# Halogenated Mazindol Analogs as Potential Inhibitors of the Cocaine Binding Site at the Dopamine Transporter

William J. Houlihan,*,† John W. Boja,‡ Vincent A. Parrino,§ Theresa A. Kopajtic,‡ and Michael J. Kuhar‡,⊥

*Charles A. Dana Research Institute, Drew University, Hall of Sciences, Room 331, Madison, New Jersey 07940, Sandoz Research Institute, Route 10, East Hanover, New Jersey 07936, and National Institute on Drug Abuse, Addiction Research Center, P.O. Box 5180, Baltimore, Maryland 21224*

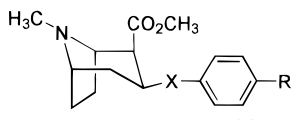
*Received April 17, 1996*⊗

A series of halogenated (F, Cl, Br, I), pyrimido and diazepino homologs of mazindol were prepared and evaluated for their ability to displace [$^3$H]WIN 35,428 binding and to inhibit uptake of [$^3$H]dopamine (DA) in rat striatal tissue. All of the compounds except for the 2′-chloro (**6**) and 2′-bromo (**16**) analogs of mazindol displaced [$^3$H]WIN 35,428 binding and inhibited [$^3$H]DA uptake more effectively than (*R*)-cocaine. Structure−activity studies indicated that best inhibition of [$^3$H]WIN 35,428 binding occurred in the imidazo series with compounds containing one or two Cl or Br atoms in the 3′- or 4′-position of the free phenyl group. Replacement of the imidazo ring by a pyrimido or diazepino ring enhanced binding inhibition. The most potent inhibitors of [$^3$H]WIN 35,428 binding and [$^3$H]DA uptake were 6-(3′-chlorophenyl)-2,3,4,6-tetrahydropyrimido[2,1-*a*]isoindol-6-ol (**23**; $IC_{50}$ 1.0 nM; 8× mazindol) and 7-(3′,4′-dichlorophenyl)-2,3,4,5-tetrahydro-7*H*-diazepino[2,1-*a*]isoindol-7-ol (**28**; $IC_{50}$ 0.26 nM; 32× mazindol), respectively. No significant differences was found between binding and uptake inhibition. Mazindol and the pyrimido and diazepino homologs **24** and **27** showed a selectivity for the DA uptake over the serotonin (5-HT) uptake site of 5-, 250-, and 465-fold, respectively, and displayed weak or no affinity for a variety of neurotransmitter receptor sites.

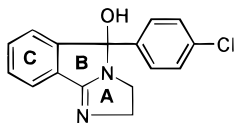
## Introduction

(*R*)-Cocaine (**1a**) is a tropane alkaloid isolated from the leaves of *Erythroxylon coca*. In humans cocaine can produce a variety of physiological effects such as local anesthesia, vasoconstriction, and increased heart rate and blood pressure. As a drug of abuse, the most relevant effects include euphoria and its reinforcement. It is available to abusers as the hydrochloride which is administered orally, intravenously, or by nasal insufflation or as the free base ("crack"), which is generally administered by inhalation (smoking). Medical complications encountered with cocaine abuse are numerous[1−3] and include death[4] and morbidity through cardiovascular complications,[5,6] neuropsychiatric disorders,[5,7] and psychiatric/behavior problems.[8] Cocaine use in the prenatal period is associated with increased incidence of prematurity, intrauterine growth retardation, and microcephaly, while postnatal effects include a neonatal neurologic syndrome ("crack babies").[9] In addition, cocaine use has been associated with the spread of sexually transmitted diseases,[10] including infection with the human immunodeficiency virus (HIV),[11] botulism,[12] fungal infections,[13] and viral hepatitis.[5]

Cocaine has several sites of action in the brain. It has relatively high affinity binding only at uptake sites for dopamine (DA), serotonin (5-HT), and norepinephrine (NE) where it blocks reuptake of these amines.[14,15]




**1a** R =H, X=OCO
**1b** R =F, X=bond




**2**

Strong binding has also been found at the $\sigma$ opiate[16] and muscarinic cholinergic[17] receptors. The potencies of cocaine and cocaine-like drugs in self-administration studies correlates with their binding to the DA transporter in the rat striatum.[18] This binding site related to DA uptake inhibition is proposed to be the transporter implicated in the reinforcing properties of cocaine.[18−20]

A possible approach to depress cocaine self-administration or block "craving" could involve the administration of a substance that blocks the cocaine binding site on the DA transporter in the striatum, but does not possess the addictive or euphoric properties associated with cocaine.[21] Mazindol (**2**, SaH42-548, AN-448), a substance that is currently marketed in the United States for the management of exogenous obesity and as an orphan drug for the treatment of Duchenne muscular dystrophy,[22] appears to be a good starting point for the discovery of such a compound.

In preclinical studies mazindol was active in a variety of mouse, rat, and monkey assays that are used to identify potential appetite suppressant and antidepressant agents.[23,24] It is a potent inhibitor of uptake and binding at the transporter sites for DA, NE, and 5-HT.[15,18,23,24] It inhibits the uptake of DA in rat striatal synaptosomes and cells expressing the human and rat DA transporter and also inhibits binding of [$^3$H]cocaine and [$^3$H]WIN 35,428 in the nanomolar range.[15,25] Although mazindol and cocaine appear to occupy a similar

* To whom correspondence should be addressed. E-mail address: whouliha@drew.edu.
† Charles A. Dana Research Institute.
‡ National Institute on Drug Abuse.
§ Sandoz Research Institute.
⊥ Present address: Yerkes Regional Primate Center, Division of Neuroscience, Emory University, 954 Gatewood Road NE, Atlanta, GA 30329.
⊗ Abstract published in *Advance ACS Abstracts,* November 15, 1996.

S0022-2623(96)00288-9 CCC: $12.00 

**Table 1.** Physical Properties of Novel 5-Aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols and 6-Aryl-2,3,4,6-tetrahydropyrimido[2,1-*a*]isoindol-6-ols

| compd[a] | yield, % | mp, °C (recryst solvent)[b] | ultraviolet[c] maxima, nm ($\epsilon$) 95% EtOH | 95% EtOH−2 N HCl | formula[d] | anal. |
|---|---|---|---|---|---|---|
| **6** | 31 | 187 dec (A) | | | $C_{16}H_{13}ClN_2O$ | C, H, Cl, N |
| **8** | 39 | 199 dec (A) | 204 (43500)<br>223 (22350)<br>267 (6250)<br>274 (5900) | 202 (34650)<br>266 (14600) | $C_{18}H_{17}ClN_2O$ | C, H, Cl, N |
| **13** | 30 | 173 dec (A) | 206 (55850)<br>275 (4250) | 204 (49600)<br>247 (12700) | $C_{16}H_{12}Cl_2N_2O$ | C, H, Cl, N |
| **16** | 19 | 147 dec (B) | 204 (40000) | 203 (39150) | $C_{16}H_{13}BrN_2O$ | C, H, N |
| **17** | 49 | 207 dec (A)[e] | 204 (43600)<br>227 (21800)<br>275 (5150) | 203 (36200)<br>247 (12000)<br>270 (12100) | $C_{16}H_{13}BrN_2O$ | C, H, N |
| **18** | 52 | 197 dec(A)[e] | 204 (50300)<br>235 (26300)<br>275 (6500) | 202 (40050)<br>237 (18150)<br>281 (11350) | $C_{16}H_{13}IN_2O$ | C, H, N |
| **20** | 22 | 211 dec (C) | | | $C_{17}H_{15}FN_2O$ | C, H, N |
| **21** | 28 | 240 dec (D) | 205 (37650)<br>263 (5450)<br>270 (5400) | 205 (34400)<br>240 (14300)<br>269 (5000) | $C_{17}H_{15}FN_2O$ | C, H, N |
| **22** | 36 | 236−238 dec (D) | | | $C_{17}H_{15}FN_2O$ | C, H, N |
| **23** | 24 | 248 dec (A) | 207 (44600)<br>269 (4800) | 204 (41600)<br>240 (14950)<br>268 (4800) | $C_{17}H_{15}ClN_2O$ | C, H Cl, N |
| **25** | 31 | 277 dec (E) | 204 (38200)<br>224 (21250)<br>271 (4150) | 202 (39400)<br>224 (23550)<br>242sh (13650)<br>267sh (3950) | $C_{19}H_{19}ClN_2O$ | C, H, Cl, N |

