Journal of
Medicinal
Chemistry

Volume 48, Number 23 November 17, 2005

Letters

7-(1,1-Dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine: A Functionally Selective γ-Aminobutyric Acid$_A$ (GABA$_A$) α2/α3-Subtype Selective Agonist That Exhibits Potent Anxiolytic Activity but Is Not Sedating in Animal Models

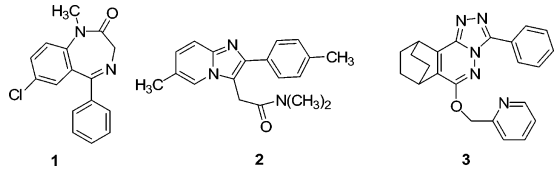
Robert W. Carling,* Andrew Madin, Alec Guiblin, Michael G. N. Russell, Kevin W. Moore, Andrew Mitchinson, Bindi Sohal, Andrew Pike, Susan M. Cook, Ian C. Ragan, Ruth M. McKernan, Kathleen Quirk, Pushpinder Ferris, George Marshall, Sally Ann Thompson, Keith A. Wafford, Gerard R. Dawson, John R. Atack, Timothy Harrison, José L. Castro,* and Leslie J. Street*

Departments of Medicinal Chemistry, Biochemistry, and Pharmacology, Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K.

Received June 16, 2005

Abstract: There is increasing evidence that compounds with selectivity for γ-aminobutyric acid$_A$ (GABA$_A$) α2- and/or α3-subtypes may retain the desirable anxiolytic activity of nonselective benzodiazepines but possess an improved side effect profile. Herein we describe a novel series of GABA$_A$ α2/α3 subtype-selective agonists leading to the identification of the development candidate **17**, a nonsedating anxiolytic in preclinical animal assays.

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter in the brain,[1] and GABA$_A$ receptors constitute the largest population of inhibitory neurotransmitter receptors.[2] The purification, sequencing, and cloning of the GABA$_A$ receptor have led to the identification of 16 subunits arranged within 7 families (α1−α6, β1−β3, γ1−γ3, δ, ϵ, π, and θ).[3] Expression of recombinant receptors shows that at least one α, one β, and one γ (or δ or ϵ) subunit are required to form a pentameric, functional GABA-gated chloride ion channel,[3,4] with recent studies suggesting a subunit stoichiometry of two α, two β, and one γ subunit.[5] As well as an agonist (GABA) binding site, GABA$_A$ receptors also have multiple allosteric modulatory sites for barbiturates, neurosteroids, anesthetics, avermectins, and benzodiazepines that all modulate opening of the channel.[6] Of these, the benzodiazepine site is the best characterized because of its role in mediating the clinical effects of anxiolytics such as diazepam (**1**). It has been shown that the major benzodiazepine sensitive GABA$_A$ receptor subtypes in brain are α1βγ2, α2βγ2, α3βγ2, and α5βγ2.[4] Currently used anxiolytic benzodiazepines such as diazepam (**1**) are nonselective, high-efficacy agonists, and these compounds show sedative,[7] muscle-relaxant,[8] and amnesic[9] properties. Zolpidem (**2**), which has higher affinity for α1- (the major subtype of GABA$_A$ receptors in the central nervous system)[4] over α2-, α3-, and α5-containing receptors, is particularly sedative in animal tests and in man.[10] This suggests that compounds with



