Alpha-ethyltryptamines as dual dopamine–serotonin releasers

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ABSTRACT

The dopamine (DA), serotonin (5-HT), and norepinephrine (NE) transporter releasing activity and serotonin-2A ($5\text{-}HT_{2A}$) receptor agonist activity of a series of substituted tryptamines are reported. Three compounds, **7b**, (+)-**7d** and **7f**, were found to be potent dual DA/5-HT releasers and were >10-fold less potent as NE releasers. Additionally, these compounds had different activity profiles at the $5\text{-}HT_{2A}$ receptor. The unique combination of dual DA/5-HT releasing activity and $5\text{-}HT_{2A}$ receptor activity suggests that these compounds could represent a new class of neurotransmitter releasers with therapeutic potential.

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Biogenic amine neurotransmitters—dopamine (DA), serotonin (5-HT) and norepinephrine (NE)—are critically involved in the pathogenesis and treatment of various psychiatric disorders.[1] The three biogenic amine transporters (BATs) are principal sites of action for cocaine and amphetamines. It is useful to divide BAT ligands into two categories based on their molecular mechanism of action: uptake inhibitors and substrates (for a review[2]). The uptake inhibitor cocaine binds to BATs and inhibits neurotransmitter uptake, leading to increases in synaptic transmitter levels. The cocaine-induced rise in extracellular neurotransmitters is dependent upon impulse-driven exocytosis and is sensitive to negative feedback loops. Amphetamine-like compounds are BAT substrates that release transmitters via carrier-mediated exchange, a process that is not dependent on impulse-driven exocytosis and is not sensitive to negative feedback loops. As a result, administration of BAT substrates tends to produce larger elevations in extracellular neurotransmitters than administration of uptake inhibitors.[3]

A major goal of our laboratory has been the development of medications that ameliorate the symptoms of stimulant withdrawal and thereby facilitate abstinence. Although many strategies for addressing this problem are possible (for recent reviews[4–7]) we decided to first focus our efforts on dual selective DA and 5-HT releasing agents for several reasons. First, preliminary clinical observations indicated that co-administration of phentermine (an amphetamine-like DA-releaser) and fenfluramine (a 5-HT releaser)

showed promise in treating cocaine and alcohol dependence.[8] Second, administration of DA and 5-HT releasing agents alone or together decrease drug-seeking behavior.[9–12] Third, based on literature suggesting cocaine withdrawal causes dysfunction in both the DA and 5-HT systems (see above), it seemed logical to develop a medication that normalizes deficits in both neurotransmitter systems, rather than just one. Fourth, a series of investigations indicated that concurrent 'global' elevation of brain extracellular 5-HT attenuates the psychomotor stimulant and rewarding effects that result from elevation of extracellular DA, without actually decreasing extracellular DA.[13,14] Similar findings with DA/5-HT uptake inhibitors broadly reinforce the validity of our findings.[15] Finally, we believed that candidate medications for stimulant addictions should target the same 'receptors' as the primary drug of abuse. This strategy, known as 'agonist therapy', is a proven approach for treating substance use disorders as exemplified by the efficacious treatments for cigarette smoking (e.g., the nicotine patch) and opioid dependence (e.g., methadone and buprenorphine).[16] In the context of stimulant dependence, the target 'receptors' of interest are BATs.

It is now well established that DA releasing agents, such as D-amphetamine, decrease cocaine self-administration behavior in animals[10,11,17,18] and that D-amphetamine and methamphetamine are two of the few medications to show promise as a treatment agent for stimulant addiction in controlled clinical trials.[16,19,20] These data provide support for using the agonist substitution approach for developing potential medications for the treatment of stimulant dependence. However, a significant limitation of this approach is the abuse liability of DA releasing agents.[21] As noted

above, concurrent elevation of extracellular 5-HT reduces D-amphetamine-induced stimulant and rewarding effects without reducing D-amphetamine increases in extracellular DA, and without altering the ability of D-amphetamine to decrease cocaine self-administration.[3] Seen from this perspective, concurrent elevation of extracellular 5-HT can reduce the abuse liability of D-amphetamine-like agents without altering the therapeutic effect, which is mediated by the increased release of DA.

