Synthesis and Hypoglycemic Activity of Substituted 8-(1-Piperazinyl)imidazo[1,2-a]pyrazines†

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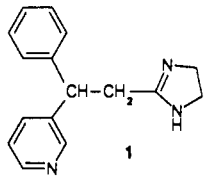
A series of alkyl- and halo-substituted 8-(1-piperazinyl)imidazo[1,2-a]pyrazines were prepared using two approaches, the condensation of α-halocarbonyl derivatives with an aminopyrazine or the oxidation–dehydration of a [(β-hydroxyalkyl)amino]pyrazine. These imidazo[1,2-a]pyrazines were evaluated for their binding affinity to the α_1, α_2, β_1, and β_2 adrenergic receptors as well as their ability to lower blood glucose in insulin resistant hyperglycemic ob/ob mice. Modifications on 8-(1-piperazinyl)imidazo[1,2-a]pyrazine (**4**) reduced α_2 binding, lowered hypoglycemic potency, and showed variations in binding to the α_1, β_1, and β_2 adrenergic receptors. In addition to **4**, the 2-methyl, 3-methyl, and 5-methyl 8-(1-piperazinyl)imidazo[1,2-a]pyrazines (**16k**, **25m**, and **16f**, respectively) displayed high affinity for the α_2 receptor and were potent hypoglycemic agents when compared to 2-amino-7,8-dihydro-4-(1-piperazinyl)-6*H*-thiopyrano[3,2-*d*]pyrimidine (MTP-1403, **2**). Receptor binding was modified by use of a 4-methylpiperazine moiety which reduced α_1 and β_1 binding while retaining some hypoglycemic activity. The structure–activity relationship for heterocyclic alkyl and halo substitution on biological activity is discussed.

Certain α_2-adrenergic antagonists have been shown to be insulin secretagogues and to be useful as hypoglycemic agents. Midaglizole[1] (DG-5128, 1), a selective α_2 antagonist related to phentolamine, was shown to be effective in lowering blood glucose in vitro and in vivo in animal studies as well as in clinical studies. Also L-657,743, an extremely potent α_2 antagonist related to yohimbine, has been shown[2] to be a potent hypoglycemic agent. The mechanism[1c] of blood glucose lowering by α-adrenergic agents is not straightforward as illustrated by the fact that not all α_2 antagonists are effective in stimulating insulin secretion in man (e.g. idazoxan[3]). Phentolamine has been shown to exhibit insulin-releasing activity through inhibition of ATP-sensitive K^+ channels independently of α-adrenergic activity.[4] Members of the arylpiperazine class, whose structures are more distantly related to phentolamine, have been shown to possess various α-adrenergic as well as hypoglycemic activities.

As a general class of compounds, heteroaromatic arylpiperazines have long been known to exhibit a wide range of



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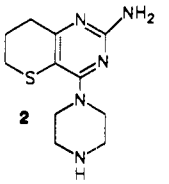

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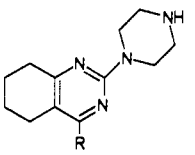
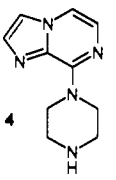


3 R=NH_2, alkoxy



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pharmacological properties including α_2-adrenergic antagonism as well as hypoglycemic, antihypertensive, and serotoninmimetic activity.[5-15] Several arylpiperazines including 2-amino-7,8-dihydro-4-(1-piperazinyl)-6*H*-thi-

† In honor of Dr. Ralph F. Hirschmann on the occasion of his 70th birthday. Dr. Hirschmann was an unflagging supporter of diabetes efforts and adrenergic receptor studies at Merck.

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opyrano[3,2-*d*]pyrimidine (MTP-1403 **2**)[5] and variously substituted 2-(1-piperazinyl)-5,6-polymethylene-pyrimidines **3**[6,7] have been shown to be insulin secretagogues and to improve glucose tolerance in mice. In addition, piperazinylpyrazines[8,9] and piperazinylimidazo[1,2-*a*]pyrazines[10,11] have recently been investigated because of their interesting pharmacological activities which include α_2 antagonism, β-blocking, and serotoninmimetic activity. The unsubstituted 8-(1-piperazinyl)imidazo[1,2-*a*]pyrazine (**4**) was shown to have a strong selective affinity for the α_2-adrenergic receptor from calf cerebral cortex.[10]

Recent studies of imidazo[1,2-*a*]pyrazines have also described a variety of biological activities including antiinflammatory, antiulcer, uterine-relaxing, antibronchospastic, cardiac-stimulating, and inotropic properties.[16-21] The present study of variously substituted 8-(1-piperazinyl)imidazo[1,2-*a*]pyrazines was initiated to examine the effects of heteroaromatic alkyl and halo substitution on the ability to lower blood glucose in insulin-resistant hyperglycemic ob/ob mice and to examine effects upon binding to the α_2 as well as to the α_1-, β_1-, and β_2-adrenergic receptors. The effects of the various substitution patterns on the above parameters were evaluated in order to better understand the overall pharmacological profile of these interesting heteroaromatic piperazine derivatives.

Chemistry

Two approaches to the imidazo[1,2-*a*]pyrazine ring system examined in this work have been previously described in the literature. The first approach utilizes the condensation of an α-halocarbonyl compound with an aminopyrazine,[10,11,18-23] and the second method uses the reaction of a vicinal amino alcohol with a chloropyrazine, followed by oxidation of the alcohol to a ketone and dehydrative ring closure.[10,11]

Synthesis of the alkyl-substituted 8-(1-piperazinyl)-imidazo[1,2-*a*]pyrazines **16d-k** and **20**, shown in Schemes I and II, utilized the reaction of substituted α-bromo carbonyl derivatives with the appropriate substituted 2-amino-3-chloropyrazines **6a-c**. The α-bromo carbonyl derivatives **7-10** required for this sequence were prepared by bromination[24] of the appropriate carbonyl compound with the bromine–dioxane complex,[25] or were generated in situ[10] from the α-bromo acetals **11-13** by treatment with 48% HBr at reflux (see Table I). The required isomeric 2-amino-3-chloro-5- and 6-methylpyrazines (**6a,b**) were prepared by a modification of literature methods.[26,27] Thus, a condensation of aminomalonamide and methylglyoxal in the presence of sodium bisulfite according to the method of Muehlmann and Day[26] afforded a 21% yield of 2-carbamoyl-3-hydroxy-5-methylpyrazine (**5b**) after chromatography and recrystallization. A low-temperature condensation of aminomalonamide and methylglyoxal described by Jones[27] to give a 59% yield of **5a** as the sole isomer gave, in our hands, poor yields of both isomers **5a** and **5b**, which could be separated by chromatography. A Hoffman reaction of **5a** and **5b** followed by a $POCl_3$ chlorination afforded **6a** and **6b**, respectively.[26,28] The condensation of **7-13** with **6a-c** proceeded with moderate yields in refluxing 2-propanol and provided **14d-l** as a mixture of 8-bromo- and 8-chloro-substituted imidazo-[1,2-*a*]pyrazines. While the NMR and TLC indicated single entities, this Br/Cl mixture was apparent from the mass spectra. This mixture is due to the general halogen scrambling that occurs in reactions of halo aldehydes and haloaminopyrazines and has been observed earlier by Lumma et al.[10]

Following construction of the 8-haloimidazo[1,2-*a*]-pyrazines **14d-l**, 1-[(*tert*-butyloxy)carbonyl]piperazine (Boc-piperazine), prepared by a modification of a literature method,[29,30] was utilized to introduce the piperazine moiety. Use of this blocked piperazine allowed facile chromatographic purifications on silica gel and gave rise to excellent isolated yields of the desired products **15d-l**. Acidic deblocking afforded high yields of the 8-(1-piperazinyl)imidazo[1,2-*a*]pyrazines **16d-k** and **20** which were isolated as their dihydrochloride salts.

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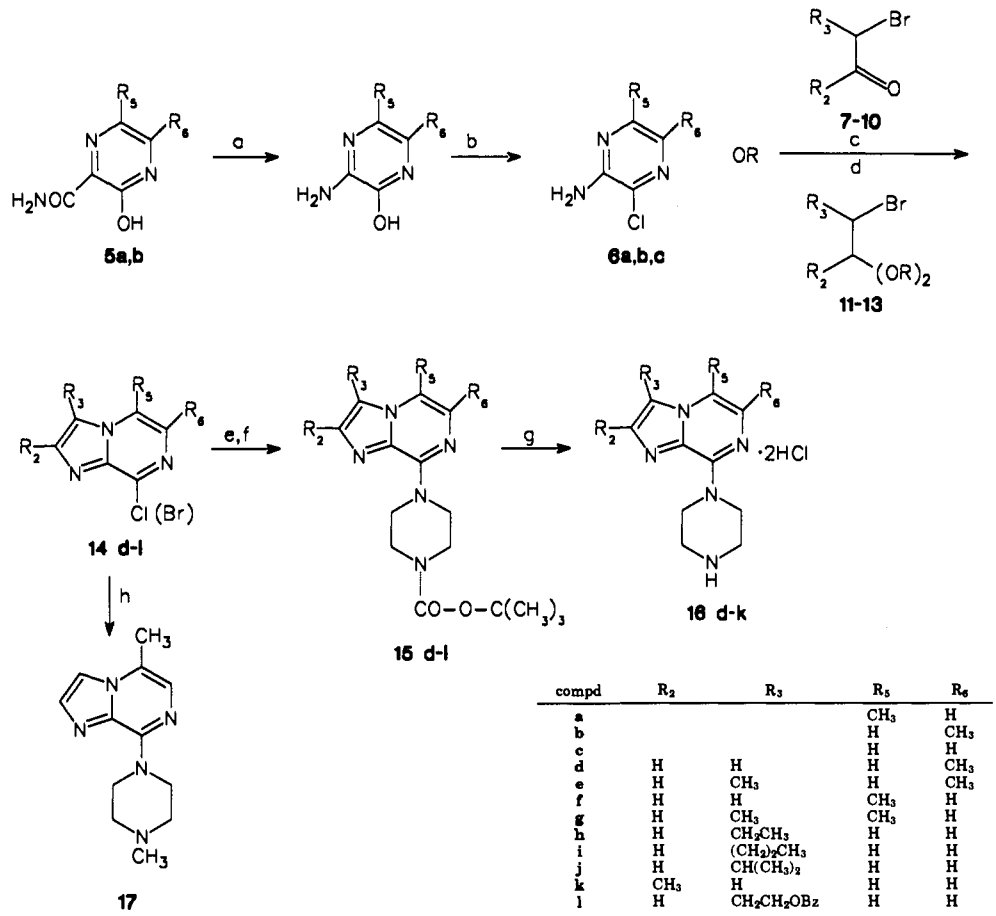
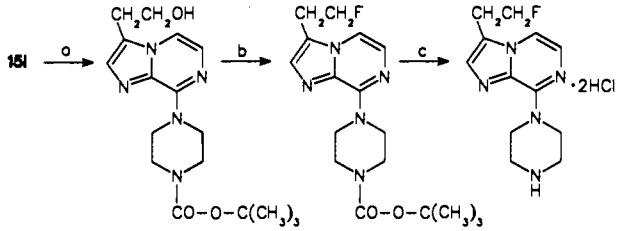
Scheme I [a]



compd	R_2	R_3	R_5	R_6
a			CH_3	H
b			H	CH_3
c			H	H
d	H	H	H	CH_3
e	H	CH_3	H	CH_3
f	H	H	CH_3	H
g	H	CH_3	CH_3	H
h	H	CH_2CH_3	H	H
i	H	$(CH_2)_2CH_3$	H	H
j	H	$CH(CH_3)_2$	H	H
k	CH_3	H	H	H
l	H	CH_2CH_2OBz	H	H

