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Some new 7-aryloxyalkyltheophyllines as bronchodilators

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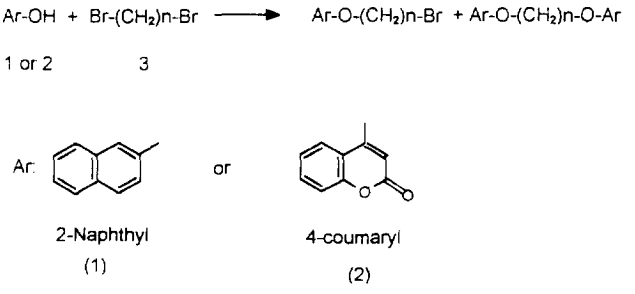
Introduction

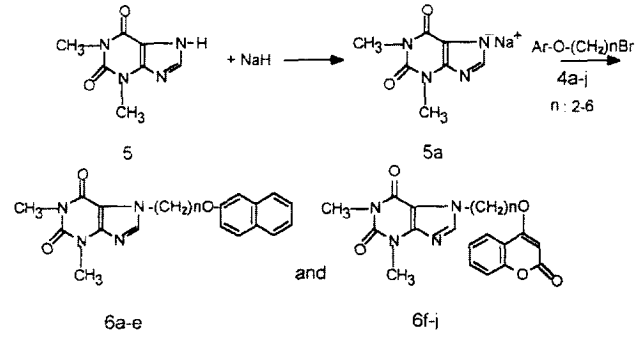
1,3-Dimethylxanthines represented by theophylline-(1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione) have been used in asthma therapy since 1921 [1]. The bronchodilatory action of theophylline is attributable to the inhibition of c-AMP phosphodiesterase activity [2, 3]. Since theophylline has some adverse reactions such as tachycardia, stimulates the central nervous system and has a very narrow therapeutic range [4, 5], the synthesis and pharmacological evaluation of many new theophylline derivatives with several groups linked to the 7 position have been reported in the literature [6–15]. Among these, proxyphylline (7-(2-hydroxypropyl)theophylline) [11], dyphylline (7-(2,3-dihydroxypropyl)theophylline) [12], etofylline (7-(2-hydroxyethyl)theophylline) [13] and doxofylline (7-(1,3-dioxolan-2-ylmethyl)theophylline) [14, 15] are in therapeutic use. None of these compounds, however, have replaced theophylline as a useful therapeutic drug for asthma. Thus, this situation prompted us to synthesize various 7-[(2-naphthyloxy)alkyl]theophylline and 7-[(4-coumaryloxy)alkyl]theophylline derivatives.

Chemistry

(2-Naphthyloxy)alkyl (**4a–e**) and (4-coumaryloxy)-alkyl bromides (**4f–j**) were prepared by using 2-naphthol, 4-hydroxycoumarin and corresponding dibromoalkanes (scheme 1). Theophylline (**5**) was treated with NaH in dry DMF to produce the sodium salt of **5** (**5a**) which was then refluxed at 60 °C with those aryloxyalkyl halides in dry DMF to obtain the target compounds (**6a–j**) (scheme 2).



Scheme 1. Synthesis of aryloxyalkyl halides.



Scheme 2. Synthesis of 7-substituted theophyllines.

Pharmacology

The bronchodilator activities of the target compounds were investigated in tracheas of male and female guinea pigs in isolated organ baths. The contractions,

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induced by acetylcholine and histamine were recorded after the samples had been incubated with various concentrations of the target compounds. Aminophylline was used as a reference substance for experiments involving acetylcholine-induced contractions.

Results and discussion

We synthesized a new series of theophylline derivatives having alkyl side chains of various lengths carrying two different aromatic rings at the 7 position of the theophylline using the procedure outlined in schemes 1 and 2. The starting compounds (**4a–j**) were prepared from 2-naphthol or 4-hydroxycoumarin and corresponding dihaloalkanes in the presence of KOH in absolute ethanol according to the general procedure A. Various other procedures are reported in the literature for the preparation of these compounds [16–18]. ω-Bis-2-naphthyloxy and ω-bis-4-coumaryloxyalkanes were the side products of the reaction (scheme 1). The physical properties and the yields of the compounds are summarized in table I. The procedure used for introduction of the alkyl groups at the 7 position of the theophylline is a modified version of one of the several methods found in the literature [19]. The compounds bearing the (2-naphthyloxy)alkyl (**6a–e**) and 4-(coumaryloxy)alkyl (**6f–j**) moieties at the 7 position of theophylline were prepared by reacting theophylline sodium with corresponding aryloxyalkyl bromides in dry DMF at 60 °C for 3 h. Bronchodilator activity (in vitro) of 7-(naphthyloxy)alkyl and 7-(coumaryloxy)alkyl theophylline derivatives (**6a–j**) was examined by inhibition of acetylcholine and histamine-induced contractions in trachea isolated from guinea pigs. The pharmacological activity results of these compounds are summarized in table II.