This type of profile was observed with PAL-287 (compound **1**, 1-naphthyl-2-aminopropane), a universal BAT releaser evaluated as our original proof of principle.[22] PAL-287 was found to induce transporter mediated release of DA, 5-HT, and NE with EC$_{50}$ values of 12.6 nM, 3.4 nM, and 11.1 nM, respectively. In vivo microdialysis in rats demonstrated that PAL-287 (1-3 mg/kg, iv) increased extracellular DA and 5-HT with the effects on 5-HT being somewhat greater. PAL-287 induced substantially less locomotor stimulation than (+)-amphetamine, a drug that increases only extracellular DA. PAL-287 did not produce serotonergic 'neurotoxicity' and had little or no reinforcing properties in rhesus monkeys trained to self-administer cocaine. Yet, PAL-287 produced a dose-dependent decrease in responding for cocaine when infused at a dose of 1.0 mg/kg/h. Although the addition of 5-HT releasing activity to a DA releaser decreases behavioral selectivity (less separation between cocaine vs food responding behavior),[17,18] the clinical implications of these findings are not clear, in view of the fact that patients treated with various serotonergic medications do not appear to suffer from non-specific disruptions of behaviors related to the reward pathways. Our results with PAL-287 support the hypothesis that a non-amphetamine substrate at DATs and SERTs will release DA and 5-HT from neurons in vivo, be minimally reinforcing, and also suppress ongoing cocaine self-administration.

The inclusion of NE release in a pharmacotherapy for the treatment of substance abuse is less clear. Dual DA/NE releasing agents, such as amphetamine and phentermine, continue to be safely used in the clinic.[3] NE reuptake inhibitors, either administered alone or as dual NE/5-HT reuptake inhibitors, have been safely used as antidepressants.[23] Despite the favorable safety record associated with using NE reuptake inhibitors and releasing agents in the clinic, some studies suggest an undesirable cardiotoxic component may exist with NE elevation. Ephedrine and analogs, which have been shown to be primarily NE releasing agents,[24] have been linked to adverse cardiovascular events including sudden cardiac death.[25] Furthermore, NE has been shown to increase oxidative stress on the cardiac cells of rats by auto-oxidation,[26] and myocardial ischemia has been shown to be enhanced by NE elevation mediated by superoxide anion radicals.[27] Because of these issues, one goal of our releaser medications development program has been to identify compounds that induce DA and 5-HT release without having NE releasing properties in order to avoid cardiotoxicity complications. We hypothesized that such a molecule would maximize therapeutic effects while minimizing potential toxicities. Herein, we report the identification of the first class of dual DA/5-HT releasers with at least 10-fold less releasing activity at the NE transporter (NET) over the DAT and SERT.

Twenty-five tryptamines were studied in BAT release and uptake inhibition assays as well as in a 5-HT 2A (5-HT$_{2A}$) receptor assay since tryptamines are known to interact with the 5-HT$_{2A}$ receptor and 5HT$_{2A}$ agonists are thought to be hallucinogenic.[28] The transporter activity of all compounds was assessed using the previously described protocol for identifying releasers and uptake inhibitors, using synaptosomes generated from rat brain homogenate.[29,30] Compounds were binned as releasing substrates or uptake inhibitors by assessment in both synaptosomal release assays and uptake inhibition assays. Once the functional activity of a compound was determined, dose response curves were completed for the binned activity. 5-HT$_{2A}$ receptor agonist activity

