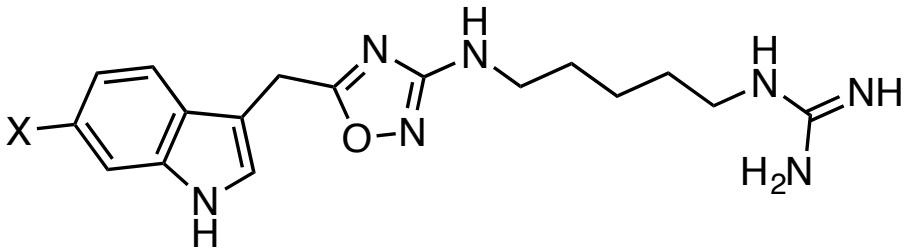
Total Synthesis and Biological Evaluation of Phidianidines A and B Uncovers Unique Pharmacological Profiles at CNS Targets

John T. Brogan, Sydney L. Stoops, Brenda C. Crews, Lawrence J. Marnett, and Craig W. Lindsley

Background

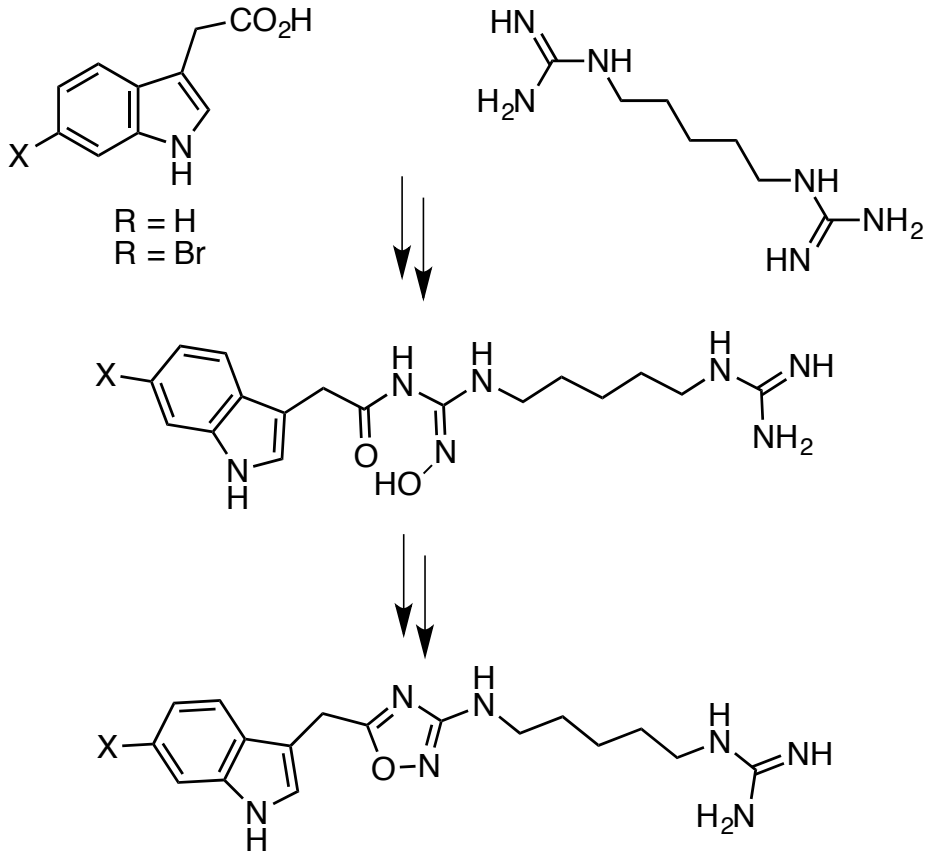


Phidianidine A, X = Br
Phidianidine B, X = H

- Isolated in 2011, from a shell-less mollusk, aeolid opisthobranch *Phidiana militaris*
- Structurally characterized by HRMS/NMR spectroscopy
- Novel 1,2,4-oxadiazole
- IC_{50} 0.1-30 µM cytotoxicity against a variety of tumor cell lines

