Bronchodilator Activity of Theophylline Derivatives Substituted at the 7-Position

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Theophylline derivatives with several groups linked at the 7-position were synthesized and their pharmacological activities were studied on guinea pig. Relaxant action in the tracheal muscle was increased in comparison with that of theophylline when the 3(2*H*)-pyridazinone system was linked to 7-(2-ethyl)-theophylline through the piperazine ring, but decreased when the 7-(2-ethyl)-theophylline was linked to 3(2*H*)-pyridazinone ring through an amino group.

7-Substituierte Theophyllin-Derivate mit bronchodilatierenden Eigenschaften

Theophyllin-Derivate mit verschiedenen Substituenten an der 7-Position wurden hergestellt, ihre pharmakologischen Eigenschaften wurden am Meerschweinchen untersucht. Der Tracheal-Muskel wurde stärker als durch Theophyllin relaxiert, wenn ein 3(2*H*)-Pyridazinon-System durch Piperazin mit 7-Ethyltheophyllin verknüpft ist. Im Gegensatz dazu vermindert die Verknüpfung über eine Aminogruppe diese Wirkung.

Theophylline is a potent bronchodilator for the relief of acute asthma attacks[1]. The pharmacodynamic of theophylline as an antiasthmatic was reviewed[2]. The bronchodilatory action of theophylline is attributable to the inhibition of c-AMP phosphodiesterase activity[3]. Some piperazine and piperidine derivatives of theophylline, flufylline and fluprophylline, possess bronchodilator and hypotensive properties with low toxicity[4].

Some pyridazinone derivatives as **1**[5], **1a**[6] show bronchospasmolytic activity, since a high level of c-AMP can be maintained by inhibition of phosphodiesterase. Recently we have synthesized compound **2** which shows an activity comparable with that of theophylline[7].

With the aim of designing new, more potent theophylline analogues useful in the treatment of asthma we have synthesized compounds in which the pyridazinone moiety is bound through a piperazine ring or an amino group to the 7-(2-ethyl)-theophylline fragment.

Substitution of 7-(2-piperazinethyl)-theophylline (**3**) with 4,5-dichloro-3(2*H*)-pyridazinone (**4**) or 2-methyl-4,5-dichloro-3(2*H*)-pyridazinone (**5**) in 1,4-dioxane and $KHCO_3$ gave a mixture of 4- and 5-substituted products **6**, **8** or **7**, **9**; only 5-substituted isomers were obtained by arylation of **3** with **4** and **5** in a polar solvent like EtOH.

Using the same method the substitution of 7-(2-aminoethyl)-theophylline with **4** and **5** gave the isomers **11**, **13** and **12**, **14** (Scheme 2).The synthesis of compounds **15**, **16**, **21**, **24** is shown in Scheme 3. Catalytic hydrogenation of **8** and **9** gave compounds **15** and **16** which were obtained also by alkylation of 7-(2-chloroethyl)-theophylline with 5-(1-piperazinyl)-3(2*H*)-pyridazinone (**18**) and with 2-methyl-5-(1-piperazinyl)-3(2*H*)-pyridazinone (**19**) in isoamylic alcohol and anhydrous Na_2CO_3. Alkylation of **17** with 6-piperazinyl-3(2*H*)-pyridazinone (**20**) in isoamylic alcohol and Na_2CO_3 yielded compound **21**. Compound **24** was prepared by alkylation of 7-(2-aminoethyl)-theophylline (**10**) with 3,6-dichloropyridazine, followed by hydrolysis with glacial acetic acid.

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Experimental Part

MP: Reichert microhostage devise, uncorr.- ^{1}H-NMR-spectra: Varian EM 390, 90 MHz, $CDCl_3$, MeOD, [D_6]DMSO, TMS int. Stand.- Purity was checked by TLC.- Elemental analyses are within ± 0.4% of theoretical values.

