New Bronchodilators. II.[1] 3*H*-Imidazo[4,5-*c*]quinolin-4(5*H*)-ones

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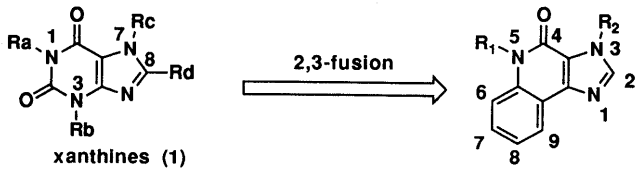
A series of novel 3-substituted imidazo[4,5-*c*]quinolin-4(5*H*)-ones (2a—w) was prepared by the reaction of imidazo[4,5-*c*]quinolin-4(5*H*)-ones (6) with several electrophiles under basic conditions. The bronchodilatory activity of these compounds was evaluated on the basis of their protective effects against antigen-induced contraction (the Schultz–Dale reaction) of guinea-pig trachea (*in vitro*) and antigen inhalation-induced bronchospasm in passively sensitized guinea-pigs (*in vivo*). Although correlations between *in vitro* and *in vivo* activities were not clear, short alkyl chains such as the methyl and ethyl groups at the 3-position were important for potent activity, especially *in vivo*. Substituents at the 5-position were more tolerant of the activity than those at the 3-position. 5-Ethyl-3-methyl-3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one (2l) exhibits the most potent bronchodilatory activity among our tested compounds and is at least 5-fold more active than theophylline *in vivo*.

Keywords 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one; xanthine; theophylline; bronchodilator; structure–activity relationship

Despite the appearance of new classes of antiasthmatic agents, theophylline (**1a**) has been used extensively in the treatment of asthma.[2] However, like other xanthines, theophylline has a narrow optimum therapeutic range due to its side effects such as central nervous system (CNS) stimulation and cardiotonic activity.[3,4] A variety of such pharmacological activities of xanthines (**1**) are proposed[5] to be based on many biochemical mechanisms such as adenosine receptor antagonism, inhibition of phosphodiesterase (PDE), inhibition of regulatory protein, Gi,[6] and so on. Therefore, a major goal in the development of new xanthine derivatives depends on the feasibility of the separation of their bronchodilatory activity from other activities. Much effort has been made with regard to the modification of the substituents at the 7-position of the xanthine.[7] Though this modification has allowed many groups to develop compounds such as proxyphylline (**1b**),[8] bamiphylline (**1c**),[9] diphylline (**1d**),[10] doxophylline (**1e**),[11] and tazifylline (**1f**),[7b] which were reported to possess more potent activity and less toxicity than theophylline in animal models, none of them presents any greater clinical usefulness than theophylline. These situations have prompted us to investigate a new approach, which involves modification of the xanthine skeleton itself.

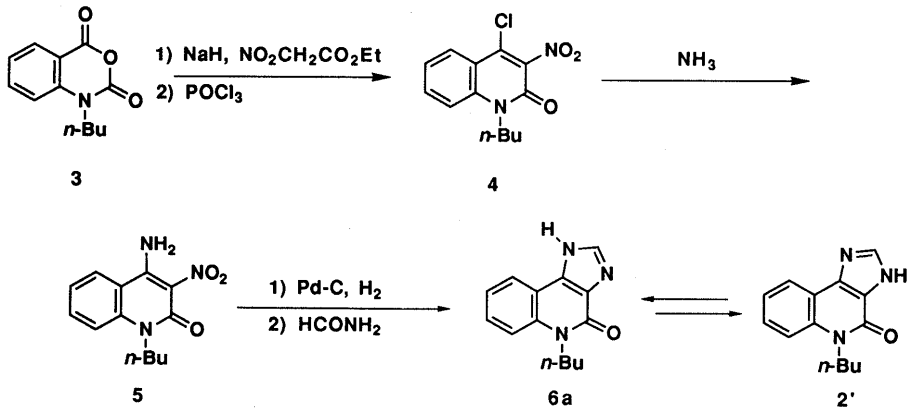
The previous study[3] with respect to xanthine derivatives suggests that the introduction of a lipophilic moiety into a xanthine skeleton may enhance one of its activities to some extent. Enprofylline (**1g**), which is a weak adenosine receptor antagonist, possesses more potent bronchodilatory activity than theophylline.[12] On the basis of this knowledge, new nonxanthine compounds, 3*H*-imidazo[4,5-*c*]quinolin-4(5-



xanthines (1) 2

theophylline (1a)
$R^a=R^b=CH_3$, $R^c=R^d=H$
proxyphylline (1b)
$R^a=R^b=CH_3$, $R^c=CH_2CH(OH)CH_3$, $R^d=H$
bamiphylline (1c)
$R^a=R^b=CH_3$, $R^c=CH_2CH_2N(C_2H_5)CH_2CH_2OH$, $R^d=CH_2C_6H_5$
diphylline (1d)
$R^a=R^b=CH_3$, $R^c=CH_2CH(OH)CH_2OH$, $R^d=H$
doxophylline (1e)
$R^a=R^b=CH_3$, R^c=1,3-dioxolan-2-ylmethyl, $R^d=H$
tazifylline (1f)
$R^a=R^b=CH_3$,
$R^c=CH_2CH(OH)CH_2N\langle\rangle N(CH_2)_3SC_6H_5$
$R^d=H$
enprofylline (1g)
$R^a=R^c=R^d=H$, $R^b=n\text{-}C_3H_7$

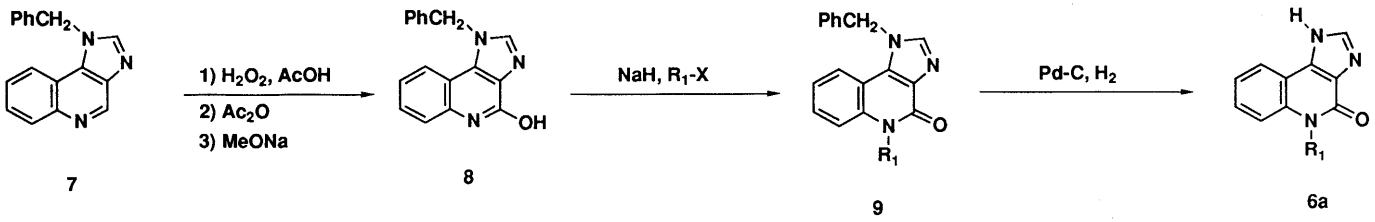
Chart 1



3 4 5 6a 2'