was measured in an in vitro calcium mobilization assay using cells over-expressing the 5-HT$_{2A}$ receptor. All of the compounds were either purchased or synthesized in our laboratory. Tryptamines **4a**, **4b**, **4d**, **4g**, **4h**, **4j**, **4l**, and **4m** were purchased commercially. Tryptamines **4c**, **4e**, **4f**, **4i**, **4k**, **4n**, **4o**, **4p** and **4q** were synthesized by reacting the requisite substituted indole with oxalyl chloride followed by reaction with either ammonia or ethylamine in dioxane and subsequent reduction with lithium aluminum hydride (Scheme 1).[31] The racemic α-alkyl tryptamines **7a**, **7b**, **7c**, **7d**, **7e**, and **7f** were synthesized by nitro olefin formation followed by lithium ammonium hydride reduction (Scheme 2).[32] The optically active tryptamines (−)-**7d** and (+)-**7d** were synthesized by reacting the N-protected 3-bromoindole with *n*-butyllithium, then adding (+)- or (−)-propylene oxide to form optically active alcohols **8** (Scheme 3, shown for (+)-**7d**).[33] The secondary alcohol was then converted to the amine by forming the tosylates **9** followed by azide displacement, azide reduction, and finally deprotection to form the optically active tryptamines (−)-**7d** and (+)-**7d**.

All but one compound, 4-methoxytryptamine (**4f**) were 5-HT-releasing substrates (Table 1). Twenty-two of the twenty-four 5-HT releasers were very potent, with EC$_{50}$ values under 140 nM. The most potent 5-HT releaser was 7-chlorotryptamine (**4p**) with an EC$_{50}$ value of 8 nM. This is comparable to PAL-287, with an EC$_{50}$ value of 4 nM. It was also one of the most selective 5-HT releasers, as were all the 7-substituted analogs. Tryptamines are not normally known to possess strong stimulant activity, yet ten of the compounds had EC$_{50}$ values for DA release of less than 165 nM. All five fluoro derivatives tested, 4-fluorotryptamine (**4e**), 5-fluorotryptamine (**4j**), 6-fluorotryptamine (**4l**), 5-fluoro-α-methyltryptamine (**4c**), and 5-fluoro-α-ethyltryptamine (**7f**) were potent DA releasers with EC$_{50}$ values of 106 nM, 82.3 nM, 104 nM, 31.8 nM and 150 nM, respectively. The other five compounds were tryptamine (**4a**), 6-methoxytryptamine (**4m**), α-methyltryptamine (**7a**), 5-chloro-α-methyltryptamine (**7b**) and (*S*)-α-ethyltryptamine ((+)-**7d**).

Surprisingly, most of the compounds were not active as NE releasers. To date we have screened over 1000 small arylalkylamines for activity at all three biogenic amine transporters and normally NE release parallels DA release, and is usually slightly more potent. However in the case of the tryptamines, the NE releasing activity of the DA releasers was weaker in almost every case, and often by at least an order of magnitude (>10-fold). This activity profile implies that these compounds do not interact with the NET as well as they interact with the DAT. The NE release potencies for (*S*)-α-ethyltryptamine ((**+**)-**7d**), 4-fluorotryptamine (**4e**), 6-fluorotryptamine (**4l**), 5-fluoro-α-ethyltryptamine (**7f**), and 5-chloro-α-methyltryptamine (**7b**) were 10-, 11-, 30-, and 64-, and 36-fold weaker than their DA release potencies. In addition, several compounds including 5-chlorotryptamine (**4h**), 5-bromotryptamine (**4i**), and 6-methyltryptamine (**4n**) were inactive as NE releasers at 10 μM but maintained reasonable potencies as DA releasers (EC$_{50}$ values < 500 nM). In addition, these compounds were found to have fairly robust 5-HT releasing potencies with EC$_{50}$ values from 12.9 nM to 75 nM making them the first dual selective DA/5-HT releasers discovered in our project.

