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Diarylacetylene piperidinyl amides as novel anxiolytics

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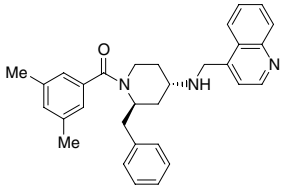
Abstract—*N*-Phenyl-2-[1-[3-(2-pyridinylethynyl)benzoyl]-4-piperidine]acetamide (**9**) and related piperidine acetamide derivatives have good oral activity in the elevated plus maze, an animal model predictive of clinical efficacy for the treatment of anxiety. Modest affinity was observed for the neurokinin NK-1 and 2 receptors, which are known to be involved in the regulation of mood and emotion.

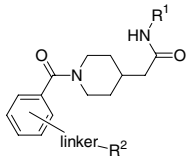
The pathological condition of anxiety is a prevalent and debilitating disorder.[1] Clinical anxiety disorders are described in the *Diagnostic and Statistical Manual*, *Vol. 4* and include generalized anxiety disorder, panic disorder, agoraphobia, and obsessive-compulsive disorder.[2] There are significant opportunities for new anxiolytics that are not sedating or addictive and are broadly effective across different patient populations and types of anxiety. Neurokinin receptors NK-1 and 2 have been implicated in mood and emotion, and investigated as targets for the treatment of anxiety.[3] No drug currently marketed for anxiety acts through this unique mechanism of action, although the NK-1 antagonist aprepitant has recently been approved as an anti-emetic.[4]

Neurokinin receptors are currently divided into three main subtypes, designated NK-1, 2, and 3. Their endogenous agonists are the tachykinin family of peptides, exemplified by substance P (NK-1 selective) and neurokinins A and B (NK-2 and 3 selective, respectively). Considerable attention has focused on the development of small-molecule antagonists of the NK-1 receptor for depression, since early clinical trials appeared to suggest that NK-1 receptor antagonists may alleviate depression in humans.[5]

When the antidepressant activity for aprepitant was described, we initiated a program to discover new neurokinin receptor antagonists. We focused our early efforts on modifications of the neurokinin modulator CGP-48923 (**1**).[6] In our design strategy, the chiral centers were removed, while several of the electrostatic and hydrophobic interactions were retained. Specifically, we proposed to add hydrophobic substitution appended to the benzyl group of **1** via a suitable spacer (viz., **2**).



1, CGP 48923



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The synthesis was initiated by the reaction of *N*-benzyl-4-piperidinone (**3**) with the appropriate stabilized Wittig reagent to give **4** (Scheme 1). Hydrogenolysis of **4** provided **5**, which was then reacted with 3-iodobenzoyl chloride to afford **6**. Copper- and palladium-mediated coupling[7] of 3-ethynylpiperidine provided **7**, which was converted to amide targets first by base-mediated hydrolysis of the ester to form **8** followed by amide formation under standard conditions to give **9** (Table 1). In addition, we prepared 4-hydroxyphenyl congener **10** because it was a metabolite of **9** (see below) and fluorinated derivatives **11**–**13** in order to block this metabolism, by

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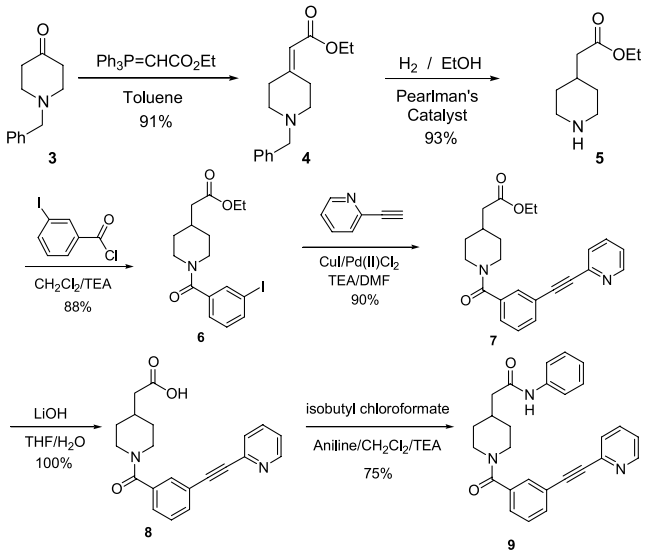
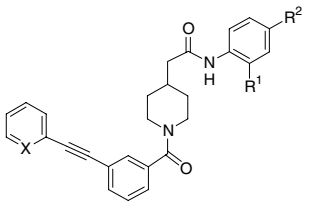


Scheme 1. General synthetic pathway.

