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Synthesis of Novel Selenium Containing Sulfa Drugs and Their Antibacterial Activities[1]

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Abstract—Synthesis of 3-[4-(*N*-**substituted** sulfamoyl)phenyl]-3,4-dihydro-4-oxo-7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-*d*]**pyrimidines**,7-[4-(*N*-**substituted** sulfamoyl)phenyl]-7,8-dihydro-8-oxo-3,4-diphenylpyrimido[4',5':4,5]selenolo [2,3-*c*]**pyridazines** and 1-[4-(*N*-**substituted** sulfamoyl)phenyl]-1,11-dihydro 11-oxo-4-methylpyrimido[4',5':4,5]selenolo[2,3-*b*]**quinolines** is reported. 4-Amino-*N*-pyrimidine-2-yl-benzene sulfonamide (a), 4-amino-*N*-(2,6-dimethylpyrimidin-4-yl)benzene sulfonamide (b), *N*-[(4-aminophenyl)sulfonyl] acetamide (c) with *N*-ethoxymethyleneamino of selenolo pyridine, selenolo pyridazine and selenolo quinoline derivatives respectively were obtained starting from 1-amino-N^4-**substituted** sulfanilamides. Spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and Mass spectral) confirmed the structure of the newly synthesized compounds**. Substituted pyrimidines**, **pyridazines** and **quinolines** were screened for antibacterial activity against gram-positive and gram-negative bacteria. Selenolo derivative of *N*-[(4-aminophenyl)sulfonyl] acetamide (substitutent of sulfacetamide c) showed strong bactericidal effect against all the tested organisms. Selenolo[3,2-*d*]pyrimidin (substitutent a) showed a good bactericidal effect against *Serratia marcescens, Staphylococcus aureus* and *Escherichia coli*. Compounds selenolo[2,3-*c*]pyridazine (substitutent b), selenolo[2,3-*b*]quinoline(substitutents c)) exhibited a moderate bactericidal effect against *Serratia marcescens*. None of the synthesized seleno pyridazines has a considerable antimicrobial activity against the tested organisms. The minimum inhibitory concentration (MIC) of the most active compound—3-[4-(*N*-acetyl sulfamoyl)phenyl]-3,4-dihydro-4-oxo-7,9-dimethylpyrido[3',2':4,5]selenolo [3,2-*d*]pyrimidine was 10 mg ml^{-1}.

Key words: sulfa drugs, selenolo pyridine, selenolo pyridazine, selenolo quinoline, antibacterial activity

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INTRODUCTION

Our laboratory has a long standing in the chemistry of selenium containing heterocycles with discovery and development of the synthesis of new heterocyclic systems to search for biological active compounds [1–4]. Recently, the explosive growth of the interest in organoselenium chemistry can be attributed to the specific properties and pharmaceutical applications [5–10]. On the other hand sulfonamide drugs (known widely as "sulfa drugs") were the first antimicrobial drugs, and paved the way for the antibiotic revolution in medicine. Moreover, sulfonamides have a variety of biological activities such as antibacterial [11], insulin releasing [12], anti-inflammatory [13] and anti-tumor activities [14]. Previous work in our laboratory describes the synthesis of selenolo[2,3-*b*]pyridine, selenolo[2,3-*c*]pyridazine, selenolo [2,3-*b*]quinoline derivatives, which indicate that certain compounds bearing the selenophene with pyridine, pyridazine and quinoline nucleus possess significant anti-inflammatory and analgesic activities with strong fungicidal effects [1–4]. For this reason the synthetic connection of sulfa drugs with selenium containing heterocyclic compounds may increase the biological activities and act as antiinflammatory, analgesic, fungicidal and bactericidal. Considering the foregoing benefits, we aimed to link biologically active sulfonamides (e.g. Sulfadiazine, Sulfadimidine and Sulfacetamide) with organo selenium derivatives to access new classes of biologically active compounds.

CHEMISTRY

In order to obtain compounds containing selenium in their structures, nitrile compounds (**2**), (**6**) or (**9**) were used as the precursors, since these compounds are readily obtained by previously described procedures [1–4]. The synthetic method for compounds (**4a**)–(**4c**), (**7a**)–(**7c**) and (**10a**)–(**10c**) is modification of hitherto known procedure [15, 16]. Upon treatment of *N*-ethoxymethyleneaminoselenolo pyridine (**2**), selenolo pyridazine (**6**) or selenolo quinoline (**9**) derivatives with 1-amino-N^4-substituted sulfanilamides (**3a**)–(**3c**) to give 3-[4-(*N*-substituted sulfamoyl)phenyl]-3,4-dihydro-4-oxo-7,9-dimethylpyrido[3',2':4,5]selenolo [3,2-*d*] pyrimidine (**4a**)–(**4c**) (Scheme 1), 7-[4-(*N*-substituted sulfamoyl)phenyl]-7,8-dihy-

