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Synthesis and reactions of thiosemicarbazides, triazoles, and *Schiff* bases as antihypertensive α-blocking agents

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Abstract Methyl 2-(thiazol-2-ylcarbamoyl)acetate was synthesized and used as starting material. It was treated with hydrazine hydrate to afford the hydrazide, which was reacted with nitromethane and formaldehyde to give the saturated nitropyrimidine. The hydrazide was reacted with phenyl isothiocyanate to afford the thiosemicarbazide, which was cyclized with ethyl bromoacetate, sodium hydroxide, or sulfuric acid to afford *N*-phenylthiazolidinone, *N*-phenyltriazole, and thiadiazolyl derivatives. The methyl 2-(thiazol-2-ylcarbamoyl)acetate was coupled with diazonium salts of aniline, 4-chloroaniline, 4-bromoaniline, or 4-aminobenzenesulfonamide to afford the carbamoyl acetates, which were reacted with 2-aminobenzimidazole, 1,2,4,5-tetrachlorophthalic anhydride, and hydrazine hydrate to afford the corresponding thiazolylmalonamide, tetrachloroisoindolylimide, and triazole derivatives. *Schiff* bases and imides are newly synthesized candidates obtained *via* simple condensation of the hydrazide with aldehydes, 2,3-pyridinedicarboxylic anhydride, or 1,8-naphthalenedicarboxylic anhydride. The pharmacological screening showed that many of these compounds have good antihypertensive α-blocking activity and low toxicity.

Keywords Methyl 2-(thiazol-2-ylcarbamoyl)acetate; Thiazoles; Thiadiazoles; Antihypertensive α-blocking agents.

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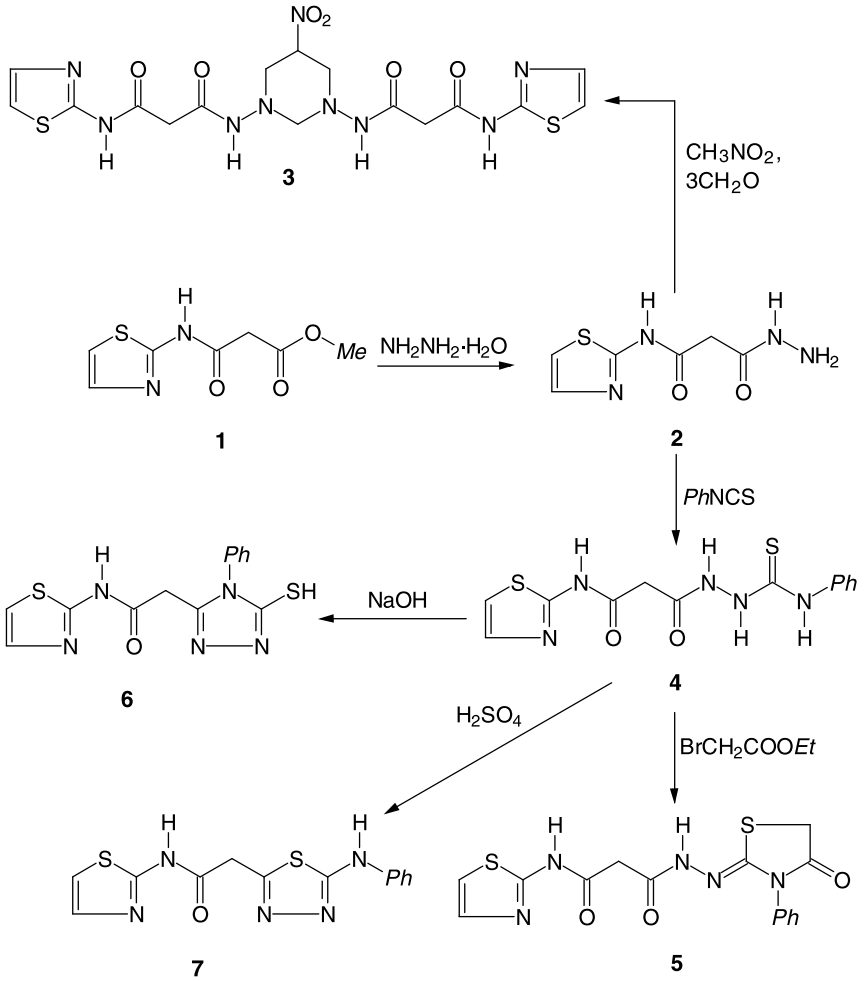
Introduction

