Directing Bitopic or Bivalent Molecules to Dopamine D_3 Receptors for the Treatment of Substance Use Disorders

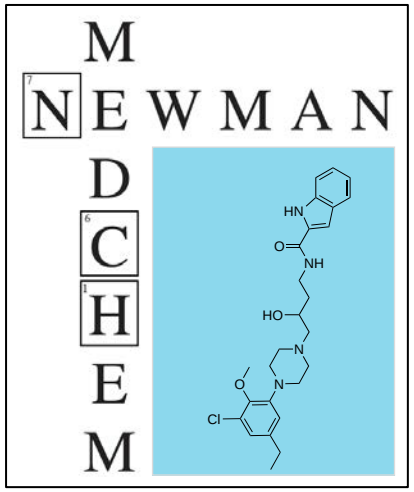
Amy Hauck Newman, Ph.D.

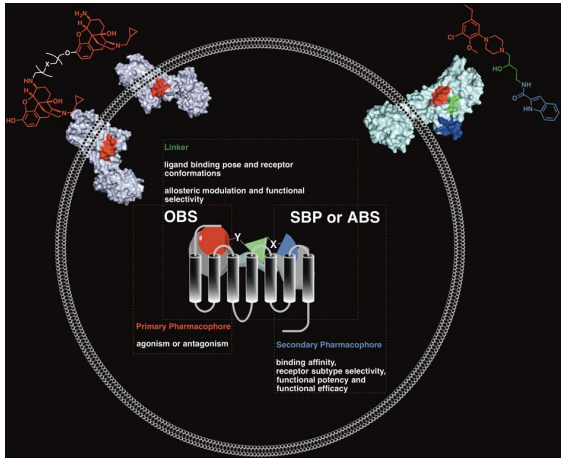
Scientific Director

NIDA – IRP

http://irp.drugabuse.gov/Newman.php

@anewman2014





Penn-Yale Addiction Center of Excellence
Addictions Seminar Series
April 12, 2021

Journal of Medicinal Chemistry

Perspective

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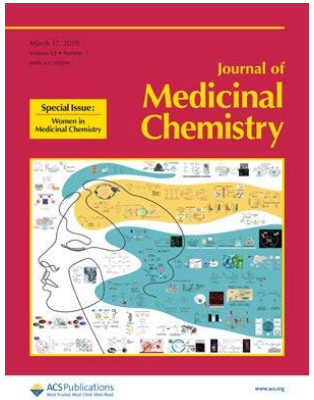
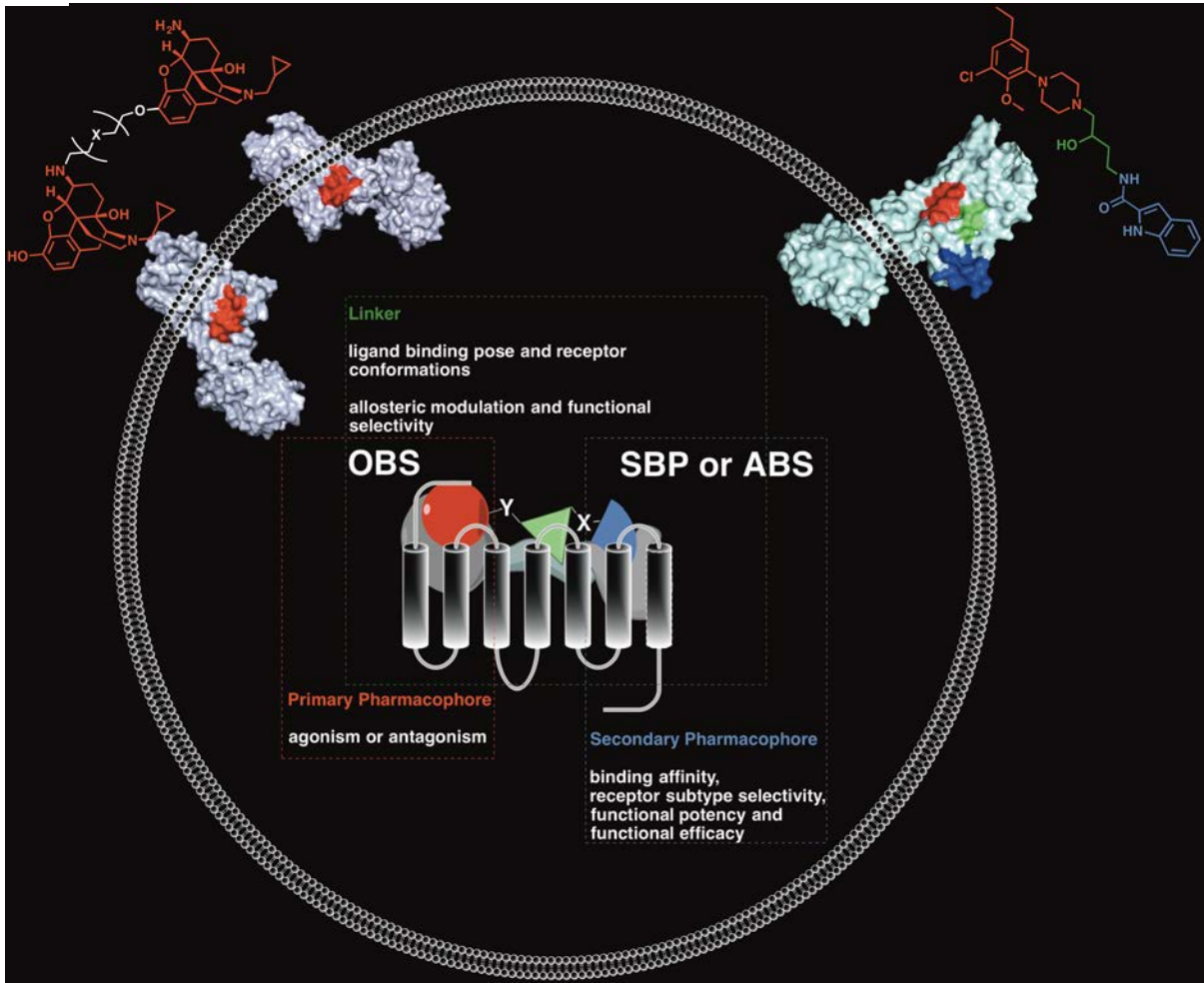
2016 Philip S. Portoghese Medicinal Chemistry Lectureship: Designing Bivalent or Bitopic Molecules for G-Protein Coupled Receptors. The Whole Is Greater Than the Sum of Its Parts

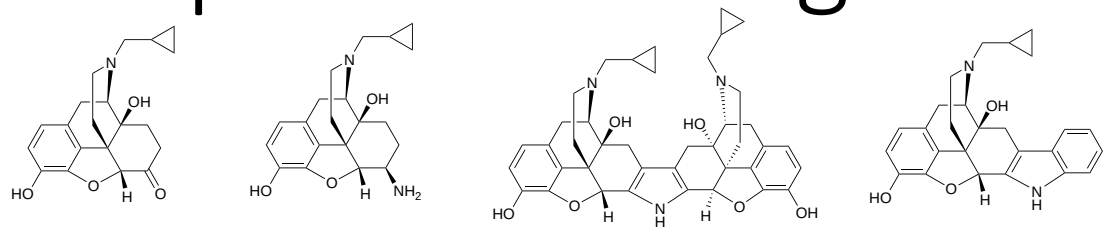
Amy Hauck Newman,*,† Francisco O. Battiti,† and Alessandro Bonifazi†

J. Med. Chem. **2020**, *62(20)* 9061-9078.





The concept: bivalent ligands

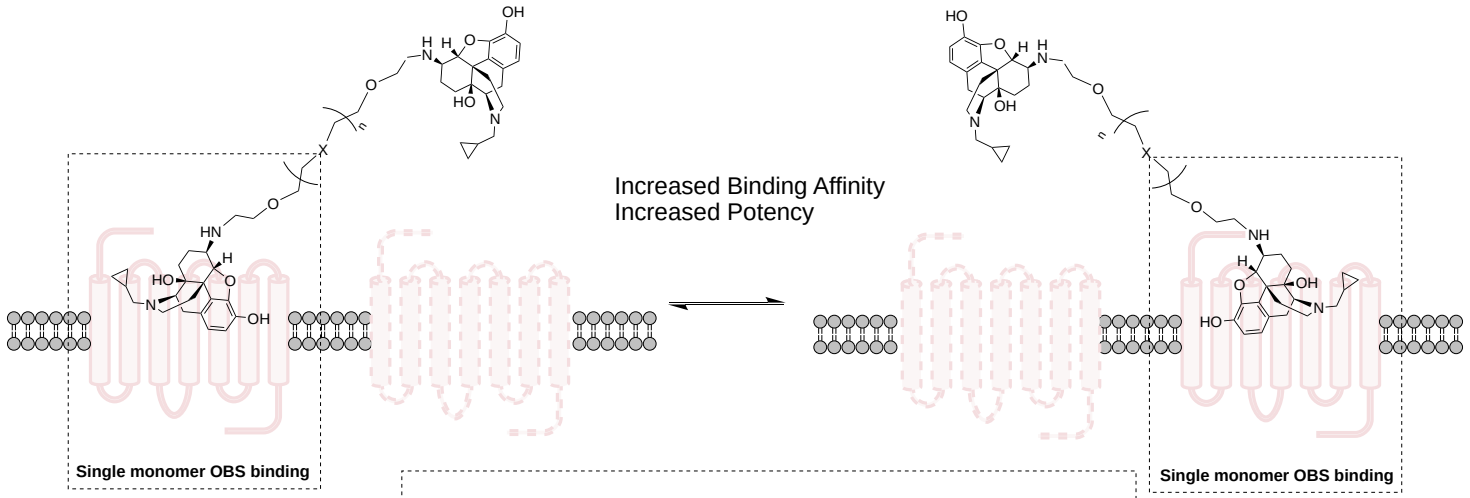


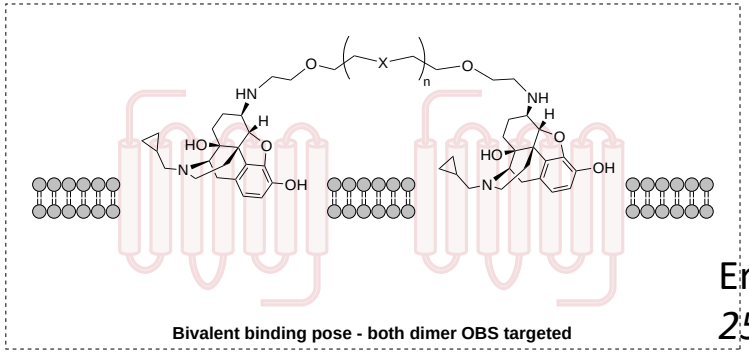
(**1**), (-)-Naltrexone

(**2**), β-Naltrexamine

(**3**), Norbinaltorphimine

(**4**), Naltrindole





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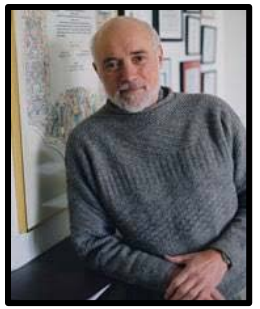
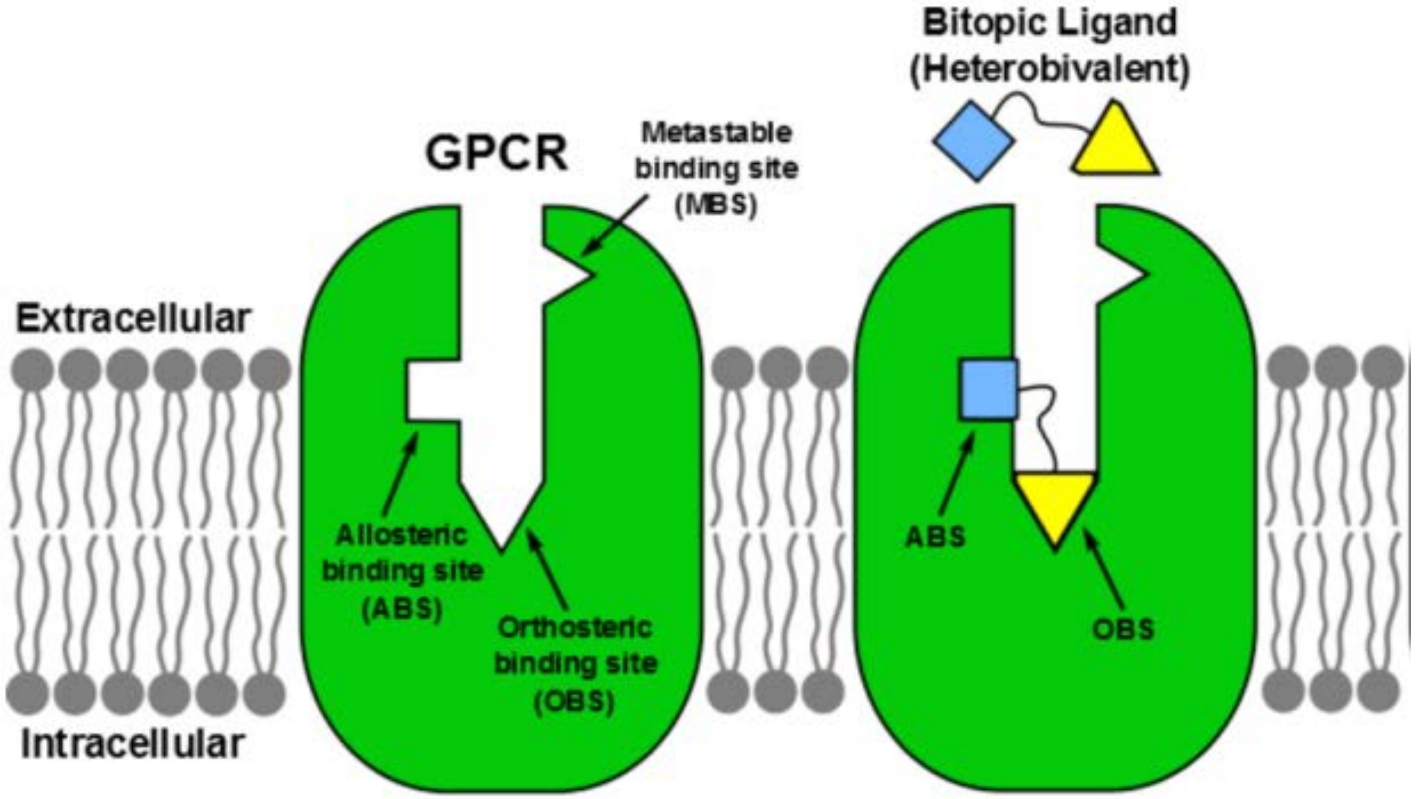


Phil Portoghese

Erez, M.; Takemori, A. E.; Portoghese, P. S. *J. Med. Chem.* 1982, *25*, 847.; Portoghese, P. S. et al., *Life Sci.* 1982, *31*, 1283.

The concept: bitopic ligands



Bridging the gap: bitopic ligands of G-protein-coupled receptors

J. Robert Lane, Patrick M. Sexton, and Arthur Christopoulos

TIPS 2013, 34, 59.

The design:

Linker

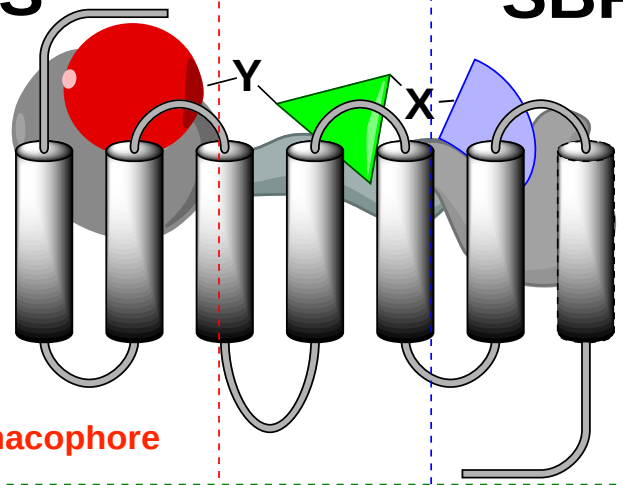
Responsible for unique binding interactions

Helps optimal ligand binding pose and consequent receptor conformations

Often responsible for modulating allosteric profiles and enhancing functional selectivity

