Molecular Mops: An Innovative Approach to Synthetic Opioid Neutralization

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1. Introduction

Research plays a crucial role in combating the synthetic opioids crisis, particularly with substances like fentanyl, which poses unprecedented challenges due to their high potency, long half-life and the rapid evolution of their chemical analogs. As synthetic opioids become increasingly sophisticated, our current treatments and antidotes, such as naloxone, struggle to keep pace with the constant emergence of new, more dangerous compounds. Innovative research into synthetic opioid blocking technologies is therefore essential.

Narcan® (nasal spray naloxone) was originally designed to counteract overdoses from morphine and heroin, which are opioids from, or derived from natural sources. Both morphine and heroin act on opioid receptors in the brain, primarily the Mu-opioid Receptors (MOR), to produce their effects [1].

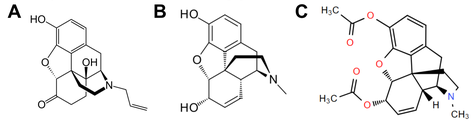

Figure 1 Naloxone (A) is structurally similar to natural opiates morphine (B) and heroin (C).

Naloxone is a lipophilic, receptor antagonist that binds to MOR [1,2]. Since fentanyl binds strongly to the same receptors, a large dose of naloxone is necessary to displace fentanyl (see Figure 2). Fentanyl is also lipophilic with a long half-life of 3 to 7 hours. Therefore, it can migrate to new receptor sites in the brain and continue to bind. Therefore, multiple doses of naloxone may be necessary for continued MOR binding to counter a fentanyl overdose (see Figure 3) [2].

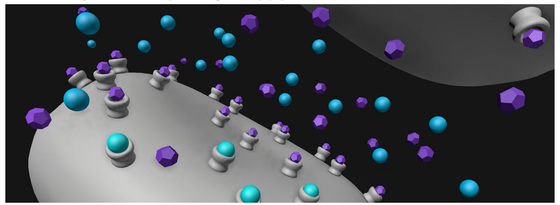

Figure 2 Naloxone, illustrated as purple shapes, competes with fentanyl, shown as blue spheres, at Mu–opioid receptor sites. Typically, a large excess of naloxone is needed to more effectively displace fentanyl.

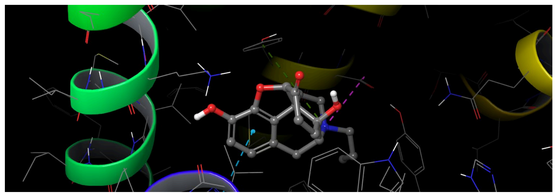

Figure 3 Molecular modeling of naloxone binding to MOR sites. Naloxone bound in the active site of PDB ID: 9BJK. In this orientation, Naloxone forms a salt bridge with Asp147, a π-π interaction with His297, and a cation–π interaction with Tyr148.

2. Molecular Modeling & In-silico Optimization

Modern synthetic opioids, such as fentanyl and its analogs, have introduced new challenges. These synthetic drugs often have different chemical structures allowing them to bind more tightly to opioid receptors compared to traditional opioids.

Introducing 'Molecular Mops'

The "molecular mop" represents a groundbreaking class of compounds designed to selectively remove unwanted molecules from critical receptor sites. Much like a physical mop absorbs and clears spills, these molecular agents function through a dual-action mechanism: first, they competitively bind to receptor sites, displacing the target molecules; then, identical compounds engage the displaced targets via precise noncovalent π-π stacking interactions, enhancing their removal (see Figure 4). By leveraging advanced molecular modeling and machine learning, these compounds are engineered with high selectivity and affinity, optimizing π-orbital overlap to maximize binding efficiency. This innovative approach holds promise for applications ranging from toxin neutralization to drug overdose reversal and beyond, offering a versatile strategy for clearing receptor sites and restoring biological balance.

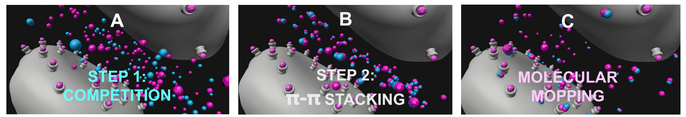

Figure 4 Molecular mops (shown as magenta shapes) are in-silico designed to work via an innovative, two-pronged approach. They are optimized to better compete with target molecules (blue spheres) for receptor binding sites [A] and simultaneously have optimized π overlap distances enabling them to π-π stack with target molecules [B]. This dual approach reduces target molecule rebinding by 'mopping' target molecules away [C].

Molecular Modeling

Molecular modeling was performed to in-silico design molecular mops that optimize receptor site affinity binding and maximize π-π stacking capabilities (see Figure 5). When π-π orbital distances are perfectly matched to target molecules the molecular mops stack like magnetic Legos™. Modeling was also employed to test binding to MOR sites (and compare various molecular mop designs to naloxone binding). [Schrödinger's software and multiple other software and shareware programs were used to study receptor site binding of various conformations and optimize the distance between aromatic rings to enhance the strength of π-π interactions.]

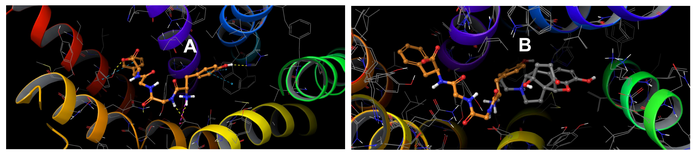

Figure 5 [A] YGGF peptide (orange) bound to the allosteric site of the Mu-opioid receptor (PDB ID: 9BJK). YGGF forms π-π interactions with Tyr75 and Trp293; hydrogen bonds with His297, Gln124, Asp147, and Tyr75; and a salt bridge with Asp147.
[B] YGGF peptide (orange) and naloxone (gray) bound to the Mu-opioid receptor (PDB ID: 9BJK). This view reveals an overlap between YGGF and naloxone, suggesting that YGGF may function both as a negative allosteric modulator (NAM) and as an orthosteric antagonist at the Mu-opioid receptor.

