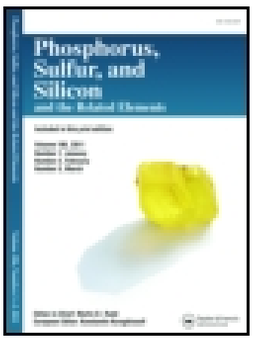

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Synthesis of 8-alkylthio- and 8-selanyl-3-*tert*-butylpyrazolo[5,1-*c*][1,2,4]triazines

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ABSTRACT

Interaction of 8-lithio-3-*tert*-butyl-4-oxopyrazolo[5,1-*c*][1,2,4]triazin-1-ide with elemental sulfur or selenium in THF with further *in situ* alkylation at –97 °C followed by warming to room temperature furnished a series of 3-*tert*-butyl-8-X-pyrazolo[5,1-*c*][1,2,4]triazin-4(6*H*)-ones (X = *n*-BuS, *n*-BuSe, MeSe, $PhCH_2S$) in good yields. 8,8′-Diselanediylbis(3-*tert*-butylpyrazolo[5,1-*c*][1,2,4]triazin-4(1*H*)-one) was also isolated as a by-product in these reactions. *One-pot* interaction of the *n*-BuSe substituted derivative with diborane/boron trifluoride led to reduction of the 1,2,4-triazine core and partial elimination of the alkylselanyl moiety. The structures of the synthesized products were established on the basis of IR, ^{1}H, 13C, 2D HMBC ^{1}H–^{77}Se NMR and high resolution mass spectra, as well as X-ray single crystal diffraction analyses. Two of the prepared compounds were also tested for antimicrobial and antifungal activities.

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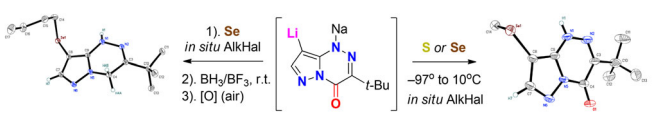
Pyrazolo[5,1-c][1; 2; 4]triazine; hetaryllithium; sulfide; selenide; X-ray diffraction

GRAPHICAL ABSTRACT



1. Introduction

1,2,4-Triazine derivatives bearing sulfur-containing substituents exhibit a broad range of biological activities,[1–3] and have found widespread use as herbicides and pharmaceuticals.[4,5] The fused thioxo- or alkylthio-substituted azolo[5,1-*c*][1,2,4]triazines are of particular research interest.[6,7] An illustrative example of such a biologically active compound is 7-methylthio-3-nitro-1,2,4-triazolo[5,1-*c*][1,2,4]triazin-4(1*H*)-one.[8]

The interaction of C(4)-metalated pyrazoles with $PhSO_2SPh$ in THF at –78 °C was described in the literature[9] as a method for introducing the phenylthio group. Selanyl-substituted pyrazoles could also be prepared using reactions of 3,5-dialkylpyrazoles with SeO_2 in pyridine.[10] However, despite their high pharmacological potency, the direct functionalization of the azolo[1,2,4]triazine heterocyclic scaffold with chalcogens has not been reported to date. In continuation of our studies on the reactivity of lithiated pyrazolo[5,1-*c*][1,2,4]triazine derivatives,[11–15] we discuss herein the reactions of 8-lithio-3-*tert*-butyl-4-oxopyrazolo[5,1-c][1,2,4]triazin-1-ide with elemental sulfur and selenium, as well as the structure and certain biological properties of the isolated products.

2. Results and discussion

8-Bromo-3-*tert*-butylpyrazolo[5,1-*c*][1,2,4]triazin-4(6*H*)-one **1** was synthesized by the halo-decarboxylation of 3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylic acid.[11] Alkyllithium compounds have been extensively used as lithium donors in metal-halogen exchange reactions with various halogenated heterocycles,[16,17] and are also well known as strong bases.[18] In order to prevent the undesirable deprotonation during the targeted lithium-bromine exchange reaction, the acidic NH hydrogen in compound **1** was completely removed using NaH in THF (Scheme 1). The resulting sodium 8-bromo-3-*tert*-butyl-4-oxo-4*H*-pyrazolo[5,1-*c*][1,2,4]triazin-1-ide **2** possessed good solubility in THF below –80 °C, and its interaction with 1.0–1.5 mol. eq. of *n*-butyllithium was fast and complete (1–3 min) at –97 °C.[11]

An attempted reaction of the formed 8-lithio-3-*tert*-butyl-4-oxopyrazolo[5,1-c][1,2,4]triazin-1-ide **3** with O_2 under various conditions[15] was unsuccessful and led to resinification. However, interaction of **3** with 1.5 mol. eq. of elemental sulfur at –97 followed by warming to 10 °C yielded a compound, which was identified as 3-*tert*-butyl-8-butylthiopyrazolo[5,1-*c*][1,2,4]triazin-4(6*H*)-one **5a** (Scheme 1). Presumably, the latter was formed by *in situ* alkylation of the intermediate 3-*tert*-

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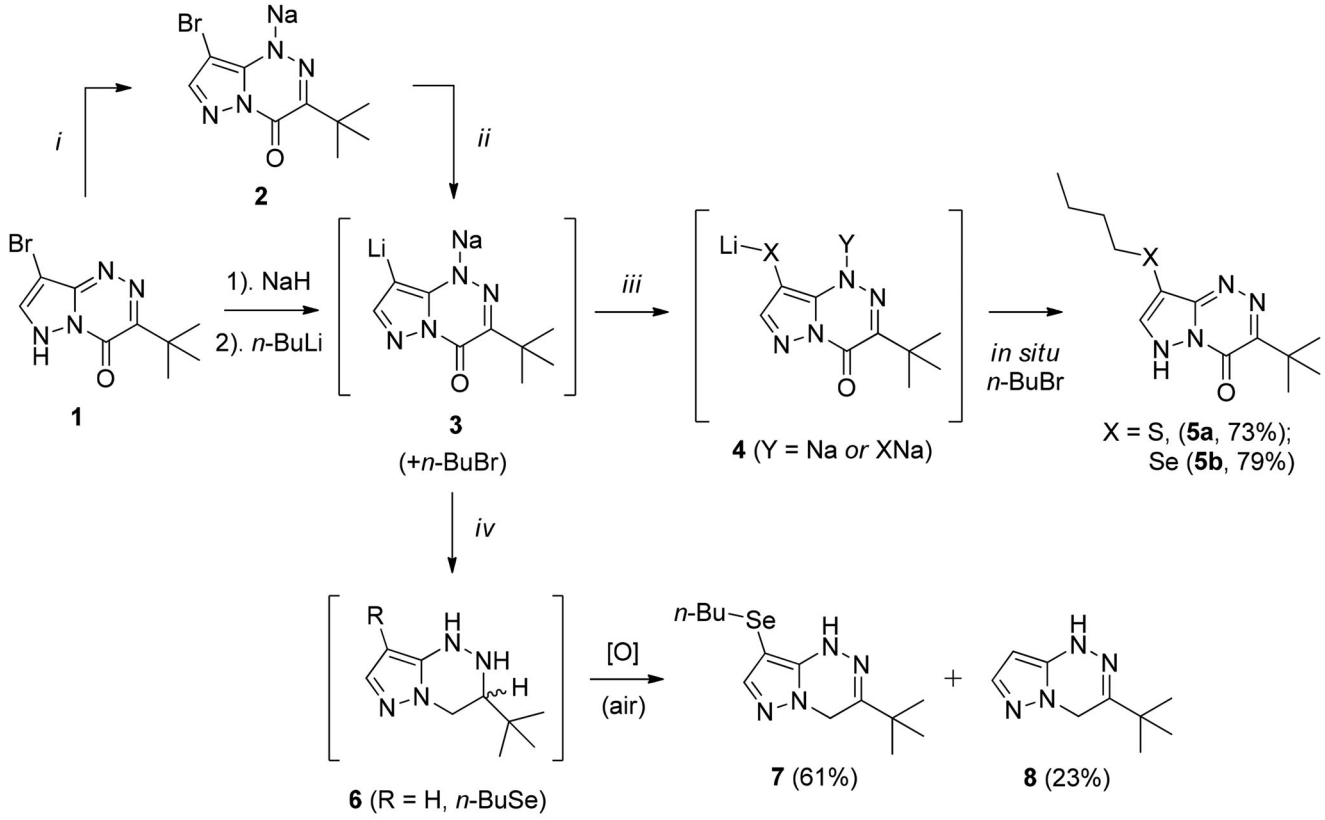


