

Azepines and Piperidines with Dual Norepinephrine Dopamine Uptake Inhibition and Antidepressant Activity

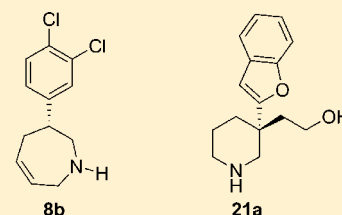
Dean G. Brown,^{*,†,§} Peter R. Bernstein,[†] Ye Wu,[†] Rebecca A. Urbanek,[†] Christopher W. Becker,[†] Scott R. Throner,[†] Bruce T. Dembofsky,[†] Gary B. Steelman,[†] Lois A. Lazor,[†] Clay W. Scott,[†] Michael W. Wood,[†] Steven S. Wesolowski,[†] David A. Nugiel, Stephanie Koch,[†] Jian Yu,[†] Donald E. Pivonka,[†] Shuang Li,[†] Carol Thompson,[†] Anna Zacco,[†] Charles S. Elmore,[†] Patricia Schroeder,[†] JianWei Liu,[†] Christopher A. Hurley,[‡] Stuart Ward,[‡] Hazel J. Hunt,[‡] Karen Williams,[‡] Joseph McLaughlin,[†] Valerie Hoesch,[†] Simon Sydserrf,[†] Donna Maier,[†] and David Aharony[†]

[†]CNS Discovery Research, AstraZeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, Delaware 19850-5437, United States

[‡]Argenta, 8/9 Spire Green Centre, Flex Meadow, Harlow, Essex, CM19 5TR, United Kingdom

Supporting Information

ABSTRACT: Herein, we describe the discovery of inhibitors of norepinephrine (NET) and dopamine (DAT) transporters with reduced activity relative to serotonin transporters (SERT). Two compounds, **8b** and **21a**, along with nomifensine were tested in a rodent receptor occupancy study and demonstrated dose-dependent displacement of radiolabeled NET and DAT ligands. These compounds were efficacious in a rat forced swim assay (model of depression) and also had activity in rat spontaneous locomotion assay.



hNET K_i = 17 nM	hNET K_i = 4.0 nM
hDAT K_i = 6.0 nM	hDAT K_i = 6.0 nM
hSERT K_i = 220 nM	hSERT K_i = 230 nM

Dose dependent activity in rat forced swim assay

KEYWORDS: norepinephrine, dopamine, uptake inhibitors, antidepressant

Despite new drugs that have helped many patients manage depressive disorders, there remains a large portion of patients who do not respond to current therapies.^{1,2} The most frequently prescribed drugs work by blocking uptake of monoamine neurotransmitters such as serotonin (SERT).³ A well-known example of a selective serotonin reuptake inhibitor (SSRI) with clinical efficacy is illustrated by fluoxetine **1** (Figure 1).⁴ Dual monoamine reuptake inhibitors such as duloxetine **2** have gained clinical acceptance and work by blocking serotonin as well as norepinephrine reuptake (SNRI).⁵ Triple reuptake inhibitors (TRI) such as amitifadine **4** are currently in clinical studies and demonstrate the ability to block SERT, norepinephrine (NET), and dopamine (DAT) reuptake.⁶

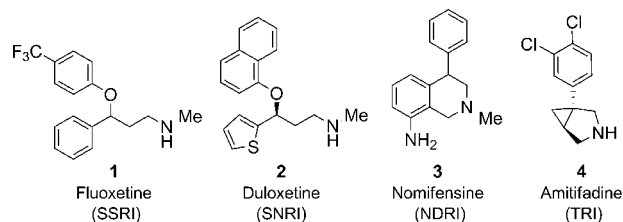


Figure 1. Examples of SSRI, SNRI, NDRI, and TRI.

Dual NET/DAT reuptake inhibitors (NDRIs) have also been utilized for the treatment of depression. The only current clinically utilized compound with NDRI activity is bupropion, but the mechanism of action is complex and may involve active metabolites.³ Nomifensine **3** was a clinically useful NDRI but was withdrawn from the market in 1986 due to increased incidence of hemolytic anemia.^{7–11}

Published reports on nomifensine **3** have hypothesized that this hemolytic anemia might have been associated with a reactive metabolite, specifically formation of a dihydroisoquinolinium ion.¹² With this in mind, we sought to identify a novel scaffold with dual NET and DAT inhibition, which would not form a dihydroisoquinolinium ion posing a potential reactive metabolite risk.

