

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
ALICIA LLOREDA RICAURTE

ASUNTO	Radicación	09-53154
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	007

12598

Patente de Invención	☐	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☐	Cap. I ☐	Cap. II ☐

No. Solicitud Internacional PCT/EP2007/063736

Fecha de Presentación Internacional 11 de diciembre de 2007

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 50 a 290	22/mayo/2009
Reivindicaciones:	Folios 21 a 30	22/mayo/2009
	Folios 292 a 301	22/mayo/2009
	Folios 303 a 308	22/mayo/2009
	Folios 312 a 318	08/junio/2009
	Folios 416 a 422	30/septiembre/2009
	Folios 429 a 457	30/noviembre/2010
Prioridad:	US 60875969	19/diciembre/2006
	US 60999561	19/octubre/2007

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque: estas solicitudes fueron presentadas dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Modificaciones no aceptadas (Art 34 D 486 y Art 19, 22 y 34 PCT)

Las modificaciones del capítulo reivindicatorio descrito en los folios 429 a 457 y en lo relacionado con la reivindicación independiente 1 (fol. 431) no son aceptables porque refieren 1.) Un disclaimer que indica una exclusión de compuestos que no habían sido considerados inicialmente, por lo cual amplían el objeto de la Solicitud.

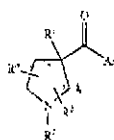
4. Objeto de la invención

Título de la solicitud: "Derivados de heteroaril-pirrolidilil y piperidinil cetona"

Expediente 09-53154 Artículo 45

El problema planteado en esta solicitud consiste proporcionar compuesto útiles para el tratamiento de enfermedades asociadas con los inhibidores de la reabsorción de monoaminas

Para resolver este problema técnico la solicitud en estudio proporciona un compuesto de la fórmula (I)



Compuesto I

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K 31/4523 y C07D 205/04; 207/08; 211/30; 401/06; 401/10; 403/06; 403/14; 405/06; 409/06; 409/14; 417/06; 417/14; 451/02; 487/04

5. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicaciones 1-21 no están debidamente sustentadas en la descripción porque de las definiciones de m, n, Ar, alquilo C₁₋₆, alqueno C₂₋₆, alquino C₂₋₆, hetero-alquilo C₁₋₆, halo-alquilo C₁₋₆, halo-alqueno C₂₋₆, cicloalquilo C₃₋₇, (cicloalquilo C₃₋₇)- alquilo C₁₋₆, alcoxi C₁₋₆, alquilsulfonilo C₁₋₆, alquilsulfanilo C₁₋₆, arilo, heteroarilo, heterociclil- alquilo C₁₋₆ aril- alquilo C₁₋₃, cuya porción heteroarilo está opcionalmente sustituida, ariloxi, aril- alcoxi C₁₋₆, heteroariloxi, heteroaril- alcoxi C₁₋₆, R^a, R^b, alquilo, haloalquilo, haloalcoxi, heteroalquilo, acilamino, mono-alquilamino, di-alquilamino, hidroxialquilo, alcoxialquilo, benciloxo, cicloalquilalquilo, cicloalcoxi, cicloalquilalcoxi, alquilsulfonilo, -(CH₂)_q-S(O)_rR^f, -(CH₂)_q-NR^gR^h, -(CH₂)_q-NR^hR^g, -(CH₂)_q-C(=O)-C(=O)-NR^gR^h, -(CH₂)_q-SO₂-NR^gR^h, -(CH₂)_q-NR^f-C(=O)Rⁱ, -(CH₂)_q-C(=O)Rⁱ, -(CH₂)_q-N(R^f)-SO₂-R^g se obtiene un gran número de compuestos, muchos de los cuales no están ejemplificados en la forma de ejemplos de la invención dentro del capítulo descriptivo, se sugiere restringir la solicitud a una razonable generalización del tipo de compuestos que han sido sintetizados o probados, es decir, que se encuentran debidamente sustentados. El siguiente cuadro ejemplifica la afirmación anterior y presenta los sustituyentes que se encuentran soportados en la descripción.

La reivindicaciones 1-21 no es concisas porque los términos alquilo, haloalquilo, haloalcoxi, heteroalquilo, acilamino, mono-alquilamino, di-alquilamino, hidroxialquilo, alcoxialquilo, benciloxo, cicloalquilalquilo, cicloalcoxi refieren a géneros funcionales se sugiere restringir la solicitud a una razonable generalización del tipo de compuestos que ha sido sintetizado ó probado, es decir, que se encuentran debidamente sustentados.

Se requiere al Solicitante hacer las aclaraciones necesarias.

6. Unidad de invención (Art 25 D 486)

La Solicitud no cumple con el Requisito de Unidad de Invención porque se refiere a 5, Grupos Inventivos.

Los Grupos Inventivos están definidos por las siguientes características esenciales:

1° Compuestos en los cuales el núcleo está caracterizado 1-aril-4-(4-(sustituido)piperidinil-il)metanona.

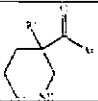
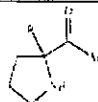
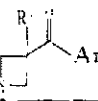
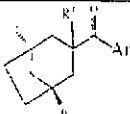
2° Compuestos en los cuales el núcleo está caracterizado 1-aril-2-(2-(sustituido)pirrolidil-il)metanona.

3° Compuestos en los cuales el núcleo está caracterizado 1-aril-3-(3-(sustituido)azetiril-il)metanona.

4° Compuestos en los cuales el núcleo está caracterizado 1-aril-4-(4-(sustituido)azepanil-il)metanona.

5° Compuestos en los cuales el núcleo está caracterizado la porción heterocíclica 1-aril- 2-(4-(sustituido)-8-azabicyclo[3.2.1]octil)metanona.

La solicitud de patente no cumple con el requisito de unidad de invención debido a refiere 5, Grupos Inventivos de acuerdo con las realizaciones preferidas, los cuales son descritos a continuación:

GRUPO INVENTIVO	CARACTERÍSTICA ESENCIAL DE GRUPO INVENTIVO (Estructura química central)	REALIZACIONES PREFERIDAS DEL GRUPO INVENTIVO (Ejemplos)
1		53-79
2		1-52
3		81
4		86
5		317-21

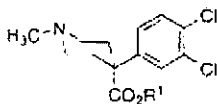
Se sugiere presentar las Solicitudes Divisionales que considere necesarias, ó limitar la solicitud inicial a una sola invención, eliminando de ella las otras invenciones.

7. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación de la solicitud de prioridad más antigua: Diciembre 19 de 2006 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación*
D1	Bioorganic & Medicinal Chemistry 13 (2005) 5623–5634	Structure–activity studies of 30-40-dichloro-meperidine analogues at dopamine and serotonin transporters	2005
D2	Journal Medicinal Chemistry 2005, 48, 1336-1343	Synthesis and Biological Evaluation of Meperidine Analogues at Monoamine Transporters	2005

D1: divulga por medio de la tabla 1 (Pág. 3) los resultados de un estudio de la relación estructura actividad de algunos derivados del compuesto 8 correspondiente a la 3'4'-dicloromeperidina, el cual es un derivado de la meperidina altamente selectivo por el transportador de dopamina DAT (Pág. 1, Col 1).



Compuesto 8

Table 1. In vitro binding data at the DAT and the SERT for the 2,4-dichloro-mepiperidine ester derivatives 8a-h

Compounds	R	IC ₅₀ DAT (nM)	IC ₅₀ SERT (nM)	DAT/SERT
8a	H	125 ± 15	18 ± 2.6	6.7
8b	CH ₃	367 ± 35	35 ± 13	10
8c	CH ₂ CH ₃	283 ± 51	200 ± 18	1.3
8d	CH ₂ CH ₂ CH ₃	670 ± 39	17 ± 1	36
8e	CH ₂ CH ₂ CH ₂ CH ₃	3310 ± 210	83 ± 3	40
8f	CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	635 ± 91	38 ± 6	17
8g	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	192 ± 31	4 ± 2	17
8h	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	165 ± 36	11 ± 1	18

Indicando que en general, los análogos ester **8a-h** (Pág. 3. Col. 1) presentan equipotente afinidad de unión por el transportador de monoaminas de serotonina SERT, en comparación con el compuesto 5. Adicionalmente, manifiesta que todos los esteres fueron más selectivos por el transportador SERT que por el transportador DAT y que una vez cuando el ester excede de cuatro átomos de carbono en longitud, la afinidad por DAT es de rango de micromolar. Lo anterior, sin afectar significativamente la afinidad por SERT e incluso menciona que el bencil ester **8h** presenta la mayor afinidad por SERT (Ki=3.9nM) de los compuestos evaluados.

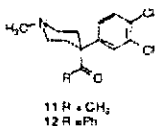
De igual modo, da a conocer a través de la tabla 3 (Pág. 4)

Table 3. In vitro binding data at DAT and SERT for the 2,4-dichloro-mepiperidine derivatives 11-17

Compounds	DAT IC ₅₀ (nM)	SERT IC ₅₀ (nM)	DAT/SERT
5	125 ± 15	18 ± 2.6	6.7
11	367 ± 35	35 ± 13	10
12	283 ± 51	200 ± 18	1.3
13	670 ± 39	17 ± 1	36
14	3310 ± 210	83 ± 3	40
15	635 ± 91	38 ± 6	17
16	192 ± 31	4 ± 2	17
17	165 ± 36	11 ± 1	18

All values are means ± SEM of three experiments performed in triplicate.
All compounds were tested as the HCl salt.

los resultados de afinidad de los compuesto 11 y 12 (Pág. 3) caracterizados por ser derivados de la (4-fenil-1-metilpiperidin-4-il)-metanona y al realizar la comparación con el compuesto 5 se evidencia 1.) que la conversión de un grupo ester por un grupo cetona resulta en una ligera disminución en la afinidad de los transportadores de DAT y SERT y 2.) que mediante la sustitución del grupo R definido para el compuesto 11 como metilo por un grupo fenilo (Compuesto 12) se logra aumentar la actividad inhibitoria del compuesto resultante por el transportador de DAT sin que su afinidad por el transportador SERT disminuya ostensiblemente y se presenta una relación de afinidad entre los transportadores DAT/SERT de 1.3.

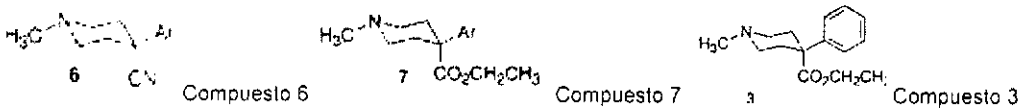


Por otra parte, en su conclusión (Pág.4) indica que los resultados de este estudio claramente demuestran que la meperidina y sus análogos son compuestos selectivos ligandos para el transportador SERT sobre DAT y que las modificaciones químicas del grupo éster generalmente conllevan a compuestos con mayor afinidad SERT, donde los sustituyentes del éster de cadena larga y grupos lipofílicos en la posición 4 favorecen el reconocimiento molecular de SERT. A continuación, indica que los grupos hidrofílicos no afecta la afinidad SERT pero reducen apreciablemente la afinidad por DAT, encontrandose que el éster bencílico era el compuesto más potente y selectivo del estudio. Finalmente, el estudio sugiere que análogos de la meperidina puede ser desarrollados como potencial inhibidores de la recaptación de serotonina (SSRIs).

D2: divulga el resultado de un estudio de la relación estructura actividad de una serie compuestos derivados de la meperidina y a través de la tabla 1 (Pág. 3) presenta los

resultados de estudio de afinidad y selectividad de los compuestos de fórmula 7 (Pág.2 Esq.1) caracterizados por ser derivados del compuesto 3 (Pág. 1) comúnmente conocido como meperidina.

Compuesto		SERT		NET		DAT	
Ar	Ar	IC ₅₀ (nM)	IC ₅₀ (nM)	IC ₅₀ (nM)	IC ₅₀ (nM)	IC ₅₀ (nM)	IC ₅₀ (nM)
6a	Ar	1.1	1.1	1.1	1.1	1.1	1.1
6b	Ar	1.1	1.1	1.1	1.1	1.1	1.1
6c	Ar	1.1	1.1	1.1	1.1	1.1	1.1
6d	Ar	1.1	1.1	1.1	1.1	1.1	1.1
6e	Ar	1.1	1.1	1.1	1.1	1.1	1.1
6f	Ar	1.1	1.1	1.1	1.1	1.1	1.1
7a	Ar	1.1	1.1	1.1	1.1	1.1	1.1
7b	Ar	1.1	1.1	1.1	1.1	1.1	1.1
7c	Ar	1.1	1.1	1.1	1.1	1.1	1.1
7d	Ar	1.1	1.1	1.1	1.1	1.1	1.1
7e	Ar	1.1	1.1	1.1	1.1	1.1	1.1
7f	Ar	1.1	1.1	1.1	1.1	1.1	1.1
3	Ar	1.1	1.1	1.1	1.1	1.1	1.1



El estudio dentro de sus objetos evaluó el impacto la modificaciones en el sustituyente Ar y su resultado fue presentado el capítulo denominado “Resultados y discusión” (Pág. 2 Col. 2) donde muestra que los derivados esterés **7a-f** son más potentes en la inhibición de los transportadores de monoaminas SERT, NET y DAT que los compuestos correspondientes con un grupo nitrilo **6a-f**. Adicionalmente, revela que los compuestos análogos a la meperidina exhiben una mayor afinidad por el transportador SERT que por el transportador DAT.

