Structure−Activity Relationships of 1,4-Dihydro-(1H,4H)-quinoxaline-2,3-diones as *N*-Methyl-D-aspartate (Glycine Site) Receptor Antagonists. 1. Heterocyclic Substituted 5-Alkyl Derivatives

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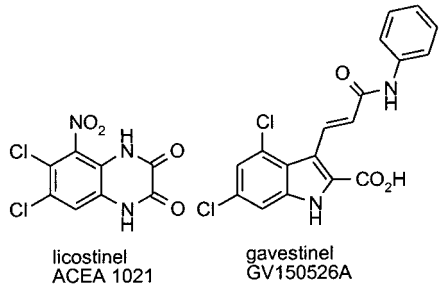
Received November 27, 2000

A series of 6,7-dichloro-1,4-dihydro-(1H, 4H)-quinoxaline-2,3-diones (**1**−**17**) were prepared in which the 5-position substituent was a heterocyclylmethyl or 1-(heterocyclyl)-1-propyl group. Structure−activity relationships were evaluated where binding affinity for the glycine site of the *N*-methyl-D-aspartate (NMDA) receptor was measured using the specific radioligand [^{3}H]-L-689,560, and functional antagonism was demonstrated by inhibition of NMDA-induced depolarizations of rat cortical wedges. The ability to prevent NMDA-induced hyperlocomotion in mice in vivo was measured for selected compounds. Binding affinity increased significantly if the heterocyclic group, e.g. 1,2,3-triazol-1-yl could participate in accepting a hydrogen bond from the receptor. It was difficult to obtain compounds with adequate aqueous solubility and strategies to improve it were investigated. The most potent compound in this series, 6,7-dichloro-5-[1-(1,2,4-triazol-4-yl)propyl]-1,4-dihydro-(1H, 4H)-quinoxaline-2,3-dione (**17**) (binding IC_{50} = 2.6 nM; cortical wedge EC_{50} = 90 nM), inhibited NMDA-induced hyperlocomotion in mice (6/9 protected at 20 mg/kg iv). Pharmacokinetic parameters, including extent of brain penetration, for **11** and **17** are reported.

Introduction

L-Glutamic acid is an important excitatory amino acid in the central nervous system. It is essential at *N*-methyl-D-aspartate (NMDA) receptors for both glycine and glutamic acid to bind to their respective sites for receptor activation to occur, and thus glycine antagonists are able to function as noncompetitive modulators of glutamic acid-induced responses in vitro and in vivo.[1−5] Overstimulation of NMDA receptors has been implicated in a number of pathological conditions involving neuronal death and degeneration and has driven the search for NMDA antagonists as possible therapies for thrombo-embolic stroke, traumatic head injury, Parkinson's, Huntington's, and Alzheimer's diseases, epilepsy, and schizophrenia.[1,2,6,7] Antagonists at the glycine binding site of the NMDA receptor may have advantages over competitive antagonists of glutamic acid (e.g. selfotel (CGS 19755) and D-CPPene (SDZ EAA 494)) and drugs which recognize the ion-channel binding site (e.g. dizocilpine (MK801) and aptiganel (CNS 1102)) due to a more attractive side effect profile.[6] However, it has, in general, been very difficult to identify compounds with sufficient potency in animal models of stroke to warrant further progression, primarily because glycine antagonists are acidic and the structural features which favor high potency tend to limit blood-brain barrier penetration and hence in vivo activity. Nevertheless, several glycine antagonists have been progressed to clinical trials (see Chart 1). Satisfactory Phase IIa safety and toleration studies with ACEA 1021 (licostinel) and GV150526A (gavestinel) have been reported,[8,9] but recently both compounds have been dropped from development.

Chart 1



A large number of papers describe structure activity relationships (SARs) for glycine antagonists and several structural series with nanomolar binding affinities have been discovered.[2,10−12] These studies have helped develop a model of the glycine binding site (Figure 1). This diagram shows schematic binding interactions for 6,7-dichloro-1,4-dihydro-2,3-quinoxalinedione (DCQX) and 5,7-dichlorokynurenic acid. The charge−charge interaction and optimum filling of the lipophilic pocket are very important for achieving high potency. SARs of both quinoxalinediones and kynurenic acids can be rationalized using the same receptor model by accommodation of the chlorines in the 6 and 7 positions of the quinoxalinedione binding to the same region of the receptor surface as the 5-chlorine and 6-hydrogen of the kynurenic

10.1021/jm001124p CCC: $20.00
Published on Web 05/05/2001

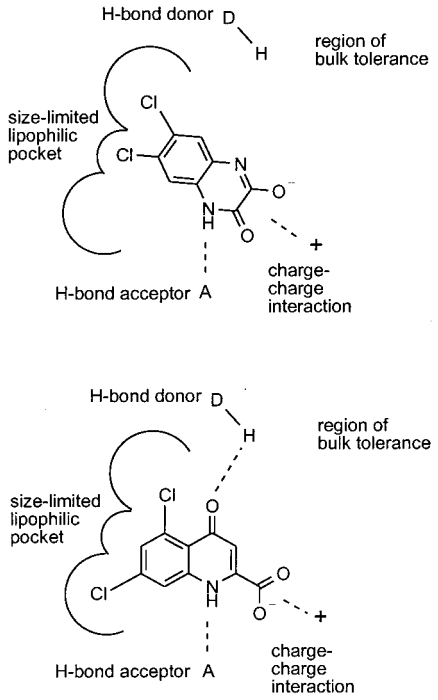


Figure 1. Schematic model of the glycine binding site with 6,7-dichloroquinoxalinedione (DCQX) (top) and 5,7-dichlorokynurenic acid docked into place.

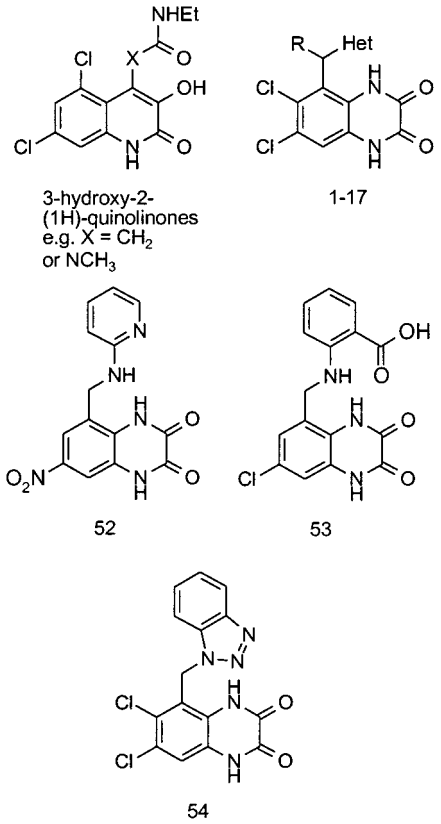
acid. This overlap led us to speculate whether some of the features of both series could be combined, and we recently reported the SARs of a series of 3-hydroxy-2(1H)-quinolinones[13] in which replacement of one of the nitrogens of a quinoxalinedione by a carbon permitted the attachment of a suitable substituent from the 4-position without loss of the acidic functionality (see Chart 2).[14]

While good in vitro binding affinity was obtained, the new hydroxyquinolone series lacked activity in vivo. Drug metabolism studies showed that compounds typically possessed very short plasma half-lives in the rat ($t_{1/2}$ < 0.2 h for the two compounds illustrated). Glucuronidation of the 3-hydroxyl was evident in rat liver microsome preparations in vitro, and we also speculate that active hepatic uptake might also have contributed to the rapid clearance rate. After many unsuccessful efforts to improve pharmacokinetic parameters of the hydroxyquinolinones, we decided to investigate quinoxalinediones, since studies with DCQX showed it to be stable toward glucuronidation by rat liver microsomes in vitro. Molecular modeling, based on the receptor model shown in Figure 1, suggested that the H-bond donor interaction could be reached easily from the 5-position. In addition, the greater potency of ACEA-1021 compared to DCQX (Table 1) could be rationalized in terms of a hydrogen bond acceptor interaction by the 5-nitro group. We therefore prepared a range of novel derivatives, all of which were designed to target this interaction. In this paper, we report SARs for a series of compounds (**1**−**17**) (Chart 2) in which the hydrogen bond acceptor is an aromatic heterocycle.

Chemistry

Quinoxalinediones are generally very insoluble so that their handling and purification are difficult. We thus sought to protect the dione functionality as the 2,3-

Chart 2



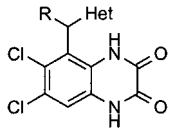
dimethoxy derivative to solve these problems and permit a variety of chemical manipulations at the 5-position. Compounds **1**−**17** (Table 1) were readily prepared by acidic hydrolysis of **18**−**34** (Scheme 1, Method A).

