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Synthesis of Selenium-Containing Amino Acid Analogues and Their Biological Study[1]

Sh. H. Abdel-Hafez[a, b, 2], H. A. Saad[a, c], M. R. E. Aly[a, d]

[a]*Chemistry Department, Faculty of Science, Taif University, 888, Alhawiya, Taif University, Taif, Kingdom of Saudi Arabia*

[b]*Chemistry Department, Faculty of Applied Science, Assiut University, Assiut, Egypt*

[c]*Chemistry Department, Faculty of Applied Science, Zagazig University, Zagazig, Egypt*

[d]*Chemistry Department, Faculty of Applied Science, Port Said University, Egypt*

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Abstract—Synthesis of selenium-containing amino acid analogues is described. These compounds were prepared in a concise and short synthetic route in good yields by nucleophilic substitution reaction of pyridineselenol and quinolineselenol derivatives with *N*-phthaloylglycyl chloride followed by hydrazinolysis. The newly synthesized compounds were screened against different strains of bacteria and fungi.

Keywords: pyridineselenol, quinolineselenol, amino acid, anti-bacterial activities, anti-fungal activities

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In recent years, the interest in organoselenium chemistry increased remarkably due to its pivotal role in the synthesis of a large number of biologically active compounds and important therapeutic products ranging from anticancer, antioxidant and antifungal to naturally occurring food supplements [1–7].

Moreover, selenium is an essential micronutrient for animals and humans: to date, its bioavailability seems to depend upon the naturally occurring selenium-containing amino acids selenocysteine, selenomethionine, other seleno amino acids, such as selenocystathionine, are also involved in seleno amino acid metabolic pathways [8, 9].

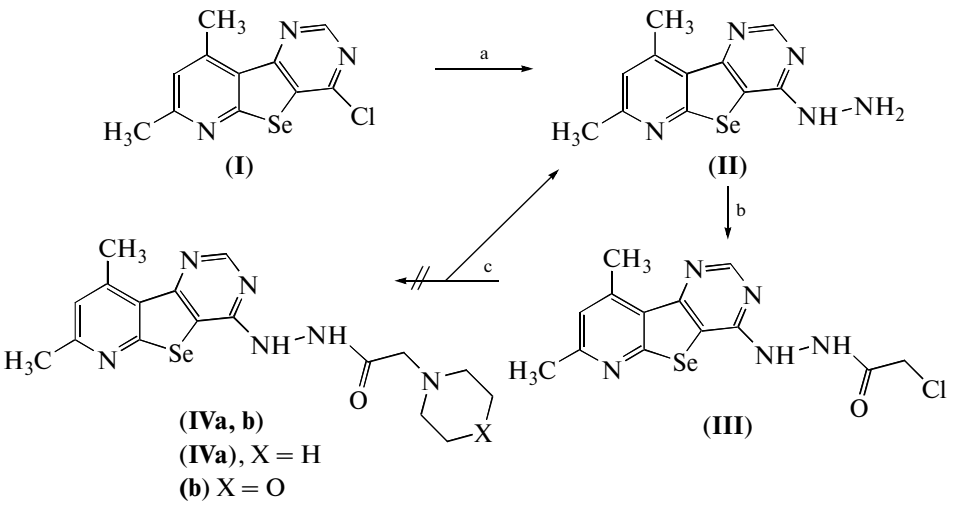
In our previous work, we described the synthesis of pyrimidoselenolo[2,3-*b*]quinoline [10], pyrimidoselenolo[2,3-*c*]pyridazine [11] and demonstrated that certain compounds manifest significant anti-inflammatory and analgesic activities with strong fungicidal effects. Stimulated by our recent work on the synthesis of selenium-containing sulfa drugs [12], we decided to expand our interest to the introduction of an organoselenium compounds in the amino acid analogues framework. To accomplish this task, we sought to functionalize the pyridineselenol and quinolineselenol derivatives with *N*-phthaloylglycyl chloride followed by hydrazinolysis by hydrazine hydrate followed by treatment with HCl.

To accomplish and attend our plan, firstly we started with compound (**I**) and prepared 4-hydrazino-7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidine (**II**) as described previously [13].

Compound (**II**) reacted with chloroacetyl chloride to furnish 2-chloro-*N*'-(7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-*d*]pyrimidin-4-yl)acetohydrazide (**III**), which, when allowed to react with piperidine or morpholine, afforded compound (**II**) instead of (**IVa**), (**IVb**). This cleavage of the amide linkage in compound (**III**) by amines instead of nucleophilic substitution is due to enhancement of the sensitivity of the carbonyl group to nucleophiles induced by the electronegativity of the β-chlorine atom (Scheme 1).

[1] The article is published in the original.

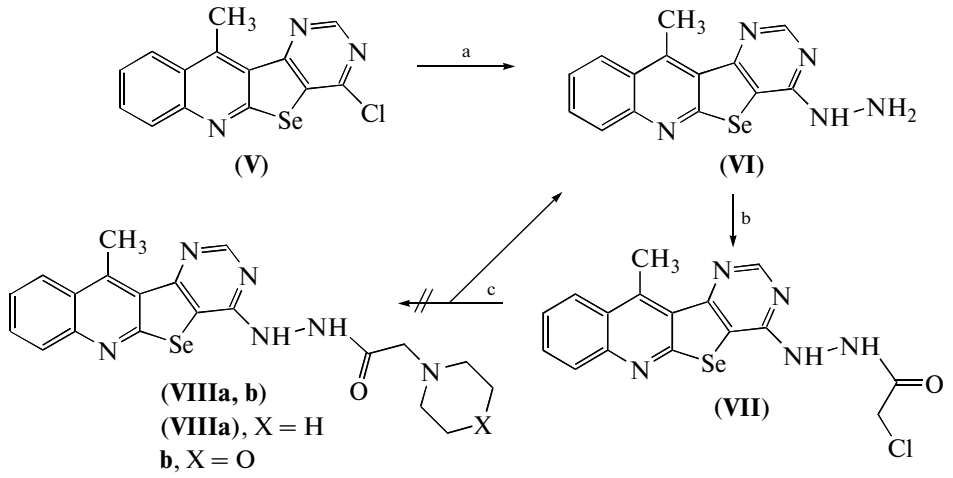
[2] Corresponding author: phone: 00966 552453944; e-mail: sabdel68@yahoo.co.uk; shams@aun.edu.eg.