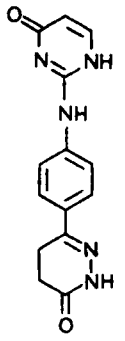
Preparation of compounds **6, 8, 7, 9.**

4-{4-[2-(7-Theophyllin)-ethyl]-1-piperazinyl}-5-chloro-3(2H)-pyridazinone (**6**)

and

4-Chloro-5-{4-[2-(7-theophyllin)-ethyl]-1-piperazinyl}-3(2H)-pyridazinone (**8**)

A mixture of 1.5 g (5.7 mmol) of 7-(2-piperazinethyl)-theophylline (**3**)[8], 0.94 g (5.7 mmol) of 4,5-dichloro-3(2*H*)-pyridazinone[9] and 0.57 g (5.7



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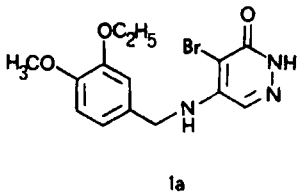
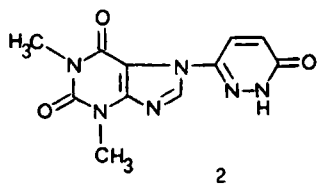


1a



2

Scheme 1

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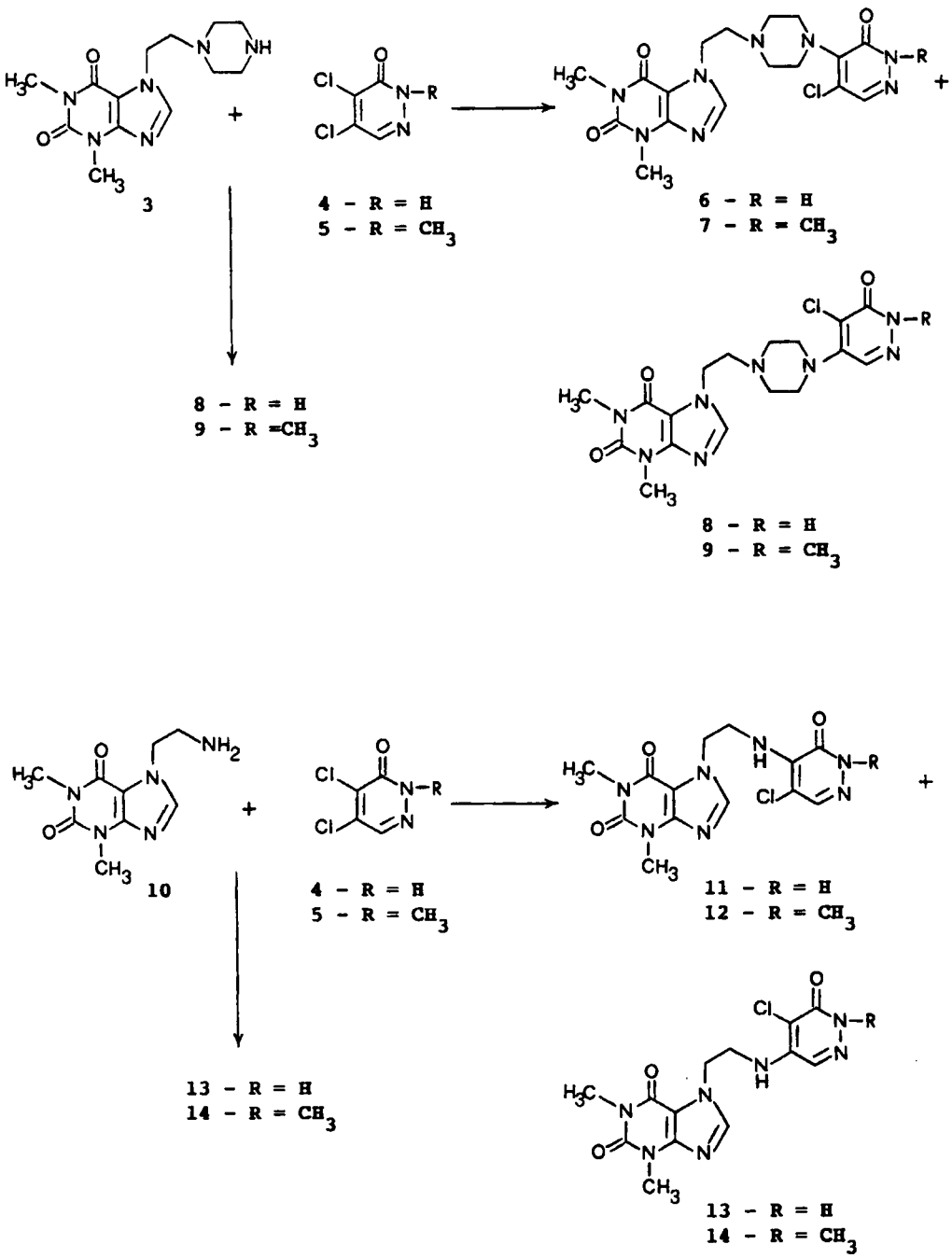


