Aust. J. Chem., 1996, **49**, 451–461

Imidazo[1,2-*b*]pyridazines. XX*†
Syntheses of Some 3-Acylaminomethyl-6-(chloro, fluoro, methoxy, methylthio, phenoxy and phenylthio)-2-(phenyl, 4-t-butylphenyl, 4-cyclohexylphenyl, β-naphthyl and styryl)imidazo[1,2-*b*]pyridazines and Their Interaction with Central and Peripheral-Type Benzodiazepine Receptors

Gordon B. Barlin,[A] *Les P. Davies,*[B] *Peter W. Harrison,*[A] *Stephen J. Ireland*[A] *and Anthony C. Willis*[C]

[A] Division of Neuroscience, John Curtin School of Medical Research, Australian National University, G.P.O. Box 334, Canberra, A.C.T. 2601.
[B] Visual Sciences Group, Research School of Biological Sciences, Australian National University, G.P.O. Box 475, Canberra, A.C.T. 2601.
[C] Research School of Chemistry, Australian National University, Canberra, A.C.T. 0200.

Some 3-(aliphatic and aromatic)acylaminomethyl derivatives of 6-(chloro, fluoro, methoxy, methylthio, phenoxy and phenylthio)-2-(phenyl, 4-t-butylphenyl, 4-cyclohexylphenyl, β-naphthyl and styryl)imidazo[1,2-*b*]pyridazines have been prepared and tested for binding to central benzodiazepine receptors present in rat brain membrane, and to peripheral-type (mitochondrial) benzodiazepine receptors present in rat kidney membrane. Some of these compounds which contained 2-(4-t-butylphenyl, 4-cyclohexylphenyl and styryl) substituents bound strongly and selectively to peripheral-type benzodiazepine receptors. For example, 2-(4′-t-butylphenyl)-6-chloro-2-(4′′-fluorobenzamidomethyl)imidazo[1,2-*b*]pyridazine in tests for the displacement of [^{3}H]diazepam from both peripheral-type and central benzodiazepine receptors gave IC_{50} <1·0 nM and 9% displacement at 1000 nM, respectively. Steric effects appeared to be more restrictive in the interaction of these ligands with central benzodiazepine receptors rather than with peripheral-type benzodiazepine receptors; X-ray structure analyses of two typical compounds are reported.

Introduction

In recent years we have prepared a large number of substituted imidazo[1,2-*b*]pyridazines which have been examined as ligands for central benzodiazepine receptors.[1] The central benzodiazepine receptor (BZR) is associated with the $GABA_A$ receptor, a ligand-gated ion channel.[2,3] The known anxiolytic, anticonvulsant and sedative effects of the benzodiazepines result from their affinity for the BZR.[4]

Pharmacologically distinct benzodiazepine binding sites have also been found on peripheral tissues, in mitochondrial fractions from kidney, liver and lung; these demonstrate [^{3}H]diazepam binding ability.[5] The structure, function and location of this peripheral-type benzodiazepine receptor (PBR) has been reviewed by Gavish *et al.*[6] and Parola *et al.*[7] The PBR is thought to be involved in a number of biological processes, in particular cellular steroidogenesis[8,9] and accumulation in tumors.[10,11]

An examination of some of our imidazo[1,2-*b*]pyridazines, prepared previously, has now shown that some of those compounds which did not bind significantly to the BZR, do bind strongly to the PBR. In order to follow this lead we now report the preparation of some 3-acylaminomethylimidazo[1,2-*b*]pyridazines and the results of an examination of their ability to displace [^{3}H]diazepam from both the PBR and the BZR.

Syntheses

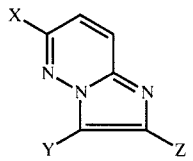
The imidazo[1,2-*b*]pyridazines reported in this paper were prepared by procedures similar to those previously

* Part XIX, *Aust. J. Chem.*, 1996, **49**, 443.
† Dedicated to Professor Miha Tišler, University of Ljubljana, in his 70th year.

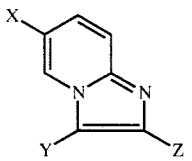
Manuscript received 11 September 1995

0004-9425/96/040451$05.00

used by us for analogous compounds.[12,13] The relevant 6-substituted pyridazin-3-amine was condensed with bromoacetyl compounds and gave the 2,6-disubstituted imidazo[1,2-*b*]pyridazine (1; Y = H); when these were heated with *N*-(hydroxymethyl)acylamines in acetic acid containing a catalytic amount of sulfuric acid, they gave the relevant 3-acylaminomethylimidazo[1,2-*b*]pyridazines (1; Y = CH_2NHCOR). In this way we prepared 3-(formamidomethyl, acetamidomethyl, propionamidomethyl, butylamidomethyl, benzamidomethyl, substituted benzamidomethyl and β-naphthamidomethyl) derivatives of 6-(chloro, fluoro, methoxy, methylthio, phenoxy and phenylthio)-2-(phenyl, 4-t-butylphenyl, 4-cyclohexylphenyl, β-naphthyl and styryl)imidazo[1,2-*b*]pyridazines.



(1)



(2)

The imidazo[1,2-*a*]pyridine (2; X = Cl, Y = H, Z = $C_6H_4Bu^t$-*p*) was prepared in an analogous manner from 5-chloropyridin-2-amine with α-bromo-4-t-butylacetophenone,[12] and the 3-benzamidomethyl group was inserted subsequently as above.

Biological Activity

The compounds reported in this paper were tested for their ability to displace [^{3}H]diazepam from the BZR in rat forebrain membrane and from the PBR in rat kidney membrane. Details of the test procedure for the determination of binding to the BZR have been reported previously,[14] and those for the determination of binding to the PBR[15] are given in the Experimental section of this paper. The results of these tests are recorded in Table 1 as IC_{50} values (nM) or as the percentage inhibition of binding at specific concentrations (in parentheses). The PBR binding data have been measured also for some compounds, for which we have previously described the syntheses and BZR affinities. Formula numbers are given for ease of comparison in the text and substituents are defined in Table 1. GBLD numbers are also recorded (as in earlier publications) in order to simplify comparisons in forthcoming publications.

An examination of the data from the imidazo[1,2-*b*]-pyridazines for binding to the BZR (Table 1) reveals for the 6-chloroimidazo[1,2-*b*]pyridazines a marked decrease in binding for those containing a 2-(4-t-butylphenyl), 2-(4-cyclohexylphenyl) or 2-styryl substituent relative to a 2-phenyl analogue. For example, compounds (12) and (7) had IC_{50} values of 1192 and 56 nM respectively, and compounds (13), (28), (34) and (8) gave 15[12] and 20%[13] displacement at 1000 nM, 17% displacement at 1000 nM and IC_{50} 140 nM,[16] respectively.

A similar situation also applied to the 6-fluoro compounds; cf. (40) and (36),[16] the 6-methoxy compounds (47), (50) and (43),[16] the 6-methylthio compounds (56), (58) and (52),[16] and the 6-phenylthio compounds (66) and (63).[16]

The large 2-(β-naphthyl) group as in compound (68) also markedly decreased binding to the BZR relative to its 2-phenyl analogue (63).[16]

The butyramidomethyl compound (7) was the most active of the series (3)–(8), whereas compound (10) differed little from its butyramidomethyl analogue (12).

The effect of substituents in 3-(substituted benzamidomethyl) compounds relative to 3-benzamidomethylimidazo[1,2-*b*]pyridazines was generally quite small; compounds (24) and (25) with *m*- and *p*-nitro groups bound most strongly.

The testing of imidazo[1,2-*b*]pyridazines for their ability to displace [^{3}H]diazepam from the PBR provided very interesting results. Whereas the 3-acylaminomethyl-2-phenylimidazo[1,2-*b*]pyridazines (3)–(8) bound to both the PBR and the BZR, with slightly greater affinity for the PBR, the situation changed dramatically in the 2-(4-t-butylphenyl) compounds (10)–(13). Each of these compounds in tests of binding to the PBR gave IC_{50} values ≤10 nM, whereas for binding to the BZR the IC_{50} values determined (or anticipated) were greater than 1000 nM, i.e. at least a hundredfold selectivity for the PBR.

Whereas 3-benzamidomethyl-2-(4′-t-butylphenyl)-6-chloroimidazo[1,2-*b*]pyridazine (13) (IC_{50} 6·2 nM) bound strongly and showed a marked preference for binding to the PBR, the 3-(substituted benzamidomethyl) analogues generally bound much less strongly with little preference for the PBR over the BZR. The marked exceptions to this were compounds (19) (IC_{50} <1·0 nM), which bound most strongly and with the greatest selectivity of the compounds reported in this paper, and compound (24) (IC_{50} 37 nM).

The 2-(4-cyclohexylphenyl) compounds (28)–(31) also exhibited significant selective binding to the PBR. The 3-(4-fluorobenzamidomethyl) compound (31) [like its 2-(4-t-butylphenyl) analogue (19)] bound more strongly than its isomers (29) or (30), but compound (29) also bound relatively strongly to the PBR.

The strong binding and high selectivity for the PBR were also shown by the 2-styryl compounds (33) and (34).

The 6-fluoro compounds (39)–(41) exhibited neither significant nor selective binding for the PBR.

Consistent with the results discussed above, the 6-chloro compounds (13) and (28) and the 6-methoxy compounds (47) and (50) showed selective binding to the PBR but the chloro substituent in compound (48) dramatically reduced binding. The 6-methylthio 2-(4-t-butylphenyl) compound (56) also exhibited significant selective binding to the PBR (IC_{50} 52 nM), but this was not shared by its 2-(4-cyclohexylphenyl) analogue (58).

Table 1. Results for the displacement of [^{3}H]diazepam from the BZR and the PBR by substituted imidazo[1,2-*b*]pyridazines

Assays for displacements from the BZR were conducted in the presence of 100 μM γ-aminobutyric acid under the standard assay conditions described in Barlin, G. B., Davies, L. P., and Ngu, M. M. L., *Aust. J. Chem.*, 1988, **41**, 1149. Assays for displacements from the PBR were conducted in the absence of γ-aminobutyric acid as described in the Experimental. For some compounds, tests were conducted over a range of concentrations, in which case the results are given as IC_{50} values (nM); other results are given as percentage inhibitions of control binding at 1000 nM (in parentheses)

