Nitrogen Bridgehead Compounds. 66.[1] Bronchodilator Nitrogen Bridgehead Compounds with a Pyrimidinone Moiety

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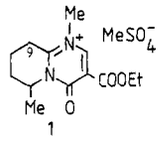
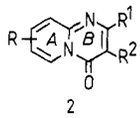
New types of bronchodilator agents, bi- and tricyclic nitrogen bridgehead compounds with a pyrimidin-4(3*H*)-one ring, were synthesized and evaluated for bronchodilator activity against serotonin-, histamine-, and acetylcholine-induced spasms in the guinea pig Konzett–Rössler test. The structure–activity relationships are discussed. The effects of some bi- and tricyclic derivatives on the human bronchus were also investigated. The homologous tricyclic compounds **68** and **69** were tested on isolated guinea pig ileum and trachea, and the effects of compound **69** were investigated in pilocarpine-treated dogs. Azepino[2,1-*b*]quinazoline (**69**; CHINOIN-1289) was selected for further biochemical and clinical investigations.

During clinical investigations of the analgetic rimazolium[2] (**1**), a favorable side effect on the respiratory system was observed.[3] Further pharmacological evaluation of compound **1** also revealed weak passive cutaneous anaphylactic (PCA) activity [ID_{50}, μmol/kg, ip], which could be enhanced by introducing various functional groups into position 9 of the pyridopyrimidinone skeleton.[4] In fact, all the compounds having antagonistic activity against serotonin inhibit quite clearly PCA in rat because, in this special species, serotonin is the most important mediator governing vascular permeability. Thus for compounds with this property PCA is not a good test to determine the antiallergic mast cell stabilization property. At the same time, compound **1** exhibited bronchodilator activity similar to that of theophylline anisate in the Konzett–Rössler test (see Table I).



1



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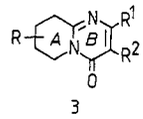
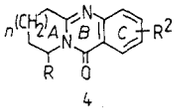


3

R = H, Me; R^1 = Me; R^2 = Et; R^1 = R^2 = $-(CH_2)_3-$; $-(CH_2)_4-$



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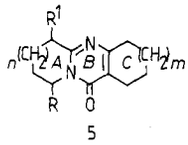


5

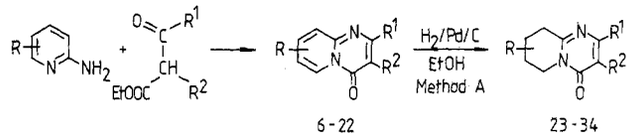
R^2 = H, Me, COOH, COOMe, COOEt, OCH_2O R = H, Me; R^1 = H, Me n = 0-3; m = 0-3

The aim of our further studies was to optimize the bronchodilator activity while eliminating the central nervous system (CNS) effect of this type of compound. In this paper we report the preparation and pharmacological investigations of bi- and tricyclic nitrogen bridgehead compounds of types **2–5**.

Of the investigated derivatives, compounds **35** and **36** are known as alkaloids.[5] Bronchodilator activity was earlier reported[6] for compounds **35–37**, without quantification, but it was noted that the bronchodilator activity of compounds **35–37** increased with increasing size of ring A.[6b]

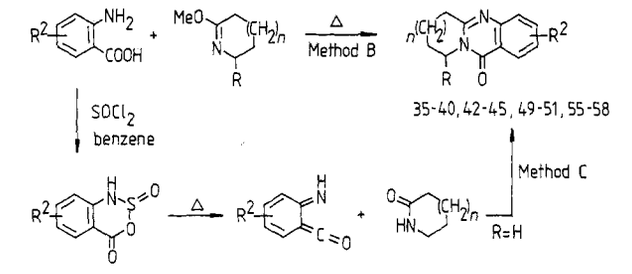
Chemistry. Pyrido[1,2-*a*]pyrimidines[7] **6–10** and **23** and tricyclic nitrogen bridgehead compounds[8,9] **11–22** and **24–34** were prepared as in the literature procedure, by

Scheme I



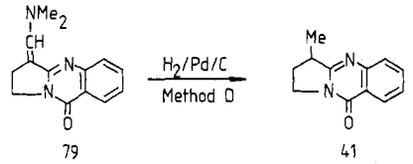
6-22 23-34

Scheme II



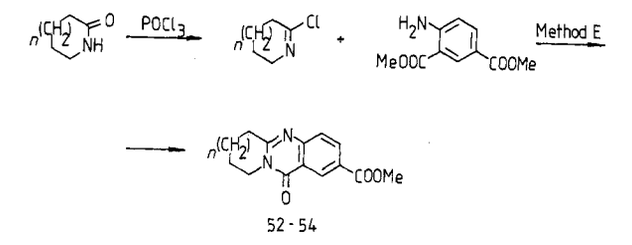
35-40, 42-45, 49-51, 55-58

Scheme III



79 41

Scheme IV



52-54

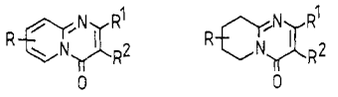
reacting 2-aminopyridines with appropriate β-oxo esters in a mixture[10] of phosphoryl chloride–polyphosphoric acid,

† Chinoin Pharmaceutical and Chemical Works Ltd.
‡ UCB Pharmaceutical Sector.

(1) Part 65. Horváth, Á.; Hermecz, I. *J. Heterocycl. Chem.* **1986**, *23*, 1295.
(2) (a) Knoll, J.; Mészáros, Z.; Szentmiklósi, P.; Fürst, Zs. *Arzneim.-Forsch.* **1971**, *21*, 717. (b) Mészáros, Z.; Knoll, J.; Szentmiklósi, P.; Dávid, Á.; Horváth, G.; Hermecz, I. *Arzneim.-Forsch.* **1972**, *22*, 815. (c) Hermecz, I.; Mészáros, Z. *Med. Res. Rev.*, in press.
(3) Graber, H.; Varga, E. *Orvostudomány* **1971**, *22*, 311.

