Organic & Supramolecular Chemistry

Synthesis of Various Derivatives of [1,3]Selenazolo[4,5-d] pyrimidine and Exploitation of These Heterocyclic Systems as Antibacterial, Antifungal, and Anticancer Agents

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A number of diversely functionalized derivatives of a novel [1,3] selenazolo[4,5-*d*]pyrimidine have been synthesized through heterocyclization of some 2,4,5-trisubstituted-1,3-selenazoles with orthoesters in refluxing acetic acid. The synthetic compounds were evaluated for their antimicrobial activity against a panel of microorganisms including Gram-negative bacteria, Gram-positive bacteria, and pathogenic fungi. The antifungal results revealed that the new selenium-containing heterocycles were as good as or sometimes better than terbinafine and fluconazole. The in vitro anticancer activities of aforementioned heterocyclic compounds were screened against human breast carcinoma MCF-7 and HeLa cervical cancer cells as well as HDF (human dermal fibroblast) normal cells. Antiproliferative results indicated that compounds with piperidine moiety on MCF-7 cells and with morpholine moiety on HeLa cells exhibited well broad-spectrum of anticancer activities with 397, 298 and 235 μM and 533, 390 and 204 μM of IC_{50} values after 24, 48 and 72 h of treatments, respectively, while they had no significant toxic effects on normal cells.

1. Introduction

Since selenium (Se) used to be considered as an essential nutrient for mammals for nearly two decades, the importance of selenium chemistry has been escalating. Selenium is the constituent of selenoproteins involved in the self-defense mechanism against oxidative stress,[1] which is essential for the activity of glutathione peroxidase, in reducing specific inflammatory processes and in detoxification phenomena.[2] In addition, it plays a pivotal role in the activity of various enzymes such as thioredoxin reductase, iodothyronine deiodinase, selenophosphate synthetase, and selenoprotein P.[3–7]

Based on a large variety of chemical, physical, and biological properties associated with the presence of selenium, the synthesis of many Se-containing heterocycles has been developed as a very active research area.[8,9,18,10–17] A diversity of organic selenium derivatives has earned well-deserved reputation for effective biocidal,[19,20] antifungal,[21–24] anti-inflammatory,[25] anti-HIV,[26–28] antioxidant,[23,29–34] free radical scavenging,[29,31,33,35–38] antimicrobial,[22,24,39] anticonvulsant,[39] histone deacetylase[40] and Mycobacterium tuberculosis (Mtb) Ag85 inhibitory[14] activities. With respect to medicine, practical application of some of the selenium-containing compounds for the treatment of tumors and cancers is a subject of current intense interest.[9,15,41–56] Moreover, in terms of material science, five-membered organoselenium heterocycles have been utilized in developing organic conductors, semiconductors, optoelectronics, and fluorescent probes.[57–62]

Amongst heterocyclic organoselenium cores, the 1,3-selenazole skeleton has received much attention in many pharmacologically active substances like selenazofurin (**I**) and amselamine (**II**). (Figure 1) Biological properties such as antioxidant,[13] anticancer,[8,63,64] human carbonic anhydrase IX

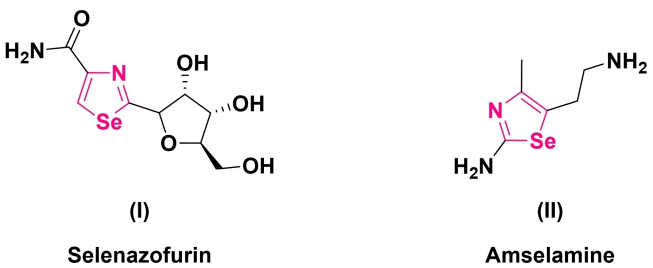

Figure 1. Examples of pharmacologically active selenazoles.

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inhibitory,[12] antimicrobial and anticonvulsant[39] activities are the other worldwide high profile of 1,3-selenazoles.

