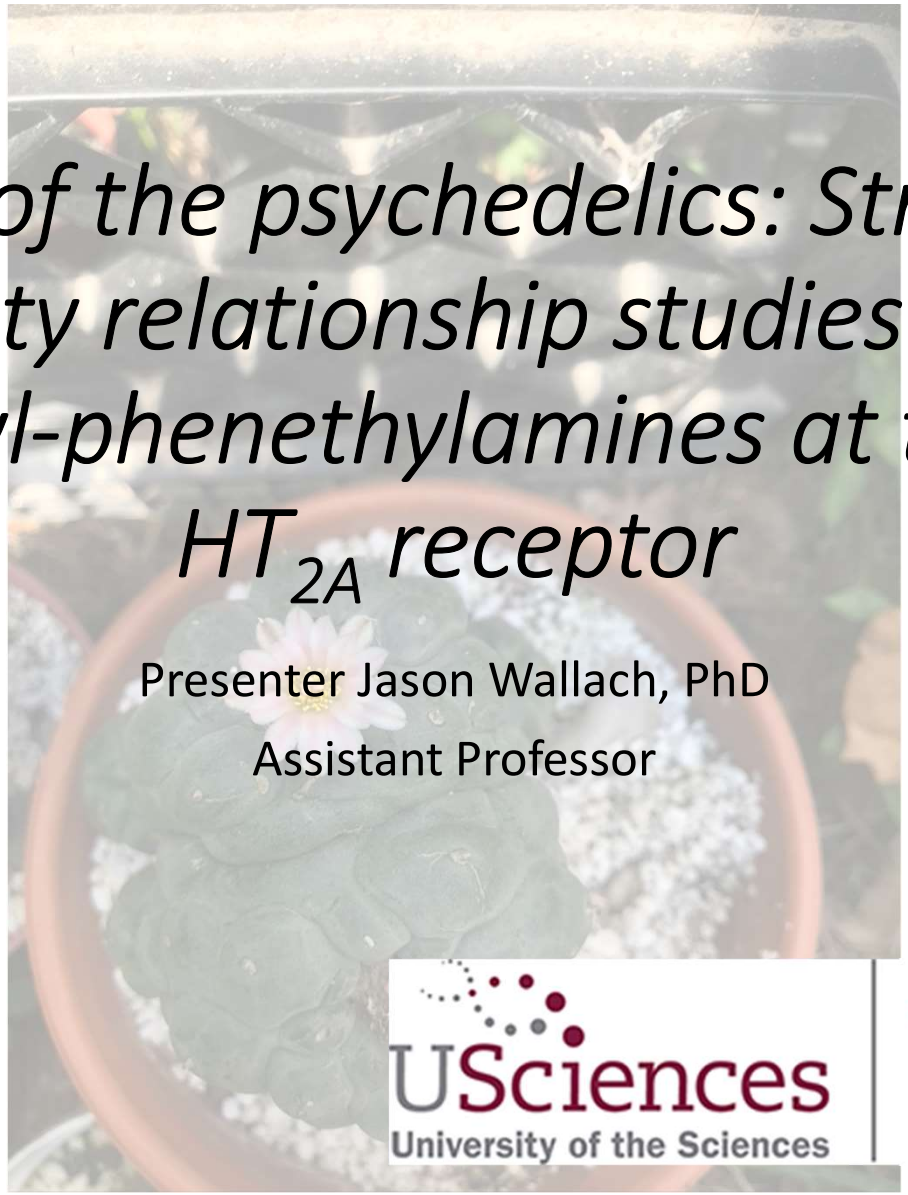


Return of the psychedelics: Structure-activity relationship studies of N-benzyl-phenethylamines at the 5-HT_{2A} receptor

Presenter Jason Wallach, PhD

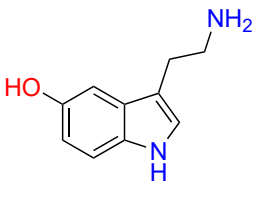
Assistant Professor

USciences
University of the Sciences

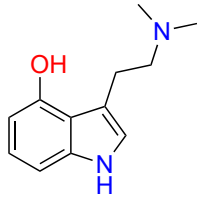
Substance Use Disorders Institute
EDUCATION • POLICY • RESEARCH

Classical Hallucinogens

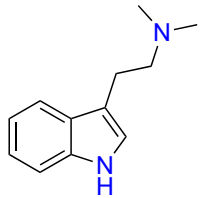
- Psychedelics
  - Magic Mushrooms: Psilocybin and psilocin
  - LSD
  - Peyote: Mescaline
  - Ayahuasca: DMT (and MAOIs)
- Act through 5-HT_{2A} receptor



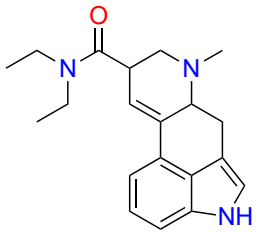
Serotonin



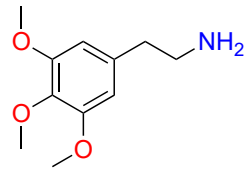
Psilocin



DMT

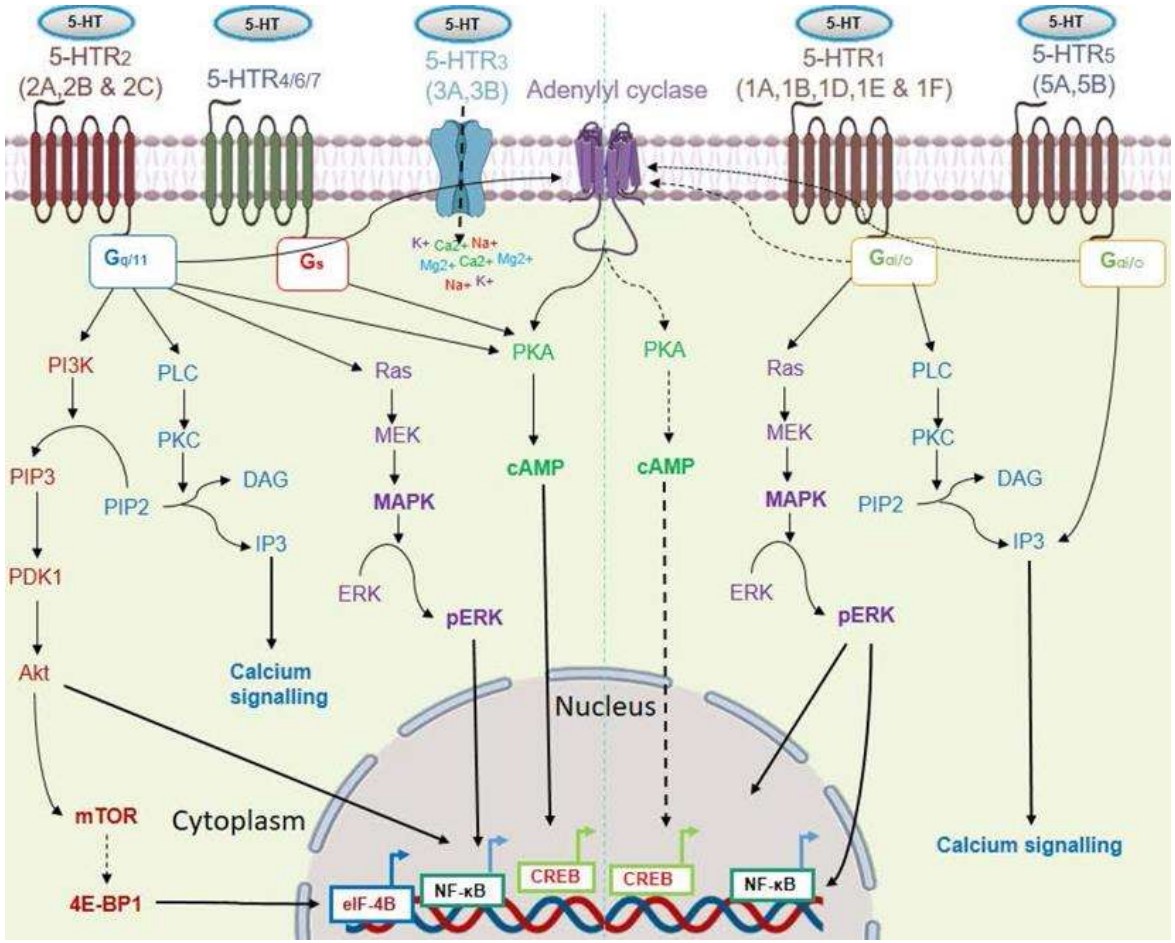


LSD



Mescaline

Serotonergic System



Karmakar and Lal. *Theranostics*. 2021

$5\text{-}HT_{2A}$

- Serotonin (5-HT) receptor
- GPCR
- Wide distribution in CNS
- Esp. abundant on excitatory PFC pyramidal neurons (on apical dendrites)
  - Pre- and post- synaptic populations
  - Also expressed on interneurons
  - Also expressed on glial cells
- Cortical layers II, III, V and VI
- Expressed in peripheral tissues
  - Smooth and skeletal muscle, platelets, kidney, liver

Serotonin 5-HT_{2A} Receptor Activation Blocks TNF-α Mediated Inflammation *In Vivo*

Felix Nau Jr.[◔], **Bangning Yu**[◔], **David Martin, Charles D. Nichols***

Department of Pharmacology and Experimental Therapeutics, Louisiana State University Health Sciences Center, New Orleans, Louisiana, United States of America

Abstract

Tumor necrosis factor alpha (TNF-α) plays a key role in inflammation, and its production and signaling contribute to many inflammatory related diseases. Recently, we discovered that selective activation of serotonin 5-HT_{2A} receptors with the agonist (*R*)-DOI produces a super-potent blockade of proinflammatory markers in primary rat aortic smooth muscle cells. Here, we demonstrate that systemic administration of (*R*)-DOI can block the systemic effects of TNF-α in whole animal, with potent anti-inflammatory effects in the aortic arch and small intestine. This includes blockade of TNF-α-induced expression of pro-inflammatory cell adhesion (*Icam-1*, *Vcam-1*), cytokine (*Il-6, IL-1b*), and chemokine (*Mcp-1*, *Cx3cl1*) genes, and expression of VCAM-1 protein in the intestine. Further, systemic (*R*)-DOI also prevents the TNF-α-induced increase of circulating IL-6. Importantly, utilizing receptor selective antagonists, we have demonstrated that the mechanism underlying the systemic anti-inflammatory effects of (*R*)-DOI is activation of serotonin 5-HT_{2A} receptors. Our results highlight a powerful new role for the serotonin 5-HT_{2A} receptor in inflammatory processes, and indicate that agonism of serotonin receptors may represent an effective and novel approach to develop powerful small molecule therapeutics for inflammatory diseases and conditions such as atherosclerosis and inflammatory bowel disease.

Citation: Nau F Jr, Yu B, Martin D, Nichols CD (2013) Serotonin 5-HT_{2A} Receptor Activation Blocks TNF-α Mediated Inflammation *In Vivo*. PLoS ONE 8(10): e75426. doi:10.1371/journal.pone.0075426

Editor: Michael Bader, Max-Delbrück Center for Molecular Medicine (MDC), Germany

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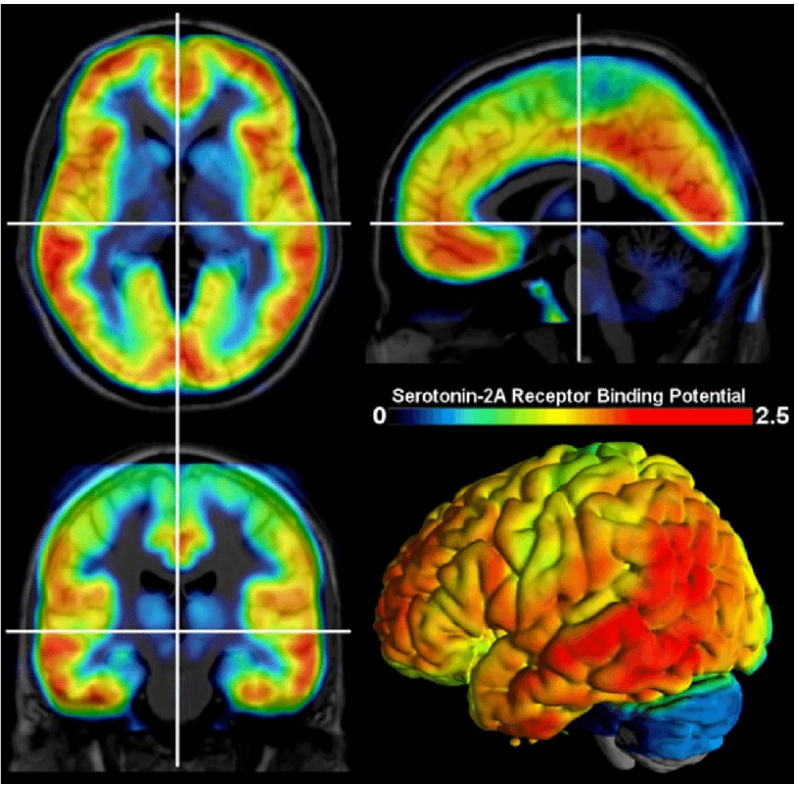
Competing Interests: The authors have declared that no competing interests exist.

