3-Phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[3,4-*a*]phthalazines and Analogues: High-Affinity γ-Aminobutyric Acid-A Benzodiazepine Receptor Ligands with α2, α3, and α5-Subtype Binding Selectivity over α1

Robert W. Carling,* Kevin W. Moore,* Leslie J. Street, Deborah Wild, Catherine Isted, Paul D. Leeson, Steven Thomas, Desmond O'Connor, Ruth M. McKernan, Katherine Quirk, Susan M. Cook, John R. Atack, Keith A. Wafford, Sally A. Thompson, Gerard R. Dawson, Pushpinder Ferris, and José L. Castro

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

Received September 4, 2003

Studies with our screening lead **5** and the literature compound **6** led to the identification of 6-benzyloxy-3-(4-methoxy)phenyl-1,2,4-triazolo[3,4-*a*]phthalazine **8** as a ligand with binding selectivity for the γ-aminobutyric acid-A (GABA-A) α3- and α5-containing receptor subtypes over the GABA-A α1 subtype (K_i: α2 = 850 nM, α3 = 170 nM, α5 = 72 nM, α1 = 1400 nM). Early optimization studies identified the close analogue **10** (K_i: α2 = 16 nM, α3 = 41 nM, α5 = 38 nM, α1 = 280 nM) as a suitable lead for further study. High-affinity ligands were identified by replacing the 6-benzyloxy group of compound **10** with 2-pyridylmethoxy (compound **29**), but binding selectivity was not enhanced (K_i: α2 = 1.7 nM, α3 = 0.71 nM, α5 = 0.33 nM, α1 = 2.7 nM). Furthermore, on evaluation in xenopus oocytes,[22] **29** was discovered to be a weak to moderate inverse agonist at all four receptor subtypes (α1, −7%; α2, −5%; α3, −16%; α5, −5%). Replacement of the 3-phenyl group of **29** with alternatives led to reduced affinity, and smaller 3-substituents led to reduced efficacy. Methyl substitution of the benzo-fused ring of **29** at the 7-, 8-, and 10-positions resulted in increased efficacy although selectivity was abolished. Increased efficacy and retention of selectivity for α3 over α1 was achieved with the 7,8,9,10-tetrahydro-(7,10-ethano)-phthalazine **62**. Compound **62** is currently one of the most binding selective GABA-A α3-benzodiazepine-site partial agonists known, and although its selectivity is limited, its good pharmacokinetic profile in the rat (33% oral bioavailability after a 3 mg/kg dose, reaching a peak plasma concentration of 179 ng/mL; half-life of 1 h) made it a useful pharmacological tool to explore the effect of a GABA-A α2/α3 agonist in vivo.

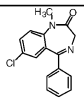
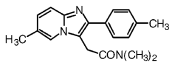
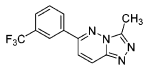
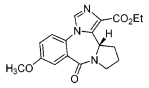
Introduction

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter in the brain.[1] There are three pharmacological classes of GABA receptors, GABA-A, GABA-B, and GABA-C, of which GABA-A[2] and GABA-C[3] are ligand-gated chloride ion channels and GABA-B is G-protein-linked. It has recently been proposed that GABA-C receptors could be classified as a subset of GABA-A receptors on the basis of similarities in molecular biology.[3] In any event, GABA-A receptors constitute the largest population of inhibitory neurotransmitter receptors.[4] The purification, cloning, and sequencing of the GABA-A receptor have led to the identification of 19 subunits from within 8 families of structurally related subunits (α1−α6, β1−β3, γ1−γ3, δ, ϵ, π, ρ1−3, and θ).[5] Expression of recombinant receptors shows that at least one α, one β, and one γ (or δ) subunit are required to form a pentameric, functional GABA-gated chloride ion channel,[5,6] with several recent studies suggesting a subunit stoichiometry of two α, two β, and one γ subunit.[7] As well as a neurotransmitter (GABA) binding site, GABA-A receptors also have multiple allosteric modulatory sites for barbiturates, steroid anesthetics, loreclezole, avermectins, and benzodiazepines that all modulate opening of the channel through different mechanisms of action.[8] Of these, the benzodiazepine (BZ) site is the best characterized because of its role in mediating the clinical effects of anxiolytics such as diazepam (**1**, Table 1). Ligands at the BZ binding site of GABA-A receptors fall into three functional classes categorized by their effect on the ion current elicited by the endogenous neurotransmitter GABA: Agonists (positive allosteric modulators) give an increased ion flux, resulting in a greater inhibitory effect on the postsynaptic neurone, while inverse agonists (negative allosteric modulators) cause a decrease in the ion flux in response to GABA. A continuum of ligand activities is possible, including antagonists (neutral allosteric modulators) that have no effect on the ion channel response to GABA but will competitively displace other BZ site ligands from the receptor. It has been shown that the benzodiazepine binding site occurs at the interface of the α and γ subunit of the GABA-A receptor, with the pharmacology of the benzodiazepine site being determined by the particular α and γ subunits present.[8] It has also been shown that the major benzodiazepine-sensitive GABA-A receptor subtypes in brain are α1β2/3γ2, α2β3γ2, α3β3γ2, and α5β3γ2.[6] Currently, only a limited number of GABA-A subtype selective ligands have been reported. Zolpidem[7] (**2**, Table 1) and

* To whom correspondence should be addressed. For R.W.C.: phone, (+1279) 440000; fax, (+1279) 440187; e-mail, robert_carling@merck.com. For K.W.M.: phone, (+1279) 440000; fax, (+1279) 440187; e-mail, kevin moore@merck.com.

10.1021/jm031020p CCC: $27.50
Published on Web 03/02/2004

Table 1. Reference Compounds: Affinities at Cloned Human GABA-A Receptors[a]

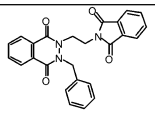
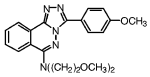
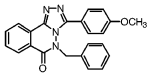
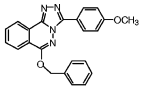
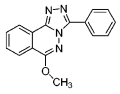
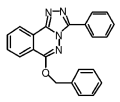
Number[b]	Structure	Ki (nM)[c] α_1	α_2	α_3	α_5
1		14	20	15	11
2		27	160	380	>15000
3		57	2000	1200	560
4		44	22	11	0.4

[a] Recombinant human GABA-A receptors $\alpha x\beta 3\gamma 2$ (x = 1, 2, 3, or 5). [b] All compounds were characterized by proton NMR and mass spectra and gave satisfactory elemental analyss results. [c] Binding data are the mean values of at least three independent determinations, and the errors of the mean are within 2-fold of the mean.

CL-218,872[9] (**3**, Table 1) have 10- to 20-fold selectivity for α1- over α3-containing subunits, and Cook has reported some *β*-carboline derivatives with similar binding selectivity.[10] The benzodiazepine **4** (Table 1) has been reported to have greater than 50-fold selectivity for α5- over α1-, α2-, and α3-containing subunits.[11] There is a recent report of some pyrazoloquinolin-3-one GABA-A ligands with minimal binding selectivity for α2-containing subunits over the α3 subtype,[12] and a series of 7,8,9,10-tetrahydroimidazo[1,2-*c*]pyrido[3,4-*e*]-pyrimidin-5(6*H*)-ones have been reported to be functionally selective GABA-A α2/α3 ligands.[13] We have recently published work from our own laboratories highlighting functionally selective GABA-A α2/3[14,15] and α5 ligands.[16]

Currently used anxiolytic benzodiazepines such as diazepam (**1**) are nonselective, high-efficacy agonists, and these compounds show sedative,[17] muscle-relaxant,[18] and amnesic[19] properties. Zolpidem (**2**) is a high-efficacy agonist that has selectivity for the α1 subtype (the major subtype of GABA-A receptors in the central nervous system),[6] and it is particularly sedative in animal tests and in man.[20] This suggests that compounds with selectivity for the α2 subtype and/or α3 subtype may retain the desirable anxiolytic activity of unselective benzodiazepines but possess an improved side effect profile. Further evidence for the role of α1-containing receptors in sedation has been provided recently by the Mohler group who bred transgenic mice where the α1 subunit was rendered BZ-insensitive.[21] On treatment with diazepam, these animals were not sedated or amnesic, but anxiolytic, anticonvulsant, and myorelaxant effects were still apparent. On the basis of this rationale, we began a medicinal chemistry program with the aim of identifying subtype-selective GABA-A α2/α3 benzodiazepine-site ligands/agonists. In this paper, we describe the identification of the 1,2,4-triazolo[3,4-*a*]phthalazine **10** as a lead compound and optimization studies that were carried out on this compound aimed at improving affinity, selectivity, and efficacy at GABA-A α2- and α3-containing receptors in particular.

Table 2. Lead Compounds and Early Optimization Studies Affinities at Cloned Human GABA-A Receptors[a]

Number[b]	Structure	Ki (nM)[c] α_1	α_2	α_3	α_5
5		6,400	1,800	1,400	4,800
6		38	41	41	80
7		>1000	>1000	>1000	>1000
8		1400	850	170	72
9		140	160	120	39
10		280	16	41	38

[a] Recombinant human GABA-A receptors $\alpha x\beta 3\gamma 2$ (x = 1, 2, 3, or 5). [b] All compounds were characterized by proton NMR and mass spectra and gave satisfactory elemental analysis results. [c] Binding data are the mean values of at least three independent determinations, and the errors of the mean are within 2-fold of the mean.

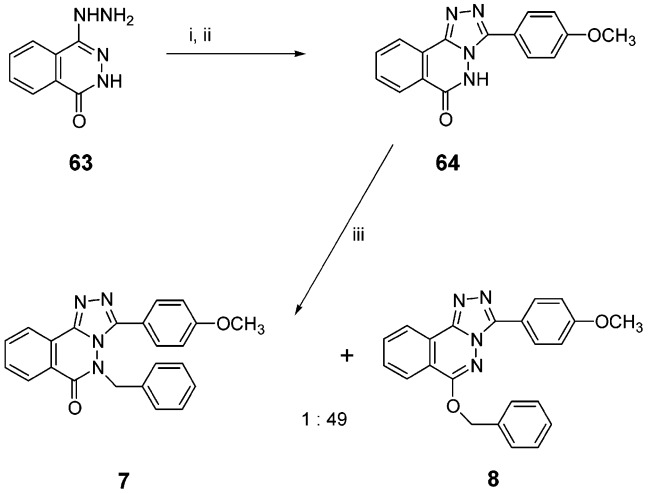
Biology

Compounds were routinely tested for their ability to displace [^{3}H]Ro15-1788 from different α-subunit-containing ($\alpha 1\beta 2\gamma 3$, $\alpha 2\beta 3\gamma 2$, $\alpha 3\ \beta 3\gamma 2$, or $\alpha 5\ \beta 3\gamma 2$) human recombinant GABA-A receptors, stably expressed in L(tk) cells.[22] The binding data for all compounds are the mean of at least three independent determinations, and the errors of the mean are within 2-fold of the mean. Efficacies of a number of compounds were determined at a maximal concentration of test ligand ($100 \times K_i$) using the EC_{20} concentration of GABA. Two electrode-voltage-clamp techniques were used on $\alpha 1\beta 3\gamma 2$, $\alpha 2\beta 3\gamma 2$, $\alpha 3\beta 3\gamma 2$, or $\alpha 5\beta 3\gamma 2$ receptors expressed in Xenopus oocytes.[23]

Lead Identification

Our strategy began with the screening of literature compounds, known to be benzodiazepine site GABA-A ligands, and the Merck sample collection for GABA-A α2/α3 subtype selective leads. The 2,3-dihydrophthalazine-1,4-dione **5**[24] (Table 2) was identified as a weakly active α2/α3 binding selective compound, but initial optimization studies involving independent deletion and replacement of hydrogen-bonding and hydrophobic groups gave only inactive compounds. We were intrigued by the similarity of **5** to the known GABA-A ligand **6** (Table 2), which has been reported to show some dissociation of anxiolysis and sedation,[25] and thus, we identified the molecule **7** as one potential target along with other hybrid molecules. Compound **7** was prepared from the hydrazine **63**[26] by acylation with 4-methoxybenzoyl chloride, subsequent cyclization in refluxing DMF to

Scheme 1[a]



[a] Reagents: (i) 4-methoxybenzoyl chloride, Et_3N, 1,4-dioxan, room temp; (ii) DMF, reflux; (iii) NaH, DMF, $PhCH_2Br$, 100 °C.

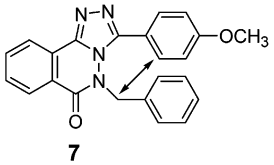


Figure 1. Nuclear Overhauser effects observed between the benzyl protons and the ortho protons of 3-aryl ring.

form a 1,2,4-triazolo[3,4-*a*]phthalazine (**64**), and finally treatment with benzyl bromide after deprotonation with sodium hydride (Scheme 1). Compound **7**, whose regiochemistry was assigned by NOE studies (see below), was isolated as a minor product from the reaction and was found to be inactive in the binding assay. Serendipitously, the major product of the alkylation reaction, the O-benzylated derivative **8**, was found to have good affinity at the α3 and α5 receptors (for K_i(**8**), α3 = 170 nM and α5 = 72 nM) with some selectivity over α1 (for K_i(**8**), α1 = 1400 nM). Direct NOE studies did not aid the assignment of the regioisomers **7** (Figure 1) and **8** (Figure 2) because enhancements between the ortho protons of the 3-aryl ring and the benzylic protons were

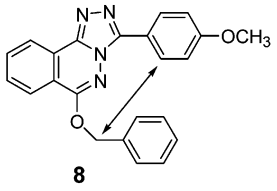


Figure 2. Nuclear Overhauser effects observed between the benzyl protons and the ortho protons of 3-aryl ring.

