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Short communication

Synthesis and *in vitro* bronchospasmolytic activity of 8-aryl, heteroaryl or arylalkyl theophyllines

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Summary — Twenty-four 8-aryl- or 8-heteroaryl-substituted theophyllines have been synthesized. The substituents are aromatic rings and heterocycles likely to induce an antiallergic effect or a spasmolytic activity. *In vitro* evaluation of the bronchospasm caused by acetylcholine or histamine shows an interesting activity for half of the compounds. Among them, the furanic **IIIs** and 2-chlorophenyl **IIIi** derivatives are, for instance, four times more active than theophylline.

theophylline / bronchodilatation / oxygenated heterocycle

Introduction

Despite its disadvantages (weak margin of safety and high toxicity) and some detractors, theophylline remains one of the most widely prescribed anti-asthma drugs worldwide. Theophylline holds a first-rank position because of its bronchodilator properties and antiinflammatory activity [1, 2]. The large number of variations of this molecule synthesised with the aim of decreasing toxicity or improving efficacy corroborates the importance of theophylline. For example, substitution at the 8-position by diphenyl methyl piperazine groups, which confer antihistaminic properties, led to potent bronchodilators useful in the treatment of allergic asthma [3]. Several products of this type, including tazifylline, have been selected for clinical trials [4].

Structural analogues of chromone, such as cromoglycate or nedocromil [5], are known to exhibit not antihistaminergic effects but antiallergic properties, which are principally useful in the prevention of asthma. Furthermore, the therapeutic association of xanthines and cromoglycate or its derivatives would decrease the immediate and delayed bronchial response [2].

The present work describes the synthesis of a series of theophylline derivatives substituted at the 8-position by oxygenated heterocycles related to chromones. Chromone derivatives exhibit a weak toxicity and can have an antiallergic activity. In this way, our aim was to obtain compounds which could both prevent and treat asthma.

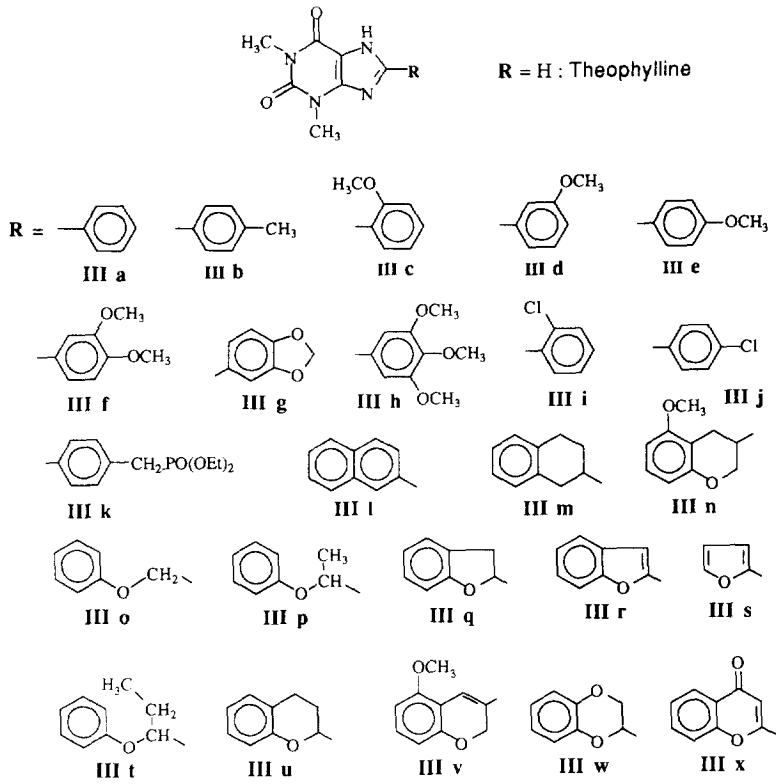
To identify the influence of this 8-substitution, we introduced aromatic groups, mono or bicyclic oxygenated heterocycles (saturated or unsaturated), and open derivatives, which could be regarded as conformationally unrestricted analogues of ring-closed structures.

Furthermore, insofar as the trimethoxybenzoic moiety is found in some spasmolytic drugs and the benzylphosphonate group has been described as having calcium antagonistic properties [6, 7], we grafted these two groups onto the theophylline moiety. Twenty-four compounds were thus synthesised, their structures are detailed in scheme 1. (Compound **IIIa** is commercially available.)

Chemistry

The 8-substituted theophyllines **III** were prepared as outlined in scheme 2.