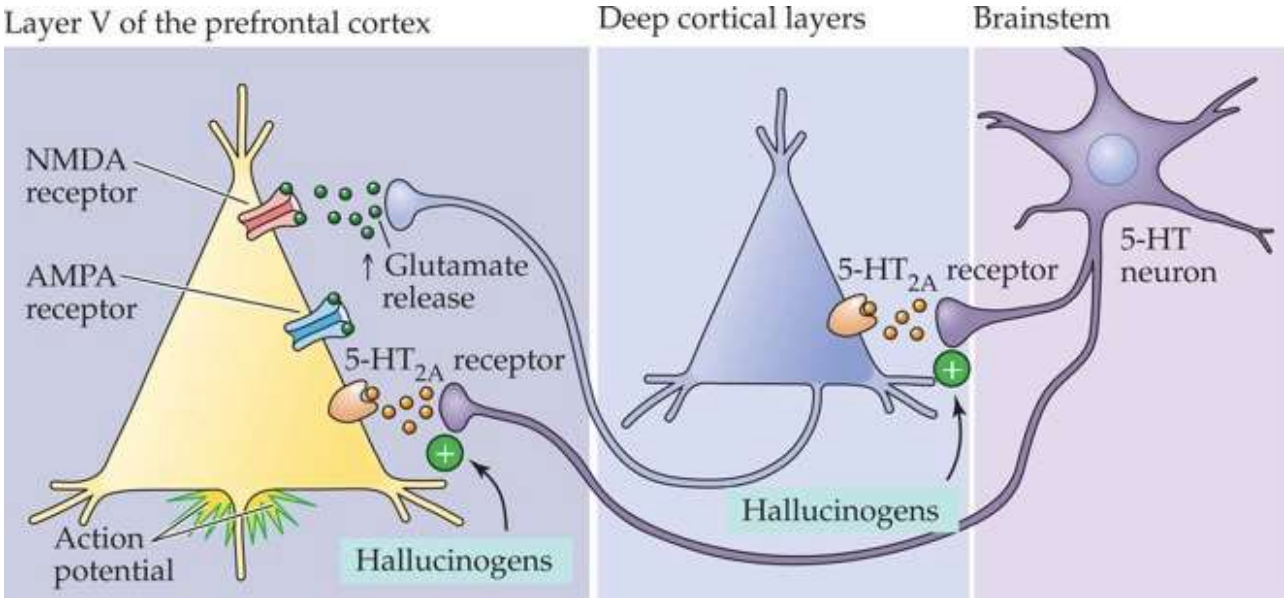
* E-mail: cnich1@lsuhsc.edu

◔ These authors contributed equally to this work.



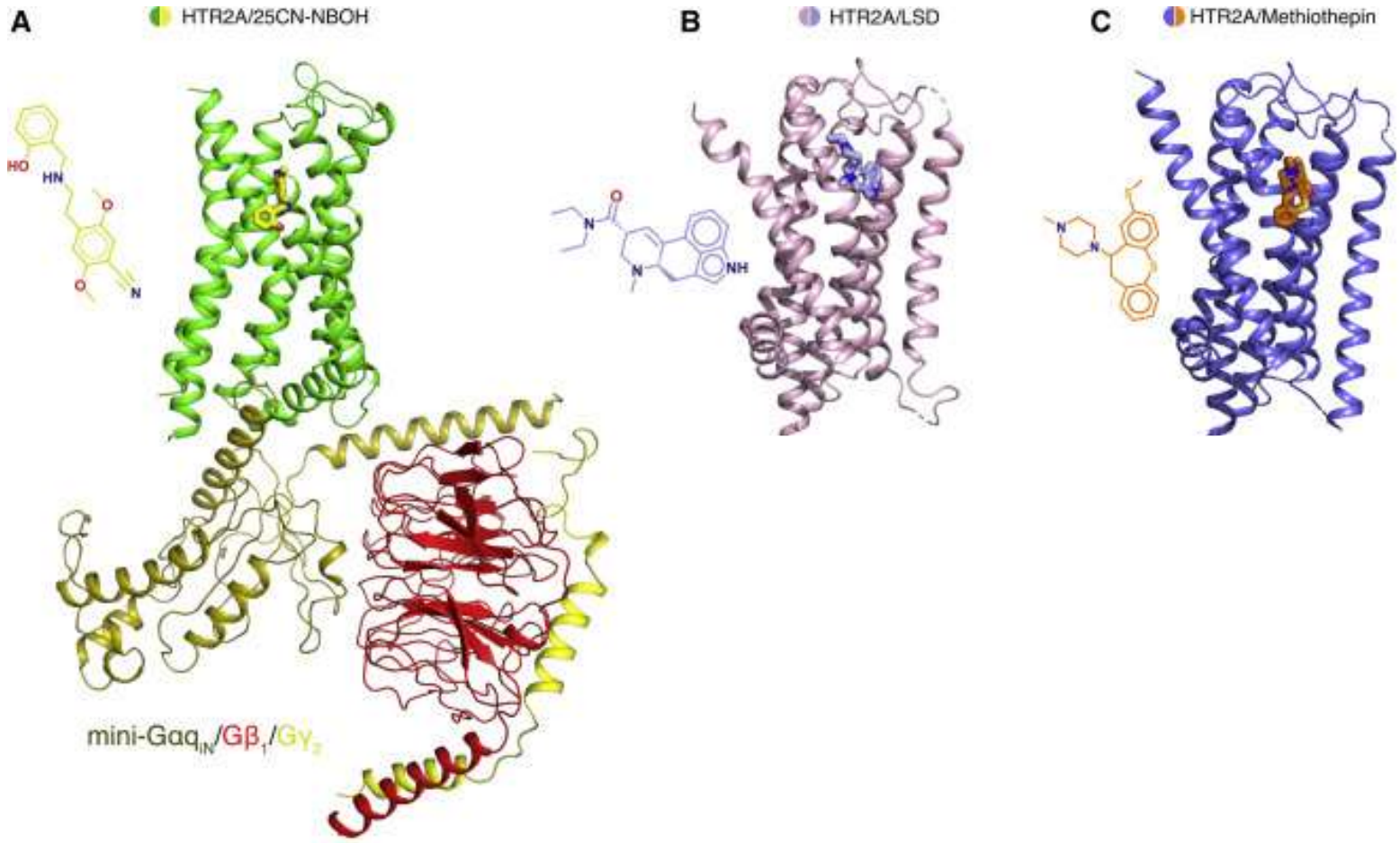
“Distribution of the serotonin 2A (5-HT2A) receptor in the human brain as measured with PET, using the 5-HT 2Aspecific radioligand [18 F]altanserin based on 17 healthy subjects”

Sauln et al. *Amino Acids*. 2012

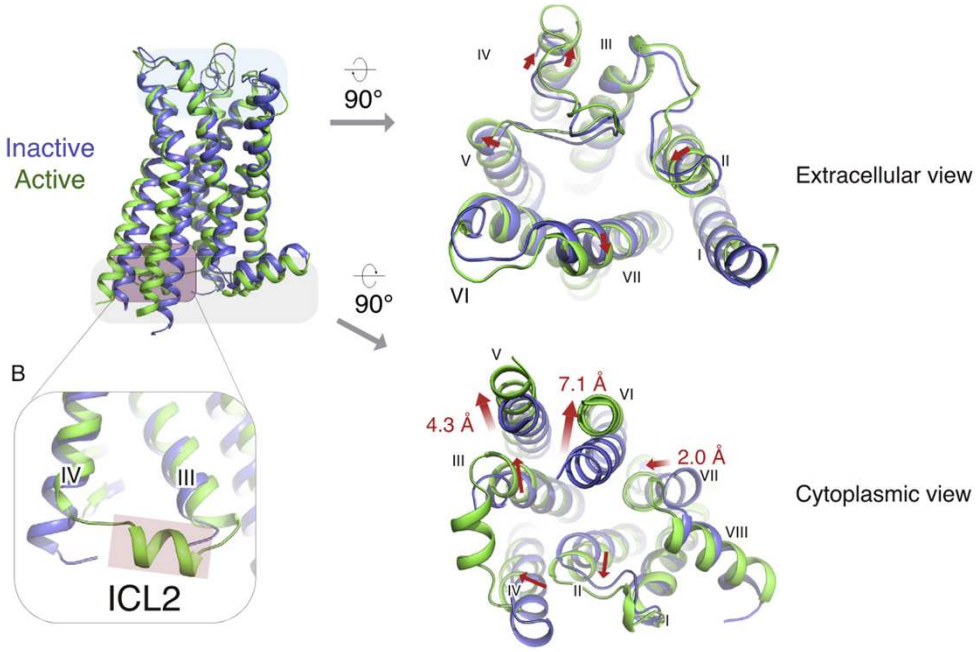


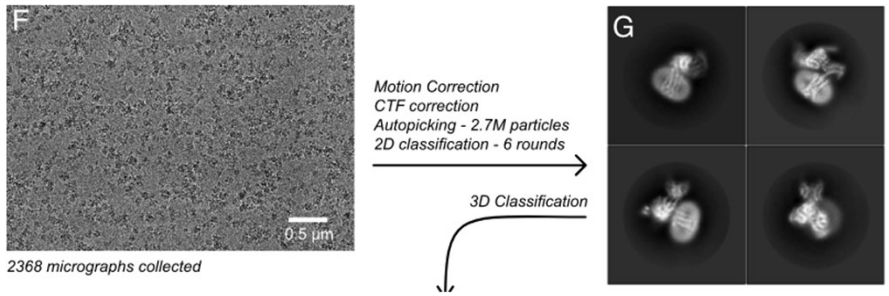
Vollenweider and Kometer. *Nat. Rev. Neurosci.* 2010

