Supplementary Materials
to
Structural insights into σ_1 receptor interactions with opioid ligands by molecular dynamics simulations

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Fig. S1. The average RMSD of the ligand-receptor complexes: FENT, HALO, MORPH, *R*- and *S*-PTZ, *R*- and *S*-PHZ; x (psec), y(Å).

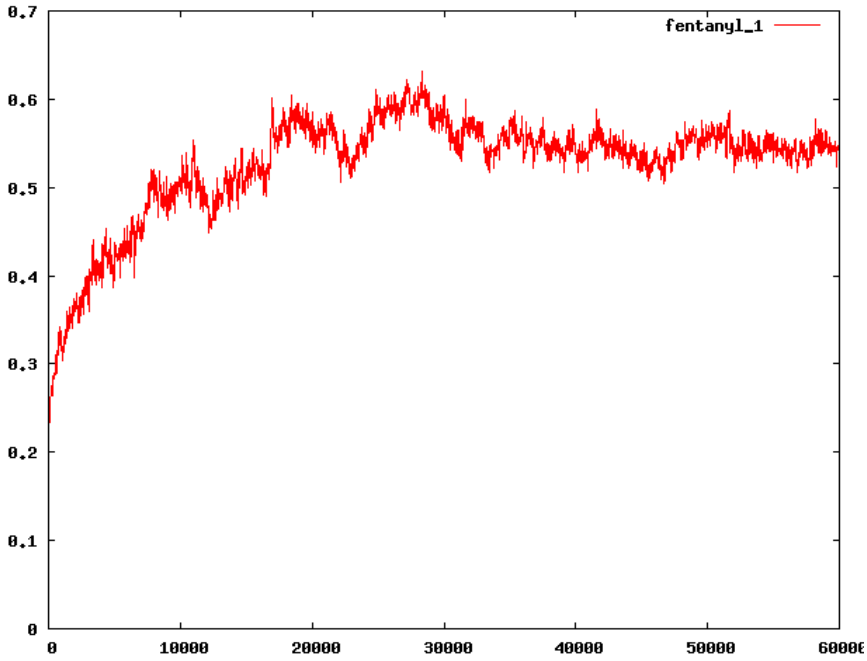
Fig. S2. 2D schematic representation of the interaction between the σ_1 receptor and the seven ligands: FENT, HALO, MORPH, *R*- and *S*-PTZ, *R*- and *S*-PHZ.

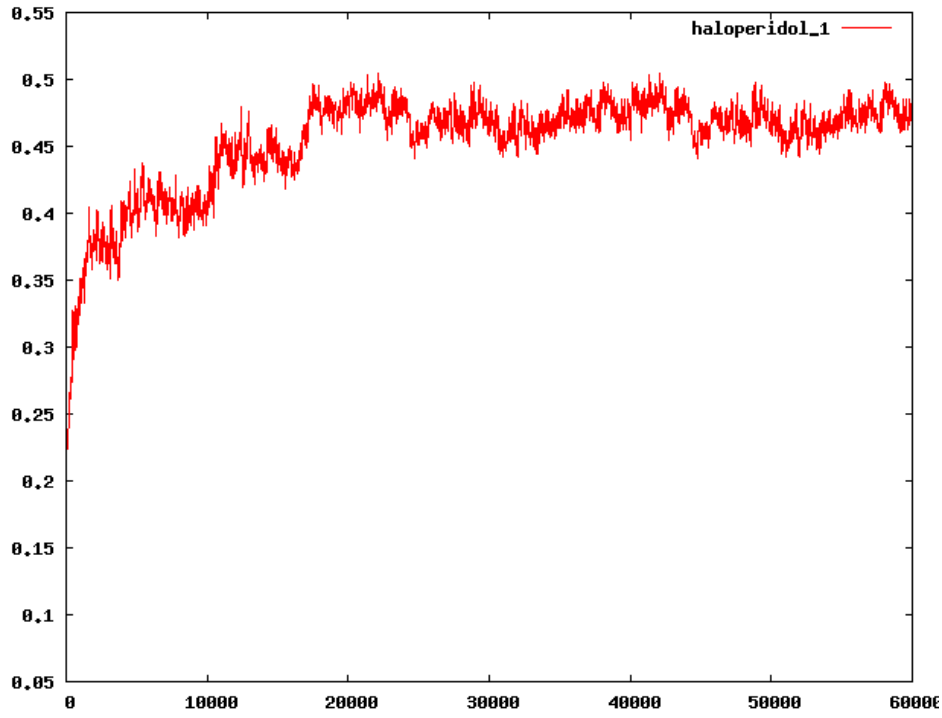
Figure S3. Spectrum of the frequency of the contacts between receptor residues and atomic centers of ligands.