Scheme 2

mmol) of $KHCO_3$ in 20 ml 1,4-dioxane was heated to 80°C for 17 h. The mixture was concentrated under reduced pressure. The residue was treated with water, filtered and the solid purified by flash-chromatography using CH_2Cl_2/EtOH. The 4-substituted isomer **6** was eluted with CH_2Cl_2/ EtOH (9.4/0.6), yield: 30%, m.p. 230-233°C.- ^{1}H-NMR (MeOD): δ (ppm) = 2.55-2.7 (m, 4H; H-pip.), 2.85 (t, 2H; J = 6 Hz, CH_2), 3.3-3.5 (m, 9H; 4H-pip., CH_2, N-CH_3), 3.55 (s, 3H; N-CH_3), 7.45 (s, 1H; 6-H-pyrid.), 7.8 (s, 1H; N=CH).- $C_{17}H_{21}ClN_8O_3$ (420.4).

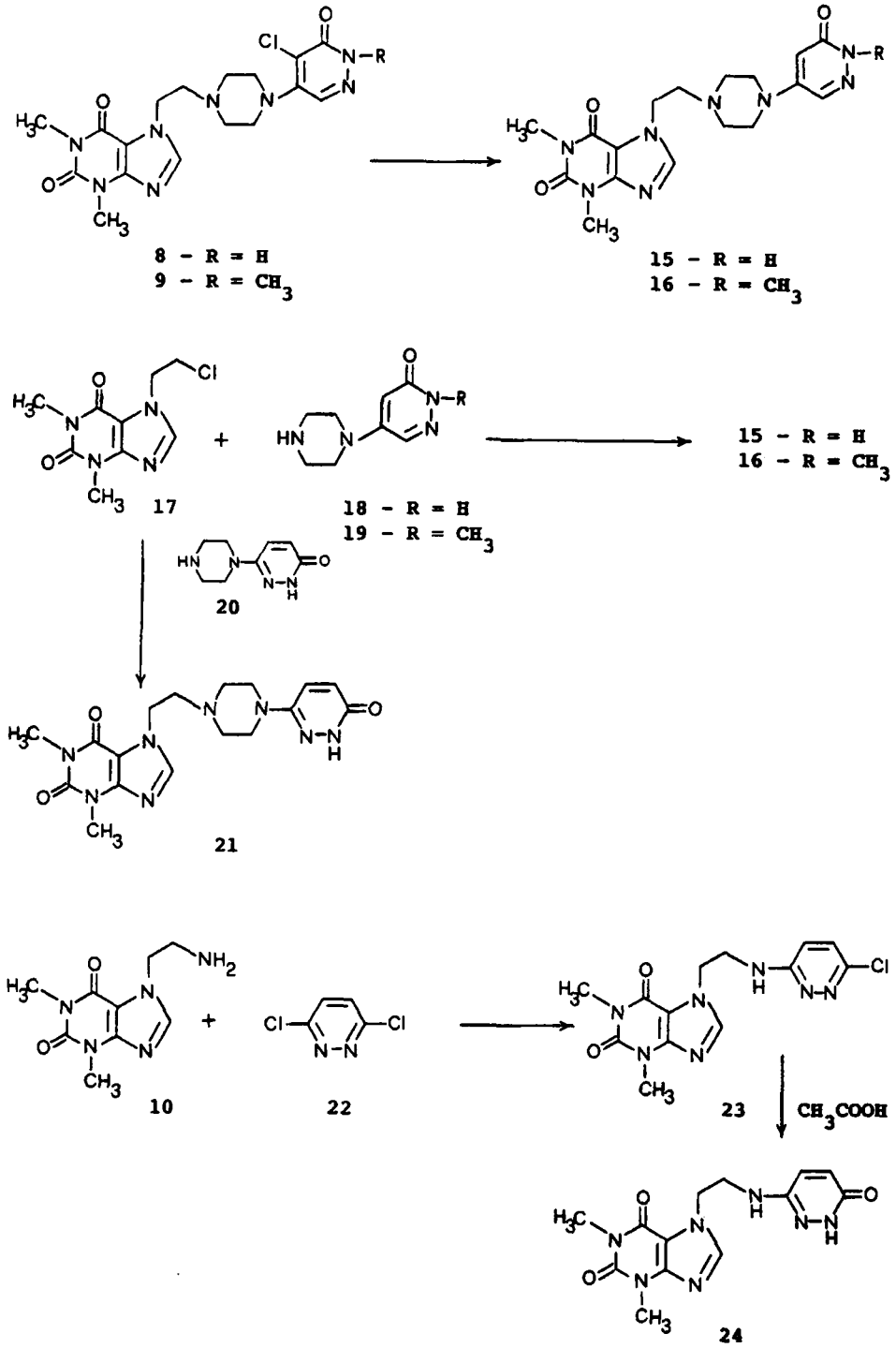
The 5-substituted isomer **8** was eluted with CH_2Cl_2/EtOH (9/1), yield: 10%, m.p. 264-268°C.