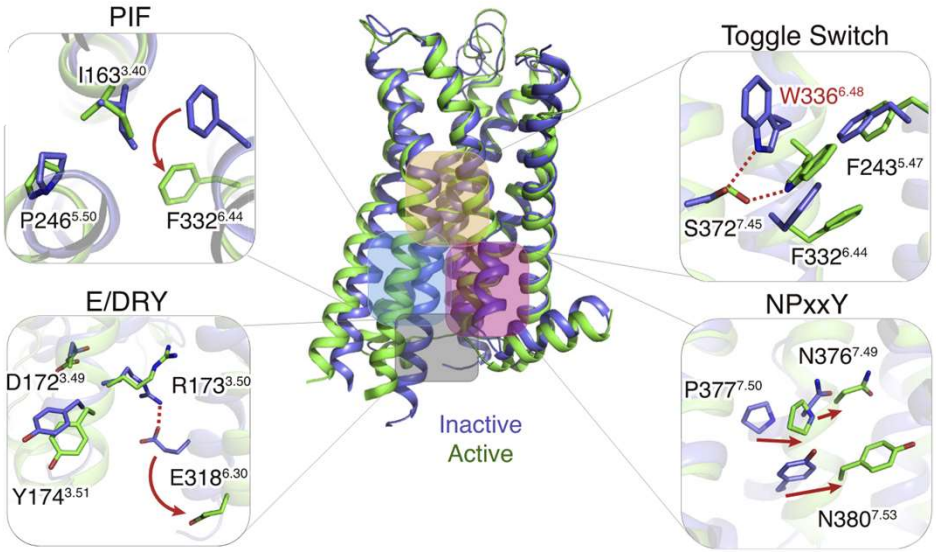
5-HT_{2A} Structure



Kim et al. *Cell*. 2020



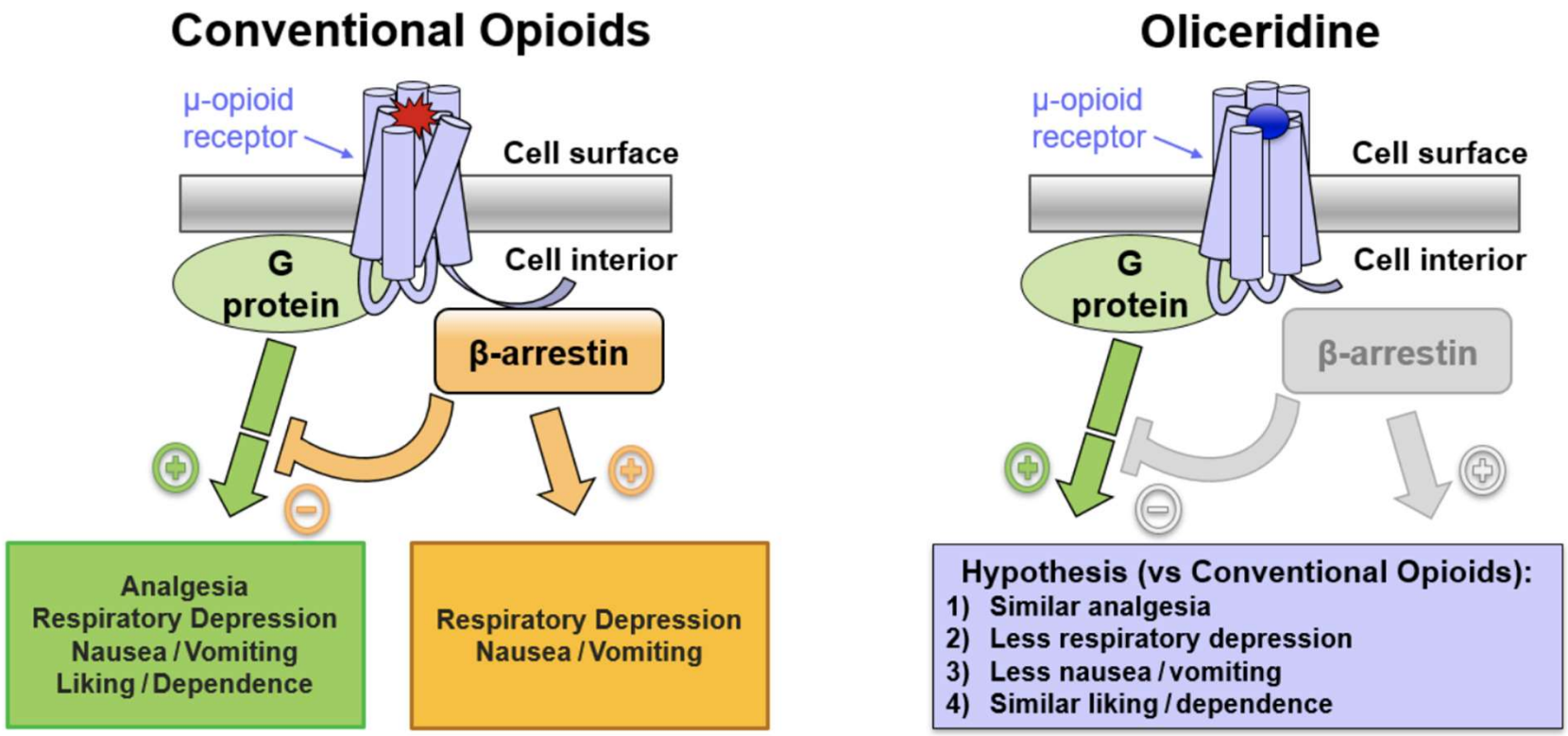




Kim et al. *Cell*. 2020

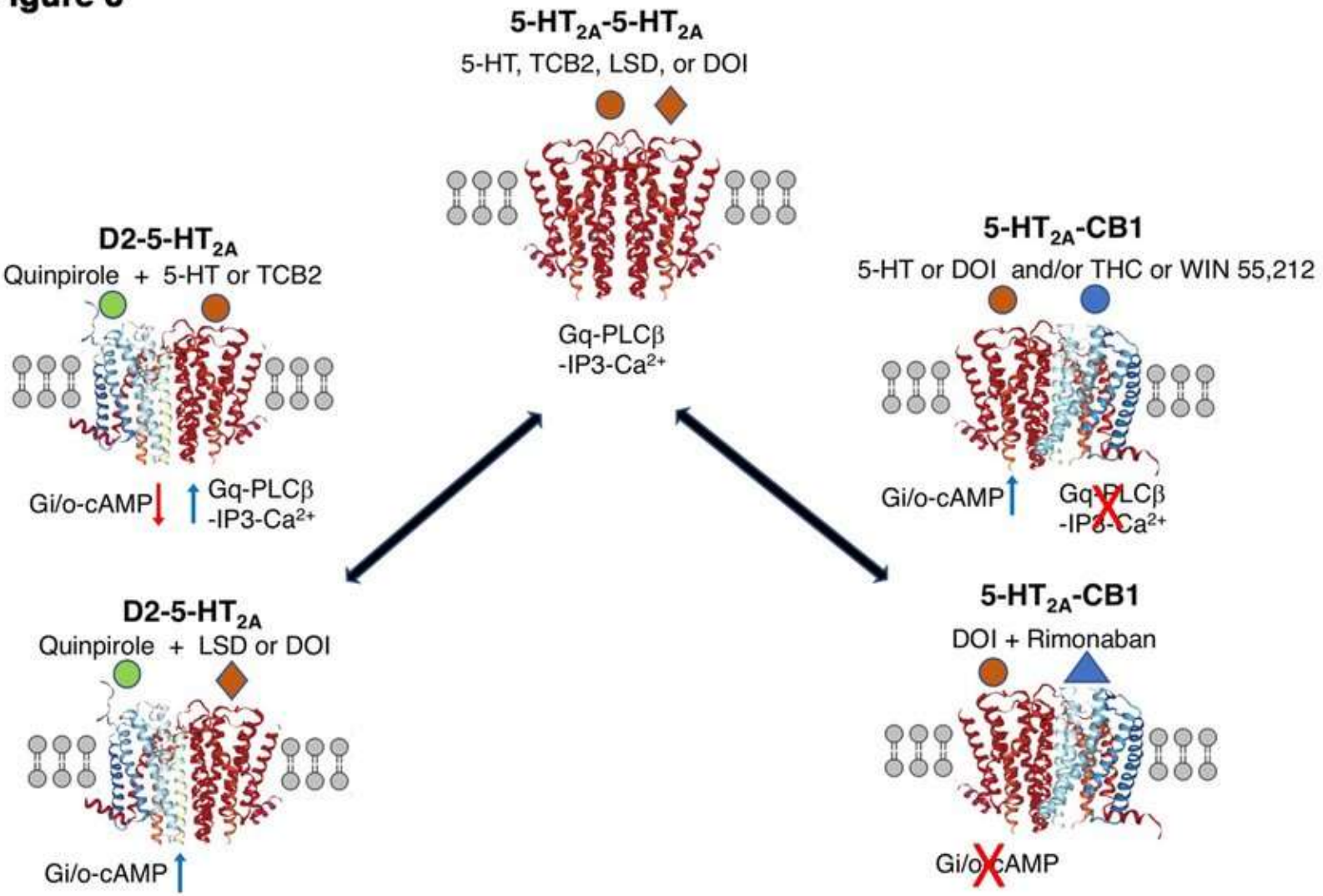
Biased Signaling

Figure 1: μ-Opioid Receptor Binding of Conventional Opioids and Oliceridine



Oliceridine. FDA ADVISORY COMMITTEE BRIEFING DOCUMENT. 2018

Figure 3



Maroteaux et al. *Biochimie* . 2019

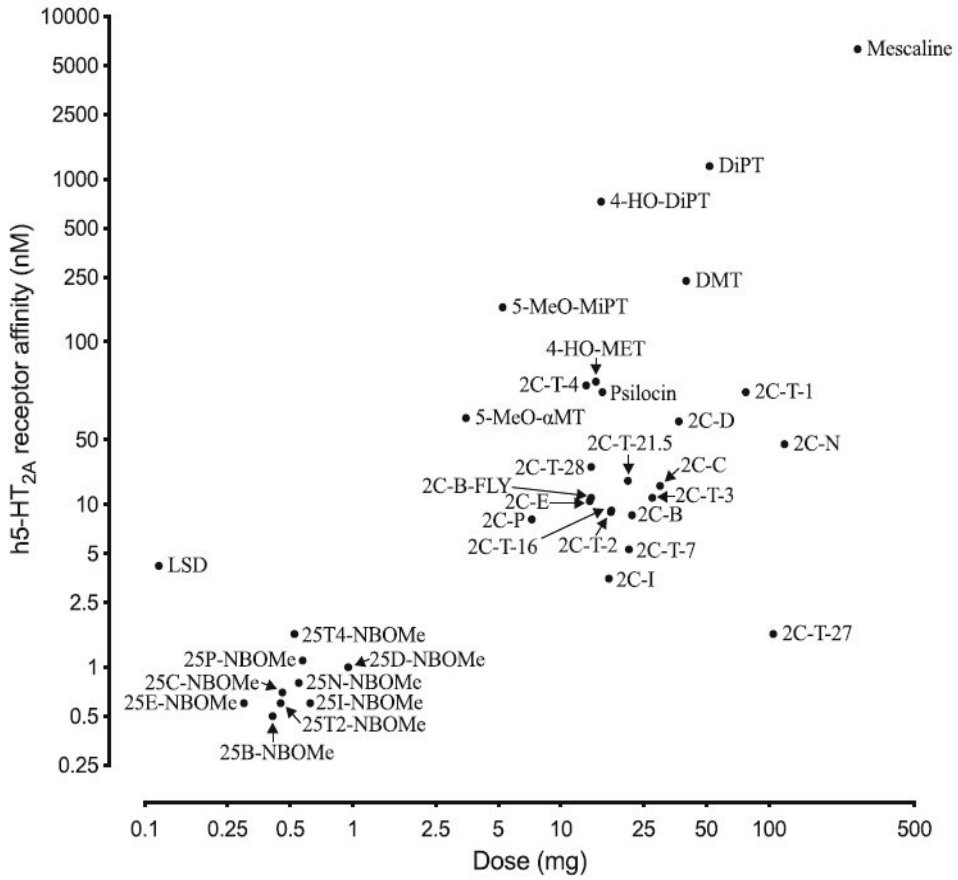


Fig 8 Correlation between reported clinical potencies and in vitro human 5-HT2A receptor affinities of a variety of psychedelics.

Luethi & Liechti. *Archives of Toxicology*. 2020

- 5-HT_{2A} binding affinities correlate with potency to induce psychedelic effects in humans

COGNITIVE NEUROSCIENCE

Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action

Vollenweider, Franz X.[1,3]; Vollenweider-Scherpenhuyzen, Margreet F. I.[2]; Bäbler, Andreas[1]; Vogel, Helen[1]; Hell, Daniel[1]

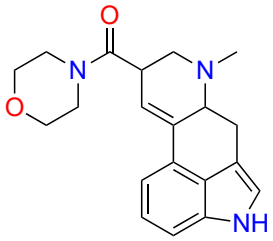
Author Information

NeuroReport: December 1, 1998 - Volume 9 - Issue 17 - p 3897-3902

Abstract

PSILOCYBIN, an indoleamine hallucinogen, produces a psychosis-like syndrome in humans that resembles first episodes of schizophrenia. In healthy human volunteers, the psychotomimetic effects of psilocybin were blocked dose-dependently by the serotonin-2A antagonist ketanserin or the atypical antipsychotic risperidone, but were increased by the dopamine antagonist and typical antipsychotic haloperidol. These data are consistent with animal studies and provide the first evidence in humans that psilocybin-induced psychosis is due to serotonin-2A receptor activation, independently of dopamine stimulation. Thus, serotonin-2A overactivity may be involved in the pathophysiology of schizophrenia and serotonin-2A antagonism may contribute to therapeutic effects of antipsychotics.

Polypharmacology: 5-HT_{1A} and 5-HT_{2A} Interactions



LSM-775

- 5-MeO-DMT
- LSM-775
- Pindolol – increased psychological effects of DMT [Strassman. 1995]
- Evidence for 5-HT_{2C} interactions in HTR too

TABLE 3 Functional activity of LSM-775 and 5-HT at selected serotonin receptors

	LSM-775		5-HT	
Receptor	EC_{50}, nM (pEC_{50} ± SEM)	E_{max} % 5-HT	EC_{50}, nM (pEC_{50} ± SEM)	E_{max} % 5-HT
h5-HT_{1A}	1.03 (8.99 ± 0.03)	98 ± 2	0.26 (9.58 ± 0.03)	100
h5-HT_{2A}	4.9 (8.31 ± 0.07)	89 ± 2	0.35 (9.50 ± 0.04)	100
m5-HT_{2A}	19 (7.72 ± 0.04)	88 ± 1	0.57 (9.24 ± 0.02)	100
h5-HT_{2B}	26 (7.58 ± 0.02)	77 ± 2	0.85 (9.07 ± 0.02)	100
h5-HT_{2C}	230 (6.64 ± 0.03)	77 ± 3	0.20 (9.58 ± 0.03)	100

Data were acquired with HEK293 cells expressing either human 5-HT_{1A} (h5-HT_{1A}), human 5-HT_{2A} (h5-HT_{2A}), mouse 5-HT_{2A} (m5-HT_{2A}), human 5-HT_{2B} (h5-HT_{2B}), or human 5-HT_{2C} INI (h5-HT_{2C}) receptors. Data represent EC_{50} and E_{max} means and standard error of the mean (SEM) from three independent experiments performed in triplicate. E_{max} is defined as percent 5-HT maximum response.