Reagents and conditions: (a) NH_2NH_2, reflux; (b) $ClCOCH_2Cl$, room temperature; (c) piperidine/morpholine, reflux

Scheme 1.

In an attempt to introduce amino acid analogues into organoselenium compounds, we tested the quinoline derivative instead of that with the pyridine nucleus. The reaction of 4-hydrazino-11-methylpyrimido[4',5':4,5]selenolo[2,3-*b*]quinoline (**VI**) [11] with chloroacetyl chloride afforded 2-chloro-*N*'-(11-methylpyrimido[4',5':4,5]selenolo[2,3-*b*]quinolin-4-yl)acetohydrazide (**VII**). Its reaction with piperidine or morpholine afforded compound (**VI**) rather than compounds (**VIIIa**), (**VIIIb**) and the reason for that seems to be the same as mentioned above (Scheme 2).

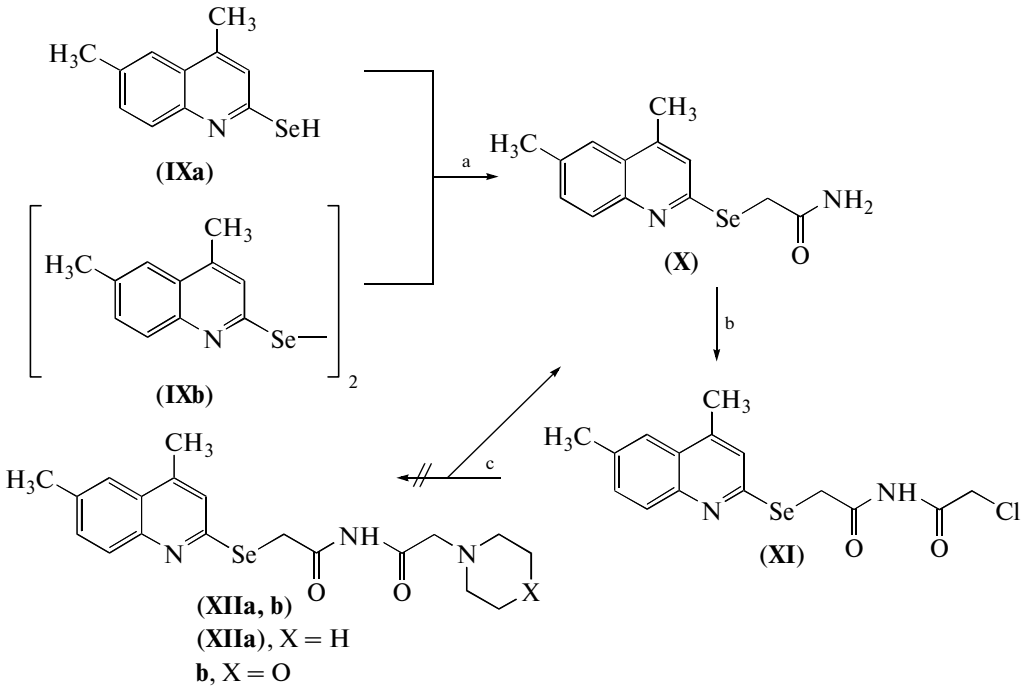


Reagents and conditions: (a) NH_2NH_2, reflux; (b) $ClCOCH_2Cl$, room temperature; (c) piperidine/morpholine, reflux

Scheme 2.

Yet another putative precursor, 4,6-dimethylquinoline-2-selenol (**IXa**), was prepared by the reaction of 2-chloro-4,6-dimethylquinoline with sodium hydrogenselenide in ethanol in low yield (10%); diquinolinyl diselenide derivative (**IXb**) formed in high yield (90%) due to self oxidation of (**IXa**) in air accelerated by heating [14]. Compounds (**IXa**) and (**IXb**) were isolated by fractional crystallization.