- ^{1}H-NMR (MeOD): δ (ppm) = 2.6-2.7 (m, 4H; H-pip.), 2.9 (t, 2H; J = 6 Hz, CH_2), 3.35-3.5 (m, 7H; 4H-pip., N-CH_3), 3.6 (s, 3H; N-CH_3), 4.45 (t, 2H; J = 6 Hz, CH_2), 7.5 (s, 1H; H6-pyrid.), 7.65 (s, 1H; N=CH).- $C_{17}H_{21}ClN_8O_3$ (420.4).

2-Methyl-4-{4-[2-(7-theophyllin)-ethyl]-1-piperazinyl}-5-chloro-3(2H)-pyridazinone (**7**)

and

2-Methyl-4-chloro-5-{4-[2-(7-theophyllin)-ethyl]-1-piperazinyl}-3(2H)-pyridazinone (**9**)

7 and **9** were prepared as described for compounds **6** and **8**. The 4-substituted isomer **7** was eluted with CH_2Cl_2/EtOH (9.8/0.2), yield: 25%, m.p. 187-189°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.55-2.65 (m, 4H; H-pip.), 2.8 (t, 2H; J = 6 Hz, CH_2), 3.4-3.55 (m, 7H; 4H-pip., N-CH_3), 3.6 (s, 3H; N-CH_3), 3.7 (s, 3H; N-CH_3), 4.4 (t, 2H; J = 6 Hz, CH_2), 7.5 (s, 1H; 6-H-pyrid.), 7.65 (s, 1H; N=CH).- $C_{18}H_{23}ClN_8O_3$ (434.4).



