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Thiazolo[3,2-a]pyrimidine derivatives as calcium antagonists

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Some new thiazolo[3,2-a]pyrimidine derivatives were prepared refluxing 2-thioxo-1,2,3,4-tetrahydropyrimidine derivatives with phenacyl bromide in glacial acetic acid. Calcium antagonistic activities of these compounds were evaluated in K^+-depolarized rat aorta, using nifedipine as reference compound.

Derivate des Thiazolo[3,2-a]pyrimidins als Calciumantagonisten

Neue Derivate des Thiazolo[3,2-a]pyrimidins wurden durch Umsetzung von 2-Thioxo-1,2,3,4-tetrahydropyrimidinen mit Phenacylbromid in siedendem Eisessig hergestellt. Die calciumantagonistische Aktivität dieser Substanzen wurde an der K^+-depolarisierten Rattenaorta mit Nifedipin als Vergleichssubstanz geprüft.

1. Introduction

1,4-Dihydropyridines, such as nifedipine, nitrendipine and amlodipine are widely used in the management of cardiovascular diseases due to their calcium channel blocking activities [1–3]. In order to enhance their intrinsic activity, several groups have prepared modifications usually by changing the ester groups and/or the substituents on the phenyl nucleus [4–6]. We also aimed to synthesize more potent calcium channel blocking agents by using the isosters of the 1,4-dihydropyridine ring, such as 2-thioxo-1,2,3,4-tetrahydropyrimidine.

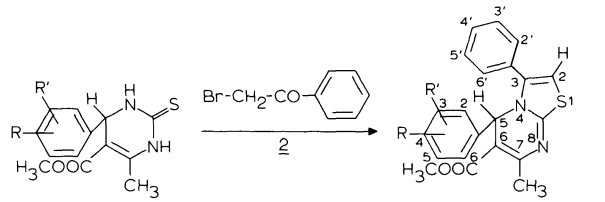
For this purpose we synthesized 2-thioxo-1,2,3,4-tetrahydropyrimidines and checked their calcium antagonistic [7, 8] and antiaggregating [8] effects *in vitro*. We later prepared [9] two new thiazolo[3,2-a]pyrimidines **3a** and **3b** from the 2-thioxo-1,2,3,4-tetrahydropyrimidines **1a** and **1b**, respectively, with phenacyl bromide according to Takamizawa et al. [10] (Scheme 1) and confirmed their structures inter alia by $^1H-^1H$ NOE technique [9, 11] indicating that the products are 5*H*-isomers. When ^1H NMR-spectra of the compounds were examined it was seen that, due to the double bond of the thiazole ring, the singlet of H-2 appeared more downfied (approximately 0.3–0.5 ppm) than that of H-5.

2. Investigations and results

Here we describe the preparation of compounds **3c–3g** using the same method [9], in order to investigate their Ca-antagonistic activities (Scheme). The pertinent efficacies of **3a–3g** were evaluated in the K^+-depolarized rat thoracic aorta. Each compound produced full relaxation at its maximal concentration (n = 5 – 7); their IC_{50} values are given in the Table. In control studies the solvent DMSO was tested: no significant relaxation was observed.

The Ca-antagonistic activities of the starting compounds **1a–1g** had been determined by the radioligand binding method and their potencies had been evaluated in terms of Ki values [7, 9] (Table). Comparison of IC_{50} and the Ki values indicates that the thiazolo[3,2-a]pyrimidines **3** are stronger Ca-antagonists than the starting compounds **1**. Even though the pharmacological methods are different, the close relation between Ki and IC_{50} values obtained for nifedipine (Table) may indicate that the results of both methods are comparable.

Scheme 1



1	R	R'	1	R	R'
a	H	4-CH_3	e	H	3-Cl
b	H	4-OCH_3	f	H	3-NO_2
c	H	H	g	2-OH	5-Br
d	H	2-OCH_3			

Table Pharmacological results

Compound	Ki* [mol/l]	Compound	IC_{50} [mol/l]
1a	$4 \cdot 10^{-5}$	**3a**	$5.6 \pm 0.3 \cdot 10^{-6}$
1b	$5 \cdot 10^{-5}$	**3b**	$8.1 \pm 0.4 \cdot 10^{-6}$
1c	$5 \cdot 10^{-5}$	**3c**	$1.4 \pm 0.3 \cdot 10^{-6}$
1d	$>10^{-4}$	**3d**	$1.6 \pm 0.3 \cdot 10^{-5}$
1e	$2 \cdot 10^{-5}$	**3e**	$2.1 \pm 0.5 \cdot 10^{-7}$
1f	10^{-4}	**3f**	$1.5 \pm 0.6 \cdot 10^{-7}$
1g	10^{-5}	**3g**	$>10^{-4}$
Nifedipine	10^{-8}		$6.9 \pm 0.08 \cdot 10^{-9}$

