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Original paper

Synthesis of basic substituted pyridines: a new class of antiasthmatic-antiallergic agents**

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Summary — A series of pyridines were synthesized and evaluated as bronchospasmolytic / anti-allergic agents. Several of these compounds were found to: 1) inhibit the release of histamine; 2) antagonize histamine, bradykinin, LTD_4 and PAF; 3) suppress the IgE-mediated passive cutaneous anaphylaxis (PCA) reaction. The most interesting substance of this series 2,6-dimethyl-3-nitro-4[(2-(4-diphenylmethyl-1-piperazinyl)ethyl)amino]pyridine **1**, (HWA 214), was selected for further pharmacological evaluation. The novel, orally active agent **1** does not have such drawbacks as causing drowsiness or being effective only as a prophylactic drug, and could provide advantages over other non-sedative compounds, such as terfenadine and astemizole, in that it is water soluble and thus can be administered through inhalation or through intravenous application.

Résumé — **Synthèse de pyridines à groupes basiques: une nouvelle classe d'anti-asthmatiques et anti-allergiques.** *Une série de pyridines a été synthétisée et testée pour l'évaluation de l'activité bronchospasmolytique et anti-allergique. Ces pyridines: 1) inhibent la libération de l'histamine; 2) antagonisent les effets de l'histamine, de la bradykinine, de la LTD_4 et du PAF; 3) suppriment la réaction passive cutanée anaphylactique (PCA) provoquée par l'IgE. Le dérivé le plus intéressant est la diméthyl-2,6 nitro-3[(diphénylméthyl-4 pipérazinyl-1)éthyl-2 amino]-4 pyridine* ***1*** *(HWA 214), active par voie orale et ne possédant pas d'inconvénients tels que sédation ou action tardive. Enfin le HWA 214 peut être utilisé par voie inhalative ou, en raison de sa solubilité dans l'eau, par voie intraveineuse. Ces propriétés constituent un avantage certain comparé aux médicaments déjà sur le marché.*

pyridines / H_1-antagonistic activity / antiallergic property / antiasthmatic property

Introduction

Antiallergic compounds at present on the market often have side-effects or disadvantages such as: 1. Causing drowsiness (*e.g.* ketotifen [1, 2], oxatomide [3]); 2.No inhalable forms available (*e.g.* ketotifen, oxatomide, astemizole [4], terfenadine [5]); 3. Intravenous application not available (*e.g.* DSCG [6], oxatomide, astemizole, terfenadine); 4. Having only prophylactic activity (*e.g.* oxatomide, DSCG). Therefore, numerous compounds which claim to possess such improved properties are currently under preclinical or clinical evaluation [7].

In this report we describe the synthesis of a series of novel agents, which possess antiasthmatic–antiallergic properties. These include inhibition of mediator release, such as histamine and products of 5-lipoxygenase, as well as antagonizing activities of histamine, bradykinin, platelet activating factor (PAF) and leukotriene D_4 (LTD_4). Further, they exhibit potent activity in the IgE-mediated passive cutaneous anaphylaxis (PCA)-reaction in the rat.

Results and Discussion

Synthesis

Scheme 1 shows the generalized synthetic pathway for the preparation of the substituted pyridines or 1-oxides bearing the NO_2, CN or COOEt group as a substituent in position 3 [8].

The 4-hydroxyalkylamine pyridines **4** were prepared from the 4-chloropyridines **2** [9] and the appropriate aminoalcohols **3a** and **3b**, respectively, in isopropanol in the presence of triethylamine (TEA). The resulting 4-piperazinyl- or piperidinyl-alkylaminopyridines **6** were obtained by reaction of compounds **5** with the corresponding amines in dimethylformamide (DMF) with TEA. The pyridine-