[a] The synthesis and physical properties of compounds **3**−**5**, **7**, **9**, **10**, **14**, and **15** are given in ref 23a, and compounds **19**, **24**, and **26**−**28** in ref 37. [b] Recrystallization solvents: A, $CH_3OH$; B, $CH_2Cl_2$−EtOH; C, $CH_2Cl_2$−$CH_3OH$; D, EtOH; E, $CH_2Cl_2$. [c] See the Experimental Section for details. The ultraviolet spectrum of **2**, **3**, **4,** and **14** in 95% EtOH and 95% EtOH−2 N HCl is reported in refs 23a and 37. [d] All compounds had spectral data consistent with assigned structures. Some representative $^1$H-NMR, IR, and MS data are given in ref 47. [e] Lit.[36] mp 216−218 °C for **17** and 206−208 °C for **18**. The melting point (decomposition point) for members of the mazindol series has been reported[23a] to be dependent on the rate of heating in the melting point apparatus.

binding site at the DA transporter,[26] a lack of correlation between their effects on [$^3$H]WIN 35,428 binding in the rat caudate putamen and stimulant effects in the mouse locomotor assay (LMA) suggests they may bind in a fundamentally different manner.[27] Mazindol also differs from cocaine in its effects on DA. Studies in cultured fetal mesencephalic DA neurons showed mazindol decreased DA uptake while cocaine did not alter dopamergic function[28] and in COS-7 cells transfected with a cloned human DA transporter cDNA mazindol inhibited both uptake and spontaneous release of DA while cocaine had no effect on DA release.[29]

Several clinical studies with mazindol in healthy volunteers have demonstrated that it is not reinforcing and actual abuse is rare.[30] These findings are inconsistent with studies in rhesus monkeys and beagle dogs where mazindol was shown to be an effective reinforcer.[30] In squirrel monkeys, mazindol maintained self-administration in only half of the monkeys studied.[32]

Clinical studies with cocaine abusers have led to inconclusive results about the efficacy of mazindol to decrease cocaine usage.[33] A recent study suggests that mazindol may be useful in preventing relapse in methadone-maintained cocaine abusers.[34]

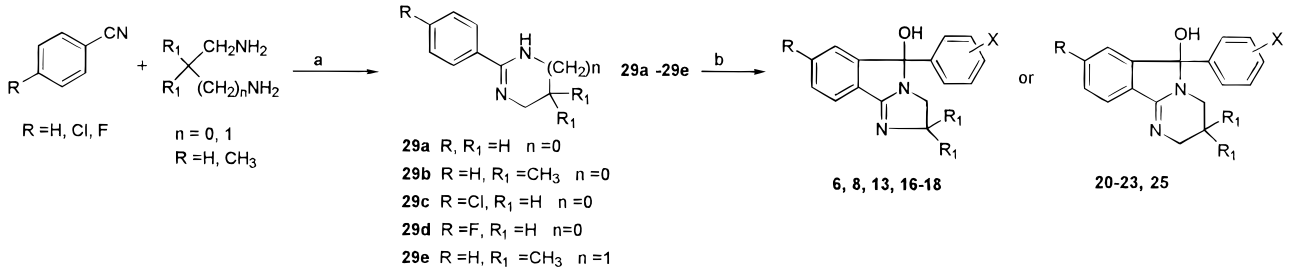
As part of an ongoing study to discover mazindol analogs that are more selective for the DA transporter and have an improved uptake/binding inhibition ratio, we report in this article on the inhibition of [$^3$H]WIN 35,428 (**1b**) binding and [$^3$H]DA uptake in rat striatal tissue for a series of halogenated mazindol analogs. These analogs are substituted in either ring C or the pendant aryl group and contain one (**4**−**10**, **16**−**18**), two (**11**−**14**), or three (**15**) F, Cl, Br, or I atoms. In addition, the six- and seven-membered ring A homologs with one Cl or F atom (**20**−**25**, **27**) or two Cl atoms (**28**) in the aryl group are also reported.

## Chemistry

The synthesis of the novel 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols **6, 8, 13,** and **16**−**18** and the 6-aryl-2,3,4,6-tetrahydropyrimido[2,1-*a*]isoindols **20**−**23**, and **25** listed in Table 1 is given in Scheme 1. Treatment of a benzonitrile with 1,2-ethanediamine or a 1,2- or 1,3-diaminopropane in refluxing ethylene glycol in the presence of p-toluenesulfonic acid gave the 2-aryl-4,5-dihydro-1*H*-imidazolines **29a**−**d** and 5,5-dimethyl-2-phenyl-1,4,5,6-tetrahydropyrimidine (**29e**). Preparation of the *N*,*o*-dilithio derivatives of **29a**−**e** by a previously reported procedure[35] followed by treatment with a methyl benzoate resulted in the formation of the 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*] isoindol-5-ols **6, 8, 13, 16**−**18** and the 6-aryl-2,3,4,6-tetrahydropyrimido-[2,1-*a*]isoindol-6-ols **20**−**23** and **25**. An earlier attempt to prepare the 2′-chloro (**6**) and 2′-bromo (**16**) analogs of mazindol by reacting the *N*,*o*-lithiation product of imidazoline **29a** with the appropriate benzoates is reported to have failed.[36]

Previously reported ultraviolet spectra studies with mazindol (**2**)[23a] and mazindol analogs[37] (**3, 4,** and **14**) indicate that the tricyclic (ol) form is favored in neutral media (95% EtOH) and the protonated benzophenone (keto) tautomer exists in acidic media (95% EtOH−HCl) (Figure 1). Comparison of the ultraviolet spectra of a group of the newly and previously synthesized compounds in 95% EtOH and 95% EtOH−HCl (Table 1) indicates that the ol form is favored in neutral and the

**Scheme 1**[a]




[a] Reagents/conditions: (a) 1,2-ethanediamine or 1,2-diamino-2-methylpropanediamine or 2,2-dimethyl-1,3-propanediamine, *p*-toluenesulfonic acid, ethylene glycol, reflux, 72 h; (b) (i) *n*-BuLi, THF, 50 °C; 3 h; (ii) methyl *X*-benzoate, THF, 50 °C, 6 h.

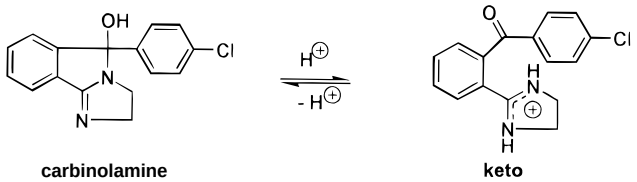



**Figure 1.** Tautomeric forms of mazindol (**2**) in neutral and acidic media.

keto form in acidic media except for the 2′-bromo analog **16**, which exists as the ol both in neutral and in acidic media.

**Receptor Binding and Uptake.** The mazindol analogs in Table 2 were tested for their ability to displace [$^3$H]WIN 35,428 (**1b**), a tropane derivative which has been shown to bind on the DA transporter of the rat striatal membrane at the same site as (*R*)-cocaine.[20] Compounds that had $IC_{50}$ values less than 100 nM in this assay were evaluated for their ability to block the uptake of [$^3$H]DA in rat striatal tissue. Mazindol and the pyrimido and diazepino homologs **24** and **27** were studied for inhibition at the DA, 5-HT, and NE uptake sites in order to determine selectivity and were also tested for their ability to bind at adrenergic, dopaminergic, muscarinic, and serotonergic receptors (Table 3).