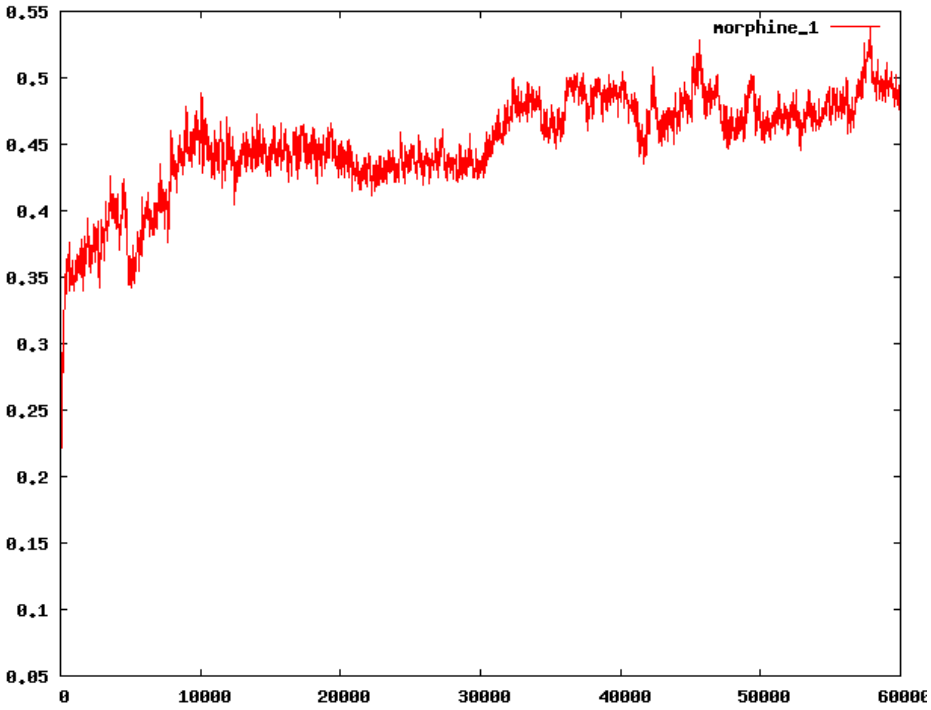
Figure S4, a-g. Spectrum of frequency of ligand contacts with receptor residues normalized according to the hydrophobic scale. The positive bars correspond to hydrophobic while negative to hydrophilic contacts.

Table S5. The contacts between residues in receptor-ligand detected in the final MD snapshots. The names of different regions of the ligands: Ar1, Ar2, Ar(T), chair, Link, Me, -CH_2, see Fig.3.

Fig.S1. The average RMSD of the ligand-receptor complexes: FENT, HALO, MORPH, *R*- and *S*-PTZ, *R*- and *S*-PHZ; x (psec), y(Å).