Chart 2

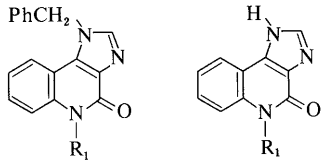
H)-one derivatives (**2**) have been designed.[13] This tricyclic heterocycle can be regarded as a fusion compound of a benzene ring to the bond between the 2- and 3-positions of 7-substituted xanthine. This modification increases the lipophilicity around the 3-position of xanthine and might result in more potent bronchodilatory activity than that of



7 8 9 6a

Chart 3

TABLE I. Physical Properties of **9** and **6**



9 **6**

Compd. No.	R_1	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
9a	CH_3	77	263—266 ($CHCl_3$–iso-Pr_2O)	$C_{18}H_{15}N_3O \cdot 2/5H_2O$	72.91 (73.00	5.37 5.42	14.17 13.88)
9b	C_2H_5	62	168—170 (EtOH–H_2O)	$C_{19}H_{17}N_3O$	75.22 (75.02	5.64 5.55	13.85 13.97)
9c	*n*-C_3H_7	70	267—273 (EtOH–H_2O)	$C_{20}H_{19}N_3O$	75.68 (75.60	6.03 5.84	13.23 13.17)
9d	iso-C_4H_9	60	>300 (EtOH–H_2O)	$C_{21}H_{21}N_3O$	76.11 (76.00	6.39 6.12	12.68 12.44)
9e	*n*-C_6H_{13}	72	189—195 ($CHCl_3$–iso-Pr_2O)	$C_{23}H_{25}N_3O$	76.85 (76.68	7.01 7.31	11.69 11.43)
6b	CH_3	66	279—282 (DMF–H_2O)	$C_{11}H_9N_3O$	66.32 (66.17	4.55 4.53	21.09 20.01)
6c	C_2H_5	93	>300 (iso-PrOH)	$C_{12}H_{11}N_3O$	67.59 (67.62	5.20 5.44	19.71 19.67)
6d	*n*-C_3H_7	94	>300 (EtOH–H_2O)	$C_{13}H_{13}N_3O$	68.71 (68.65	5.77 5.75	18.49 18.56)
6e	iso-C_4H_9	94	296—300 (EtOH–H_2O)	$C_{14}H_{15}N_3O$	69.69 (69.32	6.27 6.34	17.41 17.36)
6f	*n*-C_6H_{13}	46	>300 ($CHCl_3$–iso-Pr_2O)	$C_{16}H_{19}N_3O$	71.35 (71.68	7.11 7.12	15.60 15.78)

TABLE II. Spectral Data of **9** and **6**

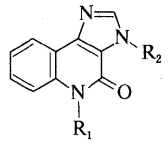
Compd. No.	IR (KBr) ν (cm^{-1})	MS *m/z* (M^+)	^{1}H-NMR	
			Solvent	δ (J=Hz)
9b	1651, 1568	303	$CDCl_3$	1.39 (3H, t, J=7), 4.49 (2H, q, J=7), 5.69 (2H, s), 6.91—7.52 (8H, m), 7.70 (1H, d, J=8), 7.81 (1H, s)
9c	1650, 1572	317	$CDCl_3$	1.06 (3H, d, J=7), 1.62—2.03 (2H, m), 4.40 (2H, t, J=7), 5.69 (2H, s), 6.97—7.52 (8H, m), 7.71 (1H, d, J=8), 7.82 (1H, s)
9d		331	$CDCl_3$	1.01 (6H, d, J=7), 1.99—2.45 (1H, m), 4.32 (2H, d, J=7), 5.69 (2H, s), 6.83—7.52 (8H, m), 7.70 (1H, d, J=8), 7.81 (1H, s)
9e	3802, 1652	359	DMSO-d_6	0.86 (3H, t, J=7), 1.27—1.62 (8H, m), 4.33 (2H, t, J=7), 5.90 (2H, s), 7.10—7.37 (6H, m), 7.49 (1H, t, J=8), 7.61 (1H, d, J=8), 7.85 (1H, d, J=8), 8.33 (1H, s)
6c	1656, 1509	213	DMSO-d_6	1.27 (3H, t, J=7), 4.42 (2H, q, J=7), 7.07—7.72 (4H, m), 7.93—8.36 (2H, m)
6d	1650, 1575	227	DMSO-d_6	0.97 (3H, t, J=7), 1.45—1.99 (2H, m), 4.30 (2H, t, J=7), 7.14—7.90 (4H, m), 7.90—8.32 (2H, m)
6e	1663, 1568	241	DMSO-d_6	0.92 (6H, d, J=7), 1.95—2.36 (1H, m), 4.27 (2H, d, J=7), 7.02—7.75 (4H, m), 7.95—8.45 (2H, m)
6f	3676, 2346, 1660	269	DMSO-d_6	0.87 (3H, t, J=7), 1.28—1.64 (8H, m), 4.35 (2H, t, J=7), 7.30—7.62 (2H, m), 8.00 (1H, d, J=8), 8.16 (1H, d, J=8), 8.24 (1H, s)

theophylline.

Now we describe here the convenient synthesis and bronchodilatory activity of this new tricyclic heterocycle, 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones (**2**).

Chemistry Compounds **6** were prepared according to the two methods shown in Charts 2 and 3. The synthetic route in Chart 2 is suitable for large scale preparation. 1-Butylisatoic anhydride (**3**)[14] was prepared from isatoic anhydride. According to the procedure reported by Coppola,[15,16] **3** was converted to the quinolone (**4**) by reaction with anions of ethyl nitroacetate, and by chlorination using phosphorus oxychloride. Amination of **4** with aqueous ammonia occurred smoothly to afford 3-aminoquinolone (**5**) in a high yield. Reduction of the nitro group in **5** followed by heating with formamide at 150 °C provided imidazo[4,5-*c*]quinolin-4(5*H*)-one (**6a**) which is chemically equivalent to its tautomer (**2'**) as shown in Chart 2. The synthesis of **6**, possessing a variety of substituents

