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1-Benzazepine derivatives acting as ATP-dependent potassium-channels antagonists

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Summary — In order to select between various pharmacological activities related to the 1-benzazepine nucleus, a set of 1-benzazepine derivatives bearing different N-1 or C-2 substituents were synthesized and tested *in vitro* as ATP-dependent K^+-channel antagonists on isolated guinea-pig trachea. Cumulative concentration curves to cromakalim were constructed in the absence or presence of the various compounds tested in comparison with glibenclamide. Products bearing N-1 substituents, especially (2-imidazolinyl)methyl showed a non-competitive antagonism towards ATP-dependent K^+ channels.

1-benzazepine / ATP-dependent K^+-channel antagonist

Introduction

The 1-benzazepine nucleus **1** (fig 1) has been extensively used in potentially active structures. Most activities related to this nucleus [1] appeared in the field of local anaesthetics, bactericidals, and cholecystokinine (CCK) or serotonin antagonists, but the most important activity concerns the central nervous system (CNS) with anxiolytic, neuroleptic, antidepressant or anorectic effects, according to the presence of unsaturation and substituents. The second main area where activity has been demonstrated is in the cardiovascular system. Inotropic and antihypertensive (angiotensine-converting enzyme inhibitors) properties have been studied and even applied for therapeutic use (benazepril).

Antiarrhythmic activity has been demonstrated in tetrahydro compounds such as **2** (fig 1). When $Z = H_2$, R^3 = phenyl and R^1 = (2-imidazolinyl)methyl, a potent antifibrillatory activity appeared in unanaesthetised cats [2–4]. The intensity of this effect was retained when the imidazoline ring was either substituted with a methyl group on its 4 position or enlarged to a tetrahydropyrimidine ring. Introduction of a chlorine atom in the *para* position of the 3-phenyl substituent caused an increase of the effect. When $R^7 = R^8$ = OMe, both effect and toxicity (epileptoid syndrome in dog) decreased. The compound selected was SU 13 197 ($Z = H_2$, R^3 = 4-Cl-phenyl and R^1 = (2-imidazolinyl)-methyl). 4-Phenyl derivatives (instead of 3-phenyl derivatives) induced a loss of activity which was more marked if $Z = H_2$ rather than oxygen.

Hypoglycaemic properties were also reported. For example [5], imines derived from 3,5-dihydro-4*H*-1-benzazepines **3** (fig 1) with the *meta*-chlorophenyl group on C-3 and an amino group on C-2 (amidine)

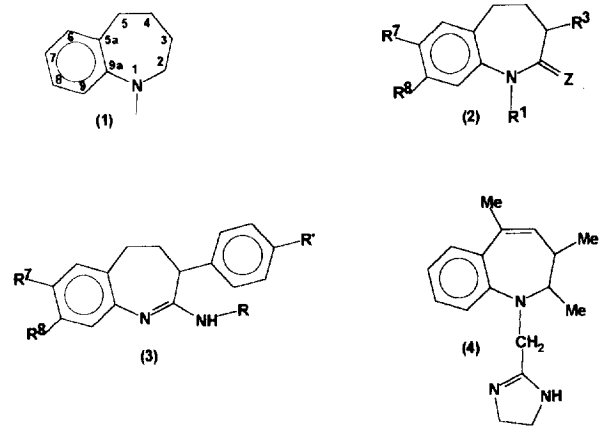


Fig 1. Structures of compounds **1–4**.

showed moderate activity in rats but was less active than tolbutamide even for the most active compound: R^7 = OMe; R^8 = R' = H; R = cyclopropyl.

In our laboratory, we have studied [6] 2-oxo (Z = O) or hydrogenated (Z = H_2) compounds derived from **2** (fig 1) with R^1 = (2-imidazolinyl)methyl or variously substituted aminoalkyls. The best activity (arrhythmias caused by light petroleum and quinidine in guinea pigs) was obtained with Z = O, R^3 = R^7 = R^9 = H and R^1 = -$(CH_2)_3$-N-*i*Pr_2.

We performed a screening programme [7] on various derivatives **4** (fig 1) with the general dihydro-1*H*-benzazepine structure. Various effects appeared; the most significant result was that the derivatives were diuretic when there was a double bond between C-3 and C-4, and hypoglycaemic when R^2 = R^3 = R^5 = Me, R^1 = (2-imidazolinyl)methyl and a 4,5-unsaturation was present. They had performances equivalent to chlorpropamide in normal rats.

These two kinds of activities, antiarrhythmic and hypoglycaemic, the adverse effects on the CNS noted with epileptoid phenomena, and the activity of K^+-channel openers as anticonvulsants [8] led us to synthesize new compounds with the 1-benzazepine nucleus and an unsaturation. These were tested *in vitro* in order to reveal any ATP-dependent K^+-channel antagonism [9–14].

Chemistry

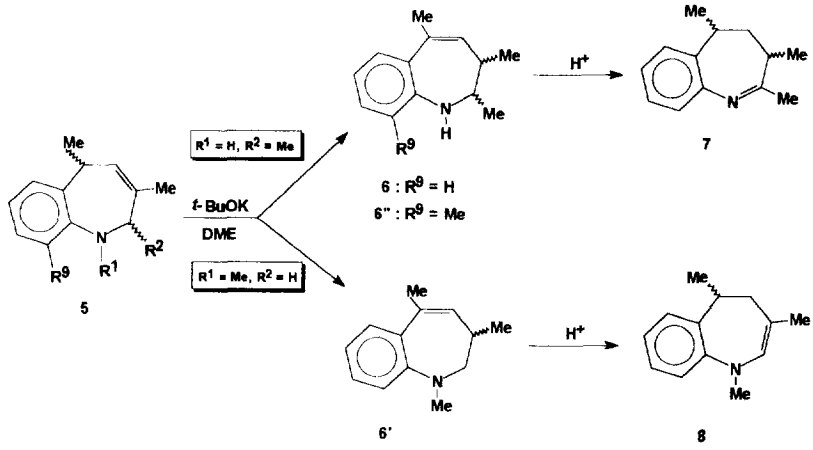
2,5-Dihydro-1*H*-1-benzazepines **5** [15] gave access [16, 17] to 2,3-dihydro derivatives **6** or **6'** whose diastereoisomers were obtained under appropriate experimental conditions in constant proportions (2*R**3*R** 95%, 2*R**3*S** 5%), except for compound **6''** whose diastereoisomer 2*R**3*S** was sterically favored. Compounds **6** and **6'** were treated with HCl [18] to give imines **7** (if R^1 = H and R^2 = Me) or enamines **8** (if R^1 = Me and R^2 = H) (scheme 1).

Various difficulties and limitations for the synthesis appeared. Compound **5** (with R^1 = H) could not undergo N-alkylation in strong basic media because it was transformed [19] into aminodiene. Monoreduction of the dihydro compounds **5** and **8** into tetrahydrobenzazepines was performed with different reagents and/or conditions. Hydrogenations with Raney Nickel or Pd/charcoal were convenient for unsaturation in any position. Only AlH_3 (mixtures of $LiAlH_4$, (3 eq) and $AlCl_3$ (1 eq)) [20] could transform aminonitrile **5a** into amine **5j** without loss of HCN or reduction of the 3,4-double bond, allowing further access to derivatives **6**. These particularities led us to various choices for the synthetic pathways.

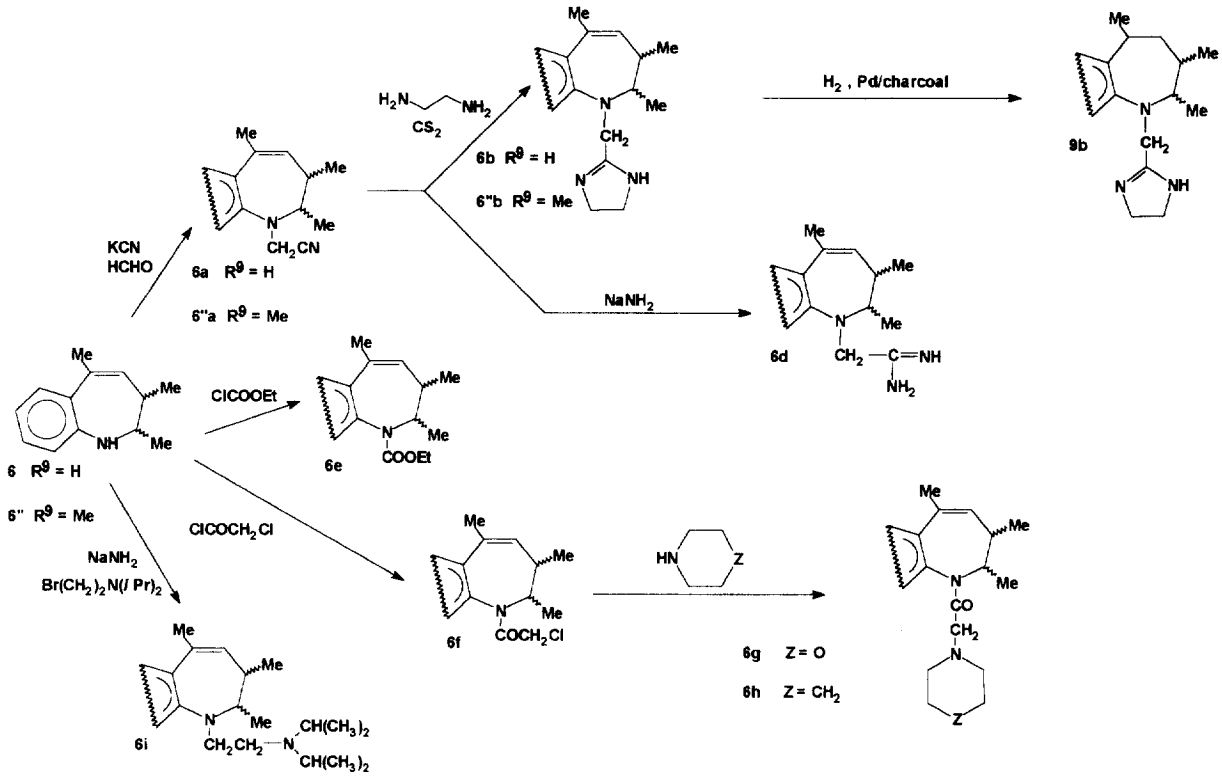
Compound **6** (scheme 2) led first to α-aminonitriles **6a**, which were easily transformed into the 1-(2-imidazolinyl)methyl derivative **6b**, whose hydrogenation (H_2, Pd/charcoal, 1 atm, RT) occurred on the azepine nucleus only giving **9b**. Compound **6a** was transformed into amidine **6d** by means of $NaNH_2$ [21]. The same sequence was applied to compound **6''**, an analogue of **6** bearing a methyl substituent in position 9 and furnished **6''a** and **6''b**.

