was generated to reproduce the three-dimensional feature fields of Peptide-71, a complex model of FF-ATC-001 bound to PD-L1 was constructed by aligning the small molecule directly onto the spatial coordinates of the template peptide in PDB 5O45 without requiring docking calculations.

A model of FF-ATC-001 in the PD-L1 binding site identified Gln66 as an opportunity for an additional interaction. The researchers designed three analogues, FF-ATC-2a, -2b, and -2c, to engage this region. Their reported Ki values were 20, 11 and 5.7 μM, respectively (Figure 5).

FF-ATC-2c improved potency by more than six-fold relative to FF-ATC-001. FMO-derived interaction-energy scores for the analogues were approximately -60 to -61 kcal/mol, compared with -50 kcal/mol for FF-ATC-001. In this series, the experimental result was directionally consistent with the structure-based prioritisation hypothesis.

Drug2drugs AI-AAM®: Strategic Discovery Applications

For biopharma drug design teams and medicinal chemists, Fujifilm's drug2drugs AI-AAM® service supports programmes in which a known active compound provides a useful interaction reference but its scaffold limits further exploration. Typical uses include alternative scaffold generation from an active lead, backup-series exploration, peptide-to-small-molecule design and expansion of a narrow medicinal-chemistry series.

The service begins with an active reference structure and project-defined objectives. It generates or screens structurally

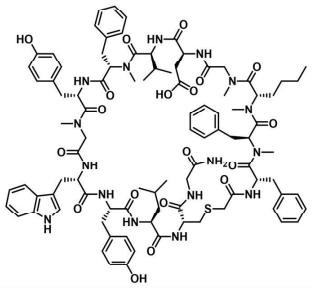
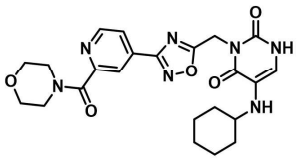
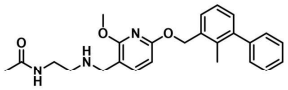
	Peptide-71	FF-ATC-001	BMS-202
			
Molecular Format	Macrocyclic Peptide	Small Molecule	Small Molecule
Ki ([μM])	0.004	39	0.034
BEI ([pK_i/Mw×1000])	4.7	9.2	17.8
MDCK-II Permeability ([10^{-6} cm/s])	0.08±0.02	11.1±0.8	Not measured

Table 1. Scaffold compression reduced molecular weight and increased the reported binding-efficiency index and membrane permeability of FF-ATC-001 relative to Peptide-71 and BMS-202

differentiated molecules, ranks them using AAM similarity and complementary computational criteria, and delivers a focused set for customer-led synthesis and testing. Where a protein structure is available, it can support optional structure-based analysis, as demonstrated in the PD-L1 study.

Scope of the Method

Peptide-to-small-molecule exploration is most tractable when key interaction features are spatially localised and can be represented within a compact scaffold. Systems with widely dispersed epitopes, highly polar or solvent-exposed contacts, extensive backbone hydrogen-bonding networks or flexible binding conformations may be more difficult to translate.

A project begins with an active reference structure and defined objectives. Drug2drugs AI-AAM® calculates the AAM profile, generates or screens alternative structures, applies ranking and diversity criteria, and delivers a prioritised set of approximately 100 molecules for customer-led synthesis, docking or biological testing.

Conclusion

The example shown in this Application Note demonstrate how Drug2drugs AI-AAM® can support scaffold exploration for a peptide-to-small-molecule challenge. In the case study, selected peptide interactions were translated into a smaller active scaffold, then improved through structure-based optimisation. We are continuing to develop our technology for the conversion of peptides into small molecules using Drug2drugs AI-AAM® and are identifying metrics to guide this process. These findings will be reported in due course.

Drug2drugs AI-AAM® gives discovery teams a route to examine alternative chemical frameworks from a known active compound before committing to a conventional analogue campaign. The output is a prioritised set of structurally differentiated molecules for synthesis, testing and further structure-activity relationship (SAR) study.

