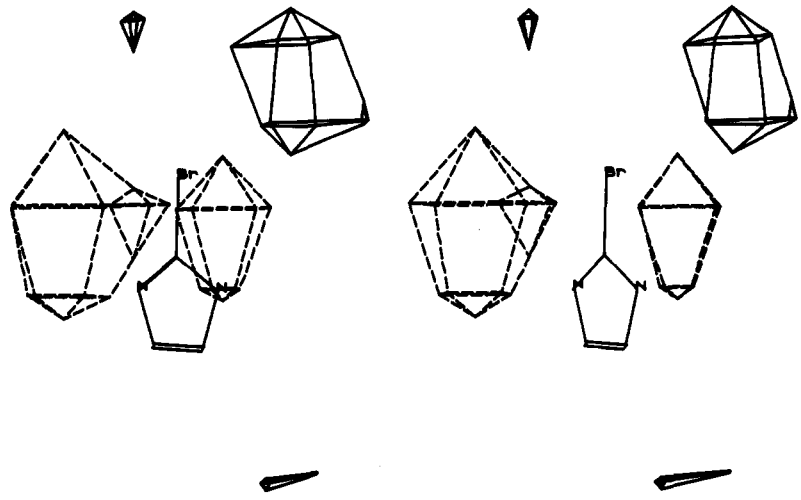

Figure 4. Stereoscopic view of the major electrostatic feature of eq 8. The negative contour regions (solid lines) decrease the pK_a values, while the positive contour regions (dashed lines) increase the pK_a values. (The contour is shown at the 0.35 coefficient level.)

Figure 4 shows important electrostatic regions in space that influence the pK_a values of imidazolines. Electron-withdrawing substituents at the 2-position make the positive contour region more electropositive and the negative contour region more electronegative. More electropositive charge in the positive contour region decreases the energy needed to remove the acidic H^+ and thus decreases the pK_a value of imidazoline analogues.

The contour regions show where strong electrostatic influences may be expected, if these compounds were placed in a biological receptor site.

We have oversimplified the description of the substituent effects on the pK_a values of the clonidine-like imidazolines and the substituted imidazoles by basing our calculation on the unsolvated, unprotonated species calculated in a vacuum, and only on one tautomer. This might explain why there are still some unaccounted-for deviations in the calculated pK_a values. Clearly, calculations considering other aspects would involve a lot more computer time and also present the ambiguity as to where to place the solvent molecules, how many solvent molecules to use, and the relative orientation of the solute and the solvent. For these reasons we chose to examine the correlations based only on the unsolvated neutral molecule. Changing any of these conditions and assumptions would likely affect the results. In ligand binding to a macromolecule, which is our primary interest, the macromolecular binding site is more fixed in space, since the side chains of a protein are not as free to move as are individual water molecules. Therefore, the substituent effect on pK_a is not a perfect model for the substituent effect on the electrostatic contribution to the binding affinity of a ligand for a macromolecule.

Conclusions

Molecular fields, calculated with an H^+ probe and AM1 partial atomic charges using a CoMFA method, reproduced and predicted the pK_a values of 28 clonidine-like imidazoline analogues and 16 imidazoles. The results of this study show that the CoMFA treatment of electrostatic effects is suitable to predict pK_a values and, along with our previous investigation[18] of this method, support its application in studies of 3D quantitative structure–activity relationships.

2-(Oxadiazolyl)- and 2-(Thiazolyl)imidazo[1,2-*a*]pyrimidines as Agonists and Inverse Agonists at Benzodiazepine Receptors

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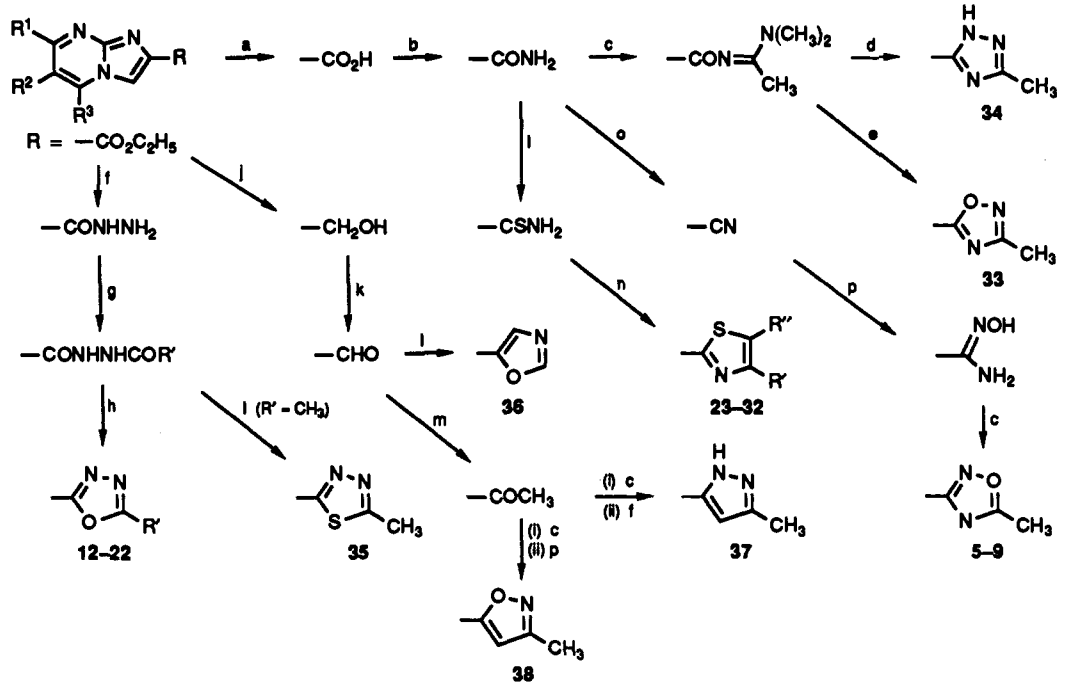
Oxadiazoles, like the benzoyl group in a series of imidazo[1,2-*a*]pyrimidines, have been found to be metabolically stable alternatives to ester groups in benzodiazepine-receptor ligands. This change has lead to a number of compounds which bind to the receptors and which exhibit potent agonist activity in a food-motivated conflict test thought to predict anxiolytic properties. Compounds **4**, **5**, and **13** were equipotent with chlordiazepoxide but showed little or no myorelaxant effects. Replacing the oxadiazole group by thiazole gave compounds such as **23** which binds to the benzodiazepine receptor but exhibits the intrinsic activity of a partial inverse agonist in vivo.