From previous work, *Schiff* bases are known to possess antimicrobial [1–4] and antiinflammatory [5, 6] activities. In addition, thiosemicarbazide and triazole derivatives have also been found to interest with potent activities including antimicrobial, analgesic, and anticonvulsant activities [7–10]. On the other hand, some synthetic thiazoles exhibit a range of biological activities, such as antitumor, antibiotic, antibacterial, antifungal, and antiinflammatory activities [11–14]. Recent studies have shown some new thiazole candidates as antimicrobial and anticancer agents [15–18]. In addition, we have reported that certain of our newly substituted heterocyclic compounds exhibited antiparkinsonian [19], antitumor [20–22], antimicrobial [23], and antiinflammatory [24] activities. In view of these reports and in continuation of our previous works in heterocyclic chemistry, we have herein synthesized some new thiazole derivatives and tested them for their antihypertensive α-blocking activity and toxicity.

Results and discussion

Synthesis

Methyl 2-(thiazol-2-ylcarbamoyl)acetate (**1**) was synthesized according to the reported procedure [25] and used as starting material. It was treated with hydrazine hydrate to afford 3-(2-thiazolylamino)-3-

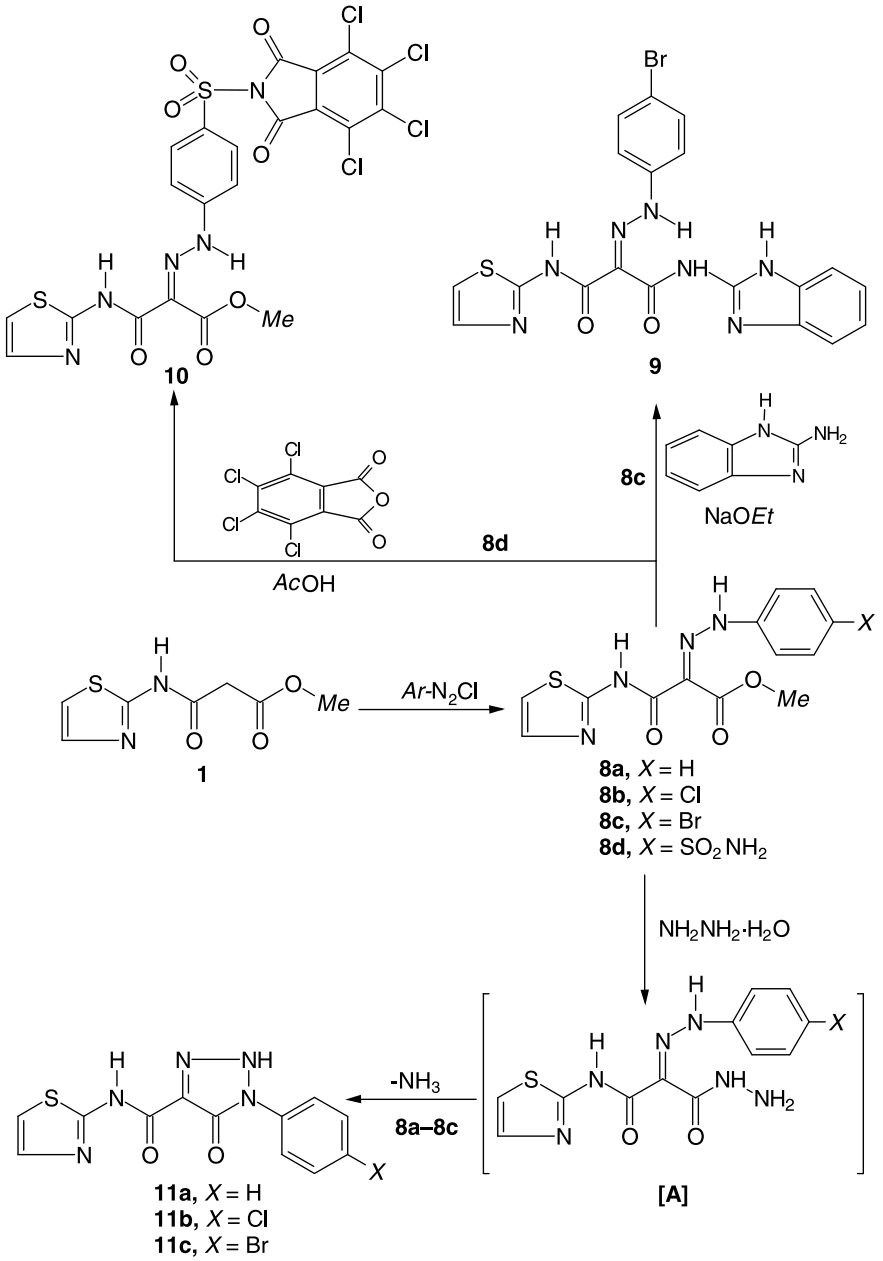


Scheme 1

oxopropanehydrazide (**2**), which was reacted with nitromethane and formaldehyde to give saturated pyrimidine **3**. Hydrazide **2** was reacted with phenyl isothiocyanate to afford the thiosemicarbazide derivative **4**, which was reacted with ethyl bromoacetate to afford the corresponding *N*-phenyl thiazolidinone derivative **5**. While, thiosemicarbazide **4** was cyclized to *N*-phenyltriazolethiol **6** by refluxing with 2 *N* NaOH, when suspension of **4** in sulfuric acid was allowed to stand overnight at room temperature, the thiadiazolyl derivative **7** was isolated in pure form and good yield (Scheme 1).

