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2,3,7-Trisubstituted pyrazolo[1,5-*d*][1,2,4]triazines: Functionally selective $GABA_A$ α3-subtype agonists

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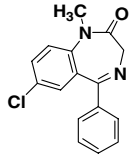
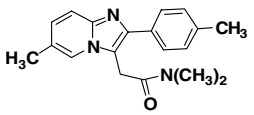
Abstract—Novel synthetic routes have been devised for the preparation of previously inaccessible 2,3,7-trisubstituted pyrazolo-[1,5-*d*][1,2,4]triazines **2**. These compounds are high affinity ligands for the $GABA_A$ benzodiazepine binding site and some analogues show functional selectivity for agonism at α3-containing receptors over α1-containing receptors with the lead compound being **32**.

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 sixteen subunits (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 is 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, anaesthetics, avermectins and benzodiazepines which all modulate opening of the channel.[6] Of these, the benzodiazepine (BZ) site is the best characterised due to its role in mediating the clinical effects of anxiolytics such as diazepam.



Diazepam



Zolpidem

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 are nonselective, high efficacy agonists and these compounds show sedative,[7] muscle-relaxant[8] and amnesic[9] properties. Zolpidem, which has higher affinity for α1- (the major subtype of $GABA_A$ receptors in the CNS)[4] over α2-, α3- and α5- containing receptors is particularly sedative in animal tests and in human.[10] This suggests that compounds with 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 BZ 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 of $GABA_A$ α2/3 subtype selective ligands have been reported in the literature.[12–16] We disclosed a series of triazolophthalazines as $GABA_A$ α2/3 agonists which had moderately higher affinity at α2- and α3- compared to α1-containing receptors[17] and we recently reported on series of triazolopyridazines,[18] imidazopyrimidines,[19] imidazotriazines[20] and imidazopyrazinones[21] as functionally selective α2/α3 agonists. In this communication, we describe our

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efforts in designing, synthesising and optimising a novel series of pyrazolotriazines as functionally selective $GABA_A$ α3 agonists.

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 (β3,γ2, plus either an α1 or α3) human recombinant $GABA_A$ receptors stably expressed in L(tk−) cells.[22] As a general screen for efficacy, modulation of chloride ion flux in cells expressing β3γ2 plus either α1 or α3 produced by an EC_{20} equivalent concentration of GABA in the presence of an approximate $1000 \times K_i$ concentration of test compound was carried out. Efficacy is expressed relative to the full agonist chlorodiazepoxide (relative efficacy = 1.0), from at least seven independent experiments.[23] For key compounds, efficacies were re-checked using whole-cell patch-clamp recordings from L(tk−) cells stably expressing α1β3γ2 or α3β3γ2 $GABA_A$ receptor subtypes using increasing concentration of test ligand to measure the concentration response.[14,24] In all cases, good agreement was observed.[23]

Compound **1** is the development compound identified from the triazolopyridazine series[18] and we sought to identify alternative leads and intellectual property. 2,3,7-Trisubstituted pyrazolo[1,5-*d*][1,2,4]triazines **2** were unique structures at the time we embarked on this strategy although since then we have published on one such molecule as a $GABA_A$ α5 selective inverse agonist for cognition enhancement.[25] Herein we report on the synthesis and SAR of 2,3,7-trisubstituted pyrazolo[1,5-*d*][1,2,4]triazines as $GABA_A$ α3 selective agonists (Fig. 1).

Starting from commercially available phenyltetronic acid **3**, reaction with hydrazine hydrate in ethanol under reflux for 10 days gave the 3-hydroxy pyrazole **4**. (Scheme 1). Alkylation at the 3-position of **4** with 3-chloromethyl-2-methyl-1,2,4-triazole followed by oxidation of the primary alcohol with manganese dioxide gave the aldehyde **6**. Condensation of **6** with (2-fluoro)benzhydrazide gave **7** which was cyclised to the target molecule **8** by heating at 200 °C in Dowtherm A for 30 h.

Compound **7** exists as two distinct tautomers in NMR solution, the structure as drawn in Scheme 1 and the tautomer (**7a**) in Scheme 2. On characterisation of **7** there was evidence for cyclisation in the mass spectrometer to **8**. A likely pericyclic mechanism for the thermal cyclisation of **7** to give **8** is outlined in Scheme 2.

