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Original article

Synthesis and pharmacology of site specific cocaine abuse treatment agents: a new synthetic methodology for methylphenidate analogs based on the Blaise reaction

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Abstract – In order to make new analogs of the dopamine (DA) uptake inhibitor methylphenidate, a synthetic methodology based on the Blaise reaction was developed. The reaction between α-bromophenylacetic acid esters, zinc and α-cyano-ω-mesylates gave stable primary enamines. After reduction of the enamines with cyanoborohydride, the amines could be cyclized to methylphenidate analogs in which the amine ring size and aromatic ring were varied. These compounds were tested for inhibitory potency against [^{3}H]WIN 35,428 binding to the cocaine recognition site and [^{3}H]DA uptake using rat striatal tissue. When the heterocyclic ring size was varied, the six-membered ring of methylphenidate appeared to be the optimum ring size. When the aryl ring was varied the 4-trifluoromethylphenyl analog was less potent than methylphenidate, the β-naphthyl congener was considerably more potent, whereas the α-naphthyl congener was less potent. Most of the compounds tested had ratios of uptake to binding inhibition (discrimination ratio) that were similar to cocaine and were therefore not lead compounds for the development of cocaine antagonists. © 2001 Éditions scientifiques et médicales Elsevier SAS

cocaine / dopamine / drug abuse / uptake inhibitor / methylphenidate / discrimination ratio

1. Introduction

Abuse of the stimulant drug cocaine is a major problem in the United States [1]. One of the actions of cocaine is to block the re-uptake of dopamine (DA) into the presynaptic neuron, thus increasing the concentration of DA in the synapse. Our work focuses on the development of treatment agents [2–5] that interact with the DA transporter, where the reinforcing effect of cocaine is thought to be mediated [6–8].

(±)-*threo*(*R*,*R*/*S*,*S*)-Methylphenidate (**1a**, Ritalin®, methyl ritalinate) was selected as a promising candidate for drug development based on several factors. It binds potently and somewhat selectively to the DA transporter [9] and has been used to study the stimulant binding site [10]. Because of its widespread use in the treatment of attention-deficit disorder, there is extensive clinical experience with this agent. We recently published the synthesis and pharmacological studies of a large number of aromatic ring-substituted methylphenidate analogs (**1b**–**1u**) using a method very similar to that which was developed originally [2].

The synthetic methodology we used to make these methylphenidate analogs is quite limiting in that the piperidine ring portion is constructed by the alkylation of 2-bromopyridine followed by hydrogenation. This produces several disadvantages: (1) very powerful nucleophiles must be used since 2-bromopyridine is a poor electrophile; (2) only six-membered rings can be constructed; (3) other parts of the molecule, for example the aromatic ring, must be able to survive the

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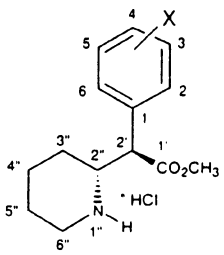


1a X=H; **1b** X=4-OH; **1c** X=3,4,5-tri-MeO;
1d X=2-Br; **1e** X=3-Br; **1f** X=4-Br; **1g** X=4-OMe;
1h X=3-I,4-OH; **1i** X=4-*t*-Bu; **1j** X=2-Cl;
1k X=3-Cl; **1l** X=4-Cl; **1m** X=3,4-di-Cl; **1n** X=2-F;
1o X=3-F; **1p** X=4-F; **1q** X=4-I; **1r** X=3-Me;
1s X=4-Me; **1t** X=3-NH_2·HCl; **1u** X=4-NH_2·HCl;
1v X=2-OH; **1w** X=3-OH; **1x** X=2-OMe;
1y X=3-OMe; **1z** X=3,4-di-OMe

strong hydrogenation conditions (Pt, HOAc, 40 psi H_2). In addition, hydrogenation always leads to a preponderance of the undesirable *erythro* isomer. Because of these limitations, we decided to attempt to develop a strategy for synthesis that would be based on the formation of the cyclic amine by ring closure. Very recently, a new total synthesis [11], an asymmetric synthesis [12], and an enantioselective synthesis [13] of methylphenidate and analogs have been published. After the work described in this paper was completed, but before it was submitted for publication [14], a stereoselective synthesis of some of the *threo*-methylphenidate analogs described herein (as well as others) was published [11]. Through the courtesy of these authors, several of their compounds have been assayed in our systems and the data included in this publication.

