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Vinylogous amide analogs of methylphenidate

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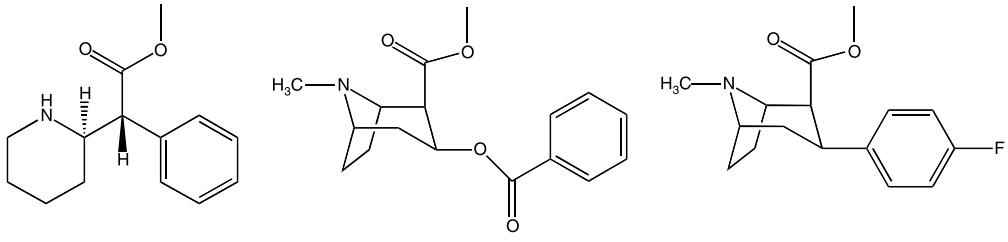
Abstract—In an effort to produce compounds with longer durations of action, we attempted to synthesize ketone analogs of methylphenidate which, however, appear to be highly unstable due to a highly acidic proton alpha to the ketone and phenyl groups. Nevertheless, vinylogous amide by products have been synthesized and tested for activity at dopamine, norepinephrine, and serotonin transporters. The compounds were found to be weak inhibitors of monoamine reuptake despite rigid three dimensional structures that are quite similar to the global minimum of threo-(*R*,*R*)-methylphenidate. The structures were confirmed by X-ray crystallography.

Methylphenidate (Scheme 1), which was first synthesized some 60 years ago,[1] is still commonly used for the treatment of attention deficit hyperactivity disorder. The therapeutic efficacy of methylphenidate is believed to be due to its ability to block the reuptake of dopamine and norepinephrine in the central nervous system.[2] However, a less desirable aspect of the clinical use of methylphenidate is that it typically must be administered two or three times/day[3] due to the presence of the ester moiety, which is rapidly metabolized to the inactive acid.[4]

Our goal has been to synthesize slow onset, long-duration blockers of dopamine reuptake as possible substitution medications for the treatment of cocaine abuse[5] since it is believed that such compounds will be considerably less abusable than dopamine uptake blockers with fast onsets and a short durations.[6,7] Since the short half life of methylphenidate is due to the presence of the easily metabolized ester group, we thought that it might be advantageous to replace the carbomethoxy with a more stable carbonyl group. This kind of substitution produces active, long-duration compounds in cocaine-like analogs (Scheme 1).[8,9] Since the carbomethoxy groups in methylphenidate and in cocaine-like compounds such as CFT have been found to correspond to each other,[10] the same substitution would be expected to produce active, long-duration analogs of methylphenidate. However, the synthesis of these analogs has proven to be more difficult than expected due to the highly



methylphenidate cocaine CFT

Scheme 1.

