SUPPORTING INFORMATION -1

Towards a Universal μ-Agonist Template for Template-based Alignment Modeling of Opioid Ligands.

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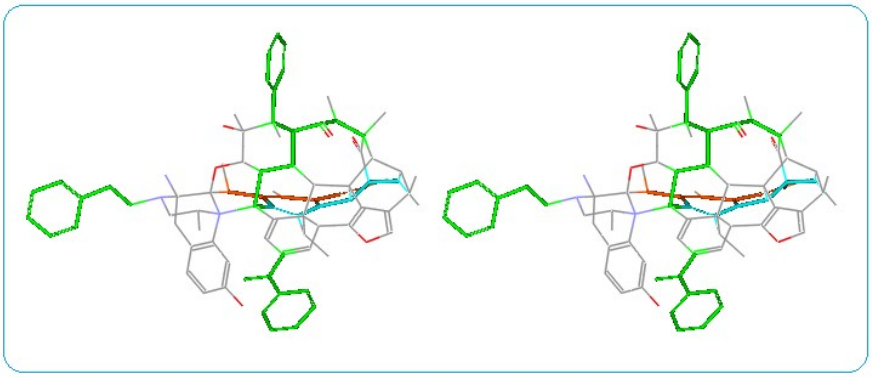

Figure S1. The template (stereoview). The green-colored moieties stand for the μ-features of the template, and the red and the blue stand for the δ-specific and the κ-specific areas, respectively.

(1) Match patterns frequently observed in the template-based alignment modeling.

a) *Bond-to-bond match*: This is a fundamental pattern applied most frequently in the template-based alignment modeling.

b) *Aromatic-to-aromatic match*: This is an often-seen pattern. There are about six aromatic regions of the template, and it is often that we first matched the aromatic ring(s) of ligand to those of the template, so as to facilitate matching the rest of ligands.

c) *Approximate conformation match*: For most of the ligands, only approximate conformational match with the template is needed, while precise fitting in conformation is not required.

d) *Branched-center match*: The branched-center match is a frequently observed pattern. And a branched center is defined as any tertiary/quaternary/carbonyl carbon, (or the sulfur atom of -SO_2-).

e) *Hetero-atom match*: A match between hetero-atoms, such as N and N, O and O, or N and O. And it can be also between N and C or O and C in some cases, depending on the overall match of the whole moiety/scaffold.

f) *Stereo-center match*: A stereo-center match is seen between moieties with same chirality. However, this pattern is not strictly applied, as it seems mostly to be sensitive with certain sites of the template, (e.g, with the Ind/Ph moiety).

g) *Non-bond-to-bond match*: Sometimes, the bond-to-bond-match pattern is not strictly observed in order for an overall fitting of a μ-agonist. As seen in our modeling, mismatch by one bond (or more) is allowed for a μ-agonist if its major scaffold is aligned well with the template.

h) *Multi-alignments*: Some ligands can be aligned with the template in more than one way. For those cases, it is necessary to assess and verify all the possible alignments.

It should be noted that the above-listed guidelines are not always observed. And exceptions are allowed from case to case, in order to get the well-balanced alignments of the whole ligand structures, e.g., being well matched at the major structural features as well as the key SARs.

(2) Additional examples of opioid antagonists featuring the backbone/scaffold mismatch