## Results and Discussion

All of the halogenated mazindol analogs and homologs, except for the 2′-chloro (**6**) and 2′-bromo (**16**) analogs, listed in Table 2 have an affinity greater than (*R*)-cocaine for the WIN 35,428 binding site (up to 90-fold) and in blocking the uptake of [$^3$H]DA (up to 800-fold) in rat striatal membranes.

The addition of one halogen atom (F, Cl, Br, or I) in the 3′- or 4′-position of the free rotating phenyl group in the imidazo- (type A, **2, 4, 7, 17,** and **18**), tetrahydropyrimido- (type B, **21**−**24**), and tetrahydro-7*H*-diazepino[2,1-*a*]isoindol-*x*-ol (type C; **27**) derivatives results in an increase in binding and uptake inhibition relative to the unsubstituted analogs **3, 19,** and **26**. A halogen (F or Cl) in the 3′-position appears to have a slightly more potent $IC_{50}$ than the 4′-analog (compare **2** and **7, 21** and **22, 23** and **24**). The rank order of binding potency of the 4′-monohalogen analogs of mazindol is Br > Cl > I > F. The same trend was found by Galinier, et al.[36] who studied halogenated mazindols binding against [$^3$H]GBR 12935, a piperazine dopamine uptake inhibitor, and a similar trend (Br > Cl > F) was reported[38] for DAT inhibitor (±)-*threo*-methylphenidate analogs against [$^3$H]WIN 35,428 binding. Carroll, et al.[20] who evaluated a series of WIN analogs against [$^3$H]-WIN 35,428 binding found a different trend with Cl ≈ I > Br > F.

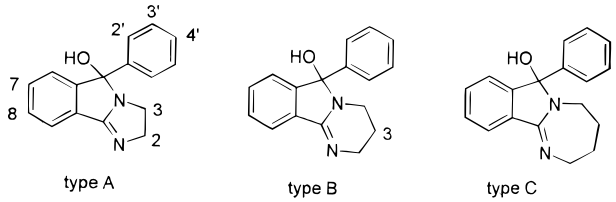
A chlorine in the 6- or 7-position (**9** or **10**) has minimal effect on binding and uptake inhibition relative to **3** while a 7-fluoro substituent (**5**) results in ca. 2-fold increase. Placement of a F, Cl, or Br in the 2′-position (**6, 16,** and **20**) results in loss in binding inhibition relative to the 4′-substituted analogs (**2, 17, 22**). The loss in binding activity as expressed by the ratio of $IC_{50}$ for the 2/4-positions was 7 (fluoro) 37 (chloro), and 515 (bromo). This effect could be correlated with the substituent size (Br > Cl > F) or inversely to electronic factors (F > Cl > Br) or a combination of both.

An "ortho effect" on binding at the DAT site has also been found in other classes of DA uptake inhibitors that have a free rotating aryl group. Davies et al.[39] reported that the 2-methylphenyl analog of the WIN (**1b**) series of compounds was 160 times less active than the 4-methylphenyl analog, and Deutsch et al.[38] found for a series of aromatic ring substituted methyl phenidate analogs an $IC_{50}$ ratio for 2/4-position of 41 (fluoro), 98 (chloro), 236 (hydroxy), and 1200 (methoxy). Interestingly, Yu et al.[40] reported that the 2′-iodobenzoyl analog of cocaine is only 4 times less active than the 4′-iodo and equal to the 3′-iodobenzoyl analog. This finding is not anticipated when compared to the results given above for 2-substituted aryl WIN analogs and suggests that the binding site requirements for the 2-benzoyloxy group in cocaine and the aryl group in the WIN analogs differ.[20] That electronic factors could also play a role in this "ortho effect" is found in the 11-fold loss in binding activity that occurred when a 2-thiophenyl group replaced the phenyl group in the WIN series,[41] and in the mazindol series[42] a 2-pyridyl group at the 5-position was 6 and 60 times less active than a 3-pyridyl or 4-pyridyl group respectively, at the same position.

The addition of a second or third halogen (F, Cl) in the 3′,4′- (**14, 28**), 4′,7- (**11, 12**), or 4′,7,8- (**15**) positions has little effect on the binding inhibition of the 3′- or 4′-monohalogen analogs. However, the introduction of a 7-Cl substitution in the 4′-F analog (**4** vs **12**) caused a ca. 4-fold loss in binding inhibition. As with the monosubstituted halogen derivatives, the addition of a 2′-Cl in mazindol (**2** vs **13**) resulted in a considerable (ca. 9-fold) loss of binding inhibition.

Both binding and uptake inhibition increase up to 11-fold as the size of ring A is increased from 5 (imidazo) to 6 (pyrimido) or 7 (diazepino) membered. Maximum increase in activity (ca. 11-fold) occurred in the unsubstituted analogs (**3** vs **19** vs **26**), while a lesser increase (ca. 4−5 fold) occurs in 3′- (**7** vs **23**) and 4′- (**2** vs **24** and **27**) chloro homologs and minimal (ca. 1.5-fold) increase occurs in 3′,4′-dichloro (**14** vs **28**) homologs. For both the unsubstituted (**19** vs **26**) and 4′-chloro (**24** vs **27**)

**Table 2.** Inhibition of [$^3$H]WIN 35,428 Binding and [$^3$H]Dopamine Uptake at the Dopamine Transporter




| compd no. | type | substituent(s) | $IC_{50}$, nM [$^3$H]WIN 35,428 binding assay[a] | $IC_{50}$, nM [$^3$H]dopamine uptake[b] | uptake/binding ratio |
|---|---|---|---|---|---|
| **1** | (*R*)-cocaine | | 89.1 ± 8 | 208 ± 12 | 2.3 |
| **2** | A | 4′-Cl | 8.1 ± 1.2 | 8.4 ± 1.3 | 1.0 |
| **3** | A | none | 66.0 ± 8.9 | 124 ± 37 | 1.9 |
| **4** | A | 4′-F | 13.3 ± 1.8 | 25.4 ± 2.7 | 1.9 |
| **5** | A | 7-F | 29.7 ± 7.0 | 78 ± 46 | 2.6 |
| **6** | A | 2′-Cl | 294 ± 6 | 770 ± 159 | 2.6 |
| **7** | A | 3′-Cl | 4.3 ± 0.4 | 9.2 ± 5.3 | 2.1 |
| **8** | A | 4′-Cl,2-$(CH_3)_2$ | 50.4 ± 5.5 | 106 ± 5.6 | 2.1 |
| **9** | A | 6-Cl | 57.2 ± 8.3 | 58 ± 6.4 | 1.0 |
| **10** | A | 7-Cl | 86.4 ± 14 | 55 ± 17 | 0.6 |
| **11** | A | 4′-Cl,7-F | 6.5 ± 1.2 | 15 ± 9 | 2.3 |
| **12** | A | 7-Cl,4′-F | 52.8 ± 8.7 | 53 ± 18 | 1.0 |
| **13** | A | 2′, 4′-$Cl_2$ | 76.5 ± 1.11 | 92 ± 19 | 1.2 |
| **14** | A | 3′, 4′-$Cl_2$ | 2.5 ± 0.5 | 1.4 ± 1.6 | 0.6 |
| **15** | A | 4′,7,8-$Cl_3$ | 13.6 ± 1.5 | | |
| **16** | A | 2′-Br | 1340 ± 179 | | |
| **17** | A | 4′-Br | 2.6 ± 1.5 | 8.6 ± 3.5 | 3.3 |
| **18** | A | 4′-I | 17.2 ± 0.9 | 14 ± 6.4 | 0.8 |
| **19** | B | none | 5.8 ± 1.6 | 18 ± 11 | 3.1 |
| **20** | B | 2′-F | 23.2 ± 1.7 | 89 ± 2.8 | 3.8 |
| **21** | B | 3′-F | 2.0 ± 0.02 | 3.1 ± 1.8 | 1.6 |
| **22** | B | 4′-F | 3.2 ± 1.7 | 8.5 ± 4.9 | 0.4 |
| **23** | B | 3′-Cl | 1.0 ± 0.2 | 1.3 ± 0.14 | 1.3 |
| **24** | B | 4′-Cl | 1.7 ± 0.2 | 1.4 ± 0.35 | 0.8 |
| **25** | B | 4′-Cl,3,3-$(CH_3)_2$ | 6.3 ± 4.5 | 1.7 ± 1.6 | 0.3 |
| **26** | C | none | 5.9 ± 0.1 | 11 ± 3.2 | 2.0 |
| **27** | C | 4′-Cl | 1.5 ± 0.1 | 3.4 ± 2.3 | 2.3 |
| **28** | C | 3′, 4′-$Cl_2$ | 1.7 ± 0.1 | 0.26 ± 0.16 | 0.2 |

[a] Values are mean ± standard error of four experiments performed in triplicate. [b] Values are average of two experiments, each conducted in triplicate.