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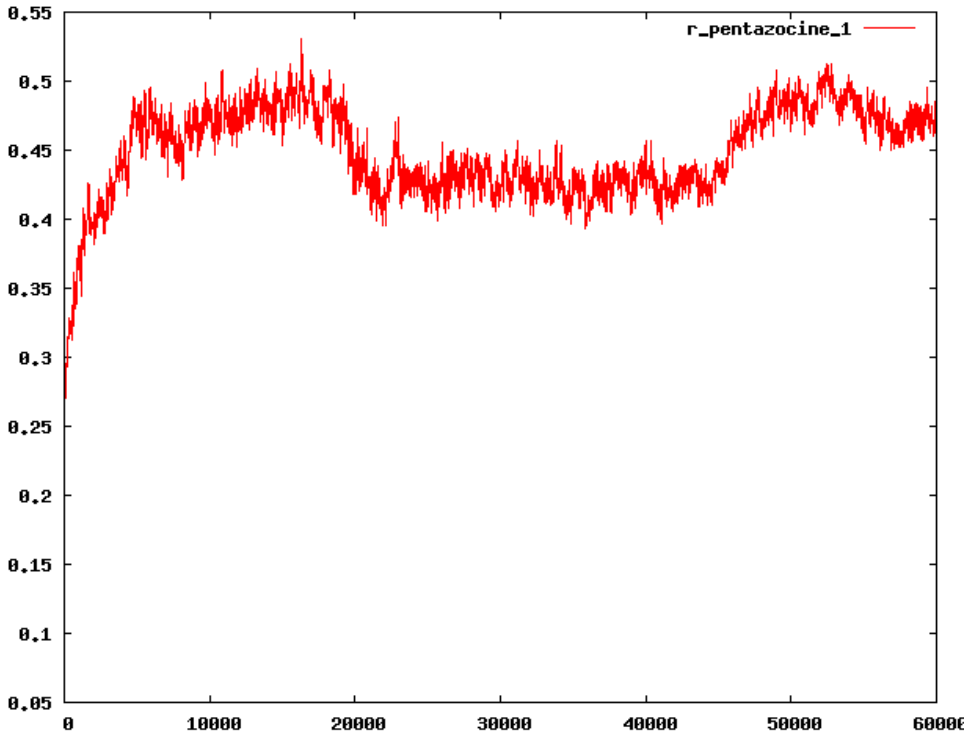
60000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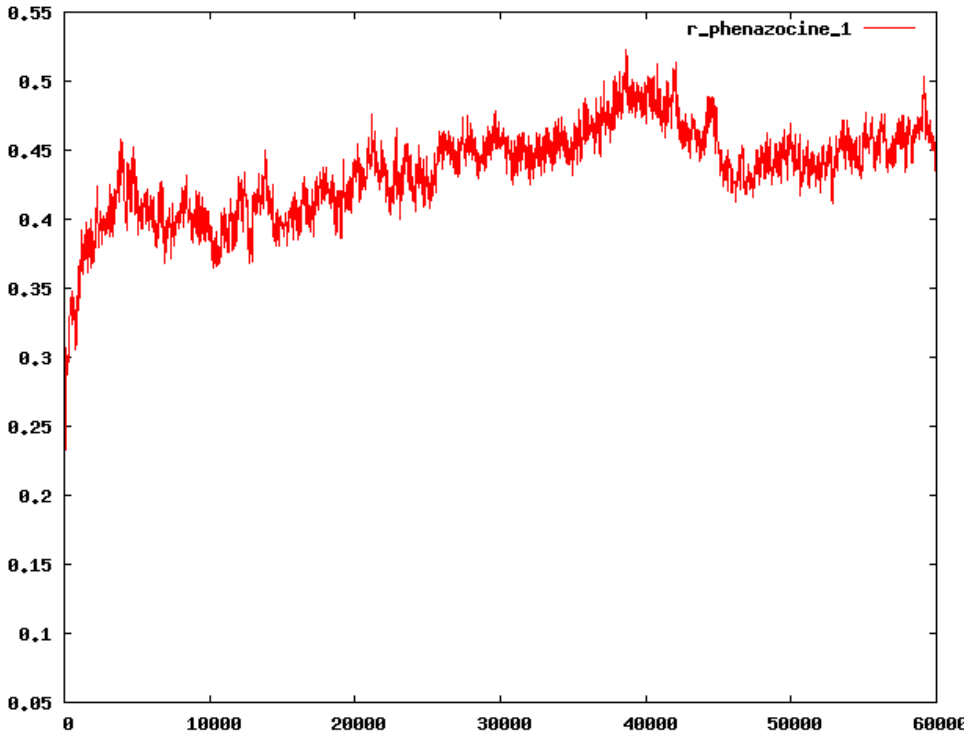
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