ORIGINAL ARTICLE

A Dimroth rearrangement approach for the synthesis of selenopheno[2,3-e][1,2,4]triazolo[1,5-c]pyrimidines with cytotoxic activity on breast cancer cells

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Abstract

New selenopheno[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives have been synthesized via Dimroth rearrangement by cyclocondensation of 7-cyano-4-hydrazinyl-6-(pyrrolidin-1-yl)selenopheno[3,2-d]pyrimidine with electrophilic carbons of either orthoesters in acetic acid or carbon disulfide in pyridine followed by S-alkylation. All the newly synthesized products have been structurally elucidated. The in vitro anticancer screening of the tricyclic Se-containing heterocycles was accomplished against human breast carcinoma MCF-7 cancerous cell line and L929 cells. Anticancer results revealed that the S-hexyl-substituted compound with an IC_{50} value of 158.9 μM in 72 h was foremost among others in cytotoxic potency. In the following order, S-pentyl and S-ethyl-substituted derivatives with IC_{50} values of 216.1 and 396.5 μM were second and third efficient compounds as in anticancer activity, respectively. The inhibitory effects of the mentioned compounds were less on the growth of L929 cells.

Graphic abstract
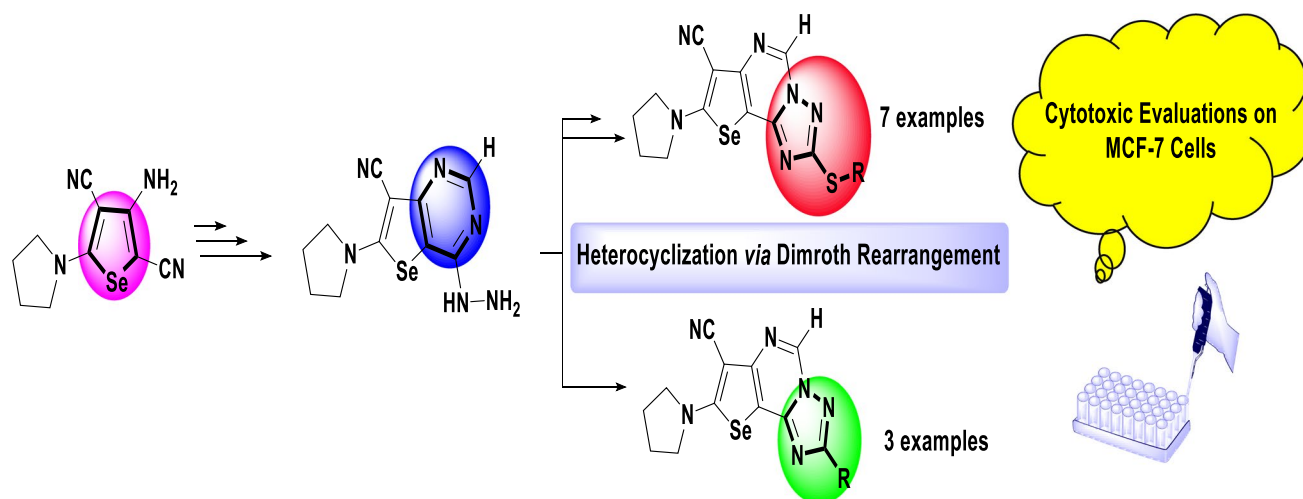
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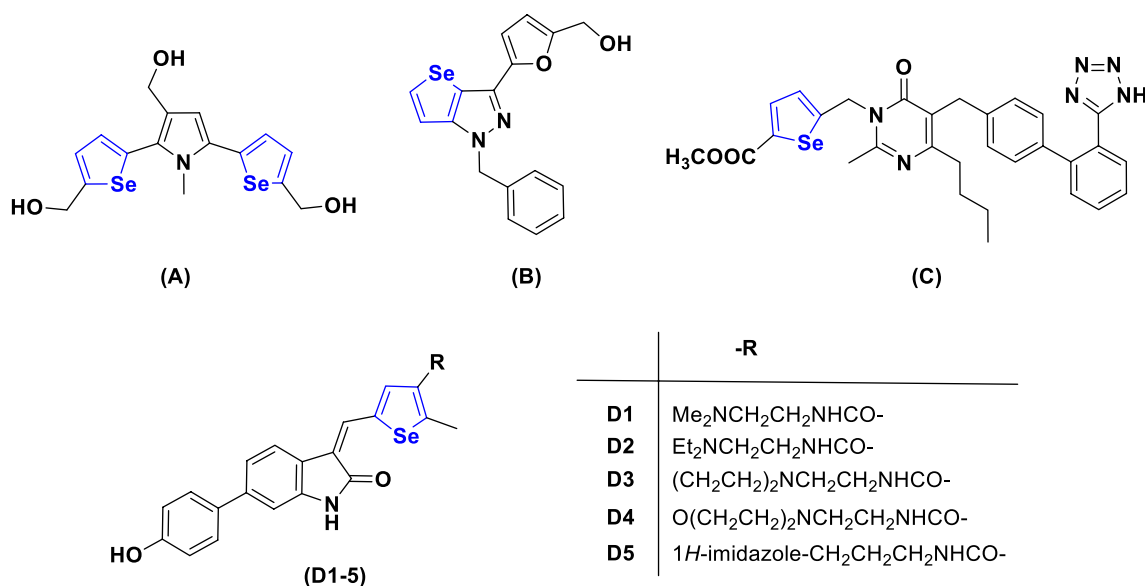
Fig. 1 Structures of biologically active selenophene compounds

	-R
D1	Me₂NCH₂CH₂NHCO-
D2	Et₂NCH₂CH₂NHCO-
D3	(CH₂CH₂)₂NCH₂CH₂NHCO-
D4	O(CH₂CH₂)₂NCH₂CH₂NHCO-
D5	1H-imidazole-CH₂CH₂CH₂NHCO-

Introduction

5-Membered heterocyclic compound containing one selenium as heteroatom is called selenophene which due to stability and electronic property play a vital role in synthesis. In 1976, Liebscher and Hartmann prepared selenophene from the treatment of selenoamide vinyl homologue using an electrophilic reagent [1]. Among chalcogenophenes, selenophenes have drawn the attention of many researchers in view of their interesting biological activities such as anti-inflammatory [2], anticonvulsant and antioxidant [3], hepatoprotective [4], anticancer [5], antihyperalgesic, and antinociceptive effects [6]. The high profile of selenophene heterocycles springs from the fact that they are a pivotal constituent of some biologically active compounds. Diselenophene derivative of 2,5-bis(5-hydroxymethyl-2-selenienyl)-3-hydroxymethyl-N-methylpyrrol (D-501036) (A) displays antitumor activity [7, 8]. Cytotoxicity effect of 1-benzyl-3-(5-hydroxymethyl-2-furyl)selenolo[3,2-c]pyrazole (B) on a number of NCI human cancerous cell lines was evaluated [9, 10], and it seems that further development of this compound may introduce it as a new therapeutic candidate for non-small cell lung and renal cancers [5]. A selenium derivative of milfasartan as one of the selenosartans (C) shows an efficient angiotensin type 1 (AT1) receptor antagonist activity [11]. 4-Hydroxyphenyl and C5-aminoalkylamide substituted selenophene derivatives of oxindole (D1-5) with IC₅₀ values in the sub-nanomolar range are excellent checkpoint kinase-1 (CHK1) enzyme inhibitors [11] (Fig. 1).

Based on the variety of biological virtues associated with the selenium, many protocols such as a sequentially one-pot four-step pathway [12], Cu-catalyzed cyclization [13], Se-metal exchange [14, 15], and microwave-assisted seleno-Clasien rearrangement under free radical conditions [16] have been developed for the synthesis of selenophene scaffolds.

