Discovery of Functionally Selective 7,8,9,10-Tetrahydro-7,10-ethano-1,2,4-triazolo[3,4-*a*]phthalazines as $GABA_A$ Receptor Agonists at the α_3 Subunit

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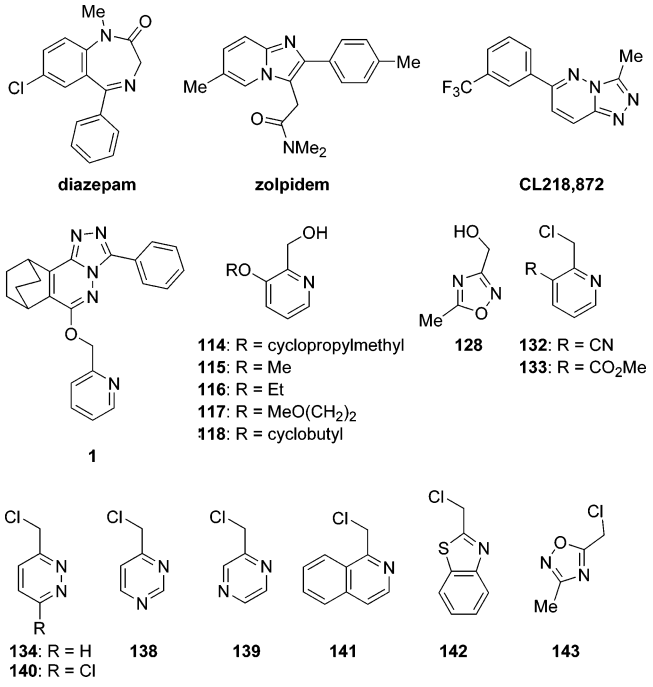
We have previously identified the 7,8,9,10-tetrahydro-7,10-ethano-1,2,4-triazolo[3,4-*a*]phthalazine (**1**) as a potent partial agonist for the α_3 receptor subtype with 5-fold selectivity in binding affinity over α_1. This paper describes a detailed investigation of the substituents on this core structure at both the 3- and 6-positions. Despite evaluating a wide range of groups, the maximum selectivity that could be achieved in terms of affinity for the α_3 subtype over the α_1 subtype was 12-fold (for **57**). Although most analogues showed no selectivity in terms of efficacy, some did show partial agonism at α_1 and antagonism at α_3 (e.g., **25** and **75**). However, two analogues tested (**93** and **96**), both with triazole substituents in the 6-position, showed significantly higher efficacy for the α_3 subtype over the α_1 subtype. This was the first indication that selectivity in efficacy in the required direction could be achieved in this series.

Introduction

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter in the mammalian central nervous system, binding to three different receptor types, $GABA_A$, $GABA_B$, and $GABA_C$. 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 (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ϵ, π, and θ).[1,2] Although this could potentially lead to a very large number of permutations, it seems that relatively few occur in vivo, with the majority of receptors comprising two α, two β, and one γ subunits.[3] The most likely arrangement of these subunits in the receptor has recently been determined by molecular modeling.[4] In addition to binding GABA, each receptor possesses a number of allosteric sites that bind a variety of ligands, leading to a modulation of the action of GABA. These include the benzodiazepine (BZ), barbiturate, neurosteroid, and loreclezole sites.

The BZ binding site is found in $GABA_A$ receptors containing β and γ_2 subunits in conjunction with an α_1, α_2, α_3, or α_5 (but not α_4 or α_6) subunit. In such receptors, it occurs at the interface of the α and γ_2 subunits with both subunits contributing to the binding.[5] BZs such as diazepam (Chart 1) are positive allosteric modulators (i.e., agonists) in that they enhance the inhibitory effects of GABA. They display anxiolytic, anticonvulsant, sedative-hypnotic, anaesthetic, and muscle-relaxant activities, but they are 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 an anxiolytic they are liabilities. Consequently, there is a need for a nonsedating anxiolytic.[6]

Chart 1



It has been found through in situ mRNA hybridization, subunit specific quantitative immunoprecipitation and autoradiography that the $\alpha_1\beta\gamma_2$ assembly is the most abundant and is located in most brain regions, while the $\alpha_2\beta\gamma_2$ and $\alpha_3\beta\gamma_2$ assemblies are of medium abundance and can be found in brain areas where the α_1 subunit is absent or at low levels. The $\alpha_5\beta\gamma_2$ receptors are low in abundance in the whole brain but are expressed to a significant extent in the hippocampus.[7] This differential location of $GABA_A$ receptor subtypes within the brain suggests that different subtypes might

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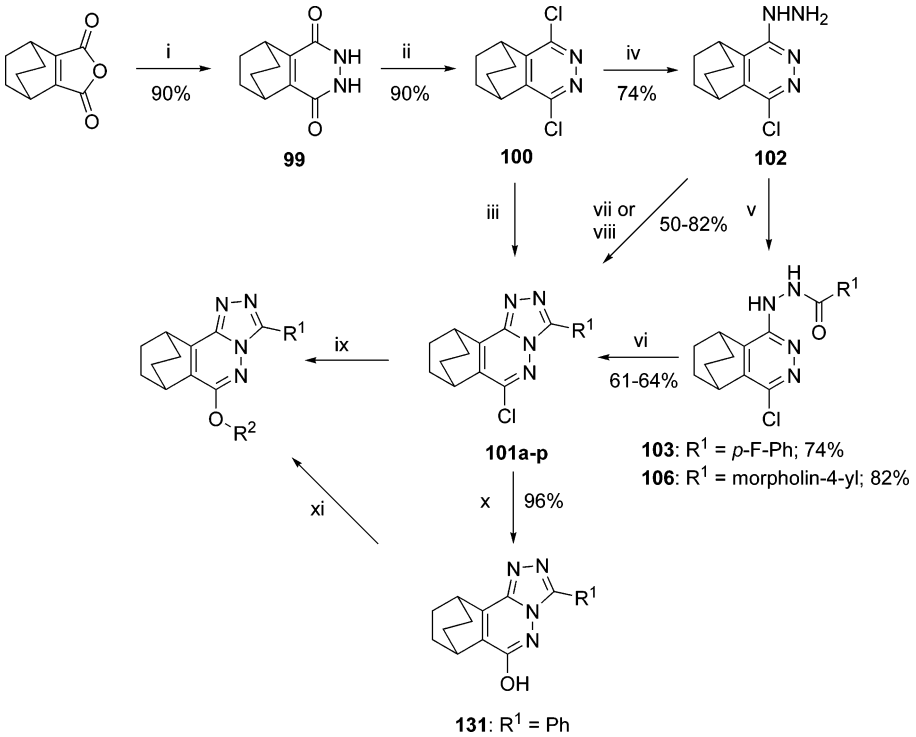
Scheme 1[a]



[a] Reagents and conditions: (i) $NH_2NH_2{\cdot}H_2O$, $NaOAc{\cdot}3H_2O$, AcOH, H_2O, reflux, 16 h; (ii) $POCl_3$, reflux, 14 h; (iii) $R^1CONHNH_2$, Et_3N, xylene, reflux, 4 d; (iv) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 18 h; (v) R^1COCl, Et_3N, $CHCl_3$, rt, 4−24 h; (vi) $POCl_3$, reflux, 2−5 h; (vii) (a) 3-thiophenecarboxylic acid, oxalyl chloride, CH_2Cl_2, DMF, rt, 1 h; (b) **102**, Et_3N, dioxane, reflux, 3 d; (viii) (a) 2-furoyl chloride, Et_3N, dioxane, rt to reflux, 36 h; (b) xylene, reflux, 5 h; (ix) R^2OH, NaH, DMF, rt; (x) 2 N NaOH(aq), dioxane, H_2O, reflux, 3 d; (xi) (a) NaH, DMF, 80 °C, 20−30 min; (b) R^2X, rt to 80 °C.

be associated with different physiological effects. BZs generally bind with equal affinity at α_1-, α_2-, α_3-, and α_5-containing subtypes with little affinity for α_4- and α_6-containing subtypes. Apart from BZs, a variety of other chemical classes bind to the BZ site, but most show no selectivity for the different subtypes. However, zolpidem (Chart 1) does possess a degree of subtype selectivity in that it has about 10-fold binding selectivity for the α_1 subunit over α_3, and >100-fold selectivity over α_5 (Table 1). This compound has primarily sedative effects and thus suggests that the α_1 subtype may play a role in the sedative properties of BZs. Moreover, zolpidem demonstrates that compounds with selectivity for discrete $GABA_A$ receptor subtypes possess different pharmacological profiles to BZs.

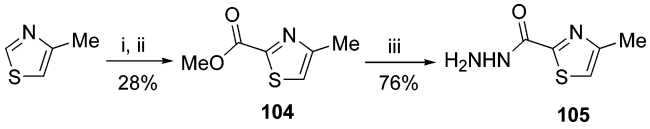
Recently, it has been shown using α_1H101R mutant mice, in which the α_1 subunit is rendered insensitive to diazepam, that diazepam retains its anxiolytic action but not its sedative effect, further supporting the notion that the α_1 subtype is involved in sedation but not anxiety.[8,9] This, therefore, implies that the α_2, α_3, and/or α_5 subtypes are likely to mediate the anxiolytic effects of BZs. There is evidence in mice lacking the α_5 subunit that this subtype is associated with memory and learning and is not involved in anxiety,[10] and it is hypothesised that the α_5 subtype may at least in part mediate the cognitive deficit seen with diazepam. Further mouse lines with α_2H101R, α_3H126R, and α_5H101R mutations have also been generated in an attempt to further define the subtypes involved in anxiety and the other actions of diazepam.[11−16] We, therefore, chose to develop BZ site agonists with selectivity for the α_2 and/or the α_3 subtype as anxiolytics with a potential for reduced side effects.

We have previously identified the 7,8,9,10-tetrahydro-7,10-ethano-1,2,4-triazolo[3,4-*a*]phthalazine **1** as a potent partial agonist for the α_3 receptor subtype with 5-fold selectivity in binding affinity over α_1.[17] This paper describes a detailed investigation of the substituents on this core structure which, although not leading to enhanced subtype selective binding affinity, did lead to the discovery of a functionally selective compound for the α_3 subtype.

Chemistry

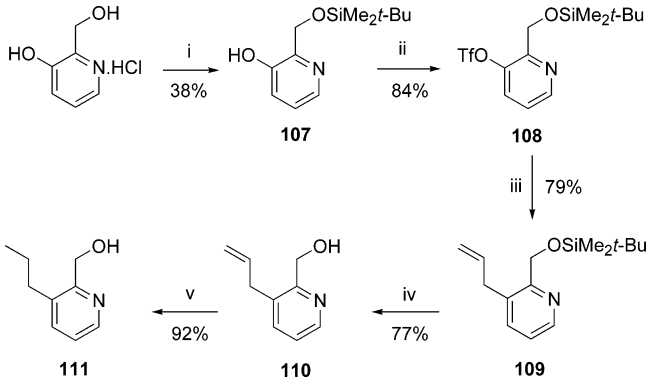
The final compounds were all synthesized through the 3-substituted 6-chloro-7,8,9,10-tetrahydro-7,10-ethano-1,2,4-triazolo[3,4-*a*]phthalazines (**101a**−**p**) (Scheme 1). These in turn were prepared by reacting 4,5,6,7-tetrahydro-4,7-ethano-2-benzofuran-1,3-dione[18] with hydrazine, and the resulting phthalazine-1,4-dione (**99**) was reacted with phosphorus oxychloride to give the 1,4-dichloro-phthalazine (**100**). This could then be cyclized directly with the appropriate acylhydrazide and triethylamine in refluxing xylene to give **101**, or a stepwise procedure could be followed by treating **100** with hydrazine to form the mono-hydrazino adduct (**102**), which in turn could be cyclized directly with the appropriate acid chloride and triethylamine in refluxing dioxane (for **101l**) or xylene (for **101m**). Alternatively, the intermediate hydrazides (**103** and **106**) were isolated by treating **102** with the corresponding acid chlorides and triethylamine in chloroform at room temperature and subsequently cyclized in phosphorus oxychloride at reflux to give **101i** and **101p**, respectively. The acylhydrazide (**105**) was prepared by treating the corresponding methyl ester (**104**) with hydrazine (Scheme 2). The chloroimidates (**101**) were then treated with an alcohol and

Scheme 2[a]



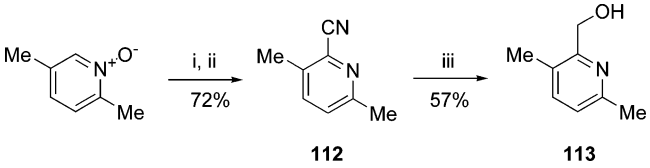
[a] Reagents and conditions: (i) (a) BuLi, THF, −78 °C, 1 h; (b) CO_2, −78 °C to room temperature, 2 h; (ii) HCl, MeOH, rt, 16 h; (iii) $NH_2NH_2{\cdot}H_2O$, MeOH, rt, 1.5 h.

Scheme 3[a]



[a] Reagents and conditions: (i) t-BuMe$_2$SiCl, imidazole, DMF, 60 °C, 16 h; (ii) Tf_2O, *i*-PrNEt$_2$, CH_2Cl_2, −10 °C to room temperature, 25 h; (iii) tetraallyltin, $(Ph_3P)_2PdCl_2$, LiCl, DMF, 80 °C, 12 h; (iv) TBAF, THF, rt, 25 min; (v) H_2, Pd/C, EtOAc, 30 psi, 30 min.

Scheme 4[a]



[a] Reagents and conditions: (i) Me_3SiCN, CH_2Cl_2, rt, 25 min; (ii) Et_2NCOCl, rt, 4 d; (iii) H_2, Pd/C, 2 N HCl(aq), 30 psi, 2 h.

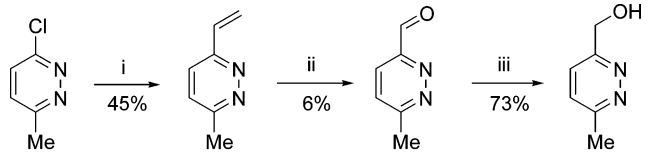
sodium hydride to give the required compounds. Alternatively, the chloroimidate could be hydrolyzed with sodium hydroxide to the corresponding amide (**131**), which was then treated with an alkyl halide and sodium hydride to afford the requisite analogues.

Although many of the alcohols were commercially available or known in the literature, some were novel. Thus, (3-propylpyridin-2-yl)methanol (**111**) was prepared by selectively protecting 3-hydroxy-2-(hydroxymethyl)pyridine with a TBDMS group, converting the free hydroxyl to a triflate and performing a Stille reaction with tetraallyltin to give **109** (Scheme 3). The silyl group was then removed, and the olefin was hydrogenated to give the required alcohol (**111**).

The (3,6-dimethylpyridin-2-yl)methanol (**113**) was synthesized from 2,5-dimethylpyridine-1-oxide[19] by treatment with trimethylsilyl cyanide, followed by *N*,*N*-diethylcarbamoyl chloride to give the 2-cyanopyridine (**112**) (Scheme 4). This was then hydrogenated in aqueous acid to give the methanol derivative (**113**).

