A Stereoselective Synthesis of *dl-threo*-Methylphenidate: Preparation and Biological Evaluation of Novel Analogues†

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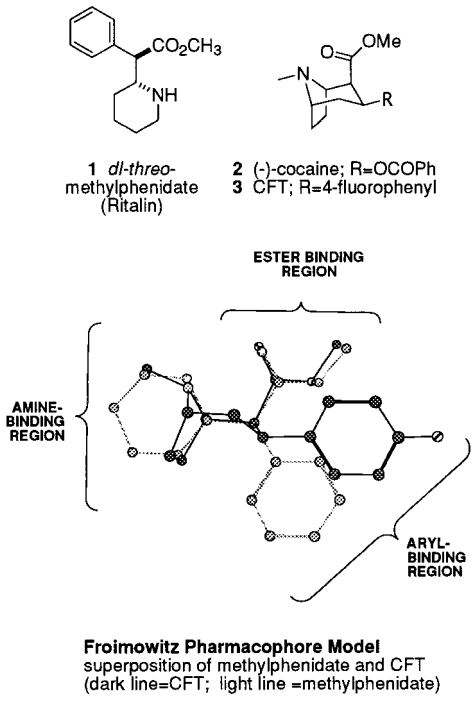
Methylphenidate (Ritalin, **1**) is the most commonly prescribed psychotropic medication for children in the United States. It is used primarily for the treatment of hyperactive children with attention deficit disorder (ADD). Both **1** and cocaine **2** have similar binding affinities for the dopamine transporter (DAT; K_i = 640 nM for (−)-cocaine and 390 nM for *d-threo*-methylphenidate), and both inhibit the reuptake of dopamine. However, it is not known whether the two drugs bind to the DAT in the same manner since X-ray structural information for the DAT is not available. Since changes in synaptic dopamine levels have been linked to a number of neurological disorders[2] as well as to cocaine abuse, the discovery of how dopamine uptake inhibitors bind to the transporter is an important goal, and the results of such studies could lead to new drug candidates to combat cocaine abuse and dependence.

Recently, Froimowitz and co-workers proposed a pharmacophore common to methylphenidate and the cocaine analogue CFT, **3**, a high-affinity ligand for the DAT, in which the β-amino ester moieties of each are superimposed (Figure 1).[3] The six-atom sequence from the ammonium group through the methyl ester includes two asymmetric centers in methylphenidate and one of the four asymmetric centers in **3**.

SAR studies on methylphenidate have been limited to modifications of the ester and substitutions on the phenyl ring due to the limitations of the previously reported syntheses of methylphenidate.[4] We describe herein a highly flexible and efficient synthesis of methylphendiate and analogues that should facilitate the establishment of the structural and functional requirements for methylphenidate binding to the DAT.

Reaction of ethyl phenylglyoxylate **4** with piperidine affords the α-ketoamide,[5] which on condensation with tosylhydrazine gives the tosylhydrazone **5** (Scheme 1). Treatment of **5** with potassium *tert*-butoxide in refluxing toluene gave **6**, which was obtained in 60% yield on crystallization of the crude reaction mixture. This procedure represents a significant improvement over previously reported work.[6] The equilibrating reaction conditions allow for the stereoselective formation of **6** (6:1 mixture of exo/endo products), in which the phenyl ring is oriented on the convex face of the bicyclic ring system. Hydrolysis of **6** with acidic methanol provides the hydrochloride salt of *threo*-methylphenidate **1** as a single diastereomer, in which the relative stereochemistry of the β-lactam **6** is completely preserved.



1 *dl-threo*-methylphenidate (Ritalin)

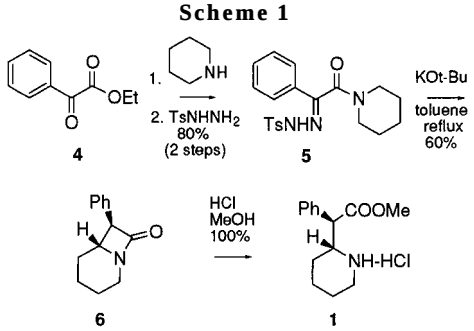
2 (-)-cocaine; R=OCOPh
3 CFT; R=4-fluorophenyl

Figure 1.

This reaction sequence has proven to be highly efficient and amenable to modification of both the piperidine and the aryl moieties of methylphenidate. The role of the piperidine ring in binding to the DAT can be evaluated by replacing it with other secondary amines (Scheme 1). Similarly, replacement of ethyl phenylglyoxylate with other arylketoacid esters leads to the incorporation of other aryl groups into the methylphenidate framework. The requisite ketoesters are available by addition of an aryllithium to diethyloxalate.[7] Using this procedure, the aryllithiums derived from 1- and 2-bromonaphthalene led to the formation of **7** and **8**, respectively (see Figure 2). The homologated phenidate analogue **9** was prepared by stereoselective alkylation of 1-azabicyclo[4.2.0]octan-8-one[8] with benzyl bromide, followed by reaction of the resulting substituted β-lactam with acidic methanol.