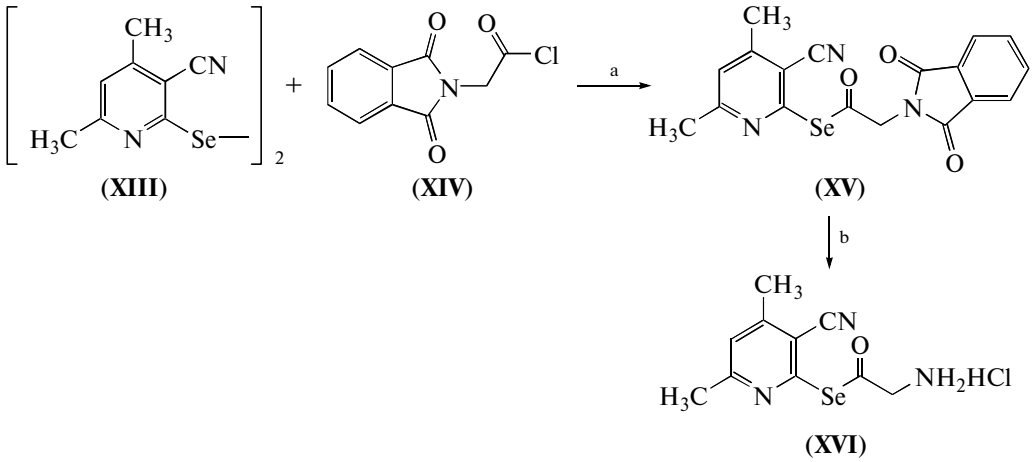
The reaction of derivatives (**IXa**) and (**IXb**) with chloroacetamide in refluxing ethanol in the presence of sodium borohydride afforded 2-[(4,6-dimethylquinolin-2-yl)selanyl]acetamide (**X**), which allowed to react with chloroacetyl chloride to yield (**XI**). Again, the reaction with piperidine or morpholine afforded compound (**X**) instead of (**XIIa**), (**XIIb**) (Scheme 3).



Reagents and conditions: (a) $ClCH_2CONH_2$, $NaBH_4$, reflux; (b) $ClCOCH_2Cl$, room temperature; (c) piperidine/morpholine, reflux

Scheme 3.

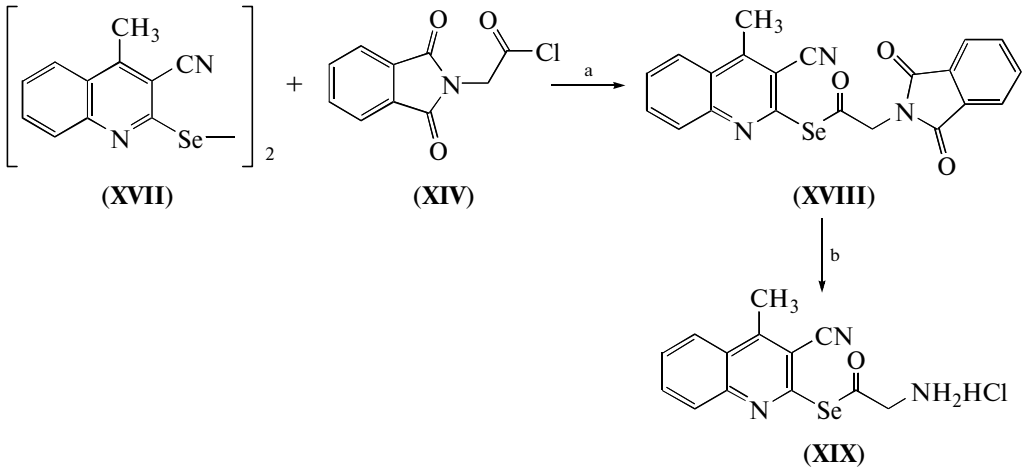
Secondly, to accomplish our target we started with another precursor, *viz.*, *N*-phthaloylglycyl chloride (**XIV**), which has been prepared long ago [15], and allowed to react with organoselenium compound (**XIII**) to yield 3-cyano-4,6-dimethyl-*Se*-[(*N*-phthalimido)glycyl]pyridine-2-selenol (**XV**), which on hydrazinolysis with NH_2NH_2 followed by treatment with 2 N HCl gave the corresponding 3-cyano-*Se*-glycyl-4,6-dimethylpyridine-2-selenol hydrochloride (**XVI**) (Scheme 4).



Reagents and conditions: (a) $NaBH_4$, EtOH, reflux; (b) (i) NH_2NH_2/reflux, (ii) 2M HCl, 40°C, 5 min

Scheme 4.

Under similar conditions, compound (**XVII**) reacted with (**XIV**) to form 3-cyano-4-methyl-*Se*-[(*N*-phthalimido)glycyl]quinoline-2-[(N-phthalimido)glycyl]quinoline-2-selenol (**XVIII**), which on hydrazinolysis furnished the corresponding 3-cyano-*Se*-glycyl-4-methylquinoline-2-selenol hydrochloride (**XIX**) (Scheme 5).

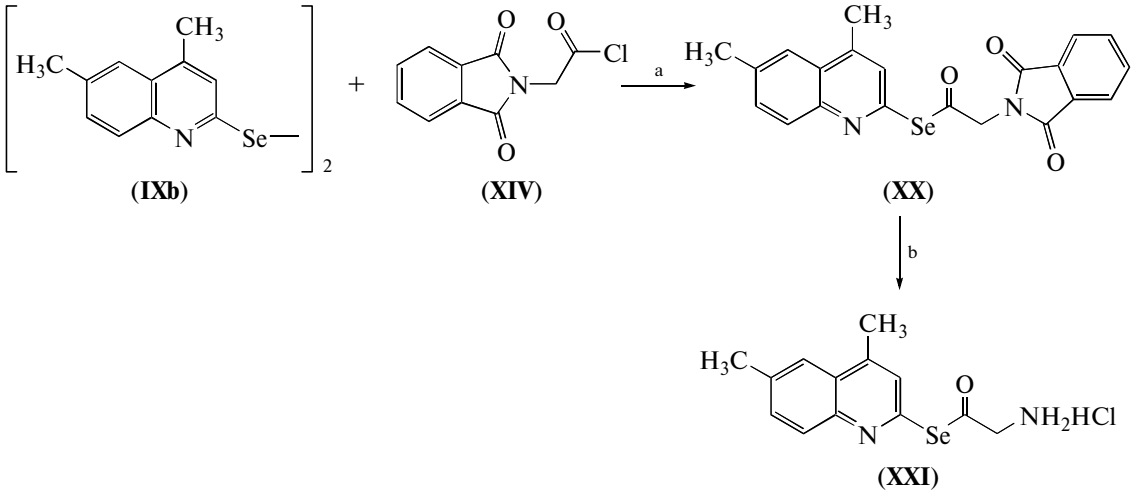


(**XVII**) (**XIV**) (**XVIII**) (**XIX**)

Reagents and conditions: (a) $NaBH_4$, EtOH, reflux; (b) (i) NH_2NH_2/reflux, (ii) 2M HCl, 40°C, 5 min

Scheme 5.