3. Methods

Experimental Validation

Experimental validation of YGGF's efficacy was conducted using MALDI MS (Shimadzu MALDImini-1, MALDI-8030 and AXIMA Performance), single and triple quadrupole LC-MS/MS and LC-Q-TOF (Shimadzu LCMS-9030) platforms. MALDI sample pH and spotting was optimized to enable peptide:opioid complex interrogation. In ESI, samples were kept at near neutral pH and instrument parameters optimized to preserve complex formation and optimize MS/MS collision energies for complex confirmation. For ESI, samples were directly infused, or a flow injection was performed with 50/50 water/ethanol. For flow injection, a 10 µL sample plug was introduced to the MS. For direct infusion, a 3 µL/min flow rate provided sufficient sensitivity and stable electrospray.

Analyses of π-π Complexes

YGGF:opioid π-π complexes were consistently observed across these platforms, confirming the robustness of the π-π complexes of YGGF peptide with multiple synthetic opioids (Figure 6). In particular, intact complexes were observed via electrospray and MALDI for fentanyl. Using the MS/MS capabilities of ESI Q-TOF, peptide-opioid complexes were confirmed for fentanyl as well as several synthetic opioid complexes including norcarfentanil, carfentanil, remifentanil, alfentanil, and tianeptine. Flow-injection was determined to be an acceptable method of sample introduction for increasing throughput as the complex was largely preserved for MS/MS detection. However, direct infusion at ~ 3 µL/min was preferred to preserve concentration and provide minimal perturbation.

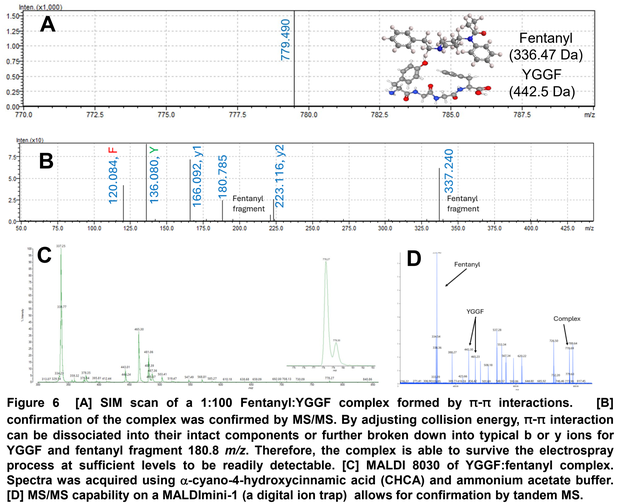

Figure 6 [A] SIM scan of a 1:100 Fentanyl:YGGF complex formed by π-π interactions. [B] confirmation of the complex was confirmed by MS/MS. By adjusting collision energy, π-π interaction can be dissociated into their intact components or further broken down into typical b or y ions for YGGF and fentanyl fragment 180.8 *m/z*. Therefore, the complex is able to survive the electrospray process at sufficient levels to be readily detectable. [C] MALDI 8030 of YGGF:fentanyl complex. Spectra was acquired using α-cyano-4-hydroxycinnamic acid (CHCA) and ammonium acetate buffer. [D] MS/MS capability on a MALDImini-1 (a digital ion trap) allows for confirmation by tandem MS.

4. Conclusion

π-π bonding is a powerful non-covalent interaction and we herein demonstrate how precise tuning of molecular mop aromatic structure distances can be applied to optimize stacking with target compounds, adding a neutralizing dimension to enhance the competitive binding efficiency against synthetic opioids.

These fentanyl complexes were detectable in the presence of sphingomyelin and at multiple opioid to peptide ratios. Furthermore, introduction of naloxone did not prevent the formation of the YGGF:opioid complex.

In drug design and therapeutic interventions, π-π interactions in these molecular mops can be leveraged to improve the specificity and efficacy of treatments. For instance, in the case of synthetic opioid antagonists, incorporating compounds that engage in π-π interactions may enhance their ability to precisely bind to target sites and displace harmful substances.

Beyond opioid antagonists, the π-π stacking of molecular mops can be applied to targeted cancer therapy, environmental remediation, neutralizing toxins, anti-allergic therapies, removing hormonal contaminants, inhibiting bacterial quorum sensing, reversing drug toxicity, targeted delivery of therapeutics, cosmetic applications and much more.

We believe that as AI and molecular modeling continue to improve, the ability to design new molecular mops to selectively bind targets will be vastly improved and new molecular mops will be designed in-silico. We intend to explore π-π stacking capabilities of molecular mops to address a variety of challenges in medical, environmental, and industrial fields.

This proof-of-principle work with synthetic opioids focused on sandwich (or eclipsed) stacking but can be extended with T and offset stacking as well as extension to cation π considerations.

5. References

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In Memory of Dr. Amina S. Woods (1943–2025):

Visionary Mass Spectrometrist, Trailblazer in Molecular Neurobiology, Devoted Mentor & Dear Friend.

The authors honor the life and legacy of Dr. Amina Woods—a colleague, a brilliant mind, and above all, a dear friend. It was not just the science that made Amina extraordinary—it was the spirit behind it. She was generous with her knowledge, gracious in collaboration, and always carried herself with humility, even as her brilliance lit up every room.

COI Disclosure: The authors declare no competing financial interest.