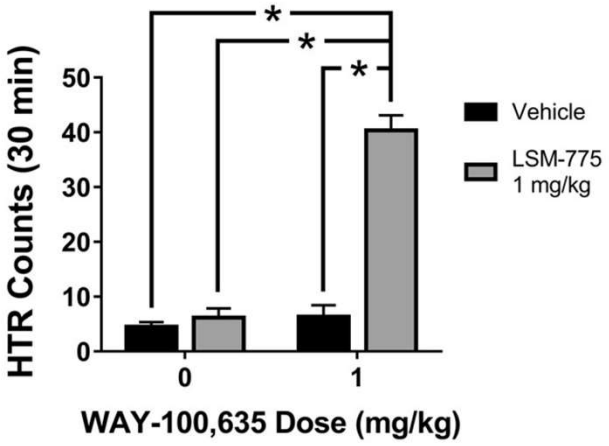
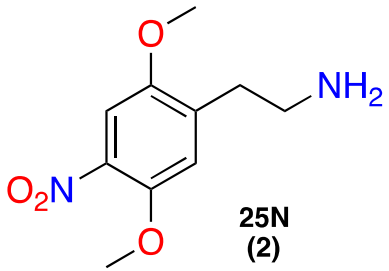


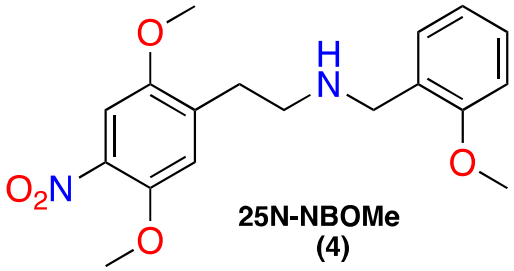
FIGURE 7 LSM-775 induced the head twitch response (HTR) in mice pretreated with the 5-HT_{1A} antagonist WAY-100,635 but not in mice pretreated with vehicle. Data are presented as group means ± SEM for the entire 30-min test session. *$p < 0.001$, significant differences between groups (Tukey's test)

Brandt et al. *Drug Testing and Analysis*. 2018

NBOMe Addition Increases 5-HT$_{2A}$ Affinity 100X



25N
(2)

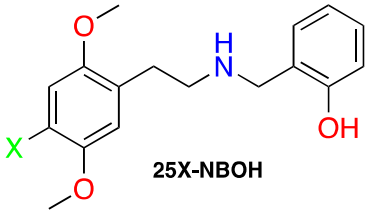


25N-NBOMe
(4)

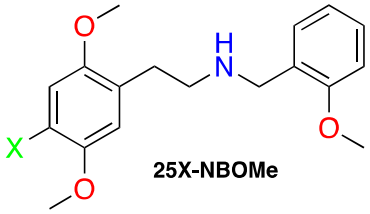
5-HT$_{2A}$ pK$_i$: 7.14 ± 0.02

9.26 ± 0.15

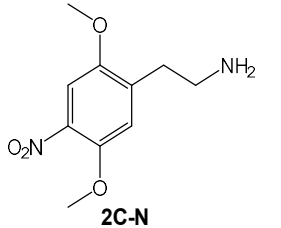
Highest Affinity Compounds in Series: H Bond Acceptors



25X-NBOH

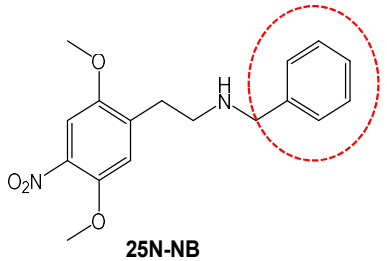


25X-NBOMe

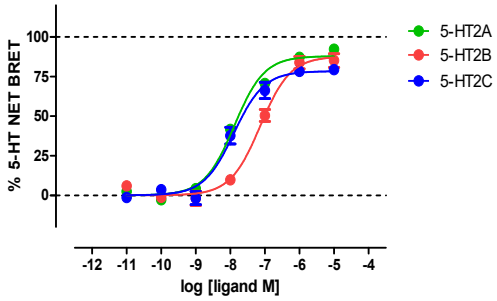


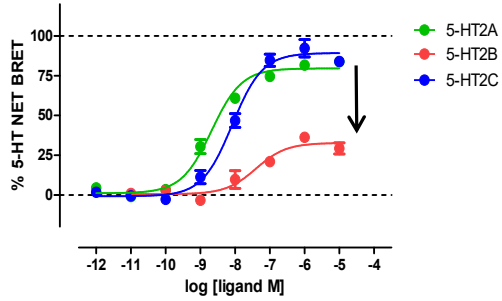
2C-N

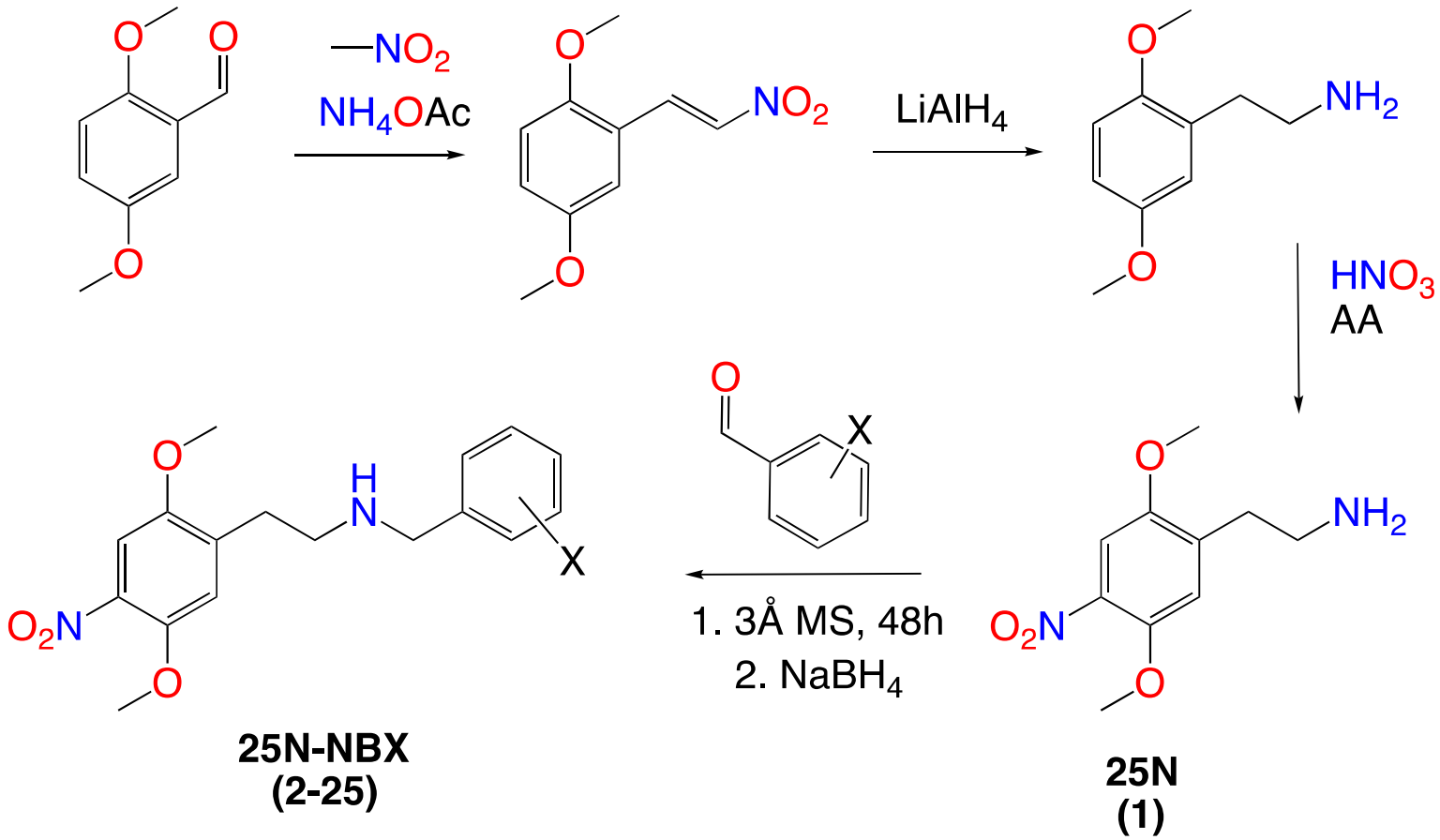
Reduce 5-HT$_{2B}$ agonist activity



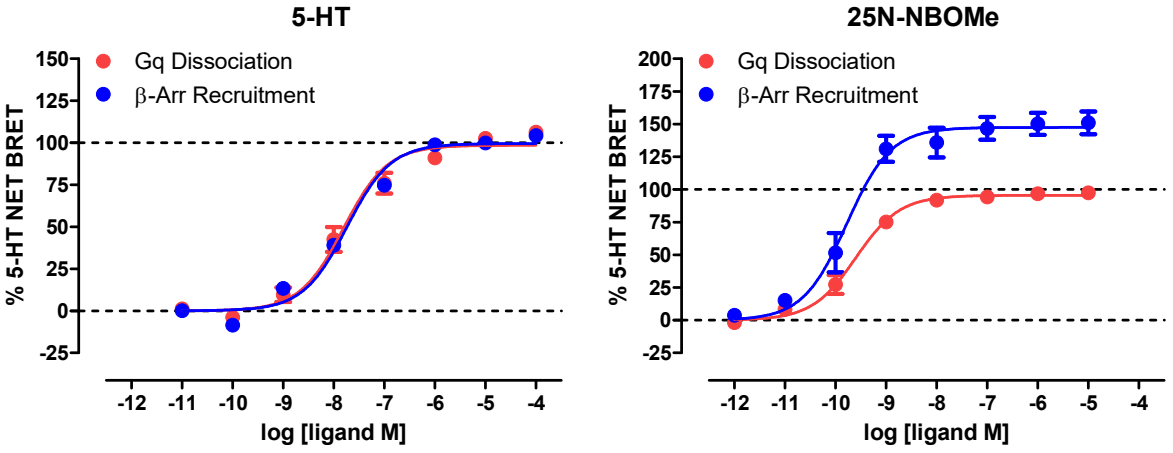
25N-NB






—NO2
NH4OAc
LiAlH4
HNO3
AA
1. 3Å MS, 48h
2. NaBH4
25N-NBX
(2-25)
25N
(1)