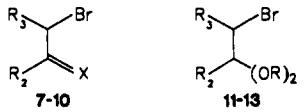
[a] (a) Br_2, KOH, H_2O, 80 °C; (b) $POCl_3$, H_2O, 115 °C; (c) $(CH_3)_2CHOH$, reflux; (d) (1) 48% HBr, (2) Na_2CO_3, (3) $(CH_3)_2CHOH$, reflux; (e) Boc-piperazine, EtOH, reflux; (f) Boc-piperazine, Et_3N, EtOH, reflux; (g) HCl/EtOH; (h) 1-methylpiperazine, EtOH, Et_3N, reflux.

Scheme II [a]



[a] (a) 40% aqueous $MeNH_2$, MeOH, 60 °C; (b) DAST, MgO, CH_2Cl_2, −70 °C; (c) TFA, HCl/EtOH.

Table I. α-Bromocarbonyl Derivatives



compd	R_2	R_3	X	R	ref
7	H	CH_3	O		24
8	H	$CH(CH_3)_2$	O		24
9	H	CH_2CH_2OBz	O		*a*
10	CH_3	H	O		*b*
11	H	H		OCH_3	*b*
12	H	CH_2CH_3		OCH_2CH_3	*c*
13	H	$CH_2CH_2CH_3$		OCH_3	39

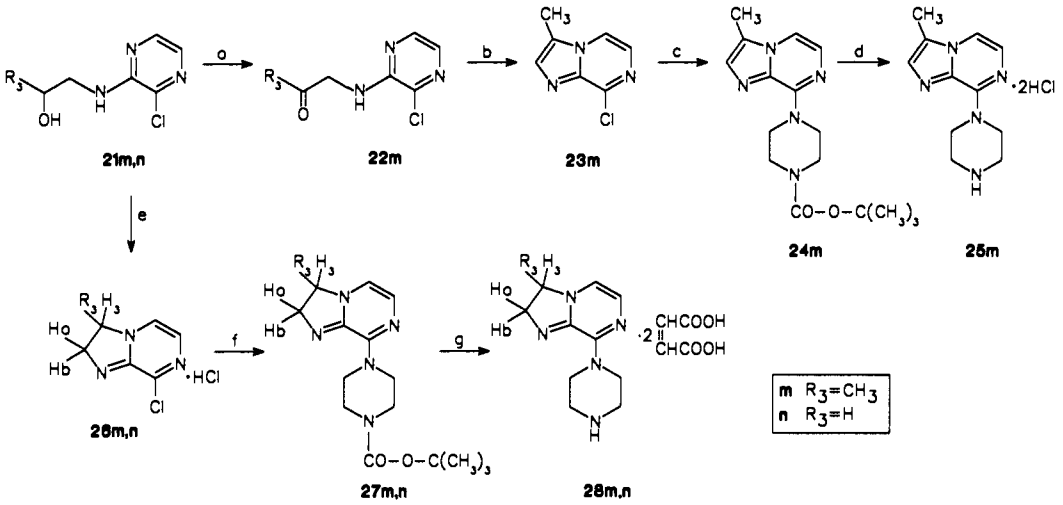
[a] See Experimental Section. [b] Aldrich. [c] Pfaltz & Bauer.

In the preparation of the hydroxyethyl and fluoroethyl derivatives **18–20** (see Scheme II), the hydroxyethyl group was introduced utilizing benzoyl protection on the hydroxyl moiety and the 3-[(benzoyloxy)ethyl] analog **15l** was further transformed prior to removal of the Boc moiety. Thus, debenzoylation of **15l** with 40% aqueous $MeNH_2$ gave the alcohol **18** which was treated with (diethylamino)-sulfur trifluoride (DAST) to provide the 2-fluoroethyl analog **19** which was deblocked in the usual fashion to give **20** (Scheme II).

The second synthetic approach to imidazo[1,2-*a*]pyrazines (Scheme III) was used to prepare **25m**. This followed the regiospecific approach described by Lumma et al.[10,11] and utilized 2,3-dichloropyrazine which was heated at reflux with 1-amino-2-propanol in dioxane to give **21m**. Oxidation to the ketone **22m** using trimethylamine–sulfur trioxide, followed by a dehydration–cyclization with trifluoroacetic acid/trifluoroacetic anhydride afforded **23m** in high yield. Conversion of **23m** and **25m** followed the same procedures described above for conversion of **14d–l** to **16d–k**.

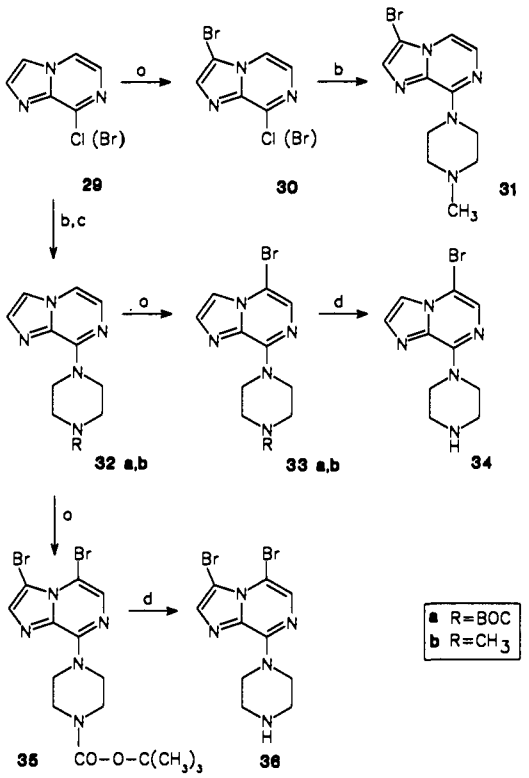
The intermediate **21m**, and a homolog **21n**, served in the synthesis of the 2,3-dihydroimidazo[1,2-*a*]pyrazines **28m** and **28n** as shown in Scheme III, using similar approaches to that described by Lumma et al.[10,11] The reaction of **21m** and **21n** with thionyl chloride in xylenes gave the intermediate chloroethyl derivatives, which could be ring-closed to the cyclic materials **26m** and **26n** by heating. Substitution of the 8-chloro moiety of **26m** and **26n** with Boc-piperazine to give **27m** and **27n** required heating at 125 °C in the dihydroimidazo[1,2-*a*]pyrazine series. Removal of the Boc group in this series was effected with trifluoroacetic acid, followed by Dowex 1×2 OH^- ion-exchange chromatography to provide the free

Scheme III [a]



[a] (a) Et_3N, $(CH_3)_3N{\cdot}SO_3$, DMSO; (b) CF_3CO_2H, $(CF_3O)_2O$; (c) Boc-piperazine, Et_3N, EtOH, reflux; (d) HCl/EtOH; (e) $SOCl_2$, xylenes, 80–100 °C; (f) (1) 10% Na_2CO_3, CH_2Cl_2 (2) Boc-piperazine, Et_3N, $(CH_3)_2CH(CH_2)_2OH$, 125 °C; (g) (1) CF_3CO_2H, (2) Dowex 1×2 OH^- resin, (3) maleic acid, EtOH.

Scheme IV [a]



[a] (a) NBS, $CHCl_3$, reflux; (b) 1-methylpiperazine, Et_3N, EtOH, reflux; (c) Boc-piperazine, Et_3N, EtOH, reflux; (d) HCl–EtOH.

base, which was then converted to the maleate salt **28m** and **28n** for isolation and biological evaluation.

Three derivatives which contained the 4-methylpiperazine moiety, **17**, **31**, and **32b** were prepared by treating their respective 8-chloroimidazo[1,2-*a*]pyrazines precursors with 1-methylpiperazine. Bromination of **32b** gave the 5-bromo derivative **33b** (see Schemes I and IV).

Electrophilic and Nucleophilic Substitution

Halogenations on the parent imidazo[1,2-*a*]pyrazine with *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS) have been shown to occur initially at C_3[22,31] in agreement with predictions based on electron density calculations.[32] When electron withdrawing halogens were present at C_8, electrophilic halogenation with NBS was also directed to C_3 (i.e. when 8-chloro/8-bromo imidazo-[1,2-*a*]pyrazine **29** was used as a substrate the 3,8-dihalo derivative **30** was obtained,[10] see Scheme IV.) With this in mind, it was of interest to examine electrophilic substitution with NBS in the presence of an electron-donating group, such as the piperazine moiety, at C_8. Thus, bromination of the 8-piperazinyl derivatives **32a** and **32b** with NBS was examined. This gave the 5-bromo derivatives **33a** and **33b**, in contrast to the 3-isomers formed with the 8-halo derivatives (see above[10]) suggesting that the 8-piperazinyl moiety increases the electron density of C_5 relative to C_3, and thus the site of electrophilic halogenation in this series can be modified by the substitution pattern on the imidazo[1,2-*a*]pyrazine.