Class of compound	GBLD No.	Compound	Substituents in (1) or (2) X (position 6)	Y (position 3)	Z (position 2)	IC_{50} (nM) (or percentage displacement[A]) BZR	PBR
Imidazo[1,2-*b*]pyridazine (1)	325	(3)	Cl	H	Ph	>3000[B]	0%
	937	(4)	Cl	CH_2NHCOH	Ph	847	(65%)
	318	(5)	Cl	$CH_2NHCOMe$	Ph	474[B]	177
	933	(6)	Cl	$CH_2NHCOEt$	Ph	198	32
	942	(7)	Cl	$CH_2NHCOPr$	Ph	56	36
	302	(8)	Cl	$CH_2NHCOPh$	Ph	140[B]	114
	699	(9)	Cl	H	$C_6H_4Bu^t$-*p*	(12%)[C]	(4%)
	934	(10)	Cl	$CH_2NHCOMe$	$C_6H_4Bu^t$-*p*	(39%)	10
	939	(11)	Cl	$CH_2NHCOEt$	$C_6H_4Bu^t$-*p*	1183	7
	941	(12)	Cl	$CH_2NHCOPr$	$C_6H_4Bu^t$-*p*	1192	9
	700	(13)	Cl	$CH_2NHCOPh$	$C_6H_4Bu^t$-*p*	(15%)[C]	6·2
	881	(14)	Cl	$CH_2NHCOC_6H_4Me$-*o*	$C_6H_4Bu^t$-*p*	(27%)	(60%)
	882	(15)	Cl	$CH_2NHCOC_6H_4Me$-*m*	$C_6H_4Bu^t$-*p*	(12%)	(85%)
	883	(16)	Cl	$CH_2NHCOC_6H_4Me$-*p*	$C_6H_4Bu^t$-*p*	(27%)	(39%)
	701	(17)	Cl	$CH_2NHCOC_6H_4F$-*o*	$C_6H_4Bu^t$-*p*	(18%)[C]	(69%)
	702	(18)	Cl	$CH_2NHCOC_6H_4F$-*m*	$C_6H_4Bu^t$-*p*	(42%)[D]	(52%)
	703	(19)	Cl	$CH_2NHCOC_6H_4F$-*p*	$C_6H_4Bu^t$-*p*	(9%)[C]	<1·0
	878	(20)	Cl	$CH_2NHCOC_6H_4Cl$-*o*	$C_6H_4Bu^t$-*p*	(25%)	(48%)
	879	(21)	Cl	$CH_2NHCOC_6H_4Cl$-*m*	$C_6H_4Bu^t$-*p*	(5%)	(63%)
	880	(22)	Cl	$CH_2NHCOC_6H_4Cl$-*p*	$C_6H_4Bu^t$-*p*	(19%)	(68%)
	884	(23)	Cl	$CH_2NHCOC_6H_4NO_2$-*o*	$C_6H_4Bu^t$-*p*	(10%)	(54%)
	885	(24)	Cl	$CH_2NHCOC_6H_4NO_2$-*m*	$C_6H_4Bu^t$-*p*	(49%)	37
	886	(25)	Cl	$CH_2NHCOC_6H_4NO_2$-*p*	$C_6H_4Bu^t$-*p*	(54%)	(50%)
	896	(26)	Cl	$CH_2NHCOC_{10}H_7$-β[E]	$C_6H_4Bu^t$-*p*	(30%)	(66%)
	704	(27)	Cl	H	$C_6H_4C_6H_{11}$-*p*[F]	(0%)[C]	(3%)
	705	(28)	Cl	$CH_2NHCOPh$	$C_6H_4C_6H_{11}$-*p*	(20%)[C]	24
	706	(29)	Cl	$CH_2NHCOC_6H_4F$-*o*	$C_6H_4C_6H_{11}$-*p*	(7%)	40
	707	(30)	Cl	$CH_2NHCOC_6H_4F$-*m*	$C_6H_4C_6H_{11}$-*p*	(8%)[C]	97
	708	(31)	Cl	$CH_2NHCOC_6H_4F$-*p*	$C_6H_4C_6H_{11}$-*p*	(19%)[C]	23
	695	(32)	Cl	H	CH=CHPh	(8%)[G]	(26%)
	897	(33)	Cl	$CH_2NHCOMe$	CH=CHPh	(2%)	24
	696	(34)	Cl	$CH_2NHCOPh$	CH=CHPh	(17%)[G]	5
	577	(35)	F	H	Ph	(21%)[B]	(18%)
	487	(36)	F	$CH_2NHCOPh$	Ph	68[B]	(66%)
	578	(37)	F	H	C_6H_4Me-*p*	383[B]	(13%)
	322	(38)	F	$CH_2NHCOPh$	C_6H_4Me-*p*	8[B]	168
	874	(39)	F	H	$C_6H_4Bu^t$-*p*	(9%)	(0%)
	887	(40)	F	$CH_2NHCOPh$	$C_6H_4Bu^t$-*p*	(16%)	(43%)
	888	(41)	F	$CH_2NHCOC_6H_4Cl$-*p*	$C_6H_4Bu^t$-*p*	(8%)	(29%)
	563	(42)	OMe	H	Ph	(18%)[B]	(16%)
	333	(43)	OMe	$CH_2NHCOPh$	Ph	79[B]	463
	566	(44)	OMe	H	Ph	1704[B]	(21%)
	570	(45)	OMe	$CH_2NHCOPh$	C_6H_4Me-*p*	23[B]	(71%)
	875	(46)	OMe	H	$C_6H_4Bu^t$-*p*	(14%)	(22%)
	890	(47)	OMe	$CH_2NHCOPh$	$C_6H_4Bu^t$-*p*	(52%)	32
	893	(48)	OMe	$CH_2NHCOC_6H_4Cl$-*p*	$C_6H_4Bu^t$-*p*	(0%)	(21%)
	894	(49)	OMe	H	$C_6H_4C_6H_{11}$-*p*	(0%)	(27%)
	891	(50)	OMe	$CH_2NHCOPh$	$C_6H_4C_6H_{11}$-*p*	(9%)	155
	557	(51)	SMe	H	Ph	(21%)[B]	(19%)
	332	(52)	SMe	$CH_2NHCOPh$	Ph	19·5[B]	(68%)
	558	(53)	SMe	H	C_6H_4Me-*p*	(35%)[B]	(11%)
	562	(54)	SMe	$CH_2NHCOPh$	C_6H_4Me-*p*	7[B]	(72%)

Table 1 *(Continued)*

Class of compound	GBLD No.	Compound	Substituents in (1) or (2) X (position 6)	Y (position 3)	Z (position 2)	IC50 (nM) (or percentage displacement[A]) BZR	PBR
Imidazo[1,2-*b*]pyridazine (1) *(continued)*	876	(55)	SMe	H	$C_6H_4Bu^t$-*p*	(13%)	(20%)
	889	(56)	SMe	$CH_2NHCOPh$	$C_6H_4Bu^t$-*p*	(45%)	52
	893	(57)	SMe	H	$C_6H_4C_6H_{11}$-*p*	(0%)	(25%)
	892	(58)	SMe	$CH_2NHCOPh$	$C_6H_4C_6H_{11}$-*p*	(6%)	(66%)
	921	(59)	OPh	H	$C_6H_4Bu^t$-*p*	(10%)	(5%)
	924	(60)	OPh	$CH_2NHCOMe$	$C_6H_4Bu^t$-*p*	(12%)	(12%)
	922	(61)	OPh	$CH_2NHCOPh$	$C_6H_4Bu^t$-*p*	(21%)	(40%)
	580	(62)	SPh	H	Ph	(43%)[B]	(31%)
	583	(63)	SPh	$CH_2NHCOPh$	Ph	9[B]	(65%)
	923	(64)	SPh	H	$C_6H_4Bu^t$-*p*	(0%)	(32%)
	929	(65)	SPh	$CH_2NHCOMe$	$C_6H_4Bu^t$-*p*	(39%)	(46%)
	926	(66)	SPh	$CH_2NHCOPh$	$C_6H_4Bu^t$-*p*	(11%)	(26%)
	928	(67)	SPh	H	$C_{10}H_7$-β	(5%)	(13%)
	927	(68)	SPh	$CH_2NHCOPh$	$C_{10}H_7$-β	(55%)	(46%)
Imidazo[1,2-*a*]pyridine (2)	873	(69)	Cl	H	$C_6H_4Bu^t$-*p*	(43%)	134
	877	(70)	Cl	$CH_2NHCOPh$	$C_6H_4Bu^t$-*p*	(3%)	487
Diazepam						4·3	73

[A] At 1000 nM. [B] Ref. 16. [C] Cf. ref. 12. [D] Differs from that reported in ref. 12. [E] β-Naphthyl. [F] *p*-Cyclohexylphenyl. [G] Ref. 13.

None of the 2-(4-t-butylphenyl) 6-phenoxy or 2-(4-t-butylphenyl or β-naphthyl) 6-phenylthio compounds (60) or (61), (65) or (66), or (68) respectively bound significantly or selectively to the PBR; this is probably related to steric effects at the 6-position.

The structures of compound (38) (which bound strongly to the BZR and also to the PBR) and compound (50) (which did not bind significantly to the BZR but did bind moderately to the PBR) were determined by X-ray structure analyses. The structure of the latter (Fig. 1) clearly illustrated the significant steric bulk of the 2-(4-cyclohexylphenyl) compound, which decreases binding to the BZR relative to 2-phenyl- or 2-(4-tolyl)-analogues.

In summary, it has been found that an increase in the size of the substituent in the 2-position of imidazo[1,2-*b*]pyridazine [from 2-phenyl to 2-(4-t-butylphenyl), 2-(4-cyclohexylphenyl), 2-styryl or 2-β-naphthyl] markedly decreases binding to the BZR, and in some circumstances the resulting compounds are strong and highly selective ligands for the PBR. This indicates that ligands for central benzodiazepine receptors are subject to greater steric constraints than those of peripheral-type benzodiazepine receptors.

An examination of the results in Table 1 for the imidazo[1,2-*a*]pyridines in binding to the BZR revealed that compound (69) had comparable activity to its 2-(4-tolyl) analogue (GBLD 648; 49% displacement at 1000 nM),[17] but compound (70), as might be expected from the results discussed above, bound much less strongly.

The results for binding to the PBR, however, did not parallel those for the imidazo[1,2-*b*]pyridazines. Whereas compound (69) bound much more strongly than compound (9), compound (70) bound *c.* 80-fold less strongly than compound (13).

Crystallography

Crystal Data for $C_{21}H_{17}FN_4O$ (1; X = F, Y = $CH_2NHCOPh$, Z = C_6H_4Me-p) (38)

$C_{21}H_{17}FN_4O$, *M* 360·39, monoclinic, space group $P2_1/c$, *a* 10·168(4), *b* 10·527(4), *c* 33·45(2) Å, β 90·85(4)°, *V* 3580(2) Å^3, D_c 1·337 g cm^{-3}, *Z* 8, *F*(000) 1504, μ_{Cu} 7·2 cm^{-1}. Crystal size 0·05 by 0·07 by 0·33 mm. Intensities of 5686 unique reflections were measured, of which 2259 with $I > 3\sigma(I)$ were considered observed. Weights in least-squares refinement were based on counter statistics. Final residuals *R* 0·049, R_w 0·045.

Crystal Data for $C_{27}H_{28}N_4O_2$ (1; X = OMe, Y = $CH_2NHCOPh$, Z = $C_6H_4C_6H_{11}$-p) (50)

$C_{27}H_{28}N_4O_2$, *M* 440·54, triclinic, space group $P\bar{1}$, *a* 9·931(1), *b* 16·412(3), *c* 16·694(3) Å, α 108·22(1), β 103·98(1), γ 103·73(1)°, *V* 2359·2(7) Å^3, D_c 1·240 g cm^{-3}, *Z* 4, *F*(000) 936, μ_{Cu} 6·4 cm^{-1}. Crystal size 0·18 by 0·20 by 0·23 mm. Intensities of 7004 unique reflections were measured, of which 4495 with $I > 3\sigma(I)$ were considered observed. Weights in least-squares refinement were based on counter statistics. Final residuals *R* 0·068, R_w 0·071.