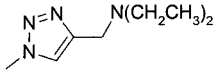
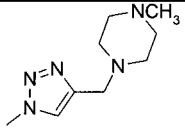
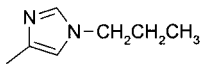
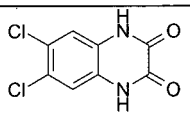
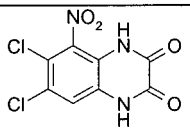
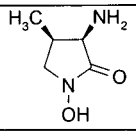
Intermediates **18**−**25** were most conveniently prepared by reaction of the benzylic bromide **35** with heterocycles such as imidazole, pyrazole, and triazole (Scheme 2, Method B). 3-Methyl-1,2,4-triazole afforded a mixture of regioisomers (**24** and **25**), whereas a single product was isolated from the reactions of 1,2,3-triazole and 1,2,4-triazole. Performing the alkylation with 1,2,4-triazole under melt conditions (Method C)[15] gave access to the 1,2,4-triazol-4-yl isomer (**22**).

Compound **35** was prepared in seven steps from commercially available 2,4,5-trichloronitrobenzene (**36**) (Scheme 2). First, a vicarious nucleophilic aromatic substitution reaction[16] with *tert*-butyl chloroacetate gave **37**, which underwent concurrent replacement of the *ortho* chlorine and hydrolysis and decarboxylation of the ester to give the nitrotoluene **38** on treatment with concentrated aqueous ammonia at high temperature. The moderate yield for this reaction is partly due to the vigorous conditions and the formation of side products arising from displacement of the *para* chlorine, but this two-step sequence[17] was preferred to the seven-step literature route.[18] Next, reduction of the nitro group and condensation with oxalic acid[19] gave **39**. Treatment with thionyl chloride gave the 2,3-dichloroquinoxaline which reacted smoothly with sodium methoxide to give **40**. Finally, bromination with *N*-bromosuccinimide afforded **35**.

Two 1,2,3-triazole derivatives (**26** and **27**) bearing amine-containing side chains were prepared. Thus, reaction of **35** with methyl 1,2,3-triazole-4-carboxylate[20]

Table 1. NMDA Receptor Binding Affinity, Functional Potency in Vitro, and Inhibition of NMDA Induced Hyperlocomotion in the Mouse by Quinoxalinedione Derivatives



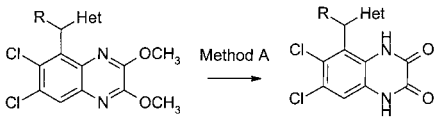
Compd	R	Het	IC_{50}[a] (nM)	EC_{50}[b] (nM)	Mouse hyperlocomotion[c]	
					no. protected / no. dosed	i.v. dose used (mg/kg)
1	H	imidazol-1-yl	23	1300		
2	H	pyrazol-1-yl	5	NT[d]		
3	H	1,2,4-triazol-1-yl	25	NT		
4	H	1,2,3-triazol-1-yl	1	350		
5	H	1,2,4-triazol-4-yl	81	1,090		
6	H	2-methylimidazol-1-yl	109	NT		
7	H	3-methyl-1,2,4-triazol-1-yl	24	640		
8	H	5-methyl-1,2,4-triazol-1-yl	190	NT		
9	H		6	150	0/9	20
10	H		7.6	88	1/9	20
11	H		4.4	350	6/9	20
						
12	H	2-pyridyl	30	4,100		
13	H	2-methyltetrazol-5-yl	78	NT		
14	CH_2CH_3	imidazol-1-yl	3.1	90	0/9	20
15	CH_2CH_3	1,2,3-triazol-1-yl	0.75	290	0/6	20
16	CH_2CH_3	1,2,4-triazol-1-yl	4.0	420		
17	CH_2CH_3	1,2,4-triazol-4-yl	2.6	90	0/9 2/9 6/9 5/9	3 10 20 30
DCQX			2,000	NT		
ACEA-1021 (**47**)			1.4	1,100	3/10 5/10 3/10	3 10 15
L-687,414			1,200	16,000	5/10 10/10	10 30

[a] Displacement of [^{3}H]-L-689,560 from rat cortical membranes. Results are the average of two determinations, and a 2-fold difference between compounds should not be regarded as significant. [b] Inhibition of NMDA-induced depolarizations in rat cortical wedges. Results are the average of two determinations, and a 2-fold difference between compounds should not be regarded as significant. [c] Ability to prevent NMDA-induced hyperlocomotion in the mouse following iv administration. [d] NT = not tested

(Scheme 3) followed by reduction of **41** to the aldehyde **42** and reductive amination with diethylamine or *N*-methylpiperazine gave **26** and **27**, respectively.

Compound **35** was also a useful intermediate for the synthesis of carbon-linked heterocyclic derivatives **28**–**30** (Scheme 4). We found that the benzylic zinc reagent could be formed under mild conditions by treating **35** with activated zinc dust in THF at room temperature.[21] Cross-coupling with chloracetyl chloride[22] (at room temperature) or 2-bromopyridine[23] (reflux) with tetrakistri(2-furylphosphine)palladium(0) catalysis[24] gave chloroketone **43** and the pyridine **29**, respectively. Reaction of **43** with 2-amino-5,6-dihydro-4H-1,3-thiazine[25] followed by Raney nickel desulfurization of **44** was used

Scheme 1[a,b]



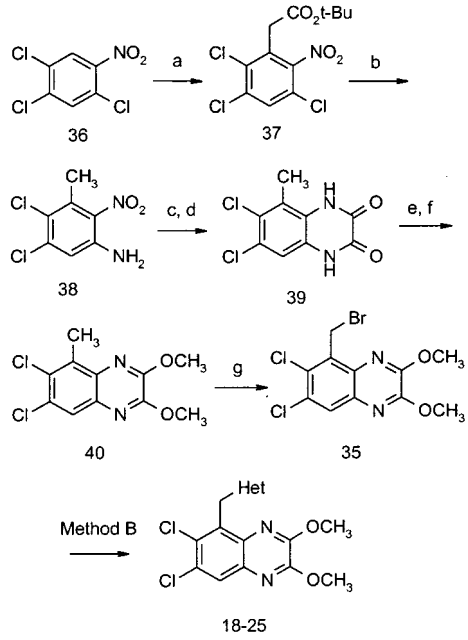
Product	Starting material	Formula	Anal.	m.p. (°C)	yield (%)	Aqueous solubility
1	18	$C_{12}H_8Cl_2N_4O_2$•HCl•0.75H_2O	C,H,N	315-6 (dec)	95	
2	19	$C_{12}H_8Cl_2N_4O_2$•0.75H_2O	C,H,N	>320	95	<10 μg/mL[c]
3	20	$C_{11}H_7Cl_2N_3O_2$•1.25H_2O	C,H,N	>320	62	<10 μg/mL[c]
4	21	$C_{11}H_7Cl_2N_3O_2$•HCl•0.5H_2O	C,H,N	323-5 (dec)	73	
5	22	$C_{11}H_7Cl_2N_3O_2$•HCl•0.25H_2O	C,H,N	>300	81	
6	23	$C_{13}H_{10}Cl_2N_4O_2$•HCl	C,H,N	>300	81	
7	24	$C_{12}H_9Cl_2N_3O_2$•HCl	C,H,N	>320	56	
8	25	$C_{12}H_9Cl_2N_3O_2$•HCl•H_2O	C,H,N	302-4 (dec)	40	
9	26	$C_{16}H_{18}Cl_2N_6O_2$•HCl•H_2O	C,H,N	236	96	
10	27	$C_{17}H_{19}Cl_2N_7O_2$•HCl•H_2O	C,H,N	265	79	>10 mg/mL[d]
11	28	$C_{15}H_{14}Cl_2N_4O_2$•HCl•H_2O	C,H,N	310	66	>10 mg/mL[d]
12	29	$C_{14}H_9Cl_2N_3O_2$•HCl	C,H,N	>290 (dec)	88	<1 mg/mL[d]
13	30	$C_{11}H_8Cl_2N_6O_2$	[e]	>300	35	
14	31	$C_{14}H_{12}Cl_2N_4O_2$•HCl•0.75H_2O	C,H,N	>300	25	~5 mg/mL[f]
15	32	$C_{13}H_{11}Cl_2N_5O_2$•0.3H_2O	C,H,N	>300	57	<1 mg/mL[f]
16	33	$C_{13}H_{11}Cl_2N_5O_2$•HCl•0.5H_2O•0.15dioxane	C,H,N	Hygroscopic foam	55	~1 mg/mL[f]
17	34	$C_{13}H_{11}Cl_2N_5O_2$•HCl•1.75H_2O	C,H,N	224-6	49	>5 mg/mL[f]

[a] Reagents and conditions: 2 M $HCl_{(aq)}$, dioxane, reflux. [b] For details of R and Het, see Table 1. [c] Solubility in water, pH 7. [d] Solubility in water as hydrochloride salt, pH 4−5. [e] No combustion analysis obtained due to the high level of nitrogen present. Compound characterized by spectroscopic means: ^{1}H NMR (300 MHz, DMSO-d_6) 4.23 (3H, s), 4.62 (2H, s), 7.30 (1H, s), 1.66 (1H, s), 12.1 (1H, s), *m/z* (thermospray) 344 (MNH_4^+). [f] Solubility in 0.1 M aqueous D-arginine, pH 9.

to ensure formation of the *N*-propylimidazole **28** regioselectively. Preparation of the tetrazole **30** proceeded via the nitrile **45**, 1,3-dipolar cycloaddition with azidotributylstannane and *N*-methylation of **46**. Compound **30** was obtained together with its 1-methyl isomer, and the two isomers were separated by column chromatography. Measurement of nuclear Overhauser enhancements between the quinoxaline 5-position methylene hydrogens and the tetrazole *N*-methyl hydrogens permitted a clear structural assignment for the two isomers.