The NH group of **6** underwent *N*-acylation with ethyl chloroformate in the presence of triethylamine to give carbamate **6e**, or with chloroacetic acid chloride in the same conditions to give *N*-chloracetamide **6f**, whose treatment by morpholine or piperidine led to **6g** or **6h**.

The use of $NaNH_2$ was necessary for *N*-alkylation and we chose to prepare **6i**, which bears the diisopro-



Scheme 1.



Scheme 2.

pylaminoethyl moiety. This moiety has previously produced good results in an antiarrhythmic test [6].

Starting from **5** (scheme 3), the same method was used to prepare aminonitrile **5a**, whose treatment with AlH_3 led to diamine **5j** with conservation of the 3,4-double bond. Transposition by potassium *tert*-butoxide in 1,2-dimethoxyethane (DME) allowed preparation of the 4,5-unsaturated diamine **6j**. Reaction of **6j** with phenylisocyanate or *p*-toluenesulfonylchloride furnished urea **6k** or sulfonamide **6l**. Treatment of **5j** by the same method gave urea **5k**.

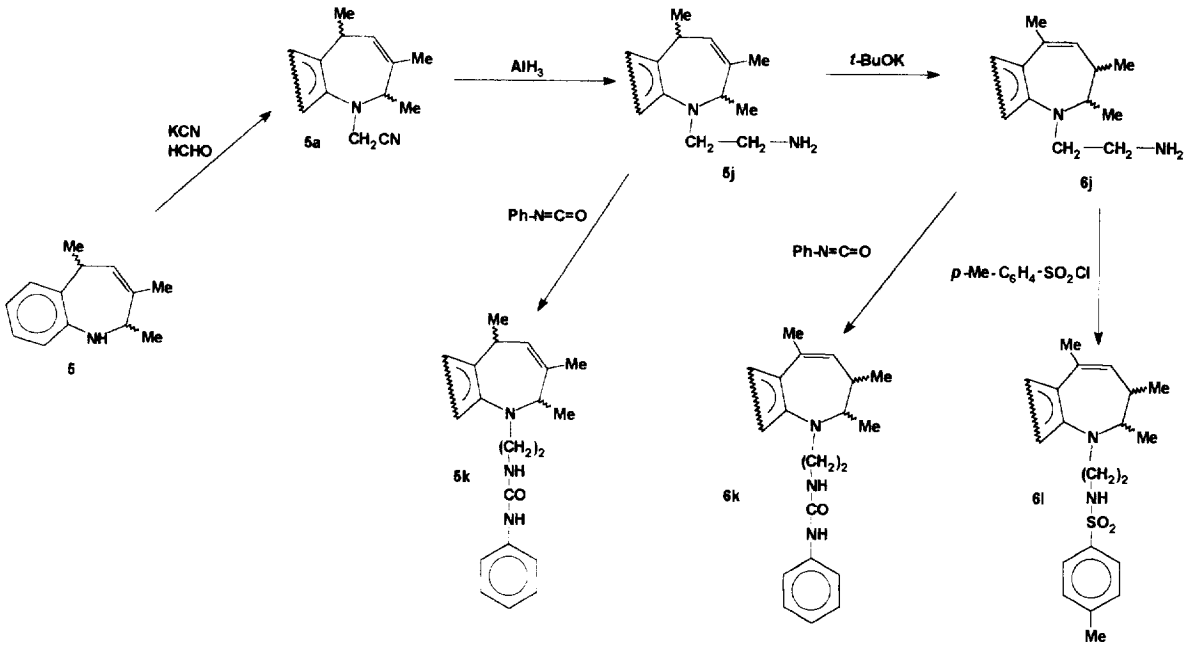
With the enamine **8** (scheme 4), the iminium salt generated by anhydrous HCl was treated with KCN [22–24] and was transformed into aminonitrile **9a** *via* stereoselective addition. Compound **9a** was very sensitive to acidic or basic medium (loss of HCN) but was reduced by means of $LiAlH_4$ into diamine **9j** whose transformation by the same methods as above furnished **9k** and **9l**.

The imine **7** (scheme 4) led stereoselectively to good yields of a 2-aminonitrile derivative by reaction with trimethylsilylcyanide (TMSCN) [25]. This derivative is far more sensitive than its analogues **6a** and **9a** and any attempt to reduce or transform the cyano group caused loss of HCN and gave back **7**. Another attempt was performed by *N*-methylation of **7** to give an iminium salt whose treatment by KCN [26] gave **9'a**. This compound was very sensitive to all the reagents tried (acidic or basic medium and hydrides) and each assay led to 2-methylated enamine **8'**.

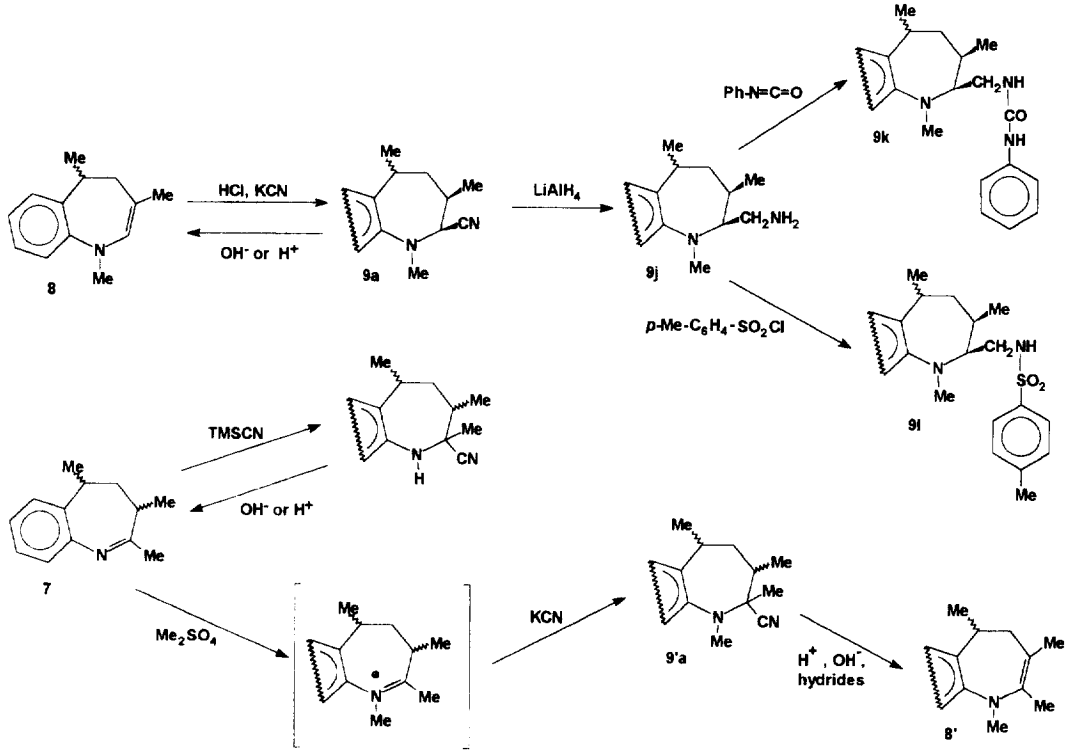
The structures of all these compounds were established by IR spectrometry, ^1H- and ^{13}C-NMR and mass spectra. All data are in concordance with those described in previous work [6, 15–19].

Pharmacology

The relaxant and antispasmogenic effects of K^+-channel openers (KCOs) have been demonstrated *in vivo* and *in vitro* on airway smooth muscle in animals and/or humans, for cromakalim (BRL 39315) and its enantiomer lemakalim (BRL 38227) [27, 28]. One of the criteria used to define KCOs is the inhibition of their effects by the sulfonylurea glibenclamide, which is selective for ATP-dependent K^+ channels [28, 29].



Scheme 3.



Scheme 4.

The aim of the pharmacological study was to investigate a similar antagonistic effect to glibenclamide on isolated guinea-pig trachea for the compounds presented in this paper.

On isolated guinea-pig tracheal tissues precontracted with histamine (10^{-5} M), the KCO cromakalim induced concentration-dependent relaxations. The sulfonylurea glibenclamide (10^{-5} M) produced rightward shifts of the concentration–response curves to cromakalim (10^{-8} to 10^{-5} M) with a significant reduction of maximum response (fig 2).