De igual manera, expresa que: 1.) El análogo 2-naftil es 59 veces más potente presentado que la meperidina frente a transportador SERT 2.), En general ninguno de los derivados **7a-f** exhiben afinidad significativa frente al transportador NET y 3.) Los esterés **7e** y **7f** muestran inhibición bifásica de dopamina con una alta afinidad inhibidora.

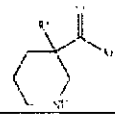
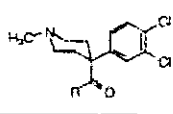
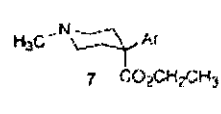
Adicionalmente, el documento (Pág. 4, Col. 1) concluye que la serie de compuesto meperidina aril-sustituida evaluados se caracteriza en porque 1.) Los análogos evaluados en el documento muestran un incremento en la selectividad por DAT y SERT sobre los receptores opiodes μ al ser comparados con la meperidina 2.) Los análogos 3,4-diclorofenil presentan una mayor selectividad sobre DAT que sobre los receptores opiodes μ 3.) Los compuestos análogos al 2-naftil muestran mayor selectividad sobre SERT que sobre los receptores opiodes μ.

8. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 para el primer grupo inventivo consiste en 1-aril-4-(4-(sustituido)piperidinil-il)metanona.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D8	D9
Un compuesto de fórmula 	Un compuesto de fórmula 	Un compuesto de fórmula 
Ar	R	Etoxilo
Indolilo Indazolilo azaíndolilo	Metilo Fenilo	

azaindazolilo 2,3-dihidro-indolilo 1,3-dihidro-indol-2-on-ilo benzotiofenilo bencimidazolilo benzoxazolilo benzotiazolilo bencisotiazolilo quinolinilo 1,2,3,4-tetrahidroquinolino quinolin-2-on-ilo isoquinolinilo piridinilo tiofenilo		
R¹ alquilo C ₁₋₆ alquenilo C ₂₋₆ alquinilo C ₂₋₆ hetero-alquilo C ₁₋₆ halo-alquilo C ₁₋₆ halo-alquenilo C ₂₋₆ cicloalquilo C ₃₋₇ (cicloalquilo C ₃₋₇)-alquilo C ₁₋₆ alcoxi C ₁₋₆ alquilsulfonilo C ₁₋₆ alquilsulfanilo C ₁₋₆ arilo heteroarilo heterocicilil-alquilo C ₁₋₆ aril-alquilo C ₁₋₃ ariloxi aril-alcoxi C ₁₋₆ heteroariloxi heteroaril-alcoxi C ₁₋₆	Diclorofenilo	Ar fenilo 4-fluorfenilo 4-yodofenilo 4-metilfenilo 3,4-diclorofenilo 2-naftil
R² alquilo C ₁₋₆ hidrógeno	Metilo	Metilo
R^a y R^b	Hidrógeno	Hidrógeno
hidrógeno alquilo C ₁₋₆ alcoxi C ₁₋₆ halógeno hidroxi oxo juntos alquilenos condicionado		

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 para el primer grupo inventivo porque divulgan compuestos derivados 1-aril-4-(4-(sustituido)piperidinil-il)metanona como inhibidores de la reabsorción de monoaminas endógenas.

La diferencia entre la invención, definida en la reivindicación 1 y los compuestos 11 o 12 divulgados en el documento D1 consiste en la característica correspondiente el sustituyente R, el cual está definido para la invención como un grupo arilo o heteroarilo seleccionado y para el documento D1 está definido como fenilo para el compuesto 12 o metilo para el compuesto 11. Sin embargo, D1 da a conocer 1.) que la conversión de un grupo éster por un grupo cetona resulta en una ligera disminución en la afinidad de los transportadores de DAT y SERT 2.) que análogos de la meperidina puede ser desarrollados como potencial inhibidores de la recaptación de serotonina (SSRIs) y 3.) que las modificaciones químicas del grupo éster generalmente conllevan a compuestos con mayor afinidad por el transportador SERT donde sustituyentes del éster de cadena larga y grupos lipofílicos en la posición 4 favorecen el reconocimiento molecular de SERT.

La diferencia entre la invención, definida en la reivindicación 1 y el compuesto divulgado en el documento D2 consiste 1.) En que el compuesto es un derivado éster y la invención lo define como una cetona y 2.) El radical R₁ es un grupo etoxilo entre tanto la invención lo define como un grupo arilo o heteroarilo.

El efecto que logra al cambiar el sustituyente R en los compuestos 11 o 12 del

documento D1 por grupo arilo o heteroarilo seleccionado es obtener nuevos compuestos inhibidores de la reabsorción de monoaminas endógenas

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo modificar los compuesto 11 o 12 conocidos en D1 para obtener compuestos inhibidores de la reabsorción de monoaminas endógenas".

En consecuencia, la persona del oficio normalmente versada en la materia, tendría suficiente motivación para reemplazar el sustituyente fenilo o metilo de los compuestos divulgados en D1 por un sustituyente arilo o heteroarilo u otro grupos lipofílicos de más de cuatro átomos de carbono como es divulgado en el documento D2 en los compuestos 11 o 12 del documento D1 para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Puesto que las reivindicaciones dependientes 2-14 y 20-21 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

9. Conclusión

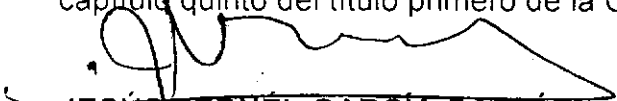
Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	Bioorganic & Medicinal Chemistry 13 (2005) 5623-5634	1-14 y 20-21	Nivel Inventivo
D2	Journal Medicinal Chemistry 2005, 48, 1336-1343	1-14 y 20-21	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante y presentarla por escrito

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.


JESÚS FERNÉL GARCÍA GARCÍA
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha 18 JUL 2012

Elaborado por: Lenin Roberto Guerrero
Revisado Por: Consuelo Leguizamón Leguizamón.
Aprobado por: Jesús Fernél García García.

Structure–activity studies of 3',4'-dichloro-meperidine analogues at dopamine and serotonin transporters

Jill B. Riedel,^a Maud Bouvet,^a Sam Leinweber,^b Dean Wade,^b Stacey A. Lomenzo^a and Mark L. Trudell^{a,*}

^aDepartment of Chemistry, University of New Orleans, New Orleans, LA 70148, USA
^bDepartment of Psychiatry and Behavioral Sciences, University of Miami School of Medicine, Miami, FL 33136, USA
 Received 10 March 2008; revised 18 May 2008; accepted 18 May 2008
 Available online 1 July 2008

Abstract—The structure–activity relationships of 3',4'-dichloro-meperidine were investigated at dopamine (DAT) and serotonin transporters (SERT). Large ester substituents and lipophilic groups at the 4-position favored molecular recognition at the SERT. The benzyl ester of 3',4'-dichloro-meperidine exhibited high potency and high selectivity for the SERT (DAT/SERT = 760). Chemical modification of the ester group and N-substitution generally led to compounds with decreased DAT affinity. Only small esters and alkyl groups were tolerated at the 4-position of the meperidine ring system by the DAT. Overall, the meperidine analogues were generally more selective for the SERT than for the DAT.
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1. Introduction

Recent studies in our laboratory have focused upon the structure–activity relationships (SAR) of meperidine, 1, an atypical μ -opioid agonist, at monoamine transporters.^{1,2} Meperidine was initially found to be selective for the serotonin transporter (SERT) over the dopamine transporter (DAT) (SERT/DAT = 43).¹ Further exploration of various aryl-substituted meperidine analogues 2 revealed that although the DAT affinity of these compounds could be enhanced, high SERT affinity and selectivity predominated throughout the series.² Effects of the aryl substituent on the DAT affinity of meperidine analogues paralleled the SAR previously reported for 2-(carboxyethoxy-3-aryl) tropanes 3,^{3,4} and α -alkoxy-benzyloxy-4-aryl piperidines 4.^{5,6} From the SAR of the meperidine analogues, the 3',4'-dichlorophenyl group was identified as an important moiety for molecular recognition at the DAT. Similar effects of the 3',4'-dichlorophenyl group on DAT affinity have been reported for other tropane derivatives,^{3,4} non-nitrogen tropane analogues,^{1,12} and piperidine derivatives.¹¹ However, unlike these tropane, tropane-related, and piperidine ligands that are DAT selective, 3',4'-dichloromeperidine, 5, exhibited high potency at the

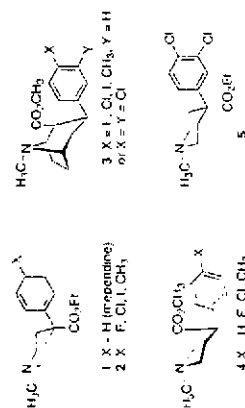


Figure 1.

Keywords: Meperidine; Dopamine transporter; Serotonin transporter
 *Corresponding author. Tel.: +1 504 280 7157; fax: +1 504 280 6600; e-mail: mltrudell@uno.edu

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both the DAT and the SERT. Herein, we report the synthesis and biological evaluation of a series of modified ester and N-substituted analogues of 3',4'-dichloromeperidine, 5, at the dopamine and serotonin transporters.

2. Results

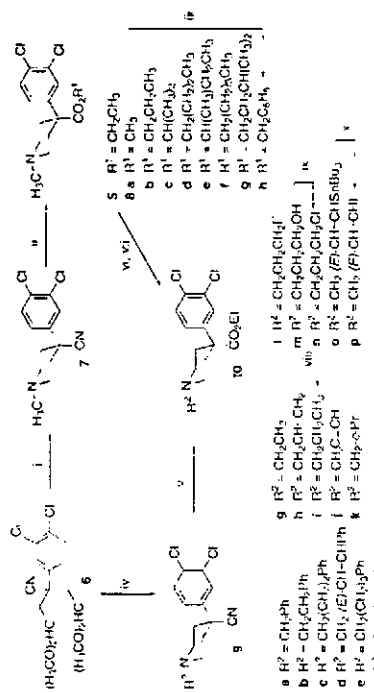
In an attempt to specifically increase potency and selectivity for either the DAT or the SERT, various substitutions on the ester group and on the nitrogen atom as well as modifications of the ester moiety were considered. As illustrated in Scheme 1, ester analogues of 5 were prepared from the diacetal 6 using a synthetic approach that was previously developed in our laboratory.¹³ Hydrolysis of 6 and concomitant reductive amination with methylamine furnished the piperidine nitrile 7. The ester derivatives 8 were then obtained using a one-pot hydrolysis/esterification process. Hydrolysis of the nitrile 7 with aqueous sulfuric acid at 120 °C was followed by the addition of an appropriate alcohol in excess. Azeotropic distillation of the alcohol/water excess afforded the desired ester substitutions 8a–g in good overall yield. However, this process was not amenable to high boiling alcohols. To this end, the benzyl ester 8h was obtained in 51% yield from the methyl ester 8a using the 1,3-bis(trimethylsilyl)imidazol-2-ylidene (TMSI) carbene catalyzed transesterification method.¹⁴

The N-substituted 3',4'-dichloro-meperidine derivatives were synthesized using two different methods (Scheme 1). The N-alkylaryl congeners 9a–e were synthesized by a reductive amination sequence in which the N-alkylaryl group was introduced during construction of the piperidine ring system. The diacetal 6 was converted into the N-alkylaryl piperidine nitriles 9a–e by hydrolysis of the

acetal moieties, followed by selective amination with the corresponding arylalkyls. Subsequent transformation of the nitrile group of 9a–e into the desired ester ester of 10a–e took place with a one-pot hydrolysis/esterification process. Alternatively, the remaining N-alkylaryl (10d–f), N-alkyl, N-alkenyl, and N-alkynyl congeners (10g–p) were prepared from 5 via a demethyla-tion/alkylation sequence. The N-3-chloropropyl derivative 10h was prepared from the hydroxy derivative 10i via the corresponding mesylate. Attempts to directly prepare 10h from the 1,3-dichloropropene or 1-bromo-3-chloropropane afforded an intractable mixture. Finally, the N-(1,3-oxo-2-propenyl) analogue 10p was prepared from the corresponding diamine 10b.¹⁵

As illustrated in Scheme 2, functional group transformation at the 4-position took place in a straightforward fashion. Treatment of 5 with 1 equiv of a Grignard reagent (methylmagnesium bromide and phenylmagnesium bromide) afforded the corresponding ketones 11 and 12, respectively. Sodium borohydride reduction of 11 gave the alcohol 13 in 96% yield. Lithium aluminum hydride reduction of 5 furnished the alcohol 14 in 98% yield. Subsequent conversion of 14 into the acetate 15, the vinyl derivative 16, and ethyl analogue 17 was effected using standard synthetic methods.