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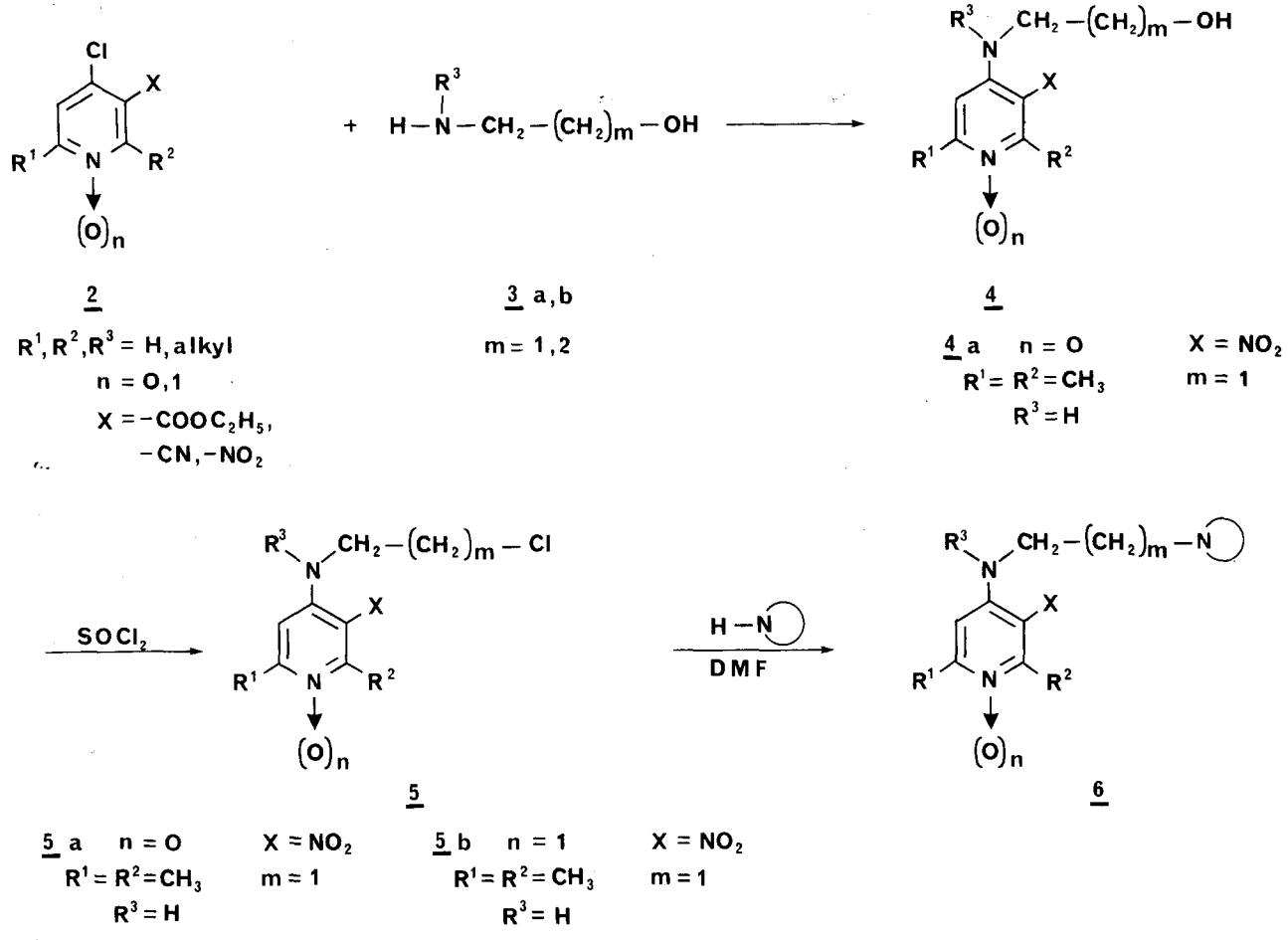
**Dedicated to Doctor Erhard Wolf on the occasion of his 60th birthday.*



Scheme 1.

carbonic ester **7** was hydrolysed by potassium hydroxide to give the acidic compound **8** (Figure 1).

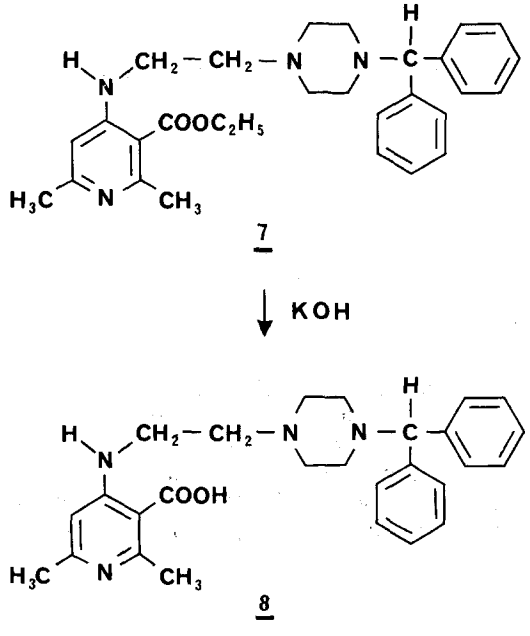


Fig. 1. Hydrolysis of compound **7**.

