Synthesis and DPPH radical-scavenging effect of novel heterocyclic derivatives of 2-amino-4-(1-benzoylindol-3-yl) selenophene-3-carbonitrile

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Background and objectives
Selenophene moiety is one of the heterocyclic compounds with a selenium atom that plays a vital role in biological fields such as antioxidant, antidepressant, anticonvulsant, antimicrobial, and anticancer activities. The aim of this study was to describe the synthesis of some new heterocycles derived from 2-amino-4-(1-benzoylindol-3-yl)selenophene-3-carbonitrile derivatives and to evaluate their 2,2¢-diphenyl-1-picrylhydrazyl radical-scavenging activity.

Materials and methods
2-Amino-4-(1-benzoylindol-3-yl)selenophene-3-carbonitrile (**3**) was prepared and allowed to react with each of formic acid, formamide, carbon disulfide, urea, thiourea, malononitrile, or ethyl cyanoacetate to yield selenolo[2,3-*d*]pyrimidines **4–7** and selenolo[2,3-*b*]pyridine derivatives **8** and **9**, respectively. Moreover, reaction of compound **3** with hydrochloric acid or acetic anhydride in glacial acetic acid yielded selenolo[2,3-*d*]pyrimidin-4-one **10** and selenoacetamide derivative **11**, respectively. In contrast, reaction of Schiff base **12** with thioglycolic acid, phenacyl bromide, or chloroacetyl chloride yielded thiazolidine **13** and azidatine derivatives **14** and **15**, respectively. Reaction of compound **3** with some substituted benzenesulfonyl chlorides yielded sulfonamide derivatives **16a, b, c**, respectively. Moreover, 2-amino-1,3,4-thiadiazole **19** and 4-oxo-2-iminothiazolidine derivatives **21** were prepared through cyclization of hydrazinecarbothioamide **18** or chloroacetamido derivative **20,** respectively. The fusion of **3** with succinic anhydride yielded pyrrolidine-2,5-dione **23**, whereas heating of **3** with succinic anhydride in ethanol yielded succinamic acid derivative **24**. The newly synthesized compounds were screened for their 2,2′-diphenyl-1-picrylhydrazyl radical-scavenging activity.

Results and conclusion
Compound **8** showed promising activity with a radical-scavenging effect (IC_{50}) of 166.40 µg/ml compared with ascorbic acid (an IC_{50} of 129.64 µg/ml) as a reference standard.

Keywords:
2-aminoselenophene-3-carbonitrile, 1-benzoyl-3-acetylindole, DPPH radical-scavenging activity, selenolo[2,3-*d*]pyrimidine, seleno[2,3-*b*]pyridine

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Introduction

Organoselenium chemistry has provided fertile ground for the discovery of novel synthetic methodology and for the design of bioactive molecules with potential therapeutic activities [1–4]. The selenophene moiety is one of the heterocyclic compounds with a selenium atom that plays a vital role in biological fields such as antioxidant, antidepressant, anticonvulsant, antimicrobial, and anticancer activities [5–9]. In addition, indole, which is the potent basic pharmacodynamic nucleus, has been reported to possess a wide variety of biological properties, that is, antioxidant, anti-inflammatory, anticancer, and antimicrobial activities [10–14]. On the basis of the above observations and in continuation of our work on the preparation of new indole compounds containing sulfur and selenium atoms [14–16], the present work deals with the synthesis of some new 1-benzoyl-3-indolyselenophenes and the evaluation of their 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging activity.

Materials and methods

Chemistry

Melting points were determined in open capillary tubes on an Electrothermal 9100 digital melting point apparatus (serial no. 8694; Electrothermal Engineering Ltd, Rochford, UK) and were uncorrected. Elemental analyses were performed on a PerkinElmer 2400 analyzer (PerkinElmer, Waltham, Massachusetts, USA) and were found within±0.4% of the theoretical values (Table 1). IR spectra were recorded on a PerkinElmer

1600 (PerkinElmer, Waltham, Massachusetts, USA) Fourier Transform Infrared Spectroscopy against KBr disks. ^{1}H NMR spectra were measured with a Bruker Avance digital spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) 500 MHz in dimethyl sulfoxide (DMSO-d_6), and chemical shifts were recorded in δ ppm relative to trimethylsilane (TMS) as the internal standard. Mass spectra (EI) were run at 70 eV with JEOL-JMS-AX500 mass spectrometer (JEOL Ltd, Tokyo, Japan). All reagents and solvents were of commercial grade. 1-Benzoyl-3-acetylindole (**1**) was prepared as reported [17].

2-Amino-4-(1-benzoylindol-3-yl)selenophene-3-carbonitrile (3)

To a solution of compound **2** (15.5 g, 50 mmol) and selenium (1.6 g, 50 mmol) in absolute methanol (50 ml), triethylamine (6 ml) was added dropwise while stirring in an ice bath, and then the reaction mixture was heated under reflux for 37 h. After cooling, the reaction mixture was filtered off and the filtrate was poured onto ice water (50 ml). The solid that formed was filtered off, washed with water, air dried, and crystallized from absolute ethanol (Scheme 1, Table 1).

5-(1-Benzoylindol-3-yl)selenolo[2,3-*d*]pyrimidin-4(3H)-one (4)

A solution of compound **3** (0.19 g, 0.5 mmol) in formic acid solution (85%, 10 ml) was heated at reflux for 4 h. The solid that formed while hot was filtered off, air dried, and crystallized from absolute ethanol (Scheme 1, Table 1).

5-(1-Benzoylindol-3-yl)selenolo[2,3-*d*]pyrimidin-4-amine (5)

A solution of compound **3** (0.19 g, 0.5 mmol) in formamide (10 ml) was heated at reflux for 3 h. The solid that formed while hot was filtered off, air dried, and crystallized from absolute ethanol (Scheme 1, Table 1).

5-(1-Benzoylindol-3-yl)-1,2,3,4-tetrahydroselenolo[2,3-*d*]pyrimidine-2,4-dithiones (6)

A mixture of compound **3** (0.19 g, 0.5 mmol) and an excess of carbon disulfide (5 ml) in ethanolic potassium hydroxide solution (0.056 g, 1 mmol of KOH in 10 ml absolute EtOH) was heated under reflux for 12 h. The excess of carbon disulfide was evaporated under vacuum and the residue obtained was dissolved in water (10 ml). The reaction mixture was filtered off and the filtrate was acidified with diluted hydrochloric acid. The precipitate formed was collected by filtration, washed with water, air dried, and crystallized from dimethylformamide (DMF) water (Scheme 1, Table 1).