0022-2623/87/1830-1543$01.50/0

Table I. Pyrido[1,2-*a*]pyrimidinones, Cyclopenta[*d*]pyrido[1,2-*a*]pyrimidinones, and Pyrido[2,1-*b*]quinazolinones (1 and 6–34)



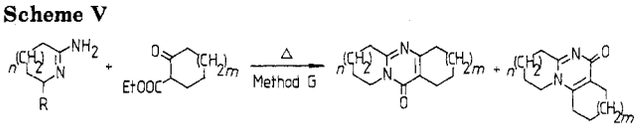
6-22 23-34

compd	R	R^1	R^2	meth	yield, %	mp, °C base	mp, °C HCl salt	recrystn solvent	lit., mp °C	ref	formula	Konzett–Rössler test: ID_{50},[a,b] μmol/kg serotonin	histamine	acetylcholine
theophylline anisate												10.0	10.0	22.0
1 (rimazolium)												14.0	8.0	31.0
6	H	Me	Et				248–250	EtOH	185–190	7	$C_{11}H_{13}ClN_2O$	12.0	8.6	29.4
7	6-Me	Me	Et				232	EtOH	233	7	$C_{12}H_{15}ClN_2O$	9.6	10.2	25.6
8	7-Me	Me	Et				>240	EtOH	210–220	7	$C_{12}H_{15}ClN_2O$	16.6	12.4	24.0
9	8-Me	Me	Et				>240	EtOH	195–200	7	$C_{12}H_{15}ClN_2O$	29.7	20.9	36.7
10	9-Me	Me	Et				>240	EtOH	125–130	7	$C_{12}H_{15}ClN_2O$	12.3	5.1	36.4
11	H	$(CH_2)_3$					>240	EtOH	165–167	8	$C_{11}H_{11}ClN_2O$	17.6	10.5	32.4
12	6-Me	$(CH_2)_3$					>240	EtOH	221–224	8	$C_{12}H_{13}ClN_2O$	11.2	10.2	21.6
13	7-Me	$(CH_2)_3$					>240	EtOH	206–215	8	$C_{12}H_{13}ClN_2O$	22.6	15.7	29.6
14	8-Me	$(CH_2)_3$					242–243	EtOH	202–210	8	$C_{12}H_{13}ClN_2O$	14.4	29.2	29.1
15	9-Me	$(CH_2)_3$					204–205	EtOH	170–180	8	$C_{12}H_{13}ClN_2O$	4.3	7.2	29.3
16	H	$(CH_2)_4$					>240	EtOH	178–183	8	$C_{12}H_{13}ClN_2O$	16.7	6.1	18.2
17	6-Me	$(CH_2)_4$					>240	EtOH	211–218	8	$C_{13}H_{15}ClN_2O$	15.6	7.0	15.7
18	7-Me	$(CH_2)_4$					>240	EtOH	240	9	$C_{13}H_{15}ClN_2O$	21.9	20.4	37.7
19	8-Me	$(CH_2)_4$					>240	EtOH	240	9	$C_{13}H_{15}ClN_2O$	20.4	15.6	32.0
20	9-Me	$(CH_2)_4$					214–215	EtOH	214–215	9	$C_{13}H_{15}ClN_2O$	6.1	9.7	10.0
21	H	$(CH_2)_6$					229–230	EtOH	193–203	8	$C_{14}H_{17}ClN_2O$	49.0	32.7	53.3
22	6-Me	$(CH_2)_6$					215–216	EtOH	200–206	8	$C_{15}H_{19}ClN_2O$	14.3	23.8	42.6
23	6-Me	Me	Et			40–42			oil	7	$C_{12}H_{18}N_2O$	18.4	23.2	28.2
24	H	$(CH_2)_3$				95–96		acetone	96–97	8	$C_{11}H_{14}N_2O$	24.1	25.7	23.7
25	6-Me	$(CH_2)_3$				88–89		acetone	86–87	8	$C_{12}H_{16}N_2O$	22.5	18.9	56.4
26	7-Me	$(CH_2)_3$		A	92	97–98		acetone			$C_{12}H_{16}N_2O$	39.6	7.2	17.6
27	8-Me	$(CH_2)_3$		A	95	85–86		acetone			$C_{12}H_{16}N_2O$	13.8	11.7	18.2
28	9-Me	$(CH_2)_3$		A	91	88–90		EtOAc			$C_{12}H_{16}N_2O$	7.7	11.5	12.8
29	H	$(CH_2)_4$				171–172		acetone	172–173	8	$C_{12}H_{16}N_2O$	33.3	22.0	44.5
30	6-Me	$(CH_2)_4$				135–136		acetone	128–130	8	$C_{13}H_{18}N_2O$	36.2	19.8	47.1
31	7-Me	$(CH_2)_4$				119–120		EtOAc	116–117	9	$C_{13}H_{18}N_2O$	39.3	25.7	29.9
32	8-Me	$(CH_2)_4$				109–110		EtOAc	108–109	9	$C_{13}H_{18}N_2O$	38.1	23.6	28.9
33	9-Me	$(CH_2)_4$				101–102		EtOAc	100–101	9	$C_{13}H_{18}N_2O$	14.0	24.7	20.3
34	H	$(CH_2)_5$		A	88	160–161		hexane			$C_{13}H_{18}N_2O$	12.7	15.2	11.8

[a] All data are considered significant at $p \leq 0.05$ as determined by Student's *t* test. [b] Compounds **6–22** were investigated as the hydrochloride salts and compounds **23–34** as the free bases.

and in some cases the bi- and tricyclic products were subsequently hydrogenated over 10% palladium-on-carbon catalyst in ethanol (Scheme I, method A).

Scheme V



59, 61, 63, 64, 66, 68, 69, 71-75 60, 62, 65, 67, 70, 76

In the preparation of compounds **35–40**, **49–51**, and **55–57**, the procedure of Petersen and Tietze[11] was adopted. The appropriate 2-aminobenzoic acid was reacted with a lactim ether in boiling benzene (method B-1) or in DMF (method B-2) at 80–90 °C (Scheme II, Table II).

To prepare compounds **42–45** and **58**, the method of Kametani[12] was applied. From the respective 2-aminobenzoic acid, a sulfinamide anhydride was prepared with thionyl chloride; this was then reacted with the required lactam in benzene to give tricyclic compounds **42–45** and **58** (method C, Scheme II).

3-Methyltetrahydropyrrolo[2,1-*b*]quinazolin-9-one (**41**) was obtained from 3-[(dimethylamino)methylene]tetrahydropyrrolo[2,1-*b*]quinazolin-9-one[13] (**79**) by catalytic

(4) (a) Hermecz, I.; Breining, T.; Mészáros, Z.; Horváth, Á.; Vasvári-Debreczy, L.; Dessy, F.; DeVos, C.; Rodriguez, L. *J. Med. Chem.* **1982**, *25*, 1140. (b) DeVos, C.; Dessy, F.; Hermecz, I.; Breining, T.; Mészáros, Z. *Int. Arch. Allergy Appl. Immunol.* **1982**, *67*, 362. (c) Hermecz, I.; Breining, T.; Mészáros, Z.; Kökösi, J.; Mészáros, L.; Dessy, F.; DeVos, C. *J. Med. Chem.* **1983**, *26*, 1126. (d) Hermecz, I.; Breining, T.; Vasvári-Debreczy, L.; Horváth, Á.; Mészáros, Z.; Bitter, I.; DeVos, C.; Rodriguez, L. *J. Med. Chem.* **1983**, *26*, 1494. (e) Hermecz, I.; Horváth, Á.; Mészáros, Z.; DeVos, C.; Rodriguez, L. *J. Med. Chem.* **1984**, *27*, 1253.