TABLE III. Physical Properties of 3*H*-Imidazo[4,5-*c*]quinolin-4(5*H*)-ones



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Compd. No.	R_1	R_2	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
2a	*n*-C_4H_9	CH_3	75	151—153 (MeOH–H_2O)	$C_{15}H_{17}N_3O$	70.56 (70.76)	6.71 7.00	16.46 16.54)
2b·HCl	*n*-C_4H_9	C_2H_5	84	215—218[a]	$C_{16}H_{19}N_3O$·HCl	62.84 (62.84)	6.59 6.80	13.74 13.64)
2c·HCl	*n*-C_4H_9	*n*-C_3H_7	80	211—214[a]	$C_{17}H_{21}N_3O$·HCl	63.84 (63.83)	6.93 7.13	13.13 13.17)
2d·HCl	*n*-C_4H_9	iso-C_3H_7	68	204—205[a]	$C_{17}H_{21}N_3O$·HCl	63.84 (63.45)	6.93 7.22	13.13 12.85)
2e·HCl	*n*-C_4H_9	*n*-C_4H_9	78	199—201[a]	$C_{18}H_{23}N_3O$·HCl	64.76 (64.89)	7.25 7.47	12.59 12.70)
2f	*n*-C_4H_9	$CH_2C_6H_5$	46	116—117 ($CHCl_3$–hexane)	$C_{21}H_{21}N_3O$	76.11 (76.13)	6.38 6.22	12.69 12.46)
2g	*n*-C_4H_9	$CH_2CH_2CH_2OH$	37	120—121 ($CHCl_3$–hexane)	$C_{17}H_{21}N_3O_2$	68.21 (67.82)	7.07 7.24	14.04 14.01)
2h	*n*-C_4H_9	CH_2COCH_3	65	140—142 (MeOH–H_2O)	$C_{17}H_{19}N_3O_2$	68.67 (68.81)	6.44 6.73	14.13 13.96)
2i	CH_3	CH_3	48	244—246 ($CHCl_3$–hexane)	$C_{12}H_{11}N_3O$	67.59 (67.89)	5.20 5.16	19.71 19.70)
2j	CH_3	C_2H_5	51	163—164 ($CHCl_3$–hexane)	$C_{13}H_{13}N_3O$	68.71 (68.71)	5.77 5.69	18.49 18.11)
2k	CH_3	iso-C_3H_7	38	95—97 ($CHCl_3$–hexane)	$C_{14}H_{15}N_3O$	69.69 (69.75)	6.27 6.35	17.41 17.27)
2l	C_2H_5	CH_3	72	137—140 ($CHCl_3$–hexane)	$C_{13}H_{13}N_3O$	68.71 (68.70)	5.77 5.93	18.49 18.64)
2m	C_2H_5	C_2H_5	70	101—102 ($CHCl_3$–hexane)	$C_{14}H_{15}N_3O$	69.69 (69.79)	6.27 6.42	17.41 17.11)
2n	C_2H_5	iso-C_3H_7	64	102—103 ($CHCl_3$–hexane)	$C_{15}H_{17}N_3O$	70.56 (70.39)	6.71 6.70	16.45 16.32)
2o	*n*-C_3H_7	CH_3	65	124—126 ($CHCl_3$–hexane)	$C_{14}H_{15}N_3O$	65.69 (69.57)	6.27 6.44	17.41 17.42)
2p	iso-C_4H_9	CH_3	95	137—140 ($CHCl_3$–hexane)	$C_{15}H_{17}N_3O$	70.56 (70.40)	6.71 6.90	16.45 16.62)
2q	iso-C_4H_9	C_2H_5	52	118—119 ($CHCl_3$–hexane)	$C_{16}H_{19}N_3O$	71.35 (71.44)	7.11 7.17	15.60 15.28)
2r	iso-C_4H_9	iso-C_3H_7	52	108—109 ($CHCl_3$–hexane)	$C_{17}H_{21}N_3O$	72.06 (71.94)	7.47 7.65	14.83 14.65)
2s·HCl	*n*-C_6H_{13}	CH_3	62	238—242[a]	$C_{17}H_{21}N_3O$·HCl	63.84 (63.83)	6.93 7.19	13.14 13.07)
2t·HCl	*n*-C_6H_{13}	C_2H_5	75	169—172[a]	$C_{18}H_{23}N_3O$·HCl	64.76 (64.63)	7.25 7.47	12.59 12.51)
2u	*n*-C_6H_{13}	iso-C_3H_7	68	60—62 ($CHCl_3$–hexane)	$C_{19}H_{25}N_3O$	73.28 (73.21)	8.09 8.32	13.49 13.51)
2v	*n*-C_4H_9	CH_2CO_2*tert*-C_4H_9	57	Crude[b]				
2w	*n*-C_4H_9	CH_2CO_2H	77	215—218 (DMF–iso-PrOH)	$C_{13}H_{11}N_3O_3$		257.0801[c] (257.0812)	

a) After purification by silica gel chromatography, 10 ml of ethyl acetate saturated with HCl gas was added to the evaporation residue. The resulting precipitate was filtered, washed with ethyl acetate, and dried to afford an analytical sample. *b*) The compound was used in the next stage without purification. *c*) High-resolution MS data (M^+). The upper value is the value calculated and the lower one in parenthesis is the value found.

other than the butyl group at the 5-position, was conducted as shown in Chart 3. Oxidation of **7**[17] with hydrogen peroxide gave *N*-oxide which was rearranged to the amide **8** by heating with acetic anhydride followed by methanolysis. Reaction of **8** with alkyl halide under basic conditions afforded mainly an *N*-alkylated product (**9**). After purification of **9**, debenzylation[18] was achieved by hydrogenolysis using 10% palladium on carbon in acetic acid to afford **6**. Yields, physical, and spectral data of **9** and **6** are listed in Tables I and II.