In the literature, many novel protocols based on the improvement of Hantzsch's reaction have been reported to synthesis of 2-amino-1,3-selenazoles. They have been prepared from the treatment of selenourea/primary selenoamides and aromatic/aliphatic α-halo carbonyls.[65–68] As an example, the synthesis through the condensation of selenourea with phenacyl bromides in eco-friendly conditions was described.[69,70] Some other miscellaneous procedures for the synthesis of mentioned amino-selenazoles are solid-state synthesis employing a Lewis acid catalyst[71] and aqueous phase one-pot synthesis under supramolecular catalysis.[69,72]

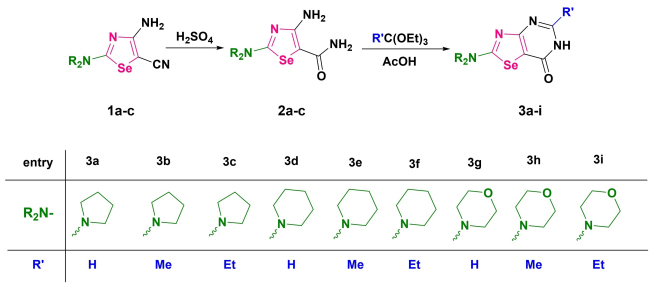
Taking into account the biological importance of the selenium-containing organic compounds and as a part of our ongoing endeavor toward developing novel heterocyclic architectures of potential pharmacological significance,[23,73–80] the present investigation is connected with the elaboration of synthetic protocols, antibacterial, antifungal and cytotoxic studies on the new derivatives of a novel [1,3]selenazolo[4,5-*d*] pyrimidine heterocyclic system **3a–i**.

2. Results and Discussion

2.1. Chemistry

In this protocol, 2,4,5-trisubstituted-1,3-selenazoles **1a–c** as starting materials were prepared through a one-pot four-step sequential procedure.[81] Then, concentrated sulfuric acid-mediated hydrolysis of compounds **1a–c** gave the corresponding substituted 1,3-selenazole-5-carboxamides **2a–c**. The latter compounds subsequently underwent cyclocondensation reaction with various triethyl orthoesters in acetic acid on heating under reflux to give the desired [1,3]selenazolo[4,5-*d*]pyrimidines **3a–i** in good yields (Scheme 1).

The structural assignments of compounds **3a–i** were validated by spectroscopic and microanalytical data. For instance, the IR spectrum of compound **2c** demonstrated the stretching vibration bands at $\nu = 3396, 3326, 3248, 3214\ cm^{-1}$ corresponding to NH_2 groups of amine and amide while the IR spectrum of compound **3i** revealed the absence of NH_2 moieties. Moreover, the C=O vibration band of **3i** was blue-shifted at $1663\ cm^{-1}$ compared to the amidic carbonyl of precursor **2c** at $1646\ cm^{-1}$. ^1HNMR spectrum of compound **3i** represented a triplet signal at δ 1.20 ppm and a quartet signal at δ 2.58 ppm due to ethyl protons, two broad multiplet signals around δ 3.58 and δ 3.73 ppm belonging to the methylene groups deshielded by nitrogen and oxygen of morpholine substituent, respectively. This spectrum showed a singlet signal at δ 12.21 ppm corresponding to the NH moiety of the newly fused pyrimidine ring, which was disappeared by adding D_2O, as well. In ^{13}CNMR, four aliphatic carbons were assigned at δ 11.9, 27.8, 49.6, and 65.9 ppm, whereas five aromatic carbons were detected from δ 108.4 to 173.5 ppm in the downfield of the spectrum. As it was expected, the appearance of the most deshielded peak at δ 173.5 ppm was due to the carbon surrounded among three heteroatoms (2 N and Se), which strongly corroborated the presence of selenazole ring in the product **3i**. Additionally, the observation of the molecular ion peak at *m/z* 313 in the mass spectrum together with the complimentary results of the elemental analysis of **3i** substantiated the fusion of the pyrimidine ring to the selenazole core of the starting material.



Scheme 1. Synthesis of [1,3]selenazolo[4,5-*d*]pyrimidine derivatives.

