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Studies Towards the Next Generation of Antidepressants. Part 1: Indolylcyclohexylamines as Potent Serotonin Reuptake Inhibitors

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Abstract—A series of indolylcyclohexylamines possessing potent and selective serotonin reuptake inhibition is reported. The most interesting compounds proved to have subnanomolar 5-HT transporter activity, and exhibited moderate 5-HT_{1A} affinity.

Depression is a debilitating disease with an overwhelming economic liability to society.[1] The treatment of depression has been revolutionized by the introduction of selective serotonin (5-HT) reuptake inhibitors (SSRIs) that possess fewer side effects than traditional tricyclic antidepressants.[2] A serious drawback to these SSRIs is the delay of therapeutic benefit, believed to be caused by the inhibitory role of the 5-HT_{1A} autoreceptors. Upon administration of an SSRI, the 5-HT_{1A} receptors decrease the firing of serotonergic neurons, resulting in no net increase of synaptic 5-HT in desired brain regions. After repeated administration and desensitization of the 5-HT_{1A} receptors the serotonergic neurons resume normal firing and therapeutic antidepressant effects are observed.[3] Co-administration of a 5-HT_{1A} antagonist and an SSRI has been shown by several groups to accelerate antidepressant effects.[4–8] By merging 5-HT_{1A} antagonism and 5-HT transporter reuptake inhibition into one molecular entity, a superior antidepressant may be achievable.

The design of new indole derivatives based on the 5-hydroxytryptamine (5-HT, **1**) structure has been known to produce compounds with serotonergic activity both at the 5-HT_{1A} receptor and 5-HT transporter site.[9,10] In this letter we wish to disclose our initial investigations directed at discovering new serotonergic agents within another series of less recognized indole derivatives. Since the cyclohexyl indoles (**2**) were known to be 5-HT transporter ligands,[11] this class was used as a starting point to systematically introduce the 5-HT_{1A} pharmacophoric requirements. We now report the synthesis and structure–activity relationships (SAR) of a new class of indole derivatives (i.e., **3**) that potently inhibit the serotonin transporter site, and begin to exhibit 5-HT_{1A} affinity (Fig. 1).[12]

Schemes 1–6 show the synthesis of the target molecules. The indolylcyclohexyl ketone was synthesized by the condensation of a 5-substituted indole with 1,4-cyclohexanedione mono-ethylene ketal.[13] Hydrolysis afforded the unsaturated ketone **7**. Ketal **4** was also hydrogenated to afford **5** followed by hydrolysis to **6**.[14] Preparation of known 5-HT transporter ligands was

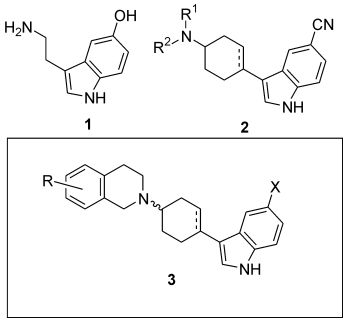

Figure 1. Serotonergic agents of interests.

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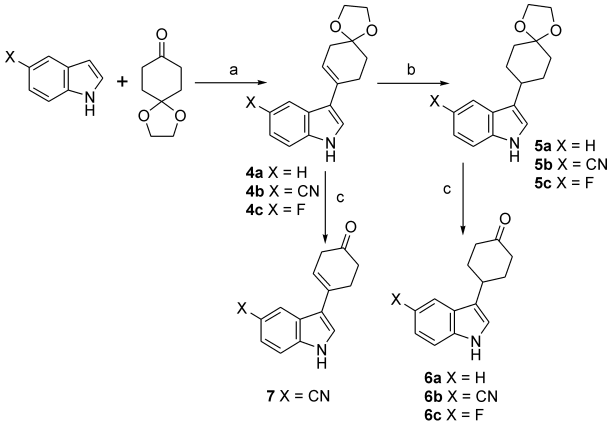
achieved by reductive amination to afford target compounds **8**–**15** as shown in Scheme 2. The *cis* and *trans* isomers could be easily separated by chromatography.

The tetrahydroisoquinoline analogue **16** was similarly prepared by reductive amination (Scheme 3). The 5-OMe analogue was prepared by the Mitsunobu reaction of 5-hydroxyisoquinoline (**17**) and MeOH to afford **18** (Scheme 4). Compound **18** was hydrogenated over Pt_2O[15] affording **19**, which was reductively aminated with **6a** to give **20a**,**b**.

