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Synthesis and biological activity of piperazine and diazepane amides that are histamine H_3 antagonists and serotonin reuptake inhibitors

Kiev S. Ly, Michael A. Letavic,* John M. Keith, Jennifer M. Miller, Emily M. Stocking, Ann J. Barbier,† Pascal Bonaventure, Brian Lord, Xiaohui Jiang, Jamin D. Boggs, Lisa Dvorak, Kirsten L. Miller, Diane Nepomuceno, Sandy J. Wilson and Nicholas I. Carruthers

Johnson & Johnson Pharmaceutical Research & Development L.L.C., 3210 Merryfield Row, San Diego, CA 92121, USA

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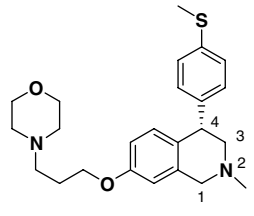
Abstract—The synthesis and biological activity of a new series of piperazine and diazepane amides is described. The new compounds are high affinity histamine H_3 ligands and serotonin reuptake inhibitors.

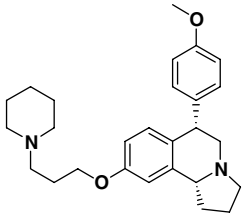
Selective serotonin reuptake inhibitors (SSRIs) are the current first line treatments for depression, a disease that affects millions of people worldwide.[1] While effective in many cases, SSRIs typically have a slow onset of action and also have little effect on cognitive impairment and fatigue, conditions that are reported by many depressed patients.[2,3] In order to address some of these issues many physicians now co-prescribe stimulants with SSRIs for the treatment of depression.[4] While this approach appears to be useful in some instances, there are a variety of reasons why stimulants are not the ideal choice for the treatment of depression, including the fact that many stimulants increase dopamine levels which can lead to unwanted behavioral effects.

We recently reported on several classes of histamine H_3 antagonists with serotonin reuptake inhibitor activity as possible alternative approaches for the treatment of depression.[5–9] Histamine H_3 antagonists have been shown to increase wakefulness[10,11] in preclinical models without showing nonspecific stimulant effects,[12] thus we hypothesized that histamine H_3 antagonists with SSRI activity might provide an improved therapy for the treatment of depression. As part of these efforts we recently detailed the in vitro and in vivo pharmacology of JNJ-28583867 (**1**), a potent histamine H_3 antagonist and serotonin reuptake inhibitor.[13]

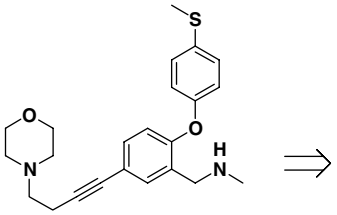
Initial leads for the histamine H_3/serotonin reuptake inhibitor program included the hexahydropyrrolo-isoquinoline **2**. Removal of the pyrrole ring led to the simplified 4-aryltetrahydroisoquinolines, including JNJ-28583867. These efforts eventually led to the discov-



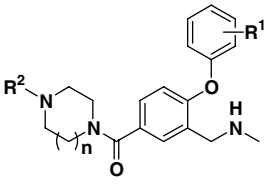
1 (JNJ-28583867)
hH_3 K_i= 10.6 nM
hSERT K_i= 3.7 nM



2, hH_3 K_i= 0.7 nM
hSERT K_i= 3.3 nM



3, hH_3 K_i= 11 nM
hSERT K_i= 0.8 nM



4 (n=1,2)

Keywords: Histamine H3 antagonist; Serotonin reuptake inhibitor; Histamine; Serotonin.
* Corresponding author. Tel.: +1 858 450 2302; e-mail: mletavic@prdus.jnj.com
† Present address: Shire Human Genetic Therapies, 700 Main street, Cambridge MA 02139, UK.

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ery of the even less complicated but related alkyne-based benzyl amines, represented by **3**.