4-Amino-5-(1-benzoylindol-3-yl)-1H-selenolo[2,3-*d*]pyrimidin-2-one (7a) and 4-amino-5-(1-benzoylindol-3-yl)-1H-selenolo[3,2-*d*]pyrimidine-2-thione (7b)

A mixture of compound **3** (0.19 g, 0.5 mmol), urea and/or thiourea (0.5 mmol) was grinded together and then heated at 180°C in a test tube on a sand bath for

Table 1 Physical and analytical data of the prepared compounds

Compound number	Formula (molecular weight)	Melting point (°C)	Yield (%)	Analysis (%; calculated/found)		
				C	H	N
3	$C_{20}H_{13}N_3OSe$ (390.30)	161–163	95	61.55/61.23	3.36/3.15	10.77/10.59
4	$C_{21}H_{13}N_3O_2Se$ (418.31)	188–190	90	60.30/60.14	3.13/3.02	10.05/9.91
5	$C_{21}H_{14}N_4OSe$ (417.32)	273 dec.	91	60.44/60.26	3.38/3.51	13.43/13.25
6	$C_{21}H_{13}N_3OS_2Se$ (466.44)	177–179	88	54.07/4.19	2.81/2.66	9.01/8.83
7a	$C_{21}H_{14}N_4O_2Se$ (433.32)	195–197	90	58.21/58.08	3.26/3.11	12.93/12.80
7b	$C_{21}H_{14}N_4OSSe$ (449.39)	221 dec.	92	56.13/56.00	3.14/3.26	12.47/12.26
8	$C_{23}H_{15}N_5OSe$ (456.36)	186–188	85	60.53/60.35	3.31/3.24	15.35/15.21
9	$C_{23}H_{14}N_4O_2Se$ (457.34)	147–149	81	60.40/60.25	3.09/2.97	12.25/12.06
10	$C_{22}H_{15}N_3O_2Se$ (432.33)	234–236	83	61.12/61.05	3.50/3.34	9.72/9.63
11	$C_{22}H_{15}N_3O_2Se$ (432.33)	144–146	78	61.12/61.02	3.50/3.41	9.72/9.55
12	$C_{27}H_{17}N_3OSe$ (478.38)	145–147	95	67.79/67.62	3.58/3.41	8.78/8.64
13	$C_{29}H_{19}N_3O_2SSe$ (552.51)	197–199	91	63.04/62.86	3.47/3.28	7.61/7.4
14	$C_{35}H_{23}N_3O_2Se$ (596.31)	124–126	69	70.47/70.29	3.89/3.71	7.04/6.87
15	$C_{29}H_{18}ClN_3O_2Se$ (554.89)	113–115	65	62.77/62.54	3.27/3.08	7.57/7.39
16a	$C_{26}H_{17}N_3O_3SSe$ (530.48)	138–140	96	58.87/58.69	3.23/3.06	7.92/7.75
16b	$C_{26}H_{16}BrN_3O_3SSe$ (609.3)	307 dec.	95	51.25/51.07	2.65/2.81	6.90/7.02
16c	$C_{26}H_{16}ClN_3O_3SSe$ (564.90)	122–124	92	55.28/55.11	2.85/2.68	7.44/7.31
17	$C_{24}H_{19}N_3O_3Se$ (476.39)	181–183	95	60.51/60.33	4.02/3.87	8.82/8.64
18	$C_{23}H_{18}N_6O_2SSe$ (521.45)	143–145	89	52.98/52.79	3.48/3.31	16.12/16.01
19	$C_{23}H_{16}N_6OSSe$ (503.44)	125–127	79	54.87/54.71	3.20/3.04	16.69/16.53
20	$C_{22}H_{14}ClN_3O_2Se$ (466.78)	112–114	92	56.61/56.45	3.02/3.12	9.00/8.88
21	$C_{23}H_{14}N_4O_2SSe$ (489.41)	133–135	94	56.44/56.26	2.88/3.04	11.45/11.27
22a	$C_{26}H_{22}N_4O_3Se$ (517.44)	171–173	81	60.35/60.51	4.29/4.08	10.83/10.65
22b	$C_{27}H_{25}N_5O_2Se$ (530.48)	128–130	78	61.13/61.01	4.75/4.58	13.20/13.11
23	$C_{24}H_{15}N_3O_3Se$ (472.35)	201–203	81	61.03/60.92	3.20/3.11	8.90/8.82
24	$C_{24}H_{17}N_3O_4Se$ (490.37)	139–141	67	58.78/58.57	3.49/3.33	8.57/8.42

4 h. On cooling, the slurry was triturated with water, filtered off, air dried, and crystallized from DMF (Scheme 1, Table 1).

2,4-Diamino-5-(1-benzoylindol-3-yl)selenolo[2,3-*b*] pyridine-3-carbonitrile (8)

A mixture of compound **3** (0.19 g, 0.5 mmol) and malononitrile (0.03 ml, 0.5 mmol) in absolute ethanol (10 ml) containing a few drops of piperidine was heated at reflux for 10 h. After cooling, the reaction mixture was poured onto ice water (20 ml), and the solid that formed was filtered off, air dried, and crystallized from dioxane (Scheme 1, Table 1).

5-Amino-6-hydroxy-3-(1-benzoylindol-3-yl)selenolo [2,3-*b*]pyridine-6-carbonitrile (9)

A mixture of compound **3** (0.19 g, 0.5 mmol) and ethyl cyanoacetate (0.056 g, 0.5 mmol) in dry dioxane (10 ml) containing a few drops of piperidine was heated at reflux for 12 h. After cooling, the reaction mixture was poured onto ice water (20 ml). The solid that formed was filtered off, air dried, and crystallized from dioxane (Scheme 1, Table 1).