A number of (imidazo[1,2-*a*]pyrimidin-2-yl)phenylmethanones and related compounds have been shown to specifically interact with benzodiazepine receptors and to possess partial agonist properties, resulting in differing degrees of separation of anxiolytic and sedative/myorelaxant effects in vivo.[1] Modification of the benzoyl group

0022-2623/91/1834-2060$02.50/0

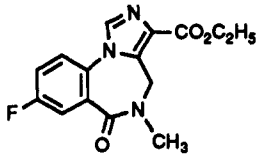
Scheme I[a]



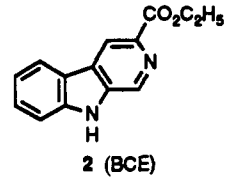
[a]Reagents: (a) K_2CO_3; H_2O, MeOH; (b) (i) CDI; DMF, (ii) NH_3; $CHCl_3$; (c) DMA acetal; (d) $NH_2NH_2 \cdot H_2O$; AcOH; (e) NH_2OH; dioxane, AcOH; (f) $NH_2NH_2 \cdot H_2O$; EtOH; (g) $(RCO)_2O$; EtOH; (h) PPA; (i) Lawesson's reagent; (j) $LiBH_4$; THF; (k) MnO_2; $CHCl_3$; (l) tosmic, K_2CO_3; MeOH; (m) (i) CH_3MgI; THF, (ii) MnO_2; $CHCl_3$; (n) R'COCHR"Cl; EtOH; (o) $(F_3CO)_2O$; Et_3N; (p) NH_2OH; EtOH.

was found in general to be detrimental to the affinity of the compounds for the receptor; therefore the search for other metabolically stable alternatives to the ester group of the initial lead compounds continued to be a major goal of the project.

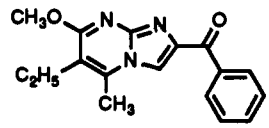
Receptor affinity appeared to be dependent upon the presence of a carbonyl group ortho to an unsubstituted heterocyclic nitrogen atom[2] as found in ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (Ro15-1788) (1) and ethyl β-carboline-3-carboxylate (BCE) (2).



1 (RO15-1788)



2 (BCE)



3 (RU32698)

In the imidazo[1,2-*a*]pyrimidine series, a particularly appealing proposal which might fulfill the electronic and steric requirements for receptor affinity was to replace the benzoyl group of (6-ethyl-7-methoxy-5-methylimidazo-[1,2-*a*]pyrimidin-2-yl)phenylmethanone (RU32698) (3) by a small heterocycle in which a nitrogen or oxygen atom would take the place of the carbonyl oxygen. This might then mimic an ester group while being stable to hydrolysis.

The first compound synthesized to test the theory was the oxadiazole **33**, which was found to have an IC_{50} of 630 nM in the displacement of [^{3}H]flunitrazepam from rat-brain preparations. Although this represented almost 1 order of magnitude less affinity than compound **3**, the minimum effective dose (MED) of **33** was found to be 5 mg/kg on oral administration in the food-motivated conflict screen for anxiolytics, compared with 2 mg/kg for **3**. It appeared that despite weaker receptor affinity, oxadiazole **33** was more bioavailable. It was decided, therefore, to investigate further the structure–activity relationships in a series of 2-heterocyclic substituted imidazo[1,2-*a*]pyrimidines.

Chemistry

The methods used to prepare the 2-substituted imidazo[1,2-*a*]pyrimidines are shown in Scheme I. The ethyl ester starting materials were synthesized by the reaction of 2-pyrimidinamines with ethyl 2-bromopyruvate as previously described.[1]

The esters were hydrolyzed to the corresponding acids, which then reacted with *N,N'*-carbonyldiimidazole to give the imidazolides. Treatment of the imidazolides with ammonia in chloroform yielded the corresponding primary amides. Reaction of the amides with Lawesson's reagent produced the thioamides while treatment with trifluoroacetic anhydride and triethylamine gave the nitriles.

The 5-substituted [1,2,4]oxadiazol-3-yl compounds **5–9**[3] (Table I) were obtained by reacting the nitriles with hydroxylamine and then cyclizing the *N*-hydroxyamidines with dimethylacetamide dimethyl acetal. Cyclization with trifluoroacetic anhydride gave the trifluoromethyl derivative **4**. The 3-bromo and 3-chloro compounds **10** and **11** were obtained by reaction of compound **5** with *N*-bromo- and *N*-chlorosuccinimide, respectively.

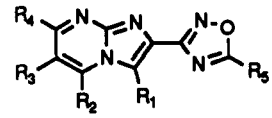
The 5-substituted [1,3,4]oxadiazol-2-yl compounds **12–22**[3] (Table II) were synthesized by reacting the esters with hydrazine hydrate to give the hydrazides, acylating

(1) Clements-Jewery, S.; Danswan, G.; Gardner, C. R.; Matharu, S. S.; Murdoch, R.; Tully, W. R.; Westwood, R. *J. Med. Chem.* **1988**, *31*, 1220.

(2) Danswan, G.; Kennewell, P. D.; Tully, W. R. *J. Heterocycl. Chem.* **1989**, *26*, 293.

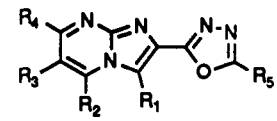
(3) Gillespie, R. J.; Tully, W. R. British Patent 2170199, 1986.

Table I. 1,2,4-Oxadiazoles



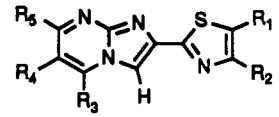
no.	R_1	R_2	R_3	R_4	R_5	mp, °C	anal.	flunitrazepam receptor binding: IC_{50}, nM	food conflict: MED, mg/kg po
4	H	CH_3	C_2H_5	CH_3O	CF_3	197–200	$C_{13}H_{12}F_3N_5O_2$	3200	2
5	H	CH_3	C_2H_5	CH_3O	CH_3	176–177	$C_{12}H_{15}N_5O_2$	500	2–5
6	H	CH_3	C_3H_7	CH_3O	CH_3	185–185.5	$C_{14}H_{17}N_5O_2$	1600	5
7	H	CH_3	CH_2=$CHCH_2$	CH_3O	CH_3	147–150	$C_{14}H_{15}N_5O_2 \cdot 0.67H_2O$	560	10
8	H	$-(CH_2)_4-$		CH_3O	CH_3	218–222	$C_{14}H_{15}N_5O_2$	560	5
9	H	CH_3	C_2H_5	CH_3S	CH_3	209–210	$C_{13}H_{15}N_5OS$	160	2
10	Br	CH_3	C_2H_5	CH_3O	CH_3	166–168	$C_{13}H_{14}BrN_5O_2$	10000	10
11	Cl	CH_3	C_2H_5	CH_3O	CH_3	155–157	$C_{13}H_{14}ClN_5O_2$	10000	10

Table II. 1,3,4-Oxadiazoles



no.	R_1	R_2	R_3	R_4	R_5	mp, °C	anal.	flunitrazepam receptor binding: IC_{50}, nM	food conflict: MED, mg/kg po
12	H	CH_3	C_2H_5	CH_3O	H	198.5–199	$C_{12}H_{13}N_5O_2$	10000	>50
13	H	CH_3	C_2H_5	CH_3O	CH_3	193.5–195	$C_{13}H_{15}N_5O_2$	6300	2
14	H	CH_3	C_2H_5	CH_3O	C_2H_5	170–172	$C_{14}H_{17}N_5O_2$	>10000	50
15	H	CH_3	C_2H_5	CH_3O	C_3H_7	180–181.5	$C_{15}H_{19}N_5O_2$	>10000	50
16	H	CH_3	C_2H_5	CH_3O	CF_3	210–211	$C_{13}H_{12}F_3N_5O_2$	>10000	10–50
17	H	CH_3	C_2H_5	CH_3O	C_6H_5	245–248	$C_{18}H_{17}N_5O_2$	>10000	>50
18	H	CH_3	C_3H_7	CH_3O	CH_3	219–220	$C_{14}H_{17}N_5O_2$	7900	10
19	H	$-(CH_2)_4-$		CH_3O	CH_3	222–226	$C_{14}H_{15}N_5O_2$	3200	>50
20	H	CH_3	CH_2=$CHCH_2$	CH_3O	CH_3	186–188	$C_{14}H_{15}N_5O_2$	2500	10
21	H	CH_3	CH_3CH=CH	CH_3O	CH_3	202–210	$C_{14}N_{15}N_5O_2$	>10000	>50
22	H	CH_3	C_2H_5	CH_3S	CH_3	175–175.5	$C_{13}H_{15}N_5OS$	320	5

