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ORIGINAL ARTICLE

Dimroth rearrangement-based synthesis of novel derivatives of [1,3] selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine as a new class of selenium-containing heterocyclic architecture

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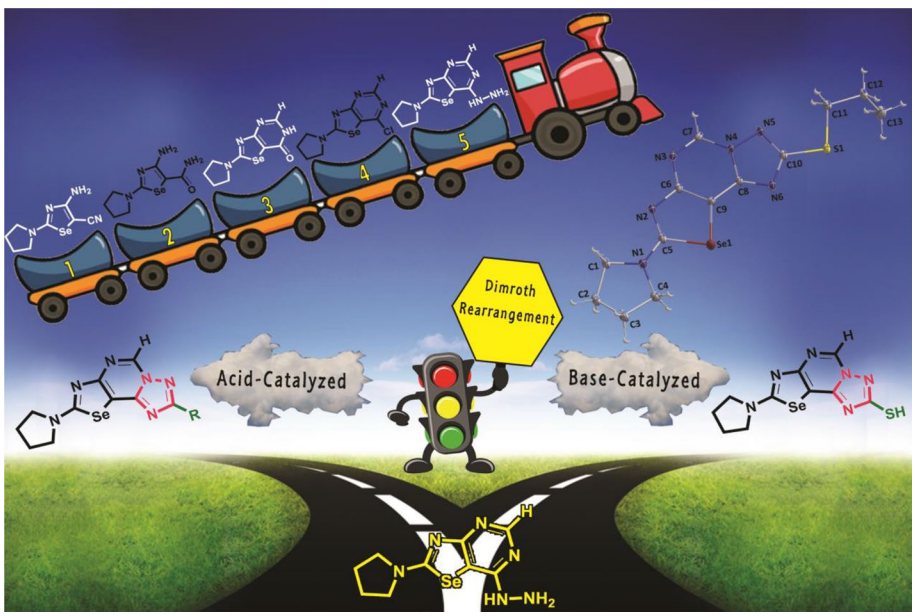
Abstract

As a part of our ongoing endeavor towards developing novel heterocyclic architectures, a number of novel *Se*-containing tricyclic heterocycles of the type [1,3]selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine have been synthesized through heteroannulation of a newly produced hydrazino derivative of selenazolo[4,5-*d*]pyrimidine with either orthoesters or carbon disulfide in pyridine followed by *S*-alkylation. Moreover, the multistep protocol employed in this investigation provides a new insight into the Dimroth rearrangement in both acidic and basic media as a means for the cyclocondensation of triazole on the selenazolopyrimidine framework leading to selenazolotriazolopyrimidines.

Graphic Abstract

The synthesis of new derivatives of novel selenazolotriazolopyrimidines via Dimroth rearrangement in both acidic and basic media is presented.



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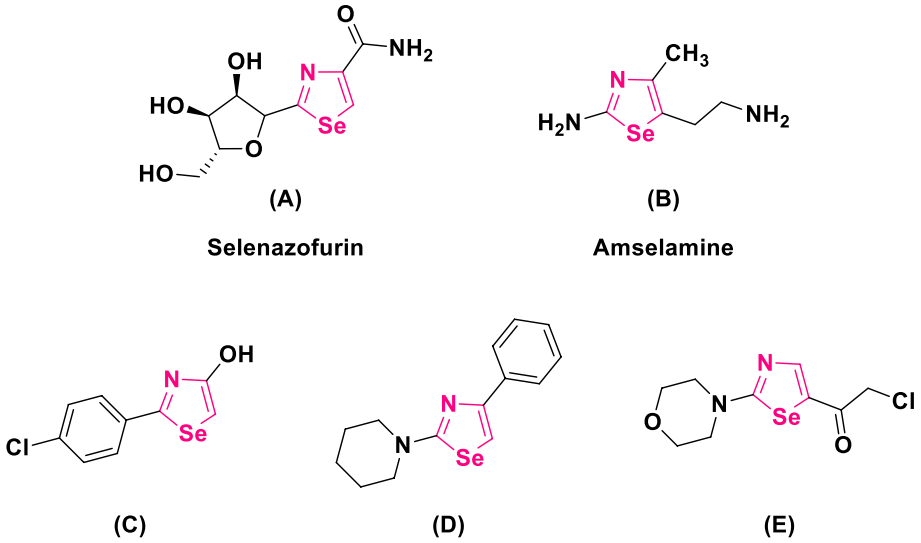


Fig. 1 Examples of bioactive synthetic selenazoles

Keywords Dimroth Rearrangement · Selenazole · Selenazolo[4,5-d]pyrimidine · Selenazolo[5,4-e][1,2,4] triazolo[1,5-c]pyrimidine · X-ray Crystallography

Introduction

Selenium has similar characteristics to its homologs oxygen and sulfur but different specific features and reactivity compared with them [1]. It is a key trace element required in small amounts by humans and animals [2, 3] and which displays an insulin-mimetic activity both in vitro and in vivo [4]. Some research indicates that it participates in the synthesis of enzymes and protects the structure and function of the biomembrane from over-oxidation and cell damage [5]. A lack of selenium could lead to the development and progression of chronic diseases [6] such as heart diseases, hypothyroidism, and weakened immune system [7, 8]. Selenium oligo-element exists in different chemical forms, each of which can determine the bioavailability and toxicity of selenium in the body [9–12]

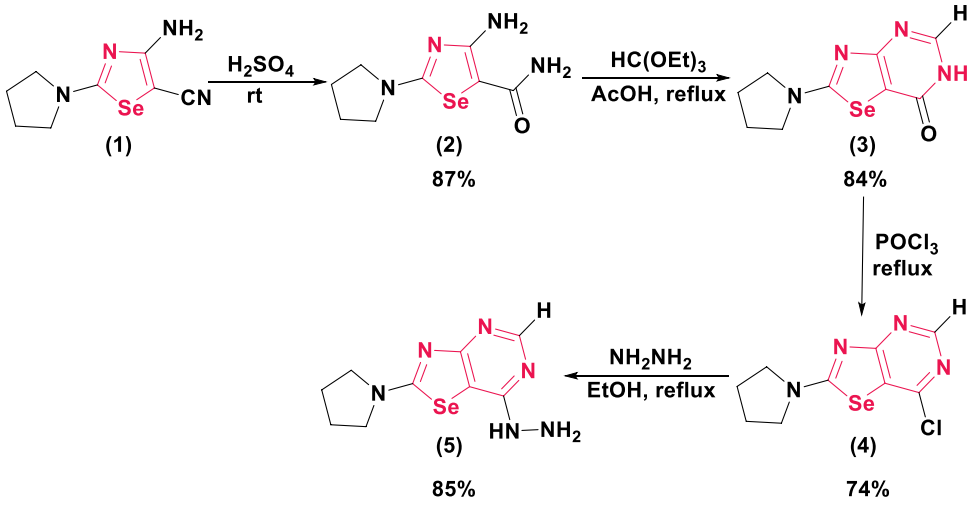
Based on the benefits associated with the presence of selenium and the importance of heterocycles in the field of medicinal chemistry, many protocols have been developed for the synthesis of organoselenium compounds containing the 1,3-selenazole ring which are characterized by a large variety of biological activities.

The selenazole ring which first appeared in 1889 [13] is present in many pharmacologically active substances such as selenazofurin and amselamine. Many functionalized 1,3-selenazole scaffolds are important constituent of bioactive synthetic compounds [14–16] (Fig. 1). Selenazofurin **(A)** is a potent known antiviral agent [17], amselamine **(B)** is a selective histamine H_2-agonist [18, 19], selenazole **(C)** is useful for prevention of nitric oxide-mediated inflammatory damages [20], 4-phenyl-2-piperidinoselenazole **(D)** exhibits superoxide anion-scavenging activity [21], while 5-(chloroacetyl)-2-morpholinoselenazole **(E)** strongly inhibits LPS-induced nitric oxide release from microglial cells [22].

Whereas 1,3-selenazoles generally act as antibiotics and cancerostatic agents [23, 24], a number of studies have indicated that 1,3-selenazole derivatives inhibit the synthesis of nitric acid [25] and they are antagonists for histamine H2 receptors [19]. This important class of heterocycles also display other significant biological effects such as inactivation of free radicals [26], antioxidant [27–31], antifungal [32, 33], antimicrobial [33–37], anticonvulsant [34], cancer cell proliferation [28, 29, 33, 36–38], protein kinase activation [39], xantine oxidase inhibitory [40], and selective human carbonic anhydrase IX inhibition with potent anti-tumor activity [41].

