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SYNTHESIS AND ANTI-HYPERTENSIVE α-BLOCKING ACTIVITY EVALUATION OF THIAZOLE DERIVATIVES BEARING PYRAZOLE MOIETY

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Abstract – A novel, facile reaction for the synthesis of series of thiazole derivatives has been developed from the reaction of the appropriate thiosemicarbazone derivatives and 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone in ethanol under reflux. The structures of the newly synthesized products were established on the basis of spectral data (mass, IR, ^{1}H and ^{13}C NMR) and elemental analyses. The pharmacological screening showed that many of the synthesized compounds exhibit a good antihypertensive α-blocking activity and having low toxicity, as compared to Minoxidil.

INTRODUCTION

Thiazoles are a familiar group of heterocyclic compounds possessing a wide variety of biological activities as antimicrobial,[1-3] antioxidant,[4] antitubercular,[5] anticonvulsant,[6] anticancer,[7] and anti-inflammatory[8] agents. Moreover, many derivatives of thiazoles are used as selective cyclooxygenase-2 inhibitors,[9] in addition to their use as 5-HT3 receptor antagonists [10] and as potent and selective acetyl Co-A carboxylase-2 inhibitors.[11] Furthermore, several pyrazole derivatives received great attention due to their biological and pharmacological activities not only as potential inhibitors of HIV-1,[12] pesticides,[13] fungicides,[14] antihypertensive agents [15] and anticancer activity.[16] In addition, thiazoles have attracted more interest not only due to their ability to enhance the lipid solubility but also they can easily metabolize through the normal biochemical reactions.[17] As a part of our research interest towards developing new routes for the synthesis of a variety of heterocyclic systems with promising biological and pharmacological

activities,[18-26] we report in the present article the synthesis of a new series of 1,3-thiazoles bearing pyrazole moiety as anti-hypertensive α-blocking agents and the results were reported against Minoxidil as reference.