On the other hand, it is a well-known fact that the combination of diverse types of heterocycles into one molecule could generate a novel skeleton with improved bioactivities. Taking the foregoing advantages into account, and in continuation of our endeavors in the development of the novel heterocyclic frameworks containing Se and/or S elements [17–23], we contemplated combining the triazolopyrimidine nucleus with selenophene ring giving selenopheno[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives in order to exert fascinating biological applications.
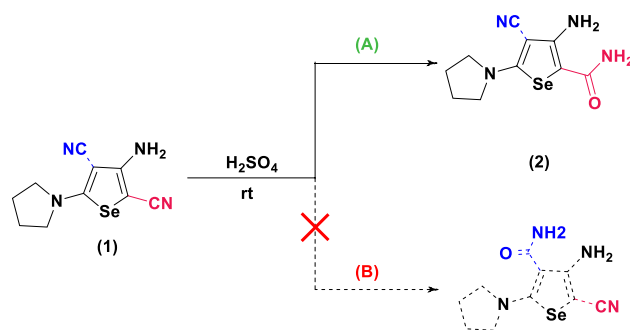
Scheme 1 Selective carbonitrile hydrolysis of 3-amino-2,4-dicyano-5-(pyrrolidin-1-yl)selenophene (1)

Result and discussion

In the present study, various poly-functionalized *Se*-containing tricyclic heterocycles have been synthesized from 3-amino-2,4-dicyano-5-(pyrrolidin-1-yl)selenophene **(1)** as starting material which was prepared through a domino four-step treatment of 2-(bis(ethylthio)methylene)malononitrile with pyrrolidine, Na_2Se, $ClCH_2CN$, and K_2CO_3 in DMF medium, respectively. As a result of vigorous stirring of compound **(1)** in concentrated sulfuric acid, the IR spectrum of compound **(2)** showed both C=O ($\nu = 1637$ cm^{-1}) and C≡N ($\nu = 2119$ cm^{-1}) absorption bands which indicates hydrolysis of only one of the C≡N groups of the starting material **(1)** to a primary amide. Taking into account both the stronger electron-withdrawing inductive effect of the selenium heteroatom along with the better electron donating mesomeric effect of the NH_2 moiety on the C^2-carbontrile

group in comparison with the C^4-position due to poor aromaticity of the selenophene heterocycle, selective carbonitrile hydrolysis leading to product **(A)** seems to be an inevitable consequence. (Scheme 1).

Then, annulation of compound **(2)** occurred in the presence of triethylorthoformate to yield selenopheno[3,2-*d*]pyrimidine **(3)**. The heterocyclization of compound **(2)** into **(3)** was deduced from the following three facts:

1. The blue-shifted amidic C=O stretching band of compound **(3)** from $\nu = 1637$ cm^{-1} to $\nu = 1642$ cm^{-1} (IR spectrum).
2. The absence of the symmetric and asymmetric stretching bands of the NH_2 group (IR spectrum).
3. The appearance of a singlet signal at δ 8.06 ppm for the C–H proton of the pyrimidine ring. (^{1}H NMR spectrum).

Scheme 2 Synthesis of 7-cyano-4-hydrazinyl-6-(pyrrolidin-1-yl)selenopheno[3,2-*d*]pyrimidine **(5)**
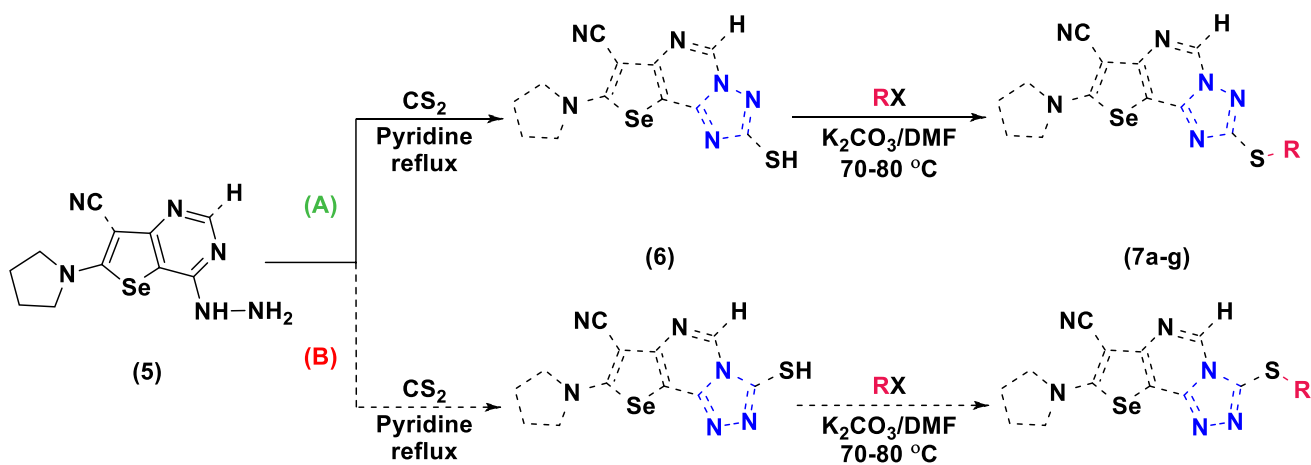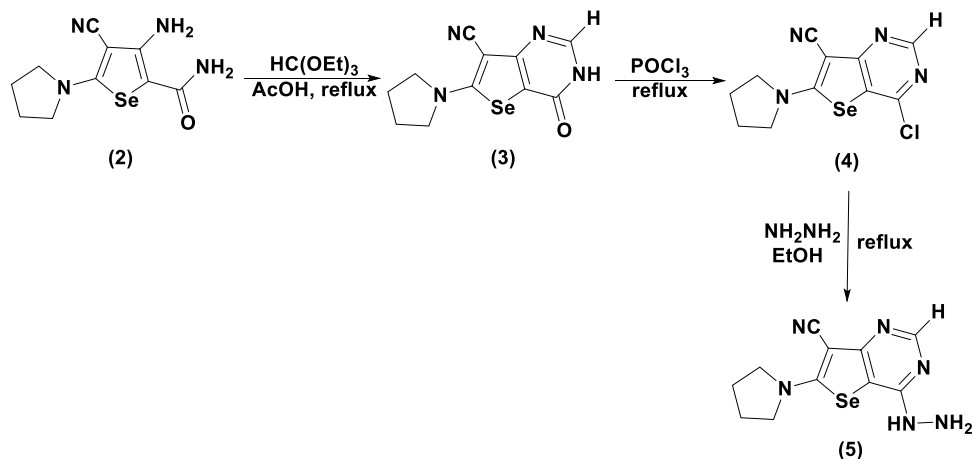
(7a): **R**= Me; **(7b):** **R**= Et; **(7c):** **R**= *n*-Pr; **(7d):** **R**= *n*-Bu; **(7e):** **R**= *n*-Pn; **(7f):** **R**= *n*-Hex; **(7g):** **R**= Bn

Scheme 3 Base-mediated synthesis of selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives

In continuation, the treatment of compound (3) with refluxing phosphoryl chloride resulted corresponding chlorinated derivative (4). The 4-chloro-selenopheno[3,2-*d*] pyrimidine (4) then underwent S_NAr hydrazination when treated with hydrazine monohydrate in boiling ethanol to generate the compound (5) (Scheme 2).

To synthesize novel tricyclic selenium-containing frameworks, cyclo-condensation of the hydrazinated compound (5) with CS_2 was conducted in boiling pyridine. Then, conversion of selenophenotriazolopyrimidine (6) when reacted with several alkyl halides in alkaline DMF resulted in its alkylated congeners (7a–f) through either pathway (A) (rearranged pathway) or pathway (B) (Scheme 3).