A literature survey revealed that 1,3-selenazoles have been mainly synthesized by application of the Hantzsch procedure [42–46]. Other efficient synthetic methodologies for the synthesis of 1,3-selenazoles have been reported to be based on *β*-cyclodextrin as a supramolecular facilitator [45, 47], $CuPy_2Cl_2$ [48]or NaF [49] catalysis, ultrasonic irradiation [50], microwave-assisted [38] and multicomponent synthesis [51].

Inspired by our experience in developing novel heterocyclic building blocks of potential pharmacological significance [52–59], the present study attempts to combine amino-selenazole and bioactive triazolopyrimidines so as to obtain *Se*-containing fused heterocycles, namely [1, 3] selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines. Aiming to reflect the reality of catalyzed Dimroth rearrangement mechanism concerning cyclization of triazole as a final ring, a consistent X-ray crystallography analysis has been conducted which truly justify the unequivocal structure of the



Scheme 1 Synthesis of 7-hydrazinyl-2-(pyrrolidin-1-yl)-[1,3]selenazolo[4,5-*d*] pyrimidine **(5)**

fused polycyclic framework of the main selenazolotriazolopyrimidine, as well.

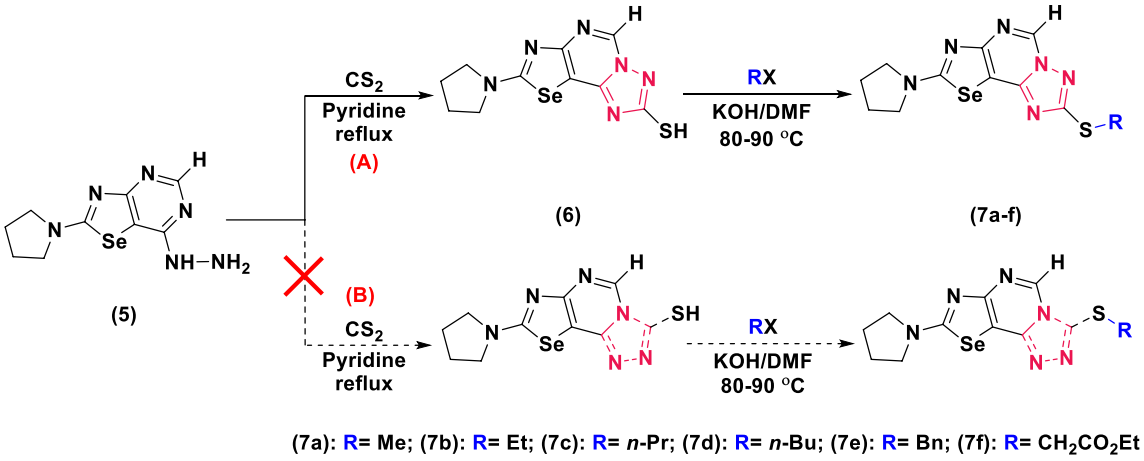
Results and discussion

Various novel selenium containing tricyclic heterocycles bearing a pyrrolidine on their selenazole core and alkyl or thioalkyl groups on their triazole ring have been synthesized from 4-amino-2-(pyrrolidin-1-yl)-1,3-selenazole-5-carbonitrile **(1)** as starting material. The protocol follows a sequence of concentrated sulfuric acid mediated hydrolysis of the carbonitrile group, ring closure in the presence of an electrophilic carbon, chlorination, S_NAr hydrazination and eventually, acid/base-catalyzed Dimroth rearrangement.

In order to prepare the trisubstituted selenazole **(1)**, dimethyl cyanodithioimidocarbonate was reacted successively with pyrrolidine, sodium selenide, chloroacetonitrile, and potassium carbonate in a one-pot four-step sequential pathway as described in the literature [60]. Hydrolysis in the concentrated sulfuric acid converted compound **(1)** into the corresponding selenazole-2-carboxamide **(2)**. The IR spectrum of **(2)** showed a carbonyl absorption band at $\nu = 1611$ cm^{-1} but C≡N ($\nu = 2165$ cm^{-1}) band of the starting material **(1)** was absent, which indicates conversion of the carbonitrile group to primary amide. Then, **(2)** underwent cyclization in the presence of $HC(OEt)_3$ to yield selenazolo[4,5-*d*] pyrimidine **(3)**. The C = O band of **(3)** was blue-shifted to $\nu = 1678$ cm^{-1} in comparison to the amidic carbonyl of precursor **(2)** ($\nu = 1611$ cm^{-1}). Both the blue-shifted amidic C = O stretching band along with the disappearance of the symmetric and asymmetric stretching bands of the NH_2 group in the IR spectrum strongly supported the possibility of the heterocyclization leading to **(3)**. In continuation, treatment of **(3)** with boiling $POCl_3$ gave the corresponding 7-chloro-pyrazolo[3,4-*d*]pyrimidine **(4)**. The chlorinated compound **(4)** was then reacted with hydrazine monohydrate in refluxing EtOH to obtain 7-hydrazino derivative **(5)** (Scheme 1).

In order to synthesize novel selenazolotriazolopyrimidine heterocycles, cyclocondensation of the hydrazinated compound **(5)** with CS_2 occurred in pyridine under reflux. The resulting tricyclic selenium-containing skeleton **(6)** was then converted to its *S*-alkylated derivatives **(7a-f)** on treatment with various alkyl halides in the presence of KOH/DMF through either path **(A)** or **(B)** (Scheme 2).

The structural assignments of all the newly synthesized compounds **(7a-f)** were validated by spectroscopic and microanalytical data. Although the formation of both isomers **(A)** and **(B)** was predicted, the experimental results did not support this prediction. Both the ^{1}H NMR and ^{13}C NMR spectra of the products revealed the formation of only one isomer, either **(A)** or **(B)**. As an example, the ^{1}H NMR spectrum of **(7c)** showed two broad multiplet peaks around δ 2.13–2.17 and 3.50–3.83 ppm belonging to the methylene groups of the pyrrolidine moiety. The thiopropyl ether signals were observed at δ 1.09 (triplet, $^3J = 7.4$ Hz), δ 1.87 (quintet, $^3J = 7.4$ Hz) and δ 3.24 ppm (triplet, $^3J = 7.3$ Hz) due to CH_3, CH_2 and SCH_2 moieties, respectively. The spectrum showed a singlet signal at δ 9.03 ppm for the C–H proton of the pyrimidine ring, as well. In the ^{13}C NMR spectrum, five aliphatic and six aromatic carbon signals were observed for **(7c)**. The number of hydrogens and carbons and their chemical shifts deduced from the ^{1}H and ^{13}C NMR spectra of **(7c)** together with the absence of the D_2O-exchangeable signal of its precursor, **(6)**, at δ 13.52 ppm verified the location of only one propyl group, probably on the thiol moiety indicating mono-alkylation as *S*-propylation. The observation of the molecular ion peak at *m/z* 367 (M^+) along with complementary results of the elemental analysis eventually confirmed the molecular formula of $C_{13}H_{16}N_6SSe$ for **(7c)**. Nevertheless, the mechanism of