Scheme 1. The reactions of sodium 8-bromo-3-*tert*-butyl-4-oxo-4*H*-pyrazolo[5,1-*c*][1,2,4]triazin-1-ide 2 with *n*-BuLi and elemental S or Se.

butyl-4-oxo-8-sulfido-4*H*-pyrazolo[5,1-*c*][1,2,4]triazin-1-ide **4** (X = S) with *n*-butyl bromide, which had been generated from *n*-butyl lithium and **1** at the Li/Br exchange reaction step. Application of elemental Se under analogous conditions led to the formation of the expected 3-*tert*-butyl-8-butylselanylpyrazolo[5,1-*c*][1,2,4]triazin-4(6*H*)-one **5b** in a good yield (Scheme 1). The molecular structure of butylthio derivative **5a** was unambiguously established by X-ray single crystal diffraction analysis (Figure 1).

In the ^{1}H NMR spectra of compounds **5a,b**, the new *n*-Bu groups showed characteristic multiplets in the aliphatic region. For example, the X-C$\underline{H}_2$CH$_2$ fragment showed triplets at 2.62 (**5a**, $^{3}J_{H,H} = 7.3$ Hz) or 2.66 ppm (**5b**, $^{3}J_{H,H} = 7.5$, $^{2}J_{Se,H} = 14.4$ Hz), and the signals of the corresponding carbon atoms (X–$\underline{C}$H$_2$) in the ^{13}C NMR spectrum were located at 36.9 for X = S, or 32.7 ppm (with the observed $^{1}J_{Se,C} = 58.9$ Hz) for X = Se. The ^{1}H–^{77}Se HMBC spectrum of **5b** possessed a single peak at 72.49 ppm (Figure 2). HRMS data were also in agreement with the assigned structures: *m/z* 281.1428 ([M + H]$^+$, $I_{rel} = 80\%$); 303.1247 ([M + Na]$^+$, $I_{rel} = 100\%$) for **5a**, and *m/z* 329.0872 ([M + H]$^+$) for **5b**, with the characteristic isotopic distribution.

One-pot reduction of the sodium salt of compound **5b** using an excess of BF_3•Et_2O and $LiBH_4$[21] was slow and completed only after two weeks at r.t. Thus, *ca.* 3: 1 3-*tert*-butyl-8-butylselanyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine **7** and 7,8-unsubstituted compound **8** were isolated in 84% overall yield, after work-up using aqueous KOH and a subsequent *in situ* oxidation of the intermediate 1,2,3,4-tetrahydropyrazolotriazines **6** (monitored by the TLC) in air at 60 °C (Scheme 1). The significant reductive elimination of the C(8)-butylselanyl group may be the result of the harsh reduction conditions used together with the strong Lewis acidity of boron trifluoride. The IR spectra of these products did not contain any characteristic C = O bands, while the ^{1}H NMR spectra possessed the singlets of C(4)H$_2$ at 4.75 ppm (**7**) or 4.70 ppm (**8**), and the corresponding carbons in the ^{13}C APT spectra were located at 43.0 or 42.6 ppm, respectively. The assigned structures were also substantiated by HRMS, as well as a single crystal diffraction analysis of compound **7** (Figure 3).

The application of CH_3Li in place of *n*-BuLi in a THF/Et_2O mixture for the generation of C(8)-lithiated compound **3**, and further addition of elemental Se led to formation of a complex mixture of products. The main product of the reaction was 3-*tert*-butyl-8-methylpyrazolo[5,1-*c*][1,2,4]triazin-4(6*H*)-one[11,21] **9** (Scheme 2). Presumably, compound **9** was formed by rapid C(8)-alkylation of the lithiated derivative **3** with MeBr, which

could be attributed to the higher reactivity of MeBr when compared to *n*-BuBr. The expected 8-methylselanyl substituted product **10** was formed in 31% yield, and a small amount of 8,8'-diselanediylbis(3-*tert*-butylpyrazolo[5,1-*c*][1,2,4]triazin-4(1*H*)-one) **11** was also isolated, presumably, as a result of spontaneous oxidation (Scheme 2).

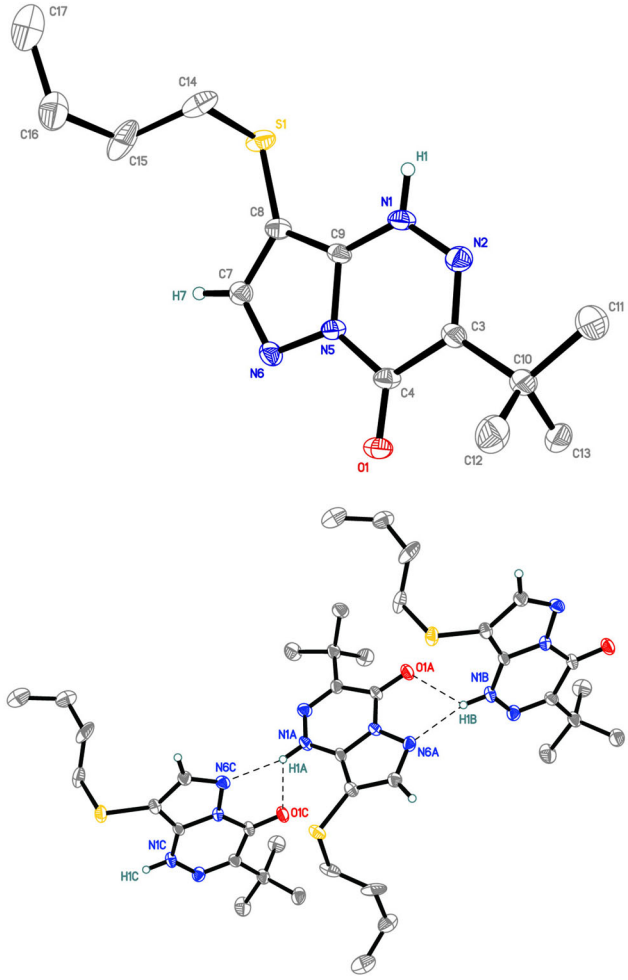


Figure 1. The molecular structure of compound **5a** and hydrogen bonding. Hydrogen atoms of Bu groups are omitted. The disorder of *n*-Bu group is not shown. Thermal ellipsoids are set to 50% probability level.[19]

The best yields of 3-*tert*-butyl-8-methylselanylpyrazolo[5,1-*c*][1,2,4]triazin-4(6*H*)-one **10** were achieved when *tert*-butyl lithium was employed at the Li/Br exchange step, with subsequent addition of Se at −97 °C → −50 °C and finally MeI at −50 °C → r.t. for 1 h. Analogously, 8-benzylthio-3-*tert*-butylpyrazolo[5,1-*c*][1,2,4]triazin-4(1*H*)-one **12** was synthesized using *t*-BuLi, elemental sulfur and benzyl chloride (Scheme 2). Apparently, the *tert*-butyl bromide formed as a by-product possessed low reactivity compared to CH_3Br, and could not participate in the competing alkylation reaction (to give the product **13**).[22]

The structures of novel compounds **10**-**12** were established by IR, heteronuclear NMR and HRMS spectral data, as well as the X-ray single crystal diffraction analysis (for **10**, Figure 4). In the ^{1}H NMR spectrum of product **10**, the two peaks in the aliphatic region at 2.16 ppm ($C\underline{H}_3Se$, $^2J_{Se,H} = 11.8$ Hz) and 1.46 ppm (*t*-Bu) were observed, while the singlets of C(7)–H and NH were located at 7.98 and 10.55 ppm, respectively. The ^{1}H–^{77}Se 2D HMBC NMR experiment (Figure 5) for diselenide **11** showed distinct cross-peaks for the NH and C(7)–H protons, while the single signal of the two seleniums was located at 365.88 ppm. The HRMS data contained peaks with the characteristic isotopic distributions, in excellent agreement with the calculated (Figure 6).

