

1.6 (m, 4 H), 1.28 (d, 3 H, CH<sub>3</sub>). Benzylic CH was obscured under HOD peak.

**Method B. N-[5-[(Cyclohexylamino)carbonyl]oxy]-2-pentyl]norepinephrine Hydrochloride (14).** A solution of compound 28 (1 g, 4.4 mmol), *dl*-norepinephrine hydrochloride (903 mg, 4.4 mmol), and NaCNBH<sub>3</sub> (416 mg, 6.6 mmol) in 35 mL of MeOH was adjusted to pH 6.0 by the addition of HOAc. The solution was then stirred for 15 h at 40 °C and then at room temperature for 36 h. Excess NaCNBH<sub>3</sub> was then destroyed by the addition of 50 mL of 0.1 N HCl; the HCN was removed under aspirator vacuum in the hood. The solution was washed three times with 50 mL of CHCl<sub>3</sub>, and the product was extracted into 100 mL of *n*-BuOH. The *n*-BuOH layer was washed three times with 50 mL of H<sub>2</sub>O and then evaporated. The product was purified by flash chromatography<sup>16</sup> using a gradient of 86:9:5 to 79:16:5 of CHCl<sub>3</sub>/MeOH/HOAc. The appropriate fractions were evaporated, added to 100 mL of 0.1 N HCl, washed with CHCl<sub>3</sub> (3 × 50 mL), extracted into 100 mL of *n*-BuOH, and evaporated. The product was dissolved in H<sub>2</sub>O and lyophilized to an amorphous white solid which was homogeneous by HPLC and TLC: NMR (D<sub>2</sub>O) δ 6.99 (m, 2 H), 6.91 (d, 2 H), 4.14 (m, 2 H, CH<sub>2</sub>O), 3.46 (m, 4 H), 1.7 (m, 14 H), 1.41 (d, 3 H, CH<sub>3</sub>). Anal. (C<sub>20</sub>H<sub>33</sub>N<sub>2</sub>O<sub>5</sub>Cl) C, H, N, O.

**SV-49 Mouse Lymphoma Cell Assay for Cyclic AMP.** The method used was essentially that described in ref 3d and is summarized here. The cells were suspended in DME (13.3 g/L) and 20 mM Hepes (pH 7.4) with 0.1% BSA at a concentration of (2–2.5 × 10<sup>6</sup>)/mL. They were then incubated for 10 min at 37 °C and added to solutions with or without test compounds for 6 min more. The solutions were cooled to 0 °C and centrifuged. The cell pellets were resuspended and boiled and cyclic AMP levels were determined by the method of Gilman.<sup>5b</sup> For each compound, a *K<sub>A</sub>* (association constant in molarity units) and an *E<sub>max</sub>* (maximal activity) was determined. Each *K<sub>A</sub>* was the average of at least three determinations measured in triplicate. The relative activity is conveniently expressed as the ratio of *K<sub>A</sub>* for isoproterenol (determined at the same time) to the *K<sub>A</sub>* for the test compound. This ratio showed no significant variation (*p* < 0.05). The *E<sub>max</sub>* for compounds 8–18 were roughly the same as for isoproterenol and are not reported here.

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26340) for subsequent financial support. We also thank Moon Ja Choo for her excellent technical assistance and Dr. Kenneth A. Jacobson, Dr. Etienne Sonveaux, and Dr. Debra Marr-Leisy for helpful discussions. Mass spectra were run by Dr. Roberto at the University of California Mass Spectrometry Biomedical Research Facility (A. L. Burlingame, Director), which is supported by National Institutes of Health Division of Research Resources Grant RR 00719/RR 01614.

**Registry No.** (±)-8, 95482-86-3; (±)-8-H<sub>3</sub>PO<sub>4</sub>, 95482-87-4; (±)-9 (isomer 1), 95482-88-5; (±)-9 (isomer 2), 95483-18-4; (±)-9-H<sub>3</sub>PO<sub>4</sub> (isomer 1), 95482-89-6; (±)-9-H<sub>3</sub>PO<sub>4</sub> (isomer 2), 95483-19-5; (±)-10 (isomer 1), 95482-90-9; (±)-10 (isomer 2), 95483-20-8; (±)-10-H<sub>3</sub>PO<sub>4</sub> (isomer 1), 95482-91-0; (±)-10-H<sub>3</sub>PO<sub>4</sub> (isomer 2), 95483-21-9; (±)-11 (isomer 1), 95482-92-1; (±)-11 (isomer 2), 95483-22-0; (±)-11-H<sub>3</sub>PO<sub>4</sub> (isomer 1), 95482-93-2; (±)-11-H<sub>3</sub>PO<sub>4</sub> (isomer 2), 95483-23-1; (±)-12 (isomer 1), 95482-94-3; (±)-12 (isomer 2), 95483-24-2; (±)-12-H<sub>3</sub>PO<sub>4</sub> (isomer 1), 95482-95-4; (±)-12-H<sub>3</sub>PO<sub>4</sub> (isomer 2), 95483-25-3; (±)-13 (isomer 1), 95482-96-5; (±)-13 (isomer 2), 95483-26-4; (±)-13-H<sub>3</sub>PO<sub>4</sub> (isomer 1), 95482-97-6; (±)-13-H<sub>3</sub>PO<sub>4</sub> (isomer 2), 95483-27-5; (±)-14 (isomer 1), 95482-98-7; (±)-14 (isomer 2), 95483-28-6; (±)-14-HCl (isomer 1), 95482-99-8; (±)-14-HCl (isomer 2), 95483-29-7; (±)-15 (isomer 1), 95483-00-4; (±)-15 (isomer 2), 95483-30-0; (±)-15-H<sub>3</sub>PO<sub>4</sub> (isomer 1), 95483-01-5; (±)-15-H<sub>3</sub>PO<sub>4</sub> (isomer 2), 95483-31-1; (±)-16 (isomer 1), 95483-02-6; (±)-16 (isomer 2), 95483-32-2; (±)-16-HCl (isomer 1), 95483-03-7; (±)-16-HCl (isomer 2), 95483-33-3; (±)-17 (isomer 1), 95512-29-1; (±)-17 (isomer 2), 95483-34-4; (±)-17-HCl (isomer 1), 95483-04-8; (±)-17-HCl (isomer 2), 95483-35-5; (±)-18 (isomer 1), 95483-05-9; (±)-18 (isomer 2), 95483-36-6; (±)-18-H<sub>3</sub>PO<sub>4</sub> (isomer 1), 95483-06-0; (±)-18-H<sub>3</sub>PO<sub>4</sub> (isomer 2), 95483-37-7; 19, 5447-02-9; (±)-20, 95483-07-1; (±)-21, 95483-08-2; (±)-21-HCl, 95483-17-3; 23, 590-90-9; 25, 21856-89-3; 26, 95483-09-3; 27, 95483-10-6; 28, 95483-11-7; 29, 95483-12-8; 30, 95483-13-9; 31, 95483-14-0; 32, 95483-15-1; 33, 82125-92-6; CH<sub>3</sub>(CH<sub>2</sub>)<sub>3</sub>NCO, 111-36-4; *p*-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>CONCO, 5843-46-9; (±)-norepinephrine, 138-65-8; *p*-toluoyl chloride, 874-60-2; (±)-norepinephrine hydrochloride, 55-27-6; *N*-(2-butyl)norepinephrine, 95483-16-2; 5-hydroxy-2-pentanone, 1071-73-4; 3-hydroxypropylamine, 156-87-6; *p*-tolyl isocyanate, 622-58-2; cyclohexyl isocyanate, 3173-53-3; *p*-tolylsulfonyl isocyanate, 4083-64-1.