Pharmacology

The compounds depicted in Table I were studied for their effects on various biological tests. It was found that many of these agents: 1) display inhibitory activity on the spasmogenic amines, histamine and bradykinin; 2) inhibit the IgE-mediated PCA reaction in the rat; and 3) inhibit the calcium ionophore A 23 187-induced histamine release from isolated rat mast cells. The results of the compounds tested are depicted in Tables II and III. Structure–activity relationship (SAR)-studies revealed that in the positions 2 and 6 methyl groups were the most favorable for pharmacological activity (except for the inhibitory action towards spasmogens; see compound **24** [Table II]). In position 3, the nitro and cyano group showed the best overall effects and the superior substituent in position 4 was diphenylmethyl-piperazine bound to the ethyl-amino moiety of the pyridine ring. The pyridine-1-oxides were equally active as the corresponding pyridines (except for inhibition of histamine release from rat mast cells; see Table III).

Conclusion

As can be concluded from the results presented, these compounds strongly inhibited the release and/or activity of spasmogenic amines and are active in the respective

Table I. Physicochemical data for the substituted pyridines **6**.

	R^1	R^2	R^3	m	N	*n*	X	Isolated as:	Melting point (°C)	Yield (%)	Formula	Recrystallized from:
1	CH_3	CH_3	H	1	4-Diphenylmethyl--piperazinyl	0	NO_2	3 HCl	248–250 (decomp.)	62	$C_{26}H_{34}N_5Cl_3O_2$ 554.95	Isopropanol
7	CH_3	CH_3	H	1	4-Diphenylmethyl--piperazinyl	0	$CO_2C_2H_5$	2 HCl 2 H_2O	220	45	$C_{29}H_{38}N_4Cl_2O_2$ 545.56	Ethanol
8	CH_3	CH_3	H	1	4-Diphenylmethyl--piperazinyl	0	CO_2H	3 HCl 2 H_2O	248–249 (decomp.)	65	$C_{27}H_{35}N_4Cl_3O_2$[a] 553.97	Ethanol Diisopropylether
9	CH_3	CH_3	H	1	4-Diphenylmethyl--piperazinyl	1	NO_2	3 HCl 2 H_2O	219 (decomp.)	22	$C_{26}H_{34}N_5Cl_3O_3$ 570.95	Methanol
10	CH_3	CH_3	H	1	4-Benzylpiperazinyl	0	NO_2	3 HCl	230	30	$C_{20}H_{30}N_5Cl_3O_2$ 478.85	Methanol Diisopropylether
11	CH_3	CH_3	H	2	4-Diphenylmethyl--piperazinyl	0	NO_2	3 HCl	203–204	35	$C_{27}H_{36}N_5Cl_3O_2$ 568.98	Isopropanol Diisopropylether
12	CH_3	CH_3	H	1	4-Cinnamylpiperazinyl	0	NO_2	3 HCl 2.5 H_2O	225–226	23	$C_{22}H_{32}N_5Cl_3O_2$ 504.89	Methanol Diisopropylether
13	CH_3	CH_3	H	1	4-Diphenylmethyl--piperazinyl	0	CN	3 HCl	225–227	23	$C_{27}H_{34}N_5Cl_3$ 534.97	Isopropanol Diisopropylether
14	CH_3	CH_3	H	1	4-Diphenylmethyl--piperazinyl	1	CN	3 HCl 1 H_2O	219	16	$C_{27}H_{34}N_5Cl_3O$ 550.96	Ethanol Methanol
15	C_3H_7	C_3H_7	H	1	4-Diphenylmethyl--piperazinyl	0	NO_2	2 HCl	222	26	$C_{30}H_{41}N_5Cl_2O_2$ 574.60	Ethanol
16	CH_3	CH_3	CH_3	1	4-Diphenylmethyl--piperazinyl	0	NO_2	3 HCl 1 H_2O	214	12	$C_{27}H_{36}N_5Cl_3O_2$ 568.98	Ethanol Diisopropylether
17	CH_3	CH_3	H	1	4-(4-Chlorophenyl--phenylmethyl)piperazinyl	0	NO_2	3 HCl 2 H_2O	210 (decomp.)	16	$C_{26}H_{33}N_5Cl_4O_2$ 589.39	*n*-Pentanol Diisopropylether
18	CH_3	CH_3	H	1	4-(*bis*(4-Fluorophenyl)-methyl)piperazinyl	0	NO_2	3 HCl 3 H_2O	197	20	$C_{26}H_{32}N_5Cl_3F_2O_2$ 590.94	Isopropanol
19	CH_3	CH_3	H	1	4(4-Chlorophenyl-pyridin-4-yl-methyl) piperazinyl	0	NO_2	4 HCl	105	23	$C_{25}H_{33}N_6Cl_5O_2$[b] 626.85	Isopropanol Diisopylether
20	CH_3	CH_3	H	1	4(Hydroxy-diphenyl--methyl)piperidinyl	0	NO_2	2 HCl	217–219	40	$C_{27}H_{34}N_4Cl_2O_3$ 533.51	Ethanol
21	CH_3	CH_3	H	1	4(4-Chlorophenyl-4-fluorophenylmethyl)piperazinyl	0	NO_2	3 HCl 2 H_2O	205	18	$C_{26}H_{32}N_5Cl_4FO_2$ 607.39	Isopropanol
22	CH_3	CH_3	H	1	4(4-Methoxyphenyl--phenyl methyl piperazinyl	0	NO_2	3 HCl 2 H_2O	155–158	28	$C_{27}H_{36}N_5Cl_3O_3$ 584.98	Isopropanol Diisopropylether
23	CH_3	CH_3	H	1	4-Diphenylmethyl--piperazinyl	0	H	3 HCl	195–196	10	$C_{26}H_{35}N_4Cl_3$ 509.96	Ethanol Diisopropylether
24	H	H	H	1	4-Diphenylmethyl--piperazinyl	0	NO_2	3 HCl 1 H_2O	198–199	26	$C_{24}H_{30}N_5Cl_3O_2$ 526.90	Methanol
25	H	CH_3	H	1	4-Diphenylmethyl--piperazinyl	0	NO_2	3 HCl	237 (decomp.)	25	$C_{25}H_{32}N_5Cl_3O_2$ 540.92	Ethanol Diisopropylether