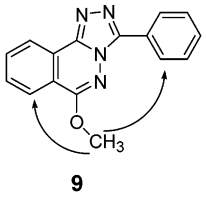
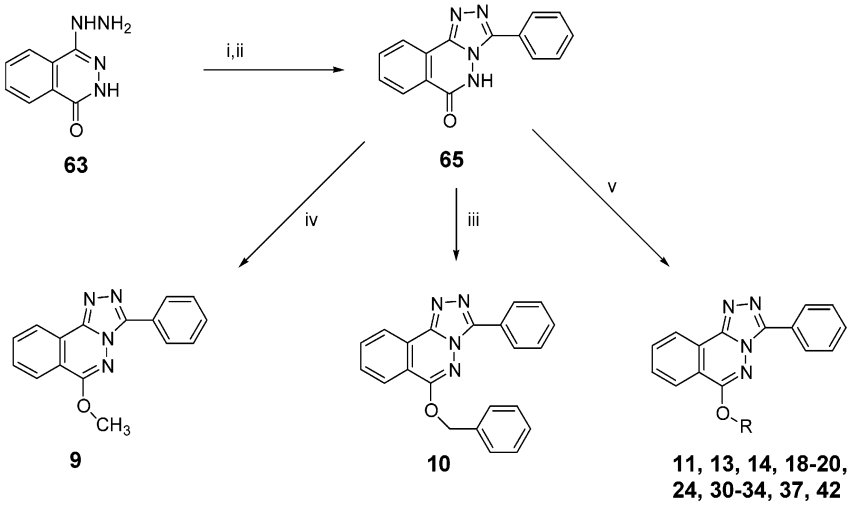


Figure 3. Nuclear Overhauser effects observed between the methyl protons and the proton at the 7-position as well as the ortho protons of the 3-aryl ring.

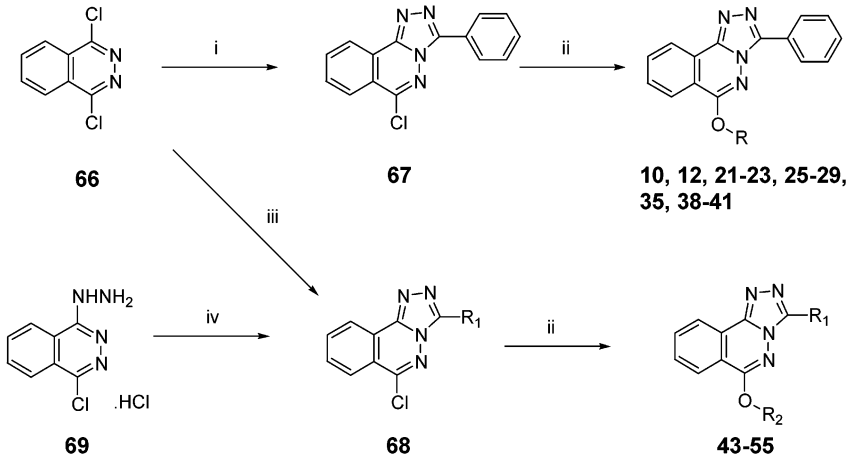
seen in both molecules. The structures of compounds **7** and **8** were assigned on the basis of the 6-methoxy-3-phenyl analogue **9** being the major regioisomer formed on reaction of the 1,2,4-triazolo[3,4-*a*]phthalazine **65** with iodomethane under analogous conditions (Scheme 2). Nuclear Overhauser effects were observed between the 6-methoxy protons and the 7-proton of **9** as well as the 3-(*o*-phenyl) protons (Figure 3; see Experimental Section for full details). The 3-phenyl analogue of the lead compound **8** was prepared by an analogous route to give compound **10** (Scheme 2). This change resulted in both a moderately improved affinity (K_i(**10**): α3 = 41 nM) and retention of selectivity. A rapid and unambiguous synthetic route for the preparation of **10** (and close analogues) was also developed (Scheme 3). This involved direct reaction of benzoic hydrazide with 3,6-dichlorophthalazine **66**[27−29] to give 6-chloro-3-phenyltriazolophthalazine **67**, which on reaction with the alkoxide of benzyl alcohol gave **10**. This unambiguous synthesis of **10** provided conclusive evidence for the original regiochemical assignments of compounds **7**, **8**, and **10**.

Scheme 2[a]



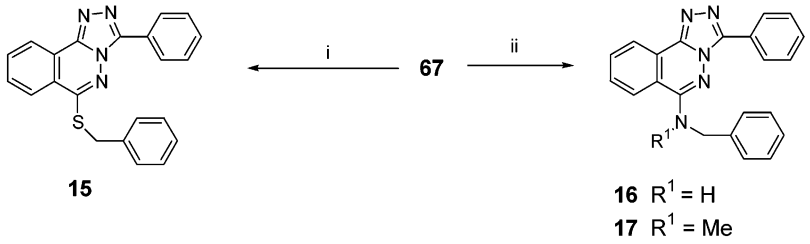
[a] Reagents: (i) benzoyl chloride, Et_3N, 1,4-dioxan, room temp; (ii) DMF, reflux; (iii) NaH, DMF, $PhCH_2Br$, 100 °C; (iv) NaH, DMF, CH_3I; (v) NaH, DMF, RCH_2Br or RCH_2Cl.

Scheme 3[a]



[a] Reagents: (i) $PhCONHNH_2$, Et_3N, dioxan, reflux; (ii) ROH, NaH, DMF; (iii) $R_1CONHNH_2$, Et_3N, xylene, reflux; (iv) R_1COCl, Et_3N, dioxan, reflux.

Scheme 4[a]



[a] Reagents: (i) $PhCH_2SH$, NaH, DMF, 80 °C; (ii) $PhCH_2NH(R^1)$, 120 °C.

Chemistry

Compounds **11**−**62** were prepared for optimization studies based on the lead compound **10**. Reaction of a range of alkyl halides with the sodium anion of compound **65** gave a number of 6-alkoxy analogues (Scheme 2). An alternative procedure for the formation of 6-alkoxy derivatives was to react the chloroimidate **67** with the sodium salt of an appropriate alcohol (Scheme 3). Alternatives to the phenyl group at the 3-position of the 1,2,4-triazolo[3,4-*a*]phthalazines were introduced by reaction of the known hydrazine **69** with an appropriate acid chloride under the conditions of Tarzia et al.[25] or by reaction of 3,6-dichlorophthalazine **66** with an appropriate acyl hydrazide in refluxing xylene to give intermediates **68** (Scheme 3). Treatment of compounds **68** with the appropriate alkoxide gave analogues **43**−**55**. The thioether **15** was prepared by reaction of **67** with the sodium salt of benzyl mercaptan, while the amidines **16** and **17** were made by heating **67** with a large excess of the appropriate amine (Scheme 4).

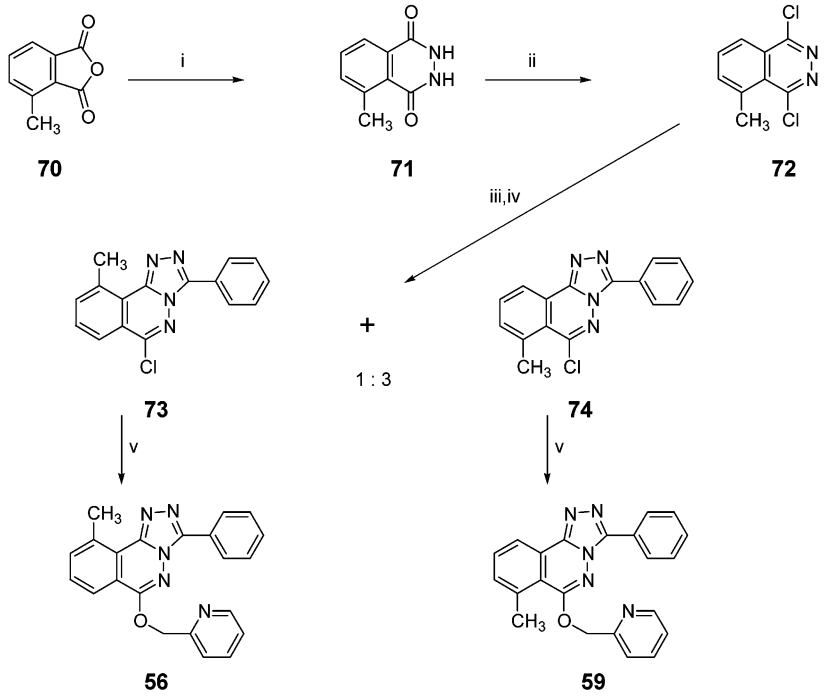
A number of changes were made to the benzo-fused ring of the phthalazine core of **10** including methyl substitution to give compounds **56**−**59** (Schemes 5 and 6). These compounds were made using the methylphthalic anhydrides **70** or **75** as starting materials with key intermediates being the dichlorophthalazines **72** and **77**, respectively. In the synthesis of **56** and **59**, the separation of the 7- and 10-methyl regioisomers was carried out after the penultimate step by chromatography of the chlorotriazolophthalazines **73** and **74** (Scheme 5). The regiochemistries of **56** and **59** were ultimately assigned by the observation of an NOE between the methyl protons and the methylene protons of **59**. In the case of the 9-methyl (**57**) and 8-methyl (**58**) isomers, chromatographic separation was carried out on the final compounds (Scheme 6) and regiochemical assignments were largely carried out through the observation of an NOE between the methylene protons and the 7-H singlet of **58** (see Experimental Section for more details). The benzo-fused ring of **10** was also replaced with a cyclohexyl group to give **60** and a 2,2,2-bridged ring system to give **62** using chemistry similar to that outlined in Scheme 5, starting from the appropriate commercially available 3,6-dichloropthalazine. In the case of the cycloheptyl compound **61**, the synthesis was carried out starting from 1-cycloheptene-1,2-dicarboxylic anhydride.[30]

Results and Discussion

Replacement of the 6-benzyloxy group of the lead compound **10** with methoxy to give **9** resulted in decreased affinity at α3 and loss of selectivity over other GABA-A receptor subtypes (Table 2). Saturation of the 6-substituent (**11**) or deletion of the methylene spacer (**12**) resulted in the abolition of binding affinity at all receptor subtypes (Table 3). Homologation of the 6-benzyloxy group (**13** and **14**) was better tolerated, but affinity at the α3 receptor was still reduced by an order of magnitude. Replacement of the 6-ether linkage with either thioether (**15**) or amino (**16** and **17**) was also not well tolerated. The data in Table 3 indicate that an imidate group with one methylene linker to a phenyl ring (**10**) is optimal for affinity at α2, α3, and α5 and for selectivity over α1.

Limited exploration of aromatic substitution on the aryl ring of the 6-benzyloxy group of **10** was carried out

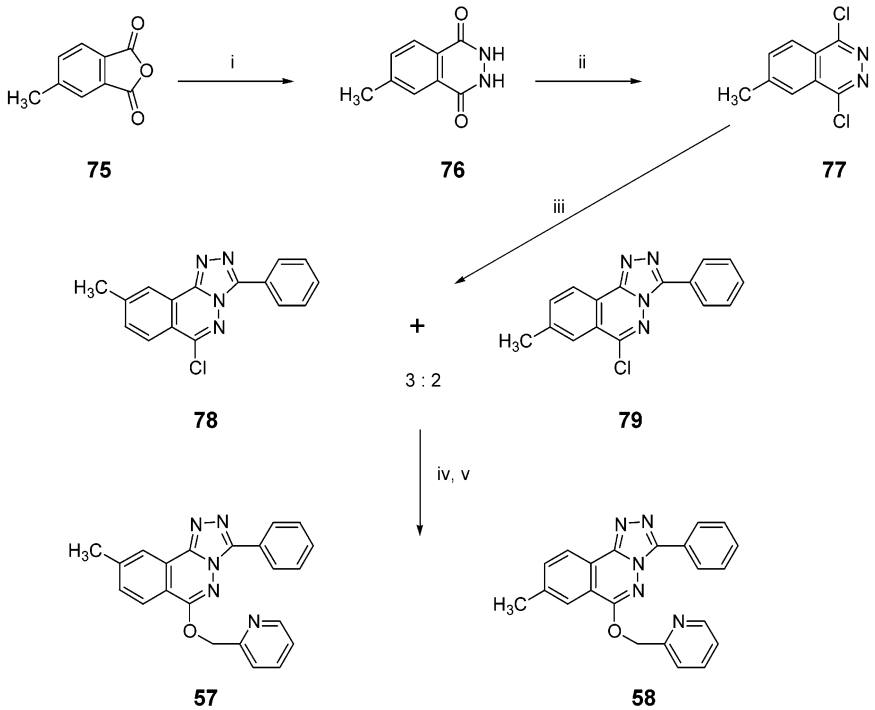
Scheme 5[a]



70 **71** **72** **73** **74** **56** **59**

[a] Reagents: (i) $NH_2NH_2 \cdot H_2O$, AcOH, NaOAc, reflux; (ii) POCl3, reflux; (iii) $PhCONHNH_2$, Et_3N, xylene, reflux; (iv) chromatography; (v) ROH, NaH, DMF.

Scheme 6[a]



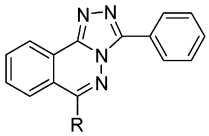
75 **76** **77** **78** **79** **57** **58**

[a] Reagents: (i) $NH_2NH_2 \cdot H_2O$, AcOH, NaOAc, reflux; (ii) POCl3, reflux; (iii) $PhCONHNH_2$, Et_3N, xylene, reflux; (iv) ROH, NaH, DMF; (v) chromatography.

(Table 4). Substitution with chlorine (**18**−**20**) and methoxy (**21** and **23**) generally led to significantly reduced affinity; however the *m*-methoxy analogue **22** retained affinity and selectivity for α3 over α1.