**Table 3.** Monoamine Transporter Binding Inhibition by Mazindol (**2**) and Homologs **24** and **27**[a]

| | **2** | **24** | **27** |
|---|---|---|---|
| | Dopamine[b] | | |
| $IC_{50}$, nM | 42.6 | 4.2 | 2.7 |
| | Serotonin[c] | | |
| $IC_{50}$, nM | 231 | 1040 | 1250 |
| | Norepinephrine[d] | | |
| % inhib at $10^{-5}$ M | 60 | 62.8 | |
| $IC_{50}$, nM | | | 7610 |
| 5HT/DA ratio | 5 | 250 | 465 |
| NE/DA ratio | >1000 | >10000 | 2820 |

[a] See the Experimental Section for details. [b] Receptor source: guinea pig striatal membrane. Reference compound: (*RS*)-bupropion in initial screen and [$^3$H]WIN 35,428 in $IC_{50}$. [c] Receptor source: rat forebrain membranes. Reference compound: imipramine in initial screen and [$^3$H]citalopram in $IC_{50}$. [d] Receptor source: rat cortical membranes. Reference compound: desmethylimipramine (DMI) in initial screen and [$^3$H]DMI in $IC_{50}$ assay.

homologs there is no difference in binding inhibition as ring A is increased from 6 to 7 membered.

Placement of geminal methyl groups in ring A of a 5-membered (**8**) or 6-membered system (**25**) results in a 4−6-fold loss of binding inhibition relative to the methyl-free analogs (**2** and **24**).

Comparison of the uptake/binding ratio (Table 2), which is a measurement of the ability of a compound to block the uptake of DA relative to inhibiting the binding site of WIN 35,428, reveals little selectivity. Compounds that gave the highest ratio (>3.0) were the 4′-Br imidazo analog **17** and the unsubstituted and 2′-F pyrimido analogs **19** and **20**. Compounds that have high uptake/binding ratios would be preferred since they in theory would not interfere with the normal function of DA but yet block the (*R*)-cocaine binding site. Although it appears possible to prepare such compounds since (*R*)-cocaine and dopamine appear not to bind at the same sites on the DA transporter, none have been reported.[20,43]

Mazindol (**2**) and the 6- and 7-membered ring A homologs **24** and **27** were evaluated for displacement of radiolabeled ligand binding at the DA, 5-HT, and NE transporter sites (Table 3). The three compounds displaced [$^3$H]WIN 35,428 binding on guinea pig striatal membranes in the same order (**27** > **24** > **2**), but with slightly less potency, as on rat striatal membranes (cf. Table 2). Moderate to weak binding affinity was found at the serotonin transporter site and the order of activity was reversed with **2** > **24** > **27**. At the norepinephrine receptor, using [$^3$H]desmethylimipramine (DMI) as the radioligand, all three compounds showed very poor affinity with **2** and **24** giving ca. 60% inhibition at $10^{-5}$ M concentration and **27** an $IC_{50}$ of 7610 nM. The three compounds (**2, 24,** and **27**) showed selectivity for the DA uptake binding site relative to the 5-HT uptake binding site. Best selectivity was shown by **27** with a 5HT/DA ratio of 465. A similar pattern of selectivity and potency was found when these compounds were assayed for their ability to block the uptake of [$^3$H]DA and [$^3$H]5-HT in

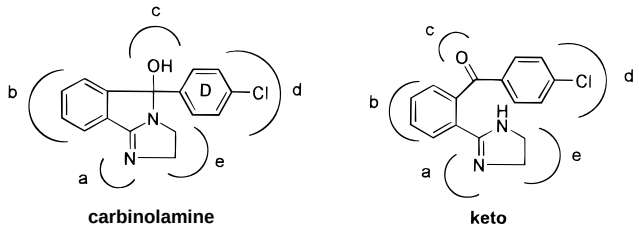



**Figure 2.** Putative interaction models of the ol and keto forms of mazindol at the dopamine transporter. Interaction sites: (a) and (c) ionic or H-bond, (b) and (d) aromatic lipophilic, and (e) aliphatic lipophilic.

rat occipital cortex membranes.[44] However, the potency of these compounds at the NE binding site with [$^3$H]-DMI is in marked contrast to that reported for their ability to inhibit uptake of [$^3$H]NE in various rat membrane preparations. In three separate studies,[24b,44,45] mazindol was found to have an $IC_{50}$ value of ca. 1.5 nM, and in one study,[24a] **24** and **27** had $IC_{50}$ values of 8.3 and 19 nM, respectively. These findings suggest that mazindol and related compounds do not occupy the same binding site as DMI.

Mazindol, **24**, and **27** showed no activity at $10^{-5}$ M concentration at the $\alpha_1$, $\alpha_2$, $\beta$, $DA_1$, $DA_2$, $H_2$, $M_2$, $M_3$, 5-$HT_1$, and 5-$HT_2$ receptors. Weak activity ($IC_{50}$ value 309−2150 nM) at the $H_1$, $M_1$, 5-$HT_{1A}$, and 5-$HT_3$ receptors was found for **24** and **27**, but not for mazindol.

**Interaction Model.** The possible interaction sites for the ol and keto forms of mazindol are given in Figure 2. The difference between these forms involves a reversal of the ionic and H-bond roles for the N and O atom (a and c in Figure 2). In the ol form the O can function as an H-acceptor or donor and the N as a H-bond acceptor while in the keto both O and N can act as H-bond acceptors.

An earlier study by Koe[44] comparing the tautomeric forms of mazindol with those of a number of potent DA and NE uptake inhibitors led to the suggestion that the keto or benzophenone form shown in Figure 2 might be the active structure at these uptake sites. Since the WIN 35,428 binding and the DA uptake assays were carried out at pH 7.40 and 7.35, respectively, the mazindol analogs in solution would be present in ol form. However, insufficient information is available to conclude whether the keto or ol form of these compounds interacts at the cocaine binding site on the DA transporter.

## Conclusion

A series of halogenated and ring A homologs of mazindol have been prepared and found to bind with high affinity to the WIN 35,428 binding site and block the uptake of DA in rat striatal tissue. Structure−activity studies indicated that one or two halogen atoms, preferably Cl or Br, in the 3′- or 4′-position of the free phenyl group gave best activity in the 5-membered ring A (imidazo) series. Replacement of the imidazo ring A by a 6-(pyrimido) or 7-(diazepino) membered ring-enhanced binding inhibition.

Mazindol and the pyrimido and diazepino homologs **24** and **27** show a selectivity for the DA uptake site over the 5-HT uptake site. The results at the NE uptake site are conflicting and require additional studies.

Mazindol, **24**, and **27** display very weak or no affinity for a variety of $\alpha$, $\beta$, DA, histamine, muscarinic, and 5-HT receptor binding sites.

