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Synthesis and Biological Activity of 5-Aryl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-1-phenyl-1*H*-pyrazole-3-carboxamides and Their Salts

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Abstract—The reaction of 4-aryl-2-hydroxy-4-oxo-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}but-2-enamides with phenylhydrazine in glacial acetic acid afforded 5-aryl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-1-phenyl-1*H*-pyrazole-3-carboxamides. Treatment of the latter with an equimolar amount of silver nitrate in ethanol–DMF (2:1) gave the corresponding silver salts, while 5-aryl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-1-phenyl-1*H*-pyrazole-3-carboxamide sodium salts were obtained by reaction with sodium methoxide in methanol–DMF (1:1). The synthesized compounds were tested for analgesic, anti-inflammatory, and antimicrobial activities.

Keywords: pyrazole-3-carboxamides, pyrazole-3-carboxamide silver and sodium salts, analgesic activity, anti-inflammatory activity, antimicrobial activity

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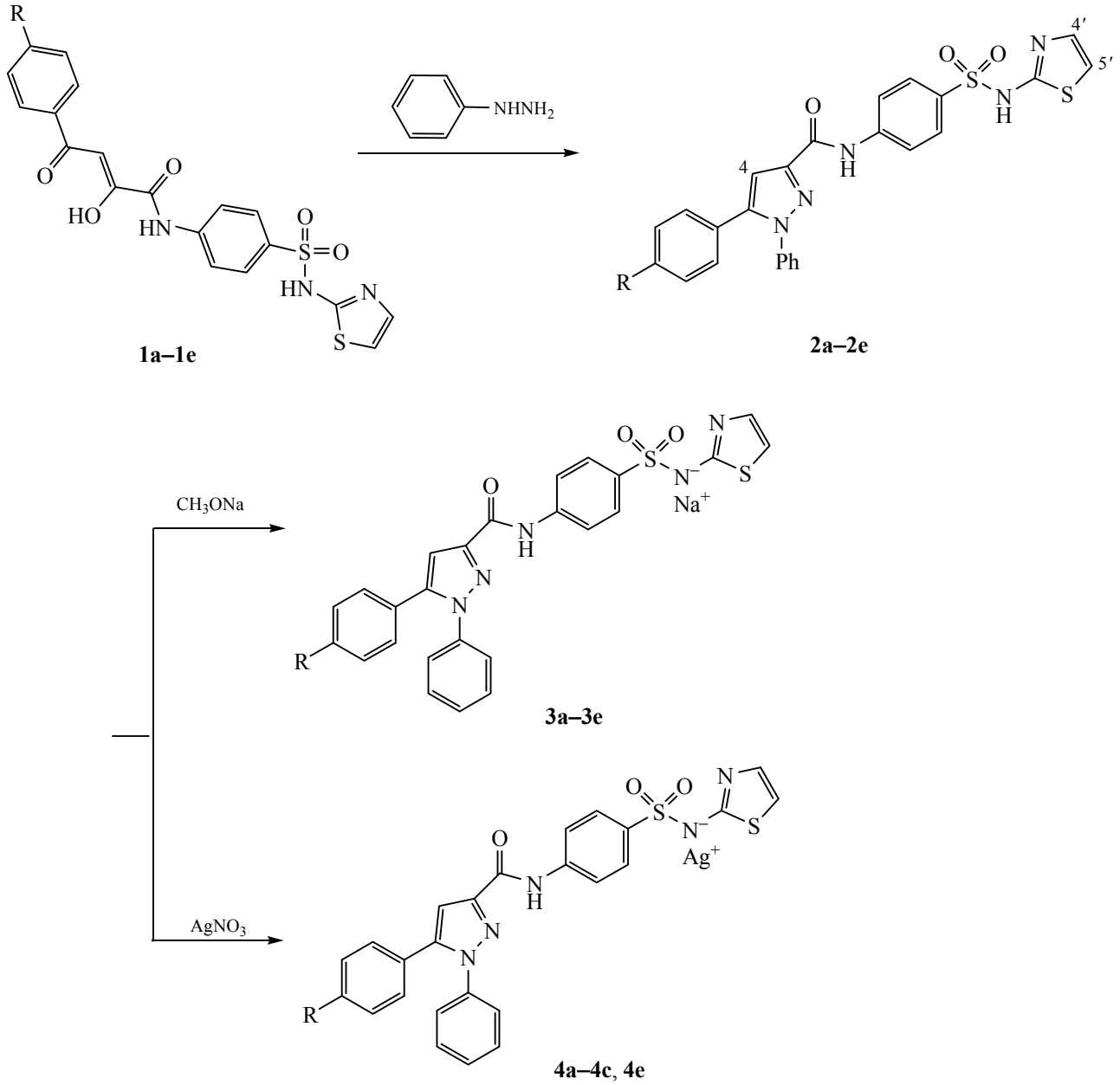
We previously synthesized pyrazole-3-carboxamides containing a 4-(acetylsulfamoyl)phenyl substituent on the amide nitrogen atom [1]. However, the formation of salts at the sulfonamido group of these compounds with silver, sodium, or other metals was not studied.