Most of the acid chlorides **I** are commercially available. Chlorides of piperonylic acid [8], tetrahydronaphthalene-2-carboxylic acid [9], 5-methoxy chroman-3-carboxylic acid [10], dihydrobenzofuran-2-carboxylic acid [11], benzofuran-2-carboxylic acid [12], chroman-2-carboxylic acid [13], 5-methoxy



Scheme 1.

chromene-3-carboxylic acid [10], benzodioxane-2-carboxylic acid [14], and chromone-2-carboxylic acid [15] were synthesised according to previously 56 256described protocol. Only the synthesis of diethylphosphonomethylbenzoyl chloride **Ik**, obtained from the appropriate acid in the presence of thionyl chloride, is described here.

Intermediate amides **II** were obtained by condensation of 5,6-diamino-1,3-dimethyl uracile with the corresponding acids chlorides. Cyclisation of amides **II** to give 8-aryl or 8-heteroaryl theophyllines was achieved with phosphoric anhydride in the presence of a catalytic amount of aluminium chloride (a), or with butanol in the presence of potassium *tert*-butoxide (b), as shown in scheme 2.

The physical properties of compounds **II** (**b–x**) and **III** (**b–x**) are listed in tables I and II, respectively.

Pharmacology

The reduction of acetylcholine or histamine-induced bronchospasm was evaluated *in vitro* on isolated guinea-pig tracheal strips; theophylline was tested for comparison. The anti-bronchoconstrictive effect was expressed as the –log IC_{50} value (pD_2) (concentration of drug required to inhibit acetylcholine/histamine effects by 50%). The results are reported in table III.

Results and discussion

Three compounds, **IIIc**, **IIIu** and **IIIs**, in order of decreasing activity, were found to be more active or as active as theophylline on acetylcholine-induced bronchospasm. The results concerning the histamine-induced bronchospasm are more interesting. Eleven compounds exhibited an antibronchospasmic activity of the same order of magnitude as theophylline. Compounds **IIIs**, **IIIi** and **IIIu**, in order of decreasing activity, were even more potent or as potent as theophylline *in vitro*.

It can be seen that the *ortho* substitution of 8-phenyl theophylline by a methoxy group (**IIIc**) or a chlorine (**IIIi**) leads to active compounds. On the contrary, the corresponding *para* compounds **IIIe** and **IIIj** and the *meta* methoxy derivative **IIId** are devoid of activity.

With regard to these results, we can assume that the introduction of a bulky group at the *ortho* position

imposes a rotation of the phenyl ring. This rotation may induce a breaking of planarity and consequently a loss of conjugation between the phenyl ring and the xanthine moiety. In the case of the inactive *meta*- and *para*-substituted phenyl theophyllines, the planarity may be preserved.

This loss of planarity and conjugation may both explain the differences of activity between compounds **IIIl** (2-naphthyl) and **IIIm** (2-tetrahydronaphthyl), **IIIr** (2-benzofuranyl) and **IIIq** (2-dihydrobenzofuranyl), **IIIv** (5-methoxy 3-chromenyl) and **IIIn** (5-methoxy-3-chromanyl). In each of these pairs, only the saturated non-aromatic derivative was active.

Finally, non-conjugated open derivatives **IIIo, p, t** exhibited an antibronchospasmic activity but were found to be less potent than the corresponding cyclised derivative **IIIu**.

The activity of 2-furyl compound **IIIs** may be explained by a slight aromaticity of furan. The latter is often considered to behave as a diene. In addition, it exhibits a weak steric hindrance.

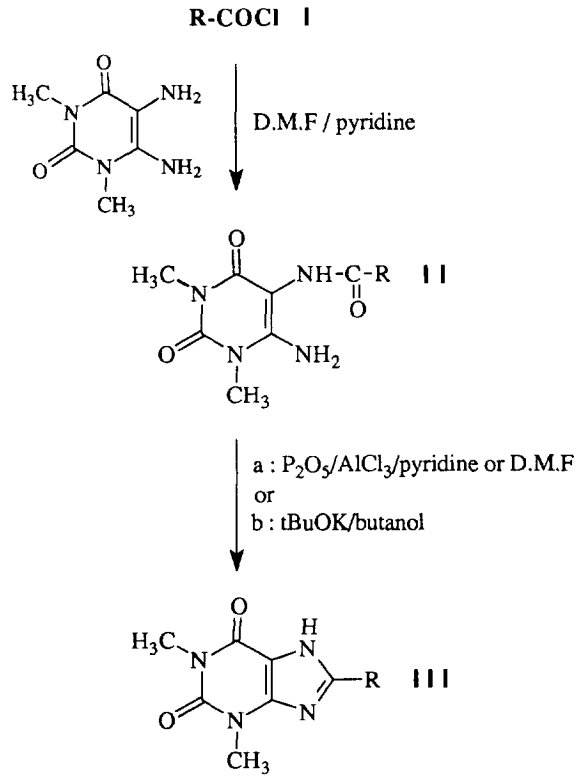
Surprisingly, the benzodioxane **IIIw** compound is totally inactive although it possesses a nonplanar saturated structure. This lack of activity may be explained by the presence of the second oxygen atom, which introduces an additional negative potential area. This further attractive zone may hinder the binding into the receptor cavity. The same remark can be applied to chromone derivative **IIIx**. On the other hand, the non-aromatic derivatives **IIIm, n, p, q, t, u** and **w** are characterised by a chiral centre and were tested as racemic mixtures; the two enantiomeric activities could be very different.