Table 1. Diarylacetylene piperidinyl amides



Compound	R^1	R^2	X	NK-1[a]	NK-2[a]
9	H	H	N	37	11
10	H	OH	N	18	n.t.
11	F	H	N	96 (0.64)	97 (0.55)
12	H	F	N	96 (1.0)	96 (1.0)
13	F	F	N	16	8
14	H	H	C	28	7

n.t. is not tested.
[a] % inhibition at 10 μM (IC_{50}, μM).

the use of the appropriate aniline in coupling with **8**. Phenylacetylene **14** was also prepared by the use of ethynylbenzene in reaction with **6**.

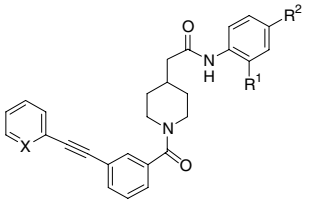
The oral bioavailability of compound **9** in rats was determined to be 65% with a $t_{1/2}$ of 3.1 h after administration of 40 mg/kg po. The metabolic stability of **9** was evaluated in human and rat liver microsomes. Significant levels of unchanged **9** remained after 90 min incubation (63% in rat and 35% in human). The major metabolite involved hydroxylation of the phenyl ring. We therefore prepared *para*-hydroxy compound **10**. Comparison of synthetic **10** with that prepared metabolically revealed that they were identical. Compound **10** was more metabolically stable than **9** with 97% and 80% remaining in rat and human liver microsomes, respectively, after 90 min incubation. However, the bioavailability of **10** was quite low (<2% at 3 and 10 mg/kg po), so that it was not considered further. In order to potentially block hydroxylation on the aryl ring, we prepared fluorinated derivatives **11**–**13**.

Compounds **9**–**14** were tested for binding at the neurokinin NK-1 and 2 receptors (hNK1-U373MG and hNK2-CHO cells, respectively). Although **9** and metabolite **10** had relatively little binding to these receptors, both the 2- and 4-fluorophenyl compounds **11** and **12** had modest binding with IC_{50}s of $\leqslant 1$ μM. Surprisingly, 2,4-difluorophenyl congener **13** had significantly less NK-1 and 2 binding. Compound **14**, in which the pyridine ring of **9** was now a phenyl, had a similar level of activity as for **9**. In addition, **9** was tested at 62 other GPCRs, ion channels, and uptakes sites at 1 and 10 μM. Other than 60% inhibition of the GABA transporter at 10 μM, only weak activities were observed at the peripheral benzodiazepine, glycine, SK^+ Ca^{2+} channels, and the peripheral imidazoline I_2 receptor.

We also determined anxiolytic efficacy of **9**, **10**, and **13** in established animal models predictive of clinical utility. The primary animal model used was the reversal of DOI-induced head shake in mice. Anti-depressant therapy is associated with down-regulation of the 5-HT_{2a} and 5-$HT_{2\,c}$ receptors. Further, antisense down-regulation of 5-HT_{2a} in mice is associated with antidepressant effects.[8] Therefore, we determined the effects of test compounds on head shakes induced by 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI), which has high affinity as an agonist for 5-$HT_{2A/2C}$ receptors.[9] This model is useful because it is expected to be sensitive to compounds that modulate serotonergic pathways, either directly or indirectly. This model may also be useful for the examination of new, atypical anxiolytic agents. Compounds **9** and **10** had the same potency in this test with 20 mg/kg po minimum effective doses (MEDs), and **13** was more active with a 0.1 mg/kg MED po (Table 2).

The elevated plus maze (EPM) is a widely used animal test of anxiety.[10] It models spontaneous behavioral patterns in response to interactions with the environment. The EPM takes advantage of the innate fear of rodents for open spaces with novelty as the major source for this fear. A conflict develops due to the stimuli of the novel environment which produces both an approach drive (curiosity) and an avoidance drive

Table 2. In vivo testing data



Compound	Elevated plus maze (MED, po)	DOI-induced headshakes (MED, po)
9	1.0	20.0
10	3.0	20.0
13	1.0	0.1

such as fear of the unknown properties of the environment. Current marketed anxiolytics are active in the EPM, which can detect both anxiolytic and anxiogenic effects. Compounds **9** and **10** displayed 1.0 and 3.0 mg/kg MEDs upon oral administration, and **13** had a 1.0 mg/kg MED po.