Structure Determination

X-Ray intensity data sets were measured to $2\theta_{max}$ 120° at room temperature by using a Rigaku AFC6R diffractometer with graphite-monochromatized Cu Kα radiation and a 12 kW rotating anode generator. Azimuthal scans of several reflections indicated no need for an absorption correction for (38), but an analytical absorption correction was applied for (50). The structures were solved by direct methods. In both structures there are two molecules to the crystallographic asymmetric unit. In the latter the cyclohexyl group of one of the molecules is disordered over two orientations. Anisotropic displacement factors were used for full-occupancy non-hydrogen atoms and

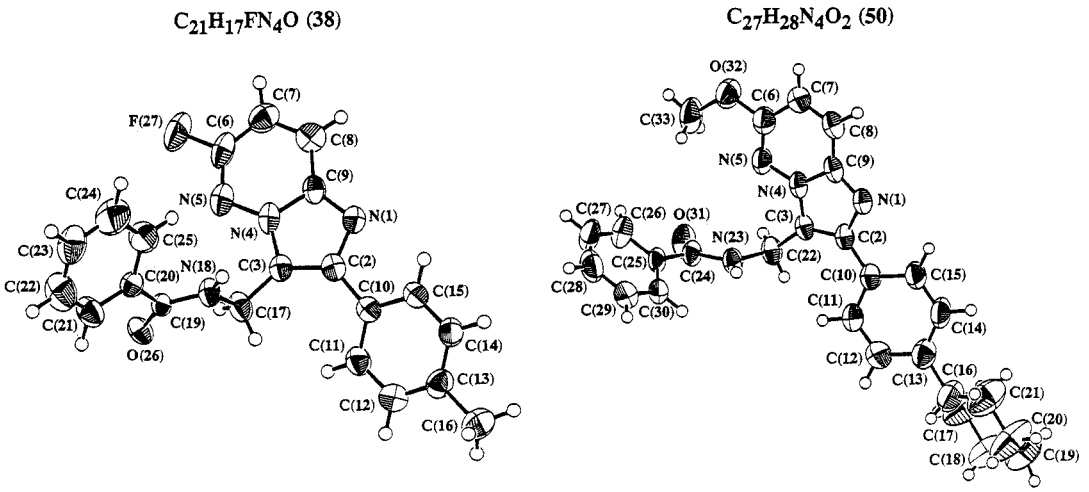


Fig. 1. Projected view of one molecule of $C_{21}H_{17}FN_4O$ (38) and one molecule of $C_{27}H_{28}N_4O_2$ (50) showing the labelling of non-hydrogen atoms. Thermal ellipsoids enclose 50% probability levels, except for hydrogen atoms which are drawn as circles of arbitrary small radius.

the isotropic form was used for the remainder. Hydrogen atoms were included at geometrically determined positions which were periodically recalculated; hydrogen atoms of the disordered cyclohexyl group have been omitted. Refinement was by full-matrix least-squares analysis, minimizing $\Sigma w(|F_o|-|F_c|)^2$. Computation was carried out with use of the teXsan program system.* Results are given in Fig. 1 and Tables 2–4; full details of data collection, refinement and results have been deposited along with structure factor listings.†

Experimental

All compounds were examined for the presence of impurities by thin-layer chromatography on alumina and by ^{1}H n.m.r. spectroscopy.

Solids for analysis were dried at 100–120°/710 mmHg for 2–24 h. Melting points are uncorrected and were taken in open Pyrex capillaries. The light petroleum used had b.p. 60–80°.

Analyses were performed by the Australian National University Analytical Services Unit.

^{1}H n.m.r. spectra (δ values) were recorded from $CDCl_3$ solutions (unless specified otherwise), with tetramethylsilane as internal standard, and at 90 MHz and 30° with a Jeol FX90Q Fourier-transform spectrometer possessing a digital resolution of 0·12 Hz.

Low-resolution mass spectra were recorded on an Incos data system attached to a VG-Micromass 7070 double-focusing mass spectrometer by using electron ionization (e.i.) at 70 eV (under the supervision of Dr J. K. MacLeod at the Research School of Chemistry).

2-(4′-t-Butylphenyl)-6-fluoroimidazo[1,2-b]pyridazine (39) and Related Compounds

A mixture of 6-fluoropyridazin-3-amine[18] (0·23 g), α-bromo-4-t-butylacetophenone[12] (0·51 g) and ethanol (15 ml) was refluxed for 3 h, sodium hydrogen carbonate (0·17 g) was added and the refluxing continued for 3 h. The ethanol was removed under vacuum and the residue extracted with chloroform. The extract was washed with water and evaporated to give a brown solid which was recrystallized from a mixture of acetone and light petroleum to give a light grey solid (0·30 g, 56%). It was then subjected to t.l.c. (alumina; chloroform/light petroleum, 1 : 1) and recrystallized from light petroleum to give white crystals of the *title compound*, m.p. 213–214° (Found: C, 71·1; H, 6·1; N, 15·5. $C_{24}H_{23}FN_4O$ requires C, 71·6; H, 5·8; N, 15·6%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 6·85, d, J 9·5 Hz, H7; 7·48, d, J 8·5 Hz, H3′,5′ (or 2′,6′); 7·88, d, J 8·5 Hz, H2′,6′ (or 3′,5′); 7·84–8·03, complex, H8; 8·12, s, H3. Mass spectrum m/z 269 (M, 45%), 254 (100), 113 (17).

In a similar manner from 6-methoxypyridazin-3-amine,[19,20] 6-methylthiopyridazin-3-amine,[21] 6-phenoxypyridazin-3-amine,[22] 6-phenylthiopyridazin-3-amine,[23] α-bromo-4-t-butylacetophenone,[12] α-bromo-4-cyclohexylacetophenone[12] and 2-bromoacetylnaphthalene [prepared by bromination of 2′-acetonaphthone at 0° in ether containing a little anhydrous aluminium chloride. It had m.p. 78–80° (lit.[24] 80°) and ^{1}H n.m.r.: δ 4·57, s, CH_2; 7·54–8·10, complex, H3,4,5,6,7,8; 8·52, br s, H1] were prepared the following compounds.

2-(4′-t-Butylphenyl)-6-methoxyimidazo[1,2-b]pyridazine (46) (55%), m.p. 126–128°, after t.l.c. (alumina; chloroform/light petroleum, 3:1) and recrystallization from light petroleum (Found: C, 71·8; H, 6·5; N, 14·7. $C_{17}H_{19}N_3O.0·15H_2O$ requires C, 72·9; H, 6·8; N, 14·8%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 4·00, s, OMe; 6·67, d, J 9·5 Hz, H7; 7·46, d, J 8·5 Hz, H3′,5′ (or 2′,6′); 7·81, d, J 9·5 Hz, H8; 7·86, d, J 8·5 Hz, H2′,6′ (or 3′,5′); 8·02, s, H3. Mass spectrum m/z 281 (M, 45%), 266 (100).

2-(4′-Cyclohexylphenyl)-6-methoxyimidazo[1,2-b]pyridazine (49) (52%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], m.p. 194–196° (from light petroleum) (Found: C, 73·4; H, 7·1; N, 13·4. $C_{19}H_{21}N_3O.0·2H_2O$ requires C, 73·4; H, 6·9; N, 13·5%). ^{1}H n.m.r.: δ 1·33–1·86, complex, cyclohexyl; 3·99, s, MeO; 6·67, d, J 9·5 Hz, H7; 7·28, d, J 8 Hz, H3′,5′ (or 2′,6′); 7·81, d, J 9·5 Hz, H8; 7·84, d, J 8 Hz, H2′,6′ (or 3′,5′); 8·00, s, H3. Mass spectrum m/z 307 (M, 100%), 264 (65), 238 (40).

2-(4′-t-Butylphenyl)-6-methylthioimidazo[1,2-b]pyridazine (55) (41%), m.p. 154–156° [after t.l.c. (alumina; chloroform/light petroleum, 1:1) and recrystallization from light petroleum] (Found: C, 68·8; H, 6·7; N, 14·2. $C_{17}H_{19}N_3S$ requires C, 68·7; H, 6·4; N, 14·1%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 2·61, s, MeS; 6·82, d, J 9·5 Hz, H7; 7·46, d, J 9 Hz, H3′,5′ (or 2′,6′); 7·71, d, J 9·5 Hz, H8; 7·88, d, J 9 Hz, H2′,6′ (or 3′,5′); 8·14, s, H3.

2-(4′-Cyclohexylphenyl)-6-methylthioimidazo[1,2-b]pyridazine (57) (65%) [after t.l.c. (alumina; chloroform/light petrol-

* teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation, The Woodlands, Texas, U.S.A. (1985 and 1992).
† Copies are available on application to the Australian Journal of Chemistry, P.O. Box 1139, Collingwood, Vic. 3066.

Table 2. Non-hydrogen atomic parameters for $C_{21}H_{17}FN_4O$ (38) and $C_{27}H_{28}N_4O_2$ (50)

In compound (38), atoms numbered 1–27 belong to molecule A and atoms 51–77 belong to molecule B. In compound (50), atoms numbered 1–33 belong to molecule A and atoms 34–66 belong to molecule B; carbon atoms labelled with suffix a have occupancy 0·51(2) and those with suffix b have occupancy 0·49(2). Estimated standard deviations in the least significant figure are given in parentheses. B_{eq} (Å^2) is the isotropic equivalent of the anisotropic displacement factor

$$B_{eq} = \tfrac{4}{3}(a^2\beta_{11} + b^2\beta_{22} + c^2\beta_{33} + 2ab\beta_{12} + 2ac\beta_{13} + 2bc\beta_{23})$$

