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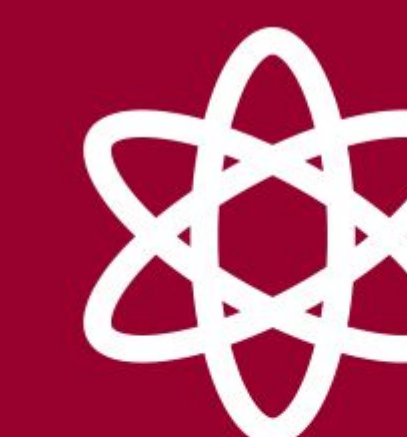
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Computational Design of β -Fluorinated Morphine Derivatives for pH-specific Binding

By: Makena Augenstein, Nayiri Alexander, and Dr. Matthew Gartner
Schmid College of Science and Technology, Chapman University



Morphine Binding

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.

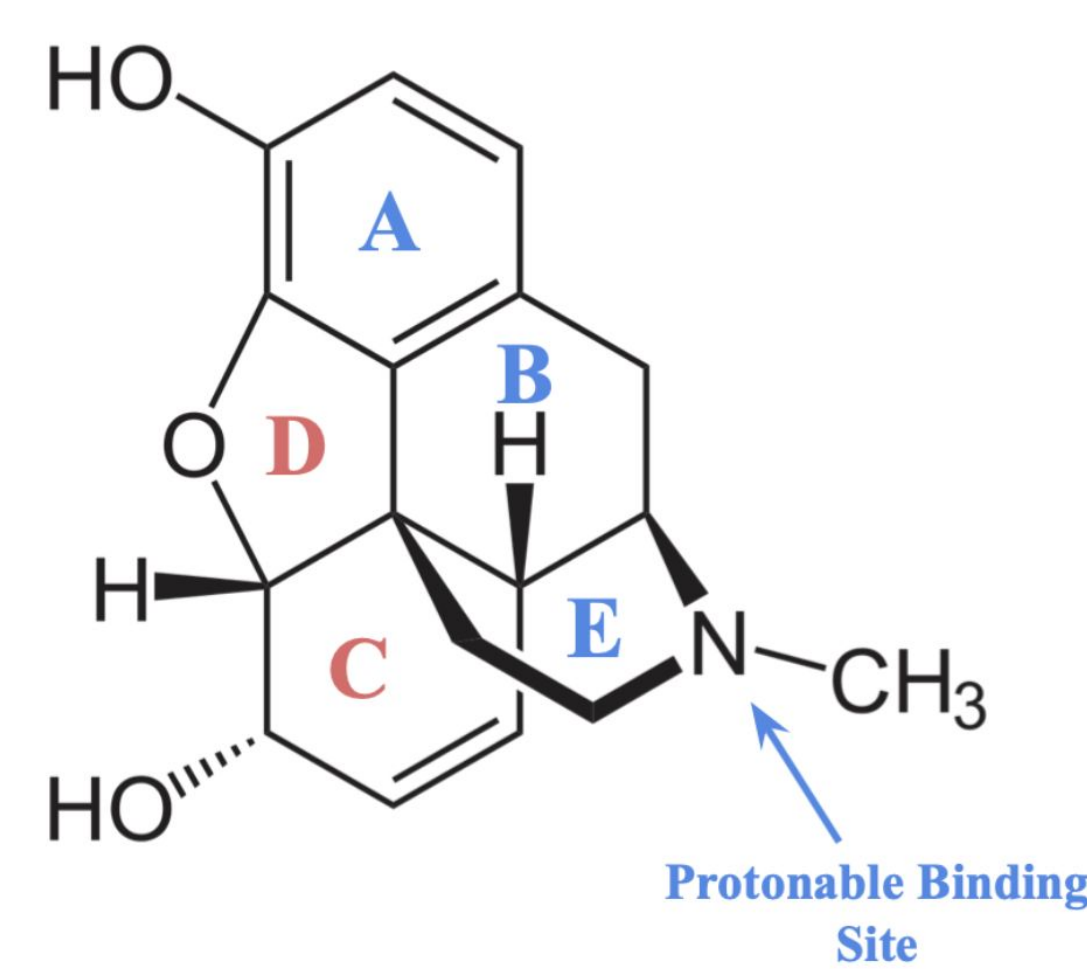
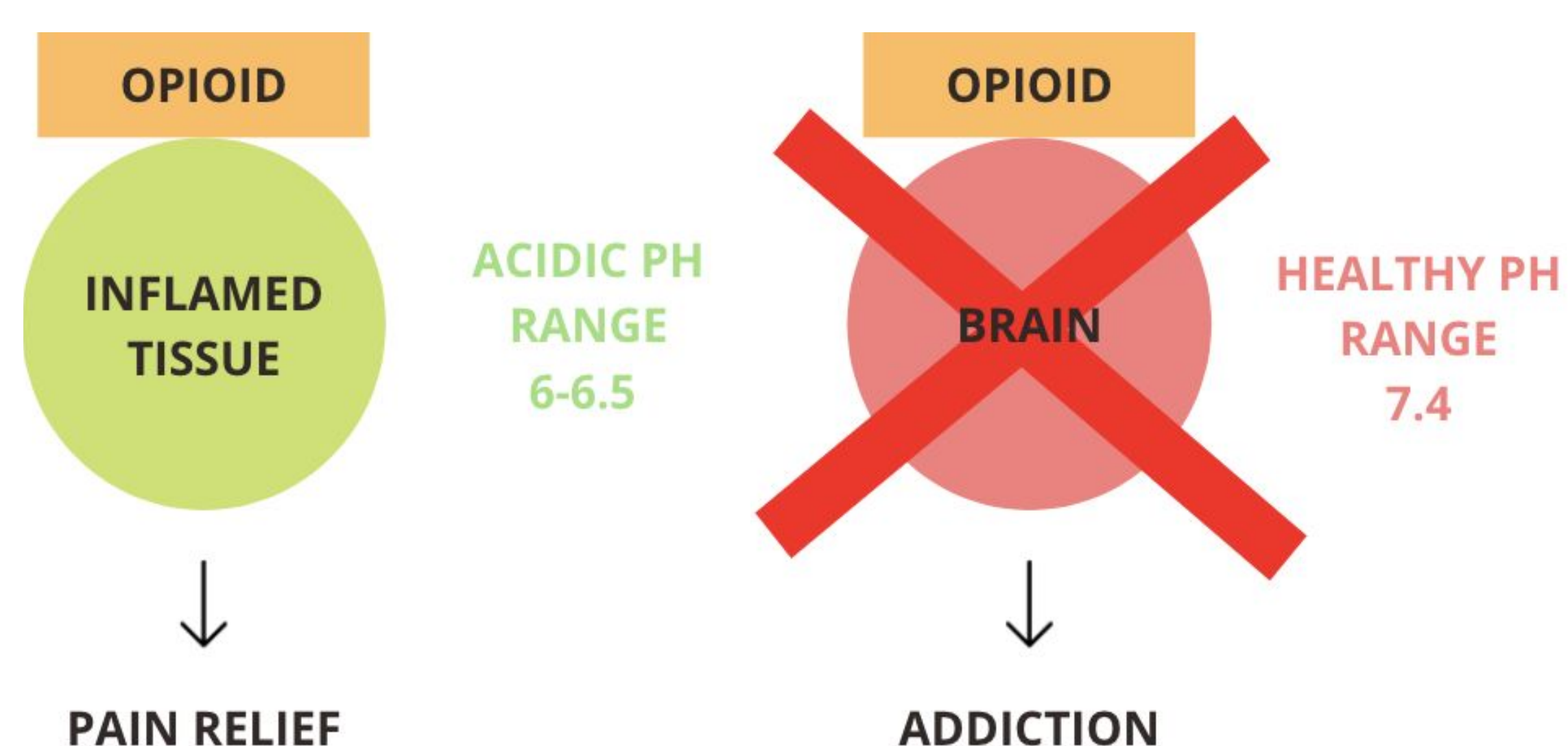