2.2. Biological Evaluation

2.2.1. In vitro antibacterial and antifungal assay

Inhibitory property of all the newly synthesized compounds **3a-i** was studied against three Gram-positive and five Gram-negative pathogenic bacteria as well as three fungal strains. The activities are presented as the minimum inhibitory concentration (MIC), the minimum bactericidal concentration (MBC), and the minimum fungicidal concentration (MFC) values in Tables 1 and 2. The results of the antibacterial evaluation were compared with those obtained with ceftriaxone and gentamicin antibiotics, while terbinafine and fluconazole were applied as positive controls in antifungal tests.

Based on the obtained results, compounds **3c**, **3e**, and **3h** were effective only against *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Listeria monocytogenes*, respectively. No inhibitory effect on tested bacteria was observed with compound **3g**. Broad-spectrum antibacterial activities were recorded for compound **3a**. This compound was the only effective selenazolo[4,5-*d*]pyrimidine on *Acinetobacter baumannii*, even though it could not inhibit the growth of *Klebsiella pneumonia* and *Streptococcus pyogenes* strains. The latter bacterium was only blocked with compound **3d**. An increase in the size of the C^5-substituents led to a drop in antibacterial effects of 2-pyrrolidinyl-selenazolo[4,5-*d*]pyrimidines **3a-c**. Completely opposite QSAR were observed with 2-morpholino-selenazolo[4,5-*d*]pyrimidines **3g-i**.

Antifungal activities of the selenium-containing heterocycles **3a-i** were more significant than their antibacterial properties, as predicted upon previous researches.[21,22] Whereas compounds **3a**, **3b** and **3i** were effective against all fungal strains, compounds **3d**, **3g** and **3h** could exclusively hinder the growth of only one fungus, effectively. The only efficient piperidine-substituted derivatives against *Aspergillus fumigatus* and *Fusarium oxysporum* were compounds **3e** and **3f**, respectively. Selenazolopyrimidines **3g–i** bearing C^2-morpho-

Table 1. Antibacterial activity of selenazolo[4,5-*d*]pyrimidine derivatives **3a–i.**

Bacteria		Selenazolo[4,5-*d*]pyrimidines									Antibiotics	
		3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	Ceftriaxone	Gentamicin
Escherichia coli	MIC	952	452	–	–	–	–	–	–	409	14	17
(PTCC 1399)	MBC	1903	452	–	–	–	–	–	–	818	14	17
Pseudomonas aeruginosa	MIC	476	905	–	–	1724	1646	–	–	204	1	0.1
(PTCC 1310)	MBC	952	1809	–	–	3448	1646	–	–	409	2	0.1
Shigella dysenteriae	MIC	952	226	–	–	–	–	–	–	–	58	0.06
(PTCC 1188)	MBC	952	452	–	–	–	–	–	–	–	116	0.1
Acinetobacter baumannii	MIC	119	–	–	–	–	–	–	–	–	29	33
(PTCC 1855)	MBC	238	–	–	–	–	–	–	–	–	58	66
Klebsiella pneumonia	MIC	–	–	–	–	–	412	–	–	204	0.1	8
(PTCC 1290)	MBC	–	–	–	–	–	823	–	–	409	1	8
Listeria monocytogenes	MIC	119	–	–	–	–	–	–	0.054	–	14	4
(PTCC 1297)	MBC	238	–	–	–	–	–	–	0.107	–	14	4
Staphylococcus epidermidis	MIC	476	–	216	449	–	–	–	–	818	1	2
(PTCC 1435)	MBC	951	–	431	898	–	–	–	–	1636	4	4
Streptococcus pyogenes	MIC	–	–	–	225	–	–	–	–	–	1	4
(PTCC 1447)	MBC	–	–	–	449	–	–	–	–	–	2	4

MIC (μM), MBC (μM)- No noticeable antibacterial effects.