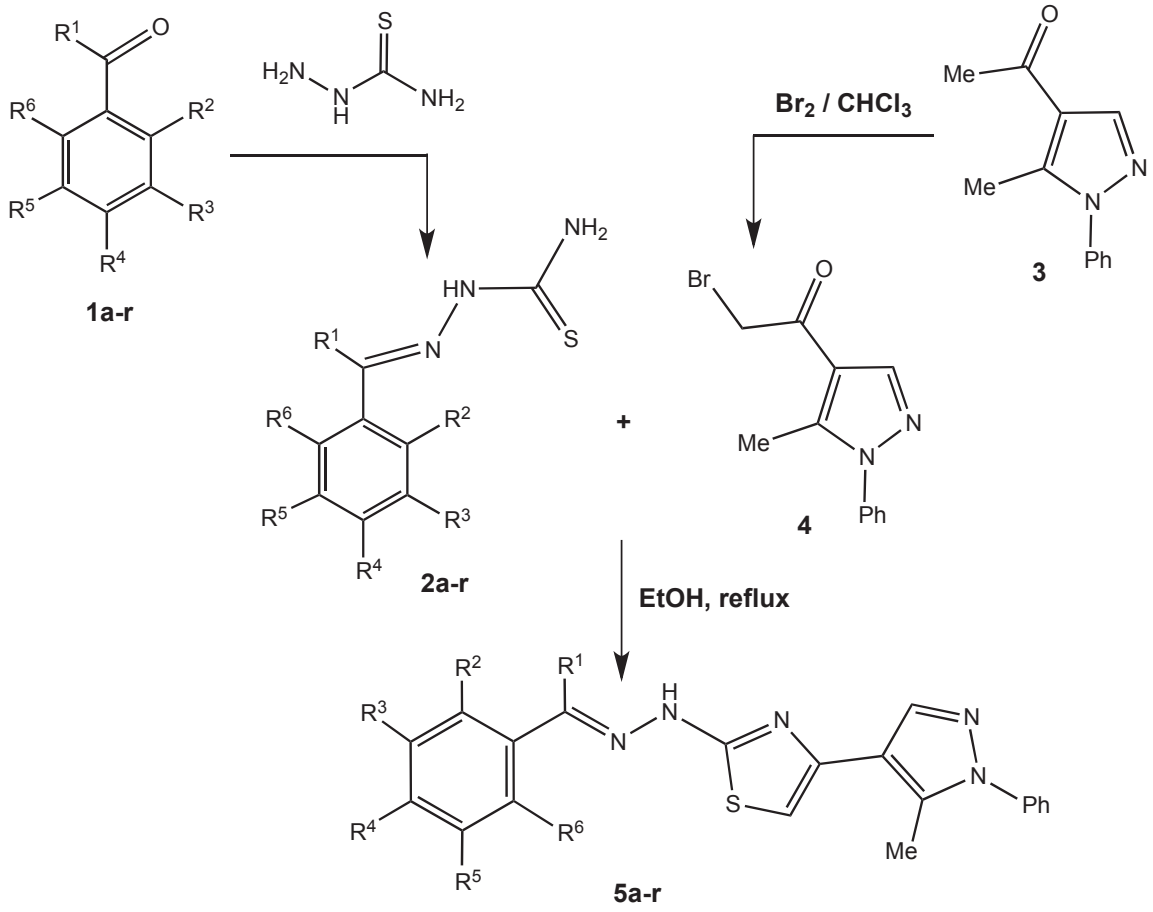
RESULTS AND DISCUSSION

The thiosemicarbazones were synthesized by treatment of the corresponding carbonyl compound with thiosemicarbazide in acid medium, unless otherwise indicated, according to the general procedure previously described.

2-Bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**4)** was prepared *via* direct bromination of the acetylpyrazole **3** with bromine in $CHCl_3$ as previously reported in the respective literature.[27]

The reaction of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**4)** with thiosemicarbazones **2a-r** in refluxing ethanol, afforded the corresponding thiazoles **5a-r** following Hantzsch thiazole synthesis.[28] The reaction proceeded through the reaction of **4** with equivalent amounts of each of thiosemicarbazones **2a-r**, to give the *S*-alkylated intermediates which cyclized *in situ* under the employed reaction conditions with elimination of water molecule furnished in each case, one isolable product (as tested by TLC). The reaction products were identified as thiazoles **5a-r** (Scheme 1). Structures of the final products were elucidated by studying their elemental analyses and spectral data. For example, the ^{1}H NMR spectrum of thiazoles **5a** revealed the absence of NH_2 protons of compound **2** and showed the signals at δ = 2.58 (s, 3H, CH_3), 6.83-7.87 (m, 12H, Ar-H), 8.44 (s, 1H, CH=N), 10.36 (br s, 1H, NH). Also, its mass spectrum showed peaks at *m/z* = 359 which matches with its molecular formula $C_{20}H_{17}N_5S$.

In the IR spectrum of compounds **5a-r**, the characteristic N–H stretching absorption band appeared around the 3299-3092 cm^{-1} regions. ^{1}H NMR spectra of compounds **5a-r** revealed the presence of the –CH=N– proton and the =N–NH– proton as two singlets at δ = 7.66-8.62 and 11.30-11.81 ppm, respectively. The thiazole proton appeared as a multiplet at 6.45-8.14 ppm together with phenyl protons. In addition, EI-MS spectra of **5a-r** showed a molecular ion peak with intensities of 95-100%.



1,2,5	R^1	R^2	R^3	R^4	R^5	R^6
a	H	H	H	H	H	H
b	H	H	H	Me	H	H
c	H	H	H	OMe	H	H
d	H	OMe	H	H	H	H
e	H	H	H	Cl	H	H
f	H	H	H	Br	H	H
g	H	H	H	NO_2	H	H
h	H	H	NO_2	H	H	H
i	H	H	H	NMe_2	H	H
j	H	OH	H	H	H	H
k	H	Cl	H	Cl	H	H
l	H	Cl	H	H	H	Cl
m	Me	H	H	H	H	H
n	Me	H	H	Me	H	H
o	Me	H	H	OMe	H	H
p	Me	H	H	Cl	H	H
q	Me	H	H	NO_2	H	H
r	Me	H	H	OH	H	H

Scheme 1. Synthesis of thiazoles **5a-r**

Pharmacological screening

Antihypertensive α-blocking activity

The newly synthesized derivatives were subjected to **α**-blocking activity model screening using **α**-sympatholytic activity in isolated vascular smooth muscle (Table 1). All the tested compounds showed antihypertensive **α**-blocking activities and they are arranged in descending order of activities as follows: **5m > 5l > 5e > 5c > 5f > 5g > 5a > 5h > 5q > 5r > 5b > 5d > 5n > 5o > 5p > 5j > 5i > 5k**.

It is worth to be mentioned that **5m** and **5l** compounds are more potent than Minoxidil, while, **5c** and **5e** are of similar activity.