Results and discussion

The maximal effect (E_{max}) allowed us to establish a preliminary selection in the efficacy of the compounds tested, showing significant differences from control for **6b**, **6"b**, **6h**, **6k**, **6d** and **9b** (10^{-6}–10^{-5} M) whereas **6e**, **6g**, **6i**, **6l**, **5k**, **9k**, and **9l** did not influence the relaxation induced by cromakalim.

Indeed, we observed that, similarly to glibenclamide, compounds **6b**, **6"b**, **6h**, **6k**, **6d** and **9b** (10^{-5} M) shifted the concentration–response curves to cromakalim to the right with a significant depression of the maximum response, indicating a non-competitive antagonism (fig 3).

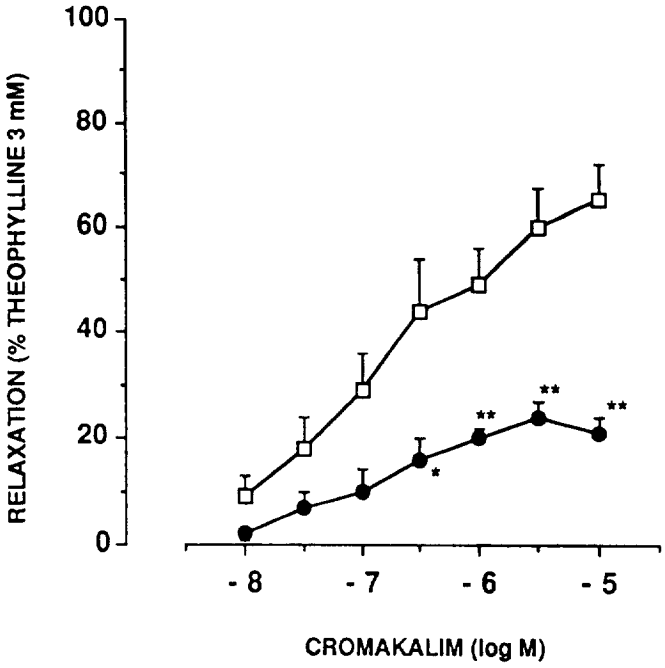


Fig 2. Cumulative concentration–response curves to cromakalim in the absence (control, □) and presence of glibenclamide (●, 10^{-5} M) in guinea-pig trachea precontacted with histamine (10^{-5} M). Means ± sem of 4 animals are shown. Significant differences from control are indicated by $*P < 0.05$ and $**P < 0.01$.

Furthermore, calculation of ED_{15} allowed us to evaluate and compare the potency of the effective compounds. A second classification based on the activity could then be made. The compounds **6b**, **6k** and **6h** (10^{-5} M) showed a similar or higher potency than glibenclamide with ED_{15} values of 5.68 ± 0.33, 6.53 ± 0.34, 6.61 ± 0.29 and 6.64 ± 0.27, respectively, which are significantly different from the control (table I).

In contrast, the compounds **9b**, **6"b** and **6d** (10^{-5} M) produced only a small rightward shift in the concentration–response curves to cromakalim with a significant depression of the maximum response; their ED_{15} values were not different from control (fig 3; table I).

A decreasing activity order can be proposed: **6b** > **6k** > **6h** > **6"b** > **9b** > **6d** > **6e** = **6g** = **6i** = **6l** = **5k** = **9k** = **9l**.

This work has also allowed a qualitative study of structure–activity relationships. Firstly, substitution of the (2-imidazolinyl)methyl moiety on N-1 gave the best activity which was lowered by *peri*-substitution on C-9 (methyl group, **6"b**), inducing conformational changes, or reduction of the 4,5-double bond (**9b**). It can be noticed that the replacement of the imidazoline ring by an open and basic analogue (amidine) gave good results (**6d**). Secondly, substitution on N-1 by an acyl group associated with a β basic site gave good activity if the basic site is in a piperidine (**6h**). Its changes to morpholine (**6g**) with weaker basicity and

Table I. Effect of the compounds **6b**, **6k**, **6h**, **6"b**, **9b**, **6d** and glibenclamide on spasmolytic action of cromakalim.

Compound	*ED_{15} (–log M)*	*E_{max} (%)*
Control	7.50 ± 0.06 (8)	60.0 ± 4.6 (9)
6b (10^{-5} M)	5.68 ± 0.33*** (5)	17.0 ± 5.1*** (6)
6k (10^{-5} M)	6.53 ± 0.34* (6)	30.0 ± 3.5*** (6)
6h (10^{-5} M)	6.61 ± 0.29* (4)	34.0 ± 7.8* (5)
6"b (10^{-5} M)	7.34 ± 0.05 (6)	36.0 ± 6.1** (6)
9b (10^{-5} M)	7.37 ± 0.13 (5)	35.0 ± 3.9** (5)
6d (10^{-5} M)	7.44 ± 0.17 (6)	38.0 ± 5.1** (6)
Glibenclamide (10^{-5} M)	6.64 ± 0.27* (4)	21.0 ± 2.9*** (4)

Values are means ± sem; the numbers in parentheses represent the number of animals per group. Significant differences from control are indicated by $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

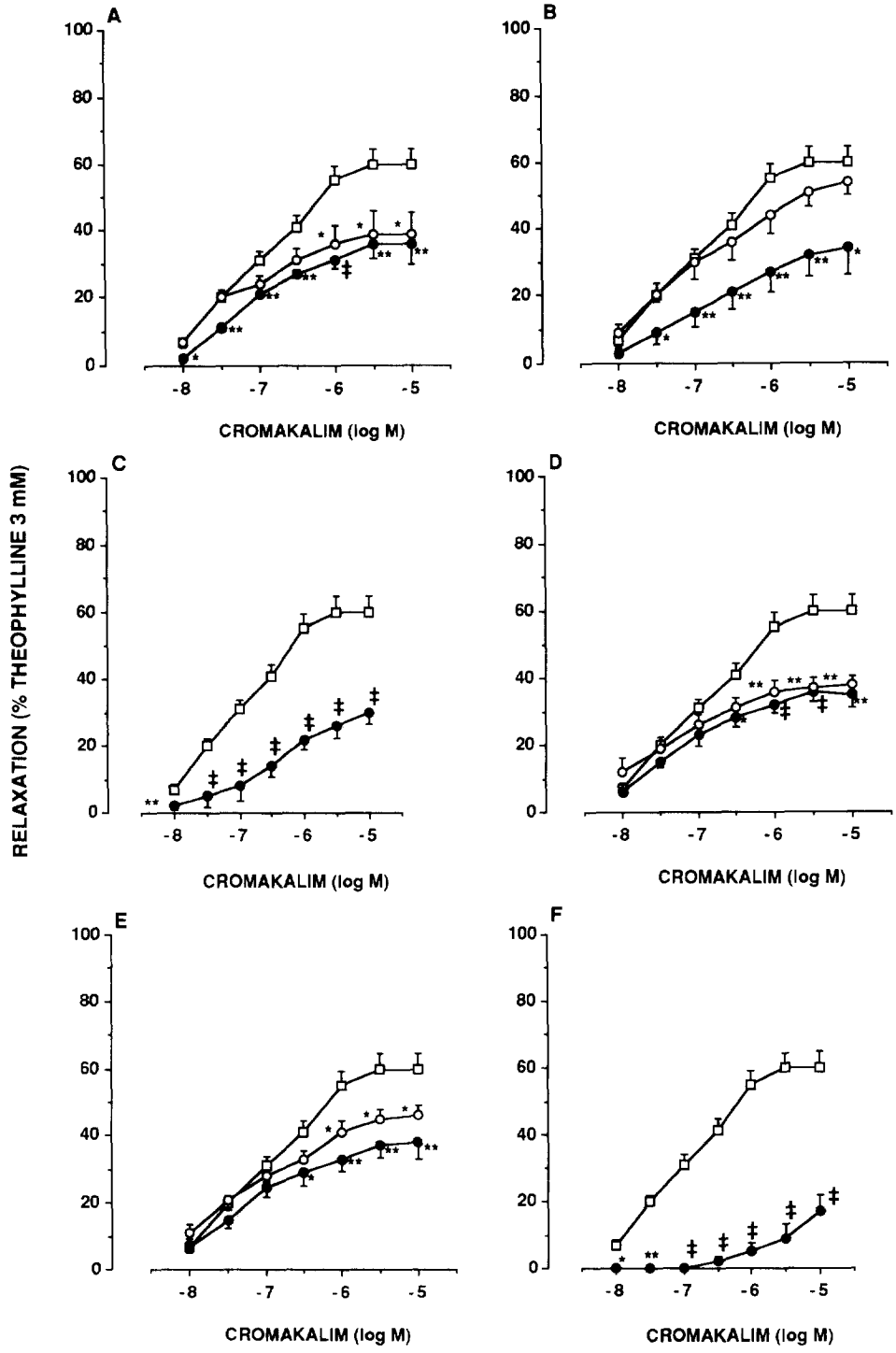


Fig 3. Cumulative concentration–response curves to cromakalim in the absence (control, □) and presence of **6"b** (A), **9b** (D), **6h** (B), **6d** (E) (○, 10^{-6} M; ●, 10^{-5} M), **6k** (C) and **6b** (F) (●, 10^{-5} M) in guinea-pig trachea precontracted with histamine (10^{-5} M). Means ± sem of 4–9 animals are shown. Significant differences from control are indicated by $^{*}P < 0.05$, $^{**}P < 0.01$, $^{\ddagger}P < 0.001$.

higher hydrophilicity led to less good results. Thirdly, when the N-1 substituent is a urea, $(CH_2)_2NHCONHPh$, a good activity was noted (**6k**), which disappeared if the azepine double bond is between C-3 and C-4 instead of C-4–C-5 (**5k**). Finally, the use of the diisopropylaminoethyl moiety on N-1 (**6i**) was disappointing considering the results previously obtained in antiarrhythmic tests [6].