On the basis of the known SAR from the literature and in-house examples,¹³ we hypothesized that the aniline was not necessary for activity, and the fused aromatic ring could be replaced in nomifensine with a cyclic aliphatic ring. Several scaffolds were investigated, but the 2,3,4,7-tetrahydro-1H-azepine proved to be useful in having the desired SAR as well as synthetic handles for further optimization.

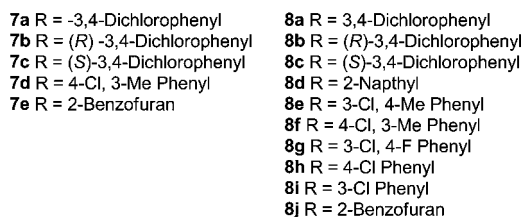
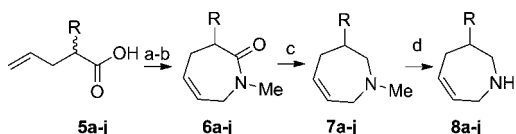
Received: August 31, 2012

Accepted: November 12, 2012

Published: November 12, 2012

Preparation of 2,3,4,7-tetrahydro-1*H*-azepines is illustrated in Scheme 1. Reaction of acid **5a–j** and *N*-methylprop-2-en-1-

Scheme 1. Preparation of Azepine Analogues^a

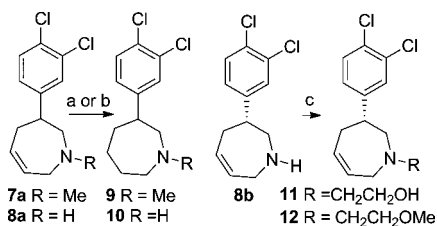


^aReagents and conditions: (a) CH=CHCH₂NHMe, 2-chloro-1-methyl pyridinium iodide, CH₂Cl₂, 25–85%. (b) Grubbs II catalyst,^{14,15} PhMe, 40 °C, 40–70%. (c) LiAlH₄, THF, 20–75%. (d) ACE-Cl, PhMe, reflux, 30–62%.

amine followed by ring closing metathesis gave the lactams **6a–j**.^{14,15} Reduction of **6a–j** with LAH provided *N*-Me analogues **7a–e** and intermediates **7f–j**. Demethylation of **7a–j** provided compounds **8a–j**.

Enantiomerically pure 2,3,4,7-tetrahydro-1*H*-azepines were prepared by starting with enantiomerically pure acid to give the (*R*) stereoisomers **7b** and **8b** and (*S*) stereoisomers **7c** and **8c**.¹⁶ Analogues **7a** and **8a** could be hydrogenated to give the azepanes **9** and **10** (Scheme 2). Alkylation of azepine **8b** provided *N*-alkyl derivatives such as **11** and **12**.

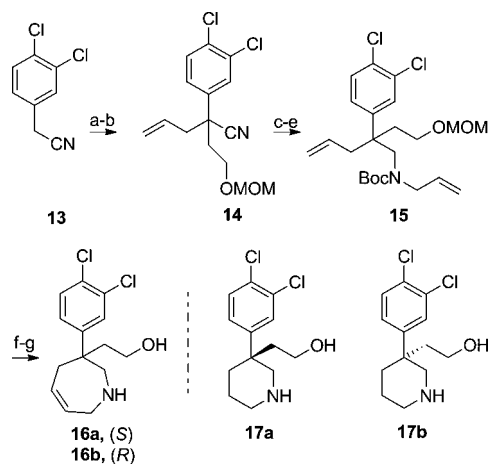
Scheme 2. Preparation of Azepine and Azepane Analogues^a



^aReagents and conditions: (a) **7a**, H₂, Pd/C, HCl, 79%. (b) **8a**, PtO₂, H₂, AcOH. (c) KOH, MeCN/H₂O, 150 °C, microwave, 75% for **11**, 35% for **12**.