Compound **1** was treated with the diazonium salts of aniline, 4-chloroaniline, 4-bromoaniline, or 4-aminobenzenesulfonamide in the presence of sodium acetate trihydrate as a catalyst in ethanol (96%) to afford the corresponding **8a**–**8d**. Compound **8c** was reacted with 2-aminobenzimidazole in the presence of sodium ethoxide to afford the thiazolylmalonamide **9**. Compound **8d** was condensed with 1,2,4,5-tetrachlorophthalic anhydride in refluxing glacial acetic acid to give the imide derivative **10**. In the present work, **8a**–**8d** were treated with hydrazine hydrate in refluxing ethanol without catalyst affording the corresponding triazoles **11a**–**11c**. Formation of **11a**–**11c** is believed to take place by the condensation of the hydrazine on the ester group of **8a**–**8c** to form the unisolable hydrazide [**A**], followed by intermolecular cyclization and removal of ammonia affording **11a**–**11c** as the final products (Scheme 2).

Compounds **12a**–**12c**, **13**, and **14** are newly suggested and synthesized candidates obtained *via* simple condensation of the hydrazide **2** with aromatic aldehydes, namely, *p*-chlorobenzaldehyde, *p*-fluorobenzaldehyde, or *p*-nitrobenzaldehyde, thus affording the *Schiff* bases **12a**–**12c.** Upon refluxing with 2,3-pyridinedicarboxylic anhydride or 1,8-naphthalinedi-



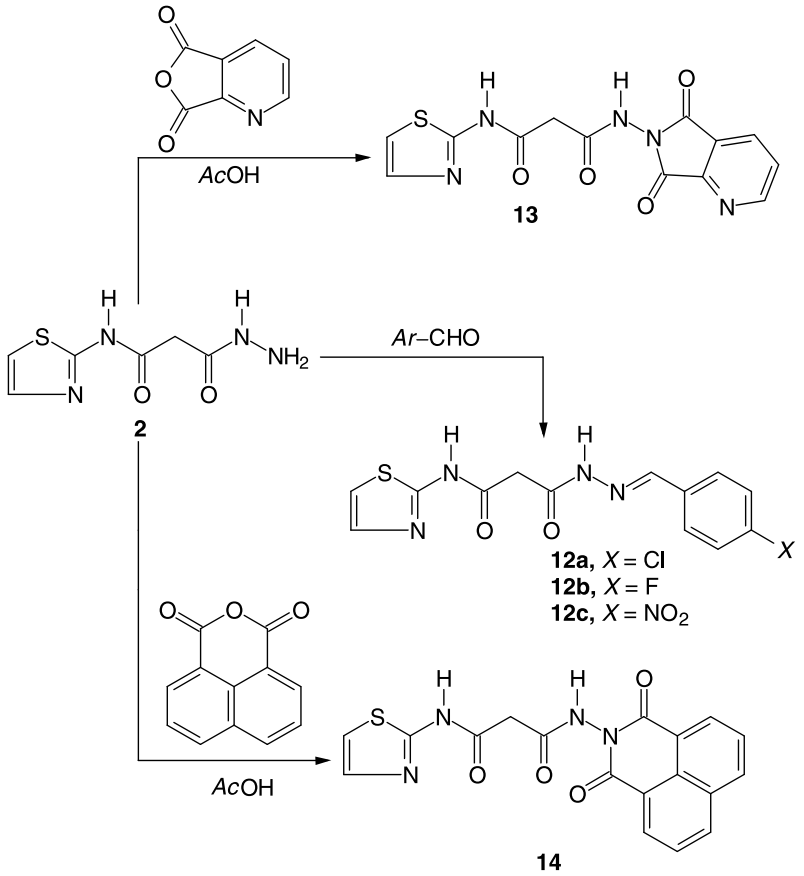
Scheme 2

carboxylic anhydride in glacial acetic acid the corresponding pyridoisoindolyl and naphthylisoindolyl derivatives **13** and **14** (Scheme 3) were obtained.