Table III. Thiazoles



no.	R_1	R_2	R_3	R_4	R_5	mp, °C	anal.	flunitrazepam receptor binding: IC_{50}, nM	food conflict: MED, mg/kg po	food conflict: CDZP antagonism:[a] MED, mg/kg po
23	H	CH_3	CH_3	C_2H_5	CH_3O	184–186	$C_{14}H_{16}N_4OS$	112	>50	10
24	H	H	CH_3	C_2H_5	CH_3O	142–144	$C_{13}H_{14}N_4OS$	200	NT[b]	10
25	H	CH_3	CH_3	C_2H_5	CH_3S	151–152	$C_{14}H_{16}N_4S_2$	80	>50	50
26	CH_3	CH_3	CH_3	C_2H_5	CH_3O	221–222	$C_{15}H_{18}N_4OS$	2500	>50	>50
27	H	$CO_2C_2H_5$	CH_3	C_2H_5	CH_3O	211–215	$C_{16}H_{16}N_4O_3S$	2800	>50	NT
28	H	CF_3	CH_3	C_2H_5	CH_3O	179–181	$C_{14}H_{13}F_3N_4OS$	2000	>50	>50
29	H	C_2H_5	CH_3	C_2H_5	CH_3O	121–122	$C_{15}H_{16}N_4OS$	220	50	50
30	H	CH_3	CH_3	C_3H_7	CH_3O	160–161	$C_{15}H_{16}N_4OS$	100	>50	50
31	H	CH_3	CH_3	CH_2=$CHCH_2$	CH_3O	149–150	$C_{15}H_{16}N_4OS$	100	>50	>50
32	H	CH_3	$-(CH_2)_4-$		CH_3O	260–263	$C_{15}H_{16}N_4OS$	22	>50	>50

[a] Conflict antagonism of chlordiazepoxide (CDZP) at 10 mg/kg po. [b] Not tested.

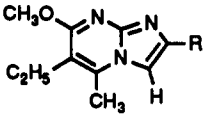
with the appropriate acid anhydride, and then cyclizing in hot polyphosphoric acid.

The 2-thiazolyl compounds **23–32**[4] (Table III) were prepared from the thioamides by reaction with α-halo ketones.

(4) Deacon, R. M. J.; Gardner, C. R.; Gillespie, R. J.; Tully, W. R. British Patent 2191196, 1987.

The miscellaneous compounds **33–38** (Table IV) were prepared as follows. Treatment of the appropriate amide with dimethylacetamide acetal yielded an acyl amidine which was cyclized with hydroxylamine to give the 3-methyl[1,2,4]oxadiazol-5-yl compound **33**.[3] Cyclization of the amidine with hydrazine hydrate gave the [1,2,4]triazole compound **34**. Cyclization of the *N*-acetylhydrazide intermediate used in the preparation of [1,3,4]oxadiazole **13**

Table IV. Miscellaneous Compounds



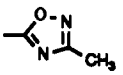
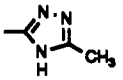
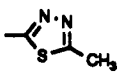
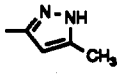
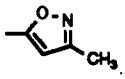
no.	R	mp, °C	anal.	flunitrazepam receptor binding: IC_{50}, nM	food conflict: MED, mg/kg po
33		204–205	$C_{12}H_{15}N_5O_2$	630	5
34		216–220	$C_{13}H_{16}N_6O \cdot 0.25H_2O$	>10000	>50
35		210–210.5	$C_{13}H_{15}N_5OS \cdot 0.25H_2O$	>10000	2–5
36		145.5–146.5	$C_{13}H_{14}N_4O_2 \cdot 0.33H_2O$	2500	>50
37		233–235	$C_{14}H_{17}H_5O$	5000	>50
38		188–190	$C_{14}H_{16}N_4O_2$	4500	50

Table V. Comparative Biological Data for Example Agonist Compounds

compound	flunitrazepam receptor binding: IC_{50}, nM	food conflict: MED[a]	antagonism of leptazol seizures: ED_{50}[a]	rotating drum: ED_{50}[a]
chlordiazepoxide	*b*	2	1.9 (1.1–3.2)	6.8 (5.0–9.2)
5	500	2–5[c]	7.4 (6.2–8.9)	17 (9.2–31.5)
6	1600	5	13 (5.2–34.2)	16.5 (11.6–23.4)
33	630	5[c]	14 (11.1–17.6)	>100
13	6300	2[c]	20 (12.7–31.6)	>200
8	560	5	55	>100
4	3200	1–2	70	>200

[a] MED (minimal effective dose) and ED_{50} values in mg/kg per os. [b] In vitro receptor binding activity for chlordiazepoxide has not been shown in view of its in vivo metabolism. [c] The anticonflict actions of these compounds were fully reversed by compound 1 (20 mg/kg ip).

with Lawesson's reagent gave instead the [1,3,4]thiadiazole **35**. Oxazole **36** was obtained from the corresponding aldehyde[5] by reaction with tosylmethyl isocyanide.

Reaction of the aldehyde with methylmagnesium iodide followed by oxidation of the resultant secondary alcohol with manganese dioxide yielded the methyl ketone.[5] Treatment of the ketone with dimethylacetamide acetal yielded a crotyl ketone which was cyclized either with hydrazine hydrate to give pyrazole **37** or with hydroxylamine to give isoxazole **38**.

Results and Discussion

Following the observed activity of the [1,2,4]oxadiazol-5-yl compound **33**, isomeric oxadiazoles **5** and **13** were synthesized, along with other five-membered heterocyclic compounds such as thiazole **23**, triazole **34**, thiadiazole **35**, oxazole **36**, pyrazole **37**, and isoxazole **38**, all of which retained the optimal substituents in the imidazo[1,2-*a*]pyrimidine ring as determined for the benzoyl compound **3**.[1] The [1,2,4]oxadiazol-3-yl compound **5** was slightly better than **33** both in terms of affinity and anxiolytic activity. The [1,3,4]oxadiazol-2-yl isomer **13** and the [1,3,4]thiadiazol-2-yl analogue **35**, however, showed little affinity in vitro while retaining some anxiolytic activity in vivo, as predicted by the food-motivated conflict test. The other replacements for the benzoyl group were less active both in vitro and in vivo, except for thiazole **23**, which possessed an IC_{50} of 112 nM with no activity at 50 mg/kg in the conflict test.