	$C_{21}H_{17}FN_4O$ (38)					$C_{27}H_{28}N_4O_2$ (50)			
Atom	x	y	z	B_{eq}	Atom	x	y	z	B_{eq}
F(27)	0·6347(4)	0·8885(4)	0·0459(1)	7·2(1)	O(31)	0·5790(4)	0·6691(3)	0·6100(3)	6·1(1)
F(77)	0·1493(4)	0·9115(4)	0·0298(1)	6·8(1)	O(32)	0·2649(5)	0·8672(3)	0·6529(3)	6·3(1)
O(26)	0·4296(4)	0·5930(4)	0·1672(1)	3·9(1)	O(64)	0·0848(4)	0·9242(3)	0·1336(2)	5·9(1)
O(76)	−0·0760(4)	0·5657(4)	0·1700(1)	4·7(1)	O(65)	0·4248(5)	0·7572(3)	0·1655(3)	7·4(1)
N(1)	0·8834(5)	0·4452(5)	0·0458(1)	3·5(1)	N(1)	−0·0616(4)	0·5383(3)	0·6175(3)	4·1(1)
N(4)	0·7344(5)	0·5835(5)	0·0671(1)	3·7(1)	N(4)	0·1414(4)	0·6392(3)	0·6290(3)	4·1(1)
N(5)	0·6617(5)	0·6930(5)	0·0693(2)	4·5(2)	N(5)	0·2364(5)	0·7194(3)	0·6366(3)	4·5(1)
N(18)	0·6444(5)	0·5579(5)	0·1542(1)	3·6(1)	N(23)	0·3503(4)	0·5621(3)	0·5410(3)	4·2(1)
N(51)	0·3807(5)	0·4615(5)	0·0453(1)	3·6(1)	N(34)	0·7143(4)	1·0473(3)	0·1178(3)	4·1(1)
N(54)	0·2399(5)	0·6146(5)	0·0619(1)	3·4(1)	N(37)	0·5227(4)	0·9591(3)	0·1324(3)	4·1(1)
N(55)	0·1739(5)	0·7276(5)	0·0600(2)	4·2(1)	N(38)	0·4355(5)	0·8885(3)	0·1451(3)	4·8(1)
N(68)	0·1366(5)	0·5823(5)	0·1544(1)	3·4(1)	N(56)	0·2147(4)	0·9724(3)	0·0532(3)	4·1(1)
C(2)	0·8081(6)	0·3918(6)	0·0752(2)	3·3(2)	C(2)	0·0474(5)	0·4998(4)	0·6147(3)	3·9(1)
C(3)	0·7153(6)	0·4748(6)	0·0894(2)	3·3(2)	C(3)	0·1757(5)	0·5622(4)	0·6210(3)	3·9(1)
C(6)	0·7059(8)	0·7800(7)	0·0447(2)	5·0(2)	C(6)	0·1801(6)	0·7835(4)	0·6460(4)	5·1(2)
C(7)	0·8119(8)	0·7740(7)	0·0193(2)	5·2(2)	C(7)	0·0347(6)	0·7775(4)	0·6479(4)	5·4(2)
C(8)	0·8777(7)	0·6625(7)	0·0166(2)	4·4(2)	C(8)	−0·0565(6)	0·6958(4)	0·6368(4)	5·2(2)
C(9)	0·8384(6)	0·5626(6)	0·0414(2)	3·4(2)	C(9)	−0·0026(5)	0·6233(4)	0·6272(3)	4·1(1)
C(10)	0·8389(6)	0·2606(6)	0·0880(2)	3·3(2)	C(10)	0·0165(5)	0·4054(4)	0·6075(3)	4·2(1)
C(11)	0·7465(6)	0·1780(6)	0·1041(2)	4·2(2)	C(11)	0·0978(6)	0·3515(4)	0·5804(4)	5·4(2)
C(12)	0·7837(7)	0·0570(7)	0·1165(2)	4·8(2)	C(12)	0·0632(7)	0·2628(4)	0·5748(4)	6·1(2)
C(13)	0·9121(8)	0·0145(6)	0·1126(2)	4·4(2)	C(13)	−0·0566(7)	0·2208(4)	0·5955(4)	5·8(2)
C(14)	1·0020(7)	0·0952(6)	0·0951(2)	4·4(2)	C(14)	−0·1376(6)	0·2752(5)	0·6224(5)	6·4(2)
C(15)	0·9664(6)	0·2169(6)	0·0833(2)	3·7(2)	C(15)	−0·1028(6)	0·3646(4)	0·6287(4)	5·5(2)
C(16)	0·9526(8)	−0·1164(7)	0·1266(2)	6·8(2)	C(16)	−0·0925(8)	0·1237(5)	0·5871(5)	6·9(2)
C(17)	0·6134(6)	0·4712(6)	0·1206(2)	4·3(2)	C(17)	−0·0072(8)	0·1131(5)	0·6627(5)	9·4(2)
C(19)	0·5474(6)	0·6145(5)	0·1735(2)	3·0(2)	C(18)	−0·036(1)	0·0139(5)	0·6534(5)	9·4(3)
C(20)	0·5911(6)	0·7094(6)	0·2050(2)	3·2(2)	C(19)	−0·199(1)	−0·0376(5)	0·6198(6)	10·4(3)
C(21)	0·5164(7)	0·7276(7)	0·2385(2)	5·0(2)	C(20)	−0·282(1)	−0·0282(6)	0·5447(7)	11·9(3)
C(22)	0·5517(8)	0·8196(9)	0·2661(2)	6·5(2)	C(21)	−0·2519(8)	0·0714(5)	0·5566(6)	10·4(3)
C(23)	0·6590(9)	0·8934(7)	0·2605(2)	6·2(3)	C(22)	0·3269(5)	0·5627(4)	0·6246(3)	4·5(1)
C(24)	0·7349(9)	0·8769(8)	0·2278(3)	7·2(3)	C(24)	0·4741(5)	0·6203(4)	0·5419(4)	4·3(1)
C(25)	0·7009(7)	0·7826(7)	0·1998(2)	5·6(2)	C(25)	0·4718(5)	0·6202(4)	0·4520(4)	4·1(1)
C(52)	0·3048(6)	0·4224(6)	0·0765(2)	3·3(2)	C(26)	0·5397(6)	0·7025(4)	0·4488(4)	6·2(2)
C(53)	0·2166(6)	0·5161(6)	0·0877(2)	3·2(2)	C(27)	0·5359(8)	0·7083(5)	0·3681(6)	7·3(2)
C(56)	0·2164(7)	0·8008(6)	0·0319(2)	4·6(2)	C(28)	0·4673(8)	0·6322(6)	0·2901(5)	7·1(2)
C(57)	0·3198(7)	0·7796(6)	0·0059(2)	4·2(2)	C(29)	0·4023(7)	0·5492(4)	0·2927(4)	6·1(2)
C(58)	0·3820(6)	0·6663(6)	0·0080(2)	3·9(2)	C(30)	0·4048(6)	0·5440(4)	0·3738(4)	4·7(2)
C(59)	0·3413(6)	0·5786(6)	0·0368(2)	3·4(2)	C(33)	0·4064(7)	0·8706(4)	0·6426(4)	7·2(2)
C(60)	0·3241(6)	0·2946(6)	0·0932(2)	3·7(2)	C(35)	0·6047(5)	1·0858(3)	0·1157(3)	3·8(1)
C(61)	0·3025(7)	0·2670(7)	0·1333(2)	5·0(2)	C(36)	0·4824(5)	1·0304(3)	0·1247(3)	3·8(1)
C(62)	0·3255(8)	0·1444(8)	0·1478(2)	6·0(2)	C(39)	0·5005(7)	0·8303(4)	0·1532(4)	5·5(2)
C(63)	0·3724(8)	0·0496(7)	0·1234(3)	5·7(2)	C(40)	0·6440(7)	0·8336(4)	0·1507(4)	6·0(2)
C(64)	0·3956(7)	0·0785(7)	0·0847(2)	5·1(2)	C(41)	0·7244(6)	0·9042(4)	0·1379(4)	5·2(2)
C(65)	0·3733(7)	0·1992(6)	0·0696(2)	4·4(2)	C(42)	0·6625(6)	0·9697(4)	0·1285(3)	4·1(1)
C(66)	0·395(1)	−0·0830(8)	0·1403(3)	9·5(3)	C(43)	0·6319(5)	1·1757(3)	0·1111(3)	3·9(1)
C(67)	0·1060(6)	0·5195(6)	0·1157(2)	3·7(2)	C(44)	0·5226(6)	1·2072(4)	0·0821(4)	5·4(2)
C(69)	0·0368(7)	0·5991(6)	0·1788(2)	3·2(2)	C(45)	0·5571(7)	1·2945(5)	0·0811(5)	6·9(2)
C(70)	0·0660(7)	0·6605(6)	0·2188(2)	3·8(2)	C(46)	0·7003(8)	1·3517(4)	0·1090(5)	6·4(2)
C(71)	−0·0149(8)	0·6297(8)	0·2502(2)	6·1(2)	C(47)	0·8070(7)	1·3183(4)	0·1376(4)	6·1(2)
C(72)	0·008(1)	0·686(1)	0·2878(2)	7·3(3)	C(48)	0·7770(6)	1·2329(4)	0·1390(4)	4·9(1)
C(73)	0·107(1)	0·772(1)	0·2927(3)	7·1(3)	C(49a)	0·705(1)	1·4377(8)	0·085(1)	4·8(3)
C(74)	0·1857(9)	0·8019(8)	0·2620(3)	7·3(3)	C(49b)	0·771(2)	1·4587(9)	0·136(1)	5·4(4)
C(75)	0·1671(7)	0·7444(7)	0·2248(2)	5·2(2)	C(50a)	0·711(1)	1·5120(8)	0·1726(9)	4·5(3)
					C(50b)	0·644(2)	1·498(1)	0·139(1)	5·3(3)
					C(51a)	0·688(2)	1·596(1)	0·141(1)	5·6(4)
					C(51b)	0·752(2)	1·611(1)	0·175(1)	5·3(3)
					C(52a)	0·854(2)	1·634(1)	0·133(1)	7·1(5)
					C(52b)	0·750(2)	1·610(1)	0·075(1)	6·9(5)
					C(53a)	0·820(2)	1·553(1)	0·032(1)	6·1(4)
					C(53b)	0·889(2)	1·570(1)	0·076(1)	5·5(4)
					C(54a)	0·854(2)	1·4712(9)	0·073(1)	5·7(4)
					C(54b)	0·781(2)	1·454(1)	0·032(1)	5·8(4)
					C(55)	0·3394(5)	1·0375(3)	0·1317(3)	4·2(1)
					C(57)	0·0970(6)	0·9188(4)	0·0608(4)	4·3(1)
					C(58)	−0·0183(5)	0·8502(4)	−0·0257(4)	4·3(1)
					C(59)	−0·0919(7)	0·7672(4)	−0·0254(4)	5·9(2)
					C(60)	−0·1997(7)	0·7011(4)	−0·1032(5)	7·3(2)
					C(61)	−0·2376(7)	0·7169(5)	−0·1796(4)	6·5(2)
					C(62)	−0·1662(6)	0·8000(4)	−0·1792(4)	5·2(2)
					C(63)	−0·0555(6)	0·8661(4)	−0·1028(4)	4·5(1)
					C(66)	0·2762(8)	0·7512(5)	0·1642(6)	9·3(3)

eum, 3:1)], m.p. 174–176° (from light petroleum) (Found: C, 70·0; H, 6·3; N, 12·7. $C_{19}H_{21}N_3S.0·15H_2O$ requires C, 70·0; H, 6·6; N, 12·9%). ^{1}H n.m.r.: δ 1·33–1·85, complex, cyclohexyl; 2·61, s, MeS; 6·85, d, *J* 9·5 Hz, H 7; 7·29, d, *J* 8 Hz, H 3′,5′ (or 2′,6′); 7·73, d, *J* 9·5 Hz, H 8; 7·86, d, *J* 8 Hz, H 2′,6′ (or 3′,5′); 8·12, s, H 3. Mass spectrum *m/z* 323 (M, 100), 280 (30), 254 (28), 233 (35).

*2-(4′-t-Butylphenyl)-6-phenoxyimidazo[1,2-*b*]pyridazine* (59) (69%), m.p. 198–200° (from ethanol) (Found: C, 77·0; H, 6·1; N, 12·2. $C_{22}H_{21}N_3O$ requires C, 76·9; H, 6·2; N, 12·2%). ^{1}H n.m.r.: δ 1·35, s, CMe_3; 6·89, d, *J* 9·5 Hz, H 7; 7·27–8·03, complex, 2×ArH and H 3,8.