The effect of replacing the aryl ring of the 6-benzyloxy group of the lead compound **10** with heterocycles was next explored (Table 5). With the exception of the 3-furan **28**, all the thiophene and furan analogues (**25**−**27**) had significantly reduced affinity at α3-containing receptors. Significantly improved binding affinity was obtained with the 2-pyridylmethyloxy compound **29**, which has subnanomolar affinity at the α5 the α3 subtypes and has some selectivity over α1 receptors. The pyridazine **32**, the pyrimidine **33**, the pyrazine **34**, and the *N*-methylimidazole **35** are also high-affinity ligands, but all have only minimal selectivity for other α receptors over α1-containing receptors. The piperidine **36** and the homologated pyridine **37** both lose significant af-

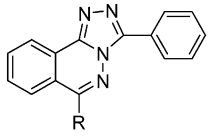
Table 3. Effect of Saturation, Chain Length, and Heteroatom Replacement at the 6-Position of Compound **9:** Affinities at Cloned Human GABA-A Receptors[a]



		Ki (nM)[c]			
Number[b]	R	α_1	α_2	α_3	α_5
11		>1000	>1000	>1000	>1000
12		>1000	>1000	>1000	>1000
13		380	>1000	720	>1000
14		300	>1000	420	>1000
15		>1000	>1000	>1000	>1000
16		>1000	>1000	>1000	>1000
17		500	>1000	>1000	240

[a] Recombinant human GABA-A receptors $\alpha x\beta 3\gamma 2$ (x = 1, 2, 3, or 5). [b] All compounds were characterized by proton NMR and mass spectra and gave satisfactory elemental analyss results. [c] Binding data are the mean values of at least three independent determinations, and the errors of the mean are within 2-fold of the mean.

Table 4. Effect of Aromatic Substitution on the Benzyl Group at the 6-Position of Compound **9**: Affinities at Cloned Human GABA-A Receptors[a]



		Ki (nM)[c]			
Number[b]	R	α_1	α_2	α_3	α_5
18		>1000	580	260	560
19		>1000	>1000	>1000	>1000
20		480	380	250	170
21		>1000	>1000	>1000	>1000
22		800	170	66	150
23		200	220	190	160
24		730	400	170	130

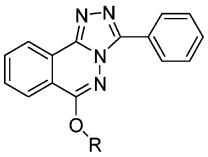
[a] Recombinant human GABA-A receptors $\alpha x\beta 3\gamma 2$ (x = 1, 2, 3, or 5). [b] All compounds were characterized by proton NMR and mass spectra and gave satisfactory elemental analysis results. [c] Binding data are the mean values of at least three independent determinations, and the errors of the mean are within 2-fold of the mean.

finity relative to the pyridine **29**. The data in Table 5 indicate that significantly improved binding affinity at all GABA-A receptor subtypes can be achieved by replacing the phenyl ring of the 6-benzyloxy group of the lead compound **10** with heterocycles containing nitrogens with H-bond-accepting potential, thus suggesting an H-bond-donating interaction from the receptor to that portion of the molecule.

Following the identification of the 2-pyridyl analogue **29** as a high-affinity but weakly selective α3 ligand, the efficacy of the compound was measured at $\alpha 1\beta 3\gamma 2$, $\alpha 2\beta 3\gamma 2$, $\alpha 3\beta 3\gamma 2$, and $\alpha 5\beta 3\gamma 2$ receptors expressed in Xenopus oocytes.[22] At all four receptor subtypes, the ligand was found to be a weak to moderate inverse agonist (α1, −7%; α2, −5%; α3, −16%; α5, −5%). Methyl substitution around the 2-pyridine ring was explored in order to determine the effect on selectivity and efficacy (Table 6). The 6-methylpyridine **38** has binding affinity at α3-containing receptors comparable to that of compound **29** but also shows a degree of binding selectivity over α1- and α2-containing receptors. Compound **38** was found to be a weak partial inverse agonist/antagonist at α1 (+1%), α2 (−4%), and α3 (−8%) and a weak partial agonist at α5 (+11%). The 5-methyl (**39**) and 4-methyl analogues (**40**) both show reduced affinity at α3 receptors. The 3-methylpyridine derivative **41** is a high-affinity GABA-A ligand but is unselective. The effect of methylation at the benzylic position of **29** to give **42** was to significantly reduce affinity, but efficacy at α1 (+36%) and α3 (+25%) was increased to give a partial agonist. The results in Table 6 show that methyl substitution at the 6-position or the 3-position of the pyridine ring is well tolerated in terms of affinity, but methylation elsewhere on the 2-pyridylmethyloxy system is detrimental.

Replacement of the 3-phenyl group of **29** with alternatives and the effect on affinity (Table 7) and efficacy were explored. The 3-methyl analogue **43** lost approximately 2 orders of magnitude in affinity at all GABA-A receptor subtypes and has significant inverse agonism at α3 (−38%). Homologation of **43** (compounds **44**−**46**) had no significant effect on α2, α3, or α5 affinity, but selectivity over α1 was reduced and the isopropyl derivative **46** is an inverse agonist at α3 (−21%). The 3-*tert*-butyl compound **47** is essentially inactive, indicating steric intolerance at that position of the molecule. The alkene **48** is approximately 10-fold lower in affinity and is clearly lower in efficacy (−31% at α3) than the lead compound **29**, while the 3-benzyl compound **49** is only weakly active at α1, α2, and α3 but has good affinity at α5-containing receptors, suggesting greater bulk tolerance for binding to the α5 receptor. The 3-cyclopropyl derivative **50** has very good affinity at α3 and α5 with good selectivity over α1, and it is an inverse agonist (−20% at α1, −26% at α3). The 6-methylpyridyl analogue of **50** (**51**) retains very good affinity, is 10-fold selective for α3 over α1, and shows less inverse agonism (−15% at α1, −13% at α3). Compound **51** is a weak partial agonist at α5 (26%) with 35-fold selectivity for α5 over α1-containing receptors and is thus one of the most selective α5 ligands yet reported. Replacing the 3-cyclopropyl group of **50** with cyclobutyl (**52**) results in reduced affinity and negligible selectivity. Introduction of a dimethylaminomethylene group to the 3-position (**53**) gives poor affinity, but interestingly very high

Table 5. Effect of Replacing the Benzyl Group at the 6-Position of Compound **9** with Heterocycles: Affinities at Cloned Human GABA-A Receptors[a]



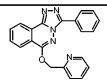
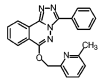
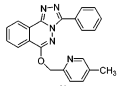
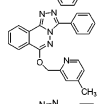
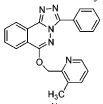
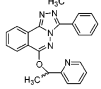
		Ki (nM)[c]			
Number[b]	R	α_1	α_2	α_3	α_5
25		240	560	300	170
26		710	510	240	250
27		250	270	180	74
28		26	38	21	13
29		2.7	1.7	0.71	0.33
30		19	16	19	31
31		24	11	7.7	6.1
32		0.82	ND[d]	0.37	0.15
33		2.3	2.9	1.3	0.5
34		2.0	1.6	0.71	0.36
35		0.51	0.7	0.22	0.17
36		32	40	37	30
37		18	25	17	15

[a] Recombinant human GABA-A receptors $\alpha x\beta 3\gamma 2$ (x = 1, 2, 3, or 5). [b] All compounds were characterized by proton NMR and mass spectra and gave satisfactory elemental analysis results. [c] Binding data are the mean values of at least three independent determinations, and the errors of the mean are within 2-fold of the mean. [d] Not determined.

inverse agonism is observed (−65% at α1 and −65% at α3). Para substitution (**54** and **55**) of the 3-phenyl ring of the lead compound **29** results in slightly lower α3 affinity. The results in Table 7 are consistent with there being a size-limited binding pocket adjacent to the 3-position of the triazolopthalazines, with unsubstituted phenyl being the best group identified for affinity. The results also indicate that reduced hydrophobicity at the 3-position generally leads to lower efficacy.

The conversion of GABA-A inverse agonists and antagonists to partial agonists, within structural series, has been accomplished with the introduction of appropriate local hydrophobicity to molecules.[31,32] With this precedent in mind, we next explored substitution of the benzo-fused ring of the lead compound **29** (Table 8). Introduction of methyl to the 10-position (**56**) results in a high-affinity ligand with moderately increased efficacy at α3 (+19%), while 9-methyl substitution (**57**) causes the complete abolition of activity. 8-Methylation (**58**) gives a high-affinity compound, but efficacy is

Table 6. Effect of Methylation of the 6-Pyridylmethyloxy Portion of **11**: Affinities and Efficacies at Cloned Human GABA-A Receptors[a]

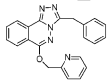
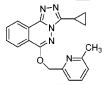
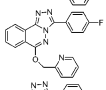
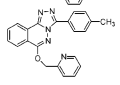
		Ki (nM)[c]			
Number[a]	Structure	α_1	α_2	α_3	α_5
29		2.7	1.7	0.71	0.33
38		8.4	8.0	1.2	2.5
39		4.8	3.6	4.3	1.1
40		18	11	10	3.7
41		2.4	2.3	1.0	0.88
42		960	520	320	140

[a] Recombinant human GABA-A receptors $\alpha x\beta 3\gamma 2$ (x = 1, 2, 3, or 5). [b] All compounds were characterized by proton NMR and mass spectra and gave satisfactory elemental analysis results. [c] Binding data are the mean values of at least three independent determinations, and the errors of the mean are within 2-fold of the mean.

increased substantially (α1, +65%; α3, +27%). The 7-methyl analogue (**59**) is 50-fold lower in α3 affinity than the lead compound **29** and efficacy is markedly higher (α1, +43%; α3, +39%), but the compound shows no binding selectivity. The data in Table 8 support the hypothesis that appropriately placed hydrophobic groups can raise efficacy but the partial agonists identified (**58** and **59**) have lost α3/α1 binding selectivity.

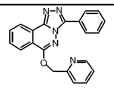
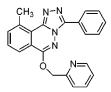
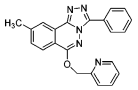
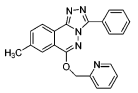
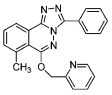
As an alternative approach toward increasing hydrophobicity around the benzo-fused ring of **29**, we constructed the 7,8,9,10-tetrahydrophthalazine **60**, and this compound retained high binding affinity and selectivity and also showed a small increase in efficacy (α1, +16%; α3, +17%) relative to the lead compound (Table 9). The seven-membered-ring homologue **61** shows significant loss of affinity and selectivity for α3 but has increased efficacy (α1, +30%; α3, +30%). In an effort to increase efficacy further, we synthesized the 7,8,9,10-tetrahydro-(7,10-ethano)-phthalazine **62**. Although the compound lost more than 10-fold binding affinity, selectivity was retained and efficacy was increased to significant levels (α1, +51%; α3, +38%). In terms of relative binding affinity, **62** is one of the most selective GABA-A α2/α3-benzodiazepine-site agonist/partial agonists known, and although its selectivity is limited, its good pharmacokinetic profile in the rat (33% oral bioavailability after a 3 mg/kg dose reaching a peak plasma concentration of 179 ng/mL; half-life 1h) made it a useful pharmacological tool to explore the effect of a GABA-A α2/α3-agonist in vivo. Compound **62** showed a statistically significant anxiolytic effect in the rat elevated plus maze[33] (at a dose of 30 mg/kg in 0.5% aqueous methyl cellulose [po] (n = 15)). Moreover, an in vivo radioligand ([^{3}H]Ro15-1788) binding assay[9] carried out on some of the test animals (n = 8) showed **62** to exhibit selective occupancy for benzodiazepine receptors in rat spinal

Table 7. Replacement of the 3-Phenyl Group: Affinities and Efficacies at Cloned Human GABA-A Receptors[a]

		Ki (nM)[c]			
Number[a]	Structure	α_1	α_2	α_3	α_5
43		900	470	81	29
44		250	130	53	16
45		160	120	52	19
46		160	56	39	8
47		>1000	>1000	>1000	>1000
48		49	28	11	3.2
49		260	340	190	18
50		16	5.8	2.6	0.74
51		32	9.7	3.1	0.92
52		56	24	23	5.1
53		140	620	840	160
54		3.9	3.7	2.4	1.7
55		18	16	11	4.0

[a] Recombinant human GABA-A receptors $\alpha x\beta 3\gamma 2$ (x = 1, 2, 3, or 5). [b] All compounds were characterized by proton NMR and mass spectra and gave satisfactory elemental analysis results. [c] Binding data are the mean values of at least three independent determinations, and the errors of the mean are within 2-fold of the mean.

Table 8. Methylation of Benzo-Fused Ring: Affinities and Efficacies at Cloned Human GABA-A Receptors[a]

		Ki (nM)[c]				Efficacy (%)[d]	
Number[a]	Structure	α_1	α_2	α_3	α_5	α_1	α_3
29		2.7	1.7	0.71	0.33	-7%	-16%
56		1.2	1.8	0.37	0.84	0%	19%
57		>1000	>1000	>1000	>1000	ND[e]	ND
58		2.2	2.2	1.2	0.64	65%	27%
59		56	44	35	20	43%	39%

[a] Recombinant human GABA-A receptors $\alpha x\beta 3\gamma 2$ (x = 1, 2, 3, or 5). [b] All compounds were characterized by proton NMR and mass spectra and gave satisfactory elemental analysis results. [c] Binding data are the mean values of at least three independent determinations, and the errors of the mean are within 2-fold of the mean. [d] % changes in electrophysiological response at a maximal concentration of test compound ($100K_i$) in the presence of GABA (EC_{20} ofconcentrated GABA) are the mean values of at least four independent determinations. [e] Not determined.