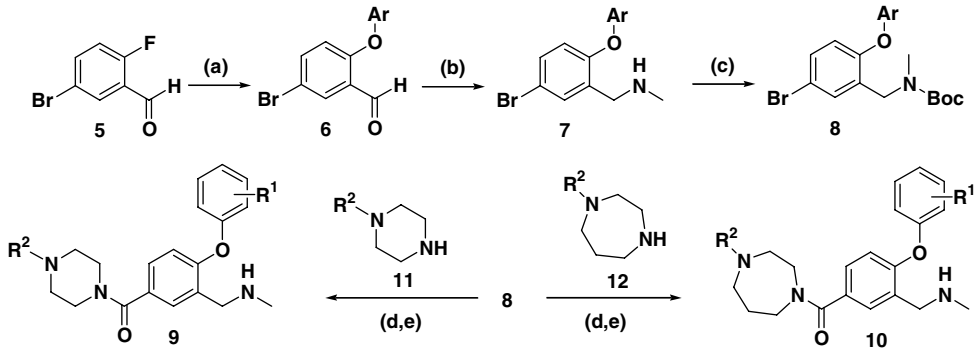
The alkyne subunit of **3** represents one of the many H_3 pharmacophores[14,15] that have been reported in the literature over the past few years. We now report on a related series of piperazine and diazepane amides **4** that are also dual H_3 antagonists/serotonin reuptake inhibitors.

Intermediates **8** were easily obtained via the procedures previously described for the synthesis of the alkynes **3**[9] from 5-bromo-2-fluorobenzaldehyde **5** by reaction with a variety of phenols, followed by reductive amination with methylamine and protection as the Boc amine **8** (Scheme 1).

Compounds **8** were then directly converted to the desired compounds **9** and **10** by microwave assisted aminocarbonylation reactions[16,17] followed by Boc deprotection.[18]

Our initial work focused on the piperazine compounds **9** (Table 1). Previous studies had demonstrated that small alkyl and cycloalkyl substituents were likely to be preferred on the piperazine (for H_3 affinity) and the compounds in Table 1 confirmed our earlier findings by affording high affinity H_3 ligands.[19] The preferred piperazine substituents in Table 1 are isopropyl and cyclobutyl. Cyclopropyl groups generally reduced H_3 affinity for this series.

The isopropyl diazepanes **10a–d** are also high affinity histamine H_3 ligands and SERT inhibitors (Table 2). We also prepared the cyclopropyl diazepanes **10e–w** (Table 3). These cyclopropyl diazepanes proved to be very high affinity histamine H_3 ligands and, with the appropriate aryloxy substituent, they are also potent SERT inhibitors. As was also observed in our earlier work with tetrahydroisoquinolines, the substituent on the aryloxy ring had a large effect on the serotonin reuptake transporter (SERT) affinity. The highest affinity for SERT was observed when the aryl ring was substituted in the 4-position. As examples, unsubstituted analogs (e.g., **9o**, **10k**), or those substituted only in the 2- or 3-positions of the ring (e.g., **9n**, **9p**, **10d**, **10o**, **10s**), had much lower affinity for

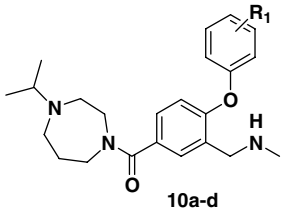


Scheme 1. Synthesis of compounds **9** and **10**. Reagents and conditions: (a) K_2CO_3, ArOH, DMF, 90 °C, 18–72 h; (b) 40% aqueous $MeNH_2$, MeOH, 0 °C, 20 min, then $NaBH_4$, 0 °C, 0.5 h, then 23 °C, 18–24 h; (c) di-*tert*-butyl dicarbonate, CH_2Cl_2, 23 °C, 1 h; (d) **11** or **12**, THF, DBU, Hermann's catalyst,[18] *t*-Bu_3PHBF_4, $Mo(CO)_6$, 125 °C, microwave, 6 min; (e) TFA, CH_2Cl_2.