The transporter binding affinities were determined for the 3',4'-dichloro-meperidine analogues by their ability to displace bound radiolabeled ligands from rat vesicular monoamine transporters.² The K_i values that are reported in Tables 1–3 are inhibition constants derived for the unlabeled ligands. The binding affinities of the meperidine analogues were determined at DAT by inhibition of [³H]WIN 35,428 binding. For compounds that were equivalent with 5 at the DAT, the SERT affinity was also determined by inhib-



Scheme 1. Reagents and conditions: (i) 1. HCl, 90 °C, then CH₃NH₂, HCl, CH₃OH, NaOH, CN, 60 °C, then R¹OH, azeotropic distillation; (ii) H₂O, 120 °C, then R²OH, HCl, 90 °C, then R²OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R²OH, azeotropic distillation; (iii) N₂, 120 °C, then R³OH, HCl, 90 °C, then R³OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R³OH, azeotropic distillation; (iv) N₂, 120 °C, then R⁴OH, HCl, 90 °C, then R⁴OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁴OH, azeotropic distillation; (v) N₂, 120 °C, then R⁵OH, HCl, 90 °C, then R⁵OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁵OH, azeotropic distillation; (vi) N₂, 120 °C, then R⁶OH, HCl, 90 °C, then R⁶OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁶OH, azeotropic distillation; (vii) N₂, 120 °C, then R⁷OH, HCl, 90 °C, then R⁷OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁷OH, azeotropic distillation; (viii) N₂, 120 °C, then R⁸OH, HCl, 90 °C, then R⁸OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁸OH, azeotropic distillation; (ix) N₂, 120 °C, then R⁹OH, HCl, 90 °C, then R⁹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁹OH, azeotropic distillation; (x) N₂, 120 °C, then R¹⁰OH, HCl, 90 °C, then R¹⁰OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R¹⁰OH, azeotropic distillation; (xi) N₂, 120 °C, then R¹¹OH, HCl, 90 °C, then R¹¹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R¹¹OH, azeotropic distillation; (xii) N₂, 120 °C, then R¹²OH, HCl, 90 °C, then R¹²OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R¹²OH, azeotropic distillation; (xiii) N₂, 120 °C, then R¹³OH, HCl, 90 °C, then R¹³OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R¹³OH, azeotropic distillation; (xiv) N₂, 120 °C, then R¹⁴OH, HCl, 90 °C, then R¹⁴OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R¹⁴OH, azeotropic distillation; (xv) N₂, 120 °C, then R¹⁵OH, HCl, 90 °C, then R¹⁵OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R¹⁵OH, azeotropic distillation; (xvi) N₂, 120 °C, then R¹⁶OH, HCl, 90 °C, then R¹⁶OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R¹⁶OH, azeotropic distillation; (xvii) N₂, 120 °C, then R¹⁷OH, HCl, 90 °C, then R¹⁷OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R¹⁷OH, azeotropic distillation; (xviii) N₂, 120 °C, then R¹⁸OH, HCl, 90 °C, then R¹⁸OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R¹⁸OH, azeotropic distillation; (xix) N₂, 120 °C, then R¹⁹OH, HCl, 90 °C, then R¹⁹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R¹⁹OH, azeotropic distillation; (xx) N₂, 120 °C, then R²⁰OH, HCl, 90 °C, then R²⁰OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R²⁰OH, azeotropic distillation; (xxi) N₂, 120 °C, then R²¹OH, HCl, 90 °C, then R²¹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R²¹OH, azeotropic distillation; (xxii) N₂, 120 °C, then R²²OH, HCl, 90 °C, then R²²OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R²²OH, azeotropic distillation; (xxiii) N₂, 120 °C, then R²³OH, HCl, 90 °C, then R²³OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R²³OH, azeotropic distillation; (xxiv) N₂, 120 °C, then R²⁴OH, HCl, 90 °C, then R²⁴OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R²⁴OH, azeotropic distillation; (xxv) N₂, 120 °C, then R²⁵OH, HCl, 90 °C, then R²⁵OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R²⁵OH, azeotropic distillation; (xxvi) N₂, 120 °C, then R²⁶OH, HCl, 90 °C, then R²⁶OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R²⁶OH, azeotropic distillation; (xxvii) N₂, 120 °C, then R²⁷OH, HCl, 90 °C, then R²⁷OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R²⁷OH, azeotropic distillation; (xxviii) N₂, 120 °C, then R²⁸OH, HCl, 90 °C, then R²⁸OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R²⁸OH, azeotropic distillation; (xxix) N₂, 120 °C, then R²⁹OH, HCl, 90 °C, then R²⁹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R²⁹OH, azeotropic distillation; (xxx) N₂, 120 °C, then R³⁰OH, HCl, 90 °C, then R³⁰OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R³⁰OH, azeotropic distillation; (xxxi) N₂, 120 °C, then R³¹OH, HCl, 90 °C, then R³¹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R³¹OH, azeotropic distillation; (xxxii) N₂, 120 °C, then R³²OH, HCl, 90 °C, then R³²OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R³²OH, azeotropic distillation; (xxxiii) N₂, 120 °C, then R³³OH, HCl, 90 °C, then R³³OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R³³OH, azeotropic distillation; (xxxiv) N₂, 120 °C, then R³⁴OH, HCl, 90 °C, then R³⁴OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R³⁴OH, azeotropic distillation; (xxxv) N₂, 120 °C, then R³⁵OH, HCl, 90 °C, then R³⁵OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R³⁵OH, azeotropic distillation; (xxxvi) N₂, 120 °C, then R³⁶OH, HCl, 90 °C, then R³⁶OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R³⁶OH, azeotropic distillation; (xxxvii) N₂, 120 °C, then R³⁷OH, HCl, 90 °C, then R³⁷OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R³⁷OH, azeotropic distillation; (xxxviii) N₂, 120 °C, then R³⁸OH, HCl, 90 °C, then R³⁸OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R³⁸OH, azeotropic distillation; (xxxix) N₂, 120 °C, then R³⁹OH, HCl, 90 °C, then R³⁹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R³⁹OH, azeotropic distillation; (xl) N₂, 120 °C, then R⁴⁰OH, HCl, 90 °C, then R⁴⁰OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁴⁰OH, azeotropic distillation; (xli) N₂, 120 °C, then R⁴¹OH, HCl, 90 °C, then R⁴¹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁴¹OH, azeotropic distillation; (xlii) N₂, 120 °C, then R⁴²OH, HCl, 90 °C, then R⁴²OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁴²OH, azeotropic distillation; (xliii) N₂, 120 °C, then R⁴³OH, HCl, 90 °C, then R⁴³OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁴³OH, azeotropic distillation; (xliv) N₂, 120 °C, then R⁴⁴OH, HCl, 90 °C, then R⁴⁴OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁴⁴OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁴⁵OH, HCl, 90 °C, then R⁴⁵OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁴⁵OH, azeotropic distillation; (xlvi) N₂, 120 °C, then R⁴⁶OH, HCl, 90 °C, then R⁴⁶OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁴⁶OH, azeotropic distillation; (xlvii) N₂, 120 °C, then R⁴⁷OH, HCl, 90 °C, then R⁴⁷OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁴⁷OH, azeotropic distillation; (xlviii) N₂, 120 °C, then R⁴⁸OH, HCl, 90 °C, then R⁴⁸OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁴⁸OH, azeotropic distillation; (xlvix) N₂, 120 °C, then R⁴⁹OH, HCl, 90 °C, then R⁴⁹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁴⁹OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁵⁰OH, HCl, 90 °C, then R⁵⁰OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁵⁰OH, azeotropic distillation; (xli) N₂, 120 °C, then R⁵¹OH, HCl, 90 °C, then R⁵¹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁵¹OH, azeotropic distillation; (xlii) N₂, 120 °C, then R⁵²OH, HCl, 90 °C, then R⁵²OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁵²OH, azeotropic distillation; (xliii) N₂, 120 °C, then R⁵³OH, HCl, 90 °C, then R⁵³OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁵³OH, azeotropic distillation; (xliv) N₂, 120 °C, then R⁵⁴OH, HCl, 90 °C, then R⁵⁴OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁵⁴OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁵⁵OH, HCl, 90 °C, then R⁵⁵OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁵⁵OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁵⁶OH, HCl, 90 °C, then R⁵⁶OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁵⁶OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁵⁷OH, HCl, 90 °C, then R⁵⁷OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁵⁷OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁵⁸OH, HCl, 90 °C, then R⁵⁸OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁵⁸OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁵⁹OH, HCl, 90 °C, then R⁵⁹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁵⁹OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁶⁰OH, HCl, 90 °C, then R⁶⁰OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁶⁰OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁶¹OH, HCl, 90 °C, then R⁶¹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁶¹OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁶²OH, HCl, 90 °C, then R⁶²OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁶²OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁶³OH, HCl, 90 °C, then R⁶³OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁶³OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁶⁴OH, HCl, 90 °C, then R⁶⁴OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁶⁴OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁶⁵OH, HCl, 90 °C, then R⁶⁵OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁶⁵OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁶⁶OH, HCl, 90 °C, then R⁶⁶OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁶⁶OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁶⁷OH, HCl, 90 °C, then R⁶⁷OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁶⁷OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁶⁸OH, HCl, 90 °C, then R⁶⁸OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁶⁸OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁶⁹OH, HCl, 90 °C, then R⁶⁹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁶⁹OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁷⁰OH, HCl, 90 °C, then R⁷⁰OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁷⁰OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁷¹OH, HCl, 90 °C, then R⁷¹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁷¹OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁷²OH, HCl, 90 °C, then R⁷²OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁷²OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁷³OH, HCl, 90 °C, then R⁷³OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁷³OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁷⁴OH, HCl, 90 °C, then R⁷⁴OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁷⁴OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁷⁵OH, HCl, 90 °C, then R⁷⁵OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁷⁵OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁷⁶OH, HCl, 90 °C, then R⁷⁶OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁷⁶OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁷⁷OH, HCl, 90 °C, then R⁷⁷OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁷⁷OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁷⁸OH, HCl, 90 °C, then R⁷⁸OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁷⁸OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁷⁹OH, HCl, 90 °C, then R⁷⁹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁷⁹OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁸⁰OH, HCl, 90 °C, then R⁸⁰OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁸⁰OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁸¹OH, HCl, 90 °C, then R⁸¹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁸¹OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁸²OH, HCl, 90 °C, then R⁸²OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁸²OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁸³OH, HCl, 90 °C, then R⁸³OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁸³OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁸⁴OH, HCl, 90 °C, then R⁸⁴OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁸⁴OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁸⁵OH, HCl, 90 °C, then R⁸⁵OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁸⁵OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁸⁶OH, HCl, 90 °C, then R⁸⁶OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁸⁶OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁸⁷OH, HCl, 90 °C, then R⁸⁷OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁸⁷OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁸⁸OH, HCl, 90 °C, then R⁸⁸OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁸⁸OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁸⁹OH, HCl, 90 °C, then R⁸⁹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁸⁹OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁹⁰OH, HCl, 90 °C, then R⁹⁰OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁹⁰OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁹¹OH, HCl, 90 °C, then R⁹¹OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁹¹OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁹²OH, HCl, 90 °C, then R⁹²OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁹²OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁹³OH, HCl, 90 °C, then R⁹³OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁹³OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁹⁴OH, HCl, 90 °C, then R⁹⁴OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁹⁴OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁹⁵OH, HCl, 90 °C, then R⁹⁵OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁹⁵OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁹⁶OH, HCl, 90 °C, then R⁹⁶OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁹⁶OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁹⁷OH, HCl, 90 °C, then R⁹⁷OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁹⁷OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁹⁸OH, HCl, 90 °C, then R⁹⁸OH, HCl, CH₃OH, NaOH, CN, 60 °C, then R⁹⁸OH, azeotropic distillation; (xlv) N₂, 120 °C, then R⁹⁹OH, HCl, 90 °C, then R⁹⁹

ation, of NMR selectivity are currently under investigation and will be reported in due course.

4. Experimental

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. THF, CH₂Cl₂ and CH₃OH were dried under the argon system. Toluene and Et₂O were dried by distillation over Na/benzophenone. Chromatography reagents were obtained from silica gel 60 (Silica Gel 60, 540–400 mesh), Petrosilum either refers to petalines with a boiling point range of 30–60 °C. Reported melting points are uncorrected. NMR spectra were recorded on a Varian-Gemini 100 MHz spectrometer. Chemical shifts are reported as δ values with tetramethylsilane (TMS), employed as the internal standard. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA.

4.1. General procedure A: Preparation of hydrochloride salts

All of the compounds were converted into the hydrochloride salts for biological testing, as well as for storage and handling purposes. The base (50–100 mg) was dissolved in a minimum amount of Et₂O (1–2 mL) and added to a saturated ethereal solution (10 mL) of anhydrous hydrogen chloride. The hydrochloride salts crystallized and were washed with Et₂O (3 × 2 mL) and purified by titration with NaOH and ethyl acetate. Fractional volumes of water could not be prevented, despite vigorous drying (110 °C, 1 h) under vacuum (0.60 mmHg). All compounds were homogeneous by thin-layer chromatography (CHCl₃/CH₂Cl₂/CH₃OH, 10:9:1).

4.2. General procedure B: Esterification of nitriles

The nitrile 7 or 9 (5.2 mmol) in an aqueous solution of sulfuric acid (6.5 mL, H₂SO₄/H₂O, 1:1) was heated in an oil bath at 120 °C for 1.5 h. The flask was then equipped with a Dean-Stark trap and excess alcohol was added. The water was azeotropically removed over 4 h and alcohol was added as needed. The reaction was heated to reflux overnight, then the reaction mixture was allowed to come to room temperature and excess alcohol was removed under reduced pressure. The flask was then cooled in an ice bath and the acid was neutralized to a pH of 10 with 1 N NaOH. The aqueous layer was extracted with Et₂O (3 × 75 mL). The combined organic fractions were dried (Na₂SO₄) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (CHCl₃/CH₂Cl₂/OH/NH₄OH, 90:9:1) to afford the esters 8a–g and 10a–c.