The goal of the present work was to synthesize biologically active pyrazole-3-carboxamide derivatives containing a 2-(4-aminobenzenesulfamido)-1,3-thiazole fragment. 2-(4-Aminobenzenesulfamido)-1,3-thiazole sodium salt is the known water-soluble antimicrobial drug sulfathiazole [2]. Therefore, a combination of (1,3-thiazol-2-yl)sulfamoyl and pyrazole-3-carboxamide fragments in a single molecule was expected to give rise to the possibility of obtaining water-soluble sodium and silver salts and thus enhancing the antimicrobial effect of the resulting compound. It is known that sulfonamide silver salts such as argosulfan (sulfathiazole silver salt) and dermazin (sulfadiazine silver salts) are used in medical practice [2].

We have synthesized 5-aryl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-1-phenyl-1*H*-pyrazole-3-carboxamides **2a**–**2e** and studied their reactions with sodium methoxide and silver nitrate. Compounds **2a**–**2e** were prepared by heating previously reported (2*Z*)-4-aryl-2-hydroxy-4-oxo-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-but-2-enamides **1a**–**1e** [3] with phenylhydrazine in boiling glacial acetic acid for 2 h (Scheme 1). Compounds **2a**–**2e** were isolated as colored crystalline solids soluble in DMSO and DMF, as well as in glacial acetic acid and dioxane on heating, and insoluble in ethanol and water.

The IR spectra of **2a**–**2e** contained absorption bands due to stretching vibrations of the N–H groups (3493–3242 cm^{-1}), amide carbonyl (1693–1673 cm^{-1}), and sulfonyl group (1320–1310, 1152–1125 cm^{-1}). The ^1H NMR spectra of **2a**–**2e** showed signals of aromatic protons (δ 6.78–8.02 ppm), 5-H and 4-H of the thiazole ring (δ 6.75–6.83 and 7.09–7.25 ppm, respectively, $J_{5,4}$ = 4.50–4.65 Hz), 4-H of the pyrazole ring (δ 7.02–7.18 ppm), and CONH (δ 10.30–10.53 ppm) and SO_2NH protons (δ 12.40–12.78 ppm); signals of other protons present in molecules **2a**–**2e**

Scheme 1.

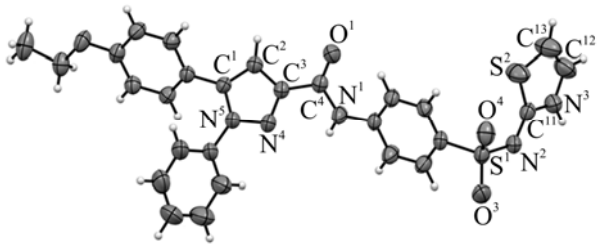


R = Cl (**a**), H (**b**), Me (**c**), EtO (**d**), MeO (**e**).

were also observed in the expected regions. The mass spectra of **2a**–**2d** displayed the molecular ion peak in support of the proposed structure.

Unlike initial amides **1a**–**1e**, 5-aryl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-1-phenyl-1*H*-pyrazole-3-carboxamides **2a**–**2e** showed a negative color test for enolic hydroxy group with an alcoholic solution of iron(III) chloroide, which (in combination with the spectral data) confirmed the given structures.

We also performed X-ray analysis of a single crystal of **2d**, which was obtained by slow crystallization from dioxane–acetic acid (1 : 1). The structure of molecule **2d** in crystal is shown in the figure. Compound **2d** crystallized in the centrosymmetric space group belonging to the triclinic crystal system. The bond lengths and bond angles in molecule **2d** do not differ appreciably from the corresponding reference values. The pyrazole and thiazole rings are planar within 0.01 and 0.02 Å, respectively, and the



Structure of the molecule of 5-(4-ethoxyphenyl)-1-phenyl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-1*H*-pyrazole-3-carboxamide (**2d**) according to the X-ray diffraction data. Non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%.

double bonds in both heterocycles are delocalized as might be expected. Molecules **2d** in crystal are linked to form centrosymmetric dimers through the hydrogen bonds N^3–$H^3\cdots N^2$ [–1 – *x*, 2 – *y*, 1 – *z*]; N^3–H^3 0.93(3), $H^3\cdots N^2$ 1.94(3), $N^3\cdots N^2$ 2.865(4) Å, $\angle N^3H^3N^2$ 168(3)°. The dimers form infinite double-stranded chains along the *a* crystallographic axis via intermolecular hydrogen bonds N^1–$H^1\cdots O^4$ [1 + *x*, *y*, *z*]; N^1–H^1 0.81(3), $H^1\cdots O^4$ 2.47(3), $N^1\cdots O^4$ 3.065(4) Å, $\angle N^1H^1O^4$ 131(2)°.

5-Aryl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-1-phenylpyrazole-3-carboxamides **2a**–**2e** are potentially tautomeric, and they can exist as two tautomers **A** and/or **B** (Scheme 2). In keeping with the X-ray diffraction data, compound **2d** in crystal has structure **B**, whereas the ^{1}H NMR data indicated that compounds **2a**–**2e** in DMSO-d_6 solution exist preferentially as tautomers **A**.

