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Synthesis and Antihypertensive Activity of 1-(2-Thiazolyl)-3,5-disubstituted -2-Pyrazolines

Several substituted 3-aryl-1-(4-aryl-2-thiazolyl)-5-(3-pyridyl)-2-pyrazolines were synthesized by reacting substituted 3-aryl-5-(3-pyridyl)-1-thiocarbamoyl-2-pyrazolines with phenacyl bromide in ethanol. The structures of all compounds were confirmed by IR, ^{1}H-NMR, mass spectral data and elemental analyses. The antihypertensive activity of compounds was examined by the tail-cuff method and compared with clonidine. Compounds **24**–**28** showed significant antihypertensive activity.

Keywords: Sympatholytics; Imidazoline; Antihypertensive; Pyridyl-thiazolyl-pyrazoline; Azachalcones

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Introduction

Hypertension is a consequence of many diseases. Therapy using antihypertensive agents evolved rapidly. In the meanwhile a number of drugs for the treatment and control of hypertensive disease have been discovered [1].

The first generation of centrally acting antihypertensive drugs such as clonidine (**1**) and its analogs were once very popular in the treatment of hypertension.

The overall mechanism of action for the centrally active sympatholytics, clonidine, guanabenz (**2**) and guanafacine (**3**) appears to be stimulation of α_2-adrenoceptors and nonadrenergic imidazoline (I1) receptors in CNS causing inhibition of sympathetic output [2, 3]. This effect results in reduced peripheral and renovascular resistance and leads to decrease in systolic and diastolic blood pressure. The central α_2-adrenergic agonists are equally effective in all age and race subgroups and can be used for patients with renal insufficiency, diabetes mellitus, bronchospastic disease and ischemic disease. As a result, many modifications of the original structure of clonidine have been studied, leading to new active compounds like thiazolo imidazoline derivative **4** which

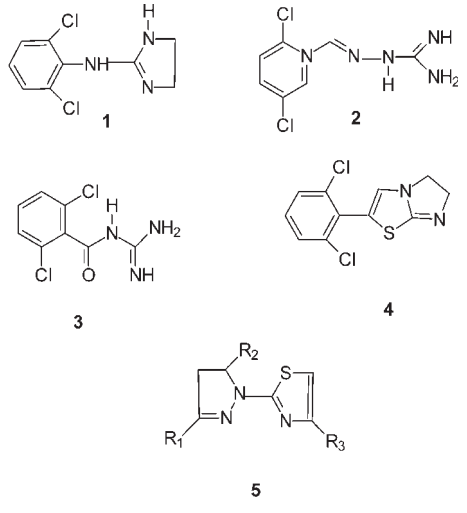

Figure 1. The structural formula of compounds having antihypertensive activity.

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in antihypertensive test was as potent as clonidine itself [4]. This result encouraged us to synthesize several pyridyl-thiazolyl-pyrazoline derivatives **5**, which are structurally similar to **4**, and to evaluate their antihypertensive activities (Figure 1).

Results and discussion

Chemistry

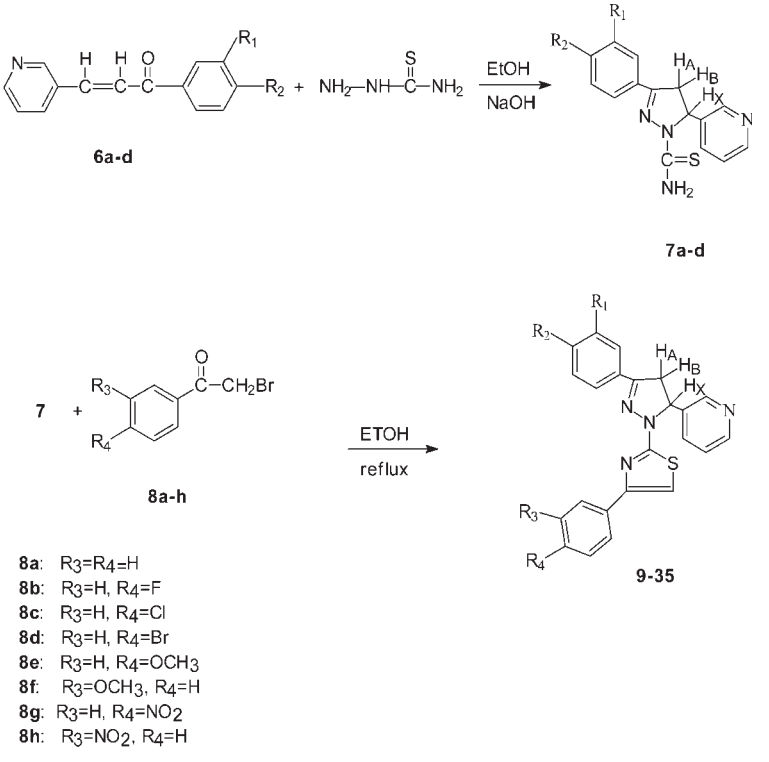
Substituted 3-aryl-1-(4-aryl-2-thiazolyl)-5-(3-pyridyl)-2-pyrazolines were synthesized for their possible antihypertensive activity. In order to prepare different 1-thiocarbamoyl-2-pyrazolines **7 a**–**d** thiosemicarbazide was allowed to react with various azachalcons **6 a**–**d** in accordance with the method described in the literature [5].