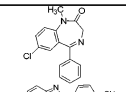
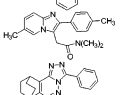
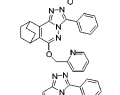
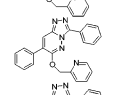
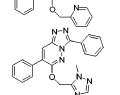
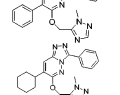
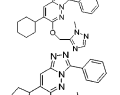
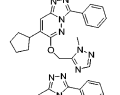
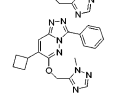
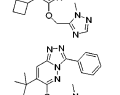
1 **2** **3**

reduced affinity and/or efficacy at α1-containing GABA$_A$ receptors, yet with affinity and efficacy at α2- and/or α3-subtypes, may retain the desirable anxiolytic activity of nonselective benzodiazepines and possess an improved side effect profile (i.e., reduced sedation). Further evidence for the role of α1-containing receptors in sedation has been provided by the use of transgenic mice in which the α1 subunit was rendered benzodiazepine-insensitive.[11,12] In these animals, the anxiolytic, anticonvulsant, and myorelaxant effects of diazepam were preserved, while its sedative and amnesic effects were significantly reduced. To date, only a limited number

* To whom correspondence should be addressed. For R. C.: phone, (+1279) 440000; fax, (+1279) 440187; e-mail, robert_carling@merck.com. For J.L.C.: phone, (+1279) 440000; fax, (+1279) 440187; e-mail, jose_castro_pineiro@merck.com. For L.J.S.: phone, (+1279) 440000; fax, (+1279) 440187; e-mail, leslie_street@merck.com.

10.1021/jm058034a CCC: $30.25
Published on Web 10/14/2005

Table 1. Affinities and Efficacies of Triazolopyridazines at Cloned Human $GABA_A$ Receptors[f]

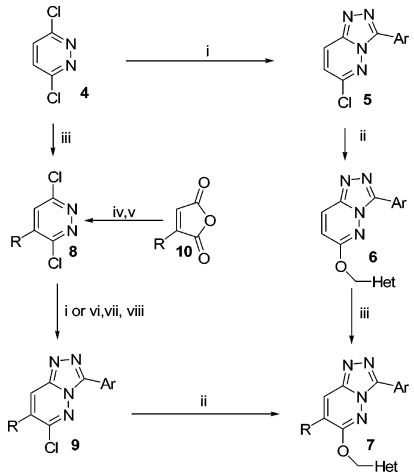
No.[a]	Structure	Ki (nM)[b]			Efficacy(%)[c, d]		
		α_1	α_2	α_3	α_1	α_2	α_3
1		14	20	15	+157%[c]	+115%[c]	+211%[c]
2		27	160	380	+160%[c]	+123%[c]	+143%[c]
3		71	26	12	+51%[c]	+23%[c]	+38%[c]
11		1.1	2.9	1.8	+80%[c]	n/d[e]	+77%[c]
12		0.78 (0.56, 1.1)	2.6 (2.3, 3.0)	1.2 (1.1, 1.3)	+94%[c]	n/d	+115%[c]
13		6.2	14	4.8	+65%[c]	n/d	+109%[c]
14		0.38 (0.37, 0.38)	0.73 (0.73, 0.74)	0.34 (0.34, 0.35)	+47%[d]	n/d	+63%[d]
15		0.23	0.25	0.17	+27%[d]	+41%[d]	+72%[d]
16		0.36	nd	0.14	0%[d]	n/d	+34%[d]
17		0.27	0.31	0.20	0%[d]	+11%[d]	+21%[d]

[a] All compounds were characterized by proton NMR and mass spectra and gave satisfactory elemental analysis results. [b] Displacement of [^{3}H]Ro 15-1788 from human recombinant $GABA_A$ receptors $\alpha x\beta 3\gamma 2$ (x = 1, 2, or 3). K_i values are the mean of at least two independent determinations (where n = 2; individual data given).. [c] Efficacy is determined as the percent modulation of the submaximal (EC_{20}) response to GABA in human $GABA_A$ receptor expressed transiently in *Xenopus laevis* oocytes. [d] Efficacy is determined as the percent modulation of the submaximal (EC_{20}) response to GABA in human $GABA_A$ receptor expressed stably in L(tk$^-$) cells. [e] n/d: not determined. [f] It is noted that as this particular series of compounds was developed, we refined our screening strategy from one in which we measured efficacy of a single drug concentration at α1, α2 and α3 subtypes transiently expressed in *Xenopus* oocytes to one in which multiple drug concentrations were assessed in stably transfected fibroblasts, the latter of which increased our precision but reduced our throughput (hence, α2 data were not available for all compounds).

