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Synthesis of 6-Selanyl-2-triazolylpurine Derivatives Using 2,6-Bistriazolylpurines as Starting Materials

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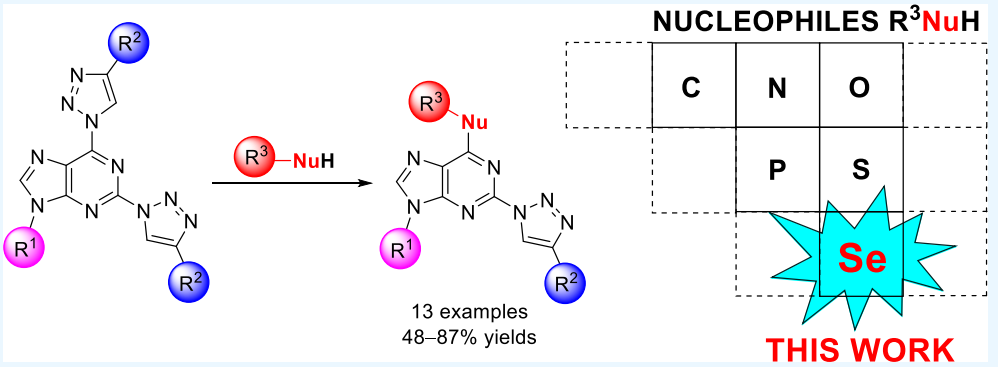

ABSTRACT: Two pathways toward 6-selanyl-2-triazolylpurine derivatives were designed. The first method involved the synthesis of 2-chloro-6-selanylpurine derivatives, further S_NAr reaction with NaN_3, and following CuAAC using different alkynes. The second method was based on the synthesis of 2,6-bistriazolylpurine derivatives as starting materials followed by S_NAr reaction with commercial or in situ generated selenols as nucleophiles. A series of 2-chloro-6-selanylpurine derivatives were obtained in yields up to 84%. It was found that in the latter compounds, 6-selanyl moiety was the better leaving group compared to 2-chlorosubstituent in S_NAr reactions. On the other hand, the S_NAr reaction between 2,6-bistriazolylpurines and selenols or diselenides was successful, and 13 examples of 6-selanyl-2-triazolylpurine derivatives were obtained in yields up to 87%. This direct approach for the Se−C bond formation proved the ability of the 1,2,3-triazolyl ring at the C6 position of purine to act as a good leaving group.

INTRODUCTION

Modified purine derivatives are a significant group of compounds that exhibit a diverse range of biological activities.[1−6] These compounds are commonly used in the fields of antiviral, anticancer, and antibacterial research. The extensive use of these compounds in medicinal chemistry calls for the continuous advancement of innovative synthetic techniques. Of particular interest are selanylpurines, as they combine the well-established applicability of the purine skeleton with the presence of selenium and as such bear intrinsic potential for biological activity (Figure 1).

Selenopurines were first synthesized in a reaction between 6-chloropurine and sodium hydroselenide or selenourea in 1956 by Mautner.[7] In the same manner, 6-selenoguanosine derivatives were prepared and further alkylated with alkyl/hetaryl bromides, yielding substituted selanylguanosines.[8] In addition, diselenides in the presence of tri-*n*-butylphosphine were used for the alkylation of selenopurines and selenoguanosines.[9] 6-Arylselanylpurines were obtained in the S_NAr reactions between 6-chloropurine and the system of aryl diselenides and $NaBH_4$ in PEG-400 and exhibited useful antioxidant and anticholinesterase activities and enhanced memory improvement effects.[10] On the other hand, alkylation of purine diselenide yielded different alkylselanylpurines.[11] Next, selenium-containing nucleoside analogs were obtained in efficient enzymatic synthesis.[12] These nucleosides play an important role in the structural study of nucleic acids.[13−15]

Simple selanylpurine analogs, similarly to 6-thioguanine, have been tested for leukemia treatment and as immunosuppressants,[16] but their selectivity and cytotoxicity levels had to be optimized.[17−19] This issue was partially overcome by selenoguanine-platinum(II) and selenopurine and selenoguanine ruthenium complexes.[20,21] These complexes were more stable and less toxic but had reduced anticancer activity.

