Synthesis and DPPH radical-scavenging activity of some new 5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazole derivatives

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Background and objectives
Heterocyclic systems with thiadiazole nucleus show a wide spectrum of biological activities such as antioxidant, analgesic, antitumor, and anti-inflammatory activities. The aim of this study is to describe the synthesis of some new 5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazole derivatives and to evaluate their antioxidant activity using 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging activity.
Materials and methods
A one-pot reaction of *N*-substituted-1*H*-indol-3-carboxaldehyde **1a**,**b** with thioglycolic acid and thiosemicarbazide in concentrated sulfuric acid yielded novel 2-amino-5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazoles **2a**,**b**. The reaction of **2a**,**b** with some benzenesulfonyl chlorides and/or benzoyl chlorides yielded sulfonamides **3a**,**b** and **4a**,**b** and benzamide **5a**,**b** and **6a**,**b** derivatives, respectively, whereas, the reaction of **2a**,**b** with chloroacetyl chloride yielded chloroacetamide derivatives **7a**,**b**, which, on cyclization with potassium thiocyanate, yielded thiazolidinone derivatives **8a**,**b**. The reaction of **2a**,**b** with sodium azide yielded tetrazole derivatives **9a**,**b**. However, the reaction of **2a**,**b** with benzaldehyde yielded Schiff bases **10a**,**b**, which cyclized with chloroacetyl chloride and/or phenacyl bromide to yield azetidinone derivatives **11a**,**b** and **12a**,**b**, respectively. However, the reaction of **10a**,**b** with sodium cyanide, followed by acid hydrolysis yielded the α-amino acid derivatives **14a**,**b**. Diazotization of **2a**,**b** yielded diazonium salt **A**, which, on coupling with sodium azide, yielded the azido derivatives **15a**,**b**. Cyclization of **15a**,**b** with ethylacetoacetate yielded tetrazole derivatives **16a**,**b**, whereas the coupling reaction of **A** with malononitrile yielded dicyano derivatives **17a**,**b**, which, on cyclization with hydrazine hydrate, yielded 3,5-diaminopyrazole derivatives **18a**,**b**. The newly synthesized compounds were screened for their antioxidant activity using 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging activity.
Results and conclusion
4-{5-[(1*H*-Indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazol-2-yl]diazo}-1*H*-pyrazole-3,5-diamine (**18a**) was highly active with radical-scavenging activity (IC_{50} of 69.14 μg/ml) compared with ascorbic acid (IC_{50} of 6.50 μg/ml).

Keywords:
DPPH radical-scavenging activity, indole-3-carboxaldehyde, synthesis, tetrazole, thiazolo[4,3-*b*]-1,3,4-thiadiazole

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Introduction

Thiadiazole is a versatile moiety that shows a wide variety of biological activities, viz, antioxidant, analgesic, anticonvulsant, anti-hepatitis B, antitubercular, antitumor, antidepressant, anti-inflammatory, antimicrobial, and anti-*Helicobacter pylori* [1–6]. Besides these, fused 5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazoles have been prepared and become a substance among 1,3,4-thiadiazoles that has drawn the attention of researchers [7–9]. Moreover, indole, which is the potent basic pharmacodynamic nucleus, has been reported to have a wide variety of biological properties, viz, antioxidant [10], anti-inflammatory [11,12], anti-cancer [13], and antimicrobial activities [12,14]. On the basis of the above observations and as a part of our continuous work on the preparation of new poly-heterocycles with pharmaceutical values [11–16], the present study focuses on the synthesis of some new *N*-substituted-3-indolyl-5*H*-thiazolor-1,3,4-thiadiazoles for the evaluation of their antioxidant activity using 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging activity starting from *N*-substituted indole-3-carboxaldehyde.

Materials and methods

Chemistry

Melting points were determined in open capillary tubes on an Electrothermal 9100 digital melting point apparatus (Electrothermal Engineering Ltd, Serial No. 8694, Rochford,

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United Kingdom) and were uncorrected. Elemental analyses were carried out on a Perkin-Elmer 2400 analyzer (940 Winter Street, Waltham, Massachusetts, USA) and were found to be within ± 0.4% of the theoretical values (Table 1). IR spectra were recorded by Perkin-Elmer 1600 Fourier transform infrared spectroscopy against KBr discs. The ^{1}H NMR spectra were measured using a mass spectrometer (JEOL Ltd. 1-2, Musashino 3-chome Akishima, Tokyo, Japan) 500 MHz in DMSO-d_6, and chemical shifts were recorded in δ ppm relative to TMS as an internal standard. Mass spectra (EI) were run at 70 eV using a JEOL-JMS-AX500 mass spectrometer (Japan). All reagents and solvents were of commercial grade. 1*H*-indole-3-carboxaldehyde (**1a**) [17] and *N*-benzyl-1*H*-indole-3-carboxaldehyde (**1b**) have been prepared as reported [18].

*2-Amino-5-(1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazole (**2a**) and 2-amino-5-(N-benzyl-1H-indol-3-yl)-5H-thiazolor-1,3,4-thiadiazole (**2b**)*

N-substituted-1*H*-indole-3-carboxaldehydes **1a** or **1b** (0.02 mol) and thioglycolic acid (1.84 ml, 0.02 mol) were mixed for 10–15 min. To the reaction mixture, thiosemicarbazide (1.82 g, 0.02 mol) was added with stirring and then concentrated sulfuric acid (10 ml) was added in portions upon cooling. The reaction mixture was homogenized and left for 24 h in a deep freezer (–20°C). The reaction mixture was then treated with crushed ice (50 g) and the suspension obtained was neutralized with an aqueous sodium hydroxide solution (40%) to pH ≃ 7–8. The precipitate that formed was filtered off, air dried, and crystallized from aqueous dioxane (Scheme 1 and Table 1).

*N-[5-(1H-Indol-3-yl1)-5H-thiazolor-1,3,4-thiadiazol-2-yl] benzenesulfonamide (**3a**), N-[5-(N-benzyl-1H-indol-3-yl)-5H-thiazolo [4,3-b]-1,3,4-thiadiazol-2-yl]benzenesulfonamide (3b), 4-chloro-N-[5-(1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl]benzene-sulfonamide (**4a**), and 4-chloro-N-[5-(N-benzyl-1H-indol-3-yl)-5H-thiazolokr-1,3,4-thiadiazol-2-yl]benzenesulfonamide (**4b**)*

A mixture of compounds **2a** or **2b** (0.001 mol) and benzenesulfonyl chloride, or 4-chlorobenzenesulfonyl chloride (0.001 mol) in dry dioxane (10 ml) containing a few drops of triethylamine was heated at reflux for 6 h. After cooling, the reaction mixture was poured onto cold water (10 ml). The solid that formed was filtered off, air dried, and crystallized from dioxane (Scheme 1 and Table 1).