In the crystal structure of compound **7**, two sets of atoms C4, N5, N6, C7, C8, C9, N1, Se1 and N1, N2, C3, C4, C10 lie in two different planes, which have the folding angle of 22.67(4)°, whereas all atoms in **10** except for Me groups are located in one plane. This fact and the bond length redistribution within the heterocyclic systems (Table 1) confirm that in the case of **7** the conjugation of the N2 and C3 atoms with the π-electron system of the N5.C9 ring is nearly lost due to the presence of the methylene group (C4), but the conjugated π-system in **10** includes all nine atoms (N1.C9, O1). Meanwhile, the Se atom is involved, to some extent, in conjugation with the π-system of a heterocycle in both structures. The both molecules form infinite chains *via* intermolecular H-bonding (N1-H1···N6 in case of **7** and **10** and N1-H1···O1 in case of **10**, see the Supplemental

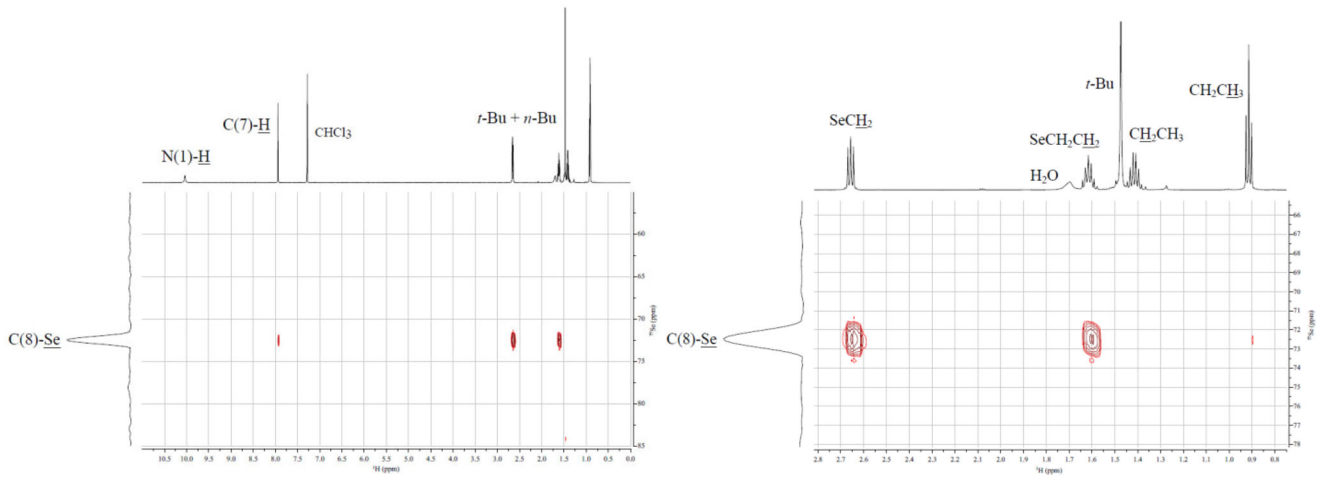


Figure 2. 2D HMBC ^{1}H–^{77}Se NMR (600 MHz, $CDCl_3$) spectrum of compound **5b**.

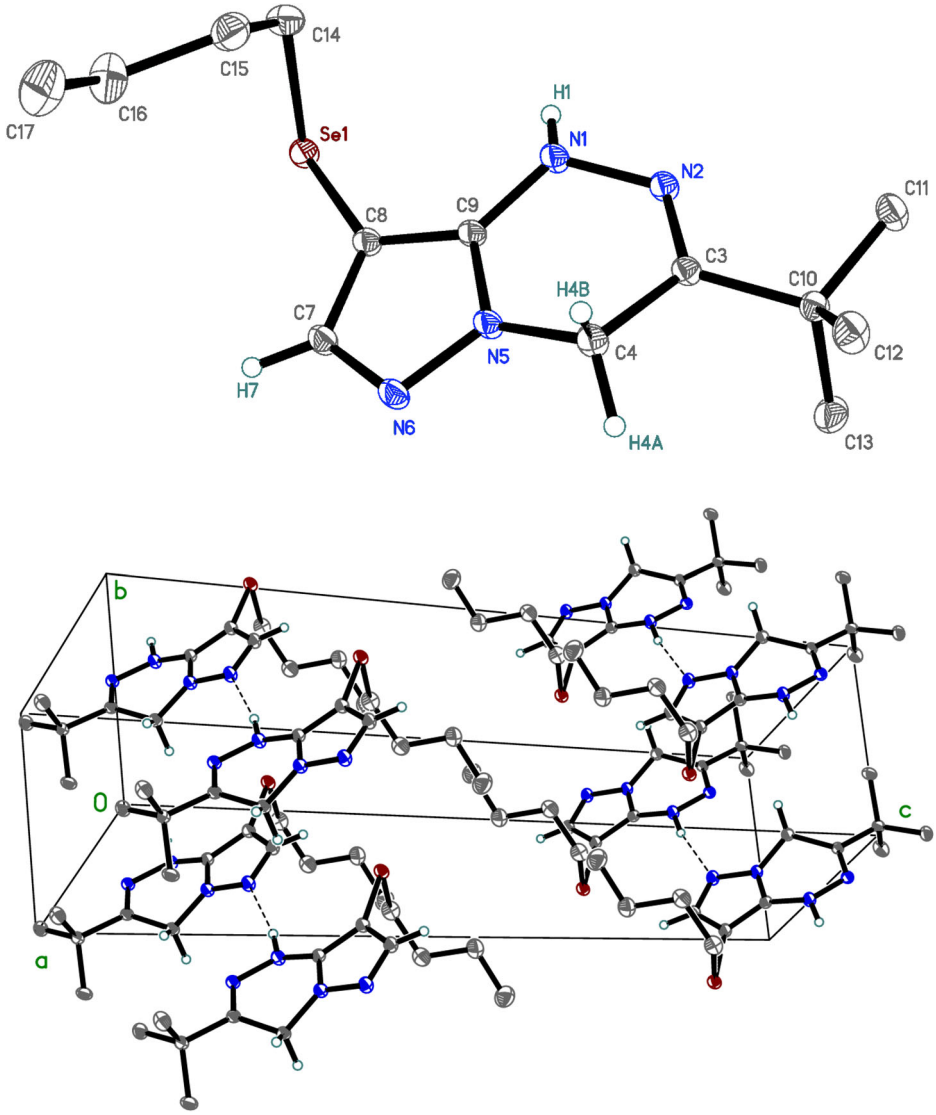


Figure 3. The molecular structure of compound **7** and hydrogen bonding. Hydrogen atoms of *t*-Bu and *n*-Bu groups are omitted. Thermal ellipsoids are set to 50% probability level.[20]

Materials for details on H-bonding and for packing plots, Figures S49–S57, Supplementary material).