It is known that chemical modification of compounds via transformation into metal salts could give water-soluble derivatives [4], appearance of new kinds of biological activity, and significant enhancement of biological effect; therefore, it seemed promising to study reactions of pyrazole-3-carboxamides **2a**–**2e** with sodium methoxide and silver nitrate.

By adding an equimolar amount of 0.2 M methanolic sodium methoxide to a warm solution of **2a**–**2e** in methanol–DMF (1:1), followed by removing the solvent, we obtained sodium salts **3a**–**3e** (Scheme 1) as white or slightly yellowish crystalline solids soluble in DMF and DMSO and (on heating) in glacial acetic acid, ethanol, and water. The IR spectra of salts **3a**–**3e** showed stretching vibration bands of the amide N–H (3476–3242 cm^{-1}), amide carbonyl (1693–1666 cm^{-1}), and SO_2 groups (1329–1314, 1150–1128 cm^{-1}). In the ^{1}H NMR spectra of **3a**–**3e** we observed signals of aromatic protons (δ 6.88–7.98 ppm), 5-H and 4-H of the thiazole ring (δ 6.53–6.75 and 6.96–7.18 ppm, respectively, $J_{5,4}$ = 4.0–4.4 Hz), 4-H of the pyrazole ring (δ 6.84–7.19 ppm), and CONH proton (δ 10.17–10.74 ppm), whereas no signal at δ 12.40–12.78 ppm assignable to proton of the SO_2NH group was present. The mass spectra of **3a**–**3e** contained the molecular ion peak in support of their structure.

5-Aryl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-1-phenyl-1*H*-pyrazole-3-carboxamide silver salts **4a**–**4c** and **4e** were synthesized by adding an equimolar amount of silver nitrate (as a 2% solution in ethanol) to a hot solution of compound **2a**–**2c** or **2e** in ethanol–DMF (2:1) (Scheme 1). Silver salts **4a**–**4c** and **4e** were isolated as colored crystalline solids soluble on heating in dimethylformamide, dimethyl sulfoxide, and glacial acetic acid and insoluble in water, ethanol, and isopropyl alcohol. The IR spectra of **4a**–**4c** and **4e** contained absorption bands due to stretching vibrations of the amide N–H group (3499–3300 cm^{-1}), amide carbonyl (1688–1681 cm^{-1}), and sulfonyl group (1319–1317, 1141–1140 cm^{-1}). In the ^{1}H NMR spectra of **4a**–**4c** and **4e**, aromatic protons resonated in the region δ 6.88–7.97 ppm, protons in positions 5 and 4 of the thiazole ring gave signals at δ 6.86–6.87 and 7.18–7.19 ppm, respectively, with a coupling constant $J_{5,4}$ of

Scheme 2.

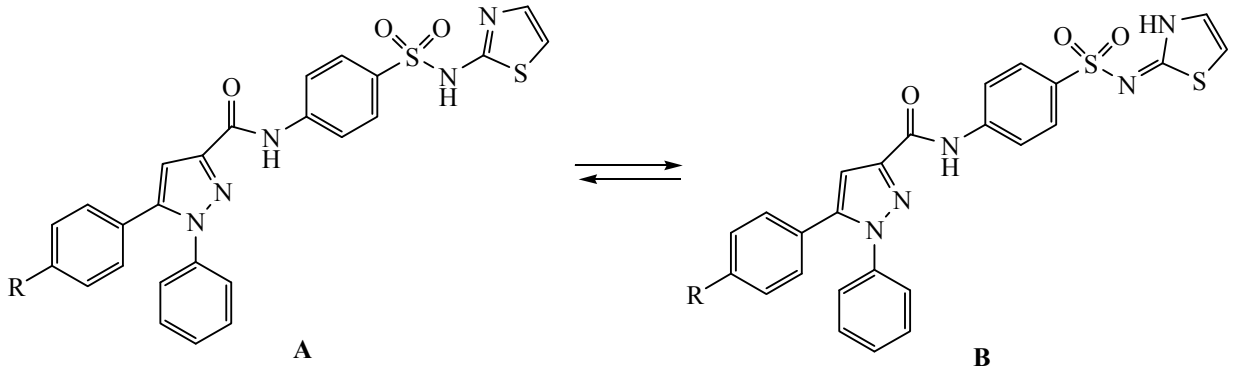


Table 1. Analgesic activity of compounds **2a**–**2c** and **3a**–**3e**

Compound no.	Defense response latency, s	*p* (with respect to control)	*p* (with respect to reference drug)
2a	16.36±1.80	<0.050	<0.05
2b	16.02±2.44	<0.050	>0.05
2c	18.73±4.36	<0.050	<0.05
3a	14.42±3.11	>0.050	>0.05
3b	18.41±3.02	<0.050	<0.05
3c	23.58±10.49	<0.001	<0.05
3d	17.03±1.64	<0.050	<0.05
3e	16.84±1.58	<0.050	<0.05
Metamizole sodium salt	12.60±1.20	<0.050	–
Control	11.30±0.90	–	–

3.9 Hz, the pyrazole 4-H signal was located at δ 7.04–7.14 ppm, and the CONH signal appeared at δ 10.25–10.29 ppm. Like sodium salts **3a**–**3e**, the ^{1}H NMR spectra of **4a**–**4c** and **4e** lacked signal at δ 12.40–12.78 ppm assignable to NH proton of sulfonamido group.