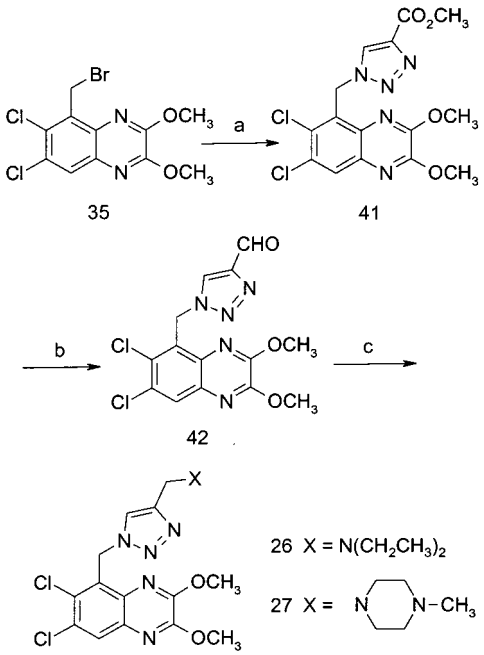
We also wished to investigate the effect of branching next to the heterocycle (Scheme 5). We prepared the necessary bromopropyl intermediate **51** in eight steps from 5-nitroquinoxalinedione **47**.[26] Thus, chlorination with thionyl chloride, reduction of the 5-nitro group, and nucleophilic displacement of the 2- and 3-position chlorines gave the 2,3-dimethoxy derivative **48**. A Sandmeyer reaction gave the iodide **49**,[27] which underwent cross-coupling with tributylvinylstannane[28] and subsequent ozonolysis and addition of ethylmagnesium bromide to give the alcohol **50**. Finally, bromination[29] of the alcohol **50** afforded bromide **51**, whose proton NMR spectrum was of interest since two diastereomers were evident. This was presumably due to hindered rotation of the 5-substituent bond and the stereogenic center contained within that substituent. Presumably, the 6-position chlorine restricts rotation of the 5-position

Scheme 2[a]



[a] Reagents and conditions: a: $ClCH_2CO_2Bu^t$, $KOBu^t$, THF, −40 °C, 30 min; b: concentrated aqueous NH_3, 2-methoxyethanol, autoclave, 150 °C, 72 h; c: $Na_2S_2O_4$, $KHCO_3$, H_2O/MeOH, 20 °C, 30 min; d: $(CO_2H)_2$, 4 M $HCl_{(aq)}$, reflux, 6 h; e: $SOCl_2$, catalyst DMF, reflux, 3 h; f: NaOMe, THF/MeOH, 20 °C, 1 h; g: *N*-bromosuccinimide, catalyst AIBN, CH_3CCl_3, sunlamp, reflux, 4 h; Method B: Het-H, K_2CO_3, CH_3CONMe_2 or THF, 50 °C, 18 h.

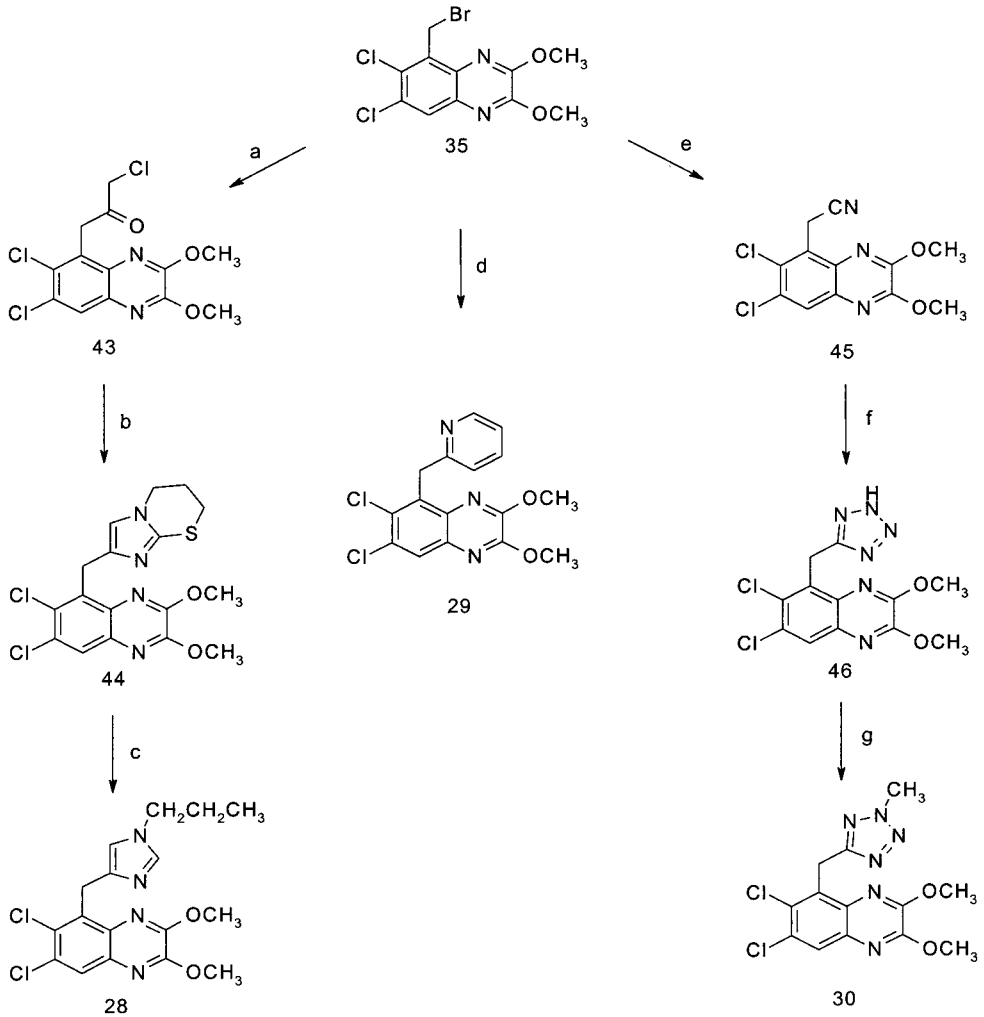
Scheme 3[a]



[a] Reagents and conditions: a: methyl 1,2,3-triazole-4-carboxylate, K_2CO_3, THF, reflux, 18h, then separation of the isomers by chromatography; b: DIBAL-H, CH_2Cl_2, −78 °C, 2.25 h; c: amine, $NaBH(OAc)_3$, HOAc, THF, 20 °C, 2 h.

substituent when the latter is sufficiently bulky. Nucleophilic substitution of the bromide was problematic presumably due to steric hindrance and competing elimination, but satisfactory yields of products **31**−**34** were obtained using a melt of the heterocycle (Method C).

Scheme 4[a]



[a] Reagents and conditions: a: zinc dust, THF, 20 °C, ultrasound, then $ClCH_2COCl$, $Pd_2(dba)_3$, tri(2-furyl)phosphine, THF, 20 °C, 45 min; b: 2-amino-5,6-dihydro-4H-1,3-thiazine, NBu^n_4 Br, K_2CO_3, DMF, 80 °C, 2 h; c: Raney nickel, EtOH, reflux, 2 days. d: zinc dust, THF, 20 °C, ultrasound, then 2-bromopyridine, $Pd_2(dba)_3$, tri(2-furyl)phosphine, THF, 65 °C, 60 min; e: NaCN, i-PrOH/H_2O, reflux, 1 h; f: azidotributylstannane, toluene, reflux, 42 h; g: CH_3I, K_2CO_3, DMF, 20 °C, 2 h, then separation of tetrazole isomers by chromatography.

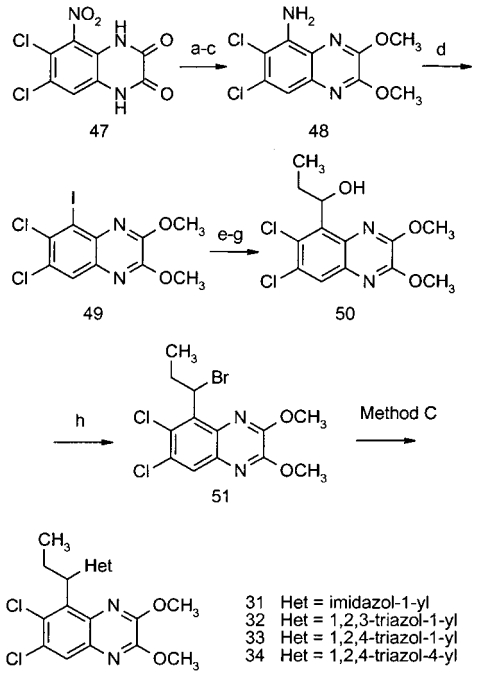
Results and Discussion

Compounds **1**−**17** were first evaluated as glycine site ligands at the NMDA receptor by measuring their ability to displace the specific glycine antagonist [^{3}H]-L-689,560 from thoroughly washed rat cortical membranes[30] (see Table 1). Functional activity in vitro was measured from compounds' ability to inhibit NMDA-induced depolarizations of rat cortical wedges.[31] Comparative data, generated in our laboratories, for three literature glycine antagonists, DCQX,[26] ACEA 1021 (**47**),[26] and L-687,414,[32] are also shown in Table 1.