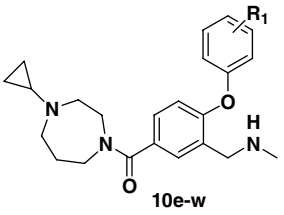
Table 1. Binding data for the rat and human serotonin reuptake transporters and for the human H_3 receptor for compounds **9**

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 H_3pA_2[a]
9a	4-MeS–	*i*-Pr	1.8 (±0.1)	5.9 (±1.5)	2.2 (±0.6)	8.57 (±0.01)
9b	4-MeS–	*c*-Pr[b]	4.0 (±0.5)	5.0 (±0.6)	29 (±5)	
9c	4-MeS, 3-Me–	*i*-Pr	5.8 (±0.6)	8.1 (±2.7)	4.3 (±1.8)	8.15 (±0.08)
9d	4-MeS, 3-Me–	*c*-Pr	4.2 (±2.2)	11 (±3)	21 (±5)	
9e	3,4 diCl–	*i*-Pr	4.9 (±0.7)	6.3 (±2.9)	2.4 (±1.1)	8.17 (±0.05)
9f	3,4 diCl–	*c*-Pr	9.3 (±0.7)	6.8 (±0.3)	23 (±4)	8.10 (±0.00)
9g	3,4 diCl–	*c*-Bu	12 (±2)	16 (±3)	7.7 (±2.5)	8.35 (±0.14)
9h	3,4 diCl–	*c*-Pent	11 (±2)	15 (±3)	20 (±7)	
9i	4-Cl–	*i*-Pr	8.2 (±2.5)	24 (±7)	1.1 (±0.3)	8.63 (±0.00)
9j	4-Cl–	*c*-Pr	9.7 (±3.7)	23 (±9)	11 (±3)	
9k	4-Cl–	*c*-Bu	10 (±2)	39 (±2)	2.4 (±0.2)	
9l	4-Cl–	*c*-Pent	8.1 (±1.2)	24 (±1)	3.4 (±1.0)	
9m	3-MeO–	*i*-Pr	18 (±6)	28 (±5)	1.1 (±0.2)	8.53 (±0.09)
9n	3-Cl–	*c*-Pr	113 (±18)	155 (±68)	14 (±5)	
9o	H	*c*-Pr	186 (±132)	535 (±203)	6.8 (±0.9)	
9p	3-F–	*c*-Pr	102 (±28)	363 (±95)	15 (±2)	
9q	4-F_3C–	*c*-Pr	16 (±2.5)	37 (±18)	37 (±4)	

[a] Values are means of at least three experiments in triplicate, standard error of the mean is in parentheses.
[b] Cyclopropyl.



10a-d



10e-w

SERT than compounds that have a substituent in the 4-position of the ring.

Select compounds were tested in a histamine H_3 functional assay and in all cases the compounds were found to be H_3 antagonists (pA_2 data, Tables 1–3). Compounds **9a** and **10h** were also screened in a commercial panel of 50 receptor, ion channel, and transporter assays (CEREP, www.cerep.com). Both compounds have weak affinity for the μ-opiate receptor and **10h** has weak muscarinic-3 receptor affinity.[20] Compounds **9a** and **10h** also have significant affinity for the norepinephrine transporter (NET) and dopamine transporter (DAT) in this assay. We confirmed this preliminary data by generating K_i's for select compounds against both of these targets. The compounds generally have very weak affinity for the dopamine transporter, however they variably have moderate affinity for the norepinephrine transporter (Table 4).

Several of the compounds in Tables 1–3 were screened in preliminary in vivo assays. Initially, plasma and brain levels of the drug in rats were measured following oral administration. This provided a crude measure of bioavailability and of brain exposure. Also, measurement of receptor/transporter occupancy could be performed in the same experiment, if warranted.

Compound **9f** is representative of the more promising analogs. Figure 1 shows the plasma and brain concentrations following a 10 mg/kg p.o. dose of **9f**. Good exposure (C_{max} in excess of 1 μM) was obtained both in plasma and in the brain. A pharmacokinetics experiment was then performed in rats (Fig. 2). Consistent with the earlier result, compound **9f** has good rat pharmacokinetic parameters (iv $t_{1/2} = 16.1 \pm 0.9$ h, $F = 93\%$, $C_l = 10.2 \pm 1.0$ mL/min/kg, and $V_{ss} = 13.0 \pm 1.2$ L/kg). An ex-vivo autoradiography[13] experiment was also performed using **9f** in order to confirm receptor occupancy at the histamine H_3 receptor and at the serotonin transporter. The results are shown in Figures 3 and 4. There is a dose dependent increase in receptor/transporter occupancy. In a similar experiment (data not shown), no significant NET occupancy was measured. In contrast to the good exposure observed for **9f** in rat, several of the compounds with higher histamine H_3 affinity had poorer PK properties. For example **9a**, **9e**, **10e**, and **10g** had very low exposure (both in plasma and brain tissue) in similar experiments.