Additional SAR studies are in progress to determine if the DA uptake/WIN 35,428 binding and the DA/NE uptake inhibition ratios can be improved and to further establish which tautomeric form of mazindol is interacting at the cocaine binding site on the DA transporter.

## Experimental Section

**General.** Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) data for $^1$H-NMR were taken on JEOL-FX-90 (90 MHZ) or Bruker (200 MHZ) spectrometers and are reported in $\delta$ (ppm) downfield from tetramethylsilane (TMS). The ultraviolet (UV) spectra (Table 1) were obtained in 95% EtOH or 95% EtOH−2 N HCl (9:1) solvent on a Shimazu Model UV-2101 PC ultraviolet spectrometer. Infrared (IR) spectra were determined on an Analect FX-6260 using KBr pellets. Mass spectra (MS) were obtained on a Finnigan MAT 4600 GC/MS instrument applying a desorption chemical ionization method using ammonia (or isobutane) as the reagent gas. Elemental analysis for carbon, hydrogen, and nitrogen were determined with a Carlo Erba Instruments Model EA1108 elemental analyzer and are within ±0.4% of theory unless noted otherwise. If not otherwise specified, chemicals and reagents were obtained from the Aldrich Chemical Co. Solvents were of reagent grade and dried prior to use. Reaction progress and purity of final products were determined on E. Merck silica gel 60 chromatography plates.

**2-Aryl-4,5-dihydro-1*H*-imidazoles and 2-Aryl-1,4,5,6-tetrahydropyrimidines (29b−e). 4,4-Dimethyl-2-phenyl-4,5-dihydro-1*H*-imidazole (29b).** A solution of 1, 2-diamino-2-methylpropane (25.0 g, 0.28 mol), benzonitrile (22.l g, 0.21 mol), *p*-toluenesulfonic acid monohydrate (24.9 g, 0.13 mol), and ethylene glycol (150 mL) was refluxed for ca. 72 h. The ethylene glycol was removed by distillation in vacuo, and the residue was treated with $H_2O$ (500 mL), made alkaline with solid NaOH (10 g), and extracted with $CH_2Cl_2$ (150 mL, twice). The $CH_2Cl_2$ phase was dried ($MgSO_4$), filtered, and concentrated to give 25.1 g (69%) of **29b**, mp 94−96 °C ($CH_2Cl_2$/hexane); $^1$H-NMR($CDCl_3$) $\delta$ 1.34 (s, 6H), 3.55 (s, 2H), 5.65 (bs, 1H), 7.43 (m, 3H), 7.78 (m, 2H); MS *m*/*z* 175 ($MH^+$). Anal. ($C_{11}H_{14}N_2$) C, H, N.

**2-(4′-Chlorophenyl)-4,5-dihydro-1*H*-imidazole (29c):** obtained as a white solid (68%); mp 182−184 °C (EtOH) (lit.[46] mp 187 °C); MS *m*/*z* 210 ($MH^+$).

**2-(4′-Fluorophenyl)-4,5-dihydro-1*H*-imidazole (29d):** obtained as a white solid (61%); mp 152−153 °C ($CH_2Cl_2$/hexane); $^1$H-NMR ($CDCl_3$) $\delta$ 3.49 (s, 4H), 4.65 (bs, 1H), 7.12−7.76 (m, 4H); MS *m*/*z* 165 ($MH^+$). Anal. ($C_9H_9FN_2$) C, H, N.

**5,5-Dimethyl-2-phenyl-1,4,5,6-tetrahydropyrimidine (29e):** obtained as a white solid (74%); mp 116−118 °C ($CH_2Cl_2$/hexane); $^1$H-NMR ($CDCl_3$) $\delta$ 1.02 (s, 6H), 3.17 (s, 4H), 7.38 (m, 3H), 7.64 (m, 2H); MS *m*/*z* 197 ($MH^+$). Anal. ($C_{12}H_{16}N_2$) C, H, N.

**5-Aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*] isoindol-5-ols (6, 8, 13, and 16−18) and 6-Aryl-2,3,4,6-tetrahydropyrimido-[2,1-*a*]isoindol-6-ols (20−23 and 25). 5-(4-Iodophenyl)-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol (18).** A stirred solution of 2-phenylimidazoline (1.75 g, 0.012 mol) in dry THF (20 mL) under a $N_2$ atmosphere was treated dropwise with 1.6 M *n*-BuLi in hexane (22.5 mL, 0.036 mol) over a 0.5 h period. The suspension was heated at 50 °C for 3 h and then treated dropwise with a solution of methyl 4-iodobenzoate (6.29 g, 0.024 mol) in THF (15 mL) over ca. 15 min. The mixture was stirred at 50 °C for an additional 6 h, cooled to 10 °C in an icebath, and then treated dropwise with saturated $NH_4Cl$ solution (15 mL). After the mixture was left to stand overnight at room temperature, the resulting solid was filtered, washed with $H_2O$ (ca. 25 mL), and recrystallized from $CH_3OH$ to give 2.32 g (52%) of **18** (Table 1).

Compounds **6, 8, 13, 16, 17, 20−23**, and **25** given in Table 1 were prepared by the same procedure.

**[$^3$H]WIN 35,428 Binding Assay.** Brains from male Sprague-Dawley rats weighing 200−250 g (Harlan Labs, Indianapolis, IN) were removed, dissected, and rapidly frozen. Ligand binding experiments are conducted in assay tubes containing 0.5 mL of buffer (10 nM sodium phosphate with

0.32 M sucrose, pH 7.40) on ice for 120 min. Each assay tube contained 0.5 mM [$^3$H]WIN 35,428 and 0.1 mg of striatal tissue (original wet weight). The nonspecific binding of [$^3$H]WIN 35,-428 was defined using 30 $\mu$M (*R*)-(−)-cocaine. Incubations were terminated by filtration with three 5 mL washes of ice-cold buffer through GF/B filters that were previously soaked in 0.05% polyethylenimine. Results were analyzed using the Equilibrium Binding Data Analysis software (EBDA, Biosoft).

**[$^3$H]Dopamine Uptake Studies.** Rat striatal tissue was homogenized in 10 volumes of 0.32 M sucrose using a glass Teflon homogenizer. The homogenates were centrifuged at 800*g* for 10 min. The supernatants were recentrifuged for 20 min at 27000*g* to generate crude synaptosomal pellets. The pellets were resuspended in 0.5 mg/mL Krebs-Hepes buffer (pH 7.35) containing 130 mM NaCl, 4.8 mM KCl, 1.2 mM $KH_2PO_4$, 1.3 mM $CaCl_2$, 1.2 mM $MgSO_4$, 25 mM Hepes, 10 mM glucose, 0.57 mM ascorbic acid, and 10 mM nialamide. The synaptosomes (1.8 mL) were equilibrated with the test compound (100 $\mu$L) for 10 min at 30 °C, and then 100 mL of 1 mM [$^3$H]dopamine was added. After 10 min, the reaction was stopped by filtration.

**Transporter Binding Assays.** Compounds **2, 24,** and **27** were tested through NOVASCREEN a division of Oceanix Biosciences Corporation, Hanover, MD. The receptor source, radioligand, and reference compound for each assay is given in Table 3. Incubation conditions for the dopamine transporter binding, 50 mM TRIS-HCl (pH 7.4) containing 100 mM NaCl, 25 °C for 2 h; for the serotonin transporter binding, 50 mM TRIS-HCl (pH 7.4) containing 120 mM NaCl and 5 mM KCl at 25 °C for 60 min; and for the norepinephrine transporter binding, 50 mM TRIS-HCl (7.4), containing 120 mM NaCl and 5 mM KCl at 30 °C for 25 min. The reaction for all three assays was terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interaction of test compound with the uptake site.