In conclusion, among these new compounds, the most active ones were characterised by non-aromatic substituents and nonplanar structures. However, even for the more active compounds, the level of activity is not much higher than for theophylline and justifies neither research into the mechanism of action nor study of toxicity.

Experimental protocols

Chemistry

Melting points were determined on a Maquenne apparatus or a Tottoli apparatus in glass capillary tubes and are uncorrected. Infrared spectra were obtained on Perkin-Elmer 983 G apparatus using films for liquids or inclusion in KBr pellets for solids. ^{1}H-NMR spectra were recorded with a Varian T60 spectrometer operating at 60 MHz and/or with a Bruker 200 MHz spectrometer at 200.13 MHz. Chemical shifts are reported in δ units (ppm) relative to TMS as internal standard. Silica-gel TLC was performed on Merck 60 F-254 precoated sheets. Elemental analyses are in agreement with the accepted norms and are not reported.



Scheme 2.

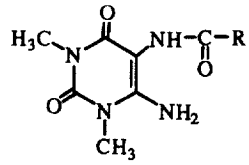
4-Diethylphosphonomethyl benzoyl chloride ***Ik***

This compound was obtained from phosphonomethyl benzoic acid [16, 17] according to the following procedure. To a solution of phosphonomethyl benzoic acid (0.013 mol) in cyclohexane (150 ml) was added thionyl chloride (0.026 mol). The reaction mixture was heated under reflux for 4 h. The solvent and the excess of reagent were then removed under reduced pressure and the resulting oil was used as crude product. $C_{12}H_{16}ClO_4P$, MW = 290.5, yield = 95%, n_D (19°C) = 1.5253. IR (film, ν cm^{-1}): 3091, 3070, 3035, 2982, 2929, 2908 (CH, CH_2, CH_3); 1772 (CO); 1603 (C=C); 1251 (PO). ^{1}H-NMR ($CDCl_3$) δ ppm: 1.00 (t, 6H, CH_2-CH_3, J = 7 Hz); 2.87 (d, 2H, CH_2P, J = 22 Hz); 3.83 (q, 4H, CH_2-CH_3, J = 7 Hz); 7.10 (d, 2H, H_3 and H_5, J = 8 Hz); 7.80 (d, 2H, H_2 and H_6, J = 8 Hz).

General procedure for the synthesis of amides ***II***

To a solution of 5,6-diamino-1,3-dimethyl uracile (0.025 mol) in 100 ml dimethylformamide (DMF) were added dry pyridine (30 ml) and the corresponding acid chloride (0.025 mol). The reaction mixture was stirred at room temperature for 12 h. After filtration, pyridine and part of the DMF was removed under reduced pressure. Water (100 ml) was added to the remaining solution; the resulting precipitate was collected by filtration, washed with water, dried and recrystallised from DMF, or from ethanol in the case of compound **IIh**.

Table I. Physical properties of amides **II**.



