resulting solid product was isolated by filtration. The solid was washed with water and dried in vacuo to provide 5.4 g of colorless solid, identified as the benzyl alcohol derivative, mp 267–271 °C. Anal. ($C_{18}H_{17}NO_4$) C, H, N.

2-[(2-Benzimidazolylthio)methyl]-3,5-dimethyl-4-methoxyaniline (47) and 2-[(2-benzimidazolylsulfinyl)methyl]-3,5-dimethyl-4-methoxyaniline (89) were prepared by methods A and C, respectively.

Registry No. **6** (R_1 = H), 583-39-1; **6** (R_1 = 5-OMe), 37052-78-1; **6** (R_1 = 5-OEt), 55489-15-1; **6** (R_1 = 4-Me), 27231-33-0; **6** (R_1 = 5-Me), 27231-36-3; **6** (R_1 = 5-Cl), 25369-78-2; **6** (R_1 = 5-CF_3), 86604-73-1; **6** (R_1 = 5,6-$(Me)_2$), 3287-79-4; **6** (R_1 = 5,6-$(OMe)_2$), 74004-74-3; **7** (R_2, R_3, R_4 = H, X = OH), 5344-90-1; **7** (R_2, R_3, R_4 = H, X = Cl), 114059-99-3; **7** (R_2 = Ac, R_3, R_4 = H, X = Cl), 90562-37-1; **7** (R_2 = Me, R_3, R_4 = H, X = Cl), 100376-52-1; **7** (R_2, R_3 = Me, R_4 = H, X = Cl), 106771-59-9; **7** (R_2, R_3 = H, R_4 = 3-Me, X = Cl), 114060-00-3; **7** (R_2, R_3 = H, R_4 = 4-Me, X = Cl), 114060-01-4; **7** (R_2, R_3 = H, R_4 = 6-Me, X = Cl), 88301-86-4; **7** (R_2, R_3 = H, R_4 = 4-Et, X = Cl), 114060-02-5; **7** (R_2, R_3 = H, R_4 = 4-Et, X = Cl)·HCl, 106746-71-8; **7** (R_2, R_3 = H, R_4 = 6-Et, X = Cl), 88301-87-5; **7** (R_2, R_3 = H, R_4 = 6-Et, X = Cl)·HCl, 88301-76-2; **7** (R_2, R_3 = H, R_4 = 4-*n*-Bu, X = Cl), 114060-03-6; **7** (R_2, R_3 = H, R_4 = 4-*m*-Bu, X = Cl)·HCl, 106746-85-4; **7** (R_2, R_3 = H, R_4 = 4-MeO, X = Cl), 114060-04-7; **7** (R_2, R_3 = H, R_4 = 4-MeO, X = Cl)·2HCl, 114060-05-8; **7** (R_2, R_3 = H, R_4 = 6-MeO, X = Cl), 88301-88-6; **7** (R_2, R_3 = H, R_4 = 4-Cl, X = Cl), 114060-06-9; **7** (R_2, R_3 = H, R_4 = 5-Cl, X = Cl), 95304-97-5; **7** (R_2, R_3 = H, R_4 = 4-CF_3, X = Cl), 114060-07-0; **7** (R_2, R_3 = H, R_4 = 4-CO_2Et, X = Cl), 114060-08-1; **7** (R_2, R_3 = H, R_4 = 6-CO_2Me, X = Cl), 88301-89-7; **7** (R_2, R_3 = H, R_4 = 3,6-$(Me)_2$, X = Cl), 114060-09-2; **7** (R_2, R_3 = H, R_4 = 3,6-$(Me)_2$, X = Cl)·HCl, 106746-89-8; **7** (R_2, R_3 = H, R_4 = 4,6-$(Me)_2$, X = Cl), 114060-10-5; **7** (R_2, R_3 = H, R_4 = 5,6-$(Me)_2$, X = Cl), 114060-11-6; **7** (R_2, R_3 = H, R_4 = 5,6-$(Me)_2$, X = Cl)·HCl, 106746-87-6; **7** (R_2, R_3 = H, R_4 = 4-Cl, 6-Me, X = Cl), 114060-12-7; **7** (R_2 = H, R_3 = COBu-*t*, R_4 = 4-CF_3, X = OH), 106746-82-1; **7** (R_2, R_3 = H, R_4 = 4-CF_3, X = Cl)·HCl, 106746-83-2; **7** (R_2, R_3 = H, R_4 = 4-Cl, 6-Me, X = Cl)·HCl, 106746-91-2; **7** (R_2, R_3 = H, R_4 = 5-Cl, 6-Me, X = Cl), 114060-13-8; **7** (R_2, R_3 = H, R_4 = 5-Cl, 6-Me, X = Cl)·HCl, 114060-14-9; **7** (R_2, R_3 = H, R_4 = 3-Me, 4-Cl, 6-OMe, X = Cl), 114060-15-0; **7** (R_2, R_3 = H, R_4 = 3-Me, 4-Cl, 6-OMe, X = Cl)·HCl, 106746-92-3; **8**, 104340-33-2; **9**, 106747-44-8; **10**, 106746-78-5; **11**, 106747-42-6; **12**, 106746-76-3; **13**, 106746-77-4; **14**, 106746-79-6; **15**, 106747-43-7; **16**, 106747-01-7; **17**, 106747-41-5; **18**, 104340-35-4; **19**, 104340-38-7; **20**, 106746-61-6; **21**, 106746-63-8; **22**, 106746-65-0; **23**, 106746-70-7; **24**, 111881-58-4; **25**, 106746-84-3; **26**, 106746-58-1; **27**, 106746-60-5; **28**, 106747-47-1; **30**, 106747-48-2; **31**, 106746-80-9; **32**, 106746-98-9; **33**, 106746-97-8; **34**, 106746-68-3; **35**, 106746-69-4; **36**, 106746-93-4; **37**, 106747-00-6; **38**, 106746-96-7; **39**, 106746-88-7; **40**, 106746-66-1; **41**, 106746-86-5; **42**, 106746-90-1; **43**, 114060-16-1; **44**, 106746-95-6; **45**, 106746-94-5; **46**, 114060-17-2; **47**, 106746-74-1; **48**, 106785-95-9; **49**, 114060-18-3; **50**, 104340-34-3; **51**, 106747-08-4; **52**, 106747-23-3; **53**, 106747-06-2; **54**, 106747-21-1; **55**, 106747-22-2; **56**, 106747-24-4; **57**, 106747-07-3; **58**, 106747-37-9; **59**, 106747-05-1; **60**, 104340-37-6; **61**, 100924-68-3; **62**, 106747-14-2; **63**, 106747-15-3; **64**, 106747-16-4; **65**, 114060-19-4; **66**, 106771-58-8; **67**, 106747-26-6; **68**, 106747-12-0; **69**, 106747-13-1; **70**, 106747-10-8; **71**, 106747-38-0; **72**, 106747-11-9; **73**, 106747-25-5; **74**, 106747-35-7; **75**, 106747-34-6; **76**, 106747-18-6; **77**, 106747-19-7; **78**, 106747-30-2; **79**, 106747-36-8; **80**, 106747-33-5; **81**, 106785-96-0; **82**, 106747-17-5; **83**, 106747-27-7; **84**, 106747-28-8; **85**, 114060-20-7; **86**, 106747-32-4; **87**, 106747-31-3; **88**, 106747-39-1; **89**, 106747-20-0; **90**, 106747-29-9; **91**, 106747-40-4; ATPase, 9000-83-3; *N*-(4-fluoro-2-methylphenyl)phthalimide, 106747-02-8; 4-fluoro-2-methylaniline, 452-71-1; phthalic anhydride, 85-44-9; *N*-[2-[(2-benzimidazolylthio)methyl]-4-fluorophenyl]phthalimide, 106771-57-7; *N*-[4-fluoro-2-(bromomethyl)phenyl]phthalimide, 106747-03-9; *N*-[2-[(2-benzimidazolylsulfinyl)methyl]-4-fluorophenyl]phthalimide, 106747-04-0; 4-(trifluoromethyl)aniline, 455-14-1; pivaloyl chloride, 3282-30-2; *N*-pivaloyl-4-(trifluoromethyl)aniline, 25617-34-9; *N*-pivaloyl-2-amino-5-(trifluoromethyl)benzaldehyde, 106746-81-0; *N*-(4-methoxy-3,5-dimethylphenyl)phthalimide, 106746-72-9; *N*-[3,5-dimethyl-2-(hydroxymethyl)-4-methoxyphenyl]phthalimide, 106746-73-0; 4-methoxy-3,5-dimethylbenzenamine, 39785-37-0; omeprazole, 73590-58-6; timoprazole, 57237-97-5; 4-ethylbenzenamine, 589-16-2; 2-ethylbenzenamine, 578-54-1; 4-*n*-butylbenzenamine, 104-13-2; 2,5-dimethylbenzenamine, 95-78-3; 2,3-dimethylbenzenamine, 87-59-2; 4-chloro-2-methylbenzenamine, 95-69-2; 3-chloro-2-methylbenzenamine, 87-60-5; 3,4,5-trimethylbenzenamine, 1639-31-2; 2-methoxy-4-chloro-5-methylbenzenamine, 6376-14-3; *N*-(3,4,5-trimethylphenyl)-phthalimide, 40101-22-2; *N*-[2-(hydroxymethyl)-3,4,5-trimethylphenyl]phthalimide, 114060-21-8.