Compounds **2a**–**2c** and **3a**–**3e** were tested for analgesic activity in mice (Table 1). The results of hot plate tests showed that all these compounds, except for **3a**, exhibited analgesic effect after intraperitoneal administration at a dose of 50 mg/kg; in all cases, the time of first response reliably increased relative to the control. The examined compounds turned out to be more effective that metamizole sodium salt taken as reference. Compound **3c** showed the most pronounced analgesic activity.

Compounds **2a**–**2c** and **3a**–**3c** were also tested for anti-inflammatory activity (Table 2). All these compounds showed pronounced anti-inflammatory activity, reliably reducing mice paw swelling after injection of a phlogogenic agent relative to the control. The activity of all the examined compounds considerably exceeded that of metamizole and was comparable to the activity of nimesulide (except for **3b**). Compound **2a** inhibited the development of edema most efficiently and was reliably ($p < 0.05$) superior to nimesulide.

Table 2. Anti-inflammatory activity of compounds **2a**–**2c** and **3a**–**3c**

Compound no.	Paw volume before carrageenin injection, mL	Paw volume after 3 h, mL	Increase in paw volume after 3 h, %	Edema inhibition after 3 h, %
2a	1.34±0.03	1.43±0.02	6.8±1.8[a–c]	89.70
2b	1.58±0.08	1.87±0.12	19.6±8.2[a,b]	70.52
2c	1.45±0.09	1.81±0.13	25.8±9.2[a,b]	61.20
3a	1.52±0.08	1.77±0.04	17.8±7.1[a,b]	73.23
3b	1.45±0.05	2.02±0.08	39.3±2.2[a,b]	40.90
3c	1.36±0.04	1.69±0.11	24.5±7.6[a,b]	63.16
Nimesulide	1.54±0.06	1.53±0.07	12.1±2.3	81.70
Metamizole sodium salt	0.94±0.07	1.60±0.08	71.6±9.8	7.72
Control	0.77±0.05	1.26±0.08	66.5±10.2	–

[a] $p < 0.05$ with respect to control. [b] $p < 0.05$ with respect to metamizole sodium salt. [c] $p < 0.05$ with respect to nimesulide.

Table 3. Antimicrobial activity of compounds **2a**–**2e**, **3a**–**3c**, **4a**–**4c**, and **4e**

Compound no.	MIC, μg/mL		
	S. aureus ATCC 6538-P	*E. coli* ATCC 25922	*C. albicans* ATCC 885-653
2a	500.0	1000.0	1000.0
2b	>1000.0	1000.0	1000.0
2c	1000.0	1000.0	>1000.0
2d	1000.0	1000.0	1000.0
2e	1000.0	1000.0	>1000.0
3a	1000.0	1000.0	1000.0
3b	>1000.0	1000.0	1000.0
3c	500.0	1000.0	1000.0
4a	7.8	2.0	1.0
4b	15.6	3.9	1.0
4c	31.2	7.8	2.0
4e	15.6	2.0	1.0
Dioxidine (1% solution)	62.5	31.2	–
Fluconazole	–	–	2.0–>64.0[a]

[a] Data of [5].

Compounds **2a**–**2e**, **3a**–**3c**, **4a**–**4c**, and **4e** were tested for antifungal and antibacterial activities against standard strains of *Staphylococcus aureus* ATCC 6538-P, *Escherichia coli* ATCC 25922, and *Candida albicans* ATCC 885-653. The results are collected in Table 3. Pyrazole-3-carboxamides **2a**–**2e** and sodium salts **3a**–**3c** showed a low antimicrobial activity. The antimicrobial effect sharply increased in going to silver salts **4a**–**4c** and **4e**, the best results being obtained for compound **4a**. The latter was subjected to extended screening with respect to other bacterial strains from the State Collection of Pathogenic Microorganisms, namely *Staphylococcus epidermidis* ATCC 14990, *Enterococcus faecalis* ATCC 29212, *Klebsiella pneumoniae* NCTC 5055, *Proteus vulgaris* HX 19/222, *Pseudomonas aeruginosa* ATCC 9027, *Salmonella abony* 103/39, and *Bacillus cereus* ATCC 10702 (Table 4). The antibacterial activity of **4a** exceeded the activity of the reference drug dioxidine (1% solution) against *Proteus vulgaris* HX 19/222, *Klebsiella pneumoniae* NCTC 5055, *Pseudomonas aeruginosa* ATCC 9027, and *Staphylococcus epidermidis* ATCC 14990, whereas the activity of **4a** against the other examined bacterial strains was moderate.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Bruker AM-300 (300 MHz) and Bruker Avance III HD (400 MHz) spectrometers using DMSO-d_6 as solvent and

Table 4. Antibacterial activity of compound **4a**

Compound	MIC, μg/mL						
	P. vulgaris HX 19/222	*K. pneumoniae* NCTC 5055	*P. aeruginosa* ATCC 9027	*S. abony* 103/39	*S. epidermidis* ATCC 14990	*E. faecalis* ATCC 29212	*B. cereus* ATCC 10702
4a	3.9	3.9	7.8	15.6	2.0	31.2	15.6
Dioxidine (1% solution)	7.8	15.6	500.0	7.8	500.0	500.0	31.2

tetramethylsilane as internal standard. The IR spectra were recorded in KBr on a Shimadzu IR Affinity-1 spectrometer (Japan) with Fourier transform. The high-resolution mass spectra were obtained with a Bruker micrOTOF mass spectrometer. The elemental compositions were determined on a Perkin Elmer 2400 analyzer. The melting points were measured with a Büchi Melting Point M-565 apparatus.