of $GABA_A$ α2/α3-subtype selective ligands have been reported in the literature.[12−16] We disclosed **3** as a $GABA_A$ α2/α3 agonist that had moderately higher affinity at α2- and α3- compared to α1-containing receptors.[17] In this communication we describe optimization studies carried out on **3** that ultimately led to the identification of the development candidate **17**, a $GABA_A$ α1 antagonist and an α2/α3 agonist that has anxiolytic activity in animal models and is not sedating.

Compounds were tested for their ability to inhibit the binding of [^{3}H]Ro15-1788 to the benzodiazepine binding site of different α-subunit-containing ($\beta 3$, $\gamma 2$, plus an α1, α2, or α3) human recombinant $GABA_A$ receptors stably expressed in L(tk$^-$) cells.[18] Efficacies of most compounds were determined at $GABA_A$ receptors containing these same subunit combinations transiently expressed in *Xenopus* oocytes by measurement of the modulatory effect on the GABA EC_{20} ion current using two-electrode voltage-clamp electrophysiology at a single maximal concentration of test ligand (100 × K_i).[19] For

Scheme 1[a]



[a] Reagents: (i) $ArCONHNH_2$, xylene or 1,4-dioxan, $Et_3N.HCl$, reflux; (ii) $HetCH_2OH$, NaH, DMF; (iii) RCO_2H, $(NH_4)_2S_2O_8$, $AgNO_3$, H_2SO_4, H_2O, 70 °C; (iv) $NH_2NH_2{\cdot}H_2O$, AcOH, NaOAc, reflux; (v) $POCl_3$, (vi) $NH_2NH_2{\cdot}H_2O$, EtOH reflux; (vii) ArCOCl, pyridine; (viii) dioxan, HCl, reflux.

key compounds, efficacies were determined using whole-cell patch clamp recordings from L(tk$^-$) cells stably expressing $\alpha 1\beta 3\gamma 2$, $\alpha 2\beta 3\gamma 2$, or $\alpha 3\beta 3\gamma 2$ $GABA_A$ receptor subtypes using increasing concentrations of test ligand to measure the concentration response.[14,20]

Replacement of the 2-pyridyl ring of the triazolopyridazine **3** with 1,2,4-triazoles linked through the 3-position led to the identification of $GABA_A$ ligands that had higher efficacy at α3- than α1-containing receptors.[21] Removal of the [2.2.2] bicyclic ring of compound **3** and substitution of the 7-position of the triazolopyridazine core with phenyl led to a nonselective high affinity/high efficacy agonist **11** (Table 1). Combining these changes led to the 3,7-diphenyl derivative **12**, which not only has high affinity at α1-, α2-, and α3-containing $GABA_A$ receptors but also has marginal functional selectivity favoring α3 (+115%) over α1 (+94%) receptors. Replacing 7-phenyl with 7-cyclohexyl to give **13** resulted in a comparable efficacy profile but somewhat reduced affinity. To lower efficacy at α1-containing receptors (ideally silent antagonist), the effect of reducing the size of the 7-substituent, therefore local hydrophobicity, was investigated.[17,22,23] These changes were carried out using the chemistry outlined in Scheme 1.[24] Thus 3,6-dichloropyridazine **4** could be transformed in two steps to a generic triazolopyridazine (**6**) and then converted to the general structure **7** by radical addition. Alternatively, **4** could be subjected to radical attack first to give **8**, which could then be converted in two steps to the target **7**. In the case of 7-phenyl, this substituent was introduced starting from phenylmaleic anhydride, which in five steps was transformed to **8**. Replacing phenyl **12** with cyclopentyl to give **14** not only reduced α1 efficacy and retained functional selectivity but also had the added benefit of increasing α3 affinity. The 7-cyclobutyl derivative **15** showed a further reduction in α1 efficacy but retained higher efficacy at α3 and high affinity. Introduction of a *tert*-butyl group at the 7-position to give **16** resulted in a high-affinity $GABA_A$ ligand that was an antagonist at α1-containing receptors and still had positive modulation at α3 receptors. However, **16** was not considered