**Supplementary Material Available:** The HPLC parameters and 360-MHz <sup>1</sup>H NMR data for compounds 8–18 (4 pages). Ordering information is given on any current masthead page.

## New Antihistaminic Theophylline or Theobromine Derivatives

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A series of 3,4-dihydro-1,3-dimethyl-7-[3-(4-substituted-piperazin-1-yl)-substituted-alkyl]-1H-purine-2,6-diones and 3,7-dihydro-3,7-dimethyl-1-[3-(4-substituted-piperazin-1-yl)-substituted-alkyl]-1H-purine-2,6-diones was synthesized and evaluated for antihistaminic activity. Some of them displayed good inhibition of both histamine-induced bronchospasm in the anesthetized guinea pig at 10 µg/kg by the intravenous route and of passive cutaneous anaphylaxis in the rat at 10 mg/kg by the oral route. Comparison of the two most active compounds revealed a higher antihistaminic activity with the compounds containing a (phenylthio)propyl group (1 and 2) as compared with that containing a phenoxy group. Compound 2 [RS-49014, 3,4-dihydro-1,3-dimethyl-7-[3-[4-[3-(phenylthio)propyl]piperazin-1-yl]-2-hydroxypropyl]-1H-purine-2,6-dione] was selected for clinical trials on the basis of a comparative pharmacological study with chlorpheniramine, ketotifen, promethazine, and theophylline.

Theophylline and its derivatives are well-known for their bronchodilator activity and consequent efficacy in the treatment of asthma. Related N-7 substituted theophylline

derivatives such as caffeine, etofylline, proxiphylline, and reproterol (I) have also been extensively studied.

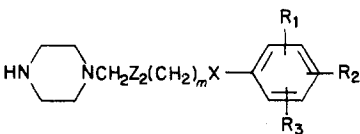
On the basis of a previous study<sup>1</sup> carried out in our laboratory, we reported that N,N'-disubstituted piper-

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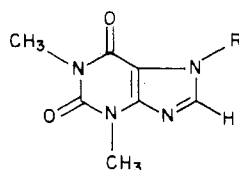
(1) Beranger, S.; Pinhas, H. French Patent 78.13.114.

**Table I.** Chemical Composition of 1-Substituted Piperazines<sup>a</sup>

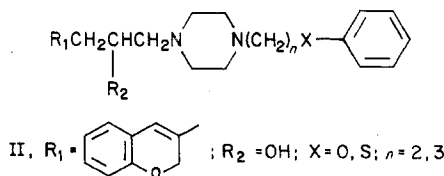
								
compd	Z <sub>2</sub>	m	X	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	yield, %	bp, °C/mm
a	CH <sub>2</sub>	1	S	H	H	H	52	140/0.05
b	CH <sub>2</sub>	0	O	2-CH <sub>3</sub>	6-CH <sub>3</sub>	H	50	190/25
c	CH <sub>2</sub>	1	O	4-Cl	H	H	40	158/0.2
d	CH <sub>2</sub>	1	S	4-Cl	H	H	60	154/0.5
e	CH <sub>2</sub>	1	O	4-OCH <sub>3</sub>	H	H	50	150/0.05
f	CH <sub>2</sub>	1	S	4-OCH <sub>3</sub>	H	H	80	225/13
g	CH <sub>2</sub>	2	S	H	H	H	62	166-168/0.5
h	CH <sub>2</sub>	2	S	4-Cl	H	H	55	160/0.01
i	CH <sub>2</sub>	1	O	3-OCH <sub>3</sub>	4-OCH <sub>3</sub>	5-OCH <sub>3</sub>	50	178-182/0.01
j	CHOH	1	S	H	H	H	50	232/13
k	CH <sub>2</sub>	2	O	H	H	H	60	140/0.01

<sup>a</sup>The NMR spectra of these compounds were in accordance with the formula.

zines typified by the general formula II were associated with potent antihistaminic effects. In that investigation, this moiety (II) was invariably linked to a polysubstituted alkylaryl ring. It therefore seemed a promising approach to link these disubstituted piperazines to the N-7 position of the theophylline ring with the aim of discovering novel N-7 substituted theophyllines exhibiting high potency as bronchodilators and antihistaminics. As part of this work, we also investigated the effect of similar substitution at the N-1 position of theobromine. This paper describes such series of compounds.



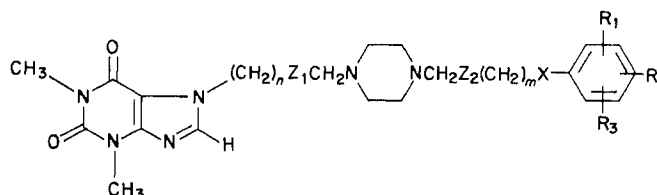
R = (CH<sub>2</sub>)<sub>3</sub>NHCH<sub>2</sub>CHOH-3,5-(OCH<sub>3</sub>)<sub>2</sub>Ph (I, reproterol)  
 R = H (theophylline)  
 R = CH<sub>3</sub> (caffeine)  
 R = CH<sub>2</sub>CH<sub>2</sub>OH (etofylline)  
 R = CH<sub>2</sub>CHOHCH<sub>3</sub> (proxiphylline)



The antihistaminic activity of the compounds was evaluated on the basis of their protective effect against passive cutaneous anaphylaxis and the cutaneous reaction provoked by exogenous histamine in the rat and against histamine-induced bronchospasm in the guinea pig. Selectivity was assessed by comparing the inhibition of histamine-induced bronchospasm with that of bronchospasm induced by acetylcholine and serotonin.