Fig. 1: The 2D chemical structure of morphine.

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.

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



Computational Design of Experimental Morphine 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.

$$(1) \Delta G_{aq} = G_{aq}(\text{Morphine}) - G_{aq}(\text{Morphine-H}^+) + G_{aq}(\text{H}^+) \quad (2) \quad pK_a = \frac{\Delta G_{aq}}{2.303RT}$$

Theoretical pKa were calculated with the direct calculation method (Eq. 2) and change in Gibbs free energy values (ΔG_{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 Asp¹⁴⁷ and Tyr¹⁴⁸ residues of the MOR (PDB ID: 4DKL). The experimental derivatives were superimposed on ligand BFO 601.

Effects of Morphine Modifications on pH Selectivity and Interactions

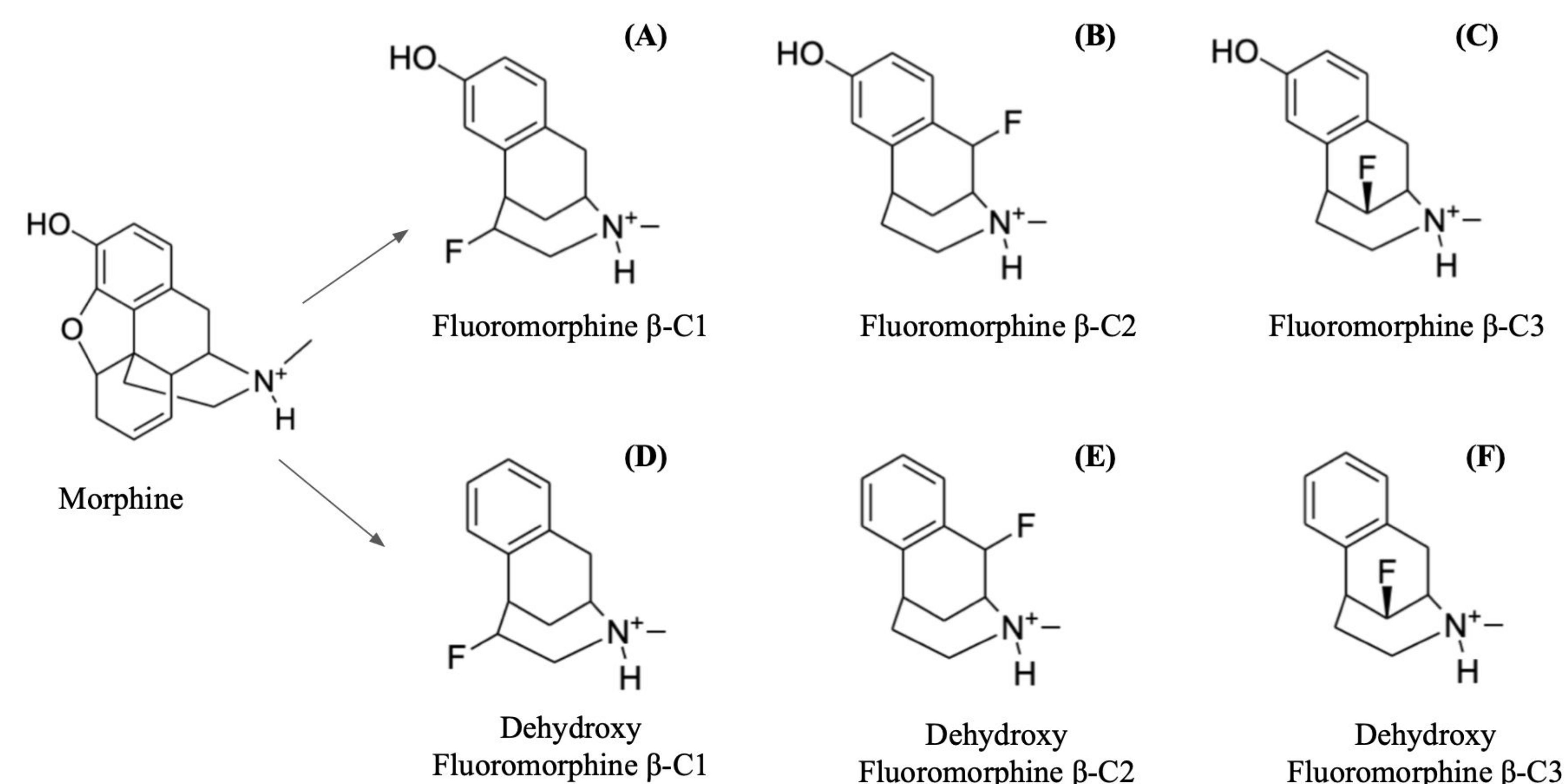


Fig. 2: Structural modifications made to protonated morphine resulting in the experimental derivatives. (A-C) depict C and D ring dissection. (D-F) depict ring dissection and hydroxyl group removal. Fluorination at various beta carbon sites are visualized on all experimental derivatives.

	pKa	% Protonation in Healthy Tissue (pH=7.4)	% Protonation in Inflamed Tissue (pH=6.5)
Morphine	8.0	86.3	98.0
Fluoromorphine β -C1	7.83 (-0.17)	73.1 (-13.2%)	95.6
Fluoromorphine β -C2	7.04 (-0.94)	30.8 (-55.5%)	77.9
Fluoromorphine β -C3	5.66 (-2.44)	1.79 (-84.5%)	12.6
Dehydroxy-fluoromorphine β -C1	7.65 (-0.35)	64.1 (-22.2%)	93.4
Dehydroxy-fluoromorphine β -C2	6.88 (-1.12)	23.2 (-63.1%)	70.5
Dehydroxy-fluoromorphine β -C3	6.66 (-1.44)	15.5 (-70.8%)	59.2

Fluoromorphine β -C1, Dehydroxy-fluoromorphine β -C2, and Dehydroxy-fluoromorphine β -C3—depict increased binding in inflamed tissue and decreased in healthy tissue. Fluorination successfully lowered the pKa values of the derivatives within the acidic tissue range. Percent protonation is reduced in healthy tissue while remaining high in inflamed tissue. The dissected structures maintain interactions needed for pain relief response and the modeled interactions depict a pi-cation bond between the protonated amine and aromatic ring on Tyr¹⁴⁸. This novel bond is potentially vital to binding affinity and specificity. *In vivo* studies discovered an unfavorable bond between the A ring hydroxyl group and His²⁹⁷ that adversely affects pain relief delivery in inflamed tissue. Removal of the hydroxyl group avoids this interaction.