Examination of the data in table II reveals that the compounds bearing (4-coumaryloxy)alkyl groups at the 7 position of the theophylline (**6f–j**) were more potent against bronchospasm induced by acetylcholine and histamine in guinea-pig trachea. It seems that replacement of the naphthyl moiety by coumaryl ring increases the bronchodilator activity. On the other hand, the substitution at the 7 position of theophylline with different alkyl chains did not change the bronchodilator activity. None of the compounds described above were more active than aminophylline.

Conclusion

In the light of these results, it is difficult to assess the relationship between the side chain length and activity, but it seems that compounds **6f–j** bearing a coumaryl ring at the side chain show better activity than those with a naphthyl ring at the side chain.

Table I. Physical and chemical properties of the compounds (**4a–j**).

		Ar-O-$(CH_2)_n$-X				
Compound	*Ar*	*X*	*n*	*Yield (%)*	*Mp (°C)*	*Crystallization solvent*
4a	2-Naphthyl	Cl	2	60.75	81–83	Ethanol/water
4b	2-Naphthyl	Br	3	65.85	54–56	Methanol
4c	2-Naphthyl	Br	4	55.45	44–46	Methanol
4d	2-Naphthyl	Br	5	40.68	Liquid	[a]
4e	2-Naphthyl	Br	6	42.50	40	Methanol
4f	4-Coumaryl	Br	2	60.22	168	Methanol/chloroform
4g	4-Coumaryl	Br	3	60.42	91	Methanol
4h	4-Coumaryl	Br	4	52.35	97	Methanol
4i	4-Coumaryl	Br	5	58.49	82–86	Methanol
4j	4-Coumaryl	Br	6	45.35	101	Methanol

[a]Compound **4d** was purified by preparative chromatography using Kieselgel $HF_{254-366}$ (Merck) 0.5 mm thick plates and *n*-hexane/ethyl acetate (20:1) solvent system (R_f = 0.88).

Table II. Bronchodilator activity results of the compounds **6a–j**.

Compound	*Concentration (mol/L)*	*Relaxation (%) Acetylcholine-induced spasm*	*Concentration (mol/L)*	*Relaxation (%) Histamine-induced spasm*
6a	10^{-6}	0	10^{-5}	9.25 ± 2.98
	10^{-5}	0	10^{-4}	29.33 ± 4.49
	10^{-4}	18.33 ± 4.51		
6b	10^{-6}	0	10^{-4}	0
	10^{-5}	6.67 ± 2.21	10^{-3}	0
	10^{-4}	15.00 ± 1.15		
6c	10^{-6}	0	10^{-4}	19.8 ± 1.40
	10^{-5}	0	5×10^{-4}	39.0 ± 1.41
	10^{-4}	8.00 ± 1.90		
6d	10^{-6}	0	5×10^{-5}	6.17 ± 3.37
	10^{-5}	0	5×10^{-4}	ND
	10^{-4}	16.00 ± 4.33		
6e	10^{-6}	0	10^{-5}	0
	10^{-5}	0	10^{-4}	17.33 ± 8.05
	10^{-4}	4.00 ± 0.66		
6f	10^{-6}	5.15 ± 2.49	10^{-5}	0
	10^{-5}	5.00 ± 2.10	10^{-4}	62.0 ± 11.62
	10^{-4}	7.67 ± 2.93		
6g	10^{-6}	0	10^{-5}	2.25 ± 1.46
	10^{-5}	0	10^{-4}	48.51 ± 6.47
	10^{-4}	3.75 ± 1.97		
6h	10^{-6}	5.50 ± 3.28	10^{-4}	12.5 ± 4.37
	10^{-5}	8.13 ± 1.58	5×10^{-4}	51.75 ± 12.66
	10^{-4}	32.60 ± 3.38		
6i	10^{-6}	0	10^{-4}	5.17 ± 2.65
	10^{-5}	0	10^{-3}	25.8 ± 2.31
	10^{-4}	21.33 ± 2.95		
6j	10^{-6}	5.67 ± 1.87	10^{-4}	27.25 ± 7.36
	10^{-5}	5.76 ± 1.65	10^{-3}	35.0 ± 15.5
	10^{-4}	12.75 ± 2.25		
Aminophylline	10^{-8}	0		
	10^{-7}	15.50 ± 6.44		
	10^{-6}	17.00 ± 7.49		
	10^{-5}	42.15 ± 5.22		
	10^{-4}	100 ± 0		

