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The synthesis and comparative receptor binding affinities of novel, isomeric pyridoindolobenzazepine scaffolds

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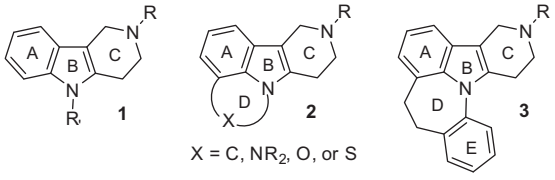
ABSTRACT

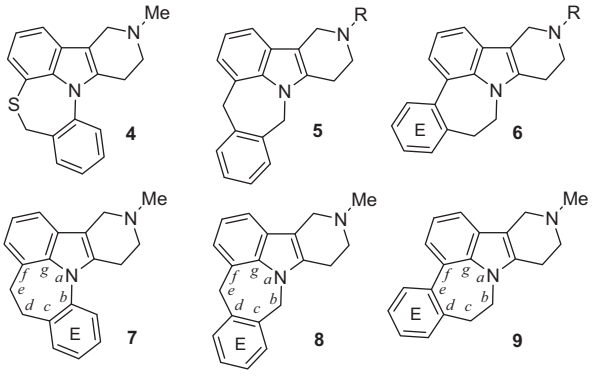
Compounds **7**, **8**, and **9**, derived from the novel scaffolds **3**, **5**, and **6**, were synthesized and evaluated in vitro. The *b,c* → *c,d* shift of the E-phenyl ring resulted in a large decrease (ca. 20- to 1000-fold) in binding to the 5-HT_{2A}, 5-HT_{2C} and H_2, receptors, and a modest decrease (ca. 10- to 20-fold) in binding to the 5-HT_{5A}, D_2, D_5, and α_{1D}, receptors. The *b,c* → *d,e* shift resulted in a large decrease in binding to the 5-HT_{1D}, 5-HT_{2C}, 5-HT_6, and H_1 receptors, a modest decrease in binding to 5-HT_{1A}, 5-HT_{5A} and D_2, D_5, α_{2B}, and H_2 receptors, and a large increase in affinity to the 5-HT_3, 5-HT_6, and σ_1 receptors.

The serotonin (5-HT) receptors continue to be important targets for the discovery and development of novel medications because of the key roles they play in the etiology of diverse central and peripheral nervous system disorders such as anxiety, depression, schizophrenia, migraine, addiction, pain, irritable bowel syndrome, etc.[1] Latest research on these receptors has also clearly defined the key roles that 5-HT_{2B} plays in psychostimulant addiction through modulation of dopamine release in reward/pleasure centers in the brain,[2–5] 5-HT_6 in cognition,[6] and 5-HT_7 in both nociceptive and neuropathic pain via descending serotonergic pathway.[7–10]

We[11–13] and others[14–23] have been extensively investigating the versatility of heterocyclic systems incorporating the tetrahydro-γ-carboline (also known as tetrahydropyridoindole) unit (**1**), which is a key pharmacophore in many small bioactive molecules. These include CNS,[14–16] immunosuppressive,[17] anti-cancer,[18] anti-arthritic,[19] and anti-asthmatic[20] agents. Hence, there is much interest in expanding the scope and utility of this system via the fusion of additional rings leading to interesting tetracyclic and pentacyclic scaffolds as (**2**)[11,21] (**3**).[12,13,22,23] Both



of these scaffolds have been shown to bind to various serotonin receptors, but our efforts were particularly directed toward the exploitation of the pentacyclic scaffold **3** for the discovery of new CNS medications. Although derivatives of this scaffold were disclosed over four decades ago as potential anti-depressants,[22] receptor binding data on these compounds have not been reported. As stated in our previous Letter,[13] the cloning and characterization of various serotonin receptor subtypes were not available at the time of its discovery. We recently reported on the synthesis and receptor binding affinities of the new pentacyclic compound **4**, a prototype of sulfur isostere of scaffold **3**.[13] The position of the E-phenyl ring in structure **4** is particularly



important for the balanced D_2 and 5-HT_{2A} receptor binding affinities of this rationally designed potential, atypical antipsychotic. However, scaffolds **5** and **6** resulting from the shifts of the E-phenyl ring to the adjacent bonds are not known. Inspection of the models