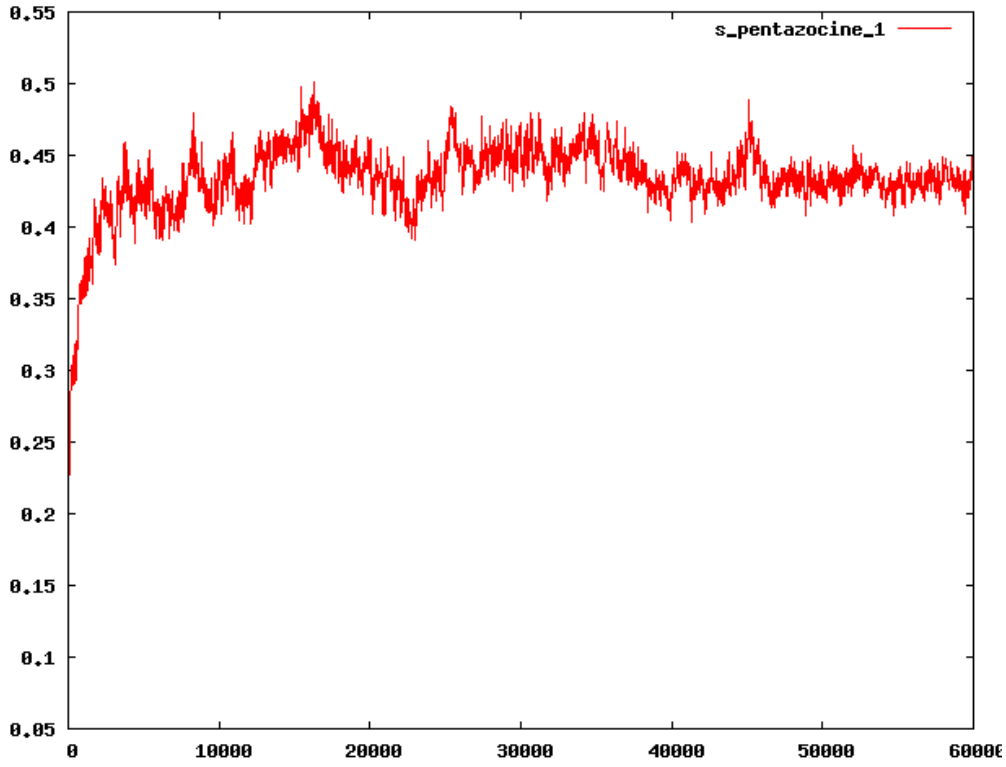
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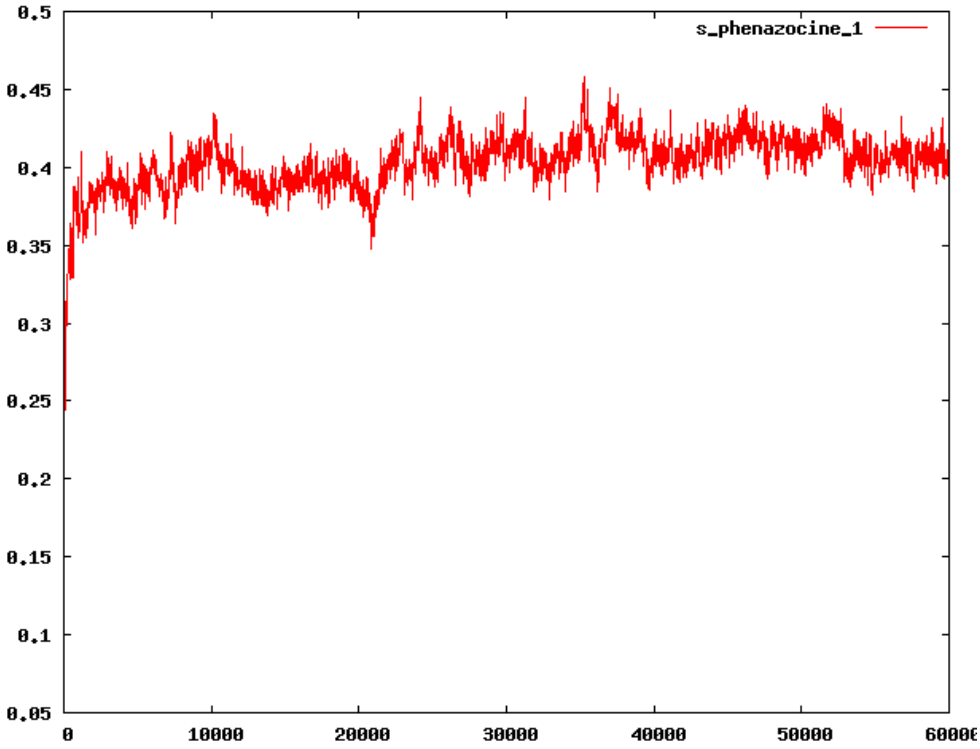
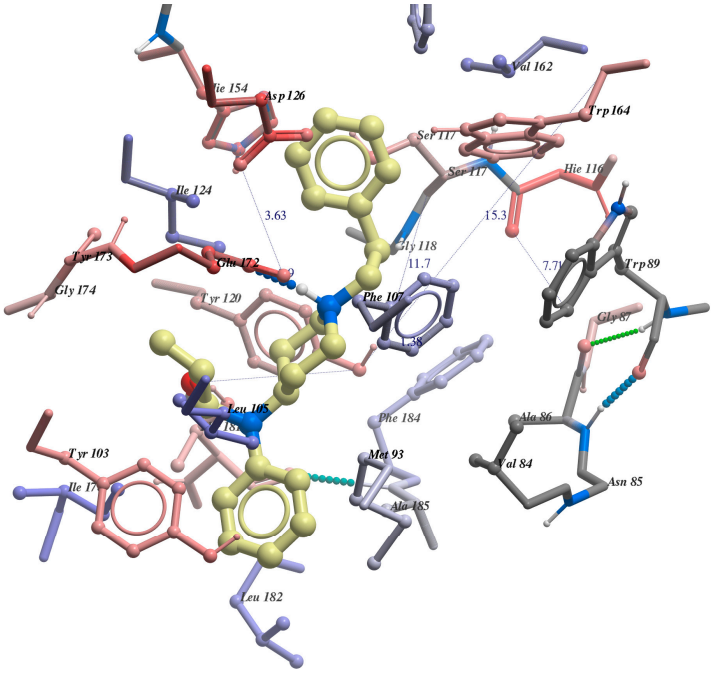
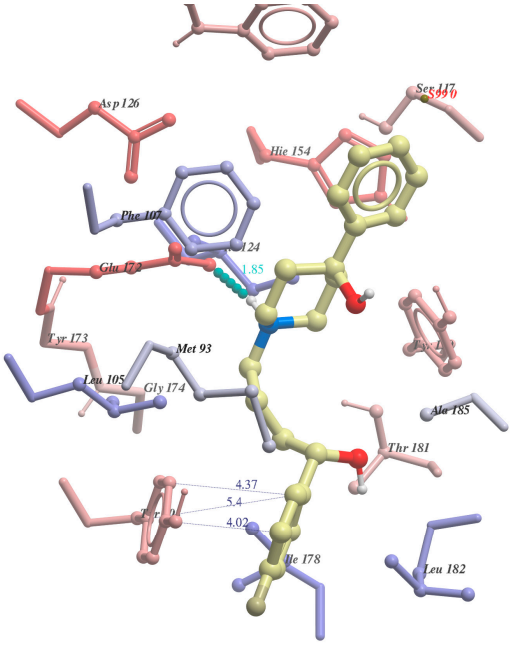


