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Synthesis and structure of novel 2,3, 5,6-tetrahydro-1*H*-imidazo [2,1-b][1,3,5]benzotriazepines with vasocontractile activity in rabbit aortic rings

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Abstract

A series of novel 2,3,5,6-tetrahydro-1*H*-imidazo[2,1-b][1,3,5]benzotriazepines (**3a**–**n**) and hydrochlorides (**4a**–**b**) were prepared and their structure was determined by IR and NMR spectroscopic data as well as by X-ray analysis of the hydrochloride **4a**. The newly synthesized benzotriazepine **4b** exhibited concentration-dependent vasocontractile activity in isolated rabbit aortic rings. Rimalkalim was found to induce a relaxation in rabbit aortic rings precontracted by **4b** (3×10^{-5} mol). Present results indicate that K_{ATP}-dependant channels may contribute in the contractile activity of benzotriazepine **4b**.

Keywords: 2,3,5,6-Tetrahydro-1*H*-imidazo[2,1-b][1,3,5]benzotriazepines; Synthesis; X-ray structure analysis; Rabbit aortic rings; K_{ATP} channel blocker

1. Introduction

Imidazoline derivatives of type A (Fig. 1) are an important class of compounds because of their wide experimental and clinical use. Imidazolines, such as phentolamine and tolazoline, have been used clinically as antagonists of peripheral alpha adrenoceptors, whereas the majority of imidazolines are used for their alpha agonist activity (e.g. oxymatazoline, naphazoline, xylometazoline).

Clonidine, another therapeutically useful imidazoline, has been postulated to exert a centrally mediated antihypertensive effect through agonist activity on alpha$_2$-adrenoceptors. The hypotension effect of the clonidine might be mediated not only by alpha-adrenoceptors but also by separate imidazoline-prefering receptors [1,2]. It was also found that imidazolines of type A may act as inhibitors of α-adrenoceptor mediated phase of noradrenaline-induced aggregation in platelets [3–5].

Some imidazolines, including phentolamine, antazoline and tolazoline, are able to block the vasorelaxant response to nicorandil and cromalkalim, the K^+ channel openers, in the isolated rat portal vein [6] and the canine coronary artery [7]. These findings indicate that K^+ channels also play an important role in the pharmacological action of imidazoline-containing compounds.

Interconnecting the imidazoline and phenyl ring of A, as achieved in 2,3-dihydro-imidazo-[1,2-a]benzimidazole B and 1,2,3,5-tetrahydroimidazo[2,1-b]quinazoline C (Fig. 1), resulted in obtaining agents effective in lowering the blood pressure of experimental animals [8,9]. However, these compounds exhibited very low affinity at alpha-adrenoceptors [10], and mechanism involving direct vascular dilation has been excluded by studies in the isolated rabbit aortic strips [9].

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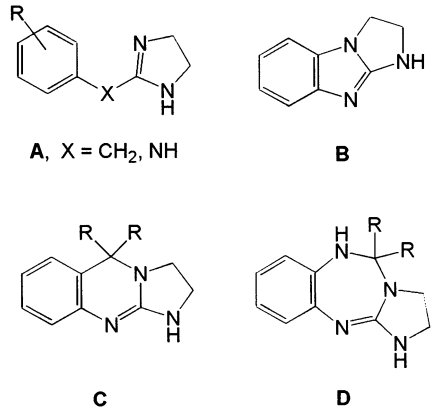


Fig. 1.

In this paper we report the synthesis, structure and biological activity of novel 2,5,6,11-tetrahydroimidazo[2,1-b][1,3,5]benzotriazepine derivatives of type D (Fig. 1) in isolated rabbit aortic rings.

2. Results and discussion

2.1. Chemistry

The previously described 2-[(2-aminophenylimino]imidazolidines (**1a**–**c**) [11] were subjected to the reaction with a variety of aldehydes and ketones in the presence of Lewis acid ($ZnCl_2$) at ambient temperature to give the title 1,2,3,5-tetrahydroimidazo[2,1-b][1,3,5]benzotriazepines in form of complexes E (Scheme 1). Free bases **3a**–**n** were liberated by treatment of the later compounds with methanolic NaOH solution.

To our knowledge, the imidazo[2,1-b][1,3,5]-benzotriazepine ring system has not been described previously in chemical literature. Structures of all newly prepared compounds **3a**–**n** was confirmed by elemental analysis as well as IR and NMR spectroscopic data (vide infra).

Due to rather low solubility of the free bases **3** in water, these compounds had to be converted into the salts suitable for biological experiments. However, the compounds **3** containing aminal group are susceptible to hydrolysis when protonated, and upon treatment with either mineral or organic acid (hydrochloric, methanesulfonic or oxalic acid) most of them decomposed within few hours to the corresponding carbonyl compounds and diamines **1**. The only compounds which proved to be stable for 1 day (NMR evidence) were these obtained from cyclohexanone (**4a**–**b**).