Experimental protocols

Chemistry

All reagents and solvents were purchased from Janssen Chimica, Aldrich and Merck. Compounds were purified on column chromatography with silica-gel 60 70-230 Mesh purchased from Merck. The purity of the synthesized substances was assessed by thin-layer chromatography (TLC), performed on silica-gel 60 F_{254} aluminium sheets (Merck). R_f values are given for guidance.

Melting points were determined on a Kofler melting point apparatus and are uncorrected. The IR spectra were obtained with a 16 PC FTIR Perkin Elmer spectrometer; ν_{max} are given in cm^{-1}. Solids were examined with a diffuse reflectance accessory. Sample mixture was obtained by grinding a 1% ratio of sample into a KBr matrix. For liquids an horizontal attenuated total reflectance (HATR) accessory with a ZnSe crystal was used.

Elemental analyses for C, H, N were performed by the Laboratoire de Microanalyse at the Faculté de Pharmacie de l'Université Paris XI, Châtenay-Malabry or the Service central d'analyse at the CNRS, Vernaison, France. Analyses indicated by the symbols of the elements were within ± 0.4% of theoretical values.

NMR data are reported in ppm with tetramethylsilane (TMS) as an internal reference and are given in δ, coupling constants (*J*) are reported in Hz. ^{1}H–NMR spectra were recorded with a Brucker AM 300 WB (300 MHz). For a few compounds (indicated in the text) a Varian EM360L CW (60 MHz) was used. AB systems are described as follows: Hα (d or m: centered) the least shielded signal; Hβ (d or m: centered) the most shielded. For recording ^{13}C-NMR spectra we used the Brucker apparatus (75 MHz). All NMR data are given for the main diastereoisomer and atoms are numbered as shown in figure 1 for compound **1**.

As regards N-1 and C-2 complex substituents all atoms are numbered as follows: 1', 2' (data with an asterisk can be inverted).

Mass spectrometric measurements were performed on a Varian Mat 311 instrument in electron impact (EI) mode (70 eV).

(2,3,5,-Trimethyl-2,5-dihydro-[1H]-benzazepin-1-yl)ethane nitrile ***5a***

A solution of KCN (3.9 g; 0.06 mol) in 10 ml H_2O was added slowly over a 15 min period to an already stirred cooled suspension (15°C) of **5** (9.35 g; 0.05 mol) in 25 ml acetic acid and 1.51 g $(CH_2O)_n$ (0.05 mol). The mixture was heated progressively up to 60°C and maintained 5 min at this temperature. The stirred suspension was cooled (35°C), and 3 ml of a 30% aqueous solution of HCHO was added. The emulsion was allowed to stand 1 night at room temperature. The crude product was neutralized with K_2CO_3 and extracted with Et_2O. The organic phase was dried over anhydrous K_2CO_3 and evaporated. The oily residue was purified by distilling under vacuum. Yield: 10 g (89%); $bp_{0.5}$ = 155°C. TLC: C_6H_6/MeOH, 99:1 (R_f: 0.8). IR: νCN: 2246. ^{1}H-NMR ($CDCl_3$): H-1'α (d, 4.13), H-1'β (d, 4.06) J_{AB} = 16.79, H-2 (q, 4.09), CH_3-2 (d, 0.96), CH_3-3 (s, 1.6), H-4 (m, 5.26), H-5 (m, 3.74), CH_3-5 (d, 1.38), Ar (m, 7–7.3). ^{13}C-NMR ($CDCl_3$): CH_2-1' (t, 41.53), CN (s, 117.67), C-2 (d, 60.27), CH_3-2 (q, 13.4), C-3 (s, 136.24), CH_3-3 (q, 22.83), C-4 (d, 128.73), C-5 (d, 31.74), CH_3-5 (q, 19.10), C-5a (s, 143.34), C-6 (d, 126.03), C-7 (d, 123.99), C-8 (d, 124.72), C-9 (d, 121.66), C-9a (s, 144.87). MS: $M^{+\bullet}$: 226 (28.5) $C_{15}H_{18}N_2$: calc: 226.1469; found: 226.146; 211 (44), 186 (100), 184 (50.7), 171 (97), 40 (2.8).

(2,3,5-Trimethyl-2,3-dihydro-[1H]-benzazepin-1-yl)ethane nitrile ***6a***

This compound was synthesized from **6** according to the same method as described above. Yield: 10.5 g (93%); $bp_{0.4}$ = 150°C. TLC: C_6H_6/MeOH, 99:1(R_f: 0.8). IR: νCN: 2222. ^{1}H-NMR ($CDCl_3$) (2*R**3*R**): H-1'α (d, 4.25), H-1'β (d, 4.0) J_{AB} = 17.96, H-2 (m, 3.71), H-3 (m, 2.55), $J_{H\text{-}2,H\text{-}3}$ = 4.42, CH_3-2 (d, 1.19), CH_3-3 (d, 1.01), H-4 (d, 5.7), $J_{H\text{-}4,H\text{-}3}$ = 5.95, CH_3-5 (s, 2.1), Ar (m, 7.2–7.32). ^{13}C-NMR ($CDCl_3$) (2*R**3*R**): CH_2-1' (t, 40.45), CN (s, 116.76), C-2 (d, 70.39), CH_3-2 (q, 13.53), C-3 (d, 35.86), CH_3-3 (q, 16.92), C-4 (d, 132.06), C-5 (s, 133.99*), CH_3-5 (q, 22.56), C-5a (s, 135.93*), C-6 (d, 127.9), C-7 (d, 122.41), C-8 (d, 127.13), C-9 (d, 119.07), C-9a (s, 146.96), $^2J_{CN,CH_2\text{-}1'}$ = 6.5. MS: $M^{+\bullet}$: 226 (83), $C_{15}H_{18}N_2$: calc: 226.1469; found: 226.148; 211 (100), 196 (9.8), 184 (48), 170 (86), 144 (21), 115 (14).

(2,3,5,9-Tetramethyl-2,3-dihydro-[1H]-benzazepin-1-yl)ethane nitrile ***6"a***

This compound was synthesized from **6"** (4 g, 20 mmol) according to the same method as described for **5a**. The oily residue was purified by column chromatography (petroleum ether/Et_2O, 80:20). Yield: 4 g (84%). TLC: petroleum ether/Et_2O 80:20 (R_f: 0.75). IR: νCN: 2242. ^{1}H-NMR ($CDCl_3$) (2*R**3*S**): H-1'α (d, 3.92), H-1'β (d, 3.79) J_{AB} = 17.38, H-2 (m, 3.29), H-3 (m, 1.96), $J_{H\text{-}2,H\text{-}3}$ = 11.1, CH_3-2 (d, 1.18), CH_3-3 (d, 0.99), H-4 (d, 5.64), CH_3-5 (s, 2.08), CH_3-9 (s, 2.33), Ar (m, 7.1–7.4). ^{13}C-NMR ($CDCl_3$) (2*R**3*S**): CH_2-1' (t, 44.27), CN (s, 117.98), C-2 (d, 74.52), CH_3-2 (q, 18.73), C-3 (d, 38.42), CH_3-3 (q, 20.02), C-4 (d, 133.85), C-5 (s, 138.79*), CH_3-5 (q, 22.41), C-5a (s, 143.16), C-6 (d, 126.53*), C-7 (d, 125.33*), C-8 (d, 129.68), C-9 (d, 135.95*), CH_3-9 (q, 18.26), C-9a (s, 143.65). MS: $M^{+\bullet}$: 240 (63.5), $C_{16}H_{20}N_2$: calc: 240.1626; found: 240.161; 225 (52), 200 (13.6), 198 (33), 184 (100), 144 (28), 115 (15).

2-Cyano-1,3,5-trimethyl-2,3,4,5-tetrahydro-[1H]-1-benzazepine ***9a***

HCl gas was bubbled through a solution of **8** (2 g, 10.7 mmol) in 30 ml anhydrous Et_2O, maintained in an ice bath for 10 min. The solvent was removed under reduced pressure. The residual solid was dissolved in 25 ml CH_2Cl_2. A solution of KCN (1 g, 15.4 mmol) in 20 ml H_2O was added dropwise under stirring over a period of 20 min. The organic phase was evaporated, dissolved in Et_2O, dried with anhydrous K_2CO_3, and the solvent was removed under reduced pressure. The crude solid was purified by recrystallization from absolute EtOH. Yield: 2 g (87%); mp: 70°C. TLC: petroleum ether/Et_2O, 80:20 (R_f: 0.8). IR: νCN: 2229.^{1}H-NMR ($CDCl_3$) (2*R**3*R**): CH_3-1 (s, 2.94), H-2 (d, 3.66), H-3 (m, 1.47), $J_{H\text{-}2,H\text{-}3}$ = 10, CH_3-3 (d, 1.11), H-4α (m, 1.73), H-4β (m, 1.35), H-5 (m, 3.39), CH_3-5 (d, 1.3), Ar (m, 7.1–7.3). ^{13}C-NMR ($CDCl_3$) (2*R**3*R**): CH_3-1 (q, 40.19), C-2 (d, 61.53), CN (117.06), C-3 (d, 34.84*), CH_3-3 (q, 18.85),

C-4 (t, 39.75), C-5 (d, 30.58*), CH_3-5 (q, 19.42), C-5a (s, 140.54), C-6 (d, 126.90), C-7 (d, 124.81), C-8 (d, 124.45), C-9 (d, 120.16), C-9a (s, 145.5). MS: $M^{+\bullet}$: 214 (100), $C_{14}H_{18}N_2$: calc: 214.1469; found: 214.147; 199 (13), 187 (6), 172 (28), 157 (30), 147 (52), 144 (19), 132 (95). Anal (C, H, N).