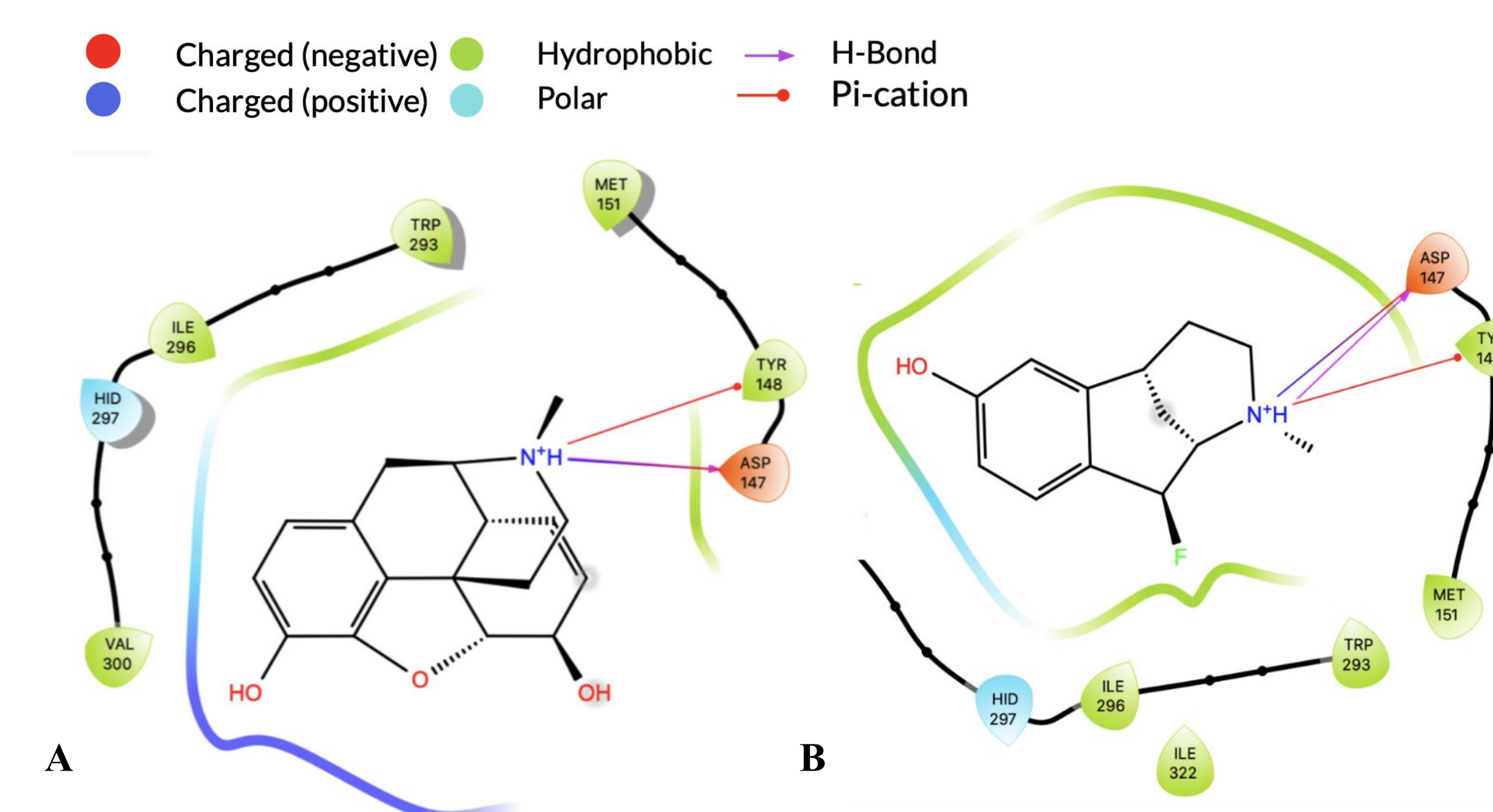


Fig. 3: Intermolecular interactions between fluoromorphine derivatives within the 4DKL MOR shown in 2D of (A) morphine and (B) Dehydroxy-fluoromorphine β -C2.

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.

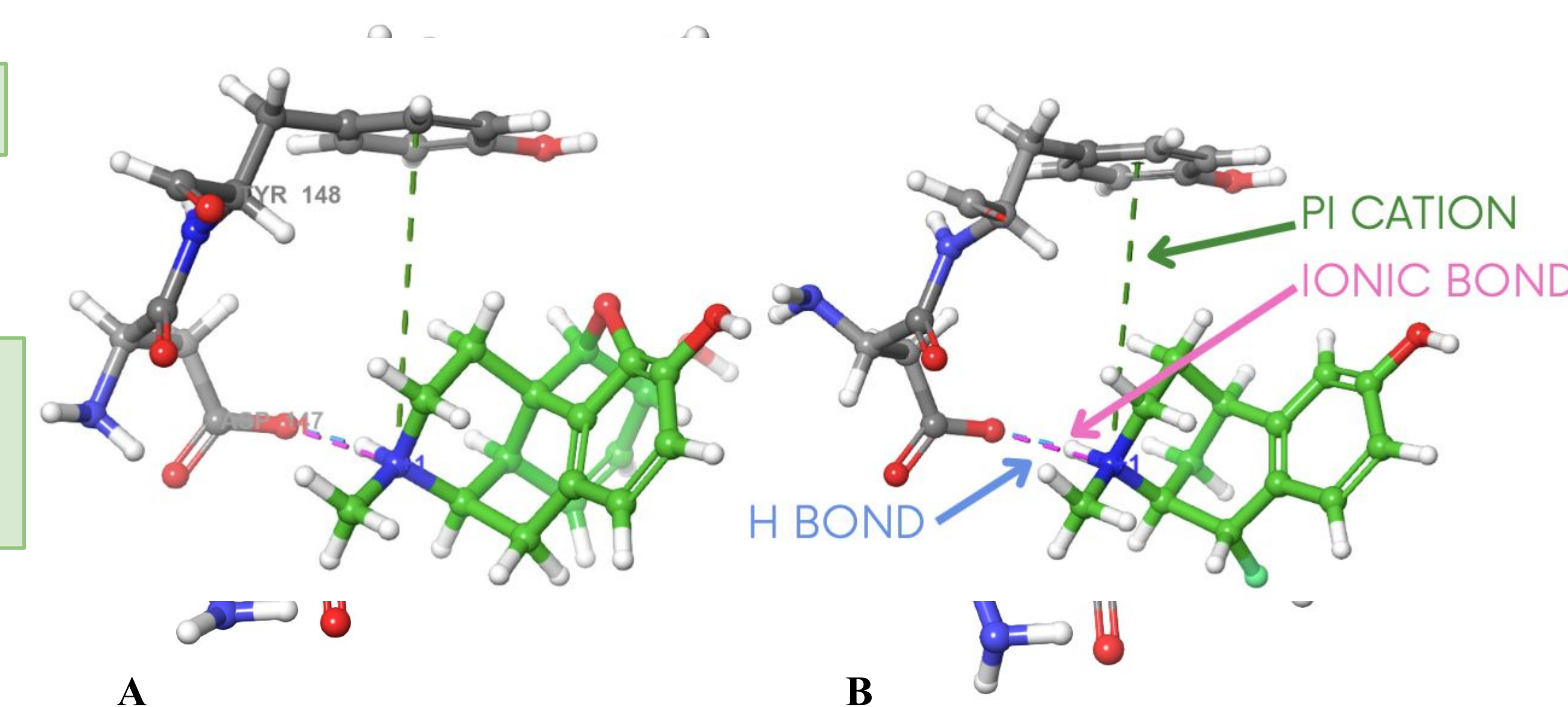


Fig. 4: 3D optimized interactions between Asp¹⁴⁷ and Tyr¹⁴⁸ of the MOR and morphine (A) and Fluoromorphine β -C1 (B).