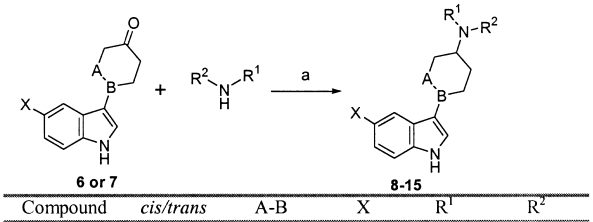
Preparation of the methoxy-tetrahydroisoquinolinyl derivatives was achieved by cyclization of the appropriate carbamate intermediates (Schemes 5 and 6).[16] Reduction with LAH, followed by reductive amination with **6a** afforded target compounds **25a**,**b**, **32a**,**b**, and **33a**,**b**.

Reacting 4-fluorophenylhydrazine with 3,4-dihydropyran afforded **34**, followed by conversion to bromide **35** (Scheme 7). Displacement with the appropriate amine provided compounds **38**–**40**.

Compounds were evaluated in vitro to determine affinity for the 5-HT transporter, 5-HT_{1A} and α_1 receptors. A protocol similar to that of Cheetham[17] was used to

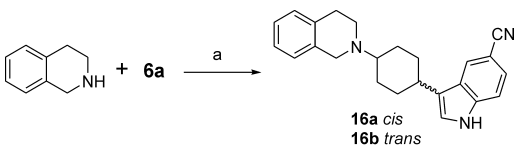


Scheme 1. Reagents and conditions: (a) 2 N KOH in MeOH, reflux; (b) H_2, 10% Pd/C, EtOH; (c) 1 M HCl, THF.

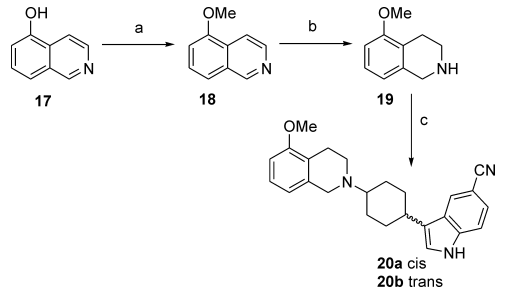


Compound	*cis/trans*	A-B	X	R^1	R^2
8a	*cis*	CH_2-CH	H	H	Bn
8b	*trans*	CH_2-CH	H	H	Bn
9	---	CH=C	CN	H	Bn
10a	*cis*	CH_2-CH	CN	H	Bn
10a	*trans*	CH_2-CH	CN	H	Bn
11a	*cis*	CH_2-CH	F	H	Bn
11b	*trans*	CH_2-CH	F	H	Bn
12	---	CH=C	CN	H	$(CH_2)_2$Ph
13a	*cis*	CH_2-CH	CN	H	$(CH_2)_2$Ph
13b	*trans*	CH_2-CH	CN	H	$(CH_2)_2$Ph
14	---	CH=C	CN		-$(CH_2)_5$-
15a	*cis*	CH_2-CH	CN		-$(CH_2)_5$-
15b	*trans*	CH_2-CH	CN		-$(CH_2)_5$-

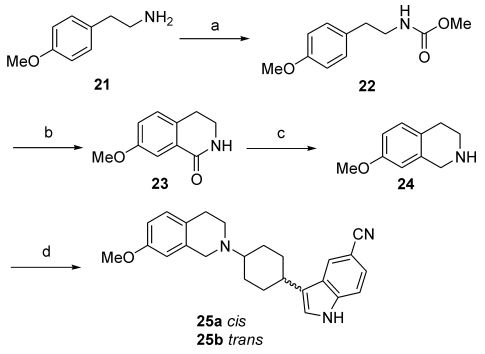
Scheme 2. Reagents and conditions: (a) $NaBH(OAc)_3$, HOAc, $ClCH_2CH_2Cl$.