Pharmacological screening

Antihypertensive α-blocking activity

Some of 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 (**7**, **8a**, and **8d**), (**2**, **8b**, **9**, and **12b**), (**3**, **6**, and **12c**), (**5**, **11a**, **11b**, and **14**), **10**, (**8c**, and **11c**), **4**, **12a**, and **13**. It is to be mentioned that **7**, **8a**, **8d**, **2**, **8b**, **9**, **12b**, **3**, **6**, and **12c** are more potent than Minoxidil®, while, **5**, **11a**, **11b**, and **14** are of similar activity as Minoxidil®.



Scheme 3

Table 1 The antihypertensive α-blocking activities of some newly synthesized compounds

Comp. No.	IC_{50} $\mu g/cm^3$
2	2
3	3
4	7
5	4
6	3
7	1
8a	1
8b	2
8c	6
8d	1
9	2
10	5
11a	4
11b	4
11c	6
12a	8
12b	2
12c	3
13	9
14	4
Minoxidil®	4

Structure activity relationship (SAR)

From the above-obtained results (Table 1), we can suggest that the antiarrhythmic activity is due to:

- a thiazole ring, which is essential for the activities,
- the presence of another heterocyclic (five membered ring system), which sharply increase activity,
- an unsubstituted phenyl ring gives more activity than substituted ones,
- steric hindrance contributes to extent to decrease of the activity, and
- saturated and partially saturated five membered ring systems lower the activity.

Determination of acute toxicity (LD_{50})

The LD_{50} was determined by using rats. They were injected with different increasing doses of the synthesized compounds. The dose that killed 50% of the animals was calculated according to *Austen et al.* [26] (Table 2).

Table 2 Acute toxicity (LD_{50}) of the synthesized compounds

Comp. No.	$LD_{50}/mg \cdot kg^{-1}$
2	286.43 ± 0.14
3	166.12 ± 0.12
4	172.80 ± 0.17
5	398.22 ± 0.38
6	468.12 ± 0.41
7	539.17 ± 0.14
8a	153.92 ± 0.12
8b	155.15 ± 0.14
8c	156.22 ± 0.16
8d	167.60 ± 0.15
9	195.17 ± 0.11
10	223.00 ± 0.17
11a	123.61 ± 0.27
11b	225.12 ± 0.22
11c	438.11 ± 0.21
12a	569.23 ± 0.39
12b	112.34 ± 0.19
12c	138.51 ± 0.18
13	724.51 ± 0.61
14	633.51 ± 0.59

Experimental

Synthesis

All melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data (in accord with the calculated values) were obtained from the microanalytical Unit, Cairo University, Cairo, Egypt. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The ^{1}H NMR spectra were recorded at 270 MHz on a Varian EM-360 spectrometer using *TMS* as an internal standard. The mass spectra were performed using a Varian MAT CH-5 spectrometer (70 eV). All reactions were followed by TLC (silica gel, aluminum sheets 60 F_{254}, and Merck). Methyl 2-(thiazol-2-ylcarbamoyl)acetate (**1**) was synthesized according to Ref. [25].

3-(2′-Thiazolylamino)-3-oxopropanehydrazide
(**2**, $C_6H_8N_4O_2S$)

A mixture of 0.2 g ester **1** (1 mmol) and 0.35 cm^3 hydrazine hydrate (8 mmol) in 25 cm^3 absolute ethanol was refluxed for 1 h. After cooling, the precipitated solid was filtered off, dried, and crystallized to afford 0.15 g (75%) hydrazide **2**. Mp 218–220°C (*Et*OH); IR (film): $\bar{\nu} = 3330–3280$ (NH, NH_2), 1682, 1675 (2C=O), 1654 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 3.82$ (s, CH_2), 4.85 (bs, NH_2, exchangeable with D_2O), 7.24, 7.28 (2d, thiazole-H), 11.35 (s, NH, exchangeable with D_2O), 12.15 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 200 [M^+, 100, base peak].