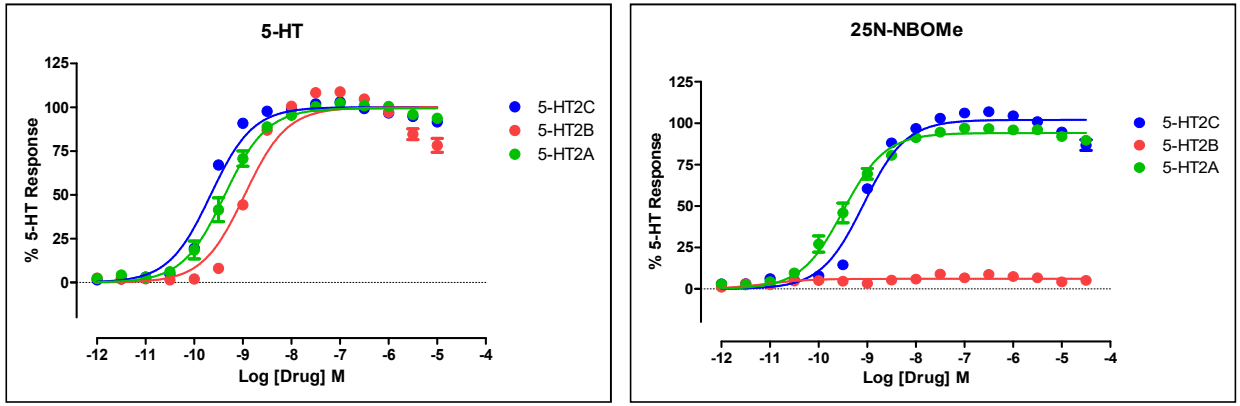
BRET

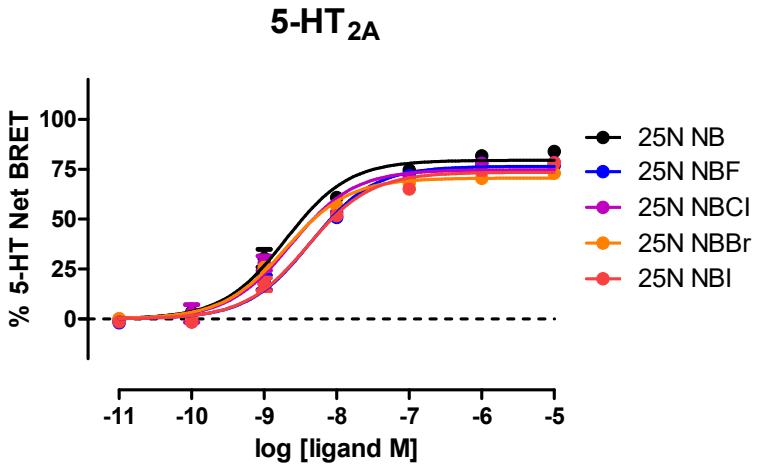


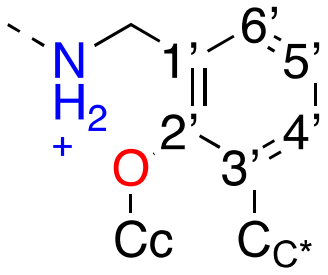
MEDICAL COLLEGE OF WISCONSIN

Dr. John McCorvy

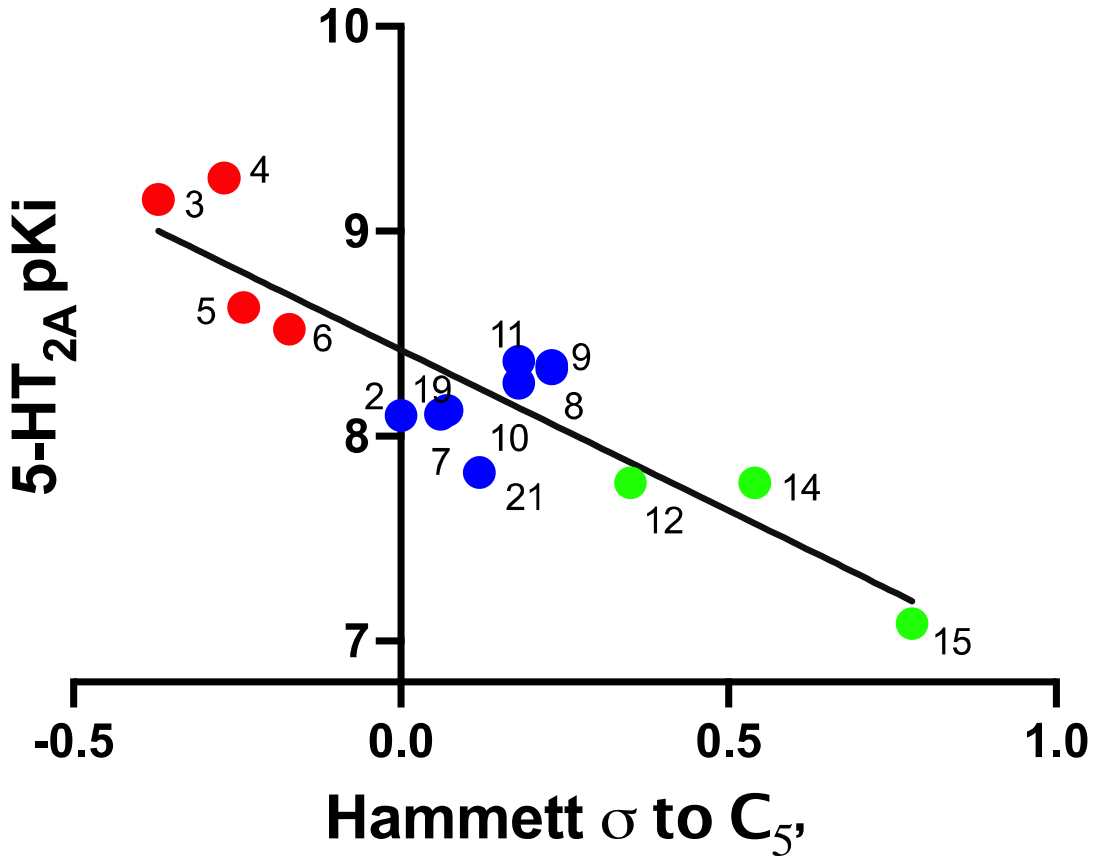
Ca^{2+} FLUX





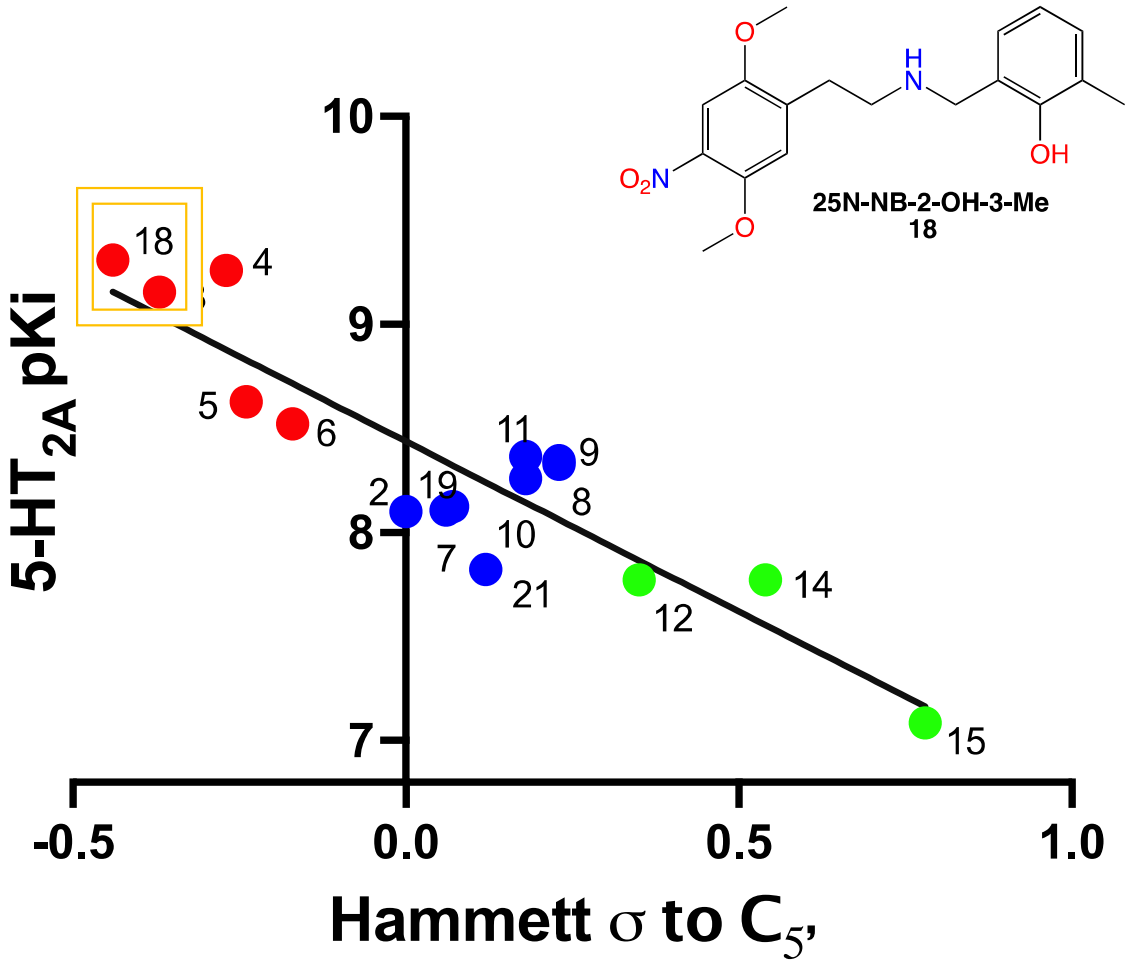


Compound	Functional Group	Hammett σ constant to $C_{5'}$
25N-NB-2-HO-3-Me (18)	2-HO-3-Me-	-0.44*
25N-NBOH (3)	2-OH	-0.37
25N-NBOMe (4)	2-OMe	-0.27
25N-NBOEt (5)	2-OEt	-0.24
25N-NBMe (6)	2-Me	-0.17
25N-NB (2)	2-H	0.00
25N-NBF (7)	2-F	0.06
25N-NBCl (8)	2-Cl	0.23
25N-NBBr (9)	2-Br	0.23
25N-NBI (10)	2-I	0.18
25N-NBOCF$_2$H (11)	2-OCF$_2$H	0.18
25NB-2-MeO-3-F (19)	2-MeO-3-F	0.07
25N-NB-3-HO (21)	3-OH	0.12
25N-NBOCF$_3$ (12)	2-OCF$_3$	0.35
25N-NBCF$_3$ (14)	2-CF$_3$	0.54
25N-NBNO$_2$ (15)	2-NO$_2$	0.78
*Additive value from corresponding σ_m and σ_p values		



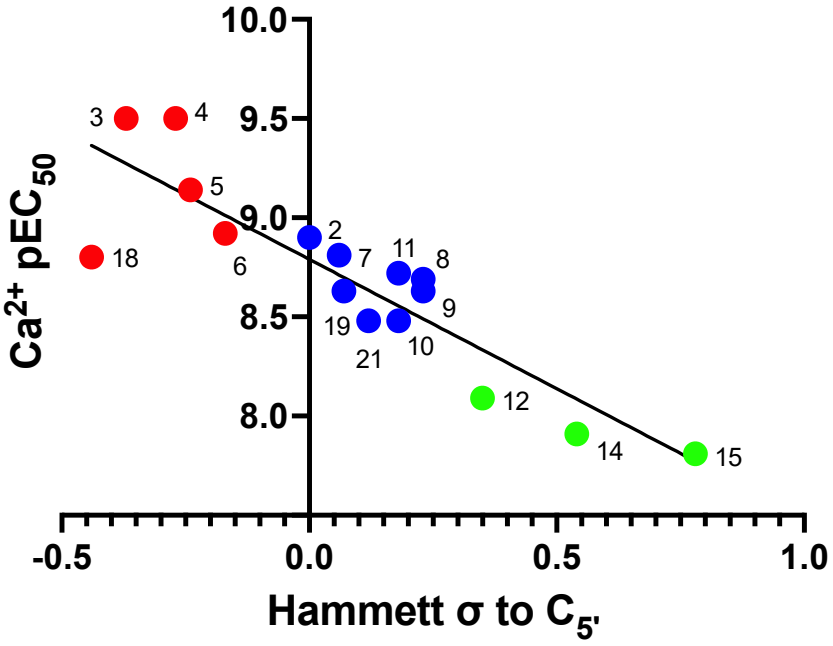
(2) 25N-NB
(3) 25N-NBOH
(4) 25N-NBOMe
(5) 25N-NBOEt
(6) 25N-NBMe
(7) 25N-NBF
(8) 25N-NBCl
(9) 25N-NBBr
(10) 25N-NBI
(11) 25N-NBOCF$_2$H
(12) 25N-NBOCF$_3$
(14) 25N-NBCF$_3$
(15) 25N-NBNO$_2$
(19) 25N-NB-2-MeO-3-F
(21) 25N-NB-3-OH

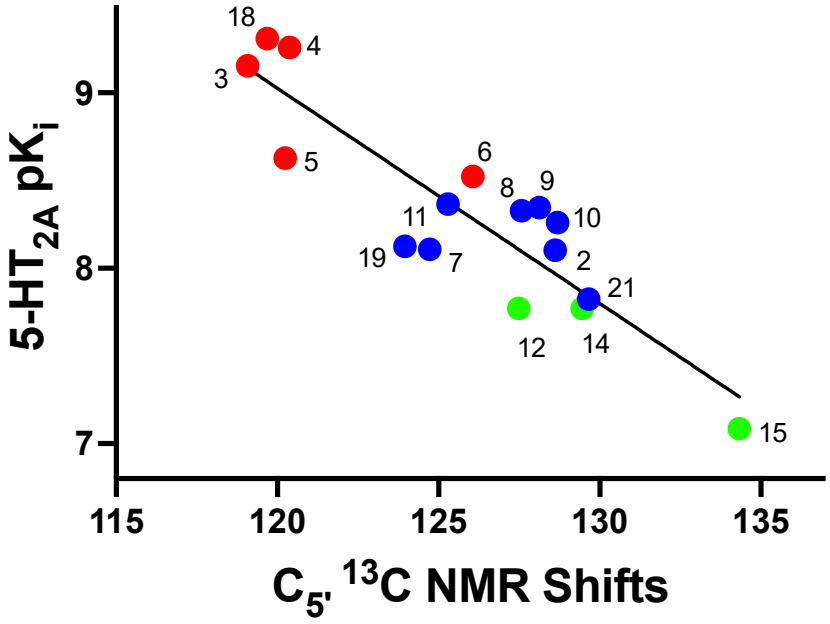
Pearson r = -0.8867, P <0.0001
R^2 = 0.7861