Fig.S2. 2D schematic representation of the interaction between the σ_1 receptor and the seven ligands: FENT, HALO, MORPH, *R*- and *S*-PTZ, *R*- and *S*-PHZ.

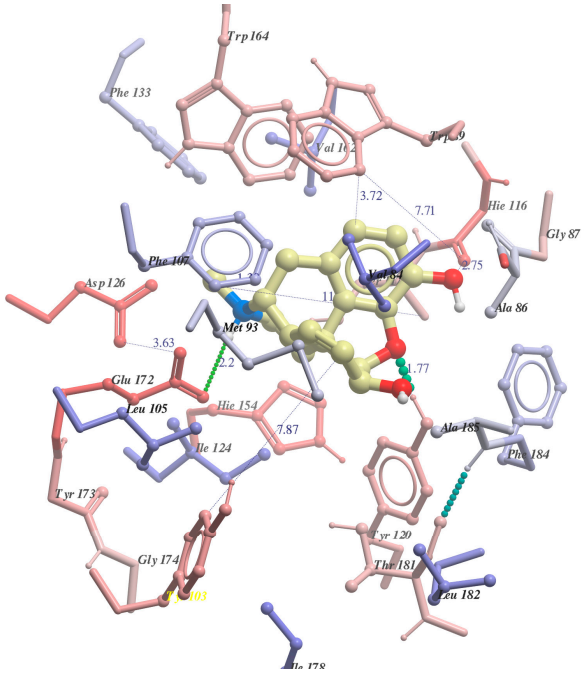
(a) FENT



(b) HALO



(c) MORPH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Val 84
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Gly 87
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Ala 86
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2.2
1.77
Glu 172
Leu 105
His 154
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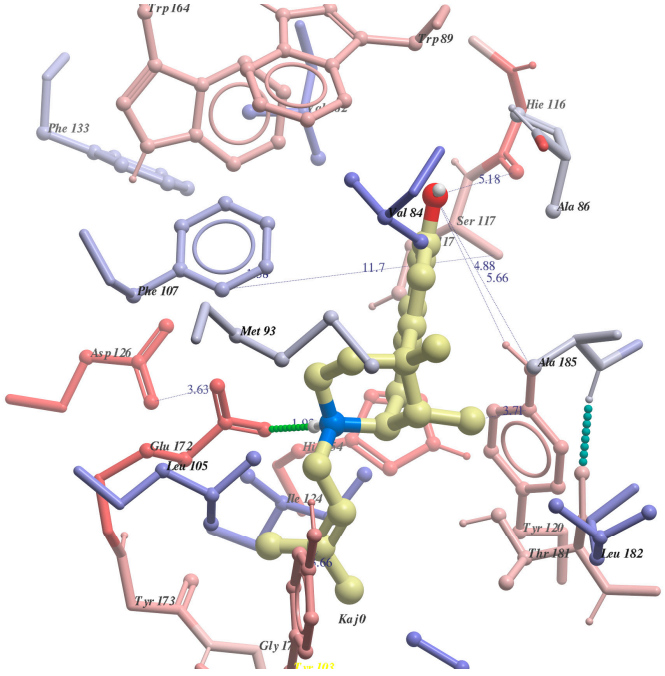
Ala 185
Ile 124
Phe 184
Tyr 173
Tyr 120
Gly 174
Thr 181
Leu 182