The preparation of the quaternary substituted 2,3,4,7-tetrahydro-1*H*-azepines is illustrated in Scheme 3. The hydroxyethyl substituent was selected based on parallel SAR emerging from studies on a piperidine scaffold. The reaction sequence began with **13**, which was alkylated with methoxymethyl ether (MOM) protected bromoethanol. A second deprotonation using KOH and tetrabutylammonium iodide (TBAI) as a phase transfer catalyst installed the quaternary center in **14**. Reduction of the nitrile with diisobutylaluminum hydride (DIBAL)-H, followed by hydrolysis, led to an intermediate aldehyde. Reductive amination and protection led to **15**, which was subjected to ring-closing metathesis and then deprotected. Chiral supercritical fluid chromatography (SFC) provided enantiomers **16a** and **16b**. Assignment of absolute configuration was done by X-ray crystallography and

Scheme 3. Quaternary Substituted Analogues^a



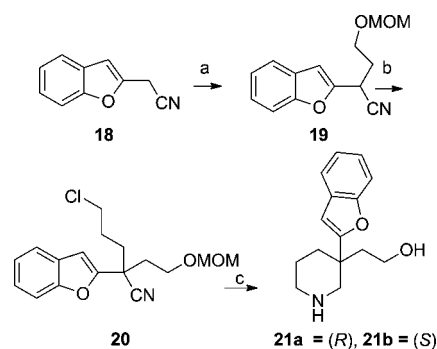
^aReagents and conditions: (a) BrCH₂CH₂OMOM, NaH, THF, 42%. (b) CH=CHCH₂Br, KOH, TBAI, MeCN, 77%. (c) DIBAL-H, PhMe. (d) CH=CHCH₂NH₂, NaBH(OAc)₃, 1,2-dichloroethane, 37% for steps c and d. (e) Boc₂O, CH₂Cl₂, 78%. (f) Grubbs II catalyst,¹⁵ CH₂Cl₂, reflux, quan. (g) HCl, MeOH, quan., chiral SFC.

confirmed by comparison of measured and computed vibrational circular dichroism (VCD) spectra.^{17,18}

Our investigation also examined piperidine analogues with substitution similar to those in the azepine series. Several 2-(3-phenylpiperidin-3-yl)ethanol type derivatives had previously been synthesized in a different project¹⁹ and were tested for activity in the NET, DAT, and SERT assays as a direct comparison to the azepines **16a** and **16b**. From this screening effort, **17a** and **17b** were identified.

The synthesis of a benzofuran analogue was accomplished in analogous fashion (Scheme 4).²⁰ The enantiomers were separated using chiral SFC to give **21a** and **21b** and assigned by measured and computed VCD spectra.

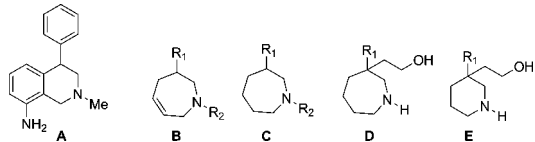
Scheme 4. Quaternary Substituted Piperidines^a



^aReagents and conditions: (a) NaH, Br(CH₂)₂OMOM. (b) NaH, Br(CH₂)₃Cl. (c) Ra Ni, NH₄OH, NaCl (aq); HCl, MeOH; chiral HPLC.

Results of NET, DAT, and SERT testing are reported in Table 1, along with cardiovascular ion channel effects (hERG), hCl_{inv} and CYP2D6 profiles. A notable observation in these results is a pronounced difference between the nomifensine stereoisomers [e.g., 3-(*S*) ≫ 3-(*R*)], which was confirmed to be consistent with the literature.²¹ All activity for nomifensine resides in the (*S*) stereoisomer, although the nomifensine racemate was used clinically. This large dependence on

