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

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

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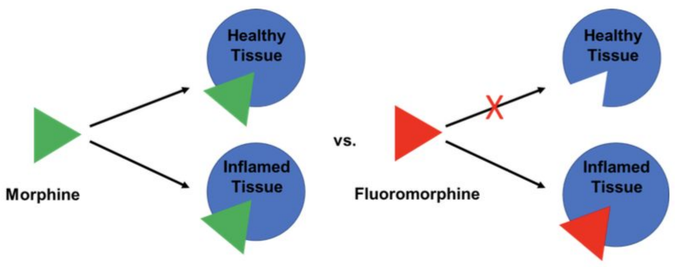
Introduction

Opioids today remain effective pain relievers, but are highly addictive. In our research, we propose a series of non-addictive opioid derivatives that will bind preferentially in peripheral tissue where inflammation occurs (pH = 6.5) and not in physiological conditions (pH = 7.4).

A pH-specific opioid derivative is aimed to induce selective binding. The pH-sensitivity is attributed to the addition of a fluorine on a beta-carbon to the ionic binding site, effectively destabilizing the amine group.

The binding of the fluoromorphine derivatives are specific to peripheral opioid receptors within inflamed tissue. Derivative will theoretically not bind to opioid receptors located in the brain, effectively lessening the central nervous system (CNS) response and lowering adverse side effects.



The benzomorphan drug class involves the dissection of C and D rings of morphine (**Tbl. 1 - Morphine**); this decreases the drug's rigidity, which encourages a more fitted binding of the ligand to the receptor.

The proposed fluoromorphine derivatives, D-fluoromorphine β-C1 and D-fluoromorphine β-C2, lack the C and D rings, similar to the benzomorphans. We hypothesize that the combination of the induction by fluorine and proposed increase in binding affinity will allow the derivatives to preferentially bind in inflamed tissue.

Methods

Electronic structure calculations were optimized with *GaussView 6* and computed with *Gaussian 16, Rev. B.01* using the Keck Computational Research Cluster at Chapman University. From direct treatment of the aqueous phase reaction (1), we calculate the overall change in Gibbs free energy for the aqueous deprotonation (2). The reported pKa values are calculated using this reported change in free energy (3).

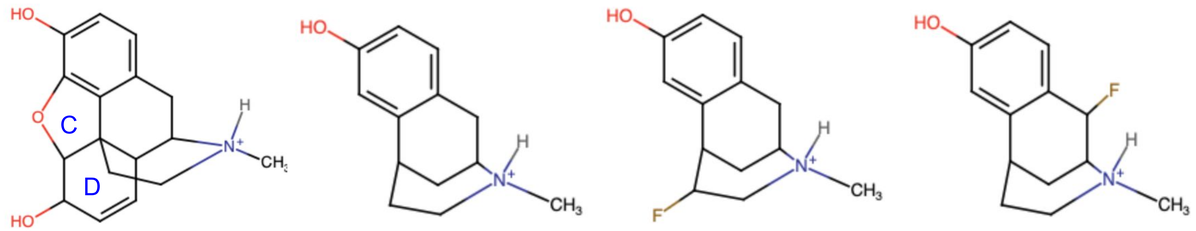
(1) $\text{Morphine-H}^{+}_{(aq)} \rightarrow \text{Morphine}_{(aq)} + \text{H}^{+}_{(aq)}$

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

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

Results

Morphine | Dissected Morphine | D-fluoromorphine β-C1 | D-fluoromorphine β-C2



Tbl. 1. The table includes the computationally calculated pKa values of morphine, dissected morphine, D-fluoromorphine β-C1, and D-fluoromorphine β-C2. The percent protonation of morphine, dissected morphine, D-fluoromorphine β-C1, and D-fluoromorphine β-C2 at physiological (pH=7.4) and inflamed tissue (pH=6.5) are listed.

	Morphine	Dissected Morphine	D-fluoromorphine β-C1	D-fluoromorphine β-C2
pKa	8.2	9.54	7.83	7.04
Percent protonation (pH 7.4)	86.3	99.3	73.1	30.8
Percent protonation (pH 6.5)	98.0	99.9	95.6	77.9

Percent protonation calculations based on pH environment are performed using a modified Henderson-Hasselbalch equation:

(4) $$pK_a - \text{pH} = \log\left(\frac{\text{Morphine} - \text{H}^{+}}{\text{Morphine}}\right)$$

(5) $$\%\ \text{protonated} = 100 \cdot \frac{\text{Morphine} - \text{H}^{+}}{\text{Morphine} - \text{H}^{+} + \text{Morphine}}$$

Discussion

Percent protonation is directly related to binding affinity. By keeping a high percent protonation in inflamed tissue, binding in inflamed peripheral tissues is encouraged while central opioid receptors at physiological pH are not activated. The most promising candidates are D-fluoromorphine β-C1 and D-fluoromorphine β-C2. Both structures maintain high protonation in inflamed tissue, while seeing a significant decrease in percent protonation in physiological tissue relative to morphine. 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

Next steps include using machine learning technology to simulate ligand-receptor binding of the derivatives to (1) the active site and (2) allosteric site of the μ-opioid receptor. Preliminary data from simulations will include basic binding affinity, as well as quantitative estimate of drug likeness (QED) and synthetic accessibility scores (SAS) to ensure derivatives remain realistic synthetic options to act on drug targets.

References/Acknowledgements

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1. V. Spahn, G.D. Vecchio, et. al, "A nontoxic pain killer designed by modeling of pathological receptor conformations" Science. 355 (2017) 966–969. https://doi.org/10.1126/science.aai8636.
2. PubChem, Morphine, NIH National Library of Medicine. (n.d.). https://pubchem.ncbi.nlm.nih.gov/compound/5288826 (accessed January 6, 2021).