**Chemistry.** The various starting compounds used in the present study were synthesized by known methods.<sup>2</sup> Condensation of 7-(2,3-epoxypropyl)theophylline<sup>3</sup> or 7-(3-chloropropyl)theophylline<sup>4</sup> with various N-substituted

piperazines (Table I) gave most of the compounds with the general formula



Compound 5 (Table II) was prepared from 7-(2-chloroethyl)theophylline<sup>5</sup> and compound 6 (Table II) from 7-(6-chlorohexyl)theophylline.<sup>6</sup> Acetylation of compounds 2 and 16 in dry pyridine/acetic anhydride afforded respectively compounds 29 and 28.

To pursue our studies on the structure-activity relationship, modified structures (Table III) were also synthesized. Replacement of the piperazine moiety in the described preparation of 1-[3-(phenylthio)propyl]piperazine by *sym*-dimethylethylenediamine or by homopiperazine afforded compounds 37 and 36, respectively.

Preparation of the Mannich's base from 7-(3-oxobutyl)theophylline<sup>7</sup> and reduction of the final product with NaBH<sub>4</sub> led to 31. Condensation of theophyllineacetyl chloride<sup>5</sup> with the N-substituted piperazine (a) (Table I) in pyridine gave 33. Synthesis of 30 was carried out by condensation of theophylline with the hydrochloride of 1-[3-(phenylthio)propyl]piperazine and poly(oxy-methylene) in refluxing EtOH. Reaction of the sodium salt of theophylline with 1,4-dichloro-2-butene followed by addition of the N-substituted piperazine (a) afforded 32.

An analogous series of reactions with theobromine in place of theophylline provided the compounds 38-50 (Table IV).

## Results and Discussion

Examination of the data in Table V on the bronchodilator activity in the guinea pig by the intravenous (iv) route reveals that compounds 1-4, 11, 12, 21-23, 25, and 36 are the most effective inhibitors of histamine-induced bronchospasm (protection ≥ 70%). Of these, compounds 3, 21, 23, and 36 were shown to be less potent against bronchospasm induced by serotonin and acetylcholine in the

(2) Favier, C.; Pinhas, H.; Beranger, S.; Pascal, J. C. Eur. Patent 81.400044.4.

(3) Fukuda, H. *Yakugaku Zasshi* 1963, 83, 925-9.

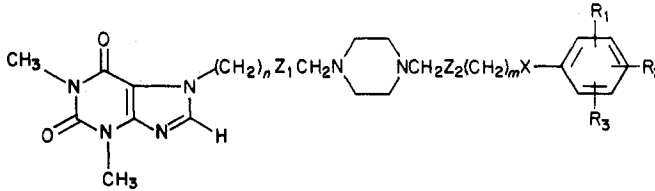
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(6) Klingler, K. H. *Arzneim.-Forsch.* 1977, 27(1A), 4-14.

(7) Zelnik, R.; Pesson, M. *Bull. Soc. Chim. Fr.* 1959, 1667-69.

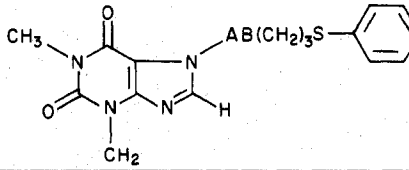
Table II. Chemical Composition of 7-Substituted Theophyllines



