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Facile synthesis and antimicrobial evaluations of some novel pyrazolo[3,4-*b*]selenolo[3,2-*e*]pyrazines and their related heterocycles

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Abstract

A new series of pyrazolopyrazinoselenolotriazolopyrimidines was synthesized by a facile method based on condensation of 5-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]selenolo[3,2-*e*]pyrazine-6-carbonitrile (**3**) with triethyl orthoformate followed by intramolecular cyclization with hydrazine to afford 7-amino-8-imino-3-methyl-1-phenyl-1,8-dihydro-7*H*-pyrazolo[3″,4″:5′,6′]pyrazino[2′,3′:4,5] selenolo [3,2-*d*]pyrimidine (**5**). The latter compound was utilized as a multipurpose precursor for the construction of other new triazoles fused to the pyrazolopyrazinoselenolopyrimidine moiety. Alternatively, acetylation and chloro-acetylation of compound **3** using acetic anhydride and chloroacetyl chloride yielded the acetyl amino **11** and chloroacetamido **12** derivatives, respectively. Compound **12** underwent nucleophilic substitution upon reaction with morpholine to provide the morpholinyl acetamide **13**. Furthermore, the pyrazolopyridoselenolopyrazine ring system **14** was synthesized by the reaction of the *o*-amino-carbonitrile **3** with malononitrile. Assignment of the chemical structures for the new compounds was confirmed depending on elemental and spectral techniques. On the other hand, most of the synthesized compounds revealed promising results against various bacterial and fungal strains.

1 | INTRODUCTION

Pyrazolo[3,4-*b*]pyrazines have occupied superior place in heterocyclic chemistry. Many pyrazolopyrazines are essential intermediates and are widely used in several applications in medicinal and pharmaceutical chemistry. Scaffolds containing pyrazolopyrazine moiety are considered as antibacterial, antifungal [1], anticancer [2], improvers of bone metabolism [3], blood platelet aggregation [4], anticonvulsant [5], antiparasitic [6], and antioxidant agents [7]. In addition to revealing anti-inflammatory and analgesic activities [8]. Moreover, these molecules are used in the treatment of conditions related to adenosine receptors as Parkinson's disease, depression, anxiety, and heart failure [9–11]. Moreover, pyrazolo[3,4-*b*]pyrazines have broad applications in the chemical industry such as fluorescent sensors [12], organic light emitting devices [13], and disperse dyes [14]. Otherwise, selenium-containing heterocycles have received great attention in the last decades because of their biological and pharmaceutical importance. Organo-selenium compounds are a fundamental class of active mediators such as antibacterial [15], fungicidal [16,17], antiviral [18], anti-arrhythmic [19,20], antioxidant [21,22], anti-inflammatory [23], and anticancer agents [24].

In the light of the prior biological performances of pyrazolopyrazines and the prominence of selenium-containing heterocycles and in continuation of our

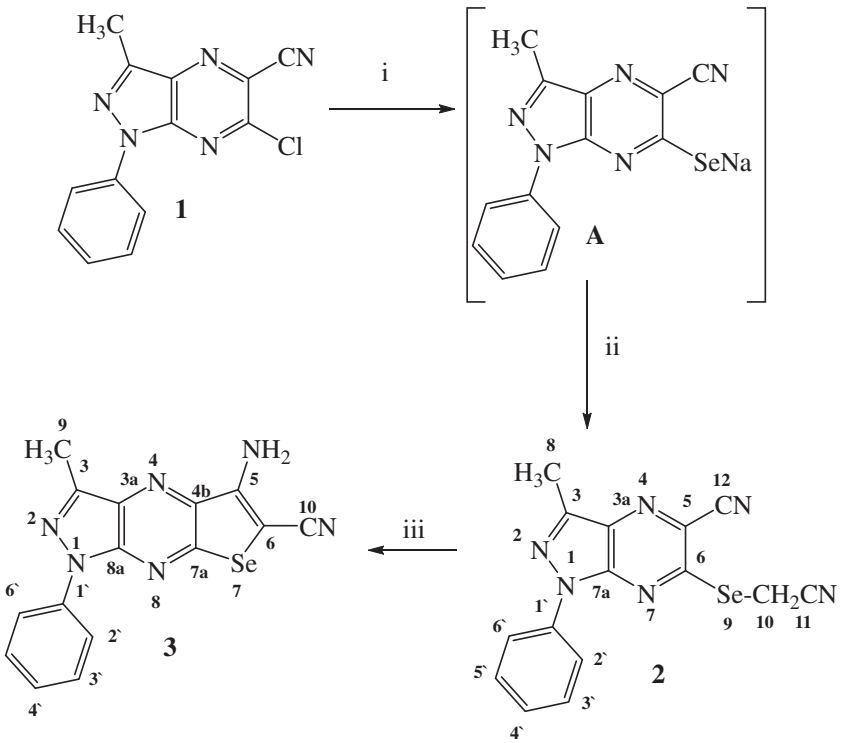
strategy for the synthesis of new heterocycles involving pyrazolopyrazine and pyrazoloselenolo pyrazine moieties [25–31]. We have reported here, synthesis of 5-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]selenolo [3,2-*e*]pyrazine-6-carbonitrile (**3**) and 7-amino-8-imino-3-methyl-1-phenyl-1,8-dihydro-7*H*-pyrazolo[3″,4″:5′,6′] pyrazino[2′,3′:4,5] selenolo[3,2-*d*]pyrimidine (**5**) which proved their adaptability as key precursors for synthesis of novel pyrazolopyrazinoselenolotriazolopyrimidine and pyrazolopyrido- selenolopyrazine heterocycles. These compounds represented favorable antibacterial and antifungal efficiencies comparable with the standard drugs.