Selenium was also introduced in the sugar moieties of various nucleoside derivatives and in the acyclic chain of antiviral acyclic compounds.[22−24] For example, selenium analogs of acyclovir and ganciclovir exhibited potent activity

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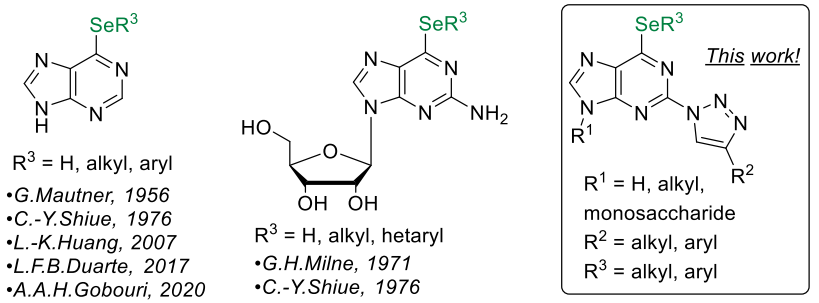


Figure 1. General structures of selanylpurine derivatives.

Scheme 1. Proposed Synthesis toward 6-Selanyl-2-triazolylpurine Derivatives 4

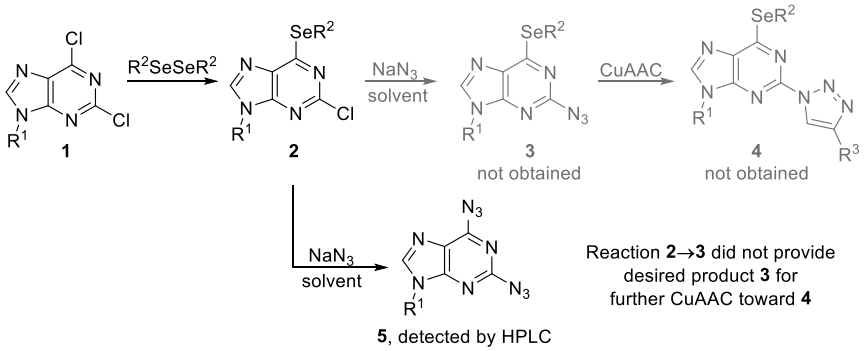
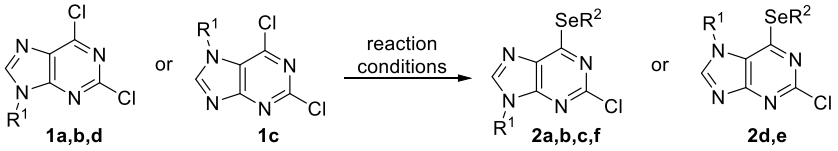


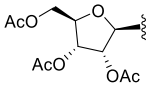
Table 1. Synthesis of 2-Chloro-6-selanylpurine Derivatives 2



Methods for R^2SeH generation:

Method A: R^2SeSeR^2, H_3PO_2 (50% H_2O), *i*-PrOH, +5°C to rt

Method B: R^2SeSeR^2, benzene, 3.0 M HCl/H_2O, Zn powder, anh. K_2CO_3, rt to 60 °C

Entry	Starting material	R^1	R^2	Method for R^2SeH generation	Yield, %
1	**1a**	H	C_6H_5	A	**2a**, 50
2	**1b**	*n*-C_7H_{15}	C_6H_5	A	**2b**, 59
3		*n*-C_7H_{15}	*n*-C_5H_{11}	A[a]	**2c**, 66
4	**1c**	*n*-C_7H_{15}	C_6H_5	A	**2d**, 60
5		*n*-C_7H_{15}	$C_6H_5CH_2$	A[b]	**2e**, 49
6	**1d**		C_6H_5	B	**2f**, 84

[a]$NaBH_4$ was used for the reduction of dipentyl diselenide, and S_NAr reaction was carried out at 60 °C. [b]S_NAr reaction was carried out at 50−60 °C.

against herpes simplex virus and human cytomegalovirus.[24] Recently, increased attention was focused on the photophysics of 6-selanylguanine, which is necessary for the further structural study of DNA/RNA duplexes containing aforementioned nucleobases.[25−27]

In the reviewed examples, 6-chloro-9*H*-purine was mostly used for S_NAr reactions with Se-nucleophiles. A few methods required a toxic gas of H_2Se for the introduction of selenol into the structure, followed by its further alkylation.[8] Some reactions required microwave irradiation to obtain 6-phenylselanylpurines in good yields.[28] Unequivocally new methods for the introduction of selanyl moieties in the purines and new structural motifs are still in high demand (Figure 1). Since only a limited number of selenium-containing unsubstituted purine derivatives were tested for their toxicity, it opens an opportunity to develop new structures and conduct further research.