no.	n	Z <sub>1</sub>	m	X	Z <sub>2</sub>	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	mp, °C	formula	yield, %	anal. <sup>a</sup>
1	1	CH <sub>2</sub>	1	S	CH <sub>2</sub>	H	H	H	260	C <sub>23</sub> H <sub>32</sub> N <sub>6</sub> O <sub>2</sub> S·2HCl	60	CHNCl
2	1	CHOH	1	S	CH <sub>2</sub>	H	H	H	209	C <sub>23</sub> H <sub>32</sub> N <sub>6</sub> O <sub>3</sub> S·2HCl	65	CHNCl
3	1	CH <sub>2</sub>	0	O	CH <sub>2</sub>	H	H	H	265	C <sub>22</sub> H <sub>30</sub> N <sub>6</sub> O <sub>3</sub> ·2HCl	48	CHNCl
4	1	CH <sub>2</sub>	1	O	CH <sub>2</sub>	H	H	H	260	C <sub>23</sub> H <sub>32</sub> N <sub>6</sub> O <sub>3</sub> ·2HCl	50	CHNCl
5	0	CH <sub>2</sub>	1	S	CH <sub>2</sub>	H	H	H	214	C <sub>22</sub> H <sub>30</sub> N <sub>6</sub> O <sub>2</sub> S·2HCl	44	CHNCl
6	1	CH <sub>2</sub>	0	O	CH <sub>2</sub>	6-CH <sub>3</sub>	2-CH <sub>3</sub>	H	244	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>3</sub> ·2HCl	54	CHNCl
7	1	CH <sub>2</sub>	1	O	CH <sub>2</sub>	4-Cl	H	H	246	C <sub>23</sub> H <sub>31</sub> ClN <sub>6</sub> O <sub>3</sub> ·2HCl	45	CHNCl
8	1	CH <sub>2</sub>	1	S	CH <sub>2</sub>	4-Cl	H	H	238	C <sub>23</sub> H <sub>31</sub> ClN <sub>6</sub> O <sub>2</sub> S·2HCl	50	CHNCl
9	1	CH <sub>2</sub>	1	O	CH <sub>2</sub>	4-OCH <sub>3</sub>	H	H	222	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>4</sub> ·2HCl	55	CHNCl
10	1	CH <sub>2</sub>	1	S	CH <sub>2</sub>	4-OCH <sub>3</sub>	H	H	224	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>3</sub> S·2HCl	55	CHNCl
11	1	CHOH	0	O	CH <sub>2</sub>	H	H	H	182	C <sub>22</sub> H <sub>30</sub> N <sub>6</sub> O <sub>4</sub> ·2HCl	60	CHNCl
12	1	CHOH	1	O	CH <sub>2</sub>	H	H	H	188	C <sub>23</sub> H <sub>32</sub> N <sub>6</sub> O <sub>4</sub> ·2HCl	65	CHNCl
13	1	CHOH	1	S	CH <sub>2</sub>	4-CH <sub>3</sub>	H	H	200	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>3</sub> S·2HCl	70	CHNCl
14	1	CHOH	1	O	CH <sub>2</sub>	4-OCH <sub>3</sub>	H	H	220	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>4</sub> ·2HCl	75	CHNCl
15	1	CHOH	1	S	CH <sub>2</sub>	4-Cl	H	H	205	C <sub>23</sub> H <sub>31</sub> ClN <sub>6</sub> O <sub>3</sub> S·2HCl	65	CHNCl
16	1	CHOH	1	O	CH <sub>2</sub>	4-Cl	H	H	206	C <sub>23</sub> H <sub>31</sub> ClN <sub>6</sub> O <sub>4</sub> ·2HCl	70	CHNCl
17	1	CHOH	2	S	CH <sub>2</sub>	4-Cl	H	H	176	C <sub>24</sub> H <sub>33</sub> ClN <sub>6</sub> O <sub>3</sub> S·2HCl	65	CHNCl
18	1	CH <sub>2</sub>	1	O	CH <sub>2</sub>	4-OCH <sub>3</sub>	3-OCH <sub>3</sub>	5-OCH <sub>3</sub>	208	C <sub>26</sub> H <sub>38</sub> N <sub>6</sub> O <sub>6</sub> ·2HCl	50	CHNCl
19	1	CH <sub>2</sub>	2	S	CH <sub>2</sub>	H	H	H	228	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>2</sub> S·2HCl	50	CHNCl
20	1	CH <sub>2</sub>	2	S	CH <sub>2</sub>	H	H	4-Cl	226	C <sub>27</sub> H <sub>40</sub> ClN <sub>6</sub> O <sub>2</sub> S·2HCl	55	CHNCl
21	1	CH <sub>2</sub>	1	S	CHOH	H	H	H	232	C <sub>23</sub> H <sub>32</sub> N <sub>6</sub> O <sub>3</sub> S·2HCl	45	CHNCl
22	1	CH <sub>2</sub>	2	O	CH <sub>2</sub>	H	H	H	230	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>3</sub> ·2HCl	40	CHNCl
23	1	CHOH	1	S	CHOH	H	H	H	182	C <sub>23</sub> H <sub>32</sub> N <sub>6</sub> O <sub>4</sub> ·2HCl	50	CHNCl
24	1	CHOH	2	S	CH <sub>2</sub>	H	H	H	198	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>3</sub> S·2HCl	60	CHNCl
25	1	CHOH	2	O	CH <sub>2</sub>	H	H	H	208	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>4</sub> ·2HCl	65	CHNCl
26	4	CH <sub>2</sub>	2	S	CH <sub>2</sub>	H	H	H	245	C <sub>26</sub> H <sub>38</sub> N <sub>6</sub> O <sub>2</sub> S·2HCl	50	CHNCl
27	1	CH <sub>2</sub>	1	S	CH <sub>2</sub>	4-CH <sub>3</sub>	H	H	238	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>2</sub> S·2HCl	40	CHNCl
28	1	CH <sub>3</sub> COOCH	1	O	CH <sub>2</sub>	4-Cl	H	H	158	C <sub>25</sub> H <sub>33</sub> ClN <sub>6</sub> O <sub>5</sub> ·2HCl	50	CHNCl
29	1	CH <sub>3</sub> COOCH	1	S	CH <sub>2</sub>	H	H	H	158	C <sub>25</sub> H <sub>34</sub> N <sub>6</sub> O <sub>4</sub> S·2C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	60	CHN

<sup>a</sup>The analytical results were within ±0.4% of the theoretical values for all elements listed.

Table III. Chemical Data of 7-Substituted Theophyllines



no.	A	B	mp, °C	formula	yield, %	anal. <sup>a</sup>
30	CH <sub>2</sub>	piperazine <sup>b</sup>	225	C <sub>21</sub> H <sub>28</sub> N <sub>6</sub> O <sub>2</sub> S·2HCl	30	CHNCl
31	(CH <sub>2</sub> ) <sub>2</sub> CHOH(CH <sub>2</sub> ) <sub>2</sub>	piperazine <sup>b</sup>	222	C <sub>25</sub> H <sub>36</sub> N <sub>6</sub> O <sub>3</sub> S·2HCl	28	CHNCl
32	CH <sub>2</sub> CH=CHCH <sub>2</sub>	piperazine <sup>b</sup>	188	C <sub>24</sub> H <sub>32</sub> N <sub>6</sub> O <sub>2</sub> S·2HCl	70	CHNCl
33	CH <sub>2</sub> CO	piperazine <sup>b</sup>	200	C <sub>23</sub> H <sub>28</sub> N <sub>6</sub> O <sub>3</sub> S·HCl	76	CHNCl
34	CH(CH <sub>3</sub> )CO	piperazine <sup>b</sup>	195	C <sub>23</sub> H <sub>30</sub> N <sub>6</sub> O <sub>3</sub> ·HCl	75	CHNCl
35	(CH <sub>2</sub> ) <sub>2</sub> CO	piperazine <sup>b</sup>	204	C <sub>23</sub> H <sub>30</sub> N <sub>6</sub> O <sub>3</sub> ·HCl	70	CHNCl
36	CH <sub>2</sub> CHOHCH <sub>2</sub>	homopiperazine <sup>b</sup>	224	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>3</sub> S·2HCl	60	CHNCl
37	(CH <sub>2</sub> ) <sub>3</sub>	CH <sub>3</sub> N(CH <sub>2</sub> ) <sub>2</sub> NCH <sub>3</sub>	190	C <sub>23</sub> H <sub>34</sub> N <sub>6</sub> O <sub>2</sub> S·2HCl	60	CHNCl

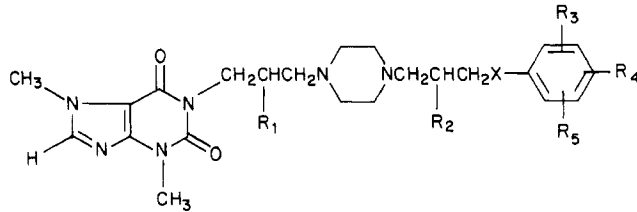
<sup>a</sup>The analytical results were within ±0.4% of the theoretical values for all elements listed. <sup>b</sup>N,N'-disubstituted.

guinea pig, and only compounds 1, 2, and 12 protected against the antibody-antigen reaction and the cutaneous reaction to exogenous histamine in the rat. The diminished activity of the other compounds enumerated above may be due to poor oral absorption and/or extensive metabolism.