[a]C: calculated, 54.97; found 54.52. [b]C; calculated, 47.91; found 47.42; Cl: calculated, 28.28; found 28.71.

Table II. Effects of compounds of Table I in different pharmacological tests.

Compound No.	% Inhibition by 50 mg/kg *p.o.* in PCA ($n = 5$)	Inhibitory activity (ED_{50} mg/kg i.v.) against histamine ($n = 5$)	bradykinin ($n = 5$)	Spasmolytic activity (lung strips guinea pig) (IC_{50} μg/ml) against 0.1 μg/ml histamine
1	85	0.3	0.15	0.1 ($n = 6$/concentration)
7	61	–	–	
8	91	1.0– 3.0	3.0	
9	91	0.3– 1.0	1.0–3.0	0.6– 1.0 ($n = 5$/c.)
10	67	3.0–10.0	10.0	1.0–10.0 ($n = 5$/c.)
11	55	3.0	3.0–10.0	
12	60	3.0	3.0–10.0	
13	64	0.3– 1.0	3.0–10.0	1.0 ($n = 5$/c.)
14	91	0.1– 0.3	1.0– 3.0	1.0 ($n = 5$/c.)
15	61	3.0	3.0	
16	68	1.0– 3.0	10.0	
17	55	1.0– 3.0	3.0–10.0	
18	59	1.0– 3.0	3.0– 6.0	10.0 ($n = 3$/c.)
19	75	1.0	1.0	
20	91	0.3	3.0–10.0	
21	24	1.0– 3.0	1.0– 3.0	
22	11	1.0– 3.0	3.0–10.0	10.0 ($n = 3$/c.)
23	41	3.0–10.0	10.0	30.0 ($n = 3$/c.)
24	69	0.02	0.03	0.1–1.0 ($n = 5$/c.)
25	71	0.1– 0.3	3.0	
Astemizole (10 mg/kg)	54	–	–	–
Terfenadine (25 mg/kg)	100	–	–	–
Ketotifen (1 mg/kg, already sedative)	67	<0.003	0.03– 1.0	0.0006 ($n = 20$/c.)