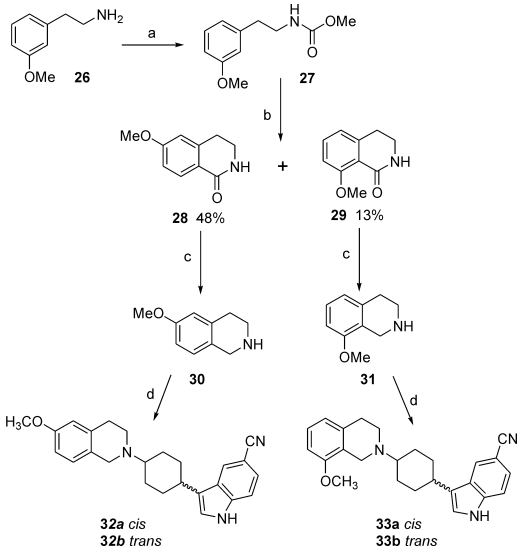
Scheme 3. Reagents and conditions: (a) $NaBH(OAc)_3$, HOAc, $ClCH_2CH_2Cl$.



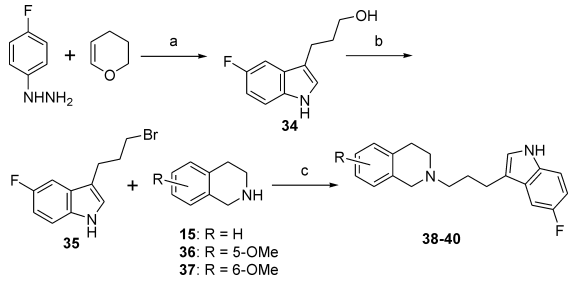
Scheme 4. Reagents and conditions: (a) DEAD, Ph_3P, MeOH, THF; (b) H_2, Pt_2O, HOAc; (c) **6a**, $NaBH(OAc)_3$, HOAc, $ClCH_2CH_2Cl$.



Scheme 5. Reagents and conditions: (a) methyl chloroformate, Et_3N, THF; (b) PPA, 140 °C; (c) LAH, THF, reflux; (d) **6a**, $NaBH(OAc)_3$, HOAc, $ClCH_2CH_2Cl$.



Scheme 6. Reagents and conditions: (a) methyl chloroformate, Et_3N, THF; (b) PPA, 140 °C; (c) LAH, THF, reflux; (d) **6a**, $NaBH(OAc)_3$, HOAc, $ClCH_2CH_2Cl$.

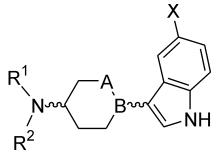


Scheme 7. Reagents and conditions: (a) H_2O, dioxane, 100 °C; (b) CBr_4, PPh_3, CH_2Cl_2; (c) Et_3N, DMSO, 100 °C.

determine affinity for the serotonin transporter (RB5-HT-T) and affinity for the α_1 receptor was determined by incubating rat cortical membranes with [^{3}H]-prazosin.[18] K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[19] Human 5-HT_{1A} receptor binding (HC5-HT_{1A}) was determined by incubating CHO cells transfected with human 5-HT_{1A} receptors with [^{3}H]-8-OH-DPAT and test compound.[20]

The biological results of the simple cyclohexylamines are shown in Table 1. These compounds exhibited moderate to high affinity for the 5-HT transporter and

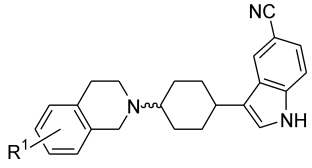
Table 1. Serotonin transporter, $5HT_{1A}$ and α_1 affinities for compounds **8**–**15**



Compound	R^1	R^2	X	A-B	*cis*/*trans*	RB5-HT-T K_i nM[a]	HC5-HT_{1A} %inhib@1μM	α_1 %inhib@1 μM
8a	H	Bn	H	CH_2–CH	*cis*	855	0%	21%
8b	H	Bn	H	CH_2–CH	*trans*	107	32%	64%[c]
9	H	Bn	CN	CH=C	—	3.13	87%[b]	27%
10a	H	Bn	CN	CH_2–CH	*cis*	7.50	15%	17%
10b	H	Bn	CN	CH_2–CH	*trans*	25	37%	28%
11a	H	Bn	F	CH_2–CH	*cis*	21	3%	9%
11b	H	Bn	F	CH_2–CH	*trans*	16	11%	8%
12	H	$(CH_2)_2$Ph	CN	CH=C	—	1.54	41%	32%
13a	H	$(CH_2)_2$Ph	CN	CH_2–CH	*cis*	7.50	0%	40%
13b	H	$(CH_2)_2$Ph	CN	CH_2–CH	*trans*	1.98	0%	56%
14	$(CH_2)_5$		CN	CH=C	—	178	0%	10%
15a	$(CH_2)_5$		CN	CH_2–CH	*cis*	22	0%	3%
15b	$(CH_2)_5$		CN	CH_2–CH	*trans*	152	0%	14%

[a]K_i values are the mean of 2–3 experiments run at six different concentrations. Each experiment was carried out in triplicate. 95% confidence limits were generally ±15% of the mean value.
[b]K_i = 374 nM.
[c]K_i = 368 nM.