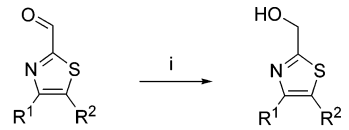
The (3-alkoxypyridin-2-yl)methanols (**114**−**118**, Chart 1) were prepared by reacting 2-(hydroxymethyl)pyridine-3-ol hydrochloride with the appropriate alkyl halide in the presence of either potassium hydroxide or potassium carbonate in DMSO or DMF. (6-Methylpyridazin-3-yl)methanol (**121**) was synthesized from 3-chloro-6-methylpyridazine by a Stille coupling with

Scheme 5[a]



[a] Reagents and conditions: (i) tetravinyltin, $(Ph_3P)_2PdCl_2$, LiCl, DMF, 100 °C, 16 h; (ii) (a) O_3, CH_2Cl_2, −78 °C to room temperature, 16 h; (b) Me_2S, −78 °C to room temperature, 1 h; (iii) $NaBH_4$, MeOH, 0 °C, 1 h.

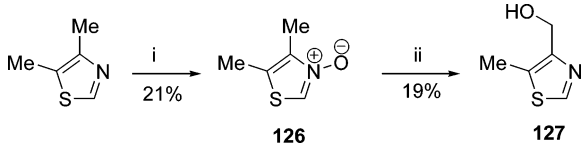
Scheme 6[a]



122: R^1 = Me, R^2 = H
124: R^1 = H, R^2 = Me
123: R^1 = Me, R^2 = H; 35%
125: R^1 = H, R^2 = Me; 65%

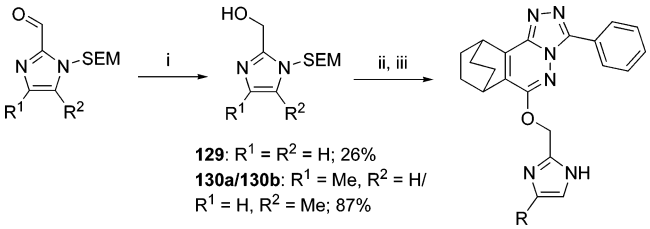
[a] Reagents and conditions: (i) $NaBH_4$, MeOH, rt, 1 h.

Scheme 7[a]



[a] Reagents and conditions: (i) m-CPBA, CH_2Cl_2, 0 °C to room temperature, 16 h; (ii) (a) Ac_2O, 110 °C, 16 h; (b) HCl, MeOH, rt, 16 h.

Scheme 8[a]



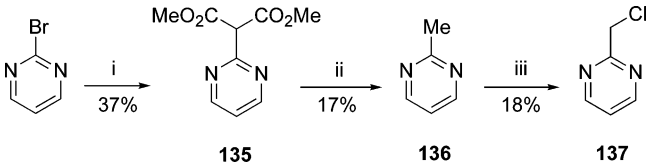
[a] Reagents and conditions: (i) $NaBH_4$, MeOH, 0 °C, 40 min; (ii) **101a**, NaH, DMF, rt; (iii) 5 N HCl(aq), 50 °C, 90 min.

tetravinyltin to give the vinylpyridazine (**119**), which was treated with ozone to give the carbaldehyde (**120**), and then reduced with sodium borohydride to give **121** (Scheme 5).

The (4- and 5-methyl-1,3-thiazol-2-yl)methanols (**123** and **125**) were prepared by reducing the carbaldehydes (**122**[20] and **124**[21]) with sodium borohydride (Scheme 6). The (5-methyl-1,3-thiazol-4-yl)methanol (**127**) was synthesized by treating 4,5-dimethylthiazole with 3-chloroperoxybenzoic acid to form the *N*-oxide (**126**), which was then reacted with acetic anhydride and subjected to an acid-catalyzed rearrangement to give the alcohol (**127**) (Scheme 7). The (5-methyl-1,2,4-oxadiazol-3-yl)methanol (**128**, Chart 1) was prepared from the THP-protected hydroxyacetamide oxime[22] by reacting with ethyl acetate and sodium hydride, followed by removal of the THP group.

The (imidazol-2-yl)methanol was reacted with chloroimidate (**101a**) as its [2-(trimethylsilyl)ethoxy]methyl

Scheme 9[a]



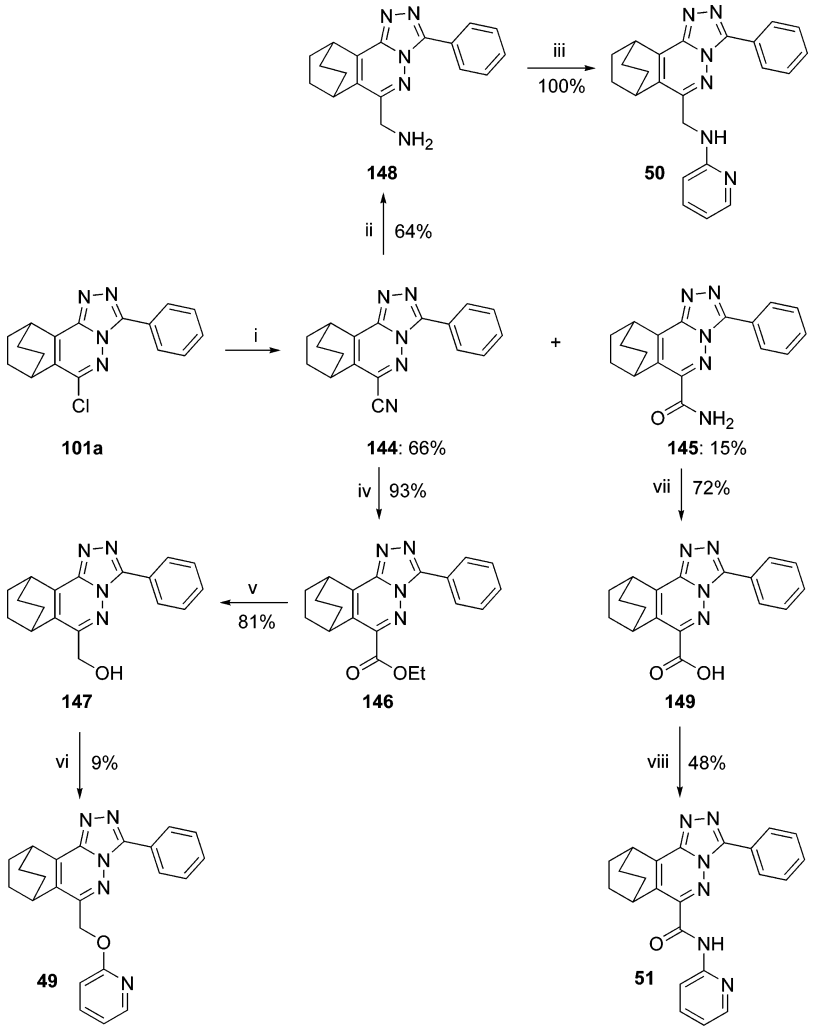
[a] Reagents and conditions: (i) NaH, $CH_2(CO_2Me)_2$, dioxane, reflux, 16 h; (ii) NaCl, DMSO, H_2O, 160 °C, 16 h; (iii) trichloroisocyanuric acid, $CHCl_3$, reflux, 9 h.

(SEM)-protected derivative (**129**), which was obtained from the carbaldehyde[23] by reduction with sodium borohydride (Scheme 8). After coupling the SEM group was removed with hydrochloric acid to give **77**. The 4-methylimidazol-2-yl analogue (**79**) was prepared in the same way from the mixture of SEM-protected imidazoles (**130a** and **130b**).

Some of the alkyl chlorides used to react with amide (**131**) also had to be prepared. In compounds where a chloromethyl substituent was in a position adjacent to a nitrogen atom in an aromatic heterocycle, these could generally be made from the corresponding methyl substituted analogue by treating with trichloroisocyanuric acid in chloroform at reflux. Thus, **132**−**134** and **138**−**142** (Chart 1) were all prepared in this manner. The preparation of (2-chloromethyl)pyrimidine (**137**) also used this chemistry in the final step, although in this case the 2-methylpyrimidine (**136**) had to be synthesized from 2-bromopyrimidine by reaction with dimethyl malonate and sodium hydride to form the malonate (**135**), followed by double decarboxylation under Krapcho conditions (Scheme 9). 5-(Chloromethyl)-3-methyl-1,2,4-oxadiazole (**143**, Chart 1) was prepared by reacting acetamide oxime with chloroacetyl chloride and sodium hydride.

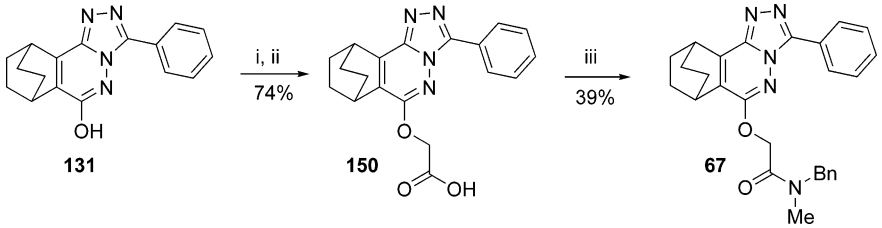
The analogues with a carbon instead of an oxygen as the first linkage atom in the side chain were all prepared from an initial reaction of the chloride (**101a**) with copper(I) cyanide to form mainly the cyanide (**144**) together with a small amount of the carboxamide (**145**) (Scheme 10). The cyanide (**144**) was hydrolyzed with sodium hydroxide to the carboxylic acid, which was then treated with thionyl chloride and ethanol to give the ethyl ester (**146**). This was then reduced with sodium borohydride and calcium chloride to the hydroxymethyl derivative (**147**), which was subjected to a Mitsunobu

Scheme 10[a]



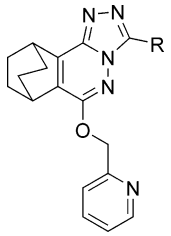
[a] Reagents and conditions: (i) CuCN, NMP, 200 °C, 36 h; (ii) H_2, Pd/C, EtOH, $CHCl_3$, 50 psi, 22 h; (iii) 2-bromopyridine, 160 °C, 6 h; (iv) (a) 4 N NaOH(aq), EtOH, reflux, 5 h; (b) 5 M HCl(aq); (c) $SOCl_2$, EtOH, reflux, 5 h; (v) $NaBH_4$, $CaCl_2$, EtOH, −10 °C to room temperature, 30 min; (vi) 2-hydroxypyridine, Ph_3P, DEAD, THF, rt, 3 h; (vii) concd HCl, 100−120 °C, 46 h; (viii) (a) $SOCl_2$, 50−60 °C, 20 h; (b) 2-aminopyridine, Et_3N, THF, rt, 3.5 h.

Scheme 11[a]



[a] Reagents and conditions: (i) $BrCH_2CO_2Me$, NaH, DMF; (ii) KOH, MeOH, H_2O, rt, 3 d; (iii) (a) N,N′-carbonyldiimidazole, DMF, rt, 2 h; (b) BnNHMe, rt, 24 h.

Table 1. Binding Affinities of 3-Substituted 6-(Pyridin-2-ylmethoxy)-7,8,9,10-tetrahydro-7,10-ethano-1,2,4-triazolo[3,4-*a*]phthalazines at Cloned Human GABA$_A$ Receptor Subtypes



compd	R	K_i (nM)[a]			
		$\alpha_1\beta_3\gamma_2$	$\alpha_2\beta_3\gamma_2$	$\alpha_3\beta_3\gamma_2$	$\alpha_5\beta_3\gamma_2$
diazepam		13 ± 1	6.6 ± 0.5	33 ± 3	11 ± 1
zolpidem		27 ± 1	103 ± 17	246 ± 18	>3333
CL218,872		66 ± 0	720 ± 110	850 ± 120	460 ± 10
1	Ph	71 ± 8	26 ± 2	13 ± 2	1.2 ± 0.1
2	2-MeO-Ph	>1000	>1000	>1000	170 ± 20
3	3-MeO-Ph	140 ± 0	79 ± 5	29 ± 7	6.0 ± 0.2
4	4-MeO-Ph	230 ± 20	74 ± 4	52 ± 4	4.2 ± 2.7
5	2-Me-Ph	>1000	280 ± 30	280 ± 0	22 ± 3
6	3-Me-Ph	570 ± 40	210 ± 20	140 ± 30	17 ± 1
7	4-Me-Ph	310 ± 20	120 ± 10	32 ± 10	4.7 ± 0.4
8	2-F−Ph	28 ± 7	16 ± 6	6.1 ± 0.1	0.54 ± 0.03
9	4-F−Ph	310 ± 60	180 ± 30	58 ± 25	27 ± 8
10	3-pyridyl	260 ± 10	54 ± 7	38 ± 1	2.7 ± 0.1
11	4-pyridyl	>1000	320 ± 10	150 ± 40	20 ± 0
12	3-thienyl	130 ± 20	52 ± 19	38 ± 20	4.4 ± 0.9
13	2-furyl	270 ± 20	110 ± 10	53 ± 11	5.3 ± 1.8
14	4-Me-thiazol-2-yl	>1000	140 ± 0	100 ± 10	26 ± 1
15	cyclopropyl	130 ± 0	24 ± 2	18 ± 2	1.8 ± 0.1
16	morpholin-4-yl	>1000	>1000	>1000	>1000

[a] Inhibition of [^{3}H]Ro15-1788 binding to recombinant hGABA$_A$ receptor subtypes stably expressed in L (tk$^-$) cells. Values are the geometric mean ± SEM for $n = 2-5$, expressed to two significant figures. Six to eight concentrations of each test compound incremented in half-log units were used in the determinations.

reaction with 2-hydroxypyridine in the presence of triphenylphosphine and diethyl azodicarboxylate to give the *N*-alkylated analogue as the major product together with a low yield of the required *O*-alkylated product (**49**). Other alkylation conditions gave only *N*-alkylated product. The cyanide (**144**) could also be hydrogenated over palladium on carbon to the aminomethyl derivative (**148**), which was then alkylated with 2-bromopyridine to give **50**. Finally, the carboxamide (**145**) was hydrolyzed by concentrated hydrochloric acid to the carboxylic acid (**149**), which was then treated with thionyl chloride, followed by 2-aminopyridine to give the amide (**51**).

The *N*-benzyl-*N*-methylacetamide analogue (**67**) was prepared by alkylating the amide (**131**) with methyl bromoacetate and then hydrolyzing the ester with potassium hydroxide to afford the acid (**150**) (Scheme 11). This was then treated with *N*,*N*′-carbonyldiimidazole, followed by *N*-benzylmethylamine to give **67**. Finally, the two propyl-substituted triazoles (**95** and **96**) were prepared by alkylation of the unsubstituted triazole (**92**) with iodopropane and sodium hydride.