We have also elaborated another method for convenient preparation of hydrochlorides **4a**–**b** which consists in the reaction of 2,3-dihydrobenzimidazole-2-spirocyclohexanes **2a**–**b** with 2-chloro-4,5-dihydroimidazole (Scheme 2). The plausible mechanism of this reaction involves initial formation of *N*-heteroalkylated 2,3-dihydrobenzimidazole (**F**), followed by the imidazoline ring scission and subsequent recyclization to the less hindered 1,3,5-triazepine ring system.

The 5-spirocyclohexyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b][1,3,5]benzotriazepine has been studied in solid state in the protonated form as the hydrochloride **4a**. Final atomic coordinates are listed in Table 1, selected bond lengths and angles in Table 2, and atom labeling is shown in Fig. 2.

2.2. Biology

The newly synthesized imidazo[2,1-b][1,3,5]benzotriazepines (**4a**–**b**) were studied for their influence on isolated rabbit aorta.

In the first series of experiments, upon construction of dose–response curves for the investigated compounds, we found that **4b** have shown no significant difference from control phenylephrine when EC_{50} values were compared (2.37 μmol versus 1.34 μmol, Table 3, Fig. 3). Unsubstituted derivative **4a**, however, produced only minimal contraction at high concentrations (E_{max} was $11.12 \pm 2.27\%$ compared to phenylephrine, Table 3).

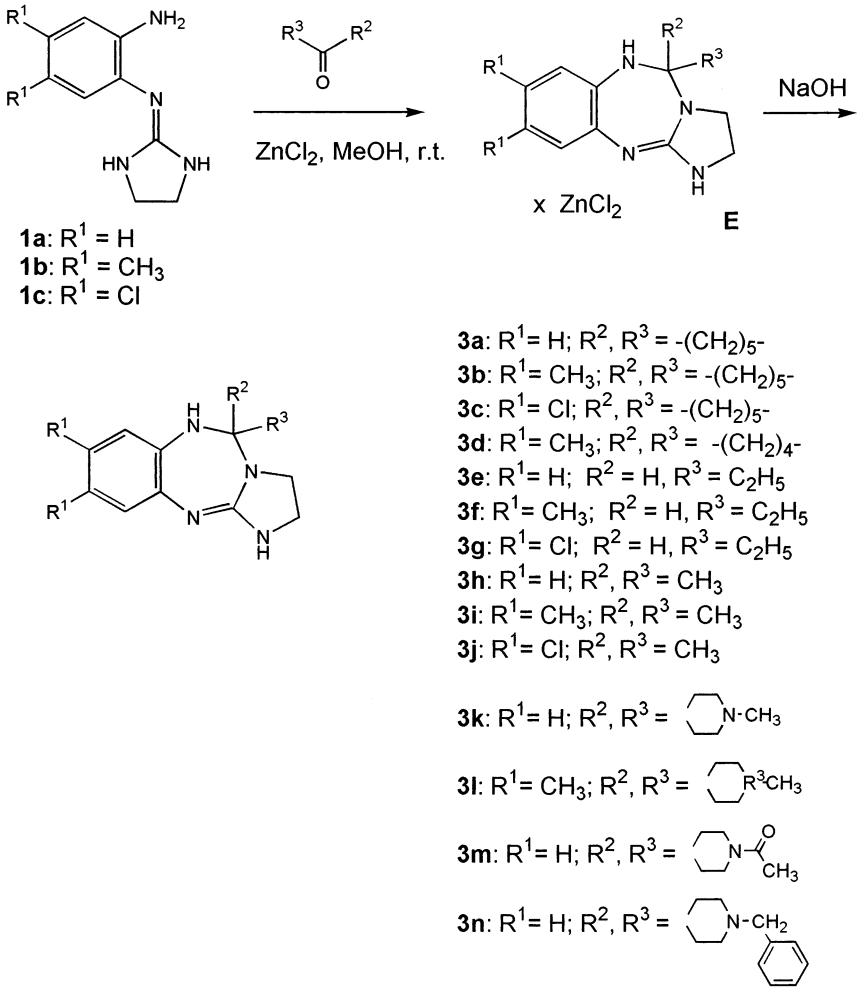
Compound **4b** has been analyzed further in the presence of rimalkalim, the K_{ATP} channel opener. It was found that in rabbit aortic rings precontracted by **4b** (3×10^{-5} mol), rimalkalim induced concentration-dependent relaxant responses (Fig. 4). These results suggest that imidazo[2,1-b][1,3,5]-benzotriazepine (**4b**) possibly acts as a blocker of K_{ATP}-dependant channels.

It is pertinent to note, that similar results showing that some imidazoline derivatives are able to antagonize the vasodilatatory effect of K^+-channel openers cromakalim and nicorandil in rat portal vein [6] and thoracic aorta [7].

3. Experimental

3.1. Chemistry

Melting points were determined on a Boetius apparatus and are uncorrected. IR spectra were obtained on a Perkin–Elmer FT 1600 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200 spectrometer at room temperature (r.t.). Elemental analyses of C, H, N agreed with theoretical values to within $\pm 0.4\%$. Solvents were dried by standard methods. Chemical reagents were used without further purification. The following substrates were prepared according to previously described procedures: 2,3-dihydrobenzimidazole-2-spirocyclohexane (**2a**) and 5,6-dimethyl-2,3-dihydrobenzimidazole-2-spirocyclohexane (**2b**) [12], 2-chloro-4,5-dihydro-imidazole [13] and 2-[(2-aminophenyl)imino]imidazolidines (**1a**–**c**) [8].