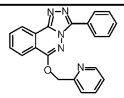
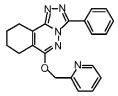
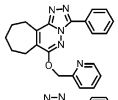
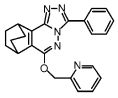
cord (α2- or α3-containing tissue, 43% receptor occupancy) over benzodiazepine receptors in rat cerebellum (α1-containing tissue, 4% receptor occupancy). These data suggest that α2/α3 subtype selective agonists are anxiolytic and support other recent evidence indicating this.[14,15]

Conclusions

We have identified 3-phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[3,4-*a*]phthalazines as a class of GABA-A receptor ligands with binding affinities in the low nanomolar to subnanomolar range. The large improvement in binding affinity on replacing the 6-benzyloxy group of **10** with 2-pyridylmethyloxy to give **29** suggests an important hydrogen-bond-donating interaction from the receptor adjacent to that portion of the molecule. A number of the analogues prepared show binding selectivity for the α3, α2, and α5 subtypes over the α1 subtype. Generally, the compounds show binding selectivity in the order α5 > α3 > α2 > α1. Overall, our attempts to optimize the triazolophthalazines for GABA-A subtype binding selectivity have met with limited success. At best, only 10-fold selectivity for α3 over α1 binding has been obtained (the 3-cyclopropyl analogue **51**), and this is consistent with the fact that the most selective α1 ligands currently known, zolpidem (**2**) and CL-218,872 (**3**), are themselves only 10- to 20-fold selective over α3.[9] It is possible to get greater (35-fold) α5/α1 binding selectivity, as evidenced by compound **51** again, where selectivity comparable to that of the literature compound **4**[11] (Table 1) is achieved. The fact that only limited binding selectivity is achievable suggests it is probable that the $\gamma 2$ subunit, which is a constant between the different receptor subtypes, is the major determinant of benzodiazepine site binding affinity (since it has been shown that the benzodiazepine binding site occurs at the interface of the α and γ subunits of the GABA-A receptor).[8]

Changes in efficacy at all the subtypes have been achieved. Reducing the size of the 3-substituent of **29** results in reduced efficacy, and increasing hydrophobicity around the benzo-fused ring of compound **29** increased efficacy. The optimal α3 binding selective agonist identified from this work was the 7,8,9,10-tetrahydro-(7,10-ethano)-phthalazine **62**. Although the compound lost more than 10-fold binding affinity relative to **29**, selectivity was retained and efficacy was increased to significant levels (α1, +51%; α3, +38%). Compound **62** showed a statistically significant anxi-

Table 9. Saturation and Homologation of the Benzo-Fused Ring Affinities and Efficacies at Cloned Human GABA-A Receptors[a]

		Ki (nM)[c]				Efficacy (%)[d]			
Number[a]	Structure	α_1	α_2	α_3	α_5	α_1	α_2	α_3	α_5
29		**2.7**	**1.7**	**0.71**	**0.33**	**-7%**	**-5%**	**-16%**	**-5%**
60		**4.3**	**1.9**	**0.85**	**0.38**	**+16%**	**+18%**	**+17%**	**+6%**
61		**41**	**17**	**17**	**2.7**	**+30%**	**+27%**	**+30%**	**+37%**
62		**71**	**26**	**12**	**1.2**	**+51%**	**+23%**	**+38%**	**+18%**

[a] Recombinant human GABA-A receptors $\alpha x\beta 3\gamma 2$ (x = 1, 2, 3, or 5). [b] All compounds were characterized by proton NMR and mass spectra and gave satisfactory elemental analysis results. [c] Binding data are the mean values of at least three independent determinations, and the errors of the mean are within 2-fold of the mean. [d] % changes in electrophysiological response at a maximal concentration of test compound ($100K_i$) in the presence of GABA (EC_{20} of concentrated GABA) are the mean values of at least four independent determinations.

olytic effect in the rat elevated plus maze[31] (at a dose of 30 mg/kg in 0.5% aqueous methyl cellulose [po] (n = 15)). These data suggest that α2/α3 subtype selective agonists are anxiolytic and support other recent evidence indicating this.[14,15]

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 instrument operating in an electrospray (ES) mode or on a VB70-250 instrument operating in the electron impact (EI) or chemical ionization (CI) mode as indicated. (Note that only the strongest peaks from the mass spectra are reported below.) Elemental analyses for carbon, hydrogen, and nitrogen were performed by Butterworth Laboratories Ltd. 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.

5-Benzyl-3-(4-methoxy)phenyl-1,2,4-triazolo[3,4-*a*]-phthalazin-6-one (7) and 6-Benzyloxy-3-(4-methoxy)-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (8). 4-Hydrazinophthalazin-1-one (**63**, 3 g, 0.17 mol) was suspended in dioxan (45 mL) with triethylamine (2.6 mL, 1.1 mol equiv), and 4-methoxybenzoyl chloride (3.2 g, 1.1 mol equiv) in dioxan (10 mL) was added dropwise over 10 min at room temperature. The reaction mixture was stirred at room temperature for 30 min, and then the dioxan was removed by rotary evaporation. The residue was dissolved in DMF (50 mL), and the mixture was then heated under reflux for 4 h, after which time water was added dropwise until the solution became cloudy. After the mixture was allowed to cool, a solid was collected by filtration, washed with water, and vacuum-dried (**64**, 2.85 g). ^{1}H NMR (360 MHz, DMSO) δ 3.87 (3 H, s), 7.15 (2 H, d, J = 8.9 Hz), 7.89 (1 H, t, J = 7.7 Hz), 8.06 (1 H, t, J = 7.3 Hz), 8.21 (1 H, d J = 8.3 Hz), 8.34 (2 H, d, J = 8.9 Hz), 8.46 (1 H, d, J = 8.0 Hz), 12.97 (1H, br s). This solid (**64**, 2.8 g, 0.0098 mol) was dissolved in DMF (80 mL), and sodium hydride (0.432 g of a 60% dispersion in oil, 1.1 mol equiv) was added in portions. When the addition was complete, the reaction mixture was heated at 100 °C for 15 min and benzyl bromide (1.29 mL, 1.1 mol equiv) was added in one portion. After 1 h, the reaction mixture was allowed to cool and the solvent was removed by rotary evaporation. The residue was heated with water (100 mL), and a solid was collected by filtration. This solid was recrystallized from methanol, and pure compound **8** was collected by filtration: 2.2 g (59%), mp 216 °C. ^{1}H NMR (360 MHz, DMSO) δ 3.87 (3 H, s), 5.65 (2 H, s), 7.17 (2 H, d, J = 8.6 Hz), 7.47 (3 H, m), 7.61 (2 H, d, J = 8.4 Hz), 7.91 (1 H, m), 8.07 (1 H, m), 8.23 (1 H, m), 8.32 (2 H, d, J = 8.4 Hz), 8.53 (1 H, m). Irradiation of the benzylic protons at δ 5.65 produced nuclear Overhauser effects to δ 8.32 (the ortho protons on the 3-aryl ring) and δ 7.61 (the ortho protons on the 6-benzyl ring). MS (ES$^+$) m/e 383 [MH]$^+$.

The mother liquors from the recrystallization, which gave pure **8**, were concentrated in vacuo and the residue obtained was purified by chromatography on silica gel using 0−40% ethyl acetate in dichloromethane as eluent to give crude **7**, which was recrystallized from diethyl ether and collected by filtration to give pure **7**: 0.045 g (1%), mp 156 °C. ^{1}H NMR (360 MHz, DMSO) δ 3.85 (3 H, s), 5.23 (2 H, s), 6.56 (2 H, d, J = 6.6 Hz), 7.04 (2 H, dd, J = 8.8 and 2.1 Hz), 7.09−7.17 (3 H, m), 7.48 (2 H, dd, J = 8.8 and 2.1 Hz), 7.86 (1 H, dd, J = 7.8 and 1.2 Hz, 7.99 (1 H, dd, J = 7.8 and 1.2 Hz, 8.33 (2 H, m). Irradiation of the benzylic protons at δ 5.23 also produced nuclear Overhauser effects to δ 7.48 (the ortho protons on the 3-aryl ring) and δ 6.56 (the ortho protons on the 6-benzyl ring). MS (ES$^+$) m/e 383 [MH]$^+$.

6-Methoxy-3-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (9). 4-Hydrazinophthalazin-1-one (**63**, 4.5 g, 0.0256 mol) was suspended in dioxan (50 mL) with triethylamine (3.92 mL, 1.1 mol equiv), and benzoyl chloride (3.27 mL, 1.1 mol equiv) in dioxan (20 mL) was added dropwise over 10 min at room temperature. The reaction mixture was stirred at room temperature for 15 min and then heated at reflux temperature for 2 h. The dioxan was then removed by rotary evaporation, and the residue was dissolved in DMF (50 mL). The mixture was then heated under reflux for 4 h, after which time water was added dropwise until the solution became cloudy. After the solution was allowed to cool, a solid was collected by filtration, washed with water, and vacuum-dried (**65**, 0.54 g, 37%). ^{1}H NMR (360 MHz, DMSO) δ 7.53−7.62 (3 H, m), 7.90 (1 H, t, J = 7.7 Hz), 8.05 (1 H, t, J = 7.3 Hz), 8.22 (1 H, d, J = 8.3 Hz), 8.39−8.41 (2 H, m), 8.50 (1 H, d, J = 8.0 Hz), 13.02 (1H, br s). This solid (**65**, 0.262 g, 0.001 mol) was dissolved in DMF (30 mL), and sodium hydride (0.044 g of a 60% dispersion in oil, 1.1 mol equiv) was added in portions. When the addition was complete, the reaction mixture was heated at 80 °C for 15 min and allowed to cool to room temperature and then methyl iodide (0.069 mL, 1.1 mol equiv) was added in one

portion. After 4 h, the solvent was removed by rotary evaporation. The residue was heated with water (50 mL), and a solid was collected by filtration. This solid was recrystallized from methanol, and pure compound **9** was collected by filtration: 0.07 g (25%), mp 230 °C. ^{1}H NMR (360 MHz, DMSO) δ 4.20 (3 H, s), 7.54−7.64 (3 H, m), 7.90 (1 H, m), 8.05 (1 H, m), 8.19 (1 H, d, J = 8.0 Hz), 8.42 (2 H, d, J = 7.2 Hz), 8.51 (1 H, d, J = 8.0 Hz). Irradiation of the methyl protons at δ 4.20 produced nuclear Overhauser effects to δ 8.42 (the ortho protons on the 3-aryl ring) and δ 8.19 (the proton at the 7-position of the triazolophthalazine ring. MS (ES$^+$) *m/e* 277 [MH]$^+$.

6-Benzyloxy-3-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (10). Method A. Compound **65** (0.262 g, 0.001 mol) was dissolved in DMF (30 mL), and sodium hydride (0.044 g of a 60% dispersion in oil, 1.1 mol equiv) was added in portions. When the addition was complete, the reaction mixture was heated at 80 °C for 15 min and then benzyl bromide (0.131 mL, 1.1 mol equiv) was added in one portion. After 1 h the solvent was removed by rotary evaporation, the residue was heated with water (50 mL), and a solid was collected by filtration. This solid was recrystallized from methanol, and pure compound **10** was collected by filtration: 0.19 g (54%), mp 211 °C. ^{1}H NMR (360 MHz, DMSO) δ 5.65 (2 H, s), 7.40−7.52 (3 H, m), 7.55−7.70 (5 H, m), 7.93 (1 H, m), 8.08 (1 H, m), 8.25 (1 H, d, J = 8.3 Hz), 8.35 (2 H, d, J = 7.8 Hz), 8.53 (1 H, m). Irradiation of the benzylic protons at δ 5.65 only produced nuclear Overhauser effects to δ 8.35 (the ortho protons on the 3-aryl ring) and δ 7.61 (the ortho protons on the 6-benzyl ring, hidden beneath the multiplet between δ 7.55 and δ 7.70). MS (ES$^+$) *m/e* 353 [MH]$^+$.

NOE studies did not aid the regiochemical assignment of **10** because only enhancements between the benzylic protons and the ortho protons of the 3-aryl ring were observed. The assignment was carried out on the basis of the nuclear Overhauser effectss seen in compound **9** and an unambiguous synthesis as described below in method B.

Method B, Part 1. To a solution of 1,4-dichlorophthalazine (**66**, 2 g, 0.01 mol) in dioxan (50 mL) was added triethylamine (1.53 mL, 1.1 mol equiv) and benzoic hydrazide (1.5 g, 1.1 mol equiv). This mixture was heated at reflux for 60 h under nitrogen. After cooling, the reaction mixture was concentrated under vacuum and the solid obtained was partitioned between dichloromethane (2 × 100 mL) and water (1 × 50 mL). The organic layer was dried (Mg SO_4), filtered, and concentrated in vacuo to leave a solid that was triturated with diethyl ether, collected by filtration, and dried under vacuum to yield 6-chloro-3-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**67**): 2.6 g (92%), mp 176 °C (dec). ^{1}H NMR (250 MHz, DMSO) δ 7.60 (3H, m), 8.00 (1H, t, J = 8.4 Hz), 8.19 (1H, t, J = 8.4 Hz), 8.31 (3H,m), 8.61 (1H, d, J = 6.3 Hz). MS *m/e* 280 [MH]$^+$.

Method B, Part 2. To a solution of benzyl alcohol (0.22 mL) in DMF (10 mL) at room temperature was added sodium hydride (0.086 g of a 60% dispersion in oil, 1.2 mol equiv), and the reaction mixture was stirred at room temperature for 15 min. After this time, **67** (0.5 g, 0.0018 mol) was added and the reaction mixture was heated at 70 °C for 3 h. Water was added until the solution became cloudy. After the solution was cooled to room temperature, a solid was collected by filtration and washed several times in the sinter funnel with water. Recrystallization from methanol gave pure **10**, 0.32 g (50%), identical in all respects to the product obtained from method A.

6-Cyclohexylmethyloxy-3-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (11). This compound was prepared using method A for the formation of **10** using cyclohexylmethylbromide instead of benzyl bromide: mp 180−181 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.19−1.38 (5 H, m), 1.74−2.02 (6H, m), 4.36 (2 H, d, J = 6.2 Hz), 7.48−7.57 (3 H, m), 7.77 (1 H, t, J = 7.2 Hz), 7.90 (1 H, t, J = 7.2 Hz), 8.20 (1 H, d, J = 7.8 Hz), 8.46 (2 H, d, J = 7.8 Hz), 8.65 (1 H, d, J = 7.8 Hz). MS (ES$^+$) *m/e* 359 [MH]$^+$.