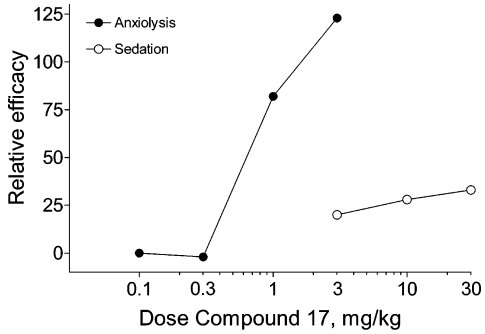


Figure 1. Efficacy of **17** expressed relative to a nonselective full agonist in the rat elevated plus maze (anxiolytic) and chain-pulling (sedation) assays. In the elevated plus maze, the percent time spent on the open arms during the 5 min trial time is expressed relative to the increase seen with the nonselective full agonist chlordiazepoxide (5 mg/kg). For the chain-pulling assay, the decrease in the mean rate of responding over the 60 min trial period was compared to diazepam (10 mg/kg). The clear separation between anxiolysis and sedation is apparent.

to be a development candidate because metabolism studies showed that triazolopyridazines with an unsubstituted 3-phenyl ring have a tendency to undergo extensive glutathione incorporation in vivo. In an attempt to overcome this problem, fluorination of the phenyl ring was explored leading to the identification of the development candidate 7-(1,1-dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine (**17**, TPA023). Compound **17** is a high-affinity antagonist at α1-containing receptors but is a high-affinity, low-efficacy partial agonist at α2 and α3 receptors; it has good pharmacokinetics in rat and dog (rat, $F = 35\%$, $t_{1/2} = 1.4$ h; dog, $F = 53\%$, $t_{1/2} = 1.5$ h) and has excellent occupancy of central $GABA_A$ receptors following oral dosing ([^{3}H]Ro15-1788) binding assay[25] $ID_{50} = 0.42$ mg/kg, $T_{max} = 0.5$ h). The pharmacokinetic properties of **17** and lack of efficacy at the α5 subtype (modulation of a GABA $EC_{20} = 6\%$) confer advantages over L-838417,[26] whereas **17** lacks both α1 and α5 efficacy relative to **15** (TP13[27]). When tested in the standard rat anxiety assay, the elevated plus maze assay (Figure 1),[28] **17** was anxiolytic at doses of 1 and 3 mg/kg po (corresponding to 70% and 88% occupancy, respectively) without causing significant impairment at a dose of 30 mg/kg po (99% occupancy) in the rat chain-pulling and mouse rotarod assays of myorelaxation and/or ataxia.[29] Compound **17** was also a nonsedating anxiolytic in primates[29] and in baboons did not cause self-administration nor did it produce subjective feelings similar to the nonselective full agonist lorazepam.[30] These data clearly suggest that **17** possesses a preclinical profile unlike existing nonselective benzodiazepines and suggest that anxiolytic efficacy can be separated from sedation and dependence.[30]