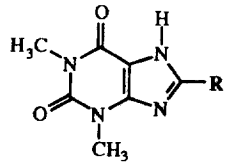
Compd	Formula	Yield (%)	MP	Rf [a]	^{1}H-NMR (DMSO-d_6) (δ ppm)
IIb	$C_{14}H_{16}N_4O_3$	60	278[c]	0.71	2.36 (s, 3H, CH_3); 3.12 (s, 3H, N-CH_3); 3.45 (s, 3H, N-CH_3); 6.83 (s wide, 2H , NH_2); 7.26 (d, 2H, H_2 & H_6, J = 8 Hz); 7.88 (d, 2H, H_3 & H_5, J = 8Hz); 8.83 (s, 1H, NH) .
IIc	$C_{14}H_{16}N_4O_4$	15	280	0.78	3.25 (s, 3H, N-CH_3); 3.45 (s, 3H, N-CH_3); 4.06 (s, 3H, OCH_3); 6.80 (s wide, 2H , NH_2); 7.19 (m, 1H, H_5); 7.31 (d, 1H, H_3, J = 8Hz); 7.64 (m, 1H, H_4) ; 8.02 (dd, 1H, H_6, J=8 & 1 Hz); 8.93 (s wide, 1H, NH)
IId	$C_{14}H_{16}N_4O_4$	10	282	0.62	3.25 (s, 3H, N-CH_3); 3.48 (s, 3H, N-CH_3); 3.93 (s, 3H, OCH_3); 6.86 (s wide, 2H , NH_2) ; 7.22 (m, 1H, H_4) ; 7.50 (m, 1H, H_5); 7.66 (m, 2H, H_2, H_6) ; 9.04 (s ,1H, NH) .
IIe	$C_{14}H_{16}N_4O_4$	10	269	0.81	3.24 (s, 3H, N-CH_3); 3.45 (s, 3H, N-CH_3); 3.94 (s, 3H, OCH_3); 6.84 (s, 2H , NH_2) ; 7.11 (d, 2H, Ar α to OCH_3, J = 9Hz) ; 8.07 (d, 2H, Ar α to CO, J = 9Hz); 8.92 (s ,1H, NH) .
IIf	$C_{15}H_{18}N_4O_5$	23	308	0.58	3.25 (s, 3H, N-CH_3); 3.45 (s, 3H, N-CH_3); 3.93 (s, 6H, $2OCH_3$); 6.83 (s wide, 2H , NH_2) ; 7.15 (d, 1H, H_5, J = 8Hz) ; 7.72 (m, 2H, H_2, H_6) ; 8.92 (s ,1H, NH) .
IIg	$C_{14}H_{14}N_4O_5$	70	270[c]	0.73	3.23 (s, 3H, N-CH_3); 3.44 (s, 3H, N-CH_3), 6.21 (s, 2H, OCH_2) ; 6.83 (s, 2H, NH_2); 7.11 (d, 1H, H_5, J=8 Hz); 7.62 (s,1H, H_2, J=1Hz); 7.64 (dd, 1H, H_6 , J=8Hz & J=1 Hz); 8.89 (s, 1H, NH).
IIh	$C_{16}H_{20}N_4O_6$	70	280[c]	0.74	3.13 (s, 3H, N-CH_3); 3.33 (s, 3H, N-CH_3); 3.71 (s, 3H, p-OCH_3); 3.84 (s, 6H, 2 m-OCH_3); 6.73 (s, 2H , NH_2) ; 7.32 (s, 2H, Ar); 8.89 (s,1H, NH) .
IIi	$C_{13}H_{13}N_4ClO_3$	24	276	0.23[b]	3.15 (s, 3H, N-CH_3); 3.36 (s, 3H, N-CH_3); 6.71 (s wide, 2H, NH_2) ; 7.45 (m, 3H, Ar); 7,80 (m, 1H, H_6); 9.11 (s wide,1H, NH) .
IIj	$C_{13}H_{13}N_4ClO_3$	78	322[c]	0.83	3.24 (s, 3H, N-CH_3); 3.45 (s, 3H, N-CH_3); 6.97 (s wide, 2H , NH_2) ; 7.66 (d, 2H, H_3, H_5, J = 8Hz); 8.11 (d, 2H, H_2, H_6, J = 8 Hz); 9.25 (s,1H, NH) .
IIk	$C_{18}H_{25}N_4O_6P$	70	184	0.73	1.27 (t, 6H, 2 OCH_2CH_3, J =7Hz) ; 3.20 (d, 2H, CH_2-P, J= 22 Hz); 3.31 (s, 3H, N-CH_3); 3.41 (s, 3H, N-CH_3); 4.03 (m, 4H, 2 OCH_2CH_3); 5.74 (s, 2H, NH_2); 7.36 (dd, 2H, H_3, H_5, J=8Hz & J=2Hz); 7.85 (d, 2H, H_2, H_6, J=8Hz); 8.05 (s,1H, NH).[d]
II l	$C_{17}H_{16}N_4O_3$	75	326[c]	0.85	3.25 (s, 3H, N-CH_3); 3.45 (s, 3H, N-CH_3) ; 6.92 (s, 2H, NH_2); 7.73 (m, 2H, Ar); 8.12 (m, 4H, Ar); 8.74 (s,1H, H_1); 9.22 (s, 1H, NH).