Experimental protocols

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are not corrected. TLC was performed on Merck $F_{254\text{-}366}$. IR spectra (KBr) were recorded on a Perkin-Elmer FT IR 1720X spectrophotometer . ^{1}H-NMR spectra were recorded on Bruker 80 and 400 MHz FT NMR spectrometer in $CDCl_3$ and DMSO-d_6. Chemical shifts are given in terms of ppm scales. TLC was performed on Kieselgel 60 $F_{254\text{-}366}$ (0.20 mm) (Merck) sheets with ethyl acetate/*n*-hexane (20:1) or benzene/methanol (95:5) and detected at UV (254 nm). Microanalyses were performed by The Scientific and Technical Research Council of Turkey, Instrumental Analysis Laboratories, Ankara, Turkey.

Aryloxyalkyl halides. General procedure A

2-Naphthol (0.02 mol; 2.88 g) or 4-hydroxycoumarin (0.02 mol; 3.25 g) and 0.02 mol KOH (1.44 g) were dissolved in absolute ethanol. The mixture was added to a mixture of 0.03 mol of the

corresponding dihaloalkane in absolute ethanol over a period of 40 min and the mixture was refluxed for 2 h. A white precipitate resulted. The solvent was removed under pressure. The precipitate was dissolved in 10 mL water and extracted with 10 mL chloroform three times. Organic layer was collected and dried on anhydrous Na_2SO_4. Removal of organic solvent yielded the corresponding aryloxyalkyl halides (see table I).

7-(2-Naphthyloxy)alkyl- and 7-[(2-oxo-2H-1-benzopyran-4-yl)-oxyalkyl-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-diones. General procedure B

NaH 60% (0.001 mol; 40 mg) was dissolved in 10 mL DMF and 0.001 mol (0.180 g) of theophylline was added slowly to this suspension. A mixture of the corresponding alkoxy halide with 10 mL DMF was then added. The mixture was refluxed for 5 h at 60 °C. This reaction mixture was decanted into an ice-water solution. The precipitate was filtered and appropriate crystallization solvents were used for purification.

7-[2-(2-Naphthyloxy)]ethyl-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione ***6a***
Starting with 0.206 g of 2-(naphthyloxy)ethyl chloride and 0.180 g of theophylline, **6a** was synthesized by general procedure B. Yield: 70.58%, mp 164–166 °C. IR (KBr) cm^{-1}: 3100, 2918, 1702, 1655, 1259, 1032. ^{1}H-NMR ($CDCl_3$): 3.35 (3H, s, NCH_3), 3.50 (3H, s, NCH_3), 4.35 (2H, t (J = 5.5 Hz), CH_2N), 4.65 (2H, t (J = 5.5 Hz), CH_2O), 7.05–7.65 (8H, m, ArH, theo C^8-H). Anal $C_{19}H_{18}N_4O_3$ (C, H, N); calc: C 65.12, H 5.18, N 15.99; found: C 65.16, H 5.16, N 15.76.

7-[3-(2-Naphthyloxy)]propyl-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione ***6b***
Starting with 0.265 g of 3-(2-naphthyloxy)propyl bromide and 0.180 g of theophylline, **6b** was synthesized by general procedure B. Yield: 65.36%, mp 115–118 °C. IR (KBr) cm^{-1}: 3100, 2900, 1703, 1650, 1255, 1028. ^{1}H-NMR (DMSO-d_6): 2.55 (2H, m, CH_2), 3.15 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 4.10 (2H, t (J = 6 Hz), CH_2N), 4.50 (2H, t (J = 6 Hz), -CH_2O), 7.00–7.85 (7H, m, ArH), 8.10 (1H, s, theo C^8-H). Anal $C_{20}H_{20}N_4O_3 \cdot 1/2H_2O$ (C, H, N); calc: C 64.34, H 5.63, N 15.01; found: C 64.24, H 5.77, N 14.90.