Supporting Information Available: Experimental procedures for synthesis and characterization of intermediates and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Rabow, L. E.; Russek, S. J.; Farb, D. H. From ion currents to genomic analysis: Recent advances in $GABA_A$ receptor research. *Synapse* **1995**, *21*, 189−274.
(2) Young, A. B.; Chu, D. Distribution of $GABA_A$ and $GABA_B$ receptors in mammalian brain: potential targets for drug development. *Drug Dev. Res.* **1990**, *21*, 161−167.
(3) (a) Luddens, H.; Korpi, E. R.; Seeburg, P. H. $GABA_A$/benzodiazepine receptor heterogeneity: Neurophysiological implications. *Neuropharmacology* **1995**, *34*, 245−254. (b) Stephenson, F. A. The GABA-A receptors. *Biochem. J.* **1995**, *310*, 1−9. (c) Davies, P. A.; Hanna, M. C.; Hales, T. G.; Kirkness, E. F. Insensitivity to anaesthetic agents conferred by a class of GABA-A receptor subunit. *Nature* **1997**, *385*, 820−823. (d) Whiting, P. J.; McAllister, G.; Vasilatis, D.; Bonnert, T. P.; Heavens, R. P.; Smith, D. W.; Hewson, L.; O'Donnell, R.; Rigby, M. R.; Sirinathsinghji, D. J. S.; Marshall, G.; Thompson, S. A.; Wafford, K. A. Neuronally restricted RNA splicing regulates the expression of a novel GABAA receptor subunit conferring atypical functional properties. *J. Neurosci.* **1997**, *17*, 5027−5037. (e) Bonnert, T. P.; McKernan, R. M.; Farrar, S.; Le Bourdelles, B.; Heavens, R. P.; Smith, D. W.; Hewson, L.; Rigby, M. R.; Sirinathsinghji, D. J. S.; Brown, N.; Wafford, K. A.; Whiting, P. J. *θ*, a novel *γ*-aminobutyric acid type A receptor subunit. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 9891−9896. (f) Barnard, E. A.; Skolnick, P.; Olsen, R. W.; Mohler, H.; Sieghart, W.; Biggio, G.; Braestrup, C.; Bateson, A. N.; Langer, S. Z. Subtypes of *γ*-aminobutyric acid A receptors: classification on the basis of subunit structure and receptor function. *Pharmacol. Rev.* **1998**, *50*, 291−313.
(4) McKernan, R. M.; Whiting, P. J. Which GABA-A receptor subtypes really occur in the brain? *Trends Neurosci.* **1996**, *19*, 139−143.
(5) Farrar, S. J.; Whiting, P. J.; Bonnert, T. P.; McKernan, R. M. Stoichiometry of a ligand-gated ion channel determined by fluorescence energy transfer. *J. Biol. Chem.* **1999**, *274*, 10100−10104.
(6) Sieghart, W. Structure and pharmacology of *γ*-aminobutyric acid-A receptor subtypes. *Pharmacol. Rev.* **1995**, *47*, 181−234.
(7) Grundstrom, R.; Holmberg, G.; Hansen, T. Degree of sedation obtained with various doses of diazepam and nitrazepam. *Acta Pharmacol. Toxicol.* **1978**, *43*, 13−18.
(8) Hudson, R. D.; Wolpert, M. K. Central muscle relaxant effects of diazepam. *Neuropharmacology* **1970**, *9*, 481−488.
(9) Clarke, P. R. F.; Eccersley, P. S.; Frisby, J. P.; Thornton, J. A. Amnesic effect of diazepam (valium). *Br. J. Anaesth.* **1970**, *42*, 690−7.