25N-NB-2-OH-3-Me
18

(2) 25N-NB
(3) 25N-NBOH
(4) 25N-NBOMe
(5) 25N-NBOEt
(6) 25N-NBMe
(7) 25N-NBF
(8) 25N-NBCl
(9) 25N-NBBr
(10) 25N-NBI
(11) 25N-NBOCF$_2$H
(12) 25N-NBOCF$_3$
(14) 25N-NBCF$_3$
(15) 25N-NBNO$_2$
(18) 25N-NB-2-OH-3-Me
(19) 25N-NB-2-MeO-3-F
(21) 25N-NB-3-OH



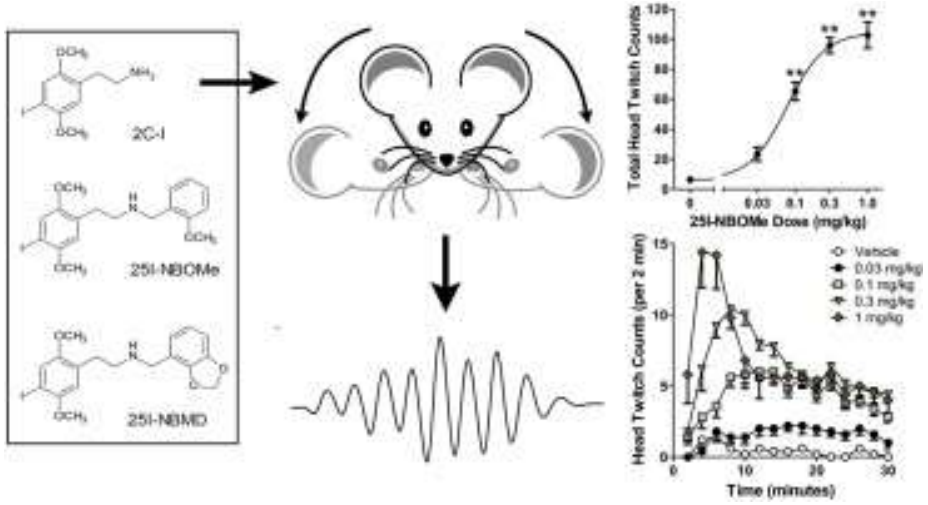


(2) 25N-NB
(3) 25N-NBOH
(4) 25N-NBOMe
(5) 25N-NBOEt
(6) 25N-NBMe
(7) 25N-NBF
(8) 25N-NBCl
(9) 25N-NBBr
(10) 25N-NBI
(11) 25N-NBOCF$_2$H
(12) 25N-NBOCF$_3$
(14) 25N-NBCF$_3$
(15) 25N-NBNO$_2$
(18) 25N-NB-2-OH-3-Me
(19) 25N-NB-2-MeO-3-F
(21) 25N-NB-3-OH

R^2 = 0.7868
Pearson r = -0.88790, p <0.0001

R^2 = 0.8009
Pearson r = -0.8949, p <0.0001

Mouse Head Twitch Response



Halberstadt and Geyer. *Neuropharmacology.* 2014

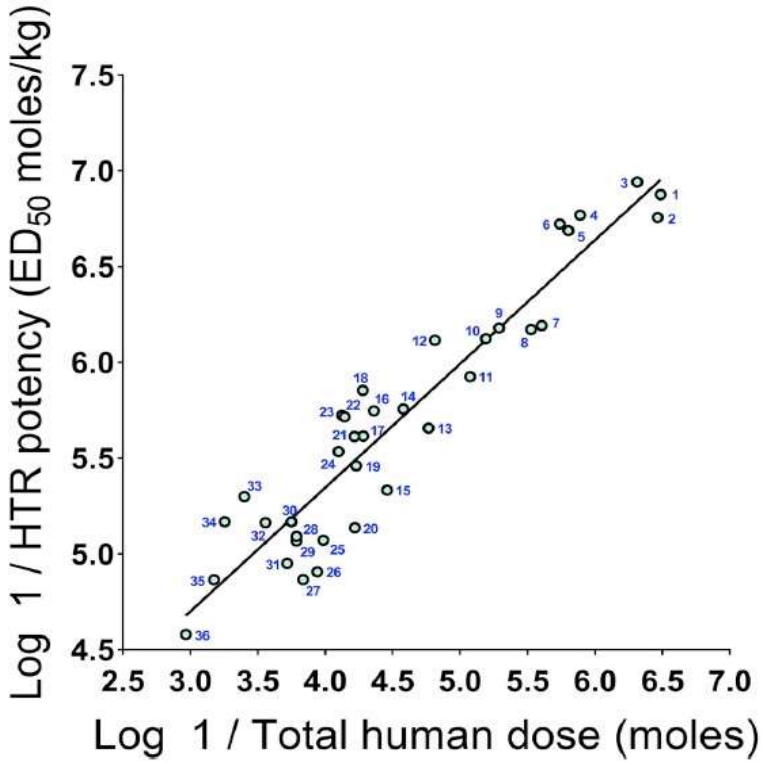
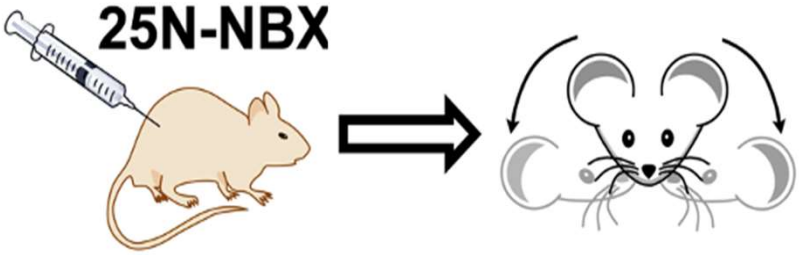


Fig. 2. Hallucinogen potencies in humans and mice are robustly correlated (r = 0.9448). The numbers correspond to the agents in Table 4. Potencies in humans are plotted as log 1/total hallucinogenic dose (in moles); potencies in the mouse head-twitch response assay are plotted as log $1/ED_{50}$ (in moles/kg).

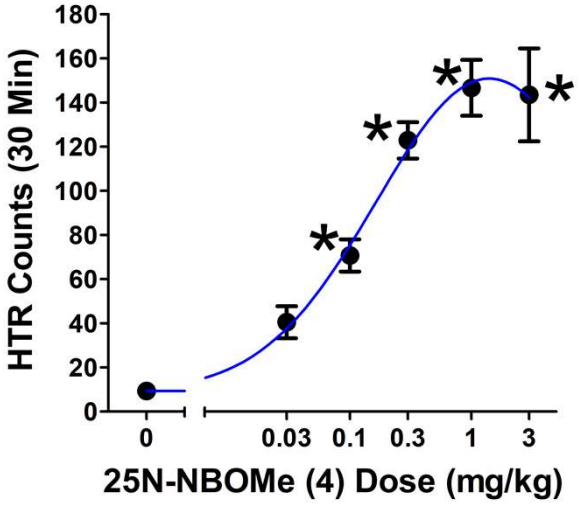
- 5-HT_{2A} agonism leads to HTR and shows high predictive validity for human hallucinogenic effects and potency.
- Compounds that do not cause psychedelic effects (lisuride, 6-F-DET) lack HTR.

Halberstadt et al. *Neuropharmacology.* 2020

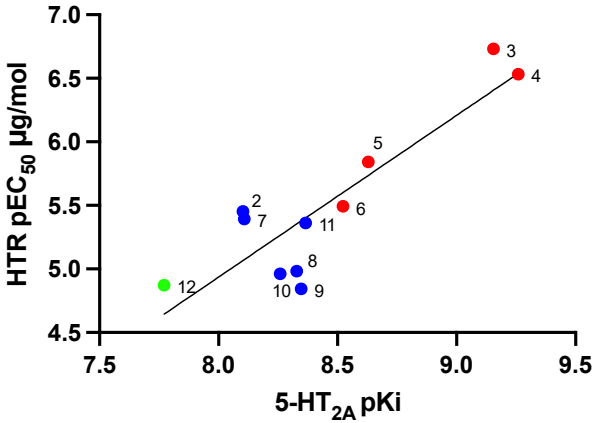


UC San Diego

Dr. Adam Halberstadt



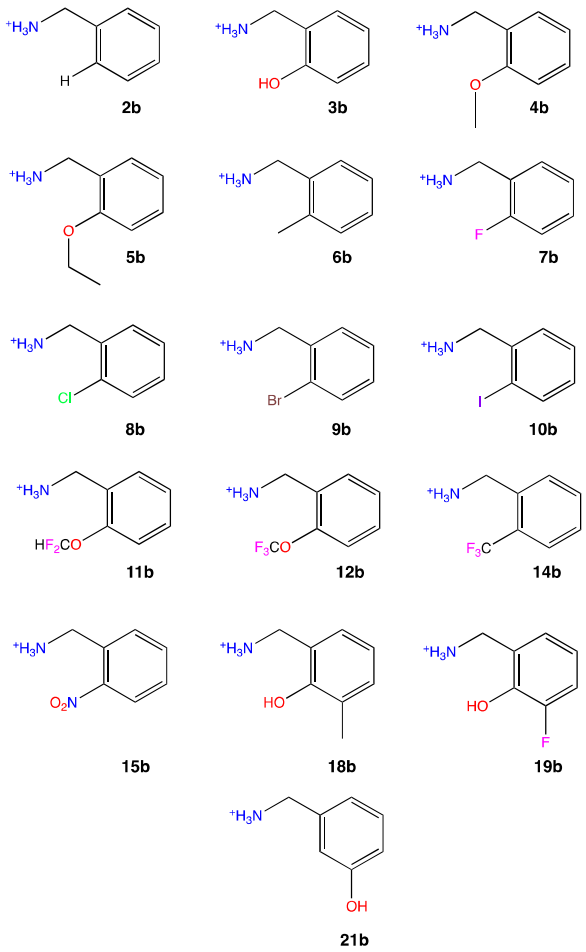
ED_{50}: 0.29 µmol/kg
95% CI: 0.20-0.43



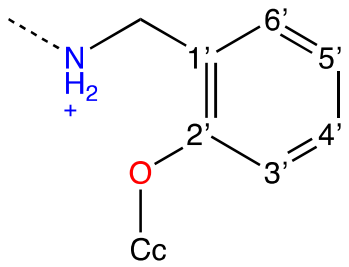
Pearson r = 0.8771, p = 0.0002
R^2 = 0.7694

(2) 25N-NB
(3) 25N-NBOH
(4) 25N-NBOMe
(5) 25N-NBOEt
(6) 25N-NBMe
(7) 25N-NBF
(8) 25N-NBCl
(9) 25N-NBBr
(10) 25N-NBI
(11) 25N-NBOCF$_2$H
(12) 25N-NBOCF$_3$

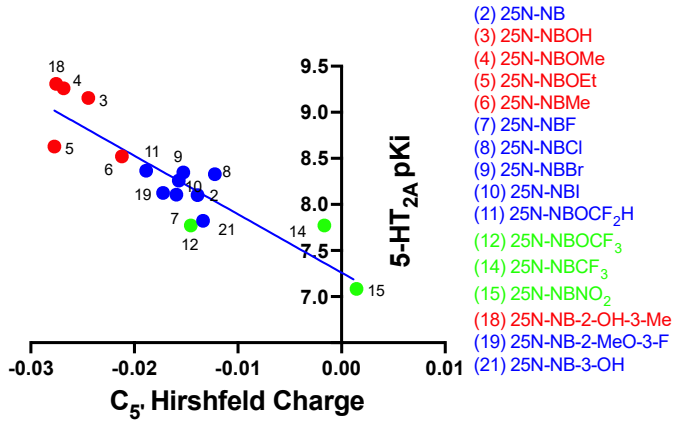
A.


2b
3b
4b
5b
6b
7b
8b
9b
10b
11b
12b
14b
15b
18b
19b
21b

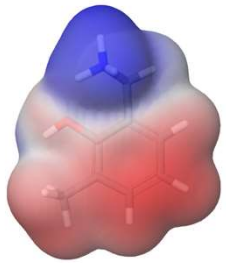
B.


N
H2
+
1'
2'
3'
4'
5'
6'
O
Cc

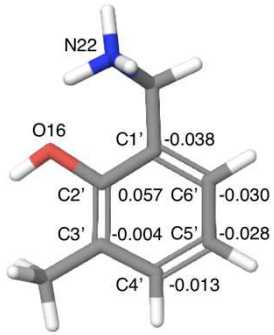
C.


(2) 25N-NB
(3) 25N-NBOH
(4) 25N-NBOMe
(5) 25N-NBOEt
(6) 25N-NBMe
(7) 25N-NBF
(8) 25N-NBCl
(9) 25N-NBBr
(10) 25N-NBI
(11) 25N-NBOCF2H
(12) 25N-NBOCF3
(14) 25N-NBCF3
(15) 25N-NBNO2
(18) 25N-NB-2-OH-3-Me
(19) 25N-NB-2-MeO-3-F
(21) 25N-NB-3-OH
5-HT2A pKi
9.5
9.0
8.5
8.0
7.5
7.0
-0.03
-0.02
-0.01
0.00
0.01
C5' Hirshfeld Charge

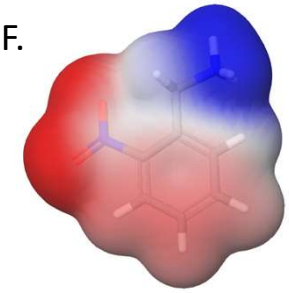
D.