7-[4-(2-Naphthyloxy)]butyl-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione ***6c***
Starting with 0.279 g of 4-(2-naphthyloxy)butyl bromide and 0.180 g of theophylline, **6b** was synthesized by general procedure B. Yield: 64.52%, mp 122 °C. IR (KBr) cm^{-1}: 3103, 2932, 1700, 1669, 1263, 1029. ^{1}H-NMR ($CDCl_3$): 1.65–2.20 (4H, m, $(CH_2)_2$, 3.10 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 4.00 (2H, t (J = 5.2 Hz), -CH_2N), 4.30 (2H, t (J = 5.2 Hz), -CH_2O), 6.90–7.60 (8H, m, ArH, theo C^8-H). Anal $C_{21}H_{22}N_4O_3$ (C, H, N); calc: C 66.65, H 5.86, N 14.81; found: C 67.12, H 5.92, N 14.80.

7-[5-(2-Naphthyloxy)]pentyl-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione ***6d***
Starting with 0.293 g of 5-(2-naphthyloxy)pentyl bromide and 0.180 g of theophylline, **6d** was synthesized by general procedure B. Yield: 70.84%, mp 221–224 °C. IR (KBr) cm^{-1}: 3100, 2953, 1702, 1656, 1289, 1029. ^{1}H-NMR ($CDCl_3$): 1.65–2.10 (6H, m, $(CH_2)_3$, 3.35 (3H, s, NCH_3), 3.55 (3H, s, NCH_3), 4.10–4.35 (4H, m, -CH_2N-, -CH_2O), 7.10–7.50 (8H, m, ArH, theo C^8-H). Anal $C_{22}H_{24}N_4O_3$ (C, H, N); calc: C 67.34, H 6.12, N 14.28; found: C 67.63, H 6.19, N 13.91.

7-[6-(2-Naphthyloxy)]hexyl-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione ***6e***
Starting with 0.307 g of 6-(2-naphthyloxy)hexyl bromide and 0.180 g of theophylline, **6e** was synthesized by general procedure B. Yield: 68.52%, mp 224–227 °C. IR (KBr) cm^{-1}: 3114, 2952, 1702, 1656, 1292, 1028. ^{1}H-NMR ($CDCl_3$): 1.50–2.05 (8H, m, $(CH_2)_4$), 3.35 (3H, s, NCH_3), 3.52 (3H, s, NCH_3), 3.95–4.30 (4H, m, -CH_2N-, -CH_2O), 7.00–7.75 (7H, m, ArH), 8.00 (1H, s, theo C^8-H). Anal $C_{23}H_{26}N_4O_3$ (C, H, N); calc: C 67.96, H 6.45, N 13.78; found: C 67.94, H 6.80, N 13.73.

7-[2-(2-Oxo-2H-1-benzopyran-4-yl)oxy]ethyl-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione ***6f***
Starting with 0.528 g of 2-[(2-oxo-2*H*-1-benzopyran-4-yl)-oxy]ethyl bromide and 0.180 g of theophylline, **6f** was synthesized by general procedure B. Yield: 40.75%, mp 242– 244 °C. IR (KBr) cm^{-1}: 3100, 2950, 1733, 1654, 1609, 1259, 1014. ^{1}H-NMR ($CDCl_3$): 3.20 (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 4.00–4.20 (4H, m, -CH_2N-, -CH_2O), 5.80 (1H, s, Ar C^3-H), 7.20–8.00 (5H, m, ArH, theo C^8-H). Anal $C_{18}H_{16}N_4O_5$ (C, H, N); calc: C 58.69, H 4.34, N 15.21; found: C 58.36, H 4.59, N 15.76.

7-[3-(2-Oxo-2H-1-benzopyran-4-yl)oxy]propyl-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione ***6g***
Starting with 0.542 g of 3-[(2-oxo-2*H*-1-benzopyran-4-yl)-oxy]propyl bromide and 0.180 g of theophylline, **6g** was synthesized by general procedure B. Yield: 50.63%, mp 248–249 °C. IR (KBr) cm^{-1}: 3083, 2952, 1699, 1656, 1626, 1259, 1027. ^{1}H-NMR (DMSO-d_6): 2.20 (2H, m, -CH_2), 2.95 (3H, s, NCH_3), 3.15 (3H, s, NCH_3), 3.85 (2H, t (J = 4.6 Hz), -CH_2N), 4.25 (2H, t (J = 4.6 Hz), -CH_2O), 5.80 (1H, s, Ar C^3-H) 6.85–7.40 (5H, m, ArH, theo C^8-H). Anal $C_{19}H_{18}N_4O_5$ (C, H, N); calc: C 59.68, H 4.71, N 14.65; found: C 59.06, H 4.43, N 14.81.