3. Biological evaluation

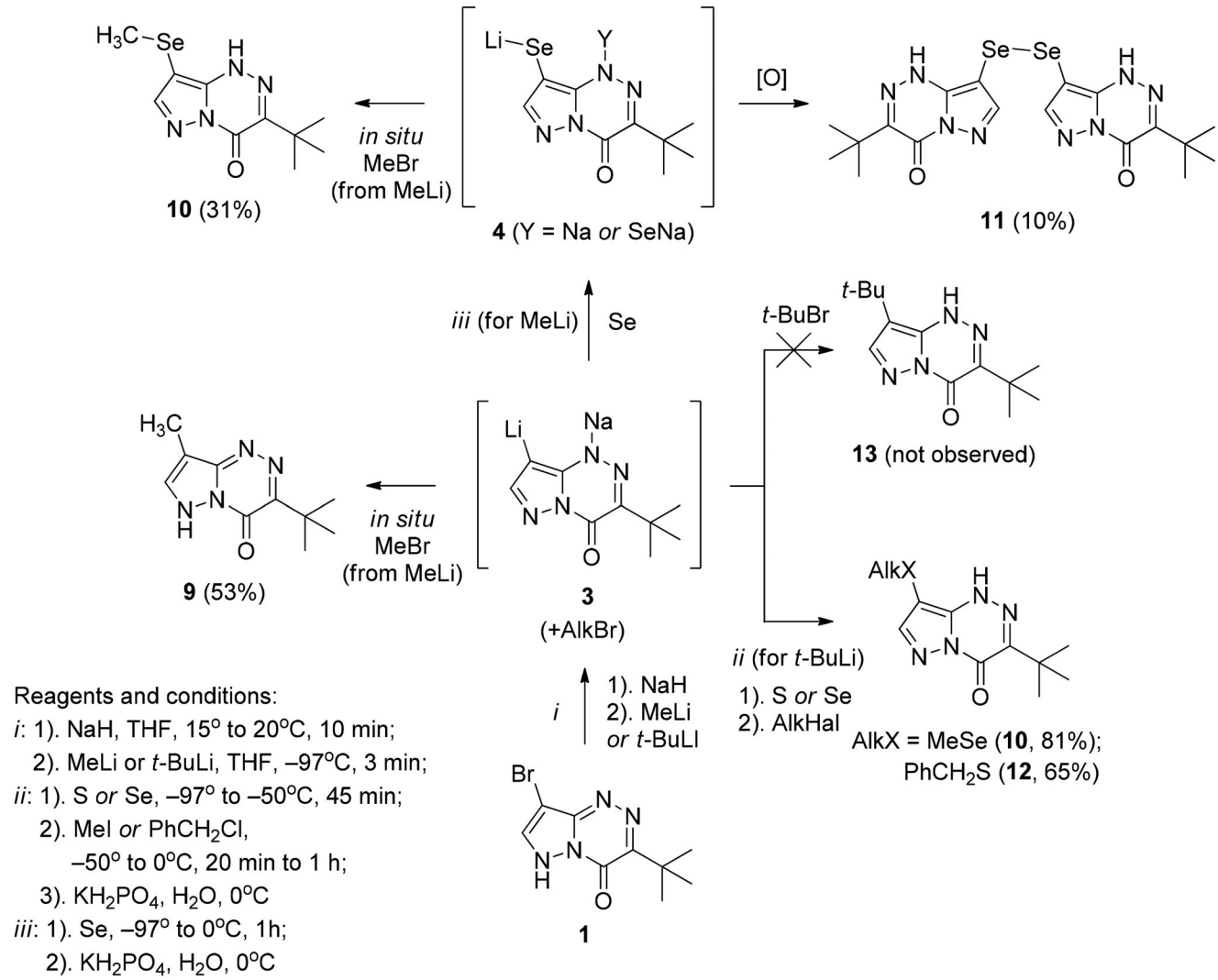
Compounds **5a** and **5b** showed poor antibacterial and antifungal activities on five bacterial and two fungal strains (Table 2). The most active sulfide **5a** exhibited 22.4% growth inhibition of *A. baumannii* at 32 $\mu g^{*}mL^{-1}$ concentration, while the analogous selenide was practically inactive toward all pathogens except for *K. pneumonia* and *P. aeruginosa* (*ca.* 18% inhibition in both cases).

4. Experimental

4.1. Materials and measurements

Melting points were determined on a STUART Melting point SMP30 apparatus (Stuart Bibby Scientific, Staffordshire, UK). IR spectra were recorded in KBr pellets using Agilent Cary 660 FTIR infrared spectrophotometer (Agilent Technologies, Inc., Santa Clara, CA). NMR spectra were recorded on a Bruker AM-300, DRX-500 or AV-600 (Bruker Corporation, Billerica, MA) operating at working frequencies of 300 or 600 MHz (^{1}H), 75 or 126 MHz (^{13}C), 114 MHz (^{77}Se). Chemical shifts were related to that of the DMSO-d_5 or $CHCl_3$ (^{1}H), DMSO-d_6 or $CDCl_3$ (^{13}C), Me_2Se (^{77}Se). High resolution mass spectra were recorded on a Bruker MicroTOF II spectrometer (Bruker Corporation) using electrospray ionization (ESI). Elemental analysis was performed on a PerkinElmer Series II 2400 Elemental Analyzer (PerkinElmer Inc., Russian Federation).

Crystal data, data collection and structure refinement details for **5a**, **7** and **10** are given in the Supplemental Materials. X-ray diffraction data were collected at 100 K on a Bruker Quest D8 diffractometer equipped with a Photon-III area-detector (graphite monochromator), using Mo K_α-radiation (0.71073 Å). The intensity data were integrated by the SAINT program[24] and were corrected for absorption and decay using SADABS[25] for **7** and **10** or TWINABS[24] for



Scheme 2. The reactions of sodium 8-bromo-3-*tert*-butyl-4-oxo-4*H*-pyrazolo[5,1-*c*][1,2,4]triazin-1-ide 2 with MeLi or *t*-BuLi and elemental S or Se.

5a. The structures were solved by direct methods using SHELXS,[26,27] and were refined on F^2 using SHELXL-2018.[26,28] The studied crystals of **5a** consisted of three major domains found by Cell_now program.[24] The merged intensity data for only one domain were used to refine **5a**. All non-hydrogen atoms were refined with anisotropic displacement parameters. The position of the H1 atom and its isotropic displacement parameter were refined in all structures. The other hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. The SHELXTL program suite[24] was used for molecular graphics.

The inner temperature of the reaction mixtures was monitored using Pt100 RTD and a Dwyer Series 32B 1/32 DIN Temperature/Process Controller (precision ±0.1 K). Flash chromatography was performed using Merck Silica gel for chromatography (60–200 μm). All operations, except for chromatography, were carried out under an atmosphere of dry argon (grade "5.0" 99.9990%), which was additionally passed through P_4O_{10} and a K/Na eutectic alloy prior to use. The syntheses were performed in a round-bottom flasks fitted with a magnetic stir bar, inert gas balloon and a rubber septum. Tetrahydrofuran and diethyl ether were boiled with potassium/sodium alloy and distilled in argon atmosphere from K/Na immediately prior to use. Commercial *n*-BuLi (2.5 M in hexane, Acros Organics) and *t*-BuLi (1.7 M in pentane, Sigma-Aldrich) solutions were used. Starting compound **1** was synthesized as described previously.[11] The Supplemental Materials contains sample ^{1}H and ^{13}C NMR and IR spectra and high resolution mass spetrometry of products **5**–**12** (Figures S1–S48, Supplementary material).

4.2. Preparation of CH_3Li (0.25 M solution in Et_2O)

MeLi was prepared from *n*-BuLi and MeI using the modified literature procedure.[29] A solution of MeI (9.5 mL, 153 mmol) in *n*-hexane (15 mL) was added dropwise over 10 min to a stirred mixture of *n*-BuLi (2.5 M in hexanes, 60.0 mL, 150 mmol) and *n*-hexane (150 mL) cooled to –40° ÷ –30°C (CH_2Cl_2/liq. N_2 cooling bath). Next, the cooling bath was removed, and the resulting mixture was stirred at –40°C → r.t. over 1 h. The precipitate formed was filtered, washed with *n*-hexane (3 × 100 mL) and dried in an argon