Scheme 3

The 5-substituted isomer **9** was eluted with CH_2Cl_2/EtOH (9.5/0.5), yield: 10%, m.p. 196-201°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.55-2.7 (m, 4H; H-pip.), 2.85 (t, 2H; J = 6 Hz, CH_2), 3.3-3.5 (m, 7H; 4H-pip., N-CH_3), 3.6 (s, 3H; N-CH_3), 3.75 (s, 3H; N-CH_3), 4.4 (t, 2H; J = 6 Hz, CH_2), 7.55 (s, 1H; 6-H-pyrid.), 7.65 (s, 1H; N=CH).- $C_{18}H_{23}ClN_8O_3$ (434.4).

5-Substituted isomers **8, 9**

A mixture of 0.01 mol of 7-(2-piperazinethyl)-theophylline (**3**), 0.01 mol of 4,5-dichloro-3(2*H*)-pyridazinone or 2-methyl-4,5-dichloro-3(2*H*)-pyridazinone and 0.01 mol of $KHCO_3$ in 100 ml EtOH was refluxed overnight. The mixture was filtered, and the filtrate was concentrated under reduced pressure and purified by flash-chromatography using a stepwise gradient of EtOH (0-10%) in CH_2Cl_2 for compound **8**, yield: 30%; while compound **9** was eluted with EtOH/CH_2Cl_2 (0.5/9.5), yield: 35%.

For spectral data see above.

4-{[2-(7-Theophyllin)-ethyl]-amino}-5-chloro-3(2H)-pyridazinone (**11**) and

4-Chloro-5-{[2-(7-theophyllin)-ethyl]-amino}-3(2H)-pyridazinone (**13**)

A mixture of 1 g (4.48 mmol) 7-(2-aminoethyl)-theophylline (**10**)[10], 0.74 g (4.48 mmol) 4,5-dichloro-3(2H)-pyridazinone and 0.45 g (4.48 mmol) of $KHCO_3$ in 10 ml of 1,4-dioxane was heated to 80°C for 10 h. The mixture was filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash-chromatography. The 4-substituted isomer **11** was eluted using a stepwise gradient of EtOH (0-4.5%) in CH_2Cl_2, yield: 20%, m.p. 186-192°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 3.2 (s, 3H; N-CH_3), 3.4 (s, 3H; N-CH_3), 4.05 (s, 2H; J = 6 Hz, CH_2), 4.4 (t, 2H; J = 6 Hz, CH_2), 6.45 (s, 1H; NH), 7.45 (s, 1H; 6-H-pyrid.), 7.8 (s, 1H; N=CH), 12.5 (s, 1H; NHCO).- $C_{13}H_{14}ClN_7O_3$ (351.4).

The 5-substituted isomer **13** was eluted with EtOH/CH_2Cl_2 (1/9), yield: 15%, m.p. 325-330°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 3.2 (s, 3H; N-CH_3), 3.4 (s, 3H; N-CH_3), 3.7 (t, 2H; J = 6 Hz, CH_2), 4.4 (t, 2H; J = 6 Hz, CH_2), 6.6 (s, 1H; NH), 7.8 (s, 1H; 6-H-pyrid.), 7.95 (s, 1H; N=CH), 13.5 (s, 1H; NHCO).- $C_{13}H_{14}ClN_7O_3$ (351.4).

2-Methyl-4-{[2-(7-theophyllin)-ethyl]-amino}-5-chloro-3(2H)-pyridazinone (**12**)

and

2-Methyl-4-chloro-5-{[2-(7-theophyllin)-ethyl]-amino}-3(2H)-pyridazinone (**14**)

A mixture of 0.5 g (2.24 mmol) of **10**, 0.4 g (2.24 mmol) of **5** and 0.23 g (2.24 mmol) of $KHCO_3$ in 20 ml of 1,4-dioxane was refluxed for 30 h. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash-chromatography using a stepwise gradient of EtOH (0-2%) in CH_2Cl_2 for 4-substituted isomer **12**, yield: 20%, m.p. 208-214°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.4 (s, 3H; N-CH_3), 3.5 (s, 3H; N-CH_3), 3.6 (s, 3H; N-CH_3), 4.2 (t, 2H; J = 6 Hz, CH_2), 4.5 (t, 2H; J = 6 Hz, CH_2), 6.8 (s, 1H; NH), 7.4 (s, 2H; 6-H-pyrid., N=CH).- $C_{14}H_{16}ClN_7O_3$ (365.4).