(5) (a) Amin, A. H.; Mehta, D. H. *Nature (London)* **1959**, *184* Suppl. No. 17, 1317. (b) John, S. R.; Lamberton, J. A. *Chem. Commun.* **1965**, 82. (c) Hermecz, I.; Vasvári-Debreczy, L. *Adv. Heterocycl. Chem.* **1986**, *39*, 282 and references cited therein.

(6) (a) Amin, A. H.; Mehta, D. R.; Samarth, S. S. *Proc. Int. Pharmacol. Meet., 1st* **1961**, 377; *Chem. Abstr.* **1964**, *61*, 7537. (b) Atal, C. K. in *Chemistry and Pharmacology of Vasicine—A New Oxytocic and Abortifacient*; Regional Research Laboratory: Jammu-Tawi, India, 1980; p 138; *Chem. Abstr.* **1981**, *95*, 198090.

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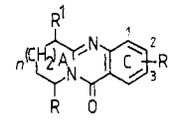
(11) Petersen, S.; Tietze, E. *Justus Liebigs Ann. Chem.* **1959**, *623*, 166.

(12) Kametani, T.; Higa, T.; Loc, C. V.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 186.

(13) Horváth, Á.; Hermecz, I.; Pongor-Csákvári, M.; Mészáros, Z.; Kökösi, J.; Tóth, G.; Szöllösy, Á. *J. Heterocycl. Chem.* **1984**, *21*, 219.

Table II. Benzo-Fused Tricyclic Nitrogen Bridgehead Derivatives (**35–58**)



35-58

compd	*n*	R	R^1	R^2	meth	yield, %	mp, °C base	mp, °C HCl salt	recrystn solvent	lit. mp, °C	ref	formula	Konzett–Rössler test: ID_{50},[a,b] μmol/kg serotonin	histamine	acetylcholine
35	0	H	H	H	B-1	95		284	EtOH	298–302	15a	$C_{11}H_{11}ClN_2O$	21.2	16.9	37.7
36	1	H	H	H	B-1	64		274–276	EtOH	269–272	15a	$C_{12}H_{13}ClN_2O$	15.2	11.1	31.1
37	2	H	H	H	B-1	72		224–225	EtOH	221–224	15a	$C_{13}H_{15}ClN_2O$	36.0	6.2	26.3
38	3	H	H	H	B-1	76		188–189	EtOH	112[c]	15b	$C_{14}H_{17}ClN_2O$	>100.0	61.8	61.8
39	0	Me	H	H	B-1	57	oil	238	EtOH			$C_{12}H_{13}ClN_2O$	12.2	10.4	48.2
40	1	Me	H	H	B-1	73		263	EtOH	265	9	$C_{13}H_{15}ClN_2O$	30.2	27.0	>100.0
41	0	H	Me	H	D	85	138–140	260	EtOH			$C_{12}H_{13}ClN_2O$	29.4	27.3	45.8
42	0	H	H	3-Me	C	78	175–176	268–271	EtOH	209–211	16	$C_{12}H_{13}ClN_2O$	11.3	29.8	29.0
43	2	H	H	1-Me	C	62	108–110	232–234	EtOH			$C_{14}H_{17}ClN_2O$	>32[d]	>32[d]	>32[d]
44	2	H	H	2-Me	C	89	100–102	262	EtOH			$C_{14}H_{17}ClN_2O$	39.4	25.6	76.0
45	2	H	H	3-Me	C	77	101–103	253–255	EtOH	189–190	16	$C_{14}H_{17}ClN_2O$	44.7	25.3	16.0
46	0	H	H	2-COOEt	F	81	130–131	238–240	EtOH			$C_{14}H_{15}ClN_2O$	>32.0	14.4	>32.0
47	1	H	H	2-COOEt	F	67	137–139	254–255	EtOH			$C_{15}H_{17}ClN_2O_3$	>32.0	15.1	>32.0
48	2	H	H	2-COOEt	F	83	118–120	233–234	EtOH			$C_{16}H_{19}ClN_2O_3$	10.0[d]	32.0[d]	24.5[d]
49	0	H	H	2-COOH	B-2	79	350–352		DMF	275–277[c]	17	$C_{12}H_{10}N_2O_3$	>100.0	>100.0	>100.0
50	1	H	H	2-COOH	B-2	82	255		EtOH			$C_{13}H_{12}N_2O_3$	>100.0	>100.0	>100.0
51	2	H	H	2-COOH	B-2	87	294		DMF			$C_{14}H_{14}N_2O_3$	>100.0	>100.0	>100.0
52	0	H	H	3-COOMe	E	68	197–198	264–266	MeOH	197–200	18	$C_{13}H_{13}ClN_2O_3$	11.7	27.0	44.1
53	1	H	H	3-COOMe	E	53	128–130	268	MeOH			$C_{14}H_{15}ClN_2O_3$	12.3	16.8	>32.0
54	2	H	H	3-COOMe	E	70	149–150	236	MeOH			$C_{15}H_{17}ClN_2O_3$	32[d]	32[d]	>32[d]
55	0	H	H	3-COOH	B-2	82	294		DMF			$C_{12}H_{10}N_2O_3$	>100.0	215.0	>100.0
56	1	H	H	3-COOH	B-2	68	273–274		DMF			$C_{13}H_{12}N_2O_3$	>100.0	>100.0	>100.0
57	2	H	H	3-COOH	B-2	80	263–266		DMF			$C_{14}H_{14}N_2O_3$	>100.0	>100.0	>100.0
58	2	H	H	2,3-OCH_2O	C	67	155–157	247–248	EtOH			$C_{14}H_{15}ClN_2O_3$	13.1	>32.0	22.7

[a] All data are considered significant at $p \leq 0.05$ as determined by Student's *t* test. [b] Compounds **35–48**, **52–54**, and **58** were investigated as the hydrochloride salts and compounds **49–51** and **55–57** as the free bases. [c] Mp of the free base. [d] Toxic range.

hydrogenation in ethanol over 10% palladium-on-carbon catalyst (method D, Scheme III).