2 | RESULTS AND DISCUSSION

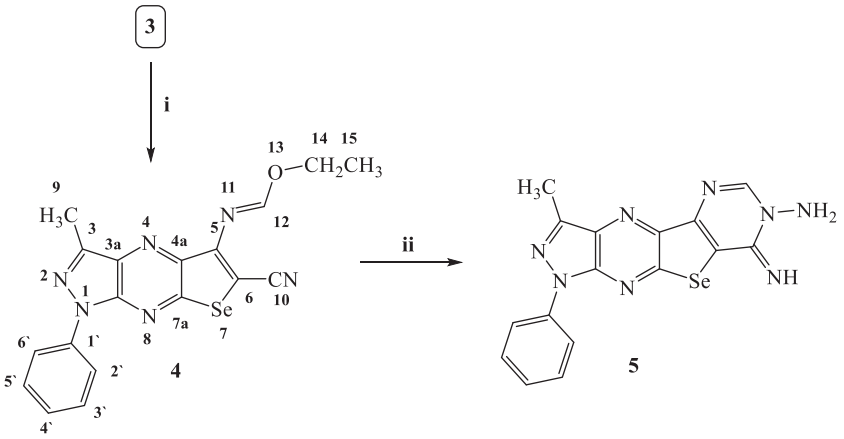
2.1 | Chemistry

Building on the indorsing expertise and in our continuing work to synthesize new pyrazolo[3,4-*b*]selenolo[3,2-*e*] pyrazine heterocycles, our goal is commenced with the synthesis of the required starting substrate **3** by a new method. Synthesis of 5-cyano-3-methyl-1-phenyl-pyrazolo[3,4-*b*]pyrazin-6-yl selanyl acetonitrile (**2**) was attained by the reduction of selenium powder with sodium borohydride in ethanol followed by addition of the preceding prepared chloropyrazolopyrazine derivative **1**. At this stage, the non-isolated selanyl sodium intermediate **A** is formed and was used in-situ for the next reaction with chloroacetonitrile. Upon heating with ethanolic sodium ethoxide solution, the selanyl acetonitrile **2** underwent *Thorpe-Ziegler* cyclization to yield the target 5-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]selenolo [3,2-*e*]pyrazine-6-carbonitrile (**3**). The chemical structures of compounds **2** and **3** were assigned by spectral data. FT-IR of **3** revealed absorption bands at 3456, 3323 cm^{-1} characteristic of NH_2, and at 2189 cm^{-1} for CN group. ^1H NMR in DMSO-d_6 exhibited singlet signal δ 7.26 ppm attributed to NH_2. While ^{13}C NMR of **3** displayed a signal at 117.0 ppm specific for CN. Mass spectrum exhibited a molecular ion peak at 353 (Scheme 1).

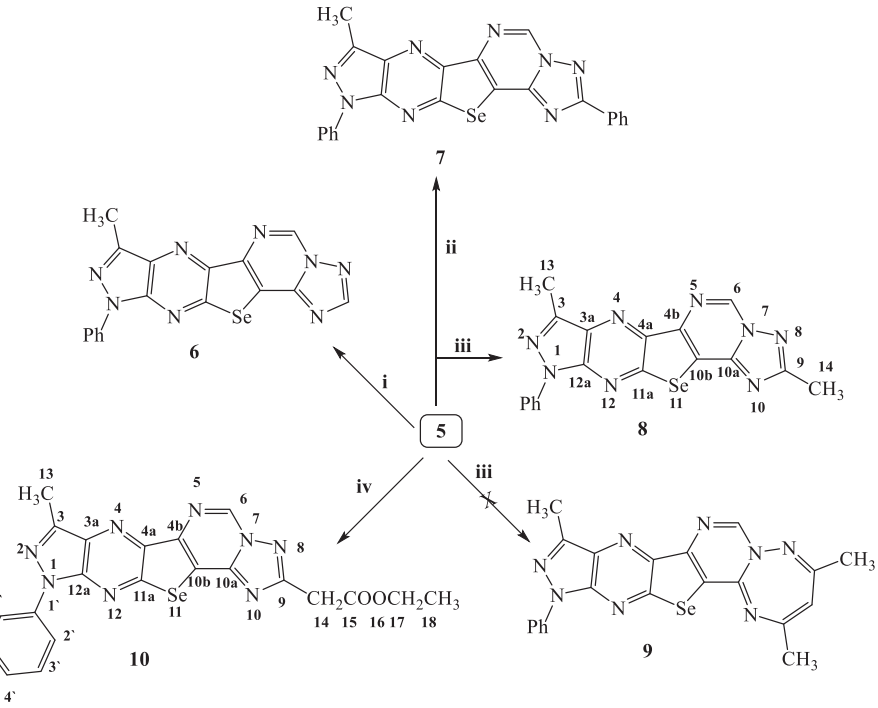
Condensation of amino group in the *o*-amino-carbonitrile **3** with triethyl orthoformate in acetic anhydride provided the ethoxymethylene amino derivative **4**. The last compound underwent nucleophilic replacement reaction followed by intramolecular cyclization upon stirring with an equimolar amount of hydrazine hydrate to furnish 7-amino-8-imino-3-methyl-1-phenyl-1,8-dihydro-7*H*-pyrazolo[3″,4″:5′,6′]pyrazino[2′,3′: 4,5]selenolo[3,2-*d*] pyrimidine (**5**). The FT-IR of compound **5** exhibited disappearance of CN group and appearance of absorption bands at 3295, 3263, and 3164 cm^{-1} assigned to NH_2 and NH groups. ^1H NMR spectrum in DMSO-d_6 displayed singlet signals at δ 5.89 and 7.61 ppm due to NH_2 and NH groups and singlet signal at δ 8.29 ppm ascribed to CH pyrimidine. The mass spectrum of **5** showed a molecular ion peak at *m/z* 396 and a base peak at *m/z* 77 (Scheme 2).



SCHEME 1 Synthesis of 5-amino-3-methyl-1-phenyl-*1H*-selenolo[3,2-*e*]pyrazolo[3,4-*b*] pyrazine-6- carbonitrile (**3**). Reagents and conditions: (i) $Se/NaBH_4/EtOH$, stirring in an ice-bath 1 h and then reflux 2 h; (ii) $ClCH_2CN$/ EtOH, stirring overnight; (iii) EtONa/ EtOH, Δ 15 min



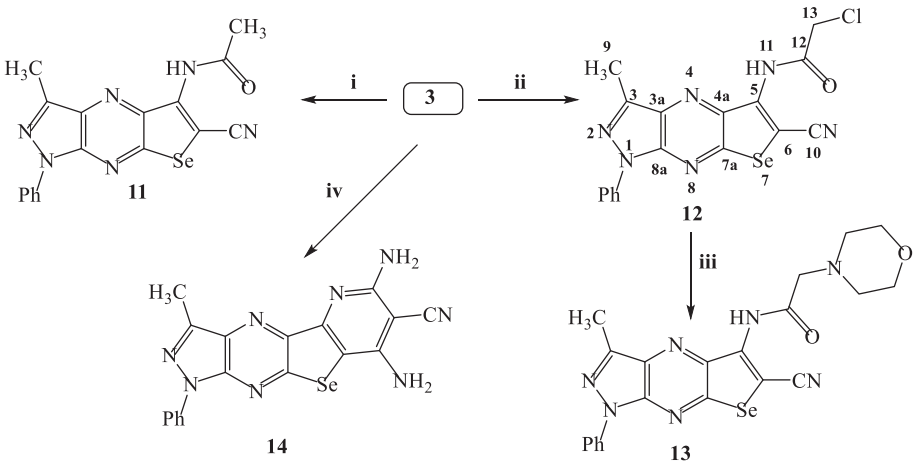
SCHEME 2 Synthesis of the versatile precursor 7-amino-8-imino-3-methyl-1-phenyl-1,8-dihydro-7*H*-pyrazolo[3″,4″:5′,6′]pyrazino[2′,3′:4,5]selenolo[3,2-*d*]pyrimidine (**5**). Reagents and conditions: (i) $CH(OEt)_3/Ac_2O$, reflux 30 min.; (ii) $H_2NNH_2.H_2O$/dioxane, stirring r.t. 30 min