Org. Lett. **2011**, *13*, 2516

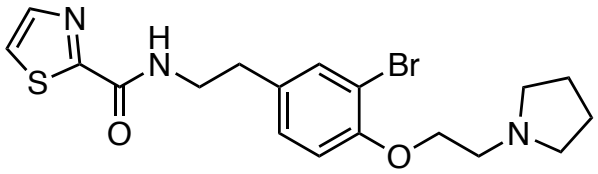
Proposed Biosynthesis



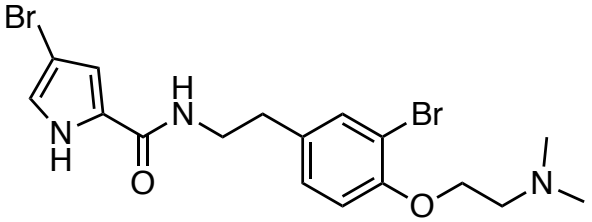
Phidianidine A, X = Br, 90%
Phidianidine B, X = H, 78%

Org. Lett. **2011**, *13*, 2516

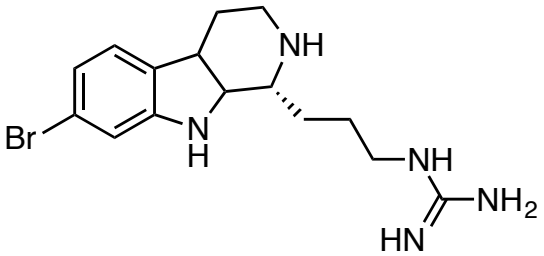
Previous H_3 Antagonists



1, Dispyrin
H_3 IC_{50} = 2.35 μM
H_3 K_i = 1.04 μM



2
H_3 IC_{50} = 30 nM
H_3 K_i = 70 nM



3 (+)-7-bromotrypargine

Target	IC_{50} (μM)	K_i (μM)
H_3	3.6	1.8
DAT	3.8	3.8
NET	1.9	1.9

ACS Chemical Neuroscience **2012**, *3*, 658

Histamine H_3 Receptor

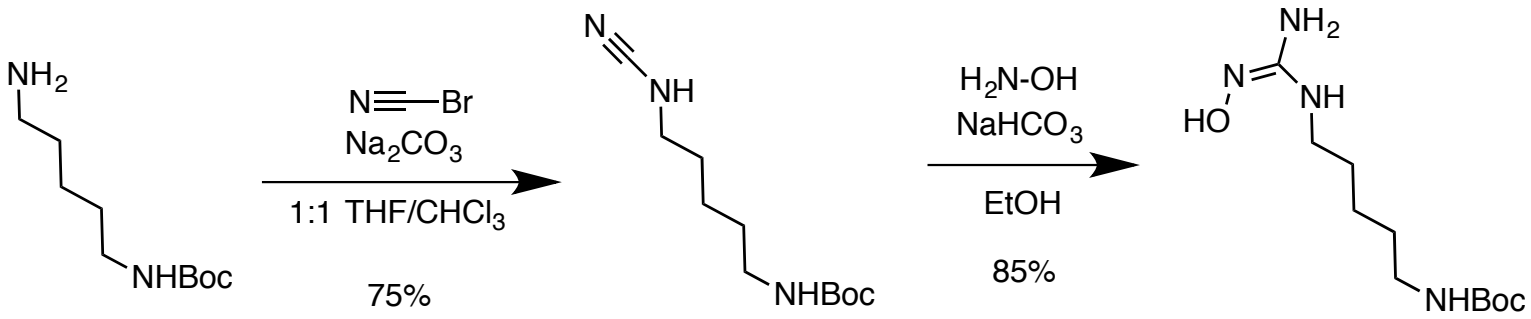
- Histamine H_3 receptors are a Class A G-protein coupled receptor

- Known to inhibit the release of: dopamine, GABA, acetylcholine, noradrenaline, and serotonin