1,3-Bis-(N′-(thiazol-2-yl)malonamido)-5-nitrohexahydropyrimidine (**3**, $C_{16}H_{19}N_9O_6S_2$)

To a solution of 0.3 g nitromethane (5 mmol) and 0.5 g formaldehyde (15 mmol) in 20 cm^3 absolute ethanol warmed 1 h, 1.0 g hydrazide **2** (5 mmol) was added. The warming was continued for another 1 h at 70°C, the precipitated solid was filtered off, dried, and crystallized to give 1.86 g (75%) **3**. Mp >300°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 3250–3202$ (NH), 1681, 1678 (C=O), 1658 (C=N), 1550 (NO_2) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.68–2.74$ (m, CH + $2CH_2$-pyrimidine), 3.38 (s, CH_2-pyrimidine), 3.73 (s, $2CH_2$), 7.21, 7.25 (2d, thiazole-H), 11.43 (s, 2NH, exchangeable with D_2O), 12.20 (s, 2NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 397 [M^+, 5] and at 57 [100, base peak].

1-(3-(2′-Thiazolylamino)-3-oxopropane)-4-phenylthiosemicarbazide (**4**, $C_{13}H_{13}N_5O_2S_2$)

A mixture of 0.2 g **2** (1 mmol) and 0.135 g phenyl isothiocyanate (1 mmol) in 50 cm^3 absolute ethanol was refluxed for 1 h. The solid formed was filtered off, dried, and crystallized to give 0.26 g (77%) **4**. Mp 231–233°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 3262–3252$ (NH), 1680, 1674 (C=O), 1655 (C=N), 1259 (C=S) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 3.63$ (s, CH_2), 7.18, 7.25 (2d, thiazole-H), 7.35–7.55 (m, *Ar*–H), 9.68 (s, NH, exchangeable with D_2O), 9.82 (s, NH, exchangeable with D_2O), 10.30 (s, NH, exchangeable with D_2O), 12.34 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 335 [M^+, 2] and at 149 [100, base peak].

2-[3-(2′-Thiazolylamino)-3-oxopropanehydrazono]-3-phenyl-4-thiazolidinone (**5**, $C_{15}H_{13}N_5O_3S_2$)

A mixture of 0.34 g **4** (1 mmol) and 0.17 g ethyl bromoacetate (1 mmol) in 30 cm^3 absolute ethanol containing 0.33 g anhydrous sodium acetate (4 mmol) was heated under reflux for 6 h. The reaction mixture was cooled, diluted with water, and allowed to stand overnight. The precipitated solid was filtered off, washed with water, and crystallized to give 0.21 g (55%) **5**. Mp 216–218°C (*Et*OH); IR (film): $\bar{\nu} = 3230$ (NH), 1745, 1692, 1682 (3C=O), 1652 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 3.91$ (s, CH_2), 4.18, 4.22 (dd, $J = 8.0$ Hz, thiazolidinone ring), 7.18, 7.22 (2d, thiazole-H), 7.25–7.39 (m, *Ar*–H), 11.98 (bs, 2NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 373 [M^+-2, 3] and at 174 [100, base peak].

2-(5-Mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)-N-(thiazol-2-yl)acetamide (**6**, $C_{13}H_{11}N_5OS_2$)

A solution of 0.34 g **4** (1 mmol) in 10 cm^3 2 *N* NaOH was refluxed for 30 min. The reaction mixture was cooled, diluted with water and neutralized with 1 *N* HCl, the formed solid was filtered off, dried, and crystallized to afford 0.20 g (62%) **6**. Mp 247–249°C (*Et*OH/H_2O); IR (film): $\bar{\nu} = 3117$ (NH), 2364 (SH), 1686 (C=O), 1659 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 3.83$ (s, CH_2), 7.20, 7.22 (2d, thiazole-H), 7.34–7.51 (m, *Ar*–H), 12.19 (s, SH, exchangeable with D_2O), 13.92 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 317 [M^+, 8] and at 71 [100, base peak].