Scheme 1.

*3.1.1. 5-Spirocyclohexyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b]benzotriazepine (**3a**)*

$ZnCl_2$ (1.53 g, 11.36 mmol) was added to a solution of 2-[(2-aminophenyl)imino]imidazolidine (**1a**) (1 g, 5.68 mmol) and cyclohexanone (0.11 g, 11.36 mol) in anhydrous methanol (10 ml) and the reaction mixture was stirred at r.t. for 12 h. The solid that precipitated was filtered off and washed with methanol. Then the crude complex E was suspended in anhydrous methanol (10 ml) followed by treatment with 5% methanolic NaOH solution (50 ml) at 0–5 °C for 0.5 h. The solvent was evaporated to dryness under reduced pressure and the viscous residue was extracted with CH_2Cl_2 (50 ml). The organic layer was dried with $MgSO_4$ and evaporated in vacuum. The product **3a** thus obtained was purified by crystallization from MeOH. Yield: 0.64 g (38%); m.p. 136–138 °C; IR (KBr): 3395 cm^{-1}, 3153, 2923, 2859, 1634, 1585, 1479, 1274, 1119, 1080; ^1H NMR ($CDCl_3$, δ ppm): 1.16–1.90 (m, 10H, $5CH_2$), 3.39–3.46 (m, 2H, CH_2), 3.51–3.64 (m, 2H, CH_2), 4.21 (s, 1H, NH), 4.40 (br s, 1H, NH), 6.63–7.01 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, δ ppm): 22.70, 25.54, 33.38, 40.97, 46.83, 70.09, 121.05, 121.77, 122.67, 127.13, 137.21, 138.60, 156.00. *Anal.* for $C_{15}H_{20}N_4$ (256.35).

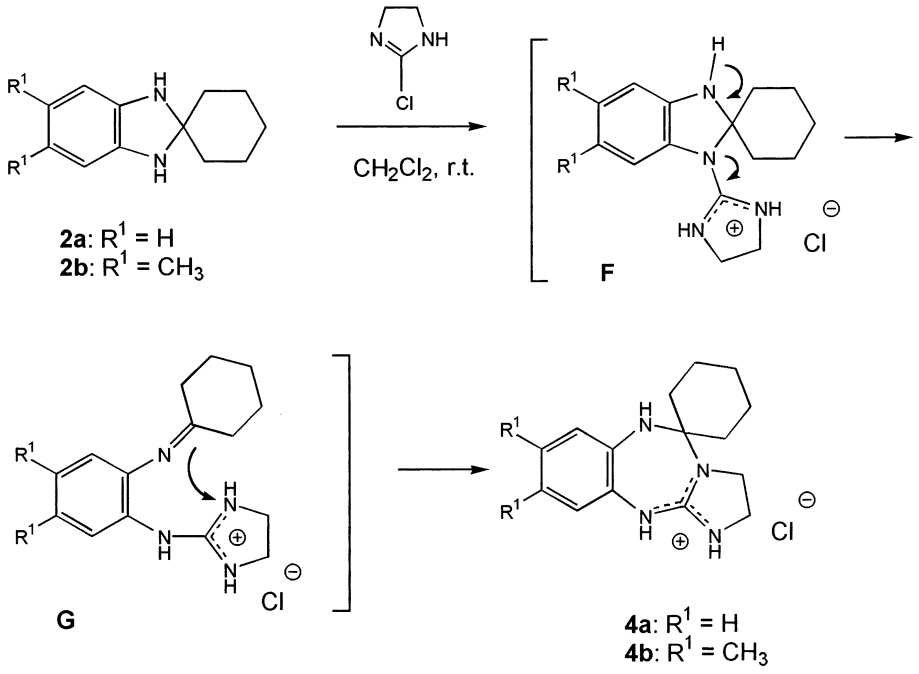
The following compounds were obtained according to the above procedure.

*3.1.2. 8,9-Dimethyl-5-spirocyclohexyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b]benzotriazepine (**3b**)*

Yield: 52%; m.p. 137–139 °C (EtOH); IR (KBr): 3403 cm^{-1}, 2923, 1643, 1600, 1472, 1436, 1280; ^1H NMR ($CDCl_3$, δ ppm): 1.54–1.88 (m, 10H, $5CH_2$), 2.14 (s, 6H, $2CH_3$), 3.40–3.44 (m, 2H, CH_2), 3.54–3.57 (m, 2H, CH_2), 4.05 (s, 1H, NH), 4.80 (br. s, 1H, NH), 6.43 (s, 1H, Ar), 6.78 (s, 1H, Ar). *Anal.* for $C_{17}H_{24}N_4$ (284.4).