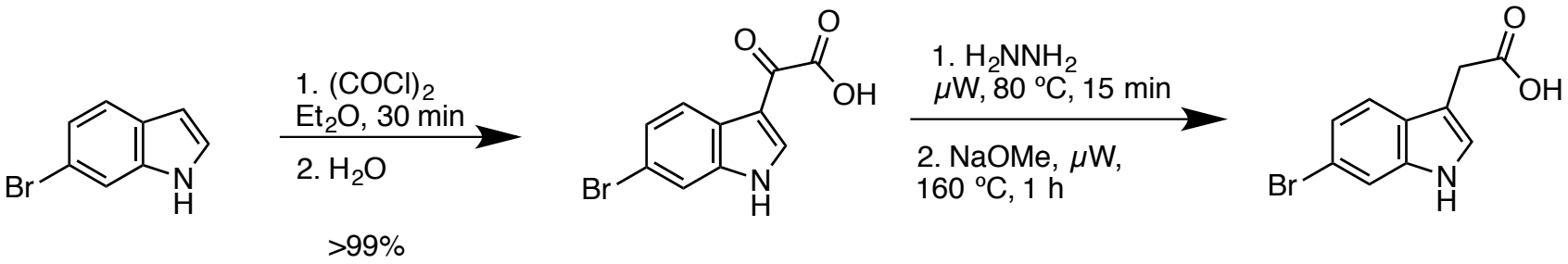
- Potential Therapeutic areas: Obesity, epilepsy, sleep/wake cycle, schizophrenia, Alzheimer's disease, neuropathic pain, and ADHD