The X-ray diffraction data for compound **2d** were obtained on a Xcalibur Ruby diffractometer with a CCD detector according to standard procedure [MoK_α radiation, 295(2) K, ω-scanning with a step of 1°]. A correction for absorption was applied empirically by SCALE3 ABSPACK algorithm [6]. Triclinic crystal system, space group *P*-1; $C_{27}H_{23}N_5O_4S_2$, *M* 545.62; unit cell parameters: *a* = 8.1680(11), *b* = 10.4424(13), *c* = 15.6117(19) Å; α = 84.769(10), β = 77.099(11), γ = 79.392(11)°; *V* = 1274.0(3) Å^3; *Z* = 2; d_{calc} = 1.422 g/cm^3; μ = 0.254 mm^{-1}. The structure was solved using Superflip [7] and was refined against F^2 by the full-matrix least-squares method in anisotropic approximation for all non-hydrogen atoms using SHELXL software package [8] with OLEX2 graphical interface [9]. Hydrogen atoms of the NH groups were refined independently in isotropic approximation, and the positions of the other hydrogens were refined according to the riding model. Final divergence factors: R_1 = 0.0623, wR_2 = 0.1377 [for 3834 reflections with $I > 2\sigma(I)$]; R_1 = 0.1008, wR_2 = 0.1688 (for all 5893 independent reflections); goodness of fit *S* = 1.050. The set of X-ray diffraction data for compound **2d** was deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1856231).

5-(4-Chlorophenyl)-1-phenyl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-1*H*-pyrazole-3-carboxamide (2a). Phenylhydrazine, 0.012 mol, was added to a suspension of 0.01 mol of (2*Z*)-4-(4-chlorophenyl)-2-hydroxy-4-oxo-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]-phenyl}but-2-enamide (**1a**) in 30 mL of glacial acetic acid. The mixture was refluxed for 2 h. After cooling, the precipitate was filtered off and recrystallized from ethanol–acetic acid (2:1). Yield 3.65 g (68%), mp 220–222°C (from EtOH–AcOH, 2:1). IR spectrum, ν, cm^{-1}: 3400 (NH), 1682 (C=O), 1313, 1148 (SO_2). ^{1}H NMR spectrum, δ, ppm: 6.79 d (1H, 5'-H, *J* = 4.7 Hz), 7.18 s (1H, 4-H), 7.19 d (1H, 4'-H, *J* = 4.7 Hz), 7.29–7.99 m (13H, H_{arom}), 10.31 s (1H, CONH), 12.44 br.s (1H, SO_2NH). Mass spectrum (ESI), *m*/*z*: 536.0614 $[M]^+$, 558.0430 $[M + Na - H]^+$, 574.0170 $[M + K - H]^+$. Found, %: C 56.13; H 3.34; N 13.15; S 12.05. $C_{25}H_{18}ClN_5O_3S_2$. Calculated, %: C 56.02; H 3.38; N 13.07; S 11.96.

Compounds **2b**–**2e** were synthesized in a similar way.

1,5-Diphenyl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]-phenyl}-1*H*-pyrazole-3-carboxamide (2b). Yield 3.82 g (76%), mp 215–217°C (from EtOH–AcOH, 2:1). IR spectrum, ν, cm^{-1}: 3493, 3274 (NH), 1673 (C=O), 1320, 1148 (SO_2). ^{1}H NMR spectrum, δ, ppm: 6.78 d (1H, 5'-H, *J* = 4.7 Hz), 7.14 s (1H, 4-H), 7.17 d (1H, 4'-H, *J* = 4.7 Hz), 7.27–7.99 m (14H, H_{arom}), 10.30 s (1H, CONH), 12.45 br.s (1H, SO_2NH). Mass spectrum (ESI), *m*/*z*: 502.0989 $[M + H]^+$, 524.0808 $[M + Na]^+$. Found, %: C 59.72; H 3.86; N 13.91; S 12.86. $C_{25}H_{19}N_5O_3S_2$. Calculated, %: C 59.86; H 3.82; N 13.96; S 12.79.

5-(4-Methylphenyl)-1-phenyl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-1*H*-pyrazole-3-carboxamide (2c). Yield 4.02 g (78%), mp 230–232°C (from EtOH–AcOH, 2:1). IR spectrum, ν, cm^{-1}: 3347, 3242 (NH), 1688 (C=O), 1310, 1125 (SO_2). ^{1}H NMR spectrum, δ, ppm: 2.29 s (3H, CH_3), 6.83 d (1H, 5'-H, *J* = 4.5 Hz), 7.14 s (1H, 4-H), 7.25 d (1H, 4'-H, *J* = 4.5 Hz), 7.17–8.02 m (13H, H_{arom}), 10.53 s (1H, CONH), 12.78 br.s (1H, SO_2NH). Mass spectrum (ESI): *m*/*z* 538.0955 $[M + Na]^+$. Found, %: C 60.45; H 4.05; N 13.65; S 12.52. $C_{26}H_{21}N_5O_3S_2$. Calculated, %: C 60.57; H 4.11; N 13.58; S 12.44.