4.3. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid methyl ester (8a)

General procedure B. This compound was obtained as a yellow solid (150 mg, 56% yield) and converted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 196–198 °C. ¹H NMR (free base): δ 7.45 (d, 1H, *J* = 2.4 Hz), 7.40 (d, 1H, *J* = 8.4 Hz), 7.21

(dd, 1H, *J* = 2.4, 8.4 Hz), 3.67 (s, 3H), 2.8 (br s, 1H), 2.55 (d, 1H, *J* = 2.8 Hz), 2.40 (s, 3H), 2.18 (t, 2H, *J* = 10.8 Hz), 1.98 (t, 2H, *J* = 10.8 Hz). ¹³C NMR (free base): δ 174.8, 119.9, 172.5, 131.1, 140.3, 128.7, 125.3, 53.2, 52.3, 48.3, 46.1, 33.7. Anal. Calcd for C₁₄H₁₄Cl₂N₂O₂: C, 48.36; H, 5.51; N, 4.63. Found: C, 48.38; H, 5.46; N, 4.69.

4.4. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid propyl ester (8b)

General procedure B. This compound was obtained as an orange oil (210 mg, 58% yield) and converted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 202–201 °C. ¹H NMR (free base): δ 7.47 (d, 1H, *J* = 2.4 Hz), 7.39 (d, 1H, *J* = 8.4 Hz), 7.23 (dd, 1H, *J* = 2.0 Hz, *J* = 8.4 Hz), 4.04 (t, *J* = 6.6 Hz, 2H), 2.79 (br s, 2H), 2.56 (d, 1H, *J* = 1.2 Hz), 2.18 (s, 3H), 2.16 (m, 2H), 1.96 (m, 2H), 1.59 (m, 2H), 0.86 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (free base): δ 173.5, 136.6, 131.2, 130.4, 128.2, 125.4, 66.8, 51.2, 48.3, 46.1, 33.6, 11.8, 10.3. Anal. Calcd for C₁₆H₁₆Cl₂N₂O₂: C, 49.95; H, 6.29; N, 3.64. Found: C, 50.19; H, 6.06; N, 3.70.

4.5. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid isopropyl ester (8c)

General procedure B. This compound was obtained as an orange oil (134 mg, 39% yield) and converted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 221–223 °C. ¹H NMR (free base): δ 7.47 (d, 1H, *J* = 2.0 Hz), 7.40 (d, 1H, *J* = 8.8 Hz), 7.22 (dd, 1H, *J* = 2.0 Hz, *J* = 8.8 Hz), 5.02 (m, 1H), 2.82 (br s, 2H), 2.54 (d, *J* = 12.8 Hz, 1H), 2.30 (s, 3H), 2.16 (m, 2H), 1.96 (m, 2H), 1.17 (d, *J* = 6.0 Hz, 6H). ¹³C NMR (free base): δ 172.8, 132.6, 131.2, 130.4, 128.2, 125.3, 66.7, 53.2, 48.2, 46.0, 33.5, 21.5. Anal. Calcd for C₁₆H₁₆Cl₂N₂O₂: C, 49.95; H, 6.29; N, 3.64. Found: C, 49.81; H, 6.26; N, 3.65.

4.6. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid butyl ester (8d)

General procedure B. This compound was obtained as an orange oil (200 mg, 54% yield) and converted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 177–179 °C. ¹H NMR (free base): δ 7.47 (d, 1H, *J* = 2.0 Hz), 7.39 (d, 1H, *J* = 8.8 Hz), 7.22 (dd, 1H, *J* = 2.4, 8.8 Hz), 4.07 (t, *J* = 6.3 Hz, 1H), 2.77 (br s, 2H), 2.54 (d, *J* = 13.2 Hz, 1H), 2.27 (s, 3H), 2.15 (t, *J* = 10.8 Hz, 2H), 1.94 (t, *J* = 11.2 Hz, 2H), 1.55 (m, *J* = 6.8 Hz, 2H), 1.28 (m, *J* = 7.5 Hz, 2H), 0.878 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (free base): δ 173.4, 143.1, 132.6, 131.1, 130.3, 128.2, 125.3, 65.0, 53.2, 48.3, 46.1, 33.6, 30.4, 19.9, 13.5. Anal. Calcd for C₁₇H₁₆Cl₂N₂O₂: C, 51.20; H, 6.57; N, 3.51. Found: C, 51.23; H, 6.54; N, 3.52.

4.7. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid sec-butyl ester (8e)

General procedure B. This compound was obtained as an orange oil (140 mg, 35% yield) and converted into

a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 193–200 °C. ¹H NMR (free base): δ 7.45 (d, 1H, *J* = 2.4 Hz), 7.39 (d, 1H, *J* = 8.4 Hz), 7.21 (dd, 1H, *J* = 2.4, 8.4 Hz), 1.83 (m, 1H), 1.80 (br s, 2H), 2.56 (d, *J* = 12.8 Hz, 1H), 2.30 (s, 3H), 2.21 (m, 2H), 1.96 (m, 2H), 1.50 (m, 2H), 1.13 (d, *J* = 6.4 Hz, 3H), 0.78 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (free base): δ 173.0, 142.6, 131.1, 130.3, 128.3, 125.3, 53.7, 48.3, 46.1, 33.5, 28.6, 19.2, 9.6. Anal. Calcd for C₁₇H₁₆Cl₂N₂O₂: C, 51.63; H, 6.35; N, 3.68. Found: C, 51.51; H, 6.27; N, 3.68.

4.8. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid pentyl ester (8f)

General procedure B. This compound was obtained as a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 158–160 °C. ¹H NMR (free base): δ 7.30 (d, *J* = 2.8 Hz, 1H), 7.35 (d, *J* = 11.6 Hz, 1H), 7.18 (dd, *J* = 2.8, 11.4 Hz, 1H), 1.01 (t, *J* = 8.8 Hz, 2H), 2.76 (d, *J* = 14.4 Hz, 2H), 2.51 (d, *J* = 16.8 Hz, 2H), 2.24 (s, 3H), 2.13 (t, *J* = 15.2 Hz, 2H), 1.91 (t, *J* = 14.1 Hz, 2H), 1.52 (m, *J* = 9.2 Hz, 2H), 1.21 (m, 4H), 0.82 (t, *J* = 9.2 Hz, 3H). ¹³C NMR (free base): δ 173.1, 142.4, 132.6, 131.3, 130.3, 125.1, 125.2, 65.1, 51.0, 48.1, 45.6, 33.0, 28.1, 28.0, 22.1, 13.9. Anal. Calcd for C₁₈H₁₈Cl₂N₂O₂: C, 52.37; H, 6.84; N, 3.39. Found: C, 51.95; H, 6.52; N, 3.21.

4.9. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid 3-methyl-butyl ester (8g)

General procedure B. This compound was obtained as an orange oil (250 mg, 70% yield) and converted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 176–178 °C. ¹H NMR (free base): δ 7.47 (d, *J* = 2.8 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.22 (dd, *J* = 2.2 Hz, *J* = 8.6 Hz, 1H), 4.10 (t, *J* = 6.6 Hz, 2H), 2.76 (br s, 2H), 2.54 (d, *J* = 12.8 Hz, 2H), 2.26 (s, 3H), 2.13 (m, 2H), 1.93 (m, 2H), 1.45 (m, 2H), 0.90 (m, 1H), 0.86 (d, *J* = 8.6 Hz, 6H). ¹³C NMR (free base): δ 173.6, 132.6, 131.2, 130.3, 128.3, 125.4, 63.8, 53.2, 48.3, 46.1, 37.1, 33.7, 25.0, 22.3. Anal. Calcd for C₁₈H₁₈Cl₂N₂O₂: C, 54.77; H, 6.64; N, 3.55. Found: C, 54.83; H, 6.63; N, 3.59.

4.10. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid benzyl ester (8h)

A flask containing oven-dried 4 Å molecular sieves (500 mg) was charged with DMF (110 mL), potassium *t*-butoxide (9.5 mol %), and THF (1 mL). The mixture was allowed to stir under an atmosphere of nitrogen for 15 min. The methyl ester (1 mmol) and benzyl alcohol (1.5 mmol) were dissolved in THF (0.5 mL) and added to the reaction mixture via cannula. The reaction was allowed to stir at room temperature and was monitored by TLC (CHCl₃/CH₂Cl₂/OH, 19:1). The mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified using column chromatography (CHCl₃/CH₂Cl₂/OH, 19:1) and obtained as a pale yellow solid (97 mg, 51% yield). The base was com-

verted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 156–158 °C. ¹H NMR (free base): δ 7.43 (d, 1H, *J* = 2.4 Hz), 7.40 (d, 1H, *J* = 8.4 Hz), 7.30 (m, 1H), 7.19 (m, 1H), 7.18 (dd, *J* = 2.4, 8.4 Hz, 1H), 5.10 (s, 1H), 2.76 (d, *J* = 8.8 Hz, 2H), 2.56 (d, *J* = 12.4 Hz, 2H), 2.24 (s, 3H), 1.70 (t, 1H, *J* = 10.8 Hz, 2H), 1.95 (t, *J* = 10.8 Hz, 2H), 1.71 (m, 2H), 1.78 (s, 1H), 1.25 (t, 6H), 51.1, 48.6, 46.1, 33.6. Anal. Calcd for C₁₉H₁₈Cl₂N₂O₂: C, 56.68; H, 5.42. Found: C, 56.51; H, 5.53; N, 3.39.

4.11. General procedure C: Reductive amination of 6 with alkylaryl amines

In a three-necked round-bottomed flask containing 3 N HCl (160 mL) at 50 °C was added the diethyl 6 (10 mmol) and the mixture was allowed to stir overnight. The acid mixture was allowed to cool to room temperature and then extracted with Et₂O (300 mL). The ethereal layer was washed with saturated NaHCO₃ (150 mL) and dried (Na₂SO₄). The Et₂O was removed under reduced pressure. The resulting residue was dissolved in dry methanol (52 mL) and then the alkylaryl amine hydrochloride (21 mmol) was added, followed by the addition of NaH/CN (9.4 mmol) and the mixture was allowed to stir for 48 h under an atmosphere of nitrogen. The methanol was removed under reduced pressure and the residue was treated with saturated NaHCO₃ (160 mL) and extracted with Et₂O (38–100 mL). The combined organic fractions were dried (Na₂SO₄) and the solvent was removed under reduced pressure. The residue was purified by chromatography (CHCl₃/CH₂Cl₂/OH, 39:1) to afford 9a–c, respectively.

4.12. 1-Benzyl-4-(3,4-dichlorophenyl)-piperidine-4-carbonitrile (9a)

General procedure C. This compound was obtained as a yellow oil (2.0 g, 56% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 271–274 °C (dec.). ¹H NMR (free base): δ 7.39 (d, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.34 (m, 4H), 7.29 (t, *J* = 4.4 Hz, 1H), 3.61 (s, 2H), 3.02 (d, *J* = 10.8 Hz, 2H), 2.51 (s, 2H), 2.08 (s, 4H). ¹³C NMR (free base): δ 140.4, 137.7, 133.1, 132.2, 130.8, 129.9, 128.2, 127.8, 127.2, 125.1, 121.1, 62.6, 50.3, 42.2, 36.3. Anal. Calcd for C₁₆H₁₄N₂Cl₂: C, 58.40; H, 3.16; N, 7.17. Found: C, 58.24; H, 4.94; N, 7.08.

4.13. 4-(3,4-Dichlorophenyl)-1-phenethyl-piperidine-4-carbonitrile (9b)

General procedure C. This compound was obtained (CHCl₃) as a white solid (120 mg, 32% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 244–250 °C (dec.). ¹H NMR (free base): δ 7.60 (d, *J* = 2.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.35 (dd, *J* = 2.4, 8.6 Hz, 1H), 7.30 (m, 2H), 7.21 (m, 1H), 3.11 (d, *J* = 12.8 Hz, 2H), 2.83 (m, 2H), 2.71 (m, 2H), 2.55 (m, 2H), 2.10 (d, *J* = 8.6 Hz, 2H), 2.08 (m, 2H). ¹³C NMR (free base): δ

0.90) (m, 3H, 0.54 ttt, 2H, 0.13 ttt, 3H) ¹C NMR (free base): δ 173.5, 143.9, 132.6, 131.2, 130.1, 128.1, 125.3, 68.6, 61.2, 51.1, 48.7, 33.5, 24.6, 8.7, 4.0 (3.7). Anal. Calcd. for C₁₇H₂₅NO₃Cl₂HCl (214.0): C, 54.4%; H, 6.22%; N, 3.35%; Found: C, 52.1%; H, 6.05%; N, 3.51.