http://en.wikipedia.org/wiki/Histamine_H3_receptor

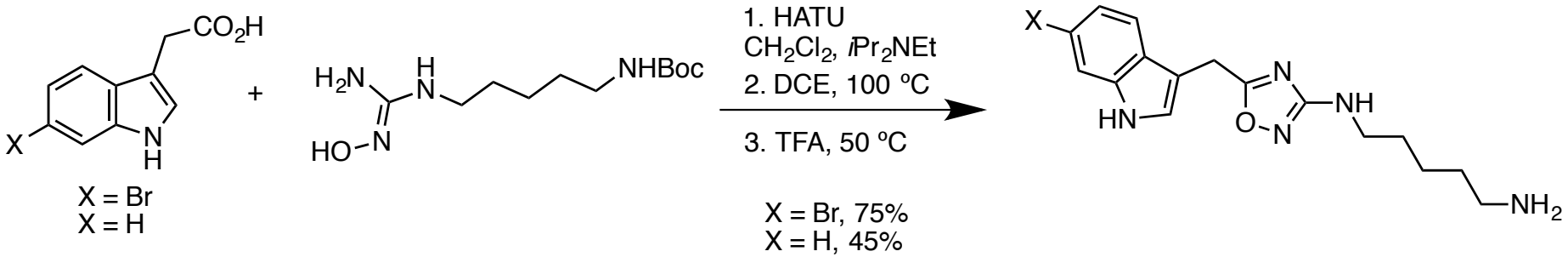
Synthesis of Fragment 1

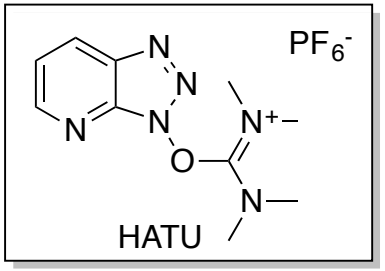


Synthesis of Fragment 2

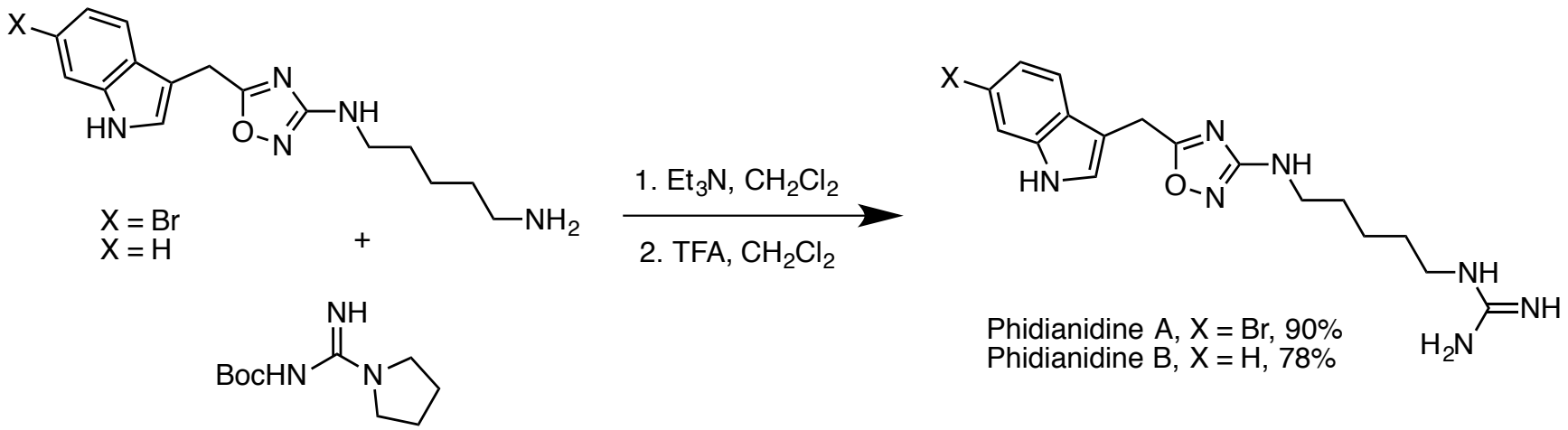


Coupling of Fragments

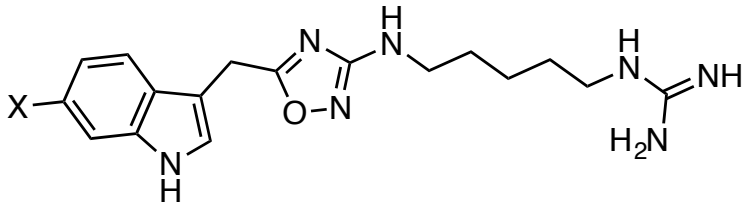




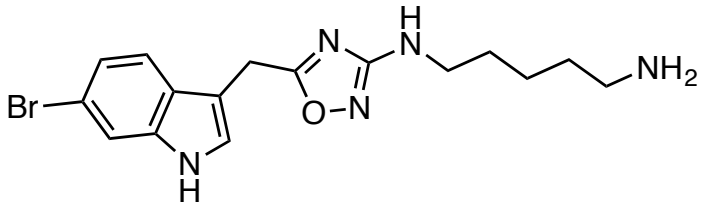
Completion of Total Synthesis



Biological Results



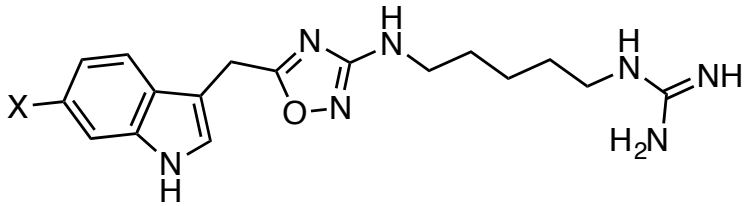
1, Phidianidine A, X = Br
2, Phidianidine B, X = H



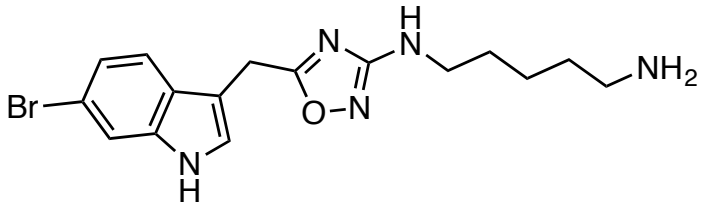
3

cmpd	H_3	DAT	NET	SERT	opioid-μ	opioid-δ	opioid-κ
			(% inhibition @ 10 μM)				
1	25	101	68	22	103	-5	3
2	33	96	45	16	97	-6	5
3	23	98	86	21	88	-2	7

Biological Results



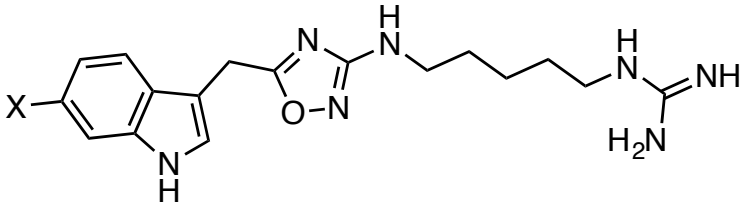
1, Phidianidine A, X = Br
2, Phidianidine B, X = H