(d) *S*-PTZ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Met 93
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Glu 172
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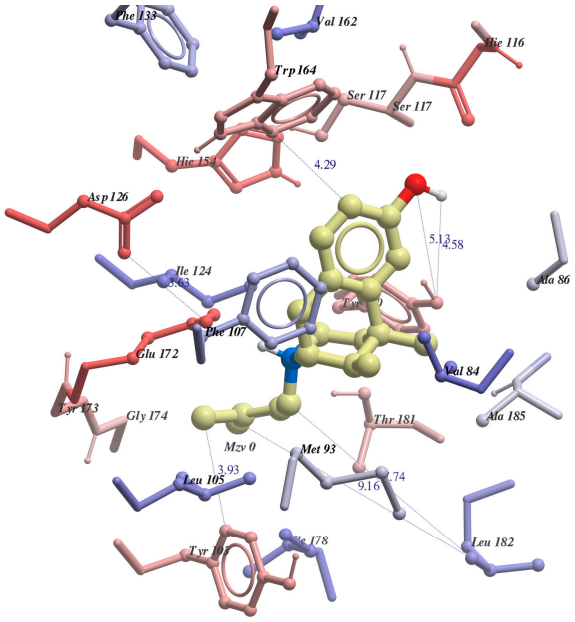
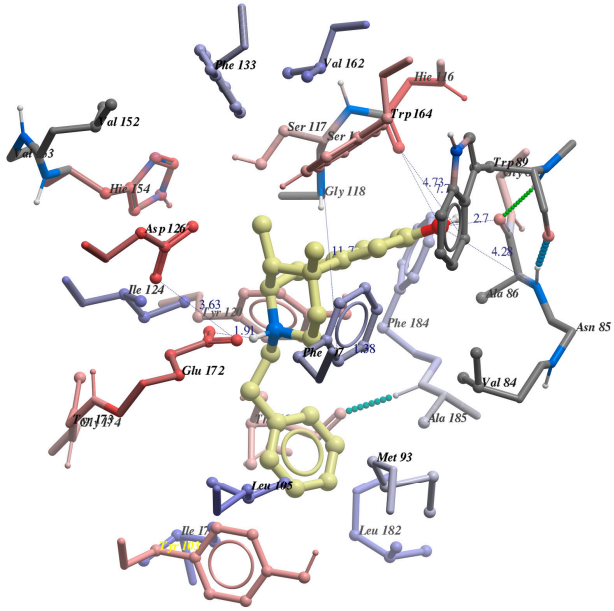
Ile 124
Tyr 120
Thr 181
Leu 182
Tyr 173
Kaj0