*2-(4′-t-Butylphenyl)-6-phenylthioimidazo[1,2-*b*]pyridazine* (64) (73%), m.p. 159–161° (from ethanol) (Found: C, 73·8; H,

Table 3. Selected bond lengths (Å) for $C_{21}H_{17}FN_4O$ (38) and $C_{27}H_{28}N_4O_2$ (50)

Estimated standard deviations in the least significant figure are given in parentheses

	$C_{21}H_{17}FN_4O$ (38)				$C_{27}H_{28}N_4O_2$ (50)		
Atoms	Distance	Atoms	Distance	Atoms	Distance	Atoms	Distance
F(27)–C(6)	1·354(7)	F(77)–C(56)	1·351(7)	O(31)–C(24)	1·217(6)	O(64)–C(57)	1·227(6)
O(26)–C(19)	1·234(6)	O(76)–C(69)	1·231(7)	O(32)–C(6)	1·383(6)	O(65)–C(39)	1·360(6)
N(1)–C(2)	1·375(7)	N(51)–C(52)	1·371(7)	O(32)–C(33)	1·446(7)	O(65)–C(66)	1·450(8)
N(1)–C(9)	1·326(7)	N(51)–C(59)	1·325(7)	N(1)–C(2)	1·380(6)	N(34)–C(35)	1·382(6)
N(4)–N(5)	1·373(7)	N(54)–N(55)	1·367(6)	N(1)–C(9)	1·319(6)	N(34)–C(42)	1·339(6)
N(4)–C(3)	1·381(7)	N(54)–C(53)	1·371(7)	N(4)–N(5)	1·375(5)	N(37)–N(38)	1·379(5)
N(4)–C(9)	1·390(7)	N(54)–C(59)	1·391(7)	N(4)–C(3)	1·360(6)	N(37)–C(36)	1·355(6)
N(5)–C(6)	1·314(9)	N(55)–C(56)	1·296(8)	N(4)–C(9)	1·383(6)	N(37)–C(42)	1·377(6)
N(18)–C(17)	1·477(7)	N(68)–C(67)	1·484(7)	N(5)–C(6)	1·289(7)	N(38)–C(39)	1·296(7)
N(18)–C(19)	1·328(7)	N(68)–C(69)	1·324(7)	N(23)–C(22)	1·467(6)	N(56)–C(55)	1·451(6)
C(2)–C(3)	1·375(8)	C(52)–C(53)	1·388(8)	N(23)–C(24)	1·359(6)	N(56)–C(57)	1·346(6)
C(2)–C(10)	1·479(8)	C(52)–C(60)	1·469(8)	C(2)–C(3)	1·390(6)	C(35)–C(36)	1·405(6)
C(3)–C(17)	1·483(8)	C(53)–C(67)	1·475(8)	C(2)–C(10)	1·466(7)	C(35)–C(43)	1·465(6)
C(6)–C(7)	1·384(9)	C(56)–C(57)	1·391(9)	C(3)–C(22)	1·486(6)	C(36)–C(55)	1·481(6)
C(7)–C(8)	1·354(9)	C(57)–C(58)	1·352(8)	C(6)–C(7)	1·432(7)	C(39)–C(40)	1·424(7)
C(8)–C(9)	1·402(8)	C(58)–C(59)	1·401(8)	C(7)–C(8)	1·356(7)	C(40)–C(41)	1·350(7)
C(13)–C(16)	1·511(9)	C(63)–C(66)	1·52(1)	C(8)–C(9)	1·396(7)	C(41)–C(42)	1·390(7)
C(19)–C(20)	1·515(8)	C(69)–C(70)	1·510(8)	C(13)–C(16)	1·501(8)	C(46)–C(49a)	1·58(1)
phenyl C–C	1·38(2)[A]	phenyl C–C	1·38(2)[A]			C(46)–C(49b)	1·60(1)
				C(24)–C(25)	1·495(7)	C(57)–C(58)	1·495(7)
				phenyl C–C	1·38(1)[A]	phenyl C–C	1·38(1)[A]
				cyclohexyl C–C	1·48(5)[A]	cyclohexyl C–C	1·66(7)[A]

[A] Average.

Table 4. Selected bond angles (degrees) for $C_{21}H_{17}FN_4O$ (38) and $C_{27}H_{28}N_4O_2$ (50)

Estimated standard deviations in the least significant figure are given in parentheses

	$C_{21}H_{17}FN_4O$ (38)				$C_{27}H_{28}N_4O_2$ (50)		
Atoms	Angle	Atoms	Angle	Atoms	Angle	Atoms	Angle
C(2)–N(1)–C(9)	105·5(5)	C(52)–N(51)–C(59)	105·7(5)	C(6)–O(32)–C(33)	114·8(5)	C(39)–O(65)–C(66)	115·6(5)
N(5)–N(4)–C(3)	125·9(5)	N(55)–N(54)–C(53)	126·7(5)	C(2)–N(1)–C(9)	106·3(4)	C(35)–N(34)–C(42)	105·9(4)
N(5)–N(4)–C(9)	125·6(6)	N(55)–N(54)–C(59)	125·2(5)	N(5)–N(4)–C(3)	124·5(4)	N(38)–N(37)–C(36)	123·6(4)
C(3)–N(4)–C(9)	108·5(5)	C(53)–N(54)–C(59)	108·0(5)	N(5)–N(4)–C(9)	126·0(5)	N(38)–N(37)–C(42)	126·1(4)
N(4)–N(5)–C(6)	111·2(6)	N(54)–N(55)–C(56)	112·5(6)	C(3)–N(4)–C(9)	109·6(4)	C(36)–N(37)–C(42)	110·2(4)
C(17)–N(18)–C(19)	119·7(5)	C(67)–N(68)–C(69)	116·5(5)	N(4)–N(5)–C(6)	113·0(5)	N(37)–N(38)–C(39)	111·9(4)
N(1)–C(2)–C(3)	112·2(6)	N(51)–C(52)–C(53)	111·4(5)	C(22)–N(23)–C(24)	121·3(4)	C(55)–N(56)–C(57)	121·3(4)
N(1)–C(2)–C(10)	118·1(6)	N(51)–C(52)–C(60)	119·5(6)	N(1)–C(2)–C(3)	110·7(5)	N(34)–C(35)–C(36)	110·4(4)
C(3)–C(2)–C(10)	129·6(6)	C(53)–C(52)–C(60)	129·1(6)	N(1)–C(2)–C(10)	119·2(4)	N(34)–C(35)–C(43)	119·5(4)
N(4)–C(3)–C(2)	103·8(5)	N(54)–C(53)–C(52)	104·5(5)	C(3)–C(2)–C(10)	130·1(5)	C(36)–C(35)–C(43)	130·0(5)
N(4)–C(3)–C(17)	120·5(6)	N(54)–C(53)–C(67)	121·4(6)	N(4)–C(3)–C(2)	104·0(4)	N(37)–C(36)–C(35)	104·0(4)
C(2)–C(3)–C(17)	135·7(6)	C(52)–C(53)–C(67)	133·6(6)	N(4)–C(3)–C(22)	120·0(5)	N(37)–C(36)–C(55)	120·7(4)
F(27)–C(6)–N(5)	112·4(7)	F(77)–C(56)–N(55)	112·1(6)	C(2)–C(3)–C(22)	135·9(5)	C(35)–C(36)–C(55)	135·2(5)
F(27)–C(6)–C(7)	118·6(8)	F(77)–C(56)–C(57)	119·4(7)	O(32)–C(6)–N(5)	118·2(5)	O(65)–C(39)–N(38)	117·3(5)
N(5)–C(6)–C(7)	129·0(7)	N(55)–C(56)–C(57)	128·4(7)	O(32)–C(6)–C(7)	114·9(6)	O(65)–C(39)–C(40)	115·3(6)
C(6)–C(7)–C(8)	118·0(7)	C(56)–C(57)–C(58)	117·8(6)	N(5)–C(6)–C(7)	126·9(6)	N(38)–C(39)–C(40)	127·4(5)
C(7)–C(8)–C(9)	117·8(6)	C(57)–C(58)–C(59)	118·3(6)	C(6)–C(7)–C(8)	117·7(6)	C(39)–C(40)–C(41)	118·2(5)
N(1)–C(9)–N(4)	110·0(6)	N(51)–C(59)–N(54)	110·4(6)	C(7)–C(8)–C(9)	118·6(5)	C(40)–C(41)–C(42)	118·0(5)
N(1)–C(9)–C(8)	131·7(6)	N(51)–C(59)–C(58)	131·9(6)	N(1)–C(9)–N(4)	109·5(5)	N(34)–C(42)–N(37)	109·4(5)
N(4)–C(9)–C(8)	118·2(6)	N(54)–C(59)–C(58)	117·7(6)	N(1)–C(9)–C(8)	132·8(5)	N(34)–C(42)–C(41)	132·2(5)
C(2)–C(10)–C(11)	123·6(6)	C(52)–C(60)–C(61)	122·4(6)	N(4)–C(9)–C(8)	117·7(5)	N(37)–C(42)–C(41)	118·4(5)
C(2)–C(10)–C(15)	118·1(6)	C(52)–C(60)–C(65)	119·7(6)	C(2)–C(10)–C(11)	124·6(5)	C(35)–C(43)–C(44)	123·6(5)
C(11)–C(10)–C(15)	118·3(6)	C(61)–C(60)–C(65)	117·7(6)	C(2)–C(10)–C(15)	119·6(5)	C(35)–C(43)–C(48)	118·7(5)
N(18)–C(17)–C(3)	112·1(5)	N(68)–C(67)–C(53)	114·4(5)	C(11)–C(10)–C(15)	115·8(5)	C(44)–C(43)–C(48)	117·8(5)
O(26)–C(19)–N(18)	124·0(6)	O(76)–C(69)–N(68)	122·3(6)	N(23)–C(22)–C(3)	110·8(4)	N(56)–C(55)–C(36)	112·7(4)
O(26)–C(19)–C(20)	121·0(6)	O(76)–C(69)–C(70)	120·3(6)	O(31)–C(24)–N(23)	123·3(5)	O(64)–C(57)–N(56)	122·8(5)
N(18)–C(19)–C(20)	115·0(6)	N(68)–C(69)–C(70)	117·4(6)	O(31)–C(24)–C(25)	122·0(5)	O(64)–C(57)–C(58)	121·6(5)
C(19)–C(20)–C(21)	119·9(6)	C(69)–C(70)–C(71)	117·5(7)	N(23)–C(24)–C(25)	114·6(5)	N(56)–C(57)–C(58)	115·6(5)
C(19)–C(20)–C(25)	120·9(6)	C(69)–C(70)–C(75)	123·1(6)	C(24)–C(25)–C(26)	117·3(5)	C(57)–C(58)–C(59)	116·7(5)
C(21)–C(20)–C(25)	119·1(6)	C(71)–C(70)–C(75)	119·5(7)	C(24)–C(25)–C(30)	123·6(5)	C(57)–C(58)–C(63)	123·7(5)
				C(26)–C(25)–C(30)	119·0(5)	C(59)–C(58)–C(63)	119·6(5)

6·2; N, 11·4. $C_{22}H_{21}N_3S$ requires C, 73·5; H, 5·9; N, 11·7%). ^{1}H n.m.r.: δ 1·35, s, CMe_3; 6·75, d, *J* 9·5 Hz, H 7; 7·39–7·92, complex, H 8 and 2×ArH; 8·10, s, H 3.

2-(Naphthalen-2′-yl)-6-phenylthioimidazo[1,2-b]-pyridazine (67)

A mixture of 6-phenylthiopyridazin-3-amine (1·0 g), 2-(bromoacetyl)naphthalene (1·41 g) and ethanol (40 ml) was refluxed with stirring in an oil bath at 95° for 1·5 h, cooled, sodium hydrogen carbonate (0·41 g) added and the refluxing continued for 14 h. The resulting mixture was then chilled and the solid (1·467 g, 84%) was filtered off and washed with ethanol, water and ethanol. A portion of this product was recrystallized from benzene to give the *title compound*, m.p. 181–183° (Found: C, 74·8; H, 4·3; N, 11·9. $C_{22}H_{15}N_3S$ requires C, 74·8; H, 4·3; N, 11·9%). ^{1}H n.m.r.: δ 6·80, d, *J* 9·5 Hz, H 7; 7·35–7·97, complex, H 8,3′,4′,5′,6′,7′,8′ and Ph; 8·24, s, H 3; 8·47, br s, H 1′.

