Discovery of Imidazo[1,2-*b*][1,2,4]triazines as $GABA_A$ α2/3 Subtype Selective Agonists for the Treatment of Anxiety

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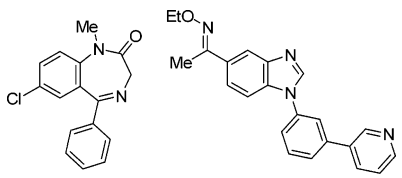
Abstract: The identification of a series of imidazo[1,2-*b*][1,2,4]triazines with high affinity and functional selectivity for the $GABA_A$ α3-containing receptor subtype is described, leading to the identification of a clinical candidate, **11**. Compound **11** shows good bioavailability and half-life in preclinical species, and it is a nonsedating anxiolytic in both rat and squirrel monkey behavioral models.

The $GABA_A$ receptor is a ligand-gated chloride ion channel that has a pentameric structure composed from a family of at least 16 subunits (α1−6, β1−3, γ1−3, δ, ϵ, π, and θ), but comprising generally of α, β, and γ subunits in a 2:2:1 stoichiometry. The benzodiazepine (BZ) binding site is an allosteric site located between the α and γ2 subunits.[1−3] Hence, benzodiazepines, exemplified by diazepam (**1**, Chart 1) interact with $GABA_A$ receptors containing β and γ2 subunits in conjunction with an α1, α2, α3, or α5 (but not α4 or α6) subunit and are full agonists at the BZ recognition site of these four subtypes, leading to a positive modulation of the actions of GABA.[4] Diazepam displays anxiolytic, anticonvulsant, sedative-hypnotic, anaesthetic, and muscle-relaxant activities, but it is also associated with side effects such as amnesia, tolerance, dependence, and alcohol potentiation. Although sedation and myorelaxation are of clinical utility for treating sleep disorders or premedication prior to procedures such as endoscopy, in terms of treating general anxiety disorder (GAD) they are liabilities. Consequently, there is a need for a nonsedating anxiolytic.[5,6]

It has been shown using α1H101R mutant mice, in which the α1 subunit is rendered insensitive to diazepam, that diazepam retains its anxiolytic but not its sedative effect.[7,8] There is also evidence in mice lacking the α5 subunit that this subtype is associated with memory and learning and is not involved in anxiety.[9] This suggests that $GABA_A$ receptors containing the α1 subtype are involved in the sedative effects of BZs whereas the α2 and/or α3 subtypes mediate the anxiolytic effects.[10,11] Therefore, BZ site agonists with selectivity for the α2/3 subtypes may be anxiolytics with a potential for reduced side effects.[6]

We have previously reported on the generation of a series of imidazopyrimidines that are structurally related to **2** (NS-2710, Chart 1).[12] In particular, the 7-trifluoromethyl-3-(2′-cyano-2,4′-difluorobiphenyl-5-yl) analogue (**3**, Table 1) and the 7-(1-hydroxy-1-methylethyl)-3-[4-fluoro-3-(pyridine-3-yl)phenyl derivative (**4**) were identified as being worthy of further development. Both compounds exhibit functional selectivity for the α2 and α3 subtype-containing receptors over the α1 and α5 subtypes and are orally bioavailable. However, although **3** has low clearance and a long half-life in rat and dog, its efficacy is low at the α3 subtype. On the other hand, **4** has higher efficacy at the α3 subtype but with a short half-life in animals. Therefore, a compound with higher efficacy at the α3 subtype and a long half-life was sought. In this manuscript, we describe the identification of a series of imidazo[1,2-*b*][1,2,4]triazines leading to the selection of a clinical candidate that meets the above criteria.