Table I. *(Continued).*

Compd	Formula	Yield (%)	MP	Rf [a]	^{1}H-NMR (DMSO-d_6) (δ ppm)
IIm	$C_{17}H_{20}N_4O_3$	34	260	0.82	1. 89 (m, 2H, Ar-CH_2-CH_2); 2.85 (m, 5H, Ar-CH_2-CH, Ar-CH_2-CH_2); 3.12 (1s, 3H, N-CH_3); 3.32 (1s, 3H, N-CH_3); 6.56 (s, 2H, NH_2); 7.08 (s, 4H, Ar); 8.42 (s, 1H, NH).
IIn	$C_{17}H_{20}N_4O_5$	14	162	0.81	2.91 (m, 3H, Ar-CH_2-CH); 3.24 (s , 3H , N-CH_3); 3.44 (s, 3H, N-CH_3); 3.90 (s, 3H, OCH_3) ; 4.35 (m, 2H , OCH_2); 6.56 (m, 2H, H_6, H_8); 6.81 (s wide, 2H, NH_2); 7.14 (m, 1H, H_7); 8.81 (s, 1H, NH).
IIo	$C_{14}H_{16}N_4O_4$	26	270[c]	0.82	3.24 (s, 3H , N-CH_3); 3.43 (s, 3H, N-CH_3); 4.71 (s, 2H, OCH_2) ; 6.85 (s, 2H, NH_2); 7.08 (m, 3H, Ar); 7.36 (m, 2H, Ar) ; 8.73 (s, 1H, NH).
IIp	$C_{15}H_{18}N_4O_4$	30	234	0.13[b]	1.64 (d, 3H, CH_3-CH); 3.29 (s, 3H, N-CH_3); 3.42 (s, 3H, N-CH_3); 4.97 (q, 1H, CH) ; 6.53 (s, 2H, NH_2); 7.23 (m, 5H, Ar) ; 8.73 (s, 1H, NH).
IIq	$C_{15}H_{16}N_4O_4$	25	260	0.84	3.21 (s, 3H, N-CH_3); 3.42 (m, 2H, ArCH_2); 3.43 (s, 3H, N-CH_3); 5.37 (dd, 1H, OCH, J = 8 & 10 Hz); 6.86 (s, 2H, NH_2); 7.14 (m, 4H, Ar); 8.69 (s, 1H, NH).
IIr	$C_{15}H_{14}N_4O_4$	60	270	0.75	3.14 (s, 3H, N-CH_3); 3.58 (s, 3H, N-CH_3); 6.90 (s, 2H, NH_2); 7.75 (s, 1H, H_3); 7.96 (m, 4H, Ar); 9.28 (s, 1H, NH).
IIs	$C_{11}H_{12}N_4O_4$	60	250	0.74	3.12 (s, 3H, N-CH_3); 3.32 (s, 3H, N-CH_3) ; 6.64 (dd, 1H, H_4, J= 1.7 & 3.5 Hz); 6.76 (s, 2H, NH_2); 7.22 (dd,1H, H_3, J =3.5 & 1Hz); 7.86 (dd,1H, H_5, J=1 & J=1.7 Hz); 8.74 (s,1H, NH).
IIt	$C_{16}H_{20}N_4O_4$	10	119	0.20[b]	1.11 (m, 3H, CH_3); 2.06 (m, 2H, CH_2); 3.23 (s, 3H, N-CH_3); 3.41 (s, 3H, N-CH_3); 4.80 (t, 1H, CH) ; 6.40 (s, 2H, NH_2); 7.09 (m, 3H, Ar); 7.41 (m, 2H, Ar); 8.74 (s, 1H, NH).
IIu	$C_{16}H_{18}N_4O_4$	60	253	0.73	2.11 (m, 2H, Ar-CH_2- CH_2); 2.86 (m, 2H, Ar-CH_2-CH_2); 3.10 (s, 3H, N-CH_3); 3.58 (s, 3H, N-CH_3); 4.6 (m, 1H, OCH); 6.69 (s, 2H, NH_2); 7.03 (m, 4H, Ar); 8.44 (s, 1H, NH).
IIv	$C_{17}H_{18}N_4O_5$	21	342[c]	0.78	3.13 (s, 3H, N-CH_3); 3.32 (s, 3H, N-CH_3); 3.85 (s, 3H, OCH_3); 4.86 (s, 2H , OCH_2); 6.50 (d, 1H, Ar, H_8); 6.64 (d, 1H, Ar, H_6, J = 8Hz); 6.72 (s, 2H, NH_2); 7.21 (m, 1H, Ar, H_7, J = 8Hz); 7.63 (s, 1H, Ar, H_4, J = 8Hz) ; 8.74 (s, 1H, NH).
IIw	$C_{15}H_{16}N_4O_5$	65	241	0.84	3.22 (s, 3H, N-CH_3); 3.43 (s, 3H, N-CH_3); 4.33 (dd,1H, H_2, J=7Hz & J=11Hz); 4.60 (dd, 1H, H_3, J=3 Hz & J=11Hz); 4.95 (dd,1H, H_3', J= 3Hz & J=7Hz); 6.81 (s, 2H, NH_2); 7.03 (m, 4H, Ar) ; 8.90 (s, 1H, NH).
IIx	$C_{16}H_{14}N_4O_5$	65	230	0.82	3.14 (s, 3H, N -CH_3); 3.58 (s, 3H, N-CH_3); 6.89 (s,1H, H_3); 6.95 (s, 2H, NH_2); 7.55 (m,1H, H_6, J=7 Hz); 7.80 (d, 1H, H_8, J=8Hz); 7.91 (m,1H, H_7, J=8Hz); 8.07 (dd,1H, H_5, J =1.5 Hz & 8Hz); 9.62 (s, 1H, NH).