From a structure activity relationship perspective, N-methylation did not improve the selectivity or potency compared to tryptamine (**4a** vs **4b**). N-ethylation caused the scaffold to lose its DA releasing activity (**4a** vs **4c**). Alkylation of the 1-position (nitrogen on the indole ring, **4d**) also caused the scaffold to lose its DA releasing activity. N-alkylation at either the side chain nitrogen or the indole ring does not appear to be a viable approach for optimizing dual DA/5-HT releasing activity. α-Alkylation of tryptamine to form α-methyltryptamine (**7a**), similar to the difference between phenethylamine and amphetamine, caused the DA releasing potency to improve 2-fold and the NE-releasing potency to
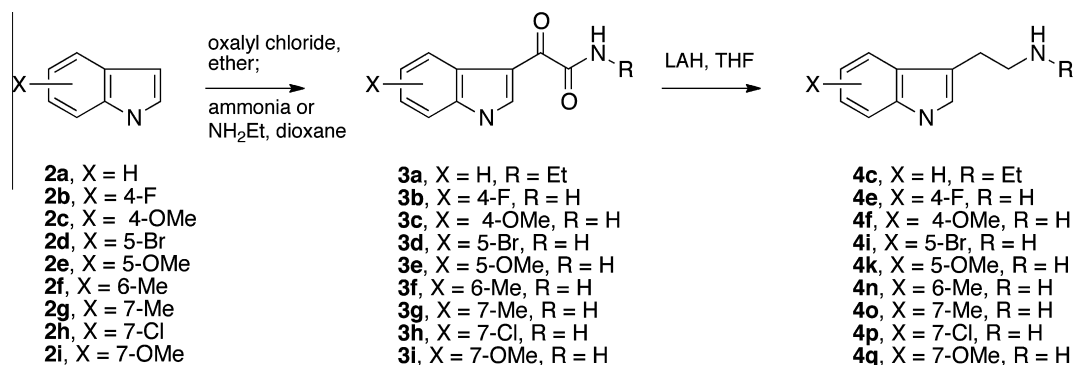
**Scheme 1.** Synthesis of tryptamine analogs.
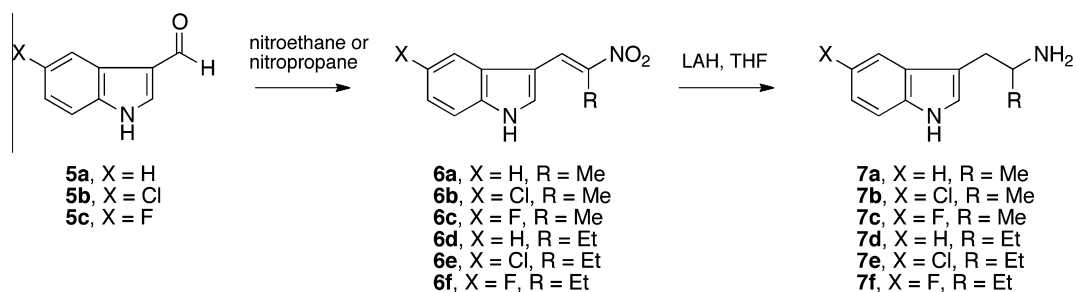
Scheme 2. Synthesis of α-alkylated tryptamine analogs.
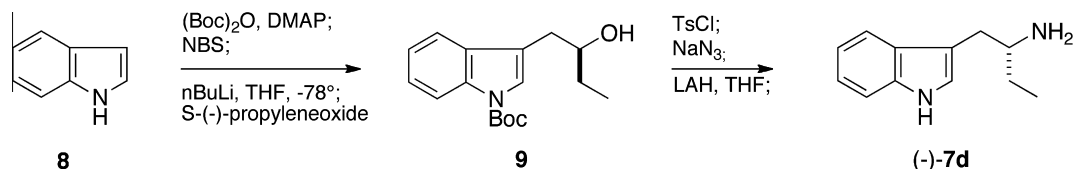
Scheme 3. Synthesis of optically-active tryptamine analogs.