Treatment of **6** with appropriate electrophiles under basic conditions gave the desired 3-substituted compounds (**2**) (Chart 4). 1-Substituted compounds were not detected. Yields, physical, and spectral data of these compounds are summarized in Tables III and IV. The position of R_2 was confirmed by ^{1}H- and ^{13}C-NMR spectroscopic analysis. Physical and spectral data of **2a** and its regioisomer **10**, which was synthesized by an alternative route,[13] were listed in Table V. Assignments of ^{13}C signals were done by the LSPD (long-range selective proton decoupling) technique. The long range couplings between C-3a and 2-H, and between C-9b and 2-H in **2a** were 4.3 and 11.8 Hz,

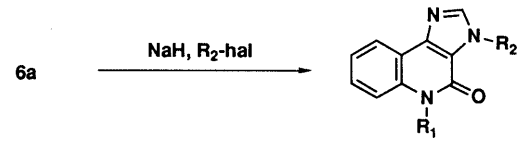

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Chart 4

TABLE IV. Spectral Data of 3*H*-Imidazo[4,5-*c*]quinorin-4(5*H*)-ones

Compd. No.	IR (KBr) ν (cm^{-1})	MS m/z (M$^+$)	^{1}H-NMR	
			Solvent	δ (J=Hz)
2b	1684	270	DMSO-d_6	0.95 (3H, t, J=7), 1.35—1.54 (2H, m), 1.50 (3H, t, J=7), 1.58—1.72 (2H, m), 4.36 (2H, t, J=7), 4.57 (2H, q, J=7), 7.42 (1H, t, J=8), 7.61—7.74 (2H, m), 8.35 (1H, d, J=8), 9.01 (1H, s)
2c	1673	284	DMSO-d_6	0.90 (3H, t, J=7), 0.95 (3H, t, J=7), 1.34—1.52 (2H, m), 1.57—1.71 (2H, m), 1.81—1.94 (2H, m), 4.35 (2H, t, J=7), 4.54 (2H, t, J=7), 7.42 (1H, t, J=8), 7.62—7.77 (2H, m), 8.39 (1H, d, J=8), 9.14 (1H, s)
2d	1673	284	DMSO-d_6	0.96 (3H, t, J=7), 1.60 (6H, d, J=7), 1.34—1.73 (4H, m), 4.37 (2H, t, J=7), 5.42—5.55 (1H, m), 7.43 (1H, t, J=8), 7.62—7.77 (2H, m), 8.43 (1H, d, J=8), 9.33 (1H, s)
2e	1668	297	DMSO-d_6	0.92 (3H, t, J=7), 0.95 (3H, t, J=7), 1.23—1.51 (4H, m), 1.54—1.71 (2H, m), 1.80—1.94 (2H, m), 4.36 (2H, t, J=7), 4.57 (2H, t, J=7), 7.43 (1H, t, J=8), 7.63—7.78 (2H, m), 8.40 (1H, d, J=8), 9.16 (1H, s)
2f	1659	331	DMSO-d_6	0.94 (3H, t, J=7), 1.30—1.51 (2H, m), 1.5—1.71 (2H, m), 4.33 (2H, t, J=7), 5.77 (2H, s), 7.24—7.62 (8H, m), 8.20 (1H, d, J=8), 8.48 (1H, s)
2g	3750, 1642	299	DMSO-d_6	0.95 (3H, t, J=7), 1.4—2.1 (6H, m), 3.1—3.7 (3H, m), 4.33 (2H, t, J=7), 4.52 (2H, t, J=7), 7.34 (1H, t, J=8), 7.52—7.64 (2H, m), 8.18 (1H, d, J=8), 8.26 (1H, s)
2h	1720, 1648	297	DMSO-d_6	0.93 (3H, t, J=7), 1.32—1.48 (2H, m), 1.53—1.68 (2H, m), 2.26 (3H, s), 4.28 (2H, t, J=7), 5.45 (2H, s), 7.35 (1H, t, J=8), 7.52—7.65 (2H, m), 8.16 (1H, s), 7.52—7.65 (2H, m), 8.16 (1H, s), 8.20 (1H, t, J=8)
2i	1658	213	DMSO-d_6	3.67 (3H, s), 4.06 (3H, s), 7.24—7.41 (1H, m), 7.50—7.63 (2H, m), 8.13 (1H, d, J=8), 8.20 (1H, s)
2j	3098, 1652	227	DMSO-d_6	1.45 (3H, t, J=7), 3.71 (3H, s), 4.50 (2H, q, J=7), 7.29—7.41 (1H, m), 7.51—7.69 (2H, m), 8.16 (1H, d, J=8), 8.30 (1H, s)
2k	3112, 1651, 1578	341	DMSO-d_6	1.58 (6H, d, J=7), 3.71 (3H, s), 5.33—5.49 (1H, m), 7.25—7.39 (1H, m), 7.51—7.68 (2H, m), 8.18 (1H, d, J=8), 8.50 (1H, s)
2l	1652, 1515	227	DMSO-d_6	1.26 (3H, t, J=7), 4.08 (3H, s), 4.38 (2H, q, J=7), 7.09—7.66 (3H, m), 8.17 (1H, d, J=8), 8.21 (1H, s)
2m	3082, 1653, 1576	241	DMSO-d_6	1.27 (3H, t, J=7), 1.45 (3H, t, J=7), 4.40 (2H, q, J=7), 4.52 (2H, q, J=7), 7.34 (1H, t, J=8), 7.56 (1H, d, J=8), 7.64 (1H, d, J=8), 8.19 (1H, d, J=8), 8.29 (1H, s)
2n	3110, 1646, 1579	255	$CDCl_3$	1.43 (3H, t, J=7), 1.63 (6H, d, J=7), 4.46 (2H, q, J=7), 5.50—5.63 (1H, m), 7.31—7.56 (3H, m), 8.01 (1H, s), 8.35 (1H, d, J=8)
2o	1659, 1574	241	DMSO-d_6	0.97 (3H, t, J=7), 1.40—1.85 (2H, m), 4.07 (3H, s), 4.28 (2H, t, J=7), 7.15—7.65 (3H, m), 8.17 (1H, d, J=8), 8.21 (1H, s)
2p	1657, 1562	255	DMSO-d_6	0.92 (6H, d, J=7), 1.97—2.30 (1H, m), 4.07 (3H, s), 4.22 (2H, d, J=7), 7.20—7.69 (3H, m), 8.12 (1H, d, J=8), 8.22 (1H, s)
2q	3734, 1646	270	DMSO-d_6	0.92 (6H, d, J=7), 1.43 (3H, t, J=7), 2.10—2.25 (1H, m), 4.25 (2H, d, J=7), 4.50 (2H, q, J=7), 7.33 (1H, t, J=8), 7.50—7.64 (2H, m), 8.18 (1H, d, J=8), 8.31 (1H, s)
2r	1657	284 (M+1) 283	DMSO-d_6	0.92 (6H, d, J=6), 1.55 (6H, d, J=7), 2.10—2.26 (1H, m), 4.25 (2H, d, J=7), 5.31—5.46 (1H, m), 7.33 (1H, t, J=8), 7.50—7.64 (2H, m), 8.14 (1H, d, J=8), 8.45 (1H, s)
2s	1668	283	DMSO-d_6	0.88 (3H, t, J=7), 1.28—1.67 (8H, m), 4.13 (3H, s), 4.32 (2H, t, J=7), 7.40 (1H, t, J=8), 7.60—7.67 (2H, m), 8.29 (1H, d, J=8), 8.83 (1H, s)
2t	3804, 1673	297	DMSO-d_6	0.87 (3H, t, J=7), 1.20—1.80 (8H, m), 1.53 (3H, t, J=7), 4.34 (2H, t, J=7), 4.61 (2H, q, J=7), 7.35—7.50 (1H, m), 7.62—7.75 (2H, m), 8.43 (1H, d, J=8), 9.22 (1H, s)
2u	3114, 1652	311	DMSO-d_6	0.87 (3H, t, J=7), 1.31—1.87 (8H, m), 1.55 (6H, d, J=7), 4.33 (2H, t, J=7), 5.33—5.44 (1H, m), 7.34 (1H, t, J=8), 7.53—7.64 (2H, m), 8.20 (1H, d, J=8), 8.46 (1H, s)