1-(2-Imidazolinyl)methyl-2,3,5-trimethyl-2,3-dihydro-[1H]-1-benzazepine ***6b***

A stirred mixture of **6a** (11.3 g, 50 mmol), diaminoethane (3.6 g, 60 mmol) freshly distilled on KOH, and 0.15 ml $CS_2$was heated at 120°C in an oil bath for 6 h. The dark crude mixture was cooled, dissolved in ethyl acetate and washed many times with water. The organic phase was dried with anhydrous K_2CO_3. The solvent was removed under reduced pressure and the crude solid was triturated with cold pentane. The precipitate was collected and recrystallized from pentane. Yield: 7.4 g (55%); mp: 74°C. TLC MeOH/Et_3N 99:1 (R_f: 0.25). IR: νNH: 3206. ^{1}H-NMR ($CDCl_3$) (2*R**3*R**): H-1'α (d, 4.77), H-1'β (d, 4.34), J_{AB} = 18.36, H-2 (m, 3.51), CH_3-2 (d, 1.09), $J_{H\text{-}2\ CH_3\text{-}2}$ = 6.33, H-3 (m, 2.53), $J_{H\text{-}2\ H\text{-}3}$ = 4.78, CH_3-3 (d, 0.96), $J_{H\text{-}3\ CH_3\text{-}3}$ = 7.11, H-4 (d, 5.74), CH_3-5 (s, 2.15), 4H-4',5' (m, 3.81), NH (s, 5.12), Ar (m, 7.02–7.30). ^{13}C-NMR ($CDCl_3$) (2*R**3*R**): CH_2-1' (t, 50.73*), C-2' (s, 167.25), C-4',5' (t, 50.34*), C-2 (d, 68.29), CH_3-2 (q, 14.02), C-3 (d, 37.51), CH_3-3 (q, 17.4), C-4 (d, 132.52), C-5 (s, 133.37*), CH_3-5 (q, 24.2), C-5a (s, 132.34*), C-6 (d, 127.58*), C-7 (d, 121.04), C-8 (d, 127.53*), C-9 (d, 119.37), C-9a (s, 146.85). MS: $M^{+\bullet}$: 269 (9.2), $C_{17}H_{23}N_3$: calc: 269.1891; found: 269.188; 254 (4.2), 186 (43.3), 144 (10), 84 (100). Anal (C, H, N).

1(2-Imidazolinyl)methyl-2,3,5,9-tetramethyl-2,3-dihydro-[1H]-1-benzazepine ***6"b***

This product was synthesized from **6"a** (2 g, 8.3 mmol) according to the same method as described for product **6b**. The oily residue was purified by column chromatography (MeOH/Et_3N, 99:1). Yield: 0.6 g (25%). TLC: MeOH/Et_3N, 99:1 (R_f: 0.29). IR: νNH: 3370. ^{1}H-NMR ($CDCl_3$) (2*R**3*S**): H-1'α (d, 4.0), H-1'β (d, 3.8), J_{AB} = 16, H-2 (m, 3.18), CH_3-2 (d, 1.12), $J_{H\text{-}2\ CH_3\text{-}2}$ = 6.13, H-3 (m, 2.14), CH_3-3 (d, 0.98), $J_{H\text{-}3\ CH_3\text{-}3}$ = 6.84, H-4 (d, 5.72), CH_3-5 (s, 2.17), CH_3-9 (s, 2.3), 4H-4',5' (m, 3.56), NH (s, 2.34), Ar (m, 7.03–7.11). ^{13}C-NMR ($CDCl_3$) (2*R**3*S**): CH_2-1' (t, 52.17*), C-2' (s, 169.06), C-3',4' (t, 51.02*), C-2 (d, 72.57), CH_3-2 (q, 19.84), C-3 (d, 36.76), CH_3-3 (q, 17.73), C-4 (d, 134.67), C-5 (s, 136.43*), CH_3-5 (q, 22.32), C-5a (s, 142.05), C-6 (d, 124.79), C-7 (d, 124.66), C-8 (d, 130.3), C-9 (d, 136.56*), CH_3-9 (q, 18.16), C-9a (s, 145.59). MS: $M^{+\bullet}$: 283 (7.5), $C_{18}H_{25}N_3$: calc: 283.2048; found: 283.206; 200 (42), 84 (100). Anal (C, H, N).

1-(2-Imidazolinyl)methyl-2,3,5-trimethyl-2,3,4,5-tetrahydro-[1H]-1-benzazepine ***9b***

A mixture of compound **6b** (0.5 g, 1.85 mmol) in 50 ml MeOH and Pd on powdered charcoal (5%) was shaken for 2 h after the theoretical amount of hydrogen had been consumed. The catalyst was filtered out and the solvent was removed under reduced pressure. The crude solid was purified by recrystallization from absolute EtOH. Yield: 0.48 g (95%); mp: 137°C. TLC: MeOH/Et_3N, 99:1 (R_f: 0.3). IR: νNH: 2400–3600, ν C=N: 1656. ^{1}H-NMR ($CDCl_3$): H-1'α (d, 3.97), H-1'β (d, 3.89) J_{AB} = 14.25, H-2 (m, 2.99), CH_3-2 (d, 0.44), $J_{H\text{-}2\ CH_3\text{-}2}$ = 6.86, H-3 (m, 2.08), CH_3-3 (d, 0.81), $J_{H\text{-}3\ CH_3\text{-}3}$ = 6.99, H-4α (m, 1.49), H-4β (m, 1 .08), H-5 (m, 2.99), CH_3-5 (d, 1.37), $J_{H\text{-}5\ CH_3\text{-}5}$ = 7.16, CH_2-4',5' (m, 3.61), NH (~ 3.61), Ar (m, 6.9–7.2). ^{13}C-NMR ($CDCl_3$): CH_2-1' (t, 50.01*), C-2' (s, 167.41), C-4',5' (t, 52.95*), C-2 (d, 58.90), CH_3-2 (q, 20.01*), C-3 (d, 35.04),CH_3-3 (q, 8.4), C-4 (t, 37.41), C-5 (d, 40.5), CH_3-5 (q, 21.22*), C-5a (s, 140.72), C-6 (d, 126.07), C-7 (d, 122.89), C-8 (d, 124.60), C-9 (d, 120.48), C-9a (s, 147.77). MS: $M^{+\bullet}$: 271 (0.19), $C_{17}H_{25}N_3$: calc: 271.2048; found: 271.205; 188 (50.5), 84 (100). Anal (C, H, N).

1-Methylamidine-2,3,5-trimethyl-2,3-dihydro-[1H]-1-benzazepine ***6d***

To a suspension of $NaNH_2$ (2 g, 50 mmol) in 15 ml anhydrous C_6H_6 under stirring, was added dropwise at room temperature over a period of 30 min, a solution of **6a** (5.65 g, 25 mmol) in 15 ml anhydrous C_6H_6. The reaction mixture was poured into cold water and extracted with Et_2O. The organic phase was treated with a 5% HCl aqueous solution. The aqueous extract was treated with a solution of NaOH (5%) in H_2O and extracted with Et_2O. The organic phase was dried by anhydrous K_2CO_3 and evaporated under vacuum. The crude solid was purified by recrystallization from absolute EtOH. Yield: 4.25 g (70%); mp: 106°C; TLC: MeOH/Et_3N, 99:1 (R_f: 0.15). IR: νNH: 3304, ν C=N: 1644. ^{1}H-NMR ($CDCl_3$) (2*R**3*R**): H-1'α (d, 4.06), H-1'β (d, 3.85) J_{AB} = 16.65, H-2 (m, 3.40), CH_3-2 (d, 1.03), $J_{H\text{-}2,CH_3\text{-}2}$ = 6.56, H-3 (m, 2.62), CH_3-3 (d, 0.97), $J_{H\text{-}3,CH_3\text{-}3}$ = 7.15, H-4 (d, 5.72), CH_3-5 (s, 2.15), NH, NH_2 (m, 5.53), Ar (m, 6.9–7.31). ^{13}C-NMR ($CDCl_3$) (2*R**3*R**): CH_2-1' (t, 55.04), C-2' (s, 166.6), C-2 (d, 65.85), CH_3-2 (q, 14.15), C-3 (d, 36.94), CH_3-3 (q, 17.31), C-4 (d, 132.51), C-5 (s, 134.65), CH_3-5 (q, 23.82), C-5a (s, 132.83), C-6 (d, 127.73), C-7 (d, 121.83), C-8 (d, 127.6), C-9 (d, 119.99), C-9a (s, 146.65). MS: $M^{+\bullet}$: 243 (0.6), $C_{15}H_{21}N_3$: calc: 243.1735; found: 243.173; 200 (10), 186 (100), 58 (30), 43 (4). Anal (C, H, N).