improve 5-fold. 5-Chloro-α-methyl-tryptamine (**7b**) was found to also have elevated DA- and NE-releasing activity compared to its non-alpha-alkylated parent (**4h**), but 9-fold and at least 3-fold respectively. This resulted in 63-fold selectivity for DA release relative to NE release, the most selective dual DA/5HT releaser found to date. 5-Fluoro-α-methyl-tryptamine (**7c**) was also found to have elevated DA- and NE-releasing potencies compared to its non-alkylated parent (**4j**), but this only resulted in 4-fold DA-NE selectivity, little different from **4j**. α-Ethyltryptamine (**7d**, also known as αET) was found to be about as potent at release as tryptamine (**4a**). The two optical isomers of **7d** were found to also induce release, with (S)-isomer (+)-**7d** being more dual selective, similar to **7b** but less selective. Interestingly, **7d** and its optical isomers were found to no longer be full NE releasers; they became partial releasers able to release only approximately 75% of the releasable pool of NE. While the implications of partial release activity versus full releasing activity are unknown, at this time we believe this type of activity reflects substrate-induced neurotransmitter release that occurs as a slower rate than with a full substrate. Partial releasers are likely compounds with suitable properties as a dual DA/5HT releaser. 5-HT partial releasers[34] and DA partial releasers have also been identified.[35] α-Ethylation of the 5-chloro and 5-fluoro substituted tryptamines, to form **7e** and **7f** respectively, also weakened NE release activity compared to their α-methyl analogs, but **7e** flipped to become a weak DA uptake inhibitor. The 5-fluoro analog **7f** also weakened as a DA releaser but maintained significant potency, 36-fold more than NE release.

All of the tryptamines were agonists at the 5-HT$_{2A}$ receptor, but with varying degrees of potencies. Overall, all the non-alkylated analogs had similar efficacies ranging from 96% to 119%, with the N-methyltryptamine analog (**4b**) being the least efficacious (96%) and the 5-methoxytryptamine analog (**4k**) being the most efficacious (119%). The 5-methoxytryptamine analog (**4k**), which had an EC$_{50}$ value of 0.5 nM, was the most potent analog, whereas the 6-methoxytryptamine analog (**4m**), which had an EC$_{50}$ value of 2443 nM, was the least potent analog. N-methylation and N-ethylation resulted in a 6.8-fold and 5.2-fold reduction in potency, respectively, compared to the non-alkylated analog (**4a**). Alkylation of the 1-position (nitrogen on the indole ring, **4d**) caused a 4-fold reduction in potency (**4d** vs **4b**). In the methyl substituted series, 5-methyltryptamine (**4g**) was 13-fold more potent than 6-methyltryptamine (**4n**) and 7-fold more potent than 7-methyltryptamine (**4o**) with similar efficacies. In the chloro substituted series, 5-chlorotryptamine (**4h**) was 5-fold more potent than 7-chlorotryptamine (**4p**). In the fluoro-substituted series, 5-fluorotryptamine (**4j**) was similar in potency to 6-fluorotryptamine (**4l**). In the methoxy substituted series, 5-methoxytryptamine (**4k**), which had an EC$_{50}$ of 0.5 nM and E_{max} of 119%, was the most potent and efficacious analog. The 4-methoxytryptamine analog (**4f**) was 18-fold less potent, the 6-methoxytryptamine analog (**4m**) was 4800-fold less potent, and the 7-methoxytryptamine analog (**4q**) was 980-fold less potent than **4k**, but had similar efficacies.

Racemic α-Ethyltryptamine (**7d**) was not potent as a 5-HT$_{2A}$ agonist, with an EC$_{50}$ value of >10,000 nM. The (−)-isomer was also