TABLE V. Melting Points and Spectral Data of **2a** and **10**

Compd. No.	mp (°C) (Recryst. solvent)	^{1}H-NMR (DMSO-d_6) δ (J=Hz)	^{13}C-NMR (DMSO-d_6) δ
2a	151—153 (MeOH–H_2O)	0.95 (3H, t, J=7), 1.36—1.52 (2H, m, C$\underline{H}_2$–CH_3), 1.58—1.71 (2H, m, N–CH_2–C$\underline{H}_2$), 4.08 (3H, s, N–CH_3), 4.31 (2H, t, J=7, N–C$\underline{H}_2$–CH_2), 7.32 (1H, t, J=8, Ar-H), 7.43 (1H, d, J=8, Ar-H), 7.56 (1H, t, J=8, Ar-H), 8.17 (1H, d, J=8, C9-H), 8.20 (1H, s, C2-H)	13.7 (C4′), 19.6 (C3′), 29.4 (C2′), 34.6 (N–Me), 40.9 (C1′), 115.3 (C9), 117.4 (C9a), 119.9 (C3a), 122.02 (C8), 122.03 (C9), 128.2 (C7), 136.3 (C5a), 143.4 (C9b), 145.1 (C2), 154.9 (C4)
10	208—209 (iso-PrOH–iso-Pr_2O)	0.94 (3H, t, J=7, CH_2–C$\underline{H}_3$), 1.37—1.45 (2H, m, C$\underline{H}_2$–CH_3), 1.55—1.64 (2H, m, N–CH_2–C$\underline{H}_2$), 4.17 (3H, s, N–CH_3), 4.34 (2H, t, J=7, N–C$\underline{H}_2$–CH_2), 7.34 (1H, br t, J=8, Ar-H), 7.55—7.56 (2H, m, Ar-H), 8.10 (1H, s, C2-H), 8.20 (1H, br d, J=8, C9-H)	13.7 (C4′), 19.6 (C3′), 29.4 (C2′), 34.6 (N–Me), 40.9 (C1′), 113.3 (C9a), 115.7 (C6), 121.7 (C8), 121.9 (C9), 128.4 (C7), 131.2 (C3a), 132.6 (C9b), 136.4 (C5a), 143.8 (C2), 157.0 (C4)

Chart 5

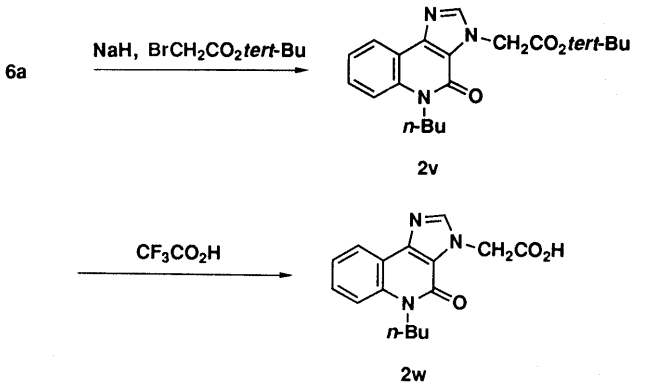


Chart 6

respectively (Chart 5). On the other hand, the long range couplings between C-3a and 2-H, and between C-9b and 2-H in **10** were 11.8 and 4.3 Hz, respectively. Thus, the location of the methyl group was determined as shown by the structure (**2a**) in Chart 5. Steric interaction between the 1-substituent and 9-H, and the linear conjugation of the double bonds in imidazole with the carbonyl group presumably favour 3-substitution of **6a** under the present alkylation conditions. Similar regioselective alkylation has been described in 5-phenylimidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-ones.[19] A 3-acetic acid derivative (**2w**) was prepared from **2v**, which was obtained by the reaction of **6a** with *tert*-butyl bromoacetate (Chart 6).

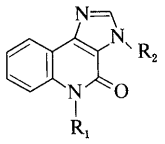
Results and Discussion

Bronchodilatory activity (*in vitro*) of 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one derivatives was examined by the inhibition of antigen-induced contraction of trachea isolated from passively sensitized guinea-pig (the Schultz–Dale (SD) reaction.[20,21] In this assay, compounds which showed more than 50% relaxation at 30 μM were regarded as active, and their IC_{50} values were determined by the cumulative method. Furthermore, active compounds were also evaluated in the antigen inhalation-induced bronchospasm model (*in vivo*).[22] The pharmacological activity of these compounds is summarized in Table VI, compared with that of theophylline. Theophylline showed moderate inhibition *in vitro* and *in vivo*, but its inhibitory effects on the antigen-induced bronchoconstriction were not significantly observed below a dose of 25 mg/kg (*p.o.*).