(Imidazo[1,2-*a*]pyrimidin-2-yl)phenylmethanones and Related Compounds as Potential Nonsedative Anxiolytics

Stephen Clements-Jewery, Geoffrey Danswan, Colin R. Gardner, Saroop S. Matharu, Robert Murdoch, W. Roger Tully,* and Robert Westwood

Roussel Laboratories Ltd., Kingfisher Drive, Covingham, Swindon, Wiltshire SN3 5BZ, U.K. *Received October 29, 1987*

Several series of heterocyclic carboxylic esters were found to be active in the benzodiazepine receptor binding assay, a typical example being ethyl 7-ethyl-5-methoxyimidazo[1,2-*a*]quinoline-2-carboxylate (**4b**) with an IC_{50} of 150 nM. The corresponding phenylmethanone **5d** was more potent with an IC_{50} of 14 nM and was orally active in animal models thought to predict anxiolytic effects. The synthesis of a large number of compounds resulted in the optimization of this activity in a series of (imidazo[1,2-*a*]pyrimidin-2-yl)phenylmethanones of which compounds **7e**, **8b**, **8h**, **8j**, and **8k** were equipotent with chlordiazepoxide while exhibiting reduced anticonvulsant activity, little or no muscle relaxation, and negligible sedative effects.

A current goal of antianxiety research is the discovery of potent anxiolytic agents which do not possess sedative side effects. Part of this endeavor has been to find compounds which lack the benzodiazepine structure but which nevertheless bind potently to the benzodiazepine receptor. A separation of antianxiety activity from muscle relaxation, sedation, and hypnotic effects might then be achieved by partial intrinsic activity at the receptor complex.[1]

With this aim we routinely screened all compounds synthesized for a variety of objectives in our laboratories for their ability to displace [^{3}H]flunitrazepam from rat-brain preparations. One of these compounds, ethyl 4,5-

(1) (a) Haefely, W. In *Clinical Neuropharmacology*; Raven: New York, 1984; Vol. 7, Suppl 1, p 658. (b) Williams, M. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1984**, *8*, 209.

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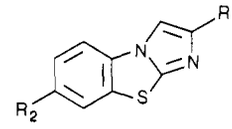
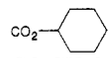
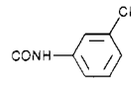
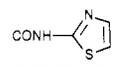
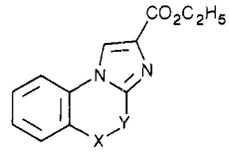
Table I. Imidazo[2,1-*b*]benzothiazoles



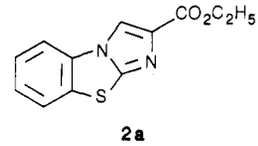
no.	R_1	R_2	method	yield, %	mp, °C	formula	anal.	flunitrazepam receptor binding: IC_{50}, nM
2a	$CO_2C_2H_5$	H	A	31	147–148[a]			120
2b	$CO_2C_2H_5$	C_2H_5	A	26	119–120	$C_{14}H_{14}N_2O_2S$	CHNS	4000
2c	COC_6H_5	H	D	87	172–173	$C_{16}H_{10}N_2OS$	CHNS	85
2d	COC_6H_5	C_2H_5	D	73	151–153	$C_{18}H_{14}N_2OS$	CHNS	740
2e	CO_2H	H	E	77	262–263[b]	$C_{10}H_6N_2O_2S$	CHNS	I[c]
2f	CO_2CH_3	H	F	56	156–157	$C_{11}H_8N_2O_2S$	CHNS	60
2g	$CO_2C_3H_7$	H	F	52	127–128	$C_{13}H_{12}N_2O_2S$	CHNS	470
2h	$CO_2CH(CH_3)_2$	H	F	10	125–126	$C_{13}H_{12}N_2O_2S$	CHNS	160
2i		H	F	37	172–174	$C_{16}H_{16}N_2O_2S$	CHN	7100
2j	$CO_2CH_2C_6H_5$	H	G	21	120–121	$C_{17}H_{12}N_2O_2S$	CHNS	50
2k		H	H	73	113–115	$C_{14}H_{13}N_3OS$	CHNS	I
2l		H	G	31	280–281	$C_{16}H_{10}ClN_3OS$	CHClNS	I
2m		H	G	37	321–323	$C_{13}H_8N_4OS_2$	CHNS	I
2n	$CH_2CO_2C_2H_5$	H	A[d]	5	84–85[e]	$C_{13}H_{12}N_2O_2S$	CHNS	I

