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Novel naphthyridines are histamine H_3 antagonists and serotonin reuptake transporter inhibitors

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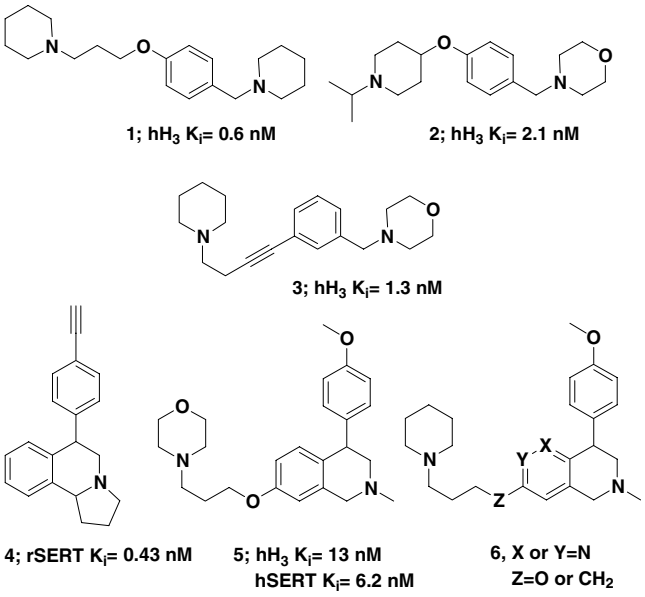
Abstract—A series of novel tetrahydronaphthyridine-based histamine H_3 ligands that have serotonin reuptake transporter inhibitor activity is described. The 1,2,3,4-tetrahydro-2,6-naphthyridine scaffold is assembled via the addition of a nitrostyrene to a metalated pyridine followed by reduction and cyclization to form the naphthyridine. In vitro biological data for these novel compounds are discussed.

Depression is a major health issue that affects millions of people worldwide.[1] Many of these individuals also suffer from cognitive impairment[2] and fatigue.[3] Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed antidepressant drugs, however these agents often fail to improve the cognitive impairment and fatigue observed in many patients even as mood improves.[4,5] Some treatments even induce fatigue and excessive sleepiness.[6,7] Co-administration of wake-promoting agents such as modafinil[8–10] with SSRIs represents one viable strategy to improve the efficacy of SSRI therapy. However, although effective, modafinil has not seen widespread use in part because it is a Schedule IV compound[11] and a P450 inhibitor.[12]

Since H_3 receptor antagonists are known to improve cognition[13] and increase wakefulness[14,15] in animal models without showing nonspecific stimulant effects[16] we hypothesized that dual H_3 antagonists/serotonin reuptake inhibitors might be useful for the treatment of depression. Toward this goal, we recently disclosed the combination of our potent propyloxypiperidine-based H_3 pharmacophore **1**[17] with tetrahydroisoquinoline-based transporter inhibitors related to **4**.[18] This work led to the discovery of potent dual H_3 antagonists/serotonin reuptake transporter (SERT) inhibitors exemplified by **5**.[19]

In this report, we describe the combination of a tetrahydronaphthyridine core **6** and previously described H_3 pharmacophores **1**, **2**,[20] and **3** to produce a new class of dual H_3 antagonists/SERT inhibitors **6**. Introduction of the nitrogen in the core naphthyridine ring structure was expected to alter the physical properties of these dual ligands, however it was not clear at the outset of this research what effect the nitrogen would have on activity at either target. We now describe the preparation and biological activity of novel 2,6- and 2,5-tetrahydronaphthyridines **6**.



Keywords: Histamine H_3 antagonists; Serotonin reuptake inhibitors; Naphthyridines.
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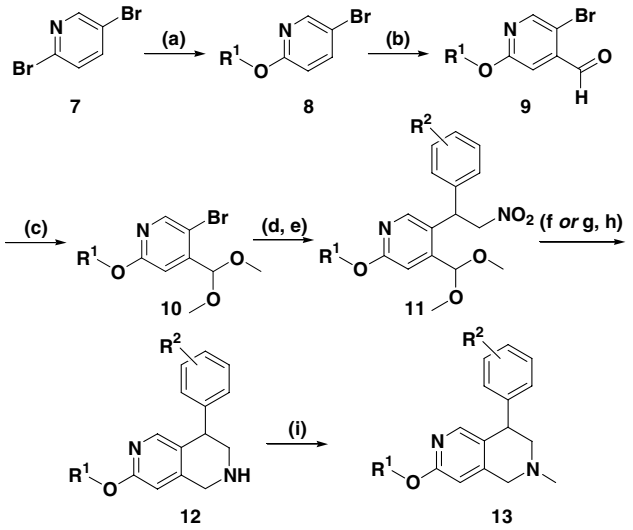