Modification of the methyl substituent on the oxadiazoles generally reduced receptor affinity and activity in food conflict with the exception of the trifluoromethyl-[1,2,4]oxadiazol-3-yl compound **4**, which was at least as potent as compound **5** in spite of an affinity of 3.2 μM. Modifications of other positions in the molecule while retaining the methyloxadiazole group at position 2 did not, in general, improve activity. Replacement of the methoxy group at position 7 by methylthio increased affinity but resulted in similar or reduced potency in vivo, as previously observed for other members of this series.[1] Likewise, a halogen substituent at position 3 reduced affinity, although some anticonflict activity was retained.

The most active of the 2-(oxadiazolyl)imidazo[1,2-a]-pyrimidines in the conflict test, in terms of potency and magnitude of response, were selected for further pharmacological study (Table V). All of these compounds may possess different degrees of partial agonism at benzodiazepine receptors because they show progressively less sedative/myorelaxant and anticonvulsant effects as indicated by the rotating drum test and the leptazol seizure model, respectively. It was confirmed for compounds **5**, **13**, and **33** that they act via benzodiazepine receptors since

(5) Tully, W. R. British Patent 2128989, 1984.

their anticonflict activity was completely blocked by the benzodiazepine antagonist compound 1. These three compounds were also tested in a stress-induced ultrasounds model in rat pups[6] and their anxiolytic-like effects found to be antagonized by compound 1 (unpublished observations).

Compound 6, the 6-propyl analogue of compound 5, showed a particularly sedative effect in the rotating drum test. However, its actions may not be due solely to agonism at benzodiazepine receptors since the compound also interacts with the associated chloride channel allosteric site, as indicated by binding studies with *tert*-butyl bicyclophosphorothionate (IC_{50} = 145 μM). Barbiturates may act partly or wholly by interacting with this site[7] and compound 6 induced barbiturate-like respiratory depression in mice at high doses (>100 mg/kg), superimposed on benzodiazepine-like effects. It is interesting that this activity should arise from a single-carbon extension to the alkyl chain at position 6. Compound 8, on the other hand, with the same number of carbon atoms in the side chains at positions 5 and 6 but cyclized into a tetramethylene bridge had receptor and conflict activity similar to that of compound 5 with no effects in the rotating drum at 100 mg/kg.

It is of particular note that there is no correlation between benzodiazepine-receptor affinity in vitro and potency in in vivo tests as exemplified by compound 13 with an IC_{50} of 6.3 μM and yet an MED at 2 mg/kg in food conflict. It is not possible to account for this lack of correlation in terms of different intrinsic activities at the receptors.[8] There are two possible explanations for such compounds which specifically interact with benzodiazepine receptors. Either they penetrate to the active site in the brain in sufficient quantities to compensate for the low affinity of the parent molecule, or they are metabolically transformed to compounds with higher affinity. Kinetic studies[9] with compound 5 have indicated high levels of parent molecule with no evidence of metabolites that have higher affinity for benzodiazepine receptors. This suggests that the in vivo effects result from the action of the parent molecule, despite its low affinity.

Some of the 2-thiazolyl derivatives (Table III) retained affinity for benzodiazepine receptors with IC_{50} values <250 nM, but were inactive in food conflict. Two of these compounds, 23 and 24, were found to be potent antagonists of chlordiazepoxide in food conflict. As with other imidazo[1,2-a]pyrimidines, replacement of the 7-methoxy group by methylthio increased receptor affinity, but this was associated with a reduction in benzodiazepine antagonism in food conflict. Modification of the alkyl substituents at positions 5 and 6 maintained affinity with the exception of the tetramethylene bridged compound 32, which was increased to 22 nM. However, there was little or no antagonism observed in food conflict, possibly due to a reduction in bioavailability. Other substitutions on the thiazole ring markedly reduced both affinity and in vivo activity, with the exception of the ethylthiazolyl compound 29, which showed weak agonistic activity.

Compound 23 was chosen for further pharmacological study. In addition to its ability to antagonise chlordiazepoxide in the conflict test, it showed intrinsic activity of its own (Table VI). Thus, it potentiated seizures induced by leptazol or by sound stimulation in DBA2 mice. This suggests that the compound possesses inverse agonist properties at benzodiazepine receptors, although these may be partial as it does not induce the seizures expected of a full inverse agonist, even at a dose of 200 mg/kg. Such properties may be useful in the treatment of cognitive disorders such as Alzheimer's disease.[10]

Table VI. Biological Activity of Compound 23[a]

flunitrazepam receptor binding: IC_{50}, nM	chlordiazepoxide antagonism in food conflict: MED po	potentiation of leptazol seizures: ED_{50} ip	potentiation of sound seizures: ED_{50} ip
112	10	1.7 (0.8–3.6)	3

[a] MED and ED_{50} values are in mg/kg/ 95% confidence limits are shown for the ED_{50} for leptazol seizure potentiation. Low maximum potentiation (<100%) of sound seizures precluded calculation of limits.

The increase in affinity of the thiazoles over the oxadiazoles might be explained by improved molecular orbital overlap of the sulfur-containing compounds with those of the receptor, similar to the 7-methylthio-substituted compounds being better than the corresponding 7-methoxy analogues. However, there is no apparent difference between the oxadiazoles and the thiazoles, except for the protrusion of the hydrogen atom at position 5 of the thiazole ring; so how can their respective agonist and inverse agonist properties be explained? A similar agonist–inverse agonist shift was observed with two methylthienyl isomers substituted at the 2-position of a series of pyrazolo[4,3-c]quinolinones.[11] Until the structure of the benzodiazepine-receptor complex is known in detail, one can only speculate about subtle differences in the physical nature of these ligands, such as polarizability, hydrophobicity, and electrostatic potential, in an attempt to explain the differences in their intrinsic activity. This is currently the subject of further study.

Conclusion

2-(Oxadiazolyl)imidazo[1,2-a]pyrimidines are a class of compounds which bind to benzodiazepine receptors with moderate to weak affinity, and yet display antianxiety properties of similar potency to chlordiazepoxide in animal models while demonstrating reduced or negligible myorelaxant effects. 2-(Thiazolyl)imidazo[1,2-a]pyrimidines on the other hand are generally more potent in binding to benzodiazepine receptors and yet are partial inverse agonists in vivo. Compounds such as these should be useful in further characterizing the nature of benzodiazepine-receptor interactions, leading to the design of molecules with a variety of therapeutic uses.

Experimental Section

Melting points were determined with a Reichert Kofler hot-stage melting point apparatus. IR spectra were determined for KBr disks with a Pye-Unicam SP 1000 spectrophotometer. NMR spectra were determined with a Bruker WP 2005Y instrument at 200 MHz, and chemical shifts are reported as δ values with respect to tetramethylsilane as internal standard. DMF and dichloromethane were dried by standing over 3-Å molecular sieves prior to use. THF was dried by distilling from $LiAlH_4$ prior to use. 2-Pyrimidinamines were synthesized by known methods.[12]

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Ethyl 6-Ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxylate. A solution of 5-ethyl-4-methoxy-6-methyl-2-pyrimidinamine (50.1 g, 0.3 mol) and ethyl bromopyruvate (70.2 g, 0.35 mol) in dry ether (300 mL) was stirred at room temperature for 24 h and the precipitated solid was filtered, washed with ether, and dried. The solid was suspended in ethanol (250 mL), and the mixture was stirred and heated under reflux for 2 h. The cooled solution was evaporated to dryness and the residue was partitioned between $CHCl_3$ and 5% $NaHCO_3$. The organic layer was separated and the aqueous layer extracted with more $CHCl_3$. Evaporation of the combined $CHCl_3$ solutions gave a solid which was purified by chromatography (silica; $CHCl_3$/EtOAc 7:3) to give the carboxylate (31.4 g, 40%), mp 151–152 °C. Anal. ($C_{13}H_{17}N_3O_3$) C, H, N. All ethyl esters were prepared in this way from the appropriate 2-pyrimidinamine.

