Supporting Information

Verifying the Role of 3-Hydroxy of 17-Cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-[(4′-pyridyl) carboxamido]morphinan Derivatives via Their Binding Affinity and Selectivity Profiles on Opioid Receptors

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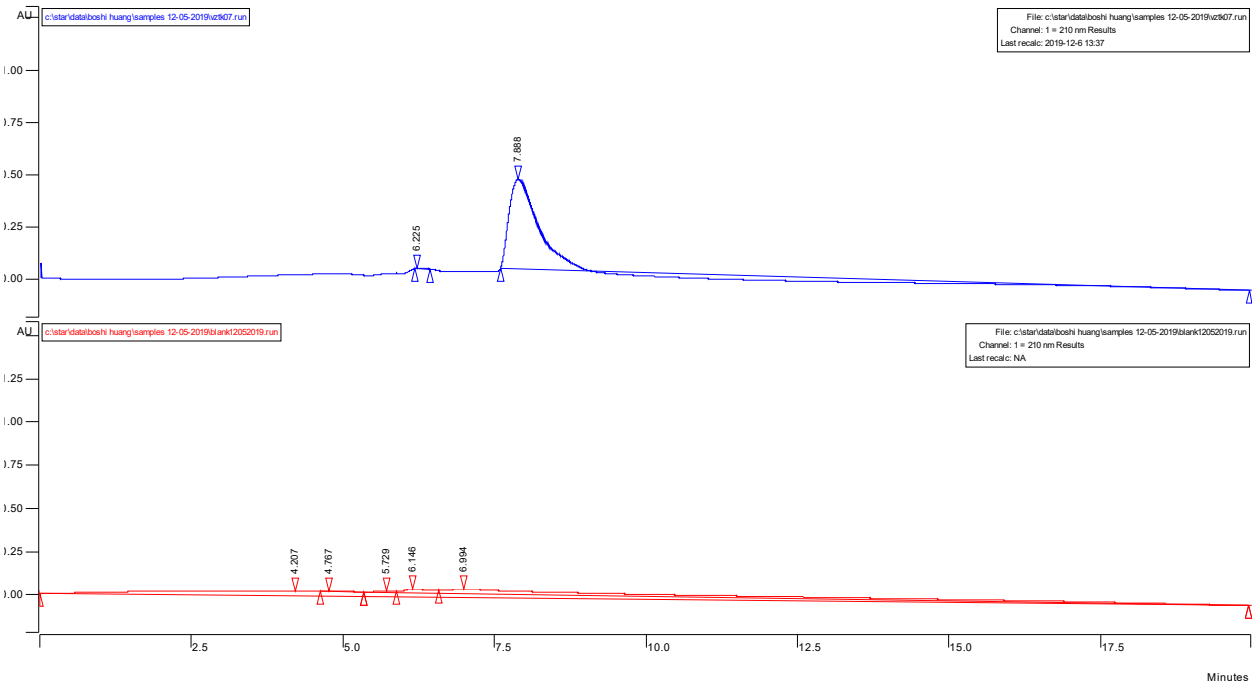
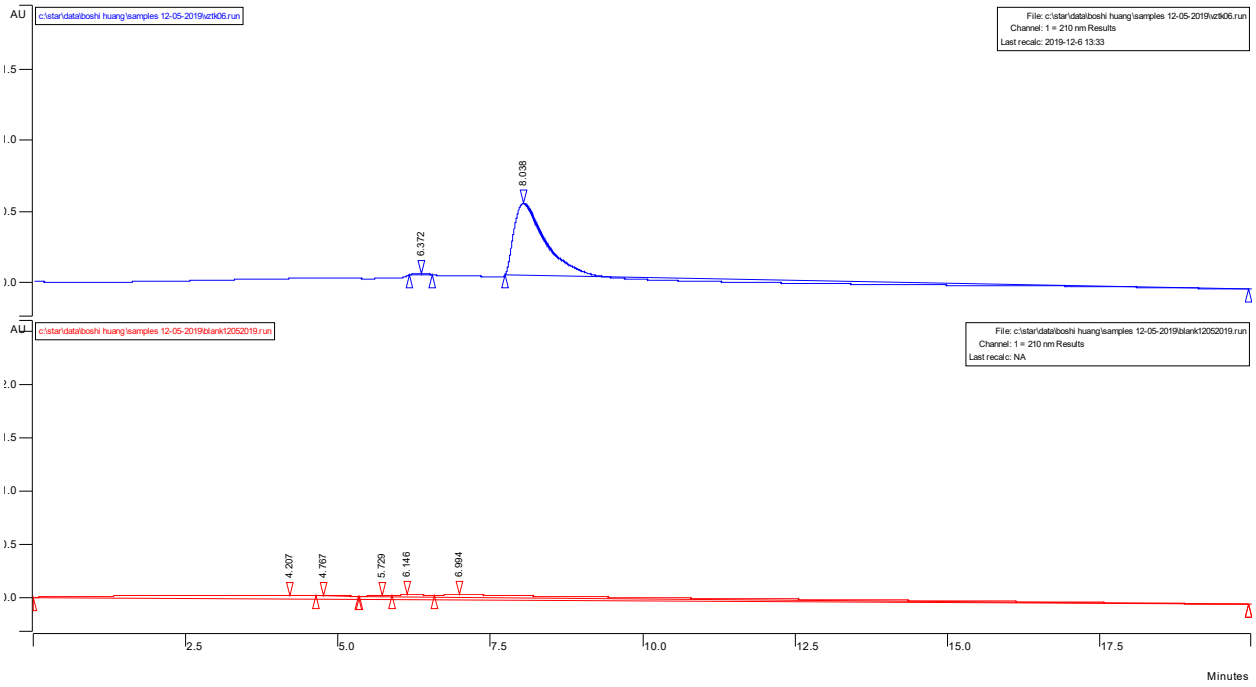
Contents:

1. Purity determination results by HPLC for target compounds ***6a-e***

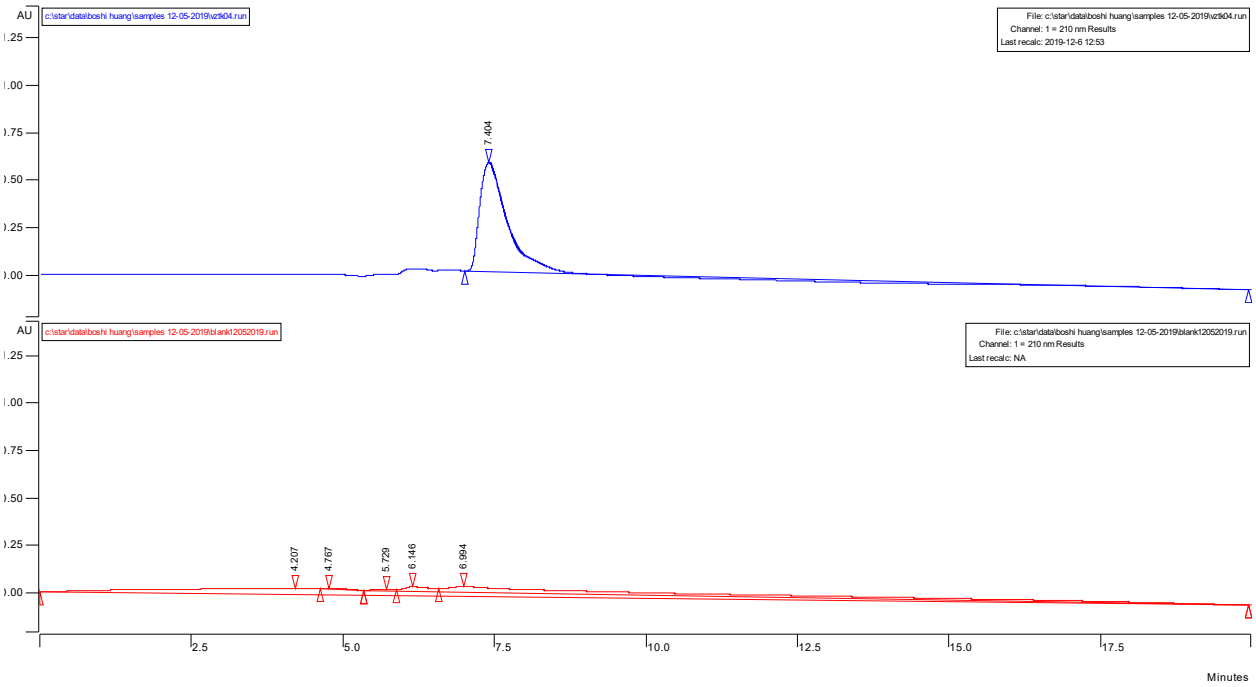
Compound ***6a***



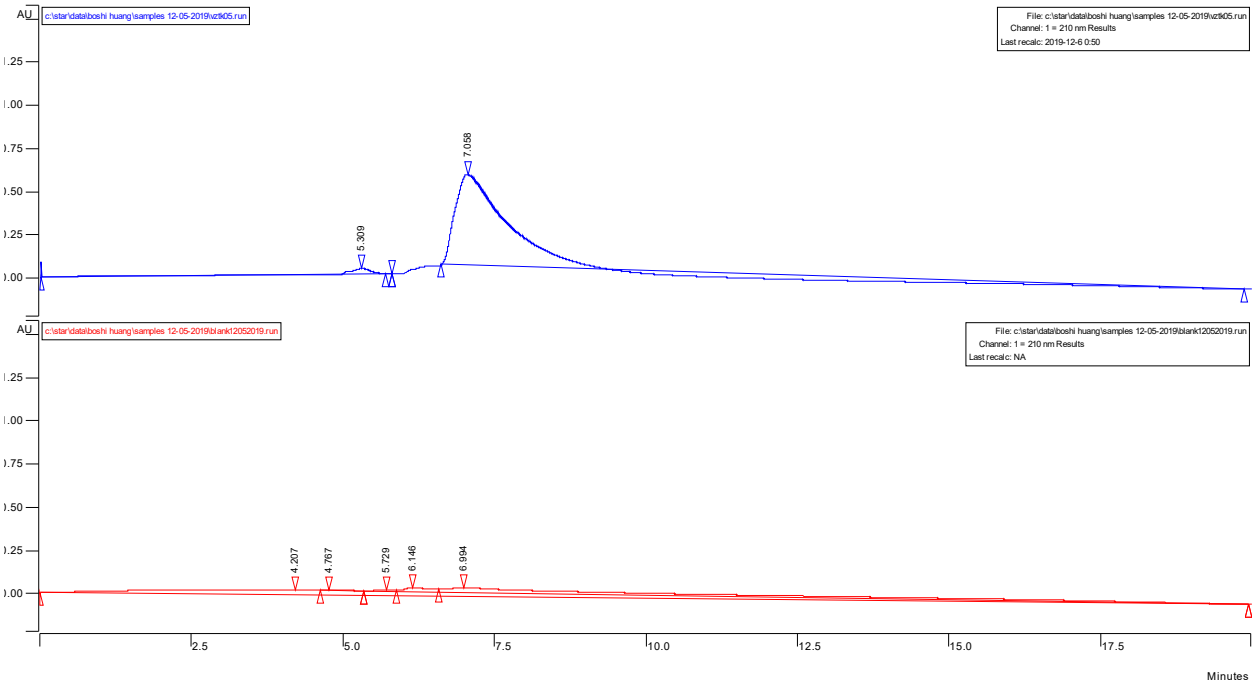
Compound ***6b***



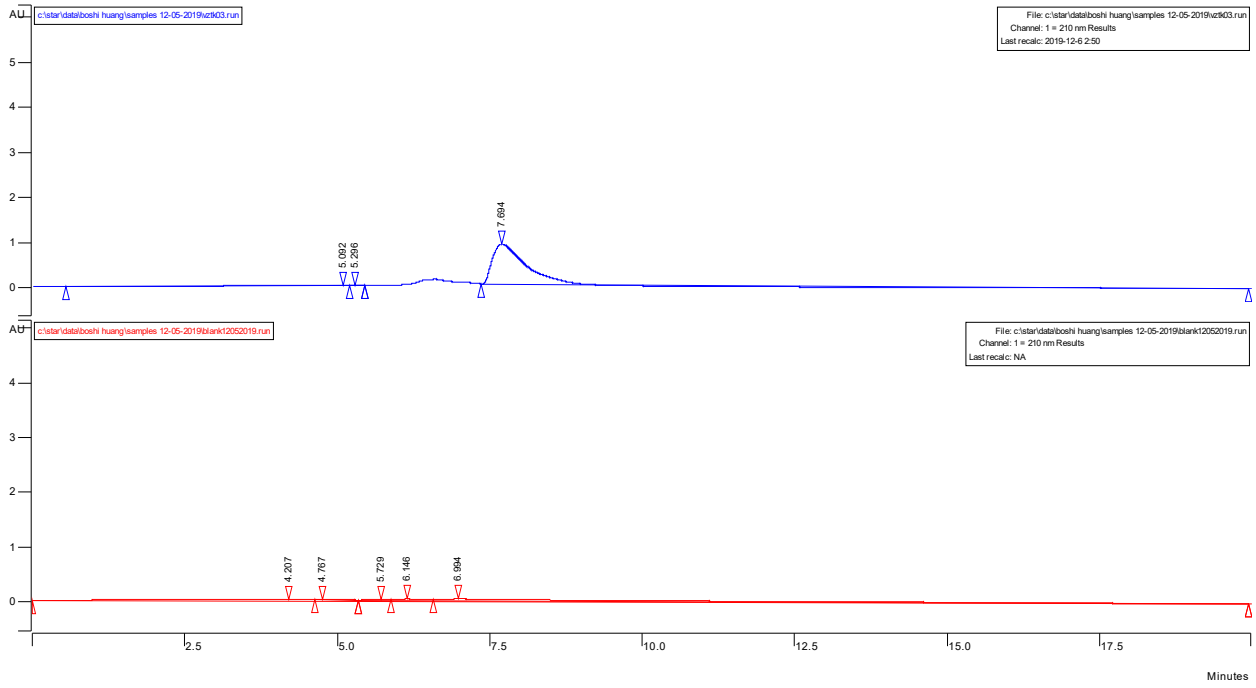
Compound ***6c***



Compound ***6d***



Compound ***6e***



2. Molecular modeling study

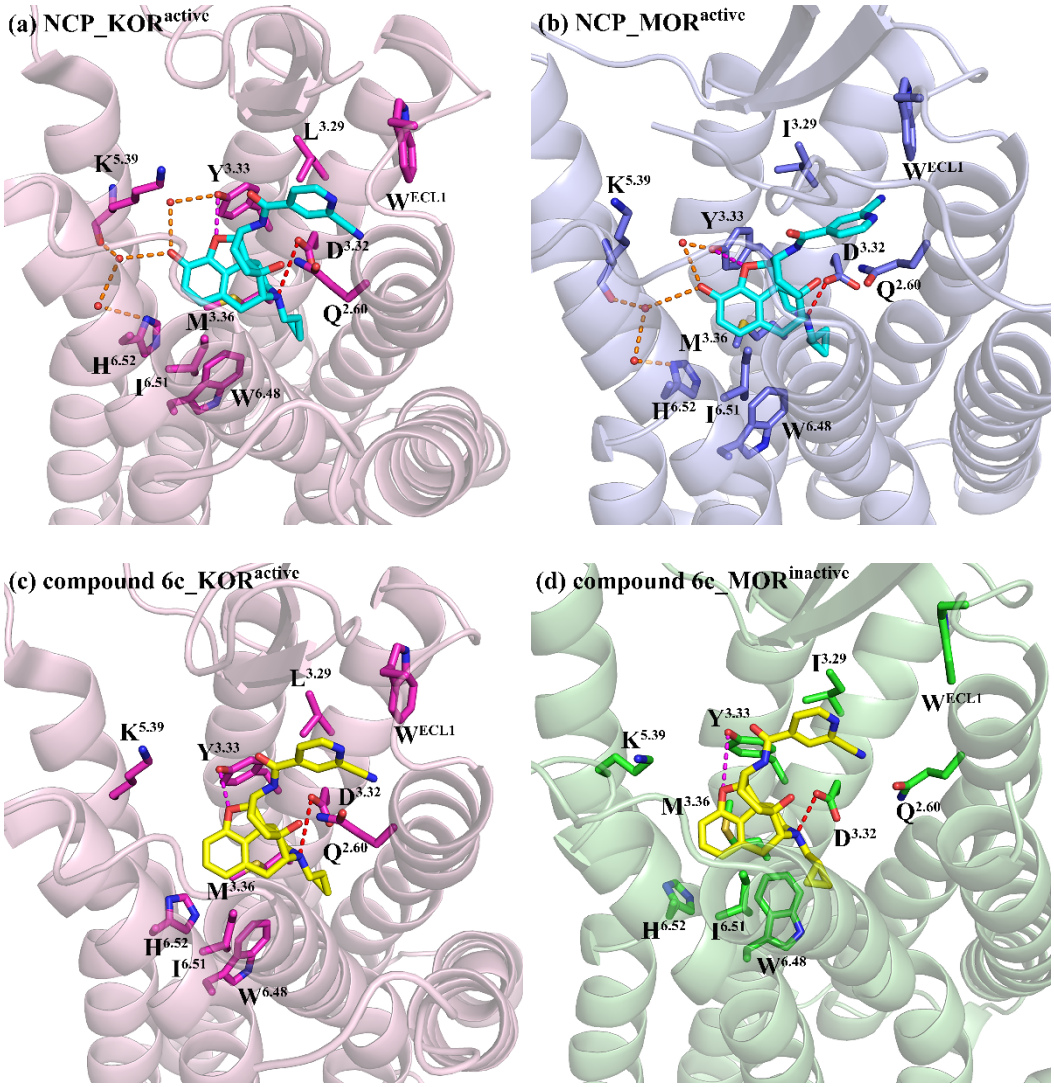