Table 1. The antihypertensive α-blocking activities of compounds 5a-r

Compound No.	IC_{50} μg/cm^3	Compound No.	IC_{50} μg/cm^3
Minoxidil	4.00	**5j**	21.56
5a	5.93	**5k**	23.78
5b	9.45	**5l**	3.91
5c	4.17	**5m**	3.79
5d	12.65	**5n**	16.54
5e	4.13	**5o**	18.67
5f	5.45	**5p**	20.86
5g	5.56	**5q**	6.54
5h	6.03	**5r**	8.32
5i	23.34		

Structure activity relationship (SAR)

As shown in Table 1, the results of the antihypertensive α-blocking activities exhibited a clear structural activity relation depending on the substitution at either aromatic ring or at the carbonyl carbon of thiosemicarbazone moiety. It has been found that, the dichloro substitution at C-2 and C-6 has been strongly affected the antihypertensive activity (IC_{50} μg/cm^3 = 3.91), even more potent than Minoxidil reference compound, as compared to the dichloro substitution at 2 and 4 carbons (IC_{50} μg/cm^3 = 23.34). On the other hand, mono aromatic substitutions with electron donating or electron withdrawing groups exhibited more antihypertensive activity through aromatic substitution at C-4 (4-OMe; 4.17) rather than at C-2 (2-OMe; 12.65). Moreover, mono substitution at C-4 with Cl and OMe groups led to similar activity to Minoxidil. Interestingly, methyl substitution at carbonyl carbon of thiosemicarbazone, with unsubstituted

benzene ring, strongly improved the antihypertensive activity (IC_{50} μg/cm^3 = 3.79) more than the exhibited activity of Minoxidil itself.

CONCCLUSIONS

This paper describes a facile and efficient synthesis of thiazole derivatives *via* cyclization reaction of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone with thiosemicarbazones. Structures of the final products were elucidated by elemental analyses and FTIR, MS, ^{1}H and ^{13}C NMR spectra. The pharmacological screening of the synthesized products showed potent antihypertensive α-blocking activity.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in KBr using Pye-Unicam SP300 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in deuterated DMSO-d_6 using a Varian Gemini 300 NMR spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and the chemical shifts were related to that of the solvent DMSO-d_6. Mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Elemental analyses of the products were carried out at the Microanalytical Centre of Cairo University, Giza, Egypt. The starting thiosemicarbazones **2a-c, 2e-j**,[29] **2d**,[30] **2m, 2p, 2r**,[31] **2n, 2o**,[32] and **2q**[33] prepared as previously described.

Synthesis of 2-(2-arylidenehydrazinyl)-4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazole (5a-r).

General procedure: A mixture of thiosemicarbazone derivatives **2a-r** (1 mmol) and 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**4**) (0.263 g, 1 mmol) in EtOH (30 mL) was refluxed for 2-4 h. (monitored by TLC). The formed precipitate was isolated by filtration, washed with methanol, dried and recrystallized from appropriate solvent to give products **5a–r**.

2-(2-Benzylidenehydrazinyl)-4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazole (5a). Yield 67%; pale yellow microcystals; mp 212-214 ºC (EtOH); IR (KBr): *v* 3431 (NH), 1608 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.58 (s, 3H, CH_3), 6.83-7.87 (m, 11H, Ar-H and thiazole-H5), 8.19 (s, 1H, pyrazole-H3), 8.44 (s, 1H, CH=N), 10.36 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 12.21(CH_3), 113.7, 128.8, 129.1, 129.4, 133.8, 137.4, 137.8, 138.6, 138.9, 139.2, 139.5, 144.1, 145.7, 153.0, 165.9; MS *m/z* (%): 359 (M^+, 27). Anal. Calcd for $C_{20}H_{17}N_5S$ (359.45): C, 66.83; H, 4.77; N, 19.48; Found: C, 66.74; H, 4.58; N, 19.29%.

4-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-(2-(4-methylbenzylidene)hydrazinyl)thiazole (5b). Yield 69%; pale yellow microcystals; mp 193-195 ºC (EtOH); IR (KBr): *v* 3412 (NH), 1602 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.18 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 6.91-7.97 (m, 10H, Ar-H and thiazole-H5), 8.25 (s, 1H, pyrazole-H3), 8.51 (s, 1H, CH=N), 10.36 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 12.21, 26.3 (CH_3), 115.5, 125.2, 125.5, 127.4, 128.6, 129.1, 129.3, 130.7, 137.8, 138.1, 141.9, 144.7, 145.9, 162.0, 167.8; MS

m/z (%): 373 (M^+, 17). Anal. Calcd for $C_{21}H_{19}N_5S$ (373.47): C, 67.53; H, 5.13; N, 18.75; Found: C, 67.42; H, 5.10; N, 18.69%.