Finally, as the last example in our target plan, the reaction of compound (**IXb**) with compound (**XIV**) afforded derivative (**XX**), i.e., 4,6-dimethyl-Se-[(*N*-phthalimido)glycyl]quinoline-2-selenol, which on hydrazinolysis furnished *Se*-glycyl-4,6-dimethylquinoline-2-selenol hydrochloride (**XXI**) (Scheme 6).



(**IXb**) (**XIV**) (**XX**) (**XXI**)

Reagents: (a) $NaBH_4$, EtOH/ref.; (b) (i) NH_2NH_2/reflux, (ii) 2N HCl/heat 5 min/40°C

Scheme 6.

The structures of the synthesized compounds were confirmed by their physical, analytical and spectral data (Table 1).

The antimicrobial screenings of the synthesized compounds were undertaken using agar well diffusion assay [16]. Table 2 lists the screening results of the tested compounds against Gram-negative and Gram-positive bacteria. Five bacterial test organisms such as *Staphylococcus aureus* (B-54), *Bacillus cereus* (B-52), *Escherichia coli* (B-53), *Serratia marcescens* (B-55), and *Pseudomonas aeruginosa* (B-73) and seven fungi test organism such as *Candida albicans* (418), *Geotrichum candidum* (226), *Trichophyton rubrum* (1804), *Fusarium oxysporum* (5119), *Scopulariopsis brevicaulis* (729), *Aspergillus flavus* (1276) were obtained from Assiut University Mycological Center. Chloramphenicol was used as an antibacterial standard, while Clotrimazole was used as an antifungal standard. DMSO was used as a blank, which exhibited no activity against any of the used organisms. The obtained data revealed that most of the compounds selected ((**II**), (**IXb**), (**X**), (**XV**), (**XVI**), (**XVIII**)–(**XXI**)) showed

Table 1. Physical and spectral data of compounds **(III)**, **(VII)**, **(IXa)**, **(IXb)**, **(X)**, **(XI)**, **(XV)**, **(XVI)**, **(XVIII)**–**(XX)** and **(XXI)**

Compd. no.	Mp °C (yield %)	Mol. formula (W/wt)	IR (cm^{-1})	^1H NMR (δ, ppm)
(III)	150–152 (60)	$C_{13}H_{12}ClN_5OSe$ (368.68)	3250–3200 (NH), 1650 (CO amide), 1610 (C=N)	$CDCl_3$: 8.04 (s, 1H, CH-pyrimidine); 7.18 (s, 1H, CH-pyridine); 5.35 (br, 1H, NH, NHNHCO); 3.96 (s, 2H, CH_2) 2.81, 2.89 (2s, 6H, $2CH_3$); 1.13 (s, 1H, NH, NHNHCO).
(VII)	160–162 (72)	$C_{16}H_{12}ClN_5OSe$ (404.71)	3400 (NH), 1660 (CO amide), 1610 (C=N)	DMSO-d_6: 8.72 (s, 1H, CH-pyrimidine); 7.30–8.31 (m, 4H, Ar-H); 4.45 (s, 2H, CH_2); 4.30 (s, 1H, NH, NHNHCO); 3.52 (s, 1H, NH, NHNH CO); 3.10 (s, 3H, CH_3).
(IXa)[a]	175–177 (10)	$C_{11}H_{11}NSe$ (236.17)	1615 (C=N)	DMSO-d_6: 7.42–7.78 (m, 4H, Ar-H); 3.60 (br, 1H, NH); 2.40 (s, 6H, $2CH_3$).
(IXb)[b]	275–277 (90)	$C_{22}H_{20}N_2Se_2$ (470.33)	1615 (C=N)	DMSO-d_6: 7.01–7.90 (m, 8H, Ar-H); 2.43 (s, 12H, $4CH_3$).
(X)[a]	180–182 (81)	$C_{13}H_{14}N_2OSe$ (293.22)	3150–3370 (NH_2); 1670 (CO-amide); 1620 (CN)	DMSO-d_6: 7.46–7.87 (m, 4H, Ar-H); 7.43 (s, 1H, NH_2); 3.82 (s, 2H, CH_2); 2.53 (s, 3H, CH_3); 2.50 (s, 3H, CH_3).
(XI)[a]	170–172 (73)	$C_{15}H_{15}ClN_2O_2Se$ (369.70)	3400 (NH); 1679 (CO-amide); 1610 (C=N)	DMSO-d_6: 8.90 (br, 1H, NH); 7.38-7.95 (m, 4H, Ar-H); 4.19 (s, 2H, $COCH_2Cl$); 3.95 (s, 2H, $SeCH_2CO$); 2.64 (s, 3H, CH_3); 2.60 (s, 3H, CH_3).
(XV)[a,b]	100–102 (90)	$C_{18}H_{13}N_3O_3Se$ (398.27)	2200 (CN); 1720, 1680,1660 (3 CO)	DMSO-d_6: 7.50–7.95 (m, 4H, Ar-H); 7.42 (s, 1H, CH-pyridine); 4.40 (s, 2H, CH_2); 2.60 (s, 3H, CH_3); 2.40 (s, 3H, CH_3).
(XVI)[a]	>300 (76)	$C_{10}H_{12}ClN_3OSe$ (304.63)	3310–3190 (NH_2); 2200 (CN); 1690 (CO)	TFA: 8.30 (s, 2H, NH_2HCl); 8.21 (s, 1H, CH-pyridine); 4.70 (s, 2H, CH_2); 3.45 (s, 3H, CH_3); 3.20 (s, 3H, CH_3).
(XVIII)[a,b]	110–112 (75)	$C_{21}H_{13}N_3O_3Se$ (434.31)	2200 (CN); 1720,1670,1660 (3 CO)	DMSO-d_6: 7.20–8.10 (m, 8H, Ar-H); 4.50 (s, 2H, CH_2); 2.81 (s, 3H, CH_3).
(XIX)[a]	>300 (76)	$C_{13}H_{12}ClN_3OSe$ (340.67)	3330–3140 (NH_2); 2200 (CN); 1680 (CO)	TFA: 8.10–8.60 (m, 4H, Ar-H); 7.55 (s, 2H, NH_2HCl); 4.40 (s, 2H, CH_2); 3.01 (s, 3H, CH_3).
(XX)[a,b]	140–142 (70)	$C_{21}H_{16}N_2O_3Se$ (423.32)	1710,1670,1660 (3 CO); 1620 (C=N)	DMSO-d_6: 7.27–7.71 (m, 7H, Ar-H); 7.26 (s, 1H, CH-pyridine); 3.92 (s, 2H, CH_2); 2.67 (s, 3H, CH_3); 2.60 (s, 3H, CH_3).
(XXI)[a]	>300 (74)	$C_{13}H_{15}ClN_2OSe$ (329.68)	3320–3120 (NH_2); 1670 (CO)	TFA: 7.48–7.89 (m, 3H, Ar-H); 7.20 (s, 1H, CH-pyridine); 7.42 (s, 2H, NH_2HCl); 3.76 (s, 2H, CH_2); 2.61 (s, 3H, CH_3); 2.34 (s, 3H, CH_3).