Chart 1



1 **2**

The binding affinities of compounds were measured by the inhibition of [^{3}H]Ro15-1788 binding to human recombinant $GABA_A$ receptor subtypes stably expressed in L(tk$^-$) cells containing α1, α2, α3, or α5 subunits in combination with β3 and γ2.[13,14] The efficacies of most compounds were determined using whole-cell patch clamp recordings on the same receptor subtype combinations. A concentration of GABA was used that elicited a response that was 20% of the maximum GABA current (EC_{20}). Modulation of this current by increasing concentrations of the test compounds was measured.[15] Alternatively, efficacies were determined in the same cell lines by measuring the modulation of ^{36}Cl ion flux produced by the EC_{20} concentration of GABA in the presence of a concentration of 1000 × K_i of the test compound.[16]

When exploring initial changes to the heterocyclic core, it was found that the imidazo[1,2-*b*]pyridazine (**5**, Scheme 1) retained the functional selectivity for the α3 subtype (Table 1), even though affinity and efficacy were slightly reduced relative to the corresponding imidazo[1,2-*a*]pyridine (**6**).[12] The previously reported introduction of another nitrogen atom to the top of the six-membered ring, to give imidazo[1,2-*a*]pyrimidine (**7**),[12] showed a 10-fold increase in affinity, and it was gratifying to find that this effect translated into the imidazo[1,2-*b*][1,2,4]-triazine (**8**). Like that of **5** compared to **6**, compound **8** had lower efficacy than **7** at both α1 and α3 subtypes but retained the selectivity window. The general synthetic route outlined in Scheme 2 was used to explore the SAR of this new scaffold. The 3-substituted imidazotriazine core (**16**) was synthesized by condensation of the corresponding 5-substituted-3-amino-1,2,4-triazine (**15**) with bromoacetaldehyde (formed immediately beforehand by treatment of bromoacetaldehyde diethyl acetal with concentrated hydrobromic acid). The 3-aminotriazines **15** were in turn prepared by the condensation of aminoguanidine and the dibromoketone (**14**) (prepared by bromination of the corresponding methyl ketone). This condensation was nonselective, producing a mixture of aminotriazines, but a regioselective synthesis of aminotriazines using bis-morpholine ketoaminals has since been reported.[17] The imidazotriazine was then brominated selectively in the 3-position to give **17**, which was then coupled with the required biaryl boronate (**18**) in a Suzuki reaction to give the final compounds.

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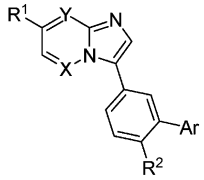
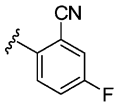
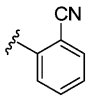
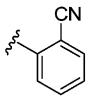
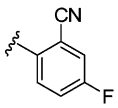
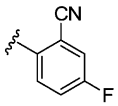
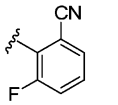
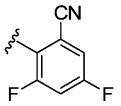
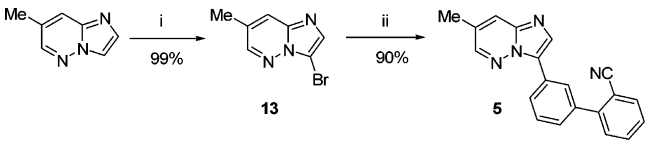
Table 1. Binding Affinities and Efficacies at Cloned Human $GABA_A$ Receptor Subtypes