2-(2-(4-Methoxybenzylidene)hydrazinyl)-4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazole (5c). Yield 62%; brown microcystals; mp 172-174 ºC (EtOH); IR (KBr): *v* 3417 (NH), 1600 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.57 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 7.00-7.89 (m, 10H, Ar-H and thiazole-H5), 8.03 (s, 1H, pyrazole-H3), 8.52 (s, 1H, CH=N), 9.87 (br s, 1H, NH); MS *m/z* (%): 389 (M^+, 23). Anal. Calcd for $C_{21}H_{19}N_5OS$ (389.47): C, 64.76; H, 4.92; N, 17.98; Found: C, 64.69; H, 4.91; N, 17.66%.

2-(2-(2-Methoxybenzylidene)hydrazinyl)-4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazole (5d). Yield 61%; brown microcystals; mp 164-166 ºC (EtOH); IR (KBr): *v* 3411 (NH), 1603 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.58 (s, 3H, CH_3), 3.54 (s, 3H, OCH_3), 7.51-7.97 (m, 10H, Ar-H and thiazole-H5), 8.14 (s, 1H, pyrazole-H3), 8.44 (s, 1H, CH=N), 9.83 (br s, 1H, NH); MS *m/z* (%): 389 (M^+, 63). Anal. Calcd for $C_{21}H_{19}N_5OS$ (389.47): C, 64.76; H, 4.92; N, 17.98; Found: C, 64.55; H, 4.90; N, 17.76%.

2-(2-(4-Chlorobenzylidene)hydrazinyl)-4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazole (5e). Yield 69%; pale yellow microcystals; mp 213-215 ºC (dioxane); IR (KBr): *v* 3436 (NH), 1605 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.74 (s, 3H, CH_3), 7.42-7.96 (m, 10H, Ar-H and thiazole-H5), 8.54 (s, 1H, pyrazole-H3), 8.87 (s, 1H, CH=N), 10.06 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.2 (CH_3), 110.7, 124.6, 124.9, 128.0, 128.9, 129.1, 130.6, 132.0, 137.2, 138.0, 139.1, 142.0, 145.3, 162.7, 164.6; MS *m/z* (%): 393 (M^+, 44). Anal. Calcd for $C_{20}H_{16}ClN_5S$ (393.89): C, 60.98; H, 4.09; N, 17.78; Found: C, 60.78; H, 4.03; N, 17.63%.

2-(2-(4-Bromobenzylidene)hydrazinyl)-4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazole (5f). Yield 66%; pale yellow microcystals; mp 251-253 ºC (dioxane); IR (KBr): *v* 3427 (NH), 1603 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.72 (s, 3H, CH_3), 7.27-7.94 (m, 10H, Ar-H and thiazole-H5), 8.53 (s, 1H, pyrazole-H3), 8.83 (s, 1H, CH=N), 10.21 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 11.62 (CH_3), 110.7, 114.7, 122.5, 125.0, 126.2, 128.2, 129.1, 132.2, 133.4, 137.5, 138.0, 139.1, 145.2,162.8, 165.8; MS *m/z* (%): 438 (M^+, 38). Anal. Calcd for $C_{20}H_{16}BrN_5S$ (438.34): C, 54.80; H, 3.68; N, 15.98; Found: C, 54.69; H, 3.62; N, 15.75%.

4-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-(2-(4-nitrobenzylidene)hydrazinyl)thiazole (5g). Yield 66%; brown microcystals; mp 237-239 ºC (dioxane); IR (KBr): *v* 3446 (NH), 1605 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.55 (s, 3H, CH_3), 6.98-7.95 (m, 10H, Ar-H and thiazole-H5), 8.12 (s, 1H, pyrazole-H3), 8.49 (s, 1H, CH=N), 10.09 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 12.0 (CH_3), 112.6, 115.8, 124.1, 124.9, 126.9, 127.7, 129.1, 135.6, 136.3, 138.8, 139.2, 140.8, 147.0, 162.0, 165.4; MS *m/z* (%): 404 (M^+, 18). Anal. Calcd for $C_{20}H_{16}N_6O_2S$ (404.45): C, 59.39; H, 3.99; N, 20.78; Found: C, 59.24; H, 3.91; N, 20.58%.

4-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-(2-(3-nitrobenzylidene)hydrazinyl)thiazole (5h). Yield 66%; brown microcystals; mp 184-186 ºC (EtOH); IR (KBr): *v* 3426 (NH), 1603 (C=N) cm^{-1}; ^1H NMR

(DMSO-d_6): δ 2.73 (s, 3H, CH_3), 7.54-7.96 (m, 10H, Ar-H and thiazole-H5), 8.23 (s, 1H, pyrazole-H3), 8.50 (s, 1H, CH=N), 10.07 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.3 (CH_3), 110.7, 123.2, 123.7, 124.5, 125.3, 126.9, 128.2, 129.6, 136.3, 137.9, 142.2, 148.7, 164.1, 166.1, 168.4; MS *m/z* (%): 404 (M^+, 72). Anal. Calcd for $C_{20}H_{16}N_6O_2S$ (404.45): C, 59.39; H, 3.99; N, 20.78; Found: C, 59.32; H, 3.85; N, 20.69%.