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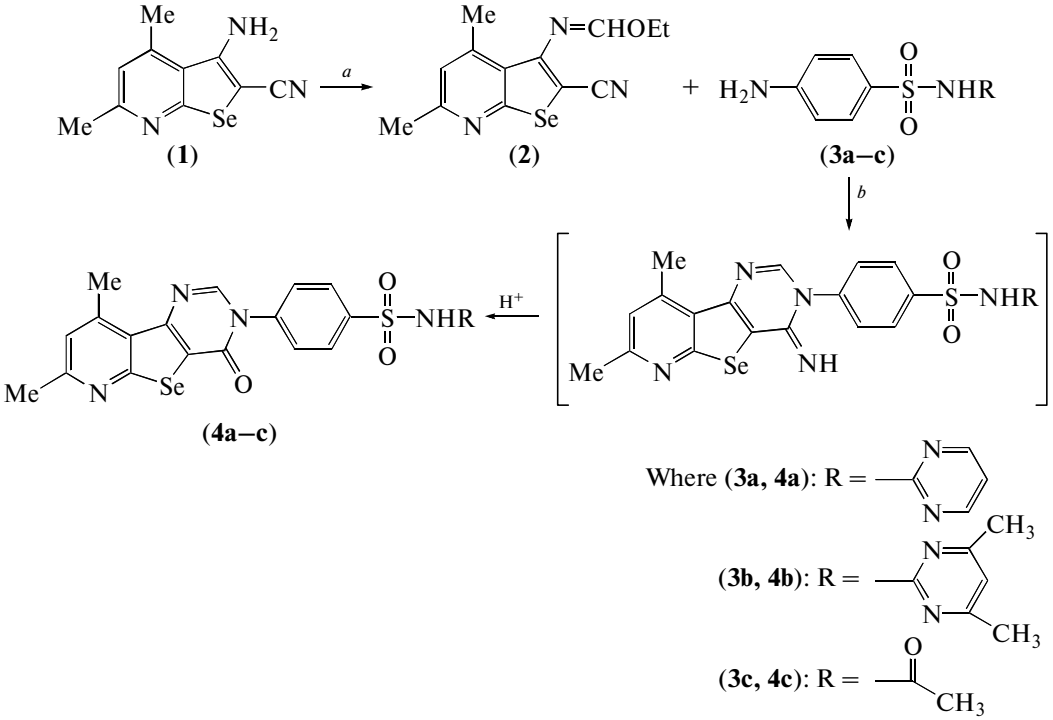
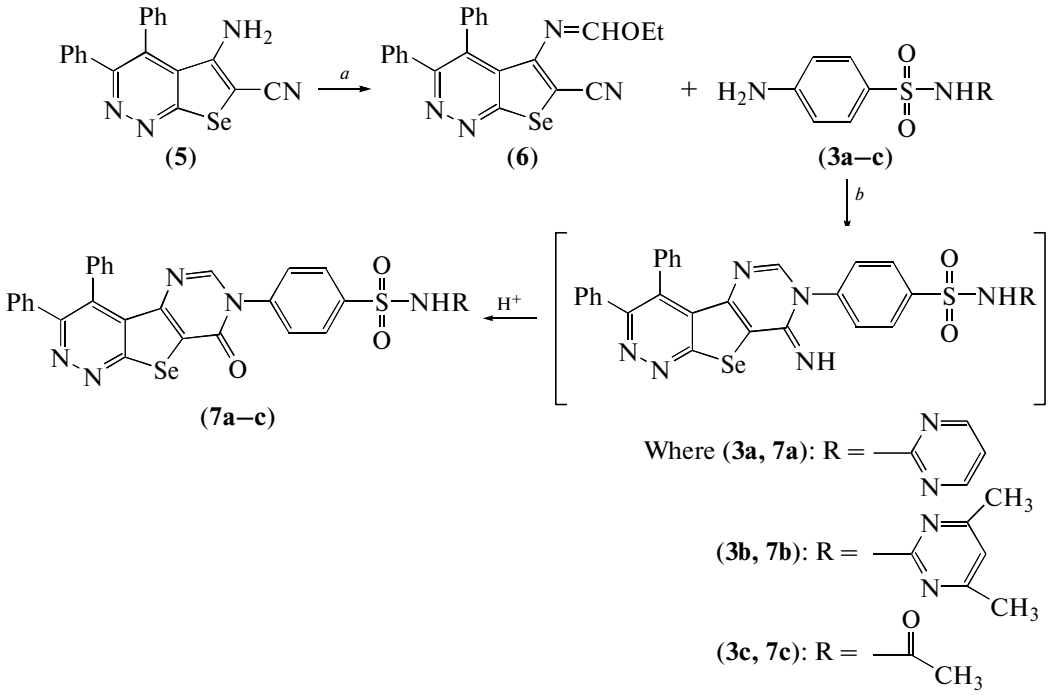
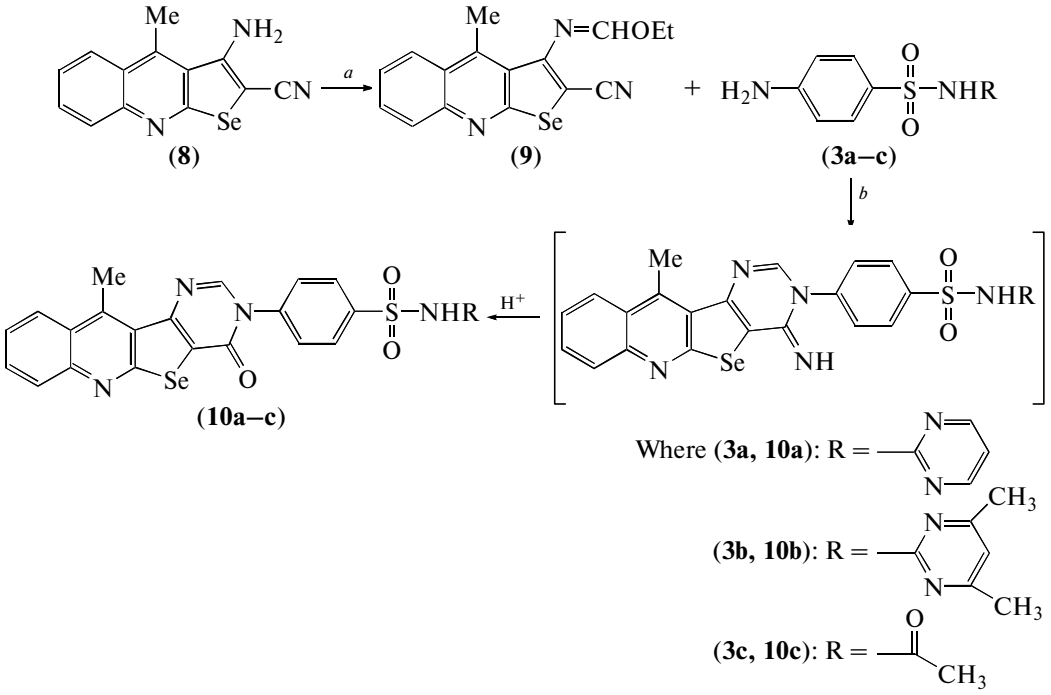
dro-8-oxo-3,4-diphenyl pyrimido [4',5':4, 5]selenolo[2,3-*c*]pyridazine (**7a**)–(**7c**) (Scheme 2) and 1-[4-(*N*-substituted sulfamoyl)phenyl]-1,11-dihydro-11-oxo-4-methylpyrimido[4',5':4,5]selenolo [2,3-*b*]quinoline (**10a**)–(**10c**) respectively (Scheme 3). It is worthy to mention that these products (**4a**)–(**4c**), (**7a**)–(**7c**) and (**10a**)–(**10c**) were obtained via oxidation of imino group in pyrimidine ring into ketone under reaction condition in acidic medium.