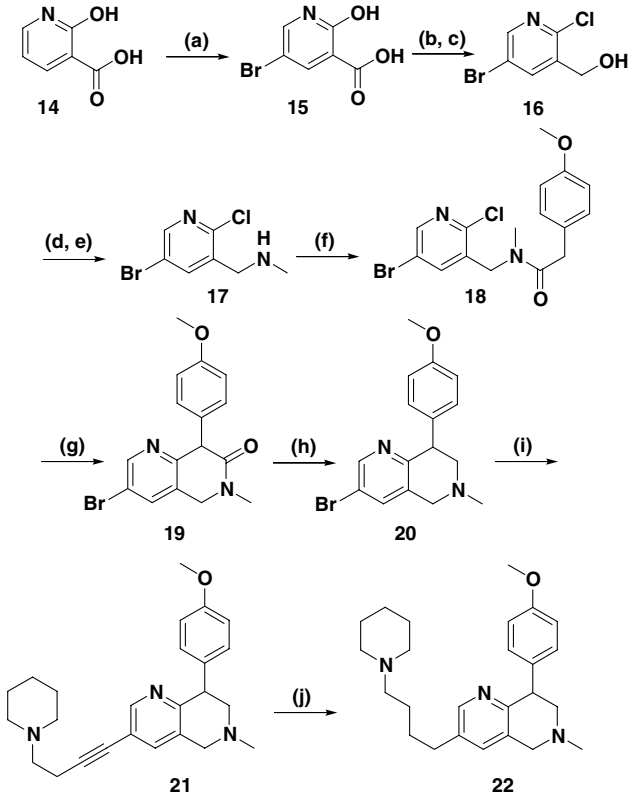
Scheme 1. Synthesis of 2,6-naphthyridines. Reagents and conditions: (a) NaH, DMF, R^1OH, 23 °C, 16 h, 37–84%; (b) diisopropylamine, *n*-butyl lithium, THF, −78 °C, then DMF, −78 °C, 0.5 h, then 23 °C, 0.5 h; (c) H_2SO_4, MeOH, 23 °C, 18 h, 38–89% for two steps; (d) *n*-butyl lithium, THF, −78 °C, 0.5 h; (e) various nitrostyrenes, −78 °C, 0.5 h, then HOAc, 21–65%; (f) Zn, HOAc, 40 °C, 18 h; (g) Zn, 6 N HCl, 18 h; (h) $NaBH_4$, EtOH, 23 °C, 1 h, 21–96% for three steps; (i) $(CH_2O)_n$, MeOH, 55 °C, then $NaBH_4$, 23 °C, 1 h, 14–51%.

The synthesis of the 2,6-naphthyridines began with the preparation of the trisubstituted pyridine **9** from 2,5-dibromopyridine as shown in Scheme 1.

Reaction of 2,5-dibromopyridine with pre-formed sodium alkoxides provided the 2-alkoxy-5-bromopyridines **8** in good yield. Subsequent metalation of the 4-position of the pyridine ring with LDA[21] was followed by reaction with DMF to form the unstable aldehydes **9**, which were converted directly to the dimethoxy acetals **10** in reasonable overall yields. The key step in the sequence was the low temperature lithium-halogen exchange on the bromopyridines **10**, followed by reaction with a nitrostyrene[22] to form the nitroalkanes **11**. It was important to maintain the temperature of this reaction at −78 °C in order to obtain reasonable yields. Yields dropped precipitously when the reaction temperatures were higher. For this reason the nitrostyrene was typically added as a pre-cooled solution in tetrahydrofuran and the reaction was quenched with acetic acid at −78 °C prior to work-up. Reduction of the nitroalkane to an alkyl amine was then accomplished by reaction with zinc in acetic acid. As this procedure variably produced a small amount of cyclized imine product, it was generally best to treat the crude mixture directly with zinc in 6 N HCl to form the imines, which were then reduced with sodium borohydride to form **12**. Alternatively, zinc in 6 N HCl could be used to form the imines directly from **11**. Reductive amination of **12** then produced the *N*-methyltetrahydronaphthyridines **13** in moderate yields.