6-Ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxamide. A mixture of ethyl 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxylate (120 g, 0.456 mol) and K_2CO_3 (120 g) in MeOH (1200 mL) and water (600 mL) was refluxed for 2 h. The MeOH was evaporated, more water (1500 mL) was added, and the resulting solution was acidified to pH = 1 (concentrated HCl). The solid obtained was filtered, washed with water and dried under vacuum over P_2O_5 at 80 °C to give 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxylic acid (87.43 g, 82%). To a solution of the acid (87.31 g, 0.371 mol) in dry DMF (1000 mL) was added *N,N'*-carbonyldiimidazole (73.9 g, 0.456 mol). After the reaction mixture was stirred at room temperature for 2 h, the product was filtered and washed with DMF followed by Et_2O to give the carboximidazolide (104.71 g, 99%). The imidazolide (93.0 g, 0.326 mol) was dissolved in $CHCl_3$ (1400 mL) and NH_3 gas bubbled through the solution for 2 h at room temperature. After stirring overnight, the solution was washed with brine (3×), dried ($MgSO_4$), and evaporated, and the resulting solid was triturated with ether to give the carboxamide (68.7 g, 90%): mp 256–259 °C (from MeOH); IR 3420, 3295, 1665, and 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (3 H, t, J = 7 Hz, 6-CH_2CH_3), 2.53 (3 H, s, 5-CH_3), 2.65 (2 H, q, J = 7 Hz, 6-CH_2CH_3), 4.05 (3 H, s, OCH_3), 6.15 (1 H, br m, NH), 7.40 (1 H, br m, NH), 7.88 (1 H, s, 3-H). Anal. ($C_{11}H_{14}N_4O_2$) C, H, N.

All carboxamides were prepared in this way from the corresponding esters.

(a) 2-([1,2,4]Oxadiazol-3-yl)imidazo[1,2-*a*]pyrimidines. 7-Methoxy-5-methyl-2-(5-methyl[1,2,4]oxadiazol-3-yl)-6-propylimidazo[1,2-*a*]pyrimidine (6). To a stirring suspension of 7-methoxy-5-methyl-6-propylimidazo[1,2-*a*]pyrimidine-2-carboxamide (6.25 g, 0.0252 mol) and triethylamine (5.09 g, 0.0503 mol) in dry CH_2Cl_2 (150 mL) was added dropwise trifluoroacetic anhydride (10.57 g, 0.0503 mol). After stirring at room temperature for 20 min, the solution was washed with water (3×) and brine and evaporated to dryness to give the carbonitrile (5.40 g, 93%) as a pale yellow solid. A mixture of the nitrile (5.30 g, 0.023 mol), hydroxylamine hydrochloride (1.76 g, 0.0253 mol), and KOH (1.42 g, 0.0253 mol) in EtOH (75 mL) was refluxed with stirring for 4.5 h. The mixture was cooled in ice and the solid was filtered and washed with cold EtOH. A suspension of the solid product in H_2O was stirred for 10 min and then filtered. The product was washed with H_2O and dried under vacuum (P_2O_5) to give the *N*-hydroxycarboxamidine (5.4 g, 89%). A mixture of the amidine (3.0 g, 0.0114 mol) and dimethylacetamide dimethyl acetal (5 mL) was heated at 100 °C for 1 h. The mixture was evaporated and the product was purified by flash chromatography (silica; $CHCl_3$) to give compound **6** (2.83 g, 87%) as colorless needles: mp 185–185.5 °C (from EtOAc); IR 3155, 1636, and 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (3 H, m, 6-$CH_2CH_2CH_3$), 1.56 (2 H, m, 6-$CH_2CH_2CH_3$), 2.57 (3 H, s, 5-CH_3), 2.67 (3 H, s, oxadiazole CH_3), 2.62 (2 H, m, 6-$CH_2CH_2CH_3$), 4.09 (3 H, s, OCH_3), 7.88 (1 H, s, 3-H). Anal. ($C_{14}H_{17}N_5O_2$) C, H, N.

Compounds **5** and **7–9** (Table I) were prepared by the same method from the appropriate carboxamides in yields of 85–95%. The 5-(trifluoromethyl)[1,2,4]oxadiazol-3-yl derivative (**4**) was prepared in the same way except that in the final stage a solution of the *N*-hydroxyamidine (2 g, 8.02 mmol) in dry CH_2Cl_2 (60 mL) containing Et_3N (0.97 g, 9.63 mmol) was treated with trifluoroacetic anhydride (5.05 g, 0.024 mol), and the mixture was heated at 45 °C for 1.5 h. The mixture was cooled, washed with H_2O, dried ($MgSO_4$), and evaporated to give compound **4** (2.49 g, 95%) as a colorless crystalline solid: mp 197–200 °C (from EtOAc); IR 3150, 1635, and 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (3 H, t, J = 7 Hz, 6-CH_2CH_3), 2.62 (3 H, s, 5-CH_3), 2.68 (2 H, q, J = 7 Hz, 6-CH_2CH_3), 4.09 (3 H, s, OCH_3), and 7.93 (1 H, s, 3-H); ^{13}C NMR δ ($CDCl_3$) 116.3 (J_{CF} = 250 Hz, CF_3) and 165.8 (J_{CF} = 45 Hz, CCF_3). Anal. ($C_{13}H_{12}N_5O_2F_3$) C, H, N, F.

Compounds **10** and **11** were prepared by reacting compound **5** with *N*-bromo- and *N*-chlorosuccinimide by using the method previously described.[1]

(b) 2-([1,3,4]Oxadiazol-2-yl)imidazo[1,2-*a*]pyrimidines. 6-Ethyl-7-methoxy-5-methyl-2-(5-propyl[1,3,4]oxadiazol-2-yl)imidazo[1,2-*a*]pyrimidine (15). A solution of ethyl 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxylate (10 g, 0.038 mol) and hydrazine hydrate (20 mL) in EtOH (150 mL) was refluxed for 4 h. Most of the EtOH was evaporated, H_2O (100 mL) was added, and the precipitate was filtered and washed with H_2O and then Et_2O to give the carbohydrazide (8.15 g, 86%). A solution of the hydrazide (2 g, 8 mmol), Et_3N (1.7 mL) and butyric anhydride (1.96 mL) in EtOH (200 mL) was refluxed for 2 h and cooled in ice. The precipitate was filtered and washed with EtOH and then Et_2O to give the 2-butyryl carbohydrazide (2.3 g, 90%). A mixture of the hydrazide (2.3 g, 7.2 mmol) and polyphosphoric acid (50 g) was stirred at 120 °C for 1 h. The mixture was cooled, poured into iced H_2O, neutralized (Na_2CO_3), and extracted with $CHCl_3$ (3×) to yield a solid which was purified by flash chromatography (silica; $CHCl_3$) to give compound **15** (1.62 g, 75%) as colorless crystals: mp 180–181.5 °C (from EtOAc); IR 3120, 1635, and 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (3 H, t, J = 7 Hz, $CH_2CH_2CH_3$), 1.12 (3 H, t, J = 7 Hz, CH_2CH_3), 1.92 (2 H, m, $CH_2CH_2CH_3$), 2.60 (3 H, s, 5-CH_3), 2.70 (2 H, q, J = 7 Hz, CH_2CH_3), 2.93 (2 H, t, J = 7 Hz, $CH_2CH_2CH_3$), 4.08 (3 H, s, OCH_3), and 7.98 (1 H, s, 3-H). Anal. ($C_{15}H_{19}N_5O_2$) C, H, N.