*3.1.3. 8,9-Dichloro-5-spirocyclohexyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b]benzotriazepine (**3c**)*

Yield: 39%; m.p. 133–136 °C ($MeOH–Et_2O$); IR (KBr): 3392 cm^{-1}, 2923, 1640, 1483, 1424, 1280; ^1H NMR ($CDCl_3$, δ ppm): 1.58–1.95 (m, 10H, $5CH_2$), 3.42–3.65 (m, 4H, $2CH_2$), 4.18 (s, 1H, NH), 5.05 (br.s, 1H, NH) 6.72 (1H, CH, Ar), 7.03 (s, 1H, Ar). *Anal.* for $C_{15}H_{18}N_4Cl_2$ (325.23).



Scheme 2.

Table 1
Compound **4a** $C_{15}H_{21}N_4^+ \cdot Cl^-$: atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$)

	x	*y*	*z*	U_{eq}
Cl(1)	−265(1)	6085(1)	10899(1)	34(1)
N(1)	−3168(2)	4104(2)	10094(1)	40(1)
C(2)	−3938(3)	3291(2)	9481(2)	44(1)
C(3)	−5409(3)	2883(2)	9951(1)	37(1)
N(4)	−4836(2)	3216(1)	10903(1)	31(1)
C(5)	−5897(2)	3053(1)	11640(1)	27(1)
N(6)	−4684(2)	2930(1)	12481(1)	28(1)
C(7)	−3969(2)	3818(1)	12956(1)	30(1)
C(8)	−3988(3)	3920(2)	13882(1)	38(1)
C(9)	−3222(3)	4773(2)	14368(2)	45(1)
C(10)	−2471(3)	5562(2)	13924(2)	48(1)
C(11)	−2447(3)	5484(2)	13008(2)	41(1)
C(12)	−3156(2)	4612(2)	12521(1)	31(1)
N(13)	−2938(2)	4574(1)	11602(1)	35(1)
C(14)	−3643(2)	3967(1)	10912(1)	30(1)
C(15)	−6928(3)	2030(2)	11444(1)	33(1)
C(16)	−8221(3)	1845(2)	12094(2)	39(1)
C(17)	−9426(3)	2790(2)	12108(2)	46(1)
C(18)	−8395(3)	3797(2)	12331(2)	41(1)
C(19)	−7150(3)	3984(2)	11655(1)	32(1)

U_{eq} is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

*3.1.4. 8,9-Dimethyl-5-spirocyclopentyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b]benzotriazepine (**3d**)*

Yield: 40%; m.p. 163–165 °C (*i*-PrOH); IR (KBr): 3358 cm^{-1}, 3154, 2960, 2855, 1645, 1600, 1509, 1476, 1272; ^1H NMR ($CDCl_3$, δ ppm): 1.68–1.92 (m, 8H, $4CH_2$), 2.15 (s, 6H, $2CH_3$) 3.39–3.58 (m, 4H, $2CH_2$),

Table 2
Bond lengths (Å) and bond angles (°) for **4a**

Bond lengths			
N(1)–C(14)	1.342(3)	C(7)–C(12)	1.401(3)
N(1)–C(2)	1.445(3)	C(8)–C(9)	1.384(3)
C(2)–C(3)	1.526(3)	C(9)–C(10)	1.379(3)
C(3)–N(4)	1.484(2)	C(10)–C(11)	1.375(3)
N(4)–C(14)	1.330(2)	C(11)–C(12)	1.389(3)
N(4)–C(5)	1.491(2)	C(12)–N(13)	1.410(2)
C(5)–N(6)	1.460(2)	N(13)–C(14)	1.333(3)
C(5)–C(15)	1.529(3)	C(15)–C(16)	1.523(3)
C(5)–C(19)	1.534(3)	C(16)–C(17)	1.524(3)
N(6)–C(7)	1.399(2)	C(17)–C(18)	1.517(3)
C(7)–C(8)	1.392(3)	C(18)–C(19)	1.525(3)
Bond angles			
C(14)–N(1)–C(2)	109.85(17)	C(10)–C(9)–C(8)	119.7(2)
N(1)–C(2)–C(3)	102.58(17)	C(10)–C(9)–H(9A)	120.4(16)
N(4)–C(3)–C(2)	102.02(16)	C(11)–C(10)–C(9)	119.9(2)
C(14)–N(4)–C(3)	108.67(16)	C(10)–C(11)–C(12)	120.9(2)
C(14)–N(4)–C(5)	123.98(15)	C(11)–C(12)–C(7)	119.94(18)
C(3)–N(4)–C(5)	123.29(15)	C(11)–C(12)–N(13)	115.98(17)
N(6)–C(5)–N(4)	106.88(14)	C(7)–C(12)–N(13)	124.04(17)
N(6)–C(5)–C(15)	108.98(15)	C(14)–N(13)–C(12)	132.33(16)
N(4)–C(5)–C(15)	108.22(14)	N(4)–C(14)–N(13)	128.71(17)
N(6)–C(5)–C(19)	113.54(15)	N(4)–C(14)–N(1)	111.95(18)
N(4)–C(5)–C(19)	109.50(14)	N(13)–C(14)–N(1)	119.33(18)
C(15)–C(5)–C(19)	109.57(15)	C(16)–C(15)–C(5)	112.99(16)
C(7)–N(6)–C(5)	120.34(15)	C(15)–C(16)–C(17)	111.08(17)
C(8)–C(7)–N(6)	120.93(17)	C(18)–C(17)–C(16)	110.83(18)
C(8)–C(7)–C(12)	118.05(17)	C(17)–C(18)–C(19)	110.84(18)
N(6)–C(7)–C(12)	120.98(17)	C(18)–C(19)–C(5)	111.39(16)
C(9)–C(8)–C(7)	121.5(2)		