5-(4-Ethoxyphenyl)-1-phenyl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-1*H*-pyrazole-3-carboxamide (2d). Yield 4.31 g (79%), mp 240–242°C (from EtOH–AcOH, 2:1). IR spectrum, ν, cm^{-1}: 3337 (NH), 1693 (C=O), 1314, 1149 (SO_2). ^{1}H NMR spectrum, δ, ppm: 1.30 t (3H, C**H**$_3$CH$_2$O, *J* = 6.9 Hz), 4.02 q (2H, CH$_3$C**H**$_2$O, *J* = 6.9 Hz), 6.83 d (1H, 5'-H, *J* = 4.7 Hz), 7.11 s (1H, 4-H), 7.25 d (1H, 4'-H, *J* = 4.7 Hz), 6.89–8.02 m (13H, H_{arom}), 10.51 s (1H, CONH), 12.67 br.s (1H, SO_2NH). Mass spectrum (ESI), *m*/*z*: 546.1251 $[M + H]^+$, 568.1074 $[M + Na]^+$. Found, %: C 59.27; H 4.21; N 12.88; S 11.68. $C_{27}H_{23}N_5O_4S_2$. Calculated, %: C 59.43; H 4.25; N 12.84; S 11.75.

5-(4-Methoxyphenyl)-1-phenyl-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-1*H*-pyrazole-3-carboxamide (2e). Yield 4.14 g (78%), mp 251–253°C (from EtOH–AcOH, 2:1). IR spectrum, ν, cm^{-1}: 3336 (NH), 1692 (C=O), 1312, 1152 (SO_2). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, CH_3O), 6.75 d (1H, 5'-H, *J* = 4.6 Hz), 7.02 s (1H, 4-H), 7.09 d (1H, 4'-H, *J* = 4.6 Hz), 6.78–7.95 m (13H, H_{arom}), 10.35 s (1H, CONH), 12.40 br.s (1H,

SO_2NH). Found, %: C 58.87; H 4.05; N 13.23; S 12.00. $C_{26}H_{21}N_5O_4S_2$. Calculated, %: C 58.74; H 3.98; N 13.17; S 12.06.

Sodium (4-{[5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-3-carbonyl]amino}benzene-1-sulfonyl)(1,3-thiazol-2-yl)azanide (3a). A 0.2 M solution of 0.005 mol of sodium methoxide in methanol was added to a warm solution of 0.005 mol of compound **2a** in methanol–DMF (1 : 1). The mixture was evaporated to dryness at room temperature, and the residue was recrystallized from ethanol. Yield 1.70 g (61%), mp 320–322°C (from EtOH). IR spectrum, ν, cm^{-1}: 3476 (NH), 1673 (C=O), 1319, 1141 (SO_2). ^1H NMR spectrum, δ, ppm: 6.55 d (1H, 5'-H, J = 4.0 Hz), 7.02 d (1H, 4'-H, J = 4.0 Hz), 7.19 s (1H, 4-H), 7.29–7.89 m (13H, H_{arom}), 10.26 s (1H, CONH). Mass spectrum (ESI), m/z: 558.0428 $[M]^+$, 580.0243 $[M + Na - H]^+$. Found, %: C 53.66; H 3.01; N 12.65; S 11.40. $C_{25}H_{17}ClN_5NaO_3S_2$. Calculated, %: C 53.81; H 3.07; N 12.55; S 11.49.

Compounds **3b**–**3e** were synthesized in a similar way.

Sodium {4-[(1,5-diphenyl-1*H*-pyrazole-3-carbonyl)-amino]benzene-1-sulfonyl}(1,3-thiazol-2-yl)azanide (3b). Yield 1.70 g (65%), mp 300°C (decomp., from EtOH). IR spectrum, ν, cm^{-1}: 3443 (NH), 1666 (C=O), 1317, 1144 (SO_2). ^1H NMR spectrum, δ, ppm: 6.53 d (1H, 5'-H, J = 4.0 Hz), 7.01 d (1H, 4'-H, J = 4.0 Hz), 7.14 s (1H, 4-H), 7.28–7.92 m (14H, H_{arom}), 10.74 s (1H, CONH). Mass spectrum (ESI): m/z 546.0632 $[M + Na]^+$. Found, %: C 57.47; H 3.39; N 13.30; S 12.19. $C_{25}H_{18}N_5NaO_3S_2$. Calculated, %: C 57.35; H 3.47; N 13.38; S 12.25.