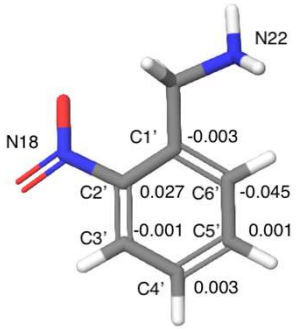
E.


N22
O16
C1'
-0.038
C2'
0.057
C6'
-0.030
C3'
-0.004
C5'
-0.028
C4'
-0.013

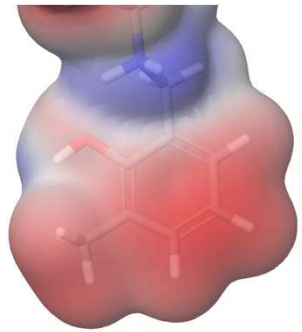
F.



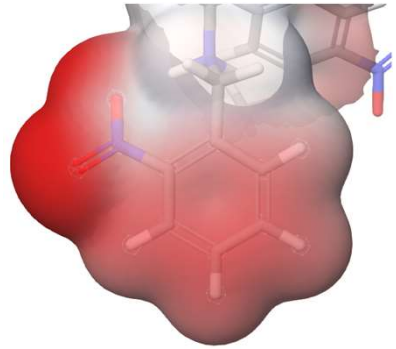
G.


N22
N18
C1'
-0.003
C2'
0.027
C6'
-0.045
C3'
-0.001
C5'
0.001
C4'
0.003

H.



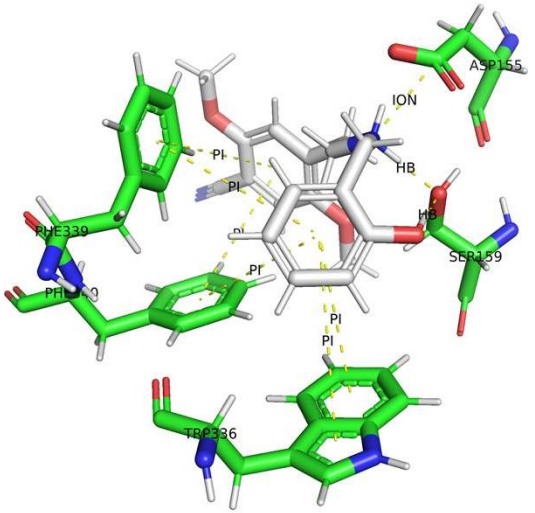
I.



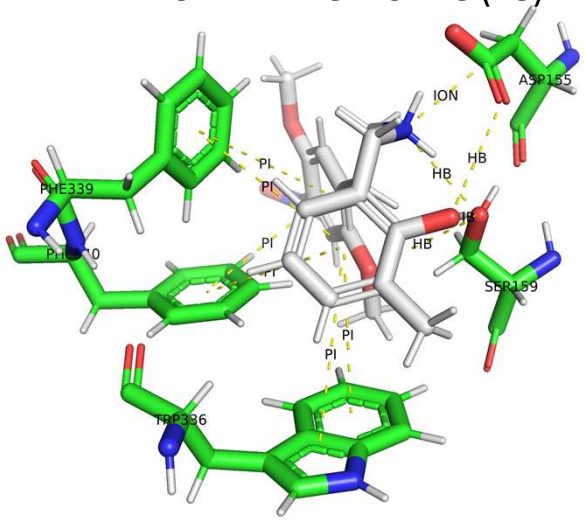
Induced Fit Docking at 5-HT_{2A}

Dr. Randy Zauhar

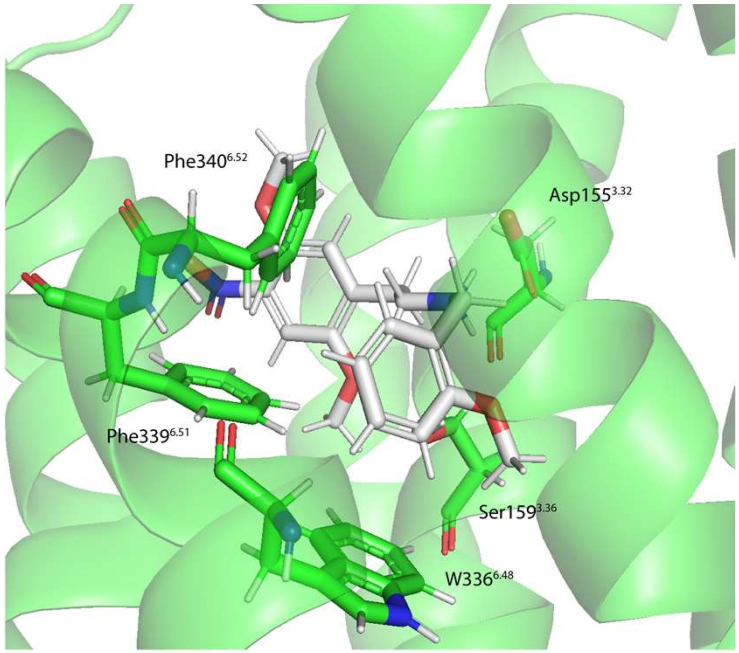
A. 25CN-NBOH

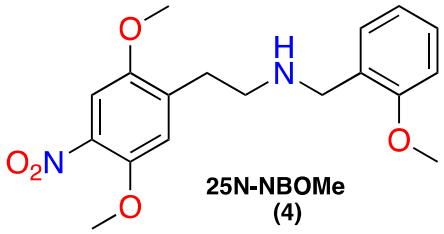


B. 25N-NB-2-OH-3-Me (18)



A.

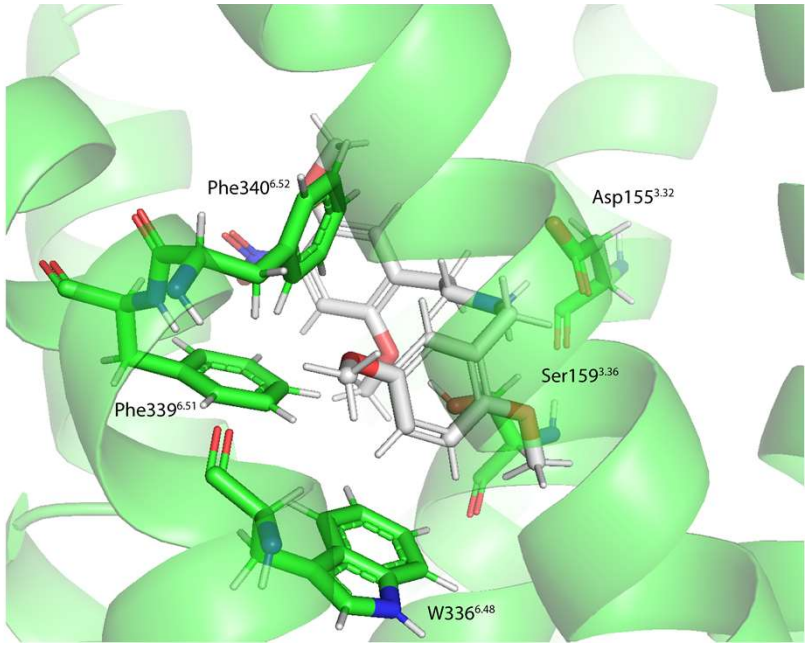


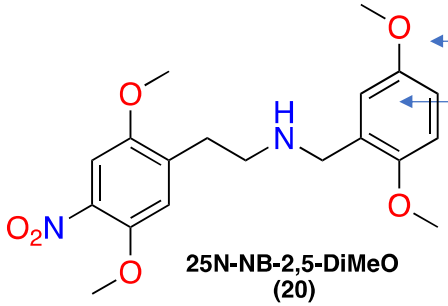


25N-NBOMe
(4)

5-HT_{2A} K_i = 0.55 ± 0.25

B.



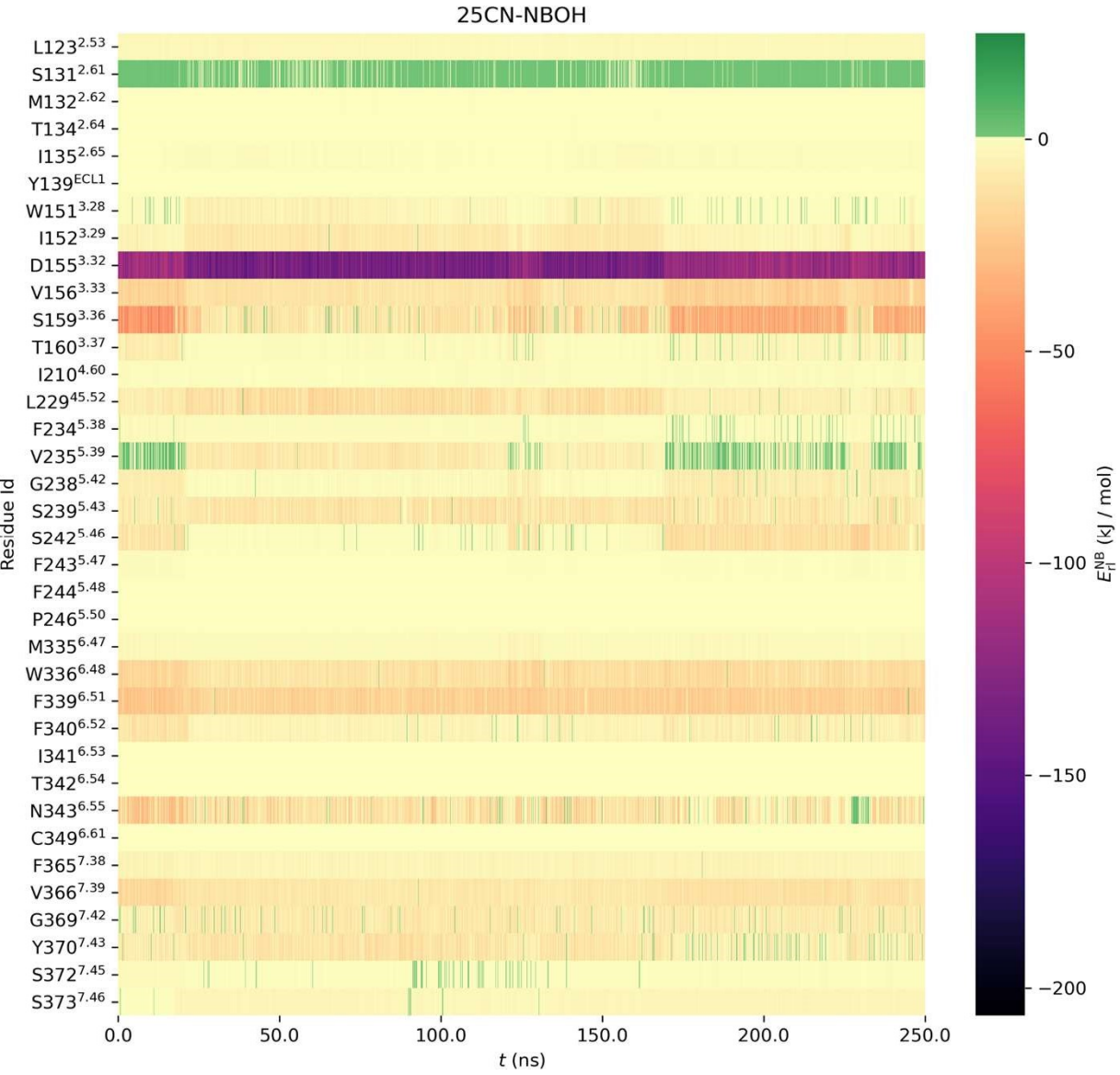


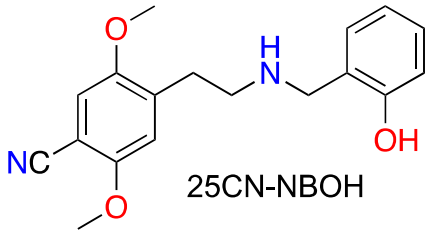
Steric bulk in C_5 position

Electron deficient

25N-NB-2,5-DiMeO
(20)