2. Results and discussion

2.1. Chemistry

The retrosynthetic analysis shown in *figure 1* has C–C bond formation via attack of an α-aryl ester enolate on a nitrile. This reaction, when the enolate is generated from zinc and an α-bromoester, is the Blaise reaction and is a variation of the Reformasky reaction. We were encouraged to attempt this reaction because of a high yield modification, which was developed by Hammick and Kishi [15]. The direct product of this reaction is actually an imine which, we hypothesized, would rearrange to the enamine (*figure 2*). This primary enamine would be expected to be stabilized on hydrolysis and have a weakly nucleophilic nitrogen because of the electron-withdrawing ester and aryl groups. Reduction of the enamine would then allow ring closure between the now nucleophilic amine and the leaving group X. To test the above approach, the appropriate starting material was synthesized (see *figure 3*) in order to make *threo*-(±)-methylphenidate ($n = 3$). Conversion of 4-chloro-1-butanol to 4-cyano-1-butanol was accomplished in low yield with KCN in water–ethanol. This alcohol was converted to the corresponding mesylate, which was then allowed to react with Zn–ethyl-α-bromophenylacetate using the exact conditions and work-up procedure described in Ref. [15]. A stable compound was isolated in 79% yield (based on the mesylate), which was assigned the *Z*-enamine structure **5b**. Reduction of the enamine was readily accomplished with sodium cyanoborohydride at pH 6 using the method of Borch et al. [16] and cyclization occurred spontaneously during the reaction or in work-up. Unfortunately, this gave a

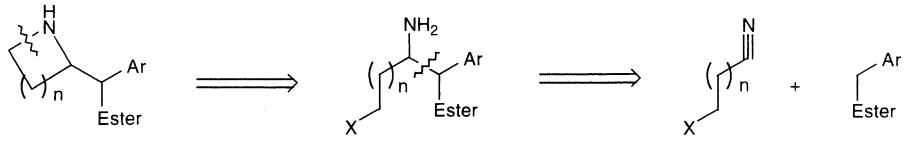


Figure 1. Retrosynthetic analysis for the synthesis of methylphenidate analogs.

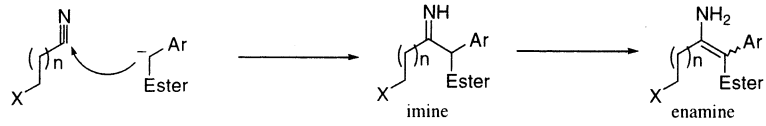


Figure 2. Blaise reaction to produce an enamine.

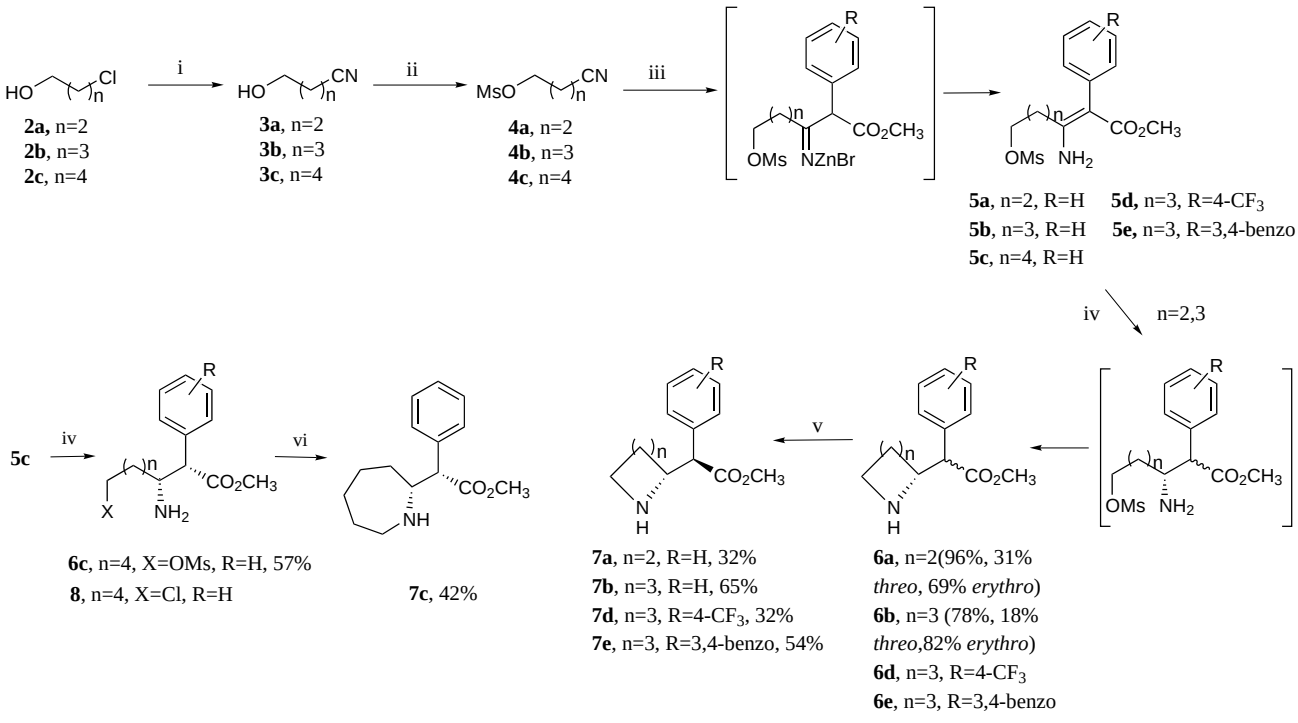


Figure 3. Synthesis of methylphenidate analogs. Reagents: (I) KCN, EtOH, H_2O; (ii) MsCl, Et_3N, CH_2Cl_2; (iii) $ArCHBrCO_2CH_3$, Zn, THF; (iv) (1) $NaBH_3CN$, MeOH, add HCl–MeOH to keep pH ~ 6, (2) NaOH, H_2O, pH>10; (v) (1) 50% KOH, reflux, (2) MeOH–HCl, (3) crystallization; (vi) K_2CO_3, DMF, 80°C.