Table 2. Antifungal activity of selenazolo[4,5-*d*]pyrimidine derivatives **3a-i.**

Fungi		Selenazolo[4,5-*d*]pyrimidines									Antifungal agents	
		3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	Terbinafine	Fluconazole
Fusarium oxysporum	MIC	476	905	–	–	–	206	224	107	51	110	418
(PTCC 5115)	MFC	952	905	–	–	–	206	224	214	51	220	836
Candida albicans	MIC	119	452	1724	449	1724	823	–	–	1636	110	836
(PTCC 5027)	MFC	238	905	1724	898	3448	1646	–	–	3272	220	1672
Aspergillus fumigatus	MIC	1903	1809	431	–	108	–	–	–	409	110	104
(PTCC 5009)	MFC	3806	3618	862	–	216	–	–	–	818	110	208

MIC (μM), MFC (μM)- No noticeable antifungal effects.

line residual showed an ascending order in antifungal potency **3g** < **3h** < **3i** against *Fusarium oxysporum* in accordance with the incremental size of the alkyl substituent at 5-position (C^5-H < C^5-Me < C^5-Et). The strongest fungal inhibitory (MIC) and fungicidal effect (MFC) of 2-morpholine-substituted derivative **3i** against the mentioned fungus, even in comparison to positive controls, probably springs from the lipophilicity increase because of the presence of a morpholine pharmacophore as well as a C^5-ethyl liner aliphatic substituent on a selenazolopyrimidine heterocyclic core which may cause a synergistic effect. Moreover, C^2-morpholine **3i**, C^2-pyrrolidine **3a**, and C^2-piperidine **3e** substituted selenazolo[4,5-*d*]pyrimidines were known as the best fungicides against *Fusarium oxysporum*, *Candida albicans*, and *Aspergillus fumigatus*, respectively.

In general, the study of in vitro sensitivity tests showed that the synthesized selenazole-based heterocyclic compounds could be suitable as antimicrobial agents, especially on pathogenic fungi. The antifungal activity of the synthetic compounds was mostly similar or higher than the activity of commonly used antifungal drugs such as terbinafine and fluconazole. Thus, they may be regarded as precursor heterocycles in the search of new derivatives showing high antifungal activity.

2.2.2. Significant cytotoxic effects of compounds 3a-i on MCF-7 and HeLa cells

Since available standard chemotherapy regimens do not offer adequate survival benefits, it has become necessary to develop new therapeutic agents to improve the treatment efficacy of various cancers and overcome this life-threatening disease. To date, many efforts have been made to discover novel drugs endowed with cytostatic action. Therefore, in the present study, we aimed to determine the anticancer properties of nine selenazolo[4,5-*d*]pyrimidine derivatives **3a–i** on MCF-7 breast cancer and HeLa cervical cancer cells by MTT assay.

Antiproliferative properties of all the newly synthesized heterocycles **3a–i** were investigated on MCF-7 human breast cancer and HeLa cervical cancer cells by measuring their viabilities using MTT colorimetric assay and the calculated IC_{50} values for different time points are presented in Table 3. To compare the cytotoxic effects of compounds **3a–i** with those of the commonly used drugs in the clinic, the well-known standard medicine doxorubicin was employed as a positive control for both MCF-7 and HeLa cells. After exposing cancer cells to various concentrations of doxorubicin at the time intervals of 24, 48 and 72 h, the respective IC_{50} values of 35, 18, 9, and 18, 16, 10 μM were obtained for MCF-7 and HeLa cells, respectively (Table 3).

Table 3. The antiproliferative activity of selenazolo[4,5-*d*]pyrimidines **3a–i** on MCF-7 and HeLa cells as determined by MTT assay.

	IC_{50} (μM) ± SD[a]						
	MCF-7			HeLa			HDF
Compounds	24 h	48 h	72 h	24 h	48 h	72 h	72 h
3a	2094 ± 1.50	894 ± 2.7	563 ± 1.7	–[b]	–[b]	–	ND[c]
3b	1036 ± 2.1	400 ± 1.7	277 ± 2.1	–[b]	–[b]	–[b]	ND[c]
3c	790 ± 1.8	442 ± 2.4	255 ± 3.4	1347 ± 1.60	1265 ± 3.31	664 ± 2.69	ND[c]
3d	482 ± 1.3	349 ± 3.4	261 ± 1.7	763 ± 5.24	568 ± 2.69	549 ± 1.08	ND[c]
3e	397 ± 1.2	298 ± 2.4	235 ± 2.1	1377 ± 1.90	405 ± 1.44	305 ± 1.65	–[d]
3f	2453 ± 2.3	1979 ± 1.5	1114 ± 3.2	822 ± 1.51	267 ± 1.14	215 ± 1.23	–[d]
3g	2238 ± 2.7	994 ± 3.1	548 ± 3.5	1288 ± 1.41	1262 ± 1.23	358 ± 1.23	ND[c]
3h	5370 ± 1.7	2793 ± 2.7	1451 ± 4.4	1323 ± 1.44	1029 ± 1.81	267 ± 1.41	ND[c]
3i	1380 ± 3.1	853 ± 2.3	659 ± 1.8	533 ± 1.14	390 ± 1.23	204 ± 1.65	–[d]
Doxorubicin	35 ± 1.19	18 ± 2.15	9 ± 3.11	18 ± 1.65	16 ± 1.14	10 ± 1.41	ND[c]