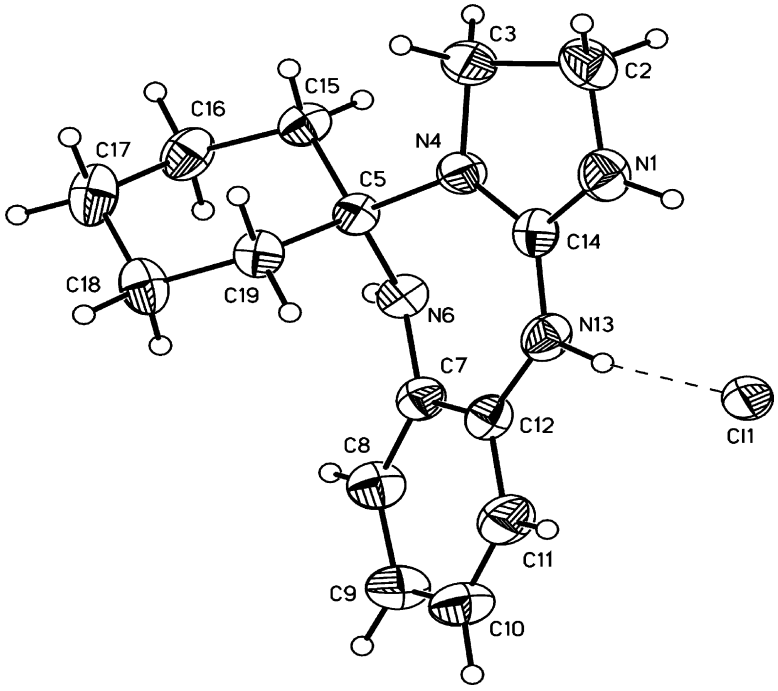


Fig. 2. ORTEP drawing of **4a**.

Table 3
Effects of test compounds **4a** and **4b** [mean EC_{50} values and maximal contraction responses (E_{max})] compared to phenylephrine (PE) in rabbit aortic rings

Compound	N	EC_{50} (μmol)	E_{max} (% control) ± SEM
Control (PE)	8	1.34	100
4a	8		11.125 ± 2.27
4b	6	2.37	91.17 ± 2.10

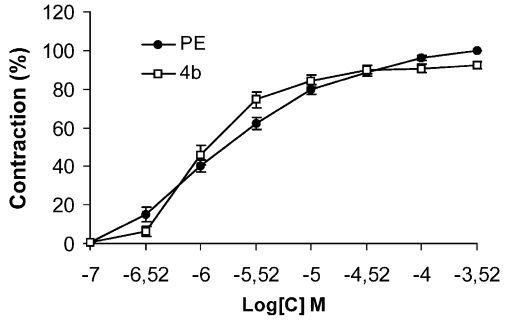


Fig. 3. Concentration–response curves for phenylephrine (PE) and **4b** in rabbit aortic rings. Results are given as mean ± SEM of six experiments.

3.70 (br s, 1H, NH), 4.35 (br. s, 1H, NH) 6.36 (s, 1H, Ar), 6.80 (s, 1H, Ar). *Anal.* for $C_{16}H_{22}N_4$ (270.37).

3.1.5. 5-Ethyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b][1,3,5]benzotriazepine (3e)

Yield: 35%; m.p. 150-154 °C (EtOH); IR (KBr): 3366 cm^{-1}, 3160, 2962, 2848, 1647, 1589, 1481, 1284, 1097;

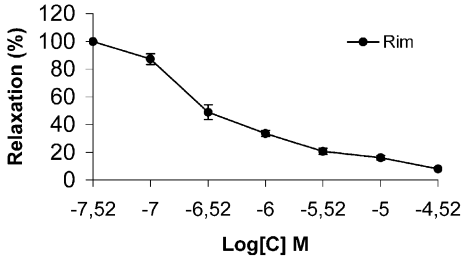


Fig. 4. The effect of relaxation of rabbit aortic rings to rimalkalim (Rim, 10^{-7}–3×10^{-5} mol). The rings were preconstricted with submaximal concentration of **4b** (3×10^{-5}mol). Values represent mean ± SEM of four experiments.