mixture that was predominately the undesired *erythro* isomer. In addition, catalytic reduction also gave a mixture that consisted of mostly the *erythro* isomer. Other methods of reduction, such as $SmCl_2$ or $NaBH_4$/acetic acid were not successful. Despite the unfavorable stereoselectivity, epimerization of the *erythro*/*threo*-methylphenidate mixture and isolation of the pure *threo* isomer was accomplished in the standard manner [2] and gave a product that was identical to (±)-*threo*-methylphenidate.

Encouraged by the results for the six-membered ring analogs, we carried out the synthesis of the five-membered ring analog of methylphenidate using the same strategy as for the six-membered ring compound. Similar yields were obtained for each step. The enamine intermediate (**5a**) was highly crystalline and single-crystal X-ray analysis, as shown in *figure 4*, verified the tendency to form the *Z* stereochemistry. Again, cyclization occurred during the reduction–isolation step and gave a mixture in which the *erythro* isomer predominated. Epimerization gave the desired *threo* isomer.

The synthesis of the seven-membered ring analog of the methylphenidate was not as straightforward. The synthesis and reduction of the corresponding enamine (**5c**) proceeded without difficulty, but spontaneous cyclization to the seven-membered ring was not observed. Instead, a yellow solid, shown to be a 5:1 mixture of *erythro* to *threo* saturated primary amine, was isolated. Washing the solid with EtOAc afforded the pure *erythro* isomer as a white solid. Unfortunately, the pure *threo*

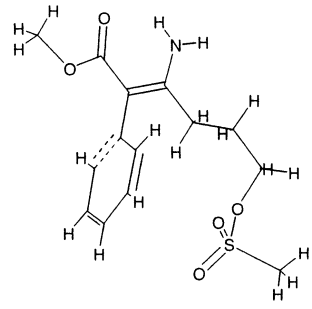


Figure 4. X-ray structure of *Z*-enamine (**5a**).

isomer could not be isolated. Cyclization (DMF, K_2CO_3, 80°C) was first carried out using the mixture of the *threo* and *erythro* open-chain compounds as the starting material. This gave a mixture that appeared to contain cyclized product, but was quite complicated by ^{1}H-NMR analysis. The assumed *threo* product was less than 10%. All attempts to isolate a pure cyclized product (*erythro* and/or *threo*) from the crude reaction mixture were not successful. This mixture was subjected to the conditions for epimerization (50% KOH, reflux) in the hope of getting more of the *threo* isomer. However, no cyclized product could be detected. It is possible that the seven-membered ring analog was destroyed by the harsh basic condition during epimerization. The cyclization was also attempted using the pure *erythro* open-chain compound as the starting material. When the hydrochloride salt was used, the crude product was a mixture of at least two compounds by ^{1}H-NMR analysis. After conversion to a hydrochloride salt, crystallization from EtOAc–MeOH (2:1) was performed. This gave a white solid, which proved not to be the desired material but rather the chloro compound (**8**) as determined by ^{1}H-NMR and MS analysis. This was, presumably, formed by the nucleophilic displacement of the mesyl group by chloride anion. The mother liquid from the isolation of **8** was evaporated and recrystallized from EtOAc–MeOH (3:1). This gave a different white solid, which proved to be the *erythro* seven-membered ring product (**7c**). It was assigned the *erythro* stereochemistry based on analogy to the known NMR patterns for *erythro* methylphenidate. When the *erythro* seven-membered ring product (**7c**) was subjected to typical epimerization conditions, neither the *erythro* nor the *threo* product could be detected by ^{1}H-NMR analysis of the methyl esters. The undesired chloro compound **8** was not formed when the free base was used as the starting material.

When the aromatic component of the Blaise reaction was varied, several new analogs were made, which could not be made by the original synthetic method. Thus, when methyl-1-bromo-1-(4-trifluoromethylphenyl)acetate or methyl-1-bromo-1-(2-naphthyl)acetate was treated with Zn and **4b**, and the isolated intermediates treated as outlined above, the corresponding *threo*-methylphenidate analogs **7d** or **7e** were isolated.

Although ^{1}H-NMR analysis (Noe, data not shown) indicated that these enamines had the *Z* stereochemistry, it was shown unambiguously by single-crystal X-ray crystallography. Semi-empirical calculations (CS MOPAC Pro) [17] indicated that the *Z* isomer was more stable, $\delta H_f = -1.6$ kcal mol^{-1}; this may account for the observed product since the more stable isomer will most likely be formed under these conditions.