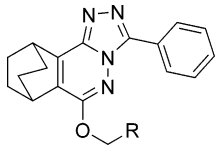
Results and Discussion

The binding affinities of compounds were measured by the inhibition of [^{3}H]Ro15-1788 binding to human recombinant GABA receptor subtypes stably expressed in L(tk$^-$) cells containing α_1, α_2, α_3, and α_5 subunits in combination with β_3 and γ_2.[24,25]

The efficacy of each compound was measured on the same combinations of receptor subtypes expressed in *Xenopus* oocytes using two-electrode voltage-clamp electrophysiology. A concentration of GABA was used that elicited a response 20% in amplitude of the maximum obtainable GABA current (EC_{20}). Modulation of this current by test compounds was carried out using a concentration of 100 × K_i of the test compound.[26, 27]

It can be seen from Table 1 that both methoxy (**2**−**4**) and methyl (**5**−**7**) substituents in any position on the

Table 2. Binding Affinities of Six-Membered Heteroarylmethoxy Groups in the 6-Position of 7,8,9,10-Tetrahydro-7,10-ethano-1,2,4-triazolo[3,4-*a*]phthalazines at Cloned Human $GABA_A$ Receptor Subtypes



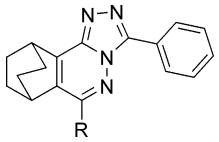
		K_i (nM)[a]			
compd	R	$\alpha_1\beta_3\gamma_2$	$\alpha_2\beta_3\gamma_2$	$\alpha_3\beta_3\gamma_2$	$\alpha_5\beta_3\gamma_2$
1	2-pyridyl	71 ± 8	26 ± 2	13 ± 2	1.2 ± 0.1
17	3-pyridyl	150 ± 10	68 ± 25	25 ± 0	6.5 ± 2.0
18	4-pyridyl	140 ± 0	82 ± 14	13 ± 1	4.7 ± 1.0
19	3-Me-2-pyridyl	9.8 ± 0.8	2.0 ± 0.1	2.1 ± 0.4	0.46 ± 0.08
20	4-Me-2-pyridyl	93 ± 2	19 ± 0	18 ± 1	2.0 ± 0.2
21	5-Me-2-pyridyl	56 ± 16	17 ± 5	15 ± 7	1.2 ± 0.3
22	6-Me-2-pyridyl	160 ± 30	36 ± 10	20 ± 5	2.6 ± 0.7
23	3-Pr-2-pyridyl	3.5 ± 1.1	9.9 ± 2.9	2.4 ± 0.9	3.1 ± 1.0
24	3,6-diMe-2-pyridyl	27 ± 2	8.7 ± 1.3	3.6 ± 0.4	0.84 ± 0.17
25	3,5-diMe-2-pyridyl	3.4 ± 0.7	3.4 ± 0.5	0.71 ± 0.5	0.20[b]
26	3,4-diMe-2-pyridyl	11 ± 2	4.0 ± 0.0	1.7 ± 0.4	1.0 ± 0.3
27	3-CN-2-pyridyl	13 ± 2	5.9 ± 1.2	1.7 ± 0.7	0.54 ± 0.01
28	3-MeO_2C-2-pyridyl	21 ± 11	30 ± 12	7.1 ± 2.7	2.5 ± 0.6
29	3-HO-2-pyridyl	270 ± 0	470 ± 60	180 ± 10	34 ± 8
30	3-MeO-2-pyridyl	17 ± 3	9.1 ± 1.0	2.4 ± 0.4	0.65 ± 0.16
31	3-EtO-2-pyridyl	3.9 ± 0.9	2.8 ± 0.9	1.1 ± 0.3	0.36 ± 0.13
32	3-methoxyethoxy-2-pyridyl	13 ± 1	9.8 ± 0.2	3.9 ± 0.2	0.50 ± 0.08
33	3-cyclopropyl-methoxy-2-pyridyl	6.9 ± 0.3	5.6 ± 0.2	2.3 ± 0.7	0.75 ± 0.02
34	3-cyclobutyloxy-2-pyridyl	32±3	43 ± 11	38 ± 7	4.2 ± 1.1
35	3-BnO-2-pyridyl	160 ± 60	100 ± 30	20 ± 7	7.0 ± 3.5
36	pyridazin-3-yl	33 ± 13	14 ± 4	8.5 ± 1.1	0.88 ± 0.30
37	pyrimidin-2-yl	87 ± 17	68 ± 7	33 ± 12	9.2 ± 3.4
38	pyrimidin-4-yl	22 ± 4	8.1 ± 1.0	3.1 ± 0.4	0.55 ± 0.03
39	pyrazin-2-yl	16 ± 6	6.5 ± 4.4	3.0 ± 2.0	0.77 ± 0.05
40	6-Me-pyridazin-3-yl	50 ± 4	22 ± 1	10 ± 1	2.1 ± 0.6
41	6-Cl-pyridazin-3-yl	73 ± 9	42 ± 16	23 ± 5	1.3 ± 0.1
42	isoquinolin-1-yl	29 ± 5	7.5 ± 0.3	4.5 ± 2.3	0.69 ± 0.15
43	quinolin-2-yl	480 ± 0	200 ± 10	77 ± 16	9.5 ± 6.7
44	quinoxalin-2-yl	82 ± 22	34 ± 5	26 ± 12	3.9 ± 0.9

[a] See corresponding footnote in Table 1. [b] Value for $n = 1$ determination.

3-phenyl ring of compound **1** resulted in a reduction in the affinity of the compounds at all receptor subtypes. Table 5 shows the efficacy values measured on some of the higher affinity analogues. It can be seen that the efficacy at the α_3 subtype for **3**, **4**, and **7** is essentially the same as **1** (33−43%), although the efficacy at α_1 shows more variability (9−51%), with both para-substituted compounds (**4** and **7**) showing a little selectivity for α_3 over α_1. The efficacies at the α_2 and α_5 subtypes were also measured for **7** and mirrored those of **1**, being somewhat lower than at the α_3 subtype, which is a general trend in this series. The only substituent that had similar affinity to **1** was 2-fluoro (**8**), but the 4-fluoro analogue (**9**) had less affinity. Replacement of the phenyl ring by six- or five-membered heteroaromatic rings (**10**−**14**) once again led to a drop in affinity. The efficacy of the 3-pyridyl analogue (**10**) was much less than for **1** at the α_3 subtype. The small cyclopropyl group gave a compound (**15**) with similar affinity to **1**, but the larger morpholinyl substituent (**16**) was completely inactive. It can be seen from this set of compounds that there was only modest selectivity in the binding affinities between the different subtypes. The affinity for the α_5 subtype was between 2- and 14-fold higher than for the α_3 subtype, while the best selectivity for the α_3 subtype over the α_1 subtype was obtained with the 4-methyl analogue (**7**), which was only 10-fold selective. The binding selectivity of the α_3 subtype over the α_2 subtype was even smaller, varying between 1- and 4-fold. In summary, substitution at the 3-position had an equivalent effect on affinity at all subtypes with the general trend of affinity (i.e. higher at α_5 than at α_1, α_2, and α_3 and modest or negligible selectivity for α_2 and α_3 over α_1) and efficacy (partial agonism with little or no selectivity) being maintained.

Table 2 shows the effect on the binding affinities produced by changes at the 6-position to the 2-pyridyl group, retaining a six-membered heteroaromatic or benzo-fused heteroaromatic ring and a 3-phenyl substituent. Thus, moving the N atom around the ring to give the 3- and 4-pyridyl analogues (**17** and **18**) led to similar affinities at the α_3 subtype compared to **1**, but the efficacies of these two analogues at the α_3 subtype were somewhat lower than for **1** (20% and 17% cf. 38%). Methylation of the 2-pyridyl group had little effect on affinity for **20**, **21**, and **22** except the 3-methyl substituent (**19**), which resulted in a 6- to 7-fold increase in affinity at the α_1 and α_3 subtypes. However, **19** had much lower efficacy at the α_3 subtype than the other three methyl analogues. The 3-propyl derivative (**23**), however, had the same affinity at the α_3 subtype as the 3-methyl analogue (**19**), although less selectivity over the α_1 subtype, but much increased efficacy at the α_3 subtype. An increase in efficacy corresponding to increased size of the alkyl group at this position is a general trend and can be seen for later compounds as well. An additional methyl group in **19** at the 5-position (**25**) led to another 3-fold rise in affinity at the α_1 and

Table 3. Binding Affinities of Other 6-Substituted-3-phenyl-7,8,9,10-tetrahydro-7,10-ethano-1,2,4-triazolo[3,4-*a*]phthalazines at Cloned Human GABA$_A$ Receptor Subtypes



		K_i (nM)[a]			
compd	R	$\alpha_1\beta_3\gamma_2$	$\alpha_2\beta_3\gamma_2$	$\alpha_3\beta_3\gamma_2$	$\alpha_5\beta_3\gamma_2$
45	3-pyridyloxy	>500	>500	>500	>500
46	2-pyridylethoxy	480 ± 20	270 ± 10	200 ± 20	44 ± 0
47	6-Me-2-pyridylpropoxy	75 ± 7	190 ± 10	240 ± 30	30 ± 3
48	1- (2-pyridyl)ethoxy	>1000	390 ± 0	550 ± 90	64 ± 20
49	2-pyridyloxymethyl	440 ± 20	230 ± 40	120 ± 10	58 ± 1
50	2-pyridylaminomethyl	>1000	>1000	>1000	>1000
51	2-pyridyl-NHCO	>1000	290 ± 30	170 ± 0	40 ± 19
52	$PhCH_2O$	>1000	>1000	>1000	110 ± 20
53	2-CN-$PhCH_2O$	190 ± 30	83 ± 18	53 ± 22	2.6 ± 1.3
54	3-CN-$PhCH_2O$	>1000	180 ± 70	66 ± 28	7.8 ± 4.6
55	4-CN-$PhCH_2O$	310 ± 20	110 ± 10	70 ± 22	9.4 ± 1.6
56	3-$HOCH_2$-$PhCH_2O$	490 ± 120	110 ± 32	43 ± 7	11 ± 2
57	4-$HOCH_2$-$PhCH_2O$	520 ± 80	76 ± 7	44 ± 3	11 ± 2
58	3-Me_2NCH_2-$PhCH_2O$	190 ± 50	64 ± 11	24 ± 8	4.5 ± 0.1
59	4-MeSO-$PhCH_2O$	96 ± 13	41 ± 5	31 ± 1	7.6 ± 1.3
60	4-CF_3O-$PhCH_2O$	>500	>500	>500	>500
61	3,4-methylenedioxy-$PhCH_2O$	>500	>500	>500	>500
62	1-Me-piperidin-2-ylmethoxy	>1000	>1000	>1000	>1000
63	1-Me-piperidin-3-ylmethoxy	750 ± 40	260 ± 40	460 ± 240	100 ± 10
64	5-oxo-2-pyrrolidinemethoxy	730 ± 170	480 ± 140	260 ± 10	59 ± 2
65	Me_2NCOCH_2O	220 ± 50	160 ± 40	89 ± 20	10 ± 3
66	1-pyrrolidine-$COCH_2O$	230 ± 20	160 ± 40	50 ± 8	9.0 ± 2.7
67	$BnMeNCOCH_2O$	21 ± 1	72 ± 10	41 ± 10	7.4 ± 0.7
68	Hydroxypropoxy	650 ± 200	310 ± 60	170 ± 10	42 ± 13
69	Hydroxybutoxy	71 ± 37	34 ± 9	19 ± 8	8.5 ± 1.0
70	*trans*-4-$HOCH_2$-cyclohexylmethoxy	150 ± 0	77 ± 1	57 ± 5	41 ± 19
71	*cis*-4-$HOCH_2$-cyclohexylmethoxy	>1000	>1000	>1000	88 ± 23

[a] See corresponding footnote in Table 1.

α_3 subtypes, making this compound the most active in this series, although an antagonist at the α_3 subtype. Extra methyl groups at the 4- and 6-positions (**26** and **24**) made little difference to the affinity or the α_3 efficacy of **19**.

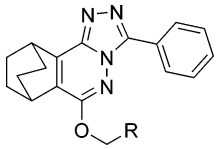
A range of other substituents at the 3-position of the 2-pyridine ring was then explored. Thus, a cyano substituent (**27**) had similar affinity and efficacy to **19**, a methyl carboxylate group (**28**) had slightly lower affinity and slightly higher efficacy, and a hydroxyl substituent (**29**) had greatly reduced affinity. However, alkylation of this hydroxyl substituent with small groups (**30**−**33**) recovered all of the affinity, although this tailed off with larger groups such as cyclobutyloxy (**34**) and benzyloxy (**35**). The efficacy at α_3 ranged from a very low partial agonist in the case of methoxy (**30**) to full agonism in the case of methoxyethoxy (**32**), cyclopropyloxy (**33**), and benzyloxy (**35**), with ethoxy (**31**) being halfway between these extremes. However, there was still no significant selectivity over α_1 in terms of either affinity or efficacy.

Addition of another N atom in the heteroaromatic ring gave similar affinity to **1** in the case of pyridazine (**36**), slightly lower affinity for the 2-pyrimidine (**37**), and higher affinity for the 4-pyrimidine (**38**) and pyrazine (**39**). However, **38** and **39** both have lower efficacy than **1** at the α_3 subtype, although **36** has slightly higher efficacy but no selectivity over the α_1 subtype. Adding a substituent to the 6-position of **36** such as methyl (**40**) or chloro (**41**) did not improve affinity, and the efficacy of **40** at α_3 was lower than for **36**. Of the benzo-fused analogues, the 2-quinoline (**43**) had significantly lower affinity, the quinoxaline (**44**) had 5- to 9-fold lower affinity across all subtypes than the corresponding non-benzo-fused pyrazine (**39**), but the 1-isoquinoline (**42**) had slightly higher affinity than **1**. However, **42** had low efficacy at α_3 and much higher efficacy at α_1.

Other more drastic changes at the 6-position were now explored (Table 3). Removing the methylene group from the linkage between the pyridine and the triazolophthalazine core led to a dramatic loss of affinity for **45**, while extending the linkage by one (**46**) or two (**47**) carbon atoms gave a significant fall in affinity compared to **1** and **22**, respectively (15- and 12-fold at α_3). An α-methyl group in the linkage (**48**) also lost over 40-fold in affinity at the α_3 subunit compared to **1**, while reversing the carbon and oxygen atoms in the linkage (**49**) led to a 9-fold reduction over **1** in affinity at α_3. If the oxygen in **49** was replaced by a nitrogen atom (**50**), affinity was lost completely, while an amide linkage (**51**) was 13-fold lower in affinity than **1** at α_3.