***N*,*N*-Dimethyl-4-((2-(4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazol-2-yl)hydrazono)methyl)aniline (5i).** Yield 66%; brown microcystals; mp 206-208 °C (EtOH); IR (KBr): *v* 3429 (NH), 1600 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.70 (s, 3H, CH_3), 3.15 (s, 6H, $2CH_3$), 6.77-7.88 (m, 10H, Ar-H and thiazole-H5), 8.30 (s, 1H, pyrazole-H3), 8.62 (s, 1H, CH=N), 9.66 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 11.9, 36.1 (CH_3), 110.9, 111.1, 120.3, 124.5, 125.2, 129.4, 131.2, 131.8, 138.1, 138.6, 141.5, 144.3, 153.0, 163.1, 164.8; MS *m/z* (%): 404 (M^+, 72). Anal. Calcd for $C_{22}H_{22}N_6S$ (402.52): C, 65.65; H, 5.51; N, 20.88; Found: C, 65.65; H, 5.51; N, 20.88%.

2-((2-(4-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazol-2-yl)hydrazono)methyl)phenol (5j). Yield 66%; yellow microcystals; mp 226-228 °C (EtOH); IR (KBr): *v* 3447, 3318 (OH and NH), 1606 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.71 (s, 3H, CH_3), 5.40 (br s, 1H, OH), 6.94-7.76 (m, 10H, Ar-H and thiazole-H5), 8.26 (s, 1H, pyrazole-H3), 8.51 (s, 1H, CH=N), 10.14 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.2 (CH_3), 110.8, 116.7, 118.8, 119.8, 125.1, 125.3, 129.1, 129.4, 129.5, 134.4, 138.0, 141.9, 145.1, 158.8, 161.8, 164.2, 167.6; MS *m/z* (%): 375 (M^+, 36). Anal. Calcd for $C_{20}H_{17}N_5OS$ (375.45): C, 63.98; H, 4.56; N, 18.65; Found: C, 63.86; H, 4.52; N, 18.48%.

2-(2-(2,4-Dichlorobenzylidene)hydrazinyl)-4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazole (5k). Yield 72%; yellow microcystals; mp 237-239 °C (EtOH); IR (KBr): *v* 3420 (NH), 1606 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.73 (s, 3H, CH_3), 7.40-7.99 (m, 9H, Ar-H and thiazole-H5), 8.17 (s, 1H, pyrazole-H3), 8.54 (s, 1H, CH=N), 10.55 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.3 (CH_3), 125.0, 125.4, 127.3, 128.2, 128.3, 129.0, 129.5, 130.0, 130.9, 131.6, 131.7, 133.8, 133.9, 135.7, 150.9, 156.4, 169.9; MS *m/z* (%): 428 (M^+, 38). Anal. Calcd for $C_{20}H_{15}Cl_2N_5S$ (428.34): C, 56.08; H, 3.53; N, 16.35; Found: C, 56.03; H, 3.47; N, 16.25%.

2-(2-(2,6-Dichlorobenzylidene)hydrazinyl)-4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazole (5l). Yield 74%; yellow microcystals; mp 249-251 °C (dioxane); IR (KBr): *v* 3434 (NH), 1604 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.73 (s, 3H, CH_3), 7.47-7.9 (m, 9H, Ar-H and thiazole-H5), 8.21 (s, 1H, pyrazole-H3), 8.50 (s, 1H, CH=N), 10.57 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.3 (CH_3), 124.1, 124.4, 127.3, 128.0, 128.7, 129.0, 129.9 130.3, 130.9, 132.1, 133.1, 133.8, 134.3, 135.3, 145.0, 156.4, 169.1; MS *m/z* (%): 428 (M^+, 73). Anal. Calcd for $C_{20}H_{15}Cl_2N_5S$ (428.34): C, 56.08; H, 3.53; N, 16.35; Found: C, 56.01; H, 3.40; N, 16.27%.