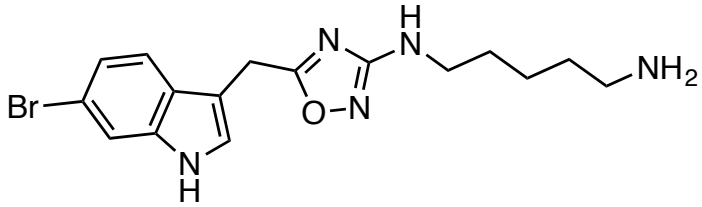
3

cmpd	H_3	DAT	NET	SERT	opioid-μ	opioid-δ	opioid-κ
		(% inhibition @ 10 μM)					
1	25	101	68	22	103	-5	3
2	33	96	45	16	97	-6	5
3	23	98	86	21	88	-2	7

Biological Results



1, Phidianidine A, X = Br
2, Phidianidine B, X = H



3

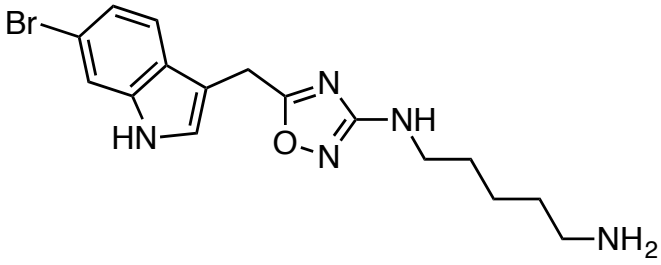
cmpd	DAT		opiod-μ	
	K_i (nM)	IC_{50} (nM)	K_i (nM)	EC_{50}[a]
1	310	390	230	17%
2	680	860	340	12%
3	690	870	800	6%

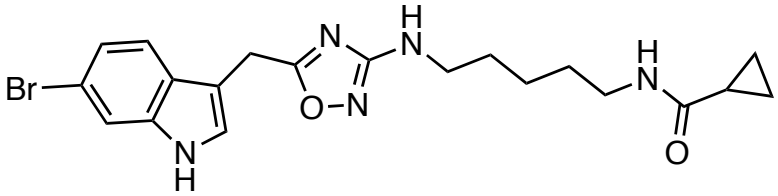
[a]Percent inhition at 10 μM reported in a GTPγS assay relative to 10 μM DAMGO control suggest potential weak, partial agonism of μOR

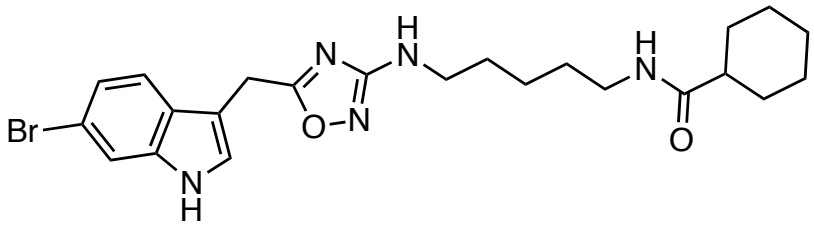
DAT = Dopamine transporter, inhibition → "rewarding" drug stimulus of drugs such as cocaine or amphetamines

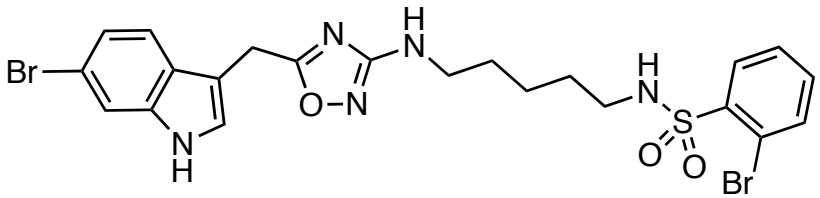
Opioid-μ = GPCR responsible for the analgesia of clinical opioids (aka morphine *etc.*)