SCHEME 3 Synthesis of new pentacyclic pyrazolopyrazinoselenolotriazolopyrimidine heterocycles **6–10** via condensation of the amino-imino pyrimidine **5** with various reagents. Reagents and conditions: (i) $CH(OEt)_3$/ AcOH, reflux 1 h.; (ii) PhCHO/AcOH, reflux 1 h; (iii). Ac_2CH_2, fusion 2 h; (iv) $CH_2(COOEt)_2$ reflux 2 h

The amino-imino pyrimidine **5** was used as adaptable precursor for synthesis of other heterocyclic rings **6–10** containing pyrazolopyrazinoselenolopyrimidine moiety. Thus, heterocyclization of compound **5** with triethyl orthoformate in acetic acid afforded the corresponding pyrazolopyrazinoselenolotriazolopyrimidine ring system **6** in a good yield. Whereas, reaction with benzaldehyde in refluxing acetic acid furnished the corresponding phenyl triazolopyrimidine derivative **7**.

A novel sequence of pentacyclic heterocycles **8–10** was produced by condensation of **5** with 1,3-dicarbonyl compounds. Therefore, condensation with acetylacetone under neat conditions did not yield the expected dimethyl triazepine **9**; the corresponding methyl triazolopyrimidine **8** was gained instead. Evidently, the suggested mechanism for formation of the methyl triazolopyrimidine **8** proceeded via cyclization of the imino group with a retro-aldol elimination of acetone. Additionally, when the amino-imino pyrimidine **5** was subjected to condense with diethyl malonate, the corresponding ethyl triazolopyrimidinyl acetate **10** was produced. The chemical structures of compounds **6–10** were illuminated based on elemental and spectral analyses. IR spectrum of compound **10** revealed a band at 1737 cm^{-1} characteristic of CO ester. ^1H NMR in DMSO-d_6 displayed triplet and quartet signals at δ 1.27 and 4.21 ppm, respectively for CH_3CH_2 ester group. In addition to singlet signal at δ 4.12 ppm characteristic to CH_2CO. ^{13}C NMR represented peaks at 14.1, 61.7 ppm specific for the ethyl ester and at 35.2 ppm for CH_2CO in addition to peak at 168.3 ppm unique for CO of the ester group. In addition, the mass spectrum of **10** showed a molecular ion peak and a base peak at *m/z* 492 (Scheme 3).



SCHEME 4 Synthesis of the morpholinyl acetamidopyrazoloselenolopyrazine **13** and the *o*-amino-pyrazolopyridoselenolopyrazine carbonitrile **14**. Reagents and conditions: (i) Ac_2O, 3 h; (ii) $ClCOCH_2Cl$/ dioxane, water bath 2 h; (iii) morpholine/ EtOH, reflux 3 h; (iv) $CH_2(CN)_2$/pyridine reflux 2 h

Acetylation of the *o*-amino-carbonitrile **3** with acetic anhydride afforded the acetamido compound **11**. While, chloroacetylation of the *o*-amino-carbonitrile compound **3** with chloroacetyl chloride in dioxane afforded the chloroacetyl amino derivative **12** which was further subjected to nucleophilic substitution with morpholine to afford the morpholinyl acetamido derivative **13**. Alternatively, association of fused pyridine ring into the pyrazoloselenolopyrazine system to afford a new tetracyclic pyrazolopyridoselenolopyrazine compound **14** was realized by the reaction of **3** with malononitrile in refluxing pyridine. IR spectrum of the chloroacetyl amino **12** showed the appearance of characteristic absorption bands at 3221 cm^{-1} for NH group and at 1696 cm^{-1} characteristic of C═O group of amide. ^1H NMR spectrum of **12** revealed the appearance of singlet signal at δ 4.57 ppm attributed to CH_2 group, as well as a singlet signal at δ 11.10 ppm belonging to NH group. ^{13}C NMR spectrum displayed peaks at 43.0 and 165.6 attributed to CH_2 and CO amide, respectively. The mass spectrum revealed a molecular ion peak at m/z 430 and a base peak at *m/z* 77 (Scheme 4).

The proposed mechanism for formation of 6,8-diamino-3-methyl-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyrido[2′,3′:4,5]selenolo[3,2-*e*]pyrazine-7-carbonitrile (**14**) is explained in Scheme 5. We suggested formation of the imino derivative **I** upon nucleophilic addition of the amino group in **3** to the cyano group of malononitrile followed by tautomerism to form the intermediate **II**. Next, heterocyclization was carried out by nucleophilic attack of the carbanion intermediate **III** formed by the action of base to the cyano group of the selenophene ring followed by tautomerism to produce the target diamino pyridine carbonitrile compound **14**.

2.2 | Antibacterial assay

The antibacterial screening was estimated by measuring the inhibition zone (mm) and was recorded in Table 1. The produced outcomes demonstrated that all screened compounds exhibited promising activities against most strains of bacteria. We observed that compounds **3**, **5**, and **6** affirmed best effects (inhibition zones 18–20 mm) against *Bacillus cereus* compared to Chloramphenicol (26 mm), whereas, compounds **4**, **7**, **8**, **10**, **11**, **12**, and **13** displayed moderate to strong activities (12–16 mm). According to *Staphylococcus aureus*, compounds **3**, **7**, and **11** parallel to the reference drug (28 mm), exhibited excellent activities with very close inhibition zones (20–23 mm), while the others displayed significant effects (12–19 mm). Moreover, compounds **3** and **8** were found to be the most active derivatives against *Pseudomonas aeruginosa* with MIC values 8.0 and 9.0 μg/ml, respectively. Compounds **3** and **7** demonstrated the highest efficacy against *Escherichia coli* with the best MIC values (7 μg/ml) comparable to Chloramphenicol (3 μg/ml). In addition, compound **6** represented the highest inhibition zone (20 mm) against *Escherichia coli*. Otherwise, compounds **8** and **13** offered inferior actions and the other compounds revealed moderate to good actions related to the reference medicine.