The in vitro SARs of N-linked heterocyclic derivatives **1**−**8** will be discussed first. The imidazole derivative **1** had good binding affinity (IC_{50} = 23 nM), suggesting that the desired hydrogen bonding interaction with the receptor had indeed been made. The affinity of the pyrazole **2** was 5-fold greater, which could be due to moving the sp^2 nitrogen atom into a better position to make the hydrogen bond. The 1,2,4-triazole **3** was only as potent as the imidazole, which can be rationalized because its dominant H-bond acceptor is the 3-position nitrogen. Enhancing the H-bond acceptor power of the heterocycle as in the 1,2,3-triazole increased binding affinity significantly (IC_{50} = 1 nM). The isomeric 1,2,4-triazole **5** was less potent than the imidazole **1**. Introduction of a methyl group adjacent to the methylene (as in **6** and **8**) was not well-tolerated in contrast to attachment to the 3-position relative to the methylene. Thus, the 3-methyltriazole **7** was equipotent with the imidazole **1**.

Compounds **1**, **4**, **5**, and **7** were found to be functional glycine antagonists in vitro with **4** being 3-fold more potent than ACEA 1021. The falloff in potency between the binding and the cortical wedge assays is probably due to the high concentration of endogenous glycine present in the cortical wedge preparation which must be overcome by the antagonist and high protein binding of the test compounds. However, it is notable that the falloff in potency is only about 13-fold for L-687,414 which has very low plasma protein binding and high water-solubility. The potency of several of the compounds **1**−**8** could not be measured in the cortical wedge assay due to low solubility. We therefore sought to append side-chains to the 4-position of the heterocycle to enhance solubility. Compounds **9** and **10** are representative of a much larger group of compounds we made in which the heterocycle (1,2,3-triazole, 1,2,3-benzotriazole, pyrazole), the amine, and its distance from the

Scheme 5[a]



[a] Reagents and conditions: a: $SOCl_2$, catalyst DMF, reflux, 3 h; b: $SnCl_2 \cdot 2H_2O$, EtOAc, reflux, 4 h; c: NaOMe, MeOH, reflux, 30 min. d: HCl, $NaNO_2$, acetone/water, 0 °C, then KI, 10 °C, 30 min; e: tributylvinylstannane, LiCl, $PdCl_2 \cdot 2PPh_3$, DMF, 100 °C, 1.5 h; f: ozone, $CHCl_3$, −60 °C, then PPh_3, 16 h; g: EtMgBr, THF, 20 °C, 30 min; h: CBr_4, PPh_3, CH_2Cl_2, 20 °C, 18 h.

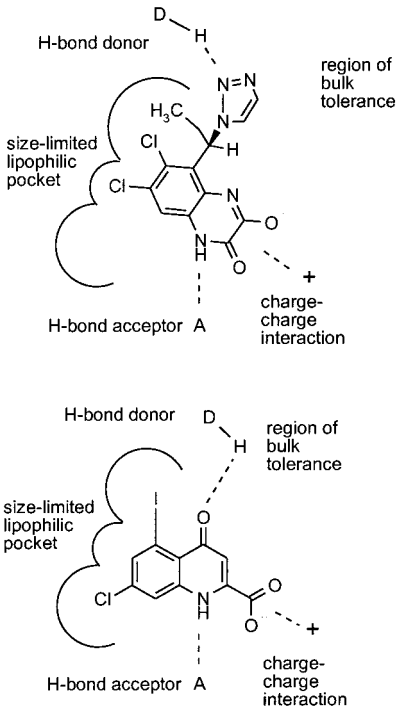


Figure 2. Schematic model of the glycine binding site with compound **15** (top) and 7-chloro-5-iodokynurenic acid docked into place.

heterocycle were varied. In general, the potency did not vary much with structure, and the amine side chains were well-tolerated by the receptor. However, functional potency and solubility improved significantly. Thus, compound **10** possessed $IC_{50} = 7.6$ nM for binding and $EC_{50} = 88$ nM in the cortical wedge assay, data which compare favorably with L-689,560 ($IC_{50} = 4$ nM, $EC_{50} = 230$ nM),[33] one of the most potent known glycine antagonists in vitro, and its solubility in water (as hydrochloride salt, pH 5) was >10 mg/mL.

The in vitro SARs for the carbon-linked heterocycles **11**−**13** will be discussed next. The imidazole **11** was designed to retain the sp^2 nitrogen atom adjacent to the methylene linker. Imidazole is a powerful H-bond acceptor,[34] and its moderate basicity was expected to help increase aqueous solubility. Table 1 shows that **11** possesses good binding affinity and functional potency, and aqueous solubility was excellent (>10 mg/mL as hydrochloride salt, pH 4). In contrast, the 2-pyridyl and tetrazolyl analogues **12** and **13** would be expected to provide similar H-bond acceptor capabilities, but they were significantly less potent than **11**. In addition, they were less soluble (<1 mg/mL).

Finally, the in vitro SARs for the branched alkyl dervatives **14**−**17** will be discussed. We believed that the poor aqueous solubility of the quinoxalinediones is due to high crystal lattice strength, as evidenced by their very high melting points. Thus, introducing groups that lie above and below the plane of the quinoxaline might be expected to disrupt the crystal packing somewhat. Examination of molecular models suggested introduction of an ethyl group next to the heterocycle might perform this function. Compounds **14**−**17** possessed very high binding affinities, with the 1,2,3-triazole **15** being the best ($IC_{50} = 0.75$ nM). In addition, compounds **14** and **17** were very potent functional antagonists. The increase in potency relative to the unbranched analogues **1**, **3**, and **5** may result from an increased conformational restriction which holds the heterocycle in a better orientation relative to the receptor, or possibly because the ethyl group helps to fill the lipophilic pocket occupied by the 6-chlorine atom (see Figure 2). It is known in the kynurenic acid series that replacement of the 5-chlorine by iodo or ethyl results in improved binding affinity.[35] In addition aqueous solubility was improved, for example **14** (as hydrochloride salt in water, pH 4) and **17** (in aqueous arginine, pH 9) could be dissolved at ≥ 5 mg/mL.

Our series of compounds bears some similarity to a group of substituted 5-(aminomethyl)quinoxalinediones such as **52** and **53** (Chart 2)[36] in which the amino, pyridyl, or carboxylate groups might be able to function as a hydrogen bond acceptors. Whereas compound **52** is reported to have little affinity for the NMDA (glycine site) (0% inhibition of [^{3}H]-5,7-dichlorokynurenic acid at 1 μM), introduction of a carboxylic acid group, as in **53,** increased potency significantly (binding $IC_{50} = 30$ nM). As part of this work we prepared benzotriazole **54** (Chart 2), which has similar potency to the 1,2,3-triazole **4**, and possesses a more marked structural resemblance to **53**. Compounds **52** and **53** also have affinity for the AMPA receptor ([^{3}H]-AMPA binding IC_{50} 1−2 μM).[36] We have measured the AMPA receptor binding affinity (displacement of [^{3}H]-AMPA from rat cortical membranes) for a number of our compounds. Of these, only compounds **3** ($IC_{50} = 0.25$ μM) and **17** ($IC_{50} = 2.3$ μM) had measurable affinity ($IC_{50} > 10$ μM for compounds **1**, **2**, **4**, **7**, **9**, and **11**).

Selected compounds were evaluated in vivo in the mouse using a modification of the published method (Table 1).[37] In this assay, administration of NMDA (300

mg/kg sc) to mice causes a series of well-characterized behavioral changes, of which the first is hyperlocomotion. The time to onset and duration of hyperlocomotion was recorded (up to a maximum of 15 min) for groups of animals receiving test compounds (as solutions intravenously via a tail vein 15 min prior to NMDA administration) or saline (as controls). Inhibition of hyperlocomotion was recorded either as the number of animals reaching 15 min post NMDA challenge at the relevant dose, or an ED_{50} was determined as the derived dose at which 50% of animals reach 15 min post NMDA administration before the end of the hyperlocomotion phase.

Only two compounds, the imidazole **11** and the α-ethyl 1,2,4-triazole **17** were able to prevent NMDA-induced hyperlocomotion. Raising the dose of **17** beyond 20 mg/kg iv did not increase the proportion of mice protected. The stringency of the test is demonstrated by the fact that ACEA 1021 also failed to inhibit the NMDA challenge completely.

