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Computational Design of β-Fluorinated Morphine Derivatives for pH-specific Binding

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Introduction

Opioids are effective pain relievers but are highly addictive. We propose several non-addictive opioid derivatives that bind preferentially in peripheral inflamed tissue (pH=6.5) and not in physiological conditions (pH=7.4). A pH-specific opioid derivative induces selective binding via the addition of a fluorine on a carbon beta to the tertiary amine. Fluorine's inductive effects destabilizes the amine group, which is the ionic binding site. The benzomorphan drug class involves the dissection of C and D rings of morphine; this decreases the drug's rigidity and encourages a more fitted binding of the ligand to the receptor. We hypothesize the derivatives will preferentially bind to peripheral opioid receptors and not central opioid receptors. This will lessen the central response and adverse side effects, such as addiction and euphoria, while maintaining analgesia. Molecular modeling techniques are used to model the derivatives' interactions with specific amino acid residues within the binding site of the μ-opioid receptor (MOR).

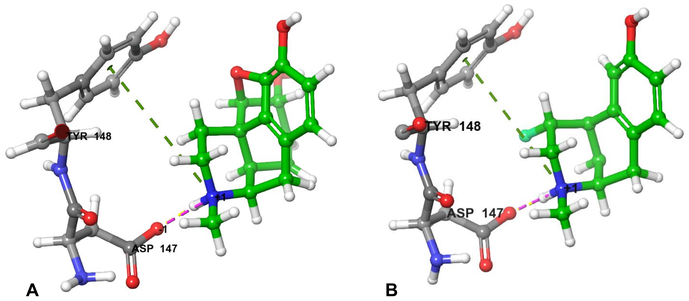

Fig. 1. Fig.1A shows optimized interactions between morphine and Asp147 and Tyr148 within the MOR. Fig.1B shows the interactions between D-fluoromorphine β-C1 and Asp147 and Tyr148 within the MOR.

Tbl. 1. The table includes the calculated pKa values from the Keck Computational Research Cluster (KCRC) and percent protonation at physiological and inflamed pH or morphine, dissected morphine, D-fluoromorphine β-C2, and D-fluoromorphine β-C2

	Morphine	Dissected Morphine	D-fluoro morphine β-C1	D-fluoro morphine β-C2
pKa	8.2	9.54	7.83	7.04
% Protonation (pH 7.4)	86.3	99.3	73.1	30.8
% Protonation (pH 6.5)	98.0	99.9	95.6	77.9

Methods

Electronic structure calculations were optimized with *GaussView 6* and computed with *Gaussian 16, Rev. B.01* using the KCRC. Percent protonation calculations based on pH environment are performed using a modified Henderson-Hasselbalch equation. From direct treatment of the aqueous phase reaction, we calculate the overall change in Gibbs free energy for the aqueous deprotonation. The reported pKa values are calculated using this reported change in free energy. Molecular modeling of the derivatives within the MOR is modeling using Schrödinger: Maestro software. Morphine, dissected morphine, and the fluoromorphine derivatives are computationally built within the crystallized MOR (PDB ID: 4dkl) file from the Protein Data Bank (PDB). A conformational search is performed within Schrödinger: Maestro and the lowest to highest energy conformations of the ligand are produced.

(1) Morphine-$H^+_{(aq)} \rightarrow$ Morphine$_{(aq)}$ + $H^+_{(aq)}$

(2) $\Delta G_{aq} = G_{aq}$(Morphine) – G_{aq}(Morphine-H^+) + G_{aq}(H^+)

(3) $$pK_a = \frac{\Delta G_{aq}}{2.303RT}$$

Results

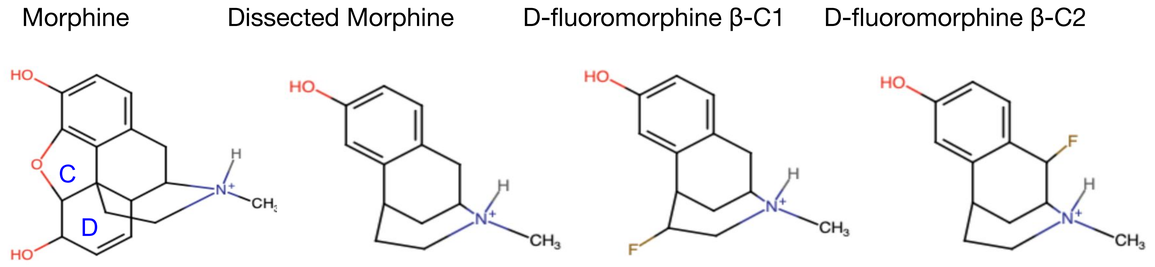

Fig. 2. 2D-line drawings of morphine, dissected morphine, and the β- fluorinated morphine derivative candidates, D-fluoromorphine β-C1 and D-fluoromorphine β-C2.

