Computational Design of $\beta$-Fluorinated Morphine Derivatives for pH-specific Binding

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In 2019, over 10 million Americans aged 12 and older abused opioids. Opioids are highly effective pain medications with dangerous side effects, such as addiction. Opioids currently bind indiscriminately to both central and peripheral μ-opioid receptors (MOR). Side effects result from central activation. There is no opioid capable of selective binding within peripheral nerves.

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**Structural Modifications and pH-Selectivity**

Inflamed tissue is more acidic (pH=6-6.5); this discrepancy in pH conditions leads to new opportunity for a novel opioid to bind preferentially in lower pH environments. Structural modifications made to protonated morphine resulting in the experimental derivatives. Structures were built within the graphical interface Gaussview6. Electronic structure calculations were submitted with Gaussian16 to the Keck Computational Research Cluster at Chapman University. Structures were optimized using M06-2X(SMD)/aug-cc-pVDZ level of theory.

\[
\Delta G_{aq} = G_{aq}^{\text{(Morphine)}} - G_{aq}^{\text{(Morphine-H\(^+\))}} + G_{aq}^{\text{(H\(^+\))}}
\]

Theoretical pK\(_a\) were calculated with the direct calculation method (Eq. 2) and change in Gibbs free energy values (\(\Delta G_{aq}\)) from (1). Percent protonation calculations were executed with the Henderson-Hasselbalch equation. Molecular modeling was performed with Maestro: Schrödinger to visualize protein-ligand interaction with Asp\(^{147}\) and Tyr\(^{148}\) residues of the MOR (PDB ID: 4DKL). The experimental derivatives were superimposed on ligand BFO 601.

Fluorination at various beta carbon sites are visualized or all experimental derivatives. (A-C) depict C and D ring dissection. (D-F) depict ring dissection and hydroxyl group removal. Fluorination at various amino acid residues are visualized or all experimental derivatives. Structurally induced pH specific binding affinity can be visualized in the 4KDL MOR shown in 2D of (A) morphine and (B) Dehydroxy-fluoromorphine β-C2-

**References**


We would like to thank Dr. Matthew Gartner for his significant contributions.
Computational Design of β-Fluorinated Morphine Derivatives for pH-specific Binding

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Introduction

In 2019, over 10 million Americans aged 12 and older abused opioids¹. Opioids are highly effective pain medications with dangerous side effects, such as addiction. Opioids currently bind indiscriminately to both central and peripheral μ-opioid receptors (MOR). Side effects result from central activation. There is no opioid capable of selective binding within peripheral nerves.

A novel morphine derivative is designed that binds specifically within peripheral MOR of inflamed conditions and avoids activation in healthy tissues. These results raise exciting possibilities for an opioid capable of providing pain relief in acidic conditions.

Methods

Structures were built within the graphical interface Gaussview. Electronic structure calculations were submitted with Gaussian16 to the Keck Computational Research Cluster at Chapman University. Structures were optimized using M06-2X(SMD)/aug-cc-pVQZ level of theory.

(1) \[ \Delta G_{aq} = G_{aq}^{*} (\text{Morphine}) - G_{aq}^{*} (\text{Morphine-H}) + G_{aq}^{*} (\text{H}) \]

Theoretical pKa were calculated with the direct calculation method (Eq. 2) and change in Gibbs free energy values (\( \Delta G \)) from Reaction 1. Percent protonation calculations were executed with the Henderson-Hasselbalch equation. Molecular modeling was performed with Maestro: Schrödinger to visualize protein-ligand interaction with Asp¹⁴⁷ and Tyr¹⁴⁸ residues of the MOR (PDB ID: 4DKL). The experimental derivatives were superimposed on ligand BFO 601.

Results and Discussion

Fig. 1: The 2D chemical structure of the morphine molecule with rings labeled A-E. The protonable binding site on the tertiary amine allows for binding.

Activation depends on the ion pair bond between the negatively charged carboxylate of Asp¹⁴⁷ and the protonated tertiary amine group on the opioid. Morphine is protonated within physiological pH conditions (pH=7.4) and can bind in all tissues.² Inflamed tissue is more acidic (pH=6-6.5); this discrepancy in pH conditions leads to new opportunity for a novel opioid to bind preferentially in lower pH environments. Structural changes to morphine leads to selective binding, such as the addition of a fluorine atom at a β-carbon site from the amine. Fluorination decreases the pKa via induction. Additionally, removal of C and D rings allow for greater flexibility when binding (Fig. 1). Subsequent removal of the hydroxyl group from the A ring maximizes the pain relief response.

Fig. 2: Structural modifications of protonated morphine along with the experimental morphine derivatives. Fluoromorphine β-C1, Fluoromorphine β-C2, and Dehydroxy-fluoromorphine β-C3 depict C and D ring dissection. Dehydroxy-fluoromorphine β-C1, Dehydroxy-fluoromorphine β-C2, and Dehydroxy-fluoromorphine β-C3 depict ring dissection and hydroxyl group removal from the A ring of morphine. Fluorination at various beta carbon sites are visualized in the chemical structures for all experimental derivatives.

A novel morphine derivative is designed that binds specifically within peripheral MOR of inflamed conditions and avoids activation in healthy tissue—the brain—that leads to addiction.

Fig. 3: Intermolecular interactions between fluoromorphine derivatives within the 4DKL MOR shown in 2D of (A) morphine and (B) Dehydroxy-fluoromorphine β-C2.

The modeled interactions contribute to the favorability of these derivatives. The pi-cation bond between the protonated amine and aromatic ring on Tyr¹⁴⁸ is novel and potentially vital to binding affinity and specificity. The dissected structures maintain important interactions while eliminating bulky rings. In vivo studies discovered an unfavorable bond between the A ring hydroxyl group and His¹⁹⁷. They suggest hydroxyl group removal as it adversely affects pain relief delivery in acidic conditions.

Derivatives preferentially bind in sites of peripheral inflammation, while discouraging binding within central tissues. These results raise exciting possibilities for medication that is capable of providing pain relief, without the addiction risk of current opioids.

The ideal derivatives—Fluoromorphine β-C1, Dehydroxy-fluoromorphine β-C2, and Dehydroxy-fluoromorphine β-C3—depict increased binding in inflamed tissue and decreased in healthy tissue. Theoretical pKa values are favorable and near the acidic range of inflamed tissue. Fluorination successfully lowered the pKa of the structures (Tab.1).

References/Acknowledgements


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