The 5-substituted isomer **14** was eluted with CH_2Cl_2/EtOH (9.4/0.6), yield: 10%, m.p. 237-242°C.- ^{1}H-NMR (MeOD): δ (ppm) = 3.4 (s, 3H; N-CH_3), 3.5 (s, 3H; N-CH_3), 3.65 (m, 5H; N-CH_3, CH_2), 4.5 (t, 2H; J = 6 Hz, CH_2), 6.0 (s, 1H; NH), 7.6 (s, 1H; 6-H-pyrid.), 7.65 (s, 1H; N=CH).- $C_{14}H_{16}ClN_7O_3$ (365.4).

5-Substituted isomers **13, 14**

These compounds were prepared similarly as compounds **8**, **9**. For spectral data see above.

5-{4-[2-(7-Theophyllin)-ethyl]-1-piperazinyl}-3(2H)-pyridazinone (**15**)

and

2-Methyl-{4-[2-(7-theophyllin)-ethyl]-1-piperazinyl}-3(2H)-pyridazinone (**16**)

Method **A**

A solution of **8** or **9** (5 mmol) and KOH (6 mmol) in MeOH (100 ml) was hydrogenated using 10% Pd/C (200 mg) at atmospheric pressure and room temp. After uptake of an equimolecular amount of H_2, the catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was treated with water and extracted with $CHCl_3$. The crude product obtained upon removal of $CHCl_3$, was purified by flash-chromatography. Compound **15** was eluted with CH_2Cl_2/EtOH (8.5/1.5), yield: 30%, m.p. 266-272°C.- ^{1}H-NMR (MeOD): δ (ppm) = 2.55-2.65 (m, 4H-pip.), 2.85 (t, 2H; J = 6 Hz, CH_2), 3.3-3.4 (m, 7H; N-CH_3, 4H-pip.), 4.0 (s, 3H; N-CH_3), 4.4 (t, 2H; J = 6 Hz, CH_2), 5.85 (d, J = 4.5 Hz, 1H; 4-H-pyrid.), 7.6 (s, 1H; N=CH), 7.65 (d, J = 4.5 Hz, 1H; 6-H-pyrid.).- $C_{17}H_{22}N_8O_3$ (386).

Compound **16** was eluted with CH_2Cl_2/EtOH (9/1), yield: 35%, m.p. 188-191°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.55-2.6 (m, 4H-pip.), 2.8 (t, 2H; J = 6 Hz, CH_2), 3.3-3.45 (m, 7H; N-CH_3, 4H-pip.), 3.5 (s, 3H; N-CH_3), 3.7 (s, 3H; N-CH_3), 4.4 (t, 2H; J = 6 Hz, CH_2), 6.15 (d, J = 4.5 Hz, 1H; 4-H-pyrid.), 7.4 (d, J = 4.5 Hz, 1H; 6-H-pyrid.), 7.5 (s, 1H; N=CH).- $C_{18}H_{24}N_8O_3$ (400).

Method **B**

A mixture of (3.3 mmol) of 7-(2-chloroethyl)-theophylline, (3.3 mmol) of 5-(1-piperazinyl)-3(2*H*)-pyridazinone (**18**) or 2-methyl-5-(1-piperazinyl)-3(2*H*)-pyridazinone (**19**) and 3.3 mmol of Na_2CO_3 in 50 ml of isoamylic alcohol was refluxed for 20 h. The mixture was filtered by suction and the filtrate was evaporated *in vacuo*. The residue was purified by flash-chromatography using a stepwise gradient of EtOH (0-15%) in CH_2Cl_2 to give compound **15** (yield: 40%), while compound **16** was eluted with EtOH/CH_2Cl_2 (1/9) (yield: 20%). For spectral data see above.