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

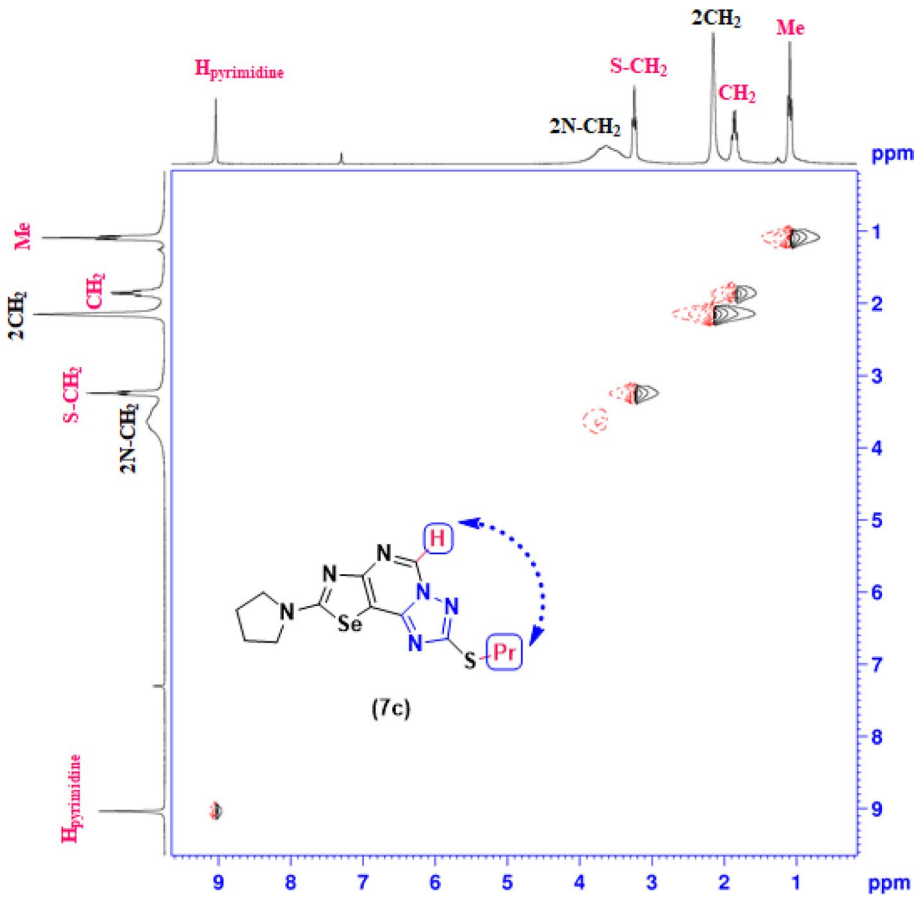


Fig. 2 ^{2}D-NOESY NMR of compound **(7c)**

annulation and the exact framework of the regioisomer was still uncertain. So a ^{2}D-NOESY NMR analysis was undertaken. The intrinsic significance of the ^{2}D-NOESY NMR was that it excluded the possibility of the cyclization through the path **(B)** due to the absence of any cross signal between the hydrogens of *S*-propyl moiety and the single hydrogen of pyrimidine ring. Taking these findings into account, it seems that the aforementioned hydrogen groups are most probably too far in space to show a spatial interaction which approximately confirms the structure **(A)** for **(7c)** (Fig. 2).

Eventually, a single crystal X-ray crystallographic analysis was established to unequivocally validate true skeleton of **(7c)**. Figure 3 which shows the molecular structure and the atom labeling of 8-(propylthio)-2-(pyrrolidin-1-yl)-[1,3]

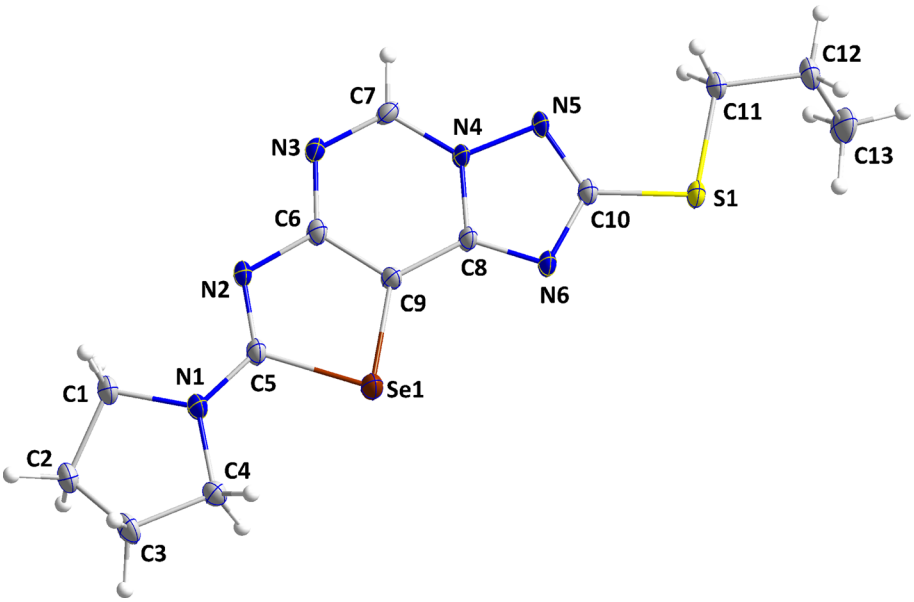


Fig. 3 ORTEP view of compound **(7c)**. The thermal displacement ellipsoids are shown at 50% probability level

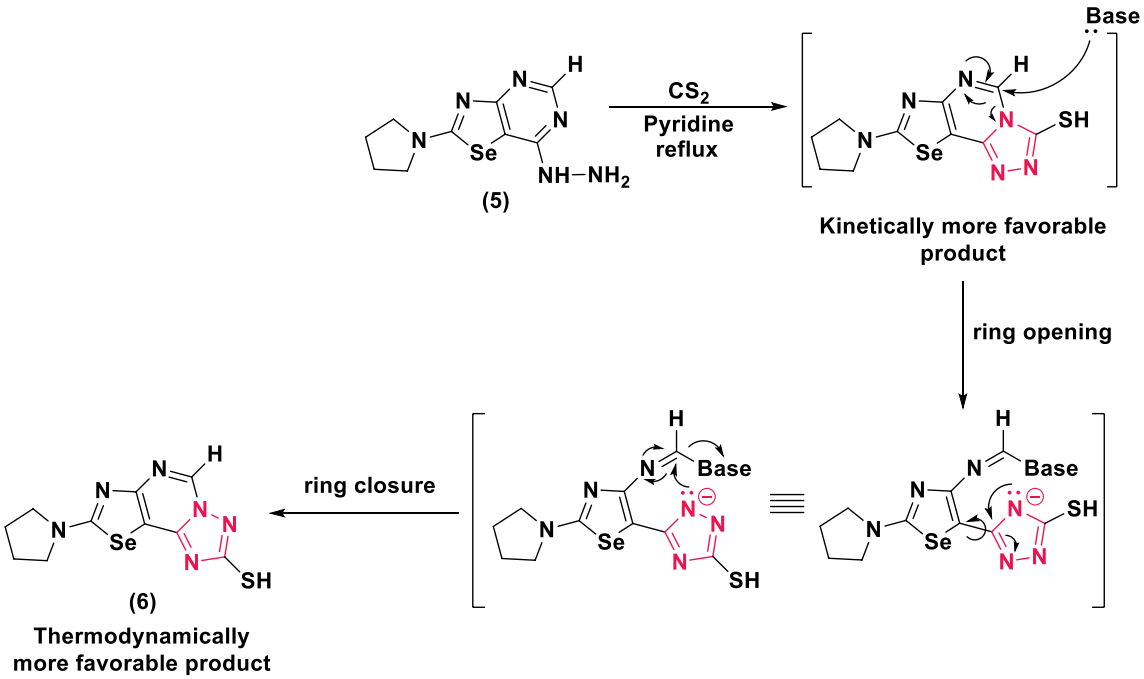


Fig. 4 Base-catalyzed Dimroth rearrangement mechanism

selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **(7c)**, clearly identifies that the regio-isomer **(A)** was unambiguously formed. Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (deposition no. CCDC 1,985,791).

These results suggest the reaction proceeds through a base-promoted, tandem ring opening/ring closure of the pyrimidine core which is associated with the base-catalyzed Dimroth rearrangement (Fig. 4).

To ascertain whether the rearrangement occurs during the treatment of **(5)** with CS_2 in pyridine, or of **(6)** with KOH and the alkyl halide, a practical experiment was designed and conducted. When the hydrazinated compound **(5)** refluxed in pyridine alone for almost the time required to triazole ring closure in the presence of CS_2, it rearranged to its regioisomeric form namely, 7-imino-2-(pyrrolidin-1-yl)-[1,3]selenazolo[4,5-*d*]pyrimidin-6(7H)-amine **(5′)**, under similar thermal and basic conditions. (Fig. 5).