4.27. 4-(3,4-Dichlorophenyl)-1-(3-fluoropropyl)-piperidine-4-carboxylic acid ethyl ester (10b)

General procedure D. This compound was obtained as an orange-brown solid (95 mg, 76% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 209 °C. ¹H NMR (free base): δ 7.47 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.22 (dd, *J* = 2.0, 8.4 Hz, 1H), 4.89 (dd, *J* = 4.7, 6.1 Hz, 2H), 3.60 (t, 2H), 4.14 (q, *J* = 7.6 Hz, 2H), 2.85 (d, 10.8 Hz, 2H), 2.55 (d, *J* = 13.2 Hz, 2H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.18 (t, *J* = 11.2 Hz, 2H), 1.90 (m, 4H), 1.20 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (free base): δ 173.1, 143.1, 132.5, 131.0, 130.3, 128.1, 125.3, 82.4, 64.0, 61.4, 58.6, 51.3, 48.6, 33.5, 28.9, 27.8, 13.9. Anal. Calcd. for C₁₇H₂₅NO₃Cl₂ (214.1): C, 54.4%; H, 6.22%; N, 3.35%; Found: C, 50.64%; H, 5.87%; N, 3.47. Found: C, 50.62%; H, 5.84%; N, 3.44.

4.28. 4-(3,4-Dichlorophenyl)-1-(4-hydroxypropyl)-piperidine-4-carboxylic acid ethyl ester (10a)

General procedure D. This compound was obtained as a yellow oil (170 mg, 70% yield) and was converted into the hydrochloride salt (Section 4.1), which was obtained as an orange solid, mp 184–186 °C. ¹H NMR (free base): δ 7.45 (d, *J* = 2.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.21 (dd, *J* = 2.4, 8.8 Hz, 1H), 4.36 (s, 1H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.81 (t, *J* = 2.1 Hz, 2H), 3.06 (br s, 2H), 2.67 (t, *J* = 6.0 Hz, 2H), 2.57 (d, *J* = 13.2 Hz, 2H), 2.27 (m, 2H), 1.95 (t, *J* = 9.2 Hz, 2H), 1.77 (m, 2H), 1.19 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (free base): δ 173.2, 142.7, 132.2, 131.4, 130.5, 128.1, 125.3, 64.0, 61.4, 58.6, 51.3, 48.6, 33.3, 27.0, 14.0. Anal. Calcd. for C₁₇H₂₅NO₃Cl₂HCl (214.1): C, 51.47%; H, 6.10%; N, 3.53%; Found: C, 51.31%; H, 6.15%; N, 3.56.

4.29. 1-(3-Chloropropyl)-4-(3,4-dichlorophenyl)-piperidine-4-carboxylic acid ethyl ester (10a)

The alcohol 10a (150 mg, 0.42 mmol) was dissolved in CH₂Cl₂ (3.2 mL) and cooled to 0 °C under an atmosphere of nitrogen. Methanesulfonyl chloride (10 μL, 0.44 mmol) was added, followed by the addition of triethylamine (90 μL, 0.62 mmol). The reaction mixture was allowed to stir for 2 h. The mixture was then allowed to warm to room temperature and stirred for an additional 48 h. The crude product was purified using column chromatography (CHCl₃/CH₂OH, 1:3) to afford a colorless oil (97 mg, 61%). This compound was converted to the hydrochloride salt to afford a white solid, mp 205 °C. ¹H NMR (free base): δ 7.47 (d, *J* = 1.6 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.22 (dd, *J* = 2.0, 8.4 Hz, 1H), 4.13 (q, *J* = 7.6 Hz, 2H), 3.59 (t, *J* = 6.4 Hz, 2H), 2.81 (d, *J* = 11.2 Hz, 2H), 2.53 (d, *J* = 12.8 Hz, 2H), 2.45 (t, *J* = 6.8 Hz, 2H), 2.16 (t, *J* = 11.2 Hz, 2H), 1.92 (m, 4H), 1.19 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (free base):

δ 173.5, 143.2, 132.6, 131.1, 130.1, 128.2, 125.4, 68.4, 61.1, 50.3, 48.8, 33.3, 24.7, 30.0, 11.0. Anal. Calcd. for C₁₇H₂₅NO₃Cl₂HCl (214.0): C, 54.4%; H, 6.22%; N, 3.35%; Found: C, 49.21%; H, 5.76%; N, 3.15.

4.30. 1-(3,4-Dichlorophenyl)-1-[3-(tri-*n*-butylstannyl)prop-2-ynyl]-4-(3-chloropropyl)-piperidine-4-carboxylic acid ethyl ester (10a)

General procedure D. with 3-(tri-*n*-butylstannyl)prop-2-ynyl ethyl ester. This compound was obtained as a yellow oil (185 mg, 84% yield). ¹H NMR (free base): δ 7.44 (d, *J* = 2.4 Hz, 1H), 7.38 (d, *J* = 8.9 Hz, 1H), 7.22 (dd, *J* = 2.4, 8.6 Hz, 1H), 6.11 (d, *J* = 19.2 Hz, 1H), 5.99 (dd, *J* = 18.8, 6.0 Hz, 1H), 4.13 (q, *J* = 6.8 Hz, 2H), 3.03 (d, *J* = 5.6 Hz, 2H), 2.85 (d, *J* = 8.8 Hz, 2H), 2.55 (d, *J* = 13.2 Hz, 2H), 2.17 (t, *J* = 10.8 Hz, 2H), 1.93 (t, *J* = 11.2 Hz, 2H), 1.50 (m, 6H), 1.30 (m, 6H), 1.49 (t, *J* = 7.2 Hz, 3H), 0.910 (3H, 18H). ¹³C NMR: δ 173.3, 145.0, 143.2, 132.6, 132.3, 131.1, 130.3, 128.2, 125.3, 65.5, 61.1, 51.0, 48.7, 33.7, 29.0, 27.2, 13.9, 13.6, 9.4.

4.31. 4-(3,4-Dichlorophenyl)-1-[3-(tri-*n*-butylstannyl)prop-2-ynyl]-piperidine-4-carboxylic acid ethyl ester (10b)

The stannyl derivative 10b (160 mg, 0.10 mmol) was dissolved in CHCl₃ (0.6 mL), and the resulting mixture was cooled to 0 °C. A solution of iodine in CHCl₃ (0.1 N) was then added dropwise to the stirred mixture until a color change resulted. The solution was allowed to come to room temperature and stirred for an additional 4 h. The reaction mixture was washed with brine (5 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure and the crude product was purified by column chromatography (Et₂O/hexanes, 1:1) to give the product as a yellow oil (21 mg, 44% yield). This compound was converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 219–221 °C (dec). ¹H NMR (free base): δ 7.46 (d, *J* = 2.4 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.21 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.57 (d, *J* = 6.8, 14.8 Hz, 1H), 6.25 (d, *J* = 14.4 Hz, 1H), 4.13 (q, *J* = 6.8 Hz, 2H), 2.93 (dd, *J* = 1.6, 6.8 Hz, 2H), 2.81 (d, *J* = 11.2 Hz, 2H), 2.54 (d, *J* = 13.2 Hz, 2H), 2.15 (t, *J* = 11.2 Hz, 2H), 1.90 (m, 2H), 1.19 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (free base): δ 173.4, 142.8, 132.7, 131.2, 130.4, 128.2, 125.3, 78.6, 62.7, 61.2, 50.9, 48.6, 33.6, 14.9. Anal. Calcd. for C₁₇H₂₅NO₃Cl₂HCl (214.0): C, 49.26%; H, 4.19%; N, 2.78%; Found: C, 49.42%; H, 4.18%; N, 2.75.

4.32. 1-[4-(3,4-Dichlorophenyl)-1-methyl-piperidin-4-yl]-ethanone (11)

To a solution of methyl magnesium bromide (0.17 mL, 1.1 mmol) in dry ether (0.2 mL) stirring under an atmosphere of nitrogen at 0 °C was added a solution of the ester 5a (20 mg, 0.37 mmol) in dry ether that had been cooled to 0 °C under an atmosphere of nitrogen. The mixture was allowed to stir for 20 min, and then allowed to return to room temperature and continue to stir overnight. Wet ether was added to the solution, followed by a deionized

water wash. The organic layer was dried (Na₂SO₄), and the solvent was removed under reduced pressure. The residue was purified by chromatography (CHCl₃/CH₂OH, 1:1) to give a yellow oil (10 mg, 65% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 254–256 °C (dec). ¹H NMR (free base): δ 7.43 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 3.4 Hz, 1H), 7.15 (dd, *J* = 2.4, 8.2 Hz, 1H), 2.60 (br s, 2H), 2.45 (t, *J* = 12.8 Hz, 2H), 2.25 (s, 3H), 2.21 (t, *J* = 10.8 Hz, 2H), 1.95 (s, 3H). ¹³C NMR (free base): δ 198.1, 141.9, 134.0, 131.7, 128.3, 125.7, 54.7, 52.6, 46.0, 32.7, 35.9. Anal. Calcd. for C₁₇H₂₅NO₃Cl₂HCl (214.0): C, 54.64%; H, 6.13%; N, 3.72%. Found: C, 44.91%; N, 3.78%; N, 3.68.

4.33. 4-(3,4-Dichlorophenyl)-1-methyl-piperidin-4-yl-phenylmethanone (12)

To a stirred solution of phenyl magnesium bromide (0.19 mL, 1.2 mmol) in dry ether (0.19 mL) under an atmosphere of nitrogen at 0 °C was added a solution of the nitrile 7 (160 mg, 0.59 mmol) in dry ether that had been cooled to 0 °C under an atmosphere of nitrogen. The mixture was allowed to stir for 20 min, and then allowed to return to room temperature and stirred overnight. Wet ether was added to the solution, followed by a deionized water wash. The organic layer was dried (Na₂SO₄), and the solvent was removed under reduced pressure. The residue was purified by chromatography (CHCl₃/CH₂OH, 2:1) to give a yellow oil (114 mg, 56% yield). This compound was converted to the hydrochloride salt (Section 4.1), which was obtained as a white solid (mp 244–246 °C (dec)). ¹H NMR (free base, 300 MHz): δ 7.51 (d, *J* = 2.1 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.44 (2.2 Hz, 5H), 7.25 (dd, *J* = 2.1, 8.6 Hz, 1H), 2.72 (m, 2H), 2.55 (m, *J* = 2.7, 8.9 Hz, 2H), 2.25 (s, 3H), 2.15 (2.07 Hz, 4H). ¹³C NMR (free base): δ 203.0, 145.5, 137.4, 133.1, 131.7, 131.5, 131.6, 128.7, 128.3, 125.2, 125.6, 52.9, 52.8, 46.0, 35.1. Anal. Calcd. for C₁₇H₂₅NO₃Cl₂HCl (214.0): C, 57.95%; H, 5.58%; N, 3.55%. Found: C, 57.98%; H, 5.34%; N, 3.47.

4.34. 1-[4-(3,4-Dichlorophenyl)-1-methyl-piperidin-4-yl]-ethanol (13)

To a stirred solution of the ketone 8 (100 mg, 0.35 mmol) in methanol (1.7 mL) was added sodium borohydride (13 mg, 0.35 mmol). The mixture was stirred at room temperature under an atmosphere of nitrogen for 2 h. The solvent was removed under reduced pressure, and water was added to the resulting residue, followed by extraction with Et₂O (3 × 5 mL), and the organic extracts were dried (Na₂SO₄). The crude product was purified using chromatography (CHCl₃/CH₂OH, 1:1) to give an off-white solid (69 mg, 89% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 185–187 °C. ¹H NMR (free base): δ 7.44 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.18 (dd, *J* = 2.4, 8.4 Hz, 1H), 3.39 (m, *J* = 6.8 Hz, 1H), 2.86 (d, *J* = 7.6 Hz, 2H), 2.45 (m, 1H), 2.28 (s, 3H), 2.15 (m, 2H), 2.05 (m, 4H), 0.925 (d, *J* = 6.4 Hz, 3H). ¹³C NMR (free base): δ 140.6, 132.6, 130.7, 130.6, 130.1, 128.1, 55.6, 51.7, 51.5, 45.4, 44.7,

3.7, 30.9, 15.0. Anal. Calcd. for C₁₇H₂₅NO₃Cl₂HCl (214.0): C, 50.51%; H, 6.06%; N, 3.71%. Found: C, 50.15%; H, 6.12%; N, 3.76.

4.35. 4-(3,4-Dichlorophenyl)-1-methyl-piperidin-4-yl-methanol (14)

To a suspension of LiAlH₄ (200 mg, 6.5 mmol) in dry Et₂O (33 mL) under an atmosphere of nitrogen was added a solution of the ethyl ester 5 (1.0 g, 3.5 mmol) in dry Et₂O (33 mL). The reaction mixture was stirred at room temperature for 3 h. Wet ether (33 mL) and 1 M NaOH (0.2 mL) were added slowly. A white precipitate began to form and the mixture was allowed to stir for 1 h. The resulting suspension was filtered through Celite, washed with Et₂O and EtOH. The filtrate was filtered and dried to give a white solid (710 mg, 83% yield). This compound was converted to the hydrochloride salt (Section 4.1) to afford a white solid, mp 224–226 °C. ¹H NMR (free base): δ 7.44 (d, *J* = 10 Hz, 1H), 7.43 (d, *J* = 0.1 Hz, 1H), 7.19 (dd, *J* = 2.4, 8.6 Hz, 1H), 3.57 (s, 2H), 2.58 (m, 2H), 2.18 (s, 3H), 2.12 (t, *J* = 14.0 Hz, 2H), 1.46 (m, 2H), 1.81 (s, 3H). ¹³C NMR (free base): δ 144.0, 142.5, 130.3, 130.2, 129.6, 126.8, 71.1, 51.5, 45.9, 41.5, 31.1. Anal. Calcd. for C₁₇H₂₅NO₃Cl₂HCl (214.0): C, 50.26%; H, 5.81%; N, 3.51%. Found: C, 50.01%; H, 5.83%; N, 3.46.