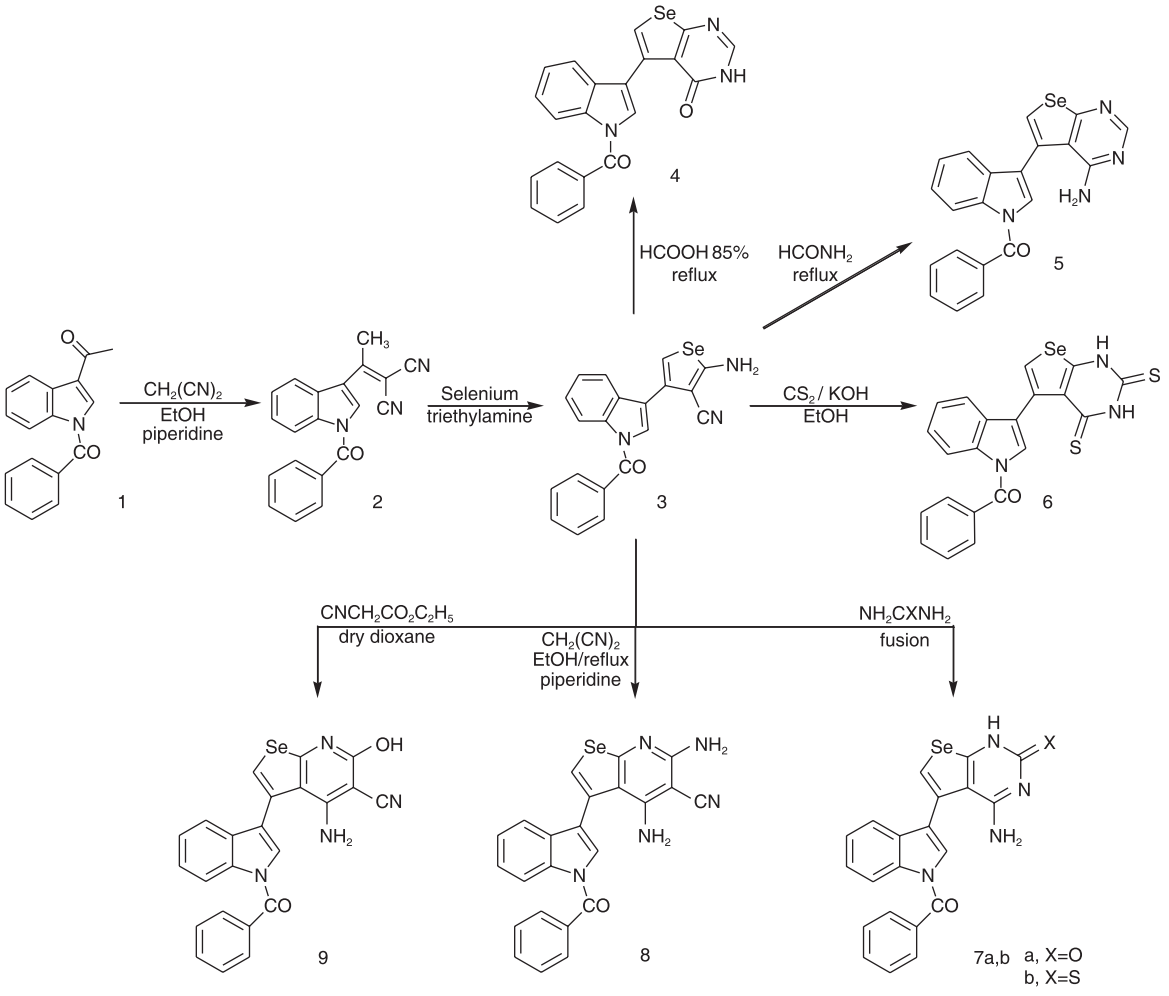
3-(1-Benzoylindol-3-yl)-6-methyl-5H-selenolo(2,3-*c*) pyrimidin-4-one (10)

A solution of compound **3** (0.19 g, 0.5 mmol) in a mixture of (10 ml) concentrated hydrochloric acid and glacial acetic acid (3 : 1) was heated at reflux for 6 h. After cooling, the reaction mixture was poured onto ice water (20 ml), and the solid that formed was filtered off, air dried, and crystallized from dioxane (Scheme 2, Table 1).

N-[3-Cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl] acetamide (11)

A solution of compound **3** (0.19 g, 0.5 mmol) in a mixture of (10 ml) acetic anhydride and glacial acetic acid (2 : 1) was heated at reflux for 10 h. After cooling, the reaction mixture was poured onto ice water (10 ml),

Scheme 1



Synthesis of compounds **1**–**9**.

and the solid that formed was filtered off, air dried, and crystallized from absolute ethanol (Scheme 2, Table 1).

2-[(Phenyl)methyleneamino)-4-(1-benzoylindol-3-yl)] selenophene-3-carbonitirile (12)

A mixture of compound **3** (3.9 g, 10 mmol) and benzaldehyde (1.06 g, 10 mmol) in glacial acetic acid (20 ml) was heated at reflux for 8 h. After cooling, the reaction mixture was poured onto ice water (30 ml). The solid that formed was filtered off, air dried, and crystallized from benzene (Scheme 2, Table 1).