Previously, we have created a method for S_NAr reactions of 2,6-bistriazolylpurine derivatives with different N-, S-, O-, C-, and P-nucleophiles and generated a library of structurally

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diverse triazolyl purine derivatives.[29−35] Thereby, we demonstrated the concept that the triazolyl ring at the C6 position of purine is acting as a good leaving group. Our previously synthesized amino-substituted triazolylpurines are fluorescent and have found application in cell imaging and OLED studies.[36−38] In this study, we focused on the necessity of new structural motifs of selenium-containing purines and methods toward them. Here, we report a novel and straightforward approach toward 6-selanylpurine derivatives using the S_NAr reactions between 2,6-dichloropurine or 2,6-bistriazolylpurine derivatives and commercial or in situ generated selenols as nucleophiles.

RESULTS AND DISCUSSION

For the methodology development, we designed and tested the first synthetic route toward 6-selanyl-2-triazolylpurine derivatives, which involved the synthesis of 2-chloro-6-selanylpurines **2** in the first step, followed by the S_NAr reaction with NaN_3 to perform CuAAC with the desired 2-azido-6-selanylpurine derivative **3** afterward (Scheme 1).

Starting materials **1b−d** were obtained from commercially available 2,6-dichloropurine, through N7/N9-derivatization. The N9-ribofuranosyl nucleoside was obtained using Vorbrüggen glycosylation conditions, while the introduction of the heptyl group at the N7/N9 positions of purine was achieved through the Mitsunobu reaction (Table 1).[29,36]

2-Chloro-6-selanylpurine derivatives **2a−f** were obtained in direct S_NAr reaction between 2,6-dichloropurine derivatives **1a−d** and in situ generated selenols (Table 1). It is known that the C6 position of purine is prone to the substitution if purine contains identical leaving groups at C2 and C6.[39,40] To participate in S_NAr reaction, diselenides should be in situ reduced back to selenols. In the literature, several reagents are used for this purpose: (1) Zn/2.9 M HCl;[41] (2) CO/H_2O;[42] (3) H_3PO_2 (50% H_2O);[10,43,44] and (4) $NaBH_4$ or KBH_4.[10,45,46] In the synthesis of compounds **2** for the reduction of diselenides, two reducing systems were used: the Zn/HCl system and 50% H_3PO_2 solution in water. By method A, the reaction smoothly proceeded in *i*-PrOH using H_3PO_2 as a reducing agent (Table 1). The reduction step was usually performed at 40 °C, but the S_NAr reaction was carried out at 0 °C for 2 h. For the synthesis of compounds **2a,b,d,e,f,** commercial diselenides such as 1,2-diphenyl diselenide and 1,2-dibenzyl diselenide were used. On the other hand, selanylpurine derivative **2c** was obtained in S_NAr reaction using dipentyl diselenide which was synthesized from *n*-pentyl bromide and Na_2Se_2 salt.[47] In the case of dipentyl diselenide, reduction to selenol was achieved only with $NaBH_4$. In the presence of H_3PO_2, the starting material was inert for S_NAr reaction. In the case of derivative **2f**, method B was used and the reduction of diselenide was completed with the Zn/HCl system in benzene (entry 6, Table 1). For reduction of diselenides, metallic indium in benzene and DMF were also tried, but no products were observed or conversion was too slow.

Next, a pathway toward triazolylpurine derivatives **4** was tested involving S_NAr with NaN_3 at the C2 position of purine and following CuAAC (Scheme 1). S_NAr reaction with NaN_3 was performed using 6-selanylpurine derivatives **2b** and **2c**, but product **3** was not observed in the reaction mixture (Scheme 1, Table 2). By HPLC analysis, starting materials **2b** and **2c** stayed unchanged or slowly degraded. During optimization study of the process with increase in temperature and change of solvents, the chlorine atom at the C2 position and the selanyl group at the C6 position were substituted, with azides providing 2,6-diazidopurine **5**[36] as the byproduct (R^1 = *n*-C_7H_{15}) (Scheme 1). The higher amounts of diazide **5** were formed by performing the reaction in DMF at 50 °C for starting material **2b** and in *i*-PrOH at 60 °C for starting material **2c** (Table 2). In addition, 2,6-diazidopurine derivatives are not suitable for S_NAr reactions with Se-nucleophiles due to the reducing properties of selenols. Indeed, a combination of **5** + R^2SeH resulted in the reduction of azido groups to amino moieties.