2-(5-(Phenylamino)-1,3,4-thiadiazol-2-yl)-N-(thiazol-2-yl)-acetamide (**7**, $C_{13}H_{11}N_5OS_2$)

A suspension of 0.34 g **4** (1 mmol) in 5 cm^3 concentrated sulfuric acid was stirred in an ice bath for 1 h. The reaction mixture was left to stand overnight, then poured into ice-water

and neutralized with 2 *N* NaOH. The formed solid was filtered off, dried, and crystallized to give 0.25 g (77%) **7**. Mp >300°C (*Et*OH); IR (film): $\bar{\nu} = 3260–3210$ (NH), 1684 (C=O), 1660 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 4.27$ (s, NH–Ph, exchangeable with D_2O), 4.15 (s, CH_2), 7.16, 7.26 (2d, thiazole-H), 7.28–7.58 (m, *Ar*–H); 11.19 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 317 [M^+, 52] and at 142 [100, base peak].

Synthesis of methyl 2-(2-arylhydrazono)-2-(thiazol-2-yl-carbamoyl)acetates ***8a–8d***

To a mixture of 0.2 g **1** (1 mmol) and 0.5 g sodium acetate trihydrate (20 mmol) in 25 cm^3 ice-cold ethanol (−5°C), the appropriate aryl diazonium salts of aniline, 4-chloroaniline, 4-bromoaniline or 4-aminobenzenesulfonamide (1 mmol) were added drop-wise with stirring. The reaction mixture was stirred in an ice bath for 2 h, the formed solid was filtered off, dried, and crystallized to give 0.22 g (74%) **8a**, 0.25 g (76%) **8b**, 0.28 g (75%) **8c**, and 0.24 g (62%) **8d**.

Methyl 2-(2-phenylhydrazono)-2-(thiazol-2-ylcarbamoyl)-acetate (**8a**, $C_{13}H_{12}N_4O_3S$)

Mp 147–149°C (*Et*OH/H_2O); IR (film): $\bar{\nu} = 3244–3235$ (NH), 1735 (C=O, ester), 1682 (C=O, amide), 1657 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.36$ (s, CH_3), 7.12, 7.19 (2d, thiazole-H), 7.28–7.59 (m, *Ar*–H), 12.24 (s, NH, exchangeable with D_2O), 13.28 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 303 [M^+-1, 2] and at 123 [100, base peak].

Methyl 2-(2-(p-chlorophenyl)hydrazono)-2-(thiazol-2-yl-carbamoyl)acetate (**8b**, $C_{13}H_{11}ClN_4O_3S$)

Mp 158–160°C (*Et*OH/H_2O); IR (film): $\bar{\nu} = 3256–3245$ (NH), 1733 (C=O, ester), 1684 (C=O, amide), 1654 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.34$ (s, CH_3), 7.11, 7.23 (2d, thiazole-H), 7.51 (d, *Ar*–H), 7.69 (d, *Ar*–H), 11.92 (s, NH, exchangeable with D_2O), 12.73 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 338 [M^+, 68] and at 307 [100, base peak].

Methyl 2-(2-(p-bromophenyl)hydrazono)-2-(thiazol-2-yl-carbamoyl)acetate (**8c**, $C_{13}H_{11}BrN_4O_3S$)

Mp 154–155°C (*Et*OH/H_2O); IR (film): $\bar{\nu} = 3262–3255$ (NH), 1736 (C=O, ester), 1680 (C=O, amide), 1652 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.37$ (s, CH_3), 7.14, 7.25 (2d, thiazole-H), 7.52 (d, *Ar*–H), 7.71 (d, *Ar*–H), 11.91 (s, NH, exchangeable with D_2O), 12.70 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 384 [$M^+ + 1$, 25] and at 127 [100, base peak].

Methyl 2-(2-(p-sulphonamidophenyl)hydrazono)-2-(thiazol-2-ylcarbamoyl)acetate (**8d**, $C_{13}H_{13}N_5O_5S_2$)

Mp 166–167°C (*Et*OH/H_2O); IR (film): $\bar{\nu} = 3366–3210$ (NH, NH_2), 1734 (C=O, ester), 1683 (C=O, amide), 1654 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.35$ (s, CH_3), 7.13, 7.26 (2d, thiazole-H), 7.58 (d, *Ar*–H), 7.78 (d, *Ar*–H), 11.96 (s, NH, exchangeable with D_2O), 12.71 (s, NH, exchangeable with D_2O); MS (EI, 70 eV): m/z (%) = 386 [$M^+ + 3$, 4] and at 309 [100, base peak].