Notes: [a] MS (see experimental Section).
[b] ^{13}C NMR of compounds **(XV)**, **(XVIII)** and **(XX)** (see Section 4).

no activity against all organisms used except for compounds **(II)** and **(XVIII)**, which showed remarkably broad-spectrum potency against *Staphylococcus aureus, Bacillus cereus, Escherichia coli*, and *Pseudomonas aeruginosa* with inhibition zone of 13, 12, 10, 8 mm for compound **(XVIII)** at concentration of 20 mg/ml and inhibition zone at 9, 9 and 12 mm for compound **(II)** at concentration of 20 mg/ml with minimum inhibition concentration (MIC) values of 8 and 12 mg/ml, respectively. Of the synthesized compounds, only compounds **(II)** and **(XVIII)** showed strong fungicidal effect against all species of fungi. The MIC of these compounds was 11, 10 mg/ml (50%). The strong fungicidal and bactericidal effect of these two compounds is presumably due to the presence of either the cyano group or quinoline nucleus in compound **(XVIII)** or amino group in addition to the pyridine nucleus in compound **(II)**. These compounds seem to be good bactericidal and fungicidal candidates against all species of bacteria and fungi. Generally, it was noticed that the activities of the tested compounds are less than those of standard antifungal and antibacterial agents used.

Thus, a new series of selenium-containing amino acid analogues were prepared in a concise and short synthetic route in good yields by a nucleophilic substitution reaction. Organoselenium compounds **(XVI)**,

Table 2. Antibacterial activity (inhibition zone in mm)

Organisms \ Sample No.	(XVIII)					(II)				(IX)*						
	20	10	5	2.5	1.25	20	10	5	2.5	20	10	5	2.5	1.25	0.6	0.3
Staphylococcus aureus (+ve) AUMC No. B-54	13	13	10	8	0	9	8	8	0	17	17	15	13	12	12	10
Bacillus cereus (+ve) AUMC No B-52	12	12	8	0	–	0	–	–	–	34	34	32	30	28	25	18
Escherichia coli (–ve) AUMC No. B-53	10	8	0	–	–	9	8	0	–	30	26	26	20	16	14	12
Serratia marcescens (–ve) AUMC No. B-55	0	–	–	–	–	0	–	–	–	41	40	38	34	28	26	20
Pseudomonas aeruginosa (–ve) AUMC No. B-73	8	8	0	–	–	12	0	–	–	16	14	12	12	10	10	10

Note: **(IX)*** = Chloramphenicol as antibacterial standard. AUMC = Assiut University Mycological Center.

Table 2. Continued: Antifungal activity (inhibition zone in mm)

Organisms \ Sample No.	(XVIII)						(II)				(IX)**						
	20	10	5	2.5	1.25	0.6	20	10	5	2.5	20	10	5	2.5	1.25	0.6	0.3
Candida albicans AUMC No. 418	12	12	10	8	8	0	14	13	8	0	30	30	30	26	26	26	26
Geotrichum candidum AUMC No. 226	10	10	9	0	–	–	16	13	0	–	24	22	22	22	22	22	22
Trichophyton rubrum AUMC No. 1804	14	11	0	–	–	–	14 p.i.	0	–	–	35	34	34	34	34	34	34
Fusarium oxysporum AUMC No. 5119	13	11	10	8	0	–	0	–	–	–	22	22	22	22	18	18	18
Scopulariopsis brevicaulis AUMC No. 729	18 p.i.	0	–	–	–	–	14	10	8	0	26	24	23	23	20	20	20
Aspergillus flavus AUMC No. 1276	15	15	11	0	–	–	18	14	10	0	27	27	27	25	25	25	25

Note: **(IX)**** = Clotrizmazole as antifungal standard. AUMC = Assiut University Mycological Center.