At first, the effects of 3-substituents (R_2) on activity were examined. Though the unsubstituted compound (**6a**) was devoid of activity, the introduction of substituents (R_2) at the 3-position resulted in pronounced bronchodilatory activity. When R_1 was *n*-butyl, compounds (**2a—d**) bearing short and small alkyl chains at the 3-position, such as a methyl, ethyl, *n*-propyl, or isopropyl group, exhibited moderate *in vitro* activity. This activity was also maintained by substitution of the acetonyl group (**2h**). Furthermore, compounds (**2a**, **b**, **d**, and **h**) exhibited significant inhibition against antigen inhalation-induced bronchospasm at a dose of 50 mg/kg (*p.o.*). A 3-isopropyl substituted compound (**2d**) produced potent activity even at a dose of 10 mg/kg (*p.o.*). However, compound (**2e**), which has a longer lipophilic substituent (*n*-butyl), lost activity. Introduction of a bulky lipophilic substituent such as benzyl and a hydrophilic substituent such as hydroxypropyl diminished *in vivo* activity without changing the *in vitro* activity (**2f** and **g**). The 3-carboxymethyl derivative (**2w**) was inactive in the SD reaction model.

Among compounds **2** bearing the *n*-butyl group at the 5-position, potent activity *in vitro* and *in vivo* was found when R_2 was methyl, ethyl or isopropyl, or an acetonyl group. Compound **2h** possessing the acetonyl group (R_2) showed CNS depressant activity at 300 mg/kg *p.o.* Thus, the effects of the 5-substituents (R_1) on bronchodilatory activity were examined, in the 3-methyl-, 3-ethyl-, and 3-isopropyl-3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones. When R_2 was then methyl group, the substitution by low alkyl chains, especially an ethyl, *n*-propyl, or isobutyl group at the 5-position, enhanced both *in vitro* and *in vivo* activities (**2l**, **o**, and **p**). Though the methyl substituted compound (**2i**) showed slightly reduced activity in two assays in comparison with the above three compounds, displacement by a longer substituent (R_1) such as *n*-hexyl caused a loss in *in vivo*

TABLE VI. Effects of 3*H*-Imidazo[4,5-*c*]quinolin-4(5*H*)-ones on the SD Reaction-Induced Contraction and Collapse Time in Antigen Inhalation-Induced Bronchospasm Model



2

Compd. No.	R_1	R_2	SD IC_{50} (μM)	Collapse time MCT (s)[a] Dose (mg/kg *p.o.*) 50	25	10
6a (2')	*n*-C_4H_9	H	>30			
2a	*n*-C_4H_9	CH_3	6.07±1.90	429±68[b]	393±63	397±42
2b·HCl	*n*-C_4H_9	C_2H_5	2.01±0.17	558±32[b]		375±52
2c·HCl	*n*-C_4H_9	*n*-C_3H_7	5.66±1.85	349±65		
2d·HCl	*n*-C_4H_9	iso-C_3H_7	3.70±0.35	412±78[c]		430±86[c]
2e·HCl	*n*-C_4H_9	*n*-C_4H_9	>30			
2f	*n*-C_4H_9	$CH_2C_6H_5$	3.62±1.76	368±82		
2g	*n*-C_4H_9	$CH_2CH_2CH_2OH$	1.12±0.34	284±53		
2h	*n*-C_4H_9	CH_2COCH_3	8.20±0.81	530±52[b]	316±31	
2i	CH_3	CH_3	4.66±2.35	509±60[b]	403±82[c]	362±50
2j	CH_3	C_2H_5	4.95±3.99	301±39		
2k	CH_3	iso-C_3H_7	1.62±0.17	289±41		
2l	C_2H_5	CH_3	0.47±0.10			597±34[b]
2m	C_2H_5	C_2H_5	2.05±0.69	587±10[b]		
2n	C_2H_5	iso-C_3H_7	3.07±0.84	373±77		
2o	*n*-C_3H_7	CH_3	1.05±0.36			518±24[b]
2p	iso-C_4H_9	CH_3	1.34±0.42			570±28[b]
2q	iso-C_4H_9	C_2H_5	2.29±0.89	590±10[b]	495±59[b]	509±28[b]
2r	iso-C_4H_9	iso-C_3H_7	3.41±1.12	261±43		
2s·HCl	*n*-C_6H_{13}	CH_3	4.49±1.44	192±26		
2t·HCl	*n*-C_6H_{13}	C_2H_5	1.35±0.35	274±40		
2u	*n*-C_6H_{13}	iso-C_3H_7	15.9±10.2	277±45		
2w	*n*-C_4H_9	CH_2CO_2H	>30			
Theophylline			6.52±1.26	414±48[b]	389±46	343±76

a) MCT indicated mean collapse time of treated animals. The mean collapse time of untreated animals was 254±18. *b*) $p<0.01$. *c*) $p<0.05$ (Duncan multiple range test).

activity (**2s**). There was a tolerance for bronchodilatory activities regarding short alkyl groups at the 5-position. When R_2 was the ethyl group, a similar tendency was observed. While **2j** (R_1=Me, R_2=Et) and **2t** (R_1=*n*-C_6H_{13}, R_2=Et) showed no significant effects *in vivo*, **2m** and **q** with the ethyl or isobutyl group as R_1 potently inhibited bronchospasm. Isopropyl substitution (**2k**, **n**, and **u**) at the 3-position (R_2) surprisingly lacked activity *in vivo* except for that of **2d**.

Structure–activity relationships were summarized as follows. Regarding R_2, short alkyl chains such as methyl and ethyl groups were important to produce potent activity, especially *in vivo*. In the case of substituents (R_1) at the 5-position, there was a tolerance for activity to some extent. Compounds, **2d**, **l**, **o**, **p**, and **q** were selected as interesting compounds. The bronchodilatory activity of **2l** was 14-fold more potent in the SD reaction model and at least 5-fold more potent in the antigen-induced bronchospasm model than that of theophylline.

Correlations between *in vitro* and *in vivo* activities were unclear. Furthermore, dose-dependency with respect to their collapse time values was not apparent. However, compounds which were significantly active against the bronchospasm model even at the dose of 10 mg/kg, also exhibited relatively potent activity *in vitro*. We speculate that these findings may be due to differences in oral bioavailability or metabolism among these compounds and to a different mechanism in the two assays. Their pharmacokinetics and effects on the CNS and cardiovascular systems are currently under study.

The present approach to nonxanthine-type compounds with the bronchodilatory activity, produced the new tricyclic heterocycle, 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones.