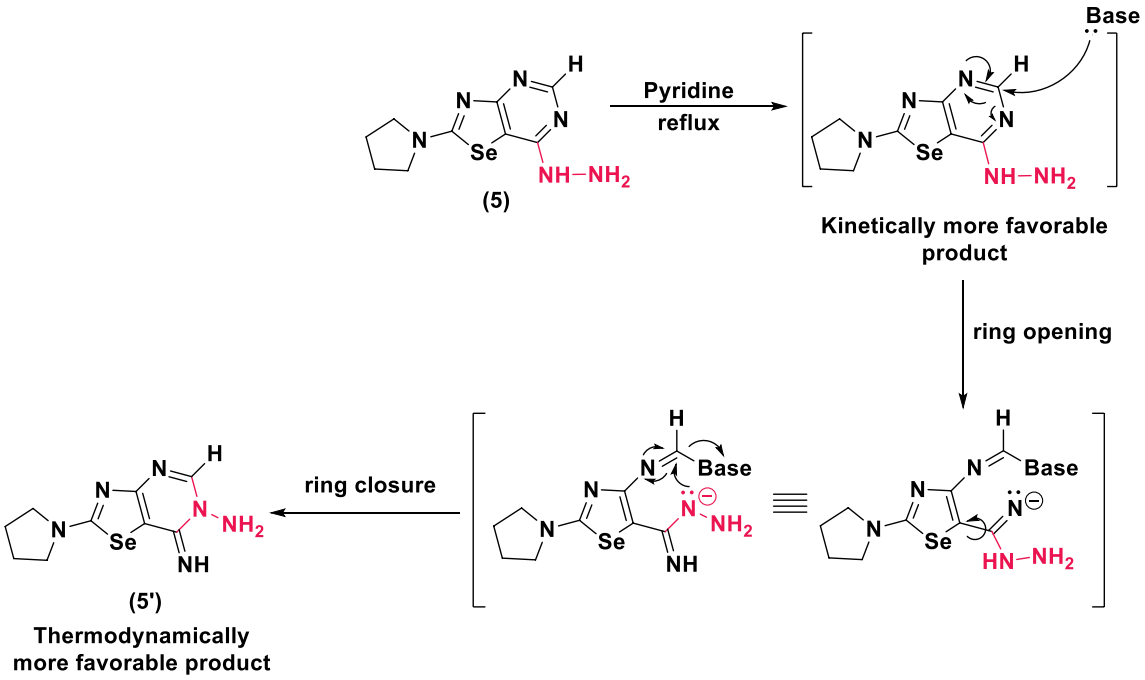


Fig. 5 Base-catalyzed Dimroth rearrangement of compound **(5)**

In Figs. 6 and 7, the ^{1}H NMR and ^{13}C NMR chemical shifts of two regioisomers have been compared thoroughly.

As a further confirmation, the present test easily substantiated that heating is the main and critical factor for the occurance of rearrangement at the presence of basic condition. So inevitably the base-catalyzed Dimroth rearrangement must be happening through the synthesis of intermediate **(5′)** during the treatment of **(5)** with CS_2 in pyridine (Scheme 3).

In other attempts, stirring the hydrazine-substituted compound **(5)** with various triethyl orthoesters in acetic acid under reflux led to annulation and formed the desired tricyclic [1, 3]selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **(8a–c)** in good yields (Scheme 4).

The spectral and microanalytical data of **(8a–c)** were in accordance with the assigned structures. For instance, in the ^{1}H NMR spectrum of **(8c)**, the ethyl signals appeared as a triplet and a quartet at δ 1.34 and 2.84 ppm, respectively, with a coupling constant of 7.6 Hz. The presence of the pyrrolidine substituent was also indicated by two multiplet peaks around δ 2.02–2.09 and 3.40–3.66 ppm corresponding to methylene groups. The only hydrogen on the pyrimidine ring was observed as a broad singlet at δ 9.02. In the ^{13}C NMR spectrum, four resolved aliphatic signals were detected at δ 11.3, 21.3, 24.6 and 49.8 ppm and six aromatic ones at δ 106.7, 137.0, 150.1, 161.6, 167.0 and 169.6 ppm. As expected, the most deshielded peak at δ 169.6 ppm was due to the carbon surrounded by three heteroatoms (2 N and Se) which strongly corroborated the presence of the C^{2}-pyrrolidine-substituted selenazole ring in **(8c)**. Furthermore, the observation of the molecular ion peak at *m/z* 321 in the mass spectrum of **(8c)** corresponding to the $C_{12}H_{14}N_6Se$ molecular formula substantiated the fusion of the triazole ring to the selenazolopyrimidine core of hydrazinated compound **(5)**.

In the absence of any X-ray crystallography, a decisive evidence for the exact tricyclic main skeleton of compounds **(8a–c)** can be provided based on the ^{2}D-NOESY NMR analysis of **(8c)** with that of crystallographically identified **(7c)** (Fig. 8).

Contrary to alkali-prepared compounds **(7a–f)**, compounds **(8a–c)** were cyclized in an acidic medium. Nevertheless, the literature survey revealed that [1, 2, 4]triazolo[4,3-*c*]pyrimidine derivatives on heating in either acidic or basic medium isomerize to the thermodynamically more stable [1, 2, 4]triazolo[1,5-*c*]pyrimidine through a series of ring opening and ring closure reactions which is consistent with a Dimroth-type rearrangement [61, 62]. Thus, it appears quite likely that just as compounds **(7a–f)** underwent base-catalyzed Dimroth rearrangement at elevated temperature, so compounds **(8a–c)** underwent an acid-catalyzed Dimroth rearrangement under similar thermal conditions (Fig. 9).

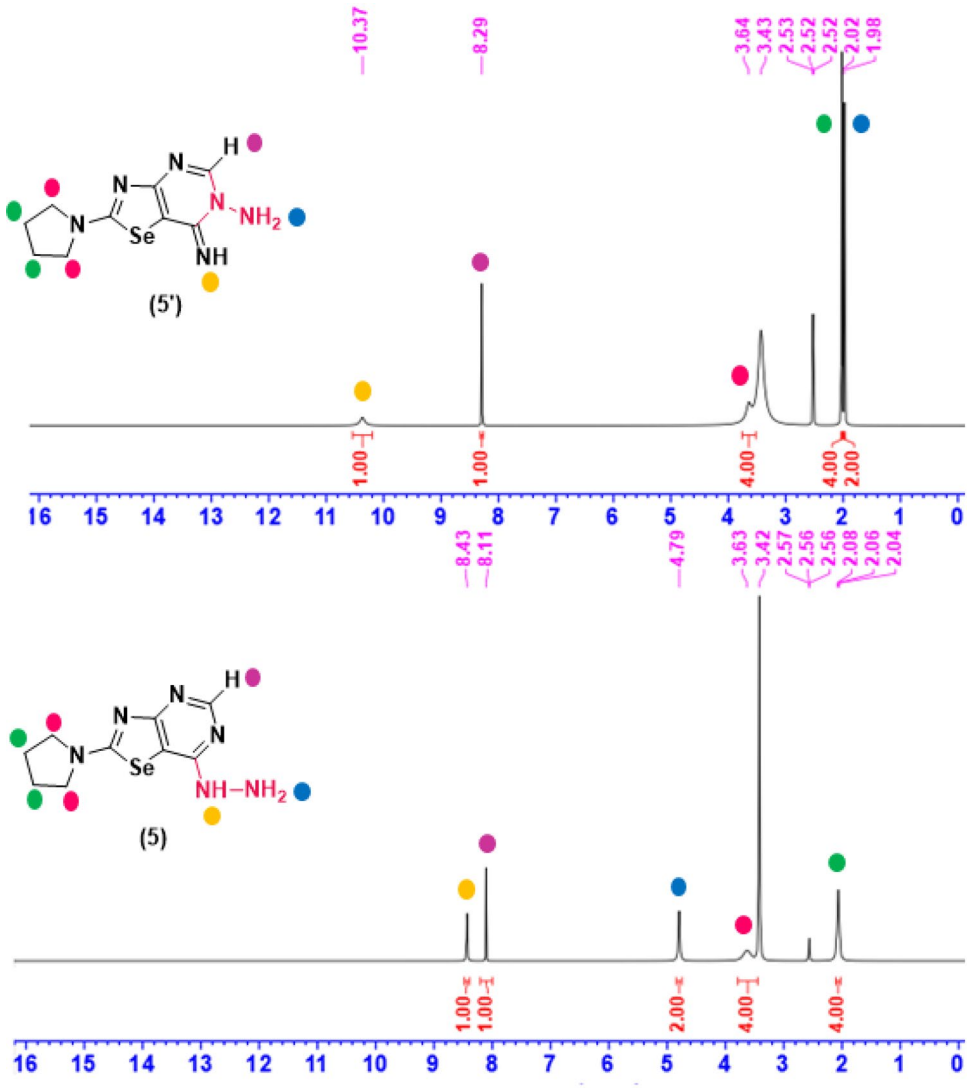


Fig. 6 ^{1}H NMR spectra of compounds **(5)** and **(5′)**

Conclusion

In summary, we disclosed a multistep strategy for the synthesis of a robust tricyclic scaffold, [1, 3]selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine, as a novel interesting fused-ring heterocyclic system with promising pharmacological activities. The synthetic strategy involves consecutive acidic hydrolysis of the carbonitrile group of starting material **(1)**, ring closure in the presence of triethylorthoformate, chlorination, hydrazination and Dimroth rearrangement in both acidic and basic media followed by *S*-alkylation. The mechanism of final cyclization and the exact structure of the regioisomer was also investigated by ^{2}D-NOESY NMR and X-ray crystallographic analyses.