Scheme 1. *a* = Triethylortho formate/Ac_2O; *b* = gl. acetic acid.



Scheme 2. *a* = Triethylortho formate/Ac_2O; *b* = gl. acetic acid.



Scheme 3. *a* = Triethylortho formate/Ac_2O; *b* = gl. acetic acid.

IR spectra of the nitrile compounds (**2**), (**6**) and (**9**) exhibited characteristic bands at 2200 cm^{-1} (CN), 1645–1640 cm^{-1} (>C=N) and disappearance of peaks at 3250–3350 cm^{-1} of amino group (NH_2) of starting compounds (**1**), (**5**) and (**8**). In ^{1}H-NMR spectra of compounds (**2**), (**6**) and (**9**) displayed a quartet and triplet like signals at 4.5–3.5 (for CH_2) and 1.5–1.2 ppm (for CH_3) corresponding to the protons of ethoxy group (OCH_2CH_3) and disappearance of signals corresponding to the protons of amino group. The structures of the final products (**4a**)–(**4c**), (**7a**)–(**7c**) and (**10a**)–(**10c**) have been elucidated based on their elemental analysis, IR, ^{1}H-NMR and ^{13}C NMR. All spectral data were in accordance with the assumed structures. In IR spectra, of compounds (**4a**)–(**4c**), (**7a**)–(**7c**) and (**10a**)–(**10c**) appeared a characteristic bands at 3300, 3310, 3320 cm^{-1} confirmed the presence of (N-H stretching) of sulfonamides fused together with selenium compounds, also, the appearance of significant bands at 1705, 1700 cm^{-1} due to ring closure of pyrimidine ring and confirmed the oxidation of imino group into carbonyl group (C=O). In ^{1}H-NMR spectra, all protons were seen according to the expected chemical shifts and integral values. The most important protons of compounds (**4a**)–(**4c**), (**7a**)–(**7c**) and (**10a**)–(**10c**) are appearance signals at 8.6–9.0 ppm due to ring closure (CH-pyrimidine).