[a] The IC_{50} values are shown as mean ± SD (n = 3)
[b] Not perceived noticeable cytotoxic effects
[c] Not determined
[d] No cytotoxic effects

Cytotoxic effects of different concentrations of compounds **3a–i** on MCF-7 and HeLa cells are depicted in Figures 2 and 3.

Based on the conclusive results demonstrated in Table 3, compounds **3a–i** displayed noteworthy dose-dependent cytotoxic effects on both cancerous cell lines. Selected selenazolo[4,5-*d*]pyrimidine derivatives **3e**, **3f**, and **3i**, which exhibited the most significant effects on cancerous cells, were used to determine their IC_{50} values on normal HDF cells. The results of the MTT assay indicated that these compounds had no cytotoxic effects on normal HDF cells.

Results revealed that after exposing MCF-7 cells to various concentrations of selenazolopyrimidines **3a–i**, the highest cytotoxic effects on breast cancer cells belonged to the piperidine-substituted **3e** bearing a methyl group on 5-position of fused heterocycle and the IC_{50} values of 397, 298 and 235 μM were acquired for it at the time intervals of 24, 48 and

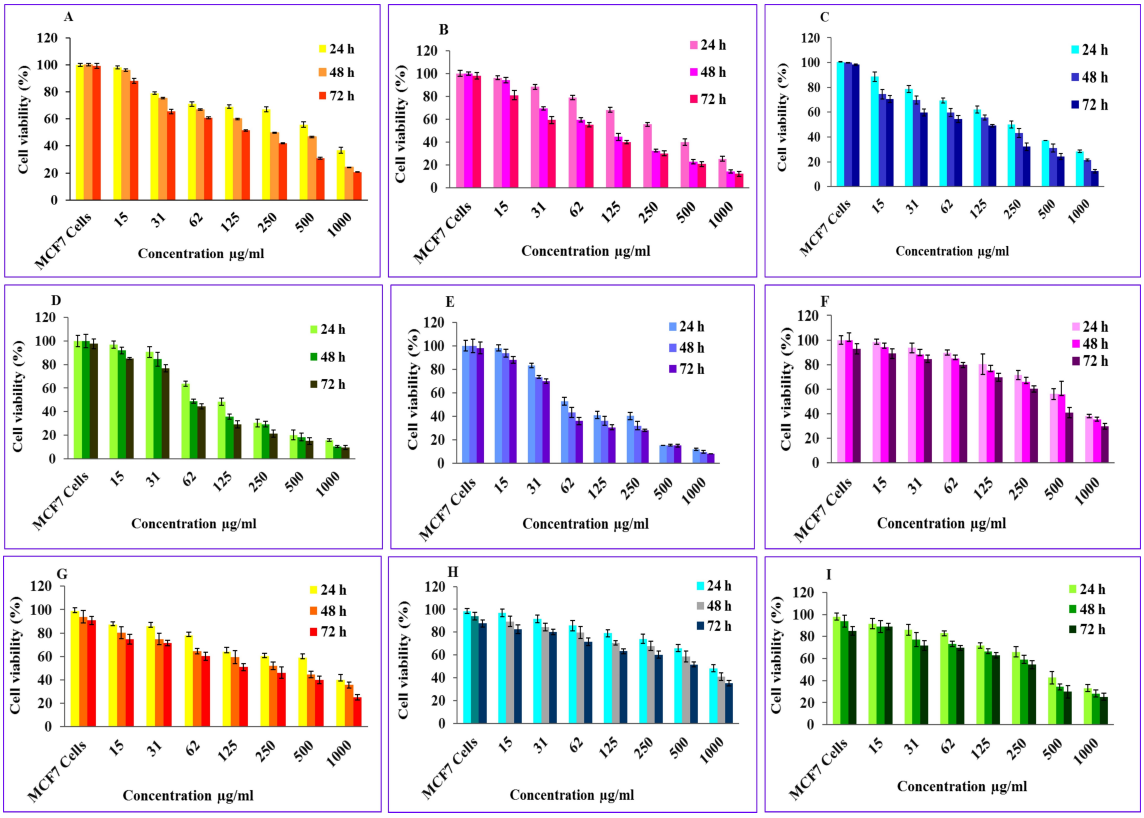


Figure 2. The cytotoxicity of selenazolo[4,5-*d*]pyrimidines **3a-i** on MCF-7 cells; A: **3a**, B: **3b**, C: **3c**, D: **3d**, E: **3e**, F: **3f**, G: **3g**, H: **3h** and I: **3i** during 24, 48 and 72 h. Results are shown as mean ± SD (n = 3).

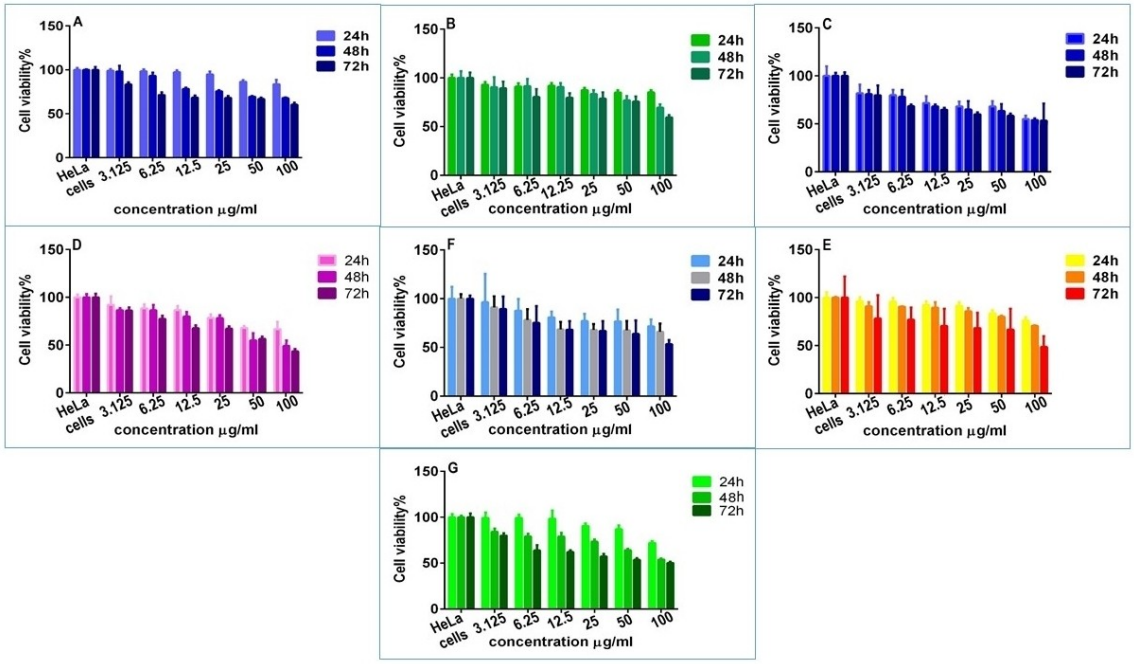


Figure 3. The cytotoxicity of selenazolo[4,5-*d*]pyrimidines **3c-i** on HeLa cells; A: **3c**, B: **3d**, C: **3e**, D: **3f**, E: **3g**, F: **3h** and G: **3i** during 24, 48 and 72 h. Results are shown as mean ± SD (n = 3).

