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Synthesis of methylphenidate analogues and their binding affinities at dopamine and serotonin transport sites

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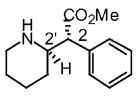
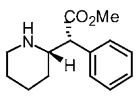
Abstract—The rhodium(II)-catalyzed intermolecular C–H insertion of methyl aryldiazoacetates with either *N*-Boc-piperidine or *N*-Boc-pyrrolidine followed by deprotection with trifluoroacetic acid is a very direct method for the synthesis of methylphenidate analogues. By using either dirhodium tetraacetate or dirhodium tetraprolinate derivatives as catalyst, either the racemic or enantioenriched methylphenidate analogues can be prepared. The binding affinities of the methylphenidate analogues to both the dopamine and the serotonin transporters are described. The most notable compounds are the *erythro*-(2-naphthyl) analogues which display high binding affinity and selectivity for the serotonin transporter.

1. Introduction

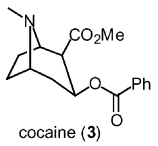
Even though the dopamine reuptake inhibitor, methylphenidate has been known for over 50 years,[1] its synthesis and biology continues to be of considerable interest. Of the *threo* and *erythro* diastereomers (**1a** and **2a**), for methylphenidate, the *threo* form is most active and is prescribed to patients as a racemate for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).[2] Additionally, *threo*-methylphenidate has undergone evaluation for its therapeutic potential for treatment of cocaine (**3**) addiction,[3–5] and shown promise in adults who have been also diagnosed to have ADHD.[3,5] Due to this intense interest, new analogues of methylphenidate continue to be explored.[6–13]



threo-methylphenidate (**1a**)



erythro-methylphenidate (**2a**)



cocaine (**3**)

As most of the therapeutic activity of *threo*-methylphenidate resides in the D-enantiomer (2*R*,2′*R*),[14] while the L-enantiomer (2*S*,2′*S*) may have undesirable side effects,[15] effective methods for the asymmetric synthesis of *threo*-methylphenidate have been explored. In the late 1990s, two new but fairly lengthy asymmetric syntheses of methylphenidate were reported.[16,17] A shorter method was then reported using an asymmetric Michael addition as the key step,[18,19] but this approach required the use of a stoichiometric amount of an expensive chiral auxiliary.

For some time, we have been designing new synthetic methods for the asymmetric synthesis of classes of compounds that inhibit monoamine transporters. The ultimate goal of this work is to apply these enabling synthetic technologies to the rapid synthesis of potential therapeutic agents for the treatment of cocaine addiction. Efficient asymmetric syntheses of many important classes of monoamine re-uptake inhibitors such as 2β-substituted 3β-aryl tropanes,[20,21] sertraline,[22] and indatraline[23] have been achieved. A hallmark of these synthetic methodologies is that they are all based on asymmetric carbenoid transformations induced by chiral rhodium prolinate catalysts, such as Rh_2(*S*-DOSP)$_4$ (**4**) and Rh_2(*S*-biDOSP)$_2$ (**5a**).[24]

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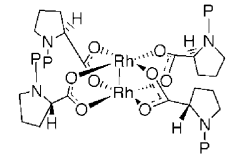
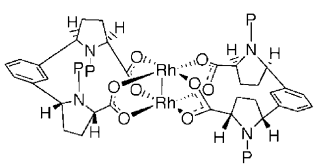
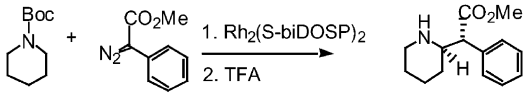


4: P = p-$C_{12}H_{25}C_6H_4SO_2$
Rh_2(*S*-DOSP)$_4$



5a: P = p-$C_{12}H_{25}C_6H_4SO_2$ Rh_2(*S*-biDOSP)$_2$
5b: P= 2,4,6-tn^{i}Pr$C_6H_2SO_2$ Rh_2(*S*-biTISP)$_2$

Recently, we described a very direct strategy for the asymmetric synthesis of *threo*-methylphenidate by an asymmetric C–H insertion *N*-Boc-piperidine (eq 1).[25–27] This new approach to *threo*-methylphenidate is unusual because it is an example of a catalytic asymmetric C–H activation process. This communication describes studies to exploit this C–H insertion for the synthesis of methylphenidate analogues, which has led to the discovery of analogues with novel binding selectivity profiles.