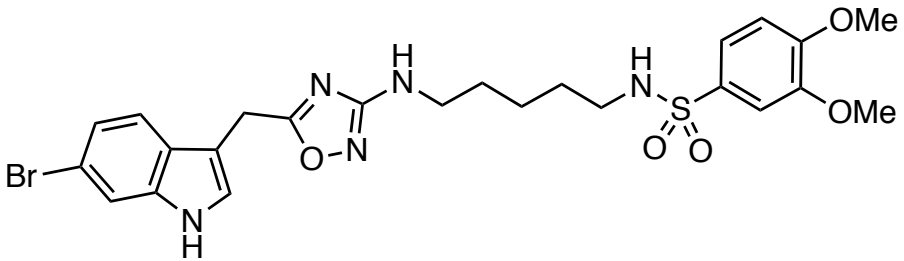
Analogues

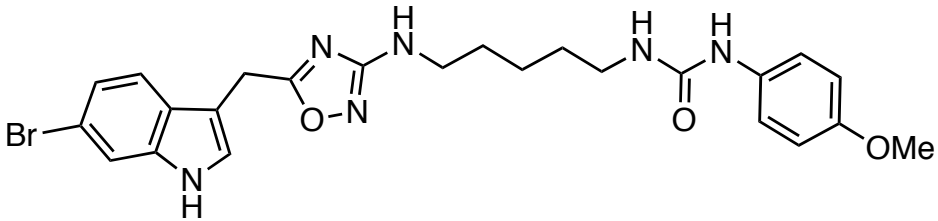

Br
HN
N
O
N
NH
NH2

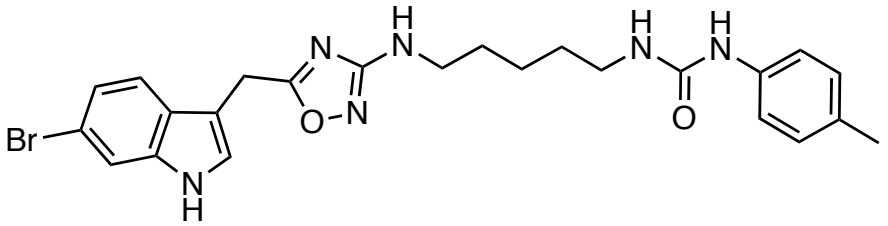

Br
N
H
O
N
H
N
H
N
O


Br
N
H
O
N
H
N
H
N
O

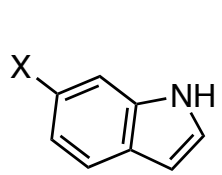

Br
N
H
O
N
H
N
S
O
O
Br


Br
N
H
O
N
H
N
S
O
O
OMe
OMe


Br
N
H
O
N
H
N
H
N
O
OMe


Br
N
H
O
N
H
N
H
N
O

N-Linked Analogue



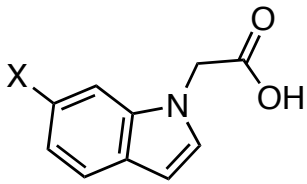
X = Br
X = H

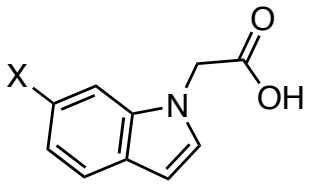
1. Br CO_2Et

K_2CO_3, KI
MeCN, μW, 160 °C

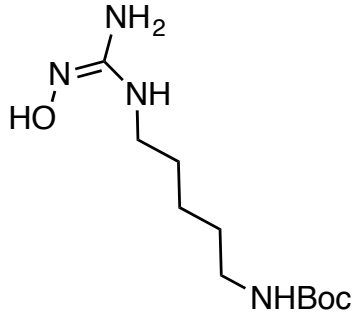
2. 1 M NaOH, dioxane

76%





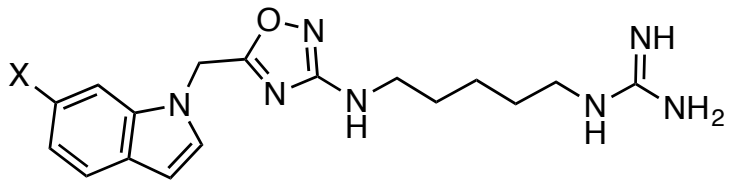
+



1. HATU
CH_2Cl_2, iPr$_2$NEt
2. DCE, 100 °C,

3. TFA, 50 °C

45%



X = Br
X = H

Conclusions

- Total Syntheses were complete
  - Phidianidine A (40% overall yield)
  - Phidianidine B (21% overall yield)
- Both A and B potent inhibitors (nM) of DAT
- Both A and B potent ligands ligands for opiod-μ
- Several analogues synthesized
- Synthetic and Biological studies are ongoing