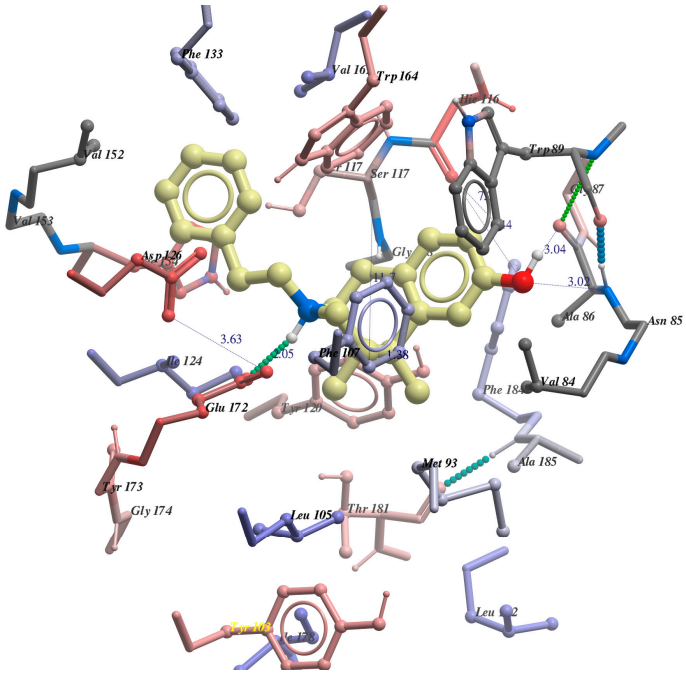
(e) *R*-PTZ



(f) *R*-PHZ



(g) *S*-PHZ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3.03
Ala 86
Asn 85
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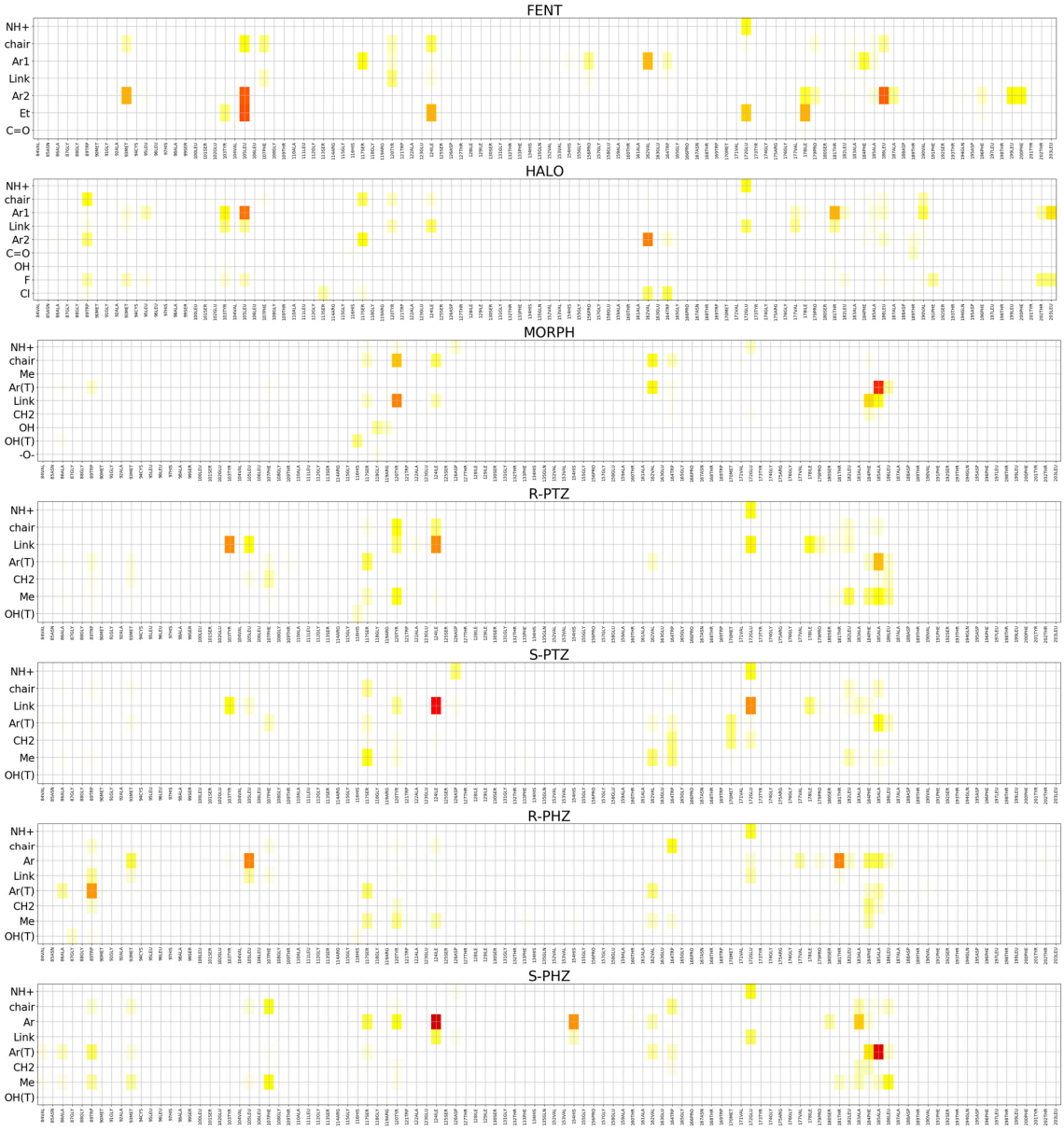
Ile 124
Phe 187
Val 84
Glu 172
Met 93
Ala 185
Ser 173
Gly 174
Leu 105
Thr 181

Table S1. The contacts between residues in receptor-ligand detected in the final MD snapshots. The names of different regions of the ligands: Ar1, Ar2, Ar(T), chair, Link, Me, -CH_2, see Fig.3.

Ligand	salt bridge	Hb between receptors residue-ligand	hydrophobic	CH- π
FENT	2.9	(Thr181) -(C=O): 3.05 Å	Ile178, Leu182, Ala185, Met93 with Ar2; Leu105, Phe107 with chair Phe133, Val162, Val152 with Ar1	Phe107- chair Tyr103-Ar2 Phe133- Ar1 Tyr120-chair Trp164-Ar1
HALO	2.8	COO^- (Thr181) (C=O): 3.7 Å (Tyr120) (C=O):3.8 Å Halogen bond: oxygen form OH group of Ser205 with Ar1 (C-F): 4.12 Å oxygen form C=O group of Thr202 with Ar1 (C-F): 4.01 Å	Trp89, Trp164, Phe107 with Ar2; Phe107, Tyr120 with chair Thr181, Leu105, Tyr103, Tyr120 with link Tyr103, Leu182 with Ar1	Trp89- Ar2 Tyr103- Ar1 Tyr120-chair, Ar2 Trp164-Ar2
MORPH	3.2 3.6	Hb oxygen atom OH (Tyr120) with oxygen –O- (C-O):2.7 Å Hb oxygen atom NH (Gly118) with oxygen –O- (C-O): 4.0 Å Hb oxygen atom C=O(backbone of Ala86) with oxygen OH (OH):2.7 Å Hb oxygen atom NH(backbone of Ala185) with oxygen OH (OH):3.5 Å + CH3(sidechain of Ala185) with OH (OH): 3.22 Å	Trp89, Trp164 with Ar(T); Phe107, Trp164 with CH2 Ile124 with chair Val84 with Link	Trp89 Phe107 Tyr103 Tyr120 Trp164 Phe184
R-PTZ	2.9		Trp164, Phe107 with Ar(T); Ala185 with Me Phe107 with CH2 Tyr120 with chair Ile178, Tyr103, Ile124, Leu105, Glu172 with Link	Phe107, Tyr120
S-PTZ	2.9	Hb oxygen atom C=O(backbone of Ala86) with oxygen OH (OH):3.2 Å	Ala185 with Me Ile124 with CH2 Phe107 with chair Ile178, Tyr103, Leu105, Glu172 with Link	Phe107, Tyr120
R-PHZ	3.8	Hb oxygen atom C=O(backbone of Ala86) with oxygen OH (OH(T)):2.7 Å	Ala86, Phe184 with Ar(T); Phe107, Trp164 with Me Tyr120 with CH2 Phe107 with chair Ile124 with Link Ile178, Tyr103, Ala185, Thr181, Leu182 with Ar	Trp89 Tyr103 Phe107, Tyr120 Trp164
S-PHZ	3.0	Hb oxygen atom C=O(backbone of Ala86) with oxygen OH (OH(T)):3.0 Å Hb oxygen atom C=O(backbone of Trp89) with oxygen OH (OH(T)):3.2 Å	Ala86, Trp89, Val84 with Ar(T); Tyr120, Ile124, Ala185 with Me Phe107 with chair Ile124 with Link Val152, Phe133, Val162, His154 with Ar	Phe107, Tyr120