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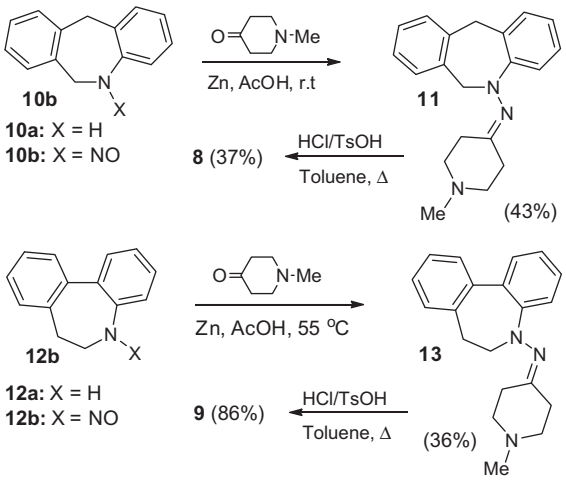
of scaffolds **3**, **5**, and **6** clearly shows their molecular topologies to be quite different and, consequently, we expected their affinities to various receptors to be different also. Therefore, we decided to synthesize compounds **8** and **9** as the simplest prototypes of scaffolds **5** and **6**, and evaluate them, together with the known **7**, for their binding affinities in a panel of thirty seven receptors and three transporters to develop 'receptor-binding profiles' on these compounds for comparison and to look for interesting leads. The results of this endeavor comprise the subject of this communication.

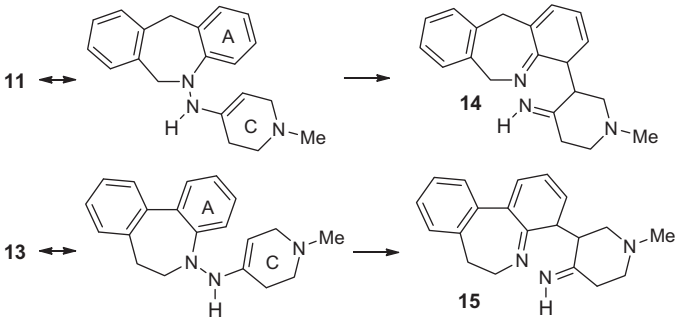
The synthesis of compound **7** has been reported earlier.[22,23] Compounds **8** and **9** were also synthesized using the Fisher indole cyclization starting from the nitroso compounds **10b** and **12b**, which were prepared from the known[24,25] tricylic amines **10a** and **11a**, respectively (Scheme 1). As mentioned in our previous Letter,[13] the reduction of the N-nitroso to the corresponding hydrazino derivative[26] has always been difficult due to the competing N–N bond cleavage. Moreover, the reduction is also dependent on the nature of the substrate. For example, whereas the reduction of the nitroso derivative **10b** proceeds at ambient temperature, **12b** requires a much higher temperature. It is interesting to note that the Fischer indole cyclization of **13** proceeded in much higher yield compared to **11**. This could be rationalized on the basis of relative energies of the transition states of the 3,3′-sigmatropic rearrangement of **11** or **13** leading to **14** or **15**, respectively, (Scheme 2). The sigmatropic shift requires that all of the participating p-orbitals in both A and C rings be in a parallel or near-parallel array. The torsional strain that would be required to align these orbitals could be greater in **14** than in **15** due to the puckering of the A-ring in **11**.

