Optimization of Novel μOR Ligands for Enhanced CNS Penetration

Alok Nerurkar[1], Sheldon Wang[1], Tom Nguyen[1], Ulhas Bhatt[1], Yihong Li[1], Pingyu Ding[1], Frederick Seidl[1], Zhi-Liang Wei[1], Corinne Sadlowski[1], Kevin Li[1], David Sperandio[1], Beth Youngblood[2], Alex Tkachenko[2], Neil Schwartz[2], Donald Gehlert[2], Julio C. Medina[1]

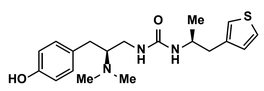
[1]R2M Pharma, Inc., South San Francisco, CA; [2]Epiodyne Inc., San Francisco, CA

Introduction

Deaths due to opioid overdose have reached epidemic levels, and this epidemic is widely recognized as a global health crisis. Full μOR agonists such as morphine, codeine, fentanyl and oxycodone are recognized as effective medications to treat pain, but their abuse leads to tolerance, dependence and death by respiratory suppression.[1] As a result of their abuse potential, approximately 130 people die daily from overdose and it is estimated that more than 10 million people in the US misuse opioids annually.[1,2] To address this epidemic, it has become increasingly apparent that there is a need for drugs that can treat pain while mitigating undesired side effects that are typically associated with opioids.

Towards this goal, Huang, Manglik, and coworkers screened a virtual library of μOR ligands, which yielded a potent and selective μOR agonist, such as PZM21[3]; however, PZM21 has poor bioavailability due to its low of CNS permeability. Here, we discuss the use of urea and phenol isosteres to optimize the CNS permeability of the PZM21 scaffold while maintaining its μOR activity.

Low CNS Permeability of PZM21

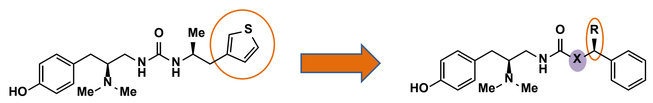


PZM21

μOR cAMP EC_{50} (% E_{max}): 13 nM (92)
MDCK-MDR1 A-B/B-A ratio: 5.1
Brain/Plasma ratio (rat and mouse): <3%
Topological Polar Surface Area (TPSA): 64.6 Å²
Hydrogen Bond Donors (HBD): 3

Optimization campaign of PZM21 will focus on:
- Improving CNS permeability.
- Reducing the number of Hydrogen Bond Donors.
- Maintaining or improving activity on μOR.

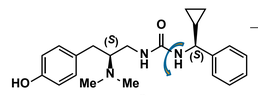
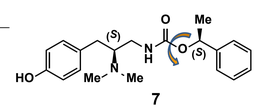
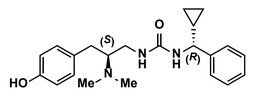
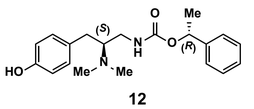
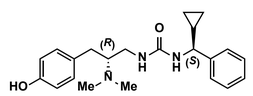
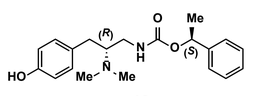
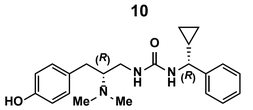
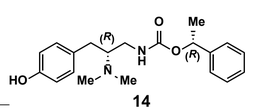
SAR of Ureas and Carbamates



Compd	R	X	μOR cAMP EC_{50} (%E_{max})+,*	μOR cAMP IC_{50} (% inhibition)+,**
1	Me	NH	21 nM (48)	-
2		NH	7.3 nM (44)	-
3		NH	>3 μM	38 nM (100)
4		NH	>3 μM	40 nM (100)
5		NH	>3 μM	56 nM (100)
6		NH	>3 μM	17 nM (105)
7	Me	O	172 nM (47)	-
8		O	771 nM (26)	-

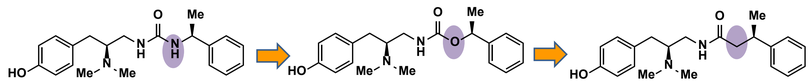
+μOR cAMP assays were performed using a stably transfected CHO cell line expressing human-uOR. Measurements were performed in triplicate.
*Agonist assay where the dose response are reported as mean values of the concentration that elicit 50% (EC_{50}) of the maximal response (%Emax) normalized to DAMGO.
**Antagonist assay was performed at the DAMGO EC90, the dose response are reported as mean values of the concentration that elicit 50% (IC_{50}) of the maximal inhibition (%inhibition) normalized to naltrexone.

Effect of Stereochemistry

	μOR cAMP EC_{50} nM (%E_{max})	
 2	7.3 (44)	172 (47)  7
 9	104 (22)	62 (33)  12
 10	346 (48)	>3 μM  13
 11	243 (17)	951 (28)  14

- The (S,S)-isomer of urea is the most potent among the four isomers.
- The S-stereochemistry at the amine-bearing stereocenter is important.