*N-[5-(1H-Indol-3-yl)-5H-thiazolor-1,3,4-thiadiazol-2-yl] benzamide (**5a**), N-[5-(N-benzyl-1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl]benzamide (**5b**), 2-chloro-N-[5-(1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl]benzamide (**6a**), and 2-chloro-N-[5-(N-benzyl-1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl]benzamide (**6b**)*

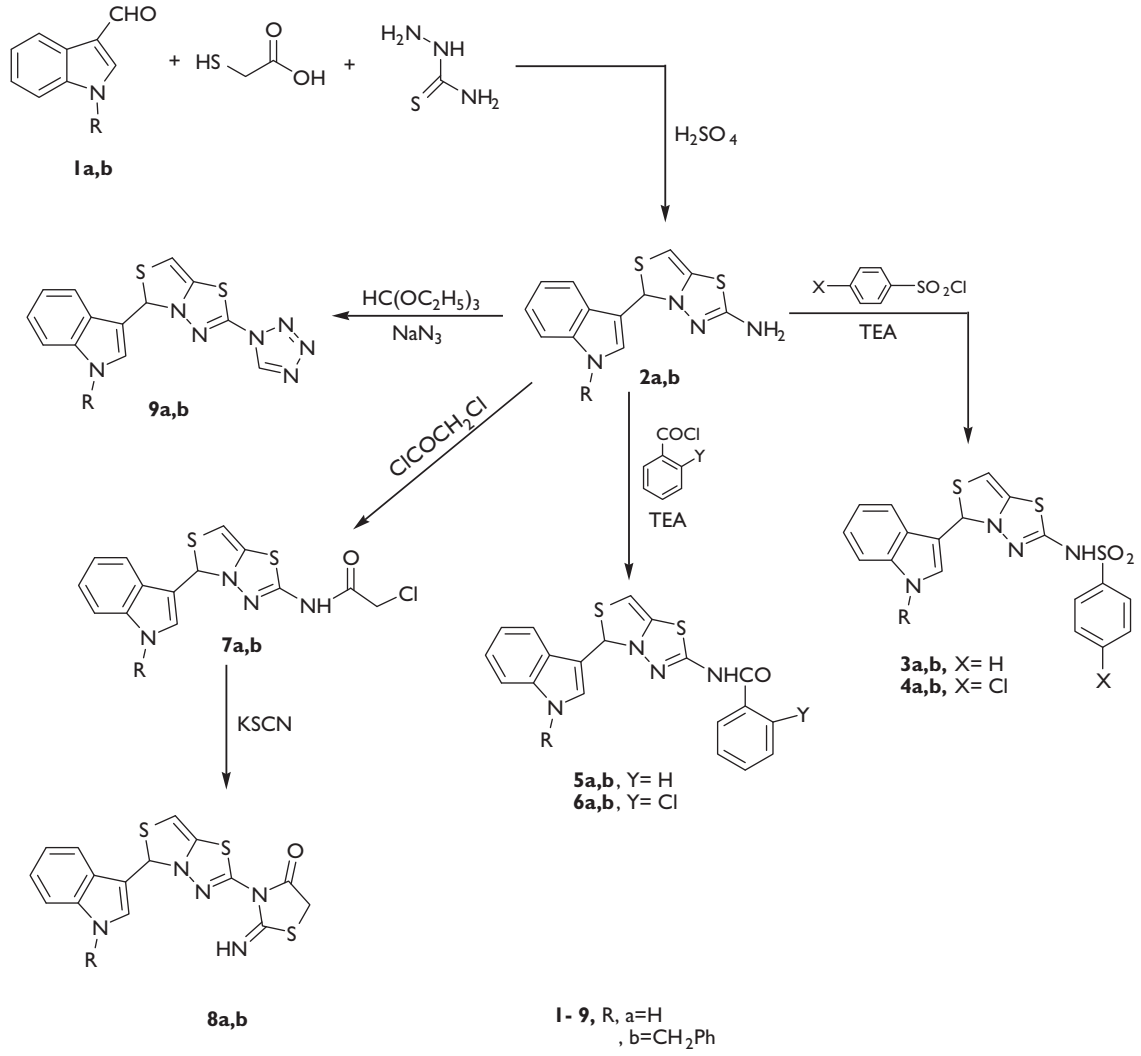
A mixture of compounds **2a** or **2b** (0.001 mol) and benzoyl chloride or 2-chlorobenzoyl chloride (0.001 mol) in dry dioxane (10 ml) containing a few drops of triethylamine was heated at reflux for 8 h. After cooling,

