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N-TOSYLCARBAMIDE DERIVATIVES OF 2-PYRAZINIUM AND 9-ACRIDINIUM SALTS AS INHIBITORS OF ACETYL-CHOLINE POTASSIUM CHANNELS IN CARDIOMYOCYTES

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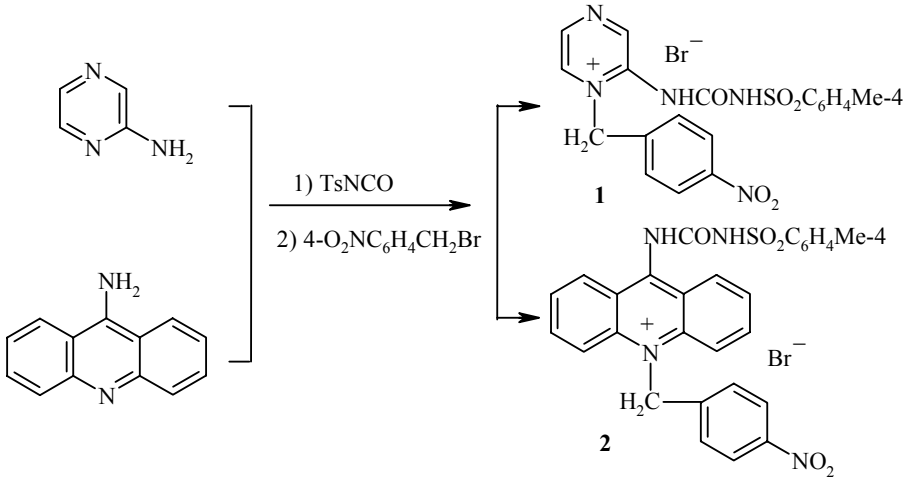
In light of the importance of correcting atrial arrhythmias [1] arising due to the increased activity of the parasympathetic nervous system or stimulation of the muscarine (acetylcholine) receptors of myocardial cells, we have continued to search for new inhibitors to potassium flow through acetylcholine channels (I_{KACh}) among sulfonylurea derivatives. According to our findings, N-tosylcarbamide derivatives of 2-pyridinium and 2-pyrimidinium salts possess such activity [2]. Thus, we have synthesized the 1,4-diazine analog of these compounds, namely, 2-pyrazinium bromide **1** as well as a condensed analog of 4-aminopyridine, namely, 9-acridinium bromide **2**, which contains a 4-nitrobenzyl group at the quaternized nitrogen atom. The activity of



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these compounds was determined relative to their capacity to increase the duration of the action potential (AP) and contractile capacity of guinea pig atrium when the AP duration was reduced to 36.4±2.1% and contraction strength was reduced to 24.4±1.7% upon the activation of I_{KACh} by 10^{-6} M carbachol according to our previous procedure [3]. 9-Acridinium bromide **2** had an especially strong effect. At a concentration of $6 \cdot 10^{-5}$ M, bromide **2** increased the AP duration by 329.1±89.4% and contraction strength by 95.0±5% in comparison with the norm taken as 100%. The activity of 2-pyrazinium bromide **1** was less pronounced.

The mass spectra were taken on a Finnigan MAT-212 mass spectrometer at 70 eV with direct sample inlet into the ion source. The reaction course and purity of the reagents were monitored by thin-layer chromatography on Silufol UV-254 plates using 8:4:1:3 1-butanol–ethanol–acetic acid–water as the eluent. The spots were developed in UV light or in iodine vapor.

1-(4-Methylphenyl)sulfonyl-3-(pyrazin-2-yl)urea. 2-Pyrazinamine (9.5 g, 100 mmol) was dissolved upon heating in 1,4-dioxane (50 ml) and cooled to room temperature. Then 4-methylphenylsulfonyl isocyanate (tosyl isocyanate) (19.7 g, 100 mmol) was added dropwise with vigorous stirring over 30 min. A white mass was formed, which was left overnight. The precipitate was separated and washed with ether. Recrystallization from 1:1 ethanol–water gave 19.9 g (68%) product, mp 163-165°C, R_f 0.65 (spot seen only in UV light, not developed by iodine vapor). Mass spectrum, *m/z* (I_{rel}, %): 292 $[M]^+$ (34), 171 (17), 155 (7), 122 (43), 121 (100), 91 (80). Found, %: C 48.91; H 3.82; N 18.87; S 10.59. $C_{12}H_{12}N_4O_3S$. Calculated, %: C 49.26; H 4.10; N 19.15; S 10.94

2-(4-Methylphenyl)sulfonylcarbamido1-(4-nitrobenzyl)pyrazinium Bromide (1). 4-Nitrobenzyl bromide (2.16 g, 10 mmol) was added to a solution of 1-(4-methylphenyl)sulfonyl-3-(pyrazin-2-yl)urea (2.92 g, 10 mmol) in 2-propanol (30 ml), heated for 2 h at 90°C, and then cooled. The precipitate was separated and washed with 2-propanol. Recrystallization from 2-propanol gave compound **1** 1.37 g (27%), mp >200°C (decomp.), R_f 0.48. Mass spectrum, *m/z* (I_{rel}, %): 506-508 (rel.) $[M]^+$, 427 (2), 257 (100), 171 (12), 155 (7), 127 (2), 91 (34). Found, %: C 44.59; H 3.32; Br 15.44; N 13.41; S 5.97. $C_{19}H_{18}BrN_5O_5S$. Calculated, %: C 44.89; H 3.57; Br 15.74; N 13.77; S 6.31.

1-(4-Methylphenyl)sulfonyl-3-(acridin-9-yl)urea. 9-Aminoacridine (9.7 g, 50 mmol) was dissolved in 1,4-dioxane (60 ml) and then cooled to room temperature. Tosyl isocyanate (9.85 g, 50 mmol) was added dropwise with vigorous stirring over 30 min. The yellowish precipitate formed was let stand for several hours, then separated, washed with 1,4-dioxane, and recrystallized from 2-propanol to give 15.8 g (81%) product, mp 183-185°C, R_f 0.60. Mass spectrum, *m/z* (I_{rel}, %): 391 $[M]^+$ (47), 221 (87), 220 (100), 194 (36), 171 (63), 155 (14), 91 (80). Found, %: C 64.05; H 4.11; N 10.42; S 7.84. $C_{21}H_{17}N_3O_3S$. Calculated, %: C 64.38; H 4.34; N 10.73; S 8.18.

9-(4-Methylphenyl)sulfonylcarbamido-10-(4-nitrobenzyl)acridinium Bromide (2). A solution of 1-(4-methylphenyl)sulfonyl-3-(acridin-9-yl)urea (3.91 g, 10 mmol) in DMF (5 ml) was diluted with 2-propanol (15 ml). Then, 4-nitrobenzyl bromide (2.16 g, 10 mmol) was added and heated at 90°C for 3 h. The mixture was cooled. The precipitate was separated and washed with 2-propanol. Recrystallization from 2-propanol gave a turbid solution, which was left stand overnight. The precipitate was separated and washed with 2-propanol to give bromide **2** 1.76 g (29%), mp >200°C (decomp.), R_f 0.43. Mass spectrum, *m/z* (I_{rel}, %): 606-608 (rel) $[M]^+$, 527 (12), 220 (85), 171 (32), 155 (9), 136 (5), 81 (29). Found, %: C 55.03; H 3.63; Br 12.81; N 9.17; S 5.02. $C_{28}H_{23}BrN_4O_5S$. Calculated, %: C 55.36; H 3.82; Br 13.15; N 9.22; S 5.28.

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