It is difficult to establish a structure-activity relationship on the basis of these two models. Nevertheless, several points are worth noting. Substitution of the phenyl ring by CH<sub>3</sub>, OCH<sub>3</sub>, or Cl resulted in a slightly diminished activity against bronchospasm induced by histamine, serotonin, or acetylcholine. Reduced activity was noted also with carbonyl substituents in the aliphatic side chains (33-35) and on replacement of piperazine by homo-

piperazine (36). When theobromine replaced the theophylline skeleton (compounds 38-50), only 40 kept good activity. Compound 2 showed a better selectivity than compound 12 in the bronchospasm test. Theophylline, known for its inhibitory effect on phosphodiesterase, was active at a high dose (100 mg/kg os) against cutaneous anaphylaxis and to a lesser extent against the cutaneous reaction provided by exogenous histamine. Theophylline inhibited histamine-induced bronchospasm, when administered intravenously, but was not selective. The activities determined for these new derivatives appear to be due to a selective antihistaminic effect in so far as their effect on passive cutaneous anaphylaxis and the cutaneous reaction provoked by exogenous histamine was similar. However,

Table IV. Chemical Composition of 1-Substituted Theobromines



no.	R <sub>1</sub>	R <sub>2</sub>	X	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	mp, °C	formula	yield, %	anal. <sup>a</sup>
38	H	H	S	H	H	H	234	C <sub>23</sub> H <sub>32</sub> N <sub>6</sub> O <sub>5</sub> S·2HCl	70	CHN
39	OH	H	O	H	H	H	234	C <sub>23</sub> H <sub>32</sub> N <sub>6</sub> O <sub>4</sub> ·2HCl	65	CHN
40	OH	H	S	H	H	H	226	C <sub>23</sub> H <sub>32</sub> N <sub>6</sub> O <sub>5</sub> S·2HCl	80	CHN
41	H	H	O	H	H	H	224	C <sub>23</sub> H <sub>32</sub> N <sub>6</sub> O <sub>4</sub> ·2HCl	85	CHN
42	OH	H	S	4-Cl	H	H	240	C <sub>23</sub> H <sub>31</sub> ClN <sub>6</sub> O <sub>5</sub> S·2HCl	60	CHN
43	OH	H	O	4-OCH <sub>3</sub>	H	H	250	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>5</sub> ·2HCl	45	CHN
44	OH	H	O	4-Cl	H	H	248	C <sub>23</sub> H <sub>31</sub> ClN <sub>6</sub> O <sub>4</sub> ·2HCl	50	CHN
45	OH	H	O	4-Cl	3-CH <sub>3</sub>	5-CH <sub>3</sub>	250	C <sub>25</sub> H <sub>35</sub> ClN <sub>6</sub> O <sub>4</sub> ·2HCl	45	CHN
46	OH	H	S	4-CH <sub>3</sub>	H	H	240	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>5</sub> S·2HCl	70	CHN
47	H	H	O	4-Cl	H	H	250	C <sub>23</sub> H <sub>31</sub> ClN <sub>6</sub> O <sub>5</sub> ·2HCl	65	CHN
48	H	H	S	4-Cl	H	H	235	C <sub>23</sub> H <sub>31</sub> ClN <sub>6</sub> O <sub>4</sub> S·2HCl	85	CHN
49	H	H	S	4-CH <sub>3</sub>	H	H	230	C <sub>24</sub> H <sub>34</sub> N <sub>6</sub> O <sub>5</sub> S·2HCl	80	CHN
50	H	OH	S	H	H	H	245	C <sub>23</sub> H <sub>32</sub> N <sub>6</sub> O <sub>6</sub> S·2HCl	70	CHN

<sup>a</sup> The analytical results were within  $\pm 0.4\%$  of the theoretical values for all elements listed.

a large number of these compounds, like promethazine and chlorpheniramine, inhibited bronchospasm induced by both histamine and serotonin. The low activity of chlorpheniramine by the oral route may be due to a rapid elimination. Compounds 1 and 2 exhibited an antihistaminic activity with potency similar to that of ketotifen and promethazine by the oral route and were more active against histamine-induced bronchospasm than any of the reference drugs.

Further investigation of the antihistaminic activity of compounds 1 and 2 revealed a significant difference between them. When given orally, 2 exerted a protective effect lasting 3 times longer than that of 1 (Table VI). This difference may be due to a disparity in the rate of metabolism. Both compounds showed a low lethality in the rat, the oral LD<sub>50</sub> values being 1.6 g/kg for 1 and 2.1 g/kg for 2. Compound 2 (LN 2974 or RS-49014) has been selected for clinical evaluation as an antihistaminic agent.

## Experimental Section

Melting points were determined on a Kofler bank and are uncorrected. The <sup>1</sup>H NMR spectra were determined with a Varian EM 360 or Brücker 300 MHz spectrometer. The proton chemical shifts are given relative to Me<sub>4</sub>Si ( $\delta = 0$ ). Elemental analyses were performed by Atlantic Microlab, Inc. Detailed experimental procedures are described only for selected compounds, which will serve to illustrate the general synthetic methods employed. The chemical-ionization (CI) mass spectra were run on a Finnigan MAT 112S spectrometer, using ammonia as the reagent gas under the following conditions: source pressure ca. 100 mtorr, source temperature 250 °C, emission current 200  $\mu$ A at 90 eV.

**3-(Phenylthio)-1-chloropropane.** To a solution containing 1.1 mol of sodium hydroxide in 500 mL of H<sub>2</sub>O were added 1 mol of thiophenol and 2 mol of 1-bromo-3-chloropropane. The mixture was then refluxed for 30 h with vigorous stirring. After cooling, the resulting mixture was extracted with 2 L of methylene chloride. After washing of the mixture with dilute NaOH and then with H<sub>2</sub>O, the solvent was dried (Na<sub>2</sub>SO<sub>4</sub>) and then evaporated in vacuo. The product, 3-(phenylthio)-1-chloropropane, was distilled at 138–140 °C (13 mm/Hg) (yield 85%).