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. (See Supporting Information file for full experimental data).

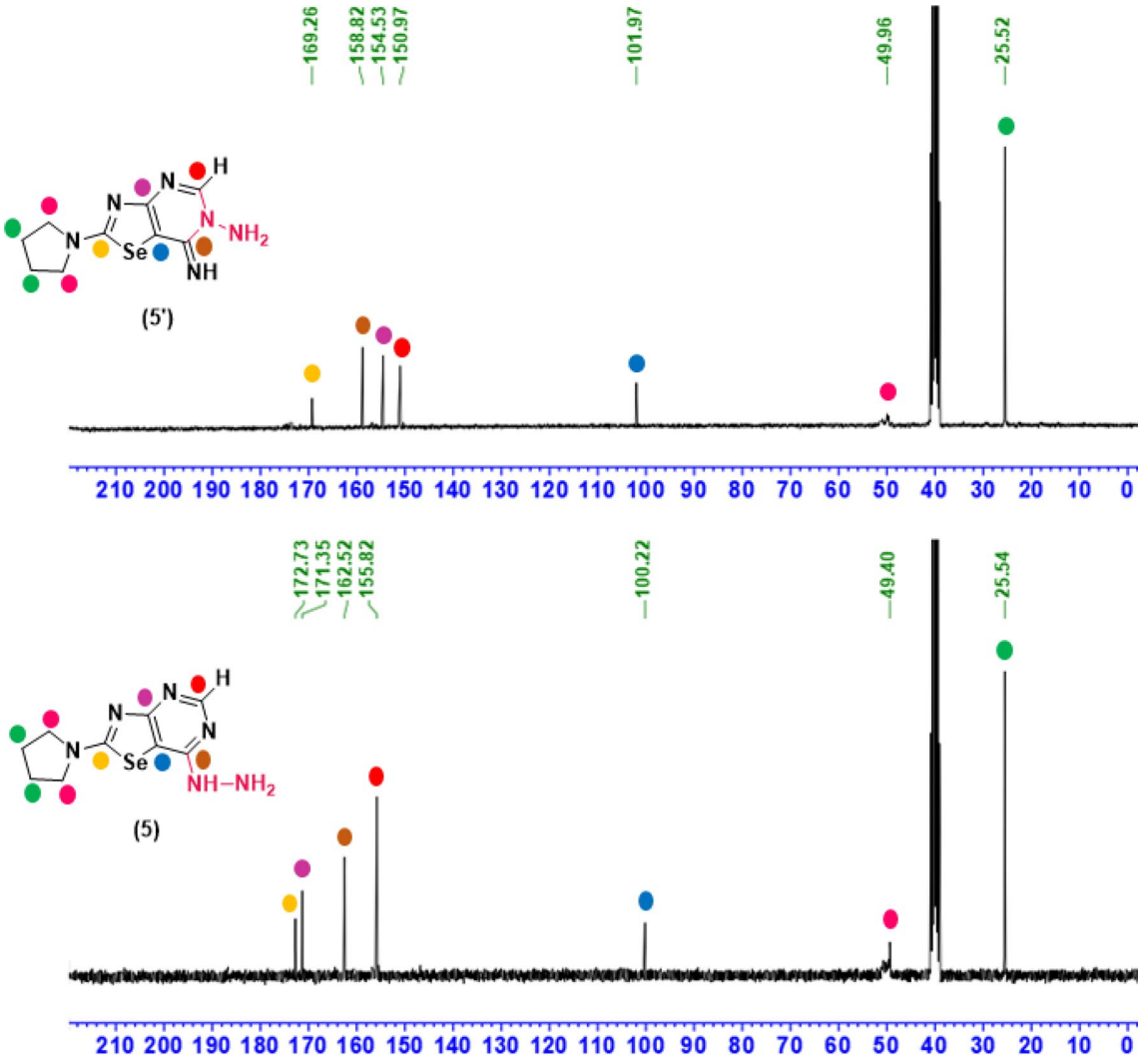


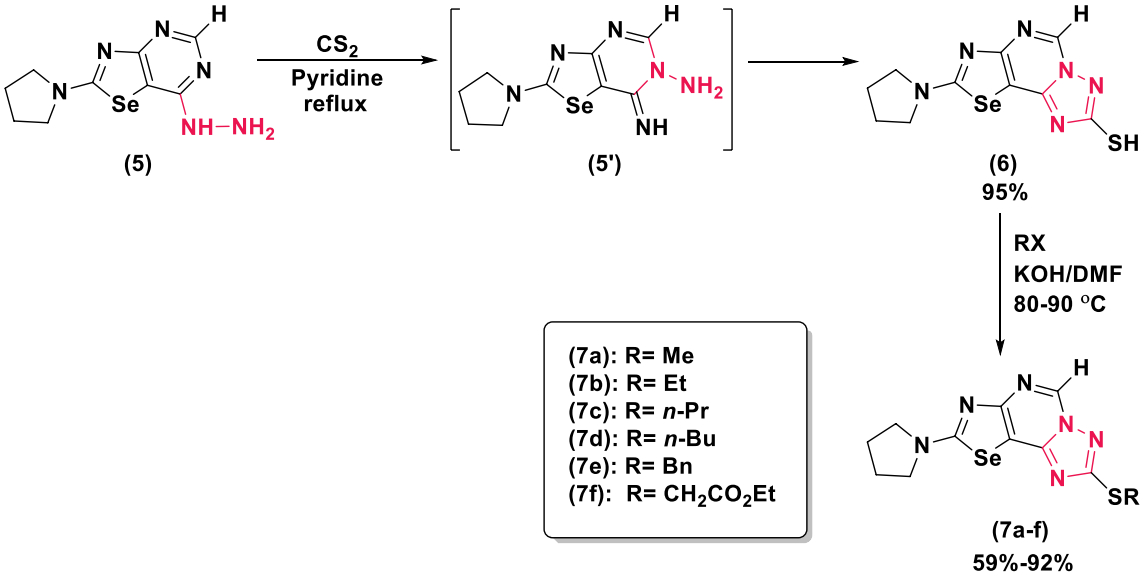
Fig. 7 ^{13}C NMR spectra of compounds **(5)** and **(5′)**

Synthesis of 4-amino-2-(1-pyrrolidinyl)-1,3-selenazole-5-carbonitrile (1)

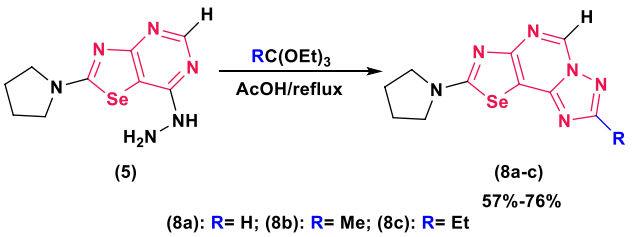
Compound **(1)** were prepared through the literature procedure [60]. Brown powder; yield: (1.82 g, 75%); mp 301–302 °C; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.96–2.01 (m, 4H, $2CH_2$), 3.34–3.37 (m, 4H, $2NCH_2$), 6.64 (br s, 2H, NH_2, D_2O-exchangable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.6, 50.9, 56.0 (CN), 119.2, 167.0, 167.5 ppm; IR (KBr): ν 3372, 3325, 3195, 3166, 2962, 2888, 2847, 2165 (CN), 1646, 1567, 1521, 1424 cm^{-1}. MS (EI, 70 eV) *m/z* = 242. *Anal.* Calcd. for $C_8H_{10}N_4Se$ (%): C, 39.84; H, 4.18; N, 23.23. Found: C, 39.81; H, 4.14; N, 23.22.

Synthesis of 4-amino-2-(1-pyrrolidinyl)-1,3-selenazole-5-carboxamide (2)

A mixture of **(1)** (10 mmol, 2.41 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 into an ice/water bath and made basic 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. Pale grey powder; yield: (2.25 g, 87%); mp 218–219 °C; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.93–2.02 (m, 4H, $2CH_2$), 3.36–3.41 (m, 4H, $2NCH_2$), 6.30 (br s, 2H, NH_2, D_2O-exchangable), 6.93 (br s, 2H, $CONH_2$, D_2O-exchangable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.6, 50.2, 83.8, 164.1, 166.2, 168.2 ppm; IR (KBr): ν 3387, 3264, 3175, 2970, 2872, 1679, 1611, 1553, 1418,



Scheme 3 The stepwise synthesis of compounds (**7a-f**) via intermediate (**5′**)



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

1303, 1076 cm^{-1}. MS (EI, 70 eV) *m/z* = 259. *Anal.* Calcd. for $C_8H_{12}N_4OSe$ (%): C, 37.08; H, 4.67; N, 21.62. Found: C, 37.05; H, 4.66; N, 21.60.