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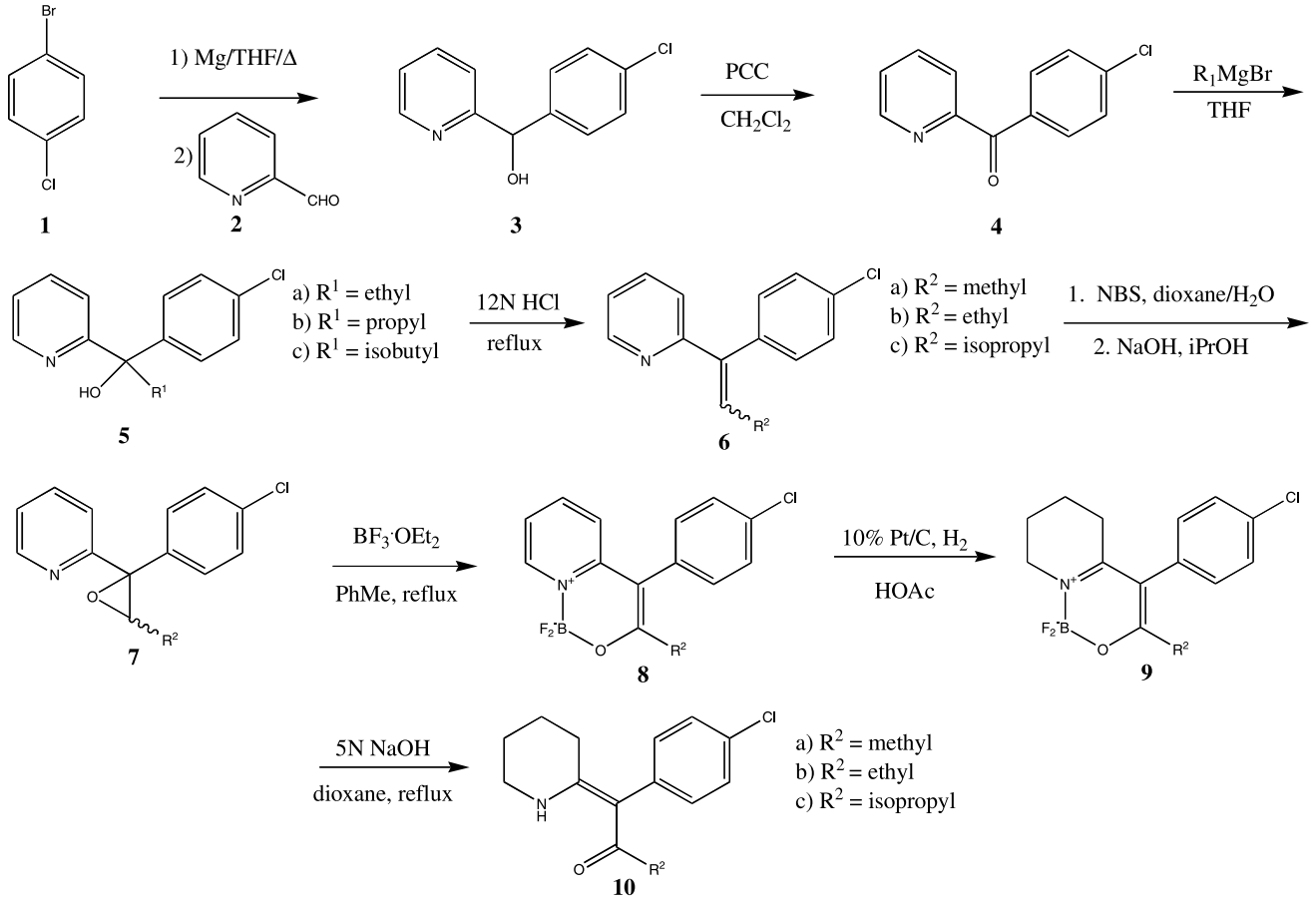
acidic proton that is alpha to both the phenyl ring and the carbonyl group of the ester. A wide variety of approaches were unsuccessful but our most recent effort has succeeded in making vinylogous amides of methylphenidate.

The novel compounds were synthesized following the sequence in Scheme 2. *para*-Bromochlorobenzene **1** was converted into a Grignard reagent with Mg/THF, which was treated with pyridine-2-carboxaldehyde **2** to produce the alcohol **3**. The alcohol **3** was oxidized with pyridinium chlorochromate to the ketone **4**, which was then treated with a series of Grignard reagents that contain various R^1 groups to produce the alcohols **5**. The alcohols **5** were dehydrated with refluxing HCl to produce *Z* and *E* olefin mixtures **6**. The olefin mixtures were converted to bromohydrins with *N*-bromosuccinimide and water, and the bromohydrins were cyclized to a *Z* and *E* mixture of epoxides **7** with NaOH. The epoxide mixtures were treated with $BF_3{\cdot}OEt_2$ to produce the BF_2-containing compounds **8**. Compounds **8** were stable to boiling 5 N NaOH overnight. The stability of these kinds of complexes has previously been noted.[11] However, after hydrogenating the pyridine rings to **9**, alkaline hydrolysis gave vinylogous amides **10**. The amide-like character of these compounds lowers the basicity of the nitrogen to the extent that an attempt to produce a salt failed and led to decomposition products.

Crystal structures were obtained for **8a**, **9a**, and all three final products **10a–c**. The crystal structure for **10c** is shown in Figure 1. The structures of all three final products show the presence of a double bond exocyclic to the piperidine ring with the four atoms attached to the double bond all lying in an approximate plane. The same geometric isomer about the double bond appears in all three compounds, presumably because of a favorable attraction between the carbonyl oxygen and the amine hydrogen. This geometric isomer corresponds to threo-methylphenidate whereas the absent geometric isomer corresponds to the inactive erythro isomer. The bond lengths for the bond range from 1.395 to 1.403 Å, showing considerable double bond character. There appear to be hydrogen bonds between the carbonyl oxygens and the amine hydrogens in the three crystal structures with distances between 1.927 and 1.957 Å.