References

We would like to thank Dr. Matthew Gartner for his significant contributions.

¹ Division of Child, Digital Communications. "Opioid Crisis Statistics." *ERIC*. 2018. <https://www.eric.gov/ops/ncsl/about-the-publications/ncsl-annual-report>.
² Kawan, Thomas H., and Eric P. George. "The Neurobiology of Opioid Dependence: Implications for Treatment." *Science of Pain* 1(2015): 1-20.
³ Augenstein, Makena, Nayiri Alexander, and Dr. Matthew Gartner. "Computational Design of β -Fluorinated Morphine Derivatives for pH-Specific Binding." *Chemical Physics Letters* 771 (August 16, 2021): 138721. <https://doi.org/10.1016/j.cpl.2021.138721>.



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



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Introduction

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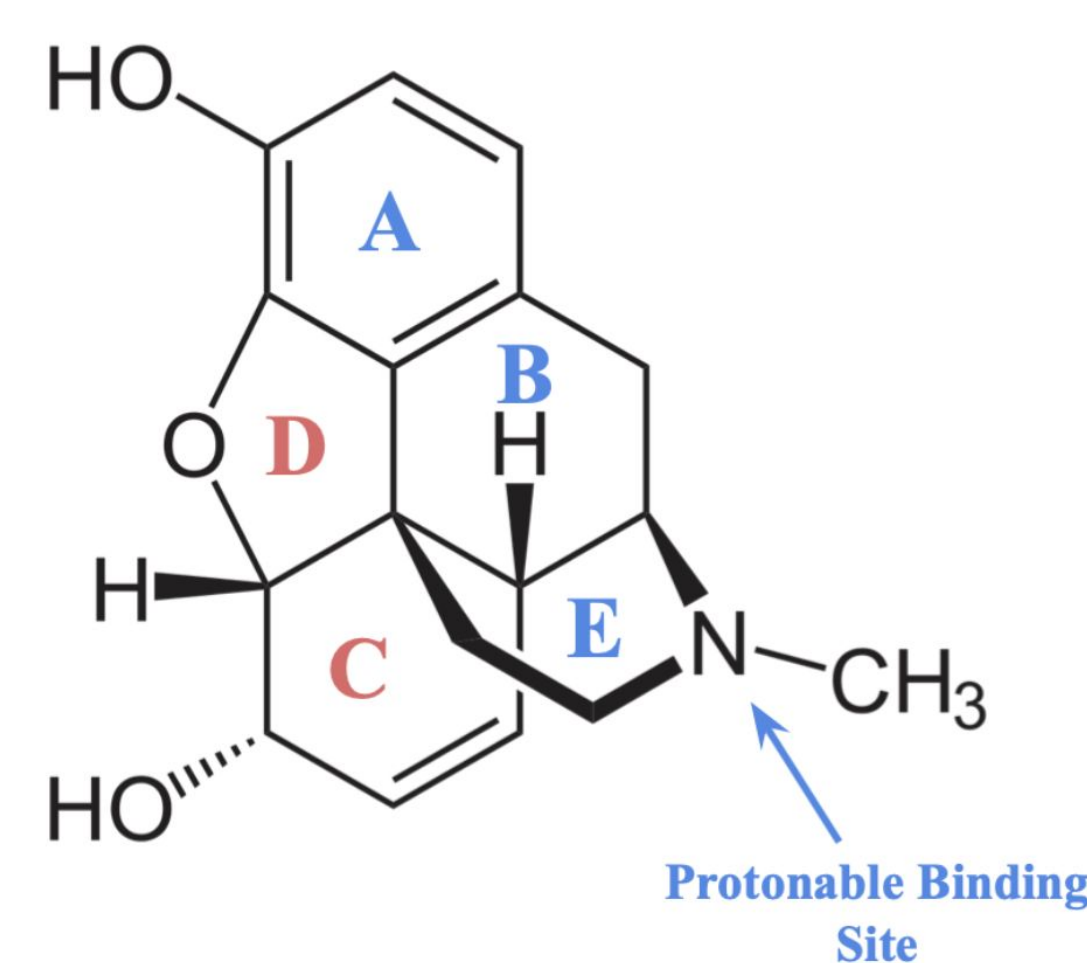
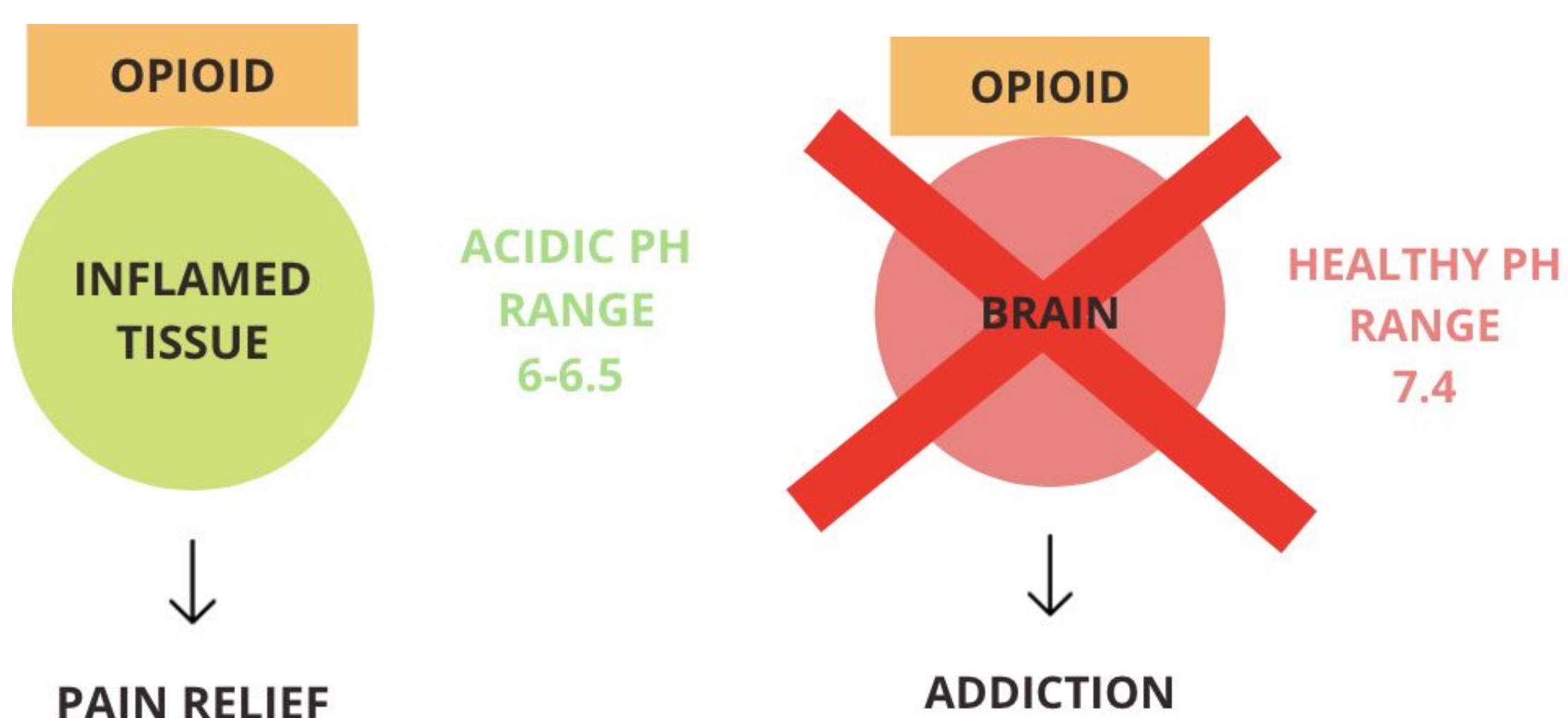