OBS

SBP or ABS



Primary Pharmacophore

Often inspired by classic orthosteric ligands

Often responsible for agonism or antagonism

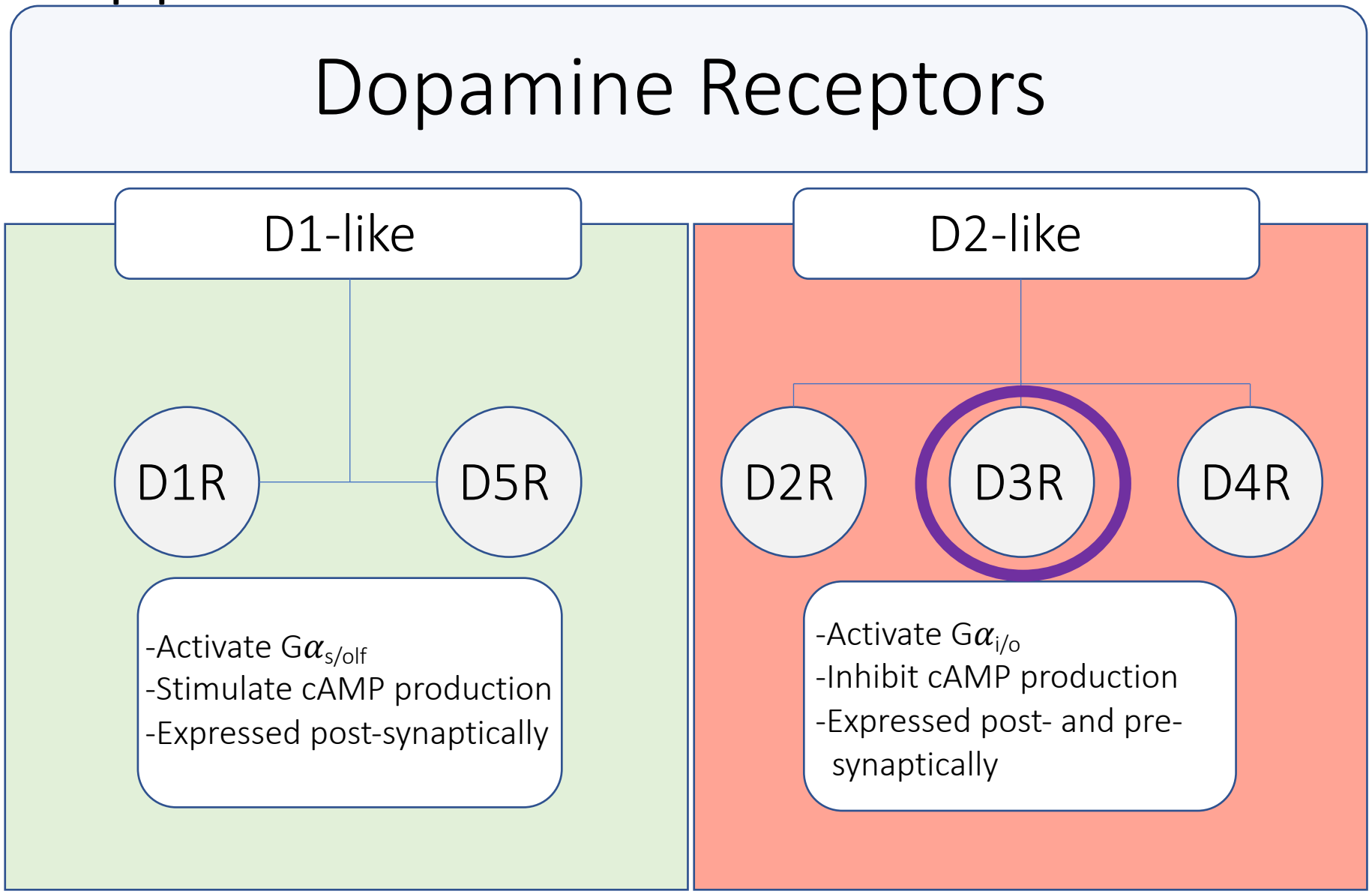
Secondary Pharmacophore

Often inspired by allosteric ligands or aromatic synthons

Often responsible for modulating binding affinity, selectivity, functional potency and efficacy

Newman, et al., J. Med. Chem. **2020**, *62(20)* 9061-9078

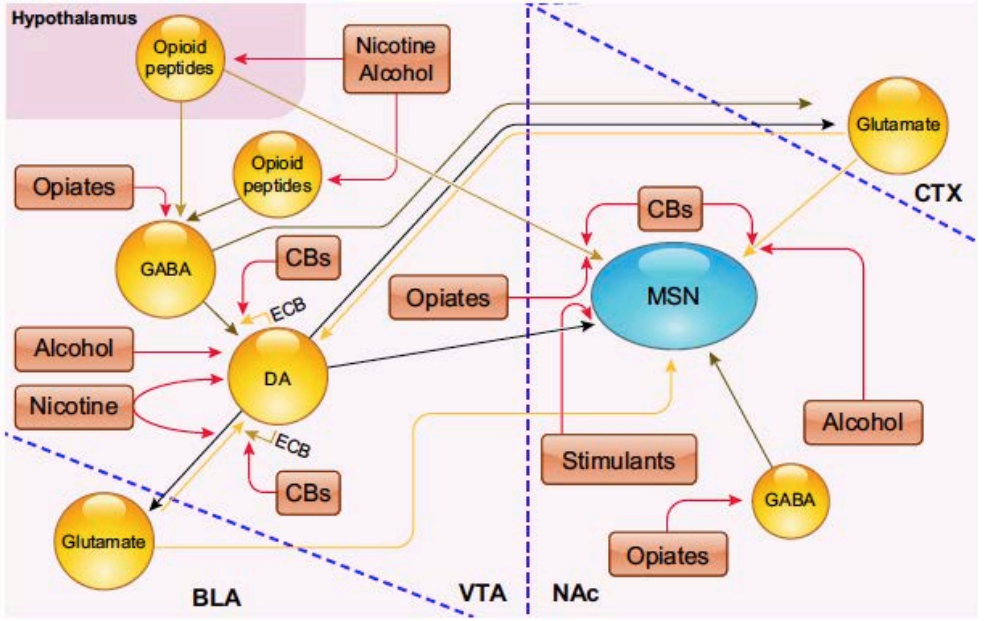
The application:



Why D_3R?

- Unlike D_2R, D_3R expression is largely localized in the mesolimbic brain region

- Reward experience induced by drugs of abuse is intrinsically connected to increased dopamine levels within this pathway
- D_3R blockade results in inhibition/reduction of self-administration of nicotine, cocaine, alcohol, methamphetamine, and heroin (Heidbreder and Newman, 2010)



Volkow et al. *Physiol Rev* (2019)

Heidbreder and Newman, *Ann. N.Y. Acad. Sci.* (2010)
Koob et al. *Science* (1997)

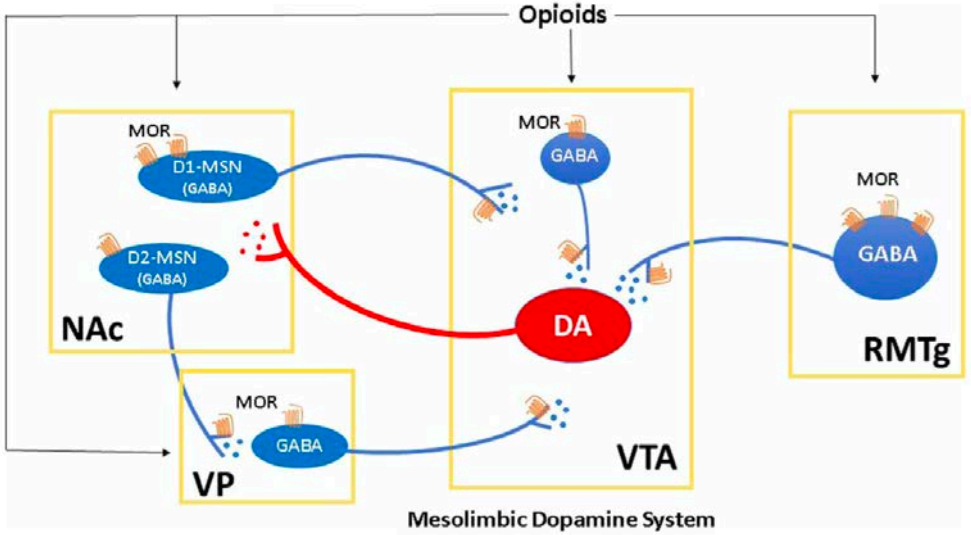
NIDA's medication development priorities in response to the Opioid Crisis: ten most wanted

Kurt Rasmussen[1], David A. White[1] and Jane B. Acri[1]

Neuropsychopharmacology (2019) 44:657–659; https://doi.org/10.1038/s41386-018-0292-5

Table 1. NIDA's DTMC ten most wanted pharmacological mechanisms for the rapid development of therapeutics in response to the Opioid Crisis

NIDA's DTMC ten most wanted
Orexin-1 or 1/2 antagonists or NAMs [17–19]
Kappa opioid antagonists or NAMs [20, 21]
GABA-B agonists or PAMs [22, 23]
Muscarinic M5 antagonists or NAMs [24, 25]
AMPA antagonists, NAMs or PAMs [26–28]
NOP/ORL agonists, antagonists, NAMs or PAMs [29–31]
mGluR2/3 agonists or PAMs [32–34]
Ghrelin antagonists or NAMs [35, 36]
Dopamine D3 partial agonists, PAMs, antagonists or NAMs [37, 38]
Cannabinoid CB-1 antagonists or NAMs [39, 40]



Dopamine D3 receptor-based medication development for the treatment of opioid use disorder: Rationale, progress, and challenges

Ewa Galaj, Amy Hauck Newman, Zheng-Xiong Xi*

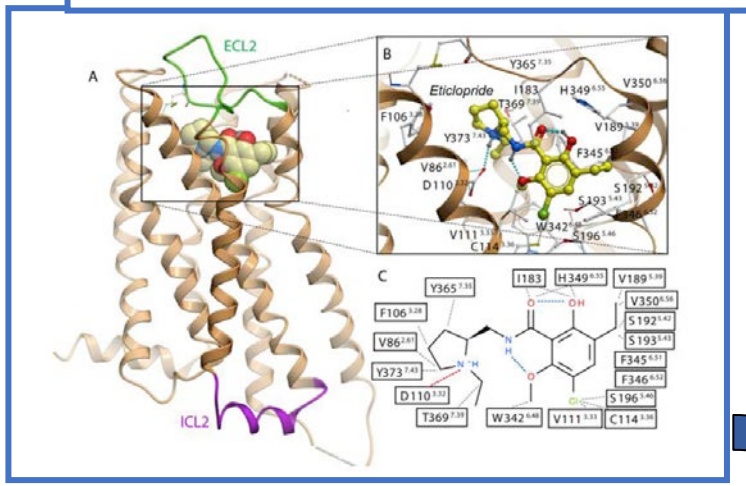
Neuroscience and Biobehavioral Reviews 114 (2020) 38–52

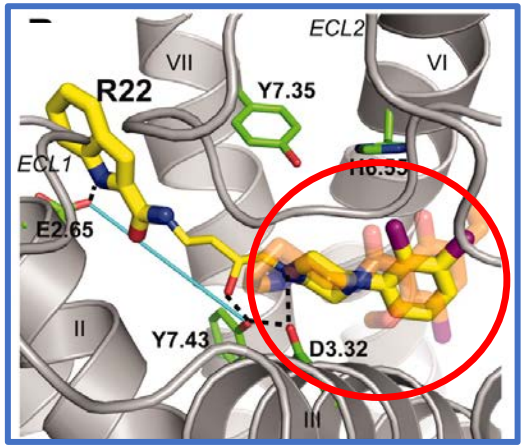
Targeting the D_3R receptor for Substance Use Disorders

- Small molecule SAR has led to the discovery of highly selective D_3R ligands,
- The D_3R crystal structure provided a template for structure-based investigation

Structure of the Human Dopamine D3 Receptor in Complex with a D2/D3 Selective Antagonist

Ellen Y. T. Chien,[1] Wei Liu,[1] Qiang Zhao,[1] Vsevolod Katritch,[2] Gye Won Han,[1] Michael A. Hanson,[3] Lei Shi,[4] Amy Hauck Newman,[5] Jonathan A. Javitch,[6] Vadim Cherezov,[1] Raymond C. Stevens[1]*



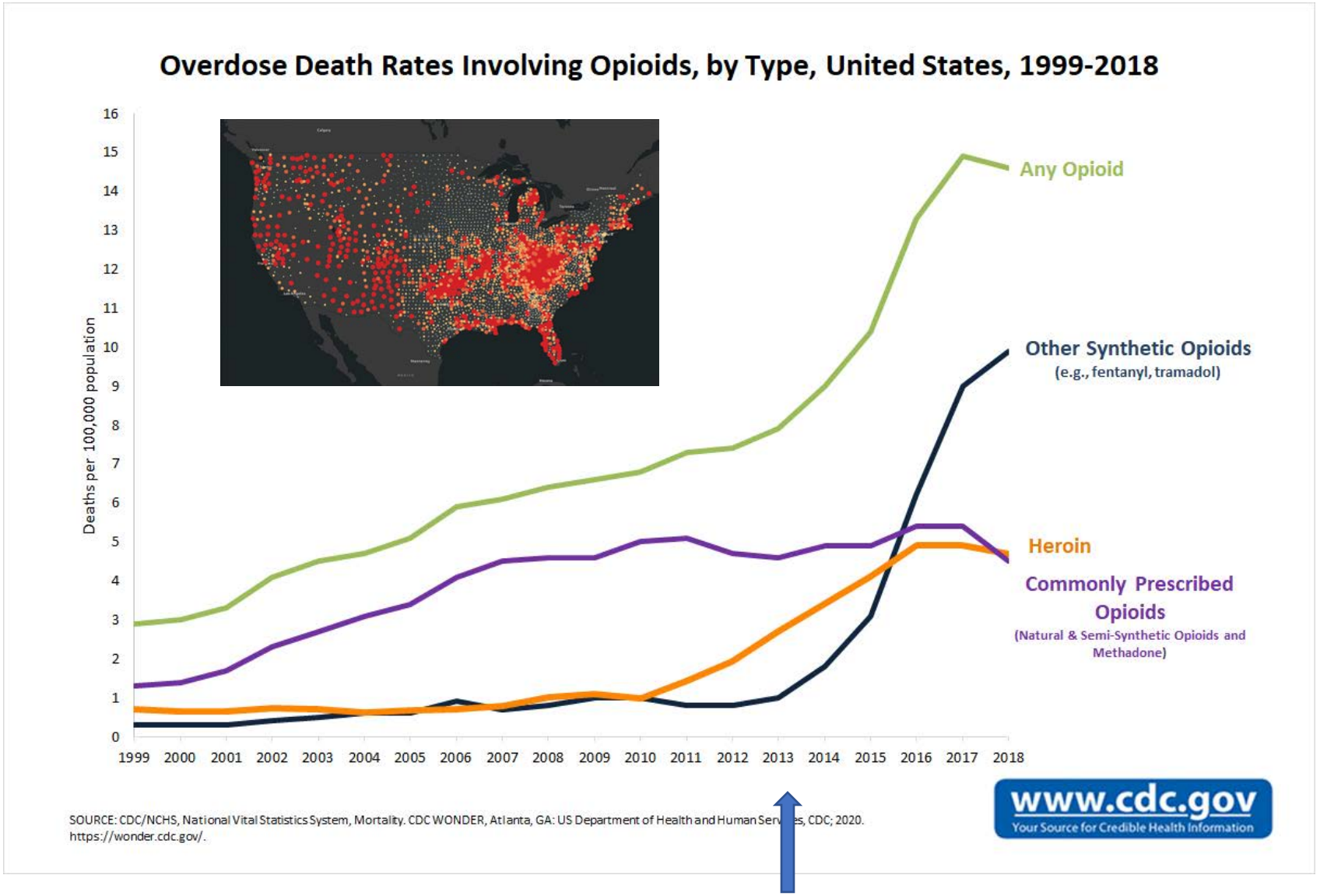


Beyond Small-Molecule SAR: Using the Dopamine D3 Receptor Crystal Structure to Guide Drug Design

Thomas M. Keck*, Caitlin Burzynski*, Lei Shi†, Amy Hauck Newman*,[1]

Advances in Pharmacology, Emerging Targets and Therapeutics for the Treatment of Psychostimulant Drug Abuse, **2014**, *69*, 267-300

The current opioid crisis in the United States



Targeting the D_3R for Opioid Use Disorder

Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

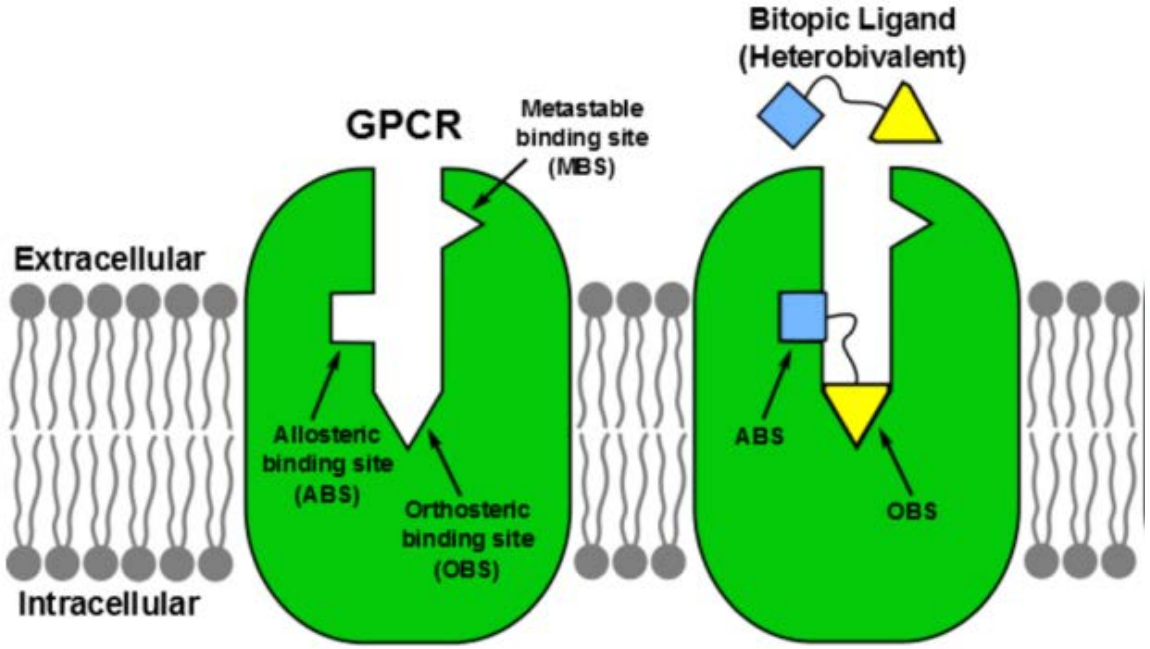
High Affinity Dopamine D_3 Receptor (D_3R)-Selective Antagonists Attenuate Heroin Self-Administration in Wild-Type but not D_3R Knockout Mice