All of the compounds were synthesized with a *para*-chloro group since this substitution increases activity by a considerable amount over methylphenidate itself.[12] The novel synthesized compounds were tested in binding and reuptake assays utilizing recombinant human dopamine, norepinephrine, and serotonin transporters stably expressed in human embryonic kidney 293 cells.[13] The binding studies measured the displacement of [^{125}I]RTI-55 by the test compounds while the reuptake studies measured the potency of the test compounds in



Scheme 2.

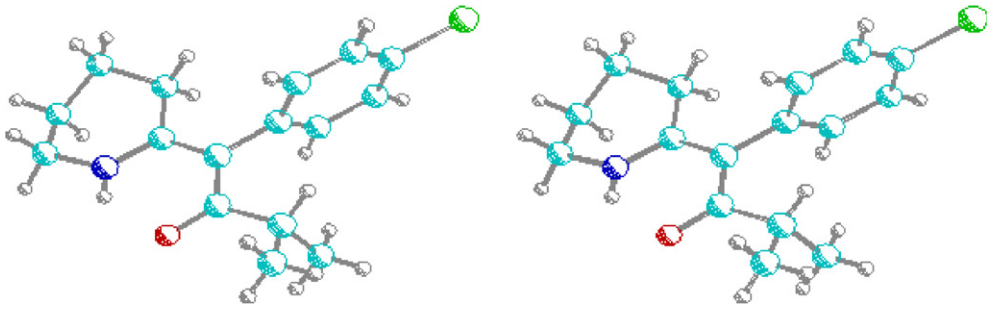


Figure 1. Stereoscopic image of crystallographic structure of **10c**.

Table 1. Binding affinity (K_i, nM) and reuptake inhibition potency (IC_{50}, nM) of compounds with recombinant human dopamine, serotonin, and norepinephrine transporters expressed in human embryonic kidney 293 cells[a]

	Dopamine		Serotonin		Norepinephrine	
	[I^{125}]-RTI-55 binding	DA Reuptake	[I^{125}]-RTI-55 binding	5HT Reuptake	[I^{125}]-RTI-55 binding	NE Reuptake
Cocaine	459 ± 69	244 ± 28	522 ± 42	314 ± 44	1970 ± 130	238 ± 33
RR/*SS*-Methylphenidate[a]	180 ± 40	190 ± 50	40,000 ± 8000	55,000 ± 16,000	1800 ± 800	38 ± 4
RR/*SS*-*para*-Cl-Methylphenidate	25 ± 8	11 ± 2	6000 ± 100	>9800	110 ± 40	11 ± 3
10a	2200 ± 800	6300 ± 1100	9000 ± 200	>10 μM	7100 ± 1200	>9500
10b	2200 ± 700	1800 ± 600	>10 μM		>10 μM	
10c	1900 ± 700	1100 ± 80	>10 μM		>10 μM	
9a	4800 ± 700	6900 ± 1400	>10 μM		>10 μM	

[a] Ref. 13.

inhibiting the reuptake of the tritiated monoamine neurotransmitters. The results of the binding assays for the vinylogous analogs along with those for cocaine, *RR*/*SS*-methylphenidate, and *RR*/*SS*-*para*-chloromethylphenidate in the same assay system are presented in Table 1.

As can be seen from Table 1, cocaine has considerable activity at all three monoamine transporters whereas methylphenidate has significant activity at just the dopamine and norepinephrine sites. As found previously,[12] the *para*-chloro analog of methylphenidate is considerably more potent than methylphenidate itself. The three vinylogous amide analogs proved to have weak activity at all three sites with the best compound, **10c**, having about 1/6 of the potency of threo-(*RR*/*SS*)-methylphenidate at the dopamine transporter and 1/100 of the potency of the *para*-chloro (*RR*/*SS*) analog. This is somewhat unexpected since the compounds **10** are rigidly held by the double bond in a conformation that is similar to the global minimum of threo-(*R*,*R*)-methylphenidate as computed with molecular mechanics calculations[10] and this conformation is also observed in a number of crystal structures of methylphenidate analogs.[14] As can be seen by comparing Figures 1 and 2, the three dimensional structures of the vinylogous amides are quite similar to the three dimensional structure of the biologically active threo-(*R*,*R*)-methylphenidate. Superimposing the heavy atoms of the piperidine and phenyl rings and the carbonyl group of **10c** with the