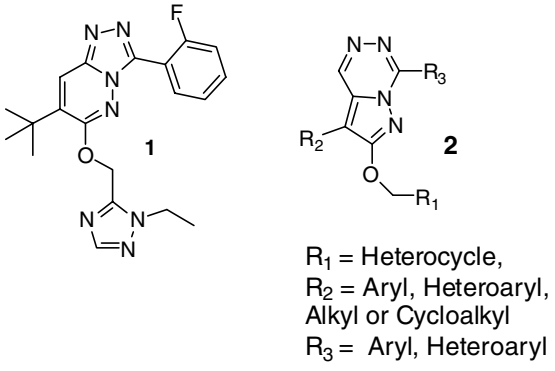
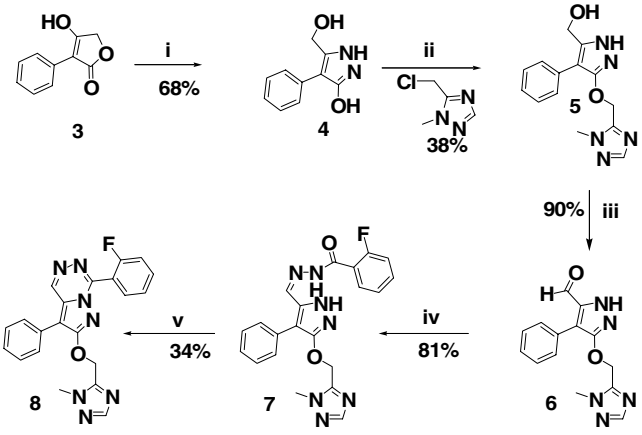
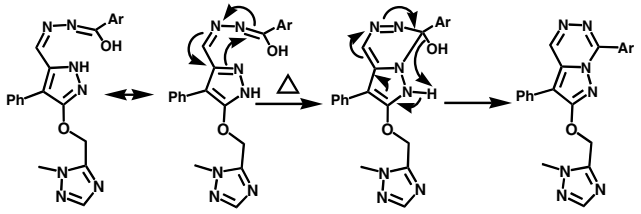


Figure 1. New class of benzodiazepine receptor ligands (**2**).



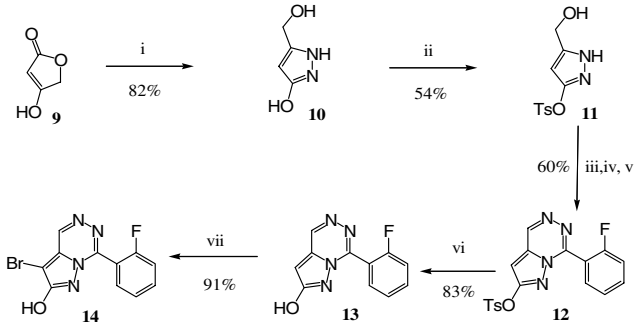
Scheme 1. Reagents and conditions: (i) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 10 days; (ii) K_2CO_3, DMF; (iii) MnO_2, $CHCl_3$, reflux, 8 h; (iv) 2-fluorobenzhydrazide, xylene, reflux, 1 h; (v) Dowtherm A, 200 °C, 30 h.



Scheme 2.

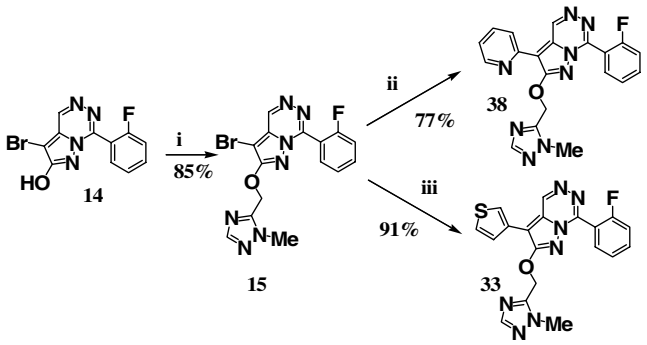
Compound **8** was evaluated in our standard biological assays and was found to be a high affinity ligand at $GABA_A$ receptors (K_i: α3 = 0.77 nM, α1 = 0.39 nM) with functional selectivity favouring α3-containing receptors (0.44 rel to CDZ) over α1-containing receptors (0.18 rel to CDZ) as measured in the electrophysiological assay.