^{1}H NMR (DMSO-d_6, δ ppm): 0.79–0.87 (t, 3H, CH_3), 1.33–1.61 (m, 1H, CH), 1.54–1.61 (m, 1H, CH), 3.22–3.51 (m, 4H, $2CH_2$), 4.06–4.15 (m, 1H, CH), 5.89–5.91 (d, 1H, NH), 6.18 (s, 1H, NH), 6.56–6.74 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, δ ppm): 10.33, 25.56, 41.02, 49.22, 70.41, 120.24, 120.54, 120.87, 126.62, 139.15, 139.93, 155.85.). *Anal.* for $C_{12}H_{16}N_4$ (216.28).

*3.1.6. 5-Ethyl-8,9-dimethyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b][1,3,5]benzotriazepine (**3f**)*

Yield: 44%; m.p. 164–167 °C (EtOH); IR (KBr): 3363 cm^{-1}, 3162, 2965, 2841, 1647, 1600, 1481, 1277, 1099; ^{1}H NMR ($CDCl_3$, δ ppm): 0.94–1.01 (t, 3H, CH_3), 1.63–1.73 (m, 2H, CH_2), 2.17 (s, 6H, CH_3), 3.44–3.63 (m, 5H, $2CH_2$ and NH), 4.16–4.23 (m, 2H, CH and NH), 6.46 (s, 1H, Ar), 6.82 (s, 1H, Ar). *Anal.* for $C_{12}H_{20}N_4$ (244.33).

*3.1.7. 8,9-Dichloro-5-ethyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b][1,3,5]benzotriazepine (**3g**)*

Yield: 20%; m.p. 170–174 °C; IR (KBr): 3376, 3156, 2959, 2870, 1646, 1577, 1481, 1277, 1071 (cm^{-1}); ^1H NMR ($CDCl_3$, δ ppm): 0.80–0.83 (t, 3H, CH_3), 1.26–1.35 (m, 1H, CH), 1.58–1.66 (m, 1H, CH), 3.22–3.53 (m, 4H, $2CH_2$), 4.11–4.17 (m, 1H, CH), 6.30 (br. s, 1H, NH), 6.33–6.34 (d, 1H, NH), 6.75 (s, 1H, Ar), 6.83 (s, 1H, Ar); ^{13}C NMR ($CDCl_3$, δ ppm): 10.18, 25.52, 40.89, 49.14, 69.66, 120.07, 120.59, 121.39, 126.79, 140.04, 140.57, 156.91. *Anal.* for $C_{12}H_{14}N_4Cl_2$ (285.17).

*3.1.8. 5,5-Dimethyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b][1,3,5]benzotriazepine (**3h**)*

Yield: 48%; m.p. 141–145 °C (EtOH); IR (KBr): 3327 cm^{-1}, 3148, 3088, 2980, 2852, 1632, 1585, 1476, 1279, 1104; ^1H NMR ($CDCl_3$, δ ppm): 1.47 (s, 6H, $2CH_3$), 3.39–3.47 (m, 2H, CH_2), 3.59–3.98 (m, 2H, CH_2), 3.98 (s, 1H, NH), 6.56–6.61 (dd, 1H, Ar), 6.71–6.89 (m, 2H, Ar), 6.97–7.02 (dd, 1H, Ar); ^{13}C NMR ($CDCl_3$, δ ppm): 26.55, 40.35, 47.23, 67.72, 119.84, 121.35, 121.96, 126.79, 136.96, 137.91, 154.96. *Anal.* for $C_{12}H_{16}N_4$ (216.28).

*3.1.9. 5,5,8,9-Tetramethyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b][1,3,5]benzotriazepine (**3i**)*

Yield: 54%; m.p. 173–176 °C (MeOH); IR (KBr): 3318 cm^{-1}, 3161, 2979, 2912, 2866, 1648, 1602, 1479, 1276; ^1H NMR (DMSO-d_6, δ ppm): 1.31 (s, 6H, $2CH_3$), 2.04 (s, 6H, $2CH_3$), 3.18–3.25 (m, 2H, CH_2), 3.39–3.47 (m, 2H, CH_2), 5.25 (s, 1H, NH), 5.95 (s, 1H, NH), 6.46 (s, 1H, Ar), 6.54 (s, 1H, Ar). *Anal.* for $C_{14}H_{20}N_4Cl_2$ (244.34).

*3.1.10. 8,9–Dichloro-5,5-dimethyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b][1,3,5]benzotriazepine (**3j**)*

Yield: 21%; m.p. 191–195 °C; IR (KBr): 3342 cm^{-1}, 3176, 2977, 2907, 1647, 1618, 1484, 1293, 1145; ^1H NMR ($CDCl_3$, δ ppm): 1.27–1.46 (s, 6H, $2CH_3$), 3.20–3.73 (m, 4H, $2CH_2$), 6.07–6.20 (br s, 1H, NH), 6.87–7.09 (m, 3H, Ar, NH). *Anal.* for $C_{12}H_{14}N_4Cl_2$ (285.17).