Table 1. Summary Results of NET, DAT, and SERT Uptake and Selected in Vitro Properties



compd	core	R1	R2	K _i (nM)			hERG IC ₅₀ (μM) ^b	hCl _{int} ^c	CYP2D6 IC ₅₀ (μM) ^d
				NET ^a	DAT ^a	SERT ^a			
3	A			5.0	10	1400	>27	37	>20
3 (S)	A			4.0	7.0	1200	NT	NT	NT
3 (R)	A			1200	450	800	NT	NT	NT
7a	B	3,4-dichlorophenyl	Me	57	5.0	100	7.6	57	10.2
7b	B	(R)-3,4-dichlorophenyl	Me	12	3.0	83	10	51	7.6
7c	B	(S)-3,4-dichlorophenyl	Me	54	13	130	NT	86	11
8a	B	3,4-dichlorophenyl	H	66	6.0	220	11	30	5.1
8b	B	(R)-3,4-dichlorophenyl	H	17	6.0	220	21	33	3.9
8c	B	(S)-3,4-dichlorophenyl	H	24	8.0	420	13.7	50	3.1
8d	B	2-naphthyl	H	25	10	63	15.4	94	6.6
8e	B	3-Cl-4-Me phenyl	H	83	49	600	>27	100	5.6
7d	B	4-Cl, 3-Me phenyl	Me	130	23	270	26	85	18
8f	B	4-Cl, 3-Me phenyl	H	170	24	NT	26	NT	NT
8g	B	3-Cl, 4-F phenyl	H	130	68	1500	23	15	6.4
8h	B	4-Cl phenyl	H	250	25	NT	>31	NT	NT
8i	B	3-Cl phenyl	H	430	240	NT	>33	NT	NT
7e	B	2-benzofuran	Me	120	60	800	15	97	6.7
8j	B	2-benzofuran	H	46	23	240	19	83	7.8
9	C	3,4-dichlorophenyl	Me	74	8.0	260	10	NT	NT
10	C	3,4-dichlorophenyl	H	130	11	140	6.1	35	2.3
11	B	3,4-dichlorophenyl	-(CH ₂) ₂ OH	12	37	150	10	52	>20
12	B	3,4-dichlorophenyl	-(CH ₂) ₂ OMe	15	9.0	540	5.3	150	3.9
16a	D	(S)-3,4-dichlorophenyl	H	5.1	4.2	31	>33	<4	18
16b	D	(R)-3,4-dichlorophenyl	H	49	91	230	>33	NT	NT
17a	E	(S)-3,4-dichlorophenyl	H	3.3	9.3	42	>33	<4	>20
17b	E	(R)-3,4-dichlorophenyl	H	250	140	250	>33	<4	>20
21a	E	(R)-2-benzofuran	H	4.0	6.0	230	>33	22	>20
21b	E	(S)-2-benzofuran	H	430	400	NT	NT	NT	NT

^aUptake inhibition measured using HEK cells overexpressed with human recombinant NET, DAT, or SERT receptors with Molecular Devices neurotransmitter kit (inhibition of a fluorescent substrate).²⁵ Results of NET, DAT, and SERT are an average of at least $n = 3$ with up to 2-fold variability. NT, not tested. ^bValues determined in CHOK1-hERG cells using electrophysiological measurements. ^cHuman liver microsomal clearance (μL/min/mg). ^dIn vitro inhibition of cytochrome P450 CYP2D6 isoforms.

stereochemistry was not observed with the 3,4-dichlorophenyl 2,3,4,7-tetrahydro-1H-azepines such as **7b** versus **7c** or **8b** versus **8c**, where only a minor difference was observed. Replacement of the 3,4-dichlorophenyl moiety resulted in a loss of potency at all transporters with the exception of the naphthyl analogue **8d** (an expected bioisosteric replacement of 3,4-dichlorophenyl). This change led to similar potency at NET and DAT but was more potent at SERT when compared to racemic 3,4-dichlorophenyl **8a**. The N-H benzofuran analogue **8j** was similar in NET activity to the 3,4-dichlorophenyl analog **8a** but showed a slight drop-off in DAT affinity.

The activities of racemic saturated azepanes **9** and **10** were similar when compared to the azepine counterparts **7a** and **8a**. The introduction of groups on the azepine N atom was generally well tolerated for NET and DAT activity. Compounds **11** and **12** illustrate that hydrophilic substituents on the N atom gave the desired NET = DAT > SERT ratio. However, N-alkylation appeared to give rise to more potent activity at hERG (cf. **12** hERG IC₅₀ = 5.3 μM vs **8b** = 21 μM) as well as an increase in hCl_{int}. Incorporation of a hydroxyethyl substituent (**16a**, **17a**, and **21a**) at the 3-position led to an increase in NET

but also an increase in SERT. In these cases, a more pronounced difference in stereochemical activity was seen, similar to nomifensine **3**.