If the pyridyl group of **1** was replaced by a phenyl ring (**52**), affinity was lost completely, although substitution of this phenyl ring by a cyano group in the ortho-, meta-, or para-position (**53**−**55**) gave compounds with only 4 to 6-fold lower affinity than **1** at α_3, with the meta-analogue (**54**) showing partial agonism at both the α_1 and α_3 subtypes. A hydroxymethyl substituent at either the meta- or para-position (**56**, **57**) gave similar affinities at α_3 to the cyano analogues with 11 to 12-

Table 4. Binding Affinities of Five-Membered Heteroarylmethoxy Groups in the 6-Position of 7,8,9,10-Tetrahydro-7,10-ethano-1,2,4-triazolo[3,4-*a*]phthalazines at Cloned Human $GABA_A$ Receptor Subtypes



		K_i (nM)[a]			
compd	R	$\alpha_1\beta_3\gamma_2$	$\alpha_2\beta_3\gamma_2$	$\alpha_3\beta_3\gamma_2$	$\alpha_5\beta_3\gamma_2$
72	2-furyl	>500	>500	>500	>500
73	2-thienyl	>500	>500	>500	>500
74	3-thienyl	>500	>500	>500	>500
75	pyrazol-1-yl	130 ± 20	43 ± 6	19 ± 1	2.7 ± 0.2
76	3,5-diMe-pyrazol-1-yl	23 ± 1	7.5 ± 2.5	2.3 ± 0.2	0.26 ± 0.01
77	imidazol-2-yl	53 ± 1	18 ± 8	6.7 ± 1.6	0.87 ± 0.05
78	1-Me-imidazol-2-yl	19 ± 4	7.1 ± 0.1	4.3 ± 0.1	0.45 ± 0.01
79	4-Me-imidazol-2-yl	85 ± 16	15 ± 4	7.8 ± 1.8	0.90 ± 0.18
80	1-Et-imidazol-2-yl	3.3 ± 0.1	2.3 ± 0.1	1.0 ± 0.1	0.29 ± 0.06
81	1-Bn-imidazol-2-yl	0.81 ± 0.07	1.7 ± 0.0	2.0 ± 0.4	0.21 ± 0.06
82	5-Me-isoxazol-3-yl	80 ± 28	35 ± 0	18 ± 7	2.7 ± 0.4
83	thiazol-2-yl	100 ± 20	35 ± 1	19 ± 5	3.6 ± 0.8
84	thiazol-4-yl	68 ± 4	21 ± 1	10 ± 5	1.2 ± 0.2
85	4-Me-thiazol-2-yl	140 ± 50	40 ± 21	30 ± 7	2.9 ± 0.8
86	5-Me-thiazol-2-yl	100 ± 30	28 ± 14	24 ± 6	2.0 ± 0.3
87	5-Me-thiazol-4-yl	35 ± 4	21 ± 2	12 ± 5	0.77 ± 0.15
88	benzothiazol-2-yl	>1000	>1000	250 ± 60	23 ± 1
89	3-Me-isothiazol-5-yl	210 ± 0	130 ± 20	99 ± 3	11 ± 2
90	3-Me-1,2,4-oxadiazol-5-yl	290 ± 20	250 ± 10	51 ± 8	12 ± 0
91	5-Me-1,2,4-oxadiazol-3-yl	140 ± 10	110 ± 20	66 ± 6	16 ± 3
92	1,2,4-triazol-3-yl	43 ± 2	25 ± 3	19 ± 5	2.8 ± 1.0
93	1-Me-1,2,4-triazol-3-yl	31 ± 4	16 ± 2	8.0 ± 0.0	2.1 ± 0.5
94	2-Me-1,2,4-triazol-3-yl	11 ± 1	5.2 ± 0.0	2.8 ± 0.7	0.39 ± 0.10
95	1-Pr-1,2,4-triazol-3-yl	78 ± 17	50 ± 1	40 ± 6	9.0 ± 0.8
96	2-Pr-1,2,4-triazol-3-yl	0.90 ± 0.02	2.5 ± 0.1	1.4 ± 0.1	0.19 ± 0.01
97	1-Me-tetrazol-5-yl	78 ± 1	59 ± 11	21 ± 1	4.4 ± 0.0
98	2-Me-tetrazol-5-yl	60 ± 5	57 ± 11	37 ± 1	6.5 ± 0.8

[a] See corresponding footnote in Table 1.

fold selectivity over α_1. A 3-(dimethylamino)methyl (**58**) and a 4-methyl sulfoxide (**59**) group also gave similar affinities at α_3 but reduced selectivity. However, **58** was a partial inverse agonist at the α_3 subunit. The 4-trifluoromethoxy (**60**) and 3,4-methylenedioxy (**61**) analogues were much lower in affinity.

Moving on to some nonaromatic substituents at the 6-position of the triazolophthalazines, it was found that saturation of the pyridine ring of **1** to piperidines (**62**, **63**) led to much reduced affinity, while a pyrrolidinone (**64**) was also some 20-fold lower in affinity than **1** at α_3. When amides were put in the position of the pyridine with various substituents on the nitrogen atom (**65**−**67**), affinities were reduced by 3- to 7-fold compared to **1**. Finally, simple hydroxyalkoxy substituents (**68**−**71**) could have reasonable affinities with the optimum being the hydroxybutoxy analogue (**69**), which had an affinity of the same order as **1** at α_3, but lower efficacy. There was a significant difference in affinity between the *trans*- and *cis*-4-(hydroxymethyl)cyclohexylmethoxy isomers (**70** and **71**).

We then turned our attention to five-membered heteroaromatic rings (Table 4). The furan and thiophene analogues (**72**−**74**) had little affinity. However, the 1-pyrazole (**75**) had similar affinity to **1**, which could be increased further by 3,5-dimethyl substitution (**76**). Although **76** was 10-fold selective in binding over α_1, both **75** and **76** had significantly higher efficacy at α_1 than at α_3. Indeed, **75** was a high partial agonist at α_1 with zero efficacy at α_3. The unsubstituted imidazole (**77**) had similar affinity to **1**, as did **78** and **79**, in which the imidazole was substituted with a methyl group in either the 1- or 4-position. However, the 1-ethyl analogue (**80**) had significantly higher affinity at the α_3 subtype, while the 1-benzyl derivative (**81**) was not much different. As expected, **81** had significantly higher efficacy than **77**−**80**, but in all compounds tested, the efficacy at the α_1 subunit was similar to that at the α_3 subtype.

The isoxazole (**82**) had similar affinity to **1**, as did the two unsubstituted thiazoles (**83** and **84**). The efficacies of **84** at α_1 and α_3 were the same but for **83** the efficacy at α_1 was significantly higher than at α_3. Substitution of the 2-thiazole (**83**) with methyl at either the 4- or 5-position (**85** and **86**) made little difference to the affinity, and the 5-methyl analogue (**87**) of the 4-thiazole had similar affinity to **84** itself. The benzo-fused derivative (**88**) had much lower affinity and the isothiazole (**89**) had 8-fold lower affinity at the α_3 subtype than **1**. The two oxadiazoles (**90** and **91**) possessed 4- to 5-fold lower affinity than **1**. The unsubstituted triazole (**92**) had similar affinity to **1**, and substituting in the 1-position with a methyl group (**93**) retained this, while a larger propyl group (**95**) resulted in a fall in affinity. On the other hand, a 2-methyl substituent (**94**) afforded nearly a 7-fold increase in affinity over **92** at the α_3 subtype, while a propyl group in this position (**96**) now gave a further 2-fold increase in affinity. The tetrazoles (**97** and **98**) both had similar or lower affinity than **1**. The interesting feature of the triazoles **93** and **96**,

Table 5. Efficacies of 7,8,9,10-Tetrahydro-7,10-ethano-1,2,4-triazolo[3,4-*a*]phthalazines at Cloned Human GABA$_A$ Receptor Subtypes

	efficacy (%)[a]			
compd	$\alpha_1\beta_3\gamma_2$	$\alpha_2\beta_3\gamma_2$	$\alpha_3\beta_3\gamma_2$	$\alpha_5\beta_3\gamma_2$
diazepam	103 ± 14 (8)	138 ± 11 (6)	118 ± 28 (6)	106 ± 3 (5)
1	51 ± 13 (5)	23 ± 4 (4)	38 ± 7 (5)	18 ± 7 (3)
3	51 ± 7 (4)	-	43 ± 8 (5)	-
4	14 ± 1 (4)	-	33 ± 5 (4)	-
7	9 ± 2 (4)	14 ± 5 (4)	40 ± 8 (6)	6 ± 2 (4)
10	36 ± 5 (4)	-	9 ± 7 (6)	31 ± 5 (3)
17	51 ± 1 (4)	-	20 ± 3 (5)	
18	38 ± 3 (4)	-	17 ± 4 (5)	-
19	17 ± 4 (4)	-	7 ± 3 (6)	-
20	41 ± 7 (4)	-	33 ± 9 (5)	-
21	100 ± 18 (6)	-	74 ± 16 (5)	-
22	53 ± 12 (4)	36 ± 6 (5)	44 ± 9 (5)	15 ± 3 (4)
23	62 ± 10 (8)	-	52 ± 7 (4)	-
24	-	-	12 ± 1 (5)	-
25	34 ± 7 (4)	-	−2 ± 2 (5)	-
26	-	-	17 ± 4 (6)	-
27	-	-	17 ± 5 (6)	-
28	-	-	29 ± 4 (4)	-
30	-	-	8 ± 3 (5)	-
31	66 ± 9 (4)	-	46 ± 8 (5)	-
32	77 ± 11 (4)	-	97 ± 21 (5)	-
33	175 ± 26 (5)	-	139 ± 22 (5)	50 ± 7 (3)
35	178 ± 24 (4)	-	132 ± 9 (4)	-
36	64 ± 11 (5)	35 ± 5 (4)	57 ± 11 (5)	39 ± 3 (3)
38	-	-	14 ± 3 (4)	-
39	-	-	27 ± 5 (4)	-
40	-	-	31 ± 1 (4)	-
42	45 ± 9 (5)	-	14 ± 4 (6)	-
54	23 ± 7 (7)	-	38 ± 8 (5)	23 ± 7 (3)
58	-	-	−16 ± 2 (4)	−25 ± 2 (3)
69	-	-	20 ± 6 (6)	-
75	76 ± 8 (6)	-	0 ± 6 (5)	-
76	31 ± 4 (4)	-	7 ± 2 (4)	1 ± 6 (3)
77	35 ± 7 (6)	-	29 ± 8 (6)	-
78	24 ± 1 (4)	-	24 ± 6 (5)	-
79	-	-	28 ± 7 (5)	-
80	26 ± 4 (4)	-	23 ± 6 (5)	-
81	73 ± 8 (7)	-	100 ± 18 (6)	-
83	84 ± 17 (5)	-	27 ± 7 (5)	-
84	33 ± 3 (4)	-	33 ± 7 (5)	-
92	-	-	49 ± 10 (5)	-
93	26 ± 9 (7)	16 ± 2 (5)	88 ± 6 (4)	26 ± 7 (2)
94	-	-	22 ± 6 (5)	-
95	-	-	83 ± 6 (4)	-
96	41 ± 5 (4)	-	78 ± 16 (5)	-

[a] Modulation of the current in response to GABA at hGABA$_A$ receptors expressed in *Xenopus* oocytes. Data represents percentage increase (or decrease) of the EC_{20} GABA concentration in the presence of a maximal concentration (~100 × K_i) of the test compound as measured by two electrode voltage-clamp electrophysiology. Values are the mean ± SEM of at least three independent determinations (with the actual number shown in brackets).

however, was that, unlike any of the other substituents at the 6-position, they showed significantly higher efficacy at the α_3 subtype compared to the α_1 subtype. Indeed, **93** was almost a full agonist at α_3 but only a very weak partial agonist at α_1. In addition, it also showed selectivity over the α_2 subunit.

To determine what, if anything, distinguished the selective triazole derivatives from other nonselective analogues, the common molecular properties were calculated for all compounds on which efficacy had been measured at both the α_1 and α_3 subtypes. It was found that when the polar surface area (PSA) (calculated using the 2D methodology derived by Ertl et al.[28]) and pK_a (calculated by ACD) were considered, one can see in Figure 1 that the triazoles lie apart from the remainder

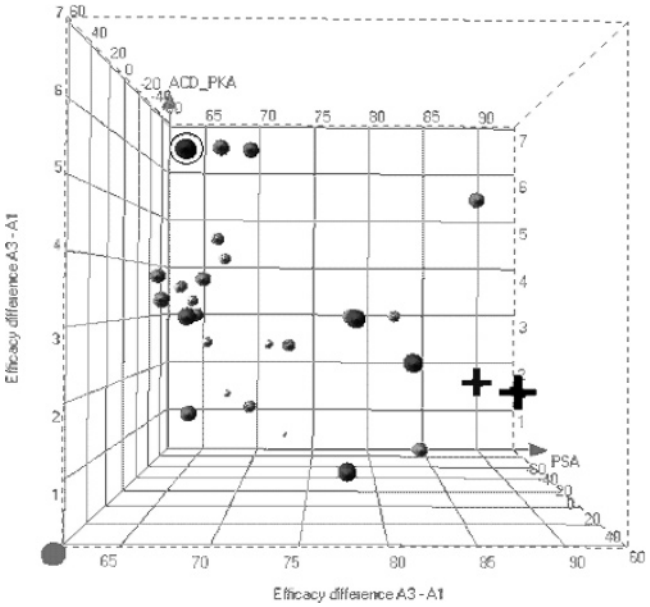


Figure 1. The above image shows a three-dimensional graph with the selective triazoles **93** and **96** illustrated as crosses. The points are shaded and sized with respect to their selective efficacy over α1 with the darker/larger points being the more selective. The axes of the graph are the selective efficacy value for the α3 subtype over α1 (A3−A1), the calculated polar surface area (PSA), and the calculated p*K*a of the molecules (ACD_PKA) using the ACDLabs desktop software version 6.0.

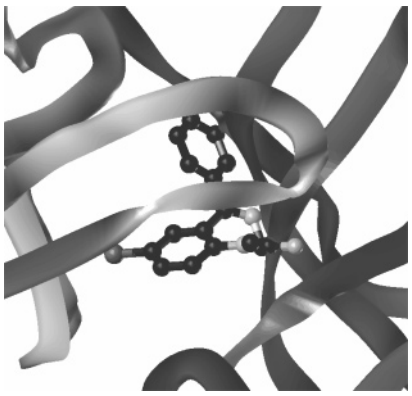


Figure 2. An image of the BZ binding site created from a homology model derived from the published crystal structure of the snail nACh binding protein with diazepam represented in ball-and-stick mode while the protein backbone is represented by a ribbon.

of the compounds with the next most selectively efficacious compound being **81** (circled) which lies distant from the triazoles and has too much agonism at the α1 subtype. The closest compound to the triazoles in terms of PSA and ACD_pK_a is compound **32** which does have limited selective efficacy (a difference of 20%) but again has too much agonism at the α1 subtype. Hence acceptable selective efficacy was produced by compounds with a PSA >85 and with a calculated pK_a of between 2 and 3.

If one considers the environment of the benzodiazepine binding site then these relationships have more meaning. Figure 2 shows an image of the binding site created from a homology model derived from the published crystal structure of the snail nACh binding protein.[29] The lighter ribbon on the left of the image corresponds to the α subunit and one can see that one

side of the benzodiazepine binding site is created by a β-sheet and loop domain. This part of the protein chain extends all the way to the putative membrane spanning domain and while some of this loop region is conserved, there are interesting differences between the various α subunits. It has been shown that mutating the α1 subunit in this region by changing Gly201 to Glu (the corresponding residue found in the α3 subunit) has an effect on the efficacy of CL218,872 (Chart 1) as well as its affinity.[30,31] The more conservative change of Val203 to Ile also has been shown to affect affinity.[32] There are other residues within this region which are different between the α subtypes, e.g., Ile202Thr (in α2), Gln204Arg (in α3), and Ser205Thr (in α5), all of which have some change in polarity and may therefore be affected by the changes in the polar nature of the ligands. Further work on mutating the other residues within this region may give a more detailed picture of the requirements for selective efficacy as well as affinity between all the subtypes.