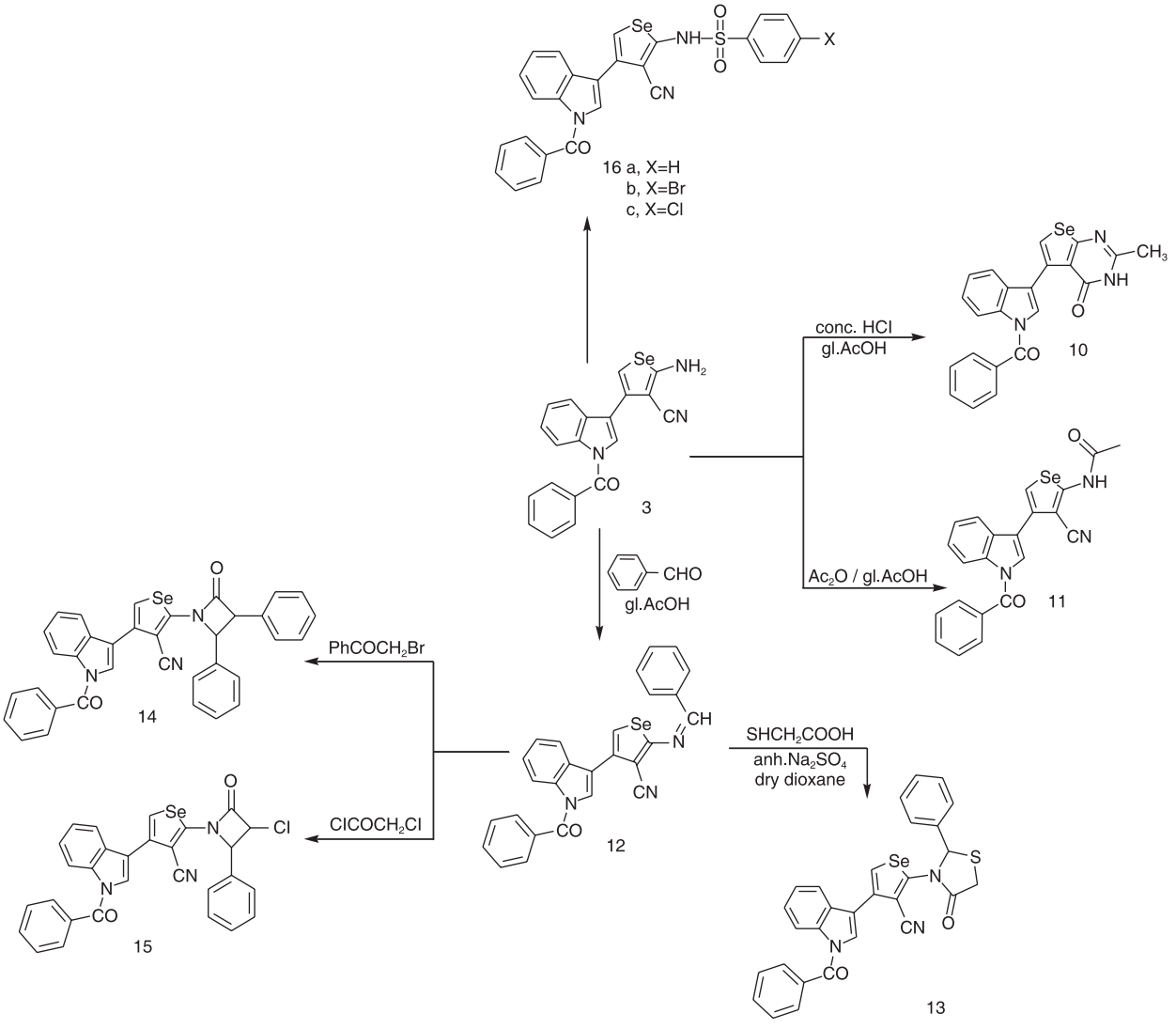
N-[3-Cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl]-4-oxo-2-phenyl thiazolidine (13)

To a stirred solution of Schiff base **12** (0.4 g, 1 mmol) in dry dioxane (10 ml), thioglycolic acid (0.13 g, 1 mmol) was added and the reaction mixture was stirred for 4 h, and then anhydrous sodium sulfate (3 g) was added. The reaction mixture was heated at reflux for 6 h. The reaction mixture was filtered while hot, and after cooling, the solid that formed was filtered off, air dried, and crystallized from chloroform (Scheme 2, Table 1).

2-(2,3-Diphenyl-4-oxoazetidin-1-yl)-4-(1-benzoylindol-3-yl)selenophene-3-carbonitrile (14) and 2-(3-chloro-2-phenyl-4-oxoazetidin-1-yl)-4-(1-benzoylindol-3-yl) selenophene-3-carbonitrile (15)

To a solution of Schiff base **12** (0.47 g, 1 mmol) in dry dioxane (10 ml) was added a solution of phenacyl bromide or chloroacetyl chloride (1 mmol) in dry dioxane (5 ml) and triethylamine (0.1 ml). The reaction mixture was heated at reflux for 13 h. After cooling, the reaction mixture was poured onto cold water (10 ml) and the solid that formed was filtered off, washed with

Scheme 2



Synthesis of compounds **10–16**.

water, air dried, and crystallized from absolute ethanol (Scheme 2, Table 1).

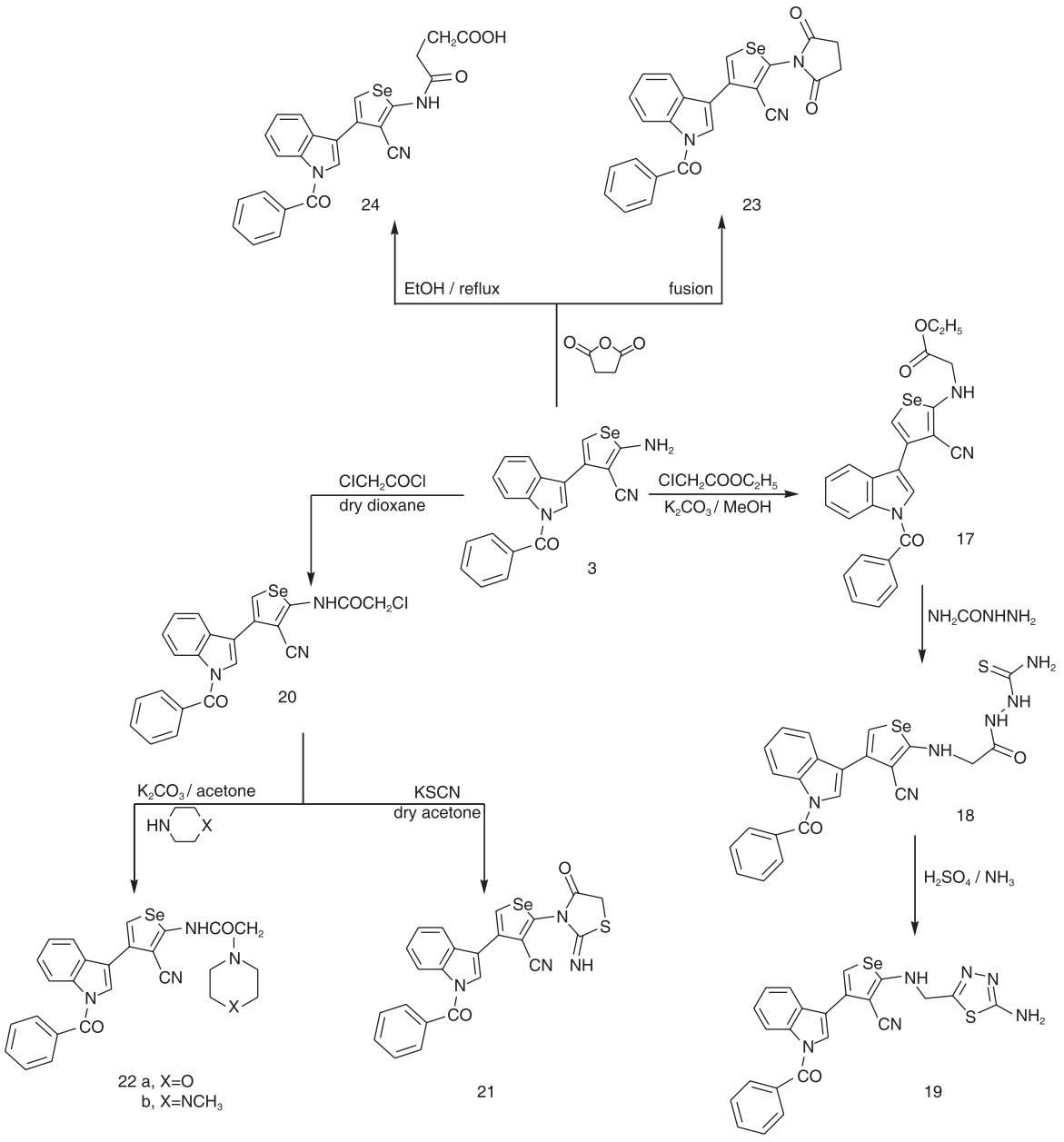
_N_-[3-Cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl]benzene- sulfonamide (16a), 4-bromo-_N_-[3-cyano-4-(1-benzoylindol-3-yl) selenophen-2-yl]benzenesulfonamide (16b) and 4-chloro-_N_-[3-cyano-4-(1-benzoylindol-3-yl) selenophen-2-yl]benzenesulfonamide (16c)