[a] Literature[3a] mp 147–148 °C. [b] Literature[3a] mp 263–265 °C. [c] I = activity > 10 μM. [d] With $ClCH_2COCH_2CO_2Et$. [e] Literature[8] mp 84–85 °C.

dihydroimidazo[1,2-*a*]quinoxaline-2-carboxylate (**1a**),[2c] was found to have an IC_{50} value of 175 nM compared with 6 nM for that of nitrazepam. This prompted us to screen a large number of heterocyclic esters which we had previously prepared[2a,b] during the course of the antiallergy program for which **1a** had been synthesized. Although the parent compound **1b** had an IC_{50} of >10 μM, the benzothiazole **2a** and the quinoline **4b** were found to be of the same order of activity as **1a** with IC_{50}'s of 120 and 150 nM, respectively. Unfortunately none of the esters were active in vivo in pharmacological screens predicting antianxiety properties, the most obvious explanation being that the esters were readily metabolized to the corresponding acids which lacked both receptor affinity (IC_{50} > 10 μM) and the lipophilicity necessary to penetrate the blood–brain barrier.

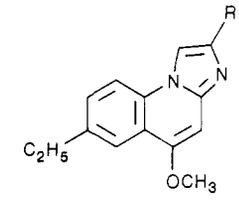


1a, X–Y = $NHCH_2$
b, X–Y = N=CH

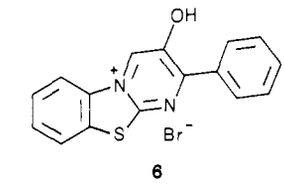


2a

The next logical step was to examine previously prepared analogues of the esters which might be receptor active and metabolically stable. In this way it was discovered that phenylmethanone **5d** was 10 times more potent on receptor binding (IC_{50} = 14 nM) and possessed oral activity in the licking-conflict screen for anxiolytics without exhibiting overt sedative effects. Compound **5d** was therefore a key lead structure on which to base our investigations into the optimum structure–activity requirements of this type of compound.



4b, R = $CO_2C_2H_5$
5d, R = COC_6H_5



6

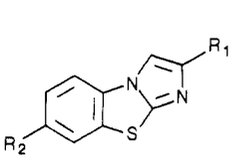
Chemistry

The routes used to prepare the fused imidazole ketones are outlined in Scheme I. The ethyl esters were synthesized by the known reaction[2b,3] of heterocyclic amines with ethyl bromopyruvate. It was found that yields were improved by isolating the salt[3b] initially formed in an inert solvent such as tetrahydrofuran and then cyclizing the intermediate in refluxing methanol or ethanol. The same procedure was employed to prepare phenylmethanones directly by using 3-bromo-1-phenyl-1,2-propanedione, except in the benzothiazole series where cyclization took place onto the wrong carbonyl group to give the pyrimido[2,1-*b*]benzothiazolium bromide **6** as supported by the lack of a carbonyl absorption in its infrared spectrum. The desired phenylmethanones **2c** and **2d** were therefore prepared from esters **2a** and **2b** via intermediates **3a–d** in Table II. Benzothiazoles **2f–m** were obtained from the corresponding acid by standard methods, and **2n** was ob-

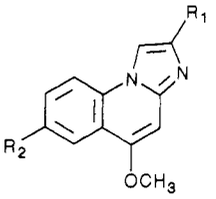
(2) (a) Rowlands, D. A.; Taylor, J. B. British Patent 1 538 479, 1979. Rowlands, D. A.; Taylor, J. B. British Patent 2 008 585, 1979. Rowlands, D. A.; Taylor, J. B. British Patent 1 576 077, 1980. (b) Barnes, A. C.; Ramm, P. J. British Patent 2 027 707, 1980. Barnes, A. C.; Kay, D. P. British Patent 2 043 064, 1980. Barnes, A. C.; Rowlands, D. A. British Patent 2 043 637, 1980. Ager, I. R.; Ramm, P. J. British Patent 1 596 652, 1980. (c) Barnes, A. C.; Kay, D. P.; Kennewell, P. D.; Parker, F. L.; Rowlands, D. A. British Patent 2 118 943, 1983.

(3) (a) Abignente, E.; Arena, F.; de Caprariis, P. *Farmaco Ed. Sci.* **1977**, *32*, 735. (b) Abignente, E.; de Caprariis, P.; Patscot, R.; Sacchi, A. *J. Heterocycl. Chem.* **1986**, *23*, 1031.

Table II. Intermediates



3a–d

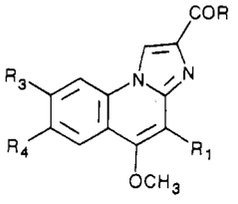


4a–f

no.	R_1	R_2	method	yield, %	mp, °C	formula	anal.
3a	CH_2OH	H	B	44	172–173	$C_{10}H_8N_2OS$	CHNS
3b	CH_2OH	C_2H_5	B	68	141–142	$C_{12}H_{12}N_2OS$	CHNS
3c	CHO	H	C	79	208–209	$C_{10}H_6N_2OS$	CHNS
3d	CHO	C_2H_5	C	85	183–184	$C_{12}H_{10}N_2OS$	CHNS
4a	$CO_2C_2H_5$	H	A	35	176–176.5[a]	$C_{15}H_{14}N_2O_3$	
4b	$CO_2C_2H_5$	C_2H_5	A	45	170–171[b]	$C_{17}H_{18}N_2O_3$	
4c	CH_2OH	H	B	89	173–175	$C_{13}H_{12}N_2O_2$	CHN
4d	CH_2OH	C_2H_5	B	47	202–203	$C_{15}H_{16}N_2O_2$	CHN
4e	CHO	H	C	75	195–196	$C_{13}H_{10}N_2O_2$	CHN
4f	CHO	C_2H_5	C	91	192–193	$C_{15}H_{14}N_2O_2$	CHN

[a] Literature[9] mp 175–176.6 °C. [b] Literature[9] mp 167–168 °C.