Table 1 Physical and analytical data of the newly synthesized compounds

Compound number	Formula (M_W)	MP (°C)	Yield (%)	Analysis (%; calculated/found)		
				C	H	N
2a	$C_{12}H_{10}N_4S_2$ (274.36)	146–148	94	52.53/52.33	3.67/3.58	20.42/20.31
2b	$C_{19}H_{16}N_4S_2$ (364.49)	86–88	88	62.61/62.44	4.42/4.26	15.37/15.20
3a	$C_{18}H_{14}N_4O_2S_3$ (414.52)	111–113	70	52.15/52.01	3.40/3.27	13.52/13.41
3b	$C_{25}H_{20}N_4O_2S_3$ (504.65)	76–78	65	59.50/59.36	3.99/3.81	11.10/10.99
4a	$C_{18}H_{13}ClN_4O_2S_3$ (448.97)	212–214	83	48.15/48.01	2.92/2.76	12.48/12.32
4b	$C_{25}H_{19}ClN_4O_2S_3$ (539.09)	187–189	76	55.70/55.54	3.55/3.41	10.39/10.22
5a	$C_{19}H_{14}N_4OS_2$ (378.47)	165–168	84	60.30/60.16	3.73/3.61	14.80/14.66
5b	$C_{26}H_{20}N_4OS_2$ (468.59)	136–138	77	66.64/66.48	4.30/4.21	11.96/11.77
6a	$C_{19}H_{13}ClN_4OS_2$ (412.92)	300–302	84	55.27/55.04	3.17/3.06	13.57/13.41
6b	$C_{26}H_{19}ClN_4OS_2$ (503.04)	300	81	62.08/62.16	3.81/3.66	11.14/11.02
7a	$C_{14}H_{11}ClN_4OS_2$ (350.85)	135–137	91	47.93/47.98	3.16/3.20	15.97/15.99
7b	$C_{21}H_{17}ClN_4OS_2$ (440.97)	127–129	95	57.20/57.28	3.89/3.76	12.71/12.68
8a	$C_{15}H_{11}N_5OS_3$ (373.48)	175–177	90	48.24/48.11	2.97/3.00	18.75/18.80
8b	$C_{22}H_{17}N_5OS_3$ (463.60)	162–164	91	57.00/57.23	3.70/3.55	15.11/15.22
9a	$C_{13}H_9N_7S_2$ (327.39)	252–254	81	47.69/47.73	2.77/2.64	29.95/29.80
9b	$C_{20}H_{15}N_7S_2$ (417.51)	175–177	82	57.53/57.40	3.62/3.58	23.48/23.40
10a	$C_{19}H_{14}N_4S_2$ (362.47)	170–172	86	62.96/62.76	3.89/3.99	15.46/15.54
10b	$C_{26}H_{20}N_4S_2$ (452.59)	158–160	83	69.00/69.11	4.45/4.33	12.38/12.55
11a	$C_{21}H_{15}ClN_4OS_2$(438.95)	100–102	78	57.46/57.66	3.44/3.68	12.76/12.56
11b	$C_{28}H_{21}ClN_4OS_2$ (529.08)	70–72	65	63.56/63.44	4.00/4.28	10.59/10.72
12a	$C_{27}H_{20}N_4OS_2$ (480.6)	159–161	75	67.48/67.50	4.19/4.32	11.66/11.45
12b	$C_{34}H_{26}N_4OS_2$ (570.73)	172–174	71	71.55/71.60	4.56/4.44	9.82/9.78
13a	$C_{20}H_{15}N_5S_2$ (389.50)	234–236	79	61.67/61.62	3.88/3.90	17.98/17.93
13b	$C_{27}H_{21}N_5S_2$ (479.62)	106–108	80	67.61/67.69	4.41/4.46	14.60/14.58
14a	$C_{20}H_{16}N_4O_2S_2$ (408.5)	196–208	76	58.80/58.77	3.95/3.90	13.72/13.69
14b	$C_{27}H_{22}N_4O_2S_2$ (498.62)	130	70	65.04/65.00	4.45/4.35	11.24/11.44
15a	$C_{12}H_8N_6S_2$ (300.36)	86–88	40	–	–	–
15b	$C_{19}H_{14}N_6S_2$ (390.48)	61–3	30	–	–	–
16a	$C_{16}H_{12}N_6O_2S_2$ (384.44)	126–128	46	49.99/49.75	3.15/3.00	21.86/21.66
16b	$C_{23}H_{18}N_6O_2S_2$ (474.56)	92–94	36	58.21/58.00	3.82/3.78	17.71/17.69
17a	$C_{15}H_9N_7S_2$ (351.41)	144–146	67	51.27/51.33	2.56/2.35	27.90/27.93
17b	$C_{22}H_{15}N_7S_2$ (441.53)	123–125	55	59.85/59.92	3.42/3.33	22.21/22.30
18a	$C_{15}H_{13}N_9S_2$ (383.45)	201–202	83	46.98/47.01	3.42/3.37	32.87/32.66
18b	$C_{22}H_{19}N_9S_2$ (473.58)	130–132	85	55.80/55.71	4.04/4.15	26.61/26.45

Compounds **15a**,**b** was decomposed slowly during the preparation of the samples analyzed.

Scheme 1



Synthesis of compounds **1a**,**b** to **9a**,**b**.

the reaction mixture was poured onto cold water (20 ml). The solid that formed was filtered off, air dried, and crystallized from dioxane (Scheme 1 and Table 1).

*N-[5-(1H-Indol-3-yl)-5H-thiazolor-1,3,4-thiadiazol-2-yl]-2-chloroacetamide (**7a**) and N-[5-(N-benzyl-1H-indol-3-yl)-5H-thiazolo [4,3-b]-1,3,4-thiadiazol-2-yl]-2-chloroacetamide (**7b**)*

To a solution of compounds **2a** or **2b** (0.02 mol) in dry benzene (60 ml), a solution of chloroacetyl chloride (5 ml, 0.04 mol) in dry benzene (20 ml) was added dropwise under vigorous stirring at 0–5°C. After complete addition, the reaction mixture was heated at reflux for 3 h. The solvent was evaporated *in vacuo* and the solid that formed was washed with sodium hydrogen carbonate (20 ml, 5%) and then with water, air dried, and crystallized from chloroform (Scheme 1 and Table 1).

*3-[5-(1H-Indol-3-yl)-5H-thiazolor-1,3,4-thiadiazol-2-yl]-2-iminothiazolidin-4-one (**8a**) and 3-[5-(N-benzyl-1H-indol-3-yl)-5H-thiazolor-1,3,4-thiadiazol-2-yl]-2-iminothiazolidin-4-one (**8b**)*

A mixture of compounds **7a** or **7b** (0.003 mol) and potassium thiocyanate (0.58 g, 0.006 mol) in dry acetone (10 ml) was heated at reflux for 3 h. The solid that formed was filtered off, air dried and crystallized from chloroform (Scheme 1 and Table 1).