Table 1
Comparison of the DAT, SERT, and NET-mediated release activity and 5-HT$_{2A}$ receptor activity of substituted tryptamines
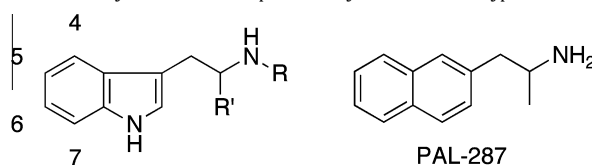
PAL	#	Substituent	R	R'	EC$_{50}$[a] (nM)			5-HT$_{2A}$[b]	
					DA	5HT	NE	EC$_{50}$ (nM)	E_{max} (%)
287	**1**	—	—	—	12.6 ± 0.4[c]	3.4 ± 0.2[c]	11.1 ± 0.9[c]	—	—
235	**4a**	—	H	H	164 ± 16	32.6 ± 2.6	716 ± 46	7.36 ± 0.56	104 ± 4
152	**4b**	—	Me	H	321 ± 23	22.4 ± 1.4	733 ± 94	50.7 ± 7.1	96 ± 2
536	**4c**	—	Et	H	6660 ± 551[d]	18.6 ± 1.6	3862 ± 635[d]	38.3 ± 2.7	99 ± 2
637	**4d**	1-Me	H	H	>10,000	53.1 ± 4.9	>10,000	209 ± 40	99 ± 3
551	**4e**	4-F	H	H	106 ± 5	108 ± 9	1123 ± 211	28.1 ± 8.4	108 ± 3
548	**4f**	4-OMe	H	H	>10,000	4114 ± 261[d]	>10,000	9.02 ± 0.65	108 ± 2
22	**4g**	5-Me	H	H	>10,000	139 ± 19	>10,000	6.00 ± 1.1	100 ± 2
441	**4h**	5-Cl	H	H	476 ± 34	19.1 ± 2.9	>10,000	4.11 ± 0.59	109 ± 3
518	**4i**	5-Br	H	H	478 ± 25	75.0 ± 7.7	>10,000	5.14 ± 0.90	108 ± 1
284	**4j**	5-F	H	H	82.3 ± 6.8	10.1 ± 0.9	464 ± 46	2.64 ± 0.36	110 ± 2
234	**4k**	5-OMe	H	H	11031 ± 580	2169 ± 259	>10,000	0.503 ± 0.09	119 ± 2
227	**4l**	6-F	H	H	106 ± 4	4.4 ± 0.4	1575 ± 104	4.56 ± 0.28	101 ± 2
263	**4m**	6-OMe	H	H	113 ± 8	53.8 ± 5.4	465 ± 45	2443 ± 491	111 ± 5
522	**4n**	6-Me	H	H	353 ± 13	51.6 ± 5.8	>10,000	75.3 ± 10	110 ± 4
286	**4o**	7-Me	H	H	3380 ± 220	23.7 ± 1.9	>10,000	44.7 ± 5.7	103 ± 3
532	**4p**	7-Cl	H	H	1330 ± 61	8.03 ± 1.3	656 ± 60	18.8 ± 4.0	102 ± 2
533	**4q**	7-OMe	H	H	2118 ± 88	44.6 ± 3.8	5600 ± 815	496 ± 50	107 ± 3
17	**7a**	—	H	Me	78.6 ± 4.0	21.7 ± 1.0	112 ± 6	23.1 ± 2.4	103 ± 3
542	**7b**	5-Cl	H	Me	54.3 ± 1.8	16.2 ± 2.2	3434 ± 516	6.27 ± 1.3	105 ± 1
212	**7c**	5-F	H	Me	37.0 ± 2	14 ± 1	78 ± 5	8.47 ± 1.9	107 ± 3
125	**7d**	—	H	Et	232 ± 17	23.2 ± 1.7	640 ± 76[e]	>10,000	21 ± 11
640	(−)-**7d**	—	H	(R)-Et	654 ± 50	54.9 ± 7.8	3670 ± 1190[e]	Inactive at 10 μM	
647	(+)-**7d**	—	H	(S)-Et	57.6 ± 3.1	34.7 ± 4.9	592 ± 97[e]	1250 ± 310	61 ± 8
526	**7e**	5-Cl	H	Et	1838 ± 150[d]	33.2 ± 3.6	>10,000	249 ± 22	87 ± 1
545	**7f**	5-F	H	Et	150 ± 7	36.6 ± 3.2	5334 ± 970	246 ± 46	87 ± 3

[a] Release EC$_{50}$ values are reported as means ± SD and are the result of N = 3 performed in triplicate.
[b] Calcium mobilization EC$_{50}$ and E_{max} values are reported as means ± SEM and are the result of three independent experiments performed in duplicate.
[c] Release data.[22]
[d] Value is IC$_{50}$ for uptake inhibition in nM.
[e] Compounds **7d**, (−)-**7d**, and (+)-**7d** were partial releasers of NE with E_{max} values of 78%, 75% and 71%, respectively.