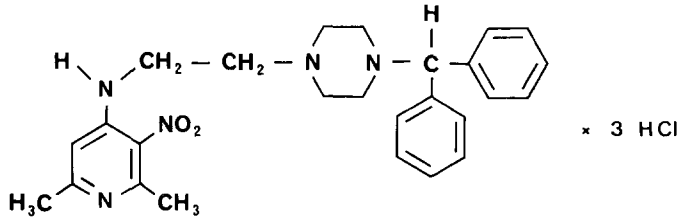
Table III. Histamine release from rat mast cells.

Compound No.	IC_{50} (μM)	r^{2*}
1	0.021	0.985
7	42.50	0.964
8	0.26	0.932
9	0.20	0.980
10	1.10	0.997
12	0.09	0.960
13	0.08	0.970
15	2.40	0.946
16	0.016	0.997
17	4.23	0.900
18	0.127	0.990
19	0.95	0.943
21	>100.00	–
22	5.18	0.870
23	2.71	0.840
25	4.40	0.999

*r^2 = Correlation coefficient.

relevant animal models as described below. Compound **1** (HWA 214) (Figure 2) was selected for further pharmacological studies [10]. Thus, a distinctive inhibition of the ovalbumin-induced allergic bronchospasm, with an ED_{50} of 0.2 mg/kg, i.v., could be demonstrated [11]. Further, the PAF-induced (20 ng/kg i.v.) bronchospasm was antagonized (ED_{50} = 2 mg/kg, i.v.) with this agent* (pre-

*Ref. 11 modified (anesthesia is performed with pentobarbital 60 mg/kg i.p. instead of 1.2 g/kg urethane i.p.).



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(HWA 214)

Fig. 2. Structure of HWA 214.

administration 5 min before PAF). The LTD_4 (1 ng/ml)-induced spasms of isolated guinea pig lung strips could be inhibited dose-dependently at a dose of 3–6 μg/ml with **1**. By inhaling a 0.3–1.0% aerosol solution of **1**, it was possible to prevent the histamine (0.1 μg/ml)-induced asthma attack in conscious guinea pigs. Interestingly, no sedative effects (rat, mouse) could be observed with this agent (data not given).

In conclusion, the novel pyridine compounds exhibit: 1) a pronounced inhibitory effect on the actions of spasmogens, *i.e.* histamine, bradykinin, PAF, LTD_4 and ovalbumin; 2) effective inhibition of the release of histamine from mast cells; 3) no sedative side-effects; and 4) they can

be administered through either parenteral (*e.g.* by inhalation or intravenously) or oral routes. These pyridines with this hitherto unknown pharmacological profile should allow more effective therapy of allergic disorders than the products now on the market, *e.g.* DSCG, oxatomid, ketotifen, terfenadine and astemizole.

Experimental protocols

Chemistry

Melting points were determined on a Büchi SMP-20 K melting point apparatus and are uncorrected. All analytical data obtained (C, H, N, Cl, F) were within ±0.4% of the theoretical values, unless otherwise indicated. ^{1}H NMR measurements were obtained on a Hitachi Perkin Elmer R-24 A (60 MHz) spectrometer. Infrared spectra were recorded on a Perkin–Elmer 257 spectrometer. All structural assignments were consistent with IR and NMR spectra. Starting materials (**4a–5b**) were prepared according to the following examples.

4-[(2-Hydroxyethyl)amino]-2,6-dimethyl-3-nitropyridine ***4a***
A mixture of 150 g (0.80 mol) 4-chloro-2,6-dimethyl-3-nitropyridine and 110 g (1.10 mol) triethylamine in 250 ml isopropanol was refluxed under stirring and 51 g (0.83 mol) 2- aminoethanol was dropped into the boiling solution. After 20 h of heating at reflux, the solution was cooled to room temperature and the precipitate was filtered off. The precipitate was extracted with refluxing ethyl acetate and the filtered solution was concentrated on a rotary evaporator to obtain a yellow residue which was used without further purification, though it could be recrystallized from isopropanol to give a yellow solid in 93% yield: mp 180–182°C; ^{1}H NMR (d^6-DMSO) δ 2.25 (S, 3H), 2.40 (s, 3H), 3.25 (t, 2H), 3.45 (t, 2H), 4.80 (s, NH), 6.50 (s, H); IR (KBr): 3287, 1650, 1620, 1540 (NO_2), 1356 (NO_2), 1071.