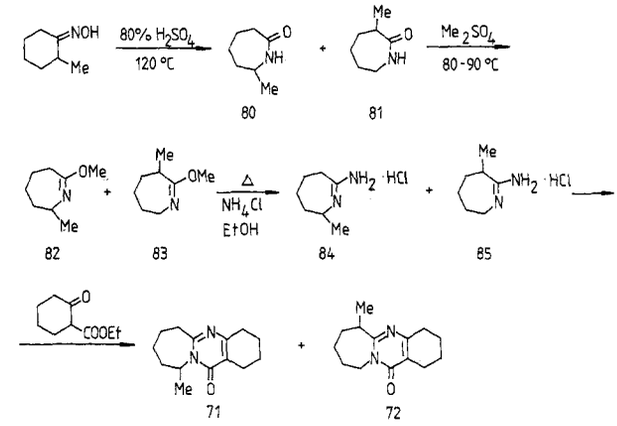
Tricyclic esters **52–54** were prepared by the method of Kadyrov and co-workers[14] from the appropriate lactam, which was first treated with phosphoryl chloride and then with dimethyl 2-aminoisophthalate (method E, Scheme IV).

The carboxylic acids **49–51** were esterified with ethanol in the presence of dry hydrogen chloride to give the corresponding ethyl esters **46–48** (method F).

Semicyclic amidines were reacted with cyclic β-oxo esters in boiling ethanol to give a mixture of the isomeric linearly and angularly annelated nitrogen bridgehead compounds **59–70** and **73–76** (Scheme V, Table III). Isomeric products could be identified by TLC. The linearly fused isomers (**59, 61, 63, 64, 66, 68, 69**, and **71–75**) with the higher R_f values (~0.6) were the major products; they were isolated by crystallization (method G-1). In some cases the minor angular products (**60, 62, 65, 67, 70**, and **76**) with lower R_f values (~0.3) were isolated from the mother liquor by preparative HPLC (method G-2).

Methylazepino[2,1-*b*]quinazolinones **71** and **72** were synthesized from 2-methylcyclohexanone oxime,[19] as depicted in Scheme VI (method H). Tricyclic compounds **71** and **72** were separated by preparative HPLC.

Scheme VI



The treatment of azepino derivatives **68** and **69** with phosphorus pentasulfide in refluxing xylene afforded thiones **77** and **78** (method I).

Biological Results and Discussion

The pharmacological data obtained on the bi- and tricyclic nitrogen bridgehead compounds in the modified Konzett–Rössler[20] test, using serotonin, histamine, and

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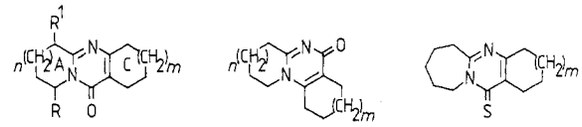
Table III. Linearly and Angularly Fused Tricyclic Nitrogen Bridgehead Derivatives (**59–78**)



59, 61, 63, 64, 66, 68, 69, 71-75 | 60, 62, 65, 67, 70, 76 | 77, 78

compd	*m*	*n*	R	R^1	meth	yield, %	mp, °C base	mp, °C HCl salt	recrystn solvent	formula	Konzett–Rössler test: ID_{50},[a,b] μmol/kg serotonin	histamine	acetylcholine
59	0	0	H	H	G-1	61	92–94		EtCOMe	$C_{10}H_{12}N_2O$	82.5	46.1	>100
60	0	0	H	H	G-2	17	170		acetone	$C_{10}H_{12}N_2O$	>100	>100	>100
61	1	0	H	H	G-1	65	129		EtCOMe	$C_{11}H_{14}N_2O$	29.8	24.1	51.1
62	1	0	H	H	G-2	12	162–164		EtOAc	$C_{11}H_{14}N_2O$	107.0	>100	>100
63	1	0	Me	H	G-1	69	94–96		Et_2O	$C_{12}H_{16}N_2O$	46.8	19.7	74.6
64	2	0	H	H	G-1	77	113–115		EtOAc	$C_{12}H_{16}N_2O$	33.0	27.6	38.5
65	2	0	H	H	G-2	15	129–131		acetone	$C_{12}H_{16}N_2O$	>32.0	>32.0	>32[c]
66	3	0	H	H	G-1	71	98		*i*-PrOH	$C_{13}H_{18}N_2O$	57.1	164	100
67	3	0	H	H	G-2	6.4	118–121		EtCOMe	$C_{13}H_{18}N_2O$			
68	0	2	H	H	G-1	87.5	98		EtCOMe	$C_{12}H_{16}N_2O$	13.8	6.5	3.7
69	1	2	H	H	G-1	82	152–153	207–208	acetone	$C_{13}H_{18}N_2O$	3.0	3.0	7.8
70	1	2	H	H	G-2	1.2	188–190		MeOH	$C_{13}H_{18}N_2O$	55.1	>32.0	>32[c]
71	1	2	Me	H	H	38	82–84		Et_2O	$C_{14}H_{20}N_2O$	>320[d]	>320[d]	>320[d]
72	1	2	H	Me	H	35	94		MeCOMe	$C_{14}H_{20}N_2O$	>320[d]	>320[d]	>320[d]
73	2	2	H	H	G-1	76	160–161	240–242	acetone	$C_{14}H_{21}ClN_2O$	30.8	33.8	7.2
74	3	2	H	H	G-1	58	113	207–209	EtOAc	$C_{15}H_{23}ClN_2O$	>100	33.0	2.26
75	1	3	H	H	G-1	60	71–73		acetone–hexane	$C_{14}H_{20}N_2O$	44.6	27.1	58.5
76	1	3	H	H	G-2	0.8	101–103		Et_2O	$C_{14}H_{20}N_2O$			
77	0				I	36	134		EtOH	$C_{12}H_{16}N_2S$	>320	>320	>320
78	1				I	45	134–135		EtOH	$C_{13}H_{18}N_2S$	>320	>320	>320

[a] All data are considered significant at $p \leq 0.05$ as determined by Student's *t* test. [b] Compounds **59–72** and **75–78** were investigated as the free bases and compounds **73** and **74** as the hydrochloride salts. [c] Toxic range. [d] It was administered by an intraduodenal route.

acetylcholine as spasmogenic agents, are presented in Tables I–III. In order to get a good bronchodilator activity, it is better to have no selectivity of action in the Konzett test. In this case, that means that the bronchodilator property is real and does not reflect an end-organ antagonism for the used bronchospasmogenic substances.

3-Ethyl-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**6**) exhibited activities similar to those of theophylline anisate or rimazolium (**1**) against the above spasmogenic agents. Introduction of a methyl group onto the pyridine ring (compounds **7–10**) or replacement of the methyl and ethyl groups in positions 2 and 3 by an alkylene chain (**11** and **16**) modified the activities only slightly. The less potent derivatives (**8**, **9**, **13**, **14**, **18**, and **19**) contain a methyl group in position 7 or 8.

Compounds **6–22** possess significant analgesic activity, too.[21] While saturation of the pyridine ring in compounds **7** and **11–20** resulted in loss of the analgesic effect, the bronchodilator activities of the tetrahydro derivatives **23–33** did not change so dramatically (see Table I).