Compounds **12–14** and **16–22** (Table II) were prepared in yields of 70–80% by the same method except for the following modifications.

The unsubstituted 1,3,4-oxadiazol-2-yl analogue **12** was prepared by heating the carbohydrazide with triethyl orthoformate at 125 °C for 6 h; the resulting intermediate was filtered, washed with Et_2O, and then cyclized with PPA as above. The trifluoromethyl analogue **16** was prepared by reaction of the carbohydrazide with trifluoroacetic anhydride at room temperature and then warming the solution at 45 °C for 30 min to cyclize the intermediate.

(c) 2-(2-Thiazolyl)imidazo[1,2-*a*]pyrimidines. 6-Ethyl-7-methoxy-5-methyl-2-(4-methyl-2-thiazolyl)imidazo[1,2-*a*]pyrimidine (23). A mixture of 6-ethyl-7-methoxy-5-methylimidazol[1,2-*a*]pyrimidine-2-carboxamide (20 g, 0.0854 mol) and Lawesson's reagent[13] (25.4 g, 0.0629 mol) in THF (470 mL) was refluxed for 4 h. The mixture was cooled and the product was filtered and washed with THF and then Et_2O to give the thiocarboxamide (12.06 g, 56%) as a yellow solid, mp 248–259 °C. A mixture of the thioamide (4.3 g, 0.017 mol) and chloroacetone (3.18 g, 0.0344 mol) in EtOH (300 mL) was refluxed for 5 h, more chloroacetone (3.18 g, 0.0344 mol) was added, and refluxing was continued for a total of 29 h. The solvent was evaporated and the residue was dissolved in H_2O (2000 mL). The solution was basified (concentrated NH_4OH) and extracted with $CHCl_3$ (3×). The $CHCl_3$ was evaporated and the product was purified by flash chromatography (silica; $CHCl_3$) to give compound **23** (3.37 g, 68%) as a buff solid: mp 184–186 °C (from EtOAc); IR 3085 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (3 H, t, J = 7 Hz, CH_2CH_3), 2.51 (3 H, s, thiazole CH_3), 2.56 (3 H, s, 5-CH_3), 2.68 (2 H, q, J = 7 Hz, CH_2CH_3), 4.08 (3 H, s, OCH_3), 6.92 (1 H, s, thiazole H), and 7.85 (1 H, s, 3-H). Anal. ($C_{14}H_{18}N_4OS$) C, H, N, S.

Compounds **24–32** (Table III) were prepared in yields of 60–70% by the same method with the following modifications. The unsubstituted thiazole **24** was prepared by reacting the thioamide with bromoacetaldehyde diethyl acetal in EtOH containing a few drops of aqueous HCl. The 4-trifluoromethyl analogue (**28**) was prepared from the thioamide by reaction with 1-bromo-3,3,3-trifluoroacetone to give the uncyclized intermediate (2 g, 5.55 mmol) which was dissolved in dry CH_2Cl_2 (50 mL) containing Et_3N (1.55 mL) and the solution was treated with

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trifluoroacetic anhydride (1.57 mL). After 20 min the mixture was washed with H_2O and evaporated, and the resulting product was purified by flash chromatography.

(d) Miscellaneous Compounds (Table IV). 6-Ethyl-7-methoxy-5-methyl-2-(3-methyl[1,2,4]oxadiazol-5-yl)-imidazo[1,2-*a*]pyrimidine (33). A mixture of 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxamide (5.4 g, 0.023 mol) and dimethylacetamide dimethyl acetal (11 g) was stirred at 110 °C for 1 h. The mixture was evaporated to dryness to give the intermediate amidine as a thick brown oil. The crude intermediate was treated with hydroxylamine hydrochloride (2.24 g, 0.0322 mol), dioxane (40 mL), glacial HOAc (40 mL), and finally aqueous NaOH (16.7 mL, 2 M), and the resulting solution was heated at 90 °C for 1.75 h. Water was added to the hot mixture which was then cooled to crystallize compound **33** (3.97 g, 63%) as colorless needles: mp 204–205 °C (from EtOAc); IR 3125, 1640, and 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (3 H, t, J = 7 Hz, CH_2CH_3), 2.44 (3 H, s, oxadiazole CH_3), 2.56 (3 H, s, 5-CH_3), 2.67 (2 H, q, J = 7 Hz, CH_2CH_3), 4.06 (3 H, s, OCH_3), and 7.96 (1 H, s, 3-H). Anal. ($C_{12}H_{15}N_5O_2$) C, H, N.

6-Ethyl-7-methoxy-5-methyl-2-(5-methyl[1,2,4]triazol-3-yl)imidazo[1,2-*a*]pyrimidine (34). Compound **34** was prepared by the same method as compound **33** except that the crude intermediate (0.012 mol) was treated with hydrazine hydrate (1.2 g, 0.024 mol) in glacial HOAc (25 mL) and heated at 90 °C for 2.5 h. The product was purified by flash chromatography (silica; $CHCl_3$) to give **34**: mp 216–220 °C (from 2-propanol); IR 3500–2700 br, 2970, 1635, and 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (3 H, t, J = 7 Hz, CH_2CH_3), 2.48 (3 H, s, triazole CH_3), 2.54 (3 H, s, 5-CH_3), 2.66 (2 H, q, J = 7 Hz, CH_2CH_3), 4.04 (3 H, s, OCH_3), and 7.95 (1 H, s, 3-H). Anal. ($C_{13}H_{16}N_6O\cdot0.25H_2O$) C, H, N.

6-Ethyl-7-methoxy-5-methyl-2-(5-methyl[1,3,4]thiadiazol-2-yl)imidazo[1,2-*a*]pyrimidine (35). Starting from the appropriate ester, compound **35** was prepared in the same way as compound **15** except that the intermediate 2-acetylhydrazide (2.67 g, 9.17 mmol) in dry toluene (90 mL) was treated with Lawesson's reagent[13] (4.7 g, 11.62 mmol) and the mixture refluxed for 45 min after which it was cooled and dissolved in $CHCl_3$. The solution was washed with aqueous $NaHCO_3$ and water and then evaporated. The product was purified by flash chromatography (silica; $CHCl_3$) to give **35** (0.9 g, 34%), mp 210.5–212 °C. Anal. ($C_{13}H_{15}N_5OS\cdot0.25H_2O$) C, H, N, S.