The results of the biological evaluation of the methylphenidate analogues using [^{125}I]-IPT **14**[9] to determine inhibition constants are shown in Table 1. While only the

Scheme 1



† Dedicated to our friend and colleague Professor Ralph F. Hirschmann, the 1999 recipient of both the Arthur C. Cope Award and the Edward E. Swissman Bristol-Myers Squibb Award.

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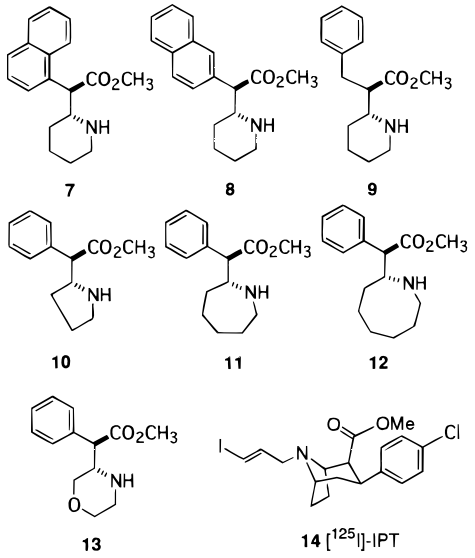

Figure 2.

aromatic moiety of methylphenidate **1** has been altered in compounds **7**−**9**, the piperidine ring has been changed in compounds **10**−**13**. These data establish for the first time that increasing the size of the aryl moiety leads to enhanced binding to the DAT in the cases of the 1-naphthyl (**7**) and 2-naphthyl (**8**) analogues relative to methylphenidate **1**, a result that is consistent with the large aryl-binding region in the pharmacophore model shown in Figure 1. A 7-fold increase in binding affinity has been achieved with the 2-naphthyl analogue **8** relative to methylphenidate **1**. Changing the aryl moiety from phenyl to benzyl, i.e., **9**, in which a methylene is added between the ester-bearing carbon and the phenyl ring, significantly attenuates the binding affinity. The data in Table 1 also indicate that the receptor is sensitive to subtle changes in the piperidine ring, as binding of each of the analogues in which the piperidine ring is modified (compounds **10**−**13**) is attenuated by a factor of 5−10.

Table 1. Inhibition of [^{125}I]-IPT Binding and [^{3}H]-Dopamine Uptake at DAT (K_i, nM)

methylphenidate analogue	[^{125}I]-IPT	[^{3}H]-dopamine
1 (*d-threo*)	324	N/A
1 (*dl-threo*)	582 ± 77	429 ± 88
7	194 ± 15	1981 ± 443
8	79.5	85.2 ± 25
9	>5000	N/A
10	1336 ± 108	N/A
11	1765 ± 113	N/A
12	3321 ± 515	N/A
13	6689 ± 1348	N/A

The differentiation between inhibition of dopamine reuptake and the inhibition of cocaine binding ($K_{i\text{-uptake}}$ vs $K_{i\text{-binding}}$) is a critical feature for the development of therapeutic agents to combat cocaine abuse. Evaluation of the naphthyl analogues **7** and **8** reveals that while **8** has a higher binding affinity for the DAT than **7**, the $K_{i\text{-uptake}}$ vs $K_{i\text{-binding}}$ ratio for the 1-naphthyl analogue **7** is 10 (the ratio for both methylphenidate and the 2-naphthyl analogue **8** is ca. 1), making it one of the most selective compounds known for the differentiation between inhibition of cocaine binding and the inhibition of dopamine reuptake. These results demonstrate that this differentiation is indeed possible, thereby validating this approach to the design of therapeutics for the treatment of cocaine abuse and addiction.[10]

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Supporting Information Available: Protocols for binding assays and synthetic procedures and spectroscopic data for compounds **4**−**13** (6 pages).

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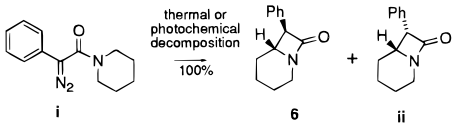
(6) In the first example of β-lactam formation from an α-diazoamide, Corey and Felix reported the stereoselective formation of a β-lactam product in 50% yield by irradiation of **i**, which was obtained by treatment of **5** with sodium hydride, although the stereochemistry of the β-lactam product was not established (Corey, E. J.; Felix, A. *J. Am. Chem. Soc.* **1965**, *87*, 2518−2519). These same authors also reported the thermal decomposition of **i** to give the same product. We have found that irradiation of **i** leads to the formation of a 4:1 mixture of *exo*-**6** and *endo*-**ii** in quantitative yield, while we observe a 3.5:1 ratio of **6**:**ii** under thermal conditions (toluene reflux). For a later example of the thermal decomposition of **i**, see: Earle, R.; Hurst, D.; Viney, M. *J. Chem. Soc. C* **1969**, 2093−2098.



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