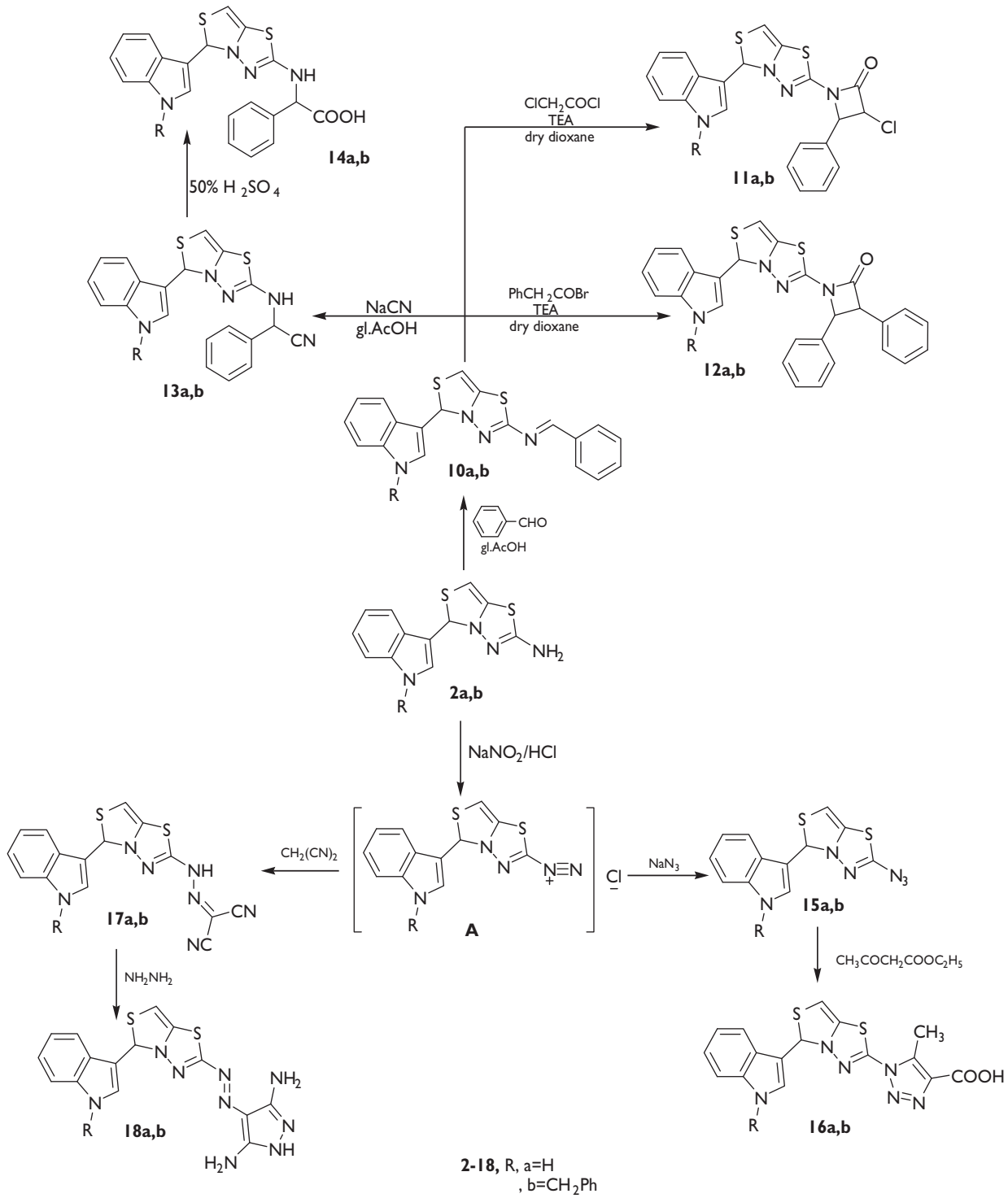
*5-(1H-Indol-3-yl)-2-(1H-tetrazol-1-yl)-5H-thiazolor-1,3,4-thiadiazole (**9a**) and 5-(N-benzyl-1H-indol-3-yl)-2-(1H-tetrazol-1-yl)-5H-thiazolor-1,3,4-thiadiazole (**9b**)*

A mixture of compounds **2a** or **2b** (0.001 mol), triethyl orthoformate (0.15 ml, 0.001 mol), and sodium azide (0.065 g, 0.001 mol) in glacial acetic acid (10 ml) was stirred under reflux for 2 h. After cooling, the reaction mixture was neutralized with concentrated hydrochloric acid (10 ml). The solid that formed was filtered off, washed with water, air dried, and crystallized from absolute ethanol (Scheme 1 and Table 1).

*N-Benzylidene-(5-(1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl)-2-amine (**10a**) and N-benzylidene-[(5-(N-benzyl-1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl]-2-amine (**10b**)*

A mixture of compounds **2a** or **2b** (0.01 mol) and benzaldehyde (1.06 g, 0.01 mol) in glacial acetic acid

Scheme 2



Synthesis of compounds **10a**,**b** to **18a**,**b**.

(20 ml) was heated at reflux for 6 and 8 h. After cooling, the reaction mixture was poured onto ice water (50 ml). The solid that formed was filtered off, air dried, and crystallized from benzene (Scheme 2 and Table 1).

*1-[5-(1H-Indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl]-3-chloro-4-phenylazetidin-2-one (**11a**), 1-[5-(N-benzyl-1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl]-3-chloro-4-phenylazetidin-2-one (**11b**), 1-(5-(1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl)-3,4-diphenylazetidin-2-one (**12a**), and 1-[5-(N-benzyl-1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl]-3,4-diphenylazetidin-2-one (**12b**)*

To a solution of Schiff bases **10a** or **10b** (0.01 mol) in dry dioxane (5 ml), a solution of chloroacetyl chloride and/or phenacyl bromide (0.01 mol) in dry dioxane (5 ml) and triethylamine (0.59 ml, 0.01 mol) was added. The reaction mixture was heated at reflux for 12–14 h. The reaction mixture was filtered off while hot and the

solvent was removed *in vacuo*. The residue solid was treated with water and filtered, air dried, and crystallized from absolute ethanol (Scheme 2 and Table 1).

*2-[5-(1H-Indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl amino]phenylacetonitrile (**13a**) and 2-[5-(N-benzyl-1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl amino]phenylacetonitrile (**13b**)*

To a solution of Schiff bases **10a** or **10b** (0.01 mol) in glacial acetic acid (20 ml) sodium cyanide (0.49 g, 0.01 mol) was added and the reaction mixture was heated at reflux for 6 h. After cooling, the reaction mixture was poured onto cold water (10 ml) and the solid that formed was filtered off, washed with water, air dried, and crystallized from acetic acid–water (Scheme 2 and Table 1).

*2-[5-(1H-Indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl amino] phenyl acetic acid (**14a**) and 2-[5-(N-benzyl-1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl amino]phenyl acetic acid (**14b**)*

A solution of compounds **13a** or **13e** (0.01 mol) in sulfuric acid (30 ml, 50%) was heated at reflux for 10 h. After cooling, the dark reaction mixture was poured onto cold water (20 ml) and then neutralized with ammonia solution (25%). The precipitate that formed was filtered off, washed with water, air dried, and crystallized from aqueous acetic acid (Scheme 2 and Table 1).