Characterization of the 5-bromo analog **33b** was based on a comparison of the ^1H NMR data with the 4′-methyl derivative **31** of the previously described 3-bromo analog **30**.[22] The ^1H NMR of **31** showed the H^2 signal as a singlet at δ 7.73 and H^6/H^5 as doublets (J = 4.5 Hz) at δ 7.51 and 7.71. Doublets for H^3/H^2 of **33b** gave a smaller coupling (J = 1.25 Hz) and were a little further downfield at δ 7.60 and 7.72, and the singlet for H^6 was at δ 7.45. The 3,5-dibromo compound **35** gave two singlets at δ 7.43 and 7.50 for H^6/H^2.

Halogenations have also been reported to favor C_5 when bromine in 95% ethanol was the reagent.[19] Other electrophilic reactions such as nitrosations[18] and hydroxylations[33] have been shown to occur at C_3 on variously substituted imidazo[1,2-*a*]pyrazines. It should be noted that when 2 equiv of NBS were used in the reaction with **32a**, a second bromine was introduced and the 3,5-dibromo derivative **35** was formed.

Nucleophilic substitution of imidazo[1,2-*a*]pyrazines is

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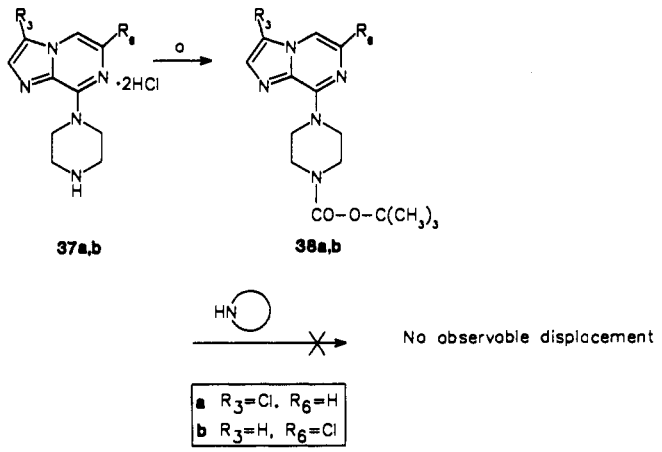
Scheme V [a]



[a] (a) $O[CO_2C(CH_3)_3]_2$, 2.5 N NaOH, H_2O, *tert*-butyl alcohol.

described in the literature to occur only at C_8 and C_5, and such observations have been validated by electron density calculations.[32] While the halogen at C_8 of **29** or **30** is readily displaced with Boc-piperazine or 1-methylpiperazine, we were not able to displace the 3-Br moiety in **31** in accord with the above mentioned observations. In order to further investigate the susceptibility of halogen at C_3 and C_6 to nucleophilic displacement we chose to evaluate **38a** and **38b** as substrates in displacement reactions with secondary amines. Thus the 3-chloro and 6-chloro compounds **37a** and **37b**[10,11] were treated with di-*tert*-butyl dicarbonate in aqueous NaOH and *tert*-butanol to provide the Boc-piperazine derivatives **38a** and **38b** (see Scheme V) which were chosen as the substrates due to their organic solubility and preferred chromatographic properties. However, attempted displacement of the 3-Cl of **38a** with pyrrolidine at 130 °C and the 6-Cl of **38b** with morpholine at 180 °C were unsuccessful, again in accordance with previous observations (see above). At temperatures above 130 °C, loss of the Boc group was observed and this decomposition of the starting material made evaluation of the displacement reaction more difficult.

In order to evaluate the susceptibility of halogen at C_5 to nucleophilic displacement, substitutions were attempted on the 5-bromo group of **33b**. Treatment of **33b** using methylamine in a bomb at 100 °C and evaluation by thin-layer chromatography showed complete disappearance of starting material and the production of several new products. One of these products was tentatively identified as the 5-(methylamino) analog by NMR but was too unstable for complete characterization. Attempted methoxide displacement of the 5-Br of **33b** was also unsuccessful at 100 °C. This apparent resistance to nucleophilic substitution at the 3-, 5- and 6-postions in this series of compounds, bearing a piperazine moiety at C_8, is in agreement with the observations of previous workers and limited the preparation of additional derivatives by these methods.

Biology

The substituted 8-(1-piperazinyl)imidazo[1,2-*a*]pyrazines were evaluated for their ability to lower blood glucose in insulin-resistant hyperglycemic ob/ob mice as well as their binding affinity for the α_1-, α_2-, β_1-, and β_2-adrenergic receptors; the results are tabulated in Table V. The measurement of hypoglycemic activity was evaluated as described by Saperstein et al.[2b] and is shown as the blood glucose level of treated animals (single dose 30 mg/kg, po) as a percentage of the blood glucose level in controls after a glucose load. In those cases where significant hypoglycemic activity was observed, more animals were utilized and a potency relative to a standard compound, in this case compound **2**, was derived. The binding to the adrenergic receptors was evaluated by measurement of the displacement of an appropriate radioligand using previously described methods[10] and is expressed as a K_i. Within this series of compounds, the parent compound **4** displayed the greatest affinity for the α_2 adrenergic receptor (K_i = 15 nM), as well as the most potent hypoglycemic activity (76× relative to **2**). On the β_1 receptor, **4** displayed a moderately high binding affinity (K_i = 400 nM) whereas α_1 and β_2 receptor binding affinity was markedly lower (K_i = 3100 nM and K_i = 1700 nM, respectively). Substitutions on **4** modified the receptor binding and effected hypoglycemic activity as described below.

α_1 Receptor Affinity

Alkyl subsitution at the 3-position of **4** displayed no apparent trend in binding affinity for the α_1 receptor. The 3-methyl analog **25m** showed an increase in α_1 binding affinity (K_i = 1800 nM) vs **4** (K_i = 3100 nM), whereas very little binding was detected for the 3-ethyl analog **16h**. A similar binding affinity was exhibited by the 3-propyl derivative **16i** as for **4**, while the branched isomer, the 3-isopropyl analog **16j**, showed a slightly reduced α_1 binding affinity (K_i = 5430 nM). The addition of a 6-methyl substituent to **4** showed a strong increase in α_1 affinity which was further increased by the addition of a second methyl group at the 3 position. (For **16d** and **16e**, K_i = 500 and 300 nM, respectively). Binding affinity for the α_1 receptor was only moderately increased relative to **4** for the 5-methyl analog **16f** (K_i = 2600 nM) which was the lowest binding affinity of the methyl-substituted series tested. Of the halo substituted analogs, the 3-chloro derivative **37a** (K_i = 2780 nM) had a lower binding affinity than the 3-methyl analog **25m** and had a similar affinity for the α_1 receptor as the parent **4**. In contrast, the 6-chloro analog **37b** displayed the greatest α_1 receptor binding affinity in this series (K_i = 250 nM). The α_1 binding affinity of the 5-bromo derivative **34** fell between that of **37a** and **37b**. The introduction of a 4-methyl group on the piperazine moiety reduced affinity for α_1 receptor binding. This is demonstrated by comparison of the 5-bromo analogs, **34** and **33b** (K_i = 1490 nM and 22% displacement of ligand at 10000 nM, respectively) and also of the 5-methyl derivatives, **16f** and **17** (K_i = 2600 nM and 45% displacement of ligand at 10000 nM, respectively).

β_1 Receptor Affinity

On the β_1 receptor, the addition of the 3-alkyl moieties dramatically reduced binding relative to the parent **4** (K_i = 400 nM); the increase in the size of the substituent paralleled the reduced binding affinity. Thus, the trend showed that the 3-methyl **25m**, the 3-ethyl **16h**, and the 3-propyl **16i** gave K_i's for β_1 receptor binding equal to 2400, 5000, 7790 nM, respectively. A small increase in binding returned with the isopropyl derivative **16j** (K_i = 2990 nM) relative to the straight chain isomer **16i**. A methyl substituent at the 6-position, exemplified by the 6-methyl **16d**, and the 3,6-dimethyl **16e** analogs resulted in a dramatic increase in β_1 receptor binding as demon-

strated by K_i's = 220 and 150 nM, respectively. Both the 5-methyl analogs **16f** and **16g** showed a β_1 binding affinity similar to the parent. The 5-bromo analog **34** displayed a greater β_1 binding affinity than the 5-methyl analog **16f**. Addition of a second bromine to **34** to give the 3,5-dibromo analog **36** reduced β_1 binding (K_i = 170 and 630 nM for **34** and **36**, respectively). As noted earlier for the α_1 receptor, the 4'-methylpiperazinyl derivatives again exhibited greatly reduced binding affinity relative to the piperazinyl derivatives as shown by the following K_i's for the β_1 receptors, **4** (K_i = 400 nM) vs **32b** (no detectable binding), the 5-methyl analogs **16f** (K_i = 360 nM) vs **17** (K_i = 2800 nM), and the 5-bromo analogs **34** (K_i = 170 nM) vs **33b** (K_i = 500 nM), respectively.

β_2 Receptor Affinity

Receptor binding affinity at β_2 was generally reduced (exception **16i**) for the 3-alkyl substituents relative to the parent **4** (K_i = 1700 nM) but with no apparent trend as shown by the K_i's for the 3-methyl **25m**, 3-ethyl **16h**, 3-propyl **16i**, and 3-isopropyl **16j** equal to 2300, 3240, 1390 and 2010 nM, respectively. However, substitution with a 5-bromo, 5-methyl, or 6-methyl moiety demonstrated a strong increase in β_2 receptor binding as seen most dramatically for the 6-methyl **16d** and 3,6-dimethyl **16e** analogs (K_i's = 280 and 250 nM, respectively).