Table 2. Continued: Antibacterial activity (inhibition zone in mm and MICs given in brackets of chemical compounds tested, Chloramphenicol (CHL) used as standard

Sample No.	*Staphylococcus aureus* (+ve)	*Bacillus cereus* (+ve)	*Escherichia coli* (–ve)	*Serratia marcescens* (–ve)	*Pseudomonas aeruginosa* (–ve)
(II)	8(5)	–	8(10)	–	12(20)
(XVIII)	8(2.5)	8(5)	8(10)	–	8(10)
(IX)*	10(0.3)	18(0.3)	12(0.3)	20(0.3)	10(0.3)

Table 2. Continued: Antifungal activity (inhibition zone in mm and MICs given in brackets of chemical compounds tested, Clotrimazole (CLO) used as standard

Sample No.	*Candida albicans*	*Geotrichum candidum*	*Trichophyton rubrum*	*Fusarium oxysporum*	*Scopulariopsis brevicaulis*	*Aspergillus flavus*
(II)	8(5)	13(10)	14 p.i.(20)	–	8(5)	10(5)
(XVIII)	8(1.25)	9(5)	11(10)	8(2.5)	18 p.i.(20)	11(5)
(IX)**	26(0.3)	22(0.3)	34(0.3)	18(0.3)	20(0.3)	25(0.3)

The authors have declared no conflict of interest.

(**XIX**) and (**XX**) that contain glycyl moiety did not have antimicrobial activity against the tested organisms.

It seems obvious that quinolineselenol and pyridineselenol derivatives in which the quinoline ring is bearing cyano and phthalimido groups (compound **XVIII**), as well as pyridine nucleus carrying hydrazino group (compound **II**) demonstrated the best results in the biological screening.

EXPERIMENTAL CHEMISTRY

Melting points were determined using a Kofler melting point apparatus and are uncorrected. IR spectra were recorded on a Pye-Unicam SP3-100 instrument in KBr wafer. The mass spectra (EI, 70 eV, ion source temperature 210°C) were recorded on a Jeol JMS600 instrument. ^{1}H NMR spectra were obtained on a Varian spectrometer (90 MHz) using tetramethylsilane as the internal reference. ^{13}C NMR spectra were recorded on a JNM-LA spectrometer (400 MHz) at Assiut University. Elemental analyses were obtained on an Elementar Vario EL 1150C analyser. Purity of the compounds was checked by TLC using silica gel plates.

Compounds (**I**), (**II**), (**V**), (**VI**), (**XIII**), and (**XVII**) were prepared as previously described [11, 13, 14].

***N*-Chloroacetylation (general procedure).** Chloroacetyl chloride (10 mmol) was added dropwise to a solution of compounds (**II**), (**VI**) or (**X**) (10 mmol) in dioxane (20 ml) and the reaction mixture was stirred for 3 h at room temperature, then poured into cold water. The precipitate was collected and recrystallized from ethanol to give yellow crystals of compound (**III**), red crystals of compound (**VII**) and yellow crystals of compound (**XI**).

2-Chloro-*N*'-(7,9-dimethylpyrido[3',2':4,5]selenolo [3,2-*d*]pyrimidin-4-yl)acetohydrazide (III). MS of compound (**III** exhibited molecular ion peak at *m/z* (I_{rel}, %) 368.22 ([*M*]$^+$, 12) and other important fragments were observed at *m/z* 364.19 (7), 353.27 (17), 327.18 (22), 198.19 (9), 80.66 (100), 79.86 (34). Found, %: C, 42.20; H, 3.00; N, 18.88; Cl, 9.45. $C_{13}H_{12}ClN_5OSe$. Calcd., %: C, 42.35; H, 3.28; N, 19.00; Cl, 9.62.

2-Chloro-*N*'-(11-methylpyrimido[4',5':4,5]selenolo [2,3-*b*]quinolin-4-yl)acetohydrazide (VII). MS of compound (**VII**) exhibited molecular ion peak at *m/z* (I_{rel}, %) 404 ([*M*]$^+$, 2) and other important fragments were observed at *m/z* 368 (44), 326 (100), 284 (18), 73 (24). Found, %: C, 47.13; H, 2.77; N, 17.10; Cl, 8.45. $C_{16}H_{12}ClN_5OSe$. Calcd., %: C, 47.48; H, 2.99; N, 17.30; Cl, 8.76.

2-Chloro-*N*-(2-(4,6-dimethylquinolin-2-ylselanyl) acetyl)acetamide (XI). MS of compound (**XI** exhibited molecular ion peak at *m/z* (I_{rel}, %) 368.85 ([*M* − 1]$^+$, and other important fragments were observed at *m/z* 293.49 (57), 249.57 (100), 246.56 (43), 235.56 (17), 155.77 (43). Found, %: C, 48.44; H, 3.88; N, 7.32; Cl, 9.29. $C_{15}H_{15}ClN_2O_2Se$. Calcd., %: C, 48.73; H, 4.09; N, 7.58; Cl, 9.59.