Discuss a known active small molecule, peptide, macrocycle, natural product or constrained lead series with Fujifilm.

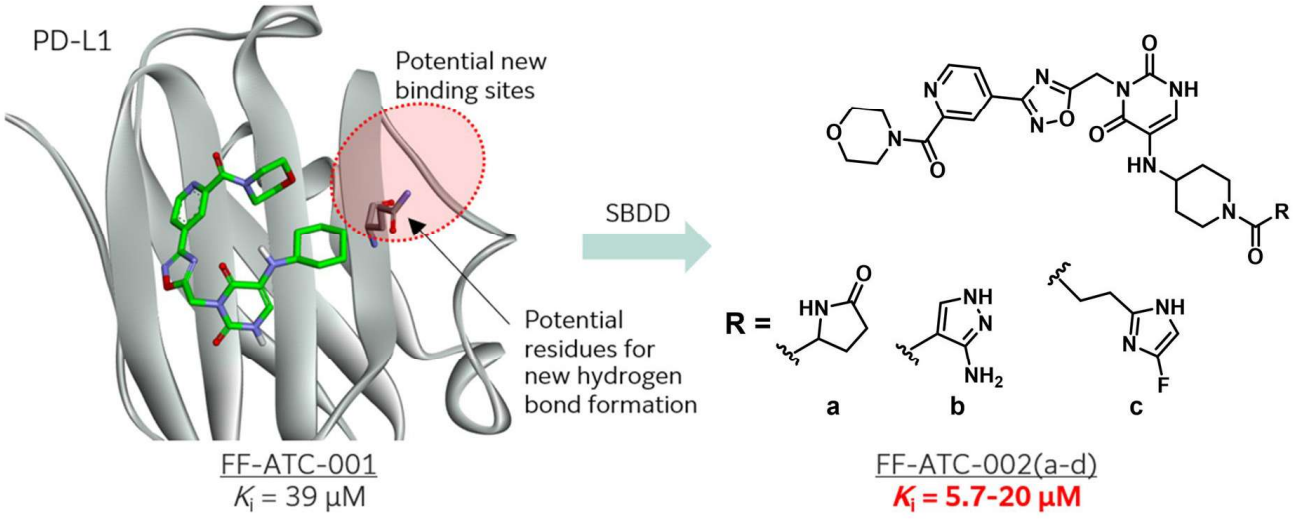
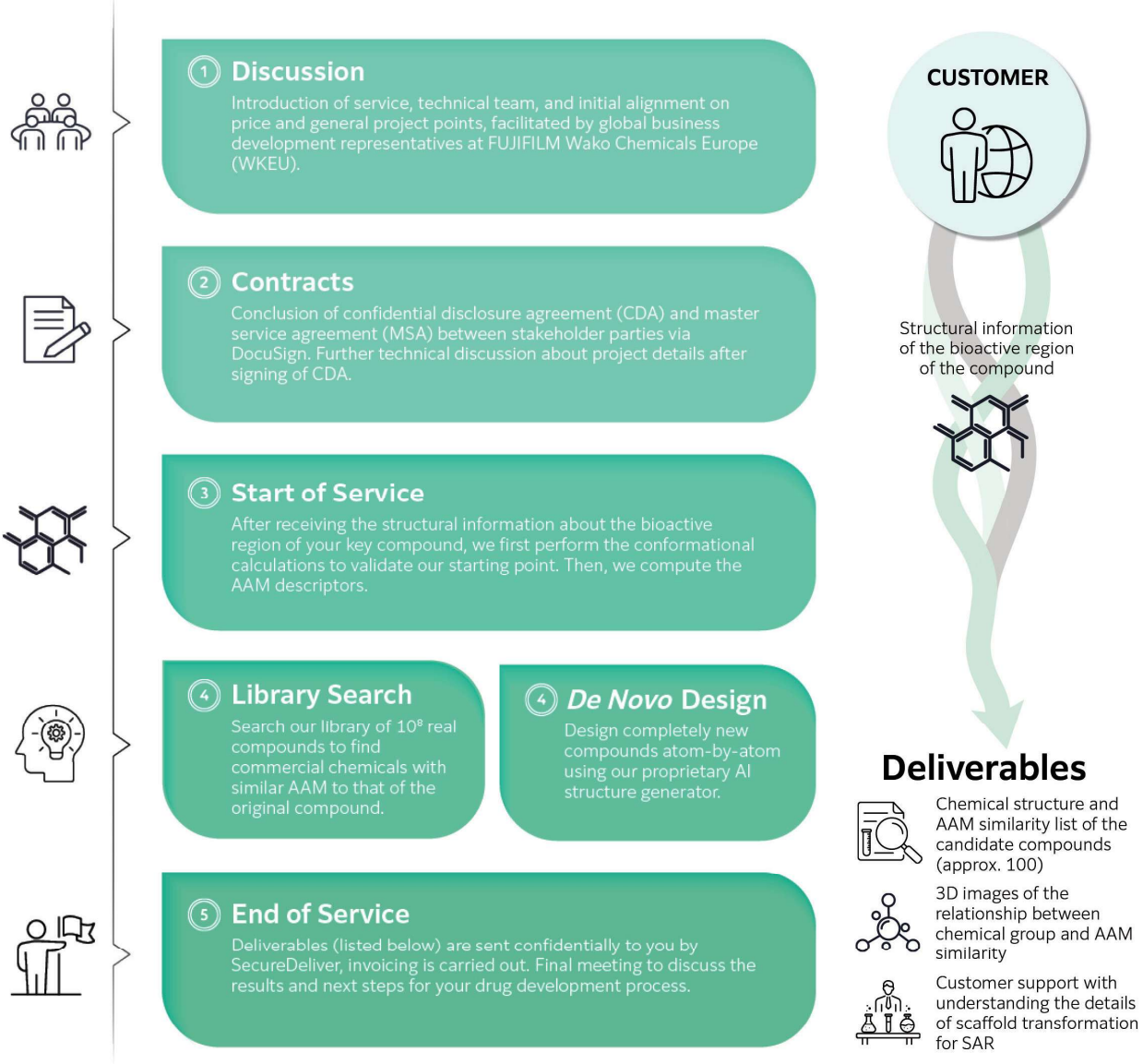