Rat pharmacokinetic parameters were measured for **11** and **17** to see if they threw light on the relatively poor in vivo performance. Compound **11** possessed moderate clearance (37 mL/min/Kg) and moderate volume of distribution (1.0 L/Kg) leading to a short plasma half-life (0.3 h). Penetration into brain tissue following a 2 mg/kg iv dose was rapid, resulting in total drug concentrations in plasma, brain tissue, and CSF of 4.6 μM, 0.38 μM, and 0.26 μM at 0.1 h post dose and 2.4 μM, 0.39 μM, and <0.1 μM at 0.25 h post dose, respectively. The brain/plasma concentration ratio of **11** was in the range 0.08−0.21, consistent with its lipophilicity (logD = 2.4). However, the CSF/plasma concentration ratio (0.06) was measurable at a single time point and was higher than expected considering the high plasma protein binding (98%) of **11**.

In comparison with compound **11**, compound **17** (2 mg/kg iv) possessed lower clearance (15 mL/min/Kg) and slightly greater volume of distribution (1.6 L/Kg) leading to a plasma half-life of 1.2 h. Penetration into brain tissue was also rapid, resulting in total drug concentrations in plasma, brain tissue, and CSF of 7.5 μM, 0.58 μM, and 0.52 μM at 0.1 h post dose and 4.6 μM, 0.22 μM, and 0.26 μM at 0.25 h post dose, respectively. The brain/plasma and CSF/plasma concentration ratios were 0.05−0.08 and 0.06−0.07, respectively (the two ratios relate to the two time points). The close similarity of the ratios is consistent with the measured logD = 0.2 (octanol, pH 7.4) (i.e. almost equal partitioning between brain cell membranes and extracellular fluid). The magnitude of the ratios is consistent with the measured rat plasma protein binding of 94%, since theoretical models of brain penetration usually propose that only an unbound drug may cross the blood-brain barrier.[38]

Thus, the relatively poor in vivo activity with **11** in the mouse probably stems from its short plasma half-life, resulting in low brain concentrations at the time of the NMDA challenge, rather than an inability to cross the blood brain barrier. In contrast, the low in vivo potency of **17** is less well understood. In principle, pharmacokinetic experiments that compare free drug concentrations in brain tissue and CSF with functional potency at the NMDA receptor (as a surrogate for the efficacious concentration) following various doses in the same species could have been undertaken, but we have not pursued this line of enquiry.

In this paper, we describe a novel series of 5-substituted quinoxalinediones possessing potent activity in vitro as glycine antagonists. However, obtaining good in vivo activity was elusive. The majority of glycine antagonists would appear to suffer from one or more problems which handicap their utility in vivo, namely acidity (low pK_a), high plasma protein binding, high hydrogen bond count, and rapid clearance. We considered that these could be overcome in the quinoxalinediones, for although the hydrogen bond count is high, we and others[13,26] had demonstrated that good potency in vitro may be achieved in other chemical series with moderate molecular weight and relatively low acidity (pK_a = 6−7.5). Furthermore, compounds with low lipophilicity or a basic center had suitable aqueous solubility and could cross the blood-brain barrier. Despite a poor understanding of the in vivo performance of **17**, we nevertheless decided to persevere with the quinoxalinediones and examine other structural series that might address the deficiencies of the compounds described here. These results will be detailed in a following paper (Part 2).[39]

Experimental Section

Biology. Ligand Binding Affinity. The method of Grimwood et al.[30] was followed with minor adjustments. Thoroughly washed membrane protein from rat brain (cortex and hippocampus) was incubated for 90 min at 4 °C with test compounds (dissolved in Tris-acetate buffer (pH 7.4) containing 1% DMSO) and [^{3}H]-L-689,560. Mixtures were filtered using a Brandel cell harvester, and the filters were added to scintillation fluid for quantification of remaining radioactivity. Displacement of the radioligand using a range of concentrations of test compounds was used to derive IC_{50} values. The binding affinity of 5,7-dichlorokynurenic acid was measured every time the assay was performed and gave IC_{50} = 210 ± 100 nM.

NMDA-Induced Depolarizations of Rat Cortical Wedges. The ability of compounds to inhibit NMDA-induced depolarization of rat cortical tissue was determined using the cortical wedge technique described by Harrison and Simmonds.[31] Compounds were dissolved in 1% DMSO/Krebs buffer and applied in increasing concentrations (up to 10 μM) for 15 min prior to a standard challenge of 12.5 μM NMDA to evoke depolarization. The percentage inhibition from control responses was used to calculate an IC_{50}. Assays were performed in duplicate and five-point dose−response curves measured. Spontaneous activity was blocked by adding 0.1 μM tetrodotoxin to the Krebs buffer.

NMDA-Induced Hyperlocomotion in Mice. In vivo potency was determined using a modification of the literature method[37] in which a larger dose of NMDA was given subcutaneously rather than intracerebroventricularly, and the hyperlocomotion phase (which precedes clonic convulsions) was used as an endpoint. Mice (CD1, Charles River, 25−30 g) were administered NMDA (300 mg/kg sc), and the time to onset and duration of hyperlocomotion were recorded (up to a maximum of 15 min). Animals were euthanased at the end of the hyperlocomotion phase or at 15 min post NMDA administration, whichever was earliest. Test compounds were dissolved in buffered saline (pH 7−9) or 0.1 M aqueous D-arginine and given intravenously (up to 30 mg/Kg) via a tail vein 15 min prior to NMDA administration, and usually 9−10 mice were used per dose. Inhibition of hyperlocomotion was recorded either as the number of animals reaching 15 min post NMDA challenge at the relevant dose, or an ED_{50} was determined as the derived dose at which 50% of animals reach 15 min post NMDA administration before the end of the hyperlocomotion phase.

Chemistry. Melting points were determined using open glass capillary tubes and a Gallenkamp melting point apparatus and are uncorrected. Spectroscopic data were recorded on a Perkin-Elmer 983 (IR), Finnigan Mat. TSQ 7000 or a Fisons Instruments Trio 1000 (MS), and Varian Unity Inova-300 or Bruker AC300 (NMR) instruments and are consistent with the assigned structures. Flash chromatography refers to column chromatography on silica gel (Kieselgel 60, 230−400 mesh, from E. Merck, Darmstadt). Kieselgel 60 F_{254} plates from E. Merck were used for TLC, and compounds were visualized using UV light, 5% aqueous potassium permanganate or chloroplatinic acid/potassium iodide solution. Where analyses are indicated only by the symbols of the elements, results obtained are within ± 0.4% of the theoretical values. In cases where compounds were analyzed as hydrates, the presence of water was evident in the enhanced peak due to water in the NMR spectra. The purity of compounds was carefully assessed using analytical TLC and proton NMR (300 MHz), and the latter was used to calculate the amount of solvent in solvated samples. In multistep sequences, the purity and structure of intermediates were verified spectroscopically by NMR.

ACEA-1021,[26] L-687,414,[40] methyl 1,2,3-triazole-4-carboxylate,[20] and 2-amino-5,6-dihydro-4H-1,3-thiazine[25] were prepared by methods in the literature.

Method A. Hydrolysis of 2,3-Dimethoxyquinoxalines 18−34 To Give 1−17. The 2,3-dimethoxyquinoxaline was added to a mixture of 2 M hydrochloric acid and dioxane (1:1, 40 mL/g) and heated at reflux until TLC analysis indicated complete consumption of starting material (2−24 h). The solvent was removed under reduced pressure, and the residue was suspended in water (or ether or acetone for the compounds forming hydrochloride salts) and filtered off. The solid was dried in vacuo.

Method B. Preparation of 2,3-Dimethoxyquinoxalines 18−21 and 23−25. (Compound **22** was prepared by Method C, below.) A mixture of **35** (1 equiv), heterocycle (2 equiv), and anhydrous potassium carbonate (2 equiv) in dry *N*,*N*-dimethylacetamide (4 mL/equiv) or THF (for compounds **21**, **24**, and **25**) was heated at 50 °C with stirring for 18 h. The mixture was diluted with ethyl acetate, washed with water, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford 2,3-dimethoxyquinoxalines **18**−**25**. The reaction of 1,2,4-triazole with **35** yielded a mixture of **24** and **25** which were separated by flash chromatography (gradient elution with ethyl acetate/hexane). The structures of **24** and **25** were confirmed by Rotating Frame Overhauser Enhancement Spectroscopy, which confirmed the proximity of the triazole methyl group to the methylene in **25**.

Physical and Spectroscopic Data for 2,3-Dimethoxyquinoxalines 18−25. 18: colorless solid, yield 68%; ^{1}H NMR (300 MHz, $CDCl_3$) 4.15 (3H, s), 4.22 (3H, s), 5.80 (2H, s), 6.97 (1H, s), 7.09 (1H, s), 7.74 (1H, s), 7.95 (1H, s). LRMS *m*/*z* (thermospray) 338 (M^+).

19: colorless solid, yield 69%; ^{1}H NMR (300 MHz, $CDCl_3$) 4.16 (3H, s), 4.17 (3H, s), 6.03 (2H, s), 6.20 (1H, m), 7.41 (1H, d, J 2 Hz)), 7.49 (1H, d, J 2 Hz), 7.94 (1H, s). LRMS *m*/*z* (thermospray) 338 (M^+).

20: colorless solid, yield 58%; ^{1}H NMR (300 MHz, $CDCl_3$) 4.15 (6H, s), 6.05 (2H, s), 7.85 (1H, s), 7.95 (1H, s), 8.10 (1H, s). LRMS *m*/*z* (thermospray) 340 (MH^+).