In summary, these data clearly show that, despite a wide variety of substituents at both the 3- and 6-positions of the central 7,8,9,10-tetrahydro-7,10-ethano-1,2,4-triazolo[3,4-*a*]phthalazine core, it was not possible to achieve greater than 12-fold binding selectivity (seen for **57**). In retrospect, this is possibly not surprising since it has been hypothesised that it is the γ subunit, which is constant between all four subtypes, that makes the major contribution to the BZ site binding energy.[33] Moreover, while compounds such as zolpidem and the triazolopyridazine CL218,872 (Chart 1) have selectivity in favor of the α_1 subtype over the α_2 and α_3 subtypes (Table 1), attributable to a single amino acid (α1G201/α3E225),[30] this is no better than our compounds in the reverse direction (i.e., α_2/α_3 over α_1 binding selectivity). Most analogues in the current work showed no selectivity in terms of efficacy, although some did show partial agonism at α_1 and antagonism at α_3 (e.g., **25** and **75**). Only two of the analogues tested (**93** and **96**) showed significantly higher efficacy for the α_3 subtype over the α_1 subtype. This was the first indication that we could obtain functional selectivity in efficacy in the required direction in this series and led us to focus on 1,2,4-triazoles in subsequent work, which will be the subject of further communications.

Experimental Section

General Methods. Melting points were obtained on a Reichert Thermovar hot stage and are uncorrected. Proton NMR spectra were obtained using either a Bruker AM360 or a Bruker AC250 spectrometer. Mass spectra were recorded on a Quattro operating in an electrospray (ES) mode. (Note that only the strongest peaks from the mass spectra are reported below.) Elemental analysis for carbon, hydrogen, and nitrogen were performed by Butterworth Laboratories Ltd. Unless otherwise stated, high performance liquid chromatography (HPLC) analysis was performed on a Hewlett-Packard HP1090 instrument using a Hichrom S5 ODS2 23 cm column, eluting with acetonitrile/water (containing 0.2% triethylamine and made to pH 3.5 with orthophosphoric acid). Analytical thin-layer chromatography (TLC) was conducted on precoated silica gel 60 F_{254} plates (Merck). Visualization of the plates was accomplished by using UV light and/or iodine and/or aqueous potassium permanganate solution. Chromatography was conducted on silica gel 60, 220−440 mesh (Fluka), under low pressure. Solutions were evaporated on a Büchi rotary evaporator under reduced pressure. All starting materials were obtained from commercial sources and used as received unless otherwise indicated.

2,3,5,6,7,8-Hexahydro-5,8-ethanophthalazine-1,4-dione (**99**) and **1,4-dichloro-5,6,7,8-tetrahydro-5,8-ethanophthalazine** (**100**) have been described by Street et al.[27]

6-Chloro-3-phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]-triazolo[3,4-*a*]phthalazine (**101a**) and **3-phenyl-6-(pyridin-2-ylmethoxy)-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]-triazolo[3,4-*a*]phthalazine** (**1**) have been described by Carling et al.[17]

6-Chloro-3-(2-methoxyphenyl)-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazine (101b). A suspension of **100** (2.5 g, 10.9 mmol) in xylene (50 mL) with 2-methoxybenzoic hydrazide (2.01 g, 12.1 mmol) and triethylamine (1.68 mL, 12.1 mmol) was heated under reflux for 4 days. The solvent was evaporated, and the residue was purified by chromatography (silica gel, 0−40% EtOAc/CH_2Cl_2) to give 1.5 g (40%) of **101b** as a solid: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.41 (4H, m), 1.92 (4H, m), 3.43 (1H, s), 3.78 (3H, s), 3.82 (1H, s), 7.15 (1H, t, J = 7.5 Hz), 7.28 (1H, d, J = 8.4 Hz), 7.51 (1H, dd, J = 7.5 and 1.7 Hz), 7.62 (1H, td, J = 8.4 and 1.7 Hz); MS (ES$^+$) *m/z* 341/343 $[M + H]^+$.

Compounds **101c**−**h**,**j**,**k**,**o** were prepared from **100** by a method similar to that described for **101b** using the corresponding commercially available hydrazides.

1-Chloro-4-hydrazino-5,6,7,8-tetrahydro-5,8-ethanophthalazine (**102**) has been described by Street et al.[27]

***N′*-(4-Chloro-5,6,7,8-tetrahydro-5,8-ethanophthalazin-1-yl)-4-fluorobenzohydrazide (103).** To a solution of **102** (2.003 g, 8.91 mmol) in chloroform (40 mL) under nitrogen was added triethylamine (1.24 mL, 8.90 mmol), and then dropwise 4-fluorobenzoyl chloride (1.07 mmol, 8.95 mmol), causing a solid to start precipitating. The mixture was stirred at room temperature for 4 h and then filtered. The collected solid was washed twice with chloroform and then with diethyl ether and dried under vacuum at 50 °C to afford 2.295 g (74%) of **103** as a white solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.37 (4H, m), 1.85 (4H, m), 3.23 (1H, s), 3.43 (1H, s), 6.97 (2H, t, J = 8.6 Hz), 7.60 (1H, br s), 7.89 (2H, dd, J = 8.8 and 5.3 Hz), 10.90 (1H, br s); MS (ES) *m/z* 347/349 $[M + H]^+$.

6-Chloro-3-(4-fluorophenyl)-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazine (101i). A solution of **103** (1.0014 g, 2.89 mmol) in phosphorus oxychloride (7 mL) was heated at reflux for 5 h. The solvent was evaporated and ice-cold water (20 mL) was added to the residue. The aqueous layer was neutralized to pH 7 with saturated aqueous sodium hydrogen carbonate (6 mL), and the resulting solid was collected by filtration, washed twice with water and then with hexane, and dried under vacuum at 50 °C. This was purified by flash chromatography (silica gel, 10% EtOAc/CH_2Cl_2) to give 0.5743 g (61%) of **101i** as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.50 (4H, m), 1.98 (4H, m), 3.57 (1H, s), 4.06 (1H, s), 7.25 (2H, t, J = 8.7 Hz), 8.50 (2H, dd); MS (ES$^+$) *m/z* 329/331 $[M + H]^+$.

6-Chloro-3-(3-thienyl)-7,8,9,10-tetrahydro-7,10-ethano-[1,2,4]triazolo[3,4-*a*]phthalazine (101l). To a solution of 3-thiophenecarboxylic acid (0.8 g, 6.25 mmol) in dichloromethane (30 mL) was added oxalyl chloride (0.645 mL, 7.39 mmol), followed by DMF (3 drops). The mixture was stirred at room temperature for 1 h and then concentrated. Dichloromethane was added to the residue and evaporated twice. This was then dissolved in dioxane (50 mL) with **102** (1.7 g, 5.7 mmol) and triethylamine (0.866 mL, 6.21 mmol). The mixture was stirred at room temperature for 15 min and then heated at reflux for 3 days. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 0−2% MeOH/CH_2Cl_2) and recrystallized from EtOAc to afford 1.2 g (50%) of **101l**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.49 (4H, m), 1.97 (4H, m), 3.57 (1H, s), 4.05 (1H, s), 7.49 (1H, dd, J = 5.1 and 3.0 Hz), 8.10 (1H, dd, J = 5.1 and 1.2 Hz), 8.60 (1H, m).

6-Chloro-3-(2-furyl)-7,8,9,10-tetrahydro-7,10-ethano-[1,2,4]triazolo[3,4-*a*]phthalazine (101m). To a solution of **102** (1.0 g, 4.4 mmol) and triethylamine (0.68 mL, 4.9 mmol) in dioxane (20 mL) was added portionwise 2-furoyl chloride

(0.44 mL, 4.4 mmol), and the mixture was stirred at room temperature for 30 min and then heated at reflux for 36 h. The solvent was replaced by xylene, and the mixture was heated at reflux for a further 5 h. The solvent was evaporated, and the residue was triturated with ethyl acetate to afford 1.07 g (82%) of **101m** as a solid: MS (ES$^+$) *m/z* 301 [M + H]$^+$.

Methyl 4-methyl-1,3-thiazole-2-carboxylate (104). To a solution of 4-methylthiazole (5 g, 50.4 mmol) in anhydrous THF (200 mL) at −78 °C was added *n*-butyllithium (1.6 M solution in hexane; 34.65 mL, 55.4 mmol) dropwise. The solution was stirred at −78 °C for 1 h, at which point solid carbon dioxide was passed through the solution for 20 min at −78 °C. The solution was then allowed to warm to room temperature over 2 h, and the precipitate was collected by filtration, dissolved in methanol (200 mL), and added to methanolic hydrogen chloride (200 mL). The solution was stirred at room temperature overnight. The solvent was evaporated, and diethyl ether was added to the residue. The resultant solid was collected by filtration to yield 2.2 g (28%) of **104** as a white solid: ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.44 (3H, s), 3.89 (3H, s), 7.74 (1H, s); MS (ES$^+$) *m/z* 158 [M + H]$^+$.

4-Methyl-1,3-thiazole-2-carbohydrazide (105). To a solution of **104** (2.1 g, 13.4 mmol) in methanol (20 mL) was added hydrazine hydrate (3.2 mL, 65.8 mmol) dropwise over 30 min. The mixture was stirred for 1.5 h and the precipitate collected by filtration and washed with diethyl ether to afford 1.6 g (76%) of **105** as a white solid: ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.64 (3H, s), 4.82 (2H, bs), 7.79 (1H, s), 10.25 (1H, bs); MS (ES$^+$) *m/z* 158 [M + H]$^+$.

6-Chloro-3-(4-methyl-1,3-thiazol-2-yl)-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazine (101n). This was prepared in 17% yield using a method similar to that described for **101b** but using **105** instead of 2-methoxybenzoic hydrazide and triethylamine hydrochloride instead of triethylamine: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.41 (4H, m), 1.94 (4H, m), 2.54 (3H, s), 3.48 (1H, s), 3.85 (1H, s), 7.66 (1H, s); MS (ES$^+$) *m/z* 332/334 [M + H]$^+$.

***N*′-(4-Chloro-5,6,7,8-tetrahydro-5,8-ethanophthalazin-1-yl)morpholine-4-carbohydrazide (106).** To a solution of **102** (1.024 g, 4.56 mmol) in chloroform (20 mL) under nitrogen was added triethylamine (0.635 mL, 4.56 mmol), followed by freshly distilled 4-morpholinecarbonyl chloride (0.532 mL, 4.56 mmol) and the mixture was stirred at room temperature for 24 h. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 4% MeOH/CH_2Cl_2) to give 1.265 g (82%) of **107** as an off-white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.38 (4H, m), 1.85 (4H, m), 3.16 (1H, s), 3.40 (1H, s), 3.53 (4H, t, J = 5.2 Hz), 3.71 (4H, t, J = 5.1 Hz), 6.85 (1H, br s), 8.53 (1H, br s); MS (ES) *m/z* 338/340 [M + H]$^+$.

6-Chloro-3-morpholin-4-yl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazine (101p). A solution of **106** (0.4021 g, 1.19 mmol) in phosphorus oxychloride (5 mL) under nitrogen was heated at reflux for 2 h. The solvent was evaporated, and a little water and dichloromethane were added to the residue. The aqueous layer was neutralized to pH 8 with saturated aqueous sodium hydrogen carbonate (21 mL), and the mixture was extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with saturated aqueous NaCl solution (30 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel, 2% MeOH/CH_2Cl_2) to give 0.2426 g (64%) of **101p** as a yellow solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.44 (4H, m), 1.92 (4H, m), 3.48 (1H, s), 3.67 (4H, t, J = 4.9 Hz), 3.94 (5H, m); MS (ES$^+$) *m/z* 320/322 [M + H]$^+$.

3-(2-Methoxyphenyl)-6-(pyridin-2-ylmethoxy)-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazine (2). To a solution of 2-pyridylcarbinol (0.199 mL, 2.06 mmol) in DMF (25 mL) was added sodium hydride (60% dispersion in oil, 80 mg, 2.00 mmol), and the reaction mixture was stirred at room temperature for 15 min. After this time, **101b** (0.50 g, 1.47 mmol) was added and the reaction mixture was stirred at room temperature for 75 min. Water was added until the solution became cloudy, and after stirring for a further 45 min, a solid was collected by filtration. This solid was recrystallized from ethyl acetate−petroleum ether to give 0.410 g (67%) of **2** as a white solid: mp 208−210 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.49 (4H, m), 1.92 (4H, m), 3.54 (1H, s), 3.80 (3H, s), 3.99 (1H, s), 5.40 (2H, s), 7.05−7.11 (2H, m), 7.24 1H, m), 7.40 (1H, d, J = 7.9 Hz), 7.51 (1H, td, J = 7.6 and 1.8 Hz), 7.57 (1H, dd, J = 7.5 and 1.8 Hz), 7.69 (1H, dt, J = 7.7 and 1.8 Hz), 8.59 (1H, m); MS (ES$^+$) *m/z* 414 [M + H]$^+$. Anal. [$C_{24}H_{23}N_5O_2$] C, H, N.

Compounds **3**−**16** were prepared in a similar manner from the corresponding chlorides **101c-101p**.

Compounds **17**−**26**, **30**−**35**, **40**, **46**, **52**, **58**, **59**, **62**−**64**, **68**, **76**, **78**, **80**−**87**, **89**, and **91**−**94** were prepared using a method similar to that described for **2** from **101a** and the corresponding alcohol. Where the alcohol was not commercially available, their preparations are described below.

(3-Methylpyridin-2-yl)methanol, used to make **19**, was prepared in similar way to that described by Iqbal et al.[34] (4-Methylpyridin-2-yl)methanol, used to make **20**, has been prepared by Kühler et al.[35] (5-Methylpyridin-2-yl)methanol used to make **21**, has been prepared by Appel et al.[36]

2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)pyridin-3-ol (107). To 3-hydroxy-2-(hydroxymethyl)pyridine hydrochloride (15.0 g, 93 mmol) in DMF (500 mL) were added imidazole (19.0 g, 0.28 mol) and *tert*-butyldimethylsilyl chloride (16.8 g, 0.11 mol) with stirring at room temperature. The mixture was then stirred at 60 °C under nitrogen overnight. The solvent was evaporated, and the crude product was partitioned between water (200 mL) and dichloromethane (200 mL). The aqueous phase was washed with more dichloromethane (2 × 200 mL), and then the combined organic layers were washed with water (200 mL) and with saturated sodium chloride solution (200 mL), dried ($MgSO_4$), and evaporated. The residual material was purified by flash chromatography (silica gel, 5−20% EtOAc/hexane, yielding 8.5 g (38%) of **107** as a colorless solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.17 (6H, s), 0.94 (9H, s), 5.08 (2H, s), 7.07−7.18 (2H, m), 8.03 (1H, dd, J = 4.4 and 1.6 Hz), 8.66 (1H, br s); MS (ES$^+$) *m/z* 240 [M + H]$^+$.