[a]Ethanol; [b]ethyl acetate; [c]decomposition; [d]$CDCl_3$.

Table II. Physical properties of 8-substituted theophyllines **III**.



Compd	Formula	Yield (%)	MP	Rf [a]	^{1}H-NMR (DMSO-d_6) (δ ppm)
IIIb	$C_{14}H_{14}N_4O_2$	45	320[c]	0.73[b]	2.48 (s, 3H, CH_3) ; 3.38 (s, 3H, N-CH_3); 3.62 (s, 3H, N-CH_3); 7.43 (d, 2H, H_2, H_6, J = 8 Hz); 8.25 (d, 2H , H_3, H_5, J = 8 Hz); 13.50 (s,1H, NH).
IIIc	$C_{14}H_{14}N_4O_3$	35	266	0.46	3.38 (s, 3H, N-CH_3) ; 3.61 (s, 3H, N-CH_3); 4.04 (s, 3H, OCH_3); 7.20 (m, 1H, H_5); 7.31 (d, 1H, H_6, J = 8 Hz); 7.60 (m, 1H, H_4); 8.12 (dd, 1H, H_3, J= 1 & 8 Hz); 12.96 (s, 1H, NH).
IIId	$C_{14}H_{14}N_4O_3$	40	312[c]	0.61	3.38 (s, 3H, N-CH_3) ; 3.61 (s, 3H, N-CH_3); 3.95 (s, 3H, OCH_3); 7.15 (m, 1H, H_4); 7.53 (m, 1H, H_5); 7.85 (m, 2H, H_2 & H_6); 13.95 (s, 1H, NH).
IIIe	$C_{14}H_{14}N_4O_3$	30	321[c]	0.54	3.38 (s, 3H, N-CH_3) ; 3.61 (s, 3H, N-CH_3); 3.94 (s, 3H, OCH_3); 7.17 (d, 2H, H_3 & H_5, J= 9 Hz); 8.19 (d. 2H. H_2 & H_6, J = 9 Hz); 13.95 (s, 1H, NH).
IIIf	$C_{15}H_{16}N_4O_4$	22	326[c]	0.39	3.38 (s, 3H, N-CH_3) ; 3.62 (s, 3H, N-CH_3); 3.94 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3); 7.20 (d, 1H, H_5, J = 9 Hz); 7.84 (m, 2H, H_2 & H_6); 13.57 (s, 1H, NH).
IIIg	$C_{14}H_{12}N_4O_4$	50	231	0.85[b]	3.38 (s, 3H, N-CH_3) ; 3.60 (s, 3H, N-CH_3); 6.23 (s, 2H, OCH_2); 7.17 (d, 1H, H_5, J=8 Hz); 7.76 (s,1H, H_2); 7.81 (d, 1H , H_6, J=8Hz); 13.77 (s, 1H, NH).
IIIh	$C_{16}H_{18}N_4O_5$	45	291	0.48	3.27 (s, 3H, N-CH_3); 3.51 (s, 3H, N-CH_3); 3.72 (s, 3H, p-OCH_3); 3.86 (s, 6H, 2 m-OCH_3); 7.48 (s, 2H, Ar); 13.77 (s, 1H, NH).
IIIi	$C_{13}H_{11}N_4ClO_2$	13	248	0.83[b]	3.38 (s, 3H, N-CH_3); 3.59 (s, 3H, N-CH_3); 7.71 (m, 4H, Ar); 14.0 (s wide, 1H, NH).
IIIj	$C_{13}H_{11}N_4ClO_2$	53	362[c]	0.87[b]	3.38 (s, 3H, N-CH_3) ; 3.61 (s, 3H, N-CH_3); 7.69 (d, 2H, H_3, H_5, J=8.5 Hz); 8.25 (d, 2H, H_2, H_6, J=8.5 Hz); 13.88 (s, 1H, NH).
IIIk	$C_{18}H_{23}N_4O_5P$	55	320[c]	0.73[b]	1.27 (t, 6H, 2 OCH_2-CH_3, J=7Hz); 3.25 (d, 2H, CH_2-P, J=22Hz); 3.53 (s, 3H, N-CH_3); 3.70 (s, 3H, N-CH_3); 4.09 (m, 4H, 2 OCH_2CH_3); 7.45 (dd, 2H, H_3, H_5, J=8Hz & J=2Hz); 8.24 (d, 2H, H_2, H_6, J=8Hz); 13.01 (s,1H, NH).[d]
III l	$C_{17}H_{14}N_4O_2$	70	356[c]	0.63	3.40 (s, 3H, N-CH_3) ; 3.67 (s, 3H, N-CH_3); 7.7 (m, 2H, H_6, H_7); 8.13 (m, 3H, H_4, H_5, H_8); 8.37 (d, 1H, H_3); 8.84 (s, 1H, H_1); 14.00 (s wide, 1H, NH).