Incorporation of the hydroxyethyl substituent also improved metabolic stability, decreased hERG, and improved CYP2D6 liability relative to **8b**. The benzofuran quaternary substituted piperidine **21a** provided the closest match to the nomifensine profile with NET ≈ DAT (K_i = 4.2 and 6.3 nM, respectively) and a large separation at SERT (K_i = 230 nM). Compounds **8b** and **21a** were also tested for reactive metabolites with GSH under in vitro metabolic activation and did not reveal any adduct formation.

In vivo receptor occupancy was selected as a pharmacodynamic assay to verify that selected ligands could block accumulation of labeled NET/DAT ligands in respective brain regions (Table 2). Test compounds were administered to the rats, followed 30 min later by administration of a radioligand specific for NET or DAT. This assay is described in more detail in the Supporting Information.

Nomifensine was chosen as the benchmark comparator compound, and [³H]-MeNER and [³H]-PE2I were used as the

Table 2. NET and DAT Receptor Occupancy Studies in Rats

compd	NET EC ₅₀ (nM) ^a	DAT EC ₅₀ (nM)	NET ED ₅₀ (mg/kg) ^d	DAT ED ₅₀ (mg/kg) ^d	% free ^e	B/P ratio ^f
3	3.1	31 ^c	0.05	0.7 ^c	60.5	10.1
8b	46	220 ^b	0.5	2.1 ^c	7.7	4.8
21a	5.6	33 ^c	0.17	0.8 ^d	75	5.8

^aEC₅₀ = unbound plasma levels equaling 50% occupancy. Utilized [³H]MeNER as NET ligand (sc) and quantified in thalamus. ^bUtilized [³H]WIN 35,428 as DAT radioligand (sc), quantified in striatum. ^cUtilized [³H] PE2I (sc) and quantified in striatum. ^dED₅₀ = dose to give 50% occupancy at the receptor. The mean value is reported. The 95% confidence interval was typically ± half of the mean value reported. Scatter plots are presented in the Supporting Information to give the reader a more detailed view of the error in the assay. ^ePercent free plasma concentrations in rat. ^fBrain to plasma ratio.

NET and DAT ligands, respectively.^{22–24} It should also be noted that early in the program, [³H]-WIN35,458 was used as the DAT ligand,²² but it was found that [³H]-PE2I gave smoother curves and a better correlation with our in vitro assays. Compound **8b** was tested using [³H]-WIN35,458 but was not repeated with the new ligand. The calculated EC₅₀ in these assays demonstrated a slight disconnect with the human recombinant transporter assays in Table 1, most notably against DAT. This was not unexpected given the differences between rat and human orthologues and the difference between a human recombinant assay and a rat receptor occupancy assay with the inherent errors therein. It is not clear why this discrepancy was more prominent in the DAT measurement. The values of 3.1 and 31 nM observed for nomifensine **3** for NET and DAT, respectively, are consistent with the values reported in a rat synaptosomal uptake assay (NET K_i = 4 nM, DAT K_i = 26 nM).⁸ This observation led us to believe that the rat receptor occupancy study could be used as a key tool in dose selection for preclinical efficacy testing in rodents. Overall,

the receptor occupancy provided rank order in NET and demonstrated potent and dose-dependent receptor occupancy at both receptors at pharmacologically relevant doses used in behavioral assays.

These compounds were then tested in a rat forced-swim assay (FST) for antidepressant effects. Results are shown in Figure 2. Nomifensine **3** demonstrated efficacy at 10, 3, and 1 mg/kg but not at 0.3 mg/kg. It should be noted that doses for the rat forced-swim were selected based on systemic exposure and receptor occupancy, described above. The 2,3,4,7-tetrahydro-1*H*-azepines **8b** demonstrated activity at 10 and 3 mg/kg but not at 1 mg/kg.