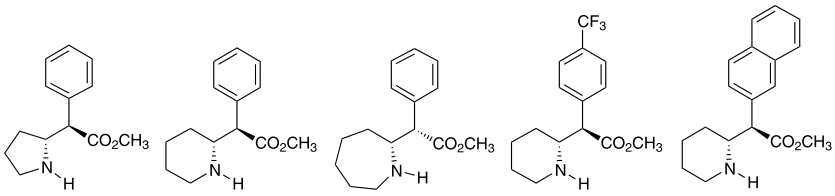
Reduction of the enamines with cyanoborohydride under neutral conditions proceeded rapidly and in high yield to give mixtures of products in which the *erythro* isomers were always produced in greater amount (70–80%) as compared to the *threo* isomers. Thus, the predominant mode of reduction is the *syn* addition of hydrogen. This process must be at least primarily under kinetic control since the *threo* isomer is more stable (based on epimerization experiments). Catalytic reduction, which would be expected to give the products of *syn* addition of hydrogen, also gave predominately the *erythro* isomers. Several other methods of reduction were also attempted, which either gave high recovery of starting material ($SmCl_2$) or complicated mixtures of products ($NaBH_4$/HOAc) that could not be analyzed. In most cases the pure *threo* compounds could be isolated in reasonable yield by epimerization of the methylphenidate analogs (after ring closure).

When enamines **5a**, **5b**, **5d** and **5e** were reduced with $NaBH_3CN$ and then worked up under basic conditions, ring closure to form the five- or six-membered ring compounds occurred spontaneously. This did not happen with the precursor to the seven-membered ring analog. In this case, the open-chain compound was isolated and then treated with K_2CO_3 and DMF at 70°C. In one case, when the hydrochloride salt of the precursor was so treated, both the seven-membered ring analog and the chloro compound **8** were isolated. In this case, the slow rate of ring closure allows for the competitive nucleophilic displacement of the mesyl group by the chloride anion. When the free base of pure *erythro* **6c** was treated with K_2CO_3 and DMF at 70°C, pure *erythro* **7c** could be isolated easily. All attempts to epimerize either pure **7c** or a mixture of **7c** and the corresponding *threo* isomer (never isolated) led to mixtures of products of undetermined structures. It appeared as though the seven-membered ring analogs were unstable under the epimerizing conditions (50% KOH, 120°C). The synthesis of the *threo*-β-naphthyl analog **7e** and the *threo*-4-trifluoromethyl analog **7d** proceeded normally. All of these compounds (**7a**, **7c**, **7d** and **7e**) are of interest chemically because they are not available by the previous methods of synthesis.

3. Pharmacology

The inhibition of [^{3}H]WIN 35,428 (WIN) binding and [^{3}H]DA uptake are shown in *table I* (compounds

Table I. Inhibition of [^{3}H]WIN 35,428 binding and [^{3}H]DA uptake for methylphenidate derivatives synthesized in this study and related compounds; value ± SEM (n).

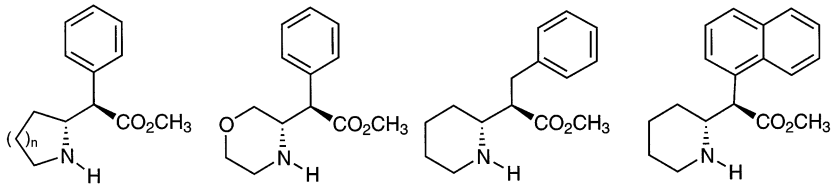


7a **7b(1a)** **7d** **7c** **7e**

Compound	Stereochemistry	IC_{50} (nM)		Hill coefficient, n_H, for WIN binding	Discrimination ratio, ratio of uptake to binding (DR)
		[^{3}H]WIN 35,428 binding	[^{3}H]DA uptake		
7a	*threo*	355 ± 45(2)	885 ± 5.0(2)	1.07 ± 0.01	2.5
7b(1a)	*threo*	83.0 ± 7.9(4)	224 ± 19(4)	0.90 ± 0.09	2.7
7c	*erythro*	4090 ± 310(2)	9030 ± 250(2)	0.81 ± 0.08	2.2
7d	*threo*	615 ± 15(2)	2370 ± 85(2)	0.97 ± 0.05	3.8
7e	*threo*	11.0 ± 2.5(3)	53.0 ± 8.0(2)	1.01 ± 0.03	4.8
COC [a]		160 ± 15(3)	404 ± 26(2)	1.03 ± 0.01	2.5

[a] (−)-Cocaine.

Table II. Inhibition of [^{3}H]WIN 35,428 binding and [^{3}H]DA uptake for methylphenidate derivatives synthesized by Axten et al. [11] value ± SEM (n).