Further confirmation of the structure was through ^{13}C NMR spectra for compounds (**9**) and final product (**4b**) only and this due to slightly solubility of the final compounds. The signals obtained were all in a good agreement with the proposed structures. In ^{13}C NMR spectrum of compound (**4b**) sixteen peaks were observed. The sulfonamide and carbonyl carbons of pyrimidine ring are resonated at 219.59 ppm and 167.41 ppm respectively. The aromatic carbon atoms in addition carbon atom of dimidine resonate at 119.99–147.91 ppm. The ^{13}C NMR spectrum of compound (**9**) twelve peaks were observed. The most important Peaks at 219.58 ppm is due to N=CHO, 125.46–132.63 ppm—to quinoline ring carbon atoms, 69.11 ppm CH_2—to ethoxy carbon atom and 14.32 ppm CH_3—to quinoline ring.

BIOLOGICAL SCREENING

Five bacterial test organisms such as *Serratia marcescens* (b-55), *Escherichia coli* (b-53) and *Pseudomonas aeruginosa* (b-73), *Bacillus cereus* (b-52) and *Staphylococcus aureus* (b-54) were obtained from Assiut University Mycological Center. The tested organisms were maintained on nutrient agar slants and were sub cultured in Petri dishes prior to testing. The media used was nutrient agar. The Minimum inhibitory concentration (MIC) was determined by the test tube dilution technique using Sulfadiazine, Sulfadimidine and Sulfacetamide as standard drugs.

RESULTS AND DISCUSSION

All the newly synthesized compounds (**4a**)–(**4c**), (**7a**)–(**7c**) and (**10a**)–(**10c**) were screened in vitro for their antibacterial activity against gram-positive

Antibacterial activity of compounds **(4a)**–**(4c)**, **(7a)**–**(7c)** and **(10a)**–**(10c)**

Organism	Inhibition zone (mm) for compounds											
	(4a)	**(4b)**	**(4c)**	**(7a)**	**(7b)**	**(7c)**	**(10a)**	**(10b)**	**(10c)**	Ref*	Ref**	Ref***
S. marcescens (-ve) AUMC b-55	12	10	14	0	0	0	10	10	10	24	22	20
B. cereus (+ve) AUMC b-52	0	0	11	0	0	0	0	0	0	20	14	14
S. aureus (+ve) AUMC b-54	14	0	18	0	0	0	0	0	0	0	0	0
E. coli (-ve) AUMC b-53	12	0	14	0	0	0	0	0	0	18	16	14
P. aeruginosa (-ve) AUMC b-73	0	0	12	0	0	0	0	0	0	0	0	0

Organisms	Minimum inhibitory concentration (mg ml^{-1}) for compounds													
	(4a)		**(4b)**	**(4c)**		**(10a)**	**(10b)**	**(10c)**	Ref*		Ref**		Ref***	
	100	50	100	100	50	100	100	100	100	50	100	50	100	50
S. marcescens (-ve) AUMC b-55	10	0	0	12	0	0	0	0	24	22	22	22	16	16
B. cereus (+ve) AUMC b-52	0	0	0	0	0	0	0	0	0	0	0	0	0	0
S. aureus (+ve) AUMC b-54	10	0	0	14	0	0	0	0	0	0	0	0	0	0
E. coli (-ve) AUMC b-53	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P. aeruginosa (-ve) AUMC b-73	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Slightly sensitive (inhibition zone 5–10), fairly sensitive (inhibition zone 11–15), highly sensitive (inhibition zone 16–20), very highly sensitive 21–25).

* Ref = Sulfadiazine, ** Ref = Sulfadimidine, *** Ref = Sulfacetamide.

Amount added from each sample = 50 µl/ pore.

AUMC = Assiut University Mycological Center.

(*B. cereus* and *S. aureus*) and gram-negative (*S. marcescens, E. coli* and *P. aeruginosa*) bacteria. Compound **(4c)** showed strong significant activity against all species of gram-positive and gram-negative bacteria (inhibition zone 14, 11, 18, 14, 12 mm respectively as in Table). We can attributed this to the presence of acetyl group in sulfacetamide. Replacing acetyl group with pirimidine-2-yl) moiety in compound **(4a)** resulted in lower activity than compound **(4c)** (inhibition zone 12 mm against *S. marcescens*, 14 mm against S. *aureus* and 12 mm against *E. coli*). Replacing pirimidine-2-yl) moiety with 4,6-dimethylpyrimidine-2-yl moiety **(4b)** showed lower activity compared to **(4c)** and **(4a)** against gram-negative bacteria *S. marcescens* with inhibition zone 10 mm. Compounds **(10a)**, **(10b)** and **(10c)** showed slightly sensitive against gram-negative bacteria *S. marcescens* (inhibition zone 10 mm). Compounds **(7a)**, **(7b)** and **(7c)** were inactive against all gram-positive and gram-negative bacteria. The minimum inhibitory concentration (MIC) of the most active compound **(4c)** which contain sulfacetamide group bearing with selenolo pyridine was 10 mg ml^{-1} with inhibition zone 14 mm against *S. aureus* bacteria and 12 mm against *S. marcescens* as shown in Table.