**1-[3-(Phenylthio)propyl]piperazine.** To 1 L of 50% aqueous alcohol were added 4 mol of piperazine, 1 mol of 3-(phenylthio)-1-chloropropane, and 1 mol of sodium hydroxide. The mixture was refluxed for 24 h with stirring. The EtOH was then evaporated, and the resulting material was extracted with 1 L of methylene chloride. The organic phase was thoroughly washed with H<sub>2</sub>O and was then concentrated and distilled to give 123 g

(52%) of 1-[3-(phenylthio)propyl]piperazine: bp 140–142 °C (0.05 mm); <sup>1</sup>H NMR (CCl<sub>4</sub>)  $\delta$  7.3 (5 H, s), 2.8 (6 H, m), 2.2 (6 H, m), 1.2 (1 H, s, NH, D<sub>2</sub>O exchangeable); mass spectrum, *m/e* 236 (M<sup>+</sup>, 20), 99 (100).

**3,7-Dihydro-1,3-dimethyl-7-[3-[4-[3-(phenylthio)propyl]piperazin-1-yl]propyl]-1H-purine-2,6-dione Dihydrochloride (1).** A mixture of 20 g (0.085 mol) of 1-[3-(phenylthio)propyl]piperazine, 21.7 g (0.085 mol) of 7-(3-chloropropyl)theophylline, and 0.085 mol of K<sub>2</sub>CO<sub>3</sub> in 200 mL of EtOH was refluxed 24 h with stirring. The solvent was evaporated and the resulting mixture was taken up with Et<sub>2</sub>O/H<sub>2</sub>O. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The solid residue was crystallized from EtOH/HCl. The crystalline product was collected to give 27 g (60%): mp 260 °C; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  8.3 (s, 1 H, 8-H theophylline), 7.3 (s, 5 H, C<sub>6</sub>H<sub>5</sub>), 4.5 (t, 2 H, N<sub>7</sub>CH<sub>2</sub>), 3.8 (br, 12 H piperazine and *N,N*-methylene groups), 3.5 (s, 3 H, CH<sub>3</sub>), 3.3 (s, 3 H, CH<sub>3</sub>), 3.1 (t, 2 H, CH<sub>2</sub>SPh), 2 (m, 4 H, aliphatic methylene).

**3,7-Dihydro-1,3-dimethyl-7-[3-[4-[3-(phenylthio)propyl]piperazin-1-yl]-2-hydroxypropyl]-1H-purine-2,6-dione Dihydrochloride (2).** A solution of 23.6 g (0.1 mol) of 7-(2,3-epoxypropyl)theophylline<sup>3</sup> and 23.6 g (0.1 mol) of 1-[3-(phenylthio)propyl]piperazine in 200 mL of H<sub>2</sub>O was heated under reflux for 3 h. It was then cooled and the solid was collected. Crystallization from ethanolic HCl gave 35.4 g (75%): mp 208–209 °C; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  8.2 (s, 1 H, 8H-theophylline), 7.3 (s, 5 H, C<sub>6</sub>H<sub>5</sub>), 3.3 (s, 3 H, CH<sub>3</sub>), 3.7 (s, 3 H, CH<sub>3</sub>), 2.2 (m, 2 H); mass spectrum (free base), *m/e* 472 (20), 454 (30), 335 (30), 275 (16), 249 (100), 98 (17).

**3,7-Dihydro-1,3-dimethyl-7-[5-[4-[3-(phenylthio)propyl]piperazin-1-yl]-3-hydroxypentyl]-1H-purine-2,6-dione Dihydrochloride (31).** To 15.6 g (0.032 mol) of 7-(3-oxobutyl)-theophylline and 16 g (0.052 mol) of 1-[3-(phenylthio)propyl]piperazine dihydrochloride in 200 mL of EtOH under reflux was added portionwise 7 g of poly(oxyethylene). After this addition, the mixture was refluxed for 12 h and cooled. The white solid was collected by filtration and dried to give 7.33 g (yield 40%). Reduction using NaBH<sub>4</sub> was carried out as usual, giving 6 g (80%) of the corresponding alcohol. The dihydrochloride salt melted at 222 °C.

**3,7-Dihydro-1,3-dimethyl-7-[4-[4-[3-(phenylthio)propyl]piperazin-1-yl]-2-butenyl]-1H-purine-2,6-dione Dihydrochloride (32).** A 21.8-g (0.1 mol) portion of the potassium salt of theophylline in 100 mL of *trans*-1,4-dichloro-2-butene was heated at 100 °C overnight. After cooling, the mixture was filtered and the filtrate evaporated to dryness. Crystallization of the residue from EtOH gave 18.5 g (70%) of 7-(4-chloro-2-buten-1-yl)theophylline, which was condensed with 1-[3-(phenylthio)propyl]piperazine according to the previously described procedure for 1 to give 23 g (70%) of 32: mp 188 °C.

Table V. Antiallergic and Bronchodilator Activity of Compounds 1-50

no.	antiallergic act. in rat by oral route, at 10 mg/kg <sup>a</sup>		bronchodilator act. in guinea pig by iv route at 250 µg/kg <sup>b</sup>		
	antigen/antibody rcn <sup>f</sup>	cutaneous rcn to histamine <sup>f</sup>	histamine- induced bronchospasm <sup>f</sup>	acetylcholine- induced bronchospasm <sup>f</sup>	serotonin- induced bronchospasm <sup>f</sup>
1	60 <sup>c</sup>	62 <sup>c</sup>	95 <sup>d</sup>	23	69 <sup>d</sup>
2	54 <sup>c</sup>	65 <sup>c</sup>	76 <sup>d</sup>	23	26
3	0	0	70 <sup>d</sup>	15	0
4	48 <sup>c</sup>	28 <sup>c</sup>	88 <sup>d</sup>	30	35
5	28 <sup>c</sup>	21 <sup>c</sup>	0	0	48
6	0	0	0	0	0
7	0	0	30	0	0
8	0	0	25	0	0
9	0	0	60 <sup>d</sup>	25	0
10	ND <sup>e</sup>	ND	53 <sup>d</sup>	0	0
11	59 <sup>c</sup>	56 <sup>c</sup>	76 <sup>d</sup>	0	21
12	94 <sup>c</sup>	78 <sup>c</sup>	87 <sup>d</sup>	23	43
13	19 <sup>c</sup>	24 <sup>c</sup>	5	0	0
14	0	0	27	0	0
15	35 <sup>c</sup>	67 <sup>c</sup>	24	0	0
16	22 <sup>c</sup>	44 <sup>c</sup>	19	0	0
17	0	0	0	0	0
18	ND	ND	0	0	0
19	0	0	47	34	24
20	0	0	3	26	23
21	0	0	88 <sup>d</sup>	0	0
22	0	0	80 <sup>d</sup>	35	26
23	0	29 <sup>c</sup>	89 <sup>d</sup>	0	0
24	0	0	13	34	0
25	0	0	82 <sup>d</sup>	45	22
26	0	0	0	23	23
27	0	0	15	35	24
28	15	24 <sup>c</sup>	0	0	0
29	54 <sup>c</sup>	62 <sup>c</sup>	50 <sup>d</sup>	17	29
30	0	0	9	0	0
31	70 <sup>c</sup>	38 <sup>c</sup>	35	20	36
32	8	4	8	0	20
33	15	10	31	16	21
34	5	6	3	4	0
35	0	0	2	3	0
36	0	4	74 <sup>d</sup>	0	0
37	ND	ND	2	12	50 <sup>d</sup>
38	15	31.5 <sup>c</sup>	56 <sup>d</sup>	10	25
39	76 <sup>c</sup>	30 <sup>c</sup>	10	0	50 <sup>d</sup>
40	43 <sup>c</sup>	10	66 <sup>d</sup>	24	96 <sup>d</sup>
41	23 <sup>c</sup>	0	28	30	47
42	0	0	0	11	8
43	0	0	28	11	3
44	23 <sup>c</sup>	24 <sup>c</sup>	19	14	11
45	8	8	2	0	53 <sup>d</sup>
46	11	4	10	29	42
47	18	12.5	14	18	30
48	17.5 <sup>c</sup>	12	0	27	47
49	0	6.5	13	24	6
50	0	0	25	2	3
ketotifen	64 <sup>c</sup>	90 <sup>c</sup>	10	ND	ND
promethazine	30	58	40	0	0
chlorpheniramine	0	15	62 <sup>d</sup>	ND	0
theophylline	45 <sup>c</sup>	15	56 <sup>d</sup>	72 <sup>c</sup>	59 <sup>d</sup>

