

Highly Selective Low Molecular Weight 5-hydroxytryptamine 2C Receptor Agonists Showing Anti-Feeding Properties and Reduced Cocaine-Induced Locomotor Activity

Andreas Svennebring¹, Sung Jin Cho¹, Niels Jensen², Sudhakar Kadari¹, Carla Elsen³, Thomas Birchfield³, Luna Abdallah⁴, Bryan L Roth², Michael Forster³, Laurence Tecott⁴, Alan P Kozikowski¹.

¹ Drug Discovery Program, University of Illinois at Chicago, Department of Medicinal Chemistry, Chicago, Illinois, 60612, United States; ² University of North Carolina Medical School, Department of Pharmacology, Psychiatry, Comprehensive Cancer center, Center for Neurobiology Division of Medicinal Chemistry and Natural Products, and NIMH Psychoactive Drug Screening Program, Chapel Hill, North Carolina, 27599, United States; ³ University of North Texas Health Science Center at Fort Worth, Department of Pharmacology and Neuroscience, Fort Worth, Texas, 76107, United States; ⁴ UCSF Center for Neurobiology and Psychiatry, Molecular Biology and Genetics in Psychiatry, San Francisco, California, 94158, United States

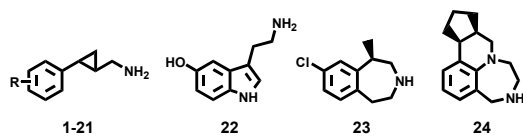
Introduction

The 5-HT_{2C} receptor is involved in the regulation of a variety of functions in the central nervous system connected to mood, cognition, attention and appetite.¹ 5-HT_{2C}-agonists have been suggested as therapeutic drugs for a multitude of disease states:

- Obesity (appetite suppressants)
- Epilepsy
- Depression
- Drug withdrawal symptoms
- Psychosis

Because of structural similarities, 5-HT₂-receptor subtypes A and B have similar ligand preferences as the C subtype. Due to the serious side-effects associated with activation of the A- (hallucinations) and B- (cardiotoxicity) subtypes, C-subtype selectivity is essential.

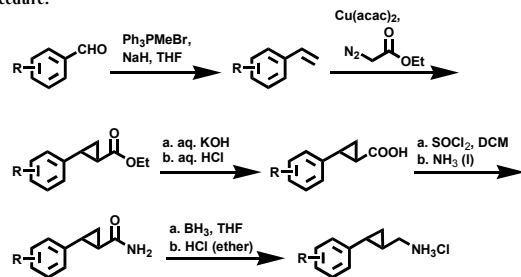
From a hit in a high-throughput screening campaign, we have identified aryl substituted *trans*-(2-phenylcyclopropyl)methylamines (1-21, Scheme 1) as potent and subtype selective 5-HT_{2C}-agonists.² The structural resemblance to 5-hydroxy tryptamine (5-HT, 22) has been helpful in understanding subtype selectivity of these molecules. Currently two 5-HT_{2C} agonists, Lorcaserin (23) and Vabicaserin (24), are undergoing clinical trials for the treatment of obesity and psychosis, respectively.



Scheme 1. Structures investigated.

Synthesis

The compounds presented have been synthesized through the following general procedure:



Scheme 2. Synthesis of 4 and its derivatives.

In vitro

The potency and efficacy at the three 5-HT₂ receptor subtypes has been evaluated in a series of cells overexpressing the different 5-HT₂ subtypes. The ability of the cells to increase calcium influx has been measured by patch clamping and verified by fluorimetric measurements (Table 1).

The structural similarities between 5-HT and the 5-HT_{2C}-selective agonists described seem to well explain the connection between the substituent pattern and 5-HT_{2C}-activity. The preference for halogens showing a weak mesomeric effect (8 and 9) in the 2-position appears rational considering the 2-aniline substituent in 5-HT. The 3-position offers a more erratic structure-activity relationship with strikingly high activity found with a 3-hydroxy substituent as in the native substrate. Any substitution at the 4-position, however, is connected to a severe loss of activity.