Compounds **9**–**35** were obtained by reacting compounds **7 a**–**d** with phenacyl bromide or its derivatives in ethanol [6] (Scheme 1). The substitution on the para or meta site of phenacyl bromide played an important role in thiazole formation step. Namely, the phenacyl bromide derivatives with a strong electron-withdrawing group like NO_2 in para or meta position of the benzene ring, gave higher yield compared to the H or Br groups (see Table 1).

The structures of compounds **9**–**35** were confirmed by IR, ^{1}H-NMR, mass spectra and elemental analyses. IR spectra of compounds **9**–**35** showed C=N and C=C stretching bands at 1640 and 1550 cm^{-1} respectively. In the ^{1}H-NMR spectra, H_A, H_B, H_X protons of the pyrazoline ring appeared as 3 doublets of doublets (dd) at 3.31–3.37, 3.93–4 and 5.65–5.7 ppm (J_{AB} = 16 Hz, J_{AX} = 8 Hz, J_{BX} = 12 Hz) respectively. Protons belonging to the aromatic ring and phenyl substituents were observed at expected chemical shift and integral values. The H_5-proton of thiazole was observed as a singlet between 6.9 to 7.1 ppm. The mass spectrum fragmentation pattern of compound **9** was also in agreement with the suggested structure. The molecular ion appeared at m/z 382. The fragment ions appeared at 304 (M^+- pyridyl), 278 (M^+- C_6H_5-CH=CH_2), 266 (M^+- C_8H_6N), 248 (M^+- C_8H_6S), 220 (M^+- C_5H_4N-C^+=N-N=C=S), 174 (M^+- C_5H_4N-CN + C_6H_5-CH=CH_2), 134 (C_8H_6S), 104 (C_5H_4N-CN or C_6H_5-CH=CH_2). Compounds **10**–**35** gave similar mass spectra. The physical constants of compounds **10**–**35** are summarized in Table 1.

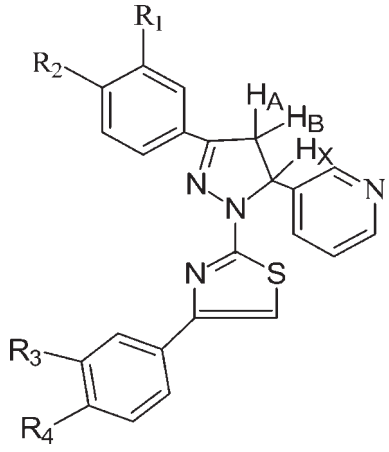
Biological activity

Adult male sparague-Dawley rats weighing 200–220 g were used in this study. Rats were housed in animals



Scheme 1. Synthesis of 1-(2-thiazolyl)-3,5-disubstituted-2-pyrazolines.

Table 1. Physical properties of pyridyl-thiazolyl-pyrazolines (**10**–**35**).



Compound	R1	R2	R3	R4	Yield (%)	Mp (°C)#	Formula†, MW	^{1}H-NMR ($CDCl_3$), MS
10	H	H	H	F	29	177–178	C23H17FN4S 400	3.4 (dd, 1 H, HA), 3.96 (dd, 1 H, HB), 5.67 (dd, 1 H, HX), 6.76 (s, 1 H, thiazole-H), 7.18 (m, 9 H, aromatic-H), 7.76 (m, 2 H, pyridine-H), 8.54 (m, 1 H, pyridine-H), 7.94 (m, 1 H, pyridine-H). MS m/z (%): 400 (M^+, 100) 367 (15), 322 (19), 282 (22), 256 (10), 221 (62), 192 (30), 151 (23).
11	H	H	H	Cl	34	221–223	C23H17ClN4S 416.5	3.33 (dd, 1 H, HA), 3.96 (dd, 1 H, HB), 5.67 (dd, 1 H, HX), 6.79 (s, 1 H, thiazole-H), 7.41 (m, 9 H, aromatic-H), 7.76 (m, 2 H, pyridine-H), 8.6 (m, 1 H, pyridine-H), 8.95 (m, 1 H, pyridine-H). MS m/z (%): 416 (M^+, 100), 383 (10) 338 (9), 312 (18), 270 (22), 208 (30), 173 (25), 139 (10).
12	H	H	H	Br	34	194–196	C23H17BrN4S 462	3.32 (dd, 1 H, HA), 3.95 (dd, 1 H, HB), 5.66 (dd, 1 H, HX), 6.83 (s, 1 H, thiazole-H), 7.56 (m, 9 H, aromatic-H), 7.79 (m, 2 H, pyridine-H), 8.67 (m, 1 H, pyridine-H), 8.95 (m, 1 H, pyridine-H). MS m/z (%): 462 (M^+, 35), 416 (100), 382 (10), 312 (15), 271 (18), 220 (30), 173 (40), 104 (38).
13	H	H	H	OCH3	30	168–170	C24H20N4OS 412	3.33 (dd, 1 H, HA), 3.80 (s, 3 H, OCH3), 3.94 (dd, 1 H, HB), 5.60 (dd, 1 H, HX), 6.68 (s, 1 H, thiazole-H), 6.85 (d, 2 H, aromatic-H), 7.44 (m, 3 H, aromatic-H), 7.56 (d, 2 H, aromatic-H), 7.75 (m, 2 H, aromatic-H), 7.80 (m, 2 H, pyridine-H), 8.60 (m, 1 H, pyridine-H), 8.90 (m, 1 H, pyridine-H). MS m/z (%): 412 (M^+, 50), 334 (10), 308 (12), 276 (18), 239 (18), 205 (25), 149 (45), 134 (55).