<sup>a</sup> Except for theophylline, tested at a dose of 100 mg/kg. <sup>b</sup> Except for theophylline, tested at a dose of 4 mg/kg. <sup>c</sup>  $P < 0.05$  for the difference between the areas of dye diffusion in control and treated animals. <sup>d</sup>  $P < 0.05$  for the difference between the bronchospasm in control and treated animals. <sup>e</sup> ND, not determined. <sup>f</sup> The results are expressed as the percent decrease in allergic reaction or bronchospasm in comparison with the control group ( $n = 10$ ).

Table VI. Kinetics of Protective Effect of Compounds 1 and 2 against Passive Cutaneous Anaphylaxis in the Rat (Dose: 100 mg/kg po)<sup>a</sup>

test	no.	% protection after (h): <sup>b</sup>				
		0.25	1	2	3	4
antigen/antibody rcn	1	98	45	45	0	0
	2	100	98	82	74	44
rcn to exogenous histamine	1	46	23	28	0	0
	2	52	49	33	52	39

<sup>a</sup> The total number of animals tested was 60 for 1 and 50 for 2. <sup>b</sup> Time intervening between compound administration and challenge.

**3,4-Dihydro-1,3-dimethyl-7-[1-[4-[3-(phenylthio)propyl]-piperazin-1-yl]methyl]-1H-purine-2,6-dione Dihydrochloride (30).** To a refluxed solution of 10 g (0.055 mol) of theophylline and 17 g (0.055 mol) of 1-[3-(phenylthio)propyl]piperazine dihydrochloride in 100 mL of EtOH was added portionwise 6.6 g (0.22 mol) of poly(oxyethylene). Heating was continued for 12 h. On cooling, the crystals separated and were recrystallized twice from EtOH/H<sub>2</sub>O to afford 9 g (30%) of 30; mp 225 °C.

**3,7-Dihydro-3,7-dimethyl-1-[3-[4-[3-(phenylthio)propyl]-piperazin-1-yl]-2-hydroxypropyl]-1H-purine-2,6-dione Dihydrochloride (40).** 3,4-Dihydro-3,7-dimethyl-1-(3-chloro-2-hydroxypropyl)-1H-purine-2,6-dione (27.2 g, 0.1 mol) and 1-[3-(phenylthio)propyl]piperazine (23.6 g, 0.1 mol) were refluxed for 24 h in a 50% aqueous alcoholic solution. On completion of the reaction, sodium hydroxide (0.1 mol) was added. The mixture was extracted with methylene chloride and washed with H<sub>2</sub>O, after which the solvent was evaporated off and the residue was recrystallized from EtOH/HCl to give 43.6 (80%) of 40, melting at 226 °C.

**Pharmacological Methods. Passive Cutaneous Anaphylaxis in the Rat.** The method has been described by Bitteau and Hertz.<sup>8</sup> The assays were carried out on male Sprague-Dawley rats (Iffa-Credo, France) weighing 240–250 g. The animals were divided into two groups. The first group received a subcutaneous injection of 1 mg of ovalbumin and 200 mg of aluminum hydroxide together with an intraperitoneal dose of *Haemophilus pertussis* vaccine (0.67 mL containing  $1.5 \times 10^{10}$  cells/mL; Vaxicoq, Institut Pasteur, France). Three weeks after sensitization, blood was withdrawn and centrifuged. The antiserum containing the reactive antibodies was stored at –20 °C. The animals of the second group received an intradermal injection of 0.1 mL of the diluted antiserum (1:10 or 1:200) at two sites on the shaved back. Twenty-four hours later, they were given an oral dose of the test compound (10 mg/kg,  $n = 10$ ) or the vehicle ( $n = 10$ ). After a further 30 min, they received an intravenous injection of ovalbumin and Evans Blue dye (5 mg of ovalbumin and 2.5 mg of Evans Blue in 1 mL of physiological saline), provoking an anaphylactic reaction at the sites of antiserum injection. Simultaneously, histamine (0.1 mL, 150 µg/kg) was injected subcutaneously at two other sites on the back to permit evaluation of the direct antihistaminic effect of the test drugs.

Thirty minutes later, the animals were anesthetized by ether inhalation and sacrificed by decapitation. The skin was removed and the amount of dye leaked at each site of antiserum or histamine injection was evaluated by measuring the area and density of the colored zone. The statistical significance of the difference between the colored areas on treated and control animals (20 sites for each group) was determined by the Student's *t* test. The inhibition percentage is expressed as follows: (mean control area – mean treated area)/mean control area.

**Bronchoconstriction in the Guinea Pig.** The method has been described by Konzett and Rossler<sup>9</sup> and Harichaux et al.<sup>10</sup> The assay was carried out on Dunkin Hartley guinea pigs (Janvier, France) weighing 250–300 g. The animals were anesthetized by an intraperitoneal injection of ethyl carbamate (1 g/kg, 0.2 mL).