4-[(2-Chloroethyl)amino]-2,6-dimethyl-3-nitropyridine ***5a***
A solution of 157.1 g (0.74 mol) of compound **4a** in 500 ml dichloromethane was heated to reflux and 183.8 g (1.5 mol) thionylchloride was slowly dropped into this solution. After the addition was complete, the solution was refluxed for a further 2 h and the solvents were distilled under reduced pressure. The resulting oil was poured on 300 ml water and the solution adjusted to pH 8 by means of a 30% solution of NaOH. Extraction with 3 × 200 ml dichloromethane (DCM), drying with sodium sulfate and removal of solvent *in vacuo* afforded a solid which was recrystallized from isopropanol in 98% yield: mp 107–108°C; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 2.60 (s, 3H), 3.48–3.65 (m, 4H), 6.30 (s, 1H); IR (KBr): 3395, 1603, 1520, 1350, 1245, 840.

4-[(2-Chloroethyl)amino]-2,6-dimethyl-3-nitropyridine-1-oxide ***5b***
A mixture of 30 g (0.15 mol) 4-chloro-2,6-dimethyl-3-nitropyridine-1-oxide [9] and 21 g (0.34 mol) 2-aminoethanol in 100 ml isopropanol was heated for 20 h at reflux. Evaporation of the solvent *in vacuo* resulted in an oil which was purified by column chromatography on silica gel with DCM/MeOH = 7/3 (v/v) to give 14 g (41% yield) of a red, amorphous solid which was immediately chlorinated as above using $NaHCO_3$ instead of NaOH to give 15.43 g of a highly viscous oil in 42% yield. ^{1}H NMR (d^6-DMSO) δ 2.45 (s, 3H), 2.50 (s, 3H), 3.55–3.90 (m, 4H), 4.30 (s, NH), 7.35 (s, 1H); IR (KBr): 3380, 1645 (C=N), 1530, 1315, 1242, 1210, 800.

Typical procedures for the last step (formation of compounds ***6*** *of Scheme 1. 2,6-Dimethyl-3-nitro-4[(2-(4-diphenylmethyl-1-piperiazinyl)-ethyl)amino]pyridine trihydrochloride* ***1***
In a 500-ml round flask 80 ml DMF, 20 g (87 mmol) 4[(2-chloroethyl)-amino]-2,6-dimethyl-3-nitropyridine **5a** 22 g (87 mmol) 1-diphenylmethylpiperazine and 10 g (0.1 mol) triethylamine were heated at reflux for 2 h. DMF was evaporated and the residue distributed between water and DCM. The organic layer was distilled off *in vacuo* to dryness and the residue recrystallized from isopropanol. In order to form the hydrochloride, the yellow solid was dissolved in hot ethanol and ethanolic HCl was added. By addition of diisopropylether compound **1** precipitated as a colorless solid in 62% yield (30 g): mp 248–250°C (decomp.); ^{1}H NMR (d^6-DMSO) δ 2.60 (s, 3H), 2.72 (s, 3H), 3.18–4.00 (d, m, 3H), 7.18–7.58 (m, 7H), 7.65–8.00 (m, 4H); IR (KBr): 3430, 1640, 1610, 1540, 1450.

2,6-Dimethyl-4-[(2-(4-diphenylmethyl-1-piperazinyl)ethyl)amino] pyridine-3-carboxylic acid trihydrochloride dihydrate ***8***
A mixture of 8 g (17 mmol) of ethyl 2,6-dimethyl-4[(2-(4-diphenylmethyl-1-piperazinyl)ethyl)amino]-pyridine-3-carboxylate **7** and 1.4 g (25 mmol) of potassium hydroxide was heated at 170°C in ethylene glycol for 2 h. After cooling to room temperature, the pH was adjusted to 4 by addition of 4 N hydrochloric acid. The precipitate was filtered off with suction, washed with water, dried and converted into the hydrochloride with ethanolic HCl. The trihydrochloride dihydrate was precipitated by addition of diisopropyl ether and recrystallized from isopropanol/diisopropylether (4:1, vol) yield: 6.5 g (65%): mp 248–249°C (decomp.), ^{1}H NMR (d^6-DMSO) δ 2.65 (s, 3H), 2.81 (s, 3H), 3.35–3.65 (m, 7H), 3.78–4.25 (m, 5H), 6.15 (s, NH), 7.40–7.85 (m, 7H), 8.15–8.35 (m, 4H), 9.15 (s, OH); IR (KBr): 3420, 1685 (C=O), 1645, 1600, 1195, 750, 705.