6-Chloro-3-formamidomethyl-2-phenylimidazo[1,2-b]-pyridazine (4)

A mixture of *N*-(hydroxymethyl)formamide[25] (0·098 g), 6-chloro-2-phenylimidazo[1,2-*b*]pyridazine[26] (0·1 g), acetic acid (3·0 ml) and concentrated sulfuric acid (0·03 ml) was refluxed with stirring in an oil bath at 120° for 14 h. The solvent was evaporated, the residue diluted with water, adjusted to pH 10 and extracted with chloroform to give an oil (0·117 g). This was subjected to t.l.c. (alumina; chloroform) and the product at low R_F was recrystallized from benzene to give crystals of the *title compound* (0·006 g), m.p. 182–183° (Found: C, 58·3; H, 4·0; N, 19·4. $C_{14}H_{11}ClN_4O$ requires C, 58·6; H, 3·9; N, 19·5%). ^{1}H n.m.r.: δ 5·07, d, *J* 5·5 Hz, CH_2N; 7·10, d, *J* 9·5 Hz, H 7; 7·43–7·99, complex, Ph; 7·94, d, *J* 9·5 Hz, H 8; 8·26, br s, CHO.

6-Chloro-2-phenyl-3-propionamidomethylimidazo[1,2-b]-pyridazine (6)

A mixture of 6-chloro-2-phenylimidazo[1,2-*b*]pyridazine[26] (0·15 g), *N*-(hydroxymethyl)propionamide[27] (0·131 g), acetic acid (3·0 ml) and concentrated sulfuric acid (0·04 ml) was heated under reflux with stirring in an oil bath at 120° for 14 h. The acetic acid was evaporated, the residue diluted with water, adjusted to pH 11 and extracted with chloroform. The product (0·219 g) was subjected to t.l.c. (alumina; chloroform/cyclohexane, 2:1) and recrystallized from ethanol to give the *title compound* (0·110 g, 53%), m.p. 225–227° (Found: C, 61·0; H, 4·7; N, 17·7. $C_{16}H_{15}ClN_4O$ requires C, 61·0; H, 4·8; N, 17·8%). ^{1}H n.m.r.: δ 1·16, t, *J* 7·5 Hz, Me; 2·25, q, *J* 7·5 Hz, C**H**$_2$CH$_3$; 5·05, d, *J* 5·5 Hz, CH_2N; 6·25, br, NH; 7·11, d, *J* 9·5 Hz, H 7; 7·40–8·05, complex, ArH and H 8.

3-Acetamidomethyl-2-(4′-t-butylphenyl)-6-phenylthioimidazo-[1,2-b]pyridazine (65) and Related Compounds

A mixture of 2-(4′-t-butylphenyl)-6-phenylthioimidazo[1,2-*b*]pyridazine (0·120 g), *N*-(hydroxymethyl)acetamide[25] (0·080 g), acetic acid (3·0 ml) and concentrated sulfuric acid (0·05 ml) was heated under reflux with stirring in an oil bath at 120° for 14 h. The solvent was evaporated under reduced pressure, the residue diluted with water, adjusted to pH 10 and extracted with chloroform. The product (0·159 g) was subjected to t.l.c. (alumina; chloroform/light petroleum, 1:2) and then extracted (0·081 g, 56%) and recrystallized from cyclohexane to give the *title compound* (0·055 g), m.p. 146–147° (Found: C, 70·0; H, 6·4; N, 13·0. $C_{25}H_{26}N_4OS$ requires C, 69·7; H, 6·1; N, 13·0%). ^{1}H n.m.r.: δ 1·34, s, CMe_3; 1·84, s, MeCO; 4·79, d, *J* 5·5 Hz, CH_2; 6·09, br, NH; 6·85, d, *J* 9·5 Hz, H 7; 7·43–7·92, complex, 2×ArH and H 8.

In a similar manner from 6-chloro-2-phenylimidazo[1,2-*b*]pyridazine,[26] 2-(4′-t-butylphenyl)-6-chloroimidazo[1,2-*b*]pyridazine,[12] 6-chloro-2-styrylimidazo[1,2-*b*]pyridazine[13] and 2-(4′-t-butylphenyl)-6-phenoxyimidazo[1,2-*b*]pyridazine (see above) with *N*-(hydroxymethyl)acetamide,[25] *N*-(hydroxymethyl)propionamide[27] and *N*-(hydroxymethyl)butyramide[28] were prepared the following compounds.

3-Butyramidomethyl-6-chloro-2-phenylimidazo[1,2-b]pyridazine (7) (88%) [after t.l.c. (alumina; chloroform)], m.p. 213–215° (from ethanol) (Found: C, 61·8; H, 5·4; N, 17·0. $C_{17}H_{17}ClN_4O$ requires C, 62·1; H, 5·2; N, 17·0%). ^{1}H n.m.r.: δ 0·93, t, *J* 7·5 Hz, CH_3; 1·65, complex, C**H**$_2$CH$_3$; 2·16, q, *J* 7·5 Hz, CH_2CO; 5·00, d, *J* 5·5 Hz, CH_2N; 6·45, br, NH; 7·05, d, *J* 9·5 Hz, H 7; 7·41–7·98, complex, Ph; 7·86, d, *J* 9·5 Hz, H 8.

3-Acetamidomethyl-2-(4′-t-butylphenyl)-6-chloroimidazo-[1,2-b]pyridazine (10) (74%) [after t.l.c. (alumina; chloroform)], m.p. 261–262° (from ethanol) (Found: C, 63·4; H, 6·1. $C_{19}H_{21}ClN_4O$ requires C, 63·9; H, 5·9%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 2·03, s, MeCO; 5·02, d, *J* 5·5 Hz, CH_2; 7·08, d, *J* 9·5 Hz, H 7; 7·52, d, *J* 8·5 Hz, H 3′,5′ (or 2′,6′); 7·90, d, *J* 8·5 Hz, H 2′,6′ (or 3′,5′); 7·95, d, *J* 9·5 Hz, H 8.

2-(4′-t-Butylphenyl)-6-chloro-3-propionamidomethylimidazo[1,2-b]pyridazine (11) (70%) [after t.l.c. (alumina; chloroform/light petroleum, 2:3, then 1:1)], m.p. 237–239° (from ethanol) (Found: C, 64·5; H, 6·4; N, 15·1. $C_{20}H_{23}ClN_4O$ requires C, 64·8; H, 6·3; N, 15·1%). ^{1}H n.m.r.: δ 1·17, t, *J* 7·5 Hz, CH_3; 1·36, s, CMe_3; 2·26, q, *J* 7·5 Hz, C**H**$_2$CH$_3$; 5·05, d, *J* 5·5 Hz, CH_2N; 7·11, d, *J* 9·5 Hz, H 7; 7·49–8·06, complex, H 8,2′,3′,5′,6′.

2-(4′-t-Butylphenyl)-3-butyramidomethyl-6-chloroimidazo-[1,2-b]pyridazine (12) (41%) [after t.l.c. (alumina; chloroform/light petroleum, 1:1)], m.p. 238–240° (from ethanol) (Found: C, 65·3; H, 6·7; N, 14·3. $C_{21}H_{25}ClN_4O$ requires C, 65·5; H, 6·5; N, 14·6%). ^{1}H n.m.r.: δ 0·93, t, *J* 7·5 Hz, CH_3; 1·36, s, CMe_3; 1·66, q, *J* 7·5 Hz, C**H**$_2$CH$_3$; 2·16, q, *J* 7·5 Hz, CH_2CO; 5·03, d, *J* 5·5 Hz, CH_2N; 7·06, d, *J* 9·5 Hz, H 7; 7·46–7·96, complex, H 8,2′,3′,5′,6′.

3-Acetamidomethyl-6-chloro-2-styrylimidazo[1,2-b]pyridazine (33) (28%) [after t.l.c. (alumina; chloroform)], m.p. 266–267° (from benzene) (Found: C, 62·3; H, 4·6. $C_{17}H_{15}ClN_4O$ requires C, 62·5; H, 4·6%). ^{1}H n.m.r.: δ 2·01, s, Me; 4·92, d, *J* 5·5 Hz, CH_2; 7·08, d, *J* 9·5 Hz, H 7; 7·30–7·62, complex, PhCH=CH; 7·89, d, *J* 9·5 Hz, H 8.

3-Acetamidomethyl-2-(4′-t-butylphenyl)-6-phenoxyimidazo[1,2-b]pyridazine (60) (51%) [after t.l.c. (alumina; chloroform/light petroleum, 2:5, developed twice, then 1:2)], m.p. 228–229° (from benzene) (Found: C, 71·1; H, 6·5; N, 13·1. $C_{25}H_{26}ClN_4O_2.0{\cdot}5H_2O$ requires C, 70·9; H, 6·4; N, 13·2%). ^{1}H n.m.r.: δ 1·35, s, CMe_3; 1·85, s, MeCO; 4·79, d, *J* 5·5 Hz, CH_2; 6·94, d, *J* 9·5 Hz, H 7; 7·20–8·07, complex, 2×ArH and H 8.

2-(4′-t-Butylphenyl)-6-chloro-3-(2″-chlorobenzamidomethyl)-imidazo[1,2-b]pyridazine (20) and Related Compounds

A mixture of 2-(4′-t-butylphenyl)-6-chloroimidazo[1,2-*b*]-pyridazine (0·14 g), 2-chloro-*N*-(hydroxymethyl)benzamide (0·093 g), acetic acid (5·0 ml) and concentrated sulfuric acid (0·1 ml) was refluxed with stirring in an oil bath at 120° for 14 h. The acetic acid was distilled off under reduced pressure, the residue diluted with water (20 ml), adjusted to pH 10 and extracted with chloroform. The product was subjected to t.l.c. (alumina; chloroform/light petroleum, 3:1) which gave some unchanged imidazo[1,2-*b*]pyridazine (0·060 g) and a white solid (0·060 g) which was recrystallized from toluene and gave the *title compound* (0·026 g, 26%), m.p. 246–248° (Found: C, 63·9; H, 5·1; N, 12·3. $C_{24}H_{22}Cl_2N_4O$ requires C, 63·6; H, 4·9; N, 12·4%). ^{1}H n.m.r.: δ 1·37, s, CMe_3; 5·25, d, *J* 5·5 Hz, CH_2; 7·09, d, *J* 9·5 Hz, H 7; 7·30–8·02, complex, 2×ArH; 7·94, d, *J* 9·5 Hz, H 8. Mass spectrum *m/z* 454, 452 (M, 10, 13%), 313 (100), 139 (30).

In a similar manner from 2-(4′-t-butylphenyl)-6-chloroimidazo[1,2-*b*]pyridazine[12] and other compounds described above with the relevant *N*-(hydroxymethyl)benzamides[16] and *N*-(hydroxymethyl)-β-naphthamide[29] were prepared the following compounds.

2-(4′-t-Butylphenyl)-6-chloro-3-(2″-methylbenzamidomethyl)imidazo[1,2-b]pyridazine (14) (54%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], m.p. 250–251° (from toluene) (Found: C, 69·3; H, 6·0; N, 12·7. $C_{25}H_{25}ClN_4O$ requires C, 69·4; H, 5·8; N, 12·9%). ^{1}H n.m.r.: δ 1·37, s, CMe_3; 2·45, s, 2″-Me; 5·25, d, *J* 5·5 Hz, CH_2; 7·10, d, *J* 9·5 Hz, H7; 7·20–7·60, complex, 2×ArH; 7·96, d, *J* 9·5 Hz, H8. Mass spectrum *m/z* 434, 432 (M, 3, 9%), 313 (100), 119 (25), 91 (23).