Hypoglycemic Potency and α_2 Receptor Affinity

The most potent hypoglycemic agents in the ob/ob mouse model in this series of alkyl- and halo-substituted 8-(1-piperazinyl)imidazo[1,2-*a*]pyrazines were the 2-methyl **16k**, 3-methyl **25m**, and 5-methyl **16f** analogs [relative potencies (to **2**) 25×, 11× and 17×, respectively]. These compounds also displayed high affinity for the α_2 receptor (K_i's = 51, 240, and 140 nM for **16k**, **25m**, and **16f**, respectively). A small increase in the size of the 3-alkyl moiety reduced α_2 binding and hypoglycemic activity as shown by the similar activity of the 3-ethyl **16h**, 3-propyl **16i**, and 3-isopropyl **16j** analogs. Replacement of a hydrogen in **16h** with fluorine to give the 3-(2-fluoroethyl) analog **20** increased hypoglycemic activity 2-fold. The 6-methyl analog **16d** displayed a K_i for α_2 binding slightly higher than the 3-methyl analog **25m** but was not as potent a hypoglycemic agent. Addition of a 3-methyl group to **16d** to give the 3,6-dimethyl derivative **16e** reduced α_2 binding affinity but unexpectedly increased hypoglycemic activity (K_i's for α_2 affinity were 190 and 620 nM, and hypoglycemic activity, determined by the % of blood glucose after a single dose were 61% and 47% for **16d** and **16e**, respectively). Addition of a 3-methyl group to the 5-methyl analog **16f** to give the 3,5-dimethyl compound **16g** also reduced α_2 binding affinity (K_i = 140 and 340 nM for **16f** and **16g**) and as expected lowered the hypoglycemic potency. Within the halo-substituted series, addition of a 3-bromo substituent to **34** to give the 3,5-dibromo analog **36** showed a great loss in α_2 binding affinity (K_i = 182 and 11860 nM, respectively). In addition **36** was inactive as a hypoglycemic agent. The 6-chloro analog **37b** exhibited a greater affinity for the α_2 receptor than the 3-chloro analog **37a** (K_i = 73 and 240 nM, respectively) and was also more effective in lowering blood glucose. As was noted for the other receptors, the introduction of a 4-methyl group on the piperazine moiety reduced α_2 binding affinity and lowered hypoglycemic potency for the parent compound **4** (K_i = 15 nM and 1020 nM, and hypoglycemic relative potency 76× and 19× relative to **2**, for **4** and **32b**, respectively). In contrast, introduction of 4-methylpiperazine in the 5-methyl series (**16f** and **17**) increased α_2 receptor binding while lowering hypoglycemic potency. For the 5-bromo analogs **34** and **33b**, the 4-methylpiperazine moiety contributed to a very small reduction in α_2 binding affinity and both compounds were essentially inactive in lowering blood glucose. However, note that the impact of the 4-methyl group on the piperazine ring on the ability to modulate hypoglycemic activity is clouded by the potential of metabolic demethylation[34] in vivo to regenerate the parent piperazine.

Summary

Piperazinyl derivatives of imidazo[1,2-*a*]pyrazine have significant hypoglycemic activity, which on the basis of binding data available does not seem to correlate with binding to α_1- or β-adrenergic receptors.

Modifications on the parent compound **4** demonstrated significant variations in binding to the α_1-, α_2-, β_1- and β_2-adrenergic receptors. In general, the decrease in α_2 receptor binding affinity upon addition of substituents to the parent **4** corresponded to a lowering of hypoglycemic activity in this series of compounds (it is not possible on the basis of binding data to distinguish agonist from antagonist from partial agonist activity). The highest affinity for the α_1 receptor was observed in analogs **16d**, **16e**, and **37b** which contained a 6-halo or 6-methyl moiety (K_i = 250–500 nM). The greatest β_1 and β_2 receptor binding was found in **16d**, **16e**, **16f**, and **34** which contained a 5- or 6-methyl or 5-halo substituent (K_i for β_1 = 150–360 nM, K_i for β_2 = 250–820 nM). In addition β_1 binding was greatly reduced for the 3-alkyl derivatives. 4-Methylation of the piperazinyl moiety dramatically reduced the binding to the α_1 and β_1 receptor. A very significant loss in binding on all the receptors was observed for the 2,3-dihydroimidazo[1,2-*a*]pyrazine analogs **28m** and **28n**. Their α_2 receptor binding affinity was among the lowest in the series (K_i = 870 and 1600 nM for **28n** and **28m**, respectively), and very little hypoglycemic activity was observed.

Experimental Section

Proton NMR spectra were recorded on Varian XL-200 or SC-300 spectrometers in $CDCl_3$–Me_4Si, DMSO–Me_4Si or D_2O–TMSP. Mass spectra were obtained with a Varian MAT 731 instrument. Column chromatography was performed on E. Merck silica gel 60 (70–230 mesh) or grade 62 (60–200 mesh). Microanalytical results in Tables II–IV are indicated by atomic symbols and are within ±0.4% of the theoretical values. Melting points (uncorrected) were determined in open capillary tubes with a Thomas-Hoover apparatus.

Method A (ring closure): 8-Chloro-3-ethylimidazo[1,2-*a*]pyrazine (14h). A mixture of 1.59 g (7.0 mmol) of α-bromobutyraldehyde diethyl acetal (**12**), 0.7 mL of 48% hydrobromic acid, and 0.7 mL of H_2O was refluxed for 1 h, cooled, and poured into a suspension of 3.2 g of $NaHCO_3$ in 20 mL of 2-propanol. After CO_2 bubbling had ceased, the mixture was filtered and 518 mg (4.0 mmol) of 2-amino-3-chloropyrazine (**6c**)[35] was added to the filtrate. The resulting solution was refluxed under N_2 for 10 h and then concentrated to a solid residue which was partitioned between CH_2Cl_2 and 10% Na_2CO_3. The organic layer was dried

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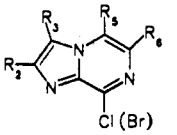
(35) Okada, S.; Kosasayama, A.; Konno, T.; Uchimaru, F. Studies on Pyrazine Derivatives. II. Synthesis, Reactions, and Spectra of Pyrazine N-Oxide Derivatives. *Chem. Pharm. Bull.* **1971**, *19*, 1344–1357.

Table II. Substituted 8-Haloimidazo[1,2-*a*]pyrazines



14 d-l, 23m, 29, 30

26m, n

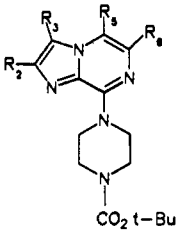
compd	R_2	R_3	R_5	R_6	method (yield, %)	*m/e*[a]	^{1}H NMR data[b]	mol formula
14d	H	H	H	CH_3	A (83)	167, 169 (Cl) 211, 213 (Br)	2.50 (s, 3 H, C6-CH_3), 7.68 (s, 1 H, H2, H3, or H5), 7.79 (s, 1 H, H2, H3, or H5), 7.87 (s, 1 H, H2, H3, or H5)	
14e	H	CH_3	H	CH_3	B (51)	181, 183 (Cl) 225, 227 (Br)	2.50 (s, 3 H, C3 or C6-CH_3), 2.52 (s, 3 H, C3 or C6-CH_3), 7.60 (s, 1 H, H2 or H5), 7.64 (s, 1 H, H2 or H5)	
14f	H	H	CH_3	H	A (74)	167, 169 (Cl) 211, 213 (Br)	2.60 (s, 3 H, C5-CH_3), 7.54 (s, 1 H, H6) 7.66 (d, 1 H, H2 or H3, J = 1.2), 7.88 (d, 1 H, H2 or H3, J = 1.2)	
14g	H	CH_3	CH_3	H	B (59)	181, 183 (Cl) 225, 227 (Br)	2.81 (s, 6 H, C3 and C5-CH_3), 7.30 (s, 1 H, H2 or H6), 7.52 (s, 1 H, H2 or H6)	
14h	H	CH_2CH_3	H	H	A (59)	181, 182 (Cl) 225, 227 (Br)	1.44 (t, 3 H, CH_3, J = 7.6), 2.92 (q, 2 H, CH_2, J = 7.6), 7.64 (s, 1 H, H3), 7.70 (m, 1 H, H5 or H6), 7.84 (m, 1 H, H5 or H6)	
14i	H	$(CH_2)_2CH_3$	H	H	A (46)	195, 197 (Cl) 239, 241 (Br)	1.04 (t, 3 H, CH_3, J = 7.2), 1.82 (dt, 2 H, CH_2CH_3, J = 7.2), 2.86 (t, 2 H, $CH_2CH_2CH_3$, J = 7.2), 7.64 (s, 1 H, H3), 7.70 (m, 1 H, H5 or H6), 7.86 (m, 1 H, H5 or H6)	
14j	H	$CH(CH_3)_2$	H	H	B (15)	195, 197 (Cl) 239, 241 (Br)	1.43 (d, 6 H, $(CH_3)_2$, J = 6.8), 3.2 (m, 1 H, CH, J = 6.8), 7.62 (s, 1 H, H2), 7.68 (d, 1 H, H5 or H6, J = 4.5), 7.85 (d, 1 H, H5 or H6, J = 4.5)	
14k[c]	CH_3	H	H	H				
14l	H	CH_2CH_2OBz	H	H	B (33)	302 (Cl)	3.40 (t, 2 H, C3-CH_2, J = 6.7), 4.66 (t, 2 H, CH_2OBz, J = 6.7), 7.39–7.62 (m, 3 H, *m,p*-Bz), 7.73 (d, 1 H, H5 or H6, J = 4.5), 7.77 (s, 1 H, H2), 7.92–8.01 (2 d, 2 H, *o*-Bz), 8.06 (d, 1 H, H5 or H6, J = 4.5)	$C_{15}H_{12}N_3O_2Cl \cdot 0.25H_2O$
23m[d]	H	CH_3	H	H	F (85)	167, 169 (Cl)	2.54 (s, 3 H, C3-CH_3), 7.64 (s, 1 H, H2), 7.71 (d, 1 H, H5 or H6), 7.82 (d, 1 H, H5 or H6)	$C_7H_6N_3Cl \cdot 0.1\ H_2O$
26m	2,3-dihydro-3-CH_3		H	H	G (45)	169, 171 (Cl)	1.69 (d, 3 H, C3-CH_3, J =6.7), 3.83 (dd, Ha or Hb, $^2J_{HaHb}$ = 11.5, $^3J_{HaH3}$ = 8.5), 4.34 (dd, Ha or Hb, $^2J_{HaHb}$ = 11.5, $^3J_{HbH3}$ = 11.5), 5.13–5.32 (m, 1 H, CH), 7.80 (d, 1 H,H5 or H6, J = 4.2), 8.07 (d,1 H, H5 or H6, J = 4.2)	$C_7H_8N_3Cl \cdot HCl \cdot 1.25H_2O$
26n	2,3-dihydro		H	H	G (89)	155	4.19 (t, 2 H, CH_2, J = 10, 4.89 (t, 2 H, CH_2, J = 10), 7.81 (d, 1 H, H5 or H6, J = 4), 8.04 (d, 1 H, H5 or H6, J = 4)	$C_6H_8N_3Cl \cdot HCl \cdot H_2O$
29[e]	H	H	H	H				
30[e]	H	Br	H	H				

[a] Mass spectra are EI except for 14l which is FAB. [b] NMR chemical shifts are in ppm and coupling constants are in hertz. NMRs are in $CDCl_3$, except **26m** and **26n** are in D_2O. [c] Reference 18. [d] Reference 11. [e] Reference 10.