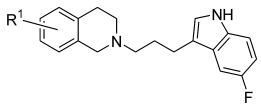
Table 2. Serotonin transporter, $5HT_{1A}$, and α_1 affinities for compounds **16**, **20**, **25**, **32** and **33**



Compound	R^1	*cis*/*trans*	RB5-HT-T K_i (nM[a])	HC5-HT_{1A} %inhib@1 μM	α_1 K_i nM
16a	H	*cis*	1.23	0%	337
16b	H	*trans*	10	10%	88
20a	5-OMe	*cis*	0.61	7%	920
20b	5-OMe	*trans*	12	47%	120
25a	7-OMe	*cis*	0.80	26%	11%@100
25b	7-OMe	*trans*	12	48%	113
32a	6-OMe	*cis*	0.10	21%	11%@100
32b	6-OMe	*trans*	8	74%[b]	228
33a	8-OMe	*cis*	1.01	14%	336
33b	8-OMe	*trans*	7.5	46%	66

[a]K_i values are the mean of 2–3 experiments run at six different concentrations. Each experiment was carried out in triplicate. 95% confidence limits were generally ±15% of the mean value.
[b]K_i = 300 nM.

Table 3. 5-HT transporter, $5HT_{1A}$, and α_1 affinities for **38–40**



Compound	R^1	RB5-HT-T K_i (nM[a])	HC5-HT_{1A} K_i (nM)	α_1 K_i (nM)
38	H	4.85	48%@1000	35
39	5-OMe	1.94	242.9	31.4
40	6-OMe	1.39	288	58

[a]K_i values are the mean of 2–3 experiments run at six different concentrations. Each experiment was carried out in triplicate. 95% confidence limits were generally ±15% of the mean value.

exhibited selectivity over the α_1 receptor. Moderate 5-HT_{1A} activity was observed only in the unsaturated analogue **9** ($K_i = 374$ nM). Substitution at the indole 5 position with a cyano or fluoro led to an improvement on 5-HT transporter affinity (**8a**,**b** vs **10a**,**b** and **11a**,**b**). Comparing the benzyl analogues to the corresponding phenethylamine analogues (i.e., **9** vs **12**: **10b** vs **13b**), an increase in 5-HT transporter affinity was observed, while the affinity of the *cis* analogues remained the same (**10a** vs **13a**). Unsaturation in the cyclohexyl ring increased 5-HT transporter and 5-HT_{1A} affinity for both the benzyl and phenethylamines (i.e., **9** and **12**). Removal of the phenyl ring, as shown with the piperidinyl derivatives (i.e., **14**, **15a**, and **15b**), resulted in a detrimental effect with respect to 5-HT transporter and 5-HT_{1A} affinities.

Incorporating the tetrahydroisoquinoline moiety (i.e., **16a** and **16b**, Table 2) led to an increase in 5-HT transporter affinity of >15-fold over the corresponding piperidine analogues **15a** and **15b** and, in general, were more potent than the benzyl and phenethylamines (i.e., **10a**, **10b**, and **13a**). In the tetrahydroisoquinolinyl series the *cis* isomers (i.e., **16a**, **20a**, **25a**, **32a**, and **33a**) were consistently more potent at the 5-HT transporter site than were the *trans* isomers (i.e., **16b**, **20b**, **25b**, **32b**, and **33b**). The *trans* isomers also were generally less selective than the *cis* isomers when compared to the α_1 receptor. An attempt to increase 5-HT_{1A} affinity by attachment of a methoxy substituent to the tetrahydroisoquinoline moiety led to only a modest improvement in affinity for the 5-HT_{1A} receptor and a slight increase in the 5-HT transporter affinity. Compound **32a** is particularly interesting as a pure SSRI, since it was observed to have subnanomolar affinity for the 5-HT transporter and high selectivity versus the 5-HT_{1A} and α_1 receptors. Results where the cyclohexyl linker was replaced with a more flexible propyl side chain are shown in Table 3. These analogues (i.e., **38–40**) still possessed potent 5-HT transporter activity and had slightly more affinity at the 5-HT_{1A} receptor. However, **38–40** also had higher affinity for the α_1 receptor.