Sodium (4-{[5-(4-methylphenyl)-1-phenyl-1*H*-pyrazole-3-carbonyl]amino}benzene-1-sulfonyl)(1,3-thiazol-2-yl)azanide (3c). Yield 1.53 g (57%), mp 298–300°C (from EtOH). IR spectrum, ν, cm^{-1}: 3346, 3242 (NH), 1687 (C=O), 1329, 1128 (SO_2). ^1H NMR spectrum, δ, ppm: 2.29 s (3H, CH_3), 6.75 d (1H, 5'-H, J = 4.4 Hz), 7.11 s (1H, 4-H), 7.18 d (1H, 4'-H, J = 4.4 Hz), 7.16–7.98 m (13H, H_{arom}), 10.33 s (1H, CONH). Mass spectrum (ESI), m/z: 538.0970 $[M + H]^+$, 560.0793 $[M + Na]^+$. Found, %: C 57.99; H 3.80; N 13.12; S 11.99. $C_{26}H_{20}N_5NaO_3S_2$. Calculated, %: C 58.09; H 3.75; N 13.03; S 11.93.

Sodium (4-{[5-(4-ethoxyphenyl)-1-phenyl-1*H*-pyrazole-3-carbonyl]amino}benzene-1-sulfonyl)(1,3-thiazol-2-yl)azanide (3d). Yield 1.62 g (57%), mp 250–252°C (from EtOH). IR spectrum, ν, cm^{-1}: 3336 (NH), 1693 (C=O), 1314, 1149 (SO_2). ^1H NMR spectrum, δ, ppm: 1.30 t (3H, C**H**$_3$CH$_2$O, J = 7.0 Hz), 4.02 q (2H, CH$_3$C**H**$_2$O, J = 7.0 Hz), 6.58 d (1H, 5'-H, J = 4.4 Hz), 7.05 d (1H, 4'-H, J = 4.4 Hz), 7.06 s (1H, 4-H), 6.88–7.90 m (13H, H_{arom}), 10.23 s (1H, CONH). Mass spectrum (ESI), m/z: 568.1081 $[M + H]^+$, 590.0906 $[M + Na]^+$. Found, %: C 57.21; H 3.87; N 12.40; S 11.37. $C_{27}H_{22}N_5NaO_4S_2$. Calculated, %: C 57.13; H 3.91; N 12.34; S 11.30.

Sodium (4-{[5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-3-carbonyl]amino}benzene-1-sulfonyl)(1,3-thiazol-2-yl)azanide (3e). Yield 1.63 g (59%), mp 250–252°C (from EtOH). IR spectrum, ν, cm^{-1}: 3339 (NH), 1691 (C=O), 1315, 1150 (SO_2). ^1H NMR spectrum, δ, ppm: 3.72 s (3H, CH_3O), 6.63 d (1H, 5'-H, J = 4.4 Hz), 6.84 s (1H, 4-H), 6.96 d (1H, 4'-H, J = 4.4 Hz), 7.04–7.90 m (13H, H_{arom}), 10.17 s (1H, CONH). Mass spectrum (ESI), m/z: 554.0906 $[M + H]^+$, 576.0727 $[M + Na]^+$. Found, %: C 56.55; H 3.60; N 12.56; S 11.67. $C_{26}H_{20}N_5NaO_4S_2$. Calculated, %: C 56.41; H 3.64; N 12.65; S 11.58.

Silver (4-{[5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-3-carbonyl]amino}benzene-1-sulfonyl)(1,3-thiazol-2-yl)azanide (4a). A hot 2% solution of 0.005 mol of silver nitrate in ethanol was added to a hot solution of 0.005 mol of compound **2a** in 30–35 mL of ethanol–DMF (2 : 1). The precipitate was filtered off, washed on a filter with ethanol and water to remove traces of silver nitrate, dried, and again washed with ethanol and dried. Yield 2.15 g (67%), mp 217–219°C (from EtOH). IR spectrum, ν, cm^{-1}: 3494, 3376 (NH), 1688 (C=O), 1319, 1141 (SO_2). ^1H NMR spectrum, δ, ppm: 6.86 d (1H, 5'-H, J = 3.9 Hz), 7.14 s (1H, 4-H), 7.19 d (1H, 4'-H, J = 3.9 Hz), 7.25–7.96 m (13H, H_{arom}), 10.29 s (1H, CONH). Found, %: C 46.82; H 2.64; N 10.97; S 9.91. $C_{25}H_{17}AgClN_5O_3S_2$. Calculated, %: C 46.71; H 2.67; N 10.89; S 9.98.

Compounds **4b**, **4c**, and **4e** were synthesized in a similar way.

Silver {4-[(1,5-diphenyl-1*H*-pyrazole-3-carbonyl)-amino]benzene-1-sulfonyl}(1,3-thiazol-2-yl)azanide (4b). Yield 2.16 g (71%), mp 219–221°C (from EtOH). IR spectrum, ν, cm^{-1}: 3499, 3312 (NH), 1681 (C=O), 1318, 1140 (SO_2). ^1H NMR spectrum, δ, ppm: 6.87 d (1H, 5'-H, J = 3.9 Hz), 7.11 s (1H, 4-H), 7.19 d (1H, 4'-H, J = 3.9 Hz), 7.24–7.97 m (14H, H_{arom}), 10.29 s (1H, CONH). Found, %: C 49.42; H 2.93; N 11.41; S 10.45. $C_{25}H_{18}AgN_5O_3S_2$. Calculated, %: C 49.35; H 2.98; N 11.51; S 10.54.