Table 1. (continued)

Compound	R1	R2	R3	R4	Yield (%)	Mp (°C)[#]	Formula[†], MW	^{1}H-NMR ($CDCl_3$), MS
14	H	H	OCH3	H	32	120–122	C24H20N4OS 412	3.34 (dd, 1 H, HA), 3.80 (s, 3 H, OCH3), 3.96 (dd, 1 H, HB), 5.67 (dd, 1 H, HX), 6.84 (s, 1 H, thiazole-H), 7.24 (m, 5 H, aromatic-H), 7.44 (m, 3 H, aromatic-H), 7.23 (m, 1 H, aromatic-H), 7.77 (m, 2 H, pyridine-H), 8.54 (m, 1 H, pyridine-H), 8.78 (m, 1 H, pyridine-H). MS m/z (%): 412 (M^+, 100), 379 (18), 334 (22), 308 (60), 276 (42), 221 (38), 205 (65), 188 (62), 160 (30).
15	H	H	H	NO2	64	221–223	C23H17N5O2S 427	3.37 (dd, 1 H, HA), 4.10 (dd, 1 H, HB), 5.68 (dd, 1 H, HX), 7.06 (s, 1 H, thiazole-H), 7.57 (m, 9 H, aromatic-H), 8.18 (m, 2 H, pyridine-H), 8.58 (m, 1 H, pyridine-H), 8.78 (m, 1 H, pyridine-H). MS m/z (%): 427 (M^+, 100), 379 (10), 349 (10), 323 (20), 291 (20), 237 (10), 220 (25), 174 (27), 104 (22).
16	H	H	NO2	H	62	202–204	C23H17N5O2S 427	3.39 (dd, 1 H, HA), 4.02 (dd, 1 H, HB), 5.69 (dd, 1 H, HX), 7.01 (s, 1 H, thiazole-H), 7.48 (m, 5 H, aromatic-H), 7.83 (m, 3 H, aromatic-H), 7.93 (m, 1 H, aromatic-H), 8.07 (m, 1 H, pyridine-H), 8.46 (m, 1 H, pyridine-H), 8.59 (m, 1 H, pyridine-H), 8.79 (m, 1 H, pyridine-H). MS m/z (%): 427 (M^+, 100), 379 (10), 349 (20), 322 (30), 291 (25), 218 (45), 172 (82), 103 (45).
17	CH3	H	H	H	35	145–147	C24H20N4S 396	2.41 (s, 3 H, CH3), 3.41 (dd, 1 H, HA), 4.16 (dd, 1 H, HB), 6.02 (dd, 1 H, HX), 6.80 (s, 1 H, thiazole-H), 7.45 (m, 9 H, aromatic-H), 8.90 (m, 2 H, pyridine-H), 8.74 (m, 1 H, pyridine-H), 9.08 (m, 1 H, pyridine-H). MS m/z (%): 396 (M^+,100), 361 (25), 317 (18), 235 (22), 221 (18), 174 (50), 128 (18).
18	CH3	H	H	Cl	32	218–220	C24H19ClN4S 430.5	2.44 (s, 3 H, CH3), 3.47 (dd, 1 H, HA), 4.21 (dd, 1 H, HB), 6.21 (dd, 1 H, HX), 6.84 (s, 1 H, thiazole-H), 7.51 (m, 8 H, aromatic-H), 8.23 (m, 2 H, pyridine-H), 8.78 (m, 1 H, pyridine-H), 9.29 (m, 1 H, pyridine-H). MS m/z (%): 430 (M^+, 100), 397 (10), 311 (15), 280 (10), 235 (18), 209 (18), 172 (22), 162 (18), 104 (10).
19	CH3	H	H	Br	30	213–215	C24H19BrN4S 476	2.43 (s, 3 H, CH3), 3.45 (dd, 1 H, HA), 4.18 (dd, 1 H, HB), 6.19 (dd, 1 H, HX), 6.82 (s, 1 H, thiazole-H), 7.48 (m, 8 H, aromatic-H), 8.21 (m, 2 H, pyridine-H), 8.78 (m, 1 H, pyridine-H), 9.27 (m, 1 H, pyridine-H). MS m/z (%): 475 (M^+, 22), 440 (10), 396 (22), 356 (40), 324 (38), 253 (45), 235 (75), 207 (65), 173 (100), 145 (20).
20	CH3	H	H	OCH3	30	161–163	C25H22N4OS 426	2.42 (s, 3 H, CH3), 3.32 (dd, 1 H, HA), 3.80 (s, 3 H, OCH3), 3.95 (dd, 1 H, HB), 5.66 (dd, 1 H, HX), 6.81 (s, 1 H, thiazole-H), 7.38 (m, 8 H, aromatic-H), 7.71 (m, 2 H, pyridine-H), 8.53 (m, 1 H, pyridine-H), 8.78 (m, 1 H, pyridine-H). MS m/z (%): 426 (M^+, 80), 393 (10), 347 (22), 308 (55), 275 (25), 234 (32), 204 (100), 188 (75), 160 (60), 103 (30).