Table II. *(Continued).*

Compd	Formula	Yield (%)	MP	Rf [a]	^{1}H-NMR (DMSO-d_6) (δ ppm)
IIIm	$C_{17}H_{18}N_4O_2$	54	252	0.61	2.03 (m, 2H, Ar-CH_2-CH_2) ; 2.87 (m, 2H, Ar-CH_2-CH); 3.12 (m, 3H, Ar-CH_2-CH_2, Ar- CH_2-CH); 3.24 (s, 3H, N-CH_3) ; 3.43 (s, 3H, N-CH_3); 7.10 (m, 4H , Ar); (NH exchanged with H_2O from DMSO)
IIIn	$C_{17}H_{18}N_4O_4$	22	332[c]	0.53	3.09 (m, 3H, Ar-CH_2-CH); 3.35 (s, 3H, N-CH_3); 3.59 (s, 3H, N-CH_3); 3.90 (s, 3H, OCH_3); 4.18 (t, 1H, OCH_2); 4.55 (m, 1H, OCH_2) ; 6.56 & 6.66 (2d, 2H, H_8 & H_6); 7.19 (m, 1H, H_7); 13.8 (s, 1H, NH).
IIIo	$C_{14}H_{14}N_4O_3$	19	222[e]	0.69	3.34 (s, 3H, N-CH_3); 3.54 (s, 3H, N-CH_3); 5.19 (s, 2H, OCH_2); 7.10 (m, 3H, Ar); 7.42 (m, 2H, Ar); 13.9 (s,1H, NH).
IIIp	$C_{15}H_{16}N_4O_3$	16	195	0.68	1.65 (d, 3H, CH_3, J=6.5 Hz); 3.21 (s, 3H, N-CH_3); 3.43 (s, 3H, N-CH_3); 5.56 (q, 1H, CH, J=6.5 Hz) ; 6.95 (m, 3H, Ar); 7.26 (m, 2H, Ar); 13.82 (s, 1H, NH).
IIIq	$C_{15}H_{14}N_4O_3$	49	300[c]	0.49	3.35 (s, 3H, N-CH_3); 3.52 (s, 3H, N-CH_3); 3.58 (m, 2H, Ar-CH_2); 5.96 (t, 1H, O-CH-) ; 6.92 (d, 1H, H_7, J=7.9 Hz); 7.00 (t, 1H, H_5, J=7.2 Hz); 7.26 (t, 1H, H_6. J = 7.4 Hz); 7.39 (d, 1H, H_4, J=7.2 Hz); 13.92 (s, 1H, NH)
IIIr	$C_{15}H_{12}N_4O_3$	30	320[c]	0.66	3.39 (s, 3H, N-CH_3); 3.63 (s, 3H, N-CH_3); 7.45 (m, 1H, H_6, J=1Hz & 8Hz); 7.57 (m, 1H, H_5, J=1Hz & J=8Hz); 7.78 (s, 1H, H_3); 7.82 (dd, 1H, H_7, J=1 & 8Hz); 7.89 (d, 1H, H_4, J=8Hz); 13.91 (s,1H, NH).
IIIs	$C_{11}H_{10}N_4O_3$	30	345[c,e]	0.55	3.25 (s, 3H, N-CH_3); 3.46 (s, 3H, N-CH_3); 6.71 (m, 1H, H_4); 7.22 (m, 1H, H_3); 7.91 (m, 1H, H_5); 13.91 (s,1H, NH).
IIIt	$C_{16}H_{18}N_4O_3$	15	132	0.72	1.07 (t, 3H, CH_2-CH_3); 2.10 (m, 2H, CH_2); 3.32 (s, 3H, N-CH_3); 3.54 (s, 3H, N-CH_3); 5.43 (t, 1H, CH) ; 7.05 (m, 3H, Ar); 7.37 (m, 2H, Ar); 13.82 (s, 1H, NH).
IIIu	$C_{16}H_{16}N_4O_3$	35	217	0.62	2.27 (m , 2H, Ar-CH_2-CH_2); 2.92 (m, 2H, Ar-CH_2-CH_2); 3.24 (s, 3H, N-CH_3); 3.44 (s, 3H, N-CH_3); 5.24 (m,1H, OCH); 6.96 (m, 4H, Ar); 13.75 (s, 1H, NH).
IIIv	$C_{17}H_{16}N_4O_4$	24	316[c]	0.64[b]	3.31 (s, 3H, N-CH_3); 3.56 (s, 3H, N-CH_3); 3.95 (s, 3H, O-CH_3); 5.23 (s, 2H, CH_2); 6.56 (d, 1H, H_8, J=8Hz); 6.67 (d, 1H, H_6, J=8Hz); 7.12 (t, 1H, H_7, J=8Hz); 7.36 (s, 1H, CH ethylene); 13.85 (s, 1H, NH).
IIIw	$C_{15}H_{14}N_4O_4$	30	255	0.64	3.24 (s, 3H, N-CH_3); 3.43 (s, 3H, N-CH_3); 4.41 (dd, 1H, H_2, J=7Hz & J=11.5Hz); 4.57 (dd, 1H, H_3, J=3 Hz & J=11.5Hz); 5.42 (dd,1H, H_3, J=3Hz & J=7Hz); 6.92 (m, 4H, Ar); 13.94 (s, 1H, NH).
IIIx	$C_{16}H_{12}N_4O_4$	30	256	0.88	3.39 (s, 3H, N-CH_3); 3.62 (s, 3H, N-CH_3); 7.11 (s,1H, H_3); 7.64 (m, 1H, H_6, J=7Hz); 7.84 (d, 1H, H_8, J=7Hz); 7.99 (m, 1H, H_7, J=2 Hz & 7Hz); 8.17 (d, 1H, H_5, J=2 & 7Hz); (NH exchanged with H_2O from DMSO).