2-(4′-t-Butylphenyl)-6-chloro-3-(3″-methylbenzamidomethyl)imidazo[1,2-b]pyridazine (15) (38%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], m.p. 226–227° (from toluene) (Found: C, 69·4; H, 5·6; N, 12·6. $C_{25}H_{25}ClN_4O$ requires C, 69·4; H, 5·8; N, 12·9%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 2·38, s, 3″-Me; 5·24, d, *J* 5·5 Hz, CH_2; 7·10, d, *J* 9·5 Hz, H7; 7·32–8·02, complex, 2×ArH; 7·94, d, *J* 9·5 Hz, H8. Mass spectrum *m/z* 434, 432 (M, 5, 18%), 313 (100), 119 (36), 91 (35).

2-(4′-t-Butylphenyl)-6-chloro-3-(4″-methylbenzamidomethyl)imidazo[1,2-b]pyridazine (16) (54%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], as a white solid, m.p. 247–248° (from toluene) (Found: C, 69·0; H, 5·8; N, 13·1. $C_{25}H_{25}ClN_4O$ requires C, 69·4; H, 5·8; N, 12·9%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 2·38, s, 4″-Me; 5·24, d, *J* 5·5 Hz, CH_2; 7·10, d, *J* 9·5 Hz, H7; 7·49–8·03, complex, 2×ArH; 7·95, d, *J* 9·5 Hz, H8. Mass spectrum *m/z* 434, 432 (M, 7, 20%), 313 (100), 119 (40), 91 (28).

2-(4′-t-Butylphenyl)-6-chloro-3-(3″-chlorobenzamidomethyl)imidazo[1,2-b]pyridazine (21) (74%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], m.p. 262–263° (from toluene) (Found: C, 63·4; H, 4·6; N, 11·9. $C_{24}H_{22}Cl_2N_4O$ requires C, 63·6; H, 4·9; N, 12·4%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 5·23, d, *J* 5·5 Hz, CH_2; 7·10, d, *J* 9·5 Hz, H7; 7·28–7·97, complex, 2×ArH; 7·97, d, *J* 9·5 Hz, H8. Mass spectrum *m/z* 454, 452 (M, 11, 16%), 313 (100), 139 (35).

2-(4′-t-Butylphenyl)-6-chloro-3-(4″-chlorobenzamidomethyl)imidazo[1,2-b]pyridazine (22) (26%) [after t.l.c. (alumina; chloroform/light petroleum, 4:1)], as yellow crystals, m.p. 248–250° (Found: C, 63·3; H, 4·7; N, 11·9. $C_{24}H_{22}Cl_2N_4O$ requires C, 63·6; H, 4·9; N, 12·4%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 5·23, d, *J* 5·5 Hz, CH_2; 7·08, d, *J* 9·5 Hz, H7; 7·92, d, *J* 9·5 Hz, H8; 7·38, d, *J* 9 Hz, 7·52, d, *J* 9 Hz, 7·71, d, *J* 9 Hz, 7·93, d, *J* 9 Hz, H2′,6′,3′,5′,2″,6″,3″,5″. Mass spectrum *m/z* 454, 452 (M, 9, 16%), 313 (100), 139 (27).

2-(4′-t-Butylphenyl)-6-chloro-3-(2″-nitrobenzamidomethyl)imidazo[1,2-b]pyridazine (23) (36%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], as a white solid, m.p. 260–262° (from toluene) (Found: C, 61·7; H, 4·6; N, 14·6. $C_{24}H_{22}ClN_5O_3$ requires C, 62·1; H, 4·8; N, 15·1%). ^{1}H n.m.r.: δ 1·37, s, CMe_3; 5·24, d, *J* 5·5 Hz, CH_2; 6·84, br, NH; 7·06, d, *J* 9·5 Hz, H7; 7·50–8·18, complex, 2×ArH; 7·92, d, *J* 9·5 Hz, H8. Mass spectrum *m/z* 465, 463 (M, 3, 8%), 446 (35), 311 (100), 295 (40).

2-(4′-t-Butylphenyl)-6-chloro-3-(3″-nitrobenzamidomethyl)imidazo[1,2-b]pyridazine (24) (82%) (from the chloroform extract), as pale yellow crystals, m.p. 232–235° [after t.l.c. (alumina; chloroform/light petroleum, 3:1)] (Found: C, 62·2; H, 4·8; N, 5·0. $C_{24}H_{22}ClN_5O_3$ requires C, 62·1; H, 4·8; N, 5·1%). ^{1}H n.m.r.: δ 1·35, s, CMe_3; 5·26, d, *J* 5·5 Hz, CH_2; 7·08, d, *J* 9·5 Hz, H7; 7·09–8·39, complex, H2′,3′,5′,6′,4″,5″,6″; 7·89, d, *J* 9·5 Hz, H8; 8·62, t, *J* 1·5 Hz, H2″. Mass spectrum *m/z* 465, 463 (M, 7, 22%), 313 (100), 150 (25).

2-(4′-t-Butylphenyl)-6-chloro-3-(4″-nitrobenzamidomethyl)imidazo[1,2-b]pyridazine (25) (22%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], as a white solid, m.p. 232–235° (from toluene) (Found: C, 61·6; H, 4·7; N, 14·8. $C_{24}H_{22}ClN_5O_3$ requires C, 62·1; H, 4·8; N, 15·1%). ^{1}H n.m.r.: δ 1·37, s, CMe_3; 5·27, d, *J* 5·5 Hz, CH_2; 7·09, d, *J* 9·5 Hz, H7; 7·50–8·33, complex, 2×ArH and H8. Mass spectrum *m/z* 465, 463 (M, 6, 15%), 313 (100), 150 (26).

2-(4′-t-Butylphenyl)-6-chloro-3-(2″-naphthamidomethyl)imidazo[1,2-b]pyridazine (26) (36%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], m.p. 255–256° (from toluene) (Found: C, 71·2; H, 5·7; N, 11·8. $C_{28}H_{25}ClN_4O$ requires C, 71·7; H, 5·4; N, 11·9%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 5·30, d, *J* 5·5 Hz, CH_2; 7·08, d, *J* 9·5 Hz, H7; 7·47–8·04, complex, H8,2′,3′,5′,6′,3″,4″,5″,6″,7″,8″; 8·30, br s, H1″.

3-Benzamidomethyl-2-(4′-t-butylphenyl)-6-fluoroimidazo[1,2-b]pyridazine (40) (50%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], as a white solid, m.p. 261–262° (from toluene) (Found: C, 71·4; H, 5·7; N, 13·8. $C_{24}H_{23}FN_4O$ requires C, 71·6; H, 5·8; N, 13·9%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 5·20, d, *J* 5·5 Hz, CH_2; 7·87, d, *J* 9·5 Hz, H7; 7·05, br, NH; 7·38–8·09, complex, 2×ArH and H8. Mass spectrum *m/z* 402 (M, 15%), 297 (100), 105 (36), 77 (25).

2-(4′-t-Butylphenyl)-3-(4″-chlorobenzamidomethyl)-6-fluoroimidazo[1,2-b]pyridazine (41) (38%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], m.p. 257–258° (from toluene) (Found: C, 65·0; H, 5·2; N, 12·5. $C_{24}H_{22}ClFN_4O.0·25H_2O$ requires C, 65·4; H, 5·1; N, 12·5%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 5·19, d, *J* 5·5 Hz, CH_2; 6·89, d, *J* 9·5 Hz, H7; 7·38, d, *J* 8·5 Hz, 7·53, d, *J* 8·5 Hz, 7·72, d, *J* 8·5 Hz, 7·92, d, *J* 8·5 Hz, H2′,3′,5′,6′,2″,3″,5″,6″; 7·99, d, *J* 9·5 Hz, H8.

3-Benzamidomethyl-2-(4′-t-butylphenyl)-6-methoxyimidazo[1,2-b]pyridazine (47) (24%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], as cream crystals, m.p. 215–217° (from toluene) (Found: C, 72·7; H, 6·7; N, 13·2. $C_{25}H_{26}N_4O_2$ requires C, 72·4; H, 6·3; N, 13·5%). ^{1}H n.m.r.: δ 1·35, s, CMe_3; 4·00, s, MeO; 5·21, d, *J* 5·5 Hz, CH_2; 6·68, d, *J* 9·5 Hz, H7; 6·70, br, NH; 7·38–7·87, complex, 2×ArH; 7·77, d, *J* 9·5 Hz, H8.

2-(4′-t-Butylphenyl)-3-(4″-chlorobenzamidomethyl)-6-methoxyimidazo[1,2-b]pyridazine (48) (22%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], as white crystals, m.p. 282–283° (from toluene) (Found: C, 66·9; H, 5·6; N, 12·5. $C_{25}H_{25}ClN_4O_2$ requires C, 66·9; H, 5·6; N, 12·5%). ^{1}H n.m.r.: δ 1·35, s, CMe_3; 4·00, s, MeO; 5·21, d, *J* 5·5 Hz, CH_2; 6·71, d, *J* 9·5 Hz, H7; 6·83, br, NH; 7·32–7·80, complex, 2×ArH; 7·79, d, *J* 9·5 Hz, H8.

3-Benzamidomethyl-2-(4′-cyclohexylphenyl)-6-methoxyimidazo[1,2-b]pyridazine (50) (45%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], m.p. 192–193° (from toluene) (Found: C, 73·8; H, 6·5; N, 12·5. $C_{27}H_{27}N_4O_2$ requires C, 73·8; H, 6·2; N, 12·7%). ^{1}H n.m.r.: δ 1·32–1·85, complex, cyclohexyl; 3·98, s, MeO; 5·19, d, *J* 5·5 Hz, CH_2; 6·65, d, *J* 9·5 Hz, H7; 6·97, br, NH; 7·23–7·84, complex, 2×ArH; 7·73, d, *J* 9·5 Hz, H8.

3-Benzamidomethyl-2-(4′-t-butylphenyl)-6-methylthioimidazo[1,2-b]pyridazine (56) (82%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], as cream crystals, m.p. 218–219° (from toluene) (Found: C, 69·1; H, 6·0; N, 12·7. $C_{25}H_{26}N_4OS.0·2H_2O$ requires C, 69·2; H, 6·1; N, 12·9%). ^{1}H n.m.r.: δ 1·35, s, CMe_3; 2·58, s, MeS; 5·24, d, *J* 5·5 Hz, CH_2; 6·84, d, *J* 9·5 Hz, H7; 6·99, br, NH; 7·37–7·52 and 7·73–7·86, complex, 2×ArH; 7·64, d, *J* 9·5 Hz, H8.

3-Benzamidomethyl-2-(4′-cyclohexylphenyl)-6-methylthioimidazo[1,2-b]pyridazine (58) (39%) [after t.l.c. (alumina; chloroform/light petroleum, 3:1)], as white crystals, m.p. 224–226° (from toluene) (Found: C, 71·1; H, 5·8; N, 12·1. $C_{27}H_{27}N_4OS$ requires C, 71·2; H, 6·0; N, 12·3%). ^{1}H n.m.r.: δ 1·33–1·86, complex, cyclohexyl; 2·61, s, MeS; 5·27, d, *J* 5·5 Hz, CH_2; 6·91, d, *J* 9·5 Hz, H7; 7·27–7·88, complex, 2×ArH and H8.

3-Benzamidomethyl-2-(4′-t-butylphenyl)-6-phenoxyimidazo[1,2-b]pyridazine (61) (53%) [after t.l.c. (alumina; chloroform/light petroleum, 1:1)], m.p. 203·5–205° (from toluene)

(Found: C, 75·3; H, 5·8; N, 11·5. $C_{30}H_{28}N_4O_2$ requires C, 75·6; H, 5·9; N, 12·0%). ^{1}H n.m.r.: δ 1·34, s, CMe_3; 4·99, d, J 5·5 Hz, CH_2; 6·87, d, J 9·5 Hz, H7; 7·26–7·99, complex, 3×ArH and H8.