2-(2-(p-Bromophenyl)hydrazono)-N^1-(1H-benzo[d]imidazol-2-yl)-N^3-(thiazol-2-yl)malonamide (**9**, $C_{19}H_{14}BrN_7O_2S$)

A mixture of 0.38 g **8c** (1 mmol) and 0.133 g 2-aminobenzimidazole (1 mmol) in 20 cm^3 absolute ethanol in the presence of 0.03 g sodium ethoxide (1.5 mmol) was refluxed for 2 h. The reaction mixture was cooled, then poured into ice-water, and acidified with diluted HCl to *pH* ~6. The formed solid was filtered off, dried, and crystallized to give 0.26 g (55%) **9**. Mp 261–263°C (*Et*OH); IR (film): $\bar{\nu} = 3244–3188$ (NH), 1678, 1658 (C=O), 1654 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.99$ (s, NH-imidazole, exchangeable with D_2O), 7.22, 7.25 (2d, thiazole-H), 7.38–7.58 (m, *Ar*–H), 11.40 (s, NH, exchangeable with D_2O), 12.31 (s, NH, exchangeable with D_2O), 12.73 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 484 [M^+, 5] and at 140 [100, base peak].

3-Hydroxy-2-{[4-(4,5,6,7-tetrachloro-1,3-dioxo-1,3-dihydro-isoindole-2-sulfonyl)phenyl]hydrazono}-3-(thiazol-2-ylamino)propionic acid methyl ester (**10**, $C_{21}H_{11}Cl_4N_5O_7S_2$)

A mixture of 0.38 g **8d** (1 mmol) and 0.29 g of 3,4,5,6-tetrachlorophthalic anhydride (1 mmol) in 50 cm^3 glacial acetic acid was heated under reflux for 6 h. The reaction mixture was evaporated under reduced pressure, the obtained residue was solidified with ether, filtered off, and crystallized to yield 0.5 g (77%) **10**. Mp 246–248°C (*Ac*OH/H_2O); IR (film): $\bar{\nu} = 3266–3238$ (NH), 1785 (2C=O), 1733 (C=O, ester), 1675 (C=O, amide), 1654 (C=N), 1330 (S=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.36$ (s, CH_3), 7.11, 7.24 (2d, thiazole-H), 7.55 (d, *Ar*–H), 7.85 (d, *Ar*–H), 11.85 (s, NH, exchangeable with D_2O), 12.22 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 651 [M^+, 15] and at 83 [100, base peak].

2,5-Dihydro-5-oxo-1-aryl-N-(thiazol-2-yl)-1H-1,2,3-triazole-4-carboxamides ***11a–11c***

A mixture of **8a–8c** (2 mmol) and 0.8 cm^3 hydrazine hydrate (16 mmol) in 30 cm^3 absolute ethanol was refluxed for 3 h. The obtained solid was filtered off, dried, and crystallized from *DMF*/*Ela* to afford 0.45 g (78%) **11a**, 0.52 g (81%) **11b**, and 0.58 g (79%) **11c**.

2,5-Dihydro-5-oxo-1-phenyl-N-(thiazol-2-yl)-1H-1,2,3-triazole-4-carboxamide (**11a**, $C_{12}H_9N_5O_2S$)

Mp 200–201°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 3273–3266$ (NH), 1678, 1674 (2C=O), 1657 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 7.23$, 7.28 (2d, thiazole-H), 7.24–7.56 (m, *Ar*–H), 13.50 (s, NH, exchangeable with D_2O), 13.88 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 287 [M^+, 4] and at 273 [100, base peak].

1-(4-Chlorophenyl)-2,5-dihydro-5-oxo-N-(thiazol-2-yl)-1H-1,2,3-triazole-4-carboxamide (**11b**, $C_{12}H_8ClN_5O_2S$)

Mp 216–217°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 3278–3255$ (NH), 1672, 1667 (2C=O), 1660 (C=N) cm^{-1}; ^1H NMR

(*DMSO*-d_6): $\delta = 7.24, 7.30$ (2d, thiazole-H), 7.26–7.68 (m, *Ar*–H), 13.42 (s, NH, exchangeable with D_2O), 13.84 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 322 [$M^+ + 1$, 100, as base peak].

1-(4-Bromophenyl)-2,5-dihydro-5-oxo-N-(thiazol-2-yl)-1H-1,2,3-triazole-4-carboxamide (**11c**, $C_{12}H_8BrN_5O_2S$)
Mp 227–228°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 3286$–3249 (NH), 1668, 1662 (2C=O), 1655 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 7.26$, 7.30 (2d, thiazole-H), 7.35–7.72 (m, *Ar*–H), 13.15 (s, NH, exchangeable with D_2O), 13.76 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 366 [M^+, 4] and at 140 [100, base peak].