Fig. S1. The binding modes of **NCP**_KOR^{active}, **NCP**_MOR^{active}, compound **6c**_KOR^{active}, and compound **6c**_MOR^{inactive} complexes after molecular docking study. The receptors were shown as cartoon models, the active KOR in light-pink, the active MOR in light-blue, and the inactive MOR in light-green. **NCP**, compound **6c**, and key amino acid residues were shown as stick models. Carbon atoms: **NCP** in cyan; compound **6c** in yellow; key amino acid residues of the active KOR in magenta, the active MOR in blue, and the inactive MOR in green. The dashed lines in red represented potential ionic interactions. The dashed lines in magenta represented a potential hydrogen bonding interactions. The dashed lines in orange represented potential water-mediated hydrogen bonds. The water molecules were shown as sphere models in red.

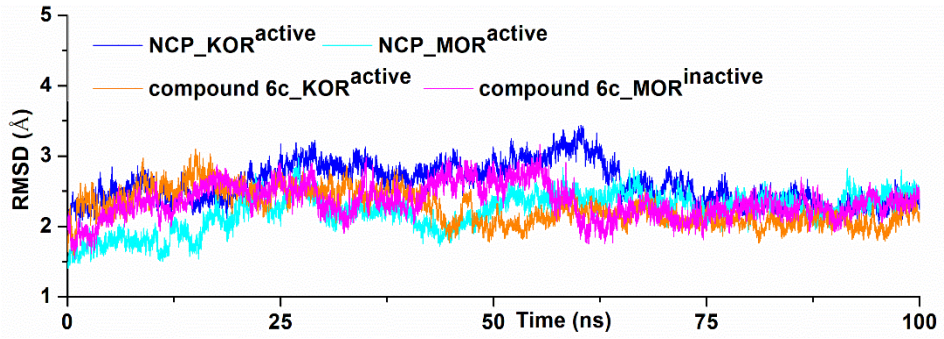


Fig. S2. The root-mean-square deviation (RMSD) of the backbone atoms of the residues in the **NCP**_KOR^{active}, **NCP**_MOR^{active}, compound **6c**_KOR^{active}, and compound **6c**_MOR^{inactive} complexes after 100 ns MD simulations.