1-Ethyloxycarbonyl-2,3,5-trimethyl-2,3-dihydro-[1H]-1-benzazepine ***6e***

To a suspension of **6** (4 g, 21.3 mmol) and K_2CO_3 (3.5 g, 25 mmol) under stirring was added dropwise a solution of ClCOOEt (4.6 g, 42.3 mmol) in 20 ml anhydrous C_6H_6. The mixture was refluxed for 48 h and the solvent was removed under reduced pressure. Afer addition of Et_2O, the crude was filtered, the organic phase was dried with anhydrous K_2CO_3 and evaporated under vacuum. The solid was purified by recrystallization from pentane. Yield: 3.87 g (70%); mp: 90°C. TLC: CH_2Cl_2/Et_2O, 95:5 (R_f: 0.65). IR: νCO: 1680. ^{1}H-NMR ($CDCl_3$) (2*R**3*R**): H-2 (m, 4.6), H-3 (m, 3.1), CH_3-2 (d, 0.72), CH_3-3 (d, 0.98), H-4 (d, 5.69), CH_3-5 (s, 2.17), O-CH_2 (q, 4.1), CH_3-4' (t, 1.18), Ar (m, 7.0–7.43). ^{13}C-NMR ($CDCl_3$) (2*R**3*R**): C-2 (d, 52.67), CH_3-2 (q, 13.03), C-3 (d, 38.65), CH_3-3 (q, 16.65), C-4 (d, 134.09), C-5 (s, 127.31), CH_3-5 (q, 26.4), C-5a (s, 135.47), C-6 (d, 127.44), C-7 (d, 126.55), C-8 (d, 130.06), C-9 (d, 126.40), C-9a (s, 136.87), CO (154.65), CH_2-3' (t, 61.38), CH_3-4' (q, 14.58). MS: $M^{+\bullet}$: 259 (100), $C_{16}H_{21}NO_2$: calc: 259.1572; found: 259.155; 244 (48.5), 230 (19.3), 203 (62), 200 (19), 186 (29). Anal (C, H, N, O).

1-(2-Chloroacetyl)-2,3,5-trimethyl-2,3-dihydro-[1H]-1-benzazepine ***6f***

A solution of $ClCH_2COCl$ (1.2 g, 10.5 mmol) in anhydrous C_6H_6 (5 ml) was slowly added to a suspension under stirring of **6** (1 g, 5.3 mmol) and K_2CO_3 (1.1 g, 8 mmol) in anhydrous C_6H_6 (5 ml). The mixture was allowed to remain under stirring at room temperature for 18 h. After filtration, the organic phase was evaporated under vacuum, the crude solid was dissolved in Et_2O and washed with water. The organic layer was dried with anhydrous K_2CO_3 and evaporated under reduced pressure. The solid was purified by recrystallization from CH_2Cl_2. Yield: 0.79 g (56%); mp: 148°C. TLC: CH_2Cl_2/Et_2O, 95:5 (R_f: 0.55). IR: νCO: 1638. ^{1}H-NMR ($CDCl_3$) (2*R**3*R**) (60 MHz): H-2 (m, 4.9), H-3 (m, 3.13), CH_3-2 (d, 0.75) CH_3-3 (d, 0.93), H-4

(d, 5.76), CH_3-5 (s, 2.15), H-2'α (d, 3.97), H-2'β (d, 3.68), J_{AB} = 13, Ar (m, 7.1–7.6). MS: M^+: 263 (25.5), $C_{15}H_{18}NOCl$: calc: 263.1076; found: 263.107; 248 (42), 234 (43), 228 (35.4), 186 (76.3), 170 (100), 158 (51.3), 144 (53), 131 (62.9), 77 (32.1). Anal (C, H, N, O, Cl).

1-[2-(1-Morpholino)acetyl]-2,3,5-trimethyl-2,3-dihydro-[1H]-1-benzazepine **6g**

Morpholine (0.66 g, 7.6 mmol) was added to a solution of **6f** (1 g, 3.8 mmol) in CH_3CN (20 ml) under stirring, with an additional amount of Et_3N. The mixture was refluxed for 18 h. The solvent was evaporated *in vacuo* (0.1 mm Hg), the resulting crude solid was treated with NaOH (10%) in H_2O, extracted with Et_2O, the extract dried over anhydrous K_2CO_3 and Et_2O evaporated under reduced pressure. The crude solid was purified by recrystallization from EtOH. Yield: 1.12 g (94%); mp: 114°C. TLC: C_6H_6/MeOH, 97:3 (R_f: 0.35). IR: νCO: 1666. ^{1}H-NMR ($CDCl_3$) (2*R**3*R**): H-2 (m, 4.92), H-3 (m, 3.13), $J_{H\text{-}2\ H\text{-}3}$ = 6.76, CH_3-2 (d, 0.7), $J_{H\text{-}2\ CH_3\text{-}2}$ = 7.25, CH_3-3 (d, 0.96), $J_{H\text{-}3\ CH_3\text{-}3}$ = 7.45, H-4 (d, 5.73), CH_3-5 (s, 2.18), H-2'α (d, 3.09), H-2'β (d, 2.86) J_{AB} = 14.92, CH_2-4',8' (m, 2.4), CH_2-5',7' (m, 3.63), Ar (m, 7.1–7.37). ^{13}C-NMR ($CDCl_3$) (2*R**3*R**): C-2 (d, 51.36), CH_3-2 (q, 13.01), C-3 (d, 38.00), CH_3-3 (q, 16.11), C-4 (d, 134.88), C-5 (s, 127.76), CH_3-5 (q, 25.93), C-5a (s, 136.59), C-6 (d, 129.02), C-7 (d, 127.49), C-8 (d, 127.60), C-9 (d, 126.92), C-9a (s, 137.24), CO (167.68), CH_2-2' (t, 60.85), CH_2-4',8' (t, 53.42), CH_2-5',7' (t, 66.72). MS: M^+: 314 (9.7), $C_{19}H_{26}O_2N_2$: calc: 314.1994; found: 314.199; 100 (100).

1-[2-(1-Piperidino)acetyl]-2,3,5-trimethyl-2,3-dihydro-[1H]-1-benzazepine **6h**

Piperidine (0.64 g, 7.6 mmol) was added to a solution of **6f** (1 g, 3.8 mmol) in CH_3CN (20 ml) under stirring, with an additional amount of Et_3N. The mixture was refluxed for 18 h. The resulting mixture was cooled, filtered, and the solvent was evaporated *in vacuo* (0.1 mm Hg). The oily residue was treated with NaOH (10%) in H_2O, extracted with Et_2O, the extract dried over anhydrous K_2CO_3 and Et_2O evaporated under reduced pressure. The viscous liquid was purified by column chromatography (eluent toluene/MeOH, 90:10).Yield: 1.12 g (94.5%). TLC: toluene/MeOH, 90:10 (R_f: 0.5). IR: νCO: 1648. ^{1}H-NMR ($CDCl_3$) (2*R**3*R**): H-2 (m, 4.92), H-3 (m, 3.13), $J_{H\text{-}2\ H\text{-}3}$ = 6.2, CH_3-2 (d, 0.69), $J_{H\text{-}2\ CH_3\text{-}2}$ = 7.25, CH_3-3 (d, 0.95), $J_{H\text{-}3\ CH_3\text{-}3}$ = 7.45, H-4 (d, 5.72), CH_3-5 (s, 2.18), H-2'α (d, 3.07), H-2'β (d, 2.83) J_{AB} = 15, CH_2-4',8' (m, 2.33), CH_2-5',7' (m, 1.5), CH_2-6' (m, 1.33), Ar (m, 7.08–7.47). ^{13}C-NMR ($CDCl_3$) (2*R**3*R**): C-2 (d, 51.3), CH_3-2 (q, 13.02), C-3 (d, 38.04), CH_3-3 (q, 16.13), C-4 (d, 134.83), C-5 (s, 127.53), CH_3-5 (q, 25.9), C-5a (s, 136.58), C-6 (d, 129.15), C-7 (d, 127.1), C-8 (d, 127.50), C-9 (d, 126.88), C-9a (s, 137.33), CO (168.12), CH_2-2' (t, 61.02), CH_2-4',8' (t, 54.22), CH_2-5',7' (t, 25.64), CH_2-6' (t, 23.84). MS: M^+: 312 (4.4), $C_{20}H_{28}ON_2$: calc: 312.2201; found: 312.221; 186 (0.65), 98 (100).

1-[2-(N-Diisopropylamino)ethyl]-2,3,5-trimethyl-2,3-dihydro-[1H]-1-benzazepine **6i**

To a suspension of $NaNH_2$ (1.25 g, 32 mmol) in DME (6 ml) under stirring was added dropwise a solution of **6** (3 g, 16 mmol) in DME (7 ml). The mixture was maintained at 40°C for 1 h. A solution of freshly distilled diisopropylaminoethyl chloride was then added progressively and the mixture was maintained under stirring at 40°C for 4 h. The crude reaction mixture was evaporated under reduced pressure and poured into cold H_2O for hydrolysis. After extraction with Et_2O, the organic phase was dried over anhydrous K_2CO_3 and Et_2O evaporated. Product **6i** was purified by column chromatography (eluent: MeOH/Et_3N, 99:1). Yield: 1.2 g (24%). TLC: MeOH/Et_3N, 99:1 (R_f: 0.25). ^{1}H-NMR ($CDCl_3$) (2*R**3*R**): H-2 (m, 3.35), H-3 (m, 1.85), CH_3-2 (d, 0.97), $J_{H\text{-}2\ CH_3\text{-}2}$ = 6.89, CH_3-3 (d, 1.05), $J_{H\text{-}3\ CH_3\text{-}3}$ = 6.83, H-4 (d, 5.74), CH_3-5 (s, 2.05), H-1'α (m, 3.35), H-1'β (m, 2.37), H-2'α (m, 2.96), H-2'β (m, 2.37), 2H isopropyl (m, 2.96), 4 CH_3 isopropyl (d, 0.95 and d, 0.97), Ar (m, 6.97–7.24). ^{13}C-NMR ($CDCl_3$) (2*R**3*R**): C-2 (d, 73.35), CH_3-2 (q, 20.93), C-3 (d, 39.45), CH_3-3 (q, 20.72), C-4 (d, 133.49), C-5 (s, 138.51), CH_3-5 (q, 22.97), C-5a (s, 134.26), C-6 (d, 126.78), C-7 (d, 122.86), C-8 (d, 126.67), C-9 (d, 121.56), C-9a (s, 146.49), CH_2-1' (t, 44.07), CH_2-2' (t, 53.69), CH-4',5' (d, 49.17), 4 CH_3 (q, 13.82). MS: M^+: 314 (3), $C_{21}H_{34}N_2$: calc: 314.2728; found: 314.271; 200 (18), 114 (100), 72 (18). Anal (C, H, N).