4,6-Dimethylquinoline-2-selenol (IXa). A mixture of 4,6-dimethyl-2-chloroquinoline (1.8 g, 10 mmol), metallic selenium (1 g, 12 mmol) and sodium borohydride (1.2 g, 32 mmol) were refluxed in 50 ml ethanol for 2 h. The mixture was cooled and poured onto ice-cold HCl. The solid thus separated which contain a mixture of compounds (**IXa**), (**IXb**) was filtered off, dried and recrystallized from ethanol to give the title compound as yellow crystals. Yield 0.2 g (10%); the mass spectrum of compound (**IXa**) exhibited molecular ion peak at *m/z* (I_{rel}, %) 236 ([*M*]$^+$, 100) and other important fragments were observed at *m/z* 155.7 (41), 140.7 (13), 75.9 (3). Found, %: C, 55.78; H, 4.47; N, 5.85. $C_{11}H_{11}NSe$. Calcd., %: C, 55.94; H, 4.69; N, 5.93.

2,2'-Bis(4,6-dimethylquinolinyl) diselenide (IXb) was not dissolved during the crystallization from ethanol. The solid was dried and recrystallized from dioxane to give (**IXb**) as an orange crystals; Yield (0.39 g, 90%).

MS of compound (**IXb**) exhibited a molecular ion peak at *m/z* (I_{rel}, %) 472.4 ([*M* + 2]$^+$, 13) and other important fragments were observed at *m/z* (I_{rel}, %) 390.1 (16), 236.4 (100), 155.7 (41), 140.7 (13), 75.9 (3). Found, %: C, 56.00; H, 4.11; N, 5.69. $C_{22}H_{20}N_2Se_2$. Calcd., %: C, 56.18; H, 4.29; N, 5.96.

2-[(4,6-Dimethylquinolin-2-yl)selanyl]acetamide (X). A mixture of compounds (**IXa**) and (**IXb**) as obtained from the reaction mixture (7.05 g, 15 mmol), sodium borohydride (0.63 g, 17 mmol) and chloroacetamide (1.40 g, 15 mmol) in 30 ml of ethanol was heated under reflux for 2 h, the reaction mixture allowed to cool and poured onto 50 ml ice water. The solid product was collected by filtration and recrystallized from dioxane as yellow crystals. Yield 8.7 g (80%); MS of compound (**X**) exhibited a molecular ion peak at *m/z* (I_{rel}, %) 294.3 ([*M* + 2]$^+$, 13) and other important fragments were observed at *m/z* (I_{rel}, %) 293.73 (10), 249.54 (15), 190.92 (100), 155.94 (40), 127.95 (20). Found, %: C, 53.10; H, 4.66; N, 9.33. $C_{13}H_{14}N_2OSe$. Calcd., %: C, 53.25; H, 4.81; N, 9.55.

***Se*-Acylation (general procedure).** A mixture of a diselenide (**XIII**), (**XVII**) and (**IXb**) (10 mmol), sodium borohydride (0.44 g, 12 mmol) and *N*-phthaloylglycyl chloride (2.2 g, 10 mmol) in 30 ml of ethanol was heated under reflux for 1 h, the reaction mixture allowed to cool and poured onto 50 ml ice water. The solid product was collected by filtration and recrystallized from petroleum ether (60–80°C) (**XV**) or ethanol ((**XVIII**) and (**XX**)).

3-Cyano-4,6-dimethyl-*Se*-[(*N*-phthalimido)glycyl] pyridine-2-selenol (XV), pale yellow crystals. ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.4, 24.3 ($2CH_3$), 38.5 (CH_2), 108.2, 114.1, 123.2, 123.5, 131.7, 134.2, 152.1, 154.4, 162.5, 167.3, 170.7 (C≡N, 7 C=C, C=N, 2 C=O); MS of compound (**XV**) exhibited molecular

ion peak at *m/z* (I_{rel}, %) 399.96 ([*M* + 1]$^+$, 4) and other important fragments were observed at *m/z* 250.99 (7), 227.93 (33), 165.94 (18), 129.98 (17), 68.97 (39). Found, %: C, 54.01; H, 3.11; N, 10.28. $C_{18}H_{13}N_3O_3Se$. Calcd., %: C, 54.28; H, 3.29; N, 10.55.

3-Cyano-4-methyl-*Se*-[(N-phthalimido)glycyllquinoline-2-selenol (XVIII), pale yellow crystals. ^{13}C NMR (DMSO-d_6, 75 MHz) δ 16.6, (CH_3), 53.4, (CH_2), 114.2, 116.9, 122.6, 123.8, 124.4, 127.1, 130.9, 131.6, 133.5, 145.8, 150.9, 153.8, 158.6, 166.4 (C≡N, 10 C=C, C=N, 2 C=O); MS of compound (**XVIII**) exhibited molecular ion peak at *m/z* (I_{rel}, %) 434.30 ([*M* + 1]$^+$, and other important fragments were observed at 290.00 (9), 222.9 (30), 247.99 (15), 168.07 (11), 78.05 (39). Found, %: C, 57.88; H,2.88; N, 9.56. $C_{21}H_{13}N_3O_3Se$. Calcd., %: C, 58.08; H, 3.02; N, 9.68.