Experimental

Melting points were determined on a Yanagimoto hot plate micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a JASCO IR-810 spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured on a JEOL JNM GX-270 spectrometer or a Hitachi R-90H spectrometer with tetramethylsilane (TMS) as an internal standard (δ value, ppm). Mass spectra (MS) were determined on a JEOL JMS-D300 instrument at an ionization potential of 70 eV. Elemental analyses were performed with a Perkin-Elmer 2400CHN. For column chromatography, Silica gel 60 (E. Merck, 0.063—0.200 mm) was used. The reactions were usually carried out under nitrogen. Organic extracts were dried over anhydrous Na_2SO_4 and concentrated by a rotary evaporator.

1-Butyl-4-chloro-3-nitroquinolin-2(1*H*)-one (4) To a solution of ethyl nitroacetate (2.4 ml, 0.026 mol) in dry *N*,*N*-dimethylacetamide (30 ml) was added 60 wt% NaH (1.0 g, 0.026 mol) at 0 °C in portions. When the evolution of hydrogen ceased, **3** (5.2 g, 0.024 mol) was added. The

temperature was slowly raised to 120 °C and maintained there for 5 h (carbon dioxide evolution occurred). After the solvent was evaporated under reduced pressure, water (15 ml) and CH_2Cl_2 (15 ml) were added to the residue. The resulting precipitate was filtered. The aqueous layer of the filtrate was acidified with conc. HCl, then the precipitate was recollected by filtration and dried together with the previously collected solid.

Next $POCl_3$ (16 ml, 0.17 mol) was added to this solid and the suspension was refluxed for 1 h. After cooling, the excess reagent was evaporated under reduced pressure and water was added to the residue. The mixture was neutralized with 2 N of a NaOH solution and extracted with $CHCl_3$. The organic layer was washed with saturated aqueous NaCl, dried, and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel using $CHCl_3$ to give **4** (1.1 g, 16%) as yellow crystals which were recrystallized from hexane, mp 100—102 °C. IR (KBr): 1655, 1541 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7 Hz), 1.20—1.98 (4H, m), 4.34 (2H, t, J=7 Hz), 7.12—7.60 (m, 2H), 7.75 (1H, br t, J=8 Hz), 8.11 (1H, br d, J=8 Hz). *Anal.* Calcd for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; N, 9.98. Found: C, 55.72; H, 4.64; N, 9.80.

4-Amino-1-butyl-3-nitroquinolin-2(1*H*)-one (5) To a solution of **4** (1.0 g, 3.6 mmol) in tetrahydrofuran (20 ml) was added 28% aqueous ammonia solution (4.5 ml, 36 mmol) with ice cooling. The solution was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure and water was added to the residue. The resulting precipitate was filtered, washed with water, and dried. Recrystallization from isopropyl alcohol–water gave **5** (0.84 g, 90%) as yellow crystals, mp 163—165 °C. IR (KBr): 1608, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7 Hz), 1.22—1.91 (4H, m), 4.26 (2H, t, J=7 Hz), 7.10—7.42 (4H, m), 7.50—7.82 (2H, m). *Anal.* Calcd for $C_{13}H_{15}N_3O_3 \cdot 1/10H_2O$: C, 59.35; H, 5.82; N, 15.97. Found: C, 59.49; H, 5,78; N, 16.22.

5-Butylimidazo[4,5-*c*]quinolin-4(5*H*)-one (6a) To a suspension of **5** (0.96 g, 3.7 mmol) in ethyl alcohol (30 ml) was added 10% Pd–C (0.20 g). The mixture was stirred under a hydrogen stream at room temperature for 5 h. Then the mixture was filtered and concentrated. Formamide (2.9 ml, 74 mmol) was added to the residue. The suspension was stirred at 150 °C for 4 h. After cooling, the solution was poured into water, and the mixture was extracted with $CHCl_3$. The organic layer was washed with a saturated aqueous NaCl, dried, and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel using $CHCl_3$ to give **6a** (0.62 g, 70%) as colorless crystals, having been recrystallized from ethyl alcohol–water, mp 269—271 °C. IR (KBr) 1651 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, t, J=7 Hz), 1.33—1.51 (2H, m), 1.57—1.73 (2H, m), 4.36 (2H, t, J=7 Hz), 7.34 (1H, br t, J=8 Hz), 7.55 (1H, br t, J=8 Hz), 7.62 (1H, br d, J=8 Hz), 8.17 (1H, br d, J=8 Hz), 8.23 (1H, s), 13.40—13.70 (1H, m). *Anal.* Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.86; H, 6.27; N, 17.41.

1-Benzyl-4-hydroxy-1*H*-imidazo[4,5-*c*]quinoline (8) A solution of **7**[17] (6.0 g, 0.023 mol) in 30% H_2O_2 (4.7 ml, 0.046 mol) and acetic acid (40 ml) was stirred at 80 °C for 12 h. After cooling, the solvent was evaporated under reduced pressure and the residue was neutralized with a saturated aqueous $NaHCO_3$. The resulting precipitate was filtered and dried. A suspension of the crude mixture in 40 ml of acetic anhydride was heated under reflux for 1 h. After cooling, the solvent was evaporated under reduced pressure and MeOH (20 ml) was added to the residue. A solution of MeONa in MeOH (28%) was added dropwise to the suspension until pH 10 was attained. The resulting precipitate was filtered, washed with MeOH, and dried. Recrystallization from dimethylformamide (DMF)–MeOH gave **8** (2.9 g, 45%) as brown crystals, mp >300 °C. IR (KBr) 1654 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.89 (2H, s), 6.95—7.55 (8H, m), 7.76 (1H, br d, J=8 Hz), 8.31 (1H, s), 11.61 (1H, s). *Anal.* Calcd for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.26. Found: C, 73.92; H, 4.92; N, 15.27.

1-Benzyl-5-methyl-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one (9a) To a suspension of **8** (0.50 g, 1.8 mmol) in dry DMF (10 ml) was added 60 wt% NaH (0.15 g, 3.6 mmol) at 0 °C in portions, followed by stirring at 50 °C for 30 min. The mixture was again ice-cooled and MeI (0.23 ml, 3.6 mmol) was added dropwise. After stirring at room temperature for 2 h, the solvent was evaporated under reduced pressure and water was added to the residue. The aqueous mixture was extracted with $CHCl_3$. The organic phase was washed with water, dried, and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel using $CHCl_3$ and recrystallized from $CHCl_3$–iso-Pr_2O to give **9a** (0.40 g, 77%) as colorless crystals. IR (KBr) 1668 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.71 (3H, s), 5.91 (2H, s), 7.10—7.38 (6H, m), 7.51 (1H, br t, J=8 Hz), 7.66 (1H, br d, J=8 Hz), 7.86 (1H, br d, J=8 Hz), 8.32 (1H, s). MS *m/z*: 289 (M^+). Compounds **9b—9e** were prepared in a similar manner to **9a**, using C_2H_5I, *n*-C_3H_7I iso-C_4H_9I and *n*-$C_6H_{13}Br$ instead of MeI, respectively, and their physical and spectral data are listed in Tables I and II.