3-Benzamidomethyl-2-(4′-t-butylphenyl)-6-phenylthioimidazo[1,2-b]pyridazine (66) (69%) [after t.l.c. (alumina; chloroform/light petroleum, 1:2)], m.p. 145–146·5° (from cyclohexane) (Found: C, 73·5; H, 5·8; N, 11·5. $C_{30}H_{28}N_4OS$ requires C, 73·1; H, 5·7; N, 11·4%). ^{1}H n.m.r.: δ 1·34, s, CMe_3; 5·03, d, J 5·5 Hz, CH_2; 6·84, d, J 9·5 Hz, H7; 7·29–7·98, complex, 3×ArH and H8.

3-Benzamidomethyl-2-(naphthalen-2′-yl)-6-phenylthioimidazo[1,2-b]pyridazine (68) (79%) [after t.l.c. (alumina; chloroform/light petroleum, 1:1)], m.p. 153–155° (from ethanol) (Found: C, 74·0; H, 4·4; N, 11·3. $C_{30}H_{22}N_4OS$ requires C, 74·0; H, 4·6; N, 11·5%). ^{1}H n.m.r.: δ 5·12, d, J 5·5 Hz, CH_2; 6·90, d, J 9·5 Hz, H7; 7·30–8·22, complex, H3′,4′,5′,6′,7′,8′ and 2×Ph; 8·53, br s, H1′.

2-(4′-t-Butylphenyl)-6-chloroimidazo[1,2-a]pyridine (69)

A mixture of 5-chloropyridin-2-amine (0·26 g, Aldrich) and α-bromo-4-t-butylacetophenone in ethanol (15 ml) was refluxed for 3 h, sodium hydrogen carbonate (0·17 g) was added and the refluxing was continued for 3 h. The ethanol was evaporated and the residue extracted with chloroform (60 ml). The resulting extract was then washed with water (3×20 ml), dried (Na_2SO_4) and evaporated, and the product was recrystallized from a mixture of acetone and light petroleum to give the *title compound* (0·22 g, 39%), m.p. 169–170° (Found: C, 71·4; H, 6·2; N, 9·9. $C_{17}H_{17}ClN_2$ requires C, 71·7; H, 6·0; N, 9·8%). ^{1}H n.m.r.: δ 1·35, s, CMe_3; 7·18, dd, J 9·5, 2 Hz, H7; 7·47, d, J 9 Hz, H2′,6′ (or 3′,5′); 7·67, d, J 9·5 Hz, H8; 7·83, s, H3; 7·88, d, J 9 Hz, H3′,5′ (or 2′,6′); 8·19, d, J 2 Hz, H5. Mass spectrum m/z 286, 284 (M, 20, 50%), 269 (100), 121 (20).

3-Benzamidomethyl-2-(4′-t-butylphenyl-6-chloroimidazo[1,2-a]pyridine (70)

A mixture of 2-(4′-t-butylphenyl)-6-chloroimidazo[1,2-*a*]-pyridine (0·14 g), *N*-(hydroxymethyl)benzamide (0·076 g), acetic acid (5·0 ml) and concentrated sulfuric acid (0·09 ml) was refluxed with stirring in an oil bath at 120° for 24 h. The acetic acid was evaporated and water (20 ml) added. The pH was adjusted to 10, the mixture extracted with chloroform, then washed with water, dried (Na_2SO_4), and the solvent evaporated to give an oil which crystallized. This product was applied in chloroform/methanol (3:1) to a t.l.c. plate (alumina) which was developed with a mixture of chloroform and light petroleum (3:1). Extraction with chloroform gave a white solid (0·19 g, 90%) which was recrystallized from toluene to give cream crystals of the *title compound* (0·045 g), m.p. 226–227° (Found: C, 71·9; H, 5·7; N, 9·7. $C_{25}H_{24}ClN_3O$ requires C, 71·8; H, 5·8; N, 10·1%). ^{1}H n.m.r.: δ 1·35, s, CMe_3; 5·12, d, J 5·5 Hz, CH_2; 6·73, br, NH; 7·15, dd, J 9·5, 2 Hz, H7; 7·30–7·70, complex, 2×ArH; 7·85, dd, J 9·5, 2 Hz, H8; 8·40, br s, H5.

Biological Testing: PBR *Binding Assays*

Young adult male Wistar rats were decapitated and the kidneys removed. The kidneys were dissected free of fat and the kidney capsule was rinsed in ice-cold saline, blotted and weighed, and then chopped with scissors and homogenized with an 'Ultra-Turrax' in 16 volumes of ice-cold 0·32 M sucrose. The homogenate thus obtained was centrifuged at 17000 rpm for 30 min, then the supernatant liquid was decanted and the remaining pellet suspended in ice-cold distilled water. After 10 min, this suspension was centrifuged a second time and the pellet resuspended in 50 mM Tris–HCl buffer, pH 7·4. Finally, this suspension was centrifuged and the pellet resuspended in Tris buffer and stored frozen. On the day of use, the suspension was thawed, recentrifuged and the pellet suspended in fresh Tris buffer.

The PBR binding assay contained aliquots of the rat kidney membrane preparations (approximately 1 mg wet weight), various concentrations of the test compounds and [^{3}H]diazepam (86·6 Ci*/mmol, 0·70±0·05 nM final concentration) in a final volume of 2 ml Tris–HCl buffer. Assays were performed in the absence of γ-aminobutyric acid as it does not stimulate benzodiazepine binding to the PBR. The assays were incubated with [^{3}H]diazepam on ice at 0–4°C for 60 min. Non-specific binding was determined in separate tubes by the addition of a large excess (10 μM) of unlabelled diazepam. After the incubation period the membranes were collected by filtration under vacuum on glass-fibre filters (Whatman GF/B, 2·5 cm) and washed with 12 ml of ice-cold buffer. Filters were placed in scintillation vials with 1 ml of toluene/Triton X-100 scintillation fluid and bound radioactivity was determined by conventional techniques.

Compounds were initially tested for their ability to displace specific [^{3}H]diazepam binding from the PBR at a single concentration of 1000 nM, and for compounds showing high percentage displacement, IC_{50} values were determined over four separate concentrations, with all assays within each experiment being performed in triplicate. The IC_{50} values for the test compounds were calculated by using log–logit analysis (with the correlation coefficients of the lines of best fit to log–logit curves not less than 0·95).

BZR *Binding Assays*

Evaluation of the compounds for their ability to displace [^{3}H]diazepam bound to rat brain membrane preparations in the presence of 100 μM γ-aminobutyric acid was carried out as described previously.[14]

Percentage inhibitions of control binding at 1000 nM were measured firstly, and in appropriate cases IC_{50} values (nM) were determined, as described above for the PBR.

The results are listed in Table 1 for the BZR and the PBR as IC_{50} values (nM), or in parentheses as percentage displacement at 1000 nM.

Acknowledgments

We thank Dr D. J. Brown for helpful discussion, and the Australian National University for the award of a scholarship to P.W.H.

References

[1] Barlin, G. B., Davies, L. P., and Harrison, P. W., *Aust. J. Chem.*, 1995, *48*, 1031, and preceding papers in this series.
[2] Sieghart, W., *Trends Pharmacol. Sci.*, 1992, **13**, 446.
[3] Lüddens, H., Korpi, E. R., and Seeburg, P. H., *Neuropharmacology*, 1995, **34**, 245.
[4] Haefely, W., Kyburz, E., Gerecke, M., and Möhler, H., *Adv. Drug Res.*, 1985, **14**, 165.
[5] Braestrup, C., and Squires, R. F., *Proc. Natl Acad. Sci. USA*, 1977, **74**, 3805.
[6] Gavish, M., Katz, Y., Bar-Ami, S., and Weizman, R., *J. Neurochem.*, 1992, **58**, 1589.
[7] Parola, A. L., Yamamura, H. I., and Laird II, H. E., *Life Sci.*, 1993, **52**, 1329.
[8] Mukhin, A. G., Papadopoulos, V., Costa, E., and Krueger, K. E., *Proc. Natl Acad. Sci. USA*, 1989, **86**, 9813.

* 1 Ci = $3·7\times10^{10}$ Bq = $3·7\times10^{10}$ s^{-1}.

[9] Krueger, K. E., and Papadopoulos, V., *J. Biol. Chem.*, 1990, **265**, 15015.
[10] Black, K. L., Ikezaki, K., Santori, E., Becker, D. P., and Vinters, H. V., *Cancer*, 1990, **65**, 93.
[11] Camins, A., Sureda, F. X., Pubill, D., Camarasa, J., and Escubedo, E., *Life Sci.*, 1994, **54**, 759.
[12] Barlin, G. B., Davies, L. P. Glenn, B., Harrison, P. W., and Ireland, S. J., *Aust. J. Chem.*, 1994, **47**, 609.
[13] Barlin, G. B., Davies, L. P., Harrison, P. W., Jacobsen, N. W., and Willis, A. C., *Aust. J. Chem.*, 1994, **47**, 1989.
[14] Barlin, G. B., Davies, L. P., and Ngu, M. M. L., *Aust. J. Chem.*, 1988, **41**, 1149.
[15] Skerritt, J. H., Chen Chow, S., Johnston, G. A. R., and Davies, L. P., *Neurosci. Lett.*, 1982, **34**, 63.
[16] Barlin, G. B., Davies, L. P., Ireland, S. J., Ngu, M. M. L., and Zhang, J., *Aust. J. Chem.*, 1992, **45**, 731.
[17] Barlin, G. B., Davies, L. P., Ireland, S. J., Ngu, M. M. L., and Zhang, J., *Aust. J. Chem.*, 1992, **45**, 877.
[18] Barlin, G. B., *Aust. J. Chem.*, 1986, **39**, 1803.
[19] Horie, T., Kinjo, K., and Ueda, T., *Chem. Pharm. Bull.*, 1962, **10**, 580.
[20] Clark, J. H., English, J. P., Jansen, G. R., Marson, H. W., Rogers, M. M., and Taft, W. E., *J. Am. Chem. Soc.*, 1958, **80**, 980.
[21] Barlin, G. B., *J. Chem. Soc., Perkin Trans. 1*, 1976, 1424.
[22] Barlin, G. B., Davies, L. P., and Ngu, M. M. L., *Aust. J. Chem.*, 1988, **41**, 1735.
[23] Barlin, G. B., and Ireland, S. J., *Aust. J. Chem.*, 1987, **40**, 1491.
[24] Immediata, T., and Day, A. R., *J. Org. Chem.*, 1940, **5**, 512.
[25] Einhorn, A., and Ladisch, C., *Justus Liebigs Ann. Chem.*, 1905, **343**, 264.
[26] Yoneda, F., Ohtaka, T., and Nitta, Y., *Chem. Pharm. Bull.*, 1964, **12**, 1351.
[27] Einhorn, A., and Hamburger, A., *Justus Liebigs Ann. Chem.*, 1908, **361**, 122.
[28] Zugravescu, I., Leonte, C., and Petrovanu, O., *An. Stiint. Univ. Al. I. Cuza Iasi, Sect. 1*, 1963, **9** (1), 219 (*Chem. Abstr.*, 1964, **60**, 1580h).
[29] Yasuda, S., Tanimoto, S., and Okano, M., *Yuki Gosei Kagaku Kyokai Shi*, 1970, **28**, 1137 (*Chem. Abstr.*, 1971, **74**, 87539g).