5-(1-Piperazinyl)-3(2H)-pyridazinone (**18**)

and

2-Methyl-5-(1-piperazinyl)-3(2H)-pyridazinone (**19**)

A solution of 5 mmol of 4-chloro-5-(1-piperazinyl)-3(2*H*)-pyridazinone[11] or 2-methyl-4-chloro-5-(1-piperazinyl)-3(2*H*)-pyridazinone[11], and 6 mmol of KOH in MeOH (100 ml) was hydrogenated catalytically using 10% palladium on carbon (200 mg) at atmospheric pressure and room temp. After uptake of an equimolecular amount of H_2, the catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was treated with dry EtOH after heating, the org. phase was filtered and concentrated. Compound **18** was crystallized from EtOH, yield: 40%, m.p. 216-220°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 2.7-2.8 (m, 5H; 4H-pip., NH), 3.2-3.3 (m, 4H-pip.), 6.65 (d, 1H; 4-H-pyrid.), 7.8 (d, 1H; 6-H-pyrid.), 12.5 (s, 1H; NHCO).

Compound **19** was purified by flash-chromatography using CH_2Cl_2/EtOH (7/3), yield: 50%, dense oil.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.85-3.0 (m, 5H; 4H-pip., NH), 3.15-3.30 (m, 4H-pip.), 3.65 (s, 3H; N-CH_3), 5.85 (d, 1H; 4-H-pyrid.), 7.55 (d, 1H; 6-H-pyrid.).

6-{4-[2-(7-Theophyllin)-ethyl]-1-piperazinyl}-3(2H)-pyridazinone (**21**)

A mixture of 0.48 g (2 mmol) of 7-(2-chloroethyl)-theophylline, 0.36 g (2 mmol) of 6-piperazinyl-3(2*H*)-pyridazinone (**20**)[12], 0.8 g of Na_2CO_3 in 25 ml of isoamylic alcohol was refluxed overnight. The mixture was filtered and the filtrate was evaporated under reduced pressure, the residue was purified by flash-chromatography using a stepwise gradient of EtOH (0-7%) in CH_2Cl_2, yield: 30%, m.p. 248-250°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.5-2.6 (m, 4H-pip.), 2.8 (t, 2H; J = 6 Hz, CH_2), 3.1-3.2 (m, 4H- pip.), 3.35 (s, 3H; N-CH_3), 3.55 (s, 3H; N-CH_3), 4.35 (t, 2H; J = 6 Hz, CH_2), 6.7 (d, 1H; J = 9.5 Hz, CH=C<u>H</u>), 7.1 (d, 1H; J = 9.5 Hz, C<u>H</u>=CH), 7.5 (s, 1H; N=CH).- $C_{17}H_{22}N_8O_3$ (386).

3-Chloro-{6-[2-(7-theophyllin)-ethyl]-amino}-piridazine (**23**)

A mixture of 2.33 g (0.01 mol) of 7-(2-aminoethyl)-theophylline (**10**) and 1.5 g (0.01 mol) of 3,6-dichloropiridazine in 20 ml isoamylic alcohol was refluxed overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash-chromatography using CH_2Cl_2/EtOH (9.3/0.7), yield: 50%, m.p. 188-192°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.4 (s, 3H; N-CH_3), 3.5 (s, 3H; N-CH_3), 3.95 (t, 2H; J = 6 Hz, CH_2), 4.6 (t, 2H; J = 6 Hz, CH_2), 5.85 (s, 1H; NH), 6.6 (d, 1H; J = 9.5 Hz, C<u>H</u>=CH), 7.05 (d, 1H; J = 9.5 Hz, CH=C<u>H</u>), 7.5 (s, 1H; N=CH).