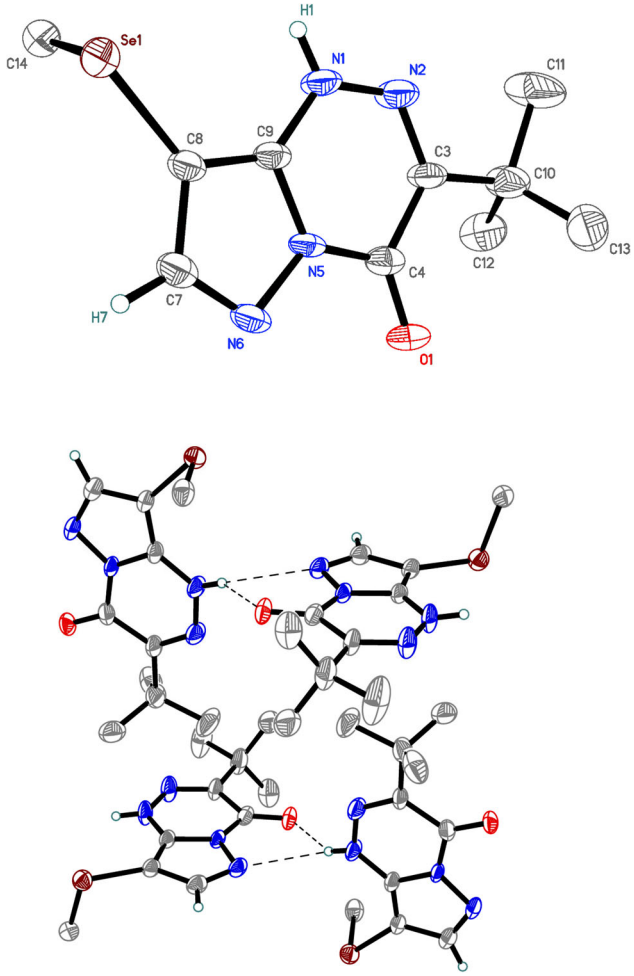


Figure 4. The molecular structure of compound **10** and hydrogen bonding. Hydrogen atoms of Me groups are omitted. Thermal ellipsoids are set to 50% probability level.[23]

flow at 25 °C. The residue was dissolved in Et_2O (0.5 L) and filtered through a glass fiber under a slight argon pressure to give a solution of MeLi, $C \sim 0.25$ M (^{1}H NMR), yield 83%. ^{1}H NMR (600 MHz, Et_2O), δ, ppm (J, Hz): 4.10 (4H, q, $3J_{H,H} = 6.9$, OCH_2CH_3); 1.83 (6H, t, $3J_{H,H} = 6.9$, OCH_2CH_3); –1.17 (~0.075 H, s, CH_3Li). 13C NMR (151 MHz, Et_2O), δ, ppm: 65.42 (OCH_2CH_3); 14.76 (OCH_2CH_3); –13.89 (CH_3Li).

4.3. Preparation of a THF solution of compound 3. General step for the synthesis of compounds 5a,b, 7–12

NaH (60% dispersion in mineral oil, 70 mg, 1.75 mmol) was added in one portion to a stirred solution of compound **1** (0.20 g, 0.74 mmol) in THF (30 mL) at 15°–20°C. Gas evolution was observed. The resulting bright yellow mixture was stirred for 10 min and cooled to –97°C (CH_2Cl_2/liq. N_2 cooling bath). Next, a pre-cooled (–25°C) solution of *n*-BuLi (2.5 M in hexanes, 0.40 mL, 1.00 mmol, for the synthesis of **5a,b**, **7**, **8**), MeLi (0.25 M in Et_2O, 4.0 mL, 1.00 mmol, for the synthesis of **9–11**) or *t*-BuLi (1.7 M in pentane, 0.9 mL, 1.53 mmol, for the synthesis of **10** and **12**) was added dropwise with vigorous stirring over 1 min. During this procedure, the reaction mixture became deep red and after several seconds turned yellow. The resulting solution of **3** was

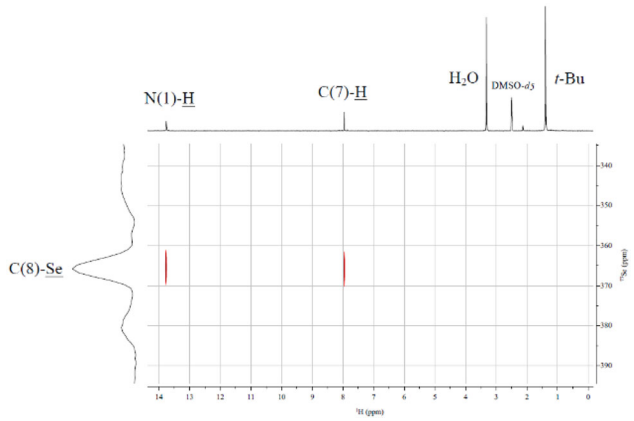


Figure 5. 2D HMBC ^{1}H–^{77}Se NMR (600 MHz, DMSO-d_6) spectrum of compound **11**.

further stirred for 2 min at –97°C and used immediately in the next reaction step.

4.4. Preparation of compounds 5a,b; general step for the synthesis of compounds 7, 8

To the prepared solution of compound **3** (0.74 mmol, *n*-BuLi was used in the previous step), freshly powdered elemental S (35 mg, 1.09 mmol) or Se (85 mg, 1.08 mmol) were added in one portion. The resulting mixtures were stirred vigorously at –97°C for 30 min, then the cooling bath was removed and the temperature was slowly raised to 10 °C in a period of 40 min. Thus prepared solution of the sodium salt of compound **5b** was used immediately in the next step (for the preparation of compounds **7, 8**), or crystalline KH_2PO_4 (1 g, 7.35 mmol, for the isolation of compounds **5a,b**) was added in one portion. Next, pre-cooled (0 °C) water (3 mL) was added dropwise with stirring over 2 min. Finally, EtOAc (30 mL) and water (20 mL) were added. The resulting mixtures were stirred vigorously at 0°–5 °C for 5 min. The organic phases were separated, and the mother liquor was further extracted with EtOAc (3 × 25 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue, which was purified by flash chromatography (eluent CH_2Cl_2:hexane 1:5–2:1) to give compound **5a**, white powder (0.15 g, 0.53 mmol, 73%), or **5b**, white powder (0.19 g, 0.58 mmol, 79%).

4.4.1. 3-tert-Butyl-8-(butylthio)pyrazolo[5,1-c][1, 2, 4]triazin-4(6H)-one 5a

M.p. 173–174 °C. IR (KBr) ν_{max}, cm^{-1}: 3221 (NH), 3136, 3030, 2956, 2929, 2871, 2828 (CH), 1700, 1686 (C = O), 1601, 1523, 1464, 1392, 1372, 1362, 1341, 1281, 1224, 1198, 1163, 1149, 1137, 1069, 1023, 998, 939, 924, 884, 842, 772, 724, 690, 635, 623, 530, 510, 440. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 0.91 (3H, t, $^3J_{H,H} = 7.2$, S–$CH_2CH_2CH_2CH_3$); 1.33–1.61 (4H, m, S–$CH_2CH_2CH_2CH_3$); 1.47 (9H, s, $C(CH_3)_3$); 2.62 (2H, t, $^3J_{H,H} = 7.3$, S–$CH_2CH_2CH_2CH_3$); 7.94 (1H, s, C(7)–H); 10.45 (1H, s, NH). ^{13}C NMR (APT, 75 MHz, $CDCl_3$), δ, ppm: 13.67

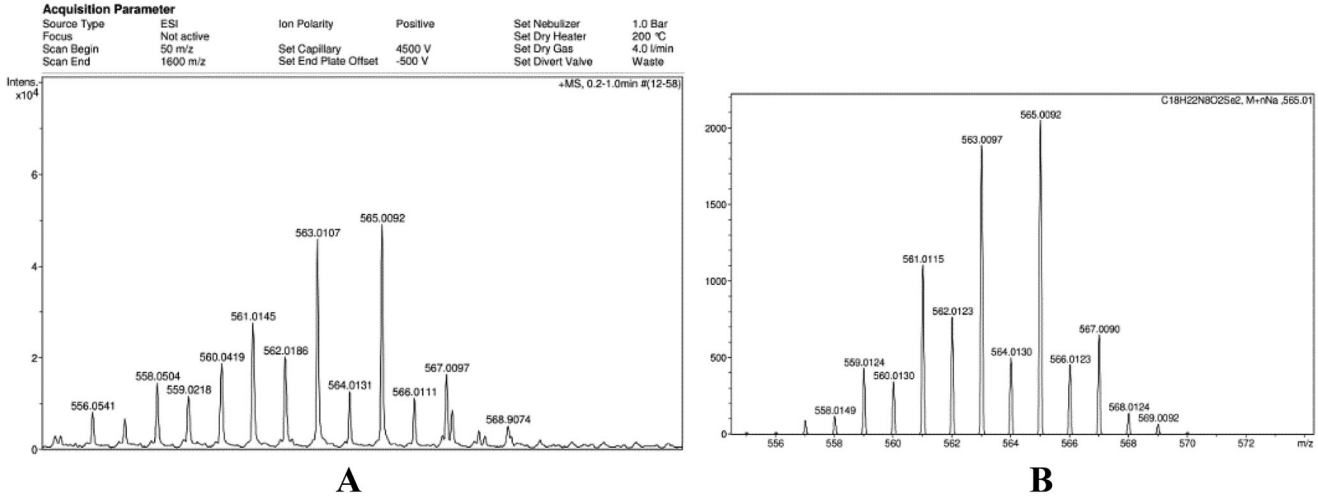


Figure 6. (A) Experimental and (B) Calculated HRMS for compound **11**.