4-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-(2-(1-phenylethylidene)hydrazinyl)thiazole (5m). Yield 68%; brown microcystals; mp 162-164 °C (EtOH); IR (KBr): *v* 3417 (NH), 1602 (C=N) cm^{-1}; ^{1}H NMR

(DMSO-d_6): δ 2.58 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 7.47-7.98 (m, 11H, Ar-H and thiazole-H5), 8.51 (s, 1H, pyrazole-H3), 10.63 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.3, 15.9 (CH_3), 110.7, 124.5, 125.0, 125.4, 125.8, 127.8, 128.1, 128.7, 129.0, 131.5, 136.5, 141.9, 164.1, 166.1, 168.4; MS *m/z* (%): 373 (M^+, 47). Anal. Calcd for $C_{21}H_{19}N_5S$ (373.47): C, 67.53; H, 5.13; N, 18.75; Found: C, 67.46; H, 5.06; N, 18.59%.

4-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-(2-(1-(*p*-tolyl)ethylidene)hydrazinyl)thiazole (5n). Yield 68%; yellowish-brown microcystals; mp 175-177 °C (EtOH); IR (KBr): *v* 3439 (NH), 1600 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 6.91-7.88 (m, 10H, Ar-H and thiazole-H5), 8.53 (s, 1H, pyrazole-H3), 10.60 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.3, 15.9 (CH_3), 110.7, 124.5, 125.0, 125.4, 125.8, 127.8, 128.1, 128.7, 129.0, 131.5, 136.5, 141.9, 164.1, 166.1, 168.4; MS *m/z* (%): 387 (M^+, 30). Anal. Calcd for $C_{22}H_{21}N_5S$ (387.50): C, 68.19; H, 5.46; N, 18.07; Found: C, 68.08; H, 5.35; N, 18.01%.

2-(2-(1-(4-Methoxyphenyl)ethylidene)hydrazinyl)-4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazole (5o). Yield 65%; yellowish-brown microcystals; mp 154-156 °C (dioxane); IR (KBr): *v* 3431 (NH), 1597 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 7.23-7.88 (m, 10H, Ar-H and thiazole-H5), 8.53 (s, 1H, pyrazole-H3), 10.12 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 12.3, 21.1, 44.2 (CH_3), 110.8, 124.7, 125.4, 126.5, 128.3, 129.7, 131.2, 138.1, 139.6, 142.0, 143.1, 145.8, 153.1, 165.2, 168.1; MS *m/z* (%): 387 (M^+, 30). Anal. Calcd for $C_{22}H_{21}N_5O_S$ (403.50): C, 65.49; H, 5.25; N, 17.36; Found: C, 65.42; H, 5.19; N, 17.27%.

2-(2-(1-(4-Chlorophenyl)ethylidene)hydrazinyl)-4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazole (5p). Yield 68%; yellow microcystals; mp 183-185 °C (dioxane); IR (KBr): *v* 3440 (NH), 1607 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 7.10-7.93 (m, 10H, Ar-H and thiazole-H5), 8.50 (s, 1H, pyrazole-H3), 10.52 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 12.9, 22.0 (CH_3), 110.8, 121.4, 125.4, 126.0, 127.2, 129.2, 130.4, 134.6, 137.5, 141.3, 143.6, 141.5, 153.3, 164.2, 169.6; MS *m/z* (%): 407 (M^+, 100). Anal. Calcd for $C_{21}H_{18}ClN_5S$ (407.92): C, 61.83; H, 4.45; N, 17.17; Found: C, 61.86; H, 4.39; N, 17.07%.

4-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-(2-(1-(4-nitrophenyl)ethylidene)hydrazinyl)thiazole(5q). Yield 62%; brown microcystals; mp 198-200 °C (dioxane); IR (KBr): *v* 3421 (NH), 1608 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 7.03-7.89 (m, 10H, Ar-H and thiazole-H5), 8.53 (s, 1H, pyrazole-H3), 10.50 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.3, 21.4 (CH_3), 110.3, 124.7, 125.4, 125.9, 127.4, 129.2, 131.5, 134.6, 137.6, 142.5, 143.8, 149.4, 150.3, 163.9, 169.0; MS *m/z* (%): 418 (M^+, 63). Anal. Calcd for $C_{21}H_{18}N_6O_2S$ (418.47): C, 60.27; H, 4.34; N, 20.08; Found: C, 60.21; H, 4.21; N, 19.93%.