6-Phenoxy-3-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (12). This compound was prepared using method B part 2 for the formation of **10** using phenol instead of benzyl alcohol: mp 189−199 °C. ^{1}H NMR (360 MHz, DMSO) δ 7.34−7.58 (8 H, m), 8.08−8.15 (4 H, m), 8.44 (1 H, d, J = 8.1 Hz), 8.61 (1 H, d, J = 8.1 Hz). MS (ES$^+$) *m/e* 339 [MH]$^+$.

6-Phenylethyloxy-3-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (13). This compound was prepared using method A for the formation of **10** using phenethylbromide instead of benzyl bromide: mp 160−161 °C. ^{1}H NMR (360 MHz, DMSO) δ 3.22 (2 H, t, J = 6.6 Hz), 4.75 (2 H, t, J = 6.6 Hz), 7.26 (1 H, m), 7.34 (2 H, t, J = 7.7 Hz), 7.42 (2 H, d, J = 7.1 Hz), 7.60 (3 H, m), 8.04 (1 H, t, J = 7.7 Hz), 8.04 (1 H, t, J = 6.4 Hz), 8.12 (1 H, d, J = 7.8 Hz), 8.14 (2 H,d, J = 7.8 Hz), 8.38 (1 H, d, J = 6.6 Hz). MS (ES$^+$) *m/e* 367 [MH]$^+$.

6-Phenylpropyloxy-3-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (14). This compound was prepared using method A for the formation of **10** using 1-bromo-3-phenylpropane instead of benzyl bromide: mp 162 °C. ^{1}H NMR (360 MHz, DMSO) δ 2.26 (2H, m), 2.87 (2 H, t, J = 6.7 Hz), 4.52 (2 H, t, J = 6.7 Hz), 7.19 (1 H, m), 7.30 (4 H, m), 7.56 (3 H, m), 7.88 (1 H, t, J = 6.5 Hz), 8.04 (1 H, t, J = 6.5 Hz), 8.13 (1 H, d, J = 7.9 Hz), 8.36 (2 H,d, J = 7.8 Hz), 8.48 (1 H, d, J = 6.6 Hz). MS (ES$^+$) *m/e* 381 [MH]$^+$.

6-Phenylmethylthio-3-phenyl-1,2,4-triazolo[3,4-*a*]-phthalazine (15). This compound was prepared using method B part 2 for the formation of **10** using benzylthiol instead of benzyl alcohol: mp 219−220 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.58 (2 H, s), 7.30−7.33 (3 H, m), 7.44−7.52 (5 H, m), 7.76 (1 H, dt, J = 1.0 and 7.1 Hz), 8.01 (1 H, t, J = 7.2 Hz), 8.10 (1 H, d, J = 8.2 Hz), 8.34−8.35 (2 H, m), 8.72 (1 H, d, J = 8.0 Hz). MS (ES$^+$) *m/e* 369 [MH]$^+$.

6-Phenylmethylamino-3-phenyl-1,2,4-triazolo[3,4-*a*]-phthalazine (16). 6-Chloro-3-phenyl-1,2,4-triazolo[3,4-*a*]-phthalazine (**67**, 0.5 g, 0.018 mol) was added to benzylamine (10 mL), and the mixture was heated at 120 °C for 8 h. After the mixture was allowed to cool, water (200 mL) was added and the aqueous layer was washed with ether (1 × 30 mL). On standing, the aqueous layer became cloudy and a solid was collected by filtration. This solid was recrystallized from a mixture of dichloromethane and methanol to give pure **16**: mp 293−294 °C. ^{1}H NMR (360 MHz, DMSO) δ 5.72 (2 H, d, J = 5.4 Hz), 7.26−7.48 (9 H, m), 7.77 (1 H, t, J = 7.7 Hz), 7.88 (1 H, t, J = 7.7 Hz), 8.28−8.30 (3H, m), 8.64 (1 H, d, J = 7.8 Hz). MS (ES$^+$) *m/e* 352 [MH]$^+$.

6-(*N*-Methyl)phenylmethylamino-3-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (17). This compound was prepared in the same way as compound **16** but using *N*-methylbenzylamine instead of benzylamine: mp 176−177 °C. ^{1}H NMR (360 MHz, DMSO) δ 3.03 (3 H, s), 5.72 (2 H, s), 7.30−7.58 (8 H, m), 7.7 (1 H, t, J = 7.7 Hz), 8.00 (1 H, t, J = 7.7 Hz), 8.22 (1H, dd, J = 1.0 and 7.8 Hz), 8.33 (2 H, dd, J = 1.0 and 8.5 Hz), 8.58 (1 H, d, J = 7.8 Hz). MS (ES$^+$) *m/e* 366 [MH]$^+$.

6-(2-Chlorophenyl)methyloxy-3-phenyl-1,2,4-triazolo-[3,4-*a*]phthalazine (18). This compound was prepared using method A for the formation of **10** using 2-chlorobenzyl bromide instead of benzyl bromide: mp 246−247 °C. ^{1}H NMR (360 MHz, DMSO) δ 5.72 (2 H, s), 7.32−7.35 (2 H, m), 7.48−7.57 (5H, m), 7.78 (1 H, t, J = 7.7 Hz), 7.96 (1 H, t, J = 7.7 Hz), 8.26 (1 H, d, J = 7.9 Hz), 8.24 (2H, d, J = 7.8 Hz), 8.71 (1 H, d, J = 7.9 Hz). MS (ES$^+$) *m/e* 387 [MH]$^+$.

6-(3-Chlorophenyl)methyloxy-3-phenyl-1,2,4-triazolo-[3,4-*a*]phthalazine (19). This compound was prepared using method A for the formation of **10** using 3-chlorobenzyl bromide instead of benzyl bromide: mp 228−229 °C. ^{1}H NMR (360 MHz, DMSO) δ 5.66 (2 H, s), 7.46−7.57 (2 H, m), 7.59−7.64 (4 H, m), 7.71 (1 H, s), 7.93 (1 H, t, J = 7.2 Hz), 8.07 (1 H, t, J = 7.2 Hz), 8.26 (1 H, d, J = 7.9 Hz), 8.35 (2H, d, J = 7.8 Hz), 8.69 (1 H, d, J = 7.9 Hz). MS (ES$^+$) *m/e* 387 [MH]$^+$.

6-(4-Chlorophenyl)methyloxy-3-phenyl-1,2,4-triazolo-[3,4-*a*]phthalazine (20). This compound was prepared using method A for the formation of **10** using 4-chlorobenzyl bromide instead of benzyl bromide: mp 204−205 °C. ^{1}H NMR (360 MHz, DMSO) δ 5.64 (2 H, s), 7.51−7.66 (7 H, m), 7.92 (1 H, t,

J = 7.2 Hz), 8.08 (1 H, t, J = 7.2 Hz), 8.25 (1 H, d, J = 7.9 Hz), 8.35 (2H, d, J = 7.8 Hz), 8.59 (1 H, d, J = 7.9 Hz). MS (ES^+) *m/e* 387 $[MH]^+$.

6-(2-Methoxyphenyl)methyloxy-3-phenyl-1,2,4-triazolo-[3,4-*a*]phthalazine (21). This compound was prepared using method B part 2 for the formation of **10** using 2-methoxybenzyl alcohol instead of benzyl alcohol: mp 209−210 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 3.88 (3 H, s), 5.65 (2 H, s), 6.97−7.03 (2 H, m), 7.37 (1 H, t, J = 7.7H), 7.48−7.56 (4 H, m), 7.74 (1 H, t, J = 7.2 Hz), 7.92 (1 H, t, J = 7.2 Hz), 8.22 (1 H, d, J = 7.9 Hz), 8.45 (2 H, d, J = 7.8 Hz), 8.68 (1 H, d, J = 7.9 Hz). MS (ES^+) *m/e* 383 $[MH]^+$.

6-(3-Methoxyphenyl)methyloxy-3-phenyl-1,2,4-triazolo-[3,4-*a*]phthalazine (22). This compound was prepared using method B part 2 for the formation of **10** using 3-methoxybenzyl alcohol instead of benzyl alcohol: mp 190−191 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 3.80 (3 H, s), 5.57 (2 H, s), 6.92 (1 H, dd, J = 5.6 and 2.2 Hz), 7.08−7.13 (2 H, m), 7.35 (1 H, t, J = 7.8 Hz), 7.50−7.57 (3 H, m), 7.78 (1 H, t, J = 7.2 Hz), 7.94 (1 H, t, J = 7.2 Hz), 8.24 (1 H, d, J = 7.9 Hz), 8.39 (2 H, d, J = 7.8 Hz), 8.68 (1 H, d, J = 7.9 Hz). MS (ES^+) *m/e* 383 $[MH]^+$.

6-(4-Methoxyphenyl)methyloxy-3-phenyl-1,2,4-triazolo-[3,4-*a*]phthalazine (23). This compound was prepared using method B part 2 for the formation of **10** using 4-methoxybenzyl alcohol instead of benzyl alcohol: mp 166−167 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 3.83 (3 H, s), 5.53 (2 H, s), 6.94 (1 H, dd, J = 6.6 and 2.9 Hz), 7.45−7.59 (5 H, m), 7.74 (1 H, t, J = 7.8 Hz), 7.89 (1 H, t, J = 7.8 Hz), 7.94 (1 H, t, J = 7.5 Hz), 8.20 (1 H, d, J = 7.8 Hz), 8.39 (2 H, d, J = 6.7 Hz), 8.68 (1 H, d, J = 7.9 Hz). MS (ES^+) *m/e* 383 $[MH]^+$.

6-(3-Cyanophenyl)methyloxy-3-phenyl-1,2,4-triazolo-[3,4-*a*]phthalazine (24). This compound was prepared using method A for the formation of **10** using 3-cyanobenzyl bromide instead of benzyl bromide: mp 226−228 °C. ^1H NMR (360 MHz, DMSO) δ 5.72 (2 H, s), 7.57−7.70 (4 H, m), 7.86−8.12 (5 H, m), 8.33 (3 H, t, J = 7.2 Hz), 8.58 (1 H, d, J = 7.9 Hz). MS (ES^+) *m/e* 378 $[MH]^+$.

3-Phenyl-6-(2-thenyl)methyloxy-1,2,4-triazolo[3,4-*a*]-phthalazine (25). This compound was prepared using method B part 2 for the formation of **10** using 2-thiophene methanol instead of benzyl alcohol: mp 229−231 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 5.65 (2 H, s), 7.04−7.06 (1 H, m), 7.27 (1 H, d, J = 1.2 Hz), 7.53 (1 H, dd, J = 1.2 and 5.2 Hz), 7.51−7.59 (3H, m), 7.76 (1 H, t, J = 7.6 Hz), 7.91 (1 H, t, J = 7.4 Hz), 8.19 (1 H, d, J = 8.1 Hz), 8.46 (2 H, d, J = 6.8 Hz), 8.68 (1 H, d, J = 7.9 Hz). MS (ES^+) *m/e* 359 $[MH]^+$.

3-Phenyl-6-(3-thenyl)methyloxy-1,2,4-triazolo[3,4-*a*]-phthalazine (26). This compound was prepared using method B part 2 for the formation of **10** using 3-thiophene methanol instead of benzyl alcohol: mp 216−217 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 5.61 (2 H, s), 7.25 (1 H, d, J = 1.2 Hz), 7.38−7.40 (1 H, m), 7.47−7.57 (4H, m), 7.76 (1 H, t, J = 7.6 Hz), 7.91 (1 H, t, J = 7.4 Hz), 8.22 (1 H, d, J = 8.1 Hz), 8.44 (2 H, d, J = 6.8 Hz), 8.69 (1 H, d, J = 7.9 Hz). MS (ES^+) *m/e* 359 $[MH]^+$.

6-(2-Furyl)methyloxy-3-phenyl-1,2,4-triazolo[3,4-*a*]-phthalazine (27). This compound was prepared using method B part 2 for the formation of **10** using 2-furfuryl alcohol instead of benzyl alcohol: mp 213−215 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 5.57 (2 H, s), 6.43 (1 H, dd, J = 1.9 and 3.3 Hz), 6.57 (1 H, d, J = 3.1 Hz), 7.50−7.59 (4 H, m), 7.70 (1 H, t, J = 7.8 Hz), 7.90 (1 H, t, J = 7.8 Hz), 8.20 (1 H, d, J = 7.8 Hz), 8.40 (2 H, d, J = 6.7 Hz), 8.65 (1 H, d, J = 7.9 Hz). MS (ES^+) *m/e* 343 $[MH]^+$.

6-(3-Furyl)methyloxy-3-phenyl-1,2,4-triazolo[3,4-*a*]-phthalazine (28). This compound was prepared using method B part 2 for the formation of **10** using 3-furfuryl alcohol instead of benzyl alcohol: mp 210−211 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 5.49 (2 H, s), 6.58 (1 H, d, J = 1.1 Hz), 7.46−7.57 (5 H, m), 7.77 (1 H, t, J = 7.8H), 7.92 (1 H, t, J = 7.8 Hz), 8.18 (1 H, d, J = 7.8 Hz), 8.45 (2 H, d, J = 6.7 Hz), 8.70 (1 H, d, J = 7.9 Hz). MS (ES^+) *m/e* 343 $[MH]^+$.

3-Phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[3,4-*a*]-phthalazine (29). This compound was prepared using method B part 2 for the formation of **9** but using 2-pyridyl carbinol instead of benzyl alcohol: mp 177−178 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 5.73 (2H, s), 7.29 (1H, m), 7.47−7.59 (4 H, m), 7.75−7.82 (2 H, m), 7.94 (1 H, m), 8.32−8.37 (3 H, m), 8.88−8.91 (2 H, m); *m/e* 354 $[MH]^+$.