Table III. Imidazo[1,2-*a*]quinolines



no.	R	R_1	R_2	R_3	method	yield, %	mp, °C	formula	anal	flunitrazepam receptor binding: IC_{50}, nM	food conflict: MED, mg/kg po
5a	C_6H_5	CH_3	C_2H_5	H	A	22	141–142	$C_{22}H_{20}N_2O_2$	CHN	7	2
5b	2-C_5H_4N	H	C_2H_5	H	D	15	185–186	$C_{20}H_{17}N_3O_2$	CHN	9	5
5c	C_6H_5	H	$CH(CH_3)_2$	H	A	23	187–188	$C_{22}H_{20}N_2O_2$	CHN	10	5
5d	C_6H_5	H	C_2H_5	H	A	37	196–198	$C_{21}H_{18}N_2O_2$	CHN	14	5
5e	C_6H_5	H	C_3H_7	H	A	30	185–186	$C_{22}H_{20}N_2O_2$	CHN	16	2
5f	C_6H_5	H	F	H	A	19	234–235	$C_{19}H_{13}FN_2O_2$	CHNF	20	10
5g	C_6H_5	H	CH_3	H	A	30	218–220	$C_{20}H_{16}N_2O_2$	CHN	21	5
5h	C_6H_5	H	C_4H_9	H	A	26	165–167	$C_{23}H_{22}N_2O_2$	CHN	25	10
5i	C_6H_5	H	H	H	A	12	190–191	$C_{19}H_{14}N_2O_2$	CHN	57	5
5j	C_6H_5	H	CH_3	CH_3	A	28	244–245	$C_{21}H_{18}N_2O_2$	CHN	100	5
5k	C_2H_5	H	C_2H_5	H	D	29	188–189	$C_{17}H_{18}N_2O_2$	CHN	135	10
5l	C_6H_5	C_2H_5	C_2H_5	H	A	18	145–146	$C_{23}H_{22}N_2O_2$	CHN	135	20
5m	C_3H_7	H	C_2H_5	H	D	39	179–180	$C_{18}H_{20}N_2O_2$	CHN	535	20
5n	CH_3	H	C_2H_5	H	A[a]	30	148	$C_{16}H_{16}N_2O_2$	CHN	1300	20
5o	4-$CH_3C_6H_4$	H	H	H	D	35	212–213	$C_{20}H_{16}N_2O_2$	CHN	19	>50
5p	2-C_4H_3S	H	H	H	D	36	257–259	$C_{17}H_{12}N_2O_2S$	CHNS	24	>50
5q	4-$CH_3OC_6H_4$	H	H	H	D	31	170–171	$C_{20}H_{16}N_2O_3$	CHN	37	>50
5r	4-ClC_6H_4	H	H	H	D	25	245–246	$C_{19}H_{13}ClN_2O_2$	CHNCl	96	>50

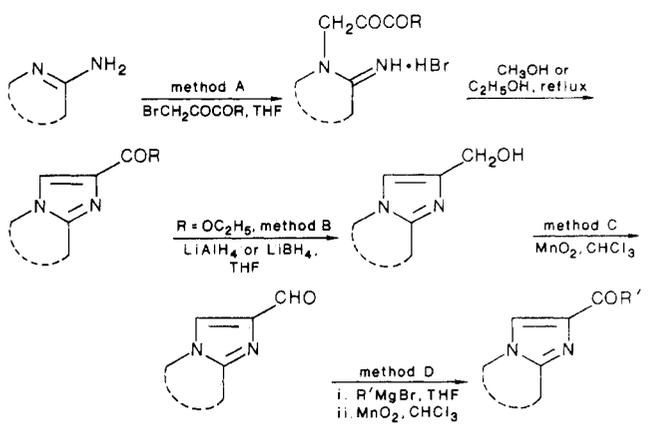
[a] With $BrCH_2COCOCH_3$.[18]

tained in low yield from the reaction of 2-benzothiazolamine with ethyl 4-chloroacetoacetate.

The (imidazo[1,2-*a*]quinolin-2-yl)methanones[4] were synthesized either directly by using the propanedione or indirectly via intermediates **4c–f** in Table II. The most potent members of the series, i.e. those with receptor binding IC_{50} values of 1 μM or less, are shown in Table III along with their oral activity in food conflict, our primary anxiolytic screen.

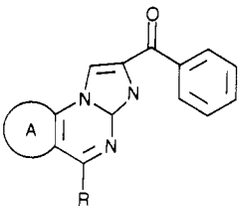
A large number of imidazo[1,2-*a*]pyrimidin-2-yl ketones[5] were likewise synthesized from 2-pyrimidinamines. With the exception of imidazo[1,2-*a*]quinazolines **7e–i**, the tri-

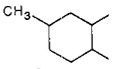
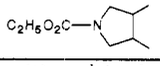
Scheme I



(4) (a) Robson, P. A.; Barnes, A. C. British Patent 2 096 143, 1982. (b) Tully, W. R. British Patent 2 127 824, 1984.
(5) Tully, W. R. British Patent 2 128 989, 1984.

Table IV. Tricyclic Imidazo[1,2-*a*]pyrimidines

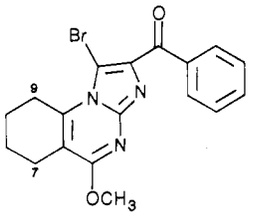


no.	A	R	yield, %	mp, °C	formula	anal.	flunitrazepam receptor binding: IC_{50}, nM	food conflict: MED, mg/kg po
7a		OCH_3	35	210–211	$C_{17}H_{15}N_3O_2$	CHN	200	20
7b		OC_2H_5	47	227–229	$C_{18}H_{17}N_3O_2$	CHN	>10000	50
7c		SCH_3	44	208–209	$C_{17}H_{15}N_3OS$	CHNS	35	2
7d		SC_2H_5	63	211–212	$C_{18}H_{17}N_3OS$	CHNS	1850	50
7e		OCH_3	52	234	$C_{18}H_{17}N_3O_2 \cdot {}^1/_2H_2O$	CHN	61	5
7f		OC_2H_5	48	250–252	$C_{19}H_{19}N_3O_2 \cdot {}^1/_2H_2O$	CHN	2000	>50
7g		SCH_3	35	225	$C_{18}H_{17}N_3OS \cdot {}^1/_4H_2O$	CHNS	9	10
7h		OCH_3	43	200–201	$C_{19}H_{19}N_3O_2$	CHN	135	10
7i		SCH_3	52	215–217	$C_{19}H_{19}N_3OS$	CHNS	76	50
7j		OCH_3	44	196–198	$C_{19}H_{19}N_3O_2$	CHN	125	10
7k		OC_2H_5	39	193–194	$C_{20}H_{21}N_3O_2$	CHN	4000	5
7l		OCH_3	60	239–240[a]	$C_{16}H_{13}N_3O_2S$	CHNS	430	>50
7m		OCH_3	21	252–254	$C_{17}H_{15}N_3O_2S$	CHNS	185	20
7n		OC_2H_5	53	262–265[a]	$C_{18}H_{17}N_3O_2S$	CHNS[b]	>10000	>50
7o		SCH_3	39	267–269[a]	$C_{17}H_{15}N_3OS_2$	CHNS[b]	24	50
7p		OCH_3	37	274–277[a]	$C_{19}H_{18}N_4O_4$	CHN[c]	10000	50

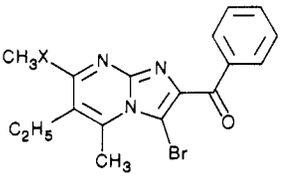
[a] Decomposition. [b] Analysis corrected for 0.1 mol of $CHCl_3$. [c] Analysis corrected for 0.2 mol of H_2O.

cyclic pyrimidines in Table IV are new ring systems. Table V lists the most potent bicyclic members of the series.