Table 1. Selected bond lengths (Å) in **7** and **10**.

	7	10		7	10
N1–N2	1.3831 (11)	1.340 (4)	C8–C9	1.3958 (12)	1.370 (4)
N2–C3	1.2824 (11)	1.305 (4)	N1–C9	1.3667 (12)	1.340 (4)
C3–C4	1.5191 (12)	1.471 (4)	N5–C9	1.3426 (11)	1.367 (4)
C4–N5	1.4418 (12)	1.393 (4)	C4–O1	–	1.213 (4)
N5–N6	1.3698 (11)	1.369 (3)	Se1–C8	1.8751 (9)	1.892 (3)
N6–C7	1.3318 (12)	1.332 (4)	Se1–C14	1.9732 (11)	1.941 (3)
C7–C8	1.4066 (13)	1.401 (4)			

(S–$CH_2CH_2CH_2\boldsymbol{C}H_3$); 21.71 (S–$CH_2CH_2\boldsymbol{C}H_2CH_3$); 28.07 (C($\boldsymbol{C}H_3)_3$); 32.15 (S–$CH_2\boldsymbol{C}H_2CH_2CH_3$); 36.86 (S–$\boldsymbol{C}H_2CH_2CH_2CH_3$); 37.45 ($\boldsymbol{C}(CH_3)_3$); 89.96 (C(8)); 143.94, 147.31, 148.34 (C(3), C(4), C(8a)); 149.75 ($\boldsymbol{C}$(7)–H). HRMS: Found, *m/z*: 281.1428 $[M+H]^+$. $C_{13}H_{20}N_4OS$. Calculated, *m/z*: 281.1431. Anal. Calcd for $C_{13}H_{20}N_4OS$: C, 55.69; H, 7.19; N, 19.98. Found: C, 55.63; H, 7.26; N, 19.90.

4.4.2. 3-tert-Butyl-8-(butylselanyl)pyrazolo[5,1-c][1, 2, 4]triazin-4(6H)-one 5b

M.p. 181–182 °C. IR (KBr) ν_{max}, cm^{-1}: 3217 (NH), 3135, 3072, 3023, 2976, 2954, 2930, 2870, 2824 (CH), 1697, 1685 (C = O), 1602, 1522, 1476, 1459, 1391, 1364, 1334, 1281, 1196, 1159, 1135, 1094, 1042, 1023, 984, 939, 923, 886, 840, 769, 715, 685, 633, 619, 571, 529, 510. ^{1}H NMR (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.91 (3H, t, $^3J_{H,H} = 7.4$, Se–$CH_2CH_2CH_2C\boldsymbol{H}_3$); 1.38–1.45 (2H, m, Se–$CH_2CH_2C\boldsymbol{H}_2CH_3$); 1.47 (9H, s, C($CH_3)_3$); 1.57–1.65 (2H, m, Se–$CH_2C\boldsymbol{H}_2CH_2CH_3$); 2.66 (2H, t, $^3J_{H,H} = 7.5$, $^2J_{Se,H} = 14.4$, Se–$C\boldsymbol{H}_2CH_2CH_2CH_3$); 7.94 (1H, s, C(7)–H); 10.04 (1H, s, NH). ^{13}C NMR (APT, 75 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 13.56 (Se–$CH_2CH_2CH_2\boldsymbol{C}H_3$); 22.75 (Se–$CH_2CH_2\boldsymbol{C}H_2CH_3$); 28.07 (C($\boldsymbol{C}H_3)_3$); 29.70 (Se–$\boldsymbol{C}H_2CH_2CH_2CH_3$, $^1J_{Se,C} = 58.9$); 32.73 (Se–$CH_2\boldsymbol{C}H_2CH_2CH_3$); 37.40 ($\boldsymbol{C}(CH_3)_3$); 80.70 (C(8), $^1J_{Se,C} = 135.0$); 144.54, 146.93, 148.39 (C(3), C(4), C(8a)); 150.37 ($\boldsymbol{C}$(7)–H). ^{77}Se NMR (^{1}H–^{77}Se HMBC, 600 MHz, $CDCl_3$), δ, ppm: 72.49 (C(8)–Se). HRMS: Found, *m/z*: 329.0872 $[M+H]^+$. $C_{13}H_{20}N_4OSe$. Calculated, *m/z*: 329.0875. Anal. Calcd for $C_{13}H_{20}N_4OSe$: C, 47.71; H, 6.16; N, 17.12. Found: C, 47.75; H, 6.22; N, 17.13.

4.5. One-pot synthesis of compounds 7, 8

To the prepared solution of sodium salt of compound **5b** (0.74 mmol), $BF_3{\bullet}Et_2O$ (7.0 mL, 56.7 mmol) was added in one portion at 0 °C. Next, $LiBH_4$ (1.0 g, 45.9 mmol) was added in small portions with stirring over 20 min. The resulting mixture was stirred at r.t. for 2 weeks (TLC monitoring). The reaction mixture was then added dropwise to a cooled (0 °C) solution of KOH (5 g, 89.1 mmol) in H_2O (100 mL) over 20 min with vigorous stirring. After the addition was complete, tetrabutylammonium bromide (10 mg, 0.031 mmol) and EtOAc (10 mL) were added, and the resulting mixture was stirred in air atmosphere at 60 °C for 1 h. Then, it was cooled and extracted with a EtOAc/hexane mixture (5:1, 7 × 30 mL). The combined organic phases were washed with water (2 × 100 mL), dried with anhydrous $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue, which was purified by flash chromatography (eluent EtOAc:hexane 1:20–2:1) to give compounds **7**, white powder (0.14 g, 0.45 mmol, 61%), and **8**, white powder (30 mg, 0.17 mmol, 23%).

4.5.1. 3-tert-Butyl-8-butylselanyl-1,4-dihydropyrazolo[5,1-c][1, 2, 4]triazine 7

M.p. 156–157 °C. IR (KBr) ν_{max}, cm^{-1}: 3259, 3204, 3153 (NH), 3110, 3074, 2959, 2920, 2869 (CH), 1562 (C = N), 1476, 1459, 1412, 1363, 1348, 1284, 1256, 1235, 1202, 1184, 1145, 1094, 1082, 1043, 998, 965, 936, 901, 868, 839, 785, 758, 735, 710, 676, 624, 609, 573, 507, 445. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.90 (3H, t, $^3J_{H,H} = 7.4$, Se–$CH_2CH_2CH_2C\boldsymbol{H}_3$); 1.23 (9H, s, C($CH_3)_3$); 1.32–1.47 (2H, m, Se–$CH_2CH_2C\boldsymbol{H}_2CH_3$); 1.53–1.66 (2H, m, Se–$CH_2C\boldsymbol{H}_2CH_2CH_3$); 2.55 (2H, t, $^3J_{H,H} = 7.4$, $^2J_{Se,H} = 14.0$, Se–$C\boldsymbol{H}_2CH_2CH_2CH_3$); 4.75 (2H, s, C(4)$H_2$); 7.45 (1H, s, C(7)–H); 7.83 (1H, s, NH). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 13.55 (Se–$CH_2CH_2CH_2\boldsymbol{C}H_3$); 22.71 (Se–$CH_2CH_2\boldsymbol{C}H_2CH_3$); 27.48 (C($\boldsymbol{C}H_3)_3$); 29.42 (Se–$\boldsymbol{C}H_2CH_2CH_2CH_3$, $^1J_{Se,C} = 60.0$); 32.60 (Se–$CH_2\boldsymbol{C}H_2CH_2CH_3$); 36.90 ($\boldsymbol{C}(CH_3)_3$); 43.02 (C(4)$H_2$); 79.62 (C(8), $^1J_{Se,C} = 122.3$); 140.42, 148.75 (C(3), C(8a)); 145.20 ($\boldsymbol{C}$(7)–H). HRMS: Found, *m/z*: 315.1077 $[M+H]^+$.