1-(2-Aminoethyl)-2,3,5-trimethyl-2,5-dihydro-[1H]-1-benzazepine **5j**

To a suspension of $LiAlH_4$ (1.9 g, 50 mmol) and $AlCl_3$ (2.22 g, 17 mmol) in anhydrous Et_2O (120 ml) freshly prepared under stirring, was added dropwise a solution of **5a** (11.3 g, 50 mmol) in anhydrous Et_2O (100 ml). The mixture was stirred for 1 h, and hydrolysed with an aqueous NaOH (15%) solution. The organic phase was dried over anhydrous K_2CO_3 and evaporated. The yellow viscous oily residue was purified by distilling under vacuum. Yield: 10.5 g (91%); $bp_{0.4}$ = 135°C. IR: $νNH_2$: 3358 and 3288. ^{1}H-NMR ($CDCl_3$): H-2 (q, 3.56), CH_3-2 (d, 0.87), $J_{H\text{-}2\ CH_3\text{-}2}$ = 6.7, CH_3-3 (s, 1 .57), H-4 (d, 5.23), H-5 (m, 4.10), CH_3-5 (d, 1.37) $J_{H\text{-}5\ CH_3\text{-}5}$ = 7.48, H-1'α (m, 3.47) H-1'β (m, 3.06) $J_{H\text{-}1'\alpha\ H\text{-}1'\beta}$ = 12.7 , CH_2-2' (m, 2.80), NH_2 (s, 2.18), Ar (m, 7–7.2). ^{13}C-NMR ($CDCl_3$): C-2 (d, 60.63), CH_3-2 (q, 13.32), C-3 (s, 137.61), CH_3-3 (q, 22.99), C-4 (d, 125.55), C-5 (d, 31.85), CH_3-5 (q, 19.22), C-5a (s, 143.74), C-6 (d, 128.44), C-7 (d, 123.22), C-8 (d, 123.37), C-9 (d, 122.94), C-9a (s, 146.37), CH_2-1' (t, 40.13), CH_2-2' (t, 55.32). MS: M^+: 230 (16.5), $C_{15}H_{22}N_2$: calc: 230.1782; found: 230.178; 200 (100), 185 (8.6), 172 (17.7), 170 (14.9).

1-(2-Aminoethyl)-2,3,5-trimethyl-2,3-dihydro-[1H]-1-benzazepine **6j**

To a solution of **5j** (10.5 g, 45.6 mmol) in DME (70 ml) at room temperature, *tert*-BuOK (3.5 g, 31 mmol) was added portionwise under continuous stirring. The mixture was stirred for 1 h, and the solvent was removed under reduced pressure. The residue was hydrolyzed and extracted with Et_2O. The organic phase was dried over anhydrous K_2CO_3 and evaporated. The oily residue was purified by distilling under reduced pressure. Yield: 10 g (95%); $bp_{0.25}$ = 139–140°C. IR: $νNH_2$: 3332. ^{1}H-NMR ($CDCl_3$) (2*R**3*R**) (60 MHz): H-2 (m, 3.2), H-3 (m, 2.66), CH_3-2 (d, 1.01), CH_3-3 (d, 0.93), H-4 (d, 5.70), CH_3-5 (s, 2.18), CH_2-1' (t, 2.76), CH_2-2' (t, 3.33), NH_2 (m, 1.3), Ar (m, 6.8–7.4).

2-Methylamino-1,3,5-trimethyl-2,3,4,5-tetrahydro-[1H]-1-benzazepine **9j**

A solution of **9a** (4 g, 18.7 mmol) in anhydrous Et_2O (15 ml) was slowly added to a 1.86 M stirred solution of $LiAlH_4$ (12 ml, 22.3 mmol). The crude mixture was maintained at room temperature under stirring for 3 h and was hydrolyzed with an aqueous NaOH (10%) solution. The organic phase was dried over anhydrous K_2CO_3, evaporated and the oily residue was purified on column chromatography (eluent: MeOH/Et_3N, 99:1). Yield: 3.8 g (93%). TLC: MeOH/Et_3N, 99:1 (R_f: 0.3). IR: $νNH_2$: 3303 and 3375. ^{1}H-NMR ($CDCl_3$): CH_3-1 (s, 3.04), H-2 (m, 2.79), H-1'α (d, 2.53), H-1'β (d, 2.27) J_{AB} = 13, H-3 (m, 1.86), $J_{H\text{-}2\ H\text{-}3}$ = 10.4, CH_3-3 (d, 1.22) $J_{H\text{-}3\ CH_3\text{-}3}$ = 6.9, 2H-4 (m, 1.42), H-5 (m, 3.11), CH_3-5 (d, 1.3) $J_{H\text{-}5\ CH_3\text{-}5}$ = 7.1, NH_2 (m,

1.5), Ar (m, 6.9–7.2). ^{13}C-NMR ($CDCl_3$): CH_3-1 (q, 43.27), C-2 (d, 68.86), CH_2-2 (t, 42.72), C-3 (d, 31.02), CH_3-3 (q, 18.97), C-4 (t, 36.91), C-5 (d, 29.42), CH_3-5 (q, 21.43), C-5a (s, 140.69), C-6 (d, 125.86), C-7 (d, 121.75), C-8 (d, 124.95), C-9 (d, 119.38), C-9a (s, 149.51); MS: $M^{+\bullet}$: 218 (1), $C_{14}H_{22}N_2$: calc: 218.1782; found: 218.178; 203 (1.5), 188 (100), 174 (27.3), 144 (10.25), 77 (3.6).

1-[2-(N-Phenylaminocarbonylamino)ethyl]-2,3,5-trimethyl-2,5-dihydro-[1H]-1-benzazepine ***5k***

A solution of PhNCO (1.43 g, 12 mmol) in anhydrous C_6H_6 (5 ml) was slowly added to a stirred solution of **5j** (2.3 g, 10 mmol) in anhydrous C_6H_6 (25 ml). The mixture was refluxed for 2 h. The crude reaction mixture was evaporated under reduced pressure. Product **5k** was purified by recrystallization from absolute EtOH. Yield: 1.4 g (40%); mp: 191°C. TLC: CH_2Cl_2/Et_2O, 90:10 (R_f: 0.15). IR: νCO: 1654, νNH: 3376. ^{1}H-NMR ($CDCl_3$): H-2 (q, 3.52), CH_3-2 (d, 0.82), $J_{H\text{-}2\ CH_3\text{-}2}$ = 6.68 ,CH_3-3 (s, 1.51), H-4 (d, 5.43), CH_3-5 (d, 1.26), H-5 (q, 3.74) $J_{H\text{-}5\ CH_3\text{-}5}$ = 7.42, CH_2-1',2' (m, 3.39), NH 3',5' (s, 5.14*, s, 6.6*), Ar (m, 7–7.3). ^{13}C-NMR ($CDCl_3$): C-2 (d, 60.31), CH_3-2 (q, 13.28), C-3 (s, 137.35*), CH_3-3 (q, 23), C-4 (d, 124.28), C-5 (d, 31.8), CH_3-5 (q, 19.36), C-5a (s, 143.27), C-6 (d, 128.25), C-7 (d, 123.56), C-8 (d, 125.74), C-9 (d, 122.66), C-9a (s, 145.78), CH_2-1' (t, 38.3), CH_2-2' (t, 51.55), CO (s, 155.99), C-6' (s, 138.3*), C-7',11' (d, 122.03), C-8',10' (d, 129.35), C-9' (d, 124.28). MS: $M^{+\bullet}$: 349 (15), $C_{22}H_{27}ON_3$: calc: 349.2154; found: 349.215; 256 (5), 230 (0.8), 200 (100), 186 (15), 119 (7), 93 (18). Anal (C, H, N).

1-[2-(N-Phenylaminocarbonylamino)ethyl]-2,3,5-trimethyl-2,3-dihydro-[1H]-1-benzazepine ***6k***

This product was synthesized from **6j** (2.3 g, 10 mmol) according to the method described for **5k**. Yield: 2 g (57%); mp: 127°C. TLC: CH_2Cl_2/Et_2O, 90:10 (R_f: 0.2). IR: νCO: 1646, νNH br: 3328. ^{1}H-NMR ($CDCl_3$) (2*R**3*R**): H-2 (m, 3.19), CH_3-2 (d, 0.91), $J_{H\text{-}2\ CH_3\text{-}2}$ = 6.43, H-3 (m, 2.59), CH_3-3 (d, 0.92), $J_{H\text{-}3\ CH_3\text{-}3}$ = 7.2, H-4 (d, 5.59), CH_3-5 (m, 2.04), CH_2-1',2' (m, 3.1–3.45), NH 3',5' (s, 5.47*, s, 3.1*), Ar (m, 6.9–7.42). ^{13}C-NMR ($CDCl_3$) (2*R**3*R**): C-2 (d, 66.92), CH_3-2 (q, 13.96), C-3 (d, 37.82), CH_3-3 (q, 17.5), C-4 (d, 132.35), C-5 (s, 134.05*), CH_3-5 (q, 24.47), C-5a (s, 138.54*), C-6 (d, 127.8*), C-7 (d, 121.26), C-8 (d, 129.18*), C-9 (d, 119.68), C-9a (s, 145.9), CH_2-1' (t, 38.02), CH_2-2' (t, 50.52), CO (s, 156.32), C-6' (s, 138.88*), C-7',11' (d, 123.76), C-8',10' (d, 129.55*), C-9' (d, 127.3*). MS: $M^{+\bullet}$: 349 (7.5), $C_{22}H_{27}ON_3$ calc: 349.2154; found: 349.215; 256 (3.5), 230 (3.35), 200 (100), 186 (4.8), 119 (38), 93 (75.5). Anal (C, H, N).