						K_i (nM)[a]		Efficacy[b]	
compd	X	Y	R^1	R^2	Ar	α1β3γ2	α3β3γ2	α1β3γ2	α3β3γ2
1						13 ±1	33 ± 3	0.93 ± 0.07	0.80 ± 0.13
2						2.0 ± 0.3	14 ± 1	0.40 ± 0.05	0.99 ± 0.04
3	CH	N	CF_3	F		1.2 ± 0.1	0.73 ± 0.03	-0.03 ± 0.02	0.25 ± 0.03
4	CH	N	$C(OH)Me_2$	F	3-pyridyl	0.85 ± 0.1	4.0 ± 0.5	0.06 ± 0.03	0.54 ± 0.08
5	N	CH	Me	H		13 ± 1	19 ± 2	-0.20 ± 0.06[c]	0.26 ± 0.03[c]
6	CH	CH	Me	H		4.5 ± 0.1	3.7 ± 0.6	-10 ± 4%	0.55 ± 0.04
7	CH	N	Me	H		0.40 ± 0.10	0.40 ± 0.1	0.07 ± 0.03	0.69 ± 0.08
8	N	N	Me	H		1.5 ± 0.2	1.2 ± 0.3	-21 ± 2%	0.34 ± 0.01
9	N	N	CF_3	F		0.25 ± 0.05	0.80 ± 0.1	-13 ± 3%	-0.06 ± 0.04
10	N	N	$C(OH)Me_2$	F		1.2 ± 0.2	2.1 ± 0.1	-15 ± 1%	0.43 ± 0.09
11	N	N	$C(OH)Me_2$	F		0.73 ± 0.21	1.8 ± 0.4	0.03 ± 0.01	0.50 ± 0.02
12	N	N	$C(OH)Me_2$	F		0.15 ± 0.05	1.0 ± 0.1	0.00 ± 0.05	0.37 ± 0.03

[a] Inhibition of [^{3}H]Ro15-1788 binding to recombinant human $GABA_A$ receptor subtypes stably expressed in L(tk$^-$) cells. Values are the geometric mean ± SEM for $n = 2-12$. Six to eight concentrations of each test compound incremented in half-log units were used in the determinations. [b] Efficacy measured at $GABA_A$ receptors stably expressed in L(tk$^-$) cells using whole cell patch clamp recording and represents the effect of the test compound on the current produced by an EC_{20}-equivalent of GABA. Values are quoted relative to the maximum response seen with the full agonist chlordiazepoxide (CDZ, efficacy = 1.00) except for those figures quoted as percentages. [c] Modulation of chloride ion flux in cells expressing $\beta 3\gamma 2$ plus either α1 or α3 produced by an EC_{20} equivalent concentration of GABA in the presence of an approximate 1000 × K_i concentration of test compound. Values are the mean of at least seven independent experiments.

Scheme 1[a]



[a] Reagents and conditions: (i) Br_2, NaOAc, AcOH, rt, 20 min; (ii) **18a**, $Pd(PPh_3)_4$, K_3PO_4, DMA, 80 °C, 21 h.

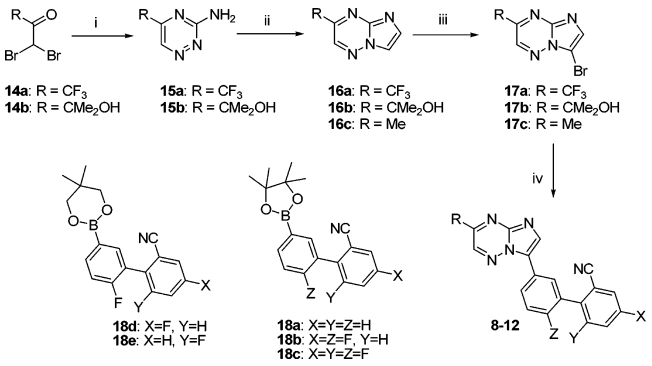
Table 2. Pharmacokinetic Data for Selected Compounds[a]

compd	species	Cl_p (mL/min/kg)	$t_{1/2}$ (h)	V_d (L/kg)	F (%)
10	rat	1.1	38	3.4	ND[b]
11	rat	2.4	11	2.1	77
11	dog	4.6	6.5	1.9	22
11	rhesus	5.8	4.9	2.1	29
12	rat	1.0	69	5.8	64

[a] Dose: 1 mg/kg iv; 1 mg/kg po. [b] Oral dose not administered.