In order to allow optimisation studies at the 2-(R_1) and 3-(R_2) positions, the versatile 3-bromo intermediate **14** was synthesised as described in Scheme 3. Reaction of



Scheme 3. Reagents and conditions: (i) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 1 h; (ii) TsCl, Et_3N, CH_2Cl_2, rt, 16 h; (iii) MnO_2, $CHCl_3$, reflux, 8 h; (iv) 2-fluorobenzhydrazide, xylene, reflux, 1 h; (v) Dowtherm A (0.025 M), 180 °C, 3 days; (vi) 4 N NaOH, dioxane–H_2O, 60 °C, 3 h; (vii) Br_2, AcOH, rt, 2.25 h.

hydrazine hydrate with tetronic acid (**9**) in refluxing ethanol for just 1 h gave the 3-hydroxy pyrazole **10**.[26] The 2-hydroxy group was protected with tosyl to give **11**, before oxidation of the primary alcohol, condensation with (2-fluoro)benzhydrazide and subsequent cyclisation at elevated temperature to give **12**. Removal of the tosyl group with sodium hydroxide in aqueous dioxane, followed by bromination of **13** in acetic acid, gave **14**.

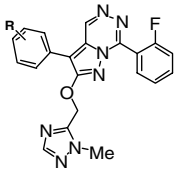


Scheme 4. Reagents and conditions: (i) 3-(chloromethyl)-2-methyl-1,2,4-triazole hydrochloride, Cs_2CO_3; DMF, rt to 60 °C, 25 h; (ii) 2-(tributylstannyl)pyridine, $Pd(PPh_3)_4$, CuI, dioxane, 100 °C, 18 h; (iii) thiophene-3-boronic acid, Pd_2dba_3, P(*t*-Bu)$_3$, Cs_2CO_3, dioxane, 80–90 °C, 41 h.

The 2-position of **14** was alkylated with 3-(chloromethyl)-2-methyl-1,2,4-triazole hydrochloride in the presence of caesium carbonate in DMF and Suzuki or Stille chemistry was used to elaborate the 3-position in high yield as shown in Scheme 4.

Fluorinated and di-fluorinated phenyl groups (compounds **16**, **20** and **26**–**30**) were introduced using the route described in Scheme 1, starting from the appropriate fluorophenyl tetronic acid. The other 3-substituted phenyl analogues (Table 1) as well as all the 3-heteroaryl analogues (Table 2) were prepared using palladium catalysed couplings in a similar way to the heterocyclic couplings described in Scheme 4. Optimisation studies at the 7-position (R_3) were easily carried out essentially using the route outlined in Scheme 1 but starting with 2-fluorophenyl tetronic acid and by using the appropriate acylhydrazides in the penultimate step (compounds **38**–**45**, Table 3; and **46**–**49** and **51**, Table 4). Compound **50** was made starting from phenyl tetronic acid as in

Table 1. Effect of 3-aryl changes on α3 affinity and α1 and α3 efficacy



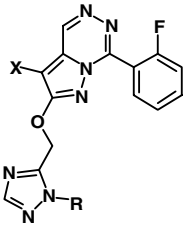
Compound	R	K_i[a] α3 (nM)	Efficacy[b,c] α1	Efficacy[b,c] α3
8	H	0.77	0.18	0.44
16	2-F	0.45	0.22	0.40
17	2-Cl	8.7	0.32	0.32
18	2-Me	23	—	—
19	2-CF_3	>33	—	—
20	3-F	0.28	0.23	0.46
21	3-Cl	1.1	0.35	0.45
22	3-CN	1.6	0.35	0.28
23	3-CF_3	0.54	0.30	0.46
24	3-CH_2OH	6.6	0.50	0.50
25	3-NH_2	14	0.42	0.38
26	4-F	6.3	0.09	0.31
27	2,3-F_2	1.5	0.27	0.40
28	2,5-F_2	0.20	0.29	0.46
29	2,6-F_2	0.55	0.23	0.45
30	3,5-F_2	>33	—	—

[a] K_i values for binding to the BZ sites of stably expressed human recombinant $GABA_A$ receptors with the composition α3β3γ2. Inhibition of the binding of 1.8 nM [^{3}H]Ro15-1788 was measured and the concentration required to inhibit binding by 50% (IC_{50}) was converted to a K_i value according to the Cheng–Prusoff equation.[22] Data shown are means of three to ten experiments.

[b] Modulation of chloride ion flux in cells expressing $\beta_3\gamma_2$ plus either α_1 or α_3 produced by an EC_{20} equivalent concentration of GABA in the presence of an approximate $1000 \times K_i$ concentration of test compound.[23] Efficacy is expressed relative to the full agonist chlorodiazepoxide (relative efficacy = 1.0), from at least seven independent experiments.

