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Discovery of Substituted 3,4-Diphenyl-thiazoles as a Novel Class of Monoamine Transporter Inhibitors through 3-D Pharmacophore Search Using a New Pharmacophore Model Derived from Mazindol

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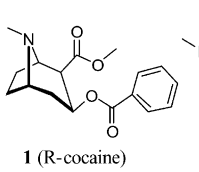
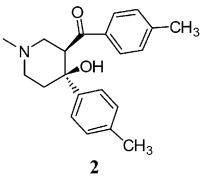
Abstract—Substituted 3,4-diphenyl-1,3-thiazols were identified as a class of novel and potent monoamine transporter inhibitors through a 3-D pharmacophore search using a new pharmacophore model derived from mazindol. The most potent compound (**13**) has K_i values of 24 and 23 nM in binding to dopamine transporter and inhibition of dopamine reuptake, respectively. © 2002 Published by Elsevier Science Ltd.

Cocaine (**1**) is considered to be one of the most reinforcing/rewarding abused drugs.[1–5] No specific medication is presently available for the treatment of cocaine addiction, dependence and abuse.[1] An effective therapy for treating cocaine abuse and addiction is needed immediately. Although cocaine potently inhibits the reuptake of serotonin (SER) and norepinephrine (NE) by the SER and NE transporters (SERT and NET), the dopamine hypothesis suggests that the reinforcing effects of cocaine are primarily due to blocking of the dopamine transporter (DAT).[6,7] Binding of cocaine to the DAT blocks the reuptake of DA, thus increasing the concentration of DA in the synapse and enhancing DA mediated signaling. However, a recent study using DAT and SERT knockout mice shows that both DAT and SERT play a role in the reinforcing mechanism of cocaine and suggests that drugs that bind to both DAT and SERT might be effective for combating cocaine addiction.[5]



1 (R-cocaine)



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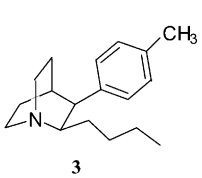

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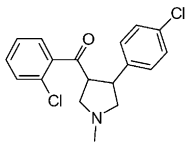

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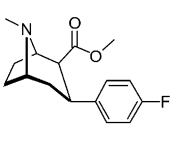
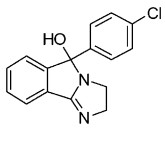


5 (WIN35,428)



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DAT inhibitors have been considered as potential therapeutic agents for treatment of cocaine addiction and dependence.[1] Our group has recently employed pharmacophore based 3-D database searching for discovering and designing novel DAT inhibitors.[8–12] Using this approach, we have discovered and developed several classes of novel DAT inhibitors such as the 3,4 disubstituted 4-hydroxypiperidines (**2**),[8,9] 2-alkyl-3-aryl quinuclidines (**3**),[11] 3,4-disubstituted pyrrolidines (**4**).[12] In our previous works, two pharmacophore models were derived primarily from cocaine and its WIN analogues, as well as some of the new DAT inhibitors that we have discovered.

Mazindol (**6**) represents a class of potent monoamine transporter inhibitor, whose chemical structure is

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different from other known classes of monoamine transporter inhibitors. Like cocaine, mazindol (**6**) potently inhibits the reuptake of DA, SER and NE. But unlike cocaine, mazindol has a low abuse liability in human.[15] The clinical use of mazindol for the treatment of cocaine addiction has been investigated with mixed results. Mazindol is currently clinically used for the treatment of opioid-induced sedation, as an anorexic agent and for the treatment of Duchenne muscular dystrophy.[13] We believe that mazindol may represent a class of DAT inhibitors with which a new pharmacophore model can be derived and used for searching for novel DAT inhibitors. Such novel DAT inhibitors might potentially have low abuse liability and may be useful as potential therapeutic agents for the treatment of cocaine abuse, as well as for other neurological disorders.

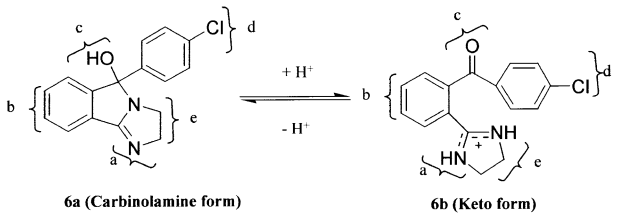


Figure 1. Two tautomeric forms of mazindol and a previously proposed putative pharmacophore model: a and c, ionic or hydrogen bond sites; b and d, lipophilic aromatic sites; e, lipophilic aliphatic site.[15]