Table 1. (continued)

Compound	R1	R2	R3	R4	Yield (%)	Mp (°C)[#]	Formula[†], MW	^{1}H-NMR ($CDCl_3$), MS
21	CH3	H	OCH3	H	17	174–176	C25H22N4OS 426	2.46 (s, 3 H, CH3), 3.34 (dd, 1 H, HA), 3.80 (s, 3 H, OCH3), 3.97 (dd, 1 H, HB), 5.68 (dd, 1 H, HX), 6.81 (s, 1 H, thiazole-H), 7.40 (m, 8 H, aromatic-H), 7.74 (m, 2 H, pyridine-H), 8.55 (m, 1 H, pyridine-H), 8.80 (m, 1 H, pyridine-H). MS m/z (%): 426 (M^+, 100), 393 (15), 348 (18), 308 (30), 237 (25), 203 (38), 158 (70), 148 (30), 103 (15).
22	CH3	H	H	NO2	65	259–261	C24H19N5O2S 441	2.42 (s, 3 H, CH3), 3.37 (dd, 1 H, HA), 3.98 (dd, 1 H, HB), 5.67 (dd, 1 H, HX), 7.06 (s, 1 H, thiazole-H), 7.54 (m, 8 H, aromatic-H), 8.18 (m, 2 H, pyridine-H), 8.56 (m, 1 H, pyridine-H), 8.70 (m, 1 H, pyridine-H). MS m/z (%): 441 (M^+, 100), 427 (20), 395 (15), 323 (18), 283 (18), 235 (25), 220 (35), 173 (22).
23	CH3	H	NO2	H	61	262–263	C24H19N5O2S 441	2.44 (s, 3 H, CH3), 3.39 (dd, 1 H, HA), 3.98 (dd, 1 H, HB), 5.69 (dd, 1 H, HX), 7.06 (s, 1 H, thiazole-H), 7.58 (m, 8 H, aromatic-H), 8.20 (m, 2H, pyridine-H), 8.59 (m, 1 H, pyridine-H), 8.78 (m, 1 H, pyridine-H). MS m/z (%): 441 (M^+, 100), 427 (17), 395 (10), 323 (21), 283 (25), 235 (30), 220 (40), 273 (25), 116 (25).
24	H	OCH3	H	H	31	169–171	C24H20N4OS 412	3.25 (dd, 1 H, HA), 3.75 (s, 3 H, OCH3), 3.86 (dd, 1 H, HB), 5.55 (dd, 1 H, HX), 6.68 (s, 1 H, thiazole-H), 6.85 (d, 2 H, aromatic-H), 7.44 (m, 3 H, aromatic-H), 7.56 (d, 2 H, aromatic-H), 7.74 (m, 2 H, aromatic-H), 7.80 (m, 2 H, pyridine-H), 8.60 (m, 1 H, pyridine-H), 8.95 (m, 1 H, pyridine-H). MS m/z (%): 412 (M^+, 45), 334 (10), 308 (20), 276 (15), 239 (18), 205 (30), 188 (22), 149 (42), 134 (55).
25	H	OCH3	OCH3	H	29	116–118	C25H22N4O2S 442	3.34 (dd, 1 H, HA), 3.80 (s, 6 H, OCH3), 3.96 (dd, 1 H, HB), 5.66 (dd, 1 H, HX), 6.84 (s, 1 H, thiazole-H), 7.47 (m, 8 H, aromatic-H), 7.78 (m, 2 H, pyridine-H), 8.53 (m, 1 H, pyridine-H), 8.78 (m, 1 H, pyridine-H). MS m/z (%): 442 (M^+, 10), 427 (90), 412 (100), 379 (10), 334 (15), 308 (35), 221 (25), 205 (58), 189 (30).
26	H	OCH3	H	OCH3	33	200–202	C25H22N4O2S 442	3.30 (dd, 1 H, HA), 3.80 (s, 3 H, OCH3), 3.87 (s, 3 H, OCH3), 3.97 (dd, 1 H, HB), 5.69 (dd, 1 H, HX), 6.70 (s, 1 H, thiazole-H), 6.86 (d, 2 H, aromatic-H), 6.96 (d, 2 H, aromatic-H), 7.46 (m, 1 H, pyridine-H), 7.55 (d, 2 H, aromatic-H), 7.71 (d, 2 H, aromatic-H), 7.92 (m, 1 H, pyridine-H), 8.58 (m, 1 H, pyridine-H), 8.82 (m, 1 H, pyridine-H). MS m/z (%): 442 (M^+, 100), 409 (15), 381 (10), 364 (15), 307 (15), 250 (18), 220 (20), 205 (320, 188 (40), 158 (50), 133 (25).