Synthesis of 2-(1-pyrrolidinyl)-[1,3] selenazolo[4,5-*d*]pyrimidin-7(6*H*)-one (3)

To a solution of (**2**) (10 mmol, 2.59 g) in acetic acid (10 mL), triethyl orthoformate (10 mmol, 1.65 mL) was added. The reaction mixture was heated under reflux for 3 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. Brown powder; yield: (2.26 g, 84%); mp 366–367 ºC [EtOH]; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.93–1.98 (m, 4H, $2CH_2$), 3.39–3.52 (m, 4H, $2NCH_2$), 7.98 (s, $1H_{aromatic}$, $H_{Pyrimidine}$), 12.18 (br s, 1H, NH, D_2O-exchangable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.6, 50.0, 110.8, 148.4, 158.7, 168.9, 169.2 ppm; IR (KBr): ν 3186, 3117, 3043, 2968, 1678, 1563, 1401 cm^{-1}. MS (EI, 70 eV) *m/z* = 269. *Anal.* Calcd. for $C_9H_{10}N_4OSe$ (%): C, 40.16; H, 3.74; N, 20.82. Found: C, 40.14; H, 3.73; N, 20.80.

Synthesis of 7-chloro-2-(pyrrolidin-1 -yl)-[1,3]selenazolo[4,5-*d*]pyrimidine (4)

Compound (**3**) (10 mmol, 2.69 g) was 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 until constant weight. Cream powder; yield: (2.13 g, 74%); mp 175–176 ºC; ^{1}H NMR (300 MHz, Chloroform-*d*): δ = 2.03–2.13 (m, 4H, $2CH_2$), 3.33 (t, *J* = 6.5 Hz, 2H, NCH_2), 3.81 (t, *J* = 6.6 Hz, 2H, NCH_2), 8.62 (s, $1H_{aromatic}$, $H_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, Chloroform-*d*): δ = 25.6, 50.6, 51.6, 125.5, 154.0, 156.3, 169.0, 172.3 ppm; IR (KBr): ν 3043, 2986, 2949, 2884, 2859, 1604, 1536, 1482, 1410, 1384, 1357, 1319, 1271, 988, 963, 887, 777 cm^{-1}. MS (EI, 70 eV) *m/z* = 288. *Anal.* Calcd. for $C_9H_9ClN_4Se$ (%): C, 37.59; H, 3.15; N, 19.48. Found: C, 37.57; H, 3.14; N, 19.45.

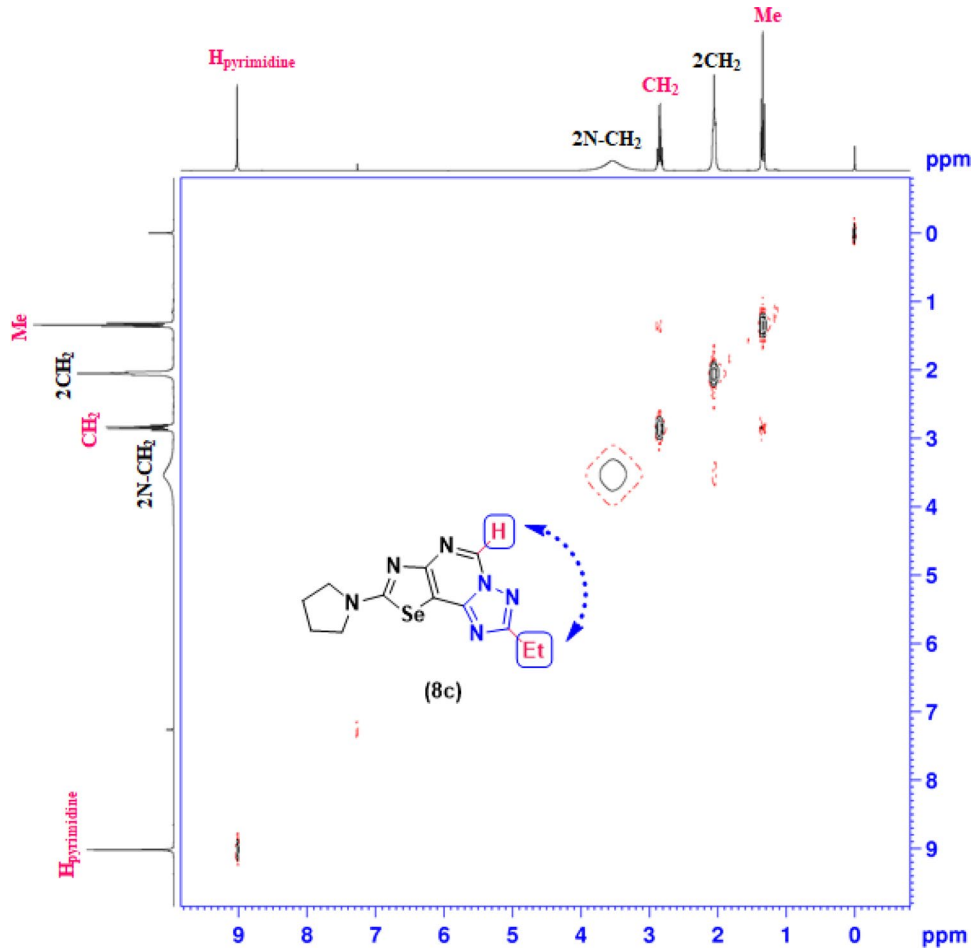


Fig. 8 ^{2}D-NOESY NMR of compound **(8c)**

Synthesis of 7-hydrazinyl-2-(pyrrolidin-1-yl)-[1,3]selenazolo[4,5-*d*]pyrimidine (5)

A mixture of **(4)** (8 mmol, 2.30 g) and excess amount of hydrazine monohydrate (1.5 mL) in EtOH (15 mL) was stirred vigorously at reflux for 2 h. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH, 20:1), the ethanol was evaporated under reduced pressure. The resulting solid was then washed with water (2 × 20 mL), filtered off and recrystallized from ethanol. Cream flakes; yield: (1.92 g, 85%); mp 268–270 ºC [EtOH]; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.02–2.12 (m, 4H, $2CH_2$), 3.53–3.73 (m, 4H, $2NCH_2$), 4.79 (br s, 2H, NH_2, D_2O-exchangable), 8.11 (s, $1H_{aromatic}$, $H_{Pyrimidine}$), 8.43 (br s, 1H, NH, D_2O-exchangable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.5, 49.4, 100.2, 155.8, 162.5, 171.4, 172.7 ppm; IR (KBr): ν 3325, 3301, 3195, 3047, 2950, 2888, 2847, 1649, 1554, 1490, 1405, 1325, 1266 cm^{-1}. MS (EI, 70 eV) *m/z* = 283. *Anal.* Calcd. for $C_9H_{12}N_6Se$ (%): C, 38.17; H, 4.27; N, 29.68. Found: C, 38.16; H, 4.25; N, 29.65.

Synthesis of 7-imino-2-(pyrrolidin-1-yl)-[1,3]selenazolo[4,5-*d*]pyrimidin-6(7H)-amine (5′)

A solution of compound **(5)** (1 mmol, 283 mg) in pyridine (10 mL) was stirred under reflux condition for 2 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 the mixture was neutralized with aqueous 5% HCl solution. The crude product was collected by filtration and recrystallized from ethanol. Bright cream powder; yield: (235 mg, 83%); mp 273–274 ºC [EtOH]; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.98 (br s, 2H, NH_2, D_2O-exchangable), 2.01–2.03 (m, 4H, $2CH_2$), 3.52–3.76 (m, 4H, $2NCH_2$), 8.29 (s, $1H_{aromatic}$, $H_{Pyrimidine}$), 10.37 (br s, 1H, NH, D_2O-exchangable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.5, 50.0, 102.0, 151.0, 154.5, 158.8, 169.3 ppm; IR (KBr): ν 3399, 3166, 3039, 2914, 2864, 1585, 1550, 1479, 1400, 1325, 1127 cm^{-1}. MS (EI, 70 eV) *m/z* = 283. *Anal.* Calcd. for $C_9H_{12}N_6Se$ (%): C, 38.17; H, 4.27; N, 29.68. Found: C, 38.15; H, 4.24; N, 29.67.