#	Compound / R ₂	R ₃	R ₄	5-HT _{2A}		5-HT _{2B}		5-HT _{2C}	
				ED ₅₀ (nM)	E _{max} (%)	ED ₅₀ (nM)	E _{max} (%)	ED ₅₀ (nM)	E _{max} (%)
22	5-HT			10	100	1	100	0.09	100
23	Lorcaserin			406	14	124	86	2.2	98
24	Vabicaserin			NA	NA	NA	NA	6.1	94
1				1399	74	85	93	13	96
2	OH			513	81	492	74	161	94
3	OCH ₃			2166	61	199	83	26	93
4	CH ₃			1606	69	53	86	2.3	99
5	Br			585	73	154	86	25	93
6	Cl			403	54	84	82	5.1	98
7	F			>1000	52	1549	65	37	94
8	CF ₃			NA	NA	350	102	49	101
9	OH			247	92	5.5	98	3.3	94
10	OCH ₃			613	90	75	96	16	97
11	CH ₃			585	86	65	93	4.8	95
12	Br			1680	55	141	74	14	90
13	Cl			1886	42	59	78	10	98
14	F			1769	71	51	106	3.9	92
15	CF ₃			1485	35	77	78	30	94
16	OH			NA	NA	NA	NA	NA	NA
17	OCH ₃			NA	NA	NA	NA	NA	NA
18	Br			>1000	26	2737	51	138	87
19	Cl			4482	64	404	80	76	106
20	F			1098	67	312	95	5.4	93
21	CF ₃			>1000	56	779	91	779	91

Table 1. ED₅₀ and efficacy for the compounds under investigation. NA = No activity.

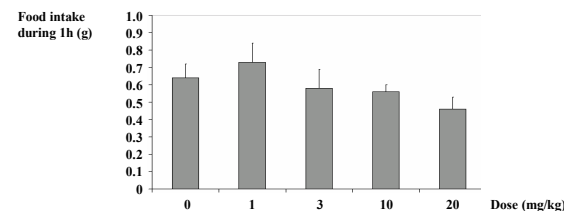
Acknowledgement and References

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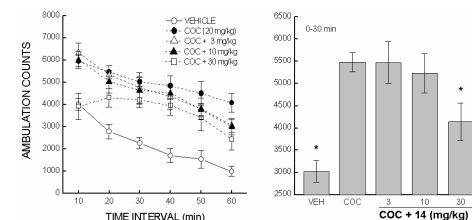
In vivo

The appetite suppressing properties of 14 has been measured in mice.³ The mice were initially presented with food in excess, then starved for 18h. Test subject was then injected with four doses ranging from 1 up to 20 mg/kg and food was again presented to the mice in excess after 30 minutes. After allowing one hour for the mice to feed, the food was removed and weighed to measure consumption. A dose dependent decrease in consumption was found (Scheme 3).



Scheme 3. Anti-feeding test performed on 14.

The ability of 14 to offset the locomotion enhancement effects of cocaine has been measured in mice (Scheme 4).⁴ A series of mice received an intraperitoneal injection with the test compound in three different doses (3, 10, 30 mg/kg) 20 minutes prior to injection with cocaine (20 mg/kg), followed by the measurement of locomotion for one hour. The ability of 14 to reduce the cocaine induced hyperlocomotion is demonstrated below. The dose necessary to offset 50% of the cocaine-induced hyperlocomotion (AD₅₀) was found to be 25 mg/kg.



Scheme 4. Effect of 14 on cocaine induced hyperlocomotion.

Conclusions

- A series of *trans*-(2-phenylcyclopropyl)methylamine derivatives has been prepared and demonstrated to be potent subtype selective 5-HT_{2C}-agonists.
- Structure-activity relationships can be hypothesized from functional data.
- Compound 14 has been demonstrated to possess appetite suppressing properties, and to reduce cocaine enhanced hyperlocomotion in mice.