In general, compounds **(4b)**, **(10a)**, **(10b)** and **(10c)** were moderate potent against *S. marcescens* as compared to the standard drugs (*Sulfadiazine, Sulfadimidine* and *Sulfacetamide*) while, compound **(4c)** was found more potent against *S. aureus, E. coli, S. marcescens, P. aeruginosa* and *B. cereus* respectively and have abroad spectrum than standard drugs. Therefore, it can be inferred that presence of donor substitute acetyl group in sulfacetamide imparts much towards antibacterial power of these compounds in addition to the presence of pyridine nucleus bearing the selenophene. The data also revealed that the activity of compounds diminished such as **(4c)** > **(4a)** > **(4b)** > **(10a)**–**(10c)** > **(7a)**–**(7c)** and this means the fusion of different heterocyclic rings (pyridine, pyridazine and quinoline) and selenophene moiety exert a significance influence on the antibacterial activity. The presence of pyridine ring showed greater activity than that of quinoline and pyridazine. The most active compound was **(4c)** which contains a selenolo pyridine ring. This indicates that the presence of pyridine moiety in addition the presence of acetyl group in sulfa drug as mentioned before is additive towards antibacterial activity in this class of compounds.

EXPERIMENTAL

Melting points were determined using a Kofler melting point apparatus (C. Reichert, Vienna, Austria) and are uncorrected. IR (KBr) spectra were recorded on a Pye-Unicam SP3-100 instrument (Pye Unicam Ltd. Cambridge, England). ^{1}H NMR spectra were obtained on a Varian EM 390 (Varian Inc., Palo Alto, CA, USA) using tetramethylsilane as an internal reference. Mass spectra were recorded on a JEOL-JMS-AX 600

(JEOL, Tokyo, Japan) at Assiut University, Assiut, Egypt. M^+ ions are given for ^{80}Se unless otherwise stated; the mass spectra were recorded via FAB inlet. ^{13}C NMR spectra were recorded on a GEMINI-200 ''NMR200'' at Cairo University. Elemental analyses were obtained on an Elementar Vario EL 1150C analyzer (Heraeus, Germany). The purity of the compounds was checked by TLC. Sulfonamides derivatives were obtained from Aldrich and used without further purification.

Compounds (**1**), (**2**), (**5**) and (**8**) were prepared as previously described [1–4].

N-Ethoxymethyleneamino Derivatives: Preparation of Compounds (2), (6) and (9)

The nitrile derivatives (**1**), (**5**) and (**8**) (10 mmol) and triethyl orthoformate (7 ml) were refluxed in acetic anhydride (3 ml) for 5 h. The precipitate that formed on cooling was collected and recrystallized from ethanol as yellow crystals.

Ethyl N-(2-cyano-4, 6-dimethylselenolo[2,3-b]pyridine-3-yl) methanimidate (**2**).

The resulted data (IR, ^1H NMR and MS) see [ref. 2]

Ethyl N-(6-cyano-3,4-diphenylselenolo[2,3-c]pyridazine-5-yl)methanimidate (**6**): crystallized from ethanol, mp = 178–180°C, yield (86%). IR (cm^{-1}) 2200 (CN); 1645 (C=N). ^1H NMR (δ, ppm), $CDCl_3$: 7.2–7.4 (10 H, m, Ar-H); 7.6 (1 H, s, N=CH); 3.5 (2 H, q, CH_2); 1.2 (3 H, t, CH_3), mass spectrum of compound (**6**) ($C_{22}H_{16}N_4OSe$) exhibited molecular ion peak at *m/z* (%) 432 (3) [M^+] and the other important fragments were observed at 403 (13), 202 (4), 103 (100). Anal: Calc. for ($C_{22}H_{16}N_4OSe$): C, 61.24; H, 3.74; N, 12.99. Found: C, 61.01; H, 3.57; N, 12.75.