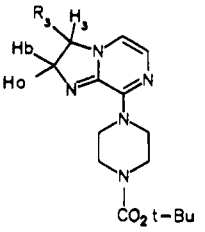
($MgSO_4$) and concentrated to 652 mg of crude solid. Chromatography on silica gel was performed with a gradient elution (70:30 to 40:60 hexane–EtOAc) to give 429 mg of pale yellow solid (59%).

Method B (ring closure): 8-Chloro-3,5-dimethylimidazo[1,2-*a*]pyrazine (14g). A mixture of 240 mg (1.67 mmol) of 2-amino-3-chloro-6-methylpyrazine (**6a**)[28] and 593 mg of 70% pure α-bromopropionaldehyde in dioxane (2.5 mmol) (**7**) in 6 mL of 2-propanol was heated at reflux overnight. The reaction was concentrated in vacuo, and the oil residue was partitioned between EtOAc and 10% Na_2CO_3. The organic layer was dried ($MgSO_4$) and chromatographed on a silica gel column (elution gradient

Table III. Substituted 8-(1-Boc-piperazinyl)imidazol[1,2-*a*]pyrazines



15d-l, 18, 19, 24m
32a, 33a, 35, 38a,b



27m,n

compd	R_2	R_3	R_5	R_6	method (yield, %)	*m/e*[a]	^{1}H NMR data[b]	mol formula
15d	H	H	H	CH_3	D (62)	317	1.48 (s, 9 H, Boc), 2.28 (s, 3 H, C6-CH_3), 3.58 (m, 4 H, pip CH_2's), 4.24 (m, 4 H, pip CH_2's), 7.34 (s, 1 H, H2, H3, or H5), 7.41 (s, 1 H, H2, H3, or H5), 7.51 (s, 1 H, H2, H3, or H5)	$C_{16}H_{23}N_5O_2$
15e	H	CH_3	H	CH_3	C (75)	331	1.48 (s, 9 H, Boc), 2.31 (s, 3 H, C2 or C5-CH_3), 2.38 (s, 3 H, C2 or C5-CH_3), 3.59 (m, 4 H, pip CH_2's), 4.23 (m, 4 H, pip CH_2's), 7.10 (s, 1 H, H2 or H5), 7.26 (s, 1 H, H2 or H5)	$C_{17}H_{25}N_5O_2$
15f	H	H	CH_3	H	C (81)	317	1.49 (s, 9 H, Boc), 2.44 (d, 3 H, CH_3, $J_{H\text{-}H}$ = 1), 3.60 (m, pip CH_2's), 4.16 (m, pip CH_2's), 7.19 (d, 1 H, H6, J = 1), 7.43 (d, 1 H, J = 1.2), 7.62 (d, 1 H, J = 1.2)	*c*
15g	H	CH_3	CH_3	H	C (47)	331	1.48 (s, 9 H, Boc), 2.67 (s, 3 H, C3 or C5-CH_3), 2.73 (s, 3 H, C3 or C5-CH_3), 3.59 (m, 4 H, pip CH_2's), 4.07 (m, 4 H, pip CH_2's), 7.00 (s, 1 H, H2 or H6), 7.24 (s, 1 H, H2 or H6)	*c*
15h	H	CH_2CH_3	H	H	C (63)	331	1.38 (t, 3 H, CH_3, J = 7.5), 1.50 (s, 9 H, Boc), 2.82 (q, 2 H, CH_2, J = 7.5), 3.61 (m, 4 H, pip CH_2's), 4.26 (m, 4 H, pip CH_2's), 7.32 (d, 1 H, H5 or H6, J = 4.5), 7.34 (s, 1 H, H2), 7.41 (d, 1 H, H5 or H6, J = 4.5)	$C_{17}H_{25}N_5O_2 \cdot 2.5H_2O$
15i	H	$CH_2CH_2CH_3$	H	H	C (78)	345	1.03 (t, 3 H, CH_3, J = 7.2), 1.48 (s, 9 H, Boc), 1.78 (dt, 2 H, CH_2CH_3, J = 7.2), 2.77 (t, 2 H, $CH_2CH_2CH_3$, J = 7.2), 3.60 (m, 4 H, pip CH_2's), 4.25 (m, 4 H, pip CH_2's), 7.31 (d, 1 H, H5 or H6), 7.32 (s, 1 H, H2), 7.38 (d, 1 H, H5 or H6)	$C_{17}H_{27}N_5O_2 \cdot 0.1H_2O$
15j	H	$CH(CH_3)_2$	H	H	C (75)	346	1.37 (d, 6 H, $(CH_3)_2$, ^3J = 6.7), 1.48 (s, 9 H, Boc), 3.04–3.18 (m, 1 H, CH, ^3J = 6.7), 3.57 (m, 4 H, pip CH_2's), 4.21 (m, 4 H, pip CH_2's), 7.29 (s, 1 H, H2), 7.32 (d, 1 H, H5 or H6), 7.37 (d, 1 H, H5 or H6)	$C_{16}H_{27}N_5O_2 \cdot 0.1H_2O$
15k	CH_3	H	H	H	C (70)	317	1.49 (s, 9 H, Boc), 2.43 (s, 3 H, C2-CH_3), 3.60 (m, 4 H, pip CH_2's), 4.21 (m, 4 H, pip CH_2's), 7.25 (s, 1 H, H3), 7.31 (d, H5 or H6, ^3J = 4.2), 7.45 (d, H5 or H6, ^3J = 4.2)	$C_{16}H_{23}N_5O_2 \cdot 0.15C_3H_6O$

Table III (Continued)

compd	R_2	R_3	R_5	R_6	method (yield, %)	*m/e*[a]	^{1}H NMR data[b]	mol formula
15l	H	CH_2CH_2OBz	H	H	C (60)	452	1.49 (s, 9 H, Boc), 3.31 (t, 2 H, C3-CH_2), 3.60 (m, 4 H, pip CH_2's), 4.26 (m, 4 H, pip CH_2's), 4.64 (t, 2 H, CH_2O, ^3J = 6.7), 7.38–7.62 (m, 6 H, H2, H5, H6, *m,p*-Bz), 7.98–8.04 (m, 2 H, *o*-Bz)	$C_{24}H_{29}N_5O_4$
18	H	CH_2CH_2OH	H	H	(82)	348	1.50 (s, 9 H, Boc), 3.07 (t, 2 H, C3-CH_2, ^3J = 6.2), 3.57 (m, 4 H, pip CH_2's), 3.97 (t, 2 H, CH_2O), 4.20 (m, 4 H, pip CH_2's),7.36–7.46 (m, 3 H, H2, H5, and H6)	*c*
19	H	CH_2CH_2F	H	H	(37)	350	1.48 (s, 9 H, Boc), 3.22 (dt, 2 H, C3-CH_2, $^3J_{H\text{-}H}$ = 6, $^3J_{H\text{-}F}$ = 23.7), 3.58 (m, 4 H, pip CH_2's), 4.24 (m, 4 H, pip CH_2's), 4.75 (dt, 2 H, CH_2F, $^3J_{H\text{-}H}$ = 6, $^2J_{H\text{-}F}$ = 47), 7.34–7.44 (m, 3 H, H2, H5, and H6)	*c*
24m	H	CH_3	H	H	D (76)	317	1.50 (s, 9 H, Boc), 2.44 (s, 3 H, C3-CH_3), 3.61 (m, 4 H, pip CH_2's), 4.27 (m, 4 H, pip CH_2's), 7.30 (d, 1 H, H5 or H6, ^3J = 4.5), 7.34 (s, 1 H, H2), 7.42 (d, 1 H, H5 or H6, ^3J = 4.5)	$C_{16}H_{23}N_5O_2$
27m	2,3-dihydro-3-CH_3		H	H	H (79)	319	1.20 (d, 3 H, C3-CH_3, ^3J = 6.5), 1.47 (s, 9 H, Boc), 3.42–3.66 (m, 5 H, pip CH_2's, H3, ^3J = 6.5), 3.78 (m, 4 H, pip CH_2's), 4.08–4.33 (m, 2 H, Ha, Hb), 6.51 (d, 1 H, H5 or H6), 6.62 (br s, 1 H, H5 or H6)	$C_{16}H_{25}N_5O_2$
27n	2,3-dihydro		H	H	H (70)	305	1.48 (s, 9 H, Boc), 3.53 (m, 4 H, pip CH_2's),3.80 (m, 4 H, pip CH_2's), 3.94–4.02 (m, 4 H, CH_2CH_2), 6.54 (br s, 2 H, H5 and H6)	*c*
32a	H	H	H	H	M (80)	304	1.49 (s, 9 H, Boc), 3.60 (m, 4 H, pip CH_2's), 4.25 (m, 4 H, pip CH_2's), 7.35 (d, 1 H, H2, H3, H5, or H6, ^3J = 4.5), 7.50 (d, 1 H, H2, H3, H5, or H6, ^3J = 1), 7.51 (d, 1 H, H2, H3, H5, or H6, ^3J = 1), 7.55 (d, 1 H, H2, H3, H5, or H6, ^3J = 4.5)	$C_{15}H_{21}N_5O_2$
33a	H	H	Br	H	K (55)	381, 383 (Br)	1.49 (s, 9 H, Boc), 3.60 (m, 4 H, pip CH_2's), 4.23 (m, 4 H, pip CH_2's) 7.46 (s, 1 H, H6), 7.60 (d, 1 H, H2, or H3, ^3J = 1.25), 7.72 (d, 1 H, H2 or H3, ^3J = 1.2)	*c*
35	H	Br	Br	H	L (59)	459, 461 (Br)	1.49 (s, 9 H, Boc), 3.58 (m, 4 H, pip CH_2's), 4.17 (m, 4 H, pip CH_2's), 7.43 (s, 1 H, H2 or H6), 7.50 (s, 1 H, H2 or H6)	$C_{16}H_{18}N_5O_2Br$
38a	H	Cl	H	H	M (85)	337, 339 (Cl)	1.49 (s, 9 H, Boc), 3.60 (m, 4 H, pip CH_2's), 4.26 (m, 4 H, pip CH_2's), 7.47 (s, 1 H, H2, H5 or H6), 7.48 (s, 2 H, H2, H5, or H6)	*c*
38b	H	H	H	Cl	M (62)	337, 339 (Cl)	1.49 (s, 9 H, Boc), 3.60 (m, 4 H, pip CH_2's), 4.33 (m, 4 H, pip CH_2's), 7.47 (s, 1 H, H2, H3, or H6), 7.54 (s, 1 H, H2, H3 or H6), 7.55 (s, 1 H, H2, H3, or H6)	$C_{15}H_{20}N_5O_2Cl$

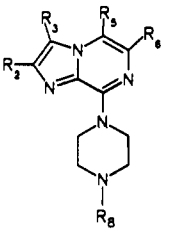
[a] Mass spectra are EI except for **15j**, **15l**, **18**, **19**, and **32a** which were FAB. [b] NMR chemical shifts are in ppm in $CDCl_3$ and coupling constants are in hertz. [c] Oil.