Fig. 1: The 2D chemical structure of the morphine molecule with rings labeled A-E. The protonable binding site on the tertiary amine allows for binding.

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.

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.



Methods

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.

$$(1) \Delta G_{aq} = G_{aq}(\text{Morphine}) - G_{aq}(\text{Morphine-H}^+) + G_{aq}(\text{H}^+) \quad (2) \quad pK_a = \frac{\Delta G_{aq}}{2.303RT}$$

Theoretical pKa were calculated with the direct calculation method (Eq. 2) and change in Gibbs free energy values (ΔG_{aq}) 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

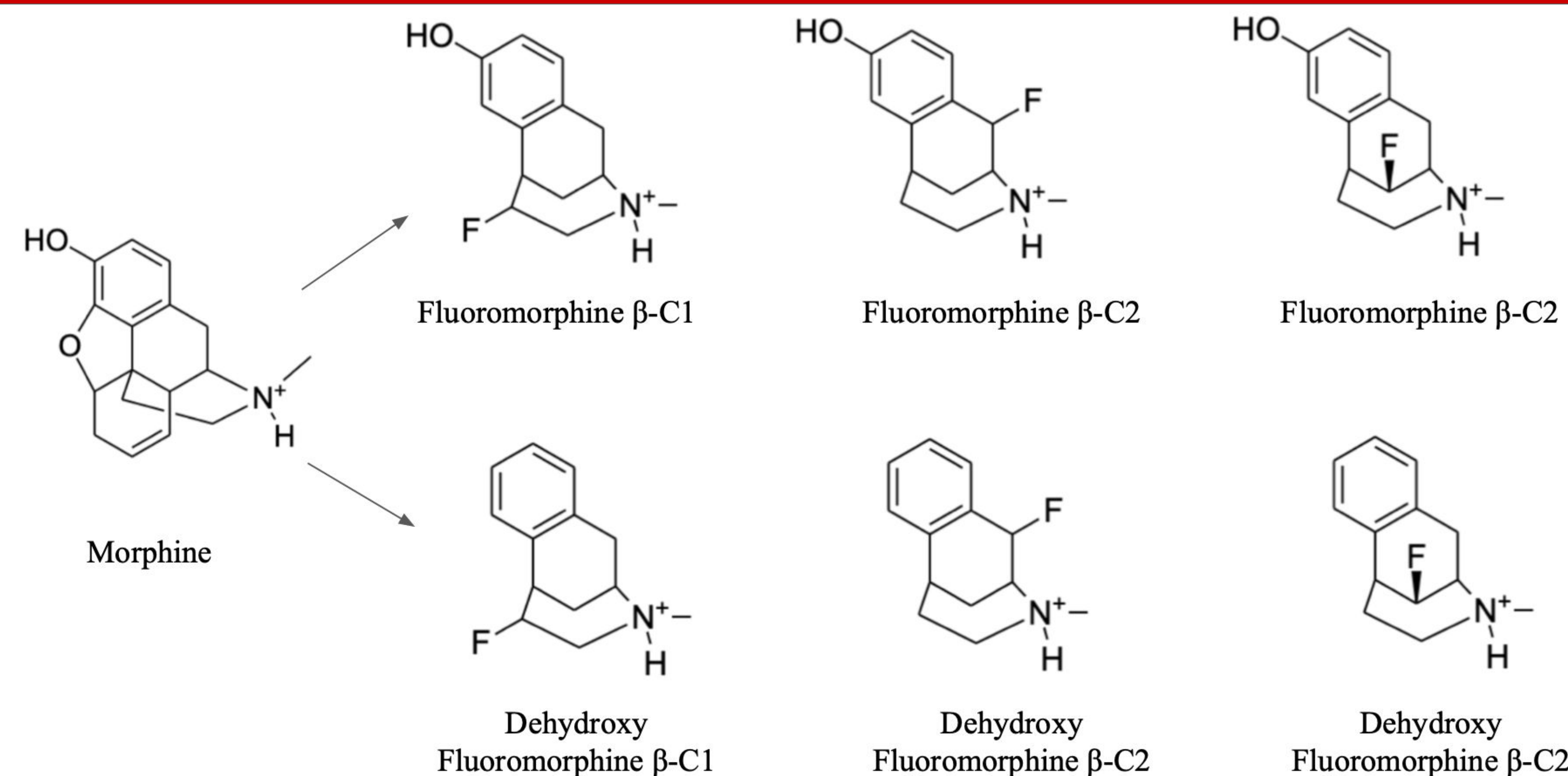


Fig. 2: Structural modifications of protonated morphine along with the experimental morphine derivatives. Fluoromorphine β -C1, Fluoromorphine β -C2, and Fluoromorphine β -C3 depict C and D ring dissection. Dehydroxy-fluoromorphine β -C1, Dehydroxy-fluoromorphine β -C2, and Dehydroxy-fluoromorphine β -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.

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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 (Tbl.1).