N′-(2-Thiazolyl)-N³-(4-substituted benzylideneimino)-malonamides ***12a–12c***
A mixture of 0.2 g **2** (1 mmol) and appropriate aromatic aldehydes, namely, 4-chlorobenzaldehyde, 4-fluorobenzaldehyde or 4-nitrobenzaldehyde (1 mmol) in 30 cm^3 absolute ethanol in the presence of few drops of glacial acetic acid was refluxed for 1 h. The solid formed was filtered off, dried, and crystallized to give 0.2 g (64%) **12a**, 0.18 g (61%) **12b**, and 0.26 g (83%) **12c**.

N′-(2-Thiazolyl)-N³-(4-chlorobenzylideneimino)malonamide (**12a**, $C_{13}H_{11}ClN_4O_2S$)
Mp 231–232°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 3271$–3180 (NH), 1682, 1671 (2C=O), 1657 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.85$ (s, CH_2), 7.20, 7.32 (2d, thiazole-H), 7.45, 7.68 (2d, *Ar*–H), 11.30 (s, N=CH), 12.00 (s, NH, exchangeable with D_2O), 12.34 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 322 [M^+, 100, base peak].

N′-(2-Thiazolyl)-N³-(4-fluorobenzylideneimino)malonamide (**12b**, $C_{13}H_{11}FN_4O_2S$)
Mp 210–212°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 3282$–3188 (NH), 1680, 1674 (2C=O), 1663 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.82$ (s, CH_2), 7.21, 7.27 (2d, thiazole-H), 7.43, 7.65 (2d, *Ar*–H), 11.24 (s, N=CH), 12.05 (s, NH, exchangeable with D_2O), 12.32 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 305 [M^+-1, 3] and at 57 [100, base peak].

N′-(2-Thiazolyl)-N³-(4-nitrobenzylideneimino)malonamide (**12c**, $C_{13}H_{11}N_5O_4S$)
Mp 241–243°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 3278$–3192 (NH), 1684, 1672 (2C=O), 1659 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.78$ (s, CH_2), 7.23, 7.28 (2d, thiazole-H), 7.40, 7.64 (2d, *Ar*–H), 11.28 (s, N=CH), 12.10 (s, NH, exchangeable with D_2O), 12.35 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 333 [M^+, 3] and at 140 [100, base peak].

Synthesis of pyridyl imide ***13*** *and naphthyl imide* ***14***
Using the same procedures for the synthesis of **10** using hydrazide **2** (1 mmol) as starting material with 2,3-pyridinedicarboxylic anhydride or 1,8-naphthalenedicarboxylic anhydride (1 mmol) as reagents.

N-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-yl)-N′-thiazol-2-yl-malonamide (**13**, $C_{13}H_9N_5O_4S$)
Yield 71%; Mp >300°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 3262$–3170 (NH), 1765 (2C=O), 1678, 1666 (2C=O), 1658 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.78$ (s, CH_2), 7.22, 7.24 (2d, thiazole-H), 8.27 (t, pyridine-H), 8.77 (d, pyridine-H), 9.10 (d, pyridine-H), 11.53 (s, NH, exchangeable with D_2O), 12.21 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 331 [M^+, 14] and at 238 [100, base peak].

N-(1,3-Dioxo-1H,3H-benzo[de]isoquinolin-2-yl)-N′-thiazol-2-yl-malonamide (**14**, $C_{18}H_{12}N_4O_4S$)
Yield 76%; Mp >300°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 3379$–3197 (NH), 1762 (2C=O), 1685, 1674 (2C=O), 1656 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.76$ (s, CH_2), 7.24, 7.27 (2d, thiazole-H), 7.42–7.68 (m, *Ar*–H), 11.48 (s, NH, exchangeable with D_2O), 12.18 (s, NH) ppm; MS (EI, 70 eV): m/z (%) = 379 [M^+-1, 12] and at 57 [100, base peak].

Pharmacological assay

Anti-hypertensive α-blocking activity [27–34]
Noradrenalin and other sympathomimetic drugs increase vascular smooth muscle tone by stimulation of α-adrenergic receptors. Contractions can be antigonized by α-adrenergic receptor blocking agents, such as phentol amine. 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°C 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 2×10^{-6} *M* for testing the contractions of the pulmonary artery and in concentrations of 2×10^{-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

phentol amine (1×10^{-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.

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