21: colorless solid, yield 36%; ^{1}H NMR (300 MHz, $CDCl_3$) 4.15 (6H, s), 6.28 (2H, s), 7.50 (1H, s), 7.63 (1H, s), 7.97 (1H, s). LRMS *m*/*z* (thermospray) 339 (M^+).

22: colorless solid, yield 37%; ^{1}H NMR (300 MHz, $CDCl_3$) 4.16 (3H, s), 4.22 (3H, s), 5.85 (2H, s), 7.97 (1H, s), 8.32 (2H, s). LRMS *m*/*z* (thermospray) 340 (MH^+).

23: colorless solid, yield 68%, mp 180 °C, ^{1}H NMR (300 MHz, $CDCl_3$) 2.42 (3H, s), 4.10 (3H, s), 4.16 (3H, s), 5.65 (2H, s), 6.55 (1H, s), 6.80 (1H, s), 7.96 (1H, s). LRMS *m*/*z* (thermospray) 353 (MH^+). Anal. ($C_{15}H_{14}Cl_2N_4O_2$) C,H,N.

24: colorless solid, yield 33%; ^{1}H NMR (300 MHz, $CDCl_3$) 2.35 (3H, s), 4.15 (6H, s), 5.95 (2H, s), 7.90 (1H, s), 7.97 (1H, s). LRMS *m*/*z* (thermospray) 354 (MH^+).

25: colorless solid, yield 23%; ^{1}H NMR (300 MHz, $CDCl_3$) 2.61 (3H, s), 4.10 (3H, s), 4.15 (3H, s), 5.90 (2H, s), 7.71 (1H, s), 7.97 (1H, s). LRMS *m*/*z* (thermospray) 353 (M^+).

5-Bromomethyl-6,7-dichloro-2,3-dimethoxyquinoxaline (**35**). A solution of 2,4,5-trichloronitrobenzene (**36**) (103 g, 0.46 mol) and *tert*-butyl chloroacetate (79 mL, 0.55 mol) in dry tetrahydrofuran (400 mL) was added dropwise over 30 min to a solution of potassium *tert*-butoxide (128 g, 1.14 mol) in dry tetrahydrofuran (800 mL) with stirring under nitrogen, keeping the temperature at −40 °C. After the addition was complete, the resulting dark blue solution was stirred for a further 30 min. The mixture was poured into 0.5 M hydrochloric acid (2 L), and the product was extracted into ethyl acetate (2.5 and 1 L). The combined organic solutions were dried ($MgSO_4$) and evaporated onto silica gel (70−200 μ, 200 g). The silica gel was applied to the top of a silica gel chromatography column (800 g), and the product was eluted using a hexane/ethyl acetate gradient. Product-containing fractions were combined and evaporated to give a yellow solid, which was triturated with hexane to give **37** (91.8 g, 59%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 1.42 (9H, s), 3.73 (2H, s), 7.60 (1H, s). LRMS *m*/*z* (thermospray) 357 (MNH_4^+). Anal. ($C_{12}H_{12}Cl_3NO_4$) C,H,N.

A mixture of compound **37** (123 g, 0.361 mol) and saturated aqueous ammonia (300 mL) in 2-methoxyethanol (360 mL) was heated in an autoclave at 150 °C for 72 h. The resulting viscous, black mixture was diluted with water (1 L) and ethyl acetate (1 L) and filtered through Arbocel filter aid. The dark red filtrate was separated, and the aqueous layer was extracted with ethyl acetate (2 × 1 L). The combined organic solutions were washed with brine (1 L), dried ($MgSO_4$), and evaporated onto silica gel (70−200 μ, 200 g). The silica gel was applied to the top of a chromatography column containing silica gel (40−60 μ, 800 g). Elution with hexane/ethyl acetate (98:2−92:8) gave **38** as a bright orange solid (39.7 g), which was contaminated with 5-amino-3,6-dichloro-2-nitrotoluene (14%). This mixture was carried onto the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) 2.48 (3H, s), 4.80 (2H, s), 6.82 (1H, s).

A solution of sodium dithionite (94 g, 0.54 mol) in water (1 L) was added to a stirred mixture of **38** (39.7 g, 0.18 mol) and potassium bicarbonate (94 g, 0.94 mmol) in methanol (1 L) at room temperature. After 30 min, the mixture was concentrated under reduced pressure, and the resulting suspension was extracted with ethyl acetate (total of 700 mL). The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 2,3-diamino-5,6-dichlorotoluene (26.1 g, 38% over two steps) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) 2.28 (3H, s), 3.36 (2H, br s), 3.42 (2H, br s), 6.72 (1H, s). LRMS *m*/*z* (thermospray) 191 (M^+).

A mixture of 2,3-diamino-5,6-dichlorotoluene (21.6 g, 0.137 mol) and oxalic acid (18.45 g, 0.206 mol) in hydrochloric acid (4 M, 900 mL) was heated at reflux for 6 h, cooled, and filtered. The dark brown solid was suspended in diethyl ether, filtered, and washed with more ether to give **39** (22.06 g, 66%). ^{1}H NMR (300 MHz, DMSO-d_6) 2.40 (3H, s), 7.14 (1H, s), 11.37 (1H, s), 11.94 (1H, s). LRMS *m*/*z* (thermospray) 262 (MNH_4^+).

A mixture of **39** (22.06 g, 90 mmol), thionyl chloride (300 mL), and dimethylformamide (1 mL) was heated at reflux for 3 h, cooled, and poured slowly into iced water. The resulting dark yellow precipitate was filtered off to give 5-methyl-2,3,6,7-tetrachloroquinoxaline (24.42 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) 2.85 (3H, s), 8.02 (1H, s). LRMS *m*/*z* (thermospray) 280 (MH^+). Anal. ($C_9H_4Cl_4N_2$) C,H,N.

A solution of sodium methoxide (38 mL, 25% solution in methanol, 175 mmol) was added over 10 min to a solution of 5-methyl-2,3,6,7-tetrachloroquinoxaline (21 g, 74 mmol) in dry tetrahydrofuran (200 mL) at 20 °C. There was a mildly exothermic reaction followed by formation of a precipitate. After 1 h the mixture was diluted with ethyl acetate (3 L), washed with water (1 L), dried ($MgSO_4$), and concentrated under reduced pressure to give **40** (20.3 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) 2.75 (3H, s), 4.15 (3H, s), 4.18 (3H, s), 7.78

(1H, s). LRMS *m/z* (thermospray) 273 (MH^+). Anal. ($C_{11}H_{10}Cl_2N_2O_2$) C,H,N.

A mixture of **40** (22.0 g, 80.5 mmol), *N*-bromosuccinimide (17.2 g, 96.6 mmol), and α,α-azoisobutyronitrile (1.3 g, 8.0 mmol) was heated at reflux in 1,1,1-trichloroethane (400 mL) for 4 h under irradiation from a 500 W sunlamp. The mixture was cooled, silica gel (50 g, 60−230 μ) was added, and the solvent was removed under reduced pressure. The residue was applied to the top of a silica gel chromatography column, and the product was eluted using a hexane/ethyl acetate gradient. The product was triturated with hexane to give **35** (25.3 g, 87%) as a fluffy white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 4.15 (3H, s), 4.22 (3H, s), 5.20 (2H, s), 7.89 (1H, s). Anal. ($C_{11}H_9BrCl_2N_2O_2$) C,H,N.

Preparation of Compounds 26 and 27. A mixture of **35** (2.11 g, 6.00 mmol), methyl 1,2,3-triazole-4-carboxylate (1.07 g, 8.4 mmol), and anhydrous potassium carbonate (1.66 g, 12 mmol) in dry tetrahydrofuran (25 mL) was heated at reflux for 18 h, cooled, and poured into water, and the solid was filtered off. Purification of the solid by flash chromatography (gradient elution with hexane/dichloromethane) gave **41** (1.278 g, 54%), R_f = 0.3 (silica gel, hexane:ethyl acetate = 1:1), as the slowest eluted of the three product isomers. ^{1}H NMR (300 MHz, $CDCl_3$) 3.90 (3H, s), 4.11 (3H, s), 4.15 (3H, s), 6.29 (2H, s), 7.93 (1H, s), 8.00 (1H, s). *m/z* (thermospray) 398 (MH^+). The structure was verified using 2D ROESY NMR, which confirmed that the triazole proton was adjacent to the methylene to which the triazole is attached.

A solution of diisobutylaluminum hydride (1 M in dichloromethane, 9 mL, 9 mmol) was added dropwise to a stirred suspension of **41** (1.087 g, 2.73 mmol) under nitrogen at −78 °C. After 2.25 h, methanol (5 mL) was added, followed by saturated aqueous ammonium chloride (25 mL) 5 min later. The mixture was allowed to warm to room temperature and filtered through Arbocel filter aid, washing the filter cake with dichloromethane. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure to give **42** (981 mg, 98%), as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 4.13 (3H, s), 4.15 (3H, s), 6.30 (2H, s), 7.99 (1H, s), 8.0 (1H, s), 10.08 (1H, s). *m/z* (thermospray) 370 (MH^+).