*3.1.11. 5-Spiro-4′-(1′-methylpiperidine) 2,3,5,6-tetrahydro-1H-imidazo[2,1-b]benzotriazepine-(**3k**)*

Yield: 41%; m.p. 158–161 °C (*i*-PrOH); IR (KBr): 3358 cm^{-1}, 3155, 2927, 2860, 2790, 1639, 1584, 1480, 1272, 1108; ^1H NMR ($CDCl_3$, δ ppm): 1.79–1.84 (d, 2H, CH_2), 1.96–2.20 (m, 4H, CH_2), 2.31 (s, 3H, CH_3), 2.73–2.78 (d, 2H, CH_2), 3.41–3.48 (m, 2H, CH_2), 3.58–3.65 (m, 2H, CH_2), 4.10 (s, 1H, NH), 4.16 (br. s, 1H, NH) 6.67–7.04 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, δ ppm): 32.78, 40.53, 46.22, 46.44, 52.04, 67.78, 121.38, 121.78, 122.86, 129.73, 135.98, 138.35, 155.71. *Anal.* for $C_{15}H_{21}N_5$ (271.36).

*3.1.12. 5-Spiro-4′-(1′-methyl-piperidine) 8,9-dimethyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b]-benzotriazepine-(**3l**)*

Yield: 32%; m.p. 197–200 °C (EtOH); IR (KBr): 3258 cm^{-1}, 3111, 2938, 2810, 2790, 1645, 1599, 1488, 1280, 1131, 997; ^1H NMR (DMSO-d_6, δ ppm): 1.51–1.57 (d, 2H, CH_2), 1.74–1.88 (t, 2H, CH_2), 2.00 (s, 3H, $2CH_3$), 2.05 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.49–2.55 (d, 4H, $2CH_2$), 3.15–3.22 (m, 2H, CH_2), 3.35–3.46 (m, 2H, CH_2), 5.13 (s, 1H, NH), 5.97 (br s, 1H, NH), 6.51 (s, 1H, Ar), 6.55 (s, 1H, Ar). *Anal.* for $C_{17}H_{25}N_5$ (299.42).

*3.1.13. 5-Spiro-4′-(1′-acetylpiperidine) 2,3,5,6-tetrahydro-1H-imidazo[2,1-b]benzotriazepine-(**3m**)*

Yield: 27% mp 162–164 °C (*i*-PrOH); IR (KBr): 3350 cm^{-1}, 3164, 2923, 1640, 1586, 1482, 1425, 1273, 1101, 998; ^1H NMR ($CDCl_3$, δ ppm): 1.73–1.96 (m, 4H, $2CH_2$), 2.09 (s, 3H, CH_3), 2.79–2.94 (m, 1H, CH), 3.17–3,41 (m, 1H, CH), 3.43–3.67 (m, 5H, $2CH_2$, CH), 3.92 (s, 1H, NH), 4.60 (d, 1H, CH), 6.79–7.03 (m, 4H, Ar). *Anal.* for $C_{16}H_{21}N_5$ (299.37).

*3.1.14. 2,3,5,6-Tetrahydro-1H-imidazo[2,1-b]benzotriazepine-5-spiro-4′-(1′-benzylpiperidine) (**3n**)*

Yield: 20% mp 184–186 °C (acetone); IR (KBr): 3377 cm^{-1}, 3160, 2949, 2852, 2765, 1643, 1585, 1486, 1270, 1110, 918; ^1H NMR ($CDCl_3$, δ ppm): 1.80–1.82 (d, 2H, CH), 2.00–2.05 (dd, 2H, CH), 2.15–2.19 (t, 2H, CH), 2.80–2.82 (d, 2H, CH), 3.44–3.47 (m, 2H, CH_2), 3.54 (s, 2H, CH_2), 3.61–3.64 (m, 2H, CH_2), 4.18 (s, 1H, NH), 6.60–6.68 (dd, 1H, Ar), 6.80–6.81 (m, 1H, Ar), 6.86–6.89 (m, 1H, Ar), 6.99–7.01 (d, 1H, Ar), 7.26–7.35 (m, 6H, Ar, NH); ^{13}C NMR ($CDCl_3$, δ ppm): 32.93, 40.63, 46.49, 49.77, 63.16, 68.60, 121.51, 122.01, 122.88, 126.38, 127.48, 128.54, 129.38,135.86, 137.77, 138.10, 155.67. *Anal.* for $C_{21}H_{25}N_5$ (345.44).

*3.1.15. 5-Spirocyclohexyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b]benzotriazepine hydrochloride (**4a**)*

To a solution of 2-chloro-4,5-dihydroimidazole (19 mol) in CH_2Cl_2 (30 ml) the 2,3-dihydro-benzimidazole (**2a**) (3 g, 15.9 mmol) was added and the reaction mixture was kept for 12 h at r.t. The solid that precipitated was separated by filtration, washed with anhydrous methanol (10 ml), dried and recrystallized from MeOH to give **4a**. Yield: 1.74 g (37%); m.p. 161–163 °C; IR (KBr): 3232 cm^{-1}, 2843, 1600, 1520, 1424, 1296, 1103; ^1H NMR ($CDCl_3$, δ ppm): 1.42–1.89 (m,10H, $5CH_2$), 3.66–3.78 (m, 4H, $2CH_2$), 4.41 (s, 1H, NH), 6.82–6.85 (m, 1H, Ar), 6.87–7.02 (m, 2H, Ar), 7.25–7.36 (m, 1H, Ar), 8.75 (br s, 1H, NH^+); ^{13}C–NMR (DMSO-d_6, δ ppm): 21.03, 23.84, 32.59, 42.64, 46.27, 72.22, 118.93, 121.91, 122.43, 124.39, 128.74, 133.58, 155.57. *Anal.* for $C_{15}H_{21}N_4Cl$ (292.85).