2.3 | Antifungal assay

The antifungal effect of the screened compounds was recoded as zones of inhibition (mm) and summarized in Table 1. It's worth to be mentioned that compound **10** demonstrated the best activity toward *Candida albicans* and *Geotrichum candidum* (MIC 6.0 and 8.0 μg/ml) compared to Clotrimazole (3.0 and 5.0 μg/ml). In case of *Geotrichum candidum*, compound **7** displayed the highest activity with very close inhibition zone (19 mm) parallel to the Clotrimazole (22 mm). While compounds **3**, **4**, **6**, **11**, and **12** affirmed good activities (12–18 mm, 8.0–9.0 μg/ml). Moreover, compounds **7**, **8**, and **13** represented inferior actions. *Geotrichum candidum* was resistant

SCHEME 5 The suggested mechanism for formation of 6,8-diamino-3-methyl-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyrido[2′,3′:4,5]selenolo[3,2-*e*]pyrazine-7-carbonitrile (**14**)

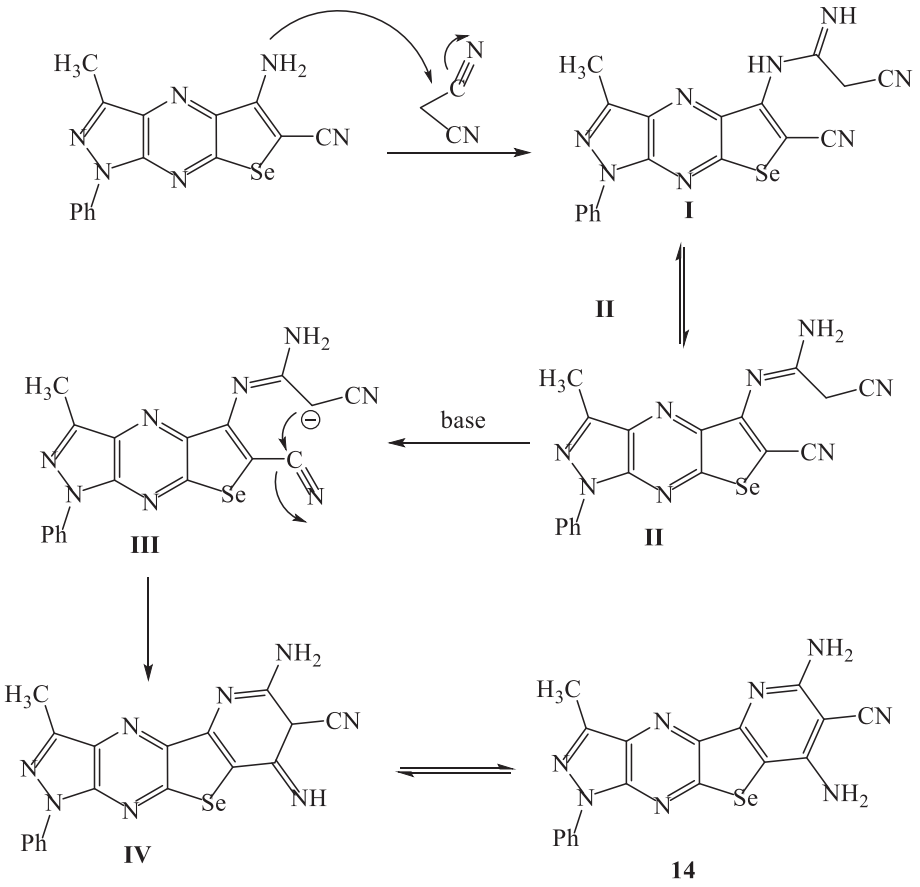


TABLE 1 In vitro antimicrobial activity and MIC (μg/ml) of the synthesized compounds

Compounds	(Inhibition zone, mm)[a] and MIC (μg/ml)[b]					
	Bacteria				Fungi	
	Gram-positive		Gram-negative			
Bacteria/Fungi	*Bacillus cereus*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Geotrichum candidum*	*Candida albicans*
3	20 (10)	23 (10)	17 (8.0)	15 (7.0)	15 (9.0)	18 (7.0)
4	16 (9.0)	19 (9.0)	18 (11)	16 (9.0)	17 (9.0)	18 (9.0)
5	18 (9.0)	18 (9.0)	14 (9.0)	17 (8.0)	-	20 (10)
6	19 (8.0)	14 (8.0)	-	20 (10)	18 (9.0)	16 (8.0)
7	16 (10)	20 (9.0)	16 (11)	17 (7.0)	19 (10)	13 (13)
8	12 (9.0)	19 (8.0)	18 (9.0)	9 (12)	10 (10)	19 (8.0)
10	16 (10)	18 (10)	14 (9.0)	11 (9.0)	14 (8.0)	20 (6.0)
11	14 (9.0)	20 (9.0)	11 (9.0)	12 (8.0)	15 (8.0)	19 (9.0)
12	15 (9.0)	18 (9.0)	15 (9.0)	17 (8.0)	12 (8.0)	-
13	15 (10)	12 (10)	15 (9.0)	10 (13)	16 (10)	13 (10)
Chloramphenicol	26 (3.0)	28 (3.0)	22 (3.0)	29 (3.0)	-	-
Clotrimazole	-	-	-	-	22 (5.0)	26 (3.0)

[a]Diameter of the inhibition zone (in mm).
[b]Minimum inhibition concentration (μg/ml).
Note: (-), no activity.

to compound **5**. In a similar manner, compounds **3**, **6**, **8**, and **13** represented significant efficacies against *Candida albicans* (MIC 7.0–9.0 μg/ml) compared to the reference antifungal drug (3.0 μg/ml). In addition, compound **5** exhibited excellent effect (inhibition zone 20 mm). Whereas, *Candida albicans* was resistant to compound **12**.

2.4 | Structure activity relationship (SAR)

Owing to the biological and pharmaceutical importance of the pyrazolopyrazine molecules and selenium-containing heterocycles, we attempted to study the influence of pyrazoloselenolopyrazine moiety on the microbial inhibitory activity. From the results which are recorded in Table 1, we can conclude that the *o*-amino-carbonitrile starting material **3** displayed excellent activities with very close inhibition zones to Chloramphenicol against all genera of pathogenic bacteria. Formation of the ethoxymethylene amino **4** slightly decreases the activities versus all bacterial strains. Cyclization of compound **4** forming the amino-imino pyrimidine **5** enhanced the antibacterial activity toward *Pseudomonas aeruginosa and Escherichia coli* with remaining the effect on *Bacillus cereus* and *Staphylococcus aureus* unchanged. Heterocyclization of **5** with triethyl orthoformate forming the triazolopyrimidine **6** strongly suppresses the activity against *Pseudomonas aeruginosa* and slightly increase the effect versus *Bacillus cereus* and *Escherichia coli*. Attendance of phenyl group in the triazole ring in compound **7** strongly promoted the activity against *Pseudomonas aeruginosa*, *Escherichia coli*, *and Staphylococcus aureus*. Replacing the phenyl by methyl group in compound **8** increased the activity against *Bacillus cereus*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* and decreased the efficacy against *Escherichia coli*. Presence of the ethyl acetate ester in the triazole ring in compound **10** highly increased the activity versus *Pseudomonas aeruginosa* compared to the triazolo compound **6** with showing almost the same activity toward the other strains. Acetylation of the *o*-amino-carbonitrile compound **3** to produce the acetyl amino derivative **11** slightly reduced the activity against all genera of bacteria. While chloroacetylation of compound **3** affording the chloroacetyl amino **12** increased the effect against *Escherichia coli*. Substitution of the chloride ion with the morpholinyl ring in compound **13** strongly diminished the efficacy against *Escherichia coli* with showing nearly the same activity against all other strains.