**Neurotransmitter Receptor Binding Assay.** Compounds **2, 24,** and **27** were tested through the NIMH/NOVASCREEN Drug Discovery and Development Program (Contract No. NIMH-2003). Briefly, competitive binding assays were performed in either 250 or 500 $\mu$L volumes containing, by volume, 80% receptor preparations, 10% radioligand, and 10% of test compound/cold ligand (nonspecific binding determinant)/4% DMSO (total binding determinant). All compounds were solubilized in neat DMSO which was diluted to a final concentration of 0.4% in the assay. Assays were terminated by rapid vacuum filtration over Whatman glass fiber filters followed by rapid washing with cold buffer. Radioactivity was determined by either liquid scintillation or $\gamma$ spectrometry. Data was reduced by a software program proprietary to NOVASCREEN.

**Acknowledgment.** Part of this work was supported by a grant (5RO3DA 08516-02) from the National Institute on Drug Abuse (NIDA). The authors thank Dr. Michael Shapiro and Jefferson Chin for NMR spectra, Mrs. Bertha Owens for mass spectra, and Dr. Linda Brady of the National Institute of Mental Health (NIMH) for the NOVASCREEN assays.

## References

(1) Stein, R. M.; Eillinwood, E. H. Medical Complications of Cocaine Abuse. *Drug Therapy* **1990**, 40−50.
(2) *Cocaine: Scientific and Social Dimensions;* Ciba Foundation Symposium Vol. 166; Bock, G. R., Whelan, J., Eds.; J. Wiley & Sons: New York, 1992; 306 pp.
(3) *Cocaine, Marijuana, Designer Drugs: Chemistry, Pharmacology and Behavior;* Redda, K. K., Walker, C. A., Barnett, G., Eds.; CRC Pres:, Boca Raton, FL, **1989**; 238 pp.
(4) National Institute on Drug Abuse Warning Network. National Clearinghouse for Drug and Alcohol Abuse Information, Rockville, MD, 1990.
(5) Bates, C. K. Medical Risks of Cocaine Use (Specialty Conference). *West J. Med.* **1988**, *148*, 440−444.
(6) (a) Kabas, J. S.; Blanchard, S. M.; Matsuyama, Y.; et al. Cocaine-mediated Impairment of Cardiac Conduction in the Dog: A Potential Mechanism for Sudden Death After Cocaine. *J. Pharmacol. Exp. Ther.* **1990**, *252*, 185−199. (b) Lange, R. A.; Cigarroa, R. G.; Flores, E. D. Potentiation of Cocaine-induced Coronary Vasoconstriction by Beta-adrenergic Blockage. *Ann. Int. Med.* **1990**, *112*, 897−903. (c) Chokshi, S. K.; Moore, R.; Pandian, N. G.; Isner, J. M. Reversible Cardiomyopathy Associated with Cocaine Intoxication. *Ann. Intern. Med.* **1989**, *111*, 1039−1040. (d) Cregler, L. L.; Mark H. Medical Complications of Cocaine Abuse. *N. Engl. J. Med.* **1986**, *315*, 1495−1499.
(7) Rowbotham, M. C. Neurologic Aspects of Cocaine Use. *West J. Med.* **1988**, *149*, 442−448.
(8) (a) *American Psychiatric Association: Diagnostic and Statistical Manual*, 3rd ed.; American Psychiatric Press: Washington, DC, 1987. (b) Merriam, A. E.; Medalla, A.; Levine, B. Partial Complex Status Epilepticus Associated with Cocaine Abuse. *Biol. Psychiatry* **1988**, *23*, 515−518.
(9) Volpe, J. J. Effect of Cocaine Use on the Fetus. *N. Engl. J. Med.* **1992**, *327*, 399−407.
(10) Fullilove, R. E.; Fullilove, M. T.; Bowser, B. P.; Gross, S. A. Risk of Sexually Transmitted Disease Among Adolescent Crack Users in Oakland and San Francisco, Calif. *J. Am. Med. Assoc.* **1990**, *263*, 250−256.
(11) Edlin, B. R.; Irwin, K. L.; Faruque, S.; McCoy, C. B.; Word, C.; Serrano, Y.; Inciard J. A.; Bowser, B. P.; Schilling, R. F.; Holmburg, S. D. Intersecting Epidemics—Crack Cocaine Use and HIV Infection Among Inter-City Young Adults. *N. Engl. J. Med.* **1992**, *331*, 1422−1427.
(12) MacDonald, K. L.; Rutherford, G. W.; Friedman, S. M.; et al. Botulism and Botulism-like Illness in Chronic Drug Abusers. *Ann. Intern. Med.* **1985**, *102*, 616−618.
(13) Wetli, C. V.; Weiss, S. D.; Cleary, T. J.; Gyori, B. Fungal Cerebritis from Intravenous Drug Abuse. *J. Forensic Sci.* **1984**, *29*, 260−268.
(14) (a) Blackburn, K. J.; French, P. C.; Merrills, R. J. 5-Hydroxytryptamine Uptake by Rat Brain in vitro. *Life Sci.* **1967**, *6*, 260−268. (b) Coyle, J. T.; Snyder, S. H. Antiparkinsonian Drugs; Inhibition of Dopamine Uptake in the Corpus Striatum as a Possible Mechanism of Action. *Science* **1969**, *166*, 889−901. (c) Ross, S. B.; Renyi, A. L. Inhibition of the Uptake of Tritiated 5-Hydroxytryptamine in Brain Tissues. *Eur. J. Pharmacol.* **1969**, *7*, 270−277. (d) Harris, J. E.; Baldessarini, R. J. Uptake of [$^3$H] Catecholamines by Homogenates of Rat Corpus Striatum and Cerebral Cortex: Effects of Amphetamine Analogue. *Neuropharmacology* **1973**, *12*, 669−679. (e) Horn, A. S.; Cuello, C.; Miller, R. J. Dopamine in the Mesolimbic System of the Rat Brain: Endogenous Levels and the Effect of Drugs on the Uptake Mechanism and Stimulation of Adenylate Cyclase Activity. *J. Neurochem.* **1974**, *22*, 265−270.
(15) Javitch, J. A.; Blaustein, R. O.; Snyder, S. H. [$^3$H] Mazindol Binding Associates with Neural Dopamine and Norepinephrine Uptake Sites. *Mol. Pharmacol.* **1984**, *26*, 35−44.
(16) Sharkey, J.; Glen, K. A.; Wolfe, F.; Kuhar, M. J. Cocaine Binding at Sigma Receptors. *Eur. J. Pharmacol.* **1988**, *246*, 1048−1052.
(17) Sharkey, J.; Ritz, M. C.; Schenden, J. A.; Hanson, R. C.; Kuhar, M. J. Cocaine Inhibits Muscarinic Cholinergic Receptor in Heart and Brain. *J. Pharmacol. Exp. Ther.* **1988**, *246*, 1048−1052.
(18) Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine Receptors on Dopamine Transporters are Related to Self-Administration of Cocaine. *Science* **1987**, *237*, 1219−1223.
(19) (a) Kuhar, M. J.; Ritz, M. C.; Sharkey, J. Cocaine Receptors on Dopamine Transporters Mediate Cocaine-reinforced Behavior in *Mechanisms of Cocaine Abuse and Toxicity*; Clouet, D., Asghar, K. and Brown, R., Eds.; US Government Printing Office, Washington, DC, 1988; pp 14−22. (b) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The Dopamine Hypothesis of the Reinforcing Properties of Cocaine. *Trends Neurosci.* **1991**, *14*, 299−302.
(20) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine receptor: Biochemical Characterization and Structure-activity Relationships of Cocaine Analogues at the Dopamine Transporter. *J. Med. Chem.* **1992**, *35*, 969−981.
(21) (a) Rothman, R. B. High Affinity Dopamine Reuptake Inhibitors as Potential Cocaine Antagonists: A Strategy for Drug Development. *Life Sci.* **1990**, *46*, 17−21. (b) For other treatment approaches, see: Carroll, F. I.; Lewis, A. H.; Biswas, J. Chemical Approaches to the Treatment of Cocaine Abuse. *Pharmaceut. News* **1994**, *1*, 11−17.
(22) (a) Silverstone, T. Appetite Suppressants. A Review. *Drugs* **1992**, *43*, 820−836. (b) Coakley, J. H.; Moorcraft, J.; Hipkin, L. J.; Smith, C. S.; Griffiths, R. D.; Edwards, R. H. The Effect of Mazindol on Growth Hormone Secretion in Boys with Duchenne Muscular Dystrophy. *J. Neurol. Neurosurg. Psychiatry* **1988**, *51*, 1551−1557. (c) Zatz, M.; Rapaport, D.; Pavanello, R. C.; Rocha, J. M.; Vainzof, M.; Nicolau, W. Nocturnal Rhythm of Growth Hormone in Duchenne Patients: Effects of Different Doses of Mazindol and Cyproheptadine. *Am. J. Med. Genet.* **1989**, *33*, 457−467. (d) Griggs, R. C.; Moxley, R. T.; Mendell, J. R.; Fenichel, G. M.; Brooke, M. H.; Miller, P. J.; Mandel, S.; Florence, J.; Schierbecker, J.; Kaiser, K. K. Randomized Double-Blind Trial of Mazindol in Duchenne Dystrophy. *Muscle Nerve* **1990**, *13*, 1169−1173.
(23) (a) Aeberli, P.; Eden, P.; Gogerty, J. H.; Houlihan, W. J.; Penberthy, C. 5-Aryl-2,3-dihydro-5H-imidazo [2,1-a] isoindol-5-ols. A Novel Class of Anorectic Agents. *J. Med. Chem.* **1975**, *18*,