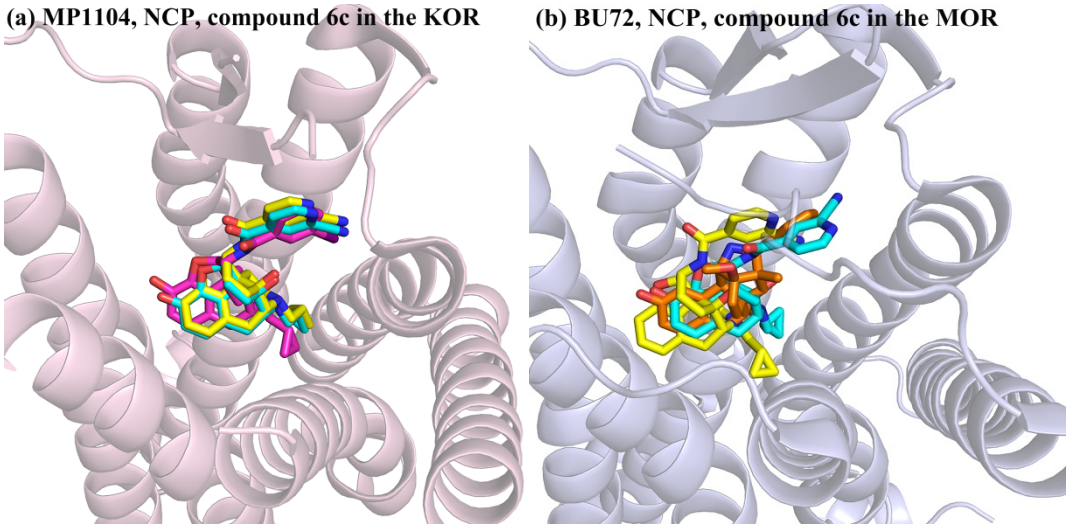


Fig. S3. The binding modes of **MP1104**, **NCP**, and compound **6c** in the KOR (**a**) and **BU72**, **NCP**, and compound **6c** in the MOR (**b**). The KOR and MOR shown as cartoon models in light-pink and light-blue, respectively. **MP1104**, **NCP**, compound **6c**, and BU72 shown as stick models in magentas, cyan, yellow, and orange, respectively.

Table S1. The average distances between atoms of ligand and atoms of receptor in **NCP**_KOR^{active}, **NCP**_MOR^{active}, compound **6c**_KOR^{active}, and compound **6c**_MOR^{inactive} complexes during 80 - 100 ns MD simulations.

Complex	Atom@Ligand	Atom@Receptor	Distance (Å)
NCP_KOR^{active}	N3@NCP	OD2@D$^{3.32}$	2.7
	O2@NCP	OH@Y$^{3.33}$	**2.9**
	O4@NCP	CB@K$^{5.39}$	**5.2**

	C12@NCP	CZ3@$W^{6.48}$	4.2
	C11@NCP	CG1@$I^{6.51}$	5.0
	C25@NCP	CE1@$H^{6.52}$	**3.5**
compound **6c**_KOR^{active}	N3@compound **6c**	OD2@$D^{3.32}$	2.7
	O2@compound **6c**	OH@$Y^{3.33}$	**3.3**
	C26@compound **6c**	CB@$K^{5.39}$	**8.3**
	C12@compound **6c**	CZ3@$W^{6.48}$	3.9
	C11@compound **6c**	CG1@$I^{6.51}$	4.9
	C25@compound **6c**	CE1@$H^{6.52}$	**4.7**
NCP_MOR^{active}	N3@NCP	OD2@$D^{3.32}$	2.6
	O2@NCP	OH@$Y^{3.33}$	**5.0**
	O4@NCP	CB@$K^{5.39}$	**4.6**
	C12@NCP	CZ3@$W^{6.48}$	3.7
	C11@NCP	CG1@$I^{6.51}$	5.0
	C25@NCP	CE1@$H^{6.52}$	**4.2**
compound **6c**_$MOR^{inactive}$	N3@compound **6c**	OD2@$D^{3.32}$	2.9
	O2@compound **6c**	OH@$Y^{3.33}$	**5.5**
	C26@compound **6c**	CB@$K^{5.39}$	**7.9**
	C12@compound **6c**	CZ3@$W^{6.48}$	4.6
	C11@compound **6c**	CG1@$I^{6.51}$	4.7
	C25@compound **6c**	NE2@$H^{6.52}$	**4.7**