6-Ethyl-7-methoxy-5-methyl-2-(5-oxazolyl)imidazo[1,2-*a*]pyrimidine (36). Lithium borohydride (11.55 g, 0.525 mol) was added over 1 h to a stirred solution of ethyl 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxylate (19.7 g, 0.075 mol) in dry THF (300 mL) and stirring was continued for 18 h. Saturated brine (300 mL) was added dropwise and the mixture was stirred for 30 min before the organic layer was separated. The aqueous phase was extracted with $CHCl_3$, and the combined organic extracts were evaporated to give (6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidin-2-yl)methanol (15.4 g, 93%) as a colorless crystalline solid, mp 186–188 °C dec. To a solution of the methanol (15.25 g, 0.069 mol) in $CHCl_3$ (200 mL) was added activated MnO_2 (40 g), and the mixture was refluxed for 18 h. More MnO_2 (20 g) was added and refluxing was continued for 4 h. The mixture was cooled, filtered through Celite, and evaporated to give 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxaldehyde (10.9 g, 72%) as a colorless crystalline solid, mp 185–186.5 °C. Anal. ($C_{11}H_{13}N_3O_2$) C, H, N. A mixture of the aldehyde (2 g, 9.12 mmol), anhydrous K_2CO_3 (2.52 g, 0.0182 mol), and tosylmethyl isocyanide[14] (1.96 g, 0.01 mol) in MeOH (100 mL) was stirred at room temperature for a few minutes until a solid precipitated and then refluxed for 30 min to give a clear solution. The solvent was evaporated and the resulting solid was partitioned between H_2O and $CHCl_3$. The aqueous phase was washed with $CHCl_3$, and the combined $CHCl_3$ extracts were washed with H_2O and evaporated. The resulting product was purified by flash chromatography (silica; $CHCl_3$) to give compound **36** (1.95 g, 66%): mp 145.5–146.5 °C (from EtOH); IR 3110 and 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (3 H, t, J = 7 Hz, CH_2CH_3), 2.55 (3 H, s, 5-CH_3), 2.66 (2 H, q, J = 7 Hz, CH_2CH_3), 4.07 (3 H, s, OCH_3), 7.45 (1 H, s, oxazole 4-H), 7.58 (1 H, s, oxazole 2-H), and 7.88 (1 H, s, 3-H). Anal. ($C_{13}H_{14}N_4O_2\cdot0.3H_2O$) C, H, N.

6-Ethyl-7-methoxy-5-methyl-2-(3-methyl-5-isoxazolyl)-imidazo[1,2-*a*]pyrimidine (38). A mixture of (6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidin-2-yl)ethanone[5] (5 g, 0.0214 mol) and dimethylacetamide dimethyl acetal (7.5 mL) was heated at 110 °C for 5 h. The resulting suspension was diluted with EtOAc and cooled in ice. The product was filtered and washed with a little cold EtOAc and Et_2O to give a light brown solid (5.02 g). A mixture of the solid (2.5 g) and hydroxylamine hydrochloride (0.86 g, 0.0124 mol) in 95% EtOH (20 mL) was heated at 90 °C for 2 h. The solvent was evaporated and the remaining solid was partitioned between H_2O and $CHCl_3$. The $CHCl_3$ phase was washed with H_2O and evaporated, and the product was purified by flash chromatography (silica; $CHCl_3$) to give **38** (1.14 g, 51%): mp 188–190 °C (from EtOH/Et_2O); IR 3125 and 1635 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.15 (3 H, t, J = 7 Hz, CH_2CH_3), 2.34 (3 H, s, isoxazole CH_3), 2.57 (3 H, s, 5-CH_3), 2.66 (2 H, q, J = 7 Hz, CH_2CH_3), 4.05 (3 H, s, OCH_3), 6.61 (1 H, s, isoxazole H), and 7.67 (1 H, s, 3-H). Anal. ($C_{14}H_{16}N_4O_2$) C, H, N.

Compound **37** was prepared by the same method except that a mixture of the crude intermediate (2 g, 6.61 mmol), EtOH (15 mL), and hydrazine hydrate (0.64 mL) was heated at 80 °C for 45 min. The mixture was cooled in ice and the product was filtered to give 6-ethyl-7-methoxy-5-methyl-2-(5-methyl-3-pyrazolyl)-imidazo[1,2-*a*]pyrimidine (**37**) (1.77 g, 99%): mp 233–235 °C (from EtOAc/MeOH); IR 3280, 3105 and 1634 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.11 (3 H, t, J = 7 Hz, CH_2CH_3), 3.31 (3 H, s, pyrazole CH_3), 2.51 (3 H, s, 5-CH_3), 2.63 (2 H, q, J = 7 Hz, CH_2CH_3), 4.02 (3 H, s, OCH_3), 6.48 (1 H, s, pyrazole H), and 7.52 (1 H, s, 3-H). Anal. ($C_{14}H_{17}N_5O$) C, H, N.

Biological Evaluation. (a) Benzodiazepine Receptor Binding Assay. The affinity of the compounds for benzodiazepine receptors was assessed by using a modification of the original method of Squires and Braestrup.[15] The values in the table are nanomolar concentrations of test drug which inhibit the specific binding of 0.6 nM [^3H]flunitrazepam to rat forebrain membrane preparations by 50% (IC_{50}, nM), and are derived from displacement curves with at least four concentrations, each assayed in triplicate.

(b) Food-Conflict Test. The food-motivated conflict test is a modification of the method of Cook and Sepinwall[16] with five alternating 4-min FI30 unpunished and five 3-min FR5 punished components using a colony of trained Lister rats. Compounds were initially tested at 50 mg/kg po in four rats (given 30 min prior to beginning testing), and if active, they were then tested at decreasing doses (20, 10, 5, 2, 1 mg/kg po) until the minimum effective dose (MED) was found. The MED was defined as the dose showing a significant increase in punished response in only one of four rats tested, as assessed by using the Mann-Whitney U test. In antagonism studies doses of test compounds were given in combination with 10 mg/kg po chlordiazepoxide, and the effect was compared with that of chlordiazepoxide alone in the same rats in separate assays.

(c) Anticonvulsant Test. Anticonvulsant activity was assessed in groups of 10 male CD-1 mice. The dose of leptazol-inducing tonic seizures in nine of the 10 mice in a 30-min observation period was titrated (approximately 120 mg/kg ip). This dose of leptazol was then repeated in combination with doses of test compounds given orally 1 h prior to seizure induction. ED_{50} values were calculated from best fit lines to at least three dose–effect points, and 95% confidence limits were calculated by using the method of Litchfield and Wilcoxon.[17]

(d) Proconvulsant Tests. Two methods were used to assess proconvulsant activity in groups of 10 male mice. In CD-1 mice the dose of leptazol-inducing tonic seizures in one of the 10 mice within 15 min was titrated (approximately 15 mg/kg ip). This

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dose of leptazol was then repeated in combination with doses of test compound given intraperitoneally at the same time as the leptazol. ED_{50} values were calculated as described above. In susceptible DBA_2 mice clonic seizures were induced by a constant 15-kHz tone for 30 s. Test compounds were administered intraperitoneally 30 min prior to the induction of seizures. This method was based on that of Jensen et al.[18]

(e) **Rotating Drum Test.** Sedative/muscle relaxant effects in male CD-1 mice were assessed with a Ugo Basile rotating drum (diameter 3 cm, 16 rev/min). The time spent on the drum was recorded 1 h after drug administration, and the mean time for groups of 10 mice was expressed as a percentage of the mean time for a control group. The dose causing 50% decrease in this time (ED_{50}) was calculated from best fit lines to at least three dose–effect points, and 95% confidence limits were calculated by using the method of Litchfield and Wilcoxon.[17]