We examined 2,4-difluoro **13** in more detail and were surprised to find that it was actually less metabolically stable than **9** in liver microsomes, with only 0.1 (rat) and 15% (human) remaining after 60 min incubation, due to oxidative metabolism of the piperidine ring. In rats it displayed a 7.0% oral bioavailability with a 2.7 h $t_{1/2}$ when dosed at 15 mg/kg po, but surprisingly had 38–71% bioavailability in cynomologous monkeys with a 3.1–3.2 h $t_{1/2}$.

Compounds **9**, **10**, and **13** have in vivo activity in animal models predictive of a clinically useful anxiolytic effect in patients. Although **11** and **12** show neurokinin NK-1 and 2 receptor binding with IC_{50}s of $\leqslant 1\ \mu M$, it is not clear if these activities contribute to the mechanism of anxiolytic action. There were no other receptor interactions identified that appeared to be relevant. Therefore, the mechanism of action of these agents is not clearly understood at the present time. We evaluated the metabolic stability and pharmacokinetics of lead **9**, preparing 4-hydroxyphenyl **10** to confirm the structure of the major metabolite. The equivalent anxiolytic activity for **9** and **10** was surprising given the poor oral bioavailability determined for **10**, and it is possible that there are biologically active metabolites of **10** in vivo. Compound **14**, in which the nitrogen of the pyridine ring of **9** was replaced with a carbon, displayed similar activity as for **9**. Among ring-fluorinated congeners prepared to block metabolism (**11**–**13**), difluoro congener **13** was examined to the greatest extent. This compound had an acceptable pharmacokinetic profile in cynomolgus monkeys and comparable activity in vivo tests as for **9**.

Acknowledgments

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References and notes

1. (a) Hood, S. D.; Argyropoulos, S. V.; Nutt, D. J. *Exp. Opin. Ther. Pat.* **2003**, *13*, 401; (b) Gordon, J. A.; Hen, R. *Annu. Rev. Neurosci.* **2004**, *27*, 193; (c) Airaksinen, E.; Larsson, M.; Forsell, Y. *J. Psychiatr. Res.* **2005**, *39*, 207; (d) Bignan, G. C.; Connolly, P. J.; Middleton, S. A. *Exp. Opin. Ther. Patents* **2005**, *15*, 357.
2. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*; 4th ed.; Text Revision, American Psychiatric Association: Washington, DC, 2000.
3. (a) McLean, S. *Curr. Pharm. Des.* **2005**, *11*, 1529; (b) Holmes, A.; Heilig, M.; Rupniak, N. M. J.; Steckler, T.; Griebel, G. *Trends Pharmacol. Sci.* **2003**, *24*, 580; (c) Rupniak, N. M. J.; Kramer, M. S. *Trends Pharm. Sci.* **1999**, *20*, 485.
4. Patel, L.; Lindley, C. *Exp. Opin. Pharmacother.* **2003**, *4*, 2279.
5. Kramer, M. S.; Cutler, N.; Feighner, J.; Shrivastava, R.; Carman, J.; Sramek, J. J.; Reines, S. A.; Liu, G.; Snavely, D.; Wyatt-Knowles, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Swain, C. J.; Harrison, T.; Hill, R. G.; Hefti, F.; Scolnick, E. M.; Cascieri, M. A.; Chicchi, G. G.; Sadowski, S.; Williams, A. R.; Hewson, L.; Smith, D.; Carlson, E. J.; Hargreaves, R. J.; Rupniak, N. M. J. *Science* **1998**, *281*, 1640.
6. Ofner, S.; Hauser, K.; Schilling, W.; Vassout, A.; Veenstra, S. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1623.
7. Negishi, E.-I.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.
8. Sibille, E.; Sarnyai, Z.; Benjamin, D.; Gal, J.; Baker, H.; Toth, M. *Mol. Pharmacol.* **1997**, *52*, 1056.
9. Willins, D. L.; Meltzer, H. Y. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 699.
10. Dubinsky, B.; Vaidya, A. H.; Rosenthal, D. I.; Hochman, C.; Crooke, J. J.; Deluca, S.; Devine, A.; Cheo-Isaacs, C. T.; Carter, A. R.; Jordan, A. D.; Reitz, A. B.; Shank, R. P. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 777.