9 n=3 **10 n=4** **11** **12** **13**

Compound	Stereochemistry	IC_{50} (nM)		Hill coefficient, n_H, for WIN binding	Discrimination ratio, ratio of uptake to binding (DR)
		[^{3}H]WIN 35,428 binding	[^{3}H]DA uptake		
9	*threo*	197 ± 16(2)	701 ± 36(2)	0.82 ± 0.02	3.6
10	*threo*	623 ± 4.5(2)	1590 ± 150(2)	0.95 ± 0.03	2.6
11	*threo*	1250 ± 210(2)	9930 ± 1400(2)	0.81 ± 0.05	7.9
12	*threo*	4470 ± 1200(2)	8450 ± 210(2)	1.04 ± 0.18	1.9
13	*threo*	716 ± 56(3)	980 ± 94(2)	0.98 ± 0.02	1.4

synthesized in this study) and *table II* (compounds synthesized by Axten et al. [11]).

WIN binding. All of the compounds with either smaller (**7**, five-membered) or larger (**11** and **12**, seven- and eight-membered) rings were somewhat less potent than methylphenidate (**1a**, six-membered) by factors of 4, 2 and 8, respectively. In agreement with earlier work [2], the *erytho* isomer **9** was 21-fold less active than the *threo* isomer **11**. When the six-membered ring is maintained but a polar oxygen atom inserted (**13**, 3-morpholino analog), the binding potency is reduced substantially (15-fold). Moving the phenyl ring one atom further away from the nitrogen, to produce a phenylpropylamine derivative, drastically reduces binding potency 54-fold. The only aromatic ring-substituted derivative was the trifluoromethyl compound **8**. Surprisingly, this compound was sevenfold less active ($IC_{50} = 615$ nM) than methylphenidate ($IC_{50} = 83.0$ nM) and 18- and 19-fold less active than 4-fluoro and 4-methylpethylphenidate [2], respectively. Most interesting were the α- and β-naphthyl derivatives **15** and **10**, respectively. Thus, **15** is 12-fold less active than MP, whereas **10** is eightfold more active than MP. This difference between the α- and β-naphthyl analogs is in good agreement with the results of Davies et al. [18] for the α- and β-naphthyl derivatives of tropanes. The differences between some of the previously reported results of Axten et al. [11] (using a different assay system) for the α- and β-naphthyl derivatives **15** and **10** and the results reported here will be addressed by these authors in a future publication [19].

[^{3}H]DA uptake. In all cases, the inhibition of [^{3}H]DA uptake closely followed WIN binding. One way to look for a divergence is to calculate the ratio of inhibitory potencies against uptake to binding using the respective IC_{50} values; the term discrimination ratio (DR) [2] has been used for this purpose. In our hands, compound **15** had a DR of only 1.4 whereas the value for compound **10** was 4.8. The compound with the highest DR reported here, 7.9, was the 3-morpholino analog **13**.

4. Conclusions

The Blaise reaction, using the modification of Hammick and Kishi [15], worked quite well giving the *Z*-ω-mesyl-enamines in 60–75% yield (based on the cyano compounds). Unfortunately, reduction of the enamines gave mostly the *erythro* isomers. Fortunately, in most cases, *threo* methylphenidate analogs could be made using an epimerization procedure. New analogs were produced, which could not be made using the previous procedure. However, the new synthetic methodology of Axten et al. [11] appears to be a more versatile way to produce these compounds. All modifications to the piperidine ring of methylphenidate produced less potent analogs. The α-naphthyl analog was less active and the β-naphthyl analog more active than methylphenidate, in agreement with the previous literature results for tropanes. While the low DR values of these compounds suggest that they may not be useful cocaine antagonists, the potent β-naphthyl analog may merit further investigation as substitution therapy for cocaine. The 3-morpholino analog **13**, although less active, may provide a lead for cocaine antagonism because of its increased DR value of 7.9, marginally higher than methylphenidate, 2.7 and cocaine, 2.5.

5. Experimental protocols

Chemistry, general. Reagents and solvents were mostly reagent grade and were used without further purification. Solvents or reagents that required drying or purification were prepared according to the procedures found in Ref. [20]. Column chromatography was carried out on Fisher Scientific Co. Silica gel (Grade 62). Extraction solvents were dried with $MgSO_4$. Melting points were obtained using a Laboratory Devices Mel-Temp II instrument without corrections. NMR spectra were recorded on a Varian Gemini 300 (300 MHz) NMR spectrometer. Mass spectra were measured on a VG 70-SE, 2 sector, forward geometry instrument. IR spectra were recorded on a Nicolet 520 FT spectrophotometer. Microanalytical data were obtained by Atlantic Microlabs, Atlanta, GA.

*4-Hydroxyl-1-butanitrile (**3a**)*. To a stirred solution of 13.4 mL (160 mmol) of 3-chloropropan-1-ol in 76 mL of ethanol–water (3:1) was added 12.7 g (200 mmol) of KCN. The solution was then boiled for 1.5 h, cooled, filtered and the solvents were distilled off under reduced pressure. This gave an oily residue, which was distilled to give 3.40 g (25%) of **3a**. ^{1}H-NMR ($CDCl_3$): δ 3.79 (t, 2H, $J = 5.8$ Hz, CH_2–O), 2.51 (t, 2H, $J = 7.1$ Hz, CH_2–CN), 1.95–1.87 (m, 2H). MS-CI; m/z: 86 (M+H).