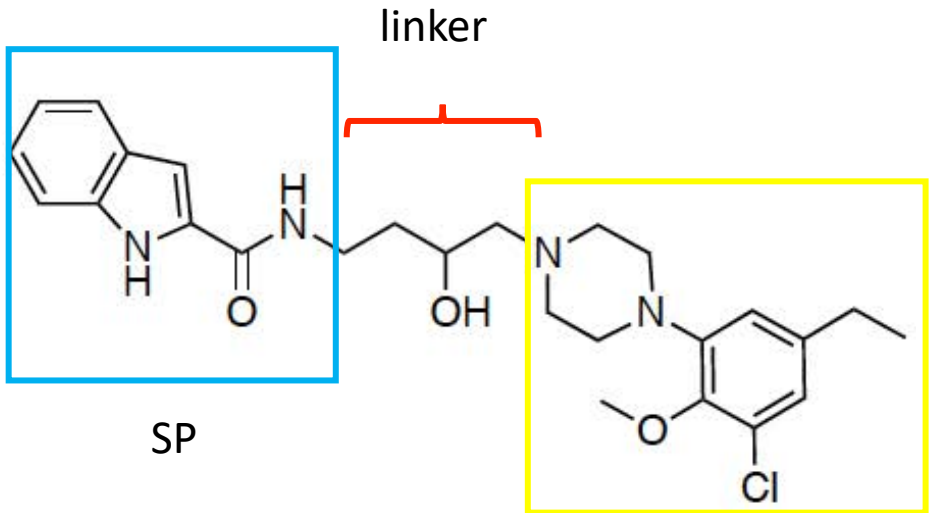
Comfort A. Boateng,[†,⊥] Oluyomi M. Bakare,[†,⊥] Jia Zhan,[†,#] Ashwini K. Banala,[†] Caitlin Burzynski,[†] Elie Pommier,[†] Thomas M. Keck,[†,‡] Prashant Donthamsetti,[∥] Jonathan A. Javitch,[∥] Rana Rais,[§] Barbara S. Slusher,[§] Zheng-Xiong Xi,[†] and Amy Hauck Newman*[,†]

J. Med. Chem. **2015**, *58(15)* 6195-6213.

Comfort Boateng

VK4-116 is a highly selective D_3R antagonist





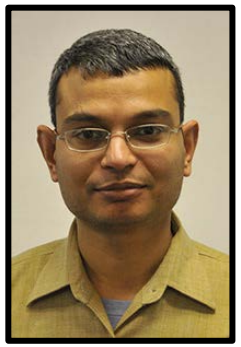
SP

PP

D_3RK_i=6.84 nM
D_2RK_i=11,400 nM

hD_3R IC_{50}=360 nM
hERG IC_{50}=43 μM

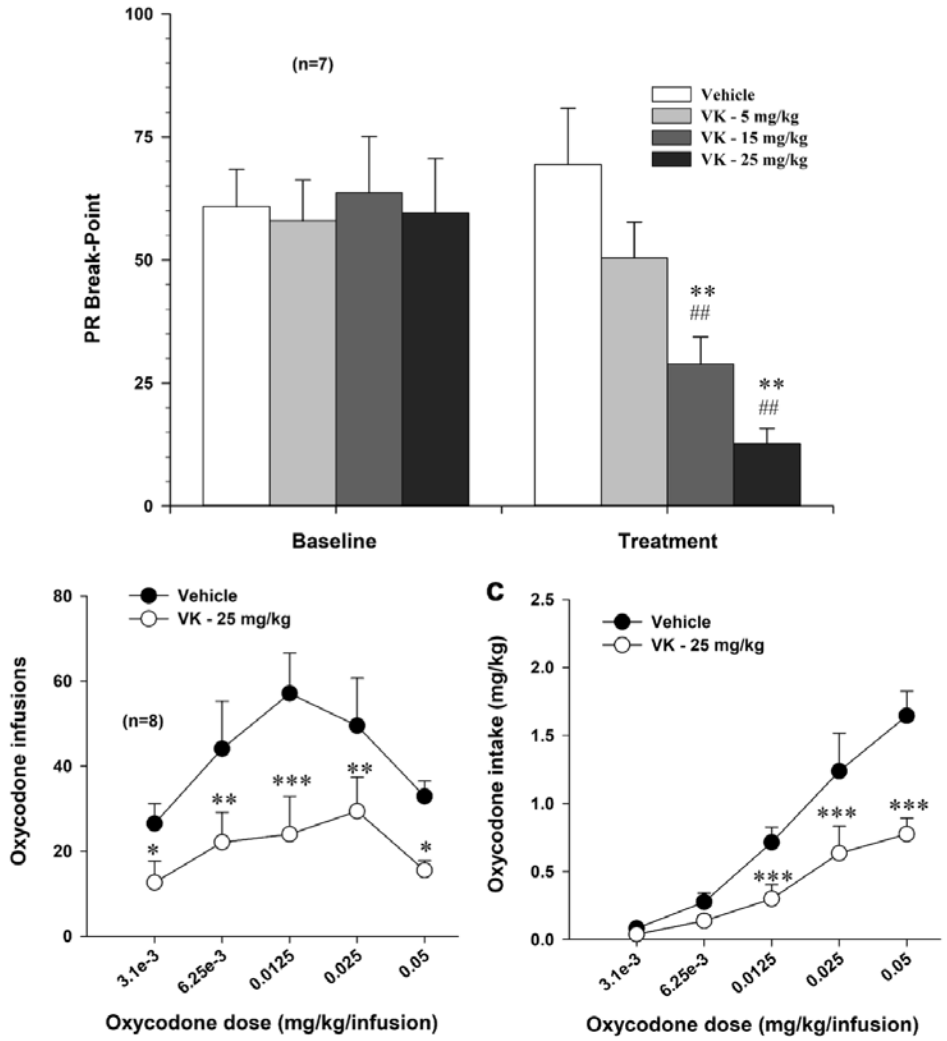
But is it "druggable"?

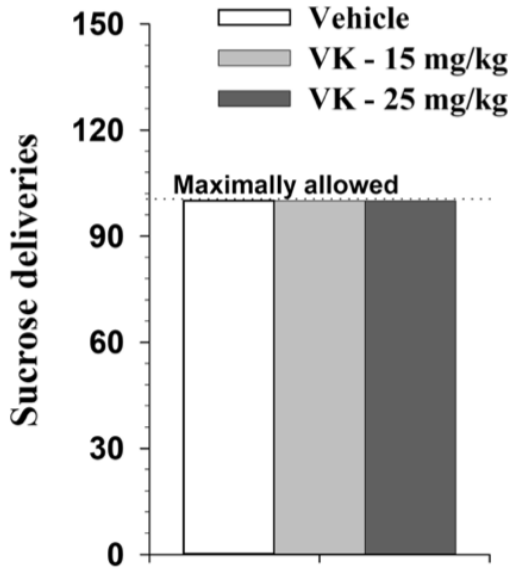


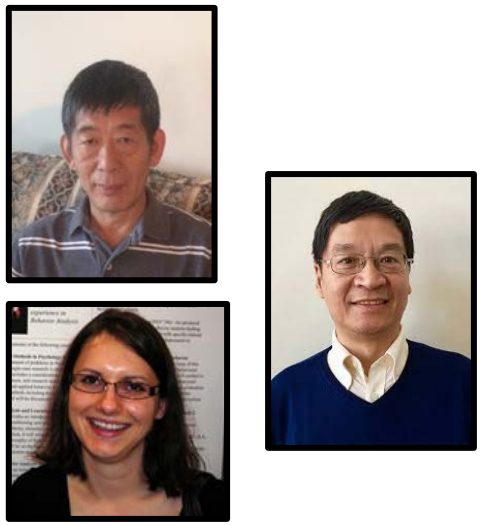
Vivek Kumar

Kumar et al, *JMC,* 2016, 59, 7634.

Pretreatment with VK4-116 dose-dependently decreases oxycodone self administration in rats and had no effect on sucrose



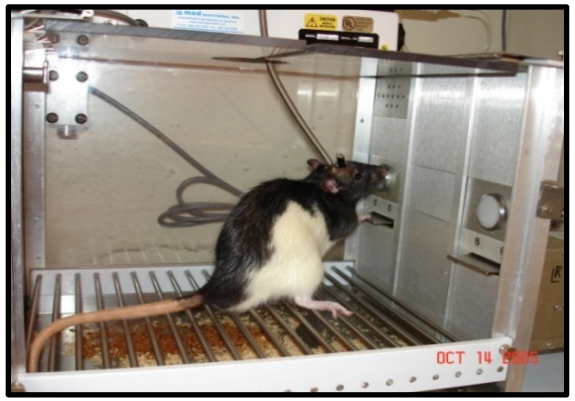


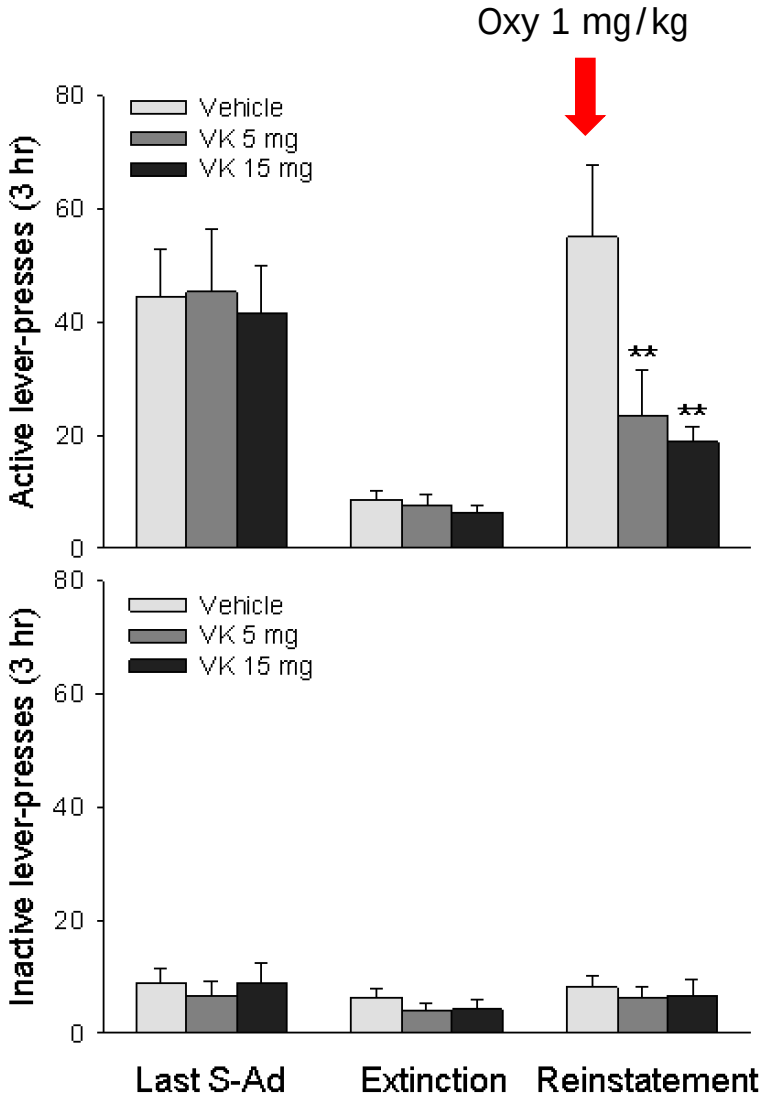


Zhi-Bing You, Ewa Galaj and Zheng-Xiong Xi

You et al., Neuropsychopharmacology, 2019, 44, 1415.

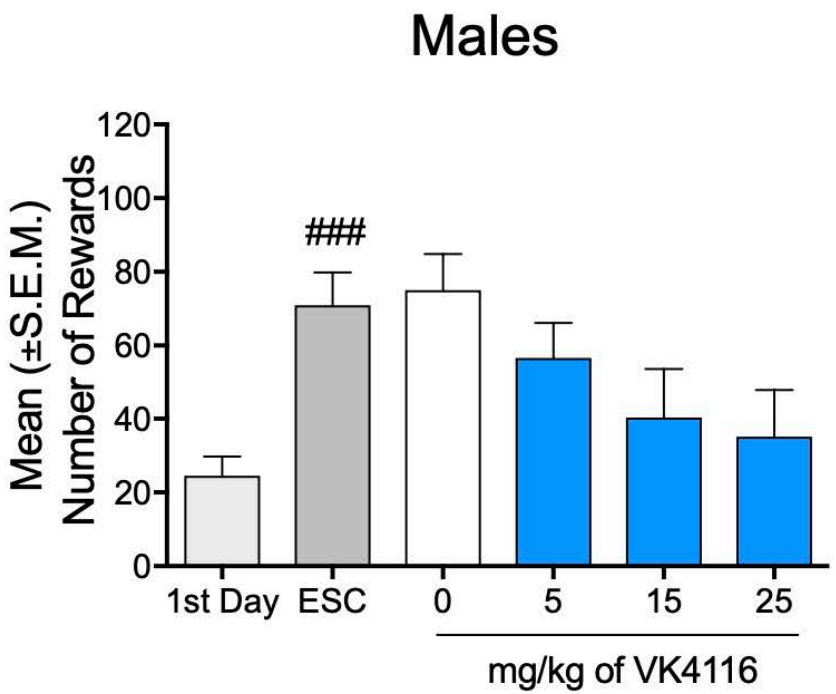
VK4-116 attenuates oxycodone induced reinstatement of drug seeking behavior

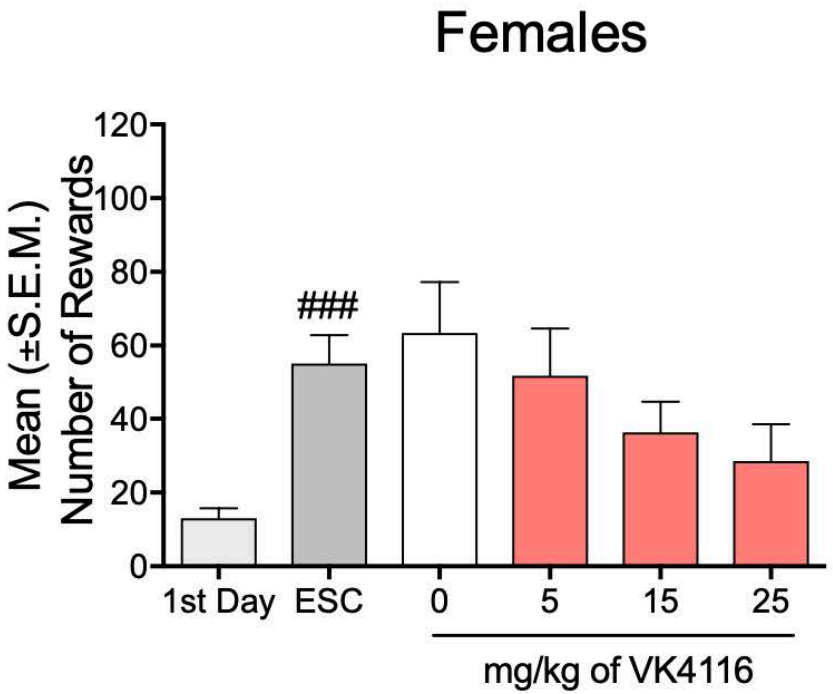




You et al., *Neuropsychopharmacology* 2019, 44, 1415.

VK4-116 prevents dose escalation in oxycodone self administering male and female rats