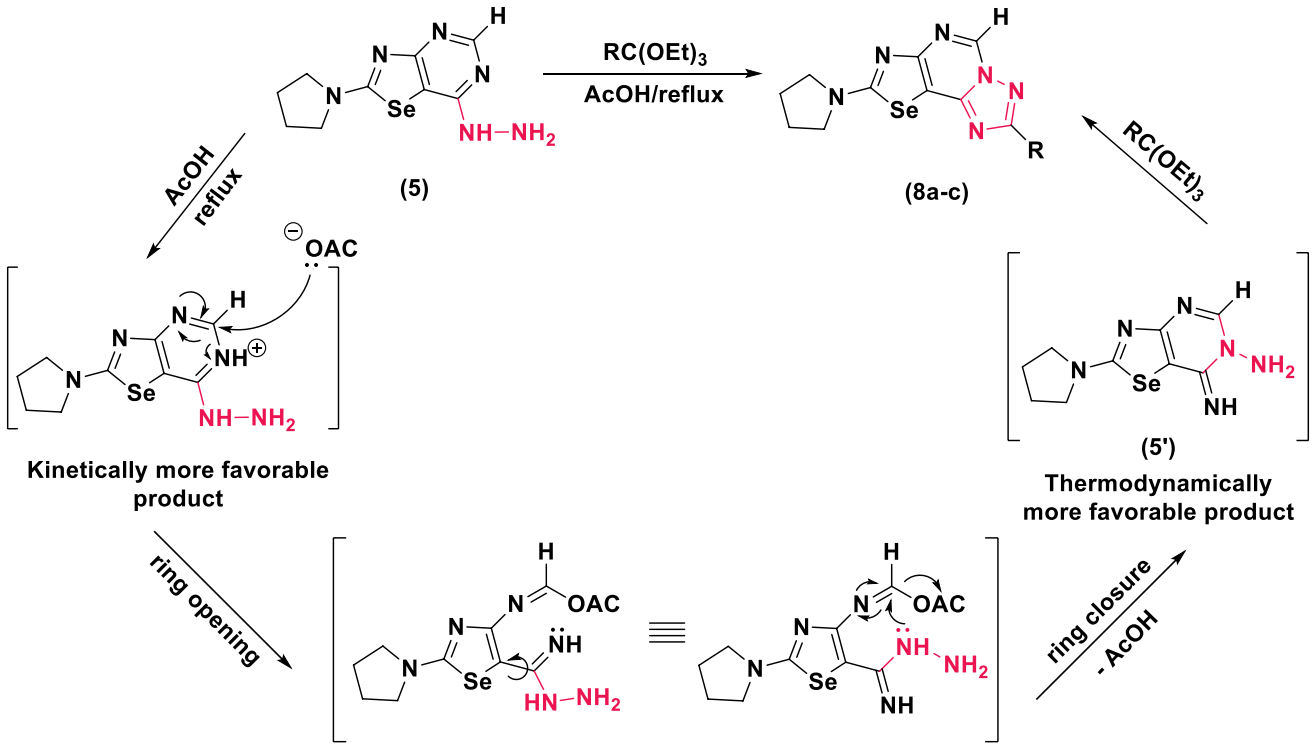


Fig. 9 Acid-catalyzed Dimroth rearrangement of compound (**5**)

Synthesis of 2-(pyrrolidin-1-yl)-[1,3] selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine-8-thiol (6)

A mixture of 7-hydrazinyl-2-(pyrrolidin-1-yl)-[1,3] selenazolo[4,5-*d*]pyrimidine **(5)** (7 mmol, 1.98 g), CS_2 (3 mL) in pyridine (10 mL) was stirred under reflux condition for 2 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 the mixture was neutralized with aqueous 5% HCl solution. The crude product was collected by filtration and recrystallized from ethanol. Bright mustard powder; yield: (2.17 g, 95%); mp 274–275 °C [EtOH]; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.99–2.06 (m, 4H, $2CH_2$), 3.33–3.46 (m, 4H, $2NCH_2$), 9.08 (s, $1H_{aromatic}$, $H_{Pyrimidine}$), 13.52 (br s, 1H, SH, D_2O-exchangable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.6, 50.6, 138.9, 147.1, 160.1, 163.6, 167.2, 167.6 ppm; IR (KBr): ν 3333, 3272, 3069, 2970, 2876, 2727, 1686, 1635, 1574, 1451, 1403, 1293, 1235 cm^{-1}. MS (EI, 70 eV) *m/z* = 325. *Anal.* Calcd. for $C_{10}H_{10}N_6SSe$ (%): C, 36.93; H, 3.10; N, 25.84; S, 9.86. Found: C, 36.91; H, 3.08; N, 25.83; S, 9.83.

Synthesis of 8-(alkylthio)-2-(pyrrolid in-1-yl)-[1,3]selenazolo[5,4-*e*][1,2,4] triazolo[1,5-*c*]pyrimidines (7a-f); general procedure

To a mixture of **(6)** (1 mmol, 325 mg) and KOH (1.2 mmol, 70 mg) in DMF (3 mL), the excess amount of the appropriate alkyl halide (0.3 mL) was added and the mixture was heated at 80–90 °C for 24 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.

8-(Methylthio)-2-(pyrrolidin-1-yl)-[1,3] selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine (7a)

(The alkyl halide is CH_3I). Pale yellow powder; yield: (200 mg, 59%); mp 241–242 °C [EtOH]; ^{1}H NMR (300 MHz, Chloroform-*d*): δ = 2.10–2.22 (m, 4H, $2CH_2$), 2.74 (s, 3H, CH_3), 3.55–3.80 (m, 4H, $2NCH_2$), 9.07 (s, $1H_{aromatic}$, $H_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, Chloroform-*d*): δ = 14.1, 25.7, 50.9, 107.0, 137.3, 151.7, 163.0, 168.3, 169.0 ppm; IR (KBr): ν 3051, 2958, 2925, 2851, 1683, 1632, 1573, 1451, 1407, 1379, 1263, 1235, 1111, 1057 cm^{-1}. MS

(EI, 70 eV) *m/z* = 339. *Anal.* Calcd. for $C_{11}H_{12}N_6SSe$ (%): C, 38.94; H, 3.57; N, 24.77; S, 9.45. Found: C, 38.92; H, 3.54; N, 24.75; S, 9.42.

8-(Ethylthio)-2-(pyrrolidin-1-yl)-[1,3]selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7b)

(The alkyl halide is C_2H_5I). Cream powder; yield: (237 mg, 67%); mp 218–220 ºC [EtOH]; ^{1}H NMR (300 MHz, Chloroform-*d*): δ = 1.42 (t, *J* = 7.4 Hz, 3H, CH_3), 2.02–2.12 (m, 4H, $2CH_2$), 3.20 (q, *J* = 7.4 Hz, 2H, SCH_2), 3.47–3.72 (m, 4H, $2NCH_2$), 8.97 (s, $1H_{aromatic}$, $H_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, Chloroform-*d*): δ = 14.9, 25.7, 30.9, 50.9, 107.1, 137.3, 151.5, 163.0, 168.2, 168.3 ppm; IR (KBr): ν 3044, 2957, 2924, 2867, 1630, 1568, 1451, 1404, 1377, 1323, 1261, 1233 cm^{-1}. MS (EI, 70 eV) *m/z* = 353. *Anal.* Calcd. for $C_{12}H_{14}N_6SSe$ (%): C, 40.80; H, 3.99; N, 23.79; S, 9.07. Found: C, 40.78; H, 3.96; N, 23.77; S, 9.05.

8-(Propylthio)-2-(pyrrolidin-1-yl)-[1,3]selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7c)

(The alkyl halide is *n*-C_3H_7Br). Pale brown powder; yield: (339 mg, 92%); mp 188–189 ºC [EtOH]; ^{1}H NMR (300 MHz, Chloroform-*d*): δ = 1.09 (t, *J* = 7.4 Hz, 3H, CH_3), 1.87 (m, *J* = 7.4 Hz, 2H, CH_2), 2.13–2.17 (m, 4H, $2CH_2$), 3.24 (t, *J* = 7.3 Hz, 2H, SCH_2), 3.50–3.83 (m, 4H, $2NCH_2$), 9.03 (s, $1H_{aromatic}$, $H_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, Chloroform-*d*): δ = 13.4, 22.9, 25.7, 33.5, 50.8, 107.0, 137.3, 151.4, 162.9, 168.2, 168.4 ppm; IR (KBr): ν 3043, 2964, 2928, 2870, 1629, 1571, 1456, 1376, 1323, 1228 cm^{-1}. MS (EI, 70 eV) *m/z* = 367. *Anal.* Calcd. for $C_{13}H_{16}N_6SSe$ (%): C, 42.51; H, 4.39; N, 22.88; S, 8.73. Found: C, 42.48; H, 4.36; N, 22.86; S, 8.72.