In conclusion, we have prepared and characterized a new class of histamine H_3 antagonists with serotonin reuptake inhibitor activity. Members of this series have acceptable preclinical pharmacokinetics, which enabled

Table 2. Binding data for the rat and human serotonin reuptake transporters and for the human H_3 receptor for compounds **10a–d**

Compound	R^1	Rat SERT K_i[a] (nM)	Human SERT K_i[a] (nM)	Human H_3 K_i[a] (nM)	Human H_3 pA_2[a]
10a	4-MeS–	1.0 (±0.3)	5.0 (±0.5)	1.1 (±0.1)	9.95 ($n = 1$)
10b	3,4 diCl–	1.9 (±0.2)	14 (±7)	1.2 (±0.2)	8.86 (±0.04)
10c	4-Cl–	1.4 (±0.4)	6.4 (±0.7)	0.5 (±0.3)	10.72 ($n = 1$)
10d	3-Cl–	14 (±4)	116 (±15)	1.0 (±0.1)	9.98 (±0.25)

[a] Values are means of at least three experiments in triplicate except where indicated, standard error of the mean is in parentheses.

Table 3. Binding data for the rat and human serotonin reuptake transporters and for the human H_3 receptor for compounds **10e–w**

Compound	R^1	Rat SERT K_i[a] (nM)	Human SERT K_i[a] (nM)	Human H_3 K_i[a] (nM)	Human H_3 pA_2[a]
10e	4-MeS–	2.2 (±0.7)	2.9 (±0.4)	1.4 (±0.3)	9.76 (±0.49)
10f	4-MeS, 3-Me–	9.5 (±4.2)	12 (±5)	4.1 (±3)	9.06 (±0.4)
10g	3,4 diCl–	9.1 (±1.2)	9.0 (±2.1)	1.8 (±0.2)	9.76 (±0.18)
10h	4-Cl–	3.8 (±0.7)	10 (±3)	1.1 (±0.1)	10.1 (±0.1)
10i	3-MeO–	4.5 (±0.7)	13 (±2)	1.0 (±0.1)	10.37 (±0.12)
10j	3-Cl–	9.7 (±2.5)	47 (±19)	0.9 (±0.2)	10.4 (±0.0)
10k	H	37 (±6)	229 (±91)	0.8 (±0.1)	10.7 (±0.0)
10l	2-F–	117 (±18)	562 (±43)	1.0 (±0.1)	
10m	3-F–	39 (±11)	236 (±94)	1.0 (±0.0)	10.00 (±0.52)
10n	4-F–	6.7 (±0.8)	68 (±6)	0.8 (±0.3)	10.65 ($n = 1$)
10o	2-F_3C–	900 (±122)	1400 (±349)	2.0 (±0.5)	9.41 ($n = 1$)
10p	4-F_3C–	11 (±2)	17 (±6)	2.0 (±0.5)	9.68 (±0.12)
10q	4-F, 3-Cl–	8.5 (±2.2)	36 (±2)	1.5 (±0.5)	10.32 (±0.06)
10r	4-Cl, 2-F–	7.9 (±1.2)	41 (±9)	1.4 (±0.4)	10.32 ($n = 1$)
10s	2-CN	238 (±125)	797 (±124)	1.0 (±0.0)	10.37 (±0.12)
10t	3-CN	13 (±6.7)	122 (±11)	0.7 (±0.1)	10.44 (±0.01)
10u	4-CN	24 (±5)	94 (±11)	1.1 (±0.2)	10.3 (±0.1)
10v	2-F_3CO–	299 (±20)	702 (±17)	2.1 (±0.6)	9.60 (±0.18)
10w	4-F_3CS–	11 (±2)	95 (±13)	5.5 (±0.5)	9.23 (±0.21)

[a] Values are means of at least three experiments in triplicate except where indicated, standard error of the mean is in parentheses.