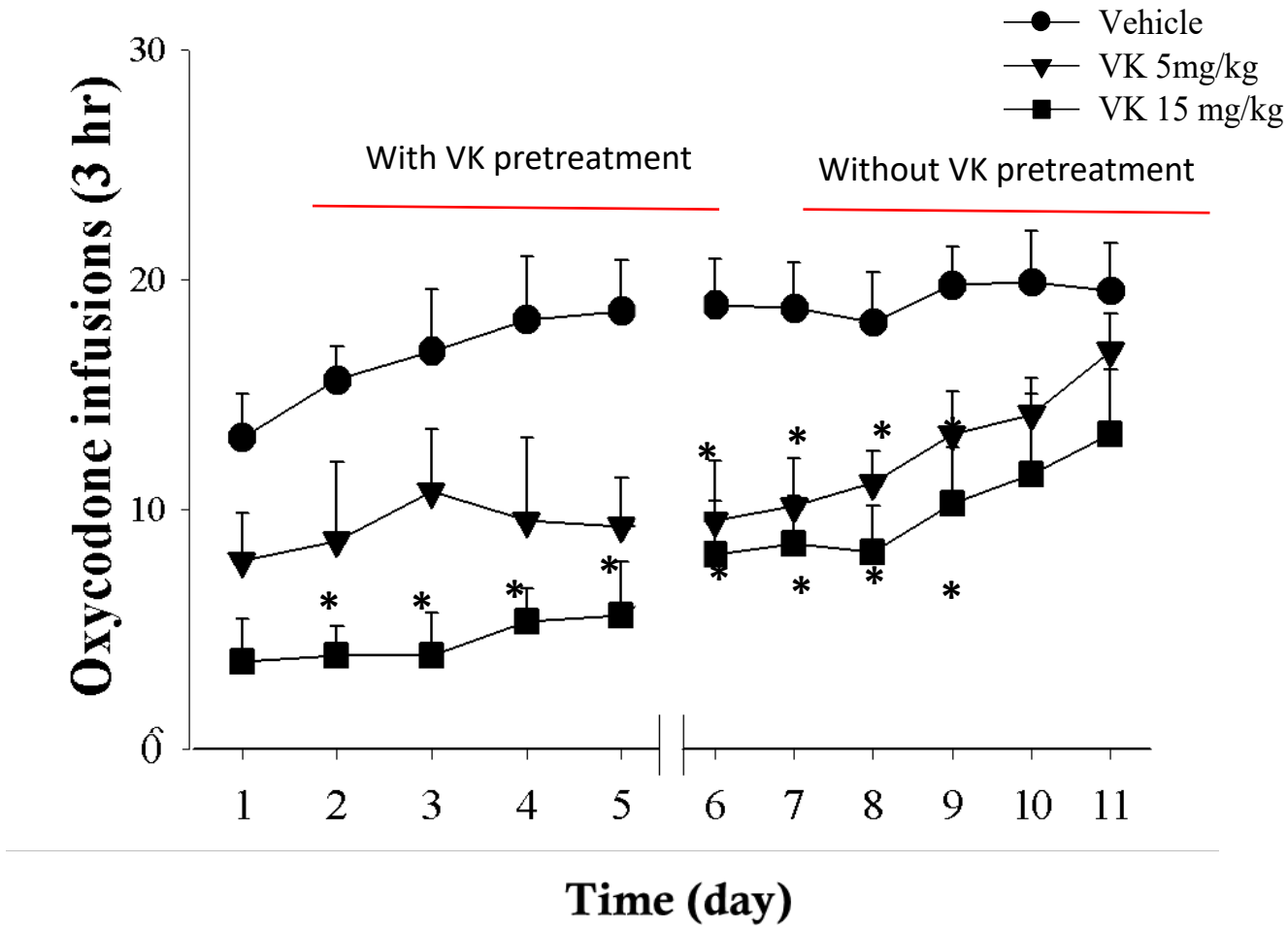




Olivier George & Giordano de Guglielmo, Scripps/UCSD

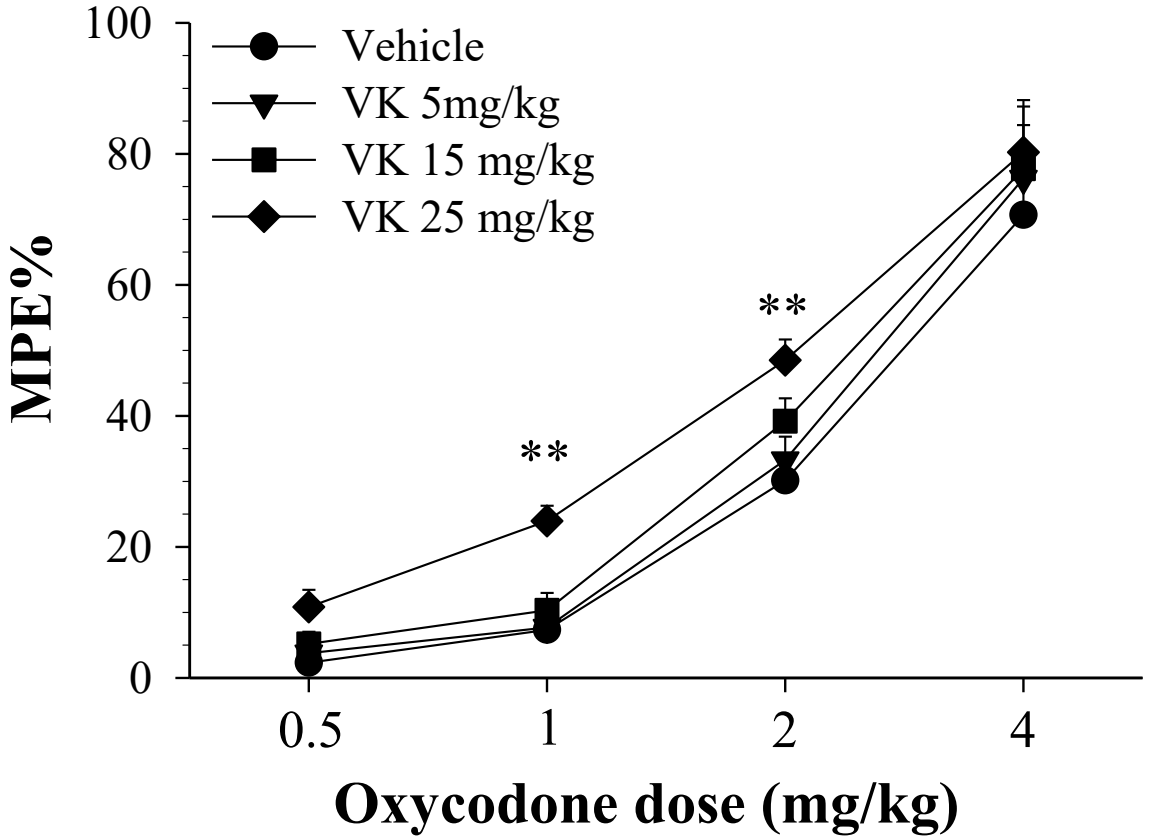
De Guglielmo et l. *Front. Behav. Neurosci* 2020, 23, 292.

Pretreatment with VK4-116 inhibits acquisition of oxycodone self administration



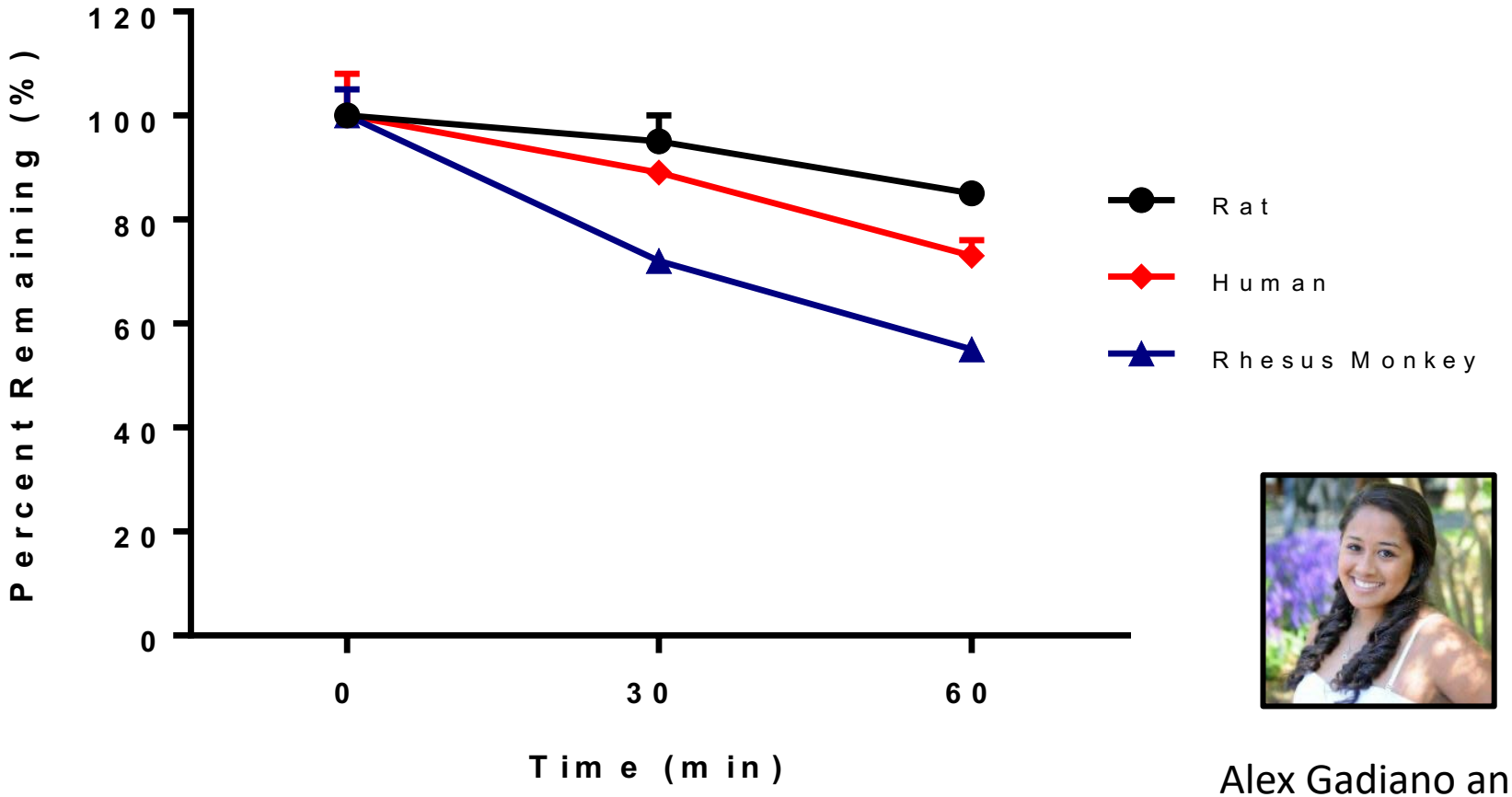
You et al., *Neuropsychopharmacology* 2019, 44, 1415.

Pretreatment with VK4-116 enhances the antinociceptive effects of low doses oxycodone (0.5-2 mg/kg) in the hot plate test



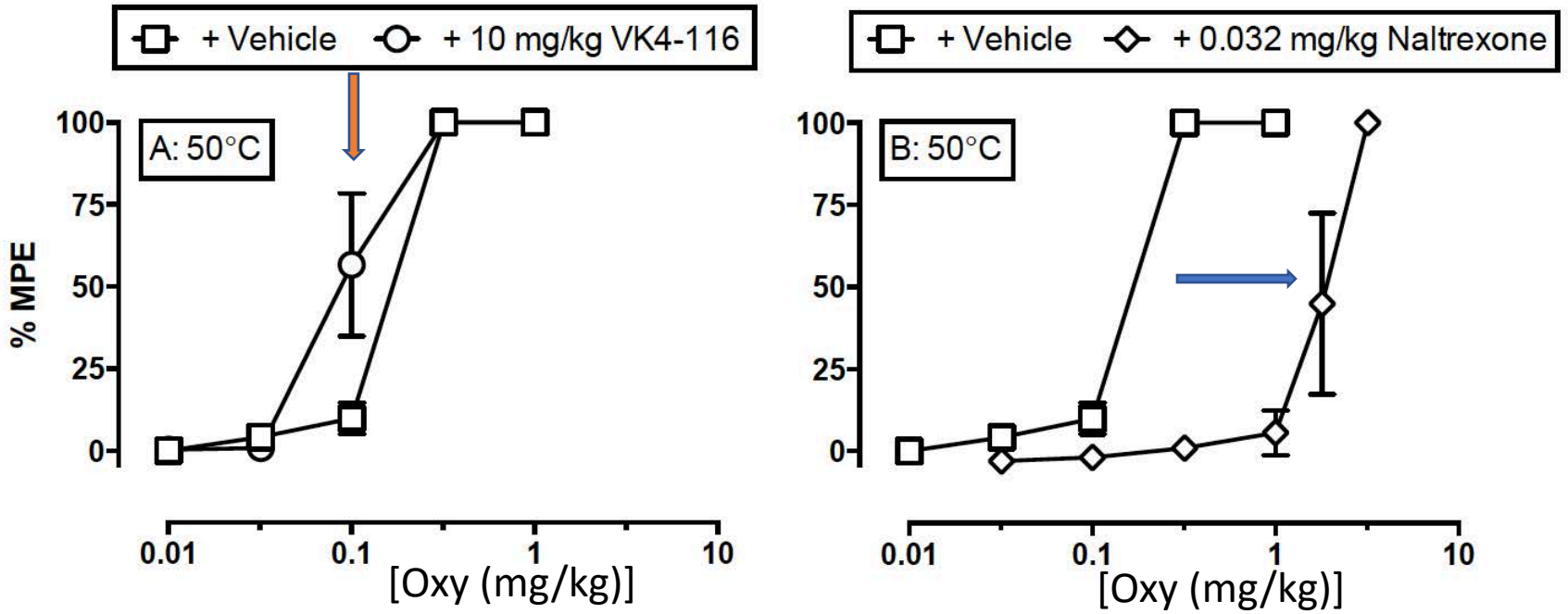
You et al., *Neuropsychopharmacology* 2019, 44, 1415.

Does VK4-116 have translational potential?



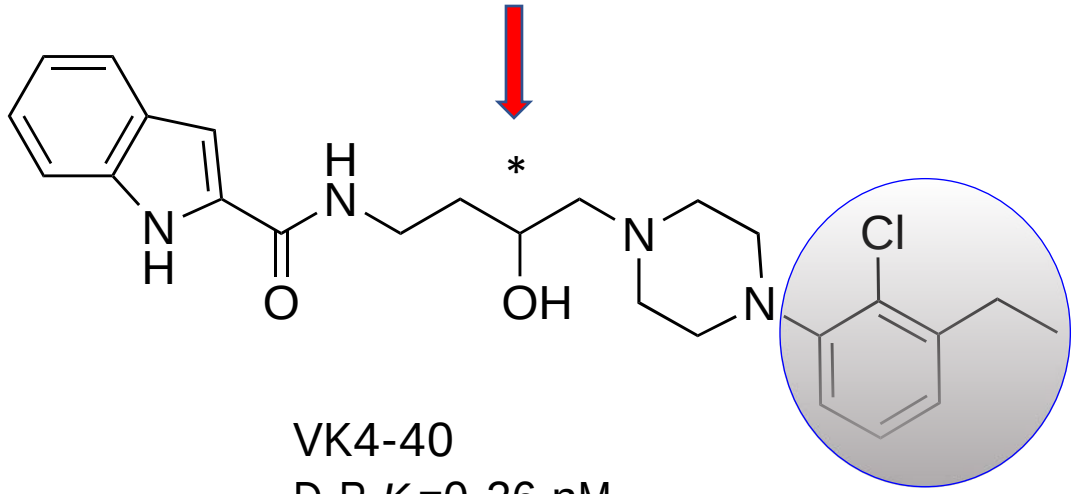
Alex Gadiano and Rana Rais, JHU

VK4-116 augments oxycodone antinociception in rhesus monkeys



Matt Banks, VCU

VK4-40 is a highly selective D_3R partial agonist

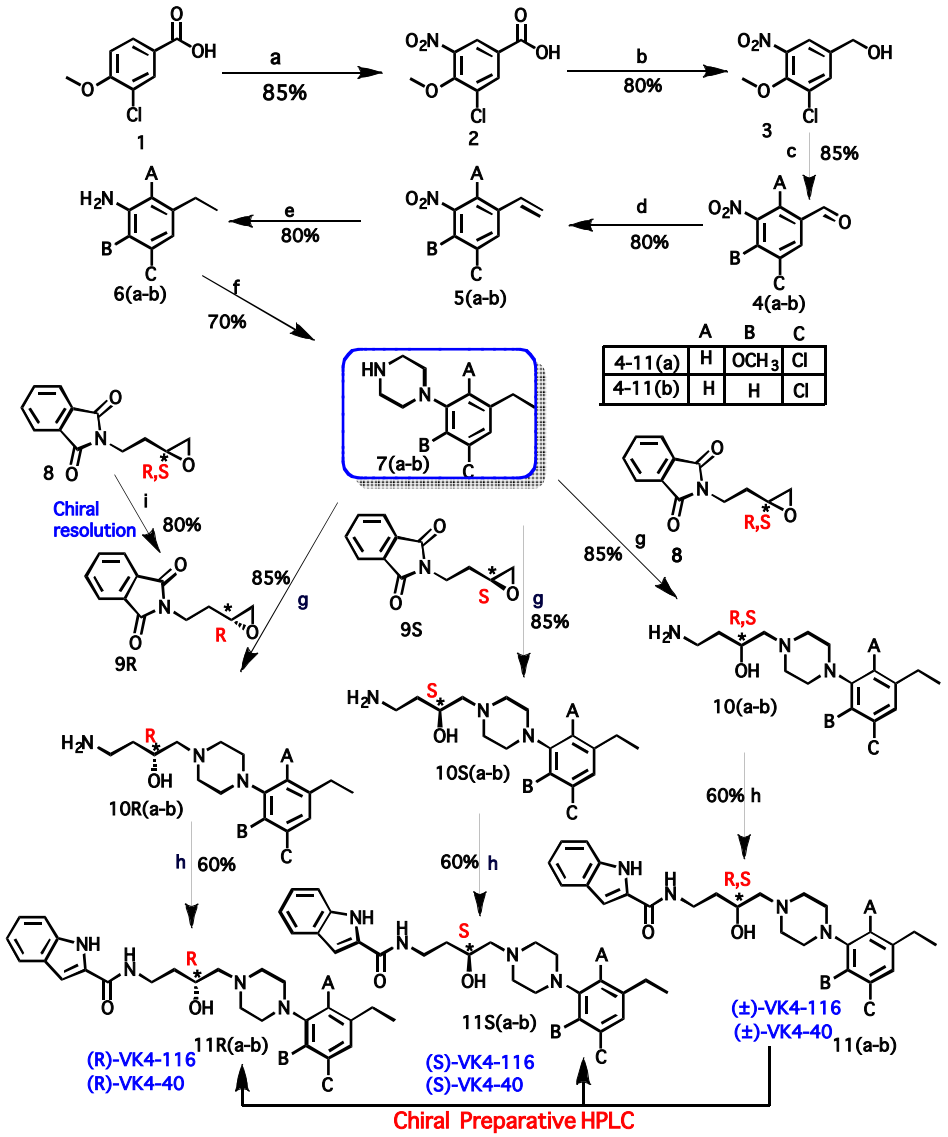


VK4-40
D_3R K_i=0.36 nM
D_2R K_i=151 nM
D_2/D_3=417

hD_3R EC_{50}=2.6 nM (18%)
hERG IC_{50}=1.4 μM

Kumar et al, JMC, 2016, 59, 7634.

Synthesis of VK4-116 and VK4-40 enantiomers



Anver Shaik

Shaik et al., JMC, 2019, 24, 9061.

D_2R and D_3R binding data

Compounds	[^{3}H]-N-methylspiperone competition[a]		
	D_2R	D_3R	
	$K_i \pm$ SEM (nM)	$K_i \pm$ SEM (nM)	D_3/D_2
(*R*)-VK04-116	10200 ± 1870	5.97 ± 1.19	1709
(*S*)-VK04-116	11600 ± 1150	33.4 ± 8.46	347
VK04-116	11400 ± 3270	6.84 ± 1.18	1667
(*R*)-VK04-40	68.1 ± 12.3	0.245 ± 0.0915	278
(*S*)-VK04-40	200 ± 57.9	0.700 ± 0.286	286
VK04-40	119 ± 11.1	0.351 ± 0.114	339

Alessandro Bonifazi

Adrian Guerrero

Shaik et al., JMC, 2019, 24, 9061.