Fig. 2 ORTEP view of compound (7f). The thermal displacement ellipsoids are shown at 50% probability level
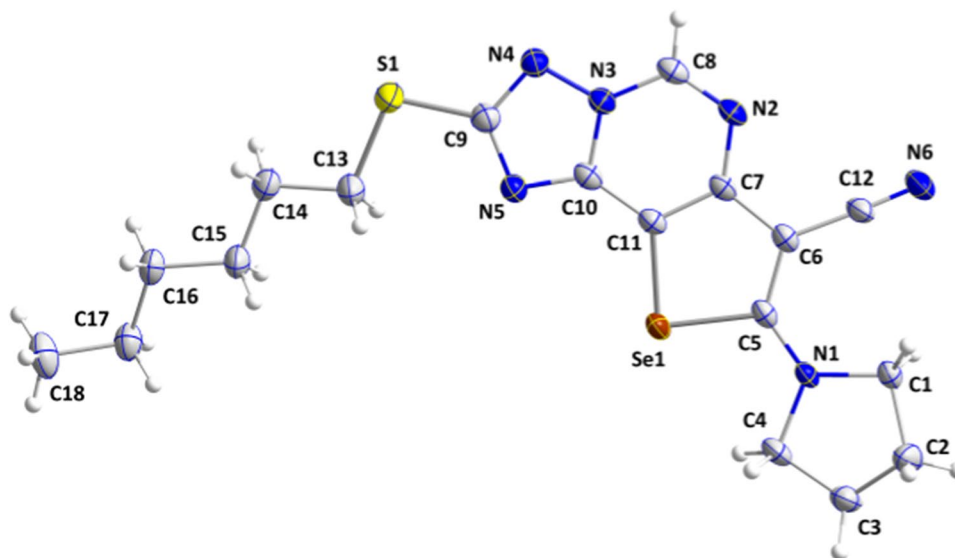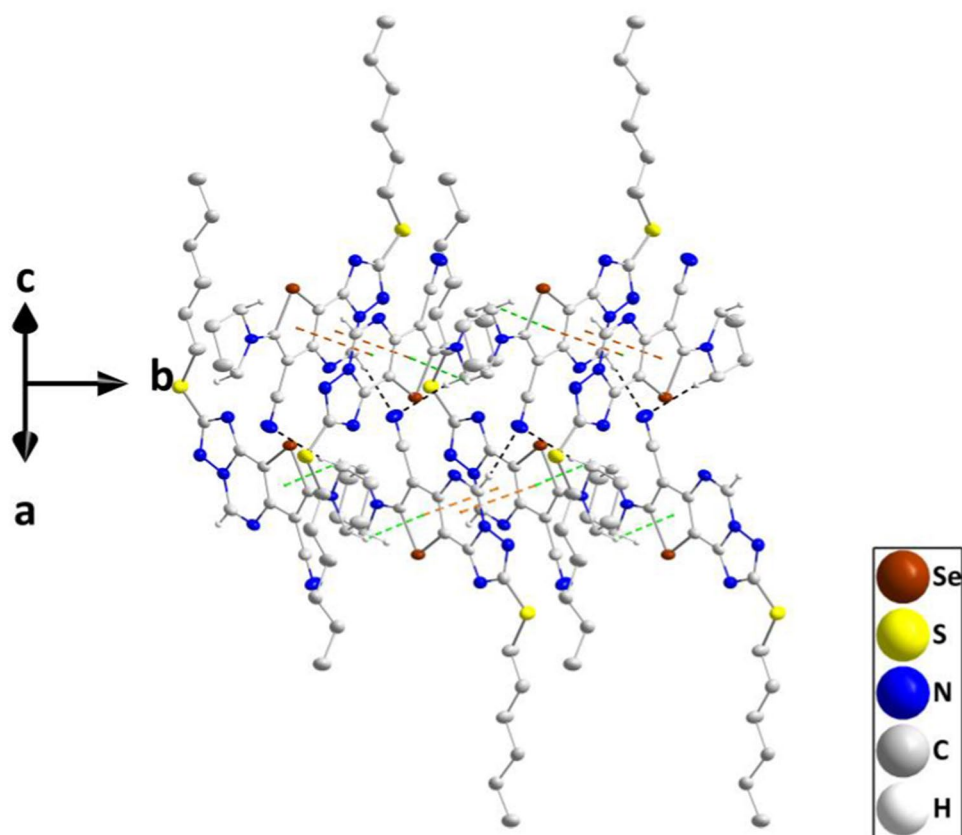

Fig. 3 Packing of (7f) projected onto (101)

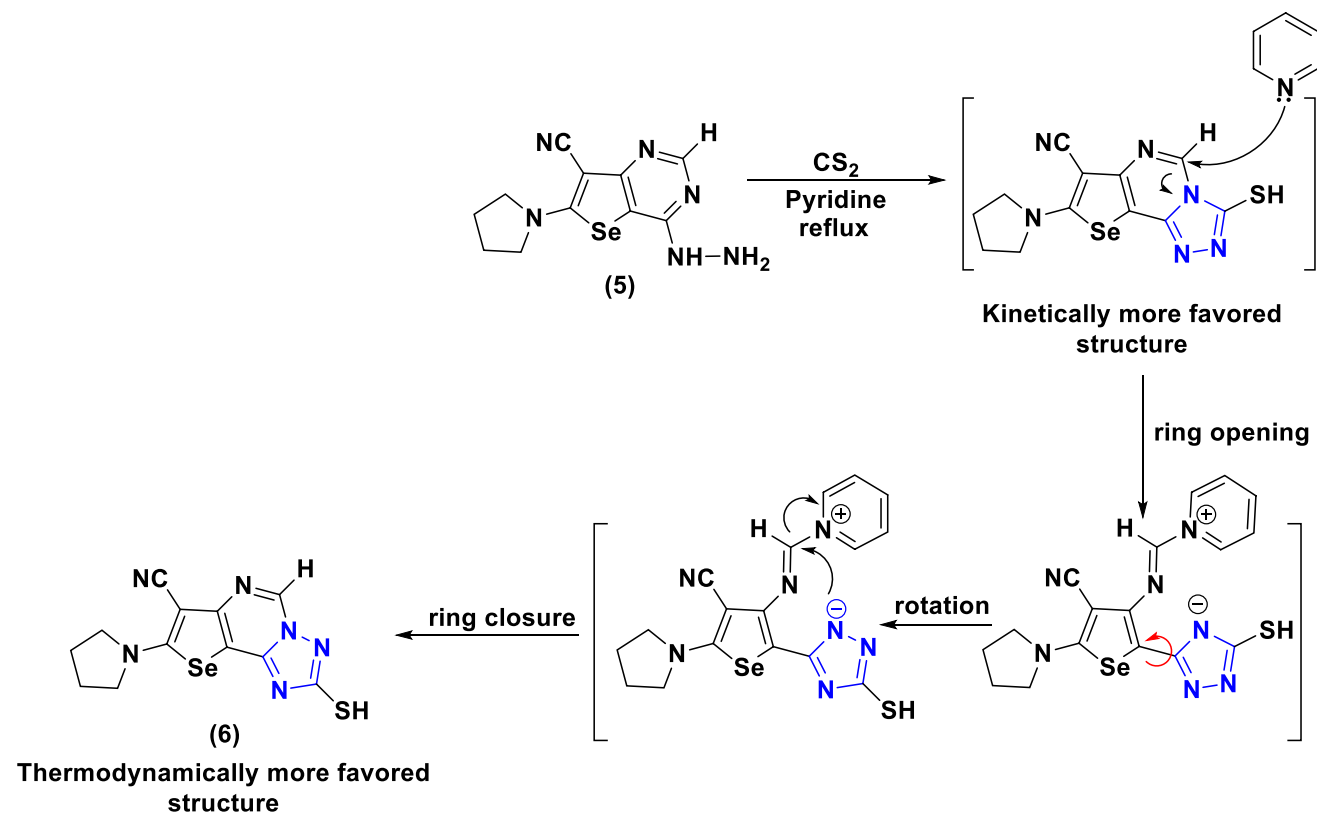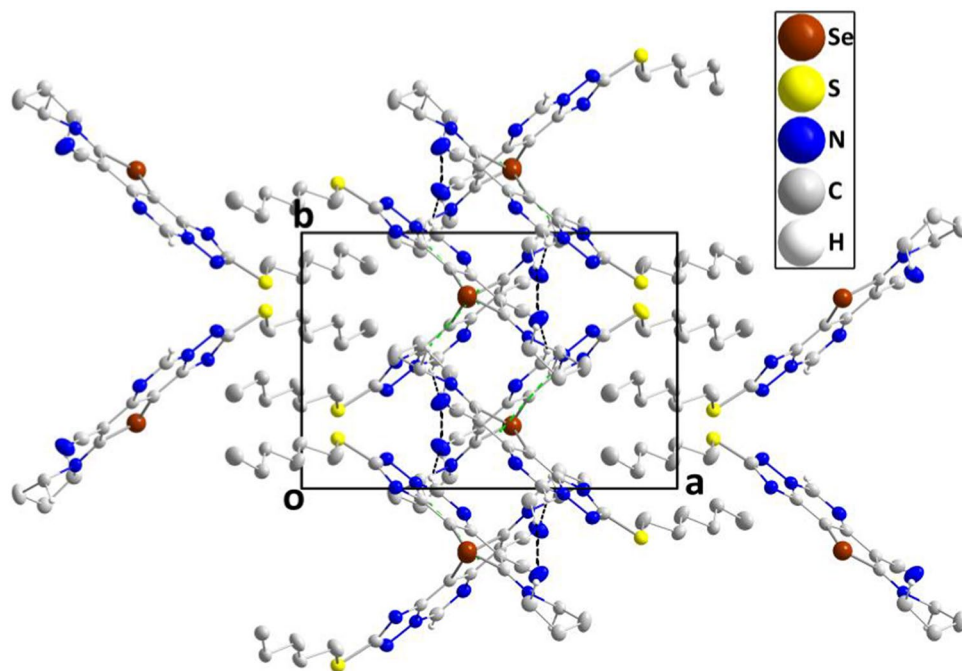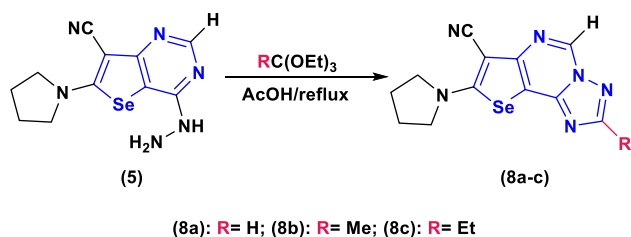**Fig. 4** Packing of **(7f)** viewed along the *c*-axis direction