5-Methylimidazo[4,5-*c*]quinolin-4(5*H*)-one (6b) To a solution of **9a** (1.0 g, 3.5 mmol) in acetic acid (50 ml) was added 10% Pd–C (0.20 g). The mixture was stirred under a hydrogen stream at 70 °C for 4 h. Then the mixture was filtered and concentrated under reduced pressure. Water was added to the residue, and the mixture was neutralized with a saturated aqueous $NaHCO_3$ solution under cooling. The resulting precipitate was collected by filtration and recrystallized from DMF–H_2O to give **6b** (0.45 g, 66%) as colorless crystals. IR (KBr) 1655 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.74 (3H, s), 7.33—7.39 (1H, m), 7.53—7.63 (2H, m), 8.16 (1H, br d, J=8 Hz), 8.26 (1H, s), 13.56 (1H, br s). MS *m/z*: 199 (M^+). Compounds **6c—f** were prepared in a similar manner to **6b** and their physical and spectral data are listed in Tables I and II.

5-Butyl-3-methyl-3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one (2a) To a suspension of **6a** (1.2 g, 5 mmol) in dry DMF (30 ml) was added 60 wt% NaH (0.30 g, 7.5 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min, and MeI (0.78 ml, 12 mmol) was added under ice cooling. Then the mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. Water was added to the residue, and the aqueous mixture was extracted with $CHCl_3$. The organic phase was washed with water, dried, and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel using $CHCl_3$: MeOH = 50 : 1 and recrystallized from MeOH to give **2a** (0.95 g, 75%) as colorless crystals. IR (KBr) 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, t, J=7 Hz), 1.36—1.52 (2H, m), 1.58—1.71 (2H, m), 4.08 (3H, s), 4.31 (2H, t, J=7 Hz), 7.32 (1H, br t, J=8 Hz), 7.43 (1H, br d, J=8 Hz), 7.56 (1H, br t, J=8 Hz), 8.17 (1H, br t, J=8 Hz), 8.20 (1H, s). MS *m/z*: 255 (M^+). Compounds **2b—v**[13b] were prepared in a manner similar to **2a** using R_2X from **6b—f** and their physical and spectral data are listed in Tables III and IV.

5-Butyl-3-carboxymethyl-3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one (2w) To a solution of **6a** (3.0 g, 15 mmol) in dry DMF (30 ml) was added 60 wt% NaH (0.40 g, 22 mmol) at 0 °C in portions. When the evolution of hydrogen ceased, *tert*-butyl bromoacetate (4.9 ml, 30 mmol) was added. After stirring at room temperature for 2 h, saturated aqueous NH_4Cl was added under cooling. The solvent was evaporated under reduced pressure and water was added to the residue. The mixture was extracted with $CHCl_3$. The organic phase was washed with water, dried and evaporated under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$ to afford **2v** (2.7 g, 57%). Without analysis, to a solution of **2v** (2.3 g, 7.3 mmol) in CH_2Cl_2 (50 ml) was added CF_3CO_2H (50 ml) under ice cooling. The mixture was stirred at room temperature for 2.5 h, and the solvent was evaporated under reduced pressure. The residue was suspended in water and 4 N of a NaOH solution was added to dissolve the residue. 2 N hydrochloric acid was added to the solution to give the resulting precipitate, which was collected by filtration. Recrystallization from DMF–iso-PrOH gave **2w** (1.5 g, 77%) as colorless crystals, IR (KBr) 3600—2200, 1725 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.93 (3H, t, J=7 Hz,), 1.32—1.50 (2H, m), 1.52—1.68 (2H, m), 4.30 (2H, t, J=7 Hz), 5.29 (2H, s), 7.36 (1H, br t, J=8 Hz), 7.54—7.64 (2H, m), 8.20 (1H, br d, J=8 Hz), 8.31 (1H, s), 12.85—13.40 (1H, m). MS *m/z*: 257 (M^+).

Antigen-Induced Contraction of Tracheal Strip Isolated from Passively Sensitized Guinea-Pig (SD Reaction)[20] Male Hartley strain guinea-pigs weighing 350—450 g were passively sensitized by intraperitoneal injection of 1 ml/animal of rabbit anti-ovalbumin (anti-OA) serum 16 to 18 h before use. The animals were killed by stunning and bleeding. Trachea were excised and cleaned adhering adipose and connective tissues. Tracheal zig-zag strips were prepared by the method of Emmerson and Mackay,[21] followed by equilibration for 1 h in Krebs–Henseleit solution with 95% O_2–5% CO_2 at 37 °C. OA was administered at 10 μg/ml in a final bath concentration. Test drugs were added cumulatively at 7 min intervals after the contraction of tracheal strips reached a plateau. Contractions were recorded isotonically using isotonic transducers (TD-112S: Nihon Kohden) connected to recorders (TYPE30066: Yokokawahokusin Electric). The inhibitory effects were calculated as a percentage of the relaxation induced by papaverine (10^{-4} M) added at the end of the experiment. The concentration of each drug required to produce 50% relaxation (IC_{50}) was determined from least-squares regression analysis.

Antigen Inhalation-Induced Bronchospasm Model in Passively Sensitized Guinea-Pigs Herxheimer's method[22] was modified as follows. Male Hartley guinea-pigs (350—450 g) were passively sensitized by intraperitoneal injection of 1 ml/animal of rabbit anti-OA serum 16—24 h before use. Guinea-pigs were placed individually in a clear plastic container (13 × 18 × 25 cm) and challenged with 1.5% OA using a nebulizer (V type: Nihon Shoji) at a rate of about 0.83 l/min. The time (s) of onset of the

asphyxial convulsion was defined as the collapse time. Animals not responding until 600 s were regarded to be fully protected and their collapse time was determined to be 600 s. Test drugs were orally administered 1 h before antigen exposure and animals were pretreated with diphenhydramine (20 mg/kg i.p.) and propranolol (5 mg/kg i.p.) 30 min before antigen exposure.

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