6-{[2-(7-Theophyllin)-ethyl]-amino}-3(2H)-pyridazinone (**24**)

A solution of 0.5 g (1.5 mmol) of **23** in 10 ml glacial acetic acid was refluxed for 14 h. After concentration under reduced pressure, the residue was purified by flash-chromatography using CH_2Cl_2/EtOH (8.5/1.5), yield: 25%, m.p. 298-300°C.- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 3.2 (s, 3H; N-CH_3), 3.3 (s, 3H; N-CH_3), 3.6 (t, 2H; J = 6 Hz, CH_2), 4.3 (t, 2H; J = 6 Hz, CH_2), 6.2 (s, 1H; NH), 6.5 (d, 1H; J = 9.5 Hz, CH=CH), 6.7 (d, 1H; J = 9.5 Hz, CH=CH), 7.8 (s, 1H; N=CH), 11.85 (s, 1H; NHCO).- $C_{13}H_{15}N_7O_3$ (317).

Pharmacology

Material and methods

Bronchial relaxation (in vitro)

The isolated guinea pig lung is perfused and constricted by physiological salt solution containing methacholine (0.05 μg/ml) at 37°C. The test substance (μg/ml) is injected as a bolus just proximal to the entry of the cannula into the trachea. An increase in the perfusion flow rate of more than 50% indicates significant activity. The increased % in the velocity of the flux of perfusion was calculated using the method of *Luduena*[13].

Discussion

The broncholytic profile of these compounds was determined in vitro on guinea pig trachea and compared with theophylline using the method of *Luduena*[13]. The increased % in the velocity of the flux of perfusion was measured for these compounds. An increase in the perfusion flow rate by more than 50% indicates significant activity. The biological results are shown in Table 1. Only compounds **6**, **7**, **8**, in which the pyridazinone ring is linked through a piperazine ring to the 7-(2-ethyl)-theophylline, show an increase in the perfusion flow rate more than that of theophylline. Compounds **6** and **7** in which a H-atom or a methyl group is bound at 2-position of the pyridazinone ring show a similar activity; on the contrary for compounds **8** and **9**, the activity is lowered when a methyl group is bound at the same position. The chlorine in the pyridazinone ring is necessary for activity, as the corresponding dehalogenated compounds (compounds **15** and **16**) show reduced activity. For compounds **11**, **12**, **13**, and **14**, in which the 7-(2-ethyl)-theophylline is linked to a pyridazinone ring through an amino group, the activity decreases. We obtained the same results for compounds **21** and **24** in which the pyridazinone ring is linked in 6-position. In conclusion for compound **6** which shows the highest increase % in the velocity of the perfusion, the pD_2 values has been determined and compared to that of compound **2** and theophylline (Table 2). These results show that compound **6** has an activity higher than that of compound **2**.

Table 1: Evaluation of tracheal relax (*in vitro*)[a]

Compound	Formula	Tissue: Guinea Pig Trachea Increase % in the velocity of the flux of perfusion[b]
Theophylline		62
6	$C_{17}H_{21}ClN_8O_3$	78
7	$C_{18}H_{23}ClN_8O_3$	73
8	$C_{17}H_{21}ClN_8O_3$	75
9	$C_{18}H_{23}ClN_8O_3$	27
11	$C_{13}H_{14}ClN_7O_3$	7
12	$C_{14}H_{16}ClN_7O_3$	10
13	$C_{13}H_{14}ClN_7O_3$	3
14	$C_{14}H_{16}ClN_7O_3$	6
15	$C_{17}H_{22}N_8O_3$	6
16	$C_{18}H_{24}N_8O_3$	13
21	$C_{17}H_{22}N_8O_3$	30
24	$C_{13}H_{15}N_7O_3$	16

a) The response was measured at the concentration of 30 μg/ml for all compounds. The reported values are the medium of three measurements.

b) The broncholytic date are the result of the screening performed by Panlabs Incorporated Taiwan.

Table 2

	pD_2
6	4.39±0.05
2	4.00±0.05
Theophylline	4.00±0.01

PD_2 = -log of molar concentration which gives a half-maximal relaxing effect.

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