(10) Rush, C. R. Behavioral pharmacology of zolpidem relative to benzodiazepines: a review. *Pharmacol., Biochem. Behav.* **1998**, *61*, 253−269.
(11) McKernan, R. M.; Rosahl, T. W.; Reynolds, D. S.; Sur, C.; Wafford, K. A.; Atack, J. R.; Farrar, S.; Myers, J.; Cook, G.; Ferris, P.; Garrett, L.; Bristow, L.; Marshall, G.; Macaulay, A.; Brown, N.; Howell, O.; Moore, K. W.; Carling, R. W.; Street, L. J.; Castro, J. L.; Ragan, C. I.; Dawson, G. R.; Whiting, P. J. Sedative but not anxiolytic properties of benzodiazepines are mediated by the $GABA_A$ receptor α_1 subtype. *Nat. Neurosci.* **2000**, *3*, 587−592.
(12) Rudolph, U.; Crestani, F.; Benke, D.; Brünig, I.; Benson, J. A.; Fritschy, J.-M.; Martin, J. R.; Bluethmann, H.; Möhler, H. Benzodiazepine actions mediated by specific *γ*-aminobutyric $acid_A$ receptor subtypes. *Nature* **1999**, *401*, 796−800.
(13) Yu, S.; He, X.; Ma, C.; McKernan, R.; Cook, J. M. Studies in search of α2 selective ligands for $GABA_A$/BzR receptor subtypes. Part 1. Evidence for the conservation of pharmacophoric descriptors for DS subtypes. *Med. Chem. Res.* **1999**, *9*, 186−202.
(14) Albaugh, P. A.; Marshall, L.; Gregory, J.; White, G.; Hutchison, A.; Ross, P. C.; Gallagher, D. W.; Tallman, J. F.; Crago, M.; Casella, J. V. Synthesis and biological evaluation of 7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]pyrimidin-5(6*H*)-ones as functionally selective ligands of the benzodiazepine receptor site on the GABA-A receptor. *J. Med. Chem.* **2002**, *45*, 5043−5051.
(15) Collins, I.; Moyes, C.; Davey, W. B.; Rowley, M.; Castro, J. L.; Bromidge, F.; Quirk, K.; Atack, J. R.; McKernan, R. M.; Thompson, S. A.; Wafford, K.; Dawson, G. R.; Pike, A.; Sohal, B.; Tsou, N. N.; Ball, R. G. 3-Heteroaryl-2-pyridones: Benzodiazepine site agonists with functional selectivity for α2/α3-subtypes of human $GABA_A$ receptor-ion channels. *J. Med. Chem.* **2002**, *45*, 1887−1900.
(16) Crawforth, J.; Atack, J. R.; Cook, S. M.; Gibson, K. R.; Nadin, A.; Owens, A. P.; Pike, A.; Rowley, M.; Smith, A. J.; Sohal, B.; Sternfeld, F.; Wafford, K.; Street, L. J. Tricyclic pyridones as functionally selective human $GABA_A$ $\alpha_{2/3}$ receptor-ion channel ligands. *Bioorg. Med. Chem.* **2004**, *14*, 1679−1682.
(17) Carling, R. W.; Moore, K. W.; Street, L. J.; Wild, D.; Isted, C.; Leeson, P. D.; Thomas, S.; O'Connor, D.; McKernan, R. M.; Quirk, K.; Cook, S. M.; Atack, J. R.; Wafford, K. A.; Thompson, S. A.; Dawson, G. R.; Ferris, P.; Castro, J. L. 3-Phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[3,4-*a*]phthalazines and analogues: High affinity $GABA_A$ benzodiazepine receptor ligands with α2, α3, and α5-subtype binding selectivity over α1. *J. Med. Chem.* **2004**, *47*, 1807−1822.