Fig. 5 Base-catalyzed Dimroth rearrangement mechanism of compound **(6)**

Structural characterization of the products **(7a–g)** was corroborated by experimental spectroscopic and elemental analysis data. The NMR data of the newly synthesized compounds validated the formation of only one of the **(A)** or **(B)** isomers. For instance, the ^{1}H NMR spectrum of **(7f)** showed two broad multiplet peaks around δ 2.10–2.14 and 3.69–3.73 ppm belonging to the methylene groups of the pyrrolidine substituent. The thiohexyl ether hydrogen signals were observed at δ 0.82 (triplet), δ 1.26–1.36 (multiplet), δ 1.40–1.76 (multiplet), and δ 3.17 ppm (triplet) due to CH_3, 2CH_2, 2CH_2, and SCH_2 moieties, respectively. A singlet signal at δ 9.02 ppm was identified for the C–H aromatic proton of the pyrimidine moiety, as well. In the ^{13}C NMR, 19 distinct signals were observed for the carbon atoms of compound **(7f)**. Assignment of the detected signal at δ 81.1 ppm to the carbon of C≡N functional group divided the spectrum into aliphatic carbon region with eight dissimilar signals at δ 14.0, 22.5, 26.0, 28.4, 29.3, 31.3, 31.5, and 53.5 ppm and aromatic carbon area with seven resolved signals at δ 104.9, 116.9, 137.9, 149.8, 154.3, 165.9, and 168.4 ppm. Eventually, emerging a molecular ion peak at m/z 435 (M$^+$) in addition to complementary results of microanalytical data assessments confirmed the molecular formula of $C_{18}H_{22}N_6SSe$ for **(7f)**.

In order to support the proposed mechanism of heterocyclization and the actual skeleton of the regioisomer obtained, an X-ray crystallography analysis was undertaken. Figures 2, 3 and 4, which show the ORTEP and the atom labeling of 7-cyano-2-(hexylthio)-8-(pyrrolidin-1-yl) selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **(7f)**, thoroughly substantiate that the *S*-hexyl regioisomer **(A)** was formed through the plausible base-catalyzed Dimroth rearrangement. Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (deposition no. CCDC 1,985,796).

Therefore, the mechanism of the reaction is likely to proceed through the structures depicted in Fig. 5.

In other attempts, the 4-hydrazinyl-selenophenopyrimidine **(5)** was stirred with some triethyl orthoesters in refluxing AcOH to yield tricyclic selenopheno[2,3-*e*][1,2,4]
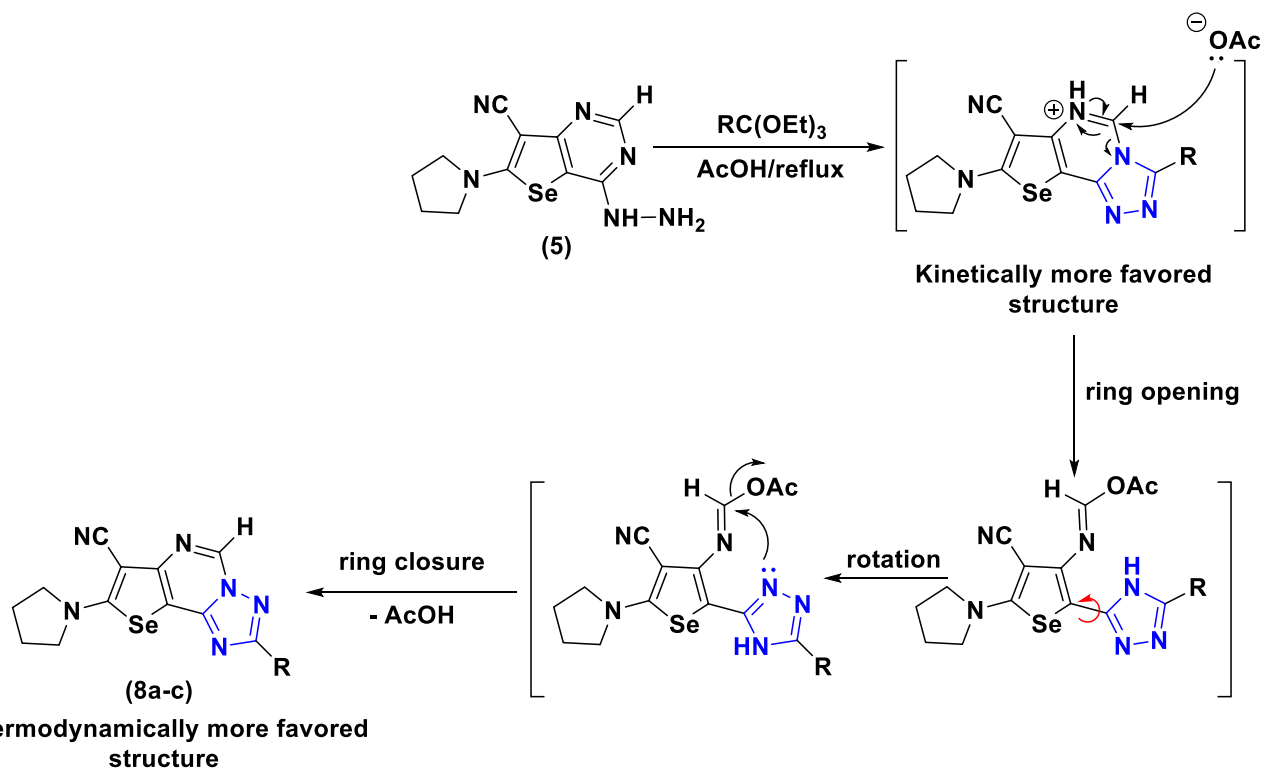

Scheme 4 Acid-mediated synthesis of selenopheno[2,3-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine derivatives

(8a): **R**= H; (8b): **R**= Me; (8c): **R**= Et

Fig. 6 Acid-catalyzed Dimroth rearrangement mechanism of products **(8a–c)**

triazolo[1,5-*c*]pyrimidines **(8a–c)** through cyclization. (Scheme 4).