inactive as a 5-HT$_{2A}$ agonist at 10 μM, but the (+)-isomer was found to be a weak partial 5-HT$_{2A}$ agonist with an EC$_{50}$ value of 1250 nM and 61% efficacy compared with 5-HT. The (+)-isomer is 170-fold less potent than the non-alkylated analog (**4a**) and 54-fold less potent than the α-methyltryptamine analog (**7a**). In the α-methyltryptamine series, the 5-chloro analog (**7b**) was 4-fold more potent as a 5-HT$_{2A}$ agonist and the 5-fluoro analog (**7c**) was 3-fold more potent than the unsubstituted α-methyltryptamine (**7a**). In the α-ethyltryptamine series, the 5-chloro analog (**7e**) and 5-fluoro analog (**7f**) both weakened substantially as 5-HT$_{2A}$ agonists compared to their α-methyl- and non-alkylated trypt-amine analogs (**7b**/**7c** and **4h**/**4j**), with EC$_{50}$ values of 249 nM and 246 nM, respectively.

Both **7a** and **7d** have been found to induce mild euphoria in humans,[31] but **7d** has also produced amphetamine-like locomotor stimulation in rodents.[36] This combination of psychoactive effects is somewhat unique and similar to 3,4-methylenedioxymetham-phetamine (MDMA). A study by Hong et al. addressed the possibility that the optical isomers of **7d** may each be responsible for one of the observed properties by conducting discriminative stimulus assays using (+)-amphetamine, 2,5-dimethoxy-4-methylamphet-amine (DOM), and MDMA.[37,38] It was found that (−)-**7d** general-ized to (+)-amphetamine and MDMA, but only partially to DOM, and that (+)-**7d** generalized to DOM and MDMA, but only partially to (+)-amphetamine. The authors concluded that while there was significant variance in effects of individual animals, the amphet-amine-like properties of **7d** primarily resided in the (−)-isomer.

This seems to be contrary to what one might expect based solely on the transporter data. (−)-**7d** was much weaker at DA release than the (+)-**7d** isomer, and consequently more selective for 5-HT. Compounds with amphetamine-like stimulant activity are nor-mally thought to be more active as DAT ligands, either as uptake inhibitors or releasers.[39] One might have postulated based on the data that the compound with higher DA releasing activity would be the stimulant. (+)-**7d** has equipotent activity as a DA and 5-HT releaser so one explanation may be that the 5-HT releasing activity may blunt the stimulant effects similar to PAL-287 (**1**).[22] One addi-tional factor that must be involved is the 5-HT$_{2A}$ receptor activity. In our assays, (−)-**7d** is inactive while (+)-**7d** is a weak partial ago-nist (EC$_{50}$ > 1 uM, 61% E_{max}). Since 5-HT$_{2A}$ agonist activity is responsible for the effects of hallucinogens, it is possible that the 5-HT$_{2A}$ activity contributes to (+)-**7d** being responsible for the hal-lucinogenic effects and lack of 5-HT$_{2A}$ activity contributes to the generalization to amphetamine produced by (−)-**7d**.

In summary, a series of substituted tryptamines was studied resulting in the discovery of three DA/5HT releasers, **7b**, (+)-**7d**, and **7f**. All three compounds are potent releasers of both DA and 5HT, and are at least 10-fold less potent as NE releasers. While less potent as DA and 5-HT releasers compared to PAL-287, all display therapeutically relevant EC$_{50}$ values as DA and 5HT releasers. They also possess α-alkyl groups known to block rapid metabolism, at least in the case for β-phenethylamine, and should make good in vivo probes. These compounds represent a new class of neuro-transmitter releasers with therapeutic potential. In addition, **7d**

and its stereoisomers were found to be NE partial releasers, a property that has unknown pharmacological implications but which nonetheless is novel. Additional tryptamines are being studied for their BAT release and behavioral properties. A full report of them will be published shortly.

Acknowledgments

Supplementary data

Supplementary data (experimental procedures for all new compounds and assay conditions) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl. 2014.07.062.

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