Figure 5. The model of FF-ATC-001 identified Gln66 as an opportunity for an additional PD-L1 interaction

Service Flow & Deliverables



Drug2drugs AI-AAM® can assess whether its AAM interaction profile is suitable for scaffold exploration and define a new scaffold-generation strategy around the objectives and constraints of the programme.

Consider drug2drugs AI-AAM® if your programme needs to:

- Explore structurally differentiated backup series
- Translate selected peptide or macrocycle interactions into smaller scaffolds
- Expand beyond a narrow analogue series
- Investigate alternative chemical matter around an active reference compound
- Generate a prioritised set of molecules for synthesis and biological testing

REFERENCES

1. Ohira, S., Doi, I., Nakabayashi, J., Tanaka, H., Sonoda, Y., Ben Ammar, Y., Kochi, M., Tanaka, T., and Tsumura, K. (2026). AI-assisted transformation of PD-L1 inhibitory peptides into small molecules using amino acid mapping descriptor and activity improvement through structure-based drug design. Bioorganic and Medicinal Chemistry Letters, 137, 130655.

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Kyosuke Tsumura is a principal research scientist at FUJIFILM Corporation, specialising in theoretical physics, computational chemistry and computational biology for drug discovery. Since joining FUJIFILM in 2006, he has applied his theoretical physics background to chemical and biological systems to accelerate product development. This work led to AI and simulation technologies, including AI-AAM. His current focus is converting PPI interfaces and their peptide or protein ligands into small-molecule starting points for drug discovery.