Similarly, it's worth to be mentioned that the tested compounds revealed strong antifungal activities against all fungal strains as shown in Table 1. The *o*-amino-carbonitrile **3** and the ethoxy methyleneamino derivative **4** exhibited similar activities against *Geotrichum candidum* and *Candida albicans*. Formation of the amino-imino pyrimidine **5** strongly inhibited the activity against *Geotrichum candidum* and enlarged the effect against *Candida albicans*. Condensation of **5** with triethyl orthoformate to yield the triazolopyrimidine **6** strongly improved the activity against *Geotrichum candidum* with slightly decrease in the effect against *Candida albicans*. Formation of the phenyl group in the triazole ring in compound **7** highly diminished the activity toward *Candida albicans* with increasing the effect against *Geotrichum candidum*. In a contrary manner, replacing the phenyl with the methyl group increased the activity against *Candida albicans* and decreased efficacy versus *Geotrichum candidum*. The ethyl acetate triazole **10** represented excellent activity against all strains. Alternatively, the acetyl amino derivative **11** offered similar activity against the fungal strains compared to the amino-carbonitrile **3**. Furthermore, chloroacetylation of **3** to produce the chloroacetyl amino derivative **12** highly endorsed the activity toward *Geotrichum candidum* and completely prohibited the activity against *Candida albicans*. Replacing the chloride ion by the morpholinyl in compound **13** remarkably increased the activity against all tested strains.

3 | EXPERIMENTAL

Melting points were determined and uncorrected on a Gallen Kamp electric melting point apparatus. Elemental analyses were carried out at the Micro Analytical Center - Assiut University, Assiut. FT-IR spectra were recorded on a FT-IR 8201 PC Shimadzu (KBr disks). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer (400 MHz) in DMSO-d_6 as solvent with Me_4Si as an internal standard, chemical shifts were measured in δ ppm. Mass spectra (EI-MS) were determined on Shimadzu Qp-2010 and at Micro Analytical Center - Cairo University, Cairo. Progress of the reaction and purity of the compounds were followed by TLC plates (silica gel. 60 F_{254}, Merck). The preliminary compound 6-chloro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyrazine-5-carbonitrile (**1**) was prepared in accordance with literature procedure [32,33].

3.1 | 6-((Cyanomethyl)selanyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyrazine-5-carbonitrile (2)

In a closed two necked flask, (0.58 g, 7.40 mmol) of selenium powder in absolute ethanol (20 ml) was dissolved completely by adding sodium borohydride (0.56 g,

14.80 mmol) in small portions with stirring under cooling at 0–5°C for 15 min. Then, the chloro pyrazolopyrazine carbonitrile **1** (2.00 g, 7.40 mmol) was added to the reaction mixture with stirring for 1 h. After that, the mixture was refluxed for 2 h. At this stage, the non-isolated selanyl sodium salt **C** was formed. Next, the chloroacetonitrile (0.47 ml, 7.40 mmol) was appended to the mixture and was left overnight with stirring. The solid precipitate that formed on cooling, was filtered, washed with water, dried, and recrystallized from ethanol as white crystals in 77% (2.00 g) yield. m. p. 195–197°C; FT-IR (KBr): ν 3050 (CH aromatic), 2986, 2935 (CH aliphatic), 2243, and 2224 (2CN), 1596 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.25–7.43 (m, 5H, ArH), 4.29 (s, 2H, Se-CH_2), 2.68 (s, 3H, CH_3 pyrazole) ppm. ^{13}C NMR (DMSO-d_6): δ 154.9 (C3), 145.5 (C6), 141.2 (C7a), 137.6 (C1′: Ph), 132.6 (C5), 129.4 (C3′, C5′: Ph), 127.4 (C4′: Ph), 121.8 (C3a), 121.0 (C2′, C6′: Ph), 115.1 (C11: CH_2CN), 114.2 (C12: CN pyrazine), 16.1 (C10: CH_2), 11.2 (C8: CH_3 pyrazole) ppm. Anal. Calcd. for $C_{15}H_{10}N_6Se$ (353.25): C, 51.00; H, 2.85; N, 23.79%. Found: C, 51.17; H, 2.93; N, 23.67%.

3.2 | 5-Amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]selenolo[3,2-*e*]pyrazine-6-carbonitrile (3)

A solution of the selanyl acetonitrile compound **2** (2.00 g, 6 mmol) in absolute ethanol (20 ml) and sodium ethoxide solution (6 mmol) was gently heated with stirring for 10 min. The solid product which separated out during reflux was collected, dried, and recrystallized from dioxane as orange powder in 71% (1.50 g) yield; m.p. 270–272°C; FT-IR (KBr) ν/cm^{-1} = 3456, 3323 (NH_2), 3084 (CH aromatic), 2910 (CH aliphatic), 2189 (CN), 1598 (C═N); ^{1}H NMR (DMSO-d_6): δ 8.22–7.38 (m, 5H, Ar—H), 7.26 (s, 2H, NH_2), 2.74 (s, 3H, CH_3 pyrazole) ppm; ^{13}C NMR (DMSO-d_6): δ 157.2 (C3), 150.3 (C4a), 144.7 (C5), 143.1 (C7a), 140.2 (C8a), 138.7 (C1′: Ph), 133.5 (C6), 129.9 (C3′, C5′: Ph), 126.7 (C4′: Ph), 120.7 (C2′, C6′: Ph), 120.3 (C3a), 117.0 (C10: CN), 11.8 (C9: CH_3 pyrazole) ppm; EI-MS: *m/z* 353 (M^+, 60%), 326 (M^+-HCN, 92%), 314 (M^+-CH_3CN, 36%), 93 ($C_6H_5NH_2^+$, 75%), 77 ($C_6H_5^+$, 100%). Anal. Calcd. for $C_{15}H_{10}N_6Se$ (353.25): C, 51.00; H, 2.85; N, 23.79%. Found: C, 51.10; H, 2.94; N, 23.71%.