Registry No. **4**, 106072-92-8; **5**, 106100-65-6; **6**, 106072-98-4; **7**, 106073-00-1; **8**, 106073-01-2; **9**, 106072-99-5; **10**, 133602-69-4; **11**, 133602-70-7; **12**, 106072-93-9; **13**, 106072-89-3; **14**, 106072-94-0; **15**, 106072-88-2; **16**, 106072-91-7; **17**, 133602-71-8; **18**, 106072-97-3; **19**, 106072-96-2; **20**, 106073-02-3; **21**, 106100-66-7; **22**, 106072-95-1; **23**, 118506-64-2; **24**, 118506-73-3; **25**, 118506-68-6; **26**, 118506-66-4; **27**, 118506-67-5; **28**, 118506-69-7; **29**, 118506-65-3; **30**, 118506-72-2; **31**, 118506-71-1; **32**, 118506-70-0; **33**, 106072-87-1; **34**, 133602-72-9; **35**, 106072-90-6; **36**, 133602-73-0; **37**, 133602-74-1; **38**, 133602-75-2; H_3CCOCH_2Cl, 78-95-5; $BrC(OEt)_2CH_3$, 133603-12-0; $H_3CCOCHClCH_3$, 4091-39-8; $EtOCOCOCH_2Cl$, 65868-37-3; F_3CCOCH_2Br, 431-35-6; $H_3CCH_2COCH_2Cl$, 616-27-3; $AcOCOCH_3$, 108-24-7; $H_3CCH_2COOCOCH_2CH_3$, 123-62-6; $H_3C(CH_2)_2COOCO(CH_2)_2CH_3$, 106-31-0; $F_3CCOOCOCF_3$, 407-25-0; $PhCOOCOPh$, 93-97-0; H_2NNH_2, 302-01-2; H_2NOH, 7803-49-8; ethyl 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxylate, 90808-77-8; ethyl 6-propyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxylate, 133602-76-3; ethyl 6-allyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxylate, 133602-77-4; ethyl 5-methoxy-6,7,8,9-tetrahydroimidazo[1,2-*a*]quinazoline-2-carboxylate, 133602-78-5; ethyl 6-ethyl-7-(methylthio)-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxylate, 133625-31-7; ethyl 6-(1-propenyl)-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxylate, 133602-79-6; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carbohydrazide, 106073-06-7; 5-methyl-7-methoxy-6-propylimidazo[1,2-*a*]pyrimidine-2-carbohydrazide, 133602-80-9; 6-allyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carbohydrazide, 106073-10-3; 5-methoxy-6,7,8,9-tetrahydroimidazo[1,2-*a*]quinazoline-2-carbohydrazide, 133602-81-0; 6-ethyl-7-(methylthio)-5-methylimidazo[1,2-*a*]pyrimidine-2-carbohydrazide, 133602-82-1; 6-(1-propenyl)-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carbohydrazide, 133602-83-2; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-(2-formylcarbohydrazide), 133602-84-3; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-(2-acetylcarbohydrazide), 106073-08-9; 6-propyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-(2-acetylcarbohydrazide), 133602-85-4; 6-allyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-(2-acetylcarbohydrazide), 133602-86-5; 5-methoxy-6,7,8,9-tetrahydroimidazo[1,2-*a*]quinazoline-2-(2-acetylcarbohydrazide), 133602-87-6; 7-(methylthio)-6-ethyl-5-methylimidazo[1,2-*a*]pyrimidine-2-(2-acetylcarbohydrazide), 133625-32-8; 7-methoxy-5-methyl-6-(1-propenyl)imidazo[1,2-*a*]pyrimidine-2-(2-acetylcarbohydrazide), 133602-88-7; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-[2-(1-oxopropyl)carbohydrazide], 133602-89-8; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-(2-butyrylcarbohydrazide), 106073-07-8; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-(2-(1-oxo-2,2,2-trifluoroethyl)carbohydrazide), 133602-90-1; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-(2-benzoylcarbohydrazide), 133602-91-2; 6-ethyl-7-methoxy-5-methylimidazolo[1,2-*a*]pyrimidine-2-carboxylic acid, 118506-74-4; 6-propyl-7-methoxy-5-methylimidazolo[1,2-*a*]pyrimidine-2-carboxylic acid, 133602-92-3; 6-allyl-7-methoxy-5-methylimidazolo[1,2-*a*]pyrimidine-2-carboxylic acid, 133602-93-4; 5-methoxy-6,7,8,9-tetrahydroimidazo[1,2-*a*]quinazoline-2-carboxylic acid, 133602-94-5; 6-ethyl-7-(methylthio)-5-methylimidazo[1,2-*a*]quinazoline-2-carboxylic acid, 133602-95-6; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxamide, 106073-04-5; 6-propyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxamide, 133602-96-7; 6-allyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxamide, 133602-97-8; 5-methoxy-6,7,8,9-tetrahydroimidazo[1,2-*a*]quinazoline-2-carboxamide, 133602-98-9; 6-ethyl-7-(methylthio)-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxamide, 133602-99-0; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-[(*N'*,*N'*-dimethyl)methylcarbonimidamide], 133603-00-6; (6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidin-2-yl)methanol, 90808-79-0; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxaldehyde, 90808-80-3; (6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidin-2-yl)ethanone, 90808-60-9; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-thiocarboxamide, 118506-76-6; 6-propyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-thiocarboxamide, 133603-01-7; 6-allyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-thiocarboxamide, 133603-02-8; 5-methoxy-6,7,8,9-tetrahydroimidazo[1,2-*a*]quinazoline-2-thiocarboxamide, 133603-03-9; 6-(1-propenyl)-7-methoxy-7-methylimidazo[1,2-*a*]pyrimidine-2-thiocarboxamide, 133603-04-0; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carbonitrile, 106073-03-4; 6-propyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carbonitrile, 133603-05-1; 6-allyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carbonitrile, 133603-06-2; 5-methoxy-6,7,8,9-tetrahydroimidazo[1,2-*a*]quinazoline-2-carbonitrile, 133603-07-3; 6-ethyl-7-(methylthio)-5-methylimidazo[1,2-*a*]pyrimidine-2-carbonitrile, 133625-33-9; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxamide oxime, 106073-05-6; 6-propyl-7-methoxy-7-methylimidazo[1,2-*a*]pyrimidine-2-carboxamide oxime, 133603-08-4; 6-allyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxamide oxime, 133603-09-5; 5-methoxy-6,7,8,9-tetrahydroimidazo[1,2-*a*]quinazoline-2-carboxamide oxime, 133603-10-8; 6-ethyl-7-(methylthio)-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxamide oxime, 133603-11-9; 5-ethyl-4-methoxy-6-methyl-2-pyrimidinamine, 90808-78-9; ethyl bromopyruvate, 70-23-5; *N,N'*-carbonyldiimidazole, 530-62-1; 6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidine-2-carboimidazolide, 118506-75-5; dimethylacetamide dimethyl acetal, 18871-66-4; trifluoroacetic anhydride, 407-25-0; triethyl orthoformate, 122-51-0; tosylmethyl isocyanaide, 36635-61-7.

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