The assigned structures of **(8a–c)** were supported by the spectral and microanalytical data. For example, in the ^{1}H NMR spectrum of **(8b)**, methyl signal appeared as a singlet at δ 2.61 ppm and the presence of the secondary amine substituent (pyrrolidine) was specified by two multiplet peaks around δ 2.19–2.24 and 3.79–3.84 ppm belonging to methylene groups. The hydrogen of the pyrimidine ring as the one and only aromatic hydrogen was also observed as a singlet at δ 9.17 ppm. In the ^{13}C NMR spectrum, four aliphatic and seven aromatic carbon signals were detected for **(8b)**. As it was foreseeable, the most deshielded peak at δ 165.9 ppm was for the carbon surrounded by N and Se heteroatoms in **(8b)** which clearly substantiated the existence of the pyrrolidine substitution on C^2 position of selenophene ring. Moreover, emerging of the molecular ion peak at *m/z* 332 and the assessment of its fragmentation in mass spectrum along with other spectroscopic data corroborated the fusion of the triazole ring on selenophenopyrimidine skeleton of **(5)**.
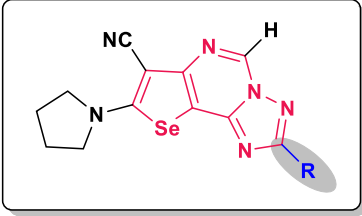
A confident prediction of the true main architecture of compounds **(8a–c)** can be proved on the basis of almost identical ^{13}C chemical shifts with that of crystallographically identified **(7f)**. Unlike alkaline catalytically prepared products **(7a–f)**, compounds **(8a–c)** were cyclized acid-catalytically. In the manner of Dimroth rearrangement, the literature-based investigations revealed that at elevated temperature, the thermodynamically more stable [1, 2, 4] triazolo[1,5-*c*]pyrimidines have been derived from isomerization of [1, 2, 4]triazolo[4,3-*c*] pyrimidines through a tandem ring opening/ring closure Dimroth-type rearrangement of pyrimidine in either acidic or basic medium [23–25]. Therefore, the acid-catalyzed Dimroth rearrangement seemed to be performed in the synthesis of compounds **(8a–c)** (Fig. 6).

Antiproliferative study

In this study, the significant cytotoxicity of the synthesized selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **(6)**, **(7a–g)** and **(8a–c)** on MCF-7 breast cancerous cells and cell line L929 (fibroblast) through assessment of their viabilities employing in vitro tetrazolium-based colorimetric assay (MTT assay protocol) was investigated for certain time intervals [26–28] and presented as the half maximal-inhibitory concentrations (IC_{50} values) in Table 1. To compare the antiproliferative properties of all the newly synthesized compounds with those of standard clinical medicines, doxorubicin as the commonly used standard drug was selected. MCF-7 cancer cells were exposed to various concentrations of the doxorubicin at 24, 48, and 72 h and the IC_{50} values

of 36.6, 20.1, and 17.1 μM were obtained, respectively (Table 1).

Table 1 The cytotoxicity effects of selenopheno[2,3-*e*][1,2,4] triazolo[1,5-*c*]pyrimidines **(6)**, **(7a–g)** and **(8a–c)** on MCF-7 and L929 determined by MTT assay

Compounds	-R	IC_{50} (μM) ± SD[a] (MCF-7)		
		24 h	48 h	72 h
6	-SH	4420.8 ± 2.61	1719.1 ± 3.52	1460.2 ± 2.61
(7a)	-SMe	1366.7 ± 2.54	715.3 ± 1.73	547.8 ± 1.18
(7b)	-SEt	823.2 ± 3.71	451.5 ± 3.28	396.5 ± 3.73
(7c)	-SPr	908.6 ± 1.28	541.5 ± 4.72	453.5 ± 4.39
(7d)	-SBu	14,994.8 ± 4.8	1511.0 ± 2.68	1210.0 ± 3.27
(7e)	-SPn	426.4 ± 0.64	253.8 ± 3.51	216.1 ± 2.64
(7f)	-SHex	222.6 ± 3.1	209.2 ± 4.2	158.9 ± 4.5
(7 g)	-SBn	815.2 ± 2.48	458.6 ± 2.38	390.6 ± 2.42
(8a)	-H	1831.7 ± 1.72	1022.0 ± 1.34	822.0 ± 2.41
(8b)	-Me	3168.9 ± 2.43	777.4 ± 2.61	625.3 ± 4.53
(8c)	-Et	2610.6 ± 2.45	614.4 ± 1.35	569.6 ± 3.34
Doxorubicin	–	36.6 ± 2.12	20.1 ± 1.36	17.1 ± 2.22
		IC_{50} (μM) ± SD[a] (L929)		
		24 h	48 h	72 h
(7b)	-SEt	831.2 ± 2.6	545.0 ± 2.11	485.0 ± 4.1
(7e)	-SPn	469.1 ± 1.24	470.5 ± 3.51	336.6 ± 1.55
(7f)	-SHex	389.7 ± 2.5	380.1 ± 1.5	374.5 ± 3.6
Doxorubicin	–	27.8 ± 3.1	16.7 ± 3.4	14.9 ± 1.2

[a]The IC_{50} values are shown as mean ± SD ($n=3$)

The graphs of MCF-7 cell viability percentages affected by various concentrations of compounds **(6)**, **(7a–g)** and **(8a–c)** are depicted in Fig. 7.

On the basis of antiproliferative data given in Table 1, all the tricyclic derivatives represented noteworthy dose-dependent cytotoxicity. Selected derivatives **(7b)**, **(7e)**, and **(7f)**, which displayed the highest cytotoxicity against MCF-7 cells, were affected on normal L929 cell line to determine their IC_{50} values. The results demonstrated that the aforementioned compounds had toxicity to L929 cells in higher concentrations.

Results of the cytotoxic evaluation of the studied compounds on MCF-7 cells revealed that the presence of a lipophilic chain on the triazole skeleton is of crucial