A mixture of compound **3** (0.19 g, 0.5 mmol) and benzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, or 4-chlorobenzenesulfonyl chloride (0.5 mmol) in dry dioxane (10 ml) containing a few drops of triethylamine was heated at reflux for 8–10 h. After cooling, the reaction mixture was poured onto cold water (20 ml). The solid that formed was filtered off, air dried, and crystallized from dioxane (Scheme 2, Table 1).

Ethyl-_N_-[3-cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl] aminoacetate (17)

A mixture of compound **3** (0.78 g, 2 mmol), ethyl chloroacetate (0.24 g, 2 mmol) and potassium carbonate (0.31 g, 2 mmol) in absolute methanol (10 ml) was kept overnight at room temperature. The reaction mixture was heated on a water bath for 1 h. After cooling, the reaction mixture was poured onto ice water (20 ml), and the solid that formed was filtered off, air dried, and crystallized from absolute ethanol (Scheme 3, Table 1).

Scheme 3



Synthesis of compounds **17–24**.

2-[2-(4-(1-Benzoylindol-3-yl)-3-cyanoselenophen-2-yl) amino)acetyl) hydrazine carbothioamide (18)

A mixture of compound **17** (0.57 g, 1 mmol) and thiosemicarbazide (0.11 g, 1 mmol) in absolute methanol (10 ml) was heated at reflux on a water bath for 10 h. The reaction mixture was filtered while hot, and then poured onto cold water (20 ml). The solid that formed was filtered off, air dried, and crystallized from absolute ethanol (Scheme 3, Table 1).

2-Amino-5-[(3-cyano-4-(1-benzoylindol-3-yl) selenophen-2-yl) methylamino]-1,2,4-thidiazole (19)

A mixture of compound **18** (0.35 g, 0.6 mmol) and concentrated sulfuric acid (1 ml, 1 mmol) in absolute methanol (10 ml) was kept overnight at room temperature. The reaction mixture was heated on a water bath for 8 h. After cooling, the reaction mixture was neutralized with ammonia solution (25%). The solid that formed was filtered off, washed with water, air dried, and crystallized from absolute ethanol (Scheme 3, Table 1).

***N*-[3-Cyano-4-(1-benzoylindol-3-yl)selenophen-3-yl] chloroacetamide (20)**

To a solution of compound **3** (0.78 g, 2 mmol) in dry benzene (10 ml), a solution of chloroacetyl chloride (0.45 ml, 4 mmol) in dry benzene (10 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 under vacuum and the solid that formed was washed with 5% sodium bicarbonate solution and then with water, air dried, and crystallized from chloroform (Scheme 3, Table 1).

3-[3-Cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl]-2-imino-4-thiazolidenone (21)

A mixture of compound **20** (0.14 g, 0.3 mmol) and potassium thiocyanate (0.058 g, 0.6 mmol) in dry acetone (20 ml) was heated at reflux for 3 h. The solid that formed was filtered off, air dried, and crystallized from chloroform (Scheme 3, Table 1).

***N*-[3-Cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl]-2-morpholinoacetamide (22a) and *N*-[3-cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl]-2-(*N*-methylpiprazino)acetamide (22b)**

A mixture of compound **20** (0.27 g, 0.6 mmol) and morpholine or *N*-methylpiprazine (0.6 mmol) in acetone (20 ml) containing potassium carbonate (0.16 g, 1 mmol) was heated at reflux for 15–17 h. The solvent was evaporated under vacuum to half of its volume, and the solid that formed was filtered off, washed with 5% sodium bicarbonate solution and then with water, air dried, and crystallized from absolute ethanol (Scheme 3, Table 1).

***N*-[3-Cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl] pyrrolidine-2,5-dione (23)**

A mixture of compound **3** (0.19 g, 0.5 mmol) and succinic anhydride (0.05 g, 0.5 mmol) was ground together and then heated at 180°C in a test tube on a sand bath for 4 h. After cooling, the solid that formed was collected, washed with water, air dried, and crystallized from dimethylformamide (Scheme 3, Table 1).

***N*-[3-Cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl] succinamic acid (24)**

A mixture of compound **3** (0.19 g, 0.5 mmol) and succinic anhydride (0.05 g, 0.5 mmol) in absolute ethanol (10 ml) was heated at reflux for 10 h. After cooling, the reaction mixture was poured onto ice water (20 ml). The solid that formed was filtered off, air dried, and crystallized from absolute ethanol (Scheme 3, Table 1).