2-[(N-Phenylaminocarbonylamino)methyl]-1,3,5-trimethyl-2,3,4,5-tetrahydro-[1H]-1-benzazepine ***9k***

This product was synthesized from **9j** (1.9 g, 8.7 mmol) according to the same method as described for compound **5k** with a solution of PhNCO (1.24 g, 10.4 mmol). Product **9k** was purified by column chromatography (CH_2Cl_2/Et_2O 90:10). Yield: 1.76 g (60%). TLC: CH_2Cl_2/Et_2O 90:10 (R_f: 0.4). IR: νCO: 1648, νNH br: 3322. ^{1}H-NMR ($CDCl_3$): CH_3-1 (s, 2.95), H-2 (m, 3.06), H-1'α (m, 3.05), H-1'β (m, 2.83), H-3 (m, 1.74), CH_3-3 (d, 1.16), $J_{H\text{-}3\ CH_3\text{-}3}$ = 6.88, 2H-4 (m, 1.39), CH_3-5 (d, 1.27), H-5 (m, 3.06), $J_{H\text{-}5\ CH_3\text{-}5}$ = 7.12, NH (t, 4.87), Ar (m, 6.7–7.4). ^{13}C-NMR ($CDCl_3$): CH_3-1 (q, 43.77), C-2 (d, 65.19), C-3 (d, 31.51*), CH_3-3 (q, 18.84), C-4 (t, 36.84), C-5 (d, 29.46*), CH_3-5 (q, 21.4), C-5a (s, 138.31), C-6 (d, 125.70), C-7 (d, 122.02), C-8 (d, 126.08), C-9 (d, 119.27), C-9a (s, 149.20), CH_2-1' (t, 41.33), CO (s, 155.99), C-5' (s, 140 74), C-6', 10' (d, 122.1), C-7',9' (d, 129.41), C-8' (d, 124.23). MS: $M^{+\bullet}$: 337 (0.7), $C_{21}H_{27}N_3O$: calc: 337.2154; found: 337.215; 244 (0.2), 218 (0.05), 188 (100), 119 (10).

1-[2-(para-Toluenesulfonamido)ethyl]-2,3,5-trimethyl-2,3-dihydro-[1H]-1-benzazepine ***6l***

To a solution of **6j** (2.3 g, 10 mmol) and Et_3N (5 g, 49.5 mmol) in anhydrous C_6H_6 (15 ml), was added dropwise a solution of *p*-toluenesulfonylchloride (3 g, 13 mmol) in anhydrous C_6H_6 (30 ml) dried with a Dean–Stark apparatus. The reaction mixture was refluxed for an additional 3 h, cooled and filtered. The solvent was removed under reduced pressure and the oily residue was purified by column chromatography (eluent C_6H_6/MeOH, 99:1). Yield: 2.96 g (77%). TLC: C_6H_6/MeOH, 99:1 (R_f: 0.5). IR: νNH br: 3280. ^{1}H-NMR ($CDCl_3$) (2*R**3*R**): H-2 (m, 3.26), CH_3-2 (d, 0.95), $J_{H\text{-}2\ CH_3\text{-}2}$ = 6.43, H-3 (m, 2.46), CH_3-3 (d, 0.88), $J_{H\text{-}3\ CH_3\text{-}3}$ = 7.15, H-4 (d, 5.69), CH_3-5 (m, 2.14), CH_2-1' (m, 3.33), H-2'α (m, 3), H-2'β (m, 2.84), NH (s, 4.74), CH_3-8' (s, 2.36), Ar (m, 6.79–7.47). ^{13}C-NMR ($CDCl_3$) (2*R**3*R**): C-2 (d, 68.13), CH_3-2 (q, 14.14), C-3 (d, 37.69), CH_3-3 (q, 17.05), C-4 (d, 132.71), C-5 (s, 132.71), CH_3-5 (q, 24.03), C-5a (s, 135.56), C-6 (d, 127.01), C-7 (d, 121.47), C-8 (d, 127.55), C-9 (d, 119.99), C-9a (s, 145.10*), CH_2-1' (t, 40.26*), CH_2-2' (t, 48.28*), C-5' (s, 136.08), C-6',10' (d, 126.78), C-7',9' (d, 129.50), C-8' (s, 143.03*). MS: $M^{+\bullet}$: 384 (13.6), $C_{22}H_{28}N_2SO_2$: calc: 384.1871, found: 384.186; 200 (100), 184 (12.1), 155 (62), 91(94). Anal (C, H, N, O).

2-(para-Toluenesulfonamidomethyl)-1,3,5-trimethyl-2,3,4,5-tetrahydro-[1H]-1-benzazepine ***9l***

This product was synthesized from **9j** (1.9 g, 8.7 mmol) according to the same method as described for **6l**. Compound **9l** was purified by column chromatography (CH_2Cl_2) and recrystallization from EtOH. Yield: 2.3 g (71%). TLC: CH_2Cl_2/Et_2O, 90:10 (R_2: 0.85). IR: νNH: 3284, νSO_2: 1330 and 1158. ^{1}H-NMR ($CDCl_3$): CH_3-1 (s, 2.95), H-2 (m, 3), CH_2-1' (m, 2.67), H-3 (m, 1 .74), CH_3-3 (d, 1.12), $J_{H\text{-}3\ CH_3\text{-}3}$ = 7.5, 2H-4 (m, 1.36), CH_3-5 (d, 1.25), H-5 (m, 3), $J_{H\text{-}5\ CH_3\text{-}5}$ = 7.06, CH_3-7' (s, 2.40), NH (4.34), Ar (m, 6.9–7.7). ^{13}C-NMR ($CDCl_3$): CH_3-1 (q, 43.40), C-2 (d, 65.18), C-3 (d, 31.27*), CH_3-3 (q, 18.68), C-4 (t, 37.19), C-5 (d, 29.48*), CH_3-5 (q, 21.48*), C-5a (s, 136.79), C-6 (d, 126.95), C-7 (d, 122.45), C-8 (d, 125.29), C-9 (d, 120.06), C-9a (s, 148.79), CH_2-1' (t, 43.73), C-4' (s, 140.62), C-5',9' (d, 126.34), C-6',8' (d, 129.63), C-7' (s, 143.32), CH_3-7' (q, 21.2*) . MS: $M^{+\bullet}$: 372 (0.35), $C_{21}H_{28}N_2SO_2$: calc: 372.1871; found: 372.188; 188 (100). calc: 188,1439; found: 188,143; 91 (10.7).

Pharmacology

Tissue preparations

Tracheal bronchial rings were obtained from tricoloured guinea pigs of either sex (Hartley, 250–350 g) anaesthetized with urethane (1.25 g•kg^{-1}, ip) and suspended under an initial tension of 2.0 g in Krebs solution at 37°C gassed with 95% O_2/5% CO_2. After an equilibration period of 60 min, the resting tension was between 1.5 and 2.0 g. Under these conditions, responses to agonists were measured isometrically with Pioden strain gauges (UF-1), amplifiers (EMKA, France) and displayed on a recorder (Linseis 1.65514, France). The composition of the Krebs solution was (mM): NaCl 118.0; KCl 5.4; $CaCl_2$ 2.5; KH_2PO_4 1.2; $MgSO_4$ 1,2; $NaHCO_3$ 25.0; and glucose 11.7.

Protocols

In all experiments, after an equilibration period of 60 min, guinea-pig tracheal rings were contracted to maximal tension

with acetylcholine (3 mM) and relaxed to maximal relaxation with theophylline (3 mM), then allowed to equilibrate for 60 min while they were washed with Krebs' solution every 15 min.

Preparations were allowed to remain under resting tension then were contracted with histamine (10^{-5} M). Cumulative concentration curves were obtained with addition of different compounds every 15–20 min until a plateau was reached. The relaxant effects of the drugs were expressed as percentages of the maximal relaxation induced by theophylline (3 mM).

Statistical analysis of results

Data are expressed as mean ± SE mean. Statistical analysis of the results was performed with variance analysis and Student's test for paired or unpaired data as appropriate. Probability values of $P < 0.05$ were considered significant.

ED_{15} values were calculated from the log concentation–response curves and were defined as the negative log of the drug concentration that caused 15% of the maximal effect (E_{max})

Substances

The substances used were: acetylcholine HCl (PCH Paris); cromakalim (BRL 34915, ic (±)-6-cyano-3,4-dihydro-2,2-(dimethyl-*trans*-4-[2-oxo-1-pyrrolidyl]-2*H*-1-benzopyran-3-ol); glibenclamide (gift from Sanofi, Montpellier, France); histamine (Sigma, Saint Louis, USA); and theophylline sodium anisate (Bruneau, Paris).

All drugs were dissolved in distilled water and then diluted in Krebs' solution, except cromakalim, glibenclamide and the compounds tested, which were dissolved in EtOH or DMSO and then diluted in Krebs' solution. The maximal amount of EtOH (0.4%) or DMSO (0,4%) added to the bath did not alter acetylcholine or histamine reactivity.

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