[c] Efficacy measurement of effect of test compound on a current at GABA EC_{20} using whole-cell patch-clamp electrophysiological recording.[14,24] Efficacy is expressed relative to the full agonist chlorodiazepoxide (relative efficacy = 1.0), from at least seven independent experiments.

Table 2. Effect of 3-heteroaryl changes on α3 affinity and α1 and α3 efficacy



Compound	X	K_i[a] α3 (nM)	Efficacy[b,c] α1	Efficacy[b,c] α3
31	2-Thienyl	0.10	0.01	0.12
32	3-Thienyl	0.10	−0.02	0.21
33	2-Furyl	0.11	−0.09	0.16
34	2-Pyridyl	1.4	0.45	0.56
35	3-Pyridyl	0.98	0.35	0.52
36	4-Pyridyl	0.14	0.10	0.19
37	5-Pyrimidyl	>33	—	—

[a] K_i values for binding to the BZ sites of stably expressed human recombinant $GABA_A$ receptors with the composition α3β3γ2. Inhibition of the binding of 1.8 nM [^{3}H]Ro15-1788 was measured and the concentration required to inhibit binding by 50% (IC_{50}) was converted to a K_i value according to the Cheng–Prusoff equation.[22] Data shown are means of three to ten experiments.

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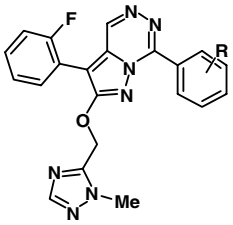
[c] Efficacy measurement of effect of test compound on a current at GABA EC_{20} using whole-cell patch-clamp electrophysiological recording.[14,24] Efficacy is expressed relative to the full agonist chlorodiazepoxide (relative efficacy = 1.0), from at least seven independent experiments.

Table 3. Effect of 7-aryl changes on α3 affinity and α1 and α3 efficacy



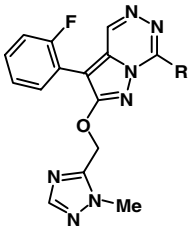
Compound	R	K_i[a] α3 (nM)	Efficacy[b,c] α1	Efficacy[b,c] α3
16	2-F	0.45	0.22	0.40
38	3-F	1.2	0.38	0.57
39	4-F	0.94	0.36	0.60
40	2,4-F_2	2.0	0.42	0.78
41	2,5-F_2	1.3	0.52	0.52
42	2,6-F_2	0.52	0.29	0.55
43	2,3,6-F_3	2.7	0.45	0.55
44	2,4,6-F_3	2.6	0.37	0.59
45	2-Cl	21	−0.02	0.02

[a] K_i values for binding to the BZ sites of stably expressed human recombinant $GABA_A$ receptors with the composition α3β3γ2. Inhibition of the binding of 1.8 nM [^{3}H]Ro15-1788 was measured and the concentration required to inhibit binding by 50% (IC_{50}) was converted to a K_i value according to the Cheng–Prusoff equation.[22] Data shown are means of three to ten experiments.

[b] Modulation of chloride ion flux in cells expressing $\beta_3\gamma_2$ plus either α_1 or α_3 produced by an EC_{20} equivalent concentration of GABA in the presence of an approximate $1000 \times K_i$ concentration of test compound.[23] Efficacy is expressed relative to the full agonist chlorodiazepoxide (relative efficacy = 1.0), from at least seven independent experiments.

[c] Efficacy measurement of effect of test compound on a current at GABA EC_{20} using whole-cell patch-clamp electrophysiological recording.[14,24] Efficacy is expressed relative to the full agonist chlorodiazepoxide (relative efficacy = 1.0), from at least seven independent experiments.

Table 4. Effect of 7-heteroaryl changes on α3 affinity and α1 and α3 efficacy



Compound	R	K_i[a] α3 (nM)	Efficacy[b,c] α1	Efficacy[b,c] α3
46	3-Pyridyl	1.1	0.15	0.16
47	Pyrazinyl	2.7	0.03	0.18
48	2-Furyl	0.85	0.01	0.19
49	3-Furyl	0.61	0.07	−0.12
50[d]	2-Thienyl	1.6	−0.03	0.19
51	cy-Propyl	0.36	−0.08	−0.01

[a] K_i values for binding to the BZ sites of stably expressed human recombinant $GABA_A$ receptors with the composition α3β3γ2. Inhibition of the binding of 1.8 nM [^{3}H]Ro15-1788 was measured and the concentration required to inhibit binding by 50% (IC_{50}) was converted to a K_i value according to the Cheng–Prusoff equation.[22] Data shown are means of three to ten experiments.