(18) Hadingham, K. L.; Wingrove, P.; Le Bourdelles, B.; Palmer, K. J.; Ragan, C. I.; Whiting, P. J. Cloning of cDNA sequences encoding human α2 and α3 γ-aminobutyric acid A receptor subunits and characterization of the benzodiazepine pharmacology of recombinant α1-, α2-, α3-, and α5-containing human γ-aminobutyric acidA receptors. *Mol. Pharmacol.* **1993**, *43*, 970−975.
(19) Wafford, K. A.; Whiting, P. D.; Kemp, J. A. Differences in affinity and efficacy of benzodiazepine receptor ligands on recombinant GABA-A receptor subtypes. *Mol. Pharmacol.* **1992**, *43*, 240−244.
(20) Whiting, P. J.; McAllister, G.; Vasilatis, D.; Bonnert, T. P.; Heavens, R. P.; Smith, D. W.; Hewson, L.; O'Donnell, R.; Rigby, M. R.; Sirinathsinghji, D. J. S.; Marshall, G. R.; Thompson, S. A.; Wafford, K. A. Neuronally restricted RNA splicing regulates the expression of a novel $GABA_A$ receptor subunit conferring atypical functional properties. *J. Neurosci.* **1997**, *17*, 5027−5037.
(21) Russell, M. G. N.; Carling, R. W.; Atack, J. R.; Bromidge, F. A.; Cook, S. M.; Isted, C.; Lucas, M.; McKernan, R. M.; Mitchinson, A.; Moore, K. W.; Narquizian, R.; Macaulay, A. J.; Thomas, D.; Thompson, S. A.; Wafford, K. A.; Castro, J. L. Discovery of functionally selective 7,8,9,19-tetrahydro-7,10-ethano-1,2,4-triazolo[3,4-*a*]pthalazines as GABAA receptor agonists at the α3 subunit. *J. Med. Chem* **2005**, *48*, 1367−1383.
(22) Hollinshead, S. P.; Trudell, M. L.; Skolnick, P.; Cook, J. M. Structural requirements for agonist actions at the benzodiazepine receptor: studies with analogs of 6-(benzyloxy)-4-(methoxymethyl)-β-carboline-3-carboxylic acid ethyl ester. *J. Med. Chem.* **1990**, *33*, 1062−1069.
(23) Colotta, V.; Cecchi, L.; Melani, F.; Filacchioni, G.; Martini, C.; Giannaccini, G.; Lucacchini, A. Tricyclic heteroaromatic systems. [1]Benzopyranopyrrol-4-ones and [1]benzopyrano-1,2,3-triazol-4-ones as benzodiazepine receptor ligands. Synthesis and structure−activity relationships. *J. Med. Chem.* **1990**, *33*, 2646−2651.
(24) Broughton, H. B.; Carling, W. R.; Castro-Pineiro, J. L.; Guiblin, A. R.; Madin, A.; Moore, K. W.; Russell, M. G.; Street, L. J. Preparation of triazolopyridazine derivatives as ligands for GABA receptors. U.S. 6,255,305 B1, 2001.
(25) Atack, J. R.; Smith, A. J.; Emms, F.; McKernan, R. M. Regional differences in the inhibition of mouse in vivo [3H]Ro 15-1788 binding reflect selectivity for α1 versus α3 Subunit-Containing $GABA_A$ Receptors. *Neuropsychopharmacology* **1999**, *20*, 255−262.
(26) Scott-Stevens, P.; Atack, J. R.; Sohal, B.; Worboys, P. Rodent pharmacokinetics and receptor occupancy of the $GABA_A$ receptor subtype selective benzodiazepine site ligand L-838417. *Biopharm. Drug Dispos*. **2005**, *26*, 13−20.
(27) McCabe, C.; Leslie, J. C.; Atack, J. R.; Street, L. J.; Wafford, K. A.; Dawson, G. R.; Reynolds, D.; Shaw, D. Subtype selective GABAergic drugs facilitate extinction of mouse operant behaviour. *Neuropharmacology* **2004**, *46*, 171−178.
(28) Dawson, G. R.; Tricklebank, M. D. Use of the elevated plus maze in the search of novel anxiolytic agents. *Trends Pharmacol. Sci.* **1995**, *16*, 33−36.
(29) Atack, J. R.; Wafford, K. A.; Tye, S. J.; Cook, S. M.; Sohal, S.; Pike, A.; Sur, C.; Melillo, D.; Bristow, L.; Bromidge, F.; Ragan, C. I.; Kerby, J.; Street, L.; Carling, R.; Castro, J.-L.; Whiting, P.; Dawson, G. R.; McKernan, R. M. TPA023, an agonist selective for α2- and α3-containing $GABA_A$ receptors, is a non-sedating anxiolytic in rodents and primates. *J. Pharmacol. Exp. Ther.*, in press.
(30) Ator, N. A. Contributions of $GABA_A$ receptor subtype selectivity to abuse liability and dependence potential of pharmacological treatments for anxiety and sleep disorders. *CNS Spectrosc*. **2005**, *10*, 31−39.

JM058034A