Ethyl N-(2-cyano-4-methylselenolo[2,3-b]quinoline-3-yl)methanimidate (**9**): crystallized from ethanol, mp = 150–152°C, yield (76%). IR (cm^{-1}) 2200 (CN); 1640 (C=N). ^1H NMR (δ, ppm), DMSO: 7.6–8.3 (4 H, m, Ar-H); 7.6 (1 H, s, N=CH); 4.4 (2 H, q, CH_2); 3.0 (3 H, s, CH_3-quinoline); 1.4 (3 H, t, CH_3); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 219.58 (–N=CH–O), 211.51, 190.07, 132.63, 131.36, 128.30, 125.46 (Aryl), 111.16 (C–CN), 72.65, 69.11 (CH_2 and CH_3), 14.32 (CH_3 of quinoline), mass spectrum of compound (**9**) ($C_{16}H_{13}N_3OSe$) exhibited molecular ion peak at *m/z* (%) 343 (100) (M^+) and the other important fragments were observed at 344 (22) [$M^+ + 1$], 345 (23) [$M^+ + 2$], 295 (39), 287 (59), 140 (68), 77 (11). Anal: Calc. for ($C_{16}H_{13}N_3OSe$): C, 56.14; H, 3.83; N, 12.27. Found: C, 56.12; H, 3.64; N, 12.43.

3-[4-(N-Substituted sulfamoyl)phenyl]-3,4-dihydro-4-oxo-7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-d]pyrimidines (4a)–(4c), 7-[4-(N-substituted sulfamoyl)phenyl]-7,8-dihydro-8-oxo-3,4-diphenylpyrimido[4',5':4,5] selenolo[2,3-c]pyridazines (7a)–(7c) and 1-[4-(N-substitutedsulfamoyl)phenyl]-1,11-dihydro-11-oxo-4-methylpyrimido[4',5':4,5]selenolo[2,3-b]quinolines (**10a**)–(**10c**).

General Procedures

The iminoethers (**2**), (**6**) or (**9**) (10 mmol) were heated under reflux with compounds (**3a**)–(**3c**) (10 mmol) for 4 h in gl. acetic acid. The solid that separated was collected and recrystallized from proper solvent.

3-[4-(N-Pyrimidinyl sulfamoyl)phenyl]-3,4-dihydro-4-oxo-7,9-dimethylpyrido[3',2':4,5]selenolo[3,2-d]pyrimidine (**4a**): crystallized from dioxan, mp = 280–282°C, yield (80%). IR (cm^{-1}) 3300 (NH); 1700 (C=O), 1640 (C=N). ^1H NMR (δ, ppm), TFA: 9.0 (1 H, s, CH-pyrimidine); 7.8–8.6 (7 H, m, Ar-H sulfapyridazine, Ar-H phenyl); 7.6 (1 H, s, CH-pyridine); 3.0 (3 H, s, CH_3); 2.2 (3 H, s, CH_3), mass spectrum of compound (**4a**) ($C_{21}H_{16}N_6O_3SSe$) exhibited molecular ion peak at *m/z* (%) 512 (8) [M^+] and the other important fragments were observed at 252 (52), 250 (23), 185 (36), 115 (76), 93 (100). Anal: Calc. for ($C_{21}H_{16}N_6O_3SSe$): C, 49.29; H, 3.15; N, 16.43; S, 6.27. Found: C, 49.92; H, 3.20; N, 16.06; S, 5.80.

3-[4-(N-2,4-Dimethylpyrimidinyl sulfamoyl)phenyl]-3,4-dihydro-4-oxo-7,9-dimethylpyrido[3',2':4,5]selenolo [3,2-d]pyrimidine (**4b**)**:** crystallized from dioxan, mp > 300°C, yield (75%). IR (cm^{-1}) 3310 (NH); 1700 (C=O), 1600 (C=N). ^1H NMR (δ, ppm), DMSO: 9.7 (1 H, s, SO_2NH), 8.72 (1 H, s, CH-pyrimidine); 6.7–8.70 (5 H, m, Ar-H dimidine, Ar-H phenyl); 7.2 (1 H, s, CH-pyridine); 2.8 (3 H, s, CH_3); 2.4 (3 H, s, CH_3); 2.2 (3 H, s, CH_3); 1.8 (3 H, s, CH_3); ^{13}C NMR (DMSO-d_6, 50 MHz), δ 219.59 (–SO_2NH–C of dimidine), 205.44, 167.41 (C=O of pyrimidine ring), 159.66, 156.31, 154.05, 147.91, 143.26, 134.12, 129.52, 128.93, 119.99, (Aryl), 97.87 (C of dimidine), 23.84, 22.91, 21.02 (CH_3 of dimidine and pyridine rings); mass spectrum of compound (**4b**) ($C_{23}H_{20}N_6O_3SSe$) exhibited molecular ion peak at *m/z* (%) 540 (33) [$M^+ - 1$], 541 (5) [M^+] and the other important fragments were observed at 538 (19), 353 (27), 185 (58), 115 (5), 93 (100). Anal: Calc. for ($C_{23}H_{20}N_6O_3SSe$): C, 51.19; H, 3.74; N, 15.58; S, 5.94. Found: C, 50.98; H, 3.69; N, 15.84; S, 5.79.