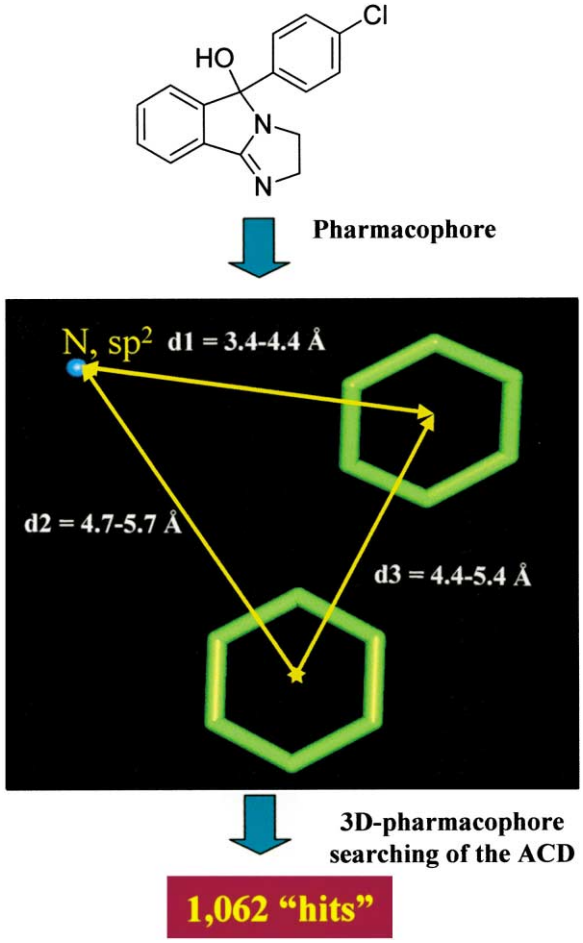
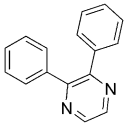
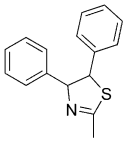
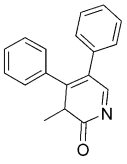
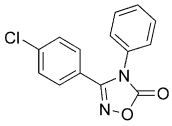
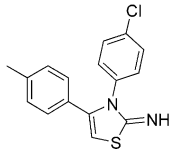
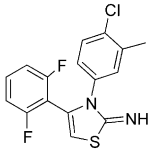
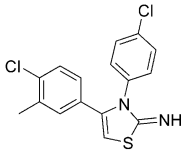


Figure 2. A new and simple pharmacophore model used for 3-D-database pharmacophore searching.

Mazindol is known to exist in two tautomeric forms, a carbinolamine form **6a** and a keto form **6b** (Fig. 1). Since the binding and uptake assays are performed at pH 7.40 and 7.35, respectively, the tricyclic form (carbinolamine) is expected to be the predominant tautomer in solution.[15] An earlier study comparing the tautomeric forms of mazindol with those of a number of potent DA and NE uptake inhibitors suggested that the keto form might be the active structure of mazindol at these uptake sites,[14] but insufficient information is available to conclude whether the keto or carbinolamine form of these compounds interacts at the cocaine binding site on the DA transporter.[15] A putative pharmacophore model for mazindol was proposed based upon available structure–activity relationships on mazindol, which includes

Table 1. Screening of 'hits' identified from 3-D pharmacophore searching in displacing [^{3}H]WIN35,428 binding to DAT

Compd	Structure	[^{3}H]WIN binding ($K_i \pm$SE, μM)
7		>1[a]
8		2.28±0.07
9		>1[a]
10		9.18±0.31
11		0.124±0.007
12		0.048±0.004
13		0.024±0.002

Standard errors were obtained with 2–3 experiments.
[a]Higher concentrations were not tested due to poor solubility.

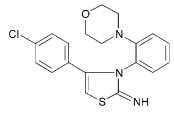
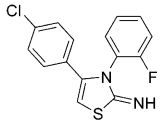
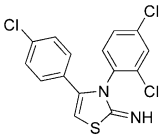
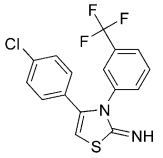
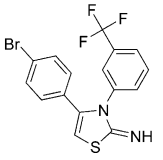
two ionic/hydrogen bonding sites, two lipophilic aromatic rings and one lipophilic aliphatic site (Fig. 1).[15]

Previously, we have successfully used a pharmacophore model comprising one hydrogen bonding site and two hydrophobic sites for discovering and designing novel and potent DAT inhibitors.[12] Thus, we postulated that among the five binding sites for mazindol (Fig. 1), it is possible that only three binding sites, (i.e., two aromatic rings and one nitrogen) are mainly responsible for binding to the DAT. Accordingly, we proposed a simple pharmacophore model comprising only of these three binding sites for 3-D-database pharmacophore searching (Fig. 2). Distances between these three pharmacophore centers were obtained from conformational analysis of both tautomeric forms **6a** and **6b**. One advantage using a simple pharmacophore model such as that depicted in Figure 2 is that it can lead to the discovery of new inhibitors with great structure diversity and novelty. One potential disadvantage is that since many more compounds will be identified as 'hits', additional criteria will need to be applied to select compounds for testing if no high throughput assay is available.