3-Phenyl-6-(3-pyridyl)methyloxy-1,2,4-triazolo[3,4-*a*]-phthalazine (30). This compound was prepared using method A for the formation of **10** using 3-picolyl chloride hydrochloride instead of benzyl bromide: mp 182−183 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 5.55 (2 H, s), 7.30−7.33 (1 H, m), 7.45−7.52 (3 H, m), 7.70−8.12 (3 H, m), 8.13 (1 H, d, J = 8.0 Hz), 8.2−8.29 (2 H, m), 8.64 (2 H, m), 8.78 (1 H s). MS (ES^+) *m/e* 354 $[MH]^+$.

3-Phenyl-6-(4-pyridyl)methyloxy-1,2,4-triazolo[3,4-*a*]-phthalazine (31). This compound was prepared using method A for the formation of **10** using 4-picolyl chloride hydrochloride instead of benzyl bromide: mp 229−230 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 5.62 (2 H, s), 7.45−7.53 (5 H, m), 7.81−7.96 (2 H, m), 8.26−8.29 (3 H, m), 8.70 (3 H, m). MS (ES^+) *m/e* 354 $[MH]^+$.

3-Phenyl-6-(3-pyridazinyl)methyloxy-1,2,4-triazolo[3,4-*a*]phthalazine (32). A solution of 3-methylpyridazine (3 g, 0.32 mol) in chloroform (100 mL) was heated to reflux, and solid trichloroisocyanuric acid (3.11 g, 0.42 mol equiv) was carefully added over 1 h. The solution was refluxed for a further 2 h. Once the reaction mixture had cooled to room temperature, it was filtered through Hyflo and washed with 1 N sodium hydroxide. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give 3-chloromethylpyridazine (3.6 g). ^1H NMR (250 MHz, $CDCl_3$) δ 4.90 (2 H, s), 7.48−7.60 (1 H, m), 7.76 (1 H, dd, J = 2.3 and 12.2 Hz), 9.21 (1 H, m).

This compound was prepared using method A for the formation of **10** using 3-chloromethylpyridazine (as described above) instead of benzyl bromide: mp 187−189 °C. ^1H NMR (360 MHz, DMSO) δ 5.74 (2 H, s), 7.52−7.54 (3 H, m), 7.82−7.96 (1 H, m), 7.99 (1 H, t, J = 7.2 Hz), 8.11−8.15 (3 H, m), 8.41 (1 H, d, J = 7.8 Hz), 8.58 (1 H, d, J = 7.8 Hz), 8.86 (1 H, d, J = 5.2 Hz), 9.25 (1 H, d, J = 1.3 Hz). (ES^+) *m/e* 355 $[MH]^+$.

3-Phenyl-6-(4-pyrimidinyl)methyloxy-1,2,4-triazolo-[3,4-*a*]phthalazine (33). This compound was prepared using the method described above for the formation of **32** using 4-methylpyrimidine instead of 3-methylpyridazine: mp 199−201 °C. ^1H NMR (360 MHz, DMSO) δ 5.74 (2 H, s), 7.53−7.55 (3 H, m), 7.83 (1 H, d, J = 5.3 Hz), 8.00 (1 H, t, J = 7.3 Hz), 8.13−8.16 (3 H, m), 8.40 (1 H, d, J = 7.8 Hz), 8.58 (1 H, d, J = 7.8 Hz), 8.87 (1 H, d, J = 5.2 Hz), 9.25 (1 H, d, J = 1.3 Hz). MS (ES^+) *m/e* 355 $[MH]^+$.

3-Phenyl-6-(2-pyrazinyl)methyloxy-1,2,4-triazolo[3,4-*a*]phthalazine (34). This compound was prepared using the method above for the formation of **32** using 2-methylpyrazine instead of 3-methylpyridazine: mp 163−165 °C. ^1H NMR (360 MHz, DMSO) δ 5.79 (2 H, s), 7.56−7.59 (3 H, m), 7.96 (1 H, t, J = 7.2 Hz), 8.10 (1 H, t, J = 7.3 Hz), 8.22−8.25 (2 H, m), 8.34 (1 H, d, J = 7.8 Hz), 8.58 (1 H, d, J = 7.8 Hz), 8.70 (2 H, dd, J = 10.2 and 1.3 Hz), 8.99 (1 H, d, J = 1.3 Hz). MS (ES^+) *m/e* 355 $[MH]^+$.

3-Phenyl-6-(2-(1-methyl)imidazoyl)methyloxy-1,2,4-triazolo[3,4-*a*]phthalazine (35). This compound was prepared using method B part 2 described above for the formation of **10** using 1-methyl-2-imidazoylmethanol instead of benzyl alcohol: mp 240 °C. ^1H NMR (360 MHz, DMSO) δ 3.79 (3 H, s), 5.69 (2 H, s), 6.97 (1 H, s), 7.30 (1 H, s), 7.58−7.67 (3 H, m), 7.90 (1 H, t, J = 7.2 Hz), 8.10 (1 H, t, J = 7.2 Hz), 8.18 (1 H, d, J = 7.9 Hz), 8.46−8.58 (3 H, m). MS (ES^+) *m/e* 357 $[MH]^+$.

3-Phenyl-6-(4-piperidyl)methyloxy-1,2,4-triazolo[3,4-*a*]-phthalazine Bishydrochoride (36). This compound was prepared using method B part 2 for the formation of **10** using 4-hydroxymethyl-*N*-*tert*-butyloyxcarbonylpiperidine (0.499 mg) instead of benzyl alcohol. The crude product was dissolved in methanol (50 mL), and a 10% solution of hydrogen chloride in methanol (20 mL) was added. The reaction mixture was stirred for 18 h at room temperature, the solvent was removed under vacuum, and the crude product was purified by recrystallization from a mixture of ethyl acetate and methanol to yield compound **36**: mp 287−289 °C. ^1H NMR (360 MHz, D_2O) δ

1.41 (2 H, m), 1.81 (2 H, m), 2.95 (2H, m), 3.44 (3H, m), 4.78 (2 H, s), 7.14−7.56 (9 H, m). MS (ES^+) *m/e* 360 $[MH]^+$.

3-Phenyl-6-(2-pyridyl)ethyloxy-1,2,4-triazolo[3,4-*a*]-phthalazine (37). This compound was prepared using method A for the formation of **10** using 2-chloroethylpyridine instead of benzyl bromide: mp 171−173 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 3.45 (2H, t, J = 6.4 Hz), 4.90 (2 H, t, J = 6.4 Hz), 7.16−7.20 (1H, m), 7.32 (1 H, d, J = 7.8 Hz), 7.49−7.59 (3 H, m), 7.63−7.75 (2H, m), 7.89 (1H, t, J = 8.2 Hz), 8.07 (1 H, d, J = 8.0 Hz), 8.44−8.62 (4H, m). MS (ES^+) *m/e* 368 $[MH]^+$.

3-Phenyl-6-(6-methylpyrid-2-yl)methyloxy-1,2,4-triazolo-[3,4-*a*]phthalazine (38). This compound was prepared using method B part 2 for the formation of **10** using 6-methyl-2-pyridylmethanol (prepared by the method of Katsuhiro et al.)[34] instead of benzyl alcohol: mp 186−187 °C. ^1H NMR (360 MHz, DMSO) δ 2.34 (3 H, s), 5.66 (2 H, s), 7.53−7.58 (4 H, m), 7.68 (1 H, d, J = 8.0 Hz), 7.93 (1 H, t, J = 7.7 Hz), 8.07 (1 H, t, J = 7.7 Hz), 8.25−8.30 (3 H, m), 8.46 (1 H, s), 8.59 (1H, d, J = 7.7 Hz). MS (ES^+) *m/e* 368 $[MH]^+$.

3-Phenyl-6-(5-methylpyrid-2-yl)methyloxy-1,2,4-triazolo-[3,4-*a*]phthalazine (39). This compound was prepared using method B part 2 for the formation of **10** using 5-methyl-2-pyridylmethanol[34] instead of benzyl alcohol: mp 213 °C (dec). ^1H NMR (360 MHz, DMSO) δ 2.52 (3 H, s), 5.65 (2 H, s), 7.25 (1 H, d, J = 7.7 Hz), 7.47−7.58 (4 H, m), 7.78 (1 H, t, J = 7.7 Hz), 7.94 (1 H, t, J = 7.7 Hz), 8.28 (1 H, t, J = 7.7 Hz), 8.30−8.33 (3 H, m), 8.58 (1H, d, J = 7.7 Hz). MS (ES^+) *m/e* 368 $[MH]^+$.

3-Phenyl-6-(4-methylpyrid-2-yl)methyloxy-1,2,4-triazolo-[3,4-*a*]phthalazine (40). This compound was prepared using method B part 2 for the formation of **10** using 4-methyl-2-pyridylmethanol[34] instead of benzyl alcohol: mp 199−201 °C. ^1H NMR (360 MHz, DMSO) δ 2.34 (3 H, s), 5.66 (2 H, s), 7.21 (1 H, d, J = 7.7 Hz), 7.52−7.60 (4 H, m), 7.96 (1 H, t, J = 7.7 Hz), 8.06 (1 H, t, J = 7.7 Hz), 8.26−8.29 (3 H, m), 8.48 (1H, d, J = 5.2 Hz), 8.58 (1 H, d, J = 7.8). MS (ES^+) *m/e* 368 $[MH]^+$.

3-Phenyl-6-(3-methylpyrid-2-yl)methyloxy-1,2,4-triazolo-[3,4-*a*]phthalazine (41). This compound was prepared using method B part 2 for the formation of **10** using 3-methyl-2-pyridylmethanol[34] instead of benzyl alcohol: mp 210 °C (dec). ^1H NMR (360 MHz, DMSO) δ 2.44 (3 H, s), 5.76 (2 H, s), 7.31−7.34 (1 H, m), 7.55−7.58 (3 H, m), 7.92 (1 H, d, J = 7.7HZ), 7.94 (1 H, t, J = 7.7 Hz), 8.23 (1 H, t, J = 7.7 Hz), 8.25−8.28 (3 H, m), 8.30 (1H, m), 8.58 (1 H, d, J = 7.8). MS (ES^+) *m/e* 368 $[MH]^+$.

3-Phenyl-6-(1-(2-pyridyl)ethyl)oxy-1,2,4-triazolo[3,4-*a*]-phthalazine (42). This compound was prepared using method A for the formation of **10** using 1-chloroethylpyridine instead of benzyl bromide: mp 220−221 °C. ^1H NMR (360 MHz, D_6-MSO) δ 1.81 (3H, d, J = 6.6 Hz), 6.15 (1 H, q, J = 6.6 Hz), 7.31−7.35 (1H, m), 7.52−7.61 (4 H, m), 7.80 (1 H, t, J = 1.7 Hz), 7.97 (1 H, t, J = 1.7 Hz), 8.07−8.09 (3H, m), 8.38 (1 H, d, J = 7.9 Hz), 8.52 (1H, d, J = 7.9 Hz), 8.60 (1H, m). MS (ES^+) *m/e* 368 $[MH]^+$.

6-(2-Pyridylmethyl)oxy-3-methyl-1,2,4-triazolo[3,4-*a*]-phthalazine (43). This compound was prepared using the method above for the formation of **9** using acetyl chloride in place of benzoyl chloride and 2-picolyl chloride instead of methyl iodide: mp 165−166 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 2.71 (3H, s), 5.70 (2 H, s), 7.28−7.32 (1H, m), 7.59 (1H, d, J = 7.9 Hz), 7.79−7.93 (3H, m), 8.27 (1 H, d, J = 7.9 Hz), 8.61 (1H, d, J = 7.9 Hz), 8.64 (1H, m). MS (ES^+) *m/e* 292 $[MH]^+$.

3-Ethyl-6-(2-pyridylmethyl)oxy-1,2,4-triazolo[3,4-*a*]-phthalazine (44). 4-Hydrazino-1-chlorophthalazine (**69**, 2 g, 0.087 mol) was suspended in dioxan (200 mL) with triethylamine (1.46 mL, 1.2 mol equiv), and propionyl chloride (0.91 mL, 1.2 mol equiv) was added. The reaction mixture was stirred at room temperature for 2 h and then heated under reflux for 14 h. After cooling, the reaction mixture was concentrated under vacuum and the solid obtained was partitioned between dichloromethane (200 mL) and water (2 × 200 mL). The organic layer was dried (Mg SO_4), filtered, and concentrated in vacuo to yield 6-chloro-3-ethyl-1,2,4-triazolo[3,4-*a*]phthalazine: 1.88 g (94%). ^1H NMR (250 MHz, $CDCl_3$) δ 1.52 (3H, t, J = 7.5 Hz), 3.22 (2H, q, J = 7.5 and 15 Hz), 7.79−8.00 (2H, m), 8.28 (1H, dd, J = 0.5 and 8.0 Hz), 8.65 (1H, dd, J = 0.5 and 8.0 Hz).

To a solution of 2-pyridylcarbinol (0.27 mL) in DMF (20 mL) at room temperature was added sodium hydride (0.112 g of a 60% dispersion in oil, 1.3 mol equiv), and the reaction mixture was stirred at room temperature for 20 min. After this time, 6-chloro-3-ethyl-1,2,4-triazolo[3,4-*a*]phthalazine from above (0.5 g, 0.0021 mol) was added and the reaction mixture was stirred for 14 h at room temperature. The reaction mixture was concentrated under vacuum, and the solid obtained was partitioned between dichloromethane (150 mL) and water (3 × 100 mL). The organic layer was washed with brine, dried (Mg SO_4), filtered, and concentrated in vacuo to yield a solid that was recrystallized from a mixture of ethyl acetate and hexane to give pure **44**: 0.142 g (22%), mp 157−158 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 1.41 (3H, t, J = 7.5 Hz), 3.11 (2H, q, J = 7.5 and 15 Hz), 5.69 (2H, s), 7.28−7.33 (1H, m), 7.52 (1H,d, J = 11.2 Hz), 7.75−7.94 (3H, m), 8.29 (1H, dd, J = 0.5 and 8.0 Hz), 8.60−8.7 (2H, m). MS (ES^+) *m/e* 306 $[MH]^+$.