2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)pyridin-3-yl Trifluoromethanesulfonate (108). To **107** (11.5 g, 48.2 mmol) in dichloromethane (200 mL) was added *N*,*N*-diisopropylethylamine (8.38 mL, 6.22 g, 48 mmol) dropwise with stirring. The mixture was then cooled to −10 °C (salt-ice bath), and trifluoromethanesulfonic anhydride (8.09 mL, 13.6 g, 48 mmol) was added dropwise with stirring. The solution was stirred at −10 °C for 1 h and then was allowed to warm to room temperature and stirred under nitrogen for 24 h. The solution was washed with water (3 × 200 mL), and then the combined aqueous layers were extracted with dichloromethane (200 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residual brown oil was purified by flash chromatography (silica gel, 5−10% EtOAc/hexane, yielding 15.1 g (84%) of **108** as a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.11 (6H, s), 0.90 (9H, s), 4.92 (2H, s), 7.32−7.38 (1H, m), 7.63 (1H, dd, J = 8.4, 1.3 Hz), 8.49 (1H, m); MS (ES$^+$) *m/z* 372 [M + H]$^+$.

3-Allyl-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-pyridine (109). To **108** (5.00 g, 13.5 mmol) in DMF (100 mL) were added tetraallyltin (6.47 mL, 7.63 g, 27 mmol) and lithium chloride (1.17 g, 28 mmol), and the mixture was degassed by bubbling nitrogen through for 15 min. Bis-(triphenylphosphine)palladium(II) chloride (949 mg, 1.35 mmol) was added, and the mixture was degassed as before and then was heated at 80 °C under nitrogen for 12 h. The mixture was filtered to remove inorganics, and then the filtrate was diluted with water (200 mL) and washed with hexane (3 × 200 mL). The combined organic layers were washed with water (200 mL) and then with saturated sodium chloride solution (200 mL), dried ($MgSO_4$), and evaporated to give a yellow oil. This was purified by flash chromatography (silica gel, 5−20% EtOAc/hexane) to yield 2.79 g (79%) of **109** as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.89 (9H, s), 3.57 (2H, d, J = 6.5 Hz), 4.84 (2H, s), 5.00−5.14 (2H, m), 5.88−5.04 (1H, m), 7.15−7.20 (1H, m), 7.51 (1H, dd, J = 7.7 and 1.6 Hz), 8.39 (1H, dd, J = 4.8 and 1.7 Hz); MS (ES$^+$) *m/z* 264 [M + H]$^+$.

(3-Allylpyridin-2-yl)methanol (110). A solution of **109** (2.50 g, 9.51 mmol) in 1 M tetrabutylammonium fluoride solution in THF (25 mL) was stirred at room temperature for 25 min. The solvent was removed in vacuo, and the residue was taken up in water (50 mL). The resulting solution was washed with dichloromethane (3 × 50 mL). The combined organic layers were washed with saturated sodium chloride solution (50 mL), dried ($MgSO_4$), and evaporated. The residual yellow oil was purified by flash chromatography (silica gel, 50% EtOAc/isohexane), yielding 1.10 g (77%) of **110** as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.30 (2H, d, J = 6.3 Hz), 4.73 (2H, s), 4.99−5.17 (2H, m), 5.81−5.97 (1H, m), 7.18−7.23 (1H, m), 7.51 (1H, dd, J = 7.6 and 1.5 Hz), 8.45 (1H, dd, J = 4.9 and 1.5 Hz); MS (ES^+) *m/z* 150 $[M + H]^+$.

(3-Propylpyridin-2-yl)methanol (111). A solution of **110** (400 mg, 2.68 mmol) in ethyl acetate (10 mL) was hydrogenated over 10% palladium on carbon (40 mg) at 30 psi on a Parr apparatus for 30 min. The catalyst was separated by filtration, and the filtrate was evaporated, yielding 371 mg (92%) of **111** as a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.3 Hz), 1.55−1.70 (2H, m), 2.49 (2H, t, J = 7.7 Hz), 4.74 (2H, s), 7.16−7.21 (1H, m), 7.49 (1H, dd, J = 7.6 and 0.9 Hz), 8.41 (1H, d, J = 4.0 Hz); MS (ES^+) *m/z* 152 $[M + H]^+$. This was used to prepare **23**.

3,6-Dimethylpyridine-2-carbonitrile (112). To 2,5-dimethylpyridine 1-oxide[16] (12.5 g, 0.102 mol) in dichloromethane (180 mL) was added trimethylsilyl cyanide (14.3 mL, 10.6 g, 0.107 mol) with stirring at room temperature. The mixture was stirred at room temperature under nitrogen for 25 min, *N*,*N*-diethylcarbamoyl chloride (13.6 mL, 14.6 g, 0.107 mol) was added, and the solution was stirred as before for 4 days. Aqueous potassium carbonate (400 mL of 10% solution) was added, and the mixture was stirred vigorously for 15 min. The aqueous phase was separated and washed with dichloromethane (3 × 200 mL). The combined organic layers were washed with more 10% potassium carbonate solution (200 mL) and then with saturated sodium chloride solution (200 mL), dried (Na_2SO_4), and evaporated. The residual brown oil was purified by flash chromatography (silica gel, 5−20% EtOAc/hexane) yielding 9.72 g (72%) of **112** as a colorless low melting point solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.52 (3H, s), 2.56 (3H, s), 7.28 (1H, d, J = 8.0 Hz), 7.56 (1H, d, J = 8.0 Hz); MS (ES^+) *m/z* 133 $[M + H]^+$.

(3,6-Dimethylpyridin-2-yl)methanol (113). A solution of **112** (1.15 g, 8.71 mmol) in 2 N hydrochloric acid (20 mL) was hydrogenated at 30 psi over 10% palladium on carbon (200 mg) for 2 h. The catalyst was removed by filtration, and the filtrate was basified by the addition of saturated sodium hydrogen carbonate solution. The resulting mixture was washed with ethyl acetate (3 × 50 mL), and then the combined organic layers were dried ($MgSO_4$) and evaporated, yielding 0.68 g (57%) of **113** as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.16 (3H, s), 2.52 (3H, s), 4.64 (2H, s), 6.98 (1H, d, J = 7.6 Hz), 7.35 (1H, d, J = 7.6 Hz); MS (ES^+) *m/z* 138 $[M + H]^+$. This was used to prepare **24**.

(3,5-Dimethylpyridin-2-yl)methanol was prepared by a similar procedure to that described by Kühler et al.[35] and used to make **25**. (3,4-Dimethylpyridin-2-yl)methanol was prepared by the method of Katz et al.[37] and used to make **26**.

[3-(Cyclopropylmethoxy)pyridin-2-yl]methanol (114). Potassium hydroxide (5.2 g, 0.093 mol) was ground to a powder under nitrogen, added to DMSO (30 mL) and stirred for 20 min under nitrogen at room temperature. The mixture was cooled to 0 °C, and 2-(hydroxymethyl)pyridin-3-ol hydrochloride (5.0 g, 0.031 mol) was added. The slurry was stirred at 0 °C for 1 h before the addition of cyclopropylmethyl bromide (3.01 mL, 4.2 g, 0.031 mol). The mixture was allowed to warm to room temperature and stirred under nitrogen overnight. Water (100 mL) was added, and the resultant solution was acidified to pH 1 with hydrochloric acid (5 N). The solution was washed with dichloromethane (3 × 100 mL), basified to pH 14 with sodium hydroxide solution (4 N), and extracted with dichloromethane (3 × 100 mL). The organic extracts were combined, washed with water (100 mL), and saturated sodium chloride solution (100 mL), dried ($MgSO_4$), and evaporated to give 2.40 g (43%) of **114** as a dark brown solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.35 (2H, m), 0.65 (2H, m), 1.26 (1H, m), 3.85 (2H, d, J = 6.8 Hz), 4.33 (1H, br s), 4.77 (2H, s), 7.13 (2H, m), 8.13 (1H, m); MS (ES^+) *m/z* 180 $[M + H]^+$. This was used to prepare **33**.

The (3-alkoxypyridin-2-yl)methanols **115**−**117** were prepared by the same procedure as that described for **114** employing the corresponding alkyl halide and used to synthesize **30**−**32**, respectively.

[3-(Cyclobutyloxy)pyridin-2-yl]methanol (118). 3-Hydroxy-2-hydroxymethylpyridine hydrochloride (1.57 g, 9.73 mmol), cyclobutyl bromide (5.00 g, 37.0 mmol), and potassium carbonate (8.09 g, 58.5 mmol) were stirred together in DMF (20 mL) at 50 °C for 24 h. Water (40 mL) was added, and the resulting mixture was acidified by the addition of 5 N hydrochloric acid and was then washed with dichloromethane (3 × 100 mL). The aqueous phase was basified with 4 N sodium hydroxide solution and washed with more dichloromethane (3 × 100 mL). The combined organic layers from the second extraction were washed with water (100 mL), dried ($MgSO_4$), and evaporated. The residual pale brown solid was recrystallized from hexane, yielding 443 mg (25%) of **118** as a tan colored solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.62−1.96 (2H, m), 2.10−2.25 (2H, m), 2.40−2.52 (2H, m), 4.31 (1H, br s), 4.60−4.71 (1H, m), 4.74 (2H, s), 6.97 (1H, dd, J = 8.2 and 1.2 Hz), 7.14 (1H, dd, J = 8.2 and 4.8 Hz), 8.13 (1H, dd, J = 4.8 and 1.1 Hz); MS (ES^+) *m/z* 180 $[M + H]^+$. This was used to prepare **34**.

[3-(Benzyloxy)pyridin-2-yl]methanol used to prepare **35** has been synthesized by Takeda et al.[38] {3-[(Dimethylamino)-methyl]phenyl}methanol used to make **58** has been prepared by Brown and Ife.[39] [4-(Methylsulfinyl)phenyl]methanol used to make **59** has been prepared by Samanen and Brandeis.[40]

3-Methyl-6-vinylpyridazine (119). A solution of 3-chloro-6-methyl pyridazine (20 g, 156 mmol), tetravinyltin (50 mL, 264 mmol), and lithium chloride (13.2 g, 311 mmol) in DMF (250 mL) was degassed with nitrogen for 10 min. The flask was then evacuated and refilled with nitrogen before adding dichlorobis(triphenylphosphine)palladium(II) (11.0 g, 15.6 mmol). The mixture was heated at 100 °C overnight. The solvent was evaporated, and water (100 mL) and dichloromethane (100 mL) was added to the residue. The mixture was filtered, and the aqueous layer was extracted further with dichloromethane (100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica gel, 0−5% MeOH/CH_2Cl_2) to give 8.37 g (45%) of **119**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.71 (3H, s), 5.63 (1H, d, J = 11.1 Hz), 6.71 (1H, d, J = 17.8 Hz), 7.03 (1H, dd, J = 17.8 and 11.0 Hz), 7.28 (1H, d, J = 8.8 Hz), 7.49 (1H, d, J = 8.7 Hz).

6-Methylpyridazine-3-carbaldehyde (120). A solution of **119** (8.37 g, 69.8 mmol) in dichloromethane (200 mL) cooled to −78 °C was treated with ozone for 5 h. The mixture was then allowed to warm to room temperature overnight before it was recooled to −78 °C and nitrogen bubbled through it for 10 min. Dimethyl sulfide (5 mL) was added and the mixture left for 1 h and then warmed to room temperature. The mixture was diluted with water (100 mL) and neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was further extracted with dichloromethane (2 × 100 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated to afford 0.50 g (6%) of **120**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.85 (3H, s), 7.52 (1H, d, J = 8.5 Hz), 7.94 (1H, d, J = 8.6 Hz), 10.37 (1H, s); MS (ES^+) *m/z* 123 $[M + H]^+$.

(6-Methylpyridazin-3-yl)methanol (121). To a solution of **120** (0.50 g, 4.07 mmol) in methanol (10 mL) at 0 °C under nitrogen was added sodium borohydride (0.05 g, 1.30 mmol), and the solution was stirred at 0 °C for 1 h. Saturated aqueous NaCl (5 mL) was added, and the mixture was stirred at room temperature for 15 min. The methanol was evaporated, and the aqueous residue was extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, dried (Na_2SO_4), and evaporated to give 370 mg (73%) of **121** as an oil: ^{1}H NMR

(360 MHz, $CDCl_3$) δ 2.69 (3H, s), 4.94 (2H, s), 7.33 (1H, d, J = 8.6 Hz), 7.41 (1H, d, J = 8.6 Hz); MS (ES^+) *m/z* 125 $[M + H]^+$. This was used to prepare **40**.

1-Ethyl-2-(hydroxymethyl)imidazole was prepared according to the procedure of Tasaka et al.[41] and used to prepare **80**. 1,3-Thiazol-2-ylmethanol has been prepared by Dondoni and Perrone[42] and was used to make **83**. 4-Hydroxymethylthiazole has been prepared by Houssin et al.[43] and was used to prepare **84**.

(4-Methyl-1,3-thiazol-2-yl)methanol (123). To a solution of 4-methyl-1,3-thiazole-2-carbaldehyde (**122**)[20] (2.23 g, 0.0175 mmol) in methanol (50 mL) was added sodium borohydride (0.664 g, 0.0175 mmol). After 1 h, the mixture was evaporated and the residue was partitioned between dichloromethane and water. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford 1.12 g (35%) of **123**: ^1H NMR (250 MHz, $CDCl_3$) δ 2.42 (3H, d, J = 1.1 Hz), 3.74 (1H, br s), 4.90 (2H, s), 6.84 (1H, q, J = 1.0 Hz). This was used to prepare **85**.

(5-Methyl-1,3-thiazol-2-yl)methanol (125). This was prepared by the same procedure as that described for **123** but using 5-methyl-1,3-thiazole-2-carbaldehyde (**124**).[21] Yield 65%: ^1H NMR (250 MHz, $CDCl_3$) δ 2.46 (3H, d, J = 1.0 Hz), 3.70 (1H, br s), 4.85 (2H, s), 7.35 (1H, q, J = 1.2 Hz). This was used to prepare **86**.

4,5-Dimethyl-1,3-thiazole 3-oxide (126). To a solution of 4,5-dimethylthiazole (20 g, 0.177 mol) in dichloromethane (100 mL) at 0 °C was added slowly a solution of 3-chloroperoxybenzoic acid (60 g) in dichloromethane (400 mL), and the mixture was stirred at room temperature overnight. 4 N Aqueous NaOH solution (40 mL) was added, and the pH was adjusted to 8−9. The aqueous layer was extracted several more times with dichloromethane, and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was triturated with diethyl ether, and the resulting solid was collected by filtration to give 4.8 g (21%) of **126**: ^1H NMR (360 MHz, $CDCl_3$) δ 2.30 (3H, s), 2.39 (3H, s), 8.07 (1H, s).