80:20 to 40:60 hexane–EtOAc) to yield 177.8 mg (59%) of a white solid: mp 163–164.5 °C.

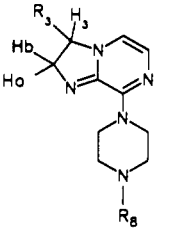
Method C: (introduction of piperazine without Et_3N): 6-Methyl-8-(4-Boc-piperazinyl)imidazo[1,2-a]pyrazine (15d). To 301 mg (1.8 mmol) of **14d** dissolved in 12 mL of absolute ethanol was added 1.0 g (5.4 mmol) of Boc-piperazine. The resulting solution was stirred at room temperature under N_2 overnight and then heated at 60 °C for 3 h. Concentration in vacuo gave a residual oil which was taken up in CH_2Cl_2 and washed with 10% Na_2CO_3, followed by H_2O. The CH_2Cl_2 layer was dried ($MgSO_4$), filtered, and concentrated onto 8 mL of silica gel. Chromatography on silica gel (elution gradient 80:20 to 50:50 hexane–EtOAc) gave 356 mg (62%) of a light pink solid: mp 127.0–129.0 °C.

Method D (introduction of piperazine with Et_3N): 3,6-Dimethyl-8-(4-Boc-piperazinyl)imidazo[1,2-a]pyrazine (15e). A solution of 100 mg (0.55 mmol) of **14e**, 205 mg (1.1 mmol) of Boc-piperazine, and 92 μL (0.660 mmol) of Et_3N in 2 mL of ethanol

Table IV. Substituted 8-(1-Piperazinyl)imidazo[1,2-*a*]pyrazines



16d-k, 17, 20, 25m, 31
32b, 33b, 34, 36, 37a, b



28m, n

compd	R_2	R_3	R_5	R_6	R_8	method (yield, %)	*m/e*[a]	^{1}H NMR data[b]	mol formula
16d	H	H	H	CH_3	H	E (85)	217	2.40 (s, 3 H, C6-CH_3), 3.56 (m, 4 H, pip CH_2's), 4.38 (m, 4 H, pip CH_2's), 7.83 (s, 1 H, H2, H3, or H5), 7.88 (s, 1 H, H2, H3, or H5), 7.98 (s, 1 H, H2, H3, or H5)	$C_{11}H_{15}N_5 \cdot 2HCl \cdot H_2O$
16e	H	CH_3	H	CH_3	H	E (84)	231	2.34 (s, 3 H, C3 or C6-CH_3), 2.41 (s, 3 H, C3 or C6-CH_3), 3.46 (m, 4 H, pip CH_2's), 4.20 (m, 4 H, pip CH_2's), 7.37 (s, 1 H, H2 or H5), 7.57 (s, 1 H, H2 or H5)	$C_{12}H_{17}N_5 \cdot 2HCl \cdot 1.5H_2O$
16f	H	H	CH_3	H	H	E (71)	217	2.58 (s, 3 H, C5-CH_3), 3.59 (m, 4 H, pip CH_2's), 4.41 (m, 4 H, pip CH_2's), 7.31 (s, 1 H, H6), 7.96 (d, 1 H, H2 or H3, ^3J = 1.1), 8.08 (d, 1 H, H2 or H3, ^3J = 1.1)	$C_{11}H_{15}N_5 \cdot 2.5HCl \cdot 0.5H_2O \cdot 0.5CH_3CH_2OH$[c]
16g	H	CH_3	CH_3	H	H	E (86)	231	2.78 (s, 3 H, C3 or C5-CH_3), 2.81 (s, 3 H, C3 or C5-CH_3), 3.57 (m, 4 H, pip CH_2's), 4.28 (m, 4 H, pip CH_2's), 7.16 (s, 1 H, H2 or H6), 7.65 (s, 1 H, H2 or H6)	$C_{12}H_{17}N_5 \cdot 3HCl \cdot H_2O$
16h	H	CH_2CH_3	H	H	H	E (37)	231	1.38 (t, 3 H, CH_3), 2.96 (q, 2 H, CH_2), 3.60 (m, 4 H, pip CH_2's), 4.40 (m, 4 H, pip CH_2's), 7.52 (d, 1 H, H5 or H6, ^3J = 5.2), 7.76 (s, 1 H, H2), 7.98 (d, 1 H, H5 or H6, ^3J = 5.2)	$C_{12}H_{17}N_5 \cdot 2HCl \cdot 2H_2O$
16i	H	$CH_2CH_2CH_3$	H	H	H	E (82)	245	0.98 (t, 3 H, CH_3), 1.78 (m, 2 H, CH_2CH_3), 2.88 (t, 2 H, C3-CH_2), 3.54 (m, 4 H, pip CH_2's), 4.29 (m, 4 H, pip CH_2's), 7.45 (d, 1 H, H5 or H6, ^3J = 6.7), 7.58 (s, 1 H, H2), 7.78 (d, 1 H, H5 or H6, ^3J = 6.7)	$C_{13}H_{19}N_5 \cdot 2HCl \cdot 0.1C_3H_6O$[c]
16j	H	$CH(CH_3)_2$	H	H	H	E (59)	245	1.38 (d, 6 H, $(CH_3)_2$), ^3J = 6.7), 3.25–3.39 (m, H, CH, ^3J = 6.7), 3.56 (m, 4 H, pip CH_2's), 4.34 (m, 4 H, pip CH_2's), 7.50 (d, 1 H, H5 or H6, ^3J = 5.5), 7.75 (s, 1 H, H2), 8.04 (d, 1 H, H5 or H6, ^3J = 5.5)	$C_{13}H_{19}N_5 \cdot 2HCl \cdot 2H_2O$
16k	CH_3	H	H	H	H	E (82)	217	2.49 (s, 3 H, C2-CH_3), 3.54 (m, 4 H, pip CH_2's), 4.24 (m, 4 H, pip CH_2's), 7.50 (d, 1 H, H5 or H6, ^3J = 5), 7.82 (s, 1 H, H3), 8.04 (d, 1 H, H5 or H6, ^3J = 5)	$C_{11}H_{15}N_5 \cdot 2HCl \cdot 0.5H_2O$
17	H	H	CH_3	H	CH_3	J (84)	231	2.29 (s, 3 H, N-CH_3), 2.36 (br s, 3 H, C_5-CH_3, ^4J = 1), 2.54 (m, 4 H, pip CH_2's), 4.16 (m, 4 H, pip CH_2's), 7.13 (d, 1 H, H6, ^4J = 1), 7.35 (d, 1 H, H2 or H3, ^3J = 1), 7.54 (d, 1 H, H2 or H3, ^3J = 1)	$C_{12}H_{17}N_5 \cdot 0.25H_2O$
20	H	CH_2CH_2F	H	H	H	N (35)	250	3.40 (dt, 2 H, C3-CH_2, $^3J_{H\text{-}H}$ = 5.5, $^3J_{H\text{-}F}$ = 27), 3.56 (m, 4 H, pip CH_2's), 4.41 (m, 4 H, pip CH_2's), 4.40 (dt, 2 H, CH_2F, $^3J_{H\text{-}H}$ = 5.5, $^3J_{H\text{-}F}$ = 41.2), 7.44 (d, 1 H, H5 or H6), 7.78 (s, 1 H, H2), 7.99 (d, 1 H, H5 or H6)	$C_{12}H_{16}N_5F \cdot 2HCl \cdot H_2O \cdot 0.15CF_3CO_2H$
25m	H	CH_3	H	H	H	E (40)	217	2.52 (s, 3 H, C3-CH_3), 3.56 (m, 4 H, pip CH_2's), 4.36 (m, 4 H, pip CH_2's), 7.64 (s, 1 H, H2), 7.48 (d, 1 H, H5 or H6), 7.89 (d, 1 H, H5 or H6)	$C_{11}H_{19}N_5 \cdot 2HCl \cdot 0.75H_2O$