Table 4. Binding data for human NET and DAT

Compound	Human NET K_i[a] (nM)	Human DAT K_i[a] (nM)
9a	530 (±150)	7300 (±2000)
9b	3700 (±1500)	8300 (±810)
9c	470 (n = 1)	4000 (n = 1)
9d	4800 (±350)	7000 (±1200)
9e	82 (±32)	330 (±88)
9f	3200 (±720)	490 (±120)
9j	1300 (±470)	3000 (±690)
9m	730 (n = 1)	7000 (n = 1)
9n	2000 (n = 1)	7000 (±1200)
10f	3300 (±710)	7700 (±410)
10g	140 (±50)	330 (±85)
10h	112 (±15)	770 (±150)
10j	420 (±70)	2500 (±320)
10k	470 (±150)	7300 (±810)
10m	760 (±220)	8000 (±1200)
10p	5700 (±2000)	9000 (±0)

[a] Values are means of at least three experiments in triplicate except where indicated, standard error of the mean is in parentheses.

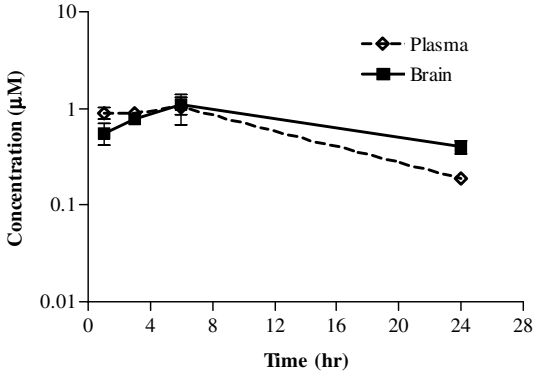


Figure 1. Brain and plasma concentrations of compound **9f** after oral administration to the rat (10 mg/kg). Results are represented as average ± SEM of n = 3.

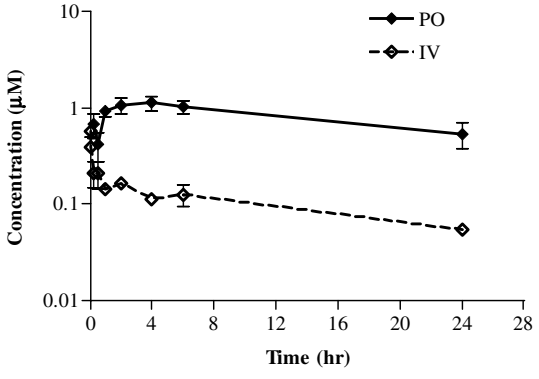


Figure 2. Plasma concentrations of compound **9f** in rat following po (10 mg/kg) and iv (1 mg/kg) administration. Results are represented as average ± SEM of n = 3.

us to demonstrate that a representative compound penetrates the rat brain and occupies both the histamine H_3 receptor and the serotonin transporter with an extended duration of action. Further in vivo studies will be required in order to determine the optimal PK profile

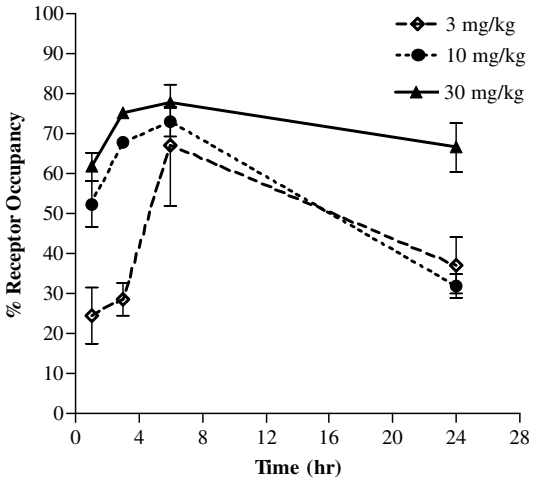


Figure 3. Ex-vivo histamine H_3 receptor occupancy data in rat striatum for compound **9f**. Time-dependency and dose dependency after oral administration (3, 10, and 30 mg/kg). Results are represented as average ± SEM of n = 3.