4.36. Acetic acid 4-(3,4-dichlorophenyl)-1-methyl-piperidin-4-yl methyl ester (15)

The alcohol 14 (190 mg, 0.70 mmol) was dried under vacuum and 4-(dimethylamino) pyridine (9 mg, 0.0697 mmol) was added to the flask and flushed with nitrogen. Dry CH₂Cl₂ (12 mL), fresh triethylamine (370 μL, 2.7 mmol), and acetyl chloride (70 μL, 1.04 mmol) were added dropwise at 0 °C. The mixture was allowed to stir on ice for 30 min, and then overnight at room temperature. To the mixture 1 N NaOH was added dropwise to adjust the pH to 10–11, followed by the addition of deionized water (10 mL). The mixture was extracted with CH₂Cl₂ (3 × 15 mL) and the organic layers were dried (Na₂SO₄). The crude product was purified using chromatography (CHCl₃/CH₂OH, 1:1) to give a white solid (110 mg, 65% yield). This compound was converted into the hydrochloride salt (Section 4.1) to afford a white foam. ¹H NMR (free base): δ 7.43 (d, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 6.0 Hz, 1H), 7.18 (dd, *J* = 3.2, 11.4 Hz, 1H), 4.03 (s, 2H), 2.60 (m, 2H), 2.24 (s, 3H), 2.17 (m, 4H), 1.97 (m, 2H), 1.97 (s, 3H). ¹³C NMR (free base): δ 170.5, 143.3, 132.4, 130.4, 130.2, 129.4, 126.5, 71.2, 51.4, 46.6, 39.6, 32.0, 20.7. Anal. Calcd. for C₁₇H₂₅NO₃Cl₂HCl (214.0): C, 47.44%; H, 6.11%; N, 3.69%. Found: C, 47.11%; H, 5.72%; N, 3.35.

4.37. 4-(3,4-Dichlorophenyl)-1-methyl-4-vinyl-piperidine (16)

To a two-necked round-bottom-flask under an atmosphere of nitrogen was added a solution of vinyl chloride (280 μL, 3.2 mmol) in dichloromethane (4.9 mL). The solution was cooled to 78 °C. A solution of dimethylsulfoxide (450 μL, 6.3 mmol) in dichloromethane

Synthesis and Biological Evaluation of Meperidine Analogues at Monoamine Transporters

Y. Li, A. B. Leach, J. G. Roden, S. M. Y. Lee, D. A. Clark, J. A. Smith, L. C. E. K. Lee, and M. J. Cook

Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60607-7159, United States; Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60607-7159, United States; Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60607-7159, United States; Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60607-7159, United States; Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60607-7159, United States; Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60607-7159, United States

A series of *N*-substituted meperidine analogues were synthesized and their binding affinities were determined at the DAT, SERT, and NET as well as μ -opioid receptors. Generally the analogues exhibited increased affinity for the DAT and SERT relative to meperidine but exhibited low binding affinity for the NET. The 2-(*trifluoromethyl*) derivative **7f** was the most potent ligand at the SERT ($K_i = 0.0072$ nM) and was the most selective ligand for the SERT over the DAT (DAT/SERT = 261). The 3,4-dichlorophenyl derivative **7e** was the most potent ligand at the DAT ($K_i = 0.125$ nM) and was the most selective ligand for the DAT over the SERT (DAT/SERT = 168). These compounds, the 3,4-dichlorophenyl derivative **7e** and the 2-naphthyl analogue **8f** and **7f** were identified that were more potent at the DAT than meperidine and that exhibited well-defined biphasic dopamine uptake inhibition similar to meperidine. However, none of the analogues tested produced locomotor effects or substituted for cocaine in drug discrimination studies, suggesting that the μ -opioid effects of these analogues may contribute to the poor effects observed *in vivo*.

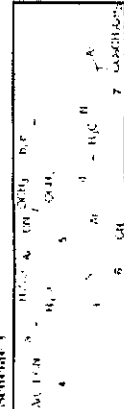
Introduction

Cocaine (1) binding at the dopamine transporter (DAT) has been well established.¹⁻¹¹ Initially, specific binding sites were identified in rodent brain that bind [³H]cocaine at a single saturable site.¹⁻³ Subsequent studies using rodent,³ human,⁴ and nonhuman primate^{5,6} brain tissue preparations (striatum and caudate putamen) later provided evidence that suggests that cocaine binding at the dopamine transporter is heterogeneous. Two distinct binding sites on the dopamine transporter have been proposed: a high affinity and a low affinity site.⁷⁻¹¹ These sites are termed high and low based upon the relative affinity of cocaine for these sites. The phenyltropane analogues of cocaine, specifically WLS 35,425 (2a), WIN 35,065-2 (2b), and WIN 35,061 (2c), in addition to several other cocaine-like compounds, also have binding curves that are better fit with a two-site than a one-site model.¹² However, it is uncertain if these compounds interact at the high and low affinity site in a fashion similar to that of cocaine. It may be possible for compounds other than cocaine to have low affinity for the high affinity site and vice versa. Also, naturally DAT inhibitors such as marindone (10) and CHR 12508¹³ exhibit only single site affinity for the DAT.

A strong correlation between binding affinity at the dopamine transporter (DAT) and potency for reinforcing effects among cocaine (1) and its analogues has been reported.¹⁴ For other effects of cocaine and its ana-

¹ To whom correspondence should be addressed. Phone: 773/508-7375; Fax: 773/508-7376; E-mail: mcook@uic.edu.
² Present address: Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60607-7159, United States.
³ Present address: Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60607-7159, United States.