Using this simple pharmacophore model, we searched the Available Chemicals Directory (ACD, version 99.2)[16] of 225,000 compounds using the Chem-X program.[17] A total of 1,062 (0.4%) compounds were identified from the ACD database that met the pharmacophore requirements as specified in Figure 2. These 1062 'hits' were considered to be potential DAT inhibitors. Since our binding and reuptake assays were quite time-consuming, we were unable to screen a large number of compounds. Therefore, we have manually screened these 1062 compounds for their structural diversity, novelty and simplicity. We have selected 7 'hits' from these 1062 compounds for screening their binding to DAT.

Of these seven compounds, three compounds (**11**, **12**, and **13**) were found to have K_i values 124, 48 and 24 nM, respectively (Table 1). Two other compounds (**7** and **9**) were found to have K_i values of 2.3 and 9.2 μM, respectively. Compounds **8** and **10** did not show appreciable binding to DAT at 1 μM. They were not tested at higher concentrations due to their poor solubility. The K_i values of these seven compounds and the chemical

Table 2. K_i values of substituted 3,4-diphenyl-1,3-thiazols in displacing [^{3}H]WIN35,428 binding to DAT and in inhibition of [^{3}H]DA, [^{3}H]SER and [^{3}H]NE uptake into DAT, SERT and NET, respectively

Compd	Structure	$K_i \pm$SE (nM)				Selectivity (ratio)		
		[^{3}H]WIN binding	[^{3}H]DA uptake	[^{3}H]SER uptake	[^{3}H]NE uptake	SER/DA	NE/DA	NE/SER
R-cocaine			274±20	155±0.4	108±4	0.56	0.39	0.69
11		124±7	171±1	2617±8	801±121	15.3	4.68	0.31
12		48±4	102±8	433±5	86±8	4.25	0.84	0.20
13		24±2	23±2	225±9	99±8	9.4	4.1	0.44
14		42±2 (μM)	76.4±6.9 (μM)	424±55	22.1±0.6 (μM)	0.006	0.29	52.1
15		189±9	210±31	1.41±0.02 (μM)	36±1	6.69	0.17	0.026
16		533±79	254±9	843±7	141±16	3.32	0.55	0.17
17		86±13	101±14	398±18	26±4	3.94	0.26	0.065
18		71±1	120±7	67±8	140±20	0.56	1.17	2.09

Standard errors were obtained with 2–3 experiments.

structures of these seven compounds are provided in Table 1. Our results showed that the simple pharmacophore model we used is effective in identifying novel DAT inhibitors. Among these new DAT inhibitors identified (Table 1), substituted 3,4-diphenyl-1,3-thiazols (**11**, **12**, and **13**) in fact represent one class of very potent inhibitors. It is of note that these compounds satisfy the pharmacophore model shown in Figure 2, but not the previously proposed pharmacophore model as shown in Figure 1.

To gain an insight into the structure–activity relationships for substituted 3,4-diphenyl-1,3-thiazols, we have identified and tested several closely related analogues available from the ACD database (**14**–**18** in Table 2). First, these compounds were tested for their activity in [^{3}H] WIN35,428 binding and inhibition of DA reuptake assays. The results are shown in Table 2. Four analogues (**15**–**18**) are potent DAT inhibitors and have K_i values better than cocaine in inhibition of DA reuptake. Compound **14** with a bulky substituent in one phenyl ring has very weak activity.

To achieve a further insight into the selectivity of these compounds among the three monoamine transporters (DAT, SERT and NET), we also evaluated their activity in inhibition of SER and NE reuptake (Table 2). Our data showed that some of these compounds are potent and/or selective DAT, NET and SERT inhibitors. Compound **13** is the most potent DAT inhibitor among all the analogues tested, with K_i values of 24 and 23 nM in binding and inhibition of DA reuptake, respectively. Furthermore, **13** has a moderate selectivity of 9.4-fold between DAT and SERT, and of 4.1-fold between DAT and NET. Although compound **14** is essentially inactive at DAT and NET, it is a quite potent inhibitor at SERT with a K_i value of 424 nM. Thus, compound **14** is a quite selective inhibitor at SERT, with a selectivity of 180- and 52-fold between SERT and DAT, and between SERT and NET, respectively. Compound **18** is a potent but non-selective inhibitor at these three monoamine transporters. Since all these compounds only differ in the nature and position of the substituents in the two phenyl rings, further chemical modifications should lead to new inhibitors with improved potency and selectivity.

In summary, using a new and very simple pharmacophore model (Fig. 2) derived from mazindol, we have discovered several classes of DAT inhibitors (Table 1). Of which, substituted 3,4-diphenyl-1,3-thiazols (**11**–**18** in Table 2) represent a new class of potent monoamine transporter inhibitors. Some of these compounds display significant selectivity toward one transporter. Preliminary SAR studies showed that the nature and position of the substituents in the two phenyl rings greatly affect the potency and selectivity of this class of compounds. We are performing extensive chemical modifications to further explore the structure–activity relationships for this class of compounds and the results will be reported in due course.

Acknowledgements

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