The quaternary piperidine **21a** demonstrated efficacy at 7.3 and 2.4 mg/kg but not at 0.7 mg/kg. The compounds were also examined in a rat spontaneous locomotion assay (LMA) as a behavioral measure of activation of the DAT system. In contrast, selective NET inhibitors have been reported to suppress locomotor activity.²⁶ The compounds were evaluated for both distance traveled and stereotypic behaviors in the last 15 min of the assay. Nomifensine **3** dose dependently induced both locomotor activity and stereotypic behavior with an inverted U-shaped curve. The reductions in LMA could be related to hyperactivation of the dopaminergic system and a shift toward stereotypic behaviors. Alternatively, LMA suppression may be driven by increasing activation of the NET system. Compound **8b** exhibited a profile similar to that of nomifensine **3**. Although dose-dependent increases in LMA and stereotypy were observed, dose-dependent decreases in LMA and stereotypy were not observed with compound **21a**. Perhaps, declines in these measures might be observed at higher doses. Given the overall precision of the FST, LMA, and stereotypy assays and the challenge in interpreting the behavioral manifestations of activating two major neuro-modulatory systems, it can be argued that nomifensine **3** and compounds **8b** and **21a** displayed similar overall behavioral profiles. No severe stereotype such as self-biting was observed

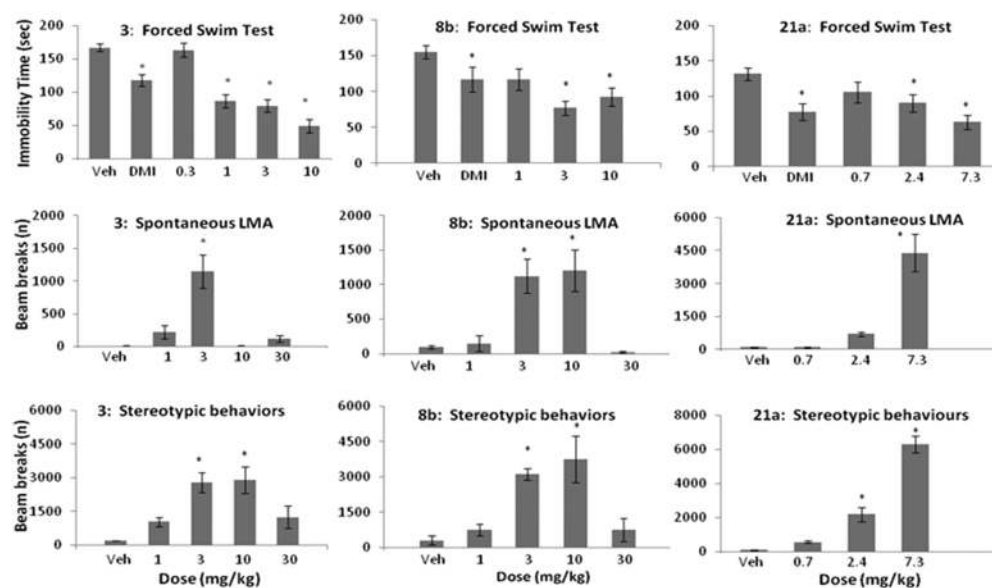


Figure 2. In vivo activity in FST, spontaneous LMA. Top row: Immobility time in FST for compounds **3**, **8b**, and **21a** following dosing (sc) in Sprague–Dawley rats. Middle row: Distance traveled in spontaneous locomotive activity (LMA) in rats as measured by beam breaks. Bottom row: Stereotypic behavior in the locomotive activity assay as measured by number of times the same beam is broken. DMI = desipramine (positive control, dosed 15 mg/kg ip). Data presented as group means ± SEMs. An asterisk indicates statistical significance from vehicle (Veh), using one-way ANOVA analysis.

with any compound at any dose. Because the objective of the project was to identify an "activating" antidepressant with a DAT uptake inhibition profile, increases in LMA were expected. However, it remains to be determined whether increased activation of the DAT system will afford an adequate therapeutic index.

Plasma levels of **8b** were measured at all doses in the FST experiment. On the basis of an assumption that free plasma would equal free brain levels, it was estimated that the free plasma concentration at the lowest effective dose in FST (3 mg/kg) was equivalent to the free concentration that gave between 50 and 70% occupancy at DAT and >90% at NET (based on receptor occupancy studies, see the Supporting Information for more details).