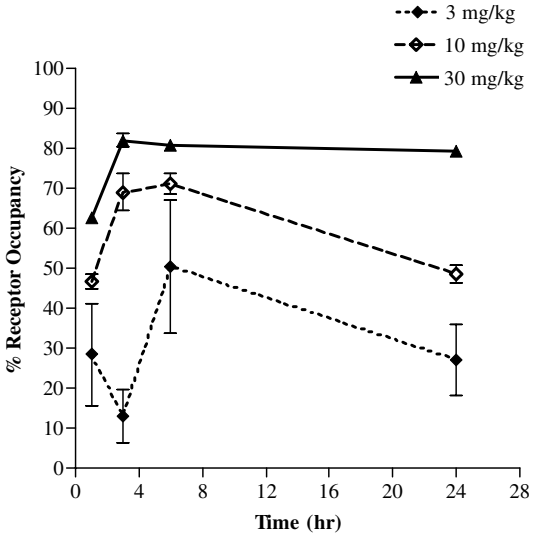


Figure 4. Ex-vivo SERT occupancy data in rat cortex for compound **9f**. Time-dependency and dose dependency after oral administration (3, 10, and 30 mg/kg). Results are represented as average ± SEM of n = 3.

for a histamine H_3 antagonist with serotonin reuptake inhibitor activity for use as an alternative to the current treatments for depression.

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18. Representative procedure for the synthesis of compounds **9** and **10**. **6c**: 5-bromo-2-fluorobenzaldehyde (5.13 g, 25.2 mmol) was dissolved in *N*,*N*-dimethylformamide (25 mL) and treated with 4-(methylthio)-*m*-cresol (4.42 g, 28.7 mmol) and potassium carbonate (7.40 g, 53.5 mmol). The mixture was heated to 90 °C for 48 h and then cooled and diluted with water and extracted into diethyl ether and concentrated. Chromatography on silica gel (EtOAc/hex) gave **6c** (6.07 g, 71%). **7c**: Compound **6c** (6.07 g, 18.0 mmol) was dissolved in methanol (250 mL) and treated with 40% aqueous methylamine (30 mL, 387 mmol). The mixture was stirred at 23 °C for 20 min until homogeneous then was cooled to 0 °C prior to the addition of sodium borohydride (in portions, 1.048 g, 27.7 mmol). The reaction mixture was then allowed to warm to 23 °C and was stirred at that temperature for 25 h. The mixture was diluted with 1 N NaOH and was extracted with dichloromethane (3×). The organic layers were dried over sodium sulfate and concentrated to give **7c** (5.76 g, 91%) as an oil. **8c**: Compound **7c** (5.76 g, 17.1 mmol) was dissolved in dichloromethane (250 mL) and was treated with triethylamine (4.8 mL, 34.4 mmol) and di-*tert*-butyl dicarbonate (4.51 g, 20.6 mmol). The mixture was stirred at 23 °C for 1 h, then was added to 1 N NaOH and extracted with dichloromethane. The organic layer was dried with sodium sulfate and concentrated to give crude **8c** (8.18 g, 106%) containing a small amount of triethylamine as an oil. The material was used as it is for the next step. **9c**: **8c** (0.292 g, 0.646 mmol) was dissolved in tetrahydrofuran (2 mL) and treated with 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) (0.3 mL), isopropylpiperazine (0.3 mL), trans-di-μ-acetatobis[2-(di-*o*-tolyl-phosphino)benzyl]di-palladium(II) (Hermann's catalyst) (28.7 mg), tri-*tert*-butylphosphonium tetrafluoroborate (26.9 mg), and molybdenum hexacarbonyl (177.4 mg) were then sequentially added to the vial. The vial was sealed and heated to 125 °C in a microwave reactor for 6 min. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The resulting oil was applied directly to a silica gel column and chromatographed using a mixture of dichloromethane and 10% methanol containing 0.1% ammonium hydroxide as eluent to give the Boc protected amine, which was directly treated with dichloromethane (2 mL) and TFA (1 mL), stirred for 1 h at 23 °C, then concentrated and chromatographed using the above eluent to give **9c** (0.0958 g, 35% over 2 steps).
19. A detailed description of the histamine H_3 assay and the histamine H_3 functional assay can be found in Ref. 12. A detailed description of the SERT, NET, and DAT assays can be found in Ref. 13.
20. Compound **9a** had 73% inhibition of the μ-opiate receptor at 1 μM and compound **10h** had 66% inhibition of the μ-opiate receptor at 1 μM and 64% inhibition of the muscarinic-3 receptor at 1 μM.