D_2R and D_3R binding data

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(*S*)-VK04-40	200 ± 57.9	0.700 ± 0.286	286
VK04-40	119 ± 11.1	0.351 ± 0.114	339

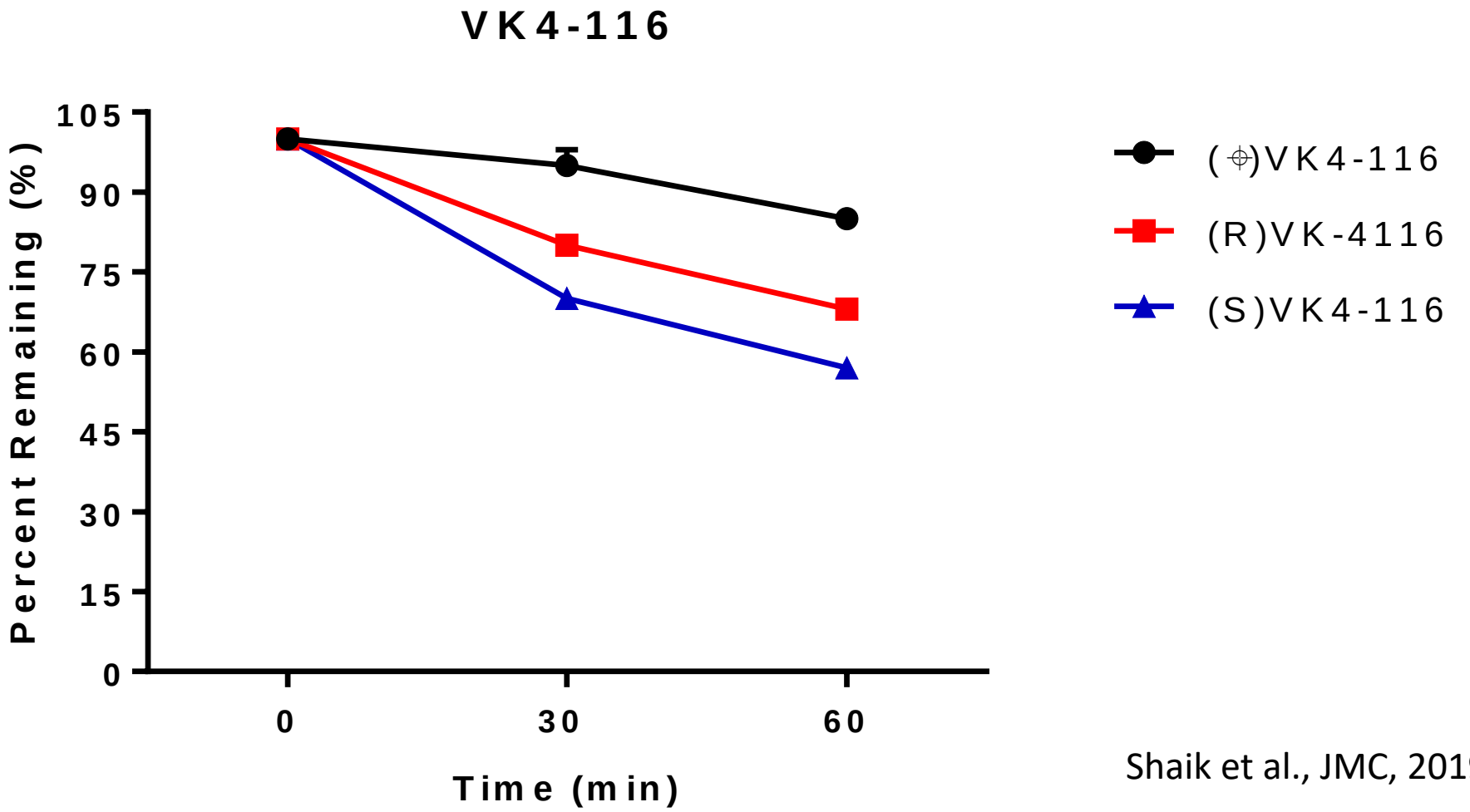
D_3R antagonists

D_3R antagonist

D_3R partial agonists

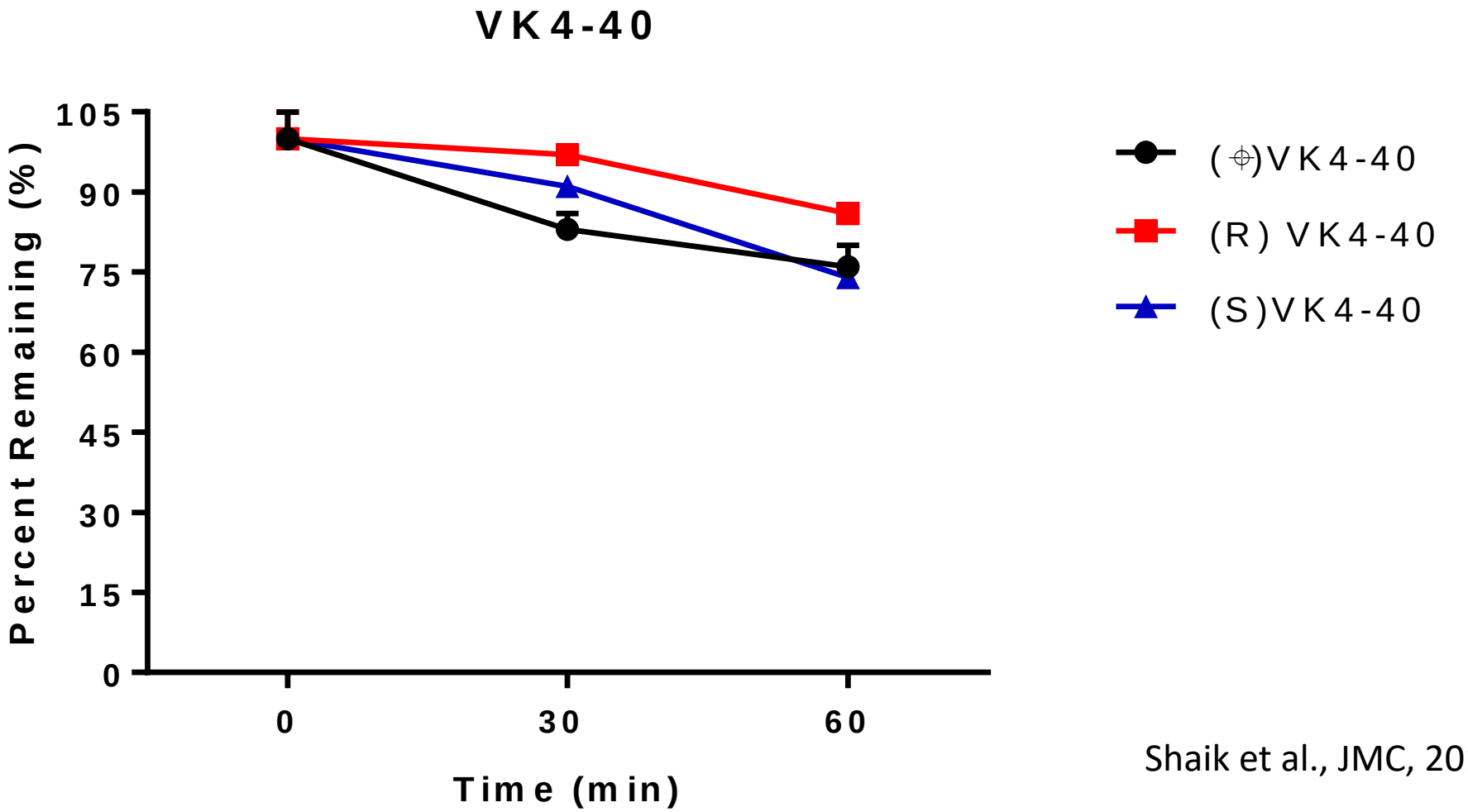
Data from NIDA CTDP

VK4-116 is highly metabolically stable in rat liver microsomes



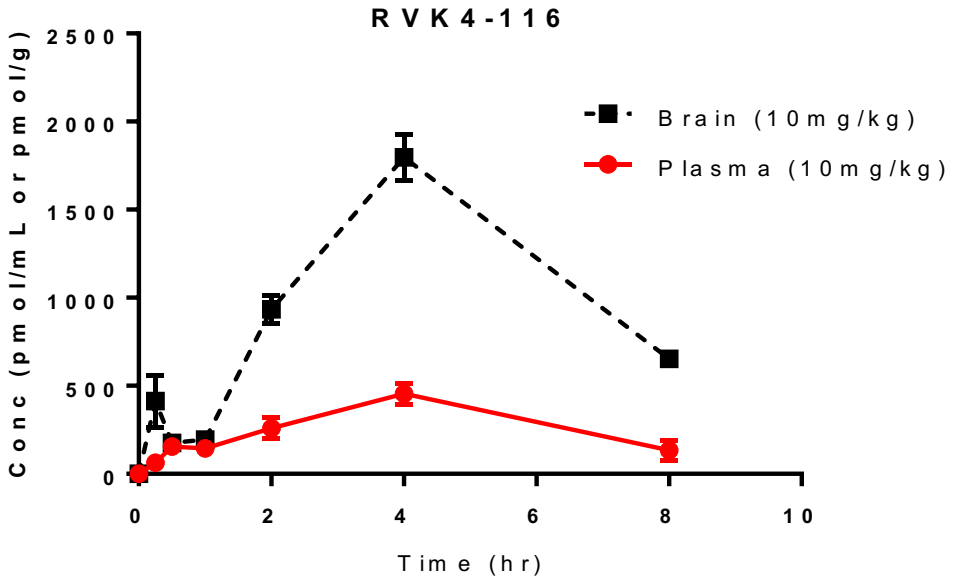
Shaik et al., JMC, 2019, 24, 9061.

VK4-40 is highly metabolically stable in rat liver microsomes

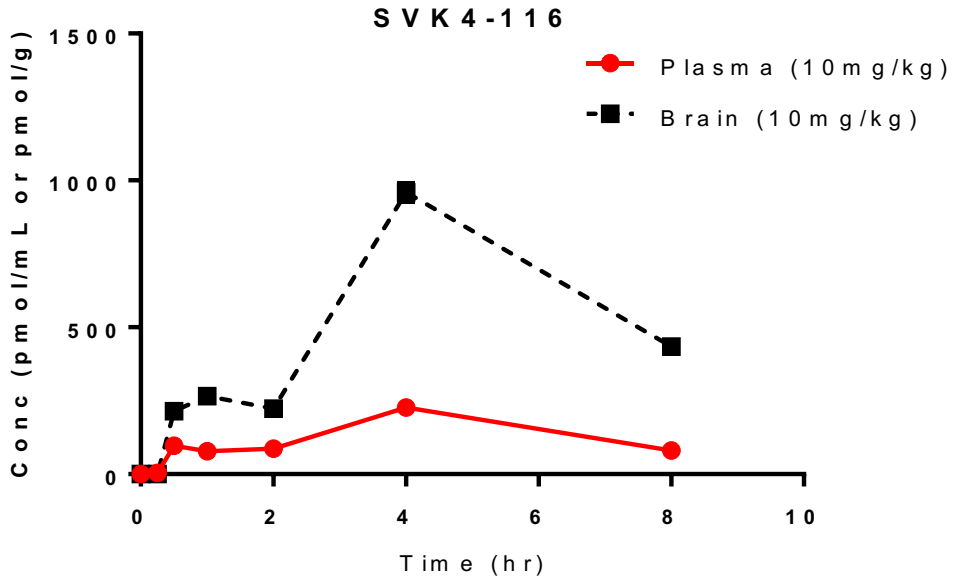


Shaik et al., JMC, 2019, 24, 9061.

R-and *S*-VK4-116 are both orally available and highly brain penetrant



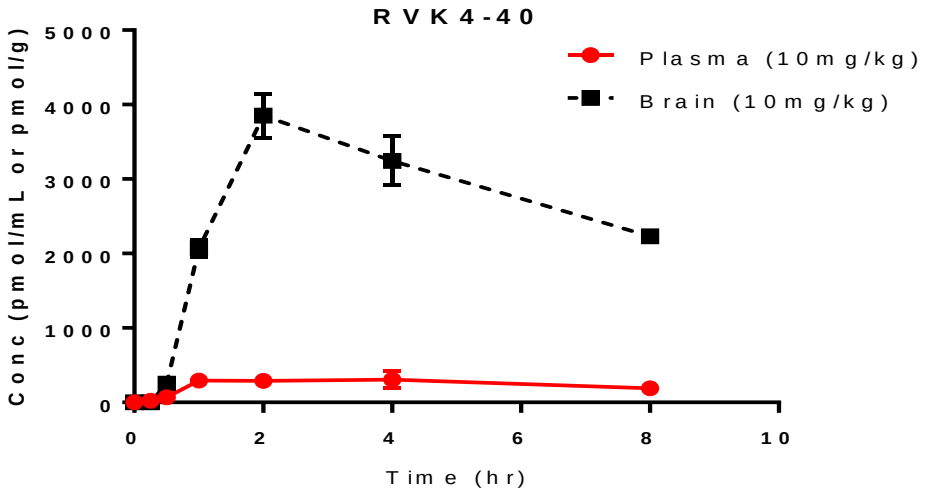
	Plasma (10mg/kg)	Brain (10mg/kg)
Area=	2201	8412



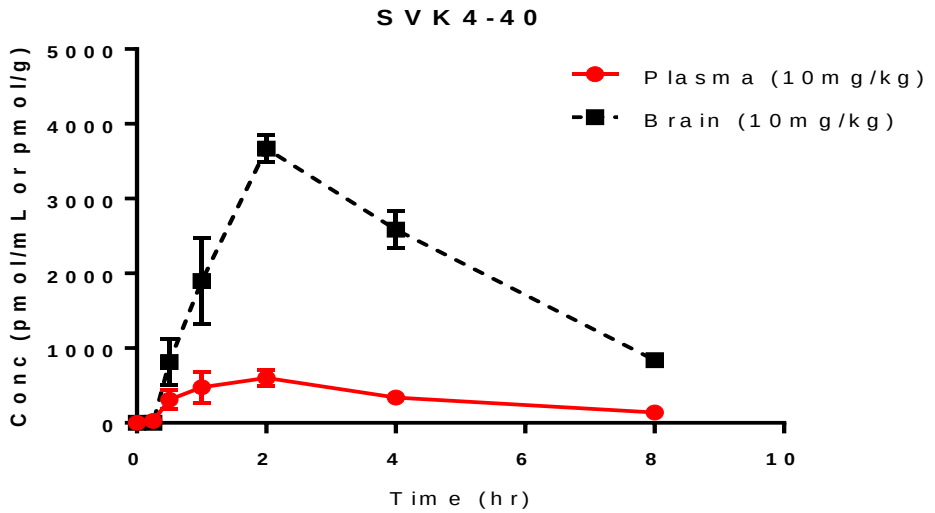
	Plasma (10mg/kg)	Brain (10mg/kg)
Area=	1068	4360

Shaik et al., JMC, 2019, 24, 9061.

R-and *S*-VK4-40 are both orally available and highly brain penetrant



	Plasma (10mg/kg)	Brain (10mg/kg)
Area=	1985	21609



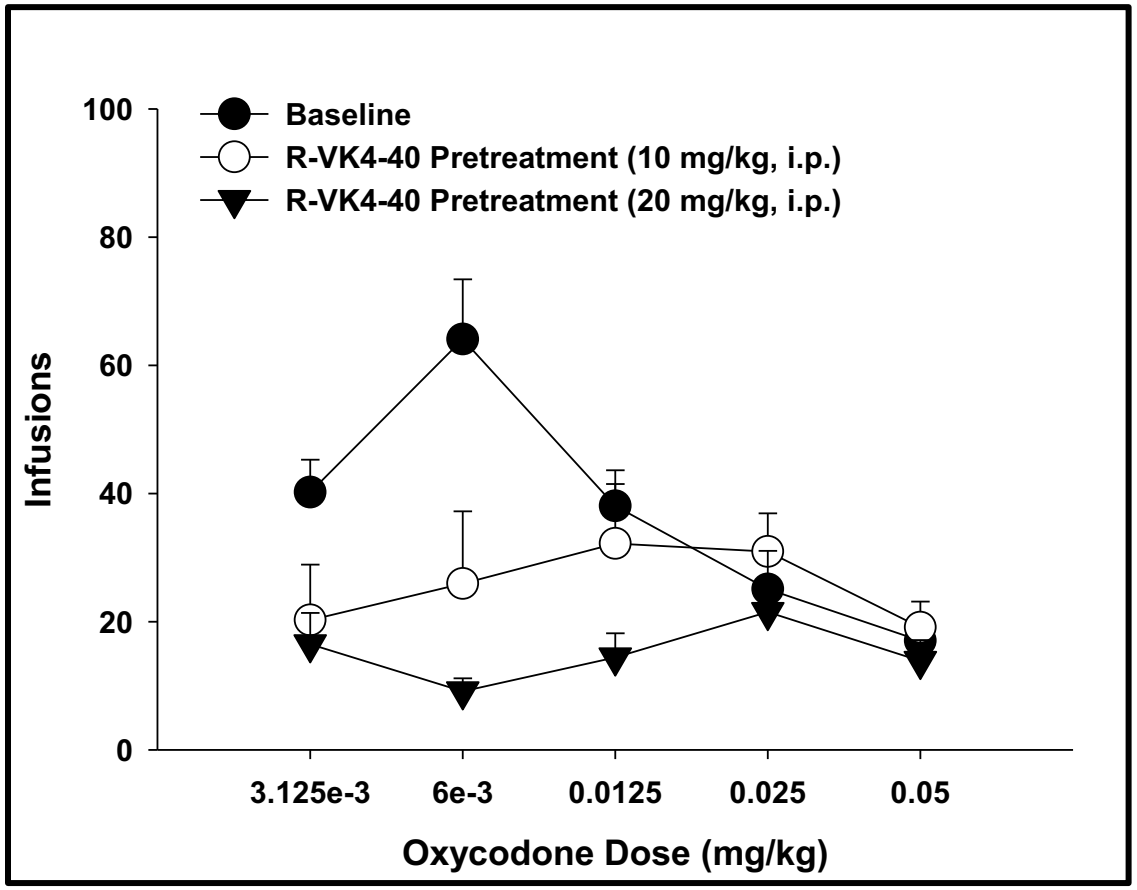
	Plasma (10mg/kg)	Brain (10mg/kg)
Area=	2678	16665

The brain to plasma ratios were similar for each enantiomeric pair, but VK4-40 demonstrated higher ratios overall.

Shaik et al., JMC, 2019, 24, 9061.