The most potent derivatives of this series against serotonin-induced spasms were compounds **15**, **20**, and **28**, against histamine-induced spasms were compounds **10**, **15–17**, and **26**, and against acetylcholine-induced spasms were compounds **20**, **28**, and **34**.

None of the benzo-fused tricyclic analogues (**35–58**) in which the size of the saturated ring A varies from 5 to 8 has a bronchodilator activity surpassing those of the above-mentioned compounds (Table II).

As observed earlier,[6b] the activities of the benzo-fused analogues against histamine- and acetylcholine-induced spasms increase as the size of the ring A increases from 5 to 7 (compounds **35–37**). As concerns the serotonin-induced spasms, however, the activities of compounds **35–37** vary with the size of ring A in the sequence 6 > 5 > 7. Further increase of the size of ring A (compound **38**) results in a significant decrease of activity (see Table II).

The linearly fused tricyclic derivative is more active than the angularly fused isomer (i.e., **59**, **61** and **60**, **62**; see Table III).

For the tricyclic homologues with a saturated six-membered ring C (compounds **61**, **16**, and **69**), the activities against the spasms induced with all three agents increase with the increase in size of saturated ring A from 5 to 7. For the higher homologue containing an eight-membered ring A, compound **75**, the bronchodilator activity is again significantly lower (see Table III).

Compound **69**, with a saturated seven-membered ring A and a saturated six-membered ring C, proved to be one of the most potent of the investigated derivatives. It is interesting to note that, for the octahydropyrido[2,1-*b*]-quinazolinone (**16**) and similarly for compound **11**, introduction of a methyl group into one of the peri positions of the piperidine ring (compounds **12**, **15**, **17**, or **20**) does not change the activities of these derivatives substantially, whereas introduction of a methyl group into one of the peri positions of the azepine ring of compound **69** (compounds **71** and **72**) results in the complete loss of bronchodilator activity.

Oxo to thioxo exchange also resulted in loss of the bronchodilator activity (see compounds **68**, **69** and **77**, **78** in Table III).

Changes in the size of rings A and C in **69** (compound **34**) resulted in a decreased bronchodilator activity.

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Table IV. Bronchodilator Activity on Isolated Human Bronchus Contracted by Carbachol

compd	IC_{50},[a] μmol/L	rel potency: IC_{50} theoph/IC_{50} compd
theophylline anisate	151	1
6	127	1.19
7	71.8	2.10
11	879.0	0.17
12	97.7	1.54
16	127	1.18
17	66.6	2.26
23	74.6	2.02
25	141.0	1.07
68	15.2	9.93
69·HCl	5.4	27.97

[a] All data arre considered significant at $p \leq 0.05$ as determined by Student's t test.

Table V. Activities of Compounds **68** and **69**·HCl on Isolated Guinea Pig Ileum against Different Spasmogenic Agents

	IC_{50},[a] μmol/L	
spasmogenic agent	**68**	**69**·HCl
serotonin	112	752
histamine	>100	>100
acetylcholine	2.53	5.01
nicotinate	75.0	49.5
$BaCl_2$	113.0	123.0

[a] All data are considered significant at $p \geq 0.05$ as determined by Student's t test.

Table VI. Activities of Compounds **68** and **69**·HCl on Isolated Guinea Pig Trachea Contracted by Carbachol

compd	pA_2[a]	pD_2'[a]	pA_2/pD_2'
68	6.64	5.37	1.23
69·HCl	5.72	5.39	1.06

[a] All data are considered significant at $p \geq 0.05$ as determined by Student's t test.

The bronchodilator activities of some compounds were also investigated in connection with the carbachol-induced contraction of the isolated human bronchus (Table IV). The two most potent derivatives, compounds **68** and **69**, contain a seven-membered ring A. The ratio between the IC_{50} of theophylline anisate and that of the tested compound shows that compounds **68** and **69** are 10 and 28 times more potent, respectively, than theophylline anisate in this assay.

Some further experiments on the isolated guinea pig ileum and trachea were also carried out with compounds **68** and **69** (see Tables V and VI). These compounds exert a selective brief anticholinergic activity on the guinea pig ileum (Table V). With the guinea pig trachea, the pA_2 values of these derivatives in the case of carbachol are relatively low, and the pA_2/pD_2' ratios are almost equal to 1. This means that the mode of action of these compounds is a combination of competitive antagonism for cholinergic receptors and noncompetitive inhibition of carbachol action. Moreover, it must be stated that compounds **68** and **69** are able to relax the basal tone of both the human bronchus and the guinea pig trachea and exhibit physiological bronchodilator activity (data not shown).

Guinea pig ileum studies showed that the tested compounds probably displayed an end-organ antagonistic property only for acetylcholine. This was confirmed by pA_2 values on isolated guinea pig trachea contracted by carbachol. Thus, the results obtained on isolated human bronchus contracted by carbachol are not explained only by a general bronchodilator property of both compounds, perhaps by some action at smooth muscle level, but also probably by antagonism at the cholinergic receptor level.

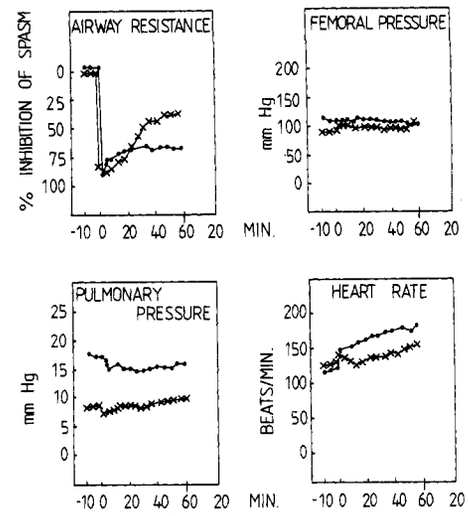

Figure 1. Bronchodilator and cardiovascular effects of the hydrochloride of compound **69** (32 μmol/kg i.v.; x) and of theophylline anisate (177 μmol/kg iv; ·) in pilocarpine-bronchoconstricted anesthetized dogs. (Resistance data of **69** and theophylline anisate and heart rate data of theophylline anisate are considered significant at $p \leq 0.05$ as determined by paired t test. Femoral pressure data of **69** are statistically different from the control period only at 6, 10, and 15 min and pulmonary pressure data of theophylline anisate at 35 and 40 min as determined by paired t test. All the femoral pressure data of theophylline anisate and pulmonary pressure and heart rate data of **69** are statistically nonsignificant vs. values during control period.)