Figure S3. Spectrum of the frequency of the contacts between receptor residues and atomic centers of ligands.



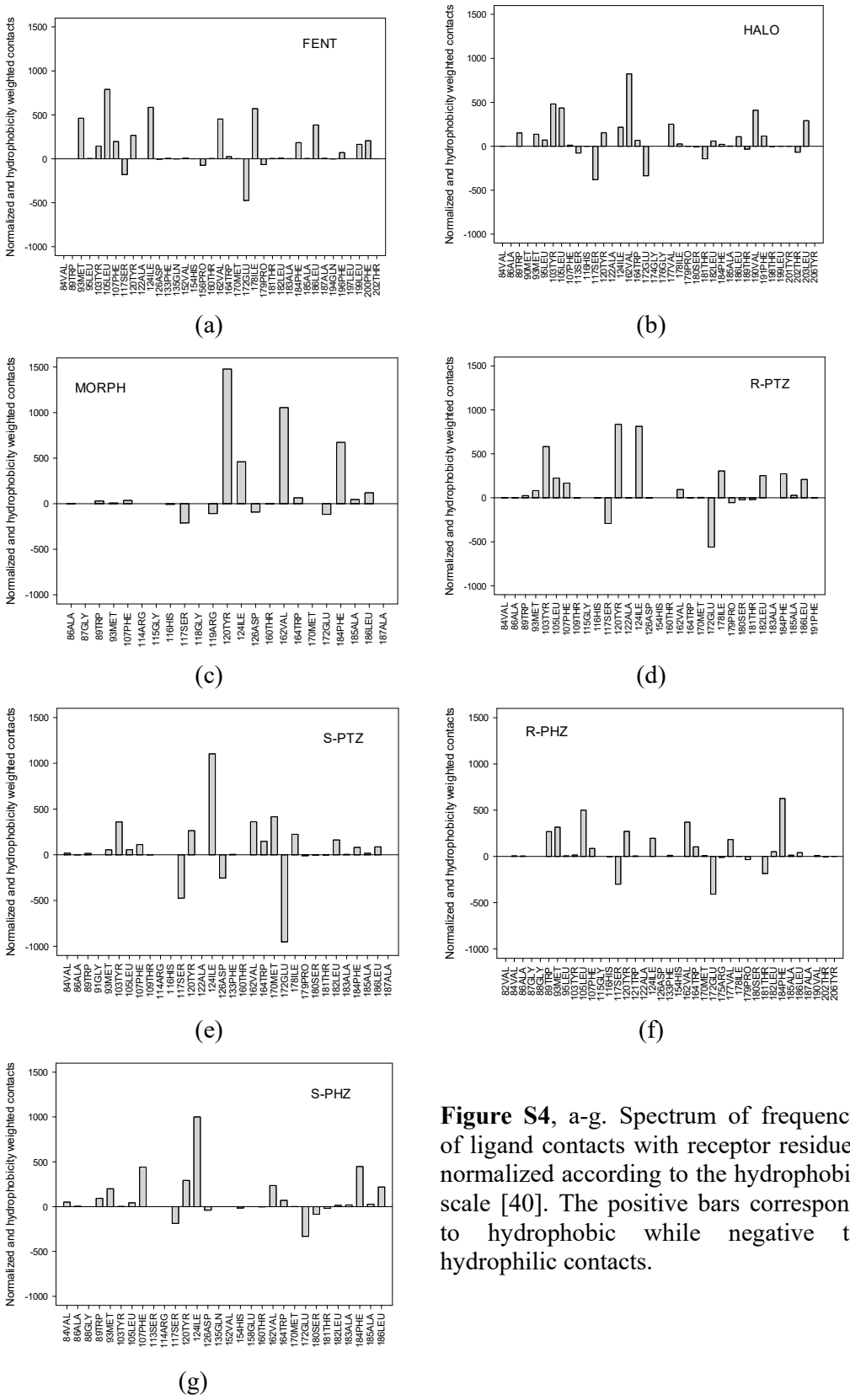


Figure S4, a-g. Spectrum of frequency of ligand contacts with receptor residues normalized according to the hydrophobic scale [40]. The positive bars correspond to hydrophobic while negative to hydrophilic contacts.