*4-Mesylate-1-butanitrile (**4a**).* With stirring, 1.0 g (12 mmol) of compound **3a** was dissolved in 60 mL of dry CH_2Cl_2 and 2.5 mL (18 mmol) of triethylamine was then added. The solution was cooled to about −10°C, 1.0 mL (13 mmol) of methanesulfonyl chloride was slowly added over a 10-min period and it was then stirred for an additional 15 min. The reaction mixture was extracted with ice-water, followed by cold 10% of HCl, saturated $NaHCO_3$ solution and brine. Drying and evaporation gave 1.82 g (93%) of **4a**, which showed: ^{1}H-NMR ($CDCl_3$): δ 4.37 (t, 2H, $J = 5.8$ Hz, CH_2–O), 3.07 (s, 3H, CH_3), 2.56 (t, 2H, $J = 7.1$ Hz, CH_2–CN), 2.18 (br), 2.09 (m, 2H); MS-CI; m/z: 164 (M + H).

*Methyl-7-mesylate-3-amino-2-phenyl-2-hexenoate (**5a**).* To a suspension of 0.780 g (12 mmol) of activated Zn dust in 7.5 mL of refluxing dry THF under N_2 was added four 0.05-mL portions of methyl-α-bromophenylacetate. The suspension was heated under reflux for 0.5 h until a green color appeared. Then, 0.392 g (2.40 mmol) of compound **4a** in 1.5 mL of dry THF was added in one portion, followed by 1.3 mL (total 9.6 mmol) of methyl-α-bromophenylacetate in 1.8 mL of dry THF over a 45-min period. The mixture was heated under reflux for an additional 10 min, cooled to room temperature (r.t.), diluted with 21 mL of THF and quenched with 3.1 mL of 50% aqueous K_2CO_3. Rapid stirring for 30 min gave two layers. The upper layer was decanted and the lower layer washed three times with THF. The combined organic layers were dried and the solvent removed in vacuo. This gave an oily residue, which was purified by column chromatography (30 g of silica gel) with an elutant of EtOAc–hexane (1:2, v/v) yielding 0.48 g (63%) of **5a** as a pale yellow solid. When washed with EtOAc–hexane (1:1), a pure white solid was produced, which showed: m.p. 105–106°C; ^{1}H-NMR ($CDCl_3$): δ 7.35–7.14 (m, 5H, Ar), 4.11 (t, 2H, $J = 6.1$ Hz, CH_2–OSO_2), 3.59 (s. 3H, CH_3O), 2.92 (s, 3H, CH_3–S), 2.16 (t, 2H, $J = 7.4$ Hz, CH_2–C=C), 1.85–1.80 (m, 2H).

*(±)-threo-Methyl-2-phenyl-2-(2-azacyclopentyl)-acetate (**7a**).* To a solution of 0.50 g (1.6 mmol) of **5a** in 15 mL of MeOH was added a trace of bromocresol green, followed by 0.40 g (6.3 mmol) of $NaBH_3CN$. Dilute HCl–MeOH solution was added until the color turned yellow. The solution was stirred at r.t. for 1 h. More HCl–MeOH was added dropwise during the reaction to maintain the yellow color. The reaction mixture was poured into 30 mL (0.1 N) of NaOH solution (saturated with NaCl), extracted with EtOAc and the organic layer washed with brine and dried. Removal of the solvent gave 337 mg (96%) of **6a**, which contained 31% of *threo* and 69% of *erythro* isomers based on ^{1}H-NMR analysis. This crude product was mixed with 9 mL of 50% KOH and heated under reflux for three days. Top oil was collected and dissolved in MeOH. Concentrated HCl was added and evaporated to dryness to give a solid. The solid was mixed with MeOH (20 mL) and thionyl chloride (0.5 mL) and stirred at r.t. for 24 h. The solvent was evaporated and water added. The solution was then made basic with NaOH (15%), extracted with EtOAc, washed with water and dried. Evaporation gave 168 mg of the *threo*-enriched mixture (4:1 *threo–erythro* by ^{1}H-NMR analysis). This mixture was converted to an HCl salt and crystallized from a mixture of acetone and diethyl ether to give a white solid, which was the pure *threo* isomer (**7a**) (130 mg, 32%): m.p. 192–194°C; ^{1}H-NMR (D_2O): δ *threo* isomer 7.31–7.26 (m, 3H, Ar), 7.20–7.17 (m, 2H, Ar), 4.06–4.01 (m, 1H, HC2″), 3.88 (d, 1H, $J = 10.6$ Hz, HC2′), 3.56 (s, 3H, CH_3), 3.25–3.18 (m, 2H, HC5″), 1.87–1.47 (m, 4H); *erythro* isomer (not isolated) 7.32–7.25 (m, 5H, Ar), 4.07–4.04 (m, 1H, HC2″), 3.90 (d, 1H, $J = 10.5$ Hz, HC2′), 3.53 (s, 3H, CH_3), 3.16–3.07 (m, 2H, HC5″), 2.27–2.23 (m, 1H), 1.98–1.90 (m, 2H), 1.70–1.66 (m, 1H); MS-EI; m/z: 220 (M+H). Anal. Calc. for $C_{13}H_{18}ClNO_2$: C, H, N, Cl.