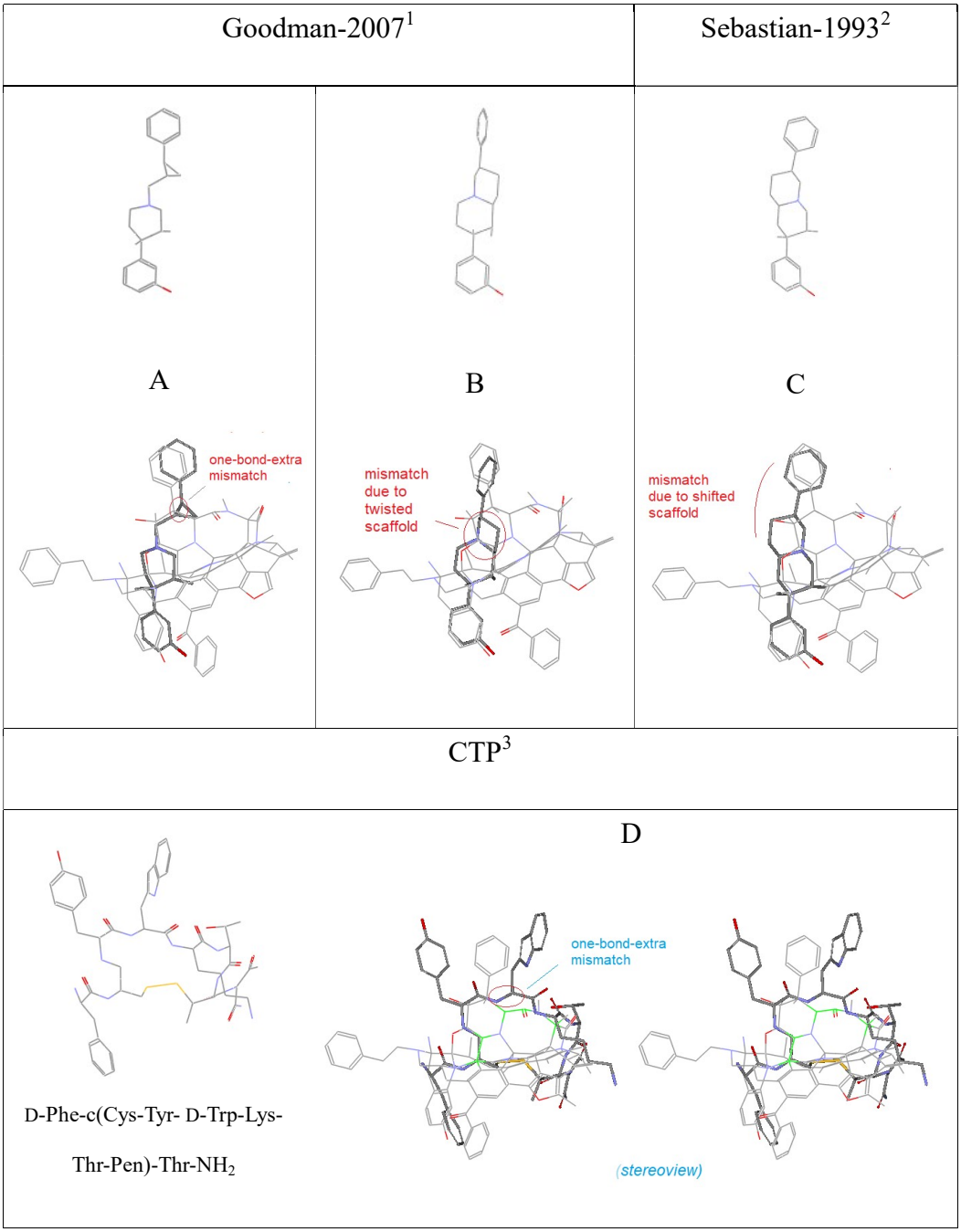

Figure S2. Examples of opioid antagonists with the backbone/scaffold mismatch. (A) with one-bond-extra mismatch; (B) with twisted scaffold-mismatch; (C) with shifted-scaffold mismatch; (D) with one-bond-extra mismatch.

References

1. Goodman, A. J.; Le Bourdonnec, B.; Dolle, R. E., Mu opioid receptor antagonists: recent developments. *ChemMedChem* **2007**, 2, (*11*), 1552-1570.

2. Sebastian, A.; Bidlack, J. M.; Jiang, Q.; Deecher, D.; Teitler, M.; Glick, S. D.; Archer, S., 14 beta-[(p-nitrocinnamoyl)amino]morphinones, 14 beta-[(p-nitrocinnamoyl)amino]-7,8-dihydromorphinones, and their codeinone analogues: synthesis and receptor activity. *J Med Chem* **1993**, 36, (*21*), 3154-3160.

3. Kazmierski, W.; Hruby, V. J., A new approach to receptor ligand design: synthesis and conformation of a new class of potent and highly selective μ opioid antagonists utilizing tetrahydroisoouinoline carroxylic acid. *Tetrahedron* **1988**, 44, (*3*), 697-710.