Biological assay

DPPH radical-scavenging activity: The newly synthesized compounds were screened for their DPPH radical-scavenging activity using the procedure of Viuda-Martos *et al*. [18]. A volume of 50 µl of DMSO stock solution of test compounds of four different concentrations (50, 100, 200, and 300 µg/ml) was added to 2 ml of 6×10^{-5} mol/l DPPH solution (2.3659 mg of DPPH in 100 ml DMSO). The mixtures were shaken in a vortex (2500 rpm) for 1 min and then placed in a dark room. Ascorbic acid (Sigma-Aldrich Chemie GmeH, Taufkirchen, Germany) was used as a reference. The decrease in absorbance at 517 nm was determined with JENWAY 6315 spectrophotometer (Keison International LTd, United Kingdom) after 1 h for all samples. DMSO was used to zero the spectrophotometer. Absorbance of the radical without the sample was used as the negative control. The amount of the sample necessary to decrease the absorbance of DPPH (IC_{50}) by 50% was calculated. The inhibition percentage of the DPPH radical (scavenging activity) was calculated according to the formula

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

where I is the DPPH inhibition percentage, A_B the absorbance of the 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

Reaction routes for the syntheses of the title compounds are described in Scheme 1–3. The starting 2-(1-benzoylindole-3-yl)ethylidine) malononitrile

(**2**) was prepared by a base-catalyzed reaction of 1-benzoyl-3-acetylindole with malononitrile [14]. Ring closure of compound **2** with selenium in absolute methanol in the presence of excess triethylamine by the second version of the Gewald reaction led to the formation of 2-amino-4-(1-benzoylindol-3-yl) selenophene-3-carbonitrile (**3**) as in Scheme 1. The IR spectra of compound **3** showed characteristic absorption bands for NH_2 and CN groups at 3366, 3224, and 2220 cm^{-1}, respectively (Table 2). Its ^1H NMR (DMSO-d_6) spectrum revealed singlet signals at 11.89 and 8.2 ppm for NH_2 and selenophenyl 5-H, respectively, besides other aromatic protons (Table 2).

Table 2 Spectral characterization of the prepared compounds

Compound number	IR (γ_{max}, cm^{-1})	^1H NMR (δ, ppm)	Mass (*m/z*, %)
3	3366 and 3224 (NH_2), 2220 (CN), 1644 (C=O), 1605 (C=C)	11.89 (s, 2H, NH_2), 8.27 (s,1H, indolyl 2-H), 8.26 (s, 1H, selenophenyl 5-H), 8.13 (d, 2H, indolyl 4-H, and 7-H), 7.43 (m, 2H, indolyl 5-H, and 6-H), 7.17–7.13 (m, 5H, Ar–H)	390 (M^+, 20), 362 (2), 350 (50), 193 (72), 144 (100), 77(30)
4	3201 (NH), 1721 and 1657 (C=O), 1622 (C=N), 1566 (C=C)	8.56 (s, 1H, pyrimidinyl 2-H), 8.38 (s, 1H, selenolyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.67–7.05 (m, 9H, Ar–H), 6.67 (s, 1H, NH)	418 (M^+, 2), 314 (10), 271 (5), 144 (100), 116 (20)
5	3399 and 3295 (NH_2), 1681 (C=O), 1649 (C=N), 1617 (C=C)	9.09 (s, 2H, NH_2), 8.57 (s, 1H, pyrimidinyl 2-H), 8.36 (s, 1H, selenolyl 5-H), 8.21 (s, 1H, indolyl 2-H), 7.86–7.01 (m, 9H, Ar–H)	
6	3270 and 3134 (NH), 1736 (C=O), 1620 (C=C), 1238 (C=S)	9.01 (s, 1H, NH), 8.38 (s, 1H, selenolyl 5-H), 8.15 (s, 1H, indolyl 2-H), 7.81–7.05 (m, 9H, Ar–H), 7.91 (s, 1H, NH)	
7a	3422 (NH_2), 3160 (NH), 1775 (C=O), 1647 (C=N), 1564 (C=C)	8.51 (s, 1H, selenolyl 5-H), 8.33 (s, 1H, indolyl 2-H), 8.16–7.21 (m, 9H, Ar–H), 6.61 (s, 1H, NH), 2.88 (s, 2H, NH_2)	
7b	3365 (NH_2), 3132 (NH), 1701 (C=O), 1636 (C=N), 1551 (C=C), 1240 (C=S)		449 (M^+, 5), 421 (10), 385 (10), 193 (5), 184 (100), 116 (10)
8	3366 and 3245 (NH_2), 2240 (CN), 1679 (C=O), 1628 (C=N), 1576 (C=C)	11.88 (s, 2H, NH_2), 8.38 (s, 1H, selenolyl 5-H), 8.22 (s, 1H, indolyl 2-H), 8.01–7.15 (m, 9H, Ar–H), 2.98 (s, 2H, NH_2)	
9	3458 (OH), 3325 (NH_2), 2195 (CN), 1695 (C=O), 1629 (C=N), 1552 (C=C)		457 (M^+, 41), 401 (12), 373 (15), 193 (50), 144 (100)
10	3232 (NH), 1720 (C=O), 1624 (C=N), 1610 (C=C)	8.57 (s, 1H, NH), 8.23 (s, 1H, selenolyl 5-H), 8.03 (s, 1H, indolyl 2-H), 7.73–7.05 (m, 9H, Ar–H), 1.52 (s, 3H, CH_3)	
11	3216 (NH), 2225 (CN), 1736 (C=O), 1611 (C=C)		432 (M^+, 3), 375 (20), 350 (41), 116 (50), 57 (100).
12	2217 (CN), 1710 (C=O), 1628 (C=N), 1599 (C=C)	10.12 (s, 1H, CH=N), 8.21 (s, 1H, indolyl 2-H), 8.07 (s, 1H, selenolyl 5-H), 8.00–7.01 (m, 14H, Ar–H)	478 (M^+, 1), 365 (11), 312 (5), 221 (100).
13	2208 (CN), 1676 and 1692 (C=O), 1585 (C=C)	8.38 (s, 1H, indolyl 2-H), 8.26 (s, 1H, selenolyl 5-H), 8.14–7.13 (m, 14H, Ar–H), 5.15 (s, 1H, thiazolidinyl 2-H), 4.10 and 3.99 (dd, 2H, thiazolidinyl 5-H)	
14	2195 (CN), 1701 and 1665 (C=O), 1605 (C=C)		596 (M^+, 29), 540 (10), 464 (20), 144 (100).
15	2210 (CN), 1692 and 1681 (C=O), 1522 (C=C), 745 (C–Cl)	8.54 (s, 1H, indolyl 2-H), 8.38 (s, 1H, selenolyl 5-H), 8.04–7.16 (m, 14H, Ar–H), 4.85 (d, 1H, azetidinyl 3-H), 4.10 (d, 1H, azetidinyl 2-H)	
16a	3218 (NH), 2235 (CN), 1715 (C=O), 1578 (C=C), 1366 and 1142 (SO_2–N)		530 (M^+, 31), 454 (2), 390 (2), 193 (100), 115 (15)
16b	3157 (NH), 2204 (CN), 1710 (C=O), 1567 (C=C), 1377 and 1176 (SO_2–N), 751 (C–Br)	8.25 (s, 1H, indolyl 2-H), 8.11 (s, 1H, selenolyl 5-H), 7.82–7.07 (m, 13H, Ar–H), 4.35 (1H, s, NH)	
16c	3157 (NH), 2204 (CN), 1710 (C=O), 1567 (C=C), 1377 and 1176 (SO_2–N), 759 (C–Cl)		564/566 (M^+/M^++2, 39/13), 528 (1),, 221 (100), 116 (20)