Fig. 7 The cytotoxicity of selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (**6**), (**7a–g**) and (**8a–c**) on MCF-7 cells at 24, 48 and 72 h. Results are mean ± SD (*n* = 3)
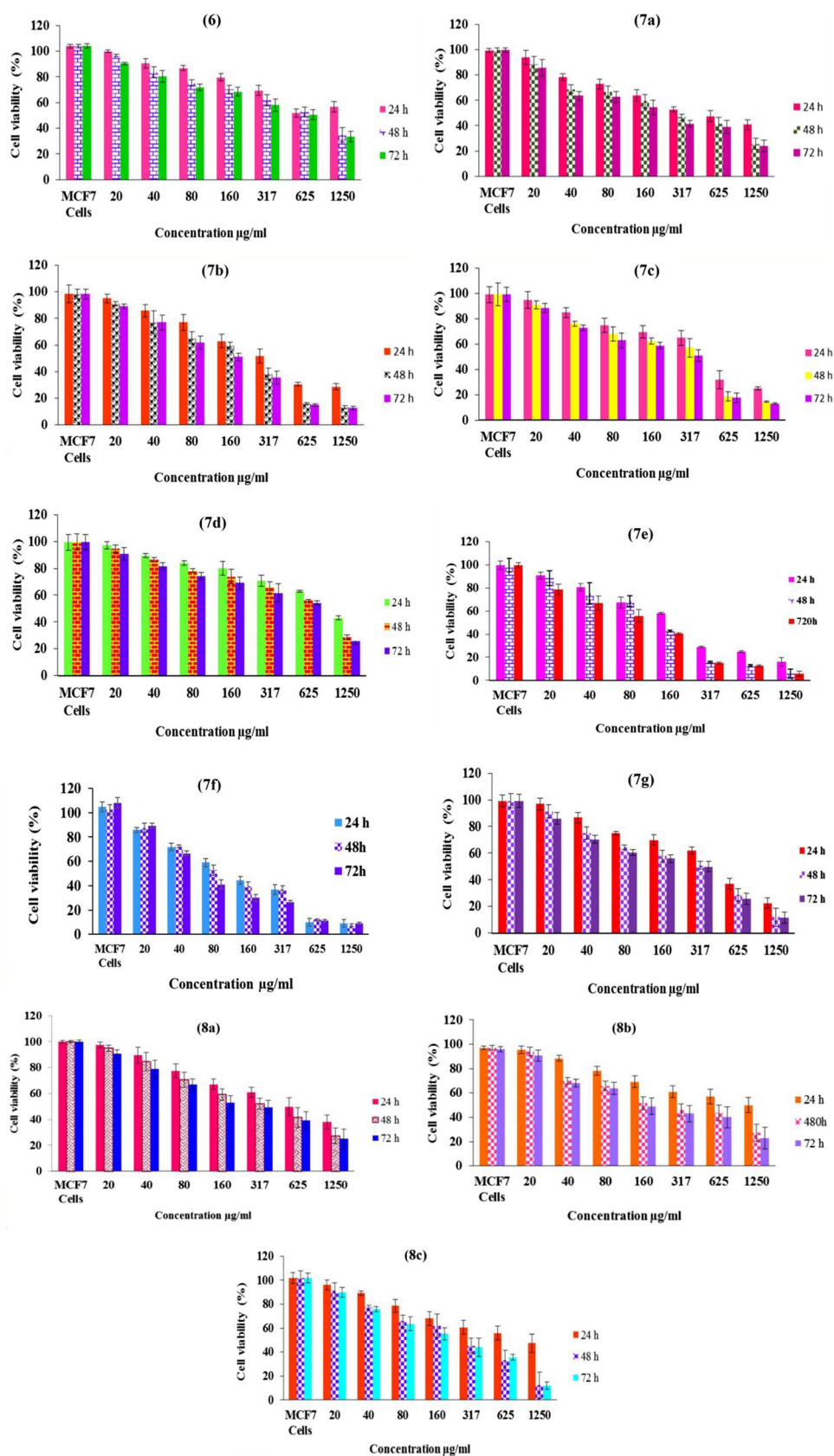
importance in the anticancer activity of selenazolotria-zolopyrimidines. Taking the length of the hydrocarbon chain into account, the antiproliferative efficacy of the selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines on breast cancerous cells improved with growing the length of C^2-alkyl or S-alkyl substituent. Among the heterocyclic compounds used in this screening, **(7f)** bearing the longest S-alkylated chain on the C-2 position of selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine skeleton was the most effective compound against MCF-7 cells with IC_{50} value of 158.9 μM after 72 h treatment while C^2-SH substituted **(6)** with IC_{50} value of 1460.2 μM was ranked in the last place of potency as the weakest cytotoxic compound. Thus, an analogy between the structure–activity relationships of the derivatives supports the conclusion that enhanced lipophilicity of the investigated heterocycles because of the size of the C^2-linear aliphatic substituents along with the presence of the C^8-pyrrolidine pharmacophore might easily cause a synergistic effect to facilitate their infiltration into MCF-7 cells and intensify the cytotoxic potencies [29, 30].

Conclusion

Various interesting selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines as novel *Se*-containing tricyclic heterocyclic building blocks bearing an alkyl or *S*-alkyl moieties on their triazole ring and pyrrolidine on their selenophene core have been synthesized from 3-amino-2,4-dicyano-5-(pyrrolidin-1-yl)selenophene **(1)**. The stepwise of the present synthetic procedure follows a concentrated H_2SO_4-mediated hydrolysis of the C≡N moiety, heterocyclization with triethyl orthoformate, chlorination in the presence of $POCl_3$, S_NAr hydrazination and ultimately, Dimroth rearrangement in both acidic and basic media. The anticancer potential of the new compounds was evaluated against carcinoma MCF-7 cancer cells and the C^2-alkyl/thioalkyl substituted heterocycles were found to be more potent than the C^2-SH substituted one. Fortunately, compounds **(7b)**, **(7e)**, and **(7f)** with maximum cytotoxic effects on cancerous cells displayed less toxicity on L929 cells.

However, the IC_{50} values of the newly synthesized selenium-containing heterocyclic compounds are not promising, further investigations on the impacts of the synthetic derivatives on other cancer cell lines and in vivo evaluations can better clarify their structure–activity relationships (SAR) for antiproliferative efficacies.

Experimental

Melting points were recorded on an Electro thermal type 9200 melting point apparatus. The IR spectra were obtained on Avatar 370 FT-IR Thermo Nicolet instrument and only noteworthy absorptions are listed. The ^{1}H NMR (300 MHz) and the ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance-III 300 NMR Fourier transformer spectrometer. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 microanalyzer.

Synthesis of 3-amino-2,4-dicyano-5-(pyrrolidin-1-yl) selenophene (1): A solution of 2-(bis(ethylthio)methylene) malononitrile (5 mmol, 0.99 g) and pyrrolidine (5 mmol, 0.41 ml) in DMF (3 ml) was stirred for 75 min at 70 ℃. Fresh Na_2Se (5 mmol) was added and heating continued for 20 min. In the next step, chloroacetonitrile (10 mmol, 0.63 ml) was added gently to the mixture at 70 ℃. After 2 h stirring at 70 ℃, K_2CO_3 (5 mmol, 0.69 g) was added and the reaction was stirred at 70 ℃ for 1 h more. After the completion of the reaction which was monitored by TLC using $CHCl_3$:MeOH (20:1), the mixture was poured onto cold water (100 ml) with good stirring. When precipitate appeared, it was filtered, washed with water, dried at room temperature until constant weight. Dark brown powder; yield = 82%; mp 217–220 ℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.98–2.04 (m, 4H, 2CH$_2$), 3.51–3.58 (m, 4H, 2NCH$_2$), 6.33 (br s, 2H, NH$_2$, D$_2$O-exchangable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.8, 53.4, 57.5 (CN), 76.5 (CN), 117.2, 117.9, 159.0, 166.1 ppm; IR (KBr): ν 3427, 3327, 3227, 2193 (CN), 2168 (CN), 1634, 1559, 1529, 1426, 1342 cm^{-1}. MS (*m/z*) 266. *Anal*. Calcd. for $C_{10}H_{10}N_4Se$ (%): C, 45.29; H, 3.80; N, 21.13. Found: C, 45.28; H, 3.78; N, 21.10.

Synthesis of 3-amino-2-carboxamide-4-cyano-5-(pyrrolidin-1-yl)selenophene (2): A mixture of compound **(1)** (10 mmol, 2.66 g) in concentrated H_2SO_4 (5 mL) was stirred vigorously at room temperature for 1 h. After the completion of the reaction, the mixture was cooled, poured onto an ice/water bath and basified with ammonium hydroxide up to pH ~ 8–9. The resulting solid product was collected by filtration, washed with water (2 × 30 mL), dried and used without further purification. Cream powder; yield = 83%; mp 261–266 °C; IR (KBr): ν 3431, 3317, 3141, 2191 (CN), 1637, 1581, 1551, 1492, 1093 cm^{-1}. MS (*m/z*) 284. *Anal*. Calcd. for $C_{10}H_{12}N_4OSe$ (%): C, 42.41; H, 4.27; N, 19.78. Found: C, 42.38; H, 4.25; N, 19.74.

Synthesis of 7-cyano-4-oxo-6-(pyrrolidin-1-yl)-3,4-dihydroselenopheno[3,2-*d*]pyrimidine (3): To a solution of compound **(2)** (10 mmol, 2.84 g) in acetic acid (10 mL), triethyl orthoformate (10 mmol, 1.65 mL) was added. The reaction mixture was heated under reflux for

6 h. After the completion of the reaction (monitored by TLC, CHCl$_3$:MeOH, 20:1), the solvent was removed under reduced pressure and the resulting crude product was washed with water (2×20 mL) and recrystallized from ethanol. Light brown powder; yield = 92%; mp 244–246 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.96–2.01 (m, 4H, 2CH$_2$), 3.54–3.59 (m, 4H, 2NCH$_2$), 8.06 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.9, 53.9, 80.4 (CN), 109.0, 117.3, 148.9, 156.9, 161.6, 167.0 ppm; IR (KBr): ν 3252, 3178, 3113, 2954, 2876, 2197 (CN), 1642, 1543, 1424, 1330 cm^{-1}. MS (*m/z*) 293. *Anal.* Calcd. for C$_{11}$H$_{10}$N$_4$OSe (%): C, 45.06; H, 3.44; N, 19.11. Found: C, 45.02; H, 3.41; N, 19.10.