3.3 | 5-Ethoxymethyleneamino-3-methyl-1-phenyl-*1H*-selenolo[3,2-*e*]pyrazolo[3,4-*b*]pyrazine-6-carbonitrile (4)

Compound **3** (3.00 g, 8.50 mmol) and triethyl orthoformate (3.00 ml) were refluxed in presence of acetic anhydride (10 ml) for 30 min. After cooling, the solid product was filtered, dried and recrystallized from dioxane as yellow crystals in 72% (2.50 g) yield; m.p. 240–242°C. FT-IR (KBr): ν 3020 (CH aromatic), 2981 (CH aliphatic), 2212 (CN), 1625 (C═N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.69 (s, 1H, N═CH), 7.38–8.26 (m, 5H, Ar—H), 4.51 (q, J = 7.10 Hz, 2H, CH_2), 2.73 (s, 3H, CH_3 pyrazole), 1.45 (t, J = 7.12 Hz, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6): δ 160.1 (C12), 154.1 (C3), 147.8 (C7a), 144.7 (C5), 141.9 (C4a), 138.6 (C1′: Ph), 138.4 (C8a), 129.2 (C3′, C5′: Ph), 126.7 (C4′: Ph), 126.3 (C3a), 120.1 (C2′, C6′: Ph), 113.5 (C10: CN), 99.5 (C6), 63.4 (C14: CH_2 ester), 14.0 (C15: CH_3 ester), 11.4 (C9: CH_3 pyrazole), ppm. EI-MS: *m/z*: 410 ([M^++1], 55%), 381 (M^+-C_2H_6, 100%). Anal. Calcd. for $C_{18}H_{14}N_6OSe$ (409.31): C, 52.82; H, 3.45; N, 20.53%. Found: C, 52.93; H, 3.40; N, 20.60%.

3.4 | 7-Amino-8-imino-3-methyl-1-phenyl-1,8-dihydro-*7H*-pyrazolo[4″,3″:5′,6′]pyrazino[3′,2′:4,5]selenolo[3,2-*d*]pyrimidine (5)

A solution of ethoxymethyleneamino **4** (2.00 g, 4.88 mmol) in warm dioxane (10 ml) and hydrazine hydrate (0.30 ml, 6.00 mmol) was stirred for 30 min. at room temperature. The solid product formed was filtered, washed with ethanol and recrystallized from dioxane as yellow powder in 84% (1.60 g) yield; m.p. 320–322°C. FT-IR (KBr): ν 3293, 3258 and 3158 (NH, NH_2), 2918, 2849 (CH aliphatic), 1637 (C═N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.27 (s, 1H, CH-pyrimidine), 8.29–7.40 (m, 5H, Ar—H), 7.61 (s, 1H, NH), 5.89 (s, 2H, NH_2), 2.78 (s, 3H, CH_3 pyrazole) ppm. ^{13}C NMR (DMSO-d_6): δ 163.1 (C8: C═NH), 155.7 (C3), 145.1 (C4a), 142.6 (C6), 142.1 (C9a), 139.8 (C4b), 138.9 (C8a), 138.6 (C1′: Ph), 135.1 (C10a), 129.3 (C3′, C5′: Ph), 126.4 (C4′: Ph), 121.2 (C3a), 120.4 (C2′: C6′: Ph), 11.7 (C11: CH_3) ppm. EI-MS: *m/z* 396 ([M^++1], 32%), 77.00 ($C_6H_5^+$, 100%). Anal. Calcd. For $C_{16}H_{12}N_8Se$ (395.29): C, 48.62; H, 3.06; N, 28.35%. Found: C, 48.71; H, 3.11; N, 28.28%.

3.5 | 8-Methyl-10-phenyl pyrazolo[3″,4″:5′,6′]pyrazino[2′,3′:4,5]selenolo[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (6)

A mixture of the amino-imino pyrimidine **5** (0.40 g, 1.00 mmol) and triethyl orthoformate (3 ml) in a catalytic amount of glacial acetic acid (0.30 ml) was refluxed for 1 h. The precipitated solid was collected and recrystallized from dioxane as yellow powder; yield 0.28 g (70%); m.p. >360°C. FT-IR (KBr): ν 3089, 3058 (CH aromatic), 1612 (C═N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ

10.00 (s, 1H, CH-pyrimidine), 8.89 (s, 1H, CH-triazole), 7.43–8.33 (m, 5H, Ar—H), 2.85 (s, 3H, CH_3 pyrazole) ppm. ^{13}C NMR (DMSO-d_6): δ 163.1 (C9), 155.1 (C3), 149.6 (C10a), 145.6 (C6), 142.8 (C4b), 142.1 (C4a), 139.4 (C1′: Ph), 138.9 (C11a), 138.2 (C10b), 135.4 (C12a), 129.3 (C3′, C5′: Ph), 126.4 (C4′: Ph), 121.6 (C3a), 120.7 (C2′, C6′: Ph), 11.7 (C13: CH_3) ppm. EI-MS: *m/z* 406 ([M^++1], 100%). Anal. Calcd. for $C_{17}H_{10}N_8Se$ (405.28): C, 50.38; H, 2.49; N, 27.65%. Found: C, 50.29; H, 2.61; N, 27.70%.

3.6 | 8-Methyl-2,10-diphenyl-10*H*-pyrazolo[3″,4″:5′,6′]pyrazino[2′,3′:4,5]selenolo[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7)

A sample of the amino-imino pyrimidine **5** (0.40 g, 1.00 mmol) and benzaldehyde (0.15 ml, 1.42 mmol) was refluxed in acetic acid (15 ml) for 1 h. The solid precipitate which separated out while hot was collected, dried and recrystallized from dioxane as yellow powder; yield 0.31 g (66%); m.p. >360°C. FT-IR (KBr): ν 3051 (CH aromatic), 2917 (CH aliphatic), 1618 (C═N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.00 (s, 1H, CH pyrimidine), 7.43–8.33 (m, 10H, Ar—H), 2.85 (s, 3H, CH_3 pyrazole) ppm. ^{13}C NMR (DMSO-d_6): δ 166.1 (C9), 155.7 (C3), 149.0 (C10a), 145.1 (C6), 142.6 (C4b), 142.1 (C4a), 139.8 (C1′: Ph), 138.9 (C11a), 138.6 (C10b), 137.8 (C1″: Ph), 137.1 (C4″: Ph), 136.7 (C3″, C5″: Ph), 135.1 (C12a), 129.3 (C3′, C5′: Ph), 126.4 (C4′: Ph), 124.3 (C2″, C6″: Ph triazole), 121.2 (C3a), 120.4 (C2′, C6′: Ph pyrazole), 12.2 (C13: CH_3 pyrazole) ppm. EI-MS: *m/z* 482 ([M^++1], 84%), 77 ($C_6H_5^+$, 100%). Anal. Calcd. for $C_{23}H_{14}N_8Se$ (481.38): C, 57.39; H, 2.93; N, 23.28%. Found: C, 57.33; H, 2.89; N, 23.31%.