4-(1-(2-(4-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazol-2-yl)hydrazono)ethyl)phenol (5r). Yield 66%;

brown microcystals; mp 198-200 ºC (dioxane); IR (KBr): *v* 3414 (NH and OH), 1605 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 4.11 (br s, 1H, OH), 7.02-7.97 (m, 10H, Ar-H and thiazole-H5), 8.51 (s, 1H, pyrazole-H3), 10.38 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 12.6, 26.8 (CH_3), 111.2, 115.3, 125.2, 125.8, 129.8, 130.3, 130.9, 138.5, 142.3, 145.2, 162.5, 163.5, 164.1, 166.6, 168.0; MS *m/z* (%): 389 (M^+, 31). Anal. Calcd for $C_{21}H_{19}N_5OS$ (389.47): C, 64.76; H, 4.92; N, 17.98; Found: C, 64.71; H, 4.82; N, 17.74%.

Pharmacological assay

Anti-hypertensive α-blocking activity [34–38]

Noradrenalin and other sympathomimetic drugs increase vascular smooth muscle tone by stimulation of **α**-adrenergic receptors. Contractions can be antagonized by adrenergic **α**-receptor blocking agents, such as phentolamine. Drugs can be tested for their capacity of reducing vascular smooth muscle contractions induced by the adrenergic receptor-activating agent noradrenaline. Moreover, effects of peptides, such as bradykinin, can be tested with strips of aorta or pulmonary artery.

Procedure

As donor animals, white guinea pigs of either sex weighing about 400 g are used. The vessels to be tested are the thoracic aorta or the arteria pulmonalis. The animals are sacrificed by stunning and exsanguinations. The pulmonary artery is quickly removed and cut into helical strips of 1–2 mm width and 15–20 mm length. The strips are mounted in an organ bath with a preload of 1 g. Krebs-Henseleit buffer solution containing 11.5 M glucose is maintained at 37 ºC and oxygenated with 95% O_2, 5% CO_2. Isotonic or isometric registration is performed. Changes in length are recorded isotonically using a lever transducer, isometric force is measured with a force transducer.

Experimental course

Following an equilibration period of 60 min, contractions are induced by repeated administration of (–)-noradrenalin HCl in concentrations of 2 x 10^{-6} M for testing the contractions of the pulmonary artery and in concentrations of 2 x 10^{-8} M for testing the contractions of the aorta. After obtaining a state plateau of identically sized contractions, cumulative doses of the test compound are added into the organ bath. Concentrations are given when the response of the previous dose has reached a plateau.

Controls at the end of the experiment

If a compound does not show vaso relating activity at any dose, the sensitivity of the preparation is tested by adding phentolamine (1 x 10^{-7} M). If a compound shows vaso relating activity, increasing the noradrenalin concentration tests the reversibility of the relaxation.

Evaluation

The contractile force is determined before and after drug administration. Percent inhibition of spas Mogen-induced contraction by test drug is calculated as compared to the maximal contraction with a spas Mogen alone (= 100%). IC_{50} values are determined from the individual dose response curves. IC_{50} is defined as the dose of drug leading to a 50% relaxation of noradrenaline induced contraction.

The small values of IC_{50} for the selected compounds indicate that, for more anticancer effect higher concentrations can be used.

REFERENCES

1. P. Karegoudar, M. S. Karthikeyan, D. J. Prasad, M. Mahalinga, B. S. Holla, and N. S. Kumari, *Eur. J. Med. Chem.*, 2008, **43**, 261.
2. A. Cukurovali, I. Yilmaz, S. Gur, and C. Kazaz, *Eur. J. Med. Chem.*, 2006**, 41**, 201.
3. B. F. Abdel-Wahab, H. A. Abdel-Aziz, and E. M. Ahmed*, Eur. J. Med. Chem.*, 2009, **44**, 2632.
4. M. H. Shih and K. F. Ying, *Bioorg. Med. Chem.*, 2004, **12**, 4633.
5. M. Shiradkar, G. V. S. Kumar, V. Dasari, S. Tatikonda, K. C. Akula, and R. Shah, *Eur. J. Med. Chem.*, 2007, **42**, 807.
6. K. M. Amin, A. D. E. Rahman, and Y. A. Al-Eryani, *Bioorg. Med. Chem.*, 2008, **16**, 5377.
7. S. M. Gomha, S. M. Riyadh, I. M. Abbas, and M. A. Bauomi, *Heterocycles*, 2013, **87**, 341.
8. K. M. Dawood, H. A. Gawad, E. A. Rageb, M. Ellithey, and H. A. Mohamed, *Bioorg. Med. Chem.,* 2006, **14**, 3672.
9. J. S. Carter, S. Kramer, J. J. Talley, T. Penning, P. Collins, M. J. Graneto, K. Seibert, C. Koboldt, J. Masferrer, and B. Zweifel, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1171.
10. L. P. Zhu, D. Y. Ye, and Y. Tang, *J. Mol. Model,* 2007, **13**, 121.
11. R. F. Clark, T. Zhang, X. Wang, R. Wang, X. Zhang, H. S. Camp, B. A. Beutel, H. L. Sham, and Y. J. Gu, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1961.
12. A. M. Kamal El-Dean, A. M. Elkhawaga, S. M. Radwan, and M. M. Ahmed, *Phosphorous, Sulfur Silicon Relat. Elem.*, 2009, **184**, 2034.
13. M. Ge, E. Cline, and L. Yang, *Tetrahedron Lett*., 2006, **47**, 5797.
14. H. A. El-Sherief, A. M. Mahmoud, and A. A. Ismaiel, *J. Chem. Res.* (S), 1997, **9**, 322.
15. A. A. Aly, *Phosphorous, Sulfur Silicon Relat. Elem.,* 2006, **181**, 2395.
16. A. E. Rashad, M. I. Hegab, R. E. Abdel-Megeid, N. F. Fathalla, and M. E. Abdel-Megied, *Eur. J. Med. Chem.*, 2009, **44**, 3285.
17. G. Saravanan, V. Alagarsamy, C. R. Prakash, P. Kumar, Dinesh and T. P. Selvam, *Asian J. Res. Pharm. Sci.*, 2011, **1**, 134.
18. S. M. Gomha and H. A. Abdel-Aziz, *Bull. Korean Chem. Soc.*, 2012, **33**, 2985.