Synthesis of 4-chloro-7-cyano-6-(pyrrolidin-1-yl) selenopheno[3,2-*d*]pyrimidine (4): Compound (**3**) (10 mmol, 2.93 g) were heated under reflux in POCl$_3$ (15 mL) for 3 h. After the completion of the reaction (monitored by TLC, CHCl$_3$:MeOH, 20:1), the mixture was poured into an ice/water bath and neutralized with saturated NaHCO$_3$ solution. The resulting solid was filtered off, washed with cold water, and dried at room temperature. Brown powder; yield = 85%; mp 251–254 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.17–2.22 (m, 4H, 2CH$_2$), 3.78–3.82 (m, 4H, 2NCH$_2$), 8.77 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 26.0, 54.0, 80.9 (CN), 108.6, 116.2, 153.5, 156.3, 165.9, 167.1 ppm; IR (KBr): ν 2922, 2847, 2201 (CN), 1574, 1534, 1491, 1439, 1287, 1033, 864, 767 cm^1. MS (*m/z*) 312. *Anal.* Calcd. for C$_{11}$H$_9$ClN$_4$Se (%): C, 42.40; H, 2.91; N, 17.98. Found: C, 42.38; H, 2.89; N, 17.97.

Synthesis of 7-cyano-4-hydrazinyl-6-(pyrrolidin-1-yl)selenopheno[3,2-*d*]pyrimidine (5): A mixture of compound (**4**) (10 mmol, 3.12 g) and excess amount of hydrazine monohydrate (1.5 mL) in EtOH (15 mL) was stirred vigorously at reflux for 16 h. After the completion of the reaction (monitored by TLC, CHCl$_3$:MeOH, 20:1), ethanol was evaporated under reduced pressure. The resulting solid was then washed with water (2×20 mL), filtered off and recrystallized from ethanol. Dark brown powder; yield = 73%; mp 290 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.03–2.08 (m, 4H, 2CH$_2$), 3.64–3.72 (m, 4H, 2NCH$_2$), 8.35 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$), 10.54 (br s, 1H, NH, D$_2$O-exchangable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.8, 53.2, 79.2 (CN), 100.8, 118.1, 155.5, 157.2, 164.2, 170.6 ppm; IR (KBr): ν 3323, 3288, 3189, 2954, 2864, 2191 (CN), 1653, 1653, 1584, 1535, 1433, 1346 cm^{-1}. MS (*m/z*) 308. *Anal.* Calcd for C$_{11}$H$_{12}$N$_6$Se (%): C, 43.01; H, 3.94; N, 27.36; found: C, 43.00; H, 3.91; N, 27.33.

Synthesis of 7-cyano-2-mercapto-8-(pyrrolidin-1-yl) selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (6): A mixture of compound (**5**) (10 mmol, 3.08 g) and CS$_2$ (3 mL) in pyridine (7 mL) was stirred under reflux

for 6 h. After the completion of the reaction, (monitored by TLC, CHCl$_3$:MeOH, 20:1), the solvent was removed under reduced pressure. Water was added to the solid product and neutralized with aqueous 5% HCl solution. The crude product was collected by filtration and recrystallized from ethanol. Green powder; yield = 87%; mp 339 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.98–2.12 (m, 4H, 2CH$_2$), 3.63–3.72 (m, 4H, 2NCH$_2$), 9.01 (s, 1H$_{aromatic}$, H$_{pyrimidine}$), 14.56 (br s, 1H, SH, D$_2$O-exchangable) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.0, 54.0, 80.5 (CN), 101.9, 117.2, 143.7, 152.1, 160.5, 165.8 ppm; IR (KBr): ν 3122, 2990, 2951, 2212 (CN), 1630, 1561, 1470, 1278 cm^{-1}. MS (*m/z*) 350. *Anal.* Calcd for C$_{12}$H$_{10}$N$_6$SSe (%): C, 41.27; H, 2.89; N, 24.06; S, 9.18; found: C, 41.26; H, 2.87; N, 24.03; S, 9.15.

Synthesis of *S*-alkylated selenopheno[2,3-*e*][1,2,4] triazolo[1,5-*c*]pyrimidines (7a-g); General procedure: To a mixture of compound (**6**) (1 mmol, 0.35 g) and K$_2$CO$_3$ (1.2 mmol, 0. 3 g) in DMF (3 mL), the excess amount of the appropriate alkyl halide (0.3 mL) was added and the mixture was heated at 70–80 ºC for 5 h. After the completion of the reaction, the mixture was cooled, poured into an ice/water bath and neutralized with aqueous 5% HCl solution. The resulting solid product was collected by filtration and recrystallized from ethanol.

7-Cyano-2-(methylthio)-8-(pyrrolidin-1-yl) selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7a): (The alkyl halide is CH$_3$I). Brown powder; yield = 78%; mp 244–247 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.20–2.24 (m, 4H, 2CH$_2$), 2.72 (s, 3H, CH$_3$), 3.78–3.82 (m, 4H, 2NCH$_2$), 9.12 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.2, 26.1, 53.6, 81.0 (CN), 105.0, 117.0, 138.0, 150.0, 154.5, 166.0, 169.0 ppm; IR (KBr): ν 3064, 2978, 2924, 2872, 2198 (CN), 1626, 1548, 1244 cm^{-1}. MS (*m/z*) 364. *Anal.* Calcd for C$_{13}$H$_{12}$N$_6$SSe (%): C, 42.98; H, 3.33; N, 23.13; S, 8.82; found: C, 42.96; H, 3.32; N, 23.11; S, 8.79.

7-Cyano-2-(ethylthio)-8-(pyrrolidin-1-yl) selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7b): (The alkyl halide is C$_2$H$_5$I). Golden powder; yield = 63%; mp 295–298 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.42 (t, *J* = 7.3 Hz, 3H, CH$_3$), 2.10–2.14 (m, 4H, 2CH$_2$), 3.16–3.23 (q, *J* = 7.4 Hz, 2H, SCH$_2$), 3.71–3.74 (m, 4H, 2NCH$_2$), 9.10 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.9, 25.9, 26.0, 53.5, 81.2 (CN), 105.1, 114.0, 117.0, 127.8, 138.0, 150.0, 154.5, 166.0, 168.2 ppm: IR (KBr): ν 3068, 2962, 2924, 2871, 2203 (CN), 1625, 1553, 1344, 1238 cm^{-1}. MS (*m/z*) 378. *Anal.* Calcd for C$_{14}$H$_{14}$N$_6$SSe (%): C, 44.56; H, 3.74; N, 22.27; S, 8.50; found: C, 44.53; H, 3.72; N, 22.25; S, 8.48.

7-Cyano-2-(propylthio)-8-(pyrrolidin-1-yl) selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7c): (The alkyl halide is *n*-C$_3$H$_7$Br). Brown powder; yield = 88%; mp 256 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.11 (t, *J* = 7.2 Hz, 3H, CH$_3$), 1.87 (m, 2H, CH$_2$), 2.20–2.24

(m, 4H, 2CH$_2$), 3.26 (t, $J = 7.2$ Hz, 2H, SCH$_2$), 3.81 (m, 4H, 2NCH$_2$), 9.12 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.4, 22.9, 26.0, 33.5, 53.5, 81.1 (CN), 105.0, 117.0, 138.0, 149.9, 154.4, 166.0, 168.4 ppm; IR (KBr): ν 3068, 2961, 2872, 2203 (CN), 1623, 1555, 1345, 1235 cm^{-1}. MS (*m/z*) 392. *Anal*. Calcd for C$_{15}$H$_{16}$N$_6$SSe (%): C, 46.04; H, 4.12; N, 21.47; S, 8.19; found: C, 46.02; H, 4.11; N, 21.44; S, 8.17.