Amide Replacements for Ureas and Carbamates



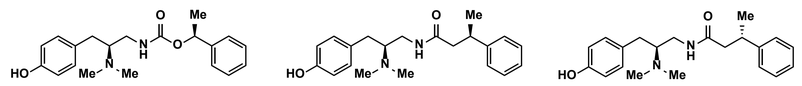
1
μOR EC_{50} = 21 nM

7
μOR EC_{50} = 172 nM

15
μOR EC_{50} = 29 nM

- Amide linkers afford similar potency to the urea linkers.
- Amides are acid stable replacements for carbamates.

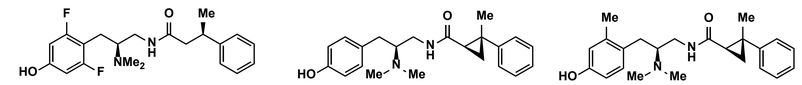
Amides Exhibit Enhanced CNS Penetration



7
μOR EC_{50} = 172 nM
%E_{max} = 47
Brain/Plasma: 323%
CSF/Plasma: 38%

15
μOR EC_{50} = 29 nM
%E_{max} = 70
Brain/Plasma: 125%
CSF/Plasma: 37%

16
μOR EC_{50} = 10 nM
%E_{max} = 69
Brain/Plasma: 96%
CSF/Plasma: 21%



17
μOR EC_{50} = 15 nM
%E_{max} = 33
Brain/Plasma: 76%

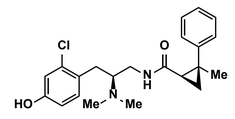
18
μOR EC_{50} = 0.88 nM
%E_{max} = 90
Brain/Plasma: 112%

19
μOR EC_{50} = 0.33 nM
%E_{max} = 100

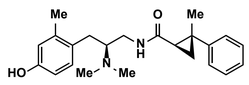
In vivo rat PK: route: P.O., Dose: 30 mg/kg, Time: 60 min

- Amide and carbamate derivatives, have good CNS permeability.
- Amide analogs afford increased μOR activity vs. carbamates.

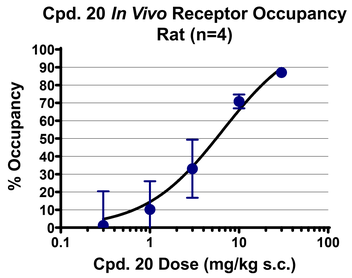
In-vivo Studies of Compound 20



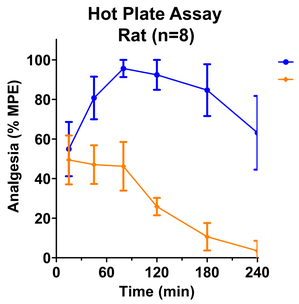
20
μOR IC_{50} (%inhibition) = 29 nM (100)



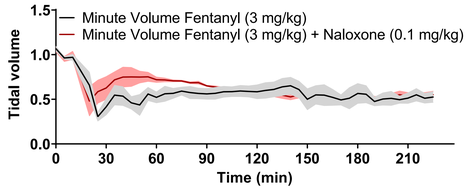
19
μOR EC_{50} (%E_{max}) = 0.33 nM (100)



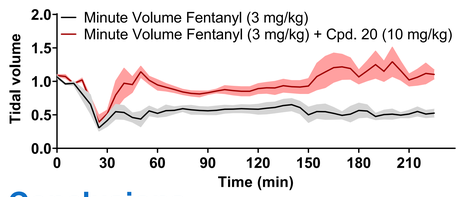
In vivo receptor occupancy was preformed using a previously described protocol.[4] Vehicle or test compounds were injected s.c.; 40 minutes later the tracer (carfentanil 1μg/kg) was injected i.v. through a lateral tail vein. After 20 minutes, animals were sacrificed, thalamic tissue samples were collected and processed for LC/MS/MS.



When co-administered with a full agonist such as **19**, **20** displays strong blockade of analgesic effect in rat hot plate assay.



Compound **20** reverts fentanyl-induced respiratory suppression. The effect appears to be more pronounced and lasts longer than naloxone.



Conclusions

- Structural optimization of PZM21 has led to a novel series of carboxamides with improved potency, tunable μOR efficacy and significantly enhanced CNS permeability.
- Compound **20** at 10 mg/kg in rat, achieved 70% occupancy of CNS MORs, inhibited the analgesic effect of **19** (a full μOR agonist), and rescues fentanyl-induced respiratory suppression.

References

1. Patterson Silver Wolf, D. A.; Gold, M.; . *J. Neurol. Sci.* **2020**, *411*,116718.; **2.** Wide ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; **2020**. http://wonder.cdc.gov.; **3.** Manglik, A.; Lin, H.; Aryal, D. K.; McCorvy, J. D.; Dengler, D.; Corder, G.; Levit, A.; Kling, R. C.; Bernat, V.; Hübner, H.; Huang, X.-P.; Sassano, M. F.; Giguère, P. M.; Löber, S.; Da Duan; Scherrer, G.; Kobilka, B. K.; Gmeiner, P.; Roth, B. L.; Shoichet, B. K.; *Nature* **2016**, *537 (7619)*, 185–190.; **4.** Need AB, McKinzie JH, Mitch CH, Statnick MA, Phebus LA. *Life Sci.* **2007**; *81*, 1389–1396.

Acknowledgements

This work was supported by the National Institutes of Health-National Institute of Drug Abuse grants 1R43DA047723-01 and 1UG3DA049598-01.