In summary, several potent dual NET/DAT uptake inhibitors have been reported, which have in vivo efficacy similar to nomifensine in a rat model of depression. Further work will need to be done to understand clinical doses and potential dose-limiting side effects such as abuse liability.

■ ASSOCIATED CONTENT

■ Supporting Information

Synthetic procedures and assay details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: 781-839-4101. E-mail: dean.brown@astrazeneca.com.

Present Address

[§]AstraZeneca Pharmaceuticals, 35 Gatehouse Drive, Waltham, Massachusetts 02451.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Amy Hehman, Lynne Neveras, Lisa Leon, Laurie Ross, Donna Sottung, John Zysk, Yan Li, William Potts, Chengwei Fang, and Peter Dorff.

■ ABBREVIATIONS

TBAI, tetrabutylammonium iodide; DIBAL, diisobutylaluminum hydride; MOM, methoxymethyl ether protecting group; CYP, cytochrome P450 metabolic enzymes; hERG, human ether a-go-go related gene; SFC, supercritical fluid chromatography; ACE, 1-chloroethyl chloroformate

■ REFERENCES

- (1) Nemeroff, C. B. Prevalence and Management of Treatment-Resistant Depression. *J. Clin. Psychiatry* **2007**, *68* (Suppl. 8), 17–25.
- (2) Papakostas, G. Limitations of Contemporary Antidepressants: Tolerability. *J. Clin. Psychiatry* **2007**, *68*, 11–17.
- (3) Liu, S.; Molino, B. F. Recent Developments in Monoamine Reuptake Inhibitors. *Annu. Rep. Med. Chem.* **2007**, *42*, 13–26.
- (4) Wong, D. T.; Perry, K. W.; Bymaster, F. P. The Discovery of Fluoxetine Hydrochloride (Prozac). *Nat. Rev. Drug Discovery* **2005**, *4* (9), 764–774.
- (5) Schatzberg, A. F. Efficacy and Tolerability of Duloxetine, a Novel Dual Uptake Inhibitor, in the Treatment of Major Depressive Disorder. *J. Clin. Psychiatry* **2003**, *64* (Suppl. 13), 30–37.
- (6) Tran, P.; Skolnick, P.; Czobor, P.; Huang, N. Y.; Bradshaw, M.; McKinney, A.; Fava, M. Efficacy and Tolerability of the Novel Triple Uptake Inhibitor Amitifadine in the Treatment of Patients with Major

Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial. *J. Psychiatric Res.* **2012**, *46*, 692–693.

- (7) Hunt, P.; Kannengiesser, M.-H.; Raynaud, J.-P. Nomifensine: A New Potent Inhibitor of Dopamine Uptake into Synaptosomes from Rat Brain Corpus Striatum. *J. Pharm. Pharmacol.* **1974**, *26* (5), 370–371.

- (8) Tuomisto, J. Nomifensine and its Derivatives as Possible Tools for Studying Amine Uptake. *Eur. J. Pharmacol.* **1977**, *42* (2), 101–106.

- (9) Nielson, J. L.; Lund, N. O. Drug Fever due to Nomifensine Treatment in Patients with Endogenous Depression. *Int. Pharmacopsychiatry* **1981**, *16*, 66–68.

- (10) Salama, A.; Mueller-Eckhardt, C. Two Types of Nomifensine-Induced Immune Haemolytic Anaemias: Drug-Dependent Sensitization and/or Autoimmunization. *Br. J. Haematol.* **1986**, *64*, 613–620.

- (11) List of Drug Products That Have Been Removed From the Market for Reasons of Safety or Effectiveness. *Fed. Regist.* **1998**, *63* (195), 54082–54089.

- (12) Obach, S. R.; Dalvie, D. K. Metabolism of Nomifensine to a Dihydroisoquinolinium Ion Metabolite by Human Myeloperoxidase, Hemoglobin, Monoamine Oxidase A, and Cytochrome P450 Enzymes. *Drug Metab. Dispos.* **2006**, *34* (8), 1310–1316.