(*Continued*)

Table 2 (Continued)

Compound number	IR (γ_{max}, cm^{-1})	^1H NMR (δ, ppm)	Mass (*m/z*, %)
17	3223 (NH), 2215 (CN), 1716 (C=O), 1655 (C=C), 1084 (C–O–C)	8.34 (s, 1H, indolyl 2-H), 8.12 (s, 1H, selenolyl 5-H), 7.95–7.14 (m, 9H, Ar–H), 4.92 (s, 2H, CH_2–N), 4.21 (s, 1H, NH), 3.83 (q, 2H, CH_2), 1.56 (t, 3H, CH_3)	
18	3423 (NH_2), 3260 and 3112 (NH), 2209 (CN), 1735 (C=O), 1571 (C=C), 1245 (C=S)		
19	3402 (NH_2), 3208 (NH), 2202 (CN), 1741 (C=O), 1636 (C=N), 1607 (C=C)	8.23 (s, 1H, indolyl 2-H), 8.02 (s, 1H, selenolyl 5-H), 7.86–7.11 (m, 9H, Ar–H), 6.34 (s, 2H, NH_2), 5.15 (s, 2H, CH_2–N), 4.06 (s, 1H, NH)	503 (M^+, 16), 474 (20), 434 (11), 311 (7), 193 (100), 117 (7)
20	3122 (NH), 2212 (CN), 1707 (C=O), 1612 (C=C), 752 (C–Cl)		466/468 (M^+/M^++2, 12/4), 430 (2), 374 (2), 144 (100), 115 (15)
21	3153 (NH), 2215 (CN), 1729 (C=O), 1645 (C=N), 1546 (C=C)	8.66 (s, 1H, indolyl 2-H), 8.40 (s, 1H, selenolyl 5-H), 8.08–7.23 (m, 9H, Ar–H), 5.03 (s, 2H, CH_2), 2.46 (1H, s, NH)	
22a	3158 (NH), 2227 (CN), 1705 (C=O), 1571 (C=C), 1132 (C–O–C)	8.53 (s, 1H, indolyl 2-H), 8.36 (s, 1H, selenolyl 5-H), 8.01–7.23 (m, 9H, Ar–H), 6.12 (s, 1H, NH), 4.54 (s, 2H, CH_2–N), 3.99–2.05 (m, 8H, CH_2)	
22b	3232 (NH), 2197 (CN), 1686 (C=O), 1525 (C=C)		530 (M^+, 20), 431(20), 404 (10), 115 (15), 100 (100)
23	2214 (CN), 1710 and 1699 (C=O), 1552 (C=C)	8.46 (s, 1H, indolyl 2-H), 8.31 (s, 1H, selenolyl 5-H), 7.98–7.18 (m, 9H, Ar–H), 3.36–3.20 (m, 4H, CH_2–CH_2)	472 (M^+), 416 (11), 374 (8), 193 (50), 144 (100)
24	3408 (OH), 3135 (NH), 2215 (CN), 1695 and 1639 (C=O), 1587 (C=C)	12.12 (s, 1H, OH), 8.77 (s, 1H, indolyl 2-H), 8.22 (s, 1H, selenolyl 5-H), 8.01–7.21 (m, 9H, Ar–H), 3.95–3.73 (m, 4H, CH_2–CH_2), 6.26 (s, 1H, NH)	

Compound **3** was used as the starting material for building up fused and unfused heterocyclic systems by the reactions of α,β-bifunctional amino and cyano groups. The cyclocondensation reaction of compound **3** with either formic acid solution 85% or formamide under reflux condition led to the formation of the fused 5-(1-benzoylindol-3-yl)selenolo[2,3-*d*] pyrimidin-4(3H)-one (**4**) and 5-(1-benzoylindol-3-yl)selenolo[2,3-*d*]pyrimidin-4-amine (**5**), respectively (Scheme 1). In contrast, reaction of compound **3** with excess of carbon disulfide in ethanolic potassium hydroxide solution yielded the fused 5-(1-benzoylindol-3-yl)-1,2,3,4-tetrahydroselenolo[2,3-*d*]pyrimidin-2,4-dithione (**6**). Also, fusion of compound **3** with urea or thiourea yielded the fused 4-amino-5-(1-benzoylindol-3-yl)-1H-selenolo[2,3-*d*]pyrimidin-2-one (**7a**) and 4-amino-5-(1-benzoylindol-3-yl)-1H-selenolo[2,3-*d*]pyrimidin-2-thione (**7b**), respectively (Scheme 1).

Moreover, cyclocondensation of compound **3** with either malononitrile or ethyl cyanoacetate under reflux in the presence of piperidine as a catalyst yielded the fused 2,4-diamino-5-(1-benzoylindol-3-yl)selenolo[2,3-*b*] pyridine-3-carbonitrile (**8**) and 4-amino-6-hydroxy-3-(1-benzoylindol-3-yl)selenolo[2,3-*b*]pyridine-5-carbonitrile (**9**), respectively (Scheme 1).