Pharmacology

Antagonistic action towards the allergy mediators bradykinin, histamine, PAF and antigen-induced asthma attack on anesthetized guinea pigs. The compounds depicted in Table I were tested for their inhibitory activity on the spasmogenic amines histamine and bradykinin using the experimental design described by Konzett and Rössler [11]. Using this method, the inhibition of bronchospasm experimentally induced by i.v. administration of histamine, bradykinin, PAF or ovalbumin (with sensitized animals) in male guinea pigs under urethane anesthesia (1.25 g/kg i.p.) was investigated. The test substances were administered in aqueous solution, injected in a vol of 1 ml/kg. The criteria used for assessment of the inhibitory activity were the ED_{50} values and ranges, with these defined as the doses in milligrams per kilogram with which the experimentally induced spasm could be reduced to one half of that in untreated control animals.

Spasmolytic activity on the isolated lung strips of guinea pigs. Lungs of albino guinea pigs were removed during ether anesthesia. They were cut into strips of ≈ 5 cm length and after 1 h contractions were induced by histamine dihydrochloride with a concentration of 0.1 μg/ml. In this pharmacological model, histamine exhibits its activity by stimulating the H_1-receptor.

Histamine caused a long-lasting stable contraction of the organ fragments. The test compound was post-administered in different concentrations into the tissue bath at intervals of 5 min. The IC_{50} values were given in micrograms per milliliter of bath concentration.

Inhibition of the release of allergy mediators: a) passive cutaneous anaphylaxis (PCA) in the rat. Passive cutaneous anaphylaxis is an IgE-mediated hypersensitivity response of the immediate type (type I). In this model, antibodies bound to mast cells and basophilic granulocytes react with an intravenously administered antigen with release of allergic mediators. The tissue damage, due to the released mediators, can be visualized in rats by simultaneous i.v. application of Evans blue and allergen. Photometric evaluations of color intensity were used to determine the effects of compounds on mast cell degranulation. The greater the concentration of blue coloring at the site of inflammation, the greater the damage to the tissue.

Inhibition of the release of allergy mediators: b) calcium ionophore A 23 187-induced histamine release from isolated rat mast cells. Similar to the IgE-mediated response, it is possible to stimulate mast cells to release mediators of allergic reactions by non-immunological means. For instance, the release of performed mediators from mast cells may be induced by calcium ionophore, basic polypeptides and synthetic secretagogues. For our studies, we examined the ability of experimental compounds to inhibit the calcium ionophore-induced release of histamine from rat peritoneal mast cells. For this purpose, 10^5 mast cells were suspended in Hanks–Bald salt solution (Gibco) and incubated together with the dissolved drug for 15 min. After this, calcium ionophore A 23 187 (10^{-6} g/ml) was added and incubated for a further 30 min, then the

sample was centrifuged and the supernatant taken. For the determination of histamine released into the supernatant, a modified form of the methods described by Skofitsch [12] and Siraganian [13] was used. Briefly, to 500 µl supernatant, 100 µl 1 N NaOH and 100 µl 0.1% *o*-phthaldialdehyde was added, and followed by rigorous mixing. The samples were allowed to react with the *o*-phthaldialdehyde for 2 min. Then the fluorophore was converted to a more fluorescent and stable product by acidification with 50 µl 3 N hydrochloric acid. Ten µl of the supernatant were directly injected into the HPLC-system. This system consisted of a chromatograph SP 8100 (Spectra Physics) integrator SP 4270 (Spectra Physics) and a fluorescence detector LS-5 (Perkin–Elmer). The column used was a CP-TM-SPHER C8 (Chrompack, FRG). Fluorescence was monitored at 360 nm excitation and 450 nm emission wavelengths.

Acknowledgments

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