1a
73% yield, 86% ee, 42% de (1)

2. Chemistry

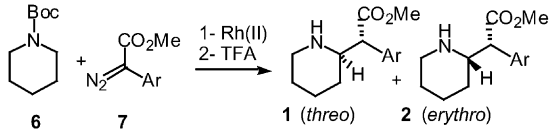
The general strategy for the synthesis of the methylphenidate analogues is based on the C–H insertion that is described in eq 1. Reaction of various aryldiazoacetates **7** with *N*-Boc-piperidine (**6**) resulted in the synthesis of a series of methylphenidate analogues as illustrated in Table 1. A major advantage of this strategy is that either racemic analogues can be prepared by using achiral catalysts or an asymmetric synthesis can be achieved using chiral catalysts. In general these reactions resulted in a slight preference for the *threo* diastereomer **1**. Rh_2(*R*-DOSP)$_4$ and Rh_2(*S*-biTISP)$_2$ generate preferentially (2*R*,2′*R*)-**1**, which is the biologically most active enantiomer of *threo*-methylphenidate. The first four entries are directed towards the synthesis of *threo* and *erythro* methylphenidate (**1a** and **2a**) and some of the more interesting methylphenidate analogues (**1b–d**) that have been studied previously.[10,11,28] As can be seen in entries 1–3, these reactions can be easily carried out with good asymmetric induction using Rh_2(*S*-DOSP)$_4$ as catalyst at −50 °C. The biphenyl analogue **1e** was prepared because the biphenyl functionality at C-3 in the tropanes resulted in very potent monoamine reuptake inhibitors.[29] The 2-naphthyl analogue **1g** and its *erythro* diastereomer (**2g**) were prepared because (±)-**1g** has been shown previously to be a potent methylphenidate analogue[9] and the 2-naphthyl functionality at C-3 in the tropanes generated extremely potent monoamine reuptake inhibitors.[29] The pure enantiomer of **1g** was readily prepared by carrying out the reaction with Rh_2(*S*-biTISP)$_2$ as catalyst at room temperature. This resulted in the formation of **1g** in 85% ee, which after a single recrystallization gave enantiomerically pure (2*R*, 2′*R*)-**1g** (>98% ee).

The C–H insertion reaction was also carried out with *N*-Boc-pyrrolidine (**8**) to generate a new series of methylphenidate analogues (Table 2). In contrast to the reaction with *N*-Boc-piperidine, the reactions with *N*-Boc-pyrrolidine are highly diastereoselective favoring the *erythro* diastereomer.[8] Indeed, when the reactions are carried out with Rh_2(*S*-DOSP)$_4$ at −50 °C, both the *de* and *ee* of the reactions are >90% favoring the (2*R*,2′*S*) enantiomer. The first four entries describe reactions with substituted phenyldiazoacetates to form **9a–c**,**f** and **10a–c**,**f**. The final four entries describe reactions with substituted 2-naphthyldiazoacetates to form **9g–j** and **10g–j**. As the naphthyl analogues **10g–j** displayed some very promising biological activity, the pure enantiomers of **10g–j** were prepared by using either Rh_2(*R*-DOSP)$_4$ or Rh_2(*S*-DOSP)$_4$ catalyst at room temperature. This resulted in the formation of **10g–j** in 65–85% *ee*. A single re-crystallization of products of 85% *ee* or above, or two recrystallizations of products of 65–84% *ee* gave enantiomerically pure **10g–j**.

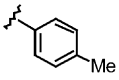
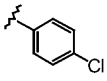
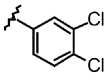
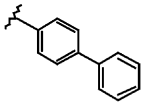
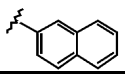
3. Biology

Table 3 summarizes the binding affinities to the dopamine and serotonin transporters (DAT and SERT) of the methylphenidate analogues **1** and **2** containing a

Table 1. Reaction of aryldiazoacetates with *N*-Boc-piperidine



6 **7** **1** (*threo*) **2** (*erythro*)