In addition, heating of compound **3** in a mixture of concentrated hydrochloric acid and glacial acetic acid (3 : 1) according to the method of Ahmed *et al.* [19] yielded the new 5-(1-benzoylindol-3-yl)-2-methyl-3H-selenolo[2,3-*d*]pyrimidin-4-one (**10**), whereas acetylation of **3** using a mixture of acetic anhydride and glacial acetic acid (2 : 1) yielded the corresponding *N*-(3-cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl) acetamide (**11**) (Scheme 1).

Acid-catalyzed reaction of compound **3** with benzaldehyde in refluxing absolute ethanol yielded the Schiff base, namely 2-[(phenyl)methyleneamino)-4-(1-benzoylindol-3-yl]selenophene-3-carbonitirile (**12**), which by cyclocondensation with thioglycolic acid in dry dioxane and in the presence of anhydrous sodium sulfate led to the formation of *N*-[3-cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl]-4-oxo-2-phenylthiazolidine (**13**). Moreover, reaction of compound **12** with phenacyl bromide or chloroacetyl chloride in dry dioxane and in the presence of triethylamine led to the formation of 2-(2,3-diphenyl-4-oxoazetidin-1-yl)-4-(1-benzoylindol-3-yl) selenophene-3-carbonitrile (**14**) and 2-(3-chloro-2-phenyl-4-oxoazetidin-1-yl)-4-(1-benzoylindol-3-yl)selenophene-3-carbonitrile (**15**), respectively (Scheme 2).

In contrast, reaction of compound **3** with benzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, or 4-chlorobenzenesulfonyl chloride under reflux in dry dioxane and in the presence of triethylamine yielded the corresponding sulfonamide derivatives **16a, b, c** (Scheme 2).

Reaction of compound **3** with chloroethyl acetate in absolute methanol and in the presence of potassium carbonate as a base yielded ethyl-*N*-[(3-cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl)amino]acetate (**17**), which on treatment with thiosemicarbazide yielded compound **18** (Scheme 3). Cyclization of compound **18** by a reaction with concentrated sulfuric acid in absolute methanol led to the formation of 2-amino-5-[(3-cyano-4-(1-benzoylindol-3-yl) selenophen-2-yl) methylamino]-1,2,4-thiadiazole (**19**) (Scheme 3).

In contrast, reaction of compound **3** with chloroacetyl chloride in dry benzene led to the formation of *N*-[3-cyano-4-(1-benzoylindol-3-yl)selenophen-3-yl]chloroacetamide (**20**), which on cyclization with potassium thiocyanate in dry acetone yielded 3-[3-cyano-4-(1-benzoylindol-3-yl) selenophen-2-yl]-2-imino-4-thiazolidenone (**21**) (Scheme 3). However, reaction of compound **20** with morpholine or *N*-methylpiprazine in acetone and in the presence of potassium carbonate yielded *N*-[3-cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl]-2-morpholinoacetamide (**22a**) and *N*-[3-cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl]-2-(*N*-methylpiprazino)acetamide (**22b**), respectively (Scheme 3).

Fusion of **3** with succinic anhydride at 180°C yielded *N*-[3-cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl]pyrrolidine-2,5-dione (**23**), whereas heating of **3** with succinic anhydride in absolute ethanol yielded *N*-[3-cyano-4-(1-benzoylindol-3-yl)selenophen-2-yl] succinamic acid (**24**) (Scheme 3).

DPPH radical-scavenging activity

The preliminary DPPH radical-scavenging activity of the newly synthesized compounds was carried out at various concentrations (50, 100, 200, and 300 μg/ml) using ascorbic acid as a reference (Table 3). From the data obtained, all compounds showed no radical-scavenging effect at concentrations of 50 and 100 μg/ml. However, compounds **8** and **14** showed free radical-scavenging effects of 65.09 and 56.00%, respectively, compared with ascorbic acid, which showed a free radical-scavenging effect of 53.56% at a concentration of 200 μg/ml. However, at a concentration of 300 μg/ml, compounds **4**, **8**, **14**, and **23** showed radical-scavenging effects of 93.45, 89.09, 94.80, and 65.09%, respectively, compared with 54.57% for ascorbic acid (Table 3).

Table 3 DPPH radical-scavenging activity percentage of the most active synthesized compounds and IC_{50} values

Compound number	Scavenging activity (%)[a]				IC_{50} (μg/ml)
	50	100	200	300	
4	1.09	12.27	16.36	93.45	236.92
5	0.00	10.18	10.18	14.91	417.75
8	19.00	21.09	65.09	89.09	166.40
13	0.00	5.82	8.00	19.63	564.88
14	0.00	25.00	56.00	94.80	186.75
19	13.81	13.81	17.09	24.00	2436.61
21	12.00	12.72	15.27	16.72	2844.95
22a	5.45	9.81	14.18	16.36	1550.20
22b	5.45	7.63	11.27	16.00	2198.62
23	17.81	18.91	21.45	65.09	251.88
Negative control	0	0	0	0	0
Ascorbic acid	45.32	50.56	53.56	54.57	129.64

DPPH, 2,2′-diphenyl-1-picrylhydrazyl, [a]Results are the mean of three independent experiments.

The amount of the sample necessary to decrease the absorbance of DPPH by 50% (IC_{50}) was calculated, and it was found that 2,4-diamino-5-(1-benzoylindol-3-yl)selenolo[2,3-*b*]pyridine-3-carbonitrile (**8**) showed promising activity with a radical-scavenging effect (IC_{50}) of 166.40 μg/ml compared with ascorbic acid (IC_{50} of 129.64 μg/ml); this may be due to the presence of two primary amino group (Table 3).

Conclusion

Some novel heterocycles derived from 2-amino-4-(1-benzoylindol-3-yl) selenophene-3-carbonitrile (**3**) were prepared and evaluated for their antioxidant activity using DPPH radical-scavenging assay. 2,4-Diamino-5-(1-benzoylindol-3-yl)selenolo[2,3-*b*] pyridine-3-carbonitrile (**8**) showed promising activity, with a radical-scavenging effect (IC_{50}) of 166.40 μg/ml compared with ascorbic acid (IC_{50} of 129.64 μg/ml) as the reference.

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Conflicts of interest

There are no conflicts of interest.

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