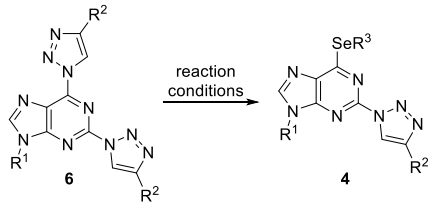
Table 2. Reaction Conditions for Transformation 2 → 3 (Scheme 1)

entry	starting material	solvent	temperature, °C	conversion to 5, %[a]
1	**2b**	*i*-PrOH	50	0
2		toluene		0
3		DMF		30
4	**2c**	DMF	60	0
5		*i*-PrOH		9

[a]Determined by HPLC, the formation of product **3** was not observed.

Next, based on our previous knowledge and achievements in purine chemistry, we designed the second route toward 6-selanyl-2-triazolylpurine derivatives, which was based on the use of 2,6-bistriazolylpurine derivatives **6** as strategic intermediates for S_NAr reactions with Se-nucleophiles (Scheme 2).

Scheme 2. S_NAr Reactions between 2,6-Bistriazolylpurines 6 and Se-Nucleophiles



Methods for R^3SeH generation:
Method B: R^3SeSeR^3, benzene, 3.0 M HCl/H_2O, Zn powder, anh. K_2CO_3, rt to 60 °C
Method C: R^3SeH, anh. K_2CO_3, benzene, 60 °C
Method D: R^3SeSeR^3, $NaBH_4$, EtOAc, AcOH, rt to 65 °C

2,6-Bistriazolylpurines **6** were synthesized using known approaches.[29,35] In the beginning, 2,6-dichloropurine derivatives **1** were generated, and then chlorine atoms were substituted with azides and the CuAAC reaction was performed, exploiting different alkyl/aryl alkynes in the presence of $CuSO_4{\cdot}5H_2O$/sodium ascorbate or CuI catalytic systems. With 2,6-bistriazolylpurine derivatives in hand, an easy and effective way for the selanyl group's introduction at the C6 position was tested using S_NAr reactions with Se-nucleophiles.

During our research, three methods were developed for the introduction of selanyl moiety into the purine core using 2,6-bistriazolylpurines **6** (Scheme 2, Table 3). First, method C was created for S_NAr reactions between 2,6-bisphenyltriazolylpurine nucleoside (**6a**) and commercially available phenylselenol in the presence of anhydrous K_2CO_3 (Table 3). Various solvents were tested for this transformation. Substitution occurred in benzene and toluene, but in toluene, a range of unidentified byproducts was observed. If alcohols, DMF, THF,

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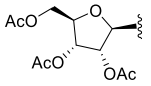
Table 3. Diversity of 6-Selanyl-2-triazolylpurine Derivatives 4 and Yields toward Them (Scheme 2)

Entry	Starting materials			Products 4a–m		
	Comp. number	R^1	R^2	R^3	Method for R^3SeH generation	Yield, %
1	**6a**		C_6H_5	C_6H_5	C	**4a**, 59
2					D	**4a**, 60
3	**6b**		4-CH_3-C_6H_4	C_6H_5	C	**4b**, 65
4					D	**4b**, 59
5				3-MeO-$C_6H_4CH_2$	D	**4c**, 59[a]
6	**6c**		4-F-C_6H_4	C_6H_5	B	**4d**, 65
7					D	**4d**, 62
8				C_2H_5	D	**4e**, 80
9	**6d**		4-CF_3-C_6H_4	C_6H_5	B	**4f**, 64
10				$C_6H_5CH_2$	D	**4g**, 82
11	**6e**		2-F-C_6H_4	C_6H_5	C	**4h**, 59
12					B[b]	**4h**, 63
13	**6f**		4-Br-C_6H_4	C_6H_5	D	**4i**, 60
14	**6g**		*n*-C_4H_9	C_6H_5	C	**4j**, 48[a]
15					D	**4j**, 73[a]
16	**6h**	*n*-C_7H_{15}	COOMe	C_6H_5	B	**4k**, 86
17					D	**4k**, 87
18				*n*-C_5H_{11}	D[c]	**4l**, 74[a]
19	**6i**		C_6H_5	4-F-$C_6H_4CH_2$	D	**4m**, 73[a]

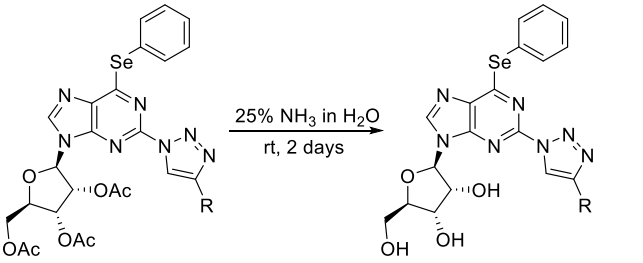
[a]Yield based on reacted starting material. [b]EtOAc was used as a solvent. [c]S_NAr was carried out for 12 h at 60 °C and 24 h at 80 °C.

and DCM were used as solvents, phenylselenol was easily oxidized to diphenyl diselenide and S_NAr reaction did not happen. For example, when the reaction bistriazole **6e** + PhSeH was performed in *i*-PrOH at 60 °C, for 5 days no conversion was observed, even with an extra addition of H_3PO_2 to reduce the formed diselenide.