For further evaluation, compound **69** and theophylline anisate were submitted to assays in which they were administered by the iv route to anesthetized pilocarpine-bronchoconstricted dogs.[22] In this assay the bronchodilator potency of 32 μmol/kg of compound **69** proved to be equal to that of 177 μmol/kg of theophylline anisate, but the duration of action of compound **69** was somewhat shorter than that of theophylline anisate (see Figure 1). At the same time, the cardiovascular side effects of compound **69** were lower than those of theophylline anisate. Femoral and pulmonary pressures were not influenced by compound **69**.

Experimental Section

Melting points were not corrected. Combustion analyses for C, H, N, and Cl gave results within 0.4% of theory. The procedures for the preparation of the reported compounds, methods A–I, may be considered general methods for preparation. Yields were not maximized. The spectra of the products (UV, Pye-Unicam SP 8-200; IR, Zeiss UR 20; ^1H and ^{13}C NMR, Bruker WP 80) are in full accord with the proposed structures.

Compounds **6–25**, **29–33**, **35–37**, and **40** were prepared in accordance with the literature methods,[7,8,11] in yields similar to those reported earlier. The hydrochlorides were prepared in the usual way.

Method A. Cyclopenta[*d*]pyrido[1,2-*a*]pyrimidinones[8] **13–15** (10 mmol) and 2,3-cyclohepta[*d*]pyrido[1,2-*a*]pyrimidinone[8] were hydrogenated in ethanol (50 mL) over 10% palladium-on-carbon catalyst (1 g) to give compounds **26–28** and **34**.

Method B-1. The appropriate lactim ether (11 mmol) and anthranilic acid (10 mmol) were reacted in refluxing benzene (200 mL) for 3 h. After the evaporation of the reaction mixture, the residue was dissolved in chloroform (120 mL). The organic solution was washed with 3% aqueous NaOH solution (2 × 20 mL) and then with water (2 × 20 mL). The dried (Na_2SO_4) organic phase was evaporated to dryness in vacuo, and the residue was

(22) (a) Lulling, J.; El Sayed, F.; Lievens, P. *Med. Pharmacol. Exp.* **1967**, *16*, 481. (b) Lulling, J.; Lievens, P.; El Sayed, F.; Prignot, J. *Arzneim.-Forsch.* **1968**, *18*, 995.

recrystallized to give compounds **38** and **39**.

Method B-2. The lactim ether (11 mmol) and the requisite 2-aminobenzoic acid[23] (10 mmol) were reacted in DMF (50 mL) at 80–90 °C for 3 h. The reaction mixture was poured into water (200 mL). The precipitated crystals were filtered off to give the tricyclic carboxylic acids **49–51** and **55–57**.

Method C. To a stirred suspension of the requisite 2-aminobenzoic acid[24] (0.1 mol) in benzene (100 mL) was added thionyl chloride dropwise at 0 °C. The reaction mixture was refluxed for 2 h and was then evaporated to dryness in vacuo. The crude sulfinamide anhydride obtained was dissolved in benzene (100 mL), and a solution of the appropriate lactam (0.1 mol) in benzene (100 mL) was added dropwise at 15 °C. The mixture was allowed to react overnight at ambient temperature. The precipitated crystals were filtered off to give compounds **42–45** and **58**.

Method D. 3-[(Dimethylamino)methylene]tetrahydropyrrolo[2,1-*b*]quinazolinone[11] (**79**) (4.8 g, 20 mmol) was hydrogenated in ethanol (100 mL) over 10% palladium-on-carbon catalyst (3 g) at ambient temperature and atmospheric pressure to give compound **41**, which was recrystallized from water.

Method E. To a solution of the requisite lactam (0.2 mol) in benzene (100 mL) was added dropwise a solution of phosphoryl chloride (15 g, 0.1 mol) in benzene (100 mL), and the reaction mixture was stirred at ambient temperature for 2 h. It was then combined with a solution of dimethyl 2-aminoisophthalate[23] (24 g, 0.1 mol) in benzene (200 mL), and the reaction mixture was refluxed for 5 h, then cooled, and treated with 10% aqueous NaOH solution (100 mL). The aqueous phase was extracted with benzene (2 × 50 mL). The combined and dried (Na_2SO_4) organic phase was evaporated to dryness in vacuo, and the residue was recrystallized from ethyl acetate to give compounds **52–54**.

Method F. A suspension of the carboxylic acids **49–51** (0.1 mol) in ethanol (200 mL) containing 28% hydrogen chloride was refluxed for 2 h, and the reaction mixture was then evaporated to dryness in vacuo. The residue was dissolved in water (200 mL), and the pH of the aqueous solution was adjusted to 7 with saturated aqueous $NaHCO_3$ solution. The precipitated crystals were filtered off, washed with water, dried, and recrystallized from ethanol to give compounds **46–48**.

Method G-1. A solution of semicyclic amidine (0.1 mol) and cyclic β-oxo ester (0.1 mol) in ethanol (100 mL) was refluxed for 10 h and then evaporated to dryness in vacuo, and the residue was crystallized from the solvent given in Table III to yield the linearly fused tricyclic compounds **59**, **61**, **63**, **64**, **66**, **68**, **69**, and **73–75**.

Method G-2. The mother liquor obtained in method G-1 was evaporated to dryness, and the residue was subjected to chromatography on a Prep-500 silica gel (Waters) column (Waters preparative liquid chromatograph) with a 2-propanol–dichloromethane–ligroin (4:1:1) eluent, to give the angularly fused tricyclic compounds **60**, **62**, **65**, **67**, **70**, and **76**.

Method H. A solution of 2-methylcyclohexanone oxime[19] (51.0 g, 0.4 mol) in 80% sulfuric acid (70 mL) was added dropwise to 80% sulfuric acid (30 mL) at 120 °C. When the exothermic reaction had ceased, the reaction mixture was cooled to 0 °C and was neutralized with concentrated ammonium hydroxide (230 mL) with intense external cooling. The aqueous solution was extracted with chloroform (3 × 100 mL). The combined and dried (Na_2SO_4) organic phase was evaporated to dryness in vacuo. The crystalline residue (44 g) was purified by vacuum distillation to give a mixture of azepinones **80** and **81** [33.3 g, 64%; bp 126–128 °C (0.6 mmHg)].

To a solution of lactams **80** and **81** (33.3 g, 0.26 mol) in dimethyl sulfate (8.0 mL) at 80 °C was added dimethyl sulfate (18.0 mL) dropwise. After the reaction mixture was stirred for 3 h at 80–90 °C, it was cooled to ambient temperature, diluted with benzene (50 mL), and then treated with 40% sodium hydroxide solution (30 mL). The separated aqueous phase was extracted with benzene (3 × 50 mL). The combined and dried (Na_2SO_4) organic phase was evaporated. The oily residue was purified by vacuum distillation to give lactim ethers **82** and **83** [28.3 g, 75%, bp 70–73 °C (8 mmHg)].