3-Propyl-6-(2-pyridylmethyl)oxy-1,2,4-triazolo[3,4-*a*]-phthalazine (45). This compound was prepared using the method above for the formation of **44** using butyryl chloride instead of propionyl chloride: mp 138−139 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 1.01 (3H, t, J = 7.4 Hz), 1.84 (2H,m), 3.07 (2H, t, J = 7.4 Hz), 5.69 (2H, s), 7.28−7.32 (1H, m), 7.57 (1H,d, J = 11.2 Hz), 7.73−7.80 (2H, m), 7.80−7.92 (1H, m), 8.27 (1H, d, J = 8.0 Hz), 8.62 (H, d, J = 8.0 Hz), 8.65 (1H, d, J = 4.0 Hz). MS (ES^+) *m/e* 320 $[MH]^+$.

3-Isopropyl-6-(2-pyridylmethyl)oxy-1,2,4-triazolo[3,4-*a*]phthalazine (46). This compound was prepared using the method above for the formation of **44** using isobutyryl chloride instead of propionyl chloride: mp 149−150 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 1.47 (6H, d, J = 7.0 Hz), 3.07 (1H, q, J = 7.0 and 14.0 Hz), 5.69 (2H, s), 7.27−7.31 (1H, m), 7.56 (1H, d, J = 7.8 Hz), 7.73−7.79 (2H, m), 7.80−7.92 (1H, m), 8.26 (1H, d, J = 8.0 Hz), 8.62 (1H, d, J = 8.0 Hz), 8.65 (1H, d, J = 3.6 Hz). MS (ES^+) *m/e* 320 $[MH]^+$.

3-*tert*-Butyl-6-(2-pyridylmethyl)oxy-1,2,4-triazolo[3,4-*a*]phthalazine (47). This compound was prepared using the method above for the formation of **44** using pivaloyl chloride instead of propionyl chloride: mp 155−157 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 1.55 (9H, s), 5.68 (2H, s), 7.29−7.31 (1H, m), 7.55 (1H, d, J = 7.9 Hz), 7.75−7.78 (2H, m), 7.89 (1H, t, J = 7.3 Hz), 8.24 (1H, d, J = 8.0 Hz), 8.6−8.70 (2H, m). MS (ES^+) *m/e* 334 $[MH]^+$.

3-Ethenyl-6-(2-pyridylmethyl)oxy-1,2,4-triazolo[3,4-*a*]-phthalazine (48). This compound was prepared using the method above for the formation of **44** using acryloyl chloride instead of propionyl chloride: mp 156−157 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 5.68 (2H, s), 5.75 (1H, dd, J = 1.9 and 16.8 Hz), 6.70 (1H, dd, J = 2.0 and 25.8 Hz), 7.02−7.14 (1H, m), 7.25−7.30 (1H, m), 7.58 (1H, d, J = 7.9 Hz), 7.78 (2H, t, J = 8.5 Hz), 7.96 (1H, t, J = 7.3 Hz), 8.24 (1H, d, J = 11.0 Hz), 8.62−8.72 (2H, m). MS (ES^+) *m/e* 304 $[MH]^+$.

3-Benzyl-6-(2-pyridylmethyl)oxy-1,2,4-triazolo[3,4-*a*]-phthalazine (49). This compound was prepared using the method above for the formation of **44** using phenylacetyl chloride instead of propionyl chloride: mp 170−171 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 4.47 (2H,s), 5.63 (2H, s), 7.17−7.31 (4H, m), 7.36 (2H, d, J = 7.2 Hz), 7.47 (1H, d, J = 7.8 Hz), 7.70−7.74 (2H, m), 7.91 (1H, t, J = 8.1 Hz), 8.25 (1H, d, J = 11.0 Hz), 8.61 (1H, d, J = 7.9 Hz), 8.64 (1H, m). MS (ES^+) *m/e* 368 $[MH]^+$.

3-Cyclopropyl-6-(2-pyridylmethyl)oxy-1,2,4-triazolo-[3,4-*a*]phthalazine (50). This compound was prepared using the method above for the formation of **44** using cyclopropanecarbonyl chloride instead of propionyl chloride: mp 157−158 °C. ^1H NMR (360 MHz, $CDCl_3$) δ 1.09−1.16 (2H, m), 1.31−1.37 (2H, m), 2.34−2.44 (1H, m), 5.70 (2H, s), 7.28−7.33 (1H, m), 7.58 (1H, d, J = 7.9 Hz), 7.74−7.79 (3H, m), 8.25 (1H, d, J = 11.1 Hz), 8.58 (1H, d, J = 11.1 Hz), 8.65 (1H, m). MS (ES^+) *m/e* 318 $[MH]^+$.

3-Cyclopropyl-6-(2-(6-methylpyridyl)methyl)oxy-1,2,4-triazolo[3,4-*a*]phthalazine (51). This compound was prepared using the method above for the formation of **44** using cyclopropanecarbonyl chloride instead of propionyl chloride and 6-methyl-2-pyridinemethanol in place of 2-pyridylcarbinol: mp 134−136 °C. ^{1}H NMR (360 MHz, DMSO) δ 1.22−1.25 (4H, m), 2.50−2.52 (1H, m), 2.74 (3H, s), 5.90 (2H, s), 7.72 (1H, d, J = 7.8 Hz), 7.96−8.10 (2H, m), 8.12 (1H, t, J = 6.8 Hz), 8.27−8.37 (2H, m), 8.5 (1H, d, J = 11.1 Hz). MS (ES$^+$) *m/e* 332 [MH]$^+$.

3-Cyclobutyl-6-(2-pyridylmethyl)oxy-1,2,4-triazolo[3,4-*a*]phthalazine (52). This compound was prepared using the method above for the formation of **44** using cyclobutanecarbonyl chloride instead of propionyl chloride: mp 170−171 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.08−2.23 (2H, m), 2.41−2.49 (2H, m), 2.59−2.70 (2H, M), 4.39−4.08 (1H, m), 5.69 (2H, s), 7.28−7.31 (1H, m), 7.56 (1H, d, J = 7.8 Hz), 7.7−7.79 (3H, m), 8.26 (1H, d, J = 7.8 Hz), 8.62−8.70 (2H, m). MS (ES$^+$) *m/e* 332 [MH]$^+$.

3-Dimethylaminomethyl-6-(2-pyridylmethyl)oxy-1,2,4-triazolo[3,4-*a*]phthalazine (53). This compound was prepared using method B for the formation of **10** using *N*,*N*-dimethylglycine hydrazide hydrochloride instead of benzoic hydrazide and 2-pyridylcarbinol instead of benzyl alcohol: mp 122−124 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.39 (6H, s), 4.02 (2H, s), 5.71 (2H, s), 7.28−7.32 (1H, m), 7.59 (1H, d, J = 7.8 Hz), 7.78 (2H, dt, J = 1.0 and 7.9 Hz), 7.90 (1H, t, J = 8.2 Hz), 8.28 (1H, d, J = 7.8 Hz), 8.65−8.72 (2H, m). MS (ES$^+$) *m/e* 335 [MH]$^+$.

3-(4-Fluorophenyl)-6-(2-pyridylmethyl)oxy-1,2,4-triazolo[3,4-*a*]phthalazine (54). This compound was prepared using the method above for the formation of **44** using 4-fluorobenzoyl chloride instead of propionyl chloride: mp 186−187 °C. ^{1}H NMR (250 MHz, DMSO) δ 5.69 (2H, s), 7.38−7.45 (3H, m), 7.70 (1H,d, J = 7.8 Hz), 7.90−7.97 (2H, m), 8.09 (1H, dt, J = 1.0 and 7.8 Hz), 8.28−8.34 (3H, m), 8.57 (H, d, J = 7.9 Hz), 8.64 (1H, d, J = 4.0 Hz). MS (ES$^+$) *m/e* 372 [MH]$^+$.

3-(4-Methylphenyl)-6-(2-pyridylmethyl)oxy-1,2,4-triazolo[3,4-*a*]phthalazine (55). This compound was prepared using method B for the formation of **10** using 4-toluic hydrazide hydrochloride instead of benzoic hydrazide and 2-pyridylcarbinol instead of benzyl alcohol: mp 224−225 °C. ^{1}H NMR (250 MHz, DMSO) δ 2.45 (3H,s), 5.72 (2H, s), 7.29−7.34 (3H, m), 7.57 (1H, d, J = 7.8 Hz), 7.75−7.81 (2H, m), 7.91−7.93 (1H, m), 8.22−8.31 (3H, m), 8.68−8.71 (2H, m). MS (ES$^+$) *m/e* 372 [MH]$^+$.

3-Phenyl-6-(2-pyridylmethyl)oxy-10-methyl-1,2,4-triazolo[3,4-*a*]phthalazine (56). To a solution of 3-methylphthalic anhydride (**70**, 15 g, 0.093 mol) in aqueous acetic acid (300 mL of 40%) was added hydrazine hydrate (5.4 mL, 0.11 mol) and sodium acetate (15.1 g, 0.11 mol), and the reaction mixture was heated at reflux for 18 h. When the mixture was cooled, the resultant solid was collected by filtration and dried, and NMR analysis showed this to be a mixture of product and starting material. This material was redissolved in aqueous acetic acid (500 mL of 40%) with hydrazine hydrate (3.6 mL, 0.072 mol) and sodium acetate (10 g, 0.072mol), and the reaction mixture was heated under reflux for a further 72 h. When the mixture was cooled, the solid was collected by filtration to yield 5-methylphthalazinedione (**71**, 5.6 g). ^{1}H NMR (250 MHz, DMSO) δ 2.81 (3H, s), 7.61 (1H, dd, J = 6.3 and 1.0 Hz), 7.37 (1H, t, J = 7.5 Hz), 7.88 (1H, dd, J = 7.5 and 1.0 Hz), 11.4 (2H, bs). MS (ES$^+$) *m/e* 177 [MH]$^+$.

A solution of 5-methylphthalazinedione (**71**, 5.5 g) in phosphorus oxychloride (200 mL) was refluxed for 18 h, cooled, and evaporated to dryness. The resulting material was dissolved in DCM (150 mL) and cold water (200 mL). Solid sodium hydrogen carbonate was added carefully until pH 11 was attained, the aqueous layer was extracted with DCM (2 × 100 mL), and then the combined organic layers were washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to yield 1,4-dichloro-5-methylphthalazine (**72**, 5.5 g). ^{1}H NMR (250 MHz, DMSO) δ 3.10 (3H,s), 8.04−8.13 (2H, m), 8.13−8.26 (1H, m).

To a solution of 1,4-dichloro-5-methylphthalazine (**72**, 5.5 g, 0.026 mol) in xylene (100 mL) was added triethylamine (4.36 mL, 1.2 mol equiv) and benzoic hydrazide (3.85 g, 1.1 mol equiv). This mixture was heated at reflux for 24 h under nitrogen. After cooling, the reaction mixture was concentrated under vacuum and the solid obtained was partitioned between dichloromethane (2 × 100 mL) and water (1 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a solid that was purified by silica gel column chromatography using 0.5−3% methanol in DCM as eluent to yield both 6-chloro-3-phenyl-7-methyl-1,2,4-triazolo[3,4-*a*]-phthalazine (**74**, high R_f product) and 6-chloro-3-phenyl-10-methyl-1,2,4-triazolo[3,4-*a*]phthalazine (**73**, low R_f product) in a ratio of 3:1. **73**: ^{1}H NMR (250 MHz, DMSO) δ 2.98 (3H,s), 7.59−7.68 (3H, m), 7.82 (1H, d, J = 7.6 Hz), 7.98 (1H, t, J = 7.6 Hz), 8.27−8.31 (2H, m), 8.51 (1H, d, J = 7.5 Hz). **74**: ^{1}H NMR (250 MHz, DMSO) δ 3.05 (3H,s), 7.57−7.67 (3H, m), 7.85−8.06 (2H, m), 8.28 (1H, d, J = 7.5 Hz), 8.27−8.28 (3H, m).

To a solution of 2-hydroxymethylpyridine (0.158 mL, 0.0016 mol) in DMF (20 mL) at room temperature was added sodium hydride (0.066 g of a 60% dispersion in oil, 0.0016 mol), and the reaction mixture was stirred at room temperature for 15 min. After this time, **73** (0.4 g, 0.0014 mol) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under vacuum, and the solid obtained was partitioned between dichloromethane (2 × 100 mL) and water (1 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a solid that was recrystallized from a mixture of ethyl acetate and dichloromethane to give pure **56**: 0.101 g, (21%), mp 197−198 °C. ^{1}H NMR (360 MHz, DMSO) δ 2.48 (3 H, s), 5.66 (2 H, s), 7.37−7.40 (1H, m), 7.54−7.56 (3 H, m), 7.66 (1H, d, J = 7.8 Hz), 7.73 (1H, d, J = 7.8 Hz), 7.86−7.94 (2H, m), 8.24 (2 H, dd, J = 1.6 and 8.0 Hz), 8.42 (1H, d, J = 8.0 Hz), 8.70 (1H, m). MS (ES$^+$) *m/e* 368 [MH]$^+$.