Table 1. (continued)

Compound	R1	R2	R3	R4	Yield (%)	Mp (°C)#	Formula†, MW	^{1}H-NMR ($CDCl_3$), MS
27	H	OCH3	H	NO2	62	196–198	C24H19N5O3S 457	3.50 (dd, 1 H, HA), 3.88 (s, 3 H, OCH3), 4.15 (dd, 1 H, HB), 5.80 (dd, 1 H, HX), 6.98 (m, 1 H, pyridine-H), 7.10 (s, 1 H, thiazole-H), 7.32 (d, 2 H, aromatic-H), 7.73 (d, 2 H, aromatic-H), 7. 78 (d, 2 H, aromatic-H), 8.20 (d, 2 H, aromatic-H), 8.40 (m, 1 H, pyridine-H), 8.78 (m, 1 H, pyridine-H), 9.11 (m, 1 H, pyridine-H). MS m/z (%): 457 (M^+, 70), 426 (10), 379 (18), 352 (10), 323 (18), 290 (15), 251 (15), 220 (30), 132 (100), 102 (15).
28	H	OCH3	NO2	H	66	199–201	C24H19N5O3S 457	3.31 (dd, 1 H, HA), 3.80 (s, 3 H, OCH3), 3.94 (dd, 1 H, HB), 5.67 (dd, 1 H, HX), 6.79 (m, 1 H, pyridine-H), 6.84 (s, 1 H, thiazole-H), 7.24 (m, 4 H, aromatic-H), 7.59 (d, 2 H, aromatic-H), 7. 63 (d, 2 H, aromatic-H), 7.72 (m, 1 H, aromatic-H), 8.54 (m, 1 H, pyridine-H), 6.77 (m, 1 H, pyridine-H). MS m/z (%): 457 (M^+, 100), 427 (50), 392 (10), 349 (25), 323 (22), 291 (22), 220 (40), 173 (42), 146 (18).
29	H	Br	H	H	29	267–269	C23H17BrN4S 462	3.33 (dd, 1 H, HA), 3.96 (dd, 1 H, HB), 5.68 (dd, 1 H, HX), 6.85 (s, 1 H, thiazole-H), 7.54 (m, 9 H, aromatic-H), 7.78 (m, 2 H, pyridine-H), 8.67 (m, 1 H, pyridine-H), 8.96 (m, 1 H, pyridine-H). MS m/z (%): 462 (M^+, 20), 460 (22), 427 (10), 382 (18), 356 (22), 323 (18), 253 (20), 221 (30), 207 (42), 172 (100), 145 (20), 104 (40).
30	H	Br	H	F	20	287–289	C23H16BrFN4S 480	3.24 (dd, 1 H, HA), 3.89 (dd, 1 H, HB), 5.52 (dd, 1 H, HX), 6.79 (s, 1 H, thiazole-H), 7.21 (d, 2 H, aromatic-H), 7.43 (d, 2 H, aromatic-H), 7.46 (m, 1 H, pyridine-H), 7.51 (d, 2 H, aromatic-H), 7.74 (d, 2 H, aromatic-H), 7.88 (m, 1 H, pyridine-H), 8.58 (m, 1 H, pyridine-H), 9.10 (m, 1 H, pyridine-H). MS m/z (%): 480 (M^+, 15), 461 (10), 442 (25), 400 (30), 261 (40), 248 (30), 177 (45), 146 (100), 103 (60).
31	H	Br	H	Cl	27	274–276	C23H16BrClN4S 496.5	3.25 (dd, 1 H, HA), 3.91 (dd, 1 H, HB), 5.56 (dd, 1 H, HX), 6.80 (s, 1 H, thiazole-H), 7.23 (d, 2 H, aromatic-H), 7.45 (d, 2 H, aromatic-H), 7.49 (m, 1 H, pyridine-H), 7. 53 (d, 2 H, aromatic-H), 7.77 (d, 2 H, aromatic-H), 7.91 (m, 1 H, pyridine-H), 8.60 (m, 1 H, pyridine-H), 9.21 (m, 1 H, pyridine-H). MS m/z (%): 496 (M^+, 10), 476 (15), 461 (17), 429 (18), 415 (100), 396 920), 386 (30), 381 (90), 371 (40), 355 (50).

Table 1. (continued)