A solution of lactim ethers **82** and **83** (28.2 g, 0.2 mol) and ammonium chloride (10.7 g, 0.2 mol) in ethanol (60 mL) was refluxed for 3 h. The reaction mixture was evaporated to dryness in vacuo to give amidine hydrochlorides **84** and **85** (31.0 g, 95%, mp 94–97 °C).

A solution of amidine hydrochlorides **84** and **85** (8.1 g, 50 mmol) in ethanol (30 mL) was treated at ambient temperature with ethanolic sodium ethoxide, prepared from sodium (1.15 g, 50 mmol) and ethanol (50 mL). After the mixture was stirred for 30 min, the precipitated sodium chloride was filtered off and ethyl 2-oxo-cyclohexanecarboxylate (8.0 g, 50 mmol) was added to the filtrate. The reaction mixture was refluxed for 6 h and was then evaporated to dryness in vacuo. From the oily residue, tricyclic products **71** (2.8 g, 24%) and **72** (2.0 g, 17.2%) were separated on a Prep-500 silica gel (Waters) column (Waters preparative liquid chromatograph) with a 2-propanol–dichloromethane–ligroin (4:1:1) eluent.

Method I. A mixture of tricyclic azepino derivatives **68** and **69** (40 mmol) and phosphorus pentasulfide (8.88 g, 40 mmol) in xylene (80 mL) was refluxed for 1 h. The solvent was decanted from the precipitate, and the residue was treated with 10% NaOH solution (80 mL). The aqueous mixture was extracted with chloroform (6 × 50 mL), and the dried (Na_2SO_4), combined organic phase was evaporated to dryness in vacuo to give thioxo derivatives **77** and **78**.

Bronchodilator Activity in Anesthetized Guinea Pigs. The following method was derived from that described by Konzett and Rössler.[20] Hartley guinea pigs of either sex weighing between 250 and 500 g were anesthetized with urethane, curarized, and artificially ventilated. The resistance to inflation of the lungs was assessed by recording changes in intratracheal pressure on inflation with a constant volume. Bronchodilator activity was expressed in terms of antagonism of bronchoconstriction elicited by the intravenous injection of spasmogenic agents 5-hydroxytryptamine, histamine, and acetylcholine. Several cumulative doses at 15-min intervals were injected into the same animal, four animals at least being used for each spasmogen. Activity was measured 5 min after each dose, and a regression line was computed to obtain the ID_{50} (dose that induces an inhibition of 50% amplitude of bronchospasms).

Bronchospasmolytic Activity on Human Bronchi. Lung tissues coming from surgery were normal tissue juxtaposed to diseased tissue.

Surgically obtained human bronchi were placed in cold physiological solution (Tris, 23 mmol/L; NaCl, 125 mmol/L; KCl, 217 mmol/L; $CaCl_2$, 1.8 mmol/L; glucose, 11 mmol/L; HCl up to pH 7.4) immediately after excision and were maintained at 4 °C for a maximum of 24 h prior to use. Each human bronchus was divided either into rings (three rings 3–4 mm in diameter and 2-mm thick, tied together) or into strips (from bronchi ranging from 4 mm to 2 cm in width), depending on the size of the received bronchus. Tissues were suspended from force displacement transducers in 5-mL baths containing physiological solution (37 °C) through which a mixture of 95% oxygen and 5% carbon dioxide was bubbled, and they were subjected to a preload tension of 1 g. Following a stabilization period, contractions were elicited with carbachol (10^{-6} mol). When the contraction had reached a maximum, the test compound was added cumulatively in increasing concentrations. The percentages of variation thereby obtained were calculated, and the EC_{50} (the concentration allowing a 50% relaxation) was extrapolated.

Pilocarpine-Induced Bronchospasm in Dog.[22] The technique used was described in detail in ref 22a and 22b. Briefly, mongrel dogs were anesthetized with morphine–chloralose, curarized with succinylcholine, and artificially ventilated. Pulmonary resistance, systemic and pulmonary arterial pressure, and heart rate were monitored throughout the experiment.

A long-acting bronchial spasm was induced with pilocarpine hydrochloride infusion. After stabilization of the spasm, the test compound was administered by the iv route. Cardiovascular and respiratory parameters were then monitored for 1 h. The effect of a compound on the airway resistance was expressed as the percentage inhibition of the induced spasm. The other parameters were expressed in absolute units (mmHg and beats/min).

(23) Doria, G.; Romeo, C.; Sberze, P.; Tibolla, M.; Corno, M. L.; Cadelli, G. *Eur. J. Med. Chem.-Chim. Ther.* **1979**, *14*, 247.

(24) (a) Friedlaender, P.; Schreiter, W. *Chem. Ber.* **1895**, *28*, 1386. (b) 2-Amino-3-, -4-, and -5-methylbenzoic acids were supplied by Aldrich Co.

Spasmolytic Activity on Guinea Pig Ileum. The ileum of a male or female fasted Dunkin–Hartley guinea pig (250–500 g) was taken from the ileocecal junction (15–20 cm). The ileum was relieved of its contents by perfusion with Tyrode's solution, and its mesenteric adventitious tissue was eliminated.

Sections 2–3 cm long, incised longitudinally at about 1-cm intervals, were attached to isometric force transducers (Hewlett-Packard FTA 1010) under a tension of 1.0 g and placed into baths thermostated at 37 ± 1 °C containing 5 mL of Tyrode–glucose (5.6 mmol/L) at pH 6, oxygenated with a mixture of 95% oxygen and 5% carbon dioxide. After a stabilization period of about 30 min, during which the tension was readjusted if necessary, the selected spasmogen was injected into the bath with a Braun perfusion pump.

The injections of spasmogens and the successive washings were automatically controlled by a microprocessor according to the predetermined cycle. The tested compounds were injected manually upon a signal emitted by the computer. Washings were made by renewing the Tyrode solution by overflow during 25 s (i.e., 6 times the volume of the bath).

All spasmogen solutions were prepared immediately before use. Histamine and acetylcholine were dissolved in water; serotonin, nicotine, and $BaCl_2$ were dissolved in Tyrode. The injected volume was 0.05 mL. Serotonin creatinine sulfate monohydrate (Fluka): 10^{-5} mol/L. Histamine dihydrochloride (Fluka): 3.2×10^{-6} mol/L. Acetylcholine chloride (Fluka): 3.2×10^{-7} mol/L. Nicotine tartrate dihydrate (BDH): 10^{-5} mol/L. Barium chloride p.a. (Merck): 10^{-3} mol/L.

For each spasmogen, the concentration of the tested compound inducing 50% inhibition of the spasms (EC_{50}) was determined by linearization of the dose vs. effect curve (by a logit/log transformation), which also allowed determination of the confidence limits. Only effects exceeding 10% were taken into consideration.