8-(Butylthio)-2-(pyrrolidin-1-yl)-[1,3]selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7d)

(The alkyl halide is *n*-C_4H_9Br). Pale brown powder; yield: (278 mg, 73%); mp 163–164 ºC [EtOH]; ^{1}H NMR (300 MHz, Chloroform-*d*): δ = 0.90 (t, *J* = 7.4 Hz, 3H, CH_3), 1.45 (m, *J* = 7.4 Hz, 2H, CH_2), 1.73 (m, *J* = 7.4 Hz, 2H, CH_2), 2.03–2.13 (m, 4H, $2CH_2$), 3.19 (t, *J* = 7.4 Hz, 2H, SCH_2), 3.45–3.75 (m, 4H, $2NCH_2$), 8.96 (s, $1H_{aromatic}$, $H_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, Chloroform-*d*): δ = 13.6, 21.9, 25.6, 31.3, 31.6, 50.8, 107.1, 137.3, 151.5, 163.0, 168.3, 168.6 ppm; IR (KBr): ν 3051, 2951, 2925, 2867, 1628, 1568, 1456, 1405, 1376, 1326, 1259, 1241 cm^{-1}. MS (EI, 70 eV) *m/z* = 381. *Anal.* Calcd. for $C_{14}H_{18}N_6SSe$ (%): C, 44.09; H, 4.76; N, 22.04; S, 8.41. Found: C, 44.07; H, 4.74; N, 22.03; S, 8.39.

8-(Benzylthio)-2-(pyrrolidin-1-yl)-[1,3]selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7e)

(The alkyl halide is $PhCH_2Br$). Brown powder; yield: (320 mg, 77%); mp 175–176 ºC [EtOH]; ^{1}H NMR (300 MHz, Chloroform-*d*): δ = 2.04–2.12 (m, 4H, $2CH_2$), 3.34–3.77 (m, 4H, $2NCH_2$), 4.44 (s, 2H, $2SCH_2Ph$), 7.21–7.43 (m, $5H_{aromatic}$, H_{Phenyl}), 8.97 (s, $1H_{aromatic}$, $H_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, Chloroform-*d*): δ = 25.7, 35.9, 50.9, 107.1, 127.5, 128.6, 129.1, 136.9, 137.4, 151.5, 163.0, 167.9, 168.3 ppm; IR (KBr): ν 3038, 2969, 2920, 2869, 1627, 1569, 1453, 1407, 1378, 1326, 1229 cm^{-1}. MS (EI, 70 eV) *m/z* = 415. *Anal.* Calcd. for $C_{17}H_{16}N_6SSe$ (%): C, 49.16; H, 3.88; N, 20.23; S, 7.72. Found: C, 49.14; H, 3.87; N, 20.21; S, 7.70.

Ethyl 2-((2-(pyrrolidin-1-yl)-[1,3]selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-8-yl)thio)acetate (7f)

(The alkyl halide is $C_2H_5CO_2CH_2Cl$). Pale brown powder; yield: (345 mg, 84%); mp 211–212 ºC [EtOH]; ^{1}H NMR (300 MHz, Chloroform-*d*): δ = 1.31 (t, *J* = 7.1 Hz, 3H, CH_3), 2.10–2.22 (m, 4H, $2CH_2$), 3.50–380 (m, 4H, $2NCH_2$), 4.07 (s, 2H, $SCH_2C=O$), 4.26 (q, *J* = 7.1 Hz, 2H, OCH_2), 9.03 (s, $1H_{aromatic}$, $H_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, Chloroform-*d*): δ = 14.2, 25.7, 33.7, 51.0, 61.9, 107.1, 137.4, 151.6, 163.0, 166.8, 168.3, 168.7 ppm; IR (KBr): ν 3043, 2965, 2917, 2867, 1716 (C = O), 1629, 1569, 1451, 1409, 1385, 1329, 1297, 1260, 1173 cm^{-1}. MS (EI, 70 eV) *m/z* = 411. *Anal.* Calcd. for $C_{14}H_{16}N_6O_2SSe$ (%): C, 40.88; H, 3.92; N, 20.43; S, 7.79. Found: C, 40.86; H, 3.90; N, 20.41; S, 7.77.

Synthesis of 8-alkyl-2-(pyrrolidin-1-yl)-[1,3]selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (8a-c); general procedure

To a solution of (**5**) (1 mmol, 283 mg) in acetic acid (3 mL), the appropriate triethylorthoester (1 mmol) was added. The reaction mixture was heated under reflux for 3 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.

2-(Pyrrolidin-1-yl)-[1,3]selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (8a)

(The triethylorthoester is $HC(OEt)_3$). Cream powder; yield: (223 mg, 76%); mp 256–257 ºC [EtOH]; ^{1}H NMR (300 MHz, Chloroform-*d*): δ = 2.14–2.24 (m, 4H, $2CH_2$), 3.59–3.79 (m, 4H, $2NCH_2$), 8.32 (s, $1H_{aromatic}$, $H_{triazole}$), 9.23 (s, $1H_{aromatic}$, $H_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, Chloroform-*d*): δ = 25.9, 50.9, 108.6, 138.5, 150.7, 155.6, 162.8, 168.3 ppm; IR (KBr): ν 3050, 2978, 2948, 2874, 1628, 1570, 1453, 1399, 1313, 1243 cm^{-1}. MS (*m/z*) 293. *Anal.* Calcd. for $C_{10}H_{10}N_6Se$ (%): C, 40.97; H, 3.44; N, 28.66. Found: C, 40.95; H, 3.41; N, 28.64.

8-Methyl-2-(pyrrolidin-1-yl)-[1,3]selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (8b)

(The triethylorthoester is $MeC(OEt)_3$). Green solid; yield: (175 mg, 57%); mp 238–239 ºC [EtOH]; ^{1}H NMR (300 MHz, Chloroform-*d*): δ = 2.09–2.16 (m, 4H, $2CH_2$), 2.57 (s, 3H, CH_3), 3.50–3.75 (m, 4H, $2NCH_2$), 9.07 (s, $1H_{aromatic}$, $H_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, Chloroform-*d*): δ = 14.5, 25.6, 50.8, 107.7, 137.9, 151.2, 162.7, 165.9, 168.1 ppm; IR (KBr): ν 3051, 2973, 2928, 2871, 1630, 1577, 1398, 1257 cm^{-1}. MS (EI, 70 eV) *m/z* = 307. *Anal.* Calcd. for $C_{11}H_{12}N_6Se$ (%): C, 43.01; H, 3.94; N, 27.36. Found: C, 42.99; H, 3.92; N, 27.34.

8-Ethyl-2-(pyrrolidin-1-yl)-[1,3]selenazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (8c)

(The triethylorthoester is $EtC(OEt)_3$). Brown powder;; yield: (212 mg, 66%); mp 223–224 ºC [EtOH]; ^{1}H NMR (300 MHz, Chloroform-*d*): δ = 1.34 (t, *J* = 7.6 Hz, 3H, CH_3), 2.02–2.09 (m, 4H, $2CH_2$), 2.84 (q, *J* = 7.6 Hz, 2H, CH_2), 3.40–3.66 (m, 4H, $2NCH_2$), 9.02 (s, $1H_{aromatic}$, $H_{Pyrimidine}$) ppm; ^{13}C NMR (75 MHz, Chloroform-*d*): δ = 11.3, 21.3, 24.6, 49.8, 106.7, 137.0, 150.1, 161.6, 167.0, 169.6 ppm; IR (KBr): ν 3047, 2973, 2936, 2855, 1629, 1576, 1497, 1391, 1362, 1259, 1240 cm^{-1}. MS (EI, 70 eV) *m/z* = 321. *Anal.* Calcd. for $C_{12}H_{14}N$ Se (%): C, 44.87; H, 4.39; N, 26.16. Found: C, 44.86; H, 4.38; N, 26.13.

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Compliance with ethical standards

Conflicts of interest The authors declares that they have no conflicts of interest.

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