3.7 | 2,8-Dimethyl-10-phenyl pyrazolo[3″,4:5′,6′]pyrazino[2′,3′:4,5]selenolo[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (8)

A suspension of the amino-imino pyrimidine derivative **5** (0.40 g, 1.00 mmol) and acetylacetone (2.5 ml, 0.025 mol) was heated under solvent-free conditions at 140°C for 2 h. The reaction mixture was triturated with EtOH (10 ml) and left to cool. The produced solid was filtered, dried and recrystallized from DMF as brown powder in 68% (0.28 g) yield; m.p. 345–47°C. FT-IR (KBr): ν 3057 (CH aromatic), 2923, 2853 (CH aliphatic), 1616 (C═N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.85 (s, 1H, CH-pyrimidine), 7.42–8.31 (m, 5H, Ar—H), 2.82 (s, 3H, CH_3 pyrazole), 2.64 (s, 3H, CH_3 triazole) ppm. ^{13}C NMR (DMSO-d_6): δ 163.6 (C9), 155.7 (C3), 149.0 (C10a), 145.1 (C6), 142.6 (C4b), 142.7 (C4a), 139.8 (C1′: Ph), 138.9 (C11a), 138.6 (C10b), 135.1 (C12a), 129.4 (C3′, C5′: Ph), 124.3 (C4′: Ph), 121.2 (C3a), 120.4 (C2′, C6′: Ph), 14.6 (C14: CH_3 triazole), 11.8 (C13: CH_3 pyrazole) ppm. EI-MS: *m/z* 420 ([M^++1], 100%). Anal. Calcd. for $C_{18}H_{12}N_8Se$ (419.31): C, 51.56; H, 2.88; N, 26.72%. Found: C, 51.43; H, 2.96; N, 26.67%.

3.8 | Ethyl 2-(8-methyl-10-phenyl pyrazolo[3″,4″:5′,6′]pyrazino[2′,3′:4,5]thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-2-yl) acetate (10)

A mixture of the amino-imino pyrimidine **5** (0.40 g, 1.00 mmol) and diethyl malonate (3 ml, 0.02 mol) was fused under neat conditions at 200°C for 2 h. The resultant precipitate was triturated with EtOH (10 ml). After cooling, the solid product formed was filtered and recrystallized from ethanol as pale yellow powder in 69% (0.33 g) yield; m.p. 292–293°C. FT-IR (KBr): ν 3046 (CH aromatic), 2921 (CH aliphatic), 1737 (C═O), 1618 (C═N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.88 (s, 1H, CH-pyrimidine), 7.37–8.27 (m, 5H, Ar—H), 4.21 (q, J = 7.10 Hz, 2H, CH_2), 4.12 (s, 2H, CH_2CO), 2.80 (s, 3H, CH_3 pyrazole), 1.27 (t, J = 7.12 Hz, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6): δ 168.3 (C15: CO ester), 163.1 (C9), 155.7 (C3), 149.0 (C10a), 145.1 (C6), 142.6 (C4b), 142.1 (C4a), 139.8 (C1′: Ph), 138.9 (C11a), 138.6 (C10b), 135.1 (C12a), 129.3 (C3′, C5′: Ph), 126.4 (C4′: Ph), 121.2 (C3a), 120.4 (C2′, C6′: Ph), 61.7 (C17: CH_2 ester), 35.2 (C14: $\underline{CH_2}CO$), 14.1 (C18: CH_3 ester), 11.7 (C13: CH_3 pyrazole) ppm. EI-MS: *m/z* 492 ([M^++1], 100%). Anal. Calcd. for $C_{21}H_{16}N_8O_2Se$ (491.37): C, 51.33; H, 3.28; N, 22.80%. Found: C, 51.50; H, 3.36; N, 22.75%.

3.9 | 5-Acetamido-3-methyl-1-phenyl-1*H*-selenolo[3,2-*e*]pyrazolo[3,4-*b*]pyrazine-6-carbonitrile (11)

The *o*-amino carbonitrile **3** (3.00 g, 8.50 mmol) was refluxed in acetic anhydride (15 ml) for 3 h. After cooling, the reaction mixture was poured onto crushed ice and the solid product was collected, dried and recrystallized from dioxane as yellowish needles; yield 68% (0.23 g); m.p. 340–342°C. FT-IR (KBr): ν 3249 (NH), 3054 (CH aromatic), 2980 (CH aliphatic), 2211 (CN), 1681 (C═O), 1596 (C═N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.94 (s, 1H, NH), 8.26–7.38 (m, 5H, Ar—H), 2.78 (s, 3H, CH_3 pyrazole), 2.33 (s, 3H, $COCH_3$) ppm. ^{13}C NMR (DMSO-d_6): δ 166.7 (C11: CONH), 150.3 (C3), 144.7 (C5), 143.1 (C7a), 140.2 (C1′: Ph), 138.7 (C4a), 133.5 (C8a), 129.9

(C3′, C5′: Ph), 126.7 (C4′: Ph), 120.0 (C2′, C6′: Ph + C3a), 118.3 (C13: CN), 99.9 (C6), 24.7 (C12: CH_3), 11.8 (C9: CH_3) ppm. EI-MS: *m/z* 396 ([M^++1], 16.42%), 77 ($C_6H_5^+$, 100%). Anal. Calcd. for $C_{17}H_{12}N_6OSe$ (395.28): C, 51.66; H, 3.06; N, 21.26%. Found: C, 51.75; H, 3.11; N, 21.21%.

3.10 | 5-Chloroacetylamino-3-methyl-1-phenyl-*1H*-selenolo[3,2-*e*]pyrazolo[3,4-*b*]pyrazine-6-carbonitrile (12)

To a solution of derivative **3** (0.40 g, 11.32 mmol) in dioxane (15 ml), chloroacetyl chloride was added (0.15 ml, 1.32 mmol). The mixture was heated on water bath at 70–80°C for 2 h. After cooling, the mixture was poured into an ice-cold water, and neutralized with diluted sodium carbonate solution. The solid product was filtered, dried and recrystallized from a dioxane as yellow crystals; yield 0.0.35 g (72%); m.p. 295–297°C. FT-IR (KBr): ν 3221 (NH), 3041 (CH aromatic), 2880 (CH aliphatic), 2216 (CN), 1696 (C═O), 1597 (C═N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 11.10 (s, 1H, NH), 8.28–7.39 (m, 5H, Ar—H), 4.57 (s, 2H, $COCH_2$), 2.79 (s, 3H, CH_3 pyrazole) ppm. ^{13}CNMR (DMSO-d_6): 165.6 (C12: CO amide), 153.1 (C3), 144.9 (C5), 142.6 (C7a), 138.6 (C1′: Ph), 136.3 (C4a), 135.4 (C8a), 129.9 (C3′, C5′: Ph), 126.9 (C4′: Ph), 121.5 (C3a), 120.5 (C2′, C6′: Ph), 113.1 (C10: CN), 99.9 (C6), 43.0 (C13: CH_2Cl), 12.1 (C9: CH_3 pyrazole) ppm. EI-MS: *m/z* 430 ([M^++1], 66%), 77 ($C_6H_5^+$, 100%). Anal. Calcd. for $C_{17}H_{11}ClN_6OSe$ (429.73): C, 47.52; H, 2.58; Cl, 8.25; N, 19.56%. Found: C, 47.45; H, 2.54; Cl, 8.31; N, 19.51%.