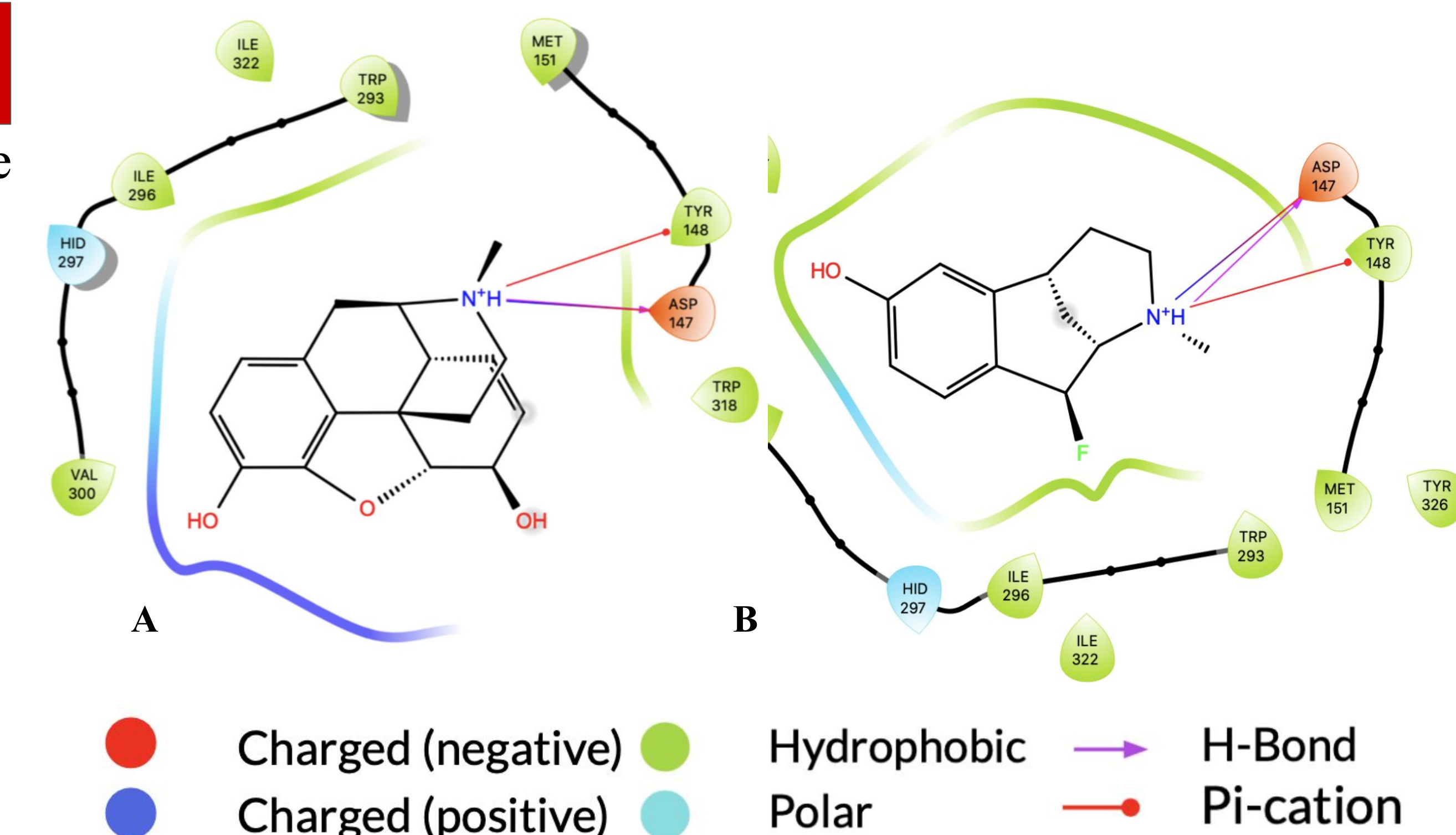


Fig. 3: Intermolecular interactions between fluoromorphine derivatives within the 4KDL MOR shown in 2D of (A) morphine and (B) Dehydroxy-fluoromorphine β -C2.

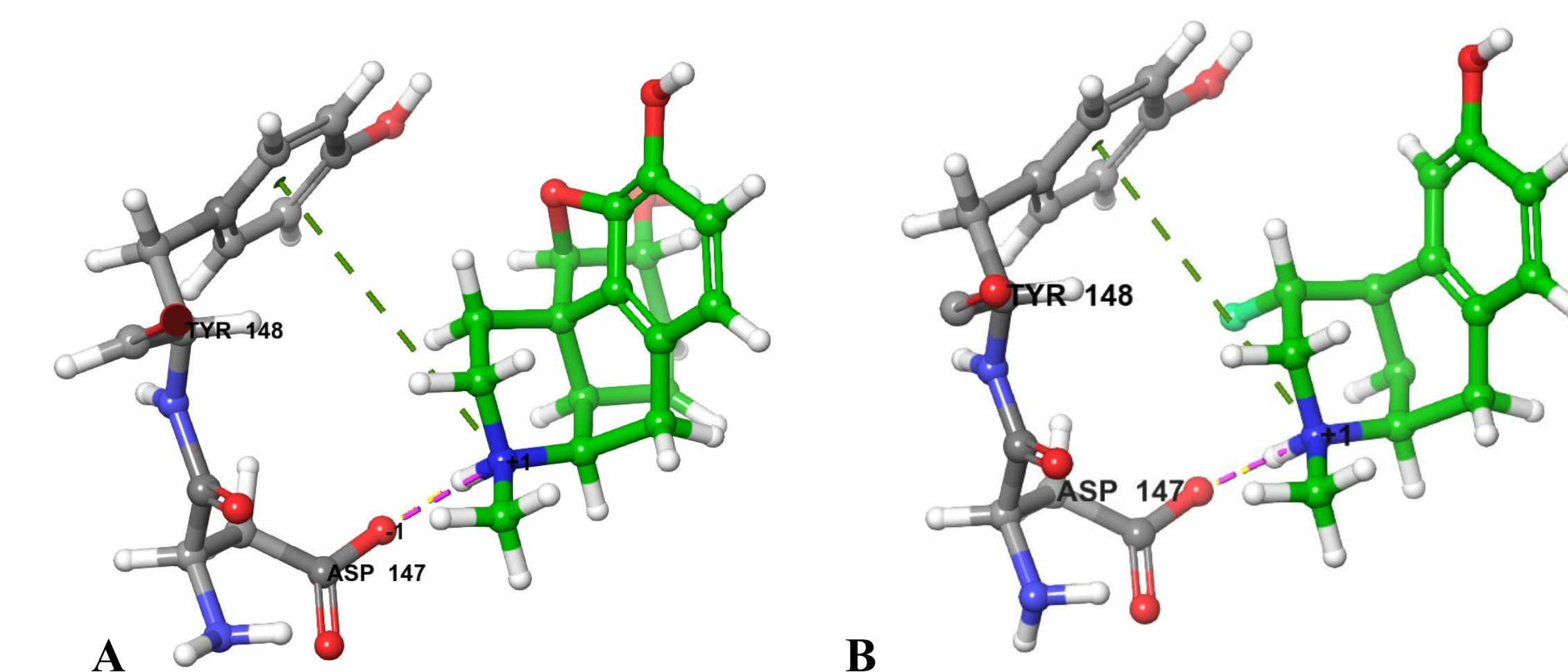


Fig. 4: 3D optimized interactions between Asp¹⁴⁷ and Tyr¹⁴⁸ of the MOR and morphine (A) and Fluoromorphine β -C1 (B).

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 His²⁹⁷. 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 issues. These results raise exciting possibilities for medication that is capable of providing pain relief, without the addiction risk of current opioids.

References/Acknowledgements

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1. Division (DCD), Digital Communications. "Opioid Crisis Statistics." Text. HHS.gov. May 8, 2018. <https://www.hhs.gov/opioids/about-the-epidemic/opioid-crisis-statistics/index.html>.
2. Kosten, Thomas R., and Tony P. George. "The Neurobiology of Opioid Dependence: Implications for Treatment." *Science & Practice Perspectives* 1, no. 1 (July 2002): 13–20.
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