The reaction between unsymmetrical 2-pyrimidinamines and α-bromo ketones can in theory give two isomeric products.[6] We have observed that the initial ring-nitrogen alkylation is hindered sterically by an adjacent phenyl substituent and electronically by an adjacent methoxy group, 4-methoxy-6-phenyl-2-pyrimidinamine and 4,6-dimethoxy-2-pyrimidinamine, for example, giving no reaction. 2-Pyrimidinamines possessing only one such group are alkylated on the unhindered ring nitrogen to yield an intermediate which then cyclizes to a single product. The structure of the fused imidazoles is supported by ^1H NMR spectroscopy where there is an observed NOE difference between the imidazole proton and the protons at position 9 in compound **7e** and likewise the 5-methyl group in compounds **8b** and **8j**. Further structural evidence was obtained by bromination of selected examples with *N*-bromosuccinimide and observation of the effects on chemical shifts. Thus compound **7e** yielded compound **9** in which there was a downfield shift of 0.7 ppm for the protons at position 9. Compounds **8b** and **8j** gave derivatives **10a** and **10b** in which the 5-methyl group moved downfield by 0.5 ppm as expected.[7] Furthermore, the structure of compound **8r** is supported by the observed allylic coupling (J = 1 Hz) between the 5-methyl group and the proton at position 6 in common with other compounds of this nature.[6b,7]



9



10a, X = S
b, X = O

Results and Discussion

Work first started on the benzothiazole series (Table I) and showed that there are steric as well as electronic requirements for potent receptor binding. Thus compound **2b** was 33 times less active than **2a** and the acetate **2n** in which the ester carbonyl cannot conjugate with the imidazole ring was inactive. Methanones **2c** and **2d**, in contrast with the orally active quinoline **5d**, were found to be less potent on the receptor and inactive in licking conflict. Attention was therefore turned to the quinoline series[4] (Table III) where we found a rough correlation between receptor affinity and oral activity in food conflict, a test giving more consistent results than licking conflict and therefore used as our primary anxiolytic screen. Notable exceptions were compounds **5o–r**, which retained receptor affinity but lost oral activity. Modification of the carbonyl

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(7) Paudler, W. W.; Kuder, J. E. *J. Org. Chem.* **1966**, *31*, 809.
(8) Abignente, E.; Arena, F.; de Caprariis, P.; Parente, L. *Farmaco Ed. Sci.* **1976**, *31*, 880.
(9) British Patent 1 542 778, 1979.
(10) Doerner, M. P. U.S. Patent 2 821 555, 1958.
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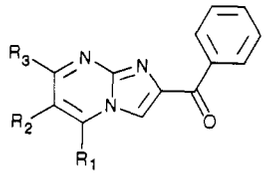
(12) Vogel, J. R.; Beer, B.; Clody, D. E. *Psychopharmacology* **1971**, *21*, 1.

Table V. Imidazo[1,2-*a*]pyrimidines



no.	R_1	R_2	R_3	yield, %	mp, °C	formula	anal.	flunitrazepam receptor binding: IC_{50}, nM	food conflict: MED, mg/kg po
8a	CH_3	CH_2=$CHCH_2$	CH_3S	45	167–169	$C_{18}H_{17}N_3OS$	CHNS	8	5
8b	CH_3	C_2H_5	CH_3S	53	182–184	$C_{17}H_{17}N_3OS$	CHNS	12	2
8c	CH_3	c-$C_3H_5CH_2$	CH_3O	32	136–137	$C_{19}H_{19}N_3O_2$	CHN	30	10
8d	C_2H_5	C_3H_7	CH_3O	26	151–152	$C_{19}H_{21}N_3O_2$	CHN	34	10
8e	C_2H_5	C_4H_9	CH_3O	20	158–159	$C_{20}H_{23}N_3O_2$	CHN	34	10
8f	CH_3	C_4H_9	CH_3O	26	141–145	$C_{19}H_{21}N_3O_2$	CHN	42	2
8g	C_2H_5	CH_2=$CHCH_2$	CH_3O		130–131	$C_{19}H_{19}N_3O_2$		42	10
8h	CH_3	CH_2=$CHCH_2$	CH_3O	68	128–131	$C_{18}H_{17}N_3O_2$	CHN	45	5
8i	C_2H_5	C_3H_7	CH_3S	24	156–158	$C_{19}H_{21}N_3OS$	CHNS	47	10
8j	CH_3	C_2H_5	CH_3O	68	148–150	$C_{17}H_{17}N_3O_2$	CHN	56	2
8k	CH_3	C_3H_7	CH_3O	54	141–142	$C_{18}H_{19}N_3O_2$	CHN	85	5
8l	C_3H_7	H	CH_3S	37	152–154	$C_{17}H_{17}N_3O_2S$	CHN	89	10
8m	C_2H_5	C_2H_5	CH_3O	23	144–145	$C_{18}H_{19}N_3O_2$	CHN	107	2
8n	CH_3	H	CH_3S	58	170–172	$C_{15}H_{13}N_3OS$	CHNS	190	5
8o	C_2H_5	H	CH_3O	49	179–182	$C_{16}H_{15}N_3O_2$	CHN	295	2
8p	C_4H_9	H	CH_3O	39	170–171	$C_{18}H_{19}N_3O_2$	CHN	340	10
8q	C_3H_7	H	CH_3O	37	152–154	$C_{17}H_{17}N_3O_2$	CHN	535	1
8r	CH_3	H	CH_3O	43	165–166	$C_{15}H_{13}N_3O_2$	CHN	800	5
8s	CH_3	CH_3O	CH_3O	28	191–193	$C_{16}H_{15}N_3O_3$	CHN	1000	5
8t	H	C_2H_5	CH_3O	52	126–129	$C_{16}H_{15}N_3O_2$	CHN	1500	5

Table VI. Comparative Biological Data for Example Compounds

compd	flunitrazepam receptor binding: IC_{50}, nM	food conflict: MED[a]	licking conflict: MED[a]	antileptazol: ED_{50}[a]	rotating drum: ED_{50}[a]	pull-up: ED_{50}[a]
chlordiazepoxide	*b*	5	2	1.9 (1.1–3.2)	6.8 (5.0–9.2)	16.0 (11.9–21.6)
5d	14	2–5[c]	2–5	3.2 (2.8–3.7)	22.5 (17.4–29.0)	640
8j	56	2	2	21.0 (14.0–31.5)	200	200
8b	12	2	2	12.5 (9.7–16.1)	100	200
8h	45	2–5	10	54	100	
8k	85	2–5	5	200	100	100
7e	61	5	5	100	200	500

[a] MED (minimal effective dose) and ED_{50} values in mg/kg per os. 95% confidence limits are shown on ED_{50} values where the doses tested allowed their calculation according to the method of Litchfield and Wilcoxon.[11] [b] In vitro receptor binding activity for chlordiazepoxide has not been shown in view of its in vivo metabolism. [c] This result was obtained by using the original method of Vogel et al.[12]

group or of the methoxyl group or insertion of a halogen in the imidazole ring reduced receptor affinity with loss of oral activity.