The affinities of compounds **7**–**9** to eight major classes of receptors and three key transporters are shown in Table 1.[27] As can readily be discerned from the table that, with the exception of compound **9** which exhibits moderate affinity to the serotonin transporter and low affinity to the norepinephrine transporter, none of these compounds binds to either of these or to the dopamine transporter. Substantial differences in binding to serotonin, α-adrenergic, histamine, and sigma receptors are apparent, consistent with changes in the position of the E-phenyl ring. Compound **7** displays strong binding (K_i <100 nM) to 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, H_1, and H_2, and moderate binding (K_i 100–500 nM) to 5-HT_6, HT_7, α_{2A}, α_{2B}, and α_{2C}; **8** exhibits strong binding to 5-HT_{1D}, 5-HT_{2B}, and H_1, and moderate affinity to 5-HT_6, HT_7; and **9** displays only moderate binding to 5-HT_{2A}, 5-HT_{2B}, HT_7, α_{1A}, α_{1D}, α_{2A}, α_{2C}, σ_1, and σ_2 receptors.

The relative changes in receptor binding of **8** and **9** compared to **7** are summarized in Table 2. Moving the E-phenyl ring from *b,c* to



Scheme 1.



Scheme 2.

Table 1
Receptor binding data, pK_i (±S.E.M.)

Receptor	7	8	9
Serotonin			
5-HT_{1A}	6.20 (0.10)	6.43 (0.07)	<5.00
5-HT_{1B}	5.87 (0.06)	6.15 (0.03)	5.91 (0.04)
5-HT_{1D}	7.07 (0.05)	7.54 (0.04)	6.02 (0.04)
5-HT_{1E}	5.39 (0.08)	<5.00	<5.00
5-HT_{2A}	7.62 (0.05)	6.13 (0.07)	6.59 (0.07)
5-HT_{2B}	7.06 (0.05)	7.25 (0.06)	6.98 (0.06)
5-HT_{2C}	7.98 (0.04)	<5.00	<5.00
5-HT_3	<5.00	<5.00	6.30 (0.10)
5-HT_{5A}	6.13 (0.05)	<5.00	<5.00
5-HT_6	6.81 (0.06)	6.56 (0.06)	<5.00
5-HT_7	7.00 (0.04)	6.70 (0.01)	6.71 (0.06)
Dopamine			
D_1	<5.00	<5.00	<5.00
D_2	6.08 (0.07)	<5.00	<5.00
D_3	<5.00	5.80 (0.10)	<5.00
D_4	<5.00	<5.00	5.91 (0.10)
D_5	6.24 (0.06)	<5.00	<5.00
Alpha adrenergic			
α_{1A}	5.62 (0.09)	<5.00	6.54 (0.06)
α_{1B}	5.50 (0.01)	<5.00	5.65 (0.09)
α_{1D}	6.23 (0.09)	<5.00	6.53 (0.08)
α_{2A}	6.64 (0.07)	5.74 (0.08)	6.39 (0.08)
α_{2B}	6.38 (0.09)	5.66 (0.07)	5.36 (0.07)
α_{2C}	6.76 (0.09)	6.11 (0.06)	6.35 (0.06)
Beta adrenergic			
β_1	<5.00	<5.00	<5.00
β_2	<5.00	<5.00	<5.00
β_3	<5.00	<5.00	<5.00
Histamine			
H_1	7.30 (0.09)	7.32 (0.05)	<5.00
H_2	7.09 (0.05)	<5.00	6.03 (0.07)
H_3	<5.00	<5.00	<5.00
Sigma			
σ_1	5.20 (0.10)	<5	6.66 (0.06)
σ_2	5.65 (0.09)	6.28 (0.05)	6.51 (0.06)
Opioid			
δ	<5.00	<5.00	<5.00
κ	5.70 (0.10)	<5.00	<5.00
μ	<5	<5.00	<5.00
Muscarinic			
M_1	5.40 (0.10)	<5.00	<5.00
M_2	<5.00	<5.00	<5.00
M_3	5.42 (0.07)	<5	<5.00
M_4	<5.00	<5.00	<5.00
M_5	5.29 (0.09)	<5.00	<5.00
Transporter			
Dopamine	<5.00	<5.00	<5.00
Norepinephrine	<5.00	5.87 (0.07)	5.71 (0.07)
Serotonin	5.66 (0.07)	<5.00	6.38 (0.09)