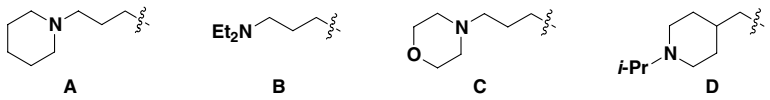
The synthesis of the 2,5-naphthyridines (Scheme 2) proceeded smoothly from 2-hydroxynicotinic acid **14** via bromination of the 5-position of the pyridine ring, which was followed by chlorination of the hydroxypyridine and reduction of the acid to form the (5-bromo-2-chloropyridin-3-yl)-methanol **16** in 54% yield over three steps. The alcohol was then converted to the mesylate and treated with methylamine to form the benzyl amine **17** (47% for two steps), which was acylated to give the acyclic amide **18**. Treatment of the amide with NaH in DMSO then gave a good yield of the lactam provided the reaction was monitored closely. Allowing the ring closure reaction to proceed beyond the time required to consume starting material consistently resulted in diminished yields. Borane reduction of the lactam then gave the desired 2,5-naphthyridine ring system **20**. Palladium-catalyzed coupling of 1-but-3-ynylpiperidine formed the alkyne **21** in good yield. The alkyne was then reduced to the alkane via hydrogenation.

Rat and human SERT data, human histamine H_3 binding data, and functional antagonist data for the 2,6-naphthyridines **12** and **13** are shown in Table 1.[16,19,20]



Scheme 2. Synthesis of 2,5-naphthyridines. Reagents and conditions: (a) Br_2, 50% NaOH, H_2O, 0–50 °C, 18 h, 78%; (b) thionyl chloride, DMF, 70 °C, 4 h, 99%; (c) isobutyl chloroformate, Et_3N, THF, 0 °C, then $NaBH_4$, 0–23 °C, 18 h, 70%; (d) $MeSO_2Cl$, DIPEA, THF, 0 °C; (e) 40% aqueous $MeNH_2$, 23 °C, 2 h, 47% two steps; (f) 4-methoxyphenylacetyl chloride, *N*-methylmorpholine, DCM, 0–23 °C, 18 h, 94%; (g) NaH, DMSO, 23 °C, 2 h, 65%; (h) BH_3THF, THF, 60 °C, 2 h, 71%; (i) PPh_3, 1-but-3-ynyl-piperidine, CuI, $(Ph_3P)_2PdCl_2$, DMF, Et_2NH, 120 °C, 75 min, 67%; (j) H_2, Pd/$BaSO_4$, EtOH, 23 °C, 4 h, 96%.

Table 1. Binding data for the rat and human serotonin reuptake transporters and for the human histamine H_3 receptor for compounds **12** and **13**



A B C D

Compound	R_1	R_2	Rat SERT K_i[a] (nM)	Human SERT K_i[a] (nM)	Human H_3 K_i[a] (nM)	Human pA_2[b]
12a	A	3,4-Dichloro	20 (±7)	32 (±23)	5 (±1)	7.95 ($n = 2$)
13a	A	3,4-Dichloro	15 (±3)	120 (±66)	18 (±8)	7.74 ($n = 3$)
12b	A	4-Chloro	30 (±5)	141 (±12)	2 (±1)	8.41
13b	A	4-Chloro	22 (±2)	106 (±7)	15 (±3)	
12c	A	2-Chloro	194 (±51)	1333 (±408)	1 (±1)	8.98
13c	A	3-Chloro	144 (±68)	826 (±214)	7 (±3)	8.01
13d	A	4-Chloro-3-fluoro	26 (±1)	147 (±66)	7 (±2)	7.78
13e	A	3-Methoxy	59 (±8)	302 (±61)	8 (±4)	7.59
12d	A	4-Methoxy	46 (±10)	147 (±17)	4 (±0)	8.23
13f	A	4-Methoxy	34 (±8)	107 (±69)	12 (±6)	
13g	A	4-Fluoro	186 (±59)	362 (±43)	9 (±3)	8.45
13h	A	H	569 (±282)	1137 (±548)	5 (±2)	7.67
12e	A	H	1667 (±408)	2333 (±548)	1 (±0)	9.14
13i	A	2-Fluoro	191 (±57)	768 (±458)	2 (±0)	8.98
12f	B	3,4-Dichloro	15 (±2)	26 (±7)	7 (±0)	7.85
13j	B	3,4-Dichloro	33 (±11)	30 (±15)	16 (±2)	
12g	B	4-Methoxy	129 (±51)	226 (±104)	23 (±5)	
13k	B	4-Methoxy	19 (±3)	66 (±12)	13 (±1)	
13l	B	H	583 (±256)	2000 (±0)	4 (±2)	9.18
12h	C	4-Methoxy	53 (±9)	189 (±19)	43 (±10)	
13m	C	4-Methoxy	29 (±15)	70 (±5)	90 (±17)	7.93 ($n = 2$)
12i	C	H	2000 (±707)	4767 (±286)	13 (±2)	
12j	D	3,4-Dichloro	18 (±3)	37 (±12)	13 (±3)	
13n	D	3,4-Dichloro	23 (±8)	31 (±5)	13 (±4)	
12k	D	4-Methoxy	15 (±6)	93 (±31)	4 (±0)	8.45
13o	D	4-Methoxy	45 (±19)	62 (±4)	13 (±1)	
Fluoxetine			2.9(±0.6)	2.2 (±0.6)	7300 (±1100)	