The tetrahydroimidazo[1,2-*a*]quinazoline **7e** was synthesized on route to the unsaturated ring system in an attempt to improve bioavailability. Dehydrogenation was not achieved but the observed activity of **7e** demonstrated that an aromatic A ring was not essential. Little improvement was obtained by varying the nature of the alicyclic ring (Table IV), but in the tricyclic series it was observed that replacing the methoxyl group by methylthio increased receptor affinity by up to eightfold (e.g., compare **7a** with 7c and **7e** with **7g**), but in some cases this had an adverse effect on oral activity, comparing **7h** with **7i**, for example. Likewise, increasing the size of the alkyl substituent on oxygen or sulfur usually reduced both receptor affinity and oral activity, presumably for steric reasons.

The A ring was then opened to produce a series of imidazo[1,2-*a*]pyrimidines[5] whose potencies were consistent with the structural requirements deduced from the other series (Table V). In some examples such as **8q** oral activity was observed in spite of poor receptor affinity. However, compounds for detailed pharmacological evaluation were chosen on the basis of both potency and efficacy in the tests for anxiolytic activity. The magnitude of the increases in punished lever pressing or punished licking in the conflict tests was taken as an indication of efficacy (see the Experimental Section). Compound **8q** was therefore excluded because it elicited only small increases in punished behavioral response.

Table VI gives comparative biological data for examples of the compounds chosen for further studies and demonstrates a consistent improvement in the ratio between doses active in models of anxiety and doses producing sedative and muscle-relaxant effects. They have similar or slightly less potency than chlordiazepoxide in the conflict tests, but none of them attained 50% inhibition at 100 mg/kg po in the pull-up test, designed specifically to detect muscle relaxation. Similarly five of the compounds showed no sedative activity on the rotating drum, the exception being compound **5d**, which also possessed the anticonvulsant activity expected of a classical benzodiazepine with equivalent anxiolytic potency. Compounds **8b**, **8h**, and **8j** showed reduced anticonvulsant activity whereas compounds **7e** and **8k** retained only the anxiolytic activity of a full benzodiazepine profile.

There is a crude correlation between in vitro benzodiazepine receptor affinity and in vivo behavioral effects

in that compounds inactive on the receptor are inactive orally, suggesting that the former may be responsible for the latter. However, the two do not correlate well in compounds having in vivo activity lower than 50 mg/kg. There are two major factors which influence this correlation. First, the in vitro binding technique assesses the affinity of compounds for the benzodiazepine receptor but does not indicate intrinsic activity. It is possible that some compounds have lower efficacy with respect to affinity, resulting in reduced oral activity. Such a hypothesis is supported by the profile of compound **7e**, which possesses benzodiazepine-like anticonflict activity but no anticonvulsant activity against leptazol in mice. On the contrary, **7e** totally antagonized the antileptazol effects of diazepam at 100 mg/kg po. This antagonism was dose related, with an ED_{50} of 54 mg/kg po, and is consistent with low efficacy and therefore only partial agonism at the benzodiazepine receptor. The compound occupies the receptors with enough intrinsic activity to produce an anticonflict effect but not an anticonvulsant effect. The affinity is sufficient however to block the anticonvulsant activity of diazepam. Secondly, there is a possible difference in bioavailability of the compounds arising from absorption, distribution, and metabolism. Selected compounds are therefore currently undergoing further studies to evaluate their potential as antianxiety drugs, the results of which will be published in due course.

Conclusion

(Imidazo[1,2-*a*]pyrimidin-2-yl)phenylmethanones represent a new class of anxiolytic agents which potently bind to the benzodiazepine receptor but do not possess the full pharmacological profile of classical benzodiazepines. While being equipotent with chlordiazepoxide in animal models of anxiety, compounds **7e**, **8b**, **8h**, **8j**, and **8k** show reduced anticonvulsant activity, little or no muscle relaxation, and neglibible sedative effects. Compounds such as these present a significant step forward in the study of benzodiazepine receptor activity and should offer a distinct advantage in the treatment of anxiety.

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 SP1000 spectrophotometer. NMR spectra were determined with a Perkin-Elmer R12A spectrometer at 60 MHz and chemical shifts are reported as τ values with respect to tetramethylsilane as internal standard; all OH and NH peaks were removed by addition of D_2O. The NOE difference spectra were run on a Brucker WP2005Y instrument at 200 MHz. Benzothiazolamines,[13] quinolinamines,[14] and pyrimidinamines[15] were synthesized by known methods. Activated manganese(IV) oxide was supplied by Aldrich.

Method A. Ethyl 7-Ethylimidazo[2,1-*b*]benzothiazole-2-carboxylate (2b). Ethyl bromopyruvate (39.9 g, 0.2 mol) was added dropwise to a stirred solution of 6-ethyl-2-benzothiazolamine (26.7 g, 0.15 mol) in dry THF (200 mL) and the mixture was stirred for 4 h. EtOH (100 mL) was added and the solution was refluxed for 3 h. Solvent was evaporated under reduced pressure, and the residue was dissolved in $CHCl_3$ (200 mL) and washed with 5% $NaHCO_3$. Evaporation of the solvent gave a residue which was subjected to chromatography (silica; CH_2Cl_2/EtOAc 96:4) to yield **2b** (10.6 g, 26%), mp 119–120 °C (from EtOAc).

Esters **4a** and **4b** were made in the same way by using the appropriate 2-quinolinamine except that the intermediate hydrobromide salt which crystallized out of the THF solution was removed by filtration and then heated in refluxing EtOH.

All phenyl methanones except **2c** and **2d** were made by method A with 3-bromo-1-phenyl-1,2-propanedione[16] instead of ethyl bromopyruvate.

Method B. 7-Ethylimidazo[2,1-*b*]benzothiazole-2-methanol (3b). Lithium aluminum hydride (1.25 g, 0.033 mol) was added to a stirred solution of **2b** (8.22 g, 0.03 mol) in dry THF (350 mL) under N_2 and the mixture was stirred for 2 h. After addition of wet THF, the mixture was poured into water (500 mL) and the product was extracted with $CHCl_3$ (300 mL), evaporation of which gave **3b** (4.8 g, 68%), mp 141–142 °C (from EtOAc).