Scheme 1



Reagents and conditions: (a) NaH, THF, 0 °C, 1 h; (b) H₂O, 1 h; (c) H₂O, 1 h; (d) H₂O, 1 h; (e) H₂O, 1 h; (f) H₂O, 1 h; (g) H₂O, 1 h; (h) H₂O, 1 h; (i) H₂O, 1 h; (j) H₂O, 1 h; (k) H₂O, 1 h; (l) H₂O, 1 h; (m) H₂O, 1 h; (n) H₂O, 1 h; (o) H₂O, 1 h; (p) H₂O, 1 h; (q) H₂O, 1 h; (r) H₂O, 1 h; (s) H₂O, 1 h; (t) H₂O, 1 h; (u) H₂O, 1 h; (v) H₂O, 1 h; (w) H₂O, 1 h; (x) H₂O, 1 h; (y) H₂O, 1 h; (z) H₂O, 1 h; (aa) H₂O, 1 h; (ab) H₂O, 1 h; (ac) H₂O, 1 h; (ad) H₂O, 1 h; (ae) H₂O, 1 h; (af) H₂O, 1 h; (ag) H₂O, 1 h; (ah) H₂O, 1 h; (ai) H₂O, 1 h; (aj) H₂O, 1 h; (ak) H₂O, 1 h; (al) H₂O, 1 h; (am) H₂O, 1 h; (an) H₂O, 1 h; (ao) H₂O, 1 h; (ap) H₂O, 1 h; (aq) H₂O, 1 h; (ar) H₂O, 1 h; (as) H₂O, 1 h; (at) H₂O, 1 h; (au) H₂O, 1 h; (av) H₂O, 1 h; (aw) H₂O, 1 h; (ax) H₂O, 1 h; (ay) H₂O, 1 h; (az) H₂O, 1 h; (ba) H₂O, 1 h; (bb) H₂O, 1 h; (bc) H₂O, 1 h; (bd) H₂O, 1 h; (be) H₂O, 1 h; (bf) H₂O, 1 h; (bg) H₂O, 1 h; (bh) H₂O, 1 h; (bi) H₂O, 1 h; (bj) H₂O, 1 h; (bk) H₂O, 1 h; (bl) H₂O, 1 h; (bm) H₂O, 1 h; (bn) H₂O, 1 h; (bo) H₂O, 1 h; (bp) H₂O, 1 h; (bq) H₂O, 1 h; (br) H₂O, 1 h; (bs) H₂O, 1 h; (bt) H₂O, 1 h; (bu) H₂O, 1 h; (bv) H₂O, 1 h; (bw) H₂O, 1 h; (bx) H₂O, 1 h; (by) H₂O, 1 h; (bz) H₂O, 1 h; (ca) H₂O, 1 h; (cb) H₂O, 1 h; (cc) H₂O, 1 h; (cd) H₂O, 1 h; (ce) H₂O, 1 h; (cf) H₂O, 1 h; (cg) H₂O, 1 h; (ch) H₂O, 1 h; (ci) H₂O, 1 h; (cj) H₂O, 1 h; (ck) H₂O, 1 h; (cl) H₂O, 1 h; (cm) H₂O, 1 h; (cn) H₂O, 1 h; (co) H₂O, 1 h; (cp) H₂O, 1 h; (cq) H₂O, 1 h; (cr) H₂O, 1 h; (cs) H₂O, 1 h; (ct) H₂O, 1 h; (cu) H₂O, 1 h; (cv) H₂O, 1 h; (cw) H₂O, 1 h; (cx) H₂O, 1 h; (cy) H₂O, 1 h; (cz) H₂O, 1 h; (da) H₂O, 1 h; (db) H₂O, 1 h; (dc) H₂O, 1 h; (dd) H₂O, 1 h; (de) H₂O, 1 h; (df) H₂O, 1 h; (dg) H₂O, 1 h; (dh) H₂O, 1 h; (di) H₂O, 1 h; (dj) H₂O, 1 h; (dk) H₂O, 1 h; (dl) H₂O, 1 h; (dm) H₂O, 1 h; (dn) H₂O, 1 h; (do) H₂O, 1 h; (dp) H₂O, 1 h; (dq) H₂O, 1 h; (dr) H₂O, 1 h; (ds) H₂O, 1 h; (dt) H₂O, 1 h; (du) H₂O, 1 h; (dv) H₂O, 1 h; (dw) H₂O, 1 h; (dx) H₂O, 1 h; (dy) H₂O, 1 h; (dz) H₂O, 1 h; (ea) H₂O, 1 h; (eb) H₂O, 1 h; (ec) H₂O, 1 h; (ed) H₂O, 1 h; (ee) H₂O, 1 h; (ef) H₂O, 1 h; (eg) H₂O, 1 h; (eh) H₂O, 1 h; (ei) H₂O, 1 h; (ej) H₂O, 1 h; (ek) H₂O, 1 h; (el) H₂O, 1 h; (em) H₂O, 1 h; (en) H₂O, 1 h; (eo) H₂O, 1 h; (ep) H₂O, 1 h; (eq) H₂O, 1 h; (er) H₂O, 1 h; (es) H₂O, 1 h; (et) H₂O, 1 h; (eu) H₂O, 1 h; (ev) H₂O, 1 h; (ew) H₂O, 1 h; (ex) H₂O, 1 h; (ey) H₂O, 1 h; (ez) H₂O, 1 h; (fa) H₂O, 1 h; (fb) H₂O, 1 h; (fc) H₂O, 1 h; (fd) H₂O, 1 h; (fe) H₂O, 1 h; (ff) H₂O, 1 h; (fg) H₂O, 1 h; (fh) H₂O, 1 h; (fi) H₂O, 1 h; (fj) H₂O, 1 h; (fk) H₂O, 1 h; (fl) H₂O, 1 h; (fm) H₂O, 1 h; (fn) H₂O, 1 h; (fo) H₂O, 1 h; (fp) H₂O, 1 h; (fq) H₂O, 1 h; (fr) H₂O, 1 h; (fs) H₂O, 1 h; (ft) H₂O, 1 h; (fu) H₂O, 1 h; (fv) H₂O, 1 h; (fw) H₂O, 1 h; (fx) H₂O, 1 h; (fy) H₂O, 1 h; (fz) H₂O, 1 h; (ga) H₂O, 1 h; (gb) H₂O, 1 h; (gc) H₂O, 1 h; (gd) H₂O, 1 h; (ge) H₂O, 1 h; (gf) H₂O, 1 h; (gg) H₂O, 1 h; (gh) H₂O, 1 h; (gi) H₂O, 1 h; (gj) H₂O, 1 h; (gk) H₂O, 1 h; (gl) H₂O, 1 h; (gm) H₂O, 1 h; (gn) H₂O, 1 h; (go) H₂O, 1 h; (gp) H₂O, 1 h; (gq) H₂O, 1 h; (gr) H₂O, 1 h; (gs) H₂O, 1 h; (gt) H₂O, 1 h; (gu) H₂O, 1 h; (gv) H₂O, 1 h; (gw) H₂O, 1 h; (gx) H₂O, 1 h; (gy) H₂O, 1 h; (gz) H₂O, 1 h; (ha) H₂O, 1 h; (hb) H₂O, 1 h; (hc) H₂O, 1 h; (hd) H₂O, 1 h; (he) H₂O, 1 h; (hf) H₂O, 1 h; (hg) H₂O, 1 h; (hh) H₂O, 1 h; (hi) H₂O, 1 h; (hj) H₂O, 1 h; (hk) H₂O, 1 h; (hl) H₂O, 1 h; (hm) H₂O, 1 h; (hn) H₂O, 1 h; (ho) H₂O, 1 h; (hp) H₂O, 1 h; (hq) H₂O, 1 h; (hr) H₂O, 1 h; (hs) H₂O, 1 h; (ht) H₂O, 1 h; (hu) H₂O, 1 h; (hv) H₂O, 1 h; (hw) H₂O, 1 h; (hx) H₂O, 1 h; (hy) H₂O, 1 h; (hz) H₂O, 1 h; (ia) H₂O, 1 h; (ib) H₂O, 1 h; (ic) H₂O, 1 h; (id) H₂O, 1 h; (ie) H₂O, 1 h; (if) H₂O, 1 h; (ig) H₂O, 1 h; (ih) H₂O, 1 h; (ii) H₂O, 1 h; (ij) H₂O, 1 h; (ik) H₂O, 1 h; (il) H₂O, 1 h; (im) H₂O, 1 h; (in) H₂O, 1 h; (io) H₂O, 1 h; (ip) H₂O, 1 h; (iq) H₂O, 1 h; (ir) H₂O, 1 h; (is) H₂O, 1 h; (it) H₂O, 1 h; (iu) H₂O, 1 h; (iv) H₂O, 1 h; (iw) H₂O, 1 h; (ix) H₂O, 1 h; (iy) H₂O, 1 h; (iz) H₂O, 1 h; (ja) H₂O, 1 h; (jb) H₂O, 1 h; (jc) H₂O, 1 h; (jd) H₂O, 1 h; (je) H₂O, 1 h; (jf) H₂O, 1 h; (jg) H₂O, 1 h; (jh) H₂O, 1 h; (ji) H₂O, 1 h; (jj) H₂O, 1 h; (jk) H₂O, 1 h; (jl) H₂O, 1 h; (jm) H₂O, 1 h; (jn) H₂O, 1 h; (jo) H₂O, 1 h; (jp) H₂O, 1 h; (jq) H₂O, 1 h; (jr) H₂O, 1 h; (js) H₂O, 1 h; (jt) H₂O, 1 h; (ju) H₂O, 1 h; (jv) H₂O, 1 h; (jw) H₂O, 1 h; (jx) H₂O, 1 h; (jy) H₂O, 1 h; (jz) H₂O, 1 h; (ka) H₂O, 1 h; (kb) H₂O, 1 h; (kc) H₂O, 1 h; (kd) H₂O, 1 h; (ke) H₂O, 1 h; (kf) H₂O, 1 h; (kg) H₂O, 1 h; (kh) H₂O, 1 h; (ki) H₂O, 1 h; (kj) H₂O, 1 h; (kk) H₂O, 1 h; (kl) H₂O, 1 h; (km) H₂O, 1 h; (kn) H₂O, 1 h; (ko) H₂O, 1 h; (kp) H₂O, 1 h; (kq) H₂O, 1 h; (kr) H₂O, 1 h; (ks) H₂O, 1 h; (kt) H₂O, 1 h; (ku) H₂O, 1 h; (kv) H₂O, 1 h; (kw) H₂O, 1 h; (kx) H₂O, 1 h; (ky) H₂O, 1 h; (kz) H₂O, 1 h; (la) H₂O, 1 h; (lb) H₂O, 1 h; (lc) H₂O, 1 h; (ld) H₂O, 1 h; (le) H₂O, 1 h; (lf) H₂O, 1 h; (lg) H₂O, 1 h; (lh) H₂O, 1 h; (li) H₂O, 1 h; (lj) H₂O, 1 h; (lk) H₂O, 1 h; (ll) H₂O, 1 h; (lm) H₂O, 1 h; (ln) H₂O, 1 h; (lo) H₂O, 1 h; (lp) H₂O, 1 h; (lq) H₂O, 1 h; (lr) H₂O, 1 h; (ls) H₂O, 1 h; (lt) H₂O, 1 h; (lu) H₂O, 1 h; (lv) H₂O, 1 h; (lw) H₂O, 1 h; (lx) H₂O, 1 h; (ly) H₂O, 1 h; (lz) H₂O, 1 h; (ma) H₂O, 1 h; (mb) H₂O, 1 h; (mc) H₂O, 1 h; (md) H₂O, 1 h; (me) H₂O, 1 h; (mf) H₂O, 1 h; (mg) H₂O, 1 h; (mh) H₂O, 1 h; (mi) H₂O, 1 h; (mj) H₂O, 1 h; (mk) H₂O, 1 h; (ml) H₂O, 1 h; (mn) H₂O, 1 h; (mo) H₂O, 1 h; (mp) H₂O, 1 h; (mq) H₂O, 1 h; (mr) H₂O, 1 h; (ms) H₂O, 1 h; (mt) H₂O, 1 h; (mu) H₂O, 1 h; (mv) H₂O, 1 h; (mw) H₂O, 1 h; (mx) H₂O, 1 h; (my) H₂O, 1 h; (mz) H₂O, 1 h; (na) H₂O, 1 h; (nb) H₂O, 1 h; (nc) H₂O, 1 h; (nd) H₂O, 1 h; (ne) H₂O, 1 h; (nf) H₂O, 1 h; (ng) H₂O, 1 h; (nh) H₂O, 1 h; (ni) H₂O, 1 h; (nj) H₂O, 1 h; (nk) H₂O, 1 h; (nl) H₂O, 1 h; (nm) H₂O, 1 h; (no) H₂O, 1 h; (np) H₂O, 1 h; (nq) H₂O, 1 h; (nr) H₂O, 1 h; (ns) H₂O, 1 h; (nt) H₂O, 1 h; (nu) H₂O, 1 h; (nv) H₂O, 1 h; (nw) H₂O, 1 h; (nx) H₂O, 1 h; (ny) H₂O, 1 h; (nz) H₂O, 1 h; (oa) H₂O, 1 h; (ob) H₂O, 1 h; (oc) H₂O, 1 h; (od) H₂O, 1 h; (oe) H₂O, 1 h; (of) H₂O, 1 h; (og) H₂O, 1 h; (oh) H₂O, 1 h; (oi) H₂O, 1 h; (oj) H₂O, 1 h; (ok) H₂O, 1 h; (ol) H₂O, 1 h; (om) H₂O, 1 h; (on) H₂O, 1 h; (oo) H₂O, 1 h; (op) H₂O, 1 h; (oq) H₂O, 1 h; (or) H₂O, 1 h; (os) H₂O, 1 h; (ot) H₂O, 1 h; (ou) H₂O, 1 h; (ov) H₂O, 1 h; (ow) H₂O, 1 h; (ox) H₂O, 1 h; (oy) H₂O, 1 h; (oz) H₂O, 1 h; (pa) H₂O, 1 h; (pb) H₂O, 1 h; (pc) H₂O, 1 h; (pd) H₂O, 1 h; (pe) H₂O, 1 h; (pf) H₂O, 1 h; (pg) H₂O, 1 h; (ph) H₂O, 1 h; (pi) H₂O, 1 h; (pj) H₂O, 1 h; (pk) H₂O, 1 h; (pl) H₂O, 1 h; (pm) H₂O, 1 h; (pn) H₂O, 1 h; (po) H₂O, 1 h; (pp) H₂O, 1 h; (pq) H₂O, 1 h; (pr) H₂O, 1 h; (ps) H₂O, 1 h; (pt) H₂O, 1 h; (pu) H₂O, 1 h; (pv) H₂O, 1 h; (pw) H₂O, 1 h; (px) H₂O, 1 h; (py) H₂O, 1 h; (pz) H₂O, 1 h; (qa) H₂O, 1 h; (qb) H₂O, 1 h; (qc) H₂O, 1 h; (qd) H₂O, 1 h; (qe) H₂O, 1 h; (qf) H₂O, 1 h; (qg) H₂O, 1 h; (qh) H₂O, 1 h; (qi) H₂O, 1 h; (qj) H₂O, 1 h; (qk) H₂O, 1 h; (ql) H₂O, 1 h; (qm) H₂O, 1 h; (qn) H₂O, 1 h; (qo) H₂O, 1 h; (qp) H₂O, 1 h; (qq) H₂O, 1 h; (qr) H₂O, 1 h; (qs) H₂O, 1 h; (qt) H₂O, 1 h; (qu) H₂O, 1 h; (qv) H₂O, 1 h; (qw) H₂O, 1 h; (qx) H₂O, 1 h; (qy) H₂O, 1 h; (qz) H₂O, 1 h; (ra) H₂O, 1 h; (rb) H₂O, 1 h; (rc) H₂O, 1 h; (rd) H₂O, 1 h; (re) H₂O, 1 h; (rf) H₂O, 1 h; (rg) H₂O, 1 h; (rh) H₂O, 1 h; (ri) H₂O, 1 h; (rj) H₂O, 1 h; (rk) H₂O, 1 h; (rl) H₂O, 1 h; (rm) H₂O, 1 h; (rn) H₂O, 1 h; (ro) H₂O, 1 h; (rp) H₂O, 1 h; (rq) H₂O, 1 h; (rr) H₂O, 1 h; (rs) H₂O, 1 h; (rt) H₂O, 1 h; (ru) H₂O, 1 h; (rv) H₂O, 1 h; (rw) H₂O, 1 h; (rx) H₂O, 1 h; (ry) H₂O, 1 h; (rz) H₂O, 1 h; (sa) H₂O, 1 h; (sb) H₂O, 1 h; (sc) H₂O, 1 h; (sd) H₂O, 1 h; (se) H₂O, 1 h; (sf) H₂O, 1 h; (sg) H₂O, 1 h; (sh) H₂O, 1 h; (si) H₂O, 1 h; (sj) H₂O, 1 h; (sk) H₂O, 1 h; (sl) H₂O, 1 h; (sm) H₂O, 1 h; (sn) H₂O, 1 h; (so) H₂O, 1 h; (sp) H₂O, 1 h; (sq) H₂O, 1 h; (sr) H₂O, 1 h; (ss) H₂O, 1 h; (st) H₂O, 1 h; (su) H₂O, 1 h; (sv) H₂O, 1 h; (sw) H₂O, 1 h; (sx) H₂O, 1 h; (sy) H₂O, 1 h; (sz) H₂O, 1 h; (ta) H₂O, 1 h; (tb) H₂O, 1 h; (tc) H₂O, 1 h; (td) H₂O, 1 h; (te) H₂O, 1 h; (tf) H₂O, 1 h; (tg) H₂O, 1 h; (th) H₂O, 1 h; (ti) H₂O, 1 h; (tj) H₂O, 1 h; (tk) H₂O, 1 h; (tl) H₂O, 1 h; (tm) H₂O, 1 h; (tn) H₂O, 1 h; (to) H₂O, 1 h; (tp) H₂O, 1 h; (tq) H₂O, 1 h; (tr) H₂O, 1 h; (ts) H₂O, 1 h; (tu) H₂O, 1 h; (tv) H₂O, 1 h; (tw) H₂O, 1 h; (tx) H₂O, 1 h; (ty) H₂O, 1 h; (tz) H₂O, 1 h; (ua) H₂O, 1 h; (ub) H₂O, 1 h; (uc) H₂O, 1 h; (ud) H₂O, 1 h; (ue) H₂O, 1 h; (uf) H₂O, 1 h; (ug) H₂O, 1 h; (uh) H₂O, 1 h; (ui) H₂O, 1 h; (uj) H₂O, 1 h; (uk) H₂O, 1 h; (ul) H₂O, 1 h; (um) H₂O, 1 h; (un) H₂O, 1 h; (uo) H₂O, 1 h; (up) H₂O, 1 h; (uq) H₂O, 1 h; (ur) H₂O, 1 h; (us) H₂O, 1 h; (ut) H₂O, 1 h; (uu) H₂O, 1 h; (uv) H₂O, 1 h; (uw) H₂O, 1 h; (ux) H₂O, 1 h; (uy) H₂O, 1 h; (uz) H₂O, 1 h; (va) H₂O, 1 h; (vb) H₂O, 1 h; (vc) H₂O, 1 h; (vd) H₂O, 1 h; (ve) H₂O, 1 h; (vf) H₂O, 1 h; (vg) H₂O, 1 h; (vh) H₂O, 1 h; (vi) H₂O, 1 h; (vj) H₂O, 1 h; (vk) H₂O, 1 h; (vl) H₂O, 1 h; (vm) H₂O, 1 h; (vn) H₂O, 1 h; (vo) H₂O, 1 h; (vp) H₂O, 1 h; (vq) H₂O, 1 h; (vr) H₂O, 1 h; (vs) H₂O, 1 h; (vt) H₂O, 1 h; (vu) H₂O, 1 h; (vv) H₂O, 1 h; (vw) H₂O, 1 h; (vx) H₂O, 1 h; (vy) H₂O, 1 h; (vz) H₂O, 1 h; (wa) H₂O, 1 h; (wb) H₂O, 1 h; (wc) H₂O, 1 h; (wd) H₂O, 1 h; (we) H₂O, 1 h; (wf) H₂O, 1 h; (wg) H₂O, 1 h; (wh) H₂O, 1 h; (wi) H₂O, 1 h; (wj) H₂O, 1 h; (wk) H₂O, 1 h; (wl) H₂O, 1 h; (wm) H₂O, 1 h; (wn) H₂O, 1 h; (wo) H₂O, 1 h; (wp) H₂O, 1 h; (wq) H₂O, 1 h; (wr) H₂O, 1 h; (ws) H₂O, 1 h; (wt) H₂O, 1 h; (wu) H₂O, 1 h; (wv) H₂O, 1 h; (ww) H₂O, 1 h; (wx) H₂O, 1 h; (wy) H₂O, 1 h; (wz) H₂O, 1 h; (xa) H₂O, 1 h; (xb) H₂O, 1 h; (xc) H₂O, 1 h; (xd) H₂O, 1 h; (xe) H₂O, 1 h; (xf) H₂O, 1 h; (xg) H₂O, 1 h; (xh) H₂O, 1 h; (xi) H₂O, 1 h; (xj) H₂O, 1 h; (xk) H₂O, 1 h; (xl) H₂O, 1 h; (xm) H₂O, 1 h; (xn) H₂O, 1 h; (xo) H₂O, 1 h; (xp) H₂O, 1 h; (xq) H₂O, 1 h; (xr) H₂O, 1 h; (xs) H₂O, 1 h; (xt) H₂O, 1 h; (xu) H₂O, 1 h; (xv) H₂O, 1 h; (xw) H₂O, 1 h; (xx) H₂O, 1 h; (xy) H₂O, 1 h; (xz) H₂O, 1 h; (ya) H₂O, 1 h; (yb) H₂O, 1 h; (yc) H₂O, 1 h; (yd) H₂O, 1 h; (ye) H₂O, 1 h; (yf) H₂O, 1 h; (yg) H₂O, 1 h; (yh) H₂O, 1 h; (yi) H₂O, 1 h; (yj) H<