[a] Values are means of at least three experiments in triplicate, standard error of the mean is in parentheses.
[b] Unless indicated, this is the result of a single experiment.

All compounds in Table 1 were tested as racemic mixtures.[23] Data for the more conformationally restricted piperidinemethanol compounds **12j–k** and **13n–o** are also detailed in Table 1. Most of the compounds in the table are potent human histamine H_3 ligands. Exceptions are the morpholine analogs **12h** and **13m**. In most cases the N–H tetrahydronaphthyridines **12** have higher affinity for the H_3 receptor than the *N*-CH_3 analogs **13**. All of the compounds tested were functional antagonists of the histamine H_3 receptor (pA_2's between 7.59 and 9.14).

Substituents on the aromatic ring (R^2) have a dramatic effect on rat and human SERT activity. Substitution in the 3- or 4-position is preferred for SERT activity. SERT activity is practically eliminated when the 3- and 4-positions of the aromatic ring are not substituted (e.g., **13h** and **12e**). The most potent analogs at the SERT are the 3,4-dichloro- or 4-methoxy derivatives. Noticeable differences between the rat and human SERT potency are observed in many cases. Typically these compounds are less potent at the human SERT than at the rat SERT, reinforcing the need to screen at the human transporter. The 2,5-naphthyridines **21** (hSERT $K_i = 1800$ nM, hH_3 $K_i = 38$ nM) and **22** (hSERT $K_i = 2500$ nM, hH_3 $K_i = 57$ nM) are significantly less potent ligands for either target, suggesting a strong preference against the presence of a nitrogen at this position on the tetrahydronaphthyridine.[24]

In order to assess the brain-penetrating ability of a prototype compound, **12i** was dosed orally at 10 mg/kg in rats and the brain and plasma concentrations were measured at 1, 6, and 24 h. In this experiment, the plasma C_{max} was 0.22 μM at 1 h and the brain C_{max} was 5.56 μM at 6 h postdose. Significant brain concentrations (>0.6 μM) were also observed at 24 h, indicating that this prototype compound should be expected to have a long duration of action.

In conclusion, we have developed viable synthetic routes to novel 4-aryl-2,6-tetrahydronaphthyridines and 4-aryl-2,5-tetrahydronaphthyridines. The 4-aryl-2,6-tetrahydronaphthyridines represent a novel class of potent dual H_3 antagonists/SERT inhibitors. A prototype compound in this series was shown to readily penetrate the brain of a rat indicating that these compounds may be viable leads for CNS targets. We have also demonstrated that the 2,5 tetrahydronaphthyridine core, at least in the case of the 7-alkyl analogs shown, is not favored for SERT affinity. Further studies detailing the pharmacology of dual histamine H_3 antagonists and serotonin reuptake inhibitors will be the subject of future disclosures.

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23. Previous studies (Ref. 19) with tetrahydroisoquinolines demonstrated that the (*R*)- and (*S*)-enantiomers of those compounds are nearly equipotent at both targets. In this study, the enantiomers of compound **12a** were also found to be essentially equipotent at the human H_3 receptor and the rat SERT.
24. The direct tetrahydroisoquinoline comparator to compound **21**, that is, 4-(4-methoxyphenyl)-2-methyl-7-(4-piperidin-1-yl-but-1-ynyl)-1,2,3,4-tetrahydroisoquinoline, is reported to have the following K_i's; human H_3 $K_i = 3$ nM, human SERT $K_i = 4$ nM (see Carruthers, N. I.; Gomez, L. A.; Jablonowski, J. A.; Keith, J. M.; Letavic, M. A.; Ly, K. S.; Miller, J. M. B.; Stocking, E. M.; Wolin, R. L. PCT Int. Appl. 2006, WO 2006066197 A1), also indicating that there is a preference against the presence of the nitrogen atom in the 2,5-naphthyridine structure, particularly with respect to SERT affinity.