19. S. M. Gomha, T. M. A. Eldebss, M. M. Abdulla, and A. S. Mayhoub, *Eur. J. Med. Chem.*, 2014, **82**, 472.
20. S. M. Gomha, *Monatsh. Chem.***,** 2009, **140**, 213.
21. S. M. Gomha and H. A. Abdel-Aziz, *J. Serb. Chem. Soc.*, 2013, **78**, 1119.
22. S. M. Gomha, T. A. Salah, and A. O. Abdelhamid, *Monatsh. Chem.*, 2015, **146**, 149.
23. S. M. Gomha and K. M. Dawood, *J. Chem. Res.*, 2014, **38**, 515.
24. S. M. Gomha, M. M. Abdulla, and S. M. Abou-Seri, *Eur. J. Med. Chem.*, 2015, **92**, 459.
25. S. M. Gomha, K. D. Khalil, A. M. El-Zanate, and S. M. Riyadh, *Heterocycles*, 2013, **87**, 1109.
26. S. M. Gomha and H. A. Abdel-Aziz, *Heterocycles*, 2012, **85**, 2291.
27. C. J. Goddard, *J. Heterocycl. Chem.*, 1991, **28**, 1607.
28. A. Hantzsch and H. J. Weber, *Ber. Dtsch. Chem. Ges.*, 1987, **20**, 3118.
29. S. A. Mohammad, L. Lijun, L. Yong-Eok, and L. Dong-Ung, *Chem. Pharm. Bull.*, 2011, **59**, 568.
30. P. Makam, P. K. Thakur, and T. Kannan. *Eur. J. Pharm. Sci*., 2014, **52**, 138.
31. F. Chimenti, B. Bizzarri, A. Bolasco, D. Secci, P. Chimenti, A. Granese, S. Carradori, M. D'Ascenzio, M. M. Scaltrito, and F. Sisto, *J. Heterocycl. Chem.*, 2010, **47**, 1269.
32. R. R. Saravanan, S. Seshadri, S. R. Gunasekaran, R. Mendoza-Meroño, and S. Garcia-Granda, *Spectrochim. Acta, Part A Mol. Biomol. Spect.*, 2015, **139**, 321.
33. A. Arshad, H. Osman, M. C. Bagley, C. K. Lam, S. Mohamad, and A. S. M. Zahariluddin, *Eur. J. Med. Chem*., 2011, **46**, 3788.
34. R. Rajagopalan, A. V. Ghate, P. Subbarayan, W. Linz, and B. A. Schoelkens, *Arzneim. Forsch/Drug Res.*, 1993, **43**, 313.
35. F. J. Hock, K. Wirth, U. Albus, W. Linz, H. J. Gerhards, G. Wiemer, S. Henke, G. Breipohl, W. König, J. Knolle, and B. A. Schölkens, *Br. J. Pharmacol*., 1991, **102**, 769.
36. C. A. Winter, E. A. Risley, and G. W. Nuss, *J. Pharmacol, Exp. Ther.*, 1963, **141**, 369.
37. K. U. Weithmann, S. Jeske, and V. Schlotte, *Agent Actions*, 1994, **41**, 164.
38. F. Herrmann, A. Lindemann, J. Gamss, and R. Mertelsmann, *Eur. J. Immunol.,* 1999, **20**, 2513.