[a]Ethyl acetate; [b]ethanol; [c]decomposition; [d]$CDCl_3$; [e]**IIIo** [19]: MP = 224°C; **IIIs** [20]: MP = 347°C.

Table III. Pharmacological activity of compounds **III**.

Compound	pD_2[a]	
	Histamine	*Acetylcholine*
IIIa	–[b]	–
IIIb	–	–
IIIc	4.00	4.52
IIId	–	–
IIIe	–	–
IIIf	–	–
IIIg	–	–
IIIh	3.75	–
IIIi	4.70	–
IIIj	–	–
IIIk	–	–
IIIl	–	–
IIIm	3.90	–
IIIn	3.60	–
IIIo	3.20	–
IIIp	4.00	–
IIIq	4.00	–
IIIr	–	–
IIIs	4.75	3.55
IIIt	3.75	–
IIIu	4.40	4.00
IIIv	–	–
IIIw	–	–
IIIx	–	–
Theophylline	4.10	3.50

[a]Log of concentration that inhibits 50% of bronchospasm induced by histamine or acetylcholine ($-\log IC_{50}$): [b]$pD_2 < 3$.

The physical specifications and NMR spectral data of amides **II** are reported in table I, except **IIa** which is commercially available. IR (KBr) ν cm^{-1} (spectral data for all compounds): 3400, 3300, 3200 (NH, NH_2); 3100, 2900 (CH, CH_3); 1690, 1650 (CO); 1610, 1500, 1450 (C=C).

Synthesis of cyclic compounds ***III***

Two alternative methods were used.

Method a. Compounds ***IIIb–k, o, q, r, s, u, w, x.*** To a solution of amide **II** (5 mmol) in 50 ml pyridine or DMF were added phosphoric anhydride (5.5 mmol) and a catalytic amount of $AlCl_3$. The mixture was heated under reflux for 4 h then cooled and filtered. After drying *in vacuo*, the residual product was recrystallized either from DMF for compounds **IIIb, c, d, e, f, g, i, j, k, r, s, x**, or from ethanol for compounds **IIIh, o, u, w**. (When the reaction was carried out in DMF, the crude product was washed with water before recrystallizing.)

Method b. Compounds ***IIIl, m, n, p, t, v.*** To a solution of amide **II** (3 mmol) in 50 ml heated butanol was added a solution of potassium *tert*-butoxide (3 mmol) in 20 ml butanol. The mixture was heated under reflux for 10 to 15 min and the reaction was followed by thin-layer chromatography. After complete reaction, the mixture was then treated with acetic acid. After cooling, the resulting precipitate was collected by filtration and recrystallized from ethanol.

The physical specifications and NMR spectral data of cyclic compounds **III** are reported in table II, except **IIIa** which is commercially available. Generally, one can observe by NMR that the signals of the two methyl groups brought by the nitrogen atoms are shifted to downfield for the ring-closed compounds **III** in comparison with the corresponding amides **II**. We also observed the disappearance of the NH_2 signals (between 6 and 7 ppm) and the amide NH signal (between 8 and 9.6 ppm); the NH signal of theophylline appears at 13–14 ppm. IR (KBr) ν cm^{-1} (spectral data for all compounds): 3400, 3200 (NH); 3100, 3000, 2900 (CH, CH_3); 1700, 1685, 1650 (CO); 1600, 1580 (C=C).

Pharmacological evaluation

These experiments were conducted according to the method described previously [18]. Drugs were dissolved in distilled water, with a minimal amount of 1 N NaOH solution.

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