Table 2. The antibacterial and antifungal activities of compounds **5a** and **5b**.

	The inhibition of growth (%)*							
	Bacteria					Fungi		
Compound	*Staphylococcus aureus*	*Escherichia coli*	*Klebsiella pneumonia*	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*	*Candida albicans*	*Cryptococcus neoformans var. Grubii*	Concentration
5a	13.84	−1.71	5.48	10.72	22.39	2.09	−11.62	32 μg/mL
5b	−3.3	2.01	18.13	18.32	−3.36	5.55	1.75	32 μg/mL

*The growth rates for all bacteria and fungi has a variation of −/+ 10%, which is within the reported normal distribution of bacterial/fungal growth.

$C_{13}H_{22}N_4Se$. Calculated, *m/z*: 315.1083. Anal. Calcd for $C_{13}H_{22}N_4Se$: C, 49.84; H, 7.08; N, 17.88. Found: C, 49.82; H, 7.15; N, 17.75.

4.5.2. 3-tert-Butyl-1,4-dihydropyrazolo[5,1-c][1, 2, 4] triazine 8

M.p. 140–150 °C (sublimation). IR (KBr) ν_{max}, cm^{-1}: 3272, 3229, 3176, 3131 (NH), 3088, 3012, 2974, 2937, 2903, 2869 (CH), 1576, 1561 (C = N), 1479, 1467, 1420, 1393, 1364, 1353, 1281, 1259, 1231, 1211, 1164, 1099, 1065, 1050, 1017, 997, 970, 939, 897, 875, 860, 836, 785, 729, 694, 663, 626, 598, 567, 501, 480, 434. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.15 (9H, s, $C(CH_3)_3$); 4.70 (2H, s, $C(4)H_2$); 5.43 (1H, d, $^3J_{H,H} = 1.9$, C(8)–H), 7.29 (1H, d, $^3J_{H,H} = 1.9$, C(7)–H); 10.10 (1H, s, NH). ^{13}C NMR (APT, 126 MHz, DMSO-d_6), δ, ppm: 27.80 ($C(\mathbf{C}H_3)_3$); 36.84 ($\mathbf{C}(CH_3)_3$); 42.56 ($C(4)H_2$); 84.66 (C(8)–H); 138.46, 146.87 (C(3), C(8a)); 139.24 (C(7)–H). HRMS: Found, *m/z*: 179.1297 $[M + H]^+$. $C_9H_{14}N_4$. Calculated, *m/z*: 179.1291. Anal. Calcd for $C_9H_{14}N_4$: C, 60.65; H, 7.92; N, 31.43. Found: C, 60.53; H, 7.95; N, 31.49.

4.6. Synthesis of compounds 9–11 from the reaction with methyllithium

To the prepared solution of compound **3** (0.74 mmol, MeLi was used in the previous step), freshly powdered elemental Se (85 mg, 1.08 mmol) was added in one portion. The resulting mixture was stirred vigorously at −97°C for 30 min. Then, the cooling bath was removed and the temperature was slowly raised to 0 °C in a period of 30 min. Next, crystalline KH_2PO_4 (1 g, 7.35 mmol) was added in one portion, and a pre-cooled (0 °C) water (3 mL) was added dropwise with stirring over 2 min. Finally, EtOAc (30 mL) and water (20 mL) were added. The resulting mixture was stirred vigorously at 0°–5 °C for 5 min. The organic phase was separated, and the mother liquor was further extracted with EtOAc (3 × 25 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue, which was purified by flash chromatography (eluent EtOAc:hexane 1:5–1:2) to give compounds **9**, white powder (80 mg, 0.39 mmol, 53%), **10**, white powder (65 mg, 0.23 mmol, 31%), and **11**, yellow crystals (20 mg, 0.037 mmol, 10%).

Spectral data and m.p. for compound **9** coincided with those described in literature.[21]

4.6.1. 3-tert-Butyl-8-methylselanylpyrazolo[5,1-c][1, 2, 4]triazin-4(1H)-one 10

M.p. 205–215 °C (sublimation). IR (KBr) ν_{max}, cm^{-1}: 3223, 3151 (NH), 3073, 3037, 2970, 2932, 2909, 2821 (CH), 1697, 1675 (C = O), 1602, 1561, 1527, 1479, 1458, 1422, 1392, 1362, 1340, 1282, 1272, 1197, 1159, 1138, 1075, 1022, 982, 938, 922, 838, 768, 683, 636, 620, 574, 527, 509. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.46 (9H, s, $C(CH_3)_3$); 2.16 (1H, s, $^2J_{Se,H} = 11.8$, $SeCH_3$), 7.98 (1H, s, C(7)–H); 10.55 (1H, s, NH). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 10.39 ($SeCH_3$, $^1J_{Se,C} = 60.5$); 28.01 ($C(\mathbf{C}H_3)_3$); 37.30 ($\mathbf{C}(CH_3)_3$); 81.87 (C(8), $^1J_{Se,C} = 127.9$); 144.18, 146.77, 148.34 (C(3), C(4), C(8a)); 149.82 (C(7)–H). HRMS: Found, *m/z*: 309.0229 $[M + Na]^+$. $C_{10}H_{14}N_4OSe$. Calculated, *m/z*: 309.0225. Anal. Calcd for $C_{10}H_{14}N_4OSe$: C, 42.11; H, 4.95; N, 19.64. Found: C, 42.05; H, 4.98; N, 19.72.

4.6.2. 8,8′-Diselanediylbis(3-tert-butylpyrazolo[5,1-c][1, 2, 4]triazin-4(1H)-one) 11

M.p. 260–263 °C (decomp.). IR (KBr) ν_{max}, cm^{-1}: 3219, 3137 (NH), 2968, 2935, 2907, 2819 (CH), 1718, 1702, 1686 (C = O), 1595, 1561, 1523, 1477, 1458, 1393, 1363, 1331, 1277, 1197, 1160, 1133, 1019, 982, 940, 921, 890, 839, 766, 731, 678, 633, 620, 571, 508. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.41 (18H, s, $2C(CH_3)_3$); 7.96 (2H, s, 2C(7)–H); 13.77 (2H, s, 2 NH). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 27.82 ($C(\mathbf{C}H_3)_3$); 36.73 ($\mathbf{C}(CH_3)_3$); 82.40 (C(8), $^1J_{Se,C} = 155.1$); 145.19, 145.37, 148.20, 149.77 (C(3), C(4), C(7), C(8a)). ^{77}Se NMR (^{1}H–^{77}Se HMBC, 600 MHz, DMSO-d_6), δ, ppm: 365.88 (C(8)–Se). HRMS: Found, *m/z*: 565.0092 $[M + Na]^+$. $C_{18}H_{22}N_8O_2Se_2$. Calculated, *m/z*: 565.0092. Anal. Calcd for $C_{18}H_{22}N_8O_2Se_2$: C, 40.01; H, 4.10; N, 20.74. Found: C, 39.92; H, 4.18; N, 20.67.

4.7. Synthesis of compounds 10 and 12 from the reaction with tert-butyllithium

To the prepared solution of compound **3** (0.74 mmol, *t*-BuLi was used in the previous step), freshly powdered elemental S (50 mg, 1.56 mmol, for the synthesis of **12**) or Se (0.12 g, 1.52 mmol, for the synthesis of **10**) were added in one portion. The resulting mixtures were stirred vigorously at −97 °C for 30 min. Then, the cooling bath was removed and the temperature was slowly raised to −50 °C in a period of 15 min. Next, MeI (0.2 mL, 3.21 mmol, for the synthesis of **10**) or $PhCH_2Cl$ (0.5 mL, 4.35 mmol, for the synthesis of **12**) were added in one portion. The resulting reaction mixtures were stirred for 20 min (for **10**) or 1 h (for **12**). Next,

crystalline KH_2PO_4 (1 g, 7.35 mmol) was added in one portion, and a pre-cooled (0 °C) water (3 ml) was added dropwise with stirring over 2 min. Finally, EtOAc (30 mL) and water (20 mL) were added. The resulting mixtures were stirred vigorously at 0 °–5 °C for 5 min. The organic phases were separated, and the mother liquor was further extracted with EtOAc (3 × 25 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue, which was purified by flash chromatography (eluent EtOAc:hexane 1:20–1:5) to give compound **10**, white powder (0.17 g, 0.60 mmol, 81%), or **12**, long bright yellow crystals (0.15 g, 0.48 mmol, 65%).