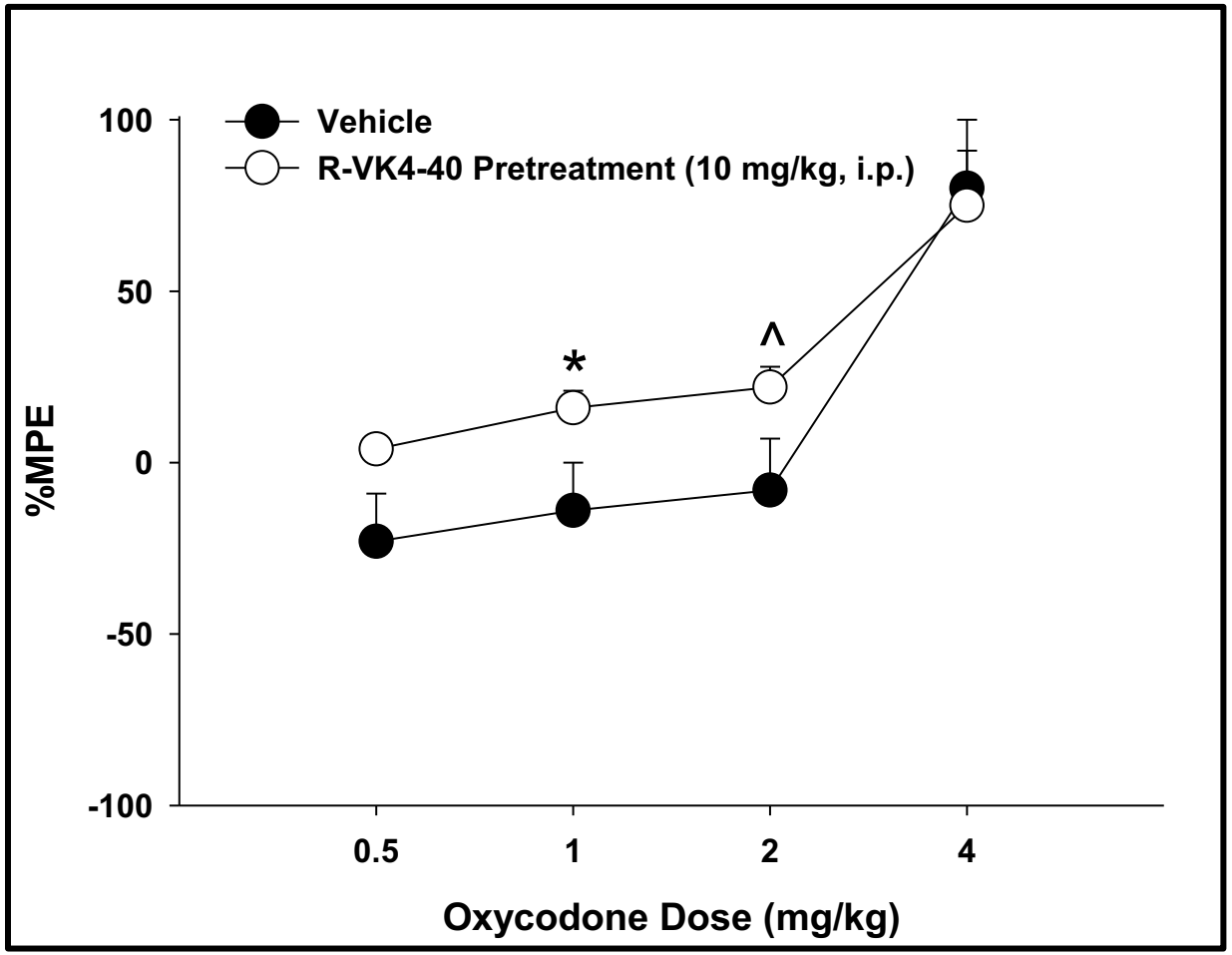
R-VK4-40 reduces oxycodone self administration

Chloe Jordan



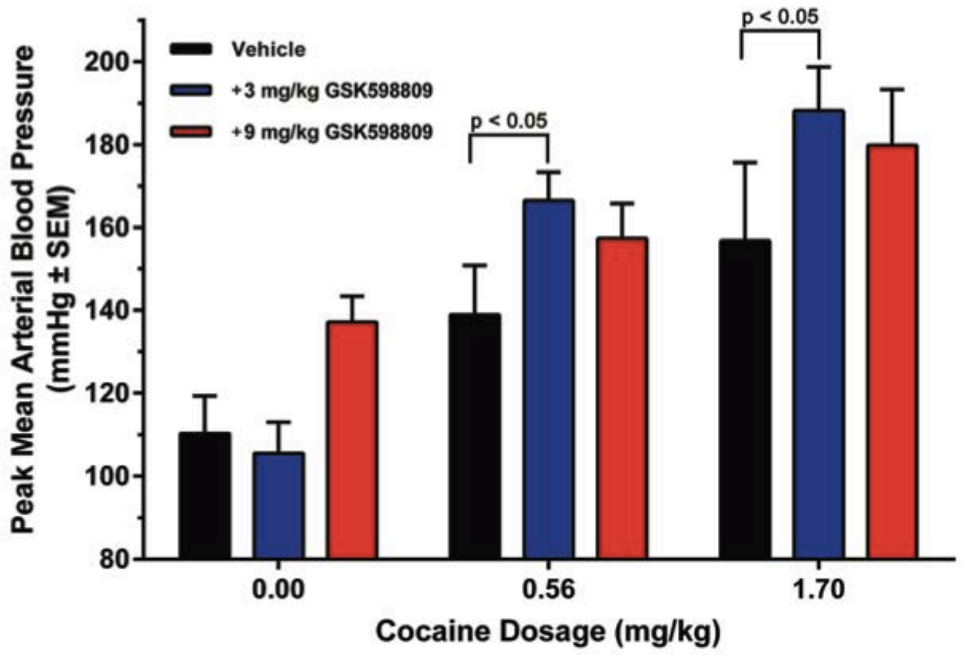
Jordan et al., Neuropharmacology 2019, 158, 107609.

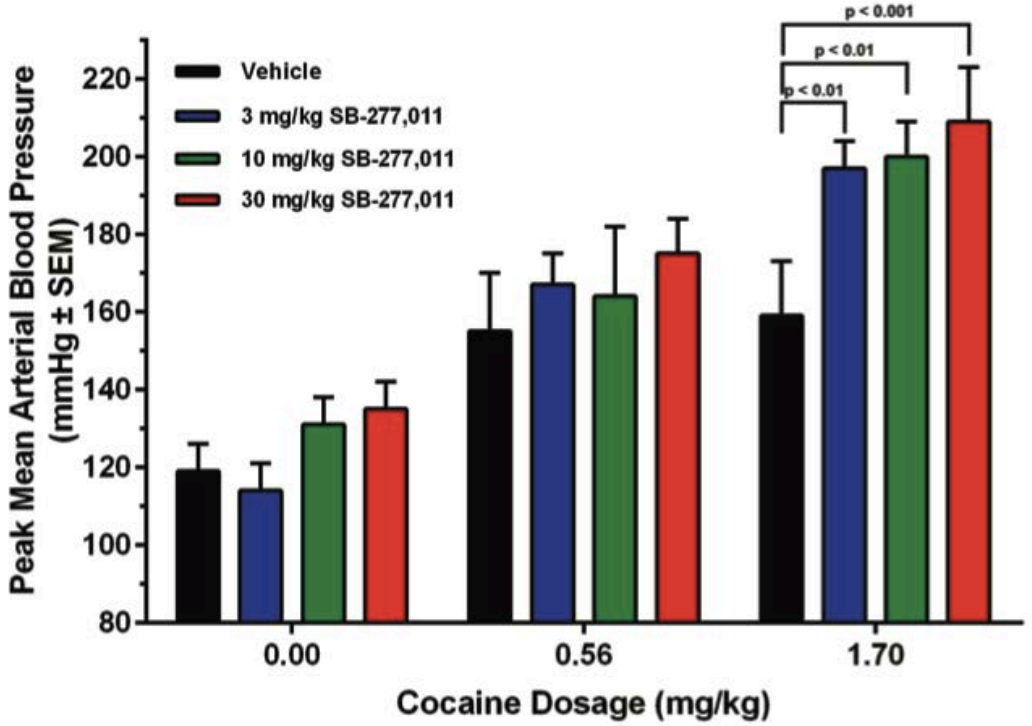
R-VK4-40 augments oxycodone-induced analgesia



Jordan et al., Neuropharmacology 2019, 158, 107609.

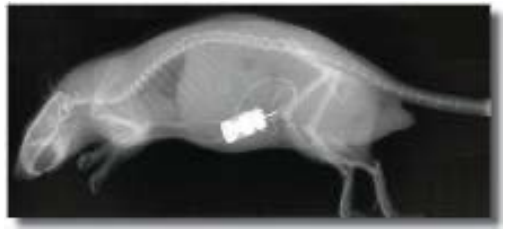
Earlier generations of D_3R antagonists increased blood pressure, especially in the presence of cocaine

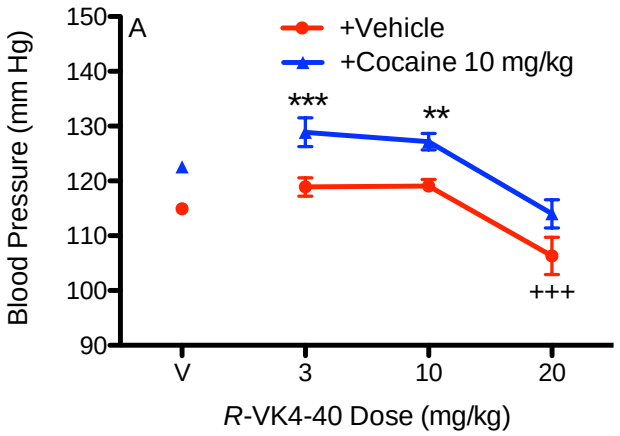


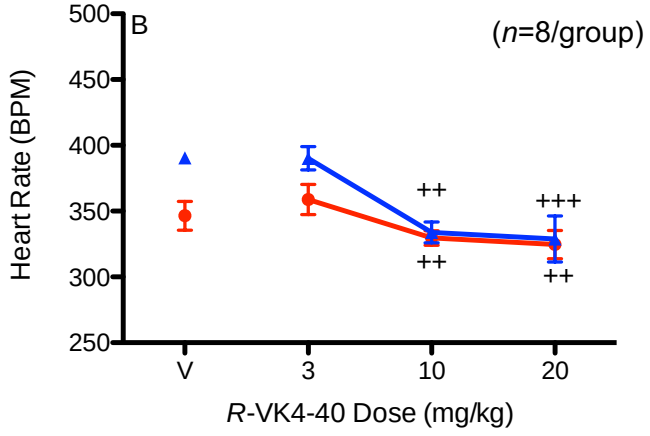


Appel & Acri, 2016; 2017

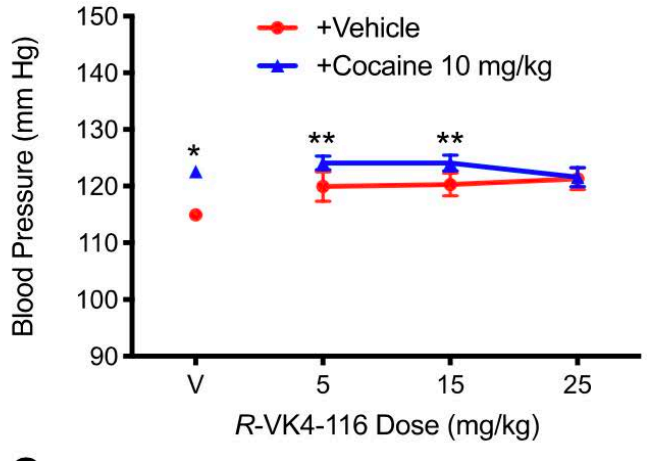
Neither R-VK4-40 nor R-VK4-116 exacerbate cocaine's cardiovascular effects

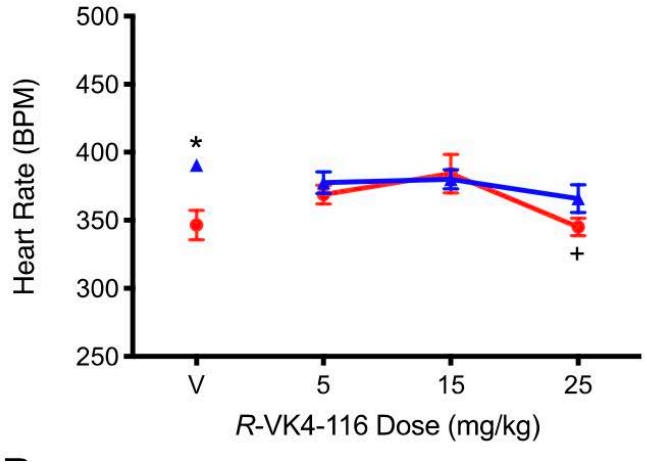






Chuck Schindler

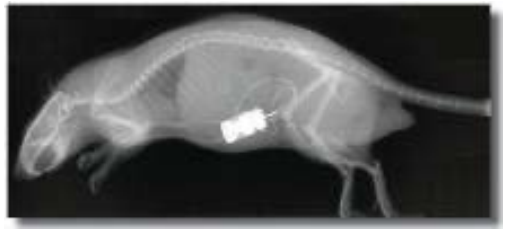


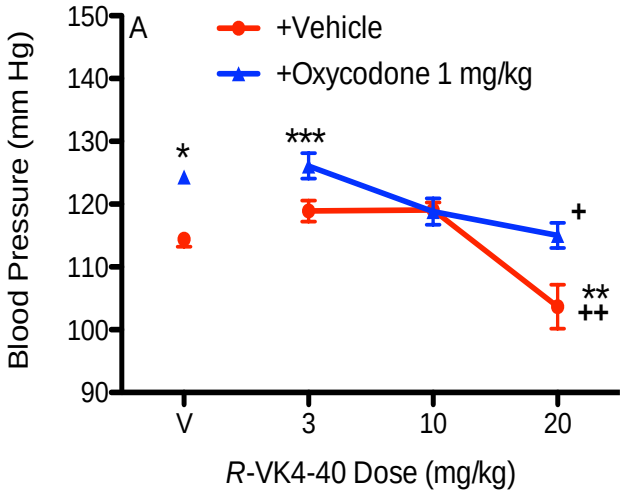


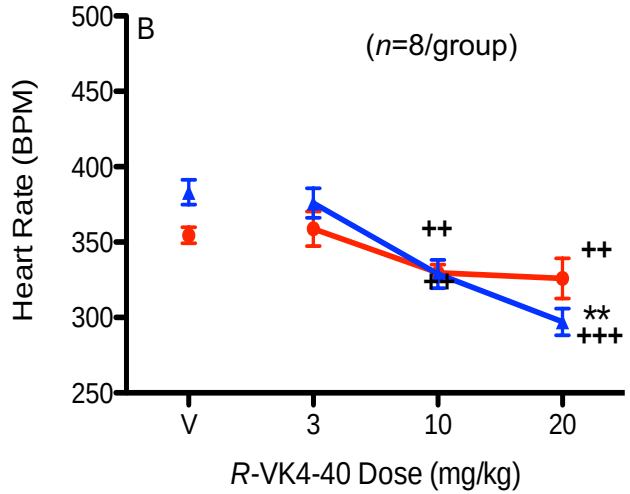
Chloe Jordan

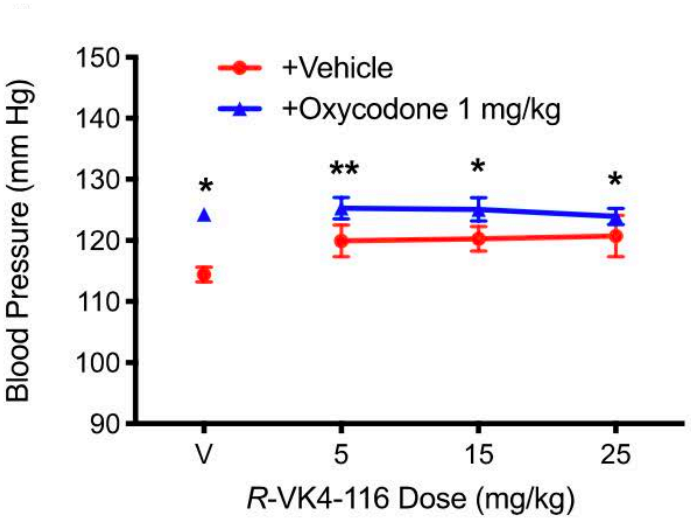
Jordan et al., JPET, 2019, 371, 602.

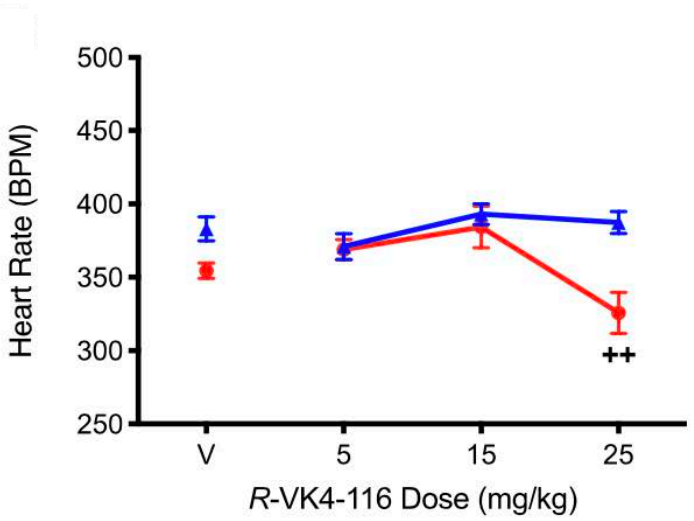
R-VK4-40 and R-VK4-116 attenuate oxycodone's cardiovascular effects



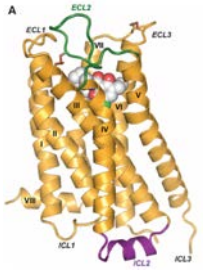








Jordan et al., JPET, 2019, 371, 602.