[illegible]

ál compounds were studied by the HPLC. All alcohols were in SFM of three experiments with a precision of better than 10%. All alcohols and esters are reported with 99 and 99.9% yield and 99.9% percent specific loading in Packed beds tested. The HPLC of three of total nucleotide inhibition.

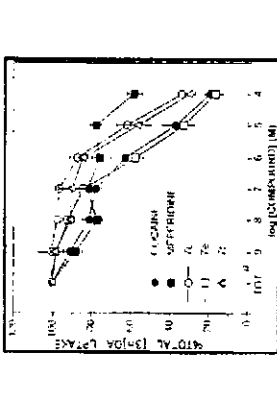


Figure 1. Meperidine like biphasic dopamine uptake inhibition of meperidine derivatives 7c and 7f.

observed for other triazine derivatives, ¹⁰ a biphenyl-*o*-propane analogues, ¹¹ and pyrazine derivatives. ¹² Though the 4-chlorophenyl group also increased the binding affinity of 7c for the SHET, the overall effect was only 15% of that observed for the DAT.

None of the morpholine analogues 7a-f exhibited significant affinity for the NER. The morpholine-ester analogues 7b, 7c, 7e, and 7f exhibited only low micromolar affinity for the NER, while all the other analogues exhibited only partial, if any, inhibition of [3H]muscetol at the highest dose tested (10 μ M).

All of the neperamine derivatives exhibited weak inhibition of dopamine uptake (Table 1). The dopamine uptake-like inhibition produced by most of the neperamine compounds modeled better for a stage state (Fig. 7c) than for a stage state (Fig. 7e). However, several of the compounds (Fig. 7c) modeled better for two states, a short affinity state and a low affinity state, similar to that observed for morphine (as illustrated in Figure 1), the isomers, 7c and 7f, and the combined bidisperse dopamine uptake inhibition with a short affinity dopamine uptake state to that for morphine (Fig. 3), of approximately 20% of the total inhibition. As the percent of total inhibition of uptake that is accounted for by the high affinity component is increased, the

a nonlinear model of the data. The group- $\log K_{\text{D}}$ values from this model, but show the actual binding constants calculated by using each of the components, that is, called better by us as "Back of the envelope," that are listed below. For two sites that one site had a high-affinity uptake component of approximately 20% of the total inhibition, which is similar to both competitive and cooperative. This is consistent with the percentage 18% of the total binding that corresponds to the high affinity component of WIN 35,429 [24]. These results that composition of the phenyl groups of 3 can increase DAT binding affinity with the retention of an ability to differentiate between the high-affinity and low affinity components of the inhibition of DA uptake of the phenyl substitutions examined. The 3-(4-chlorophenyl) (76e) and the 2-naphthyl (77b) groups were identified as important substrates for differentiating between the high and low-affinity components, whose significantly increasing binding affinity relative to nonaromatic alternatives; the 4-chlorophenyl and 1-naphthyl derivatives 76b and 7c exhibited increased DAT binding affinity relative to 3, but were unable to discriminate between the high and low affinity components.

All of the naphthalene nitrile analogues (Fig. 1) prepared in this study exhibited significant ($p < 0.05$) α -opioid receptor affinity relative to naltrexone (3). The ester analogues 7a-f exhibited only slightly reduced affinity for α -opioid receptors relative to 3, but all of the analogues exhibited a marked increase in DAT and SERT selectivity over α -opioid receptors compared to naltrexone. The 3,4-dichlorophenyl analogue 7b (90% DAT selectivity) was found to exhibit the greatest selectivity for the DAT over that of a α -opioid receptor. Table 1 exhibits the 2-methyl-5-naphthyl analogue 7f (68% SERT selectivity) the greatest selectivity for the SERT over α -opioid receptors (Table 1).

Selected compounds 7c, 7e and 7f were evaluated for their locomotor-stimulant activity in mice (Figure 2) using experimental conditions previously reported.¹⁴ Upon the basis of the high selectivity of these compounds for the dopamine and acetylcholine receptors it was believed initially that any behavior or effort's mea-

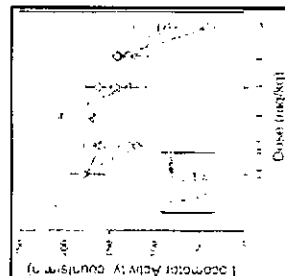


Figure 2. Dose-dependent effects of 7c, 7e, and 7f on spontaneous activity in mice. Ordinate: horizontal locomotor activity counts after drug administration in counts per second. Abscissa: dose of drug in $\mu\text{mol/kg}$ log scale. Each point represents the average effect determined in six mice. The data are from a 30-min period starting 30 min after drug administration. Note that none of the compounds produced a stimulation of activity.

ated by some receptors would be dominated relative to the one-way effects mediated by the transporters. Nevertheless, we injected in and to support activity horizontal active compounds was assessed immediately after injection for a 1-h period. Each data point is a mean $\pm$ SEM of eight subjects. None of the compounds tested produced locomotor stimulant effects similar to cocaine. Instead, each of the compounds decreased locomotor activity across a range of doses from those having no effects to those that virtually eliminated activity.

The compounds 7c (SERT selective) and 7e (DAT selective) that were tested in rats trained to discriminate intraperitoneal injections of cocaine from saline. Rats were trained to discriminate intraperitoneal injections of cocaine (10 mg/kg) from saline injections until reliable performances were obtained according to procedures previously outlined. Compounds were then tested for their effects on cocaine responding for cocaine immediately after injection during training sessions that lasted for a maximum of 20 min. At such time point is typically a mean of six subjects; however, fewer selection data was included if more than half of the subjects tested did not respond. Thus only rats that responded to the highest doses tested. Neither compound 7c nor 7e substituted for cocaine in rats trained to discriminate between cocaine and saline (Figure 3). In addition, no substitution or effects on responding were observed for these compounds, likely due to the low efficacy of these compounds. The low efficacy observed for 7c and 7e may be due to their reduced affinity, which may not be as diminished as originally envisaged. It is unlikely that actions at the SERT are directly interfered with the discriminative stimulus effect as these effects do not do so for cocaine and other drugs that have affinity for both the DAT and SERT.

In summary, a series of aryl substituted morpholine analogues were synthesized and the binding affinity determined at the DAT, SERT, and NET as well as at ion channel receptors. Generally the analogues exhibited increased inhibitory for the DAT and SERT relative to morpholine but exhibited low binding affinity for the NET. This 2-methyl derivative 7 was the most potent antagonist at the SERT and was the most selective ligand for the SERT over the DAT and channel receptors. The

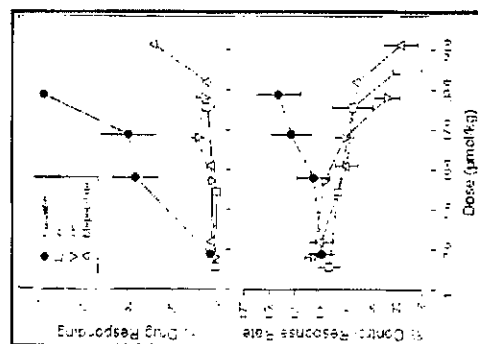


Figure 3. Effects of 7e and 7e in rats trained to discriminate injections of cocaine from saline. Ordinates for top panels: percentage of response on the cocaine-appropriate key. Ordinates for the bottom panels: rates at which responses were maintained (a percentage of response rate after saline administration). Abscissa: drug dose in $\mu\text{mol/kg}$ (log scale). Each point represents the effect in six to nine rats. The percentage error represents the standard error of the mean. The percentage error is not plotted at lower than 10% because the error would be considered unreliable, and not plotted at lower than 100% because subjects responded at that dose. Note that neither compound substituted for cocaine.

3,4-dichlorophenyl derivative 7c was the most potent antagonist at the DAT and was the most selective ligand for the DAT over α -naphthyl receptors but remained inactive for the SERT. The 3,4-dichlorophenyl derivative 7c was more selective for the SERT over the DAT than the other compounds. The 2,4-dichlorophenyl derivative 7e and the 2-naphthyl analogues 6f and 7f were identified as ligands that were potent at the DAT than naphpendine and that exhibited dopamine uptake inhibition curves that were similar to those of the dopamine transporter. The 3,4-dichlorophenyl derivative 7c inhibited the dopamine uptake of the dopamine transporter in a dose-dependent manner. However, none of the analogues tested reduced the dopamine uptake of the SERT. These results suggest that the dopamine transporter is a potential target for the treatment of cocaine addiction, suggesting that the α -naphthyl derivatives may still be significant. While the monoamine transporter affinity (SAR) of these naphpendine analogues was somewhat reminiscent of the 4-phenylthiopyranes, it was apparent from the dopamine uptake inhibition that the 3,4-dichlorophenyl and 2-naphthyl moieties are important in the monoamine system for differentiating between the high- and low-affinity components of this effect as well as between the DAT and the SERT. Additional studies directed toward the development of additional selective dopamine transporter ligands with diminished α -naphthyl derivative affinity are underway and will be reported in due course.

Experimental Section

All chemicals were purchased from Aldrich Chemical Co. (St. Louis, MO) unless otherwise noted. THF, CH₂Cl₂, and MeCN were dried under the usual conditions (toluene and Et₂O

2-(4-Iodophenyl)-2-(2,2-dimethoxyethyl)-1,4-dimethoxy-
butyronitrile (5c). General Method 2. The compound was

4-(4-Indolylphenyl)-1-methylpiperidine-carbonylnitrile (11). This compound was obtained as a yellow microcrystalline solid. The compound was converted into a hydrochloride salt (General Method A) which was obtained as a white microcrystalline solid. $[\alpha]_D^{25} + 27.0^\circ$ (in NMR, conc. base), $n_D^{25} 1.474$, $n_D^{20} 1.471$, $n_D^{15} 1.468$, $n_D^{10} 1.465$, $d_4^{25} 1.012$, $d_4^{20} 1.017$, $d_4^{15} 1.018$, $d_4^{10} 1.019$.

4-(1-Chlorophenyl)-1-methylpiperidine-4-carboxylic acid (E)-5 (7). *mp* 110–112°C. ¹H NMR (CDCl₃) δ 7.3–7.2 (m, 4H, aromatic), 6.89 (s, 1H, aromatic), 4.21 (s, 2H, CH₂), 3.11 (s, 3H, CH₃), 2.77 (s, 3H, CH₃).

the final concentration of nucleoside after all additions was approximately 0.3% w/v, corresponding to 139, 206, or 273 μM for the three nucleosides, respectively. In preparing concentrations of the drug being tested, the nucleoside was dissolved in water and added to the sample. Five minutes later, HEPES 25 mM, final concentration was added. Five minutes later, the nucleoside was added to the sample. The incubation was terminated by the addition of 10 μL of 10% TCA. The nucleoside was then filtered through Whatman 100-1000, 10 μm wet bed paper (presented in 1% HSA in water) to reduce nonspecific binding using a Brandel Cell Harvestor (Gaithersburg, MD). After filtration, the filters were washed with three 3-mL additions of 3 and 10 mM Tris, pH 7.4, containing 0.1% Tween. Absolute ethanol (95 mL) and Beckman's Ready-To-Go column Separation Cocktail 2 (25 mL) were added to the filters, which were counted the next day. An efficiency of 40% for these assays was found. In an inter-assay experiment conducted on the same day, 25 μL of the standard and 25 μL of the sample were counted. 6400 DPM total binding was obtained and 4000 DPM nonspecific binding. Nucleoside binding