The trachea was then exposed and cannulated and the cannula connected to a respiratory pump (constant stroke and airway flow). An electromanometric pressure transducer (Electromed, France), wired to an amplifier (Electromed, France) and polyrecorder (Kipp-Zonen, France), was connected to an airway shunt to measure the airway pressures. Histamine (10 µg/kg), acetylcholine

(30 µg/kg), and serotonin (10 µg/kg) were injected intravenously to evoke increases in pulmonary pressure.

After determination of two control bronchospasms at 5-min intervals, the compounds under test were injected intravenously. The various spasmogenic compounds were then injected repeatedly at 5-min intervals, and the bronchospasm was recorded.

The drugs were administered at a dose of 10.5 µg/kg iv against histamine and 250 µg/kg iv against acetylcholine and serotonin.

The statistical significance of the difference between the percentage bronchospasm in control and treated animals ( $n = 4$  for each group) was determined by the Student's *t* test. The percentage inhibition is expressed as follows: (mean control bronchospasm – mean tested bronchospasm)/mean control bronchospasm.

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**Registry No.** 1, 79730-42-0; 1-2HCl, 79712-52-0; 2, 79712-55-3; 2-2HCl, 79712-53-1; 3, 95250-18-3; 3-2HCl, 79712-25-7; 4, 95250-19-4; 4-2HCl, 79712-26-8; 5, 95250-20-7; 5-2HCl, 79712-27-9; 6, 95250-21-8; 6-2HCl, 79712-28-0; 7, 95250-22-9; 7-2HCl, 79712-29-1; 8, 95250-23-0; 8-2HCl, 79712-30-4; 9, 95250-24-1; 9-2HCl, 95250-25-2; 10, 95250-26-3; 10-2HCl, 95250-27-4; 11, 95250-28-5; 11-2HCl, 79712-33-7; 12, 95250-29-6; (E)-7-(4-chloro-2-buten-1-yl)theophylline, 79712-34-8; 13, 95250-30-9; 13-2HCl, 95250-31-0; 14, 95274-22-9; 14-2HCl, 79712-36-0; 15, 95250-32-1; 15-2HCl, 79712-37-1; 16, 95250-33-2; 16-2HCl, 79712-38-2; 17, 95250-34-3; 17-2HCl, 79712-39-3; 18, 95250-35-4; 18-2HCl, 79712-40-6; 19, 95250-36-5; 19-2HCl, 79712-41-7; 20, 95250-37-6; 20-2HCl, 79712-42-8; 21, 95250-38-7; 21-2HCl, 79712-43-9; 22, 95250-39-8; 22-2HCl, 79712-44-0; 23, 95250-40-1; 23-2HCl, 79712-45-1; 24, 95274-23-0; 24-2HCl, 79712-46-2; 25, 95250-41-2; 25-2HCl, 79712-47-3; 26, 95250-42-3; 26-2HCl, 79712-48-4; 27, 95274-24-1; 27-2HCl, 79712-32-6; 28, 95250-43-4; 28-2HCl, 79712-49-5; 29, 79712-50-8; 29-2C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>, 95250-44-5; 30, 95250-45-6; 30-2HCl, 95250-46-7; 31, 95250-47-8; 31-2HCl, 95250-48-9; 32, 95250-49-0; 32-2HCl, 95250-50-3; 33, 95250-51-4; 33-HCl, 95250-52-5; 34, 95250-53-6; 34-HCl, 95250-54-7; 35, 95250-55-8; 35-HCl, 95250-56-9; 36, 95250-57-0; 36-2HCl, 95250-58-1; 37, 95250-59-2; 37-2HCl, 95250-60-5; 38, 95250-61-6; 38-2HCl, 86591-02-8; 39, 95250-62-7; 39-2HCl, 86591-03-9; 40, 86590-99-0; 40-2HCl, 86591-00-6; 41, 86591-13-1; 41-2HCl, 86591-04-0; 42, 86591-14-2; 42-2HCl, 86591-05-1; 43, 95250-63-8; 43-2HCl, 86591-06-2; 44, 86591-15-3; 44-2HCl, 86591-07-3; 45, 86596-93-2; 45-2HCl, 86591-08-4; 46, 86596-94-3; 46-2HCl, 86591-09-5; 47, 95250-64-9; 47-2HCl, 86591-10-8; 48, 95250-65-0; 48-2HCl, 86591-11-9; 49, 95250-66-1; 49-2HCl, 86591-12-0; 50, 95250-67-2; 50-2HCl, 95250-68-3; a, 65489-00-1; a-2HCl, 95250-77-4; b, 73446-32-9; c, 93043-45-9; d, 95250-69-4; e, 95250-70-7; f, 95250-71-8; g, 95250-72-9; h, 95250-73-0; i, 95250-74-1; j, 95250-75-2; k, 92493-11-3; Cl(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>SC<sub>6</sub>H<sub>5</sub>, 4911-65-3; C<sub>6</sub>H<sub>5</sub>SH, 108-98-5; Cl(CH<sub>2</sub>)<sub>3</sub>Br, 109-70-6; trans-ClCH<sub>2</sub>CH=CHCH<sub>2</sub>Cl, 110-57-6; CH<sub>3</sub>NH(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>SC<sub>6</sub>H<sub>5</sub>, 95250-80-9; piperazine, 110-85-0; 7-(3-chloropropyl)theophylline, 2770-66-3; 7-(2,3-epoxypropyl)theophylline, 23146-07-8; 7-(3-oxobutyl)theophylline, 10226-65-0; 3,7-dihydro-1,3-dimethyl-7[5-[4-[3-(phenylthio)propyl]piperazin-1-yl]-3-oxopentyl]-1H-purine-2,6-dione, 95250-81-0; theophylline potassium salt, 57533-87-6; (E)-7-(4-chloro-2-buten-1-yl)theophylline, 95250-76-3; theophylline, 58-55-9; 3,7-dihydro-3,7-dimethyl-1-(3-chloro-2-hydroxypropyl)-1H-purine-2,6-dione, 10579-75-6; 7-(2-chloroethyl)theophylline, 5878-61-5; 7-(6-chlorohexyl)theophylline, 95250-78-5; 1-[3-(phenylthio)propyl]homopiperazine, 95250-79-6; 7-theophyllineacetyl chloride, 40421-16-7; 1-(3-chloropropyl)theobromine, 74409-52-2; 1-(2,3-epoxypropyl)theobromine, 25565-97-3.

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