Compound	R1	R2	R3	R4	Yield (%)	Mp (°C)[#]	Formula[†], MW	^{1}H-NMR ($CDCl_3$), MS
32	H	Br	H	Br	27	204–206	C23H16Br2N4S 542	3.43 (dd, 1 H, HA), 4.04 (dd, 1 H, HB), 5.73 (dd, 1 H, HX), 7.02 (s, 1 H, thiazole-H), 7.46 (d, 2 H, aromatic-H), 7.50 (d, 2 H, aromatic-H), 7.78 (d, 2 H, aromatic-H), 7.92 (m, 1 H, pyridine-H), 8.08 (d, 2 H, aromatic-H), 8.42 (m, 1 H, pyridine-H), 8.63 (m, 1 H, pyridine-H), 8.87 (m, 1 H, pyridine-H). MS m/z (%): 542 (M^+, 20), 492 (10), 460 (25), 400 (30), 385 (15), 308 (60), 293 950), 205 (100), 189 (75), 103 (25).
33	H	Br	H	OCH3	8	164–166	C24H19BrN4OS 492	3.30 (dd, 1 H, HA), 3.80 (s, 3 H, OCH3), 3.93 (dd, 1 H, HB), 5.70 (dd, 1 H, HX), 6.70 (s, 1 H, thiazole-H), 6.84 (d, 2 H, aromatic-H), 7.57 (m, 4 H, aromatic-H), 7.61 (d, 2 H, aromatic-H), 7.69 (m, 2 H, pyridine-H), 8.54 (m, 1 H, pyridine-H), 8.77 (m, 1 H, pyridine-H). MS m/z (%): 492 (M^+, 30), 412 (20), 368 (15), 308 (60), 276 (40), 267 (35), 205 (100), 188 (90), 160 (80), 104 (38).
34	H	Br	H	NO2	69	207–209	C23H16BrN5O2S 507	3.43 (dd, 1 H, HA), 4.06 (dd, 1 H, HB), 5.73 (dd, 1 H, HX), 7.02 (s, 1 H, thiazole-H), 7.46 (d, 2 H, aromatic-H), 7.63 (d, 2 H, aromatic-H), 7.78 (d, 2 H, aromatic-H), 7.92 (m, 1 H, pyridine-H), 8.01 (d, 2 H, aromatic-H), 8.42 (m, 1 H, pyridine-H), 8.62 (m, 1 H, pyridine-H), 8.86 (m, 1 H, pyridine-H). MS m/z (%): 507 (M^+, 20), 442 (30), 380 (15), 368 (30), 323 (45), 309 940), 283 (20), 220 (60), 172 (100), 172 (100), 128 (50).
35	H	Br	NO2	H	72	206–208	C23H16BrN5O2S 507	3.42 (dd, 1 H, HA), 4.06 (dd, 1 H, HB), 5.73 (dd, 1 H, HX), 7.02 (s, 1 H, thiazole-H), 7.48 (m, 4 H, aromatic-H), 7.78 (d, 2 H, aromatic-H), 7.92 (m, 1 H, pyridine-H), 8.07 (d, 2 H, aromatic-H), 8.42 (m, 1 H, pyridine-H), 8.62 (m, 1 H, pyridine-H), 8.86 (m, 1 H, pyridine-H). MS m/z (%): 507 (M^+, 10), 489 (20), 442 (55), 427 (30), 383 (17), 379 (38), 368 (56), 220 (60), 172 (100), 128 (45).

[#] – All compounds were crystallized from methanol-ether.

[†] – All compounds were analyzed for C, H, N, Analytical results obtained for these elements were within ±0.4 % of the calculated value for the formula shown.

rooms that were maintained at 23 ± 3 °C and exposed to a 12-h light-dark cycle. Animals were given a standard laboratory chow and water ad libitum. Six rats were used for each compound. The control group received 1 mL/kg DMSO intraperitoneally (i.p.) only.

To reduce spontaneous variations in blood pressure, animals were adjusted to the experimental cage 3–4 times before the start of the experiment for a period of 30–60 min. Changes of blood pressure were measured by using an indirect tail-cuff method [7–9]. Automatic measurement of systolic blood pressure was provided by a pressure transducer (International Biomedical Inc., USA) of an 8-channel polygraph apparatus (Narcotrace 80, Narco Bio-System, USA). All compounds were dissolved in DMSO (Sigma) and administrated i.p. at a 10-mg/kg dose in 0.1 mL volume. Clonidine (0.5 mg/kg) was used as a reference drug. Mean values in systolic blood pressure before and 15, 30, 60 min after drug administration were determined. **Note:** There were no significant differences between the mean blood pressures before and after DMSO administration.

Statistics

The statistical significance of differences was estimated by analysis of variance (ANOVA) followed by Tukey test. Results were expressed as the mean ± SE and reduction of arterial blood pressure (Tables 2 and 3). As shown in Table 3 most of the compounds reduced blood pressure significantly 30 min after administration with $p < 0.05$. Same results were obtained 60 min after administration of compounds. Additionally the tested samples caused a significant reduction of blood pressure in comparison to control with $p < 0.001$. In addition comparing of compounds **24**–**28** with their similar analogues which have identical structure without the -OCH_3 moiety at R_2 position, namely, **13**, **15**, **16**, **20**–**23**, **33**–**35** (see Table 2), reveals that the presence of the methoxy group at the R_2 position increased the antihypertensive activity. Finally, it should be pointed out that compounds **24**–**28** have significant antihypertensive activity.

Experimental

Most chemicals were purchased from Merck Chemical Company, Darmstadt, Germany. Azachalcons **6 a**–**d** were prepared according to the reported method [10]. Phenacyl bromides **8 a**–**h** were prepared according to the literature [11]. All chemicals were crystallized or redistilled before use. Flash chromatography was performed on silica gel HT-254 (Merck). Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^{1}H-NMR spectra were obtained using a Varian unity plus 400 MHz instrument. Tetramethylsilane was used as an in-

Table 2. Mean systolic blood pressure before and after administration of the test compounds.