2-(Butylthio)-7-cyano-8-(pyrrolidin-1-yl) selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7d): (The alkyl halide is *n*-C$_4$H$_9$Br). Cream powder; yield = 66%; mp 214–217 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.99 (t, $J = 7.3$ Hz, 3H, CH$_3$), 1.53 (m, 2H, CH$_2$), 1.82 (m, 2H, CH$_2$), 2.19–2.24 (m, 4H, 2CH$_2$), 3.28 (t, $J = 7.3$ Hz, 2H, SCH$_2$), 3.79–3.83 (m, 4H, 2NCH$_2$), 9.12 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.6, 22.0, 26.0, 31.1, 31.4, 35.5, 81.0 (CN), 105.0, 117.0, 138.0, 149.9, 154.4, 166.0, 168.5 ppm; IR (KBr): ν 2957, 2927, 2204 (CN), 1623, 1554, 1345, 1242 cm^{-1}. MS (*m/z*) 406. *Anal*. Calcd for C$_{16}$H$_{18}$N$_6$SSe (%): C, 47.41; H, 4.48; N, 20.73; S, 7.91; found: C, 47.40; H, 4.46; N, 20.70; S, 7.90.

7-Cyano-2-(pentylthio)-8-(pyrrolidin-1-yl) selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7e): (The alkyl halide is *n*-C$_5$H$_{11}$Br). White powder; yield = 62%; mp 193–196 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.80 (t, $J = 7.2$ Hz, 3H, CH$_3$), 1.26–1.44 (m, 4H, C$_2$H$_4$), 1.75 (m, 2H, CH$_2$), 2.10–2.14 (m, 4H, CH$_2$), 3.17 (t, $J = 7.3$ Hz, 2H, SCH$_2$), 3.69–3.72 (m, 4H, 2NCH$_2$), 9.03 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.0, 22.2, 26.0, 29.1, 31.0, 31.5, 53.5, 81.1 (CN), 105.0, 117.0, 149.9, 154.4, 166.0, 168.4 ppm; IR (KBr): ν 2953, 2923, 2853, 2203 (CN), 1624, 1557, 1472, 1346, 1242 cm^{-1}. MS (*m/z*) 420. *Anal*. Calcd for C$_{17}$H$_{20}$N$_6$SSe (%): C, 48.68; H, 4.81; N, 20.04; S, 7.64; found: C, 48.66; H, 4.78; N, 20.02; S, 7.63.

7-Cyano-2-(hexylthio)-8-(pyrrolidin-1-yl) selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7f): (The alkyl halide is *n*-C$_6$H$_{13}$Br). White powder; yield = 61%; mp 184–189 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.82 (t, $J = 6.9$ Hz, 3H, CH$_3$), 1.26–1.36 (m, 4H, C$_2$H$_4$), 1.40–1.76 (m, 4H, C$_2$H$_4$), 2.10–2.14 (m, 4H, CH$_2$), 3.17 (t, $J = 7.3$ Hz, 2H, SCH$_2$), 3.69–3.73 (m, 4H, 2NCH$_2$), 9.02 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.0, 22.5, 26.0, 28.4, 29.3, 31.3, 31.5, 53.5, 81.1 (CN), 104.9, 116.9, 137.9, 149.8, 154.3, 165.9, 168.4 ppm; IR (KBr): ν 3064, 2955, 2924, 2853, 2198 (CN), 1630, 1549, 1474, 1436, 1378, 1246 cm^{-1}. MS (*m/z*) 435. *Anal*. Calcd for C$_{18}$H$_{22}$N$_6$SSe (%): C, 49.88; H, 5.12; N, 19.39; S, 7.40; found: C, 49.87; H, 5.10; N, 19.36; S, 7.38.

2-(Benzylthio)-7-cyano-8-(pyrrolidin-1-yl) selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7 g): (The alkyl halide is PhCH$_2$Br). White powder; yield = 73.3%; mp 183–187 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.10–2.14 (m, 4H, 2CH$_2$), 3.71–3.73 (m, 4H, 2NCH$_2$), 4.40 (s, 2H, SCH$_2$Ph), 7.20–7.43 (m, 5H$_{aromatic}$, H$_{Phenyl}$), 9.05 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 26.0, 53.9, 53.5, 81.3 (CN), 105.3, 116.9, 127.6, 128.6, 129.1, 136.7, 138.0, 150.0, 154.5, 166.1, 167.4 ppm; IR (KBr): ν 2913, 2872, 2200 (CN), 1621, 1547, 1451, 1110 cm^{-1}. MS (*m/z*) 440. *Anal*. Calcd for C$_{19}$H$_{16}$N$_6$SSe (%): C, 51.94; H, 3.67; N, 19.13; S, 7.30; found: C, 51.92; H, 3.64; N, 19.11; S, 7.29.

Synthesis of 2-alkyl-7-cyano-8-(pyrrolidin-1-yl) selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (8a-c); general procedure: To a solution of compound (**5**) (1 mmol, 0.3 g) in acetic acid (3 mL), the appropriate triethylorthoester (1 mmol) was added. The reaction mixture was heated under reflux for 3–5 h. After the completion of the reaction (monitored by TLC, CHCl$_3$:MeOH, 20:1), the solvent was removed under reduced pressure and the resulting crude product was washed with water (2 × 10 mL) and recrystallized from ethanol.

7-Cyano-8-(pyrrolidin-1-yl)selenopheno[2,3-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine (8a): (The triethylorthoester is HC(OEt)$_3$). Cream powder; yield = 61%; mp 263–265 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.20–2.24 (m, 4H, 2CH$_2$), 3.79–3.84 (m, 4H, 2NCH$_2$), 8.3 (s, 1H$_{aromatic}$, H$_{triazole}$), 9.28 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 26.0, 53.6, 81.0 (CN), 106.6, 117.0, 139.2, 149.1, 154.1, 155.2, 166.0 ppm; IR (KBr): ν 2962, 2868, 2201 (CN), 1624, 1543, 1447 cm^{-1}. MS (*m/z*) 318. *Anal*. Calcd. for C$_{12}$H$_{10}$N$_6$Se (%): C, 45.40; H, 3.18; N, 23.49. Found: C, 45.38; H, 3.17; N, 23.46.

7-Cyano-2-methyl-8-(pyrrolidin-1-yl)selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (8b): (The triethylorthoester is MeC(OEt)$_3$). Golden powder; yield = 79%; mp 264–266 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.19–2.24 (m, 4H, 2CH$_2$), 2.61 (s, 3H, CH$_3$), 3.79–3.84 (m, 4H, 2NCH$_2$), 9.17 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.5, 26.0, 53.5, 81.1 (CN), 105.7, 117.0, 138.6, 149.6, 154.1, 165.7, 165.9 ppm; IR (KBr): 3064, 2926, 2194 (CN), 1634, 1548, 1422, 1261 cm^{-1}. MS (*m/z*) 332. *Anal*. Calcd for C$_{13}$H$_{12}$N$_6$Se (%): C, 47.14; H, 3.65; N, 25.37; found: C, 47.12; H, 3.63; N, 25.35.

7-Cyano-2-ethyl-8-(pyrrolidin-1-yl)selenopheno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (8c): (The triethylorthoester is EtC(OEt)$_3$). Golden powder; yield = 85%; mp 244–248 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.41–1.46 (t, $J = 7.6$ Hz, 3H, CH$_3$), 2.17–2.23 (m, 4H, 2CH$_2$), 2.93 (q, $J = 7.6$ Hz, 2H, CH$_2$), 3.77–3.81 (m, 4H, 2NCH$_2$), 9.17 (s, 1H$_{aromatic}$, H$_{Pyrimidine}$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ 12.2, 22.4, 26.0, 53.5, 81.0 (CN), 105.8, 117.1, 138.8, 149.6, 154.0, 165.0, 170.3 ppm; IR (KBr): ν 3064, 2976, 2872, 2200 (CN), 1629, 1551, 1421, 1239 cm^{-1}. MS (*m/z*) 346. *Anal*. Calcd. for C$_{14}$H$_{14}$N$_6$Se (%): C, 48.70; H, 4.09; N, 24.34. Found: C, 48.68; H, 4.08; N, 24.31.

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