Our initial attempts to incorporate 5-HT transporter and 5-HT_{1A} activity into a single molecule resulted in the identification of a novel class of indolylalkylamines. The indolylcyclohexylamines disclosed here generally possessed potent 5-HT transporter affinity and low to moderate 5-HT_{1A} affinity. The incorporation of the methoxy-substituted tetrahydroisoquinoline moiety led to a slight increase in 5-HT_{1A} affinity. The most potent tetrahydroisoquinoline derivative with dual activities was **32b** (5-HT transporter, $K_i = 8$ nM: 5-HT_{1A} $K_i = 300$ nM). In the course of our research we discovered a novel, potent and selective SSRI (**32a**). Research is continuing in our laboratories toward the discovery of a dual activity agent having a more balanced 5-HT reuptake and 5-HT_{1A} activity profile. SAR studies focused on the replacement of the tetrahydroisoquinoline moiety with more optimized 5-HT_{1A} pharmacophoric groups will be reported in due course.

References and Notes

1. Andrews, J. M.; Nemeroff, C. B. *Am. J. Med.* **1994**, *97*, 24S.
2. Blackwell, B. *Drugs* **1981**, *21*, 201.
3. Blier, P.; Bergeron, R. J. *J. Clin. Psychiatry* **1998**, *59*, 16.
4. Artigas, F.; Perez, V.; Alvarez, E. *Arch. Gen. Psychiatry* **1994**, *51*, 248.
5. Artigas, F.; Romero, L.; de Montigny, C.; Blier, P. *Trends Neurosci.* **1996**, *19*, 378.
6. Blier, P.; Bergeron, R. *J. Clin. Psychopharmacol.* **1995**, *15*, 217.
7. Romero, L.; Hervas, I.; Artigas, F. *Neurosci. Lett.* **1996**, *219*, 123.
8. Romero, L.; Artigas, F. *J. Neurochem.* **1997**, *68*, 2593.
9. Taylor, E. W.; Nikam, S. S.; Lambert, G.; Martin, A. R.; Nelson, D. L. *Mol. Pharm.* **1988**, *34*, 42.
10. Gueremy, C.; Audiau, F.; Champseix, A.; Uzan, A.; Le Fur, G.; Retaud, J. *J. Med. Chem.* **1980**, *23*, 1306.
11. Cipollina, J. A.; Mattson, R. J.; Sloan, C. P. US Patent 5,468,767, 1995. CAN 124:175827.
12. Mewshaw, R. E.; Meagher, K. L.; Evrard, D. A.; Smith, D. L.; Scerni, R.; Adulhawa, S.; Shi, X.; Schechter, L. E.; Andree, T. H. *Book of Abstracts*, 219th National ACS Meeting, San Francisco, CA, March 26–30, 2000.
13. Guillaume, J.; Dumont, C.; Laurent, J.; Nedelec, L. *Eur. J. Med. Chem.* **1987**, *1*, 33.
14. Wustrow, D. J.; Smith, W. J.; Corbin, A. E.; Davis, M. D.; Gerogic, L. M.; Pugsley, T. A.; Whetzel, S. Z.; Heffner, T. G.; Wise, L. D. *J. Med. Chem.* **1997**, *40*, 250.
15. Georgian, V.; Harrison, R. J.; Skaletsky, L. L. *J. Org. Chem.* **1962**, 4571.
16. Sall, D. J.; Grunewald, G. L. *J. Med. Chem.* **1987**, *30*, 2208.
17. Cheetham, S. C.; Viggers, J. A.; Slater, N. A.; Heal, D. J.; Buckett, W. R. *Neuropharmacology* **1993**, *8*, 737.
18. Morrow, A.; Creese, I. *Mol. Pharmacol.* **1986**, *29*, 321.
19. Cheng, Y.-C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *23*, 3099.
20. Dunlop, J.; Zhang, Y.; Smith, D. L.; Schechter, L. E. *J. Pharmacol. Toxicol. Methods* **1998**, *40*, 47.