*6-Hydroxy-1-hexanitrile (**3c**).* To a stirred solution of 9.20 g (75 mmol) of 5-chloro-1-pentanol in 40 mL of ethanol–water (3:1) was added 6.4 g (98 mmol) of KCN. The solution was then heated under reflux for 5.5 h. The solvents were evaporated, ether was added and the mixture was filtered. Evaporation of the filtrate gave an oil which was distilled at 125–145°C to give 5.8 g (63%) of **3c**, which showed: ^{1}H-NMR ($CDCl_3$): δ 3.66 (t, 2H, $J = 6.1$ Hz, CH_2–O), 2.38 (t, 2H, $J = 7.1$ Hz, CH_2–CN), 1.82–1.51 (m, 7H).

*6-Mesylate-1-hexanitrile (**4c**).* With stirring, 1.7 g (15 mmol) of compound **3c** was dissolved in 75 mL of dry CH_2Cl_2 and 3.0 mL (22 mmol) of triethylamine was then added. This solution was cooled to about −10°C, 1.3 mL (16 mmol) of methanesulfonyl chloride was added slowly over a 10-min period and it was stirred for an additional 15 min. The mixture was extracted with ice-water, followed by cold 10% of HCl, saturated $NaHCO_3$ solution and brine. After drying, evaporation of the solvent gave 2.8 g (97%) of **4c**, which showed: ^{1}H-NMR ($CDCl_3$): δ 4.24 (t, 2H,

$J = 6.2$ Hz, CH_2–O), 3.01 (s, 3H, CH_3), 2.38 (t, 2H, $J = 7.1$ Hz, CH_2–CN), 1.82–1.58 (m, 6H).

Methyl-8-mesylate-3-amino-2-phenyl-2-octenoate ***(5c)***. Using the same method for the synthesis of **5a**, 4.6 g (70 mmol) of activated Zn dust, 8.8 mL total (56 mmol) of methyl-α-bromophenylacetate and 2.75 g (14 mmol) of compound **4c** gave an oily residue, which was purified by column chromatography on 120 g of silica gel using an elutant of EtOAc–hexane (1:1, v/v). This gave 3.5 g (74%) of **5c**, which crystallized on standing. The solid was washed with ether to give pure **5c**, which showed: m.p. 53–55°C; ^{1}H-NMR ($CDCl_3$): δ 7.34–7.25 (m, 3H, Ar), 7.14 (m, 2H, Ar), 4.12 (t, 2H, $J = 5.9$ Hz, CH_2–O), 3.58 (s, 3H, CH_3–O), 2.97 (s, 3H, CH_3–S), 2.02 (t, 2H, $J = 7.1$ Hz, CH_2–C=), 1.60–1.25 (m, 6H).

erythro-Methyl-8-mesylate-3-amino-2-phenyl-2-octanoate ***(6c)***. Using the same method for the synthesis of **7a**, 1.62 g (4.47 mmol) of **5c** and 1.2 g (19 mmol) of $NaBH_3CN$ gave 1.77 g of crude product as a mixture of *threo* and *erythro* isomers in a ratio of about 1:5 by ^{1}H-NMR analysis. The crude product was converted to an HCl salt and yellow solid washed with EtOAc several times to afford the pure *erythro* isomer **6c** as a white solid, 0.93 g (57%), which showed: m.p. 158–160°C; ^{1}H-NMR (D_2O): δ 7.31–7.20 (m, 5H, Ar), 4.17 (t, 2H, $J = 6.1$ Hz, CH_2–O), 3.92 (d, 1H, $J = 7.2$ Hz, CH–Ar), 3.80–3.78 (m, 1H, HC–N), 3.55 (s, 3H, CH_3–O), 3.01 (s, 3H, CH_3–S), 1.63–1.32 (m, 8H).

erythro - Methyl - 2 - phenyl - 2 - (2 - azacycloheptyl)-acetate ***(7c)***. A 240-mg (7.1 mmol) portion of **6c** was added to a suspension of 570 mg of K_2CO_3 in 5 mL of DMF under a nitrogen atmosphere. The mixture was heated to 80°C for 2 h, cooled and decanted. The solid residue was rinsed with diethyl ether (4×20 mL) and the combined organic layer washed with water (5×20 mL) and dried. Evaporation of the solvent gave 160 mg crude product as a pale yellow oil which was converted to an HCl salt and crystallized from EtOAc–MeOH (2:1) to give 73 mg (42%) of white solid as the pure *erythro* isomer (**7c**) which showed: m.p. 178–180°C; ^{1}H-NMR (D_2O): δ 7.39–7.29 (m, 5H, Ar), 3.99 (d, $J = 8.8$ Hz, 1H, HC2′), 3.92 (m, 1H, HC2″), 3.60 (s, 3H, CH_3), 3.09–3.04 (m, 2H, HC7″), 1.93–1.90 (m, 1H), 1.71–1.41 (m, 7H). MS-CI; m/z: 248 (M+H). Anal. Calc. for $C_{15}H_{22}ClNO_2 \cdot 0.25H_2O$: C, H, N, Cl.