(5-Methyl-1,3-thiazol-4-yl)methanol (127). Solid **126** (4.8 g) was added in portions to a solution of acetic anhydride (30 mL) at 110 °C. The mixture was then stirred at 110 °C overnight, and the product was isolated by distillation: bp 115 °C (0.22 mbar). This was dissolved in methanolic HCl (100 mL) and left to stand overnight. The solvent was evaporated, and the residue was partitioned between 4 N aqueous NaOH solution (20 mL) and dichloromethane. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to leave 900 mg (19%) of crude **127**: ^1H NMR (250 MHz, $CDCl_3$) δ 2.48 (3H, s), 3.41 (1H, br s), 4.71 (2H, s), 8.58 (1H, s). This was used to prepare **87**.

(3-Methylisothiazol-5-yl)methanol has been prepared by Layton and Lunt[44] and was used to make **89**.

(5-Methyl-1,2,4-oxadiazol-3-yl)methanol (128). To a solution of *N*′-hydroxy-2-(tetrahydro-2*H*-pyran-2-yloxy)ethanimidamide[22] (7.0 g, 0.040 mol) in THF (100 mL) with 3 Å molecular sieves (20 g) was added sodium hydride (60% dispersion in oil, 3.2 g, 0.080 mol), and the mixture was heated at 50 °C for 1 h. Ethyl acetate (3.9 mL, 0.040 mol) was added, and the mixture was stirred for a further 2 h. After cooling, the mixture was partitioned between water (100 mL) and dichloromethane (200 mL). The aqueous layer was extracted further with dichloromethane, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in methanol (300 mL), and pyridinium *p*-toluenesulfonate (1.2 g, 4.8 mmol) was added. The mixture was stirred at room-temperature overnight and then evaporated. The residue was dissolved in dichloromethane, washed with water, dried ($MgSO_4$), and evaporated. This was redissolved in methanol, treated with *p*-toluenesulfonic acid (50 mg, 0.26 mmol), and stirred overnight at room temperature. The solvent was evaporated, and the residue was partitioned between dichloromethane and saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica gel, 0−2% MeOH/CH_2Cl_2) to give 520 mg (11%) of **128**: ^1H NMR (360 MHz, $CDCl_3$) δ 2.61 (3H, s), 3.67 (1H, br t), 4.76 (2H, d, J = 5.0 Hz). This was used to make **91**.

1*H*-1,2,4-Triazol-5-ylmethanol was prepared as described by Jones and Ainsworth[45] and used to make **92**. (1-Methyl-1*H*-1,2,4-triazol-3-yl)methanol and (1-methyl-1*H*-1,2,4-triazol-5-yl)methanol were prepared using the conditions described by Itoh and Okonogi[46] and used to make **93** and **94**, respectively.

3-Phenyl-6-(1*H*-pyrazol-1-ylmethoxy)-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazine (75). This compound was prepared using the procedure described for **2** using 1-(hydroxymethyl)pyrazole[47] and adding **101a** at the same time as the sodium hydride in order to yield the correct product. Yield 64%: mp 196 °C (EtOAc−hexane); ^1H NMR (360 MHz, DMSO-d_6) δ 1.47 (4H, m), 1.99 (4H, m), 3.38 (1H, s), 3.87 (1H, s), 6.51 (1H, m), 6.62 (2H, s), 7.73 (4H, m), 8.18 (1H, m), 8.60 (2H, m); MS (ES^+) *m/z* 373 $[M + H]^+$. Anal. $[C_{21}H_{20}N_6O]$ C, H, N.

6-(1*H*-Imidazol-2-ylmethoxy)-3-phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazine (77). This was prepared as for **2** using (1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)methanol (**129**),[27] but followed by an additional step in which the product was stirred at 50 °C in 5 N hydrochloric acid for 90 min before evaporation and recrystallization from ethyl acetate/methanol. Yield 58%: mp 219 °C (dec) (EtOAc−MeOH); ^1H NMR (360 MHz, DMSO-d_6) δ 1.42 (4H, m), 1.91 (4H, m), 3.51 (1H, s), 3.78 (1H, s), 5.84 (2H, s), 7.59 (3H, m), 7.76 (2H, s), 8.23 (2H, m); MS (ES^+) *m/z* 373 $[M + H]^+$. Anal. $[C_{21}H_{20}N_6O \cdot 2HCl \cdot 0.7H_2O]$ C, H, N.

(4-Methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)methanol (130a) and (5-Methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)methanol (130b). This mixture of compounds was prepared in an analogous manner to **129** from 4- and 5-methyl-1-{[2-(trimethylsilyl)-ethoxy]methyl}-1*H*-imidazole-2-carbaldehyde.[23] Yield 87%: ^1H NMR (250 MHz, $CDCl_3$) δ 0.00 (9H, s), 0.91 (2H, m), 2.18 and 2.25 (3H, two s), 3.53 (2H, m), 4.66 and 4.68 (2H, two s), 5.30 and 5.33 (2H, two s), 6.65 and 6.69 (1H, two s); MS (ES^+) *m/z* 243 $[M + H]^+$.

6-[(4-Methyl-1*H*-imidazol-2-yl)methoxy]-3-phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]-phthalazine (79). This compound was prepared using the procedure described for **77** using **130a/130b**. Yield 34%: mp 220 °C (dec) (EtOH−EtOAc); ^1H NMR (360 MHz, DMSO-d_6) δ 1.43 (4H, m), 1.91 (4H, m), 2.29 (3H, s), 3.50 (1H, s), 3.77 (1H, s), 5.80 (2H, s), 7.43 (1H, s), 7.59 (3H, m), 8.28 (2H, m); MS (ES^+) *m/z* 387 $[M + H]^+$. Anal. $[C_{22}H_{22}N_6O \cdot 2HCl \cdot 1.8H_2O \cdot 0.2C_4H_8O_2]$ C, H, N.

3-Phenyl-6-(pyridin-3-yloxy)-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazine (45). This compound was prepared as part of a rapid analogue library using the following methodology. To 3-hydroxypyridine (50 mg, 0.526 mmol) in a test tube with a ground glass joint sealed with a septum under nitrogen was added a solution of **101a** (50 mg, 0.161 mmol) in DMF (1.5 mL), followed by lithium bis-(trimethylsilyl)amide (1 M solution in hexanes, 0.50 mL, 0.50 mmol). The reaction was stirred at room temperature for 18 h. The mixture was poured into water (10 mL), and the precipitate formed was isolated by filtration and dried in a vacuum oven at 80 °C to yield 20 mg (34%) of **45**: MS (ES^+) *m/z* 370 $[M + H]^+$; HPLC >99% (RT 3.68 min, 50% acetonitrile/pH 3.5 phosphate buffer).

Compounds **47**, **56**, **57**, **60**, **61**, **69**, **72**−**74** were prepared by the same method as described for **45**.

(*trans*- and *cis*-4-{[(3-Phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)oxy]methyl}-cyclohexyl)methanol (70 and 71). These compounds were prepared as for **45** using a mixture of *cis*- and *trans*-1,4-cyclohexanedimethanol to give a 67% yield of **70** and **71** as an 82:18 mixture, which was separated by preparative HPLC on a Pirkle-type dinitrobenzyl-D-phenylglycine chiral stationary phase column (250 × 10 mm i.d.) eluting at 6 mL/min with 2% MeOH/chlorobutane.

70: MS (ES^+) *m/z* 419 $[M + H]^+$, HPLC >99.5% (t_R 12.68 min, using a Pirkle-type dinitrobenzyl-D-phenylglycine chiral

stationary phase column, a flow rate of 1.5 mL/min, and eluting with 2% MeOH/chlorobutane).

71: MS (ES^+) *m/z* 419 $[M + H]^+$, HPLC >99.5% (t_R 11.06 min, using a Pirkle-type dinitrobenzyl-D-phenylglycine chiral stationary phase column, a flow rate of 1.5 mL/min, and eluting with 2% MeOH/chlorobutane).

3-Phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo-[3,4-*a*]phthalazin-6-ol (131). To a solution of **101a** (3.0 g, 9.6 mmol) in 10% aqueous 1,4-dioxane (100 mL) was added 2 N sodium hydroxide solution (24 mL, 48 mmol), and the reaction mixture was heated under reflux for 3 days. The organic solvent was removed by rotary evaporation, and the residue was partitioned between water (250 mL) and diethyl ether (250 mL). The aqueous layer was separated, washed twice more with diethyl ether (100 mL), and then treated with 5 N aqueous hydrochloric acid until a pH of 2 was attained. The solid which precipitated out of solution was collected by filtration to give 2.7 g (96%) of **131** as a white solid: mp ~ 300 °C (dec); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.35 (4H, m), 2.00 (4H, m), 3.49 (1H, s), 3.84 (1H, s), 7.71 (3H, m), 8.54 (2H, d, J = 7.8 Hz); MS (ES^+) *m/z* 293 $[M + H]^+$.

2-(Chloromethyl)nicotinonitrile (132). To 2-methylnicotinonitrile[20] (2.0 g, 16.9 mmol) in chloroform (30 mL) at reflux was added trichloroisocyanuric acid (1.57 g, 6.75 mmol) in portions, and the mixture was heated at reflux overnight. After cooling, the mixture was filtered, and the filtrate was diluted with dichloromethane, washed with sodium hydroxide solution and then brine, dried ($MgSO_4$), and evaporated to give 1.5 g of impure **132**, which by NMR contained ~19% starting material and 7% dichlorinated product: ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.85 (2H, s), 7.43 (1H, dd, J = 7.9 and 4.9 Hz), 8.02 (1H, dd, J = 7.9 and 1.7 Hz), 8.81 (1H, dd, J = 4.9 and 1.7 Hz).

2-{[(3-Phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]-triazolo[3,4-*a*]phthalazin-6-yl)oxy]methyl}nicotinonitrile (27). To a stirred solution of **131** (0.3 g, 1.0 mmol) in DMF (20 mL) was added sodium hydride (60% dispersion in oil, 49 mg, 1.2 mmol), and the mixture was heated at 80 °C for 30 min before the above impure **132** (0.35 g) was added. After 1 h at 80 °C, water was added until the solution turned cloudy, and the resulting solid was collected by filtration. Recrystallization from MeOH−EtOAc afforded 140 mg (33%) of **27** as a solid: mp 278 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.51 (4H, m), 1.92 (4H, m), 3.60 (1H, s), 3.98 (1H, s), 5.78 (2H, s), 7.42 (1H, dd, J = 7.8 and 4.9 Hz), 7.47−7.54 (3H, m), 8.04 (1H, dd, J = 7.9 and 1.6 Hz), 8.37 (2H, d, J = 7.0 Hz), 8.81 (1H, dd, J = 4.9 and 1.6 Hz); MS (ES^+) *m/z* 409 $[M + H]^+$. Anal. [$C_{24}H_{20}N_6O$] C, H, N.

Compounds **28**, **36**-**39**, **41**-**44**, **48**, **53**-**55**, **66**, **88**, **90**, **97**, and **98** were prepared in essentially the same way to that described for **27** from **131** and the corresponding halide. Where the halide was not commercially available, their preparations are described below.

Chlorides **133**, **134**, **138**−**141**, and **142**[48] were prepared from the corresponding methyl analogues in the same way as that described for **132** and used to prepare **28**, **36**, **38**, **39**, **41**, **42**, and **88**, respectively.

Dimethyl Pyrimidin-2-ylmalonate (135). To dimethyl malonate (41.6 g, 0.315 mol) in 1,4-dioxane (900 mL) was added sodium hydride (60% dispersion in mineral oil; 18.9 g, 0.473 mol) portionwise. To the resultant gel was added 2-bromopyrimidine (50.0 g, 0.314 mol) in 1,4-dioxane (200 mL) dropwise. The mixture was stirred at room temperature for 1 h and then at reflux overnight. To the cooled solution was added water (400 mL), and 5 N hydrochloric acid until the pH was ~ 1. The solution was washed with ethyl acetate (2 × 400 mL), the organic layers combined, washed with saturated sodium hydrogen carbonate solution (400 mL) and saturated sodium chloride solution (400 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel, 0−20% EtOAc/CH_2Cl_2) to yield 24.1 g (37%) of **135** as a yellow-orange oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.83 (6H, s), 5.16 (1H, s), 7.28 (1H, t, J = 5.0 Hz), 8.87 (2H, d, J = 5.0 Hz); MS (ES^+) *m/z* 211 $[M + H]^+$.

2-Methylpyrimidine (136). A mixture of **135** (14.0 g, 66.6 mmol), sodium chloride (17.1 g, 293 mmol), and water (5.24 mL) were heated together in DMSO (50 mL) at 160 °C overnight. The solution was allowed to cool and the inorganic material filtered off. The filtrate was distilled at atmospheric pressure, and the fraction boiling between 95 and 112 °C was collected. The distillate was redistilled at atmospheric pressure, collecting the fraction boiling between 97 and 99 °C to give 1.41 g (17%) of **136** and dimethyl sulfide as a 2:1 mixture. This material was used in the next step without further purification. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.70 (3H, s), 7.13 (1H, t, J = 4.9 Hz), 8.66 (2H, d, J = 4.9 Hz); MS (ES^+) *m/z* 95 $[M + H]^+$.

2-(Chloromethyl)pyrimidine (137). This was prepared as for **132** from impure **136** (0.57 g) to give 0.11 g of **137** as a pale orange/brown oil, which by NMR contained ~16% starting material: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.77 (2H, s), 7.27 (1H, t, J = 4.9 Hz), 8.79 (2H, d, J = 4.9 Hz); MS (ES^+) *m/z* 129 $[M + H]^+$. This was used to prepare **37**.

2-Chloromethylquinoxaline and 2-(1-chloroethyl)pyridine were prepared as described by Jeromin et al.[49] and used to prepare **44** and **48**, respectively.

5-(Chloromethyl)-3-methyl-1,2,4-oxadiazole (143). To a solution of acetamide oxime (1 g, 0.0135 mol) in dichloromethane (30 mL) was added triethylamine (2.06 mL, 0.015 mol) and the mixture was cooled to 0 °C. Chloroacetyl chloride (1.18 mL, 0.015 mol) was added dropwise over 5 min. The reaction was stirred at 0 °C for 10 min and then at room temperature for 1 h. The reaction was diluted with dichloromethane (40 mL) and washed with water (2 × 30 mL) and then brine (30 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to yield the crude **143**. This was used to prepare **90**.

5-(Chloromethyl)-1-methyl-1*H*-tetrazole and 5-(chloromethyl)-2-methyl-2*H*-tetrazole were prepared as described by Moderhack[50] and used to prepare **97** and **98**, respectively.

3-Phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo-[3,4-*a*]phthalazine-6-carbonitrile (144) and 3-Phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]-phthalazine-6-carboxamide (145). A mixture of **101a** (1.003 g, 3.23 mmol) and copper(I) cyanide (0.522 g, 5.83 mmol) in anhydrous 1-methyl-2-pyrrolidinone (3.2 mL) under nitrogen was heated at 200 °C for 36 h. After cooling, the mixture was partitioned between aqueous ammonia solution (50 mL) and dichloromethane (50 mL). The aqueous layer was further extracted with dichloromethane (3 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel, 1−3% MeOH/CH_2Cl_2 and then 15% EtOAc/CH_2Cl_2) to afford 0.643 g (66%) of **144** as a yellow solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.53 (4H, m), 2.04 (4H, m), 3.59 (1H, s), 4.11 (1H, s), 7.53−7.62 (3H, m), 8.47 (2H, d).