Silver (4-{[5-(4-methylphenyl)-1-phenyl-1*H*-pyrazole-3-carbonyl]amino}benzene-1-sulfonyl)(1,3-thiazol-2-yl)azanide (4c). Yield 2.11 g (68%), mp 220–222°C (from EtOH). IR spectrum, ν, cm^{-1}: 3300 (NH), 1685 (C=O), 1317, 1140 (SO_2). ^1H NMR spectrum, δ, ppm: 2.29 s (3H, CH_3) 6.86 d (1H, 5'-H, J = 3.9 Hz), 7.07 s (1H, 4-H), 7.19 d (1H, 4'-H, J = 3.9 Hz), 7.14–7.95 m (13H, H_{arom}), 10.26 s (1H, CONH). Found, %: C 50.05; H 3.30; N 11.28; S 10.23. $C_{26}H_{20}AgN_5O_3S_2$. Calculated, %: C 50.17; H 3.24; N 11.25; S 10.30.

Silver (4-{[5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-3-carbonyl]amino}benzene-1-sulfonyl)(1,3-thiazol-2-yl)azanide (4e). Yield 2.04 g (64%), mp 214–216°C (from EtOH). IR spectrum, ν, cm^{-1}: 3494, 3372 (NH), 1688 (C=O), 1319, 1141 (SO_2). ^1H NMR spectrum, δ, ppm: 3.75 s (3H, CH_3O), 6.86 d (1H, 5'-H, J = 3.9 Hz), 7.04 s (1H, 4-H), 7.18 d (1H, 4'-H, J = 3.9 Hz), 6.88–7.95 m (13H, H_{arom}), 10.25 s (1H, CONH). Found, %: C 48.79; H 3.21; N 10.88; S 9.93. $C_{26}H_{20}AgN_5O_4S_2$. Calculated, %: C 48.91; H 3.16; N 10.97; S 10.04.

The analgesic activity of compounds **2a**–**2c** and **3a**–**3e** was assayed in 25–30-g outbred female mice by the hot plate test [10]. The pain sensitivity was estimated using an analgesiometer. The compounds to be tested were administered intraperitoneally at a dose of 50 mg/kg (a suspension in a 1% starch solution) 30 min before placing the animals onto a metal plate heated to 53.5°C. The pain sensitivity was assessed by the time of first response (lick, paw withdrawal, jump, attempt to escape) in seconds. The results were estimated by increase of the defense response latency relative to the initial data. Animals of the control group were administered with a 1% starch solution. Metamizole sodium at a dose of 50 mg/kg (intraperitoneal administration) was used as reference drug. The results were statistically processed by calculating Fischer–Student t test. The effect was considered to be reliable at $p < 0.05$ [11].

The anti-inflammatory activity of compounds **2a**–**2c** and **3a**–**3c** was assayed in 220–270-g white outbred male and female rats with a carrageenin-induced hind paw edema (subplantar injection of 0.1 mL of a 1% aqueous solution of carrageenin) [10]. The paw volume was measured with an oncometer before and 3 h after the injection of carrageenin. The compounds to be tested were introduced at a dose of 50 mg/kg (a suspension in a 1% starch solution) through an atraumatic metallic probe 1 h before injecting the phlogogenic agent. The reference drugs were metamizole sodium salt and nimesulide at a dose of 50 mg/kg, which were administered in a similar way. The results were statistically processed by calculating Fischer–Student t test. The effect was considered to be reliable at $p < 0.05$ [11]. The anti-inflammatory activity was evaluated by the edema growth inhibition in percent of the control group.

The antifungal and antibacterial activities of compounds **2a**–**2e**, **3a**–**3c**, **4a**–**4c**, and **4e** were estimated by the double serial dilution method using a liquid nutrient medium [10]. Stock solutions were prepared by dissolving a 0.05-g sample of a compound to be tested in 5 mL DMSO, so that their concentration was 10^4 μg/mL. The working solution had a concentration of 2×10^3 μg/mL, and it was serially diluted twofold in a series of 10 test tubes charged with a liquid nutrient medium, so that the concentration in the first test tube was 1000.0 μg/mL. Hottinger broth was used for bacterial strains, and Saburo broth, for fungal strains. Yeast cultures were prepared by incubation for 48 h on Saburo agar. Bacterial cultures were prepared by incubation for 24 h on a nutrient agar. The concentration of microbial cells was $(2–5)\times10^5$ CFU/mL for bacteria and $(2–5)\times10^4$ CFU/mL for fungi. The positive control was microbial culture inoculated onto a nutrient medium, and the negative control was an intact nutrient medium. The cultures were incubated at 25±2°C (fungi) or 37±2°C (bacteria). The growth inhibition of microorganisms was evaluated visually after 20–24 h for bacteria and after 40–48 and 70–72 h for fungi. The concentration of a compound in the last transparent test tube of the dilution series was taken as the minimal inhibitory concentration. Dioxidine and fluconazole were used as reference drugs in antibacterial and antifungal tests, respectively.

This study was performed in accordance with all applicable international, national, and institutional guidelines for treatment of animals.

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CONFLICT OF INTERESTS

No conflict of interest was declared by the authors.

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