Spasmolytic Activity on Guinea Pig Trachea. Male or female Hartley guinea pigs weighing 350–400 g were sacrificed by an electric shock to the neck. The trachea was excised immediately and transferred into a physiological solution of Krebs–Henseleit. The trachea, relieved of its adipose tissue, was cut into rings about 2 mm thick. Four rings were bound together to form a small chain, which was placed in a thermostatic bath of 5 mL and suspended from an isometric force transducer. The thermostatic bath containing the organ was at 37 °C, and the physiological solution was oxygenated by bubbling through it a mixture of 95% oxygen and 5% CO_2. The preparations were subjected to a tension of 1 g, and stabilization was maintained during 1 h.

Cumulative dose vs. response curves with carbachol were then recorded without and with the tested compound.

pA_2 and pD_2' are calculated by the methods described by Arunlakshana and Schild.[25] and Äriens and van Rossum.[26]

Registry No. **1**, 35615-72-6; **6**·HCl, 70381-33-8; **7**·HCl, 70381-39-4; **8**·HCl, 108561-72-4; **9**·HCl, 70381-66-7; **10**·HCl, 80310-21-0; **11**·HCl, 70026-57-2; **12**·HCl, 70500-18-4; **13**·HCl, 70081-29-7; **14**·HCl, 70026-66-3; **15**·HCl, 70026-67-4; **16**·HCL, 70244-83-6; **17**·HCl, 70026-60-7; **18**·HCl, 108561-73-5; **19**·HCl, 108561-74-6; **20**·HCl, 108561-75-7; **21**·HCl, 70026-59-4; **22**·HCl, 70026-62-9; **23**, 70381-46-3; **24**, 70026-79-8; **25**, 70026-82-3; **26**, 85653-87-8; **27**, 85653-88-9; **28**, 85653-89-0; **29**, 55450-48-1; **30**, 70026-83-4; **31**, 85653-84-5; **32**, 85653-85-6; **33**, 85653-86-7; **34**, 70026-80-1; **35**·HCl, 21314-56-7; **36**·HCl, 21314-58-9; **37**·HCl, 21314-60-3; **38**, 58314-97-9; **38**·HCl, 108561-76-8; **39**, 97475-24-6; **39**·HCl, 108561-77-9; **40**·HCl, 108561-78-0; **41**, 94169-31-0; **41**·HCl, 108561-79-1; **42**, 60811-38-3; **42**·HCl, 64842-91-7; **43**, 61938-73-6; **43**·HCl, 108561-80-4; **44**, 97511-55-2; **44**·HCl, 108561-81-5; **45**, 60811-48-5; **45**·HCl, 64842-97-3; **46**, 92883-90-4; **46**·HCl, 108561-82-6; **47**, 95610-22-3; **47**·HCl, 108561-83-7; **48**, 108561-84-8; **48**·HCl, 108561-85-9; **49**, 55762-24-8; **50**, 108561-86-0; **51**, 108561-87-1; **52**, 85742-71-8; **82**·HCl, 108561-88-2; **53**, 85742-95-6; **53**·HCl, 108561-89-3; **54**, 108561-90-6; **54**·HCl, 108561-91-7; **55**, 61938-67-8; **56**, 80776-94-9; **57**, 108561-92-8; **58**, 108561-93-9; **58**·HCl, 108561-94-0; **59**, 88491-49-0; **60**, 108561-95-1; **61**, 88491-50-3; **62**, 108561-96-2; **63**, 97475-23-5; **64**, 88491-51-4; **65**, 108561-97-3; **66**, 88491-52-5; **67**, 108561-98-4; **68**, 88491-53-6; **69**, 88491-54-7; **69**·HCl, 91940-24-8; **70**, 108561-99-5; **71**, 108562-00-1; **72**, 108562-01-2; **73**, 88491-55-8; **73**·HCl, 108562-02-3; **74**, 96022-55-8; **74**·HCl, 108562-03-4; **75**, 88491-57-0; **76**, 108562-04-5; **77**, 108562-05-6; **78**, 108562-06-7; **79**, 62062-75-3; **80**, 1985-48-4; **81**, 2073-32-7; **82**, 62353-42-8; **83**, 62353-57-5; **84**·HCl, 108562-07-8; **85**·HCl, 108562-08-9; theophylline sodium anisate, 71852-07-8; anthranilic acid, 118-92-3; 2,3,4,5,6,7-hexahydro-8-methoxyazocine, 1889-06-1; 5-methoxy-2-methyl-3,4-dihydro-2*H*-pyrrole, 65708-98-7; 2-amino-1,4-benzenedicarboxylic acid, 10312-55-7; 3,4-dihydro-5-methoxy-2*H*-pyrrole, 5264-35-7; 2,3,4,5-tetrahydro-6-methoxypyridine, 5693-62-9; 3,4,5,6-tetrahydro-7-methoxy-2*H*-azepine, 2525-16-8; 4-amino-1,3-benzenedicarboxylic acid, 33890-03-8; 2-amino-5-methylbenzoic acid, 2941-78-8; 2-pyrrolidinone, 616-45-5; 2-amino-3-methylbenzoic acid, 4389-45-1; hexahydro-2*H*-azepin-2-one, 105-60-2; 2-amino-4-methylbenzoic acid, 2305-36-4; 6-amino-1,3-benzodioxole-5-carboxylic acid, 20332-16-5; dimethyl 4-aminoisophthalate, 63746-12-3; 2-piperidinone, 675-20-7; 3,4-dihydro-2*H*-pyrrol-5-amine, 872-34-4; ethyl 2-oxocyclopentanecarboxylate, 611-10-9; ethyl 2-oxocyclohexanecarboxylate, 1655-07-8; 3,4-dihydro-2-methyl-2*H*-pyrrol-5-amine, 76884-40-7; ethyl 2-oxocycloheptanecarboxylate, 774-05-0; ethyl 2-oxocyclooctanecarboxylate, 4017-56-5; 3,4,5,6-tetrahydro-2*H*-azepin-7-amine, 2214-67-7; 3,4,5,6,7,8-hexahydro-2-azocinamine, 82832-98-2; 2-methylcyclohexanone oxime, 1122-26-5; 6-methyl-3,2,1-benzoxathiazin-4(1*H*)-one 2-oxide, 108562-09-0; 8-methyl-3,2,1-benzoxathiazin-4(1*H*)-one 2-oxide, 108562-10-3; 7-methyl-3,2,1-benzoxathiazin-4(1*H*)-one 2-oxide, 71955-93-6; 6,7-(methylenedioxy)-3,2,1-benzoxathiazin-4(1*H*)-one 2-oxide, 108562-11-4.

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