4.7.1. 8-Benzylthio-3-tert-butylpyrazolo[5,1-c][1, 2, 4]triazin-4(1H)-one 12

M.p. 230–231 °C. IR (KBr) ν_{max}, cm^{-1}: 3215, 3107 (NH), 3086, 3058, 3022, 2996, 2982, 2968, 2901, 2879, 2804, 2779, 2774, 2675 (CH), 1686 (C = O), 1608, 1524, 1495, 1471, 1454, 1431, 1393, 1375, 1364, 1338, 1302, 1283, 1236, 1201, 1163, 1153, 1139, 1069, 1027, 1001, 938, 927, 900, 887, 845, 768, 700, 669, 637, 624, 590, 564, 534, 511, 480, 442. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 1.38 (9H, s, $C(CH_3)_3$); 3.89 (2H, s, PhCH_2); 7.14–7.29 (5H, m, Ph); 7.66 (1H, s, C(7)–H); 13.93 (1H, s, NH). ^{13}C NMR (APT, 126 MHz, DMSO-d_6), δ, ppm: 28.31 ($C(CH_3)_3$); 37.10 ($C(CH_3)_3$); 40.45 (PhCH_2, partially overlapped with the solvent peak); 88.59 (C(8)); 127.44, 128.63, 129.51 (*p*-CH, 2 *o*-CH and 2 *m*-CH Ph); 138.12 (*ipso*-C Ph); 144.81, 145.24, 148.63 (C(3), C(4), C(8a)); 149.61 (C(7)–H). HRMS: Found, *m/z*: 337.1102 $[M + Na]^+$. $C_{16}H_{18}N_4OS$. Calculated, *m/z*: 337.1094. Anal. Calcd for $C_{16}H_{18}N_4OS$: C, 61.12; H, 5.77; N, 17.82. Found: C, 61.20; H, 5.99; N, 17.75.

4.8. Biological assay

4.8.1. Methods

4.8.1.1. Sample preparation. Samples were provided as dry material, and were made to 10 mg/mL in DMSO or water and stored at –20 °C. An aliquot of each sample was further diluted to 320 µg/mL in water in 384-well polypropylene plates (PP; Corning 3657), and 5 µL was plated in duplicate ($n = 2$) into a 384-well nonbinding surface plate (NBS; Corning 3640) for each strain assayed against.

4.8.2. Antimicrobial assay

4.8.2.1. Procedure. All bacteria (*Staphylococcus aureus* (ATCC 43300, MRSA), *Escherichia coli* (ATCC 25922, FDA control strain), *Klebsiella pneumonia* (ATCC 700603, MDR), *Pseudomonas aeruginosa* (ATCC 27853, Type strain), *Acinetobacter baumannii* (ATCC 19606, Type strain)) were cultured in Cation-adjusted Muller Hinton broth (CAMHB, Bacto Laboratories) at 37 °C overnight. A sample of each culture was then diluted 40-fold in fresh broth and incubated at 37 °C for 1.5–3 h. The resultant mid-log phase cultures were diluted (CFU/mL measured by OD_{600}), then 45 µL was added to each well of the compound containing plates, giving a cell density of 5×10^5 CFU/mL and a final compound concentration of 32 µg/mL for the tested samples. All the plates were covered and incubated at 37 °C for 18 h without shaking.

4.8.2.2. Analysis. Inhibition of bacterial growth was determined using 7-hydroxy-3*H*-phenoxazin-3-one 10-oxide (Resazurin, Sigma-Aldrich) as a marker for cell viability. Resazurin was added to each well, at 0.001% final concentration, and plates incubated at 37 °C for 2 h. Fluorescence intensity is measured, using F (top read), ex 560/10 nm, em 590/10 nm ($F_{560/590}$), using a Tecan M1000 Pro monochromator plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references. The significance of the inhibition values was determined by Z-scores, calculated using the average and standard deviation of the sample wells (no controls) on the same plate. Samples with inhibition value above 80% and Z-Score above 2.5 for either replicate ($n = 2$ on different plates) were classed as active.

4.8.3. Antifungal assay

4.8.3.1. Procedure. Fungi strains (*Candida albicans* (ATCC 90028, CLSI reference), *Cryptococcus neoformans var. Grubii* (ATCC 208821, H99–Type strain)) were cultured for 3 d on Yeast Extract-Peptone Dextrose (YPD, Becton Dickinson) agar at 30 °C. A yeast suspension of 1×10^6 to 5×10^6 cells/mL (as determined by OD_{530}) was prepared from five colonies. These stock suspensions were diluted with Yeast Nitrogen Base (YNB, Becton Dickinson) broth to a final concentration of 2.5×10^3 CFU/mL. Then, 45 µL of the fungi suspension was added to each well of the compound-containing plates, giving a final concentration of 32 µg/mL for the tested samples. Plates were covered and incubated at 35 °C for 24 h without shaking.

4.8.3.2. Analysis. Growth inhibition of *C. albicans* was determined measuring absorbance at 530 nm (OD_{530}), while the growth inhibition of *C. neoformans* was determined measuring the difference in absorbance between 600 and 570 nm ($OD_{600\text{-}570}$), after the addition of resazurin (0.001% final concentration) and incubation at 35 °C for additional 2 h. The absorbance was measured using a Biotek Synergy HTX plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (fungi without inhibitors) on the same plate as references. The significance of the inhibition values was determined by Z-scores, calculated using the average and standard deviation of the sample wells (no controls) on the same plate. Samples with inhibition value above 80% and Z-Score above 2.5 for either replicate ($n = 2$ on different plates) were classed as actives.

4.8.4. Antibiotic standards preparation and quality control

Colistin (Sigma; C4661) and Vancomycin (Sigma; 861987) were used as positive bacterial inhibitor standards for Gramnegative and Gram-positive bacteria, respectively.

Fluconazole (Sigma; F8929) was used as a positive fungal inhibitor standard for *C. albicans* and *C. neoformans*. The antibiotics were provided in 4 concentrations, with 2 above and 2 below its MIC value, and plated into the first 8 wells of column 23 of the 384-well NBS plates. The quality control (QC) of the assays was determined by the antimicrobial controls and the Z'-factor (using positive and negative controls). Each plate was deemed to fulfill the quality criteria (pass QC), if the Z'-factor was above 0.4, and the antimicrobial standards showed full range of activity, with full growth inhibition at their highest concentration, and no growth inhibition at their lowest concentration.

5. Conclusions

Previously inaccessible 8-alkylthio- and 8-selanyl-3-*tert*-butylpyrazolo[5,1-*c*][1,2,4]triazines have been synthesized for the first time from the reactions of 8-lithio-3-*tert*-butyl-4-oxopyrazolo[5,1-c][1,2,4]triazin-1-ide with elemental sulfur or selenium. The outcome of these reactions was significantly dependent on the nature of the organolithium reagent used, and a 8,8'-diselanediyl derivative was also isolated as a by-product. *One-pot* interaction of 3-*tert*-butyl-8-butylselanylpyrazolo[5,1-*c*][1,2,4]triazin-4(6*H*)-one with BH_3/BF_3 led to reduction of the 1,2,4-triazine core and partial elimination of the alkylselanyl moiety. The structures of the isolated products were established on the basis of IR, ^{1}H, ^{13}C, 2D HMBC ^{1}H–^{77}Se NMR and high resolution mass spectra, as well as X-ray single crystal diffraction analyses. 3-*tert*-Butyl-8-butylthio- and 8-butylselanylpyrazolo[5,1-*c*][1,2,4]triazin-4(6*H*)-ones were also tested for antimicrobial and antifungal activities.

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