* Ki values represent the concentration of the compounds required to cause 50% inhibition of [^{3}H]-PN 200-110 binding in rat skeletal muscle and are taken from previous studies [7, 8].

3. Experimental

3.1. Chemistry

3.1.1. Devices

M.p. (uncorr.): Hoover capillary melting point apparatus. UV-spectra: Hitachi 220 (OH). IR-spectra in KBr: Perkin Elmer 780. ^1H NMR: Bruker WM 250 (250 MHz), D_6-DMSO, TMS as internal standard. Elementary analysis: Mikroanalytisches Labor University Regensburg and Tubitak-Mae Instrumental Analysis Laboratories, Gebze, Turkey.

1,2,3,4-Tetrahydro-6-methyl-4-(substituted)phenyl-2-thioxo-5-pyrimidinecarboxylic acid methyl esters **1c–g** [7, 8] and phenacyl bromide (**2**) were prepared as reported [12].

3.1.2. Methyl 3-phenyl-5-(substituted)phenyl-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylates **3c–g**

The solutions of 7.5 mmol **1c–g** and 8 mmol (1.59 g) **2** were refluxed in glacial CH_3COOH for 6 h and kept overnight at room temp. The mixture was concentrated *in vacuo* and the residue was solidified with $(C_2H_5)_2O$. The HBr salts so obtained were converted to the corresponding bases (5% $NaHCO_3$) which were crystallized from the appropriate solvent.

3.1.2.1. Methyl 3,5-diphenyl-7-methyl-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3c**)

From 1.96 g **1c** and **2**. Yield: 1.68 g (62%). M.p. 162–163 °C [CH_3CN/H_2O (1:2)]. UV (λ_{max}, lg ε, nm): 207 (4.21), 231 (4.38, sh), 387 (4.58). IR (cm^{-1}): 1710; 1590; 1475. ^1H NMR (δ, ppm): 2.31 (s; 3 H, CH_3), 3.52 (s; 3 H, OCH_3), 6.16 (s; 1 H, py H-5), 6.61 (d; J = 8 Hz, 2 H aromat., H-2, H-6), 6.79 (s; 1 H, thia H-2), 7.09–7.12 (m; 3 H aromat., H-3–5), 7.24 (d; J = 8 Hz, 2 H aromat., H-2′, H-6′) 7.49–7.53 (m; 3 H aromat., H-3′–5′).

$C_{21}H_{18}N_2O_2S$ (362.4)
Calcd.: C 69.6 H 5.00 N 7.7
Found: C 69.4 H 5.01 N 7.9

3.1.2.2. Methyl 3-phenyl-5-(2-methoxyphenyl)-7-methyl-5*H*-thiazolo[3,2-a] pyrimidine-6-carboxylate (**3d**)

From 2.19 g **1d** and **2**. Yield: 1.12 g (38%). M.p. 239–240 °C dec. [C_2H_5OH/H_2O (1:2)]. UV (λ_{max}, lg ε, nm): 207 (4.12), 277 (4.44), 382 (4.60 sh). IR (cm^{-1}): 1710; 1610; 1490. ^1H NMR (δ, ppm): 2.44 (s; 3 H, CH_3), 3.51 (s; 3 H, $COOCH_3$), 3.92 (s; 3 H, OCH_3), 5.39 (s; 1 H py H-5), 5.67 (s; 1 H, thia H-2), 6.86–7.13 (m; 3 H aromat., H-4–6), 7.23–7.60 (m; 3 H aromat., H-3, H-2′, H-6′), 7.65–7.71 (m; 3 H aromat., H-3′–5′).
$C_{22}H_{20}N_2O_3S$ (392.5)
Calcd.: C 67.3 H 5.14 N 7.1
Found: C 67.7 H 5.53 N 7.4