SUMMARY-1

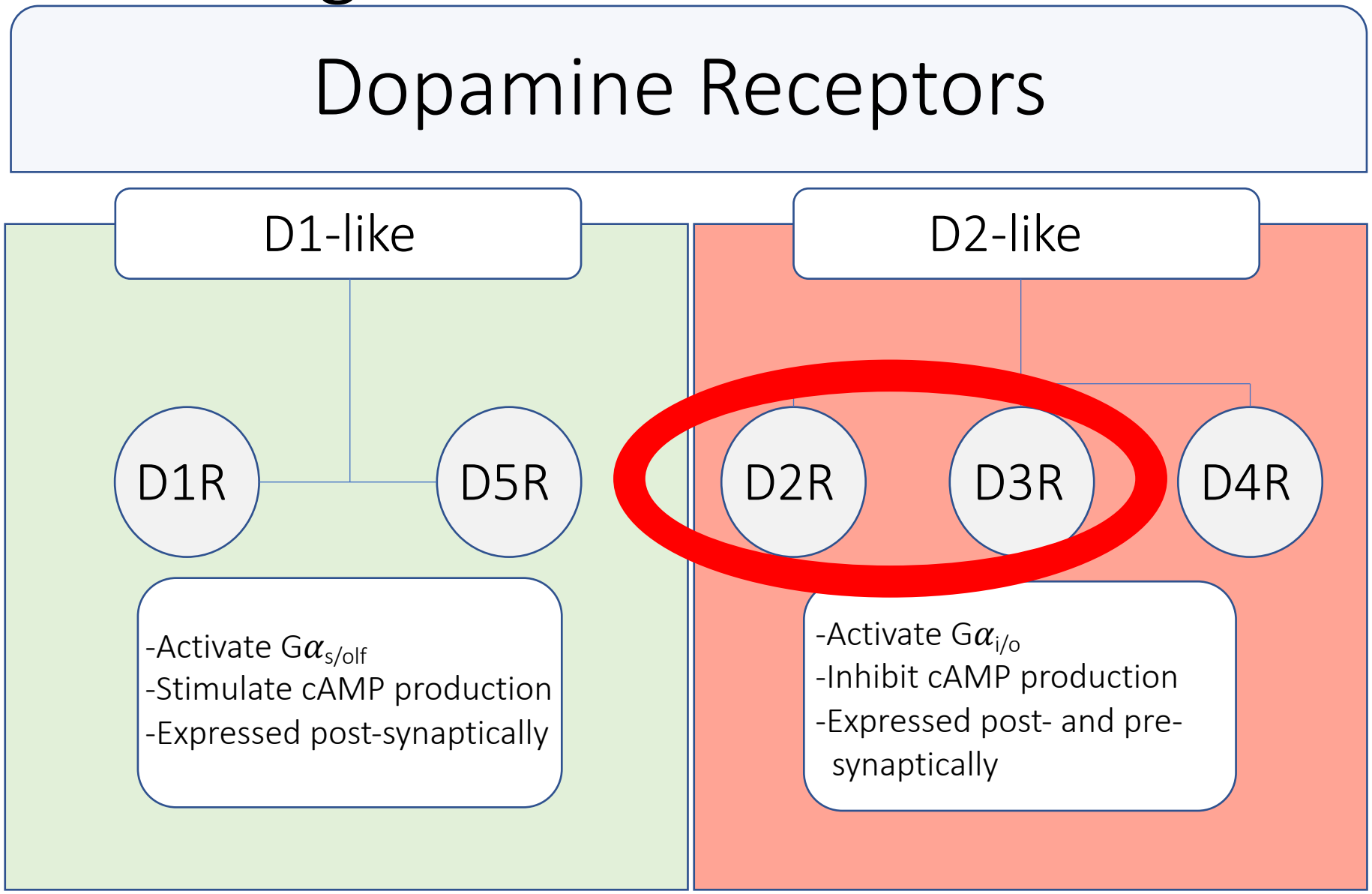
- **VK4-116** and **VK 4-40** are highly selective **bitopic** D_3R antagonists/partial agonists
- Enantiomers have been synthesized; binding, metabolism and PK studies are complete
- They do not bind to opioid (μ, δ, κ) receptors, thus the mechanism appears to be through D_3R blockade
- Significant and promising behavioral data have been collected on the antagonists **(±)VK4-116** and ***R*-VK4-40** in rats. Behavioral evaluation of a new set of 3-F analogues is underway
- Neither **R-VK4-40** nor **R-VK4-116** adversely affect peripheral biometrics or cardiovascular effects of oxycodone OR cocaine.
- Further development is underway to advance our lead molecules to clinical trials

braeburn

Newman, A. H., Kumar V., Shaik, A. Dopamine D3 receptor selective antagonists/partial agonists; method of making and uses thereof. *Int. Patent Application filed 3-8-2017.*
Newman, A. H., Kumar V., Shaik, A. Dopamine D3 receptor selective antagonists/partial agonists and uses thereof. *Provisional Patent Application filed 10-7-2018.*

NIH National Center for Advancing Translational Sciences

The challenge:



Why D_3R Agonists?

- Therapeutic Agents:

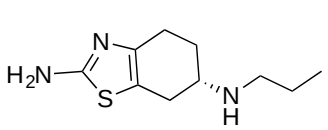
  Potentially useful in treating locomotor associated diseases:

  - Parkinson's Disease, Restless Leg Syndrome

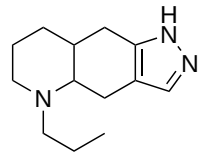
- Pharmacological Tools:

  Develop selective ligands that allow pharmacological studies of D3R function.

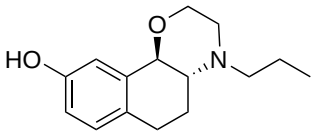
Commonly used *in vitro* and *in vivo*:



Pramipexole
D3R Ki = 1.32 nM
D2R Ki = 11.1 nM
D2R/D3R = 8.41

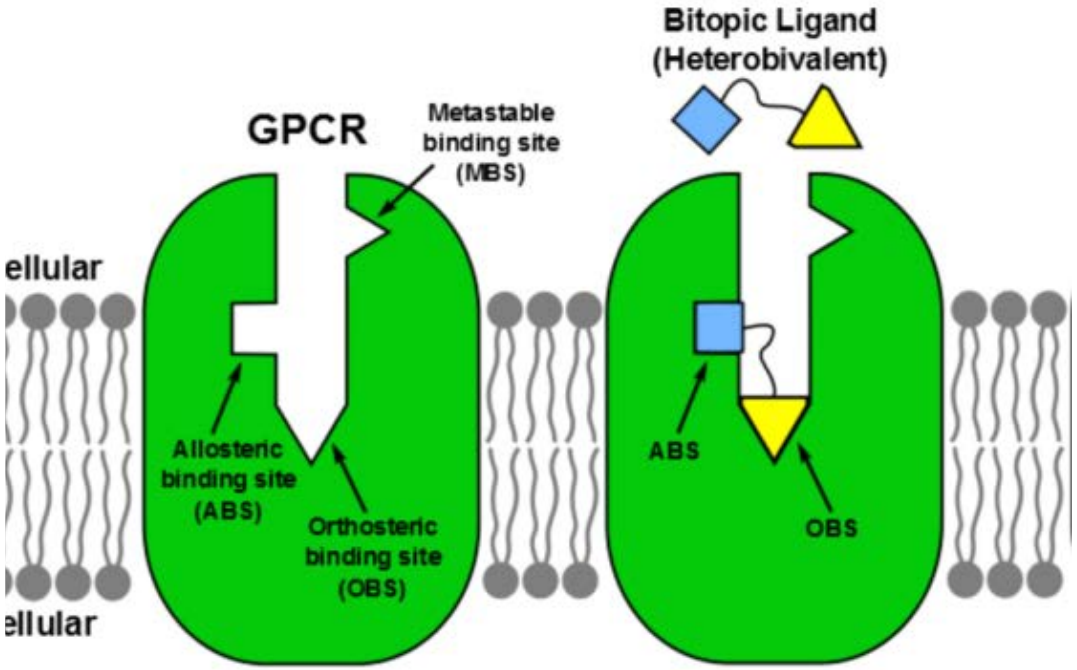


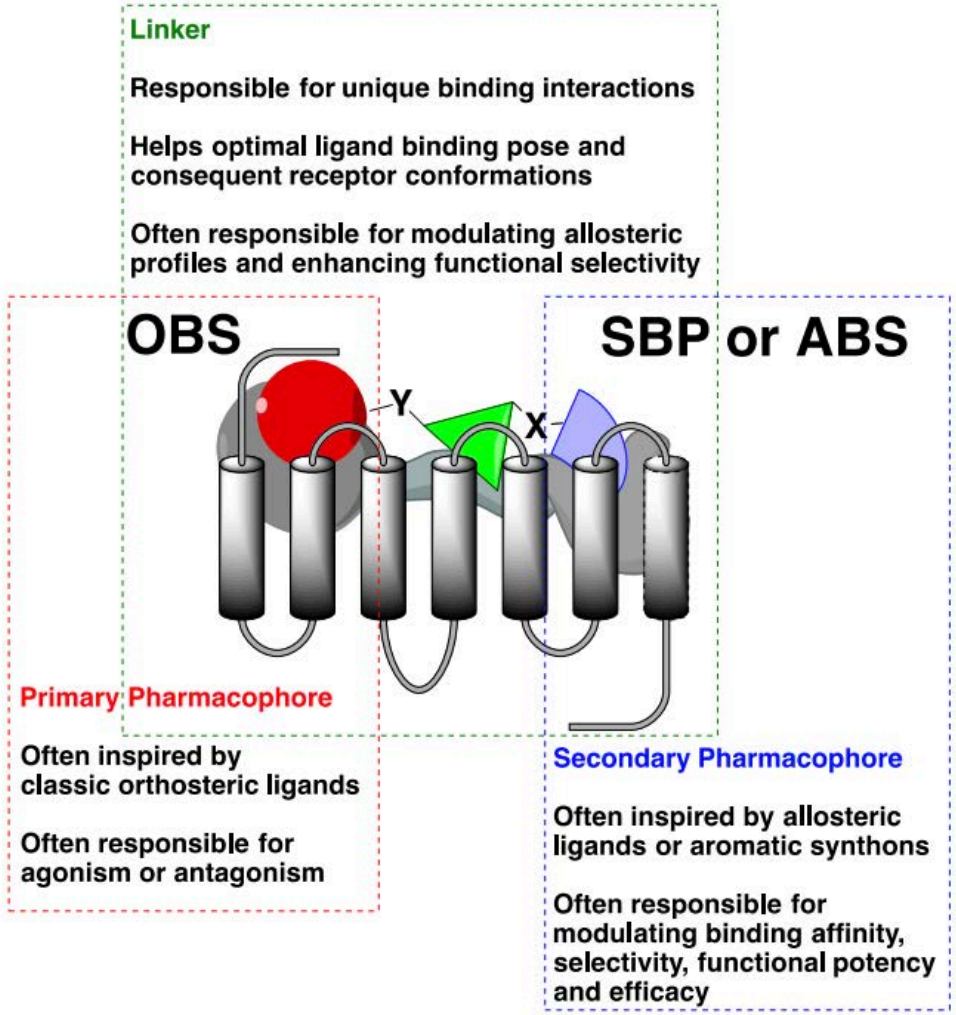
Quinpirole
D3R Ki = 24 nM
D2R Ki = 4.8 nM
D2R/D3R = 0.2



(+)-PD128,907
D3R Ki = 1.69 nM
D2R Ki = 20.5 nM
D2R/D3R = 12.1

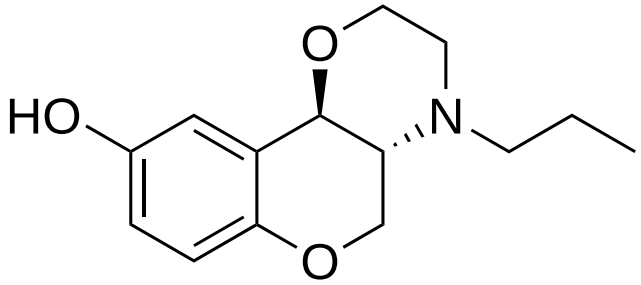
Can we apply the bitopic concept to D_3R agonists?



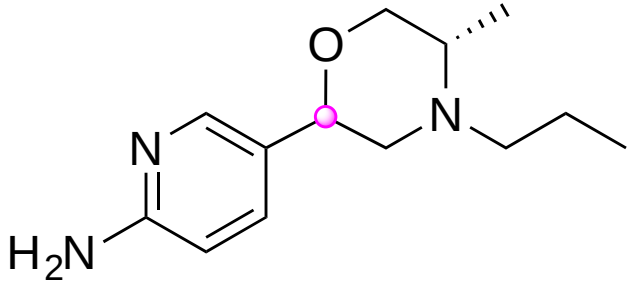


D_3R Bitopic Agonists: Design

Primary Pharmacophore Selection:



(+)-PD128,907
hD2R Ki = 20.5 nM
hD3R Ki = 1.69 nM
D2R/D3R = 12.1

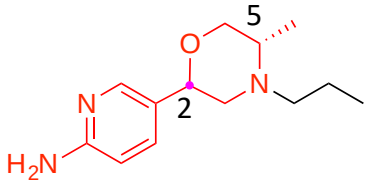


PF592,379
hD2R Ki = 1740 nM
hD3R Ki = 185 nM
D2R/D3R = 9.41

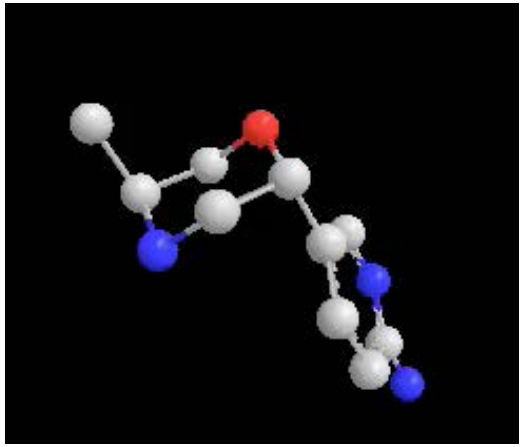
Battiti et al, *ACSMCL* 2020, *11*, 1956.

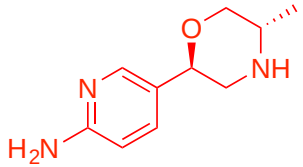
Alessandro Bonifazi, Francisco Battiti & Sophie Cemaj

D_3R Bitopic Agonists: PF592,379 Based

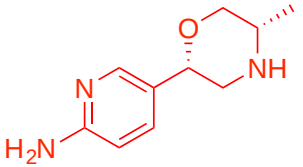


PF-592379
hD2R Ki = 1740 nM
hD3R Ki = 185 nM
D2/D3 = 9.41

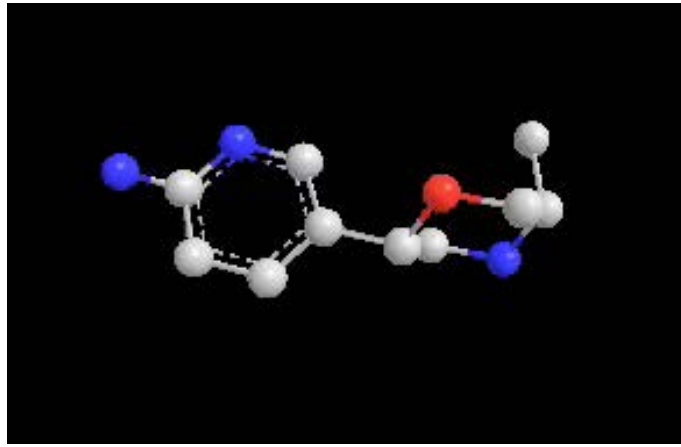




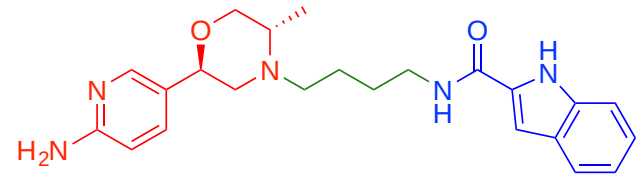
(2*R*,5*S*)-nor-PF-592379
hD2R Ki = 7100 nM
hD3R Ki = 1520 nM
D2/D3 = 4.67

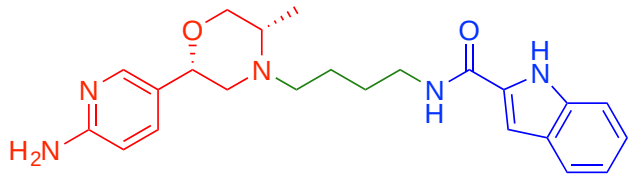


(2*S*,5*S*)-nor-PF-592379
hD2R Ki = 2340 nM
hD3R Ki = 424 nM
D2/D3 = 5.52



(2*R*,5*S*)-AB04-87
hD2R Ki = 5220 nM
hD3R Ki = 6470 nM
D2/D3 = 0.807

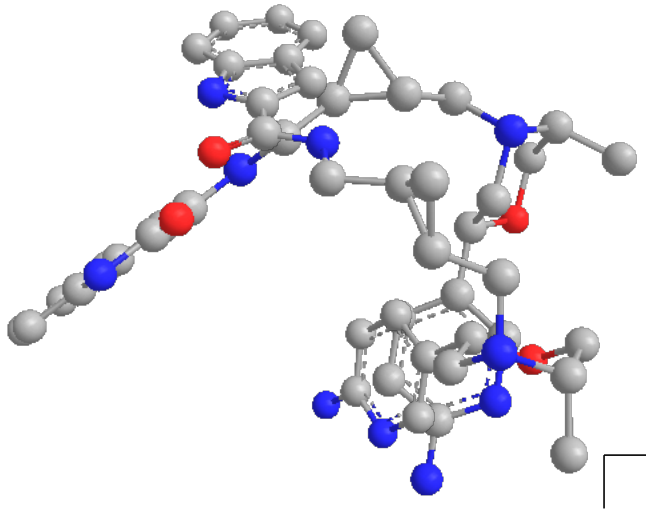


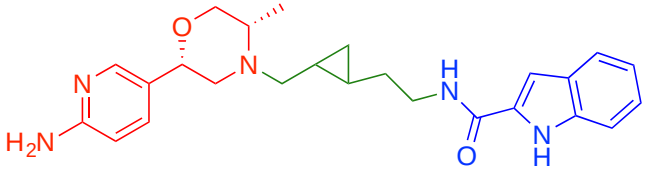


(2*S*,5*S*)-AB04-88
hD2R Ki = 134 nM
hD3R Ki = 5.96 nM
D2/D3 = 22.5

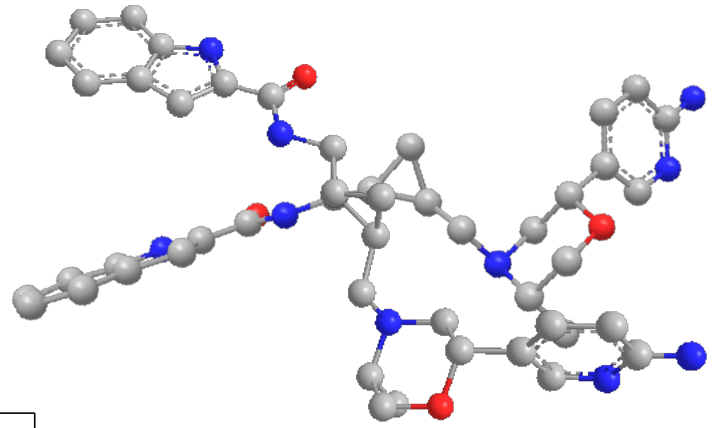
Battiti Cemaj, Guerrero et al. *JMC,* 2019 *62,* 6287