72 h, respectively. In the following order, C^2-pyrrolidine substituted compound **3c** with IC_{50} values of 790, 442 and 255 μM and C^2-piperidine substituted compound **3d** with IC_{50} values of 482, 349 and 261 μM were ranked in the second and third place of antiproliferative potency, respectively.

Furthermore, the obtained results of the present screening clarified that the presence of a hydrophobic chain on the pyrimidine ring plays a critical role in the cytotoxicity of selenazolo[4,5-*d*]pyrimidines on HeLa cells. Considering the length of the hydrocarbon chain in each series of 2-pyrrolidine-substituted **3a–c**, 2-piperidine-substituted **3d–f**, and 2-morpholine-substituted compounds **3g–i**, the antiproliferative efficacy of the selenazolopyrimidines on HeLa cells improved with the increased size of C^5-alkyl substituent. On the other hand, compounds **3d–i** bearing six-membered carbocyclic pharmacophores such as piperidine and morpholine were far superior to compounds **3a–c** bearing five-membered one, namely pyrrolidine. Thus, among the heterocyclic compounds used in this study, C^2-morpholine **3i** and C^2-piperidine **3f** substituted compounds with respective IC_{50} values of 204 and 215 μM after 72 h treatment were foremost as in anticancer potency against HeLa cells. Therefore, it can be concluded that lipophilic properties of studied compounds might easily be enhanced by growing the length of the alkyl substituent at C-5 and increasing the carbocyclic size of secondary amine functional group at C-2 position of selenazolo[4,5-*d*]pyrimidine skeleton as a new pharmacophore scaffold, which facilitated their infiltration into HeLa cells.

In terms of structure-activity relationships of other heterocyclic compounds, a newly reported investigation showed that significant cytotoxic effects on HeLa cells differ based on the length of the hydrophobic side chains attached to the main heterocyclic core.[82] Similarly, Zhou *et al.* synthesized a series of selenazolopyridine heterocycles with the capability to induce apoptosis in MCF-7 cells, which are structurally similar to our synthetic selenazolopyrimidines, both including selenazol heterocyclic framework.[8]

Eventually, making an analogy between anticancer activities of the newly synthesized compounds against two human cell lines supports the conclusion that approximately most of the tested compounds exhibited preferable toxic potencies on the HeLa cell line compared with MCF-7 cells.

3. Conclusion

In summary, we have reported an efficient protocol for the synthesis of new derivatives of a novel selenium-containing heterocyclic system of [1,3]selenazolo[4,5-*d*]pyrimidine. These potential biologically active compounds **3a–i** were prepared in almost quantitative yields through the hetero-annulation of densely functionalized 1,3-selenazoles **2a–c** with triethyl orthoesters in acetic acid under reflux condition. Since our results indicated that synthetic *Se*-containing heterocycles compared to standard drugs showed satisfactory antimicrobial activities, especially on pathogenic fungi, they can be considered as interesting new leading structures in search of new antifungal and antimicrobial drugs. Moreover, among the synthesized selenazolopyrimidines, compounds 3e and **3i** exhibited the maximum cytotoxic effects against MCF-7 and HeLa cells, respectively. This is while the derivatives **3e**, **3f**, and

3i with significant cytotoxic effects on cancerous cells, had no inhibitory effects on the growth of normal HDF cells.

In general, all investigated derivatives inhibited proliferation of human cancer cells, however, they demonstrated different degrees of cytotoxicity in different concentration ranges and had a divergent impact on the proliferation of cancer cells, which were related to both the chemical structure of compounds and the cell lines. Although the results indicated that the IC_{50} values obtained for all newly synthesized heterocycles are $>100\ \mu M$, they can present a new platform for synthesis of novel compounds with strong anticancer activities regarding the fact that selenazolo[4,5-*d*]pyrimidines were not toxic on normal cells. Further studies on the effects of these compounds on other cancerous cells and animal models can better elucidate their anticancer properties and structure-activity relationships.

Supporting Information Summary

Supplementary data associated with this article include the chemical and biological experimental section as well as the copies of ^{1}H NMR and ^{13}C NMR spectra.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Antibacterial · Antifungal · Anticancer · [1,3] Selenazolo[4,5-*d*]pyrimidine

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