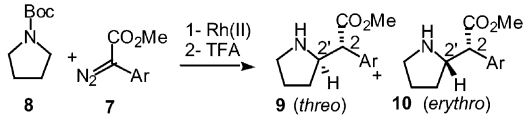
Compd	Ar	**1**&**2** yield (%)	**1**:**2**	**1** ee%	**2** ee%
a		64[a] 44[b]	2/1 1.8/1	— 68	— 89
b		55[a] 50[b]	2/1 1.4/1	— 57	— 92
c		67[a] 68[a]	1.4/1 1.5/1	— 77	— 94
d		28[c]	1.5/1	—	—
e		24[a]	1.6/1	—	—
g		30[c] 33[d]	2/1 2/1	— 85	— 90

[a] Rh_2(OOct)$_4$, reflux.
[b] Rh_2(*S*-DOSP)$_4$, −50 °C.
[c] Rh_2(*R*,*S*-DOSP)$_4$, rt.
[d] Rh_2(*S*-biTISP)$_2$, rt.

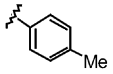
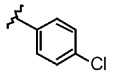
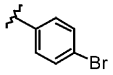
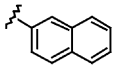
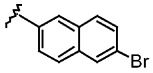
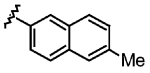
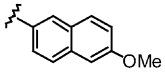
piperidine ring. Several of these racemic piperidine analogues are known and their binding affinities at the DAT have been reported.[10,11,28] The binding data for these compounds are in reasonable agreement with the published results, especially considering that the radioligand we use is different from those used in the earlier studies. For all the compounds tested, the expected trend was observed of enhanced binding of the *threo* diastereomer **1** compared to the *erythro* diastereomer **2**. The *threo* 3,4-dichlorophenyl derivative **1d** has the highest binding affinity of a methylphenidate analogue to the DAT (2.67 nM, lit[8] 5.03 nM). Even the *erythro* derivative **2d** has an IC_{50} of 33.8 nM at the DAT. The aryl functionality causes similar trends to the binding affinities at DAT as was observed for the 3-aryltropanes but there are some subtle differences. The 2-naphthyl derivative **1g** (33.9 nM) does not bind as effectively to the DAT as the 3,4-dichlorophenyl derivative **1d**, while in the 3-aryltropanes, the 2-naphthyl group leads to one of the most potent tropanes known.[29] Unlike the substituted phenyl methylphendidate analogues **1a–e**, the naphthyl derivative **1g** displays strong binding to the SERT (71.6 nM). Considering the interesting activity of **1g**, its active (2*R*,2′*R*) enantiomer was prepared and tested. The binding affinities of the *erythro* 2-naphthyl derivative **2g** was especially interesting because this compound retained the binding affinity to the SERT, even while there was the expected drop in binding affinity to the DAT compared to **1g**. Thus, **2g** is the first example of a methylphenidate analogue that binds selectively to SERT.

Table 4 summarizes the binding affinities to the DAT and SERT transporters of the methylphenidate analogues **9** and **10** containing a pyrrolidine ring. Previous studies had shown that replacement of the piperidine ring in methylphenidate with a pyrrolidine ring results in a 10-fold decrease in binding affinity to the DAT.[8,11] A similar trend is seen with a range of substituted phenyl derivatives, although certain compounds such as the *threo* 4-chlorophenyl analogue **9c** exhibit reasonable binding affinity at the DAT (272 nM). The *erythro* substituted phenyl analogues **10a–c**, **10f** display limited binding to the DAT and neither the *threo* or *erythro* substituted phenyl analogues bind effectively to the

Table 2. Reaction of aryldiazoacetate with *N*-Boc-pyrrolidine

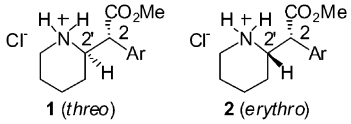


8 **7** **9** (*threo*) **10** (*erythro*)

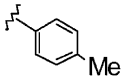
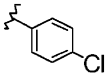
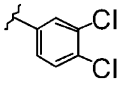
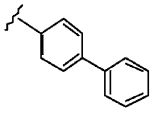
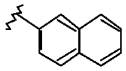
Compd	Ar	**1**&**2** yield (%)	**1**:**2**	**1** ee%
a		49[a] 72[b]	1/5 1/24	— 94
b		54[a] 67[b]	1/11 >1/25	— 94
c		43[a] 70[a]	1/4 >1/25	— 93
f		60[c]	1/21	—
g		43[c] 40[d] 40[e]	1/12 1/10 1/10	— 69 75
h		18[c] 48[d]	1/8 1/8	— 85
i		22[c] 32[d]	1/18 1/14	— 72
j		21[c] 38[d]	1/6 1/8	— 75

[a] $Rh_2(OOct)_4$, reflux.
[b] Rh_2(*S*-DOSP)$_4$, −50 °C.
[c] Rh_2(*R*,*S*-DOSP)$_4$, rt.
[d] Rh_2(*R*-DOSP)$_4$, rt.
[e] Rh_2(*S*-DOSP)$_4$, rt.