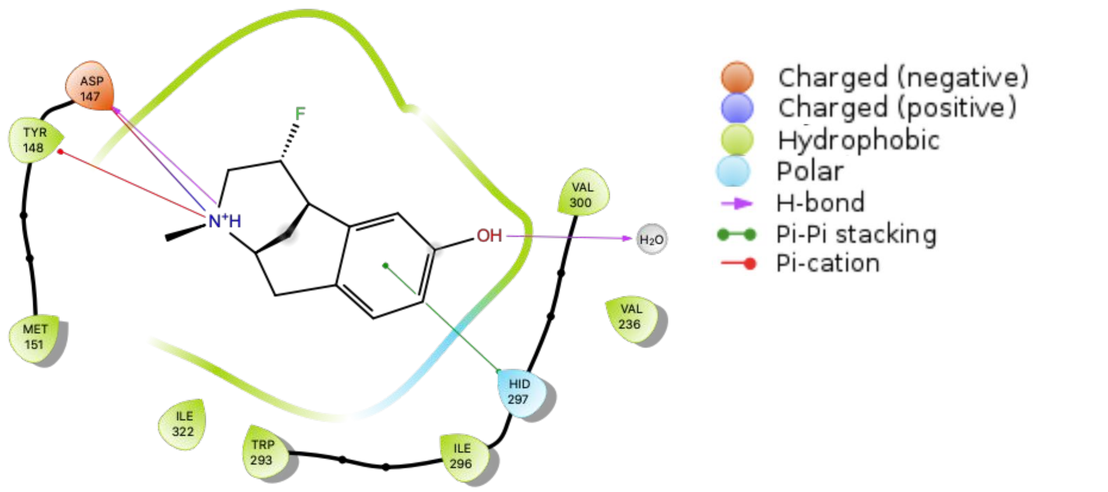

Fig. 3. The figure depicts a ligand interaction diagram of D-fluoromorphine β-C1 within an α- helix of the MOR. The crystallized structure of the MOR is 4dkl from the PDB. The ligand was built within the receptor based on the crystallized ligand of the PDB file. The conformation is optimized within a conformational search in Schrodinger: Maestro. The dissected fluoromorphine derivative maintains all vital interactions, including the ionic interaction between Asp147 and the protonated amine of the ligand.

Discussion

D-fluoromorphine β-C1 and D-fluoromorphine β-C2 maintain high percent protonation in inflamed tissue conditions, calculated pKa values, and favorable modeled interactions. Percent protonation is directly related to binding affinity. A high percent protonation in inflamed tissue encourages binding in inflamed peripheral tissue. Central opioid receptors at physiological pH are not activated. The ionic bond between the Asp147 and the tertiary amine is the primary interaction to activate the G-protein coupled receptor mechanism. The other interactions, such as hydrogen bonds and London Dispersion forces contribute to the favorability of the morphine derivatives' binding. These findings support previous computational work done modeling the MOR. The pi cation bond between the protonated amine of the morphine derivative and Tyr148 is a new discovery that may be vital in binding affinity and specificity within the MOR. Pi cation bonds have recently been studied in their importance in medicinal chemistry for their ability to induce selective binding. The dissected structures maintain important interactions, while eliminating bulky rings.The dissected ring structure encourages high binding affinity, while the fluorination beta to the binding site promotes selectivity in inflamed tissue. This encourages strong binding in sites of inflammation and pain, while discouraging binding within central tissues.

Future Directions

We aim to continue modeling the fluoromorphine derivatives within the binding site of the MOR. From the conformational searches performed using the Schrödinger: Maestro software, we will submit the ligand, receptor, and ligand-receptor complex to obtain thermodynamic data and create a reaction coordinate diagram. Thermodynamic data, such as pKa of the ligand, binding energies, etc. We also aim to continue researching the pi cation interaction and its pertinence to our present work.

References/Acknowledgements

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2. PubChem, Morphine, NIH National Library of Medicine. (n.d.). https://pubchem.ncbi.nlm.nih.gov/compound/5288826 (accessed January 6, 2021).