*2-Azido-5-(1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazole (**15a**) and 2-azido-5-(N-benzyl-1H-indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazole (**15b**)*

To a cold solution of compounds **2a** or **2b** (0.02 mol) in a mixture of concentrated hydrochloric acid (5 ml) and ice water (5 ml), a cold aqueous solution of sodium nitrite (1.73 g, 0.025 mol) in ice water (5 ml) was added dropwise under stirring at 0–5°C. After 10 min, the reaction mixture was decanted. To the decanted solution of the diazonium salt thus formed (**A**), sodium azide (1.3 g, 0.02 mol) in water (5 ml) was added dropwise. The reaction mixture was left for 15 min at room temperature and the azide was extracted by chloroform (3–10 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue was used without subsequent purification, and used in the reaction immediately after its formation because of its instability (Scheme 2 and Table 1).

*1-[5-(1H-Indol-3-yl)-5H-thiazolor-1,3,4-thiadiazol-2-yl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (**16a**) and 1-[5-(N-benzyl-1H-indol-3-yl)-5H-thiazolor-1,3,4-thiadiazol-2-yl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (**16b**)*

To a solution of sodium (0.23 g, 0.01 mol) in absolute methanol (20 ml) ethylacetoacetate (1.34 g, 0.01 mol) and compounds **15a** or **15b** (0.01 mol) were added dropwise under cooling in an ice bath. The reaction mixture was kept in an ice water bath for 30 min and then gradually heated under reflux for 1 h. After cooling, the reaction mixture was neutralized by diluted hydrochloric acid (1 : 1). The solid that formed was filtered off, washed with water, air dried, and crystallized from methanol (Scheme 2 and Table 1).

*2-{5-[(1H-Indol-3-yl)-5H-thiazolo[4,3-b]-1,3,4-thiadiazol-2-yl] hydrazono}malononitrile (**17a**) and 2-{5-[(N-benzyl-1H-indol-3-yl)-5H-thiazolor-1,3,4-thiadiazol-2-yl]hydrazono}-malononitrile (**17b**)*

To a cold solution of compounds **2a** or **2b** (0.02 mol) in a mixture of concentrated hydrochloric acid (5 ml) and ice water (5 ml), a cold aqueous solution of sodium nitrite (1.73 g, 0.025 mol) in ice water (5 ml) was added dropwise under stirring at 0–5°C. After 10 min, the reaction mixture was decanted. To the decanted solution of the diazonium salt thus formed (**A**), a cold solution of malononitrile (1.3 g, 0.02 mol) and sodium acetate trihydrate (5.4 g, 0.04 mol) in ethanol (10 ml) was added under stirring at 0–5°C. The stirring was continued for an additional 3 h at 0–5°C, and then left overnight in the refrigerator. The reaction mixture was poured onto water (250 ml) and the solid that formed was filtered off, air dried, and crystallized from absolute ethanol (Scheme 2 and Table 1).

*4-{5-[(1H-Indol-3-yl)-5H-thiazolor-1,3,4-thiadiazol-2-yl]diazo}-1H-pyrazole-3,5-diamine (**18a**) and 4-{5-[(N-benzyl-1H-indol-3-yl)-5H-thiazolor-1,3,4-thiadiazol-2-yl]diazo}-1H-pyrazole-3,5-diamine (**18b**)*

A mixture of compounds **17a** or **17b** (0.01 mol) and hydrazine hydrate (0.75 ml, 0.015 mol) in absolute ethanol (20 ml) was heated at reflux for 6 h. The solvent was evaporated *in vacuo* to half of its volume and the solid that formed was filtered off, washed with water, air dried, and crystallized from absolute ethanol (Scheme 2 and Table 1).

Biological assay

DPPH radical-scavenging activity

The antioxidant activity of the test compounds was measured in terms of hydrogen-donating or radical-scavenging ability using the stable radical 2,2′-diphenyl-1-picrylhydrazyl (DPPH) (Sigma Chemical Co., Steinheim, Germany) [19]. A volume of 50 µl of a DMSO stock solution of tested compounds at four different concentrations (50, 100, 200, and 300 µg/ml) was added to 2 ml of 6×10^{-5} mol/l dimethylsulfoxide solution of DPPH (2.3659 mg from DPPH/100 ml DMSO). The mixtures were shacked in a vortex (2500 rpm) for 1 min and then placed in a dark room. Ascorbic acid (Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany) was used as a reference. The decrease in absorbance at 517 nm was determined using a JENWAY 6315 spectrophotometer (Keison Products, Chelmsford, England) after 1 h for all samples. Dimethylsulfoxide was used to zero the spectrophotometer. The absorbance of the radical without a sample was used as a negative control. The amount of sample necessary to decrease the absorbance of DPPH (IC_{50}) by 50% was calculated graphically. The inhibition percentage of the DPPH radical (scavenging activity) was calculated according to the following formula:

$$\%I = [(A_B - A_s)/A_B] \times 100,$$

Table 2 Spectral characterization of the newly synthesized compounds

Compound number	IR (γ_{max}/cm)	^{1}H NMR (δ, ppm)	Mass (*m/z*, %)
2a	3410 (NH_2), 3169 (NH), 1635 (C=N), 1575 (C=C)	12.11 (s, 1H, NH), 11.11 (s, 1H, thiazolyl 5-H), 9.90 (s, 1H, thiazolyl 7-H), 8.25 (s, 1H, indolyl 2-H), 8.06 (d, 1H, indolyl 7-H), 7.48 (d, 1H, indolyl 4-H), 7.23-7.16 (m, 2H, indolyl 6-H and 5-H), 3.73 (s, 2H, NH_2)	274 (M^+, 1), 256 (16), 192 (5), 144 (34), 128 (14), 116 (16), 83 (47), 18 (100)
2b	3336 (NH_2), 1628 (C=N), 1543 (C=C)	12.10 (s, 1H, thiazolyl 5-H), 9.93 (s, 1H, thiazolyl 7-H), 8.25 (s, 1H, indolyl 2-H), 8.27-7.18 (m, 9H, Ar-H), 5.57 (s, 2H, CH_2-N), 3.85 (s, 2H, NH_2)	–
3a	3156 and 3111 (NH), 1636 (C=N), 1602 (C=C), 1354 and 1163 (SO_2-N)	12.14 (s, 1H, thiazolyl 5-H), 9.97 (s, 1H, thiazolyl 7-H), 8.95 (s, 1H, NH), 8.31 (s, 1H, indolyl 2-H), 8.11-7.20 (m, 9H, Ar-H), 5.08 (s, 1H, NH)	–
3b	3125 (NH), 1631 (C=N), 1574 (C=C), 1363 and 1148 (SO_2-N)	–	504 (M^+, 21), 430 (12), 353 (10), 91 (100)
4a	3232 and 3126 (NH), 1624 (C=N), 1575 (C=C), 1368 and 1136 (SO_2-N), 745 (C-Cl)	–	448/450 ($M^+/M^+ + 2$, 33/11), 330 (2), 191 (20), 113 (37), 111 (100)
4b	3168 (NH), 1618 (C=N), 1610 (C=C), 1366 and 1134 (SO_2-N), 747 (C-Cl)	12.01 (s, 1H, thiazolyl 5-H), 9.92 (s, 1H, thiazolyl 7-H), 8.69 (s, 1H, NH), 8.42 (s, 1H, indolyl 2-H), 8.21-7.18 (m, 13H, Ar-H), 5.51 (s, 2H, CH_2-N)	–
5a	3327 and 3120 (NH), 1695 (C=O), 1640 (C=N), 1585 (C=C)	11.93 (s, 1H, thiazolyl 5-H), 9.90 (s, 1H, thiazolyl 7-H), 9.59 (s, 1H, NH), 8.56 (s, 1H, indolyl 2-H), 8.32-7.37 (m, 9H, Ar-H), 4.18 (s, 1H, NH)	378 (M^+, 23), 350 (10), 274 (20), 258 (1), 105 (100)
5b	3154 (NH), 1710 (C=O), 1638 (C=N), 1563 (C=C)	12.24 (s, 1H, thiazolyl 5-H), 9.94 (s, 1H, thiazolyl 7-H), 8.26 (s, 1H, indolyl 2-H), 8.01-7.07 (m, 14H, Ar-H), 5.42 (s, 2H, CH_2-N), 3.75 (s, 1H, NH)	–
6a	3260 and 3112 (NH), 1688 (C=O), 1644 (C=N), 1585 (C=C), 775 (C-Cl)	12.12 (s, 1H, thiazolyl 5-H), 9.95 (s, 1H, thiazolyl 7-H), 8.68 (s, 1H, NH), 8.37 (s, 1H, indolyl 2-H), 7.87-7.05 (m, 8H, Ar-H), 3.96 (s, 1H, NH)	–
6b	3212 (NH), 1759 (C=O), 1643 (C=N), 1578 (C=C), 773 (C-Cl)	–	503/505 ($M^+/M^+ + 2$, 19/6), 391 (10), 113 (27), 111 (75), 91 (100)
7a	3240 and 3163 (NH), 1722 (C=O), 1618 (C=N), 1521 (C=C), 747 (C-Cl)	11.85 (s, 1H, thiazolyl 5-H), 9.91 (s, 1H, thiazolyl 7-H), 8.26 (s, 1H, indolyl 2-H), 7.94-7.26 (m, 4H, Ar-H), 6.76 (s, 1H, NH), 4.75 (s, 2H, CH_2), 4.11 (s, 1H, NH)	–
7b	3265 (NH), 1710 (C=O), 1588 (C=N), 1529 (C=C), 734 (C-Cl)	–	440/442 ($M^+/M^+ + 2$, 30/10), 349 (20), 318 (14), 91 (100)
8a	3186 and 3121 (NH), 1753 (C=O), 1616 (C=N), 1521 (C=C)	12.12 (s, 1H, thiazolyl 5-H), 9.93 (s, 1H, thiazolyl 7-H), 9.15 (s, 1H, NH), 8.29 (s, 1H, indolyl 2-H), 8.10-7.23 (m, 4H, Ar-H), 6.08 (s, 1H, NH), 4.13 (s, 2H, CH_2)	373 (M^+, 34), 345 (10), 317 (20), 142 (100), 117 (15)
8b	3265 (NH), 1725 (C=O), 1612 (C=N), 1522 (C=C)	12.15 (s, 1H, thiazolyl 5-H), 9.93 (s, 1H, thiazolyl 7-H), 8.72 (s, 1H, NH), 8.31 (s, 1H, indolyl 2-H), 8.26-7.36 (m, 9H, Ar-H), 5.21 (s, 2H, CH_2-N), 4.20 (s, 2H, CH_2)	–
9a	3160 (NH), 1643 (C=N), 1594 (C=C)	12.10 (s, 1H, thiazolyl 5-H), 9.92 (s, 1H, thiazolyl 7-H), 8.86 (s, 1H, tetrazolyl 5-H), 8.23 (s, 1H, indolyl 2-H), 7.76-7.24 (m, 4H, Ar-H), 6.90 (s, 1H, NH)	–
9b	1635 (C=N), 1572 (C=C)	11.65 (s, 1H, thiazolyl 5-H), 9.92 (s, 1H, thiazolyl 7-H), 8.82 (s, 1H, tetrazolyl 5-H), 8.42 (s, 1H, indolyl 2-H), 8.06-7.15 (m, 9H, Ar-H), 5.92 (s, 2H, CH_2-N)	417 (M^+, 17), 385 (2), 353 (21), 117 (12), 91 (100)
10a	3157 (NH), 1624 (C=N), 1565 (C=C)	12.03 (s, 1H, thiazolyl 5-H), 10.11 (s, 1H, thiazolyl 7-H), 9.90 (s, 1H, NH), 8.91 (s, 1H, CH=N), 8.50 (s, 1H, indolyl 2-H), 8.34-7.40 (m, 9H, Ar-H)	–
10b	1628 (C=N), 1571 (C=C)	12.11 (s, 1H, thiazolyl 5-H), 9.95 (s, 1H, thiazolyl 7-H), 9.01 (s, 1H, CH=N), 8.54 (s, 1H, indolyl 2-H), 8.23-7.11 (m, 14H, Ar-H), 5.66 (s, 2H, CH_2-N)	–
11a	3154 (NH), 1702 (C=O), 1633 (C=N), 1601 (C=C), 736 (C-Cl)	–	438/440 ($M^+/M^+ + 2$, 12/4), 410 (1), 402 (3), 326 (10), 77 (100)
11b	1724 (C=O), 1637 (C=N), 1563 (C=C), 745 (C-Cl)	12.22 (s, 1H, thiazolyl 5-H), 9.93 (s, 1H, thiazolyl 7-H), 8.33 (s, 1H, indolyl 2-H), 8.10-7.07 (m, 14H, Ar-H), 5.20 (d, 2H, CH), 5.07 (d, 2H, CH)	–
12a	3201 (NH), 1739 (C=O), 1640 (C=N), 1568 (C=C)	11.53 (s, 1H, thiazolyl 5-H), 9.81 (s, 1H, thiazolyl 7-H), 8.57 (s, 1H, NH), 8.25 (s, 1H, indolyl 2-H), 8.12-7.11 (m, 14H, Ar-H), 5.20 and 4.81 (2d, 2H, 2CH)	480 (M^+, 2), 328 (10), 115 (14), 103 (100)
12b	1737 (C=O), 1635 (C=N), 1570 (C=C)	12.23 (s, 1H, thiazolyl 5-H), 9.91 (s, 1H, thiazolyl 7-H), 8.65 (s, 1H, indolyl 2-H), 8.32-7.01 (m, 19H, Ar-H), 5.51 (s, 2H, CH_2-N), 5.21 and 4.99 (2d, 2H, 2CH)	–
13a	3240 and 3141 (NH), 2211 (CN), 1636 (C=N), 1583 (C=C)	12.15 (s, 1H, thiazolyl 5-H), 9.95 (s, 1H, thiazolyl 7-H), 9.34 (s, 1H, NH), 8.25 (s, 1H, indolyl 2-H), 8.11-7.25 (m, 9H, Ar-H), 6.91 (s, 1H, NH)	389 (M^+, 18), 349 (100), 333 (10), 103 (6)
13b	3118 (NH), 2216 (CN), 1625 (C=N) 1587 (C=C)	–	479 (M^+, 31), 388 (7), 312 (2), 91 (100)
14a	3418 (OH), 3265 and 3152 (NH), 1700 (C=O), 1641 (C=N), 1573 (C=C)	–	408 (M^+, 46), 392 (1), 315 (20), 287 (2), 117 (50), 116 (100)