3-[4-(N-Acetyl sulfamoyl)phenyl]-3,4-dihydro-4-oxo-7,9-dimethylpyrido[3',2':4,5]selenolo [3,2-d]pyrimidine (**4c**): crystallized from ethanol, mp = 220–222°C, yield (77%). IR (cm^{-1}) 3320 (NH); 1700, 1705 (C=O), 1620 (C=N). ^1H NMR (δ, ppm), TFA: 8.9 (1 H, s, CH-pyrimidine); 8.3 (4 H, m, Ar-H phenyl); 7.8 (1 H, s, CH-pyridine); 2.5 (3 H, s, CH_3); 2.1 (3 H, s, CH_3); 1.7 (3 H, s, CH_3), mass spectrum of compound (**4c**) ($C_{19}H_{16}N_4O_4SSe$) exhibited molecular ion peak at *m/z* (%) 476 (4) [M^+] and the other important fragments were observed at 434 (20), 278 (27), 252 (89), 250 (50), 185 (34), 115 (100), 93 (83). Anal: Calc. for

($C_{19}H_{16}N_4O_4SSe$): C, 47.99; H, 3.39; N, 11.78; S, 6.74. Found: C, 47.79; H, 3.18; N, 11.47; S, 6.54.

7-[4-(N-Pyrimidin-2-yl sulfamoyl)phenyl]-7,8-dihydro-8-oxo-3,4-diphenylpyrimido [4′,5′:4,5]selenolo[2,3-c]pyridazine (**7a**): crystallized from ethanol, mp = 202–204°C, yield (80%). IR (cm^{-1}) 3350 (NH); 1690 (C=O), 1635 (C=N). ^1H NMR (δ, ppm), DMSO: 9.2 (1 H, s, SO_2NH), 8.5 (1 H, s, CH-pyrimidine); 7.8–8.5 (17 H, m, Ar-H sulfadiazine, Ar-H phenyl); mass spectrum (EI^+) of compound (**7a**) ($C_{30}H_{19}N_7O_3SSe$) exhibited molecular ion peak at *m/z* (%) 403 (44) [$M^+ - C_{10}H_8N_3O_2S$]. Anal: Calc. for ($C_{30}H_{19}N_7O_3SSe$): C, 56.59; H, 3.01; N, 15.40; S, 5.03. Found: C, 56.38; H, 2.98; N, 15.33; S, 4.98.

7-[4-(N-4,6-Dimethylpyrimi-2-yl sulfamoyl)phenyl]-7,8-dihydro-8-oxo-3,4-diphenylpyrimido[4′,5′:4,5]selenolo[2,3-c]pyridazine (**7b**): crystallized from dioxan, mp = 220–224°C, yield (77%). IR (cm^{-1}) 3300 (NH); 1700 (C=O), 1640 (C=N). ^1H NMR (δ, ppm), DMSO: 8.9 (1 H, s, SO_2NH), 8.4 (1 H, s, CH-pyrimidine); 7.5–8.0 (15 H, m, Ar-H phenyl); 2.3 (3 H, s, CH_3), 1.8 (3 H, s, CH_3); mass spectrum (EI^+) of compound (**7b**) ($C_{32}H_{23}N_7O_3SSe$) exhibited molecular ion peak at *m/z* (%) 404 (7) [$M^+ - C_{12}H_{12}N_3O_2S$]. Anal: Calc. for ($C_{32}H_{23}N_7O_3SSe$): C, 57.82; H, 3.49; N, 14.75; S, 4.82. Found: C, 57.63; H, 3.22; N, 14.54, S, 4.71.

7-[4-(N-Acetyl sulfamoyl)phenyl]-7,8-dihydro-8-oxo-3,4-diphenylpyrimido[4′,5′:4,5]selenolo[2,3-c]pyridazine (**7c**) crystallized from dioxan, mp > 300°C, yield (75%). IR (cm^{-1}) 3300 (NH); 1700 (C=O), 1620 (C=N). ^1H NMR (δ, ppm), TFA: 9.0 (1 H, s, CH-pyrimidine); 7.5–8.3 (14 H, m, Ar-H phenyl); 1.9 (3 H, s, CH_3), mass spectrum of compound (**7c**) ($C_{28}H_{19}N_5O_4SSe$) exhibited molecular ion peak at *m/z* (%) 600 (3) [$M^+ - 1$], 601 (0.8) [M^+] and the other important fragments were observed at 493 (0.3), 297 (1.3), 277 (3.1), 241 (4.4), 185 (60), 115 (3.7), 93 (100). Anal: Calc. for ($C_{28}H_{19}N_5O_4SSe$): C, 55.99; H, 3.19; N, 11.66, S, 5.34. Found: C, 55.74; H, 3.00; N, 11.54, S, 5.19.