177−182. (b) Gogerty, J. H.; Penberthy, C.; Iorio, L. C.; Trapold, J. H. Pharmacological Analysis of a New Anorexic Substance: 5-Hydroxy-5-(4′chlorophenyl)-2,3 dihydro-5H-imidazo (2,1-a) isoindole (Mazindol). *Arch. Int. Pharmacodyn.* **1975**, *214*, 285−307. (c) Angel, I.; Taranger, M. A.; Claustre, Y.; Scatton, B.; Langer, S. A. Anorectic Activities of Serotonin Uptake Inhibitors: Correlation with Their Potencies at Inhibiting Serotonin Uptake In Vivo and 3H-Mazindol Binding In Vitro. *Life Sci.* **1988**, *43*, 651−658.

(24) (a) Heikkila, R. E.; Cabbat, F. S.; Manzino, L.; Babington, R. G.; Houlihan, W. J. Unexpected Differences between Mazindol and its Homologs on Biochemical and Behavioral Responses. *J. Pharmacol. Exp. Ther.* **1981**, *217*, 745−749. (b) Heikkila, R. E.; Babington, R. G.; Houlihan, W. J. Pharmacological Studies with Several Analogs of Mazindol: Correlation Between Effects on Dopamine Uptake and Various in vivo Responses. *Eur. J. Pharmacol.* **1981**, *71*, 277−286. (c) Engstrom, R. G.; Kelly, L. A. and Gogerty, J. H. The Effects of 5-Hydroxy-5-(4′-chlorophenyl)-2,3-dihydro-5-H-imidazo(2,1-a) isoindole (Mazindol, SaH 42-548) on the Metabolism of Brain Norepinephrine. *Arch. Int. Pharmacodyn. Ther.* **1975**, *214*, 308−321.

(25) (a) Giros, B.; Caron, M. G. Molecular Characterization of the Dopamine Transporter. *Trends Pharmacol. Sci.* **1993**, *14*, 43−44. (b) Kozikowski, A. P.; Liang, L.; Tanaka, J.; Bergmann, J. S.; Johnson, K. M. Use of Nitrile Oxide Cycle Addition (NOC) Chemistry in the Synthesis of Cocaine Analogues; Mazindol Binding and Dopamine Uptake Studies. *Med. Chem. Res.* **1991**, *1*, 312−321.

(26) (a) Johnson, K. M.; Bergman, J. S.; Kozikowski, A. P. Cocaine and Dopamine Differentially Protect [$^3$H] Mazindol Binding Sites from Alkylation by N-Ethylmaleamide. *Eur. J. Pharmacol.* **1992**, *227*, 411−415. (b) Reith, M. E.; Selmeci, G. Radiolabeling of Dopamine Uptake Sites in Mouse Striatum; Comparison of Binding Sites for Cocaine, Mazindol and GBR 12935. *Naunyn Schmiedesbergs Arch. Pharmacol.* **1992**, *345*, 309−318.

(27) Izenwasser, S.; Terry, P.; Heller, B.; Witkin, J. M.; Katz, J. L. Differential Relationships among Dopamine Transporter Affinities and Stimulant Potencies of Various Uptake Inhibitors. *Eur. J. Pharmacol.* **1994**, *263*, 277−283.

(28) Bennett, B. A.; Hyde, C. E.; Pecora, J. R.; Clodfelter, J. E. Differing Neurotoxic Potencies of Methamphetamine, Mazindol and Cocaine in Mesencephalic Cultures. *J. Neurochem.* **1993**, *60*, 1444−1452.

(29) Eshleman, A. J.; Henningsen, R. A.; Neve, K. A.; Janowsky, A. Release of Dopamine via the Human Transporter. *Mol. Pharmacol.* **1994**, *45*, 312−316.

(30) (a) Chait, L. D.; Uhlenhuth, E. H.; Johanson, C. E. Reinforcing and Subjective Effects of Several Anorectics in Normal Human Volunteers. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 777−783. (b) Chait, L. D.; Uhlenhuth, E. H.; Johanson, C. E. The Discriminative Stimulus and Subjective Effects of Phenylpropanolamine, Mazindol and d-Amphetamine in Humans. *Pharmacol. Biochem. Behavior* **1986**, *24*, 1665−1672. (c) DeFelice, E. A.; Bronstein, S.; Cohen, A. Double-blind Comparison of Placebo and 42−548, a New Appetite Suppressant, in Obese Volunteers. *Curr. Res. Ther.* **1969**, *11*, 256−262. (d) Gotetam, K. G.; Gunne, L. M. Subjective Effects of Two Anorexigenic Agents Fenfluramine and AN-448 in Amphetamine-dependent Subjects. *Br. J. Addict.* **1972**, *67*, 39−44. (e) Gotestam, K. G. Investigations of abuse potential of anorectic drugs. *Curr. Med. Res. Opin.* **1979**, *6*, 125−134. (f) Chambers, C. D. The Epidemiology of Stimulant Abuse: A Focus on the Amphetamine-related Substances. In *Amphetamine Use, Misuse and Abuse: Proceedings of the National Amphetamine Conference, 1978*; Smith, D. E., Wesson, D. R., Buxton, M. E., Seymour, R. B., Ungerledider, J. T., Morgan, J. P. Mandell, A. J., Jara, G., Eds.; G. K. Hall and Co.: Boston, MA, 1979; pp 92−103.

(31) (a) Wilson, M. C.; Schuster, C. R. Mazindol Self-Administration in the Rhesus Monkey. *Pharmacol. Biochem. Behav.* **1976**, *4*, 207−210. (b) Corwin, R. L.; Woolverton, W. L.; Schuster, C. R.; Johanson, C. E. Anorectics: Effects on Food Intake and Self-administration in Rhesus Monkeys. *Alcohol Drug Res.* **1987**, *7*, 351−361. (c) Yanagita, T.; Wakasa, Y.; Oinuma, N. Drug Dependence Potential of Mazindol Tested in Rhesus Monkeys. *Jitchuken Zenrinsho Kenkyuho* **1982**, *8*, 247−257. (d) Risner, M. E.; Silcox, D. L. Psychostimulant Self-Administration by Beagle Dogs in a Progressive-ratio Paradigm. *Psychopharmacology* **1981**, *75*, 25−30. (e) Spealman, R. D.; Madras, B. K.; Bergman, J. Effects of Cocaine and Related Drugs in Nonhuman Primates. II. Stimulant Effects on Schedule-Controlled Behavior. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 142−149. (f) Kleven, M. S.; Woolverton, W. L. Effects of Three Monoamine Uptake Inhibitors on Behavior Maintained by Cocaine or Food Presentation in Rhesus Monkeys. *Drug Alcohol Depend.* **1993**, *31*, 149−158. (g) Mansbach, R. S.; Balster, R. L. Effects of Mazindol on Behavior Maintained or Occasioned by Cocaine. *Drug Alcohol Depend.* **1993**, *31*, 183−191.