4,6-Dimethyl-*Se*-[(*N*-phthalimido)glycyl]quinoline-2-selenol (XX), pale yellow crystals. ^{13}C NMR (DMSO-d_6, 75 MHz) δ 18.6, 21.4 ($2CH_3$), 43.7, (CH_2), 122.6, 122.0, 127.4, 129.0, 130.0, 132.1, 132.3, 135, 141.8, 146.0, 150.9, 153.8, 155.6, 166.5 (10 C=C, C=N, 2 C=O); MS of compound (**XX**) exhibited molecular ion peak at *m/z* (I_{rel}, %) 423.31 ([*M* + 1]$^+$, 1) and other important fragments were observed at *m/z* (I_{rel}, %) 375.99 (5), 312.9 (16), 287.94 (11), 227.87 (54), 50.98 (100). Found, %: C, 59.35; H, 3.77; N, 6.68. $C_{21}H_{16}N_2O_3Se$. Calcd., %: C, 59.58; H, 3.81; N, 6.62.

Hydrazinolysis (general procedure). Compound (**XV**), (**XVIII**), (**XX**) (10 mmol) in ethanol (25 ml) was refluxed with hydrazine hydrate (10 ml) for 1 h, and the reaction mixture was concentrated to dryness. The residue was heated at 40°C for 10 min with 2M HCl (30 ml), allowed to stand at room temperature for 30 min and the precipitate of phthalohydrazide was filtered off. The filtrate was concentrated and the residue was recrystallized from DMF–H_2O to give pale yellow crystals.

3-Cyano-*Se*-glycyl-4,6-dimethylpyridine-2-selenol hydrochloride (XVI). MS of compound (**XVI**) exhibited molecular ion peak at *m/z* (I_{rel}, %) 302.00 ([*M* – 2]$^+$, 0.4) and other important fragments were observed at *m/z* 163.06 (100), 148.07 (15), 135.09 (8), 114.98 (18), 78.97 (34). Found, %: C, 39.22; H, 3.88; N, 13.76; Cl, 11.44. $C_{10}H_{12}ClN_3OSe$. Calcd., %: C, 39.43; H, 3.97; N, 13.79; Cl, 11.64.

3-Cyano-*Se*-glycyl-4-methylquinoline-2-selenol hydrochloride (XIX). MS of compound (**XIX**) exhibited molecular ion peak at *m/z* (I_{rel}, %) 340.70 ([*M*]$^+$, 2%) and other important fragments were observed at *m/z* 309.13 (2), 199.01 (44), 148.92 (95), 78.95 (86), 62.94 (100), 69.03 (27), 57.02 (38). Found, %: C, 45.66; H, 3.22; N, 12.02; Cl, 10.16. $C_{13}H_{12}ClN_3OSe$. Calcd., %: C, 45.83; H, 3.55; N, 12.33; Cl, 10.41.

***Se*-Glycyl-4,6-dimethylquinoline-2-selenol hydrochloride (XXI).** MS of compound (**XXI**) exhibited molecular ion peak at *m/z* (I_{rel}, %) 330.00 ([*M* + 1]$^+$, 2) and other important fragments were observed at *m/z* 294.03 (6), 237.01 (100), 157.09 (18), 143.07 (14), 119.07 (11), 109.00 (10). Found, %: C, 47.11; H, 4.38; N, 8.30; Cl, 10.66. $C_{13}H_{15}ClN_2OSe$. Calcd., %: C, 47.36; H, 4.59; N, 8.50; Cl, 10.75.

BIOLOGICAL SCREENING ASSAY

Antibacterial Activity

Five bacterial species representing both Gram-positive and Gram-negative strains were used to test the antibacterial activities of the target compounds (**II**), (**IXa**), (**IXb**), (**X**), (**XV**), (**XVI**), (**XVIII**), (**XIX**), (**XX**) and (**XXI**) in vitro, in comparison to Chloramphenicol as a reference drug using the standard agar paper disc diffusion method [16]: *S. aureus* (B-54), *B. cereus* (B-52), *E. coli* (B-53), *S. marcescens* (B-55), and *P. aeruginosa* (B-73). Cell suspensions of bacterial stains were prepared from 48 h old cultures grown on potato dextrose agar (PDA) or Sabouraud agar (SA) media. One ml of the cell suspension was added to Petri dishes of 9 cm in diameter, and then 15 ml of nutrient agar was poured onto the plates. Plates were shaken gently to homogenize the innoculum. Sterile 5 mm filter paper (Whatmann, UK) was saturated with 10 mg ml^{-1} of the test compound, Chloramphenicol solutions (200, 100, 50, 25, 15.5, 6 mg ml^{-1} concentrations) as reference drug or DMSO as negative control. Impregnated discs were then dried for 1 h and placed in the centre of each plate. The seeded plates were incubated at 35 ± 2°C for 24–48 h. The radii of the inhibition zones in mm of triplicate sets were measured and the results are given in Table 2.

Antifungal Activity

Compounds (**II**), (**IXa**), (**IXb**), (**X**), (**XV**), (**XVI**), (**XVIII**)–(**XX**) and (**XXI**) were screened for their antifungal activity in vitro, in comparison to *Clotrimazole* as a referencedrug using the standard agar paper disc diffusion method against seven fungi: *C. albicans* (418), *G. candidum* (226), *T. rubrum* (1804), *F. oxysporum* (5119), *S. brevicaulis* (729), *A. flavus* (1276). A spore suspension in sterile distilled water was prepared from 2–3 days old culture of the fungi growing on potato dextrose agar (PDA) or Sabouraud agar (SA) media. The final spore concentration was 56104 spores ml^{-1}. About 15 ml of the growth medium was placed into sterile petri dishes of 9 cm in diameter and incubated with 1 ml of the spore suspension. Plates were shaken gently to 28 ± 2°C for 7 days. The radii of the inhibition zones in mm of triplicate sets were measured and the results had shown in Table 2.

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