Table 2 (*Continued*)

Compound number	IR (γ_{max}/cm)	^{1}H NMR (δ, ppm)	Mass (*m/z*, %)
14b	3400 (OH), 1715 (C=O), 1638 (C=N), 1524 (C=C)	13.45 (s, 1H, OH), 11.70 (s, 1H, thiazolyl 5-H), 9.65 (s, 1H, thiazolyl 7-H), 8.81 (s, 1H, NH), 8.40 (s, 1H, indolyl 2-H), 8.19-7.01 (m, 14H, Ar-H), 5.51 (s, 2H, CH_2-N), 2.3 (s, 1H, CH)	–
16a	3408 (OH), 3135 (NH), 1692 (C=O), 1631 (C=N), 1563 (C=C)	13.23 (s, 1H, OH), 12.12 (s, 1H, thiazolyl 5-H), 9.93 (s, 1H, thiazolyl 7-H), 8.40 (s, 1H, NH), 8.65 (s, 1H, indolyl 2-H), 8.22-7.12 (m, 4H, Ar-H), 1.25 (s, 3H, CH_3)	–
16b	3368 (OH), 1707 (C=O), 1639 (C=N), 1585 (C=C)	–	474 (M^+, 26), 460 (11), 431 (10), 389 (8), 91 (100)
17a	3159 and 3112 (NH), 2195 (CN), 1628 (C=N), 1560 (C=C)	12.01 (s, 1H, thiazolyl 5-H), 9.92 (s, 1H, thiazolyl 7-H), 8.94 (s, 1H, NH), 8.26 (s, 1H, indolyl 2-H), 7.91-7.24 (m, 4H, Ar-H), 6.91 (s, 1H, NH)	–
17b	3160 (NH_2), 2205 (CN), 1644 (C=N), 1615 (C=C)	–	441 (M^+, 45), 413 (3), 391 (2), 381 (1), 244 (10), 91 (100)
18a	3420 (NH_2), 3192 and 3101 (NH), 1635 (C=N), 1620 (N=N), 1564 (C=C)	11.65 (s, 1H, thiazolyl 5-H), 8.90 (s, 1H, thiazolyl 7-H), 8.53 (s, 1H, NH), 8.32 (s, 1H, indolyl 2-H), 7.83-7.20 (m, 4H, Ar-H), 6.50 (s, 1H, NH), 5.21 (s, 2H, NH_2), 2.95 (s, 2H, NH_2)	–
18b	3363 and 3246 (NH_2), 3133 (NH), 1638 (C=N), 1616 (N=N), 1583 (C=C)	12.01 (s, 1H, thiazolyl 5-H), 9.91 (s, 1H, thiazolyl 7-H), 9.46 (s, 2H, NH_2), 8.42 (s, 1H, indolyl 2-H), 8.05-7.17 (m, 9H, Ar-H), 6.95 (s, 1H, NH), 5.37 (s, 2H, CH_2-N), 3.91 (s, 2H, NH_2)	473 (M^+, 66), 445 (2), 397 (21), 115 (15), 91 (100)

where I is the DPPH inhibition %, A_B the absorbance of control ($t = 0$ h), and A_S the absorbance of a tested sample at the end of the reaction ($t = 1$ h). Each assay was carried out in triplicate and the results were averaged.

Results and discussion

Chemistry

The reaction route for the synthesis of the newly synthesized compounds has been described in Schemes 1 and 2. New 2-amino-5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazoles (**2a**,**b**) were prepared by a one-pot reaction of *N*-substituted-1*H*-indole-3-carboxaldehyde with thioglycolic acid and thiosemicarbazide in concentrated sulfuric acid according to the procedure of Shukurov *et al.* [7] (Scheme 1). The IR spectra of compounds **2a**,**b** showed characteristic absorption bands at ~3241–3410/cm for (NH_2) and showed no absorption band characteristic for C = O (Table 2). Their ^{1}H NMR (DMSO-d_6) spectra showed two singlet signals at δ 12.12–9.90 ppm attributed to 5-H and 7-H of thiazolo[4,3-*b*]-1,3,4-thiadiazole moiety, besides the other aromatic protons located at their positions (Table 2).

The reaction of compounds **2a** or **2b** with benzenesulfonyl chloride and 4-chlorobenzenesulfonyl chloride in dry dioxane and in the presence of triethylamine led to the formation of *N*-[5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazol-2-yl]benzenesulfonamide derivatives **3a**,**b** and **4a**,**b**, respectively (Scheme 1). However, the reaction of **2a**,**b** with benzoyl chloride and 2-chlorobenzoyl chloride yielded *N*-[5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolor-1,3,4-thiadiazol-2-yl]-benzamide derivatives **5a**,**b** and **6a**,**b**, respectively (Scheme 1).