5-HT_{2A} K_i = 235.8 ± 33.5





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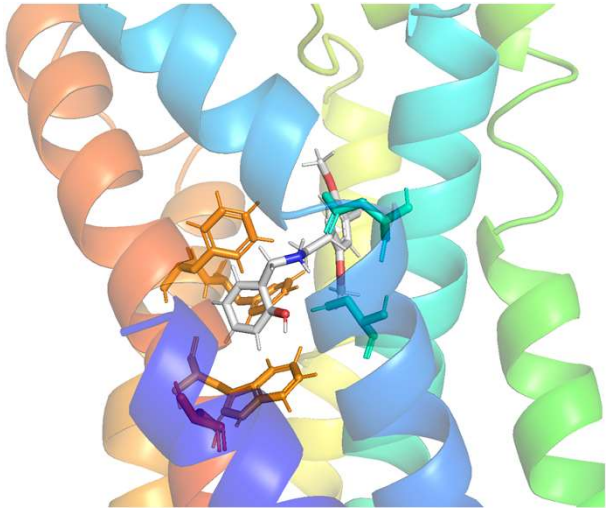
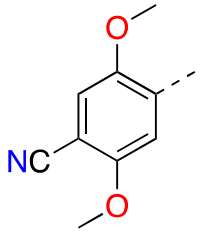
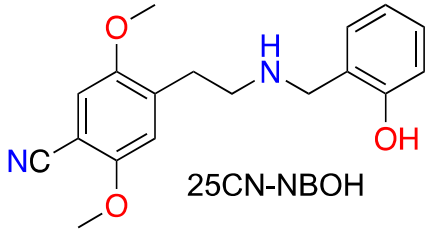
University of the Sciences

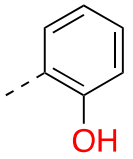




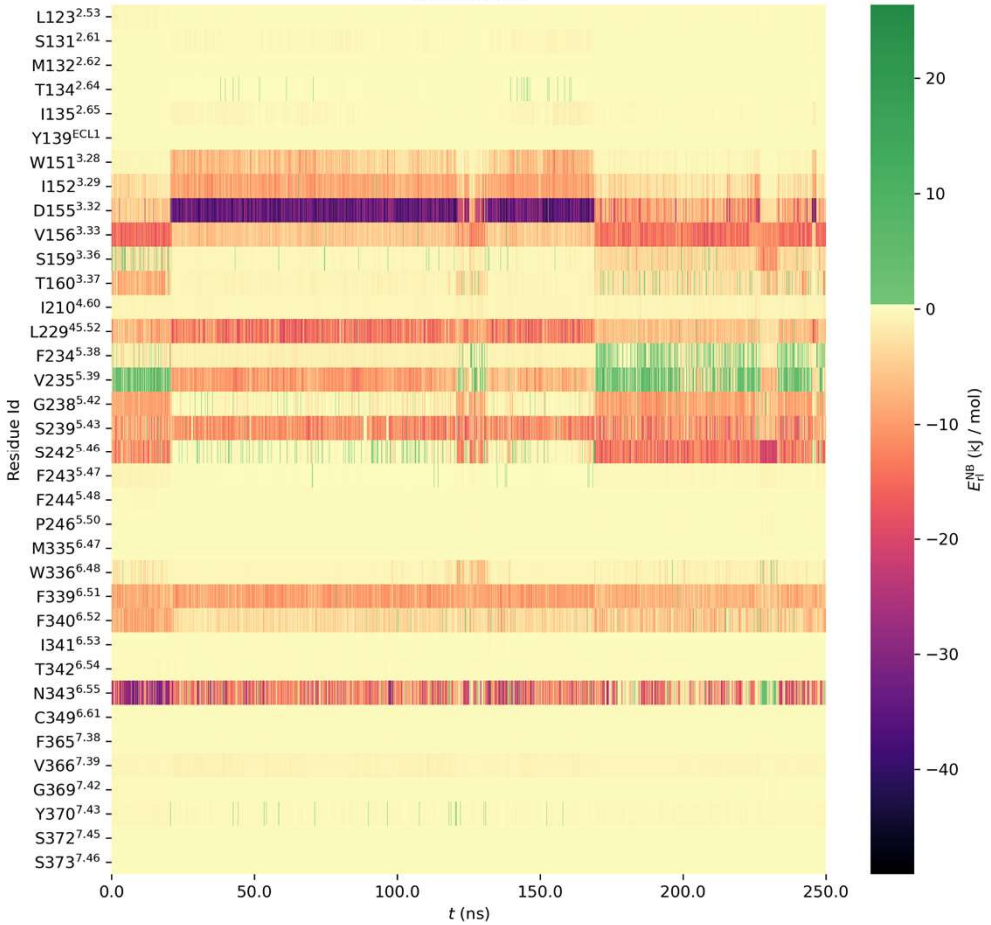
25CN-NBOH

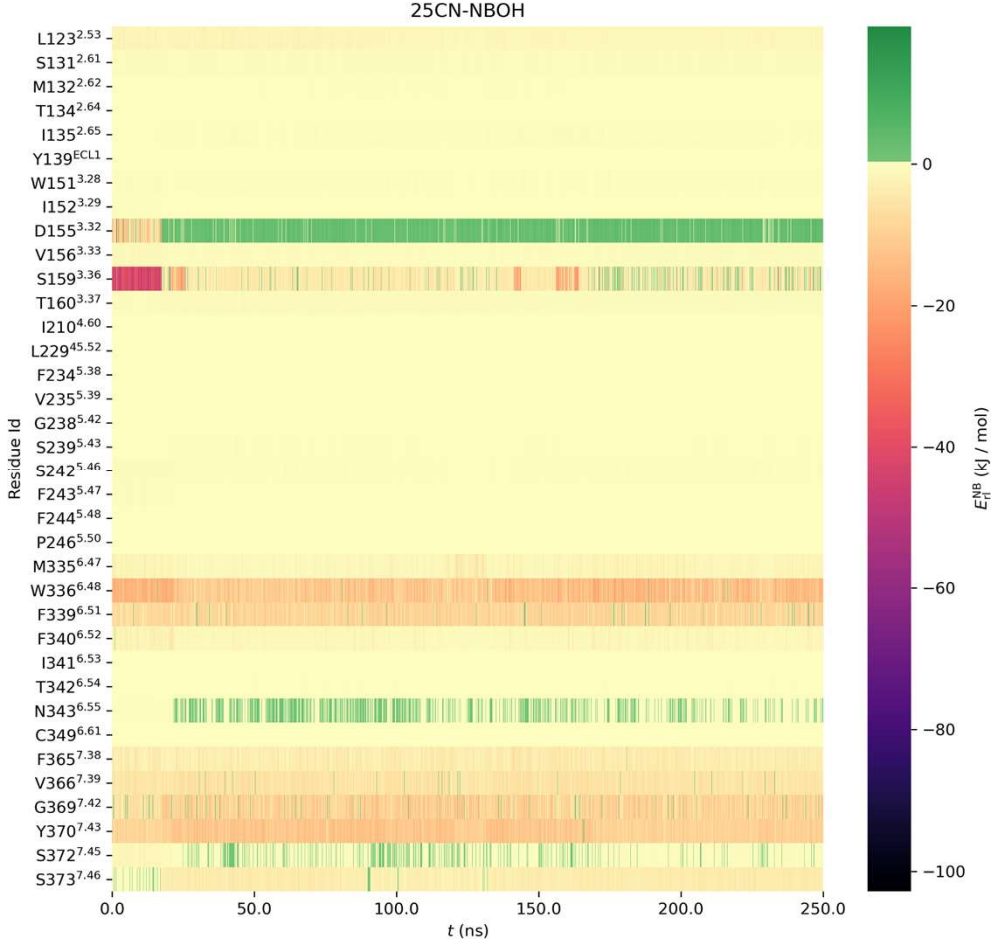


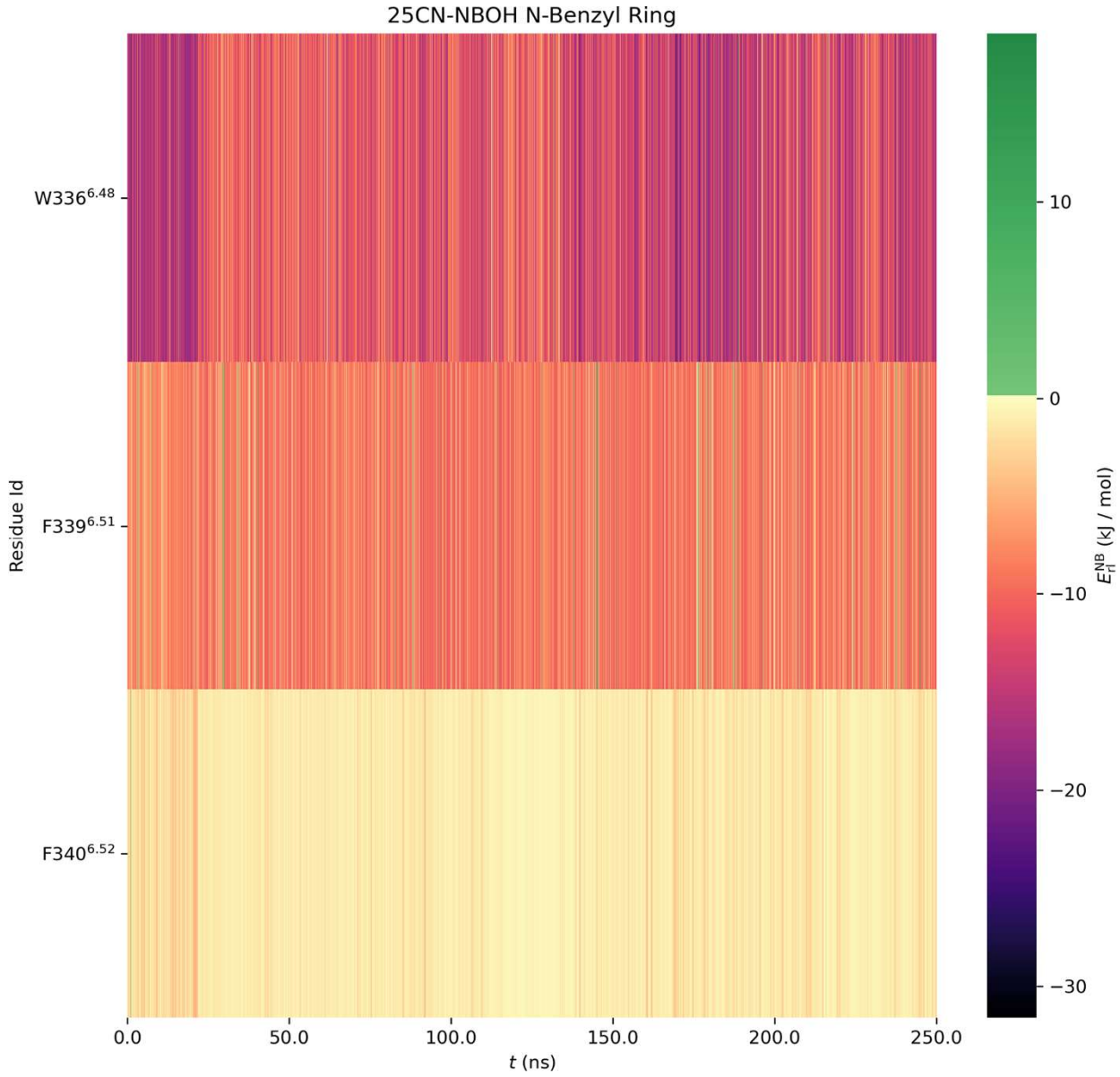
25CN-NBOH

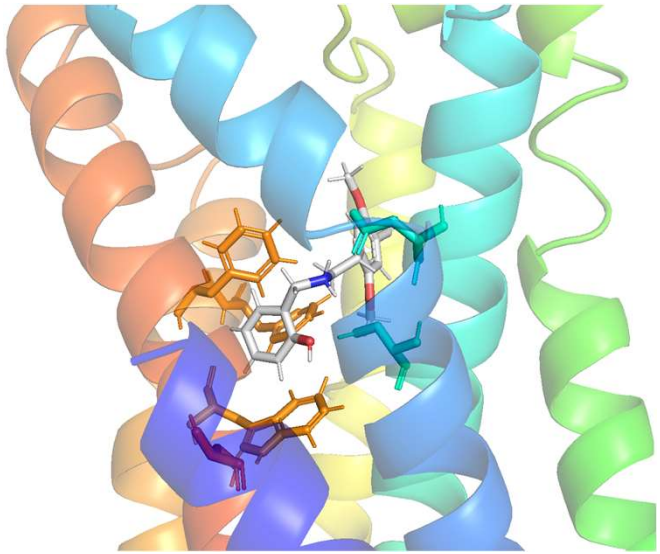


25CN-NBOH






25CN-NBOH N-Benzyl Ring
W336^6.48
F339^6.51
F340^6.52
Residue Id
0.0
50.0
100.0
150.0
200.0
250.0
t (ns)
10
0
−10
−20
−30
E_rl^NB (kJ / mol)



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Lab Members

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- Elena Ferreras
- Matt Preto

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