3-Phenyl-6-(2-pyridylmethyl)oxy-7-methyl-1,2,4-triazolo-[3,4-*a*]phthalazine (59). To a solution of 2-hydroxymethylpyridine (0.197 mL, 0.002 mol) in DMF (30 mL) at room temperature was added sodium hydride (0.082 g of a 60% dispersion in oil, 0.002 mol), and the reaction mixture was stirred at room temperature for 15 min. After this time, **74** (0.5 g, 0.0017 mol) was added and the reaction mixture was stirred at room temperature for 18 h, after which time TLC showed 80% conversion. More sodium hydride (0.016 g of a 60% dispersion in oil, 0.0004 mol) was added, and the reaction mixture was stirred for a further 3 h. The reaction mixture was concentrated under vacuum, and the solid obtained was partitioned between dichloromethane (2 × 100 mL) and water (1 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a solid. Recrystallization from a mixture of ethyl acetate and dichloromethane gave pure **59**: 0.165 g (45%), mp 169−171 °C. ^{1}H NMR (360 MHz, DMSO) δ 3.01 (3 H, s), 5.66 (2 H, s), 7.37−7.39 (1H, m), 7.53−7.56 (3H, m), 7.66 (1H, d, J = 7.8 Hz), 7.76−7.89 (3H, m), 8.13 (1H, d, J = 7.8 Hz), 8.21−8.24 (2H, m), 8.64 (1H, m). Irradiation of the benzylic protons at δ 5.66 produced a nuclear Overhauser effect to δ 3.01 (methyl group). MS (ES$^+$) *m/e* 368 [MH]$^+$.

3-Phenyl-6-(2-pyridylmethyl)oxy-9-methyl-1,2,4-triazolo-[3,4-*a*]phthalazine (57) and 3-Phenyl-6-(2-pyridylmethyl)oxy-8-methyl-1,2,4-triazolo[3,4-*a*]phthalazine (58). To a solution of 4-methylphthalic anhydride (**75**, 30 g, 0.19 mol) in aqueous acetic acid (400 mL of 40%) was added hydrazine hydrate (10.8 mL, 0.22 mol) and sodium acetate (30.2 g, 0.22 mol). The reaction mixture was heated under reflux for 18 h. When the mixture was cooled, the resultant solid was collected by filtration and dried to yield 6-methylphthalazinedione (**76**, 32 g). ^{1}H NMR (250 MHz, DMSO) δ 2.51 (3H,s), 7.70 (1H, dd, J = 1.4 and 8.2 Hz), 7.87 (1H, d, J = 1.4 Hz), 7.98 (1H, dd, J = 1.4 and 8.1 Hz), 11.47 (2H,bs). MS (ES$^+$) *m/e* 177 [MH]$^+$.

A solution of 6-methylphthalazinedione (**76**, 28 g) in phosphorus oxychloride (500 mL) was refluxed for 18 h, cooled, and evaporated to dryness. The resulting material was dissolved

in DCM (200 mL) and cold water (300 mL), and solid sodium hydrogen carbonate was added carefully until pH 11 was achieved. The aqueous layer was extracted with DCM (2 × 200), and the combined organic layers were washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to yield 1,4-dichloro-6-methylphthalizine (**77**, 29 g). ^{1}H NMR (250 MHz, DMSO) δ 2.60 (3H, s), 8.07−8.16 (2H, m), 8.24 (1H, d, J = 8.3 Hz).

To a solution of 1,4-dichloro-5-methylphthalazine (**77**, 15 g, 0.07 mol) in xylene (200 mL) was added triethylamine (11.8 mL, 1.2 mol equiv) and benzoic hydrazide (10.5 g, 1.1 mol equiv). The reaction mixture was heated under reflux for 48 h under nitrogen. After cooling, the reaction mixture was concentrated under vacuum and the solid obtained was partitioned between dichloromethane (2 × 100 mL) and water (1 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a solid that was shown to be a 3:2 mixture of two regioisomers by NMR: chloro-3-phenyl-9-methyl-1,2,4-triazolo[3,4-*a*]phthalazine (**78**) and 6-chloro-3-phenyl-8-methyl-1,2,4-triazolo[3,4-*a*]phthalazine (**79**). The two isomers were inseparable and were thus used in the next step as a mixture. NMR data for mixture: ^{1}H NMR (250 MHz, DMSO) δ 2.59 (3H, s, minor isomer), 2.63 (3H, s, major isomer), 7.58−8.30 (8H, m).

To a solution of 2-hydroxymethylpyridine (0.990 mL, 0.01 mol) in DMF (30 mL) at room temperature was added sodium hydride (0.326 g of a 60% dispersion in oil, 0.082 mol), and the reaction mixture was stirred at room temperature for 15 min. After this time the mixture of chloro-3-phenyl-9-methyl-1,2,4-triazolo[3,4-*a*]phthalazine (**78**) and 6-chloro-3-phenyl-8-methyl-1,2,4-triazolo[3,4-*a*]phthalazine (**79**, 2.0 g, 0.068 mol) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under vacuum, and the solid obtained was partitioned between dichloromethane (3 × 200 mL) and water (1 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a solid. The two products were separated by column chromatography using 3% methanol in dichloromethane as eluent, and the required products were individually recrystallized from a mixture of ethyl acetate and dichloromethane to give 3-phenyl-6-(2-pyridylmethyl)oxy-9-methyl-1,2,4-triazolo[3,4-*a*]phthalazine (**57**, 0.275 g, high R_f product) and 3-phenyl-6-(2-pyridylmethyl)oxy-8-methyl-1,2,4-triazolo[3,4-*a*]-phthalazine (**58**, 0.16 g, low R_f product). **57**: mp 190−191 °C. ^{1}H NMR (360 MHz, DMSO) δ 2.60 (3 H, s), 5.67 (2 H, s), 7.37−7.41 (1H, m), 7.53−7.56 (3H, m), 7.70 (2H, m), 7.86 (1H, t, J = 6.0), 8.18 (1H, d, J = 8.2 Hz), 8.26 (2H, m), 8.32 (1H, s), 8.68 (1H, d, J = 6.0 Hz). Irradiation of the benzylic protons at δ 5.67 did not produce an NOE to the singlet at δ 8.32. MS (ES$^+$) *m*/*e* 368 [MH]$^+$. **58**: mp 202−204 °C. ^{1}H NMR (360 MHz, DMSO) δ 2.57 (3 H, s), 5.70 (2 H, s), 7.37−7.41 (1H, m), 7.53−7.58 (3H, m), 7.68 (1H, d, J = 7.8 Hz), 7.86−7.91 (2H, m), 8.10 (1H, s), 8.22−8.24 (2H, m), 8.40 (1H, d, J = 8.1 Hz), 8.67 (1H, d, J = 6.0 Hz). Irradiation of the benzylic protons at δ 5.70 produced a nuclear Overhauser effect to the singlet at δ 8.10. MS (ES$^+$) *m*/*e* 368 [MH]$^+$.

3-Phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-*a*]phthalazine (60). To a solution of 3,6-dichloro-7,8,9,10-tetrahydrophthalazine[28] (7 g, 0.0345 mol) in dioxan (100 mL) was added triethylamine (5.2 mL, 1.1 mol equiv) and benzoic hydrazide (5.16 g, 1.1 mol equiv). This mixture was heated at reflux for 18 h under nitrogen, after which time there was little reaction. After cooling, the reaction mixture was concentrated under vacuum and the residue obtained was heated neat at 150 °C for 30 min. After the mixture was cooled, the solid obtained was recrystallized from ethanol/ethyl acetate and collected by filtration to yield 6-chloro-3-phenyl-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-*a*]phthalazine (3.2 g, 33%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.94−1.98 (4 H, m), 2.76−2.80 (2 H, m), 3.20−3.25 (2 H, m), 7.47−7.60 (3 H, m), 8.44 (2 H, d, J = 8.0 Hz). 2-Pyridylcarbinol (0.23 mL, 0.0024 mol, 1.2 mol equiv) was dissolved in DMF (20 mL), sodium hydride (0.096 g of a 60% dispersion in oil, 1.2 mol equiv) was added, and the reaction mixture was stirred at room temperature for 15 min. After this time 6-chloro-3-phenyl-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-*a*]phthalazine (0.55 g, 0,002 mol) was added and the reaction mixture was stirred for 14 h. Water was added until the solution became cloudy, and the solid that precipitated was collected by filtration and recrystallized from ethyl acetate to give pure **60** (0.2 g, 29%): mp 194 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.94 (4 H, m), 2.74 (2 H, m), 3.14 (2 H, m), 5.56 (2 H, s), 7.27 (1 H, m), 7.47 (4 H, m), 7.73 (1 H, m), 8.36 (2 H, d, J = 6.6 Hz), 8.66 (1 H, m). MS (ES$^+$) *m*/*e* 358 [MH]$^+$.

3-Phenyl-6-(2-pyridyl)methyloxy-(7,8-pentano)-1,2,4-triazolo[3,4-*a*]pyridazine (61). 1-Cycloheptene-1,2-dicarboxylic anhydride[29] (5.6 g, 0.034 mol) and sodium acetate (5.5 g, 0.040 mol, 1.2 mol equiv) were dissolved in 60% acetic acid (150 mL), and hydrazine hydrate (1.97 mL, 0.040 mol, 1.2 mol equiv) was added. The reaction mixture was heated under reflux for 16 h, allowed to cool to room temperature, and diluted with water (200 mL). The solid that precipitated was collected by filtration, washed several times with water, and dried under vacuum to give 2,3,6,7,8,9-hexahydro-5*H*-cyclohepta[*d*]pyridazine-1,4-dione: 0.88 g (15%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.47−1.78 (6 H, m), 2.49−2.67 (4 H, m), 10.8 (1 H, br s), 11.74 (1 H, br, s). MS (ES$^+$) *m*/*e* 181 [MH]$^+$. This product (0.87 g, 0.0048 mol) was dissolved in phosphorus oxychloride (100 mL), and the mixture was heated under reflux for 14 h. The reaction mixture was concentrated under vacuum, azeotroped with toluene (2 × 50 mL), then dissolved in dichloromethane (30 mL), washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), filtered, and concentrated under vacuum to give 1,4-dichloro-6,7,8,9-tetrahydro-5*H*-cyclohepta-[*d*]pyridazine: 0.63 g (60%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.48−1.98 (6 H, m), 2.59 (2 H, m), 3.08 (2 H, m). MS (ES$^+$) *m*/*e* 216 [MH]$^+$. This product (0.63 g, 0.0029 mol) and benzoic hydrazide (0.44 g, 0.000 319 mol, 1.1 mol equiv) were dissolved in xylene (30 mL) with triethylamine (0.44 mL, 1.1 mol equiv) and heated under reflux for 60 h. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel using 0−20% ethyl acetate in dichloromethane as eluent to give a crude product. Trituration with hot ethyl acetate and filtration gave purified product in the filtrate, which was further purified by recrystallization from dichloromethane to give 6-chloro-3-phenyl-(7,8-pentano)-1,2,4-triazolo[3,4-*a*]pyridazine: 0.25 g (29%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.64−2.04 (6 H, m), 3.14 (2 H, m), 3.45 (2 H, m), 7.56 (3 H, m), 8.44 (2 H, m). MS (ES$^+$) *m*/*e* 299 [MH]$^+$. 2-Pyridylcarbinol (0.078 mL, 0.001 13 mol, 1.4 mol equiv) was dissolved in DMF (20 mL), sodium hydride (0.045 g of a 60% dispersion in oil, 1.4 mol equiv) was added, and the reaction mixture was stirred at room temperature for 10 min. After this time 6-chloro-3-phenyl-(7,8-pentano)-1,2,4-triazolo[3,4-*a*]pyridazine (0.24 g, 0.000 81 mol) was added and the reaction mixture was stirred for 14 h. Water was added until the solution became cloudy, and the solid that precipitated was collected by filtration and purified by chromatography on silica gel using 0−3% methanol in dichloromethane as eluent. The crude solid was recrystallized from ethyl acetate to give pure **61** (0.076 g, 25%): mp 208 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.71 (2H, m), 1.81 (2H, m), 1.99 (2H, m), 3.01 (2H, m), 3.38 (2H, m), 5.58 (2 H, s), 7.28 (1 H, m), 7.48 (4 H, m), 7.76 (1 H, m), 8.37 (2 H, d, J = 7.8 Hz), 8.67 (1 H, m). MS (ES$^+$) *m*/*e* 372 [MH]$^+$.

3-Phenyl-6-(2-pyridyl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-*a*]phthalazine (62). 3,6-Dichloro-4,5-diazatricyclo[6.2.2.2,7]dodeca-2(7),3,5-triene[29] (2.5 g, 0.011 mol) was suspended in xylene (50 mL) with benzoic hydrazide (1.65 g, 1.1 mol equiv) and triethylamine (1.68 mL, 1.1 mol equiv), and the reaction mixture was heated under reflux for 6 days. The solvent was removed under high vacuum and the residue was purified by chromatography on silica gel using 0−50% ethyl acetate in dichloromethane as eluent followed by recrystallization from ethyl acetate/hexane to give 6-chloro-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-*a*]phthalazine: 1.3 g (38%), mp 186−188 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.43−1.59 (4 H, m), 1.91−2.05 (4 H, m),

3.57 (1 H, s), 4.07 (1 H, s), 7.58 (3 H, m), 8.58 (2 H, dd, $J = 7.8$ and 1.5 Hz). MS (ES^+) *m/e* 311 $[MH]^+$. Anal. found: C, 65.56; H, 4.83; N, 17.74. $C_{17}H_{15}ClN_4$ requires C, 65.70; H, 4.87; N, 18.03%.

To a solution of 2-pyridylcarbinol (0.263 mL, 0.0024 mol) in DMF (20 mL) was added sodium hydride (0.113 g of a 60% dispersion in oil, 1.75 mol equiv), and the reaction mixture was stirred at room temperature for 15 min. After this time 6-chloro-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-*a*]phthalazine (0.5 g, 0.0016 mol) was added and the reaction mixture was stirred at room temperature for 1 h. Water was added until the solution became cloudy. After the solution was stirred for a further 15 min, a solid was collected by filtration. This solid was recrystallized from ethyl acetate to give pure **62**: 0.112 g (18%), mp 196−198 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.45 (4 H, m), 1.95 (4 H, m), 3.58 (1 H, s), 4.00 (1 H, s), 7.26 (1H, m), 5.48 (2 H, s), 7.44−7.53 (4 H, m), 7.77 (1 H, m), 8.40 (2 H, dd, $J = 7.8$ and 1.5 Hz), 8.68 (1 H, m). MS (ES^+) *m/e* 384 $[MH]^+$.

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JM031020P