- (13) Liu, S.; Pechulis, A. D.; Beck, J. P.; Yang, Z.; Vellekoop, A. S.; Sweet, M. P.; Harms, A. E.; Wolf, M. A.; Hassler, C.; Klos, A. M.; Opalks, C. J.; Crocker, P. J.; Khmelnsky, Y.; Smith, M. A.; Molino, B. F. Heterocycle-Fused 4-Phenyl Tetrahydroisoquinolines as Dual NET/DAT Inhibitors, Presented at 243rd ACS National Meeting & Exposition, San Diego, CA, United States, March 25–March 29, 2012; MEDI-372.

- (14) Tuthill, P. A.; Seida, P. R.; Barker, W.; Cassel, J. A.; Belanger, S.; DeHaven, R. N.; Koblish, M.; Gottshall, S. L.; Little, P. J.; DeHaven-Hudkins, D. L.; Dolle, R. E. Azepinone as a Conformational Constraint in the Design of κ -Opioid Receptor Agonists. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5693–5697.

- (15) Trnka, T.; Grubbs, M. R. H. The Development of $L_2X_2R=CHR$ Olefin Metathesis Catalysts: An Organometallic Success Story. *Acc. Chem. Res.* **2001**, *34*, 18–29.

- (16) Sudhakar, A. R.; Tang, S. Optically Active Intermediates for the Preparation of Optically Active Substituted Oximes, Hydrazones and Olefins Useful as Neurokinin Antagonists, U.S. Patent 6,265,614, B1 July 24, 2001.

- (17) Nafie, L. A.; Dukor, R. K. In *Applications of Vibrational Optical Activity in the Pharmaceutical Industry*; Pivonka, D. E., Chalmers, J. M., Griffiths, P. R., Eds.; John Wiley and Sons: Chichester, West Sussex, England; pp 129–154 (2–7).

- (18) Crawford, T. D. Ab initio calculation of molecular chiroptical properties. *Theor. Chem. Acc.* **2006**, *115*, 227–245.

- (19) Emonds-Alt, X.; Gueule, P.; Proietto, V.; Van Broeck, D. 1-Azoniabicyclo [2.2.1]heptanes, Method of Preparing Them and Pharmaceutical Compositions in Which they are Present. U.S. Patent 5,679,693, October 21, 1997.

- (20) Chan, J. H. T.; Elix, J. A.; Ferguson, B. A. Anelated Furans. XVII. The Wittig Reaction of Benzofuranones. *Aust. J. Chem.* **1975**, *28*, 1097–1111.

- (21) Kunstmann, R.; Gerhards, H.; Kruse, H.; Leven, M.; Paulus, E. F.; Schacht, U.; Schmitt, K.; Witte, P. U. Resolution, Absolute Stereochemistry, and Enantioselective Activity of Nomifensine and Hexahydro-1H-indeno[1,2-b]pyridines. *J. Med. Chem.* **1987**, *30*, 798–804.

- (22) Pogun, S.; Scheffel, U.; Kuhar, M. J. Cocaine Displaces [³H]WIN 35,428 binding to Dopamine Uptake Sites in Vivo More Rapidly than Mazindol or GBR 12909. *Eur. J. Pharmacol.* **1991**, *198*, 203–205.

- (23) [³H]MeNR: Ghose, S.; Fujita, M.; Morrison, P.; Uhl, G.; Murphy, D. L.; Mozley, P. D.; Schou, M.; Hallidin, C.; Innis, R. *Synapse* **2005**, *56*, 100–104.

- (24) PE2I: Emond, P.; Guilloteau, D.; Chalon, S. [³H]PE2I: A Radiopharmaceutical for in vivo Exploration of the Dopamine Transporter. *CNS Neurosci. Ther.* **2008**, *14*, 47–64.

(25) Haunso, A.; Buchanan, D. J. Pharmacological Characterization of a Fluorescent Uptake Assay for the Noradrenaline Transporter. *J. Biomol. Screening* **2007**, *12*, 378–384.

(26) Mitchell, H. A.; Ahem, T. H.; Liles, C.; Javors, M. A.; Weinschenker, D. The Effects of Norepinephrine Transporter Inactivation on Locomotor Activity in Mice. *Biol. Psychiatry* **2006**, *60*, 1046–1052.