1-[4-(N-Pyrimidin-2-yl sulfamoyl)phenyl]-1,11-dihydro-11-oxo-4-methylpyrimido[4′,5′:4,5]selenolo[2,3-b]quinoline (**10a**): crystallized from dioxan, mp > 300°C, yield (80%). IR (cm^{-1}) 3290 (NH); 1700 (C=O), 1640 (C=N). ^1H NMR (δ, ppm), TFA: 8.5 (1 H, s, CH-pyrimidine); 7.8–8.6 (11 H, m, Ar-H); 3.0 (3 H, s, CH_3), mass spectrum of compound (**10a**) ($C_{24}H_{16}N_6O_3SSe$) exhibited molecular ion peak at *m/z* (%) 545 (0.2) [$M^+ - 3$] and the other important fragments were observed at 257 (3), 241(9), 185 (66), 115 (9), 93 (100). Anal: Calc. for ($C_{24}H_{16}N_6O_3SSe$): C, 52.64; H, 2.95; N, 15.35; S, 5.85. Found: C, 52.35; H, 3.13; N, 15.04; S, 5.45.

1-[4-(N-4,6-Dimethylpyrimidin-2-yl sulfamoyl)phenyl]-1,11-dihydro-11-oxo-4-methylpyrimido[4′,5′:4,5]selenolo[2,3-b]quinoline (**10b**): crystallized from dioxan, mp > 300°C, yield (65%). IR (cm^{-1}) 3295 (NH); 1700 (C=O), 1600 (C=N). ^1H NMR (δ, ppm), DMSO: 9.6 (1 H, s, SO_2NH); 8.6 (1 H, s, CH-dimidine); 7.5–8.0 (4 H, m, Ar-H phenyl); 6.8 (1 H, s, CH-pyrimidine); 3.6 (3 H, s, CH_3); 3.2 (3 H, s, CH_3); 2.3 (3 H, s, CH_3), mass spectrum of compound (**10b**) ($C_{26}H_{20}N_6O_3SSe$) exhibited molecular ion peak at *m/z* (%) 576 (1) [M^+], 574 (2) [$M^+ - 2$] and the other important fragments were observed at 434 (20), 228 (14), 207 (11), 185 (58), 115 (50), 93 (100). Anal: Calc. for ($C_{26}H_{20}N_6O_3SSe$): C, 54.25; H, 3.51; N, 14.60; S, 5.57 Found: C, 54.10; H, 3.34; N, 14.47, S, 5.33.

1-[4-(N-Acetyl sulfamoyl)phenyl]-1,11-dihydro-11-oxo-4-methylpyrimido[4′,5′:4,5]selenolo[2,3-b]quinoline (**10c**): crystallized from dioxan, mp = > 300°C, yield (75%). IR (cm^{-1}) 3310 (NH); 1705, 1700 (C=O), 1600 (C=N). ^1H NMR (δ, ppm), DMSO: 9.6 (1 H, s, SO_2NH); 8.9 (1 H, s, CH-pyrimidine); 7.3–8.3 (8 H, m, Ar-H phenyl); 3.2 (3 H, s, CH_3); 2.2 (3 H, s, CH_3) mass spectrum of compound (**10c**) ($C_{22}H_{16}N_4O_4SSe$) exhibited molecular ion peak at *m/z* (%) 514 (5) [$M^+ + 2$] and the other important fragments were observed at 455 (24), 373 (19), 185 (9), 101 (28), 51 (100). Anal: Calc. for ($C_{22}H_{16}N_4O_4SSe$): C, 51.66; H, 3.15; N, 10.95; S, 6.27. Found: C, 51.44; H, 3.00; N, 10.78; S, 5.98.

Anti-Bacterial Assays (in vitro)

Five bacterial species representing both gram-positive and gram-negative strains were used to test the antibacterial activities of the target compounds (**4a**)–(**4c**), (**7a**)–(**7c**) and (**10a**)–(**10c**) in vitro against (i) gram-negative bacteria: *S. marcescens* (b-55), *E. coli* (b-53) and (ii) gram-positive bacteria*: P. aeruginosa* (b-73), *B. cereus* (b-52), *S. aureus* (b-54) in comparison to sulfadiazine, sulfadimidine and Sulfacetamide as reference drug by using the standard agar paper disc diffusion method [17]. Cell suspension of bacterial stains was 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 diameter, and then 15 ml of Nutrient Agar was poured onto the plates. Plates were shaken gently to homogenize the innoculum. Sulfa drug (sulfadiazine, sulfadimidine and sulfacetamide) solutions at concentration (100 and 50 mg ml^{-1}) as reference drug. DMSO was used as a solvent control. Impregnated discs were then dried for 1 h and placed in the centre of each plate. The seeded plated 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.

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