7-[4-(2-Oxo-2H-1-benzopyran-4-yl)oxy]butyl-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione ***6h***
Starting with 0.556 g of 4-[(2-oxo-2*H*-1-benzopyran-4-yl)-oxy]butyl bromide and 0.180 g of theophylline, **6h** was synthesized by general procedure B. Yield: 55.48%, mp 188 °C. IR (KBr) cm^{-1}: 3092, 2956, 1699, 1654, 1622, 1271, 1032. ^{1}H-NMR (DMSO-d_6): 1.60–2.05 (4H, m, -$(CH_2)_2$), 3.15 (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 4.15 (2H, t (J = 5.2 Hz), -CH_2N), 4.40 (2H, t (J = 5.2 Hz), -CH_2O), 5.80 (1H, s, Ar C^3-H), 7.20–7.80 (4H, m, ArH), 8.10 (1H, s, theo C^8-H). Anal $C_{20}H_{20}N_4O_5$ (C, H, N); calc: C 60.58, H 5.09, N 14.14; found: C 60.72, H 5.27, N 13.97.

7-[5-(2-Oxo-2H-1-benzopyran-4-yl)oxy]pentyl-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione ***6i***
Starting with 0.570 g of 5-[(2-oxo-2*H*-1-benzopyran-4-yl)-oxy]pentyl bromide and 0.180 g of theophylline, **6i** was synthesized by general procedure B. Yield: 55.48%, mp 195– 197 °C. IR (KBr) cm^{-1}: 3100, 2950, 1703, 1658, 1622, 1237, 1029. ^{1}H-NMR (DMSO-d_6): 1.20–1.90 (6H, m, -$(CH_2)_3$), 3.40 (3H, s, NCH_3), 3.60 (3H, s, NCH_3), 4.05–4.40 (4H, m, -CH_2N, -CH_2O), 5.65 (1H, s, Ar C^3-H), 7.20–7.70 (5H, m, ArH, theo C^8-H). Anal $C_{21}H_{22}N_2O_5$ (C, H, N); calc: C 61.45, H 5.40, N 13.65; found: C 61.38, H 5.35, N 13.19.

7-[6-(2-Oxo-2H-1-benzopyran-4-yl)oxy]hexyl-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione ***6j***
Starting with 0.548 g of 6-[(2-oxo-2*H*-1-benzopyran-4-yl)-oxy]hexyl bromide and 0.180 g of theophylline, **6j** was synthe-

sized by general procedure B. Yield: 63.87%, mp 175 °C. IR (KBr) cm^{-1}: 3100, 2945, 1703, 1658, 1623, 1274, 1029. ^{1}H-NMR ($CDCl_3$): 1.40–2.00 (8H, m, $-(CH_2)_4$), 3.40 (3H, s, NCH_3), 3.55 (3H, s, NCH_3), 4.30 (2H, t (J = 5.2 Hz), NCH_2), 4.50 (2H, t (J = 5.2 Hz), $-CH_2O$), 5.70 (1H, s, Ar C^3-H), 7.15–7.50 (4H, m, ArH), 7.8 (1H, s, theo C^8-H). Anal $C_{22}H_{24}N_4O_5$ (C, H, N); calc: C 62.24, H 5.70, N 13.21; found: C 62.47, H 5.94, N 13.48.

Pharmacology

Male and female guinea pigs were used in the present study. After the animals were sacrificed by cervical dislocation, their trachea was immediately removed and tracheal strips were mounted vertically in a 10 mL organ bath containing Krebs–Henseleit solution of the following composition in mmol/L: NaCl: 118.3; KCl: 4.73; $CaCl_2$: 2.54; NaH_2PO4: 1.19; $MgSO_4$: 1.18; $NaHCO_3$: 26.2; glucose: 11.09. The bath contents were maintained at 37 °C and aerated by 95% O_2 and 5% CO_2. A tension of 2 g was applied and isometric recording was done using an isometric transducer (TB-65IT; Nihon-Kohden Recorder System). All compounds were diluted in dimethylsulfoxide and added to the organ bath in volumes of 0.1 mL. The preparations were allowed to equilibrate for at least 60 min, with regular washes every 15 min.

Contractions induced by 10^{-5} M acetylcholine were recorded after the samples were incubated with various concentrations of the compounds or aminophylline for 5 min.

Histamine spasm in guinea-pig trachea was induced following the same procedure in the literature [8]. The addition of the compounds (**6a–j**) in these experiments where the initial spasm was caused by histamine was performed in the 5 min after the addition of histamine. The results were compared to those of 10^{-5} M acetylcholine and 10^{-4} M histamine with the samples incubated with 0.1 mL dimethylsulfoxide. The concentration–response curves for acetylcholine and histamine were obtained. The data were expressed as mean ± SE (table II).

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