*3.1.16. 8,9-dimethyl-5-spirocyclohexyl-2,3,5,6-tetrahydro-1H-imidazo[2,1-b]benzotriazepine hydrochloride (**4b**)*

Analogously by reacting 2-chloro-4,5-dihydroimidazole with **2b**, 8,9-dimethyl-5-spirocyclohexyl-2,3,5,6-tetrahydro-1*H*-imidazo[2,1-*b*]benzotriazepine hydrochloride (**4b**) was obtained. Yield: 50%; m.p. 154-160 °C (MeOH); IR (KBr): 3295, 3201, 2931, 2778, 1642, 1578, 1507, 1443, 1296, 1020 (cm^{-1}); ^1H NMR ($CDCl_3$, δ ppm): 1.51–1.82 (m, 10H, $5CH_2$), 2.09 (s, 6H, $2CH_3$), 3.50–3.54 (m, 2H, CH_2), 3.64–3.72 (m, 2H, CH_2), 4.59 (s, 1H, NH), 6.65 (s, 1H, Ar), 6.95 (s, 1H, Ar). *Anal.* for $C_{17}H_{25}N_4Cl$ (320.91).

3.2. X-ray structure analysis of **4a**

Crystal data for $C_{15}H_{20}N_4 \cdot HCl$: monoclinic, space group $P2_1/n$, $a = 7.807(2)$, $b = 12.658(3)$, $c = 14.936(3)$ Å, $\beta = 98.94(3)^\circ$, $V = 1458.1(6)$ Å^3, $Z = 4$, $d_x = 1.334$ g/cm^3, $T = 293$ K. Data were collected for a crystal with dimensions $0.4 \times 0.3 \times 0.3$ mm^3 on a Kuma KM4 diffractometer using graphite monochromated Cu–K_α radiation. Final R indices for 2320 reflections with $I > 2\sigma(I)$ and 266 refined parameters are: $R_1 = 0.0371$, $wR_2 = 0.1022$ ($R_1 = 0.0385$, $wR_2 = 0.1029$ for all 2411 data). The structure was solved by direct methods with the program SHELXL-86 [14]. Full matrix least-squares refinement was carried out on F^2 with SHELXL-97 [15]. Only reflections with F^2 positive were used in the refinement process. Hydrogen atoms were located on ΔF map and their parameters included in the refinement process.

3.3. Biological Investigations

Rimalkalim was generously gifted by Dr. Englert, Hoechst, Germany. Phenylephrine was obtained from Sigma Chemical Co. (St. Louis, MO).

3.4. Preparation and recording of rabbit aorta ring

Adult, cross-bred rabbits of either sex weighting 2.0–2.5 kg were sacrificed by anesthetic overdose (pentobarbital 100 mg/kg, iv). The thoracic aorta was excised and placed in Krebs–Henseleit solution of the following composition (mmol) dissolved in doubly distilled water: 118 NaCl; 4.7 KCl; 1.9 $CaCl_2 \times 2H_2O$; 0.6 $MgSO_4 \times 7H_2O$; 1.2 KH_2PO_4; 25 $NaHCO_3$; 6 glucose; 2 pyruvic acid. The aorta was dissected free from connective tissue and cut into rings of approximately 4 mm that were mounted vertically by means of stainless steel hooks in 5 ml organ baths containing the physiological solution. The solution was aerated with a mixture of 95% O_2 and 5%CO_2 which produce a pH of 7.4. The temperature of the Krebs–Henseleit solution was maintained at 37 °C and the continuos flow was provided by the peristaltic pump ppl-0.5 Zalimp ('Zalimp' Warszawa, Poland) and displayed on L 6514-II four channel chart recorder (Linseis, GmBH, Selb, Germany).

The aortic rings were allowed to equilibrate under a resting tension of 3 g for 1 h before drug addition. Since we found that the first dose–response curve for most tissues differed from subsequent responses, all tissues were exposed to phenylephrine (3×10^{-7} mol) before experimentation. Subsequently, for each ring, control dose–response curve of phenylephrine (10^{-7}–3×10^{-4} mol) was constructed followed by dose–response curve of investigated compound.

Dose–response curves were constructed by increasing bath concentrations of agonists. The concentration of agonist was increased only after the previous concentration had produced its maximum response and remained constant. After completion of a dose–response curve, drugs were washed from the preparation and consecutive dose–response curves on a given tissue were always spaced at least 1 h to ensure maximum washout of agonists and to minimize receptor desensitization.

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