Compound No.	Dose (mg/kg)	Mean blood pressure (mm Hg) 0 min	15 min	30 min	60 min
9	10	106.8 ± 3.7	98.8 ± 4.4	97.5 ± 5.1	97.0 ± 5.3
13	10	103.0 ± 1.7	91.8 ± 3.2	90.7 ± 4.0	90.8 ± 4.2
15	10	99.7 ± 3.7	90.0 ± 3.7	89.0 ± 3.6	88.7 ± 3.6
16	10	103.6 ± 1.9	94.0 ± 2.0	94.0 ± 1.9	93.1 ± 1.9
17	10	104.0 ± 2.7	96.0 ± 4.5	94.9 ± 4.6	93.0 ± 4.7
20	10	102.3 ± 2.5	88.0 ± 2.9	87.5 ± 2.8	87.3 ± 2.8
21	10	99.9 ± 2.2	89.4 ± 2.1	87.5 ± 1.2	87.6 ± 4.9
22	10	99.3 ± 2.2	89.1 ± 2.0	87.5 ± 1.2	87.3 ± 4.9
23	10	107.3 ± 3.7	98.0 ± 3.6	97.0 ± 3.4	96.3 ± 3.1
24	10	95.5 ± 2.1	76.3 ± 1.9	73.5 ± 1.9	73.4 ± 1.9
25	10	101.7 ± 1.6	85.1 ± 2.7	80.0 ± 3.8	79.8 ± 3.8
26	10	103.1 ± 2.1	82.3 ± 4.6	80.8 ± 3.9	79.9 ± 3.1
27	10	100.5 ± 2.9	83.4 ± 4.7	77.4 ± 4.8	75.7 ± 4.2
28	10	101.3 ± 2.8	83.7 ± 2.7	80.3 ± 2.3	79.2 ± 1.6
29	10	99.5 ± 1.1	90.0 ± 5.1	89.0 ± 4.8	89.0 ± 4.4
31	10	91.5 ± 3.7	78.5 ± 3.9	77.1 ± 3.6	76.0 ± 4.5
33	10	97.5 ± 3.1	82.5 ± 3.4	82.5 ± 3.3	81.5 ± 3.1
34	10	103.1 ± 2.1	90.2 ± 1.7	90.0 ± 2.0	89.2 ± 2.0
35	10	98.2 ± 3.0	87.2 ± 3.2	86.1 ± 4.0	86.6 ± 4.5
Clonidine	0.5	104.4 ± 4.2	87.6 ± 3.4	87.2 ± 2.4	87.2 ± 2.4
DMSO	1 (ml/kg)	102.0 ± 0.5	100.0 ± 6.6	98.0 ± 4.5	98.0 ± 4.5

Table 3. Reduction of arterial blood pressure at 30 min after administration of the tested compounds in comparison to clonidine in rat.

Compound	Reduction of arterial blood pressure at 30 min (mm Hg) (X ± SEM)	N	P value
9	10.23 ± 1.02	6	P < 0.001
13	10.16 ± 1.16	6	P < 0.001
15	10.83 ± 0.3	6	P < 0.001
16	9.50 ± 0.61	6	P < 0.001
17	9.83 ± 0.79	6	P < 0.001
20	14.83 ± 1.10	6	P > 0.05
21	12.32 ± 2.7	6	P > 0.05
22	10.83 ± 1.07	6	P < 0.001
23	10.33 ± 0.88	6	P < 0.001
24	22.30 ± 0.36	6	P < 0.05
25	22.27 ± 0.30	6	P < 0.05
26	22.32 ± 0.28	6	P < 0.05
27	22.87 ± 0.30	6	P < 0.01
28	22.30 ± 0.33	6	P < 0.01
29	10.50 ± 0.56	6	P < 0.001
31	12.60 ± 1.28	6	P > 0.05
33	15.00 ± 1.12	6	P > 0.05
34	13.33 ± 0.21	6	P > 0.05
35	11.75 ± 1.10	6	P < 0.001
Clonidine	17.20 ± 0.73	6	–
Control *DMSO*	2.31 ± 0.21	6	P < 0.001

ternal standard. Mass spectra were obtained using a Finnigan-MAT TSQ-70 spectrophotometer at 70 eV. The IR spectra were obtained using a Nicolet FT-IR Magna 550 spectrograph (KBr disks). Elemental analyses were within ± 0.4 % of theoretical values for C, H and N.

3-Phenyl-5-(3-pyridyl)-1-thiocarbamoyl-2-pyrazoline (**7 a**)

To a suspension of azachalcon **6 a** (2.09 g, 0.01 mol) and sodium hydroxide (1 g, 0.025 mol) in ethanol (15 mL), thiosemicarbazide (0.9 g, 0.01 mol) was added. The mixture was refluxed for 1 h. The solution was poured into ice-water. The resulting precipitate was filtered off and recrystallized from methanol-ether (10:1, v/v) to yield 1.2 g (45 %) of compound **7 a** as white crystals. mp 162–164 °C. IR: ν_{max} = 3426, 3288, 1588, 1460, 1347 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 3.22 (dd, 1 H, J_{AX} = 3.6 Hz, J_{AB} = 16 Hz, H_A), 3.89 (dd, 1 H, J_{AB} = 16 Hz, J_{BX} = 12 Hz, H_B), 6.07 (dd, 1 H, J_{AX} = 3.6 Hz, J_{BX} = 12 Hz, H_X), 6.15 (brs, 1 H, NH), 7.1 (brs, 1 H, NH), 7.27 (m, 1 H, pyridine-H), 7.46 (m, 3 H, aromatic-H), 7.54 (m, 1 H, pyridine-H), 7.73 (m, 2 H, aromatic-H), 8.54 (m, 2 H, pyridine-H). MS m/z (%): 282 (M^+, 100), 268 (8), 249 (53), 222 (25), 193 (15), 177 (33), 146 (60), 137 (10), 104 (19).