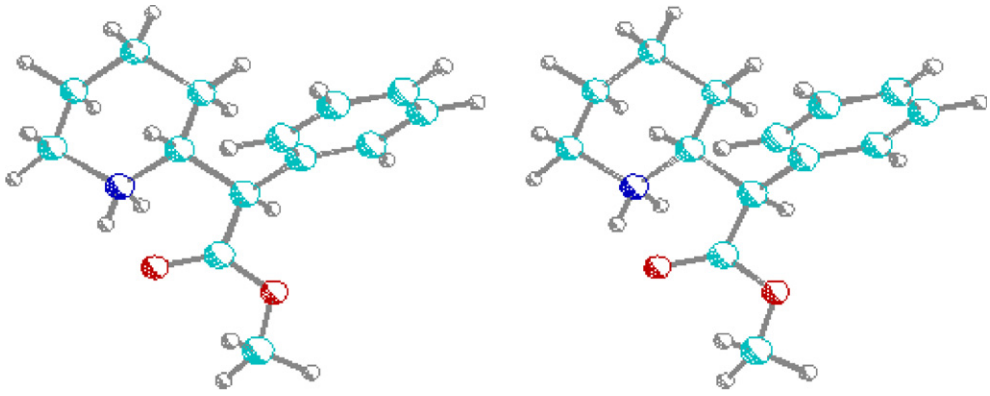


Figure 2. Stereoscopic image of the global minimum of threo-(*R*,*R*)-methylphenidate as computed by 6-31G* ab initio quantum mechanical calculations.

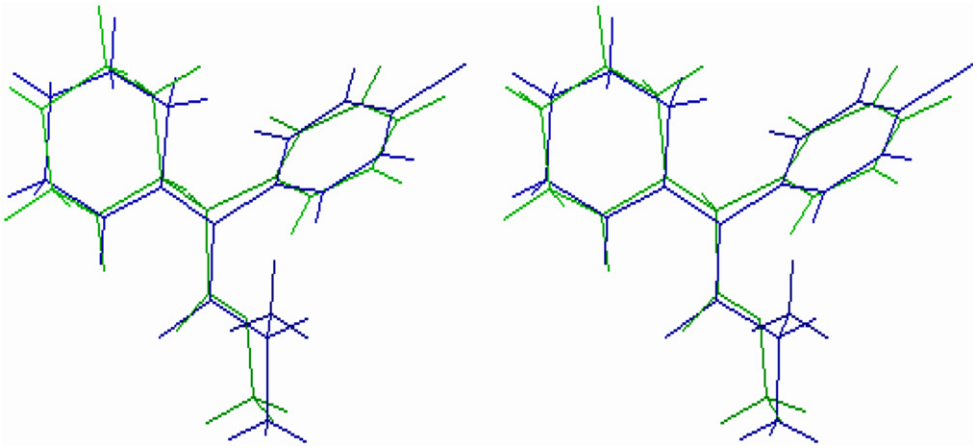


Figure 3. Stereoscopic image of the least squares superimposition of the crystal structure of **10c** (blue) with the global minimum of threo-(*R*,*R*)-methylphenidate (green).

corresponding atoms of the global minimum of threo-(*R*,*R*)-methylphenidate (as represented by a 6-31G* ab initio quantum mechanical calculation) in a least squares sense, one again sees the close three dimensional correspondence between the structures (Fig. 3), while the presence of the double bond in the vinylogous amides does reduce the basicity of the amine group, it has been shown that replacement of the nitrogen in methylphenidate by either an oxygen or carbon atom does not preclude good activity and that a basic nitrogen is not required for the activity of methylphenidate analogs.[15] Thus, the weak activity of the vinylogous amides tends to cast doubt that the biologically active conformer of threo-(*R*,*R*)-methylphenidate is similar to the global minimum of the compound. The intermediate **9a** was also tested for activity against the monoamine transporters since the boron-containing rings also forces the compound into a similar conformation. However, this compound also proved to have relatively weak activity, presumably due to the presence of the BF_2 group.

Crystallographic data (excluding structure factors) for structures **8a**, **9a**, **10a**–**10c** in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications numbers 256858, 256859, 255966, 255965, and 255964. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223-336033 or email: deposit@ccdc.cam.ac.uk].

Acknowledgments

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Supplementary data

An experimental section is available as supplementary material comprising experimental details for the syntheses and crystallographic studies, combustion analyses, and NMR, melting point, and crystallographic data. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bmcl.2005.04.034.

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