Ethyl esters **2a**, **4a**, and **4b** were reduced in the same way to give methanols **3a**, **4c**, and **4d**.

Method C. 7-Ethylimidazo[2,1-*b*]benzothiazole-2-carboxaldehyde (3d). A solution of **3b** (4.6 g, 0.02 mol) in $CHCl_3$ (200 mL) was stirred for 16 h with manganese dioxide (15.0 g, 0.17 mol) and filtered through Celite. Evaporation of the solvent gave **3d** (3.9 g, 85%), mp 183–184 °C (from EtOAc).

Aldehydes **3c**, **4e**, and **4f** were prepared in the same way.

Method D. (7-Ethylimidazo[2,1-*b*]benzothiazol-2-yl)-phenylmethanone (2d). A solution of phenylmagnesium bromide [from bromobenzene (3.8 g, 0.024 mol) and magnesium (0.58 g, 0.024 g-atom] in dry THF (15 mL) was added to a suspension of **3d** (1.84 g, 0.008 mol) in dry THF (70 mL) and the mixture was stirred for 1 h. The mixture was poured into water (300 mL) and extracted with $CHCl_3$ (200 mL), evaporation of which gave a crystalline solid (1.85 g, 75%), mp 129–130 °C (from EtOAc–petroleum ether, bp 40–60 °C). The solid (1.65 g) was treated with manganese dioxide as in method C to give **2d** (1.2 g, 73%), mp 151–153 °C (from EtOAc).

Other methanones were prepared by the same procedure by using Grignard reagents and the appropriate aldehyde.

Method E. Imidazo[2,1-*b*]benzothiazole-2-carboxylic Acid (2e). A solution of **2a** (18.45 g, 0.075 mol) and aqueous NaOH (1 N, 90 mL, 0.09 mol) in EtOH (100 mL) was heated on a steam bath for 1 h. Solvent was evaporated under reduced pressure and the residue was dissolved in water. Addition of aqueous HCl precipitated the acid **2e** (12.6 g, 77%), mp 262–263 °C (lit.[3a] mp 263–265 °C).

Method F. Methyl Imidazo[2,1-*b*]benzothiazole-2-carboxylate (2f). A mixture of **2e**, (1.09 g, 5 mmol) and boron trifluoride etherate (0.71 g, 5 mmol) in MeOH (10 mL) was refluxed for 24 h. Solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (50 mL). The solution was washed with 10% Na_2CO_3 and water and then evaporated to dryness to give the methyl ester **2f** (0.65 g, 56%), mp 156–157 °C (from EtOAc).

Esters **2g–i** were prepared in the same way except that in the case of higher boiling alcohols the reaction temperature was 120 °C.

Method G. Benzyl Imidazo[2,1-*b*]benzothiazole-2-carboxylate (2j). Oxalyl chloride (6.5 mL, 0.075 mol) was added dropwise to a stirred suspension of **2e** (10.9 g, 0.05 mol) in dry toluene (70 mL). After the mixture was stirred at room temperature for 18 h, filtration gave the acid chloride of **2e** (11.2 g, 95%), mp 232–236 °C. A mixture of the acid chloride (4.73 g, 0.02 mol) and benzyl alcohol (3.24 g, 0.03 mol) in dry CH_2Cl_2 (100 mL) was stirred at room temperature for 4 days, washed with 5% Na_2CO_3, and evaporated to dryness to give **2j** (1.3 g, 21%), mp 120–121 °C (from EtOAc).

Amides **2l** and **2m** were prepared in the same way.

Method H. 2-(4,4-Dimethyl-2-oxazolidinyl)imidazo[2,1-*b*]benzothiazole (2k). The amide obtained from reaction of acid chloride with 2-amino-2-methylpropan-1-ol as in method G (1.9 g, 6.6 mmol) was heated in polyphosphoric acid (20 mL) at 100 °C for 1 h, cooled, and poured into iced water. The solution was basified (Na_2CO_3) and extracted with CH_2Cl_2, evaporation of which gave an oil which crystallized in cold Et_2O. The product was purified by HPLC (silica; $CHCl_3$) to give **2k** (1.3 g, 73%), mp 113-135 °C; IR 2980, 1670, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) τ

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1.82 (1 H, s, 1-H), 2.15–2.75 (4 H, m, Ar H), 5.89 (2 H, s, CH_2), 8.62 (6 H, s, 2 CH_3).

2-Hydroxy-3-phenylpyrimido[2,1-*b*]benzothiazolium Bromide (6). 3-Bromo-1-phenyl-1,2-propanedione (7.5 g, 0.033 mol) was added dropwise to a solution of 2-benzothiazolamine (4.5 g, 0.03 mol) in dimethoxyethane (20 mL), and the mixture was stirred at room temperature for 16 h. Solid material was filtered off and heated for 6 h in refluxing EtOH (100 mL). After cooling, filtration yielded **6** (4.5 g, 42%) as golden-yellow crystals (from CH_3OH–EtOAc), mp 270–280 °C dec; IR 3600–3300, 3000–2300, 1600, and 1585 cm^{-1}. Anal. ($C_{16}H_{11}BrN_2OS$) C, H, Br, N, S.

(1-Bromo-5-methoxy-6,7,8,9-tetrahydroimidazo[1,2-*a*]quinazolin-2-yl)phenylmethanone (9). *N*-Bromosuccinimide (2.85 g, 0.016 mol) was added to a solution of **7e** (4.5 g, 0.015 mol) in $CHCl_3$ (20 mL). After 10 min the solution was washed with water and evaporated under reduced pressure to give **9** (4.5 g, 80%) (from EtOH), mp 162–163 °C; IR 1645 (infl) and 1634 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.65–1.86 (2 H, m, phenyl 2-H and 6-H), 2.40–2.60 (3 H, m, Ar H), 5.98 (3 H, s, CH_3), 6.30–6.62 (2 H, m, 9-CH_2), 7.20–7.55 (2 H, m, 6-CH_2), 7.90–8.35 (4 H, m, 7-CH_2 and 8-CH_2). Anal. ($C_{18}H_{16}BrN_3O_2$) C, H, Br, N.

(3-Bromo-6-ethyl-5-methyl-7-(methylthio)imidazo[1,2-*a*]pyrimidin-2-yl)phenylmethanone (10a) was prepared from **8b** as for compound **9**: mp 154–156 °C; IR 1660 and 1605 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.70–1.90 (2 H, m, phenyl 2-H and 6-H), 2.30–2.70 (3 H, m, Ar H), 6.96 (3 H, s, 5-CH_3), 7.41 (3 H, s, SCH_3), 7.27 (2 H, q, J = 7 Hz, 6-CH_2CH_3), 8.80 (3 H, t, J = 7 Hz, 6-CH_2CH_3). Anal. ($C_{17}H_{16}BrN_3OS$) C, H, Br, N, S.