A mixture of **42** (200 mg, 0.54 mmol), diethylamine (68 μL, 0.65 mmol), and glacial acetic acid (31 μL, 0.54 mmol) in anhydrous THF (3 mL) was treated with sodium triacetoxyborohydride (172 mg, 0.81 mmol) at room temperature with stirring. After 2 h, the solution was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution with ethyl acetate/methanol) to give **26** (175 mg, 74%), as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) 1.02 (6H, t, J 7 Hz), 2.49 (4H, q, J 7 Hz), 3.69 (2H, s), 4.15 (6H, s), 6.23 (2H, s), 7.96 (1H, s). *m/z* (thermospray) 425 (MH^+).

Similarly, reaction of **42** with *N*-methylpiperazine gave **27** (124 mg, 55%), as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 2.35 (3H, s), 2.60 (8H, br s), 3.65 (2H, s), 4.15 (6H, s), 6.23 (2H, s), 7.44 (1H, br s), 7.97 (1H, s). *m/z* (thermospray) 452 (MH^+).

6,7-Dichloro-[5-(1-propylimidazol-4-yl)methyl]-2,3-dimethoxyquinoxaline (**28**). A 50% aqueous suspension of Raney nickel (0.6 mL) was added to a solution of **44** (350 mg, 0.85 mmol) in ethanol (6 mL), and the mixture was heated under reflux for 16 h. Further amounts of Raney nickel suspension were added as follows (mL/total reaction time): 0.3/16 h, 0.6/30 h. After 36 h total reaction time, starting material had been consumed, so the mixture was cooled and filtered through Arbocel filter aid, washing with dichloromethane. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution with ethyl acetate/dichloromethane) to give a white solid (228 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) 0.87 (3H, t, J 7 Hz), 2.72 (2H, sextet, J 7 Hz), 3.74 (2H, t, J 7 Hz) 4.15 (6H, s), 4.68 (2H, s), 6.40 (1H, s), 7.33 (1H, s), 7.82 (1H, s). *m/z* (thermospray) 381 (MH^+).

[5-(3-Chloro-2-oxoprop-1-yl)]-6,7-dichloro-2,3-dimethoxyquinoxaline (**43**). Zinc dust (2.234 g, 34.1 mmol) was suspended in anhydrous THF (50 mL) under nitrogen. 1,2-Dibromoethane (273 μL) was added, and the mixture was heated to reflux for 1 min. After being cooled, chlorotrimethylsilane (341 μL) was added. A solution of **35** (6.00 g, 17.1 mmol) in anhydrous THF (100 mL) was added with sonication at room temperature over 45 min. Sonication was continued for 1.5 h. In a separate flask, tris(benzylideneacetone)dipalladium (0) (117 mg, 0.25 mmol) was added to a solution of tri-(2-furyl)phosphine (239 mg, 2.0 mmol) in anhydrous THF (3 mL) under nitrogen with stirring. The solution of the organozinc reagent was added by syringe to the palladium catalyst solution, and finally chloracetyl chloride (2.06 mL, 25.6 mmol) was added. The mixture was stirred for 45 min at room temperature, poured into saturated aqueous ammonium chloride (300 mL), and extracted with dichloromethane (3 × 330 mL). The extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with hexane:ethyl acetate = 9:1) to give an off-white solid (4.215 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) 4.10 (3H, s), 4.15 (3H, s), 4.24 (2H, s), 4.63 (2H, s), 7.91 (1H, s). *m/z* (thermospray) 349 (MH^+). $\nu_{max.}$ (KBr disk) 2990, 2950, 1730, 1607, 1510, 1407, 1332, 1246, 1228, 988, 888 cm^{-1}.

6,7-Dichloro-[(6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-2-yl)methyl]-2,3-dimethoxyquinoxaline (44). Anhydrous potassium carbonate (373 mg, 2.7 mmol) was added to a stirred solution of 2-amino-5,6-dihydro-4H-1,3-thiazine hydrobromide (496 mg, 2.7 mmol) at room temperature. After 45 min, **43** (524 mg, 1.5 mmol) and tetra-*n*-butylammonium bromide (484 mg, 1.5 mmol) were added, and the resulting mixture was heated at 80 °C for 2 h. The mixture was cooled, diluted with ethyl acetate, and washed with saturated aqueous sodium bicarbonate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient elution with dichloromethane/ethyl acetate) to give an off-white solid (353 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) 2.25 (2H, m), 3.10 (2H, m), 3.85 (2H, m) 4.11 (3H, s), 4.15 (3H, s), 4.60 (2H, s), 6.16 (1H, s), 7.83 (1H, s). *m/z* (thermospray) 411 (MH^+).

6,7-Dichloro-2,3-dimethoxy-[5-(2-pyridyl)methyl]quinoxaline (**29**). Zinc dust (131 mg, 2.0 mmol) was suspended in anhydrous THF (3 mL) under nitrogen. 1,2-Dibromoethane (16 μL) was added, and the mixture was heated to reflux for 1 min. After being cooled, chlorotrimethylsilane (40 μL) was added. A solution of **35** (352 mg, 1.0 mmol) in anhydrous THF (10 mL) was added with sonication at room temperature over 20 min. The mixture was stirred for 15 min and then allowed to stand. In a separate flask, tris(benzylideneacetone)dipalladium(0) (7 mg, 0.0076 mmol) was added to a solution of tri-(2-furyl)phosphine (14 mg, 0.061 mmol) in anhydrous THF (1 mL) under nitrogen with stirring. The solution of the organozinc reagent was added by syringe to the palladium catalyst solution, and finally 2-bromopyridine (114 μL, 1.2 mmol) was added. The mixture was stirred at reflux for 60 min, cooled, poured into saturated aqueous sodium bicarbonate (30 mL), and extracted with dichloromethane (3 × 25 mL). The extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give an off-white solid (205 mg, 59%), mp 126−8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) 4.00 (3H, s), 4.13 (3H, s), 6.88 (1H, d J 8 Hz), 7.06 (1H, dd, J 5 and 7 Hz), 7.47 (1H, dt, J 2 and 8 Hz), 7.88 (1H, s), 8.51 (1H, appar. d J 5 Hz).

6,7-Dichloro-2,3-dimethoxy-[5-(2-methyltetrazol-5-yl)-methyl]quinoxaline (30). Sodium cyanide (2.06 g, 42 mmol) was added to a suspension of **35** (10.0 g, 28 mmol) in 2-propanol/water (4:1, 300 mL), and the mixture was heated at reflux for 1h. After being cooled, the mixture was diluted with water (400 mL) and extracted with ethyl acetate (3 × 400 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was triturated with ether (100 mL), filtered, and dried to give **45** (6.89 g, 81%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$)

4.15 (3H, s), 4.20 (3H, s), 4.38 (2H, s), 7.92 (1H, s). *m/z* (thermospray) 298 (MH^+), $\nu_{max.}$ (KBr) 2270 cm^{-1}.

A solution of azidotributyltin (800 mg, 2.41 mmol) in toluene (5 mL) was added to a suspension of **45** (600 mg, 2.0 mmol) in toluene (20 mL), and the mixture was heated at reflux under nitrogen for 17 h. More azidotributyltin (400 mg, 1.2 mmol) was added, and heating was continued for a further 25 h. The mixture was cooled, concentrated under reduced pressure, and partitioned between water and 5% methanol in dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by repeated flash chromatography gave two fractions: the desired tetrazole **46** (132 mg) and its tributyltin derivative. The latter was dissolved in dichloromethane, washed with 1 M hydrochloric acid, dried ($MgSO_4$), and concentrated under reduced pressure. The residues were redissolved in 10% methanol/dichloromethane and washed with 5% aqueous potassium fluoride. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. Finally, trituration with acetonitrile gave additional **46** (89 mg). The total yield was 221 mg (32%). ^{1}H NMR (300 MHz, DMSO-d_6) 3.93 (3H, s), 4.05 (3H, s), 4.9 (2H, s), 8.06 (1H, s), *m/z* (thermospray) 341 (MH^+).

A mixture of **46** (175 mg, 0.5 mmol), iodomethane (34 μL, 79 mg, 0.56 mmol), and anhydrous potassium carbonate (77 mg, 0.56 mmol) in anhydrous DMF (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure, diluted with water (5 mL), and extracted with ethyl acetate (10 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography (elution with dichloromethane then dichloromethane:methanol = 99:1) to give **30** (76 mg 41%) as the faster-running of the two tetrazole isomers. ^{1}H NMR (300 MHz, DMSO-d_6) 4.07 (3H, s), 4.16 (3H, s), 4.22 (3H, s), 4.98 (2H, s), 7.87 (1H, s), *m/z* (thermospray) 355 (MH^+).

Method C: Preparation of Compounds 22 and 31−34. A mixture of **35** or **51** (1 equiv) and the heterocycle (ca. 20 equiv) was heated without solvent for 30 min at 100 °C (for reaction with imidazole or 1,2,3-triazole) or 140 °C (for reaction with 1,2,4-triazole) and then cooled. The mixture was partitioned between brine and dichloromethane. The combined organic extracts were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Crude products were purified by flash chromatography (gradient elution with dichloromethane/methanol). The reaction of 1,2,4-triazole with **51** afforded a mixture of **33** and **34** which was separated by flash chromatography (gradient elution with dichloromethane/methanol).

