Two New Sigma-1 Leads Discovered by Scaffold-Hopping

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Introduction

- "Scaffold-hopping" is a drug design strategy based on the idea that replacing one core scaffold with a structurally related group will maintain pharmacologic activity at a given target.
- We found that 3-aminopyrrolidines CWC-1-001 (**1**) and CWC-1-002 (**2**) bind dopamine 4 (D4R) receptors with preferential binding over D1-3R (**Figure 1A**).
- **Hypothesis:** we can "hop" from 3-aminopyrrolidine to piperazine without compromising D4R binding affinity and selectivity.

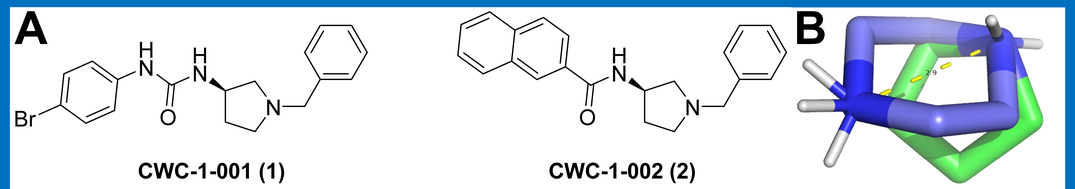
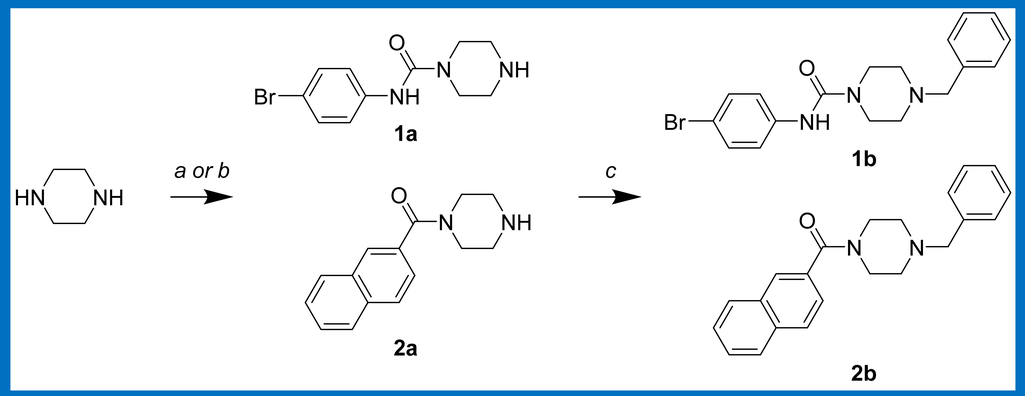


Figure 1: A) Structures of **1** and **2**, with their proposed advantages and disadvantages for drug design. B) The 3-aminopyrrolidine (green) and piperazine (blue) core scaffolds share a similar N-N distance of 2.9 Å.

Synthesis



Scheme 1: Synthesis of **2a** and **2b**. Reagents and conditions: a) 4-Bromophenylisocyanate, NEt_3 (2.2 equiv.), THF, RT, 18 hr, 77%. b) 2-Naphthoyl chloride (1.1 equiv.) NEt_3 (2.2 equiv.), THF, RT, 18 hr, 83%. c) Benzyl bromide (1.1 equiv.), DCM, RT, 18 hr, > 90%. Final product verification was completed using ^{1}H, ^{13}C NMR, HSQC, gCOSY, MS, HPLC, melting point.

Results

	D1	D2	D3	D4	D1/D4	D3/D4	σ1	σ2	σ2/σ1	Other (Ki < 100 nM)
1	> 10,000	> 10,000	1083	20	> 500	54	50	176	3.5	5-HT2B (23)
1b	> 10,000	> 10,000	> 10,000	205	> 49	> 49	14	> 10,000	> 714	
2	1977	1136	322	6.5	304	50	15	71	4.7	5-HT1A (28), 5-HT2B (4), 5-HT2C (62)
2b	> 10,000	> 10,000	528	445	23	1.2	5.1	4113	806	

Table 1: Binding data for novel compounds. Data courtesy of the NIMH Psychoactive Drug Screening Program (PDSP). Data are shown as Ki in nM.

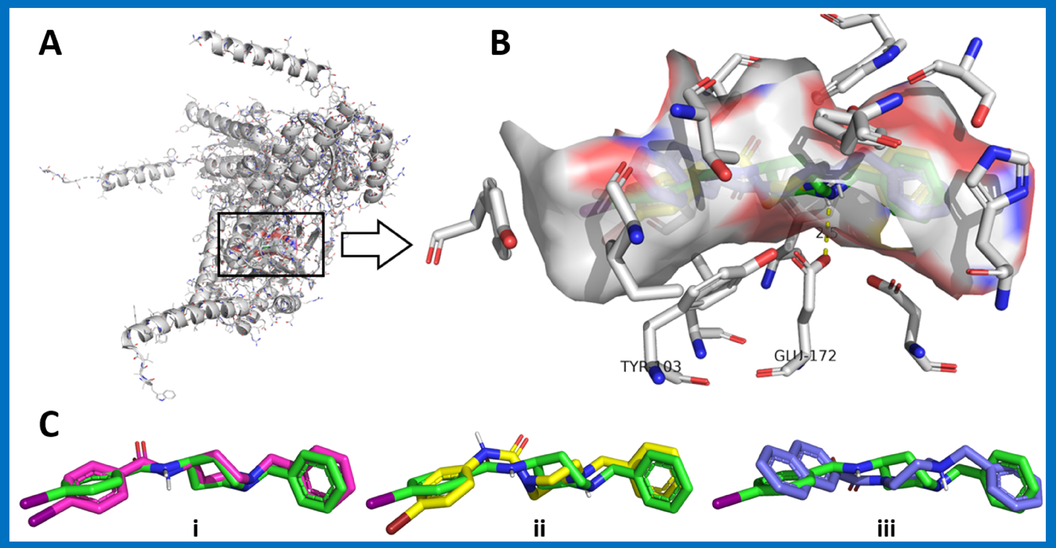


Figure 3: Docking within σ1 receptor. **A)** Global view of σ1 (pdsp 5HK2). **B)** Zoom-in on the σ1 binding pocket. **C)** Overlap of low-energy docked poses compared to co-crystallized 4-IBP (green): **i)** re-docked 4-IBP (magenta), **ii) 1b** (yellow), **iii) 2b**. (*Nature* 2016, 532: 527-530. *Mol. Neurobiol.* 2014, 50: 149-158. *J. Comput. Chem.* 2010, 31: 455-461)

Conclusions

- "Hopping" from 3-aminopyrrolidine to piperazine lowered affinity for dopamine receptors.
- 3-Aminopyrrolidines are "σ1-preferring" and piperazines are "σ1-selective" (Ki ratio > 700).
- Off-target $5\text{-}HT_{1,2}R$ activity greatly diminished.
- CWC-1-024 (**1b**) and CWC-1-025 (**2b**) are new leads for treating neuropsychiatric disorders, substance use disorder, and pain.

Acknowledgements

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