Table IV (Continued)

compd	R_2	R_3	R_5	R_6	R_8	method (yield, %)	*m/e*[a]	^{1}H NMR data[b]	mol formula
28m	2,3-dihydro-3-CH_3		H	H	H	I (34)	219	1.66 (d, 3 H, C3-CH_3, ^3J = 6.5), 3.46 (m, 4 H, pip CH_2's), 3.68 (m, 4 H, pip CH_2's), 3.77 (dd, 1 H, Ha, $^2J_{HaHb}$ = 11, $^3J_{HaH3}$ = 8.2), 4.27 (dd, 1 H, Hb, $^2J_{HaHb}$ = 8.2, $^3J_{HbH3}$ = 11), 5.02–5.19 (m, 1 H, H3), 6.28 (s, 2 H, =CH), 7.69 (br s, 2 H, H5 and H6)	$C_{11}H_{17}N_5 \cdot 1.9C_4H_4O_4$
28n	2,3-dihydro		H	H	H	I (34)	205	3.46 (m, 4 H, pip CH_2's), 3.68 (m, 4 H, pip CH_2's), 4.06–4.18 (m, 2 H, CH_2), 4.70–4.84 (m, 2 H, CH_2), 6.30 (s, 2 H, =CH), 7.61–7.68 (q, 2 H, H5 and H6)	$C_{10}H_{15}N_5 \cdot 2.2C_4H_4O_4 \cdot 0.25H_2O \cdot 0.1CH_3CH_2OH$
31	H	Br	H	H	CH_3	J (53)	296, 298 (Br)	2.21 (s, 3 H, N-CH_3), 2.44 (m, 4 H, pip CH_2's), 4.20 (m, 4 H, pip CH_2's), 7.51 (d, 1 H, H5 or H6, $^3J_{H\text{-}H}$ = 4.5), 7.71 (d, 1 H, H5 or H6, $^3J_{H\text{-}H}$ = 4.5), 7.73 (s, 1 H, H2)	$C_{11}H_{14}N_5Br \cdot 0.25H_2O$
32b	H	H	H	H	CH_3	J (82)	217	2.36 (s, 3 H, N-CH_3), 2.60 (m, 4 H, pip CH_2's), 4.32 (m, 4 H, pip CH_2's), 7.34 (d, 1 H, H2, H3, H5, or H6, $^3J_{H\text{-}H}$ = 4.5), 7.49 (d, 1 H, H2, H3, H5, or H6, $^3J_{H\text{-}H}$ = 1.2), 7.51 (d, 1 H, H2, H3, H5, or H6, $^3J_{H\text{-}H}$ = 4.5), 7.56 (d, 1 H, H2, H3, H5, or H6, $^3J_{H\text{-}H}$ = 1.2)	$C_{11}H_{15}N_5$
33b	H	H	Br	H	CH_3	J (41)	295, 297 (Br)	2.34 (s, 3 H, N-CH_3), 2.58 (m, 4 H, pip CH_2's), 4.29 (m, 4 H, pip CH_2's), 7.45 (s, 1 H, H6), 7.60 (d, 1 H, H2 or H3, $^3J_{H\text{-}H}$ = 1.25), 7.72 (d, 1 H, H2 or H3, $^3J_{H\text{-}H}$ = 1.25)	$C_{11}H_{14}N_5Br$
34	H	H	Br	H	H	E (96)	281, 283 (Br)	3.48 (m, 4 H, pip CH_2's), 4.24 (m, 4 H, pip CH_2's), 7.56 (s, 1 H, H2, H3, or H6), 7.72 (s, 1 H, H2, H3, or H6), 8.02 (s, 1 H, H2, H3, or H6)	$C_{10}H_{12}N_5Br \cdot 2HCl \cdot 0.45H_2O$
36	H	Br	Br	H	H	E (67)	361	3.46 (m, 4 H, pip CH_2's), 4.18 (m, 4 H, pip CH_2's), 7.42 (s, 1 H, H2 or H6), 7.60 (s, 1 H, H2 or H6)	$C_{10}H_{11}N_5Br \cdot 2HCl$
37a[d,e]	H	Cl	H	H	H				
37b[d,e]	H	H	H	Cl	H				

[a] Mass spectra were taken EI except for **16j**, **20**, and **31** which were FAB. [b] NMR chemical shifts are in ppm in D_2O, DMSO, or $CDCl_3$, and coupling constants are measured in hertz. [c] Solvent was observed in the NMR. [d] Reference 10. [e] Reference 11.

was heated in an oil bath (60 °C) under N_2 overnight. The reaction was cooled, concentrated, and partitioned between EtOAc and 10% Na_2CO_3. The organic layer was dried ($MgSO_4$) and concentrated to 263 mg of residual oil which was chromatographed on silica gel (gradient elution 80:20 to 60:40 hexane–EtOAc) to give 137.7 mg (75%) of a white solid: mp 130.5–132.5 °C.

Method E (Boc removal): 6-Methyl-8-(1-piperazinyl)-imidazo[1,2-*a*]pyrazine (16d). A solution of 254 mg (0.8 mmol) of **15d** in 5 mL of absolute EtOH was treated with 3 mL of ethanolic HCl. After standing for 10 min, the solvent was slowly evaporated under N_2. The residual solid was washed with 1 × (1 mL EtOH and 1 mL Et_2O) followed by 3 × 2 mL of Et_2O by centrifugation. After vacuum drying at 50 °C, 198 mg (85%) of white solid was obtained.

Method F (ring closure): 8-Chloro-3-methylimidazo[1,2-*a*]pyrazine (23m).[11] To a solution of 371 mg (2.0 mmol) of **22m**[11] in 1 mL of trifluoroacetic acid was added cautiously 0.7 mL of trifluoroacetic anhydride. After 4 h of stirring at room temperature the solution was evaporated under N_2 to a residual oil which was partitioned between $CHCl_3$ and 10% Na_2CO_3. The $CHCl_3$ layer was washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo to yield 286 mg (85%) of white solid: mp 166–168 °C.

Method G (ring closure): 2,3-Dihydro-8-chloroimidazo-[1,2-*a*]pyrazine Hydrochloride (26n). 2-Chloro-3-[(2-hydroxyethyl)amino]pyrazine[10] (**21n**) (863 mg, 5 mmol) in 10 mL of xylenes was treated with 2 mL of thionyl chloride. The nonhomogeneous mixture was heated at 80–100 °C under N_2 overnight. The precipitate was collected by filtration to yield 856 mg (89%) of pale yellow solid.

Method H (introduction of piperazine): 2,3-Dihydro-8-(4-Boc-piperazinyl)imidazo[1,2-*a*]pyrazine (27n). An amount of 400 mg (2.08 mmol) of **26n** was partitioned between CH_2Cl_2 and 10% Na_2CO_3. The aqueous phase was further extracted with 2 × 20 mL of CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), and concentrated to 301 mg (93%) of pale yellow solid. To this was added 10 mL of isoamyl alcohol, 0.54 mL (3.87 mmol) of triethylamine, and 395 mg (2.12 mmol) of Boc-piperazine. The reaction was heated for 4 h (oil bath 125 °C) under N_2 and then concentrated in vacuo. The solid residue was partitioned between CH_2Cl_2 and 10% Na_2CO_3. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated in vacuo to 897 mg of a light amber oil. Chromatography on a silica gel column (gradient elution 70:30 to 50:50 cyclohexane–acetone) gave 410 mg (70%) of **27n** as a yellow oil.

Method I (Boc removal): 2,3-Dihydro-3-methyl-8-(1-piperazinyl)imidazo[1,2-*a*]pyrazine Dimaleate (28m). A solution of 350 mg (1.09 mmol) of **27m** and 10 mL of trifluoroacetic acid was stirred for 20 min. Evaporation under N_2 gave an amber oil which was dissolved in 2 mL of H_2O and passed through a 10-mL ion-exchange column (Dowex 1 × 2 OH^- 200–400 mesh) to give 220 mg (92%) of the free base of **28m** as an amber oil. Treatment of 215 mg of the free base with 125 mg (1.07 mmol) of maleic acid dissolved in 8 mL of EtOH gave a precipitate

Table V. Receptor-Binding Data and Hypoglycemic Potency for Piperazinylimidazo[1,2-a]pyrazines

compd	α_1 K_i, nM	α_2 K_i, nM	β_1 K_i, nM	β_2 K_i, nM	blood glucose, % of control at dose of 30 mg/kg	relative potency[a]
4	3100	15	400	1700		76
16d	500	190	220	280	61	
16e	300	620	150	250	47	6
16f	2600	140	360	820	52	17
16g		340	400		72	
16h	30% @ 10000	530	3460, 5000	3240	54	4
16i	2650	480	7790	1390	59	4
16j	5430	370	2990	2010	60	3
16k		51	310		28	25, 32
17	45% @ 10000	81	2800		51	6
20					56	8
25m	1800	240	2400	2300	32	11
28n	15% @ 10000	870	17% @ 10000	2% @ 10000	71	
28m	12% @ 10000	1600	10310	17700	88	
31	4% @ 10000	1350	6300		98	
32b		1020	NB[b]		62	19
33b	22% @ 10000	270	500		100	
34	1490	182	170	520	87	
36		11860	630		NA[c]	
37a	2780	240			66	
37b	250	73			36	>5[d]

[a] Relative potency [potency MT-1403/potency of test compound] measured relative to **2** (MTP-1403) by comparison of parallel line assays obtained from blood glucose assays at multiple doses (see Experimental Section). [b] NB = not bound. [c] NA = not active. [d] Extrapolation.

which was washed with 3 × 3 mL of Et_2O by centrifugation and vacuum-dried to give 154.8 mg (34%) of **28m** as a dimaleate salt.

Method J (introduction of piperazine): 8-(4-Methylpiperazinyl)imidazo[1,2-a]pyrazine (32b). A mixture of 275 mg (1.78 mmol) of **29**,[10] 217 mL (241 mg, 2.4 mmol) of *N*-methylpiperazine, and 0.50 mL (363 mg, 3.59 mmol) of triethylamine in 8 mL of EtOH was heated in an oil bath at 70–80 °C under N_2 for 4 h. Concentration gave a crude solid which was chromatographed on silica gel (90:10:1 CH_2Cl_2–MeOH–H_2O) to give 319 mg (82%) of a light cream solid: mp 144.5–147 °C.

Method K (monobromination): 5-Bromo-8-(4-Boc-piperazinyl)imidazo[1,2-a]pyrazine (33a). A mixture of 100 mg (0.33 mmol) of **32a** and 71.2 mg (0.4 mmol) of NBS in 1.0 mL of $CHCl_3$ was refluxed for 3.5 h under N_2. The reaction was diluted with $CHCl_3$ and extracted with 10% Na_2CO_3. The organic layer was dried ($MgSO_4$) and concentrated onto 1.5 mL of silica gel which was placed on top of a 25-mL silica gel column. Gradient elution (95:5 to 75:25 hexane–EtOAc) gave 70 mg (55%) of **33a** as a viscous oil and 12 mg (8%) of **35** as a white solid.