From the first column 0.151 g (15%) of **145** was also isolated, which was triturated in boiling chloroform to leave a cream solid: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.39 (4H, m), 1.93 (4H, m), 3.65 (1H, s), 3.82 (1H, s), 7.57−7.66 (3H, m), 8.10 (1H, s), 8.34 (1H, s), 8.44 (2H, d).

Ethyl 3-Phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]-triazolo[3,4-*a*]phthalazine-6-carboxylate (146). To a solution of **144** (327 mg, 1.09 mmol) in ethanol (62 mL) was added 4 N aqueous sodium hydroxide solution (2.75 mL, 11.0 mmol), and the solution was heated at reflux for 5 h. After cooling, the mixture was acidified with 5 M hydrochloric acid to pH <2 and then evaporated. The solid was azeotroped with ethanol twice. To the residue was added more ethanol, and the mixture was cooled under nitrogen to 5 °C before thionyl chloride (0.813 mL, 11.1 mmol) was added dropwise over 5 min. The mixture was then heated at reflux for 2 h. After cooling, the solvent was evaporated, and the residue was partitioned between water (30 mL) and dichloromethane (30 mL), making the pH of the aqueous layer 7 with a few drops of saturated sodium hydrogen carbonate solution. The aqueous layer was further extracted with dichloromethane (2 × 20 mL), and the organic extracts were combined, dried ($MgSO_4$), and

evaporated to afford 353 mg (93%) of **146** as a pale yellow solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.46−1.52 (7H, m), 1.98 (4H, m), 3.82 (1H, s), 4.10 (1H, s), 4.53 (2H, q, J = 7.1 Hz), 7.54−7.57 (3H, m), 8.41 (2H, dd, J = 8.1 and 1.6 Hz); MS (ES^+) m/z 349 $[M + H]^+$.

(3-Phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo-[3,4-*a*]phthalazin-6-yl)methanol (147). A solution of **146** (701 mg, 2.01 mmol) in ethanol (10 mL) was added to a solution of anhydrous calcium chloride (90 mg, 0.81 mmol). The resulting solution was cooled to −10 °C and sodium borohydride (170 mg, 4.49 mmol) in ethanol (10 mL) was slowly added. The mixture was then allowed to stand at room temperature for 30 min. The solvent was evaporated, and the residue was diluted with 1 N aqueous HCl. The resulting solid was collected by filtration and washed several times with water to give 0.499 g (81%) of **147** as a white solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.71 (4H, m), 1.96 (4H, m), 3.35 (1H, s), 4.02 (1H, s), 4.98 (2H, s), 7.57−7.66 (3H, m), 8.41 (2H, dd, J = 8.1 and 1.6 Hz); MS (ES^+) m/z 307 $[M + H]^+$.

3-Phenyl-6-[(pyridin-2-yloxy)methyl]-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazine (49). To a solution of **147** (150 mg, 0.48 mmol), triphenylphosphine (180 mg, 0.72 mmol), and 2-hydroxypyridine (60 mg, 0.63 mmol) in THF (3.5 mL) was slowly added diethyl azodicarboxylate (0.120 mL, 0.75 mmol) at room temperature. The mixture was stirred at room temperature for 3 h. Water was then added, and the mixture was extracted with dichloromethane. The extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel, 5% MeOH/CH_2Cl_2, and then alumina, 20% EtOAc/CH_2Cl_2) and then preparative TLC (5% MeOH/CH_2Cl_2) to give 21.6 mg (9%) of **49**, which was further purified by preparative HPLC on S5 ODS 2 (250 × 4.6 mm) column, eluting with 70% MeCN/H_2O containing 0.1% TFA: HPLC >99.5% (t_R, 10 min, 70% MeCN/H_2O containing 0.1% TFA).

[(3-Phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)methyl]amine (148). A mixture of **144** (0.4974 g, 1.65 mmol) and palladium on activated charcoal (10%, 0.2516 g) in ethanol (100 mL) and chloroform (2 mL) was hydrogenated on a Parr apparatus at 50 psi for 22 h. The catalyst was removed by filtration and washed well with ethanol. The combined filtrates were evaporated in vacuo, and the residue was partitioned between 1 N NaOH solution (30 mL) and dichloromethane (100 mL). The aqueous layer was extracted further with dichloromethane (100 mL), and the combined extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (silica gel, 3% MeOH/CH_2Cl_2) to give 0.3236 g (64%) of **148** as a pale yellow solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.47 (4H, m), 1.95 (4H, m), 3.35 (1H, s), 4.02 (1H, s), 4.20 (2H, s), 7.46−7.57 (3H, m), 8.50 (2H, d).

***N*-[(3-Phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]-triazolo[3,4-*a*]phthalazin-6-yl)methyl]pyridin-2-amine (50).** A solution of **148** (0.1504 g, 0.492 mmol) and 2-bromopyridine (3.0 mL) was heated at 160 °C under nitrogen for 6 h. After cooling, the solvent was evaporated and the residue was purified by flash chromatography (silica gel, 2−5% MeOH/CH_2Cl_2) to yield 0.1909 g (100%) of **50** as a yellow solid: mp 165−170 °C (CH_2Cl_2−EtOAc−hexane); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.47 (4H, m), 1.95 (4H, m), 3.45 (1H, s), 4.03 (1H, s), 4.93 (2H, d, J = 5.5 Hz), 5.23 (1H, m), 6.58 (1H, d, J = 8.3 Hz), 6.66 (1H, t, J = 5.5 Hz), 7.46−7.53 (4H, m), 8.15 (1H, d), 8.38 (2H, d, J = 8.0 Hz); MS (ES^+) m/z 383 $[M + H]^+$. Anal. $[C_{23}H_{22}N_6 \cdot 0.06C_4H_8O_2]$ C, H, N.

3-Phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo-[3,4-*a*]phthalazine-6-carboxylic Acid (149). A solution of **145** (0.21 g, 0.66 mmol) in concentrated hydrochloric acid (5 mL) was stirred at 100−120 °C for 46 h. After cooling, the mixture was diluted with water (20 mL) and dichloromethane (20 mL) and then filtered. The solid was washed with water then dichloromethane and dried at 60 °C under vacuum. The combined filtrates were extracted with dichloromethane (12 × 50 mL), and the combined extracts were dried ($MgSO_4$) and evaporated. This was combined with the solid obtained above to give 0.151 g (72%) of **149** as a pale brown solid: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.41 (4H, m), 1.93 (4H, m), 3.77 (1H, s), 3.84 (1H, s), 7.58−7.67 (3H, m), 8.42 (2H, d).

3-Phenyl-*N*-pyridin-2-yl-7,8,9,10-tetrahydro-7,10-ethano-[1,2,4]triazolo[3,4-*a*]phthalazine-6-carboxamide (51). A mixture of **149** (0.1748 g, 0.546 mmol) in thionyl chloride (3 mL) was stirred at 50−60 °C for 20 h. The excess thionyl chloride was removed in vacuo, and the residue was azeotroped with toluene (10 mL). To the residue was added anhydrous THF (10 mL), followed by triethylamine (84 μL, 0.601 mmol), and then dropwise, over 6 min, a solution of 2-aminopyridine (56.4 mg, 0.599 mmol) in anhydrous THF (5 mL), while stirring. The mixture was stirred at room temperature under nitrogen for 3.5 h and then evaporated. The residue was partitioned between dichloromethane (25 mL) and water (25 mL) brought to pH 10 with saturated aqueous Na_2CO_3 solution. The aqueous layer was further extracted with dichloromethane (3 × 25 mL), and the combined extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica gel, 2% MeOH/CH_2Cl_2, and then alumina, 15% EtOAc/CH_2Cl_2) to afford 104.3 mg (48%) of **51** as a white solid: mp 270−275 °C (CH_2Cl_2−EtOAc−hexane); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.54 (4H, m), 2.00 (4H, m), 4.11 (1H, s), 4.42 (1H, s), 7.13 (1H, t, J = 5.9 Hz), 7.53−7.64 (3H, m), 7.80 (1H, t, J = 8.8 Hz), 8.36 (2H, d, J = 7.5 Hz), 8.43 (2H, d, J = 7.0 Hz), 9.51 (1H, s); MS (ES^+) m/z 397 $[M + H]^+$. Anal. $[C_{23}H_{20}N_6O \cdot 0.1H_2O]$ C, H, N.

[(3-Phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]-triazolo[3,4-*a*]phthalazin-6-yl)oxy]acetic Acid (150). 107 (2.50 g, 8.56 mmol) was alkylated with methyl bromoacetate using the procedure described for the preparation of **27** to give 2.98 g (96%) of crude methyl [(3-phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)oxy]acetate, which was used without further purification.

To the crude intermediate (2.50 g, 6.87 mmol) in methanol (40 mL) was added a solution of potassium hydroxide (900 mg, 16.0 mmol) in water (15 mL). The resulting yellow solution was stirred at room temperature for 3 days. The methanol was evaporated, and the remaining aqueous phase was washed with ethyl acetate (3 × 30 mL) and acidified (pH 6) by the addition of 5 N hydrochloric acid, precipitating a solid. This was separated by filtration, washed with water, and dried, to yield 1.78 g (74%) of **150** as a white solid: ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.32−1.45 (4H, m), 1.85−1.99 (4H, m), 3.43 (1H, s), 3.75 (1H, s), 4.98 (2H, s), 7.49−7.58 (3H, m), 8.33−8.35 (2H, m); MS (ES^+) m/z 351 $[M + H]^+$.

***N*-Benzyl-*N*-methyl-2-[(3-phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)oxy]-acetamide (67).** To **150** (300 mg, 0.86 mmol) in DMF (10 mL) was added *N*,*N*′-carbonyldiimidazole (153 mg, 0.945 mmol) with stirring, and the resulting mixture was stirred at room temperature under nitrogen for 2 h. *N*-Benzylmethylamine (0.111 mL, 104 mg, 0.86 mmol) was added, and the mixture was stirred as before for 24 h. Water (40 mL) was added, precipitating a hygroscopic solid which was separated by filtration and purified by flash chromatography (silica gel, 10% MeOH/CH_2Cl_2). The resulting solid was recrystallized from ethyl acetate/hexane, yielding 151 mg (39%) of **67** as a white solid: mp 168.3−169.3 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.30−1.58 (4H, m), 1.78−1.99 (4H, m), 3.04 and 3.03 (3H, 2 singlets, rotamers), 3.45 and 3.59 (1H, 2 singlets, rotamers), 3.94 and 3.98 (1H, 2 singlets, rotamers), 4.60 and 4.62 (2H, two singlets, rotamers), 5.13 and 5.17 (2H, 2 singlets, rotamers), 7.16−7.3 (5H, m), 7.36−7.52 (3H, m), 8.30−8.39 (2H, m); MS (ES^+) m/z 454 $[M + H]^+$. Anal. $[C_{27}H_{27}N_5O_2]$ C, H, N.

2-{[(3-Phenyl-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]-triazolo[3,4-*a*]phthalazin-6-yl)oxy]methyl}pyridin-3-ol (29). A solution of **33** (51.6 mg, 0.11 mmol) in methanol (2.5 mL) with concentrated hydrochloric acid (2.5 mL) was stirred at reflux for 9 h. A solid precipitated from solution upon cooling to room temperature. The solid was separated by filtration and recrystallized from methanol/ethyl acetate to yield 23.0 mg (43%) of **29** as a colorless solid. Dihydrochloride salt: mp 220 °C (dec); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.37−1.49 (4H, m),

1.80−1.99 (4H, m), 3.49 (1H, s), 3.799 (1H, s), 5.80 (2H, s), 7.54−7.62 (3H, m), 7.78 (1H, dd, J = 8.5 and 5.4 Hz), 8.11 (1H, d, J = 8.5 Hz), 8.26−8.31 (3H, m), 12.25 (1H, br s); MS (ES^+) *m/z* 400 $[M + H]^+$. Anal. $[C_{23}H_{21}N_5O_2 \cdot 2HCl \cdot 1.3H_2O]$ C, H, N.

3-Phenyl-6-[(1-propyl-1*H*-1,2,4-triazol-3-yl)methoxy]-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]triazolo[3,4-*a*]-phthalazine (95) and 3-Phenyl-6-[(1-propyl-1*H*-1,2,4-triazol-5-yl)methoxy]-7,8,9,10-tetrahydro-7,10-ethano[1,2,4]-triazolo[3,4-*a*]phthalazine (96). To a stirred mixture of sodium hydride (60% dispersion in oil, 22.1 mg, 0.553 mmol) and iodopropane (0.0553 mL, 0.567 mmol) in anhydrous DMF (2 mL) under nitrogen, at 0 °C, was added dropwise, over 8 min, a solution of **92** (0.1767 g, 0.473 mmol) in anhydrous DMF (7 mL). The mixture was then stirred for 1.5 h and allowed to warm slowly to 12 °C. More sodium hydride (60% dispersion in oil, 4.4 mg, 0.110 mmol) was added, and the mixture was stirred for another 1 h. Water (40 mL) was added, and the mixture was stirred for a few minutes. The mixture was filtered, a little saturated aqueous NaCl solution was added to the filtrate, and this was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica gel, 0−3% MeOH/EtOAc) to afford 75.8 mg (39%) of **96** and 106.9 mg (54%) of **95** as white solids:

95: mp 203−205 °C (CH_2Cl_2−EtOAc−hexane); ^1H NMR (360 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.4 Hz), 1.46 (4H, m), 1.82−1.99 (6H, m), 3.51 (1H, s), 3.96 (1H, s), 4.14 (2H, t, J = 7.1 Hz), 5.54 (2H, s), 7.45−7.56 (3H, m), 8.08 (1H, s), 8.52 (2H, d); MS (ES^+) *m/z* 416 $[M + H]^+$. Anal. $[C_{23}H_{25}N_7O \cdot 0.4H_2O]$ C, H, N.

96: mp 166−181 °C (CH_2Cl_2−EtOAc−hexane); ^1H NMR (360 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.4 Hz), 1.39 (2H, m), 1.51 (2H, m), 1.86−1.97 (6H, m), 3.41 (1H, s), 4.01 (1H, s), 4.17 (2H, t, J = 7.1 Hz), 5.61 (2H, s), 7.48−7.58 (3H, m), 7.97 (1H, s), 8.44 (2H, d, J = 6.8 Hz); MS (ES^+) *m/z* 416 $[M + H]^+$. Anal. $[C_{23}H_{25}N_7O \cdot 0.23C_6H_{14}]$ C, H, N.

Biological Methods. Radioligand Binding Studies. This procedure has been fully described by Chambers et al.[25]

Electrophysiology. Voltage Clamp in *Xenopus laevis* Oocytes. This procedure has been described by Street et al.[27]

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Supporting Information Available: Yields, melting points, and spectral data for all final compounds and intermediates not included above. This material is available free of charge via the Internet at http://pubs.acs.org.

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