Table 3. Binding affinities of piperidine derivatives

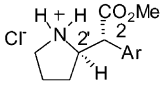


1 (*threo*) **2** (*erythro*)

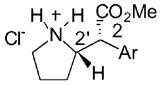
Compd	Ar	DA (IC_{50} nM)[a]	5-HT (K_i nM)[a]
1a (±)		164±40 (lit 83.0±7.9[b])	>10,000
2a (±)		>1000	>10,000
1b (±)		114±28 (lit 33.0±1.2[b])	>10,000
2b (±)		7430±1520	>10,000
1c (±)		91.2±3.7 (lit 20.6±3.4[b])	2220±220
2c (±)		2750±1200	>10,000
1d (±)		2.67±0.58 (lit 5.3±0.7[b])	>10,000
2d (±)		33.8±1.9	>10,000
1e (±)		1020±110	>10,000
2e (±)		6470±820	>10,000
1g (±)		33.9±6.4 (lit 79.5[c])	71.6±7.4
1g (2*R*,2′*R*)		11.1±2.2	94.8±23.7
2g (±)		2080±390	105±12

[a] K_i and IC_{50} values in binding assays were determined using the procedures described in ref 21.
[b] Ref 8.
[c] Ref 9.

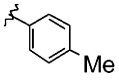
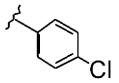
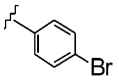
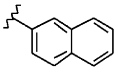
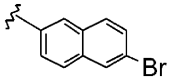
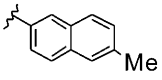
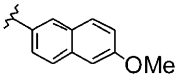
Table 4. Binding affinities of pyrrolidine derivatives



9 (*threo*)



10 (*erythro*)

Compd	Ar	DAT (IC_{50} nM)[a]	SERT (K_i nM)[a]
9a (±)		3160±380 (lit 1336±108[b])	>10,000
10a (±)		>1000	>10,000
9b (±)		1930±640	>10,000
10b (±)		>1000	>10,000
9c (±)		272±37	1080±120
10c (±)		>1000	1900±690
10f (±)		637±100	>10,000
10g (±)		805±102	4.0±1.3
10g (2*R*,2′*S*)		465±65	2.5±0.9
10g (2*S*,2′*R*)		1750±270	2020±290
10h (±)		195±54	11.4±2.2
10h (2*R*,2′*S*)		446±6	5.5±1.2
10i		1410±490	3.2±0.5
12i (2*R*,2′*S*)		850±178	2.3±0.6
10j (±)		2050±540	245±63
10j (2*R*,2′*S*)		945±114	54.6±16.7

[a] K_i and IC_{50} values in binding assays were determined using the procedures described in ref 21.
[b] Ref 9.

SERT. In contrast, a very interesting trend was found for the *erythro* substituted 2-naphthyl derivatives **10g–j**. The 2-naphthyl analogue **10g**, has decreased binding to the DAT compared to the piperidine analogue **2g**, but enhanced binding at the SERT, leading to nearly a 200-fold selectivity for the SERT ($K_i = 2.5$ nM). Similar behavior was found for the 2-(6-bromonaphthyl) **10h** (5.5 nM) and 2-(6-methylnaphthyl) **10i** (2.3 nM) derivatives, while the 2-(6-methoxynaphthyl) derivative **10j** was not as potent (54.6 nM).

In conclusion, these studies describe new methylphenidate analogues with a greater range of binding selectivity than had been previously available. Considering that recent studies indicate that *threo*-methylphenidate may not be sufficiently potent to have significant therapeutic effect on cocaine abusers other than those diagnosed with ADHD,[3–5] a compound such as the *threo*-analogue **1g**, which is 15 times more potent than *threo*-methylphenidate will be worth further evaluation. Furthermore, the new *erythro*-naphthyl analogues such as **2g** and **10g–j** are strongly SERT selective and merit further study.

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