Method L (dibromination): 3,5-Dibromo-8-(4-Boc-piperazinyl)imidazo[1,2-a]pyrazine (35). A mixture of 200 mg (0.66 mmol) of **32a** and 293.7 mg (1.65 mmol) of NBS in 2 mL of $CHCl_3$ was refluxed under N_2 for 3 h. The reaction was diluted with $CHCl_3$, extracted with 10% Na_2CO_3, dried ($MgSO_4$), and then concentrated onto 5 mL of silica gel. Chromatography on a silica gel column with a gradient elution (95:5 to 85:15 hexane–EtOAc) gave 179.5 mg (59%) of solid: mp 134–135 °C.

Method M (Boc protection): 8-(4-Boc-piperazinyl)imidazo[1,2-a]pyrazine (32a). A solution of 400 mg (1.45 mmol) of **4**[10] in 2.5 mL of H_2O was treated with 1.28 mL (3.19 mmol, 2.2 equiv) of 2.5 N NaOH, 2.5 mL of *t*-BuOH and 1.27 g (5.8 mmol, 4 equiv) of di-*tert*-butyl dicarbonate and stirred under N_2 at room temperature overnight. Concentration gave an oil residue which was taken up in CH_2Cl_2, washed with 10% Na_2CO_3, dried ($MgSO_4$), and concentrated again to give 848 mg of crude oil. Chromatography on a silica gel column (gradient elution 70:30 to 50:50 hexane–EtOAc) provided 353 mg (80%) of **32a** as a white solid: mp 107.5–109 °C.

3-(2-Hydroxyethyl)-8-(4-Boc-piperazinyl)imidazo[1,2-a]pyrazine (18). A suspension of 151 (320 mg, 0.708 mmol) in 5 mL of MeOH and 5 mL of 40% aqueous $MeNH_2$ was heated in an oil bath at 60 °C for 1.5 h. The reaction was then concentrated and partitioned between EtOAc and 10% Na_2CO_3. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on a silica gel column (1:1 EtOAc–hexane) to give 201 mg (82%) of a glasslike solid.

3-(2-Fluoroethyl)-8-(4-Boc-piperazinyl)imidazo[1,2-a]pyrazine (19). To 192 mg (0.47 mmol) of **18** dissolved in 2 mL of dry CH_2Cl_2 was added 80 mg (2.0 mmol) of MgO, and the resulting suspension was cooled in a dry ice–acetone bath. DAST (100 μL, 0.80 mmol) was added dropwise, and the reaction was allowed to warm to room temperature while stirring overnight. The tan-colored suspension was diluted with Et_2O and extracted with cold 1 M K_2HPO_4. The ethereal layer was dried ($MgSO_4$) and concentrated to 115 mg of crude oil which was chromatographed on a 1000 μm prep plate (1:1 hexane–EtOAc) to give 63.5 mg (41%) of **19** as a yellow oil.

Method N (Boc removal): 3-(2-Fluoroethyl)-8-(1-piperazinyl)imidazo[1,2-a]pyrazine (20). A solution of 63.5 mg (0.16 mmol) of **19** was dissolved in 1 mL of TFA and stirred under N_2 for 30 min. The yellow solution was then evaporated under N_2 to a crude oil which was taken up in CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and concentrated to a residual oil. The oil was then dissolved in 1 mL of EtOH and treated with 2 mL of ethanolic HCl. After standing for 1 h the solution was evaporated under N_2 to 1 mL, and a precipitate was observed. The solid was then washed with 2 × 2 mL of Et_2O by centrifugation and 20.2 mg (35%) of **20** as a light cream-colored solid was obtained.

4-(Benzoyloxy)-2-bromobutyraldehyde (9). To 4.85 g (20.2 mmol) of 4-(benzoyloxy)butyraldehyde[36] in 20 mL of Et_2O in an ice bath was added 5.02 g (20.2 mmol) of the bromine–dioxane complex[25] in 15 mL of Et_2O. The reaction was diluted with Et_2O and washed with H_2O, 5% Na_2CO_3, and H_2O. The ethereal layer was dried ($MgSO_4$) and concentrated to 5.39 g of clear oil which was chromatographed on silica gel (7:3 hexane–EtOAc) to give 1.21 g (22%) of **9** as a clear liquid.

1-Boc-piperazine.[29,30] To a solution of piperazine (668.5 g, 7.68 mol) in 8.08 L of H_2O and 9.24 L of *t*-BuOH was added 1.22 L of 2.5 N NaOH while cooling to 5 °C in an ice bath. Slowly over 60–90 min, 672 g (3.05 mol, 706 ml) of di-*tert*-butyl dicarbonate was added maintaining 5–6 °C. The reaction was stirred 1 h at 5 °C and then warmed to 25 °C and allowed to stand overnight. The above reaction was repeated on the same scale and the two homogeneous solutions were combined and evaporated to remove *t*-BuOH. This effected precipitation of a white solid which was collected by filtration and vacuum-dried at 40 °C to yield 213.4 g (24.4%) of a white solid, bis-Boc-piperazine, mp 162–163 °C. The above filtrate was extracted with 4 × 3 L of CH_2Cl_2, washed with H_2O and saturated brine, dried ($MgSO_4$), and filtered through Na_2SO_4. Concentration followed by cooling

(36) Hoffmann, H. M. R.; Rabe, J. DABCO-Catalyzed Coupling of Aldehydes with Activated Double Bonds. 4. Stereoselective Synthesis of Trisubstituted Olefins and Terpenoid Building Blocks via 2-(Hydroxyalkyl)-2-propenoic Esters. *J. Org. Chem.* **1985**, *50*, 3849–3859.

in ice gave 894.8 g (78.8%) of Boc-piperazine as a white solid: mp 47–49 °C.

Hypoglycemic Potency. Male obese mice (C57BL/6J ob/ob) were obtained from Jackson Laboratories (Bar Harbor, Maine) at approximately 6 weeks of age. They were housed in a temperature controlled room at 25 °C with a 12-h cycle of light and dark. The mice were maintained on Purina Laboratory Chow and had free access to H_2O.

Glucose was administered subcutaneously (2 g/kg) 30 min after oral administration of the test compounds. The mice were then bled via the orbital sinus 30 min after the glucose load. The data is expressed as a % of the control group (5 mice/group). In those cases where potency was determined relative to compound **2**, graded doses of compounds were administered to groups of mice (5 mice/group), and blood was obtained from the mice in the manner described above. Relative potency values were determined by the relative potency for parallel line bioassays.[37]

Glucose in the blood was determined by the potassium ferricyanide–potassium ferrocyanide oxidation–reduction reaction on the Technicon Autoanalyzer. Statistical analysis was performed using Students *t*-test to make pairwise comparisons (p less than 0.05).

α_1- and α_2-Adrenergic Receptor Binding Assay. The α_1- and α_2-adrenergic receptor binding assays were performed as described by Lumma et al.[10] and employed radiolabeled clonidine or radiolabeled prazosin.

β_1- and β_2-Adrenergic Receptor Binding Assay. The β_1- and β_2-adrenergic receptor binding assays employed the radioligand [^{125}I]CYP which was obtained from New England Nuclear. The β_1-adrenergic receptor binding assay required guinea pig frozen left heart ventricles, an enriched source of β_1 receptors. The left ventricle from a freshly killed guinea pig was weighed and rapidly frozen to −75 °C. Shortly before the assay was started, the frozen tissue was homogenized using a Polytron (setting = 6 for 10 s) in 20 mL of cold 0.05 M Tris buffer containing 0.8 M KCl, pH 7.7. The homogenate was filtered through three layers of cheesecloth and centrifuged at 700g for 10 min, and the supernatant was centrifuged at 30000g for 10 min. The pellet was resuspended in Tris buffer (no KCl) and centrifuged again at 30000g for 10 min. Centrifugation, resuspension, and centrifugation were repeated as above. The final product was resuspended in Tris buffer at a concentration of 23 fmol of β_1 adrenergic receptor/mg of protein.

For the β_2-adrenergic receptor binding assay, guinea pig lungs from freshly killed animals were placed in ice-cold saline. After removal of major bronchi, the tissue was homogenized into ice-cold pH 7.7 Tris buffer in a chilled Waring blender for 20 s. The resulting slurry was homogenized in 50 volumes of ice-cold Tris buffer using a Polytron (setting = 6 for 10 s). The homogenate was filtered through two layers of cheesecloth and then centrifuged at 30000g for 10 min. The pellet was resuspended into Tris buffer and centrifuged again. Rehomogenization and centrifugation were repeated. The final pellets were rapidly frozen in a dry ice–acetone bath and stored in a freezer at −75 °C. Shortly before the incubation phase of the assay, a single pellet was rehomogenized into 40 mL of ice-cold Tris buffer, centrifuged at 30000g for 10 min and rehomogenized into 100 mL of ice-cold Tris buffer.

The β_1 and β_2 binding assays[38] were conducted in borosilicate glass culture tubes which contained 50 μL of a radioligand solution (dilution of the commerical sample to 50 pM), 50 μL of a solution of the drug being evaluated, and 150 μL of tissue homogenate. The reaction was initiated by the addition of the tissue, and incubation continued for 60 min at 37 °C before it was terminated by rapid filtration through Whatman GF/B glass fiber filters under vacuum. The filters were removed and counted on a γ-ray spectrometer.

Specific binding was defined as the difference between total and nonspecific binding (with and without [^{125}I]CYP). Binding assay data was plotted as log concentration vs percent inhibition and analyzed by nonlinear least-squares techniques with 100% maximal inhibition assumed at the high test compound concentrations. The IC_{50} values thus obtained were used to calculate the inhibition constants from the relationship $K_i = [IC_{50}/1 + [L]/K_d]$ where [L] is the concentration of radioligand employed in the binding assay and K_d is its receptor dissociation constant.

(37) Finney, D. J. *Statistical Methods in Biological Assay*; Charles Griffin & Co., Ltd.; London, 1964; pp 99–138.

(38) Strader, C. D.; Sigal, I. S.; Register, R. B.; Candelore, M. R.; Rands, E.; Dixon, R. A. F. Identification of residues required for ligand binding to the β-adrenergic receptor. *Proc. Natl. Acad. Sci. U.S.A.* 1987, *84*, 4384–4388.

(39) Hydroxy Aldehydes and Derivatives Thereof. British Patent GB1,-215,073, 1968.