3.1.2.3. Methyl 3-phenyl-5-(3-chlorophenyl)-7-methyl-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3e**)

From 2.22 g **1e** and **2**. Yield: 1.9 g (40%). M.p. 138–139 °C [C_2H_5OH/H_2O (1:2)]. UV (λ_{max}, lg ε, nm): 208 (4.19), 271 (4.78, sh), 387 (4.64). IR (cm^{-1}): 1695; 1580; 1475. ^1H NMR (δ, ppm): 2.32 (s; 3 H, CH_3), 3.52 (s; 3 H, OCH_3), 6.13 (s; 1 H, py H-5), 6.41 (s; 1 H, thia H-2), 6.64 (d; J = 7.5 Hz, 1 H aromat., H-6), 6.83 (d; J = 1.8 Hz, 1 H aromat., H-2), 7.20–7.35 (m; 4 H aromat., H-4, H-5, H-2′, H-6′), 7.44–7.58 (m; 3 H aromat., H-3′–5′).
$C_{21}H_{17}ClN_2O_2S$ (396.9)
Calcd.: C 63.5 H 4.32 N 7.1
Found: C 63.2 H 4.35 N 7.1

3.1.2.4. Methyl 3-phenyl-5-(3-nitrophenyl)-7-methyl-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3f**)

From 2.30 g **1f** and **2**. Yield: 1.29 g (42%). M.p. 153–154 °C [C_2H_5OH/H_2O (1:2)]. UV (λ_{max}, lg ε, nm): 207 (4.20), 249 (4.44), 347 (4.71). IR (cm^{-1}): 1700; 1600; 1485. ^1H NMR (δ, ppm): 2.22 (s; 3 H, CH_3), 3.52 (s; 3 H, OCH_3), 5.50 (s; 1 H, py H-5), 6.35 (s; 1 H, thia H-2), 7.14–7.33 (m; 2 H aromat., H-5, H-6), 7.39–7.61 (m; 4 H aromat., H-2, H-4, H-2′, H-6′), 7.87–8.12 (m; 3 H aromat., H-3′–5′).
$C_{21}H_{17}N_3O_4S$ (407.5)
Calcd.: C 61.9 H 4.21 N 10.3
Found: C 62.2 H 4.48 N 10.0

3.1.2.5. Methyl 3-phenyl-5-(2-hydroxy-5-bromophenyl)-7-methyl-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3g**)

From 2.67 g **1g** and **2**. Yield: 1.40 g (41%). M.p. 134–135 °C dec. [CH_3CN/H_2O (1:2)]. UV (λ_{max}, lg ε, nm): 207 (4.16), 269 (4.85 sh), 286 (4.66) 380 (4.76 sh). IR (cm^{-1}): 1710; 1595; 1490. ^1H NMR (δ, ppm): 2.51 (s; 3 H, CH_3), 3.52 (s; 3 H, OCH_3), 5.58 (s; 1 H, py H-5), 6.63 (s; 1 H, thia H-2), 7.17–7.66 (m; 5 H aromat., H-3, H-4, H-6, H-2′, H-6′), 7.88–7.91 (m; 3 H aromat., H-3′–5′).
$C_{21}H_{17}BrN_2O_3S$ (457.3)
Calcd.: C 55.2 H 3.75 N 6.1
Found: C 55.3 H 4.01 N 5.9

3.2. Pharmacology

Male rats (200–300 g) were killed by a blow on the head and exsanguinated. Strips of thoracic aortae were isolated and mounted in organ baths containing 20 ml Ca^{2+}-free K^+-rich Krebs solution ([mmol]: NaCl 52, KCl 65, $NaHCO_3$ 25, KH_2PO_4 1.2, glucose 11.5; 37 °C; 95% O_2/5% CO_2.
1 g of resting tension was applied to the tissues and the isometric contractions were recorded by a force-displacement transducer (Ugo Basile 7004) on a Gemini recorder (model 7070).
Ca-antagonistic activities of the compounds were evaluated on the basis of their ability to relax the aortae precontracted by addition of 1.5 mmolar Ca^{2+} to the K^+-rich Ca^{2+}-free solution. Only one compound was tested in each preparation. For comparison nifedipine was used. The potencies of the compounds were determined by calculating the concentration producing 50% of the maximal relaxation (IC_{50}).

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