Physical and Spectroscopic Data for 2,3-Dimethoxyquinoxalines 31−34. 31: colorless oil, yield 70%, ^{1}H NMR (300 MHz, $CDCl_3$) 0.92 (3H, t), 2.76 (1H, m), 2.91 (1H, m), 4.08 (3H, s), 4.12 (3H, s), 6.34 (1H, m), 6.98 (1H, s), 7.01 (1H, s), 7.78 (1H, s), 7.93 (1H, s). LRMS *m/z* (thermospray) 367 (MH^+).

32: colorless oil, yield 32%, ^{1}H NMR (300 MHz, $CDCl_3$) 0.99 (3H, t), 2.98 (2H, m), 3.98 (3H, s), 4.14 (3H, s), 6.79 (1H, m), 7.60 (1H, s), 7.63 (1H, s), 7.97 (1H, s). LRMS *m/z* (thermospray) 368 (MH^+).

33: colorless solid, yield 19%, ^{1}H NMR (300 MHz, $CDCl_3$) 1.01 (3H, t), 2.86 (2H, m), 4.02 (3H, s), 4.15 (3H, s), 6.61 (1H, m), 7.84 (1H, s), 7.97 (1H, s), 8.32 (1H, s). LRMS *m/z* (thermospray) 368 (MH^+).

34: colorless foam, yield 32%, ^{1}H NMR (300 MHz, $CDCl_3$) 0.98 (3H, t), 2.74 (1H, m), 2.89 (1H, m), 4.05 (3H, s), 4.16 (3H, s), 6.40 (1H, m), 7.98 (1H, s), 8.31 (2H, s). LRMS *m/z* (thermospray) 368 (MH^+).

5-(1-Bromoprop-1-yl)-6,7-dichloro-2,3-dimethoxyquinoxaline (**51**). A mixture of 6,7-dichloro-5-nitroquinoxalin-2,3-dione (**47**) (84 g, 0.34 mol), thionyl chloride (840 mL), and dimethylformamide (0.5 mL) was heated at reflux for 3 h, cooled, and concentrated under reduced pressure. Ethyl acetate (300 mL) was added and removed under reduced pressure, followed by petroleum ether (bp 100−120 °C). The solid residue was recrystallized from hot petroleum ether (bp 100−120 °C) to give 5-nitro-2,3,6,7-tetrachloroquinoxaline (78 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) 8.6 (1H, s).

Tin(II) chloride dihydrate (346.3 g, 1.54 mol) was added to a solution of 5-nitro-2,3,6,7-tetrachloroquinoxaline (96.2 g, 0.31 mol) in ethyl acetate (1.8 L). The mixture was heated under reflux for 4 h, cooled, and poured cautiously into an excess of aqueous saturated sodium bicarbonate. The mixture was filtered through Celite, washing well with ethyl acetate. The filter cake was macerated with more ethyl acetate, and the solid material was filtered off. The combined ethyl acetate solutions were dried ($MgSO_4$) and concentrated under reduced pressure to give 5-amino-2,3,6,7-tetrachloroquinoxaline (73.4 g, 84%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) 5.45 (2H, br s), 7.47 (1H, s). *m/z* (thermospray) 385 (MH^+).

A solution of sodium methoxide (25% solution in methanol, 274 mL, 1.28 mol) was added to a suspension of 5-amino-2,3,6,7-tetrachloroquinoxaline (72.4 g, 0.256 mol) in dry methanol (1 L), and the resulting mixture was heated at reflux for 30 min. The mixture was cooled and concentrated under reduced pressure, and the residue partitioned between water and ethyl acetate (total of 8 L). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by trituration with methanol, followed by dissolution in dichloromethane (2 L) and filtration. The filtrate was concentrated under reduced pressure to give **48** as a yellow solid (55.0 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) 4.13 (3H, s), 4.14 (3H, s), 5.07 (2H, br s), 7.26 (1H, s). *m/z* (thermospray) 274 (MH^+).

Compound **48** (38.12 g, 0.14 mol) was dissolved in acetone (2 L) and cooled to 0 °C. While being agitated using a mechanical stirrer, the solution was treated first with 2 M hydrochloric acid (396 mL, 0.79 mol) and then dropwise with 1 M aqueous sodium nitrite (208 mL, 0.28 mol) while maintaining the temperature of the mixture at 0 °C. After the additions were complete, the mixture was stirred for 15 min and then treated with 5 M aqueous potassium iodide (278 mL, 1.39 mol) maintaining the temperature below 5 °C. The mixture was then allowed to warm to 10 °C over 30 min. The acetone was removed under reduced pressure, and the residue was partitioned between water and ethyl acetate (total of 4 L). The organic solution was washed with 10% aqueous sodium bisulfite and saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (eluting with toluene) gave **49** (16.9 g, 32%). ^{1}H NMR (300 MHz, $CDCl_3$) 4.17 (3H, s), 4.24 (3H, s), 7.91 (1H, s).

A mixture of compound **49** (3.0 g, 7.8 mmol), tributylvinylstannane (4.94 g, 15.6 mmol), lithium chloride (991 mg, 23.4 mmol), and bis(triphenylphosphine)palladium(II) chloride (600 mg, 1.56 mmol) in dry dimethylformamide (100 mL) was heated at 100 °C for 1.5 h. The mixture was cooled and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (elution with toluene) to give 6,7-dichloro-2,3-dimethoxy-5-ethenylquinoxaline (1.76 g, 79%), as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 4.11 (3H, s), 4.14 (3H, s), 5.84 (1H, d, J 12 Hz), 6.33 (1H, d, J 18 Hz), 7.18 (1H, dd, J 12 and 18 Hz), 7.77 (1H, s). *m/z* (thermospray) 285 (MH^+).

A mixture of ozone and oxygen was bubbled gently through a stirred solution of 6,7-dichloro-2,3-dimethoxy-5-ethenylquinoxaline (1.76 g, 6.2 mmol) in chloroform (200 mL) at −60 °C until a blue color persisted. The solution was purged with nitrogen, and then triphenylphosphine (3.23 g, 12.3 mmol) was added. The mixture was allowed to warm to room temperature and stirred for a further 16 h. The chloroform was removed under reduced pressure, and the residue was purified by flash chromatography (eluting with toluene) to give 6,7-dichloro-2,3-dimethoxy-5-formylquinoxaline (1.60 g, 90%) as a fluffy white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 4.16 (6H, s), 8.08 (1H, s), 11.06 (1H, s). *m/z* (thermospray) 287 (MH^+).

Ethylmagnesium bromide (9.08 mL, 3 M in diethyl ether, 2.3 mmol) was added to a suspension of 6,7-dichloro-2,3-dimethoxy-5-formylquinoxaline (3.91 g, 13.62 mmol) in dry tetrahydrofuran (200 mL) under nitrogen at room tempera-

ture. After 30 min, saturated ammonium chloride (50 mL) was added, and the product was extracted into ethyl acetate (2 × 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residues was purified by flash chromatography (eluting with dichloromethane) to give **50** (1.86 g, 43%), as a pale yellow solid. ^{1}H NMR (300 $CDCl_3$) 1.05 (3H, t, J 7 Hz), 1.99 (2H, m), 4.11 (3H, s), 4.12 (3H, s), 5.40 (1H, m), 5.65 (1H, d, J 11 Hz), 7.81 (1H, s).

Carbon tetrabromide (466 mg, 1.41 mmol) was added in portions to a solution **50** (223 mg, 0.70 mmol) and triphenylphosphine (369 mg, 1.41 mmol) in dry dichloromethane (15 mL) at 20 °C. The mixture was stirred for 18 h, and the solvent was removed under reduced pressure. Purification by flash chromatography eluting with hexane/dichloromethane (1:1) gave the title compound (202 mg, 46%), as a white solid, mp 134−6 °C. ^{1}H NMR (300 MHz, $CDCl_3$) diastereomers evident: 0.96 (3H, t, J 7 Hz, CH_3 both isomers), 2.60 (2H, m, CH_2 minor), 2.80 (2H, m, CH_2 major), 4.13 (3H, s, CH_3O, both isomers), 4.18 (3H, s, CH_3O, minor), 4.20 (3H, s, CH_3O, major), 5.87 (1H, t, J 7 Hz, C*H* major rotamer), 6.68 (1H, t, J 7 Hz, C*H* minor), 7.87 (1H, s, aromatic H both isomers). *m*/*z* (thermospray) 379 (MH^+).

Acknowledgment. The authors wish to thank Drs. G.T.G. Swayne and S.G. Jezequel for advice and acknowledge the able assistance of Mrs. N.S. Crouch and Miss S.-A. Thompson for ligand binding assays, Mr. M. C. MacKenny for preparing some of the compounds, Dr. J. Urenjak and Miss M. A. Parry for in vitro functional assays, Mr. G. Fox and Dr. R. A. O'Donnell for in vivo assays, and Mr. R. Webster for pharmacokinetic measurements. We also thank the staff of the Physical Sciences Department for analytical data and measuring spectroscopic data.

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JM001124P