On carrying out optimization studies, we prepared the imidazotriazine analogue (**9**) of **3** and found similar decreases on the functional efficacy to that observed with the methyl derivatives (**8** and **7**). The lower intrinsic efficacy of this core compared to the imidazopyrimidines proved useful when optimizing substitution in this series and allowed us to have different substituents to the imidazopyrimidines while still retaining antagonism at the α1 subtype. Thus, imidazotriazine

Scheme 2[a]



[a] Reagents and conditions: (i) (a) $NaOAc \cdot 3H_2O$, H_2O, reflux, 30 min; (b) aminoguanidine bicarbonate, 4 N NaOH(aq) or $KHCO_3$, rt, 1.5-39 h; (ii) $BrCH_2CHO$, EtOH, 50-80 °C, 1-2 d; (iii) Br_2, NaOAc, AcOH, rt, 0.25-6 h; (iv) **18**, $Pd(PPh_3)_4$, 2 M Na_2CO_3(aq) or K_3PO_4, THF or DME or DMA, 70-80 °C, 16-24 h.

Table 3. Binding Affinity and Efficacy of Compound **11**

subtype	K_i[a] (nM)	efficacy/CDZ[b]
$\alpha1\beta3\gamma2$	0.73 ± 0.21	0.03 ± 0.01
$\alpha2\beta3\gamma2$	2.0 ± 0.4	0.38 ± 0.04
$\alpha3\beta3\gamma2$	1.8 ± 0.4	0.50 ± 0.02
$\alpha5\beta3\gamma2$	1.1 ± 0.2	0.37 ± 0.04

[a,b] See corresponding footnotes in Table 1.

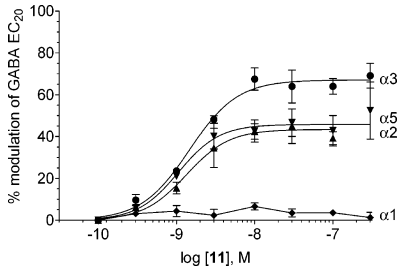


Figure 1. Efficacy of **11** at human recombinant $GABA_A$ receptors containing $\beta3$, $\gamma2$, and various α subunits. The ability of **11** to potentiate currents produced by a GABA concentration that produced a response 20% of the maximum (EC_{20}) was measured using whole-cell patch clamp electrophysiology. In comparison, a nonselective full agonist such as diazepam or chlordiazepoxide would produce a potentiation of 100−150% at each subtype. Values shown are mean ± SEM (n = 4−6).

10, for which the imidazopyrimidine analogue had too high efficacy at the α1 subtype,[12] was found to have a good binding and efficacy profile and a very long half-life in rat (38 h, Table 2). Additional fluorination on the terminal aryl ring led to the 4,6-difluoro analogue (**12**) with a similar profile to **10,** but the optimum efficacy and half-life across three species was given by the 6-fluoro derivative (**11**).

The full binding and efficacy profile of **11** is shown in Figure 1 and Table 3, which shows that it also has somewhat lower efficacy at both the α2 and α5 subtypes compared to its efficacy at α3. **11** had no significant activity at 133 other receptors and in 36 enzyme assays. In a measurement of central BZ receptor occupancy by displacement of [^{3}H]Ro15-1788 binding in rat,[18] it was found to achieve high occupancy (Occ_{50} 0.3 mg/kg po) at relatively low plasma levels (56 nM). In animal models of anxiety, **11** was active in the rat elevated plus maze[19] at 1 mg/kg po (at 88% occupancy, Figure 2) and showed no sedation up to 10 mg/kg po in the rat chain-pulling assay[20] (where 99% occupancy was achieved, Figure 3). In the squirrel monkey conditioned emotional response model[21] a significant anxiolytic effect was seen at 0.3 mg/kg po, but no significant sedation

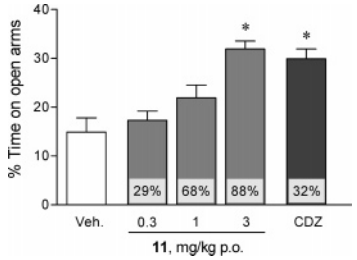


Figure 2. The anxiolytic-like effects of **11** in the rat elevated plus maze test. The mean time (± SEM, n = 18/group) spent on the open arms (expressed as a percentage of the total time, 5 min, on the maze) after 30 min pretreatment with vehicle (0.5% methyl cellulose, po), **11** (0.3, 1 or 3 mg/kg po) or chlordiazepoxide (CDZ, 5 mg/kg ip). The basis of this assay is that the less anxious an animal is, then the more time it will spend on the open arms compared to the safer, closed arms. The % figures denote the % occupancy at each dose. * = significantly different from control (vehicle), $p < 0.05$.