3.11 | 5-(2-Morpholin-4-yl acetamido)-3-methyl-1-phenyl-*1H*-selenolo[3,2-*e*]pyrazolo [3,4-*b*]pyrazine-6-carbonitrile (13)

A mixture of the chloroacetamido **12** (0.40 g, 0.93 mmol) and morpholine (0.10 ml, 1.15 mmol) was fused for 10 min, then absolute ethanol (15 ml) was added. The reaction mixture was refluxed for additional 3 h. The solid product was collected and recrystallized from dioxane as yellow crystals; yield 73% (0.33 g); mp: 263–265°C; FT-IR (KBr): ν 3312 (NH), 3057 (CH aromatic), 2852 (CH aliphatic), 2206 (CN), 1719 (CO), 1593 (C═N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.75 (s, 1H, NH), 8.25–7.40 (m, 5H, Ar—H), 3.81 (s, 2H, $COCH_2$), 3.38 (m, 4H, O[CH_2]$_2$-morpholine), 2.76 (s, 3H, CH_3 pyrazole), 2.69 (m, 4H, N[CH_2]$_2$-morpholine) ppm. ^{13}C NMR (DMSO-d_6): δ 168.3 (C11: CO), 154.2 (C3), 144.7 (C5), 143.1 (C7a), 140.2 (C1′: Ph), 138.7 (C4a), 133.5 (C8a), 129.9 (C3′, C5′: Ph), 126.7 (C4′: Ph), 120.3 (C2′, C6′: Ph + C3a), 117.1 (CN: C13), 97.3 (C6), 67.7 (C3″, C5″ morpholinyl), 60.9 (C12: CH_2), 50.2 (C2″, 6″ morpholinyl), 12.5 (C9: CH_3) ppm. (EI-MS: *m/z* 481 ([M^++1], 49.90%), 100.05 ($C_5H_{10}NO^+$, 100%). Anal. Calcd. for $C_{21}H_{19}N_7O_2Se$ (480.39): C, 52.51; H, 3.99; N, 20.41%. Found: C, 52.56; H, 4.06; N, 20.45%.

3.12 | 6,8-Diamino-3-methyl-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyrido[2′,3′:4,5]selenolo [3,2-*e*]pyrazine-7-carbonitrile (14)

Equimolar amounts of derivative **3** (0.40 g, 11.32 mmol) and malononitrile (0.75 g, 11.32 mmol) in anhydrous pyridine (10 ml) was refluxed for 2 h. After cooling, the separated product was filtered, washed with EtOH and recrystallized from dioxane as orange crystals; yield 3.60 g (75.79%); m.p. 242–244°C. FT-IR (KBr): ν 3460, 3317, 3215 and 3180 ($2NH_2$), 3066 (CH aromatic), 2920 (CH aliphatic), 2191 (CN), 1625 (C═N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.19 (s, 2H, NH_2), 7.37–8.21 (m, 5H, Ar—H), 7.14 (s, 2H, NH_2), 2.73 (s, 3H, CH_3 pyrazole) ppm. ^{13}C NMR (DMSO-d_6): δ 166.5 (C4b), 164.7 (C6), 155.3 (C8), 151.2 (C3), 144.7 (C9a), 143.1 (C4b), 140.2 (C8a), 138.7 (C1′: Ph), 133.5 (C10a), 129.9 (C3′, C5′: Ph), 126.7 (C4′: Ph), 120.3 (C2′, C6′: Ph), 118.7 (CN: C12), 88.9 (C7), 11.3 (C11: CH_3) ppm. EI-MS: *m/z* 420 ([M^++1], 17%), 77 ($C_6H_5^+$, 100%). Anal. Calcd. for $C_{18}H_{12}N_8Se$ (419.31): C, 51.56; H, 2.88; N, 26.72%. Found: C, 51.65; H, 2.95; N, 26.67%.

3.13 | *Procedure of* in vitro antimicrobial studies

Most of the newly synthesized selenolopyrazolopyrazine derivatives were evaluated for their in vitro antibacterial activity against two Gram-positive bacteria strains; *Bacillus cereus*, *Staphylococcus aureus*, and two Gram-negative bacteria strains; *Pseudomonas aeruginosa*, *Escherichia* coli. In addition, they were evaluated for their in vitro antifungal activity against two fungi strains; *Geotrichum candidium*, *Candida albicans* using Chloramphenicol and Chlotrimazole as reference drugs for antibacterial and antifungal activities, respectively and DMSO was used as negative control. All microorganisms used in the present study were obtained from the culture collection of Microbiology Department, Faculty of medicine, Assiut University. Antimicrobial activity of the newly synthesized derivatives was evaluated in vitro by disc diffusion method [34]. In this technique, a plate of 9-cm diameter containing nutrient agar (NA) for the growth of bacteria

and sabouraud's dextrose agar (SDA) for the growth of fungi. A standard 5-mm diameter sterilized filter paper disc loaded with 50 µl of the solution under investigation (2.0%) was placed on an agar plate seeded with the tested organism. The plates were incubated for 24 h at 37 ± 2°C for bacteria and 4 days at room temperature for fungi. The microdilution method [35] was employed to determine the minimum inhibitory concentration (MIC) of the tested compounds which was taken as the lowest concentration at which there were no visible bacteria observed. The MIC (µg/ml) and Inhibition zone (mm) values were determined and recorded in Table 1.

4 | CONCLUSION

In the current study, we have delivered a facile access for synthesis of a novel series of pyrazolopyrazinoselenolopyrimidine **5**, pyrazolopyrazinoselenolotriazolo pyrimidine **6–10** and pyrazolopyridoselenolopyrazine **14** ring systems. The newly synthesized compounds were isolated and purified by recrystallization. Their chemical structures were fully characterized by FT-IR, ^{1}H NMR, and mass spectroscopy in addition to ^{13}C NMR for some of them. Furthermore, most of the synthesized compounds revealed highly promising antibacterial activities against four bacterial strains (*Bacillus cereus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*) and two genera of fungi (*Geotrichum candidium*, *Candida albicans*).

DATA AVAILABILITY STATEMENT

Data available in this article supplementary material: The data that supports the findings of this study are available in the supplementary material if this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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