[b] Modulation of chloride ion flux in cells expressing $\beta_3\gamma_2$ plus either α_1 or α_3 produced by an EC_{20} equivalent concentration of GABA in the presence of an approximate $1000 \times K_i$ concentration of test compound.[23] Efficacy is expressed relative to the full agonist chlorodiazepoxide (relative efficacy = 1.0), from at least seven independent experiments.

[c] Efficacy measurement of effect of test compound on a current at GABA EC_{20} using whole-cell patch-clamp electrophysiological recording.[14,24] Efficacy is expressed relative to the full agonist chlorodiazepoxide (relative efficacy = 1.0), from at least seven independent experiments.

[d] Unsubstituted 3-phenyl group.

Scheme 1. For experimental details of the synthesis of all the compounds described in this paper, please refer to the patent literature.[27] The α-methyl 1,2,4-triazolylmethyloxy group at the 2-position was kept as a constant in all the compounds in this communication since precedent showed that in the structurally related triazolopyridazine series, it was an absolute requirement for α3/α1 functional selectivity.[18,28]

The *o*-fluoro 3-phenyl analogue **16** has essentially an identical binding and efficacy profile to the prototype molecule **8** (Table 1). However, the *o*-position of the 3-phenyl ring only tolerates small substituents since significant loss of α3 affinity is observed with chloro, methyl and in particular trifluoromethyl. The *p*-fluoro analogue **26** loses an order of magnitude in binding affinity but keeps functional selectivity for α3, whilst the *m*-position of the 3-phenyl group tolerates a wider range of substituents though polar groups lose affinity and selectivity. 2,3-, 2,5- and 2,6-Difluoro substitution (compounds **27**, **28** and **29**) is well tolerated but as with all of the analogues in Table 1, efficacy at α1 is too high with our requirement for an ideal compound being an α1 antagonist and an α3 agonist.

Of the 3-heteroaryl changes carried out, the most interesting compound is the 3-thiophene **32**, which has subnanomolar affinity at α3 receptors, is an antagonist at α1 receptors and has α3 efficacy of 0.21 relative to the full agonist CDZ. The 2-thiophene **31** and the 2-furan **33** also retain high affinity but have an inferior efficacy profile. The **2**- and **3**-pyridyl analogues (**34** and **35**) show nanomolar binding affinity at α3 receptors but both have raised efficacy at α1 receptors. The 4-pyridyl derivative (**36**) retains subnanomolar α3 affinity but has insufficient functional selectivity, whilst the 5-pyrimidyl compound **37** is significantly lower in binding affinity.

Precedent within the triazolopyridazine series suggested that large substituents on the 7-aryl ring would cause a significant reduction in binding affinity and so only the changes outlined in Table 3 were carried out. The 3- and 4- mono fluoro analogues **38** and **39** showed increased efficacy at both α1 and α3 subtypes in comparison to **16** and the prototype molecule **8** but kept a window of selectivity. Difluoro and trifluoro substitution offered no advantage, with the 2,5-difluoro analogue (**41**) in particular losing selectivity. Replacing the 2-fluoro substituent with chloro (**45**) results in reduced affinity, selectivity and efficacy.

Of the 7-heteroaryl changes carried out, the 2-furan (**48**) and the 2-thiophene (**50**) have lower efficacy than **16** and have a comparable affinity and efficacy profile to **32**.

Other heterocycles such as 3-pyridyl (**46**), 3-pyrazinyl (**47**) or 3-furyl (**49**) retained affinity but offered no improvement in efficacy or functional selectivity. Interestingly, the 7-cyclopropyl analogue (**51**) retained affinity but lost considerable efficacy in comparison to **16**.

A novel synthesis of previously inaccessible 2,3,7-trisubstituted pyrazolo[1,5-*d*][1,2,4]triazines has been developed to identify the prototype **8** as a high affinity ligand for the $GABA_A$ BZ binding site with functional selectivity for agonism at α3-containing receptors over α1-containing receptors. The chemistry has been further developed to enable efficient introduction of 2- and 3-substituents as the last steps in the synthesis. The pyrazolo[1,5-*d*][1,2,4]triazine series has produced compounds with extremely high $GABA_A$ binding affinity some of which show selective in efficacy for α3-containing subtypes over α1-containing subtypes. The best compound identified from this series is **32** which has high in vitro affinity (0.1 nM), functional selectivity favouring α3 (0.21) over α1 (−0.02), very good receptor occupancy (0.54 mg/kg po)[18] and good rat oral bioavailability (32%).

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