In contrast, the reaction of **2a** or **2b** with chloroacetyl chloride in dry benzene yielded *N*-[5-(*N*-substituted-1-*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazol-2-yl]-2-chloroacetamides (**7a**,**b**). Cyclization of the latter compounds through their reactions with potassium thiocyanate in dry acetone yielded 3-[5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolor-1,3,4-thiadiazol-2-yl]-2-iminothiazolidin-4-ones (**8a**,**b**) (Scheme 1).

The treatment of **2a** or **2b** with triethyl orthoformate and sodium azide according to Abu-Hashem *et al.* [20] yielded the new 5-(*N*-substituted-1*H*-indol-3-yl)-2-(1*H*-tetrazol-1-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazols (**9a**,**b**) (Scheme 1).

The acid-catalyzed reaction of **2a**,**b** with benzaldehyde in glacial acetic acid under reflux yielded the corresponding Schiff bases, *N*-benzylidene-[5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazol-2-yl]-2-amines (**10a**,**b**) (Scheme 2). Cyclocondensation of the latter Schiff bases with chloroacetyl chloride and/or phenacyl bromide under reflux in dry dioxane and in the presence of triethylamine yielded 3-chloro-4-phenylazetidin-2-one derivatives **11a**,**b** and 3,4-diphenylazetidin-2-one derivatives **12a**,**b**, respectively (Scheme 2).

However, the reaction of Schiff bases **10a** or **10b** with sodium cyanide in glacial acetic acid yielded 2-[5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazol-2-yl amino]phenylacetonitriles (**13a**,**b**) (Scheme 2). Acid hydrolysis of the latter compounds **13a** or **13b** yielded the corresponding α-amino acid **14a**,**b** (Scheme 2).

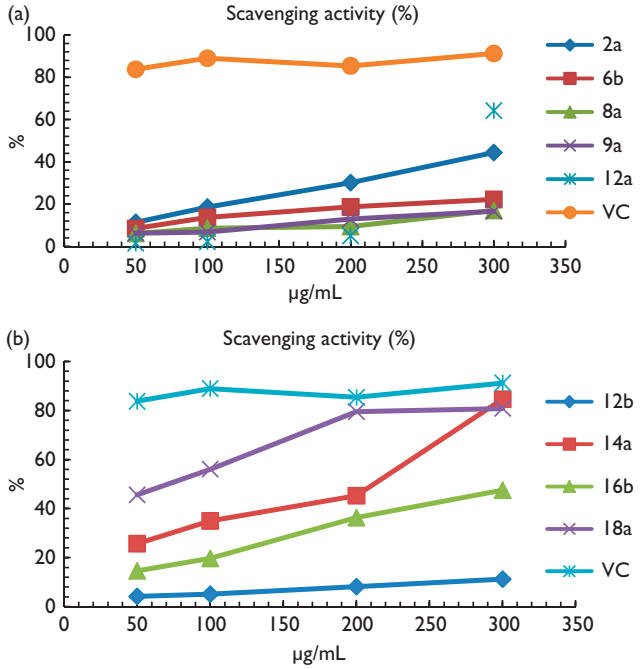
Diazotization of compounds **2a** or **2b** with concentrated hydrochloric acid and sodium nitrite at 0–5°C yielded the corresponding diazonium salts (**A**), which, under coupling with sodium azide, yielded the corresponding azides, namely, 2-azido-5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazols (**15a**,**b**). The freshly prepared azides **15a**,**b** reacted with ethylacetoacetate in dry methanol and in the presence of freshly prepared sodium methoxide and yielded 1-[5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazol-2-yl]-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acids (**16a**,**b**) (Scheme 2).

Table 3 Scavenging activity % on DPPH radicals of the most active synthesized compounds and IC_{50} values

	Scavenging activity (%)[a]				
Compound number	50	100	200	300	IC_{50} (μg/ml)
2a	11.39	18.62	30.19	44.42	368.59
6b	8.49	13.74	18.67	22.24	1254.02
8a	6.15	8.67	9.40	17.00	2243.39
9a	6.33	6.87	13.02	16.64	1731.11
12a	1.63	2.35	5.06	64.19	317.59
12b	4.15	5.06	8.13	11.21	4221.33
14a	25.67	34.9	45.26	84.61	164.15
16b	14.64	19.71	36.34	47.55	327.21
18a	45.56	56.05	79.56	80.83	69.14
Negative control	0	0	0	0	0
Ascorbic acid	83.79	88.99	85.41	91.25	6.50

[a]Results are the mean of three independent experiments.

Figure 1



Scavenging activity % on DPPH radicals of the most active synthesized compounds.

However, coupling of diazonium salts (**A**) with malononitrile in the presence of sodium acetate trihydrate yielded 2-[(5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazol-2-yl hydrazono] malononitriles (**17a**,**b**). The reaction of the latter compounds with hydrazine hydrate in absolute ethanol under reflux yielded the corresponding pyrazoles (**18a**,**b**) (Scheme 2).

DPPH radical-scavenging activity

The preliminary DPPH radical-scavenging activity of the newly synthesized compounds was determined using ascorbic acid as a reference and IC_{50} of the most active compounds were calculated (Table 3 and Fig. 1). From the data obtained, compounds **14a** and **18a** showed free radical-scavenging effects of 84.61 and 80.83% compared with that of ascorbic acid of 91.25% at a concentration of 300 μg/ml, whereas at a concentration of 200 μg/ml, only **18a** showed a radical-scavenging effect of 79.56% compared with that of ascorbic acid of 85.41%. The amount of sample necessary to decrease the absorbance of DPPH by 50% (IC_{50}) was calculated and it was found that 4-{5-[(1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazol-2-yl]diazo}-1*H*-pyrazole-3,5-diamine (**18a**) was highly active with radical-scavenging activity (IC_{50} of 69.14 μg/ml) compared with ascorbic acid (IC_{50} of 6.50 μg/ml); this may be because of the presence of the N–H moieties of the two primary aromatic amino groups and secondary amine, which act as good hydrogen bond donors (Table 3 and Fig. 1).

Conclusion

Some new heterocycles derived from novel 2-amino-5-(*N*-substituted-1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazoles (**2a**,**b**) were prepared and screened for their antioxidant activity using 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging activity. 4-{5-[(1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazol-2-yl]diazo}-1*H*-pyrazole-3,5-diamine (**18a**) was found to be highly active with radical-scavenging activity (IC_{50} of 69.14 μg/ml) compared with ascorbic acid (IC_{50} of 6.50 μg/ml); this may be because of the presence of the N–H moieties of the two primary aromatic amino groups and secondary amine, which act as good hydrogen bond donors.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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