erythro-Methyl-3-amino-8-chloro-2-phenyloctanoate ***(8)***. This compound was obtained as a byproduct when the above cyclization reaction was conducted using the HCl salt of compound **6c**. Crystallization of the crude product (HCl salt) from MeOH–EtOAc (1:2) gave pure compound **8**, which showed: m.p. 221–222°C; ^{1}H-NMR (D_2O): δ 7.35–7.23 (m, 5H, Ar), 3.94 (d, $J = 7.6$ Hz, 1H, HC–Ar), 3.85–3.81 (m, 1H), 3.59 (s, 3H, CH_3), 3.50–3.45 (m, 2H), 1.64–1.34 (m, 8H). MS-CI; m/z: 284 (M+H).

threo-4-Trifluoromethylmethylphenidate ***(7d)***. Using the same procedures described in making **5c**, 1.3 g (0.02 mmol) of activated Zn dust, 5.95 g (20.0 mmol) of methyl-α-bromo-4-trifluoromethlyphenylacetate and 0.73 g (10 mmol) of compound **4b** gave an oily residue, which was purified by column chromatography on silica gel using an elutant of EtOAc–hexane (1:1) to give 0.57 g (35%) of **5d**. Using the same method for the synthesis of **7a**, 0.57 g of **5d** and 0.36 g of $NaBH_3CN$ gave a crude product as a mixture of *threo* and *erythro* isomers in a ratio of about 1:3 by ^{1}H-NMR analysis. The crude product was converted to an HCl salt and yellow solid washed with diethyl ether several times to afford 0.37 g (75%) of **6d** as a white solid. Using the epimerization–esterification procedure described in the synthesis of **7a**, 0.37 g of **6d** gave 88 mg (24%) of **7d**, which showed: m.p. 196–197°C; ^{1}H-NMR (D_2O): δ 7.62 (d, $J = 8.2$ Hz, 2H, Ar), 7.37 (d, $J = 8.2$ Hz, 2H, Ar), 3.96 (d, $J = 9.4$ Hz, 1H, HC2′), 3.78–3.71 (m, 1H, HC2″), 3.59 (s, 3H, CH_3), 3.34–3.33 (m, 1H, HC6″), 2.95 (dt, $J = 3.3$ Hz, 12.9 Hz, HC6″), 1.76–1.19 (m, 6H). Anal. Calc. for $C_{15}H_{19}ClNO_2F_3 \cdot 0.4H_2O$: C, H, N, Cl.

threo - Methyl - 2 - piperidyl - 2 - [(2 - naphthyl)]acetate ***(7e)***. Using the same procedures described in making **5c**, 1.0 g (16 mmol) of activated Zn dust, 4.4 g (16 mmol) of methyl-α-bromo-(2-naphthyl)acetate and 0.58 g (3.2 mmol) of compound **4b** gave an oily residue, which was purified by column chromatography on silica gel using an elutant of EtOAc–hexane (1:1) to give 0.72 g (59%) of **5e**. Using the same method for the synthesis of **7a**, 0.61 g of **5e**, and 0.36 g of $NaBH_3CN$ gave a crude product as a mixture of *threo* and *erythro* isomers in a ratio of about 1:3 by ^{1}H-NMR analysis. The crude product was converted to an HCl salt and yellow solid washed with diethyl ether several times to afford 0.31 g (68%) of **6e** as a white solid. Using the epimerization–esterification procedure described in the synthesis of **7a**, 0.31 g of **6e** gave 0.13 g (54%) of **7e**, which showed: m.p. 219–220°C; ^{1}H-NMR (D_2O): δ 7.84–7.76 (m, 3H, Ar), 7.70 (m, 1H, Ar), 7.47–7.43 (m, 2H, Ar), 7.26 (dd, $J = 1.8$, 8.4 Hz, 1H, Ar), 4.00 (d, $J = 9.3$ Hz, 1H,

HC2′), 3.81–3.75 (m, 1H, HC2″), 3.57 (s, 3H, CH_3), 3.32–3.27 (m, 1H, HC6″), 2.93 (dt, $J = 3.3$ Hz, 12.9 Hz, 1H, HC6″), 1.72–1.22 (m, 6H). Anal. Calc. for $C_{18}H_{22}ClNO_2 \cdot 0.5H_2O$: C, H, N, Cl.

Pharmacology. [^{3}H]WIN 35,428 binding and [^{3}H]DA uptake assays were conducted as described previously [3].

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