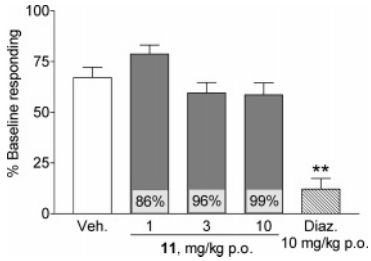


Figure 3. The lack of sedative effect of **11** in the rat chain-pulling test even at a dose, 10 mg/kg, corresponding to 99% occupancy. The mean rate of responding (± SEM; n = 11−12/group) over a 60 min trial period immediately following treatment with either vehicle, **11** or diazepam (diaz.). The % figures denote the % occupancy at each dose. ** = significantly different from control (vehicle), $p < 0.01$.

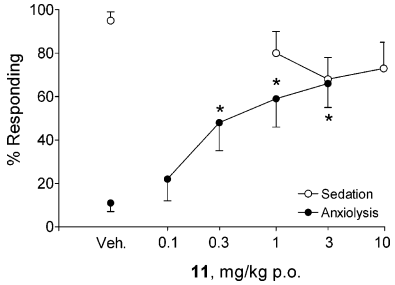


Figure 4. Nonsedating anxiolytic properties of **11** in nonhuman primates. In the squirrel monkey conditioned emotional response (CER) assay **11** has anxiolytic-like activity. In CER assay, all doses of **11** (0.3, 1, and 3 mg/kg po) reversed the inhibition of lever-pressing response produce by the presentation of the stimulus (i.e. the monkey was less anxious about the possibility of receiving an electric shock when presented with the light cue). In the sedation assay, the rate of lever pressing to obtain a fruit juice reward in squirrel monkeys was measured following treatment with either vehicle (0.5% methyl cellulose) or **11** (1, 3, or 10 mg/kg po). Values shown are mean ± SEM (n = 10−11/group). * = significantly different from control (vehicle), $p < 0.05$.

was observed up to 10 mg/kg po as measured by the response rates during the RPI30 schedule (Figure 4). **11** also showed no impairment of performance in the mouse rotarod assay[11] up to a dose of 10 mg/kg po corresponding to 100% occupancy (Figure 5).

Thus, on the basis of its excellent efficacy and pharmacokinetic profile, compound **11** was chosen as a clinical candidate. The multi-kilogram scale synthesis of this compound has already been described.[22] In Phase I clinical trials, it demonstrated a PK/PD profile suitable for once daily dosing in man. [23]

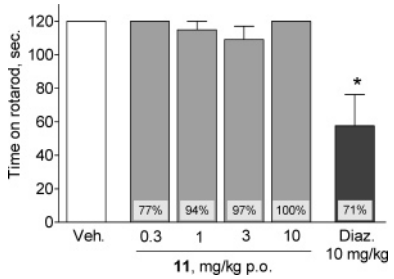


Figure 5. Lack of effect of **11** in the mouse rotarod assay of sedation and/or myorelaxation. Even at a dose of 10 mg/kg, **11** showed no sign of impaired performance whereas at the same dose, diazepam (Diaz.) showed a marked impairment. Values shown are mean ± SEM (n = 8/group). The % figures denote the % occupancy at each dose. * = significantly different from control (vehicle), $p < 0.05$.

Supporting Information Available: Full experimental details and data for all final compounds. Squirrel monkey RPI lever pressing assay. Elemental analyses and HPLC data. This information is available free of charge via the Internet at http://pubs.acs.org.

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