3-(3′-Methylphenyl)-5-(3-pyridyl)-1-thiocarbamoyl-2-pyrazoline (**7 b**)

This compound was prepared similar to **7 a** in 38 % yield, mp 203–205 °C (methanol-ether), IR: ν_{max} = 3425, 3285, 1586, 1462, 1355 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 2.39 (s, 3 H, CH_3), 3.22 (dd, 1 H, J_{AX} = 3.6 Hz, J_{AB} = 16 Hz, H_A), 3.87 (dd, 1 H, J_{AB} = 16 Hz, J_{BX} = 12 Hz, HB), 6.07 (dd, 1 H, J_{AX} = 3.6 Hz, J_{BX} =12 Hz, H_X). 6.2 (bs, 1 H, NH), 7.19 (bs, 1 H, NH), 7.29 (m, 4 H, phenyl and pyridine-H), 7.53 (m, 3 H, phenyl and pyridine-H), 8.54 (m, 2 H, pyridine-H). MS m/z (%): 296 (M^+, 40), 263 (25), 236 (30), 208 (18), 179 (42), 158 (45), 145 (100), 103 (28).

3-(4′-Methoxyphenyl)-5-(3-pyridyl)-1-thiocarbamoyl-2-pyrazoline (**7 c**)

This compound was prepared similar to **7 a** in 38 % yield, mp 163–165 °C (methanol-ether), IR: ν_{max} = 3421, 3288, 1582, 1460, 1352 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 3.18 (dd, 1 H, J_{AB} = 16 Hz, J_{AX} = 3.6 Hz, HA), 3.81 (dd, 1 H, J_{AB} = 16 Hz, J_{BX} = 12 Hz, H_B), 3.92 (s, 3 H, CH_3), 6.05 (dd, 1 H, J_{AX} = 3.6 Hz, J_{BX} = 12 Hz, H_X), 6.94 (d, 2 H, J = 8 Hz, aromatic-H), 7.22 (m, 1 H, pyridine-H), 7.54 (m, 1 H, pyridine-H), 7.67 (d, 2 H, J = 8 Hz, aromatic-H), 8.54 (m, 2 H, pyridine-H). MS m/z (%): 312 (M^+, 58), 279 (35), 252 (40), 238 (15), 177 (60), 145 (100), 133 (26), 103 (42).

3-(4′-Bromophenyl)-5-(3-pyridinyl)-1-thicarbamoyl-2-pyrazoline (**7 d**)

This compound was prepared similar to **7 a** in 42 % yield, mp 199–201 °C (methanol-ether), IR: ν_{max} = 3416, 3293, 1588, 1465, 1362 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 3.2 (dd, 1 H, J_{AB} = 16 Hz, J_{AX} = 3.6 Hz, H_A), 3.80 (dd, 1 H, J_{AB} = 16 Hz, J_{BX} = 12 Hz, H_B), 6.07 (dd, 1 H, J_{AX} = 3.6 Hz, J_{BX} = 12 Hz, H_X), 7.21 (m, 2 H, pyridine-H), 7.49 (d, 2 H, J = 8 Hz, aromatic-H), 7.61 (d, 2 H, J = 8 Hz, aromatic-H), 8.54 (m, 2 H, pyridine-H). MS m/z (%): 361 (M^+, 60), 327 (38), 301 (72), 288 (25), 223 (30), 192 (18), 178 (94), 144 (100), 137 (15), 103 (31).

General procedure for the synthesis of **9**–**35**

3-Phenyl-1-(4-phenyl-2-thiazolyl)-5-(3-pyridyl)-2-pyrazoline (**9**)

To a suspension of compound **7 a** (2.82 g, 0.01 mol) in ethanol (15 mL) phenacyl bromide (1.99 g, 0.01 mol) was added and heated to reflux for 1 h. After cooling, the precipitate was collected by suction filtration and purified by flash chromatography on silica gel with methanol-diethyl ether (50:50, v/v). The product was crystallized from chloroform to yield (1.54 g, 41 %) of compound **9**. mp 155–157 °C. ^{1}H-NMR ($CDCl_3$): δ = 3.40 (dd, 1 H, J_{AB} = 16 Hz, J_{AX} = 8 Hz, H_A), 4.19 (dd, 1 H, J_{AB} = 16 Hz, J_{BX} = 8 Hz, H_B), 5.80 (dd, 1 H, J_{AX} = 8 Hz, J_{BX} = 12 Hz, H_X), 6.91 (s, 1 H, thiazole-H), 7.57 (m, 10 H, aromatic-H), 7.94 (m, 1 H, pyridine-H), 8.54 (m, 1 H, pyridine-H), 8.72 (m, 1 H, pyridine-H), 9.02 (m, 1 H, pyridine-H). MS m/z (%): 382 (M^+, 100), 349 (10), 304 (10), 278 (20), 266 (15), 248 (31), 220 (22), 174 (60), 134 (60), 104 (38).

Compounds **10**–**35** were prepared similarly (Table 1).

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