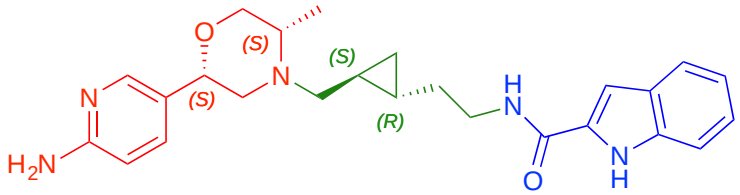
Linker: more than just a link





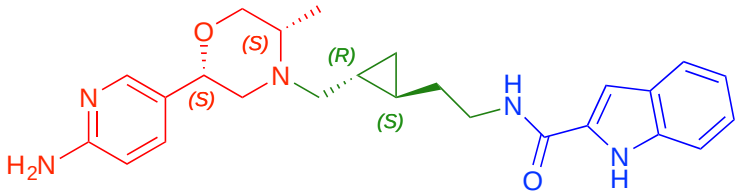
FOB02-04
hD3R Ki = 2.84 nM
hD2R Ki = 106 nM
D2/D3 = 37.3





FOB02-04A
hD3R Ki = 1.85 nM
hD2R Ki = 87.8 nM
D2/D3 = 47.5

Best Compound in Series



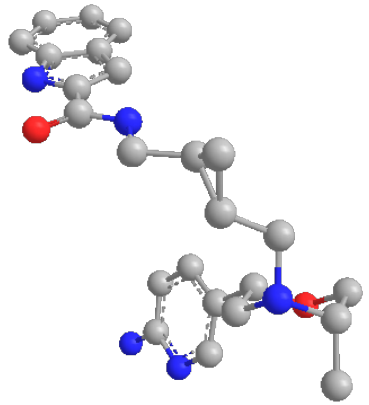
FOB02-04B
hD3R Ki = 282 nM
hD2R Ki = 831 nM
D2/D3 = 2.95

Javier Garcia Nafria, BIFI

Battiti Cemaj, Guerrero et al. *JMC,* 2019 *62,* 6287

SUMMARY-2

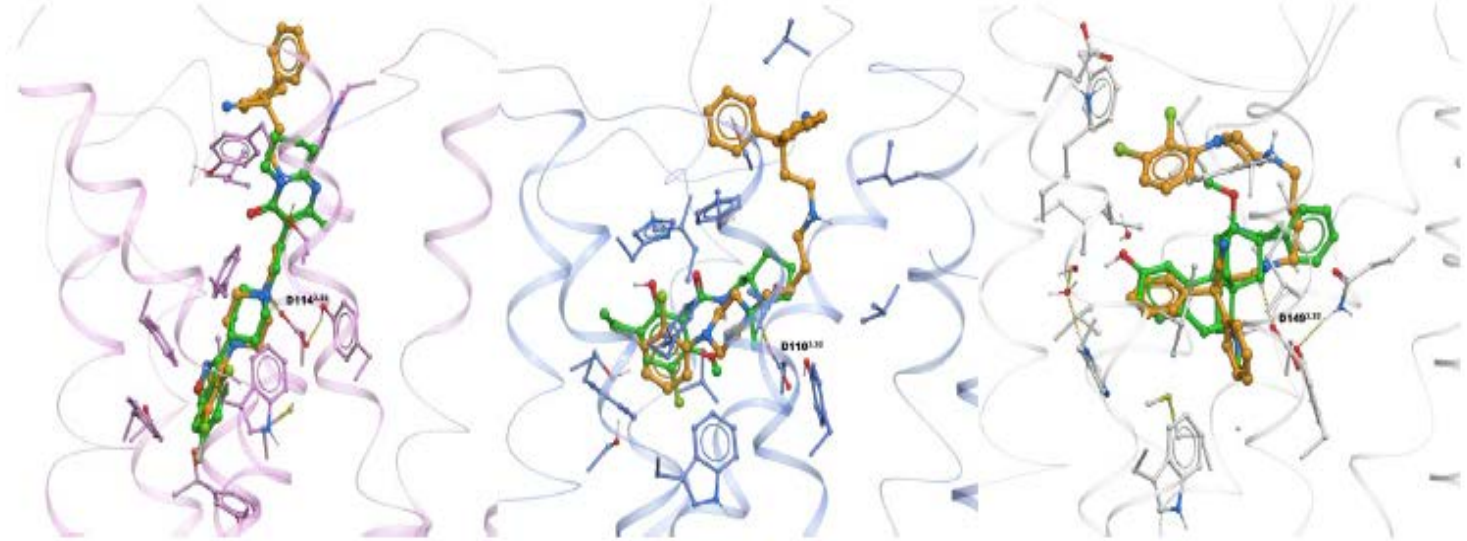
- Bitopic agonists based on PD128,907 and PF 592,379 have been synthesized
- We discovered that the 2*S*,5*S*- stereochemistry in the PF primary pharmacophore coupled with the privileged 2-indoleamide as the secondary pharmacophore and a chiral cyclopropyl linker gave the bitopic analogue, **FOB02-04** - the most D_3R-selective full agonist reported to date (EC_{50}=4.15 nM; 78%)
- Chirality in the primary pharmacophore and the linker matter!
- A cryo-EM structure would be the first to use a bitopic agonist



Our latest foray into bivalent molecules:

Novel Dual-Target Mu Opioid (MOR) and Dopamine D_3 Receptor (D_3R) Ligands as Potential Non-Addictive Pharmacotherapeutics for Pain Management

Alessandro Bonifazi,[†*] Francisco O. Battiti,[†] Julie Sanchez,[‡] Saheem Zaidi,[⊥] Eric Bow,[§] Mariia Makarova,[§] Jenny Lam,[†#] Rana Rais,[#] Kenner Rice,[§] Vsevolod Katritch,[⊥] Meritxell Canals,[‡] J. Robert Lane,[‡] Amy Hauck Newman[†*]

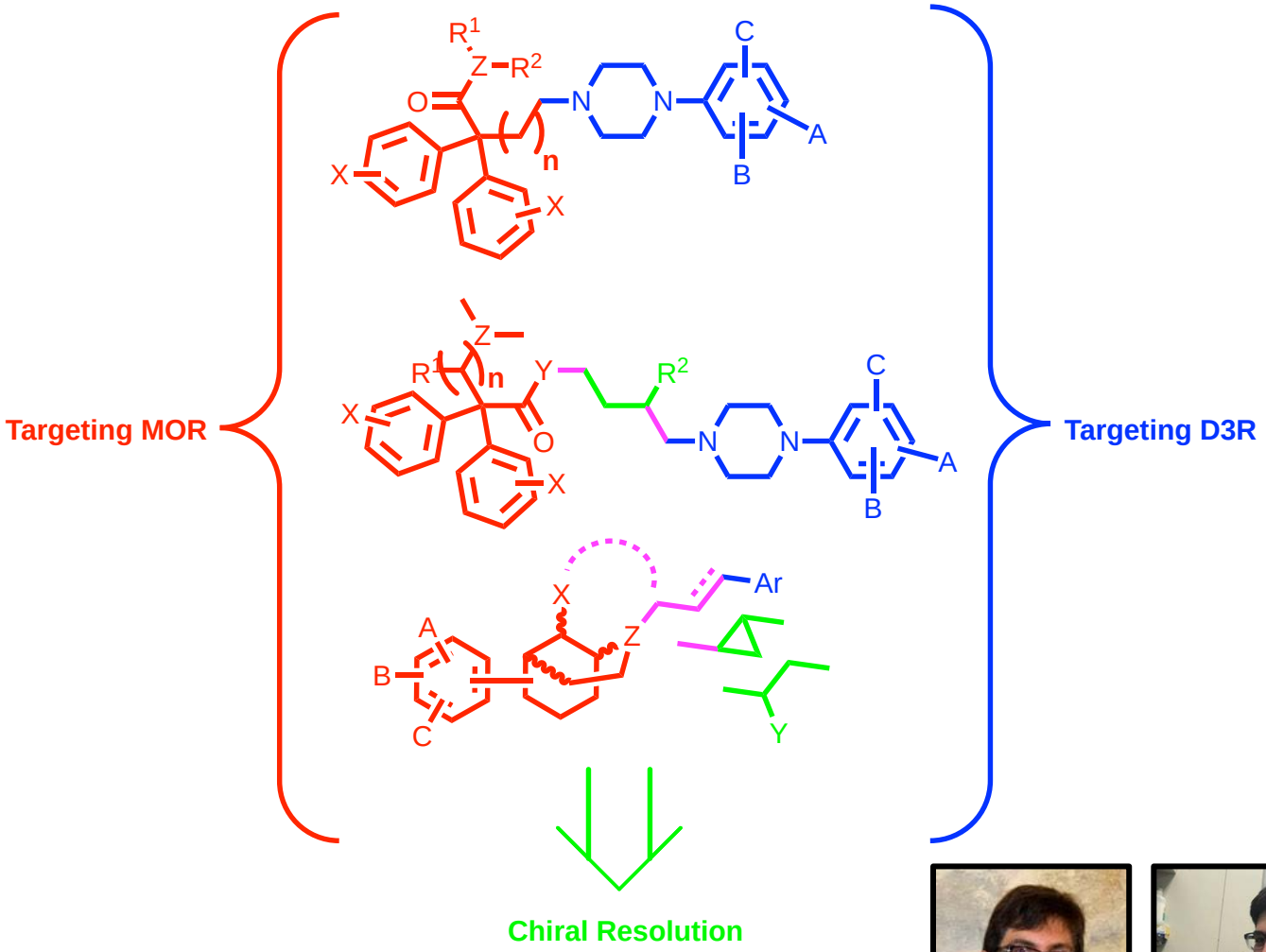


D2 docking scores/minim scores:-16.65/-33.23 D3 docking scores/minim scores:-15.62/-32.66 MOR docking scores/minim scores:-19.53/-45.42

Seva Katritch & Saheem Zaidi, USC

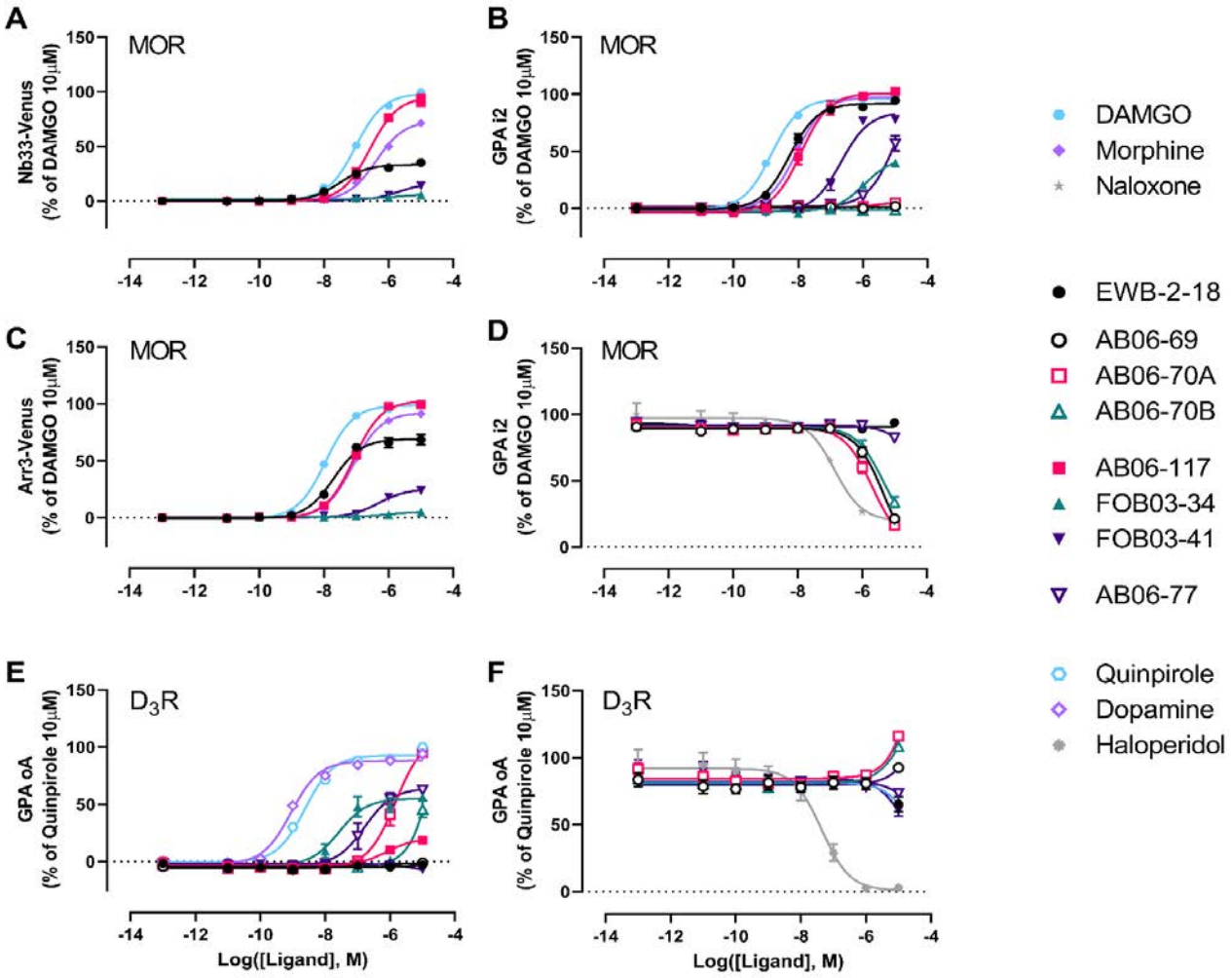
Designing bivalent MOR/D_3R molecules for the treatment of pain and OUD

- Based on SAR at both MOR and D_3R, we have synthesized a large series of novel bivalent and bitopic ligands
- In collaboration with the Rice group, we have incorporated novel MOR agonists with both primary and secondary pharmacophores for D_3R
- Several lead compounds have been discovered with nM affinities for both MOR and D_3R
- The active molecules are all bivalent (as opposed to bitopic)



Alessandro Bonifazi & Francisco Battiti

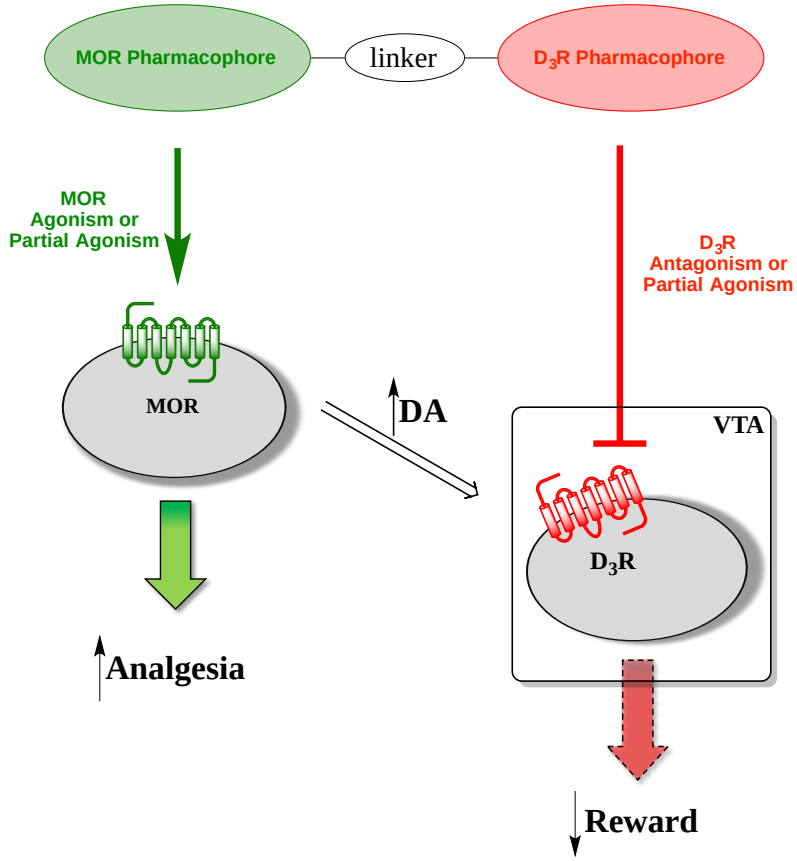
Novel MOR-D_3R ligands range in efficacies



Meri Canals & Rob Lane
U. Nottingham

SUMMARY-3

- We have discovered several bivalent MOR/D_3R partial agonists with nM affinities
- Computational studies are ongoing to elucidate key ligand-receptor interactions as a source for the wide range of affinities observed for structurally similar compounds
- Functional studies have been conducted to evaluate efficacy and G-protein vs beta-arrestin bias
- *In vivo* studies are being conducted on our 3 lead compounds
- And, of course we are designing 2nd generation compounds, further investigating novel chiral/cyclic linkers, new primary pharmacophores and improving druggability



Bonifazi et al., manuscript in revision.

Acknowledgements

Medicinal Chemistry:

Alessandro Bonifazi, Francisco Battiti, Vivek Kumar, Anver Shaik, Adrian Guerrero, Sophie Cemaj, JJ Cao – NIDA-IRP

Computational Chemistry:

Lei Shi – NIDA-IRP

Seva Katritich - USC

Pharmacology:

Zheng-Xiong Xi, Zhi-Bing You, Chloe Jordan, Guo-Hua Bi, Ewa Galaj, Bree Humburg, Pramisha Adhikari, Hideaki Yano - NIDA-IRP

Mike Nader – Wake Forest

Matt Banks, VCU

Olivier George UCSD

PK and Metabolism:

Barbara Slusher, Rana Rais – JHU

Jenny Lam, Alex Gadiano – NIDA-IRP, JHU