(3-Bromo-6-ethyl-7-methoxy-5-methylimidazo[1,2-*a*]pyrimidin-2-yl)phenylmethanone (10b) was prepared from **8j** as for compound **9**: mp 142 °C; IR 1697 and 1629 cm^{-1}; ^1H NMR ($CDCl_3$), τ 1.70–1.90 (2 H, m, phenyl 2-H and 6-H), 2.40–2.75 (3 H, m, Ar H), 5.98 (3 H, s, OCH_3), 7.01 (3 H, s, 5-CH_3), 7.38 (2 H, q, J = 7 Hz, 6-CH_2CH_3), 8.90 (3 H, t, J = 7 Hz, 6-CH_2CH_3). Anal. ($C_{17}H_{16}BrN_3O_2$) C, H, Br, N.

Benzodiazepine Receptor Binding Assay. The affinity of the compounds for the benzodiazepine receptor was assessed by using modifications of the original method of Squires and Braestrup.[17] The values in the tables are nanomolar concentration of test drug which inhibit the specific binding of 0.6 nM [^3H]-fluinitrazepam 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.

Food-Conflict Test. The food-motivated conflict test is a modification of the method of Cook and Sepinwall[18] with five alternating 4-min FI30 unpunished and 3-min FR5 punished components with male Lister rats. Compounds were initially tested at 50 mg/kg po in four rats and if active were then tested at decreasing doses until the minimum effective dose (MED) was found. The MED was based on at least one rat showing a significant increase in punished response as assessed by using the Mann–Whitney *U* test.

Licking-Conflict Test. The licking-conflict paradigm is similar to that of Petersen and Lassen[19] with the addition of a 0.5-s on–off alternating tone conditioning stimulus. After 1-min unpunished drinking, the tone stimulus began and continued for the 3-min punished period. Rats were trained to stable suppression of drinking at the onset of the tone before drugs were tested.

Anticonvulsant Test. Anticonvulsant activity was assessed in male CD-1 mice with 120 mg/kg of leptazol according to the method described by Everett and Richards.[20]

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.

Pull-Up Test. Muscle relaxation was assessed by using the pull-up test[21] in which the mean time is recorded for groups of 10 male Lister rats to pull up to the experimenter's hand after being suspended vertically by the hind limbs. Data were analyzed by using the Mann–Whitney *U* test.

Registry No. **2a**, 64951-05-9; **2b**, 81022-07-3; **2c**, 114094-91-6; **2d**, 114094-92-7; **2e**, 64951-09-3; **2e** (acid chloride), 114094-93-8; **2e** (amide), 114094-94-9; **2f**, 114094-95-0; **2g**, 114094-96-1; **2h**, 114094-97-2; **2i**, 114094-98-3; **2j**, 114094-99-4; **2k**, 114095-00-0; **2l**, 114130-38-0; **2m**, 114095-01-1; **2n**, 61984-82-5; **3a**, 114095-02-2; **3b**, 114095-03-3; **3c**, 114095-04-4; **3d**, 114095-05-5; **4a**, 66491-09-6; **4b**, 66491-19-8; **4c**, 84357-16-4; **4d**, 114095-06-6; **4e**, 84357-17-5; **4f**, 114095-07-7; **5a**, 92412-78-7; **5b**, 84357-38-0; **5c**, 84357-23-3; **5d**, 84357-04-0; **5e**, 84357-40-4; **5f**, 84357-39-1; **5g**, 84357-21-1; **5h**, 84357-24-4; **5i**, 84357-09-5; **5j**, 84357-41-5; **5k**, 114095-08-8; **5l**, 92412-80-1; **5m**, 114095-09-9; **5n**, 84357-11-9; **5o**, 84357-25-5; **5p**, 84357-29-9; **5q**, 84357-26-6; **5c**, 84357-28-8; **6**, 114095-10-2; **7a**, 90808-01-8; **7b**, 90808-02-9; **7c**, 90808-03-0; **7d**, 90808-09-6; **7e**, 90807-98-0; **7f**, 90807-99-1; **7g**, 90808-82-5; **7h**, 90808-13-2; **7i**, 90808-14-3; **7j**, 90808-05-2; **7k**, 90808-07-4; **7l**, 114095-11-3; **7m**, 114095-12-4; **7n**, 114095-13-5; **7o**, 114095-14-6; **7p**, 114095-15-7; **8a**, 90808-47-2; **8b**, 90808-45-0; **8c**, 90808-19-8; **8d**, 90808-31-4; **8e**, 90808-32-5; **8f**, 90808-26-7; **8g**, 90808-40-5; **8h**, 90808-16-5; **8i**, 90808-49-4; **8j**, 90808-12-1; **8k**, 90808-28-9; **8l**, 90808-18-7; **8m**, 90808-27-8; **8n**, 90808-17-6; **8o**, 90808-11-0; **8p**, 90808-39-2; **8q**, 90808-10-9; **8r**, 90808-00-7; **8s**, 114095-16-8; **8t**, 90808-34-7; **9**, 114095-17-9; **10a**, 114095-18-0; **10b**, 114095-19-1; $ClCH_2COCH_2CO_2Et$, 638-07-3; *m*-$ClC_6H_4NH_2$, 108-42-9; PrMgBr, 927-77-5; EtMgBr, 925-90-6; $BrCH_2COAc$, 5308-51-0; *p*-MeC_6H_4MgBr, 4294-57-9; *p*-$MeOC_6H_4MgBr$, 13139-86-1; *p*-ClC_6H_4MgBr, 873-77-8; ethyl bromopyruvate, 70-23-5; 2-amino-6-ethylbenzothiazole, 21224-16-8; 2-amino-4-methoxyquinoline, 42712-65-2; 2-amino-6-ethyl-4-methoxyquinoline, 84357-05-1; 3-bromo-1-phenyl-1,2-propanedione, 29634-62-6; 2-amino-2-methylpropan-1-ol, 124-68-5; 2-aminobenzothiazole, 136-95-8; 2-aminothiazole, 96-50-4; 2-amino-6-ethyl-4-methoxy-3-methylquinoline, 92412-82-3; 2-amino-6-isopropyl-4-methoxyquinoline, 114095-20-4; 2-amino-4-methoxy-6-propylquinoline, 114095-21-5; 2-amino-6-fluoro-4-methoxyquinoline, 5761-71-7; 2-amino-4-methoxy-6-methylquinoline, 42712-69-6; 2-amino-6-butyl-4-methoxyquinoline, 114095-22-6; 2-amino-6,7-dimethyl-4-methoxyquinoline, 77937-86-1; 2-pyridinylmagnesium bromide, 21970-13-8; 2-amino-3,6-diethyl-4-methoxyquinoline, 92412-84-5; 2-magnesium bromide thiophene, 5713-61-1.

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