(32) Bergman, J.; Madras, B. K.; Johnson, S. E.; Spealman, R. D. Effects of Cocaine and Related Drugs in Nonhuman Primates. III. Self-Administration by Squirrel Monkeys. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 150−155.

(33) (a) Berger, P.; Gawin, F.; Koster, T. R. Treatment of Cocaine Abuse with Mazindol. *Lancet* **1989**, No. 2, 283. (b) Diakogiannis, I. A.; Steinberg, M.; Kosten, T. R. Mazindol Treatment of Cocaine Abuse. A Double-blind Investigation. In *Problems of Drug Dependence 1990*;: Proceeding of the 52nd Annual Scientific Meeting of The Committee on Problems of Drug Dependence, Inc.; Harris, L., Ed.; National Institute on Drug Abuse: Rockville, MD, 1990; p 514. (c) Preston, K. L.; Sullivan, J. T.; Berger, P.; Bigelow, G. E. Effects of Cocaine Alone and in Combination with Mazindol in Human Cocaine Abusers. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 296−307.

(34) Margolin, A.; Avants, S. K.; Kosten, T. R. Mazindol for Relapse Prevention to Cocaine Abuse in Methadone - Maintained Patients. *Am. J. Drug Alcohol Abuse* **1995**, *21*, 469−481.

(35) Houlihan, W. J.; Parrino, V. A. Directed Lithiation of 2-Phenyl- and 2-(o-Methylphenyl) imidazoline. *J. Org. Chem.* **1982**, *47*, 5177−5180.

(36) Galinier, E.; Garreau, L.; Dognon, A. M.; Ombetta-Goka, J. E.; Frangin, Y.; Chalon, S.; Besnard, J. C., Guilloteau, D. Synthesis of Halogenated Analogs of 5-(4-Chlorophenyl)-2,3-dihydro-5-hydroxy-5H-imidazo [2,1-a] isoindole or Mazindol for Exploration of the Dopamine Transporter. *Eur. J. Med. Chem.* **1993**, *28*, 927−933.

(37) Aeberli, P.; Eden, P.; Gogerty, J. H.; Houlihan, W. J.; Penberthy, C. Anorectic Agents. 2. Structural Analogs of 5-(p-Chlorophenyl)-2,3-dihydro-5H-imidazo [2,1-a] isoindol-5-ol. *J. Med. Chem.* **1975**, *18*, 182−185.

(38) Deutsch, H. M.; Shi, Q.; Gruszecka-Kowalik, E.; Schweri, M. Synthesis and Pharmacology of Potential Cocaine Antagonists. 2. Structure-Activity Relationship Studies of Aromatic Ring-Substituted Methylphenidate Analogs. *J. Med. Chem.* **1996**, *39*, 1201−1209.

(39) Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliatt, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. Synthesis of 2$\beta$-Acyl-3$\beta$-aryl-8-azabicyclo [3.2.1] octanes and Their Binding Affinities at Dopamine and Serotonin Transporter Sites in Rat Striatum and Frontal Cortex. *J. Med. Chem.* **1994**, *37*, 1262−1268.

(40) Yu, D.-W.; Gatley, S. J.; Wolf, A. P.; MacGregor, R. R.; Dewey, S. L.; Fowler, J. S.; Schyler, D. J. Synthesis of Carbon-11 Labeled Iodinated Cocaine Derivatives and Their Distribution in Baboon Brain Measured Using Positron Emission Tomography. *J. Med. Chem.* **1992**, *35*, 2178−2183.

(41) Carroll, F. I.; Gao, Y.; Rahman, M. A.; Abraham, P.; Parham, K.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, Ligand Binding, QSAR and CoMFA Study of 3$\beta$-(p-Substituted phenyl) tropane-2$\beta$-carboxylic Acid Methyl Esters. *J. Med. Chem.* **1991**, *34*, 2719−2725.

(42) W. J. Houlihan, unpublished results.

(43) Kozikowski, A. P.; Eddine Saiah, M. K.; Bergmann, J. S.; Johnson, K. M. Structure-Activity Relationship Studies of N-Sulfonyl Analogs of Cocaine: Role of Ionic Interaction in Cocaine Binding. *J. Med. Chem.* **1994**, *37*, 3440−3442.

(44) Koe, B. K. Molecular Geometry of Inhibitors of the Uptake of Catecholamines and Serotonin in Synaptosomal Preparations of Rat Brain. *J. Pharmacol. Exp. Ther.* **1976**, *199*, 649−661.

(45) Hoffman, B. J. Molecular Biology of Dopamine Transporters. In *Dopamine Receptors and Transporters*; Niznik, H. B., Ed.; Marcel Dekker, Inc.: New York, 1994; pp 645−668.

(46) Oxley, P.; Short, W. F. Amidines. Part VI. Preparation of 2-substituted 4:5−dihydroglyoxalines and Ring Homologues from Cyanides and Alkylenediamines. *J. Chem. Soc.* **1947**, 497−505.

(47) $^1$H-NMR, $^{13}$C-NMR, IR, and MS data of selected compounds in Table 1. NMR were obtained in DMSO-$d_6$ and IR in KBr. **6**: $^1$H $\delta$ 3.18 (br s, 1H), 3.32 (m, 2H), 4.12 (m, 2H), 6.83 (s, 1H), 7.08−7.63 (m, 6H), 8.15 (d, 1H); $^{13}$C 40.85, 59.85, 86.32, 121.74, 123.08, 127.01, 128.51, 128.59, 129.87, 130.85, 130.97, 131.25, 136.65, 153.14, 166.85. **8**: $^1$H $\delta$ 1.35 (s, 6H), 2.92 (m, 2H), 7.20−7.74 (m, 8H); IR (cm$^{-1}$) 2990−2680, 1649; MS (CI) 313 (MH$^+$). **13**: $^{13}$C 40.73, 59.85, 86.04, 121.84, 123.05, 127.14, 128.42, 128.77, 130.13, 131.10, 131.30, 132.35, 133.59, 152.69, 166.74. **17**: $^1$H $\delta$ 2.90−3.30 (m, 2H), 4.00−4.25 (m, 2H), 6.98−7.97 (m, 8H); MS (CI) 330 (MH$^+$), 312 (MH$^+$ − H$_2$O). **18**: $^1$H $\delta$ 2.83−3.29 (m, 2H), 4.05−4.28 (m, 2H), 7.07−8.05 (m, 8H); IR (cm$^{-1}$) 2950−2620, 1655; MS (CI) 377 (MH$^+$). **20**: $^1$H $\delta$ 2.80 (m, 2H), 3.36 (m, 4H), 7.02−7.63 (m, 7H), 7.93 (d, 1H); $^{13}$C 20.58, 36.45, 43.51, 88.96, 115.79, 122.01, 124.08, 127.57, 128.44, 129.18, 130.11, 130.23, 134, 146.58, 152.94, 158.07, 160.05. **25**: $^1$H $\delta$ 0.87 (s, 3H), 0.91 (s, 3H), 2.90 (d, 1H), 2.99 (d, 1H), 3.12 (s, 2H), 6.81 (s, 1H), 7.20 (m, 1H), 7.32−7.51 (m, 6H), 7.70 (m, 1H).

JM960288W