In the methods B and D, a combination of diphenyl diselenide with a reductant (Zn/HCl or $NaBH_4$) and an appropriate solvent was used instead of phenylselenol (Table 3). In method B, reduction of diphenyl diselenide was done in a two-phase system (benzene-H_2O/HCl) where freshly formed phenylselenol was highly soluble in the benzene layer. Progress of the reduction was observed by decolorization of the reaction mixture from yellowish to colorless. After completion, benzene solutions were dried over anhydrous Na_2SO_4 and immediately used in the next step. Different solvents were tried for the optimization of the S_NAr reaction of bistriazolylpurines **6** with in situ generated selenols. Alcohols such as *i*-PrOH, glycerol, and TEG did not yield the desired products. Instead, in the reaction **6h** + PhSeSePh, the substitution of the triazolyl ring at the C6 position with *O*-nucleophile was observed. To summarize, the S_NAr reactions of **6a–i** smoothly proceed in nonpolar solvents, without the presence of water. During method B, the preparation of selenol solution in benzene should be carried out carefully using anhydrous Na_2SO_4 for drying and a prior purging reaction flask with argon. In order to make the approach more environmentally friendly and avoid the use of toxic benzene, we established a method D, switching to ethyl acetate (Table 3), and reached comparable results or higher yields (entries 14–15, Table 3).

In addition, for compounds **4a** and **4f,** acetyl groups were removed from ribosyl moieties by using 25% NH_3 solution in H_2O and stirring the reaction mixture at room temperature to avoid the substitution of selanyl moiety at the C6 position; nucleosides **7a** and **7b** were obtained in 62 and 80% yields, respectively (Scheme 3). The deprotection step makes selanyl purine nucleoside analogs more suitable for biological studies in the future due to their increased solubility in aqueous solutions in comparison to that of their acylated ribosyl analogs.

Scheme 3. Synthesis of Purine Nucleoside Analogs 7a–b



4a: R = C_6H_5
4f: R = 4-CF_3-C_6H_4
7a: R = C_6H_5, 62%
7b: R = 4-CF_3-C_6H_4, 80%

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CONCLUSIONS

A synthetic pathway to obtain 6-selanyl-2-triazolylpurine derivatives is designed. The initial attempt involved synthesis of 2-chloro-6-selanylpurine derivatives, followed by an S_NAr reaction with NaN_3, and subsequent CuAAC using various alkynes. Thus, a series of 2-chloro-6-selanylpurine derivatives with yields up to 84% were obtained. However, it appeared that the selanyl substituent at the purine C6 position is a better leaving group than chloride at the C2 position. In contrast, the second method focused on synthesizing 2,6-bistriazolylpurine derivatives as starting materials, which then underwent the C6-selective S_NAr reaction with selenols or diselenides in the presence of a reducing agent. This approach proved to be successful, resulting in the synthesis of 13 examples of 6-selanyl-2-triazolylpurine derivatives with yields up to 87%. Furthermore, this method for Se−C bond formation confirmed the favorable reactivity of the 1,2,3-triazolyl ring at the C6 position of purine and proved that it acts as an effective leaving group under mild conditions.

EXPERIMENTAL SECTION

General Information. Commercial reagents were used as received. Phenylselenol, 1,2-diethyl diselenide, 1,2-diphenyl diselenide, and 1,2-dibenzyl diselenide were obtained from commercial sources (Acros Organics, TCI Chemicals, Fluorochem Ltd.). 1,2-Bis(4-fluorobenzyl) diselenide, 1,2-bis(3-methoxybenzyl) diselenide, and 1,2-dipentyl diselenide were synthesized according to literature methods.[47−50] Starting materials **1** were synthesized according to literature procedures.[29,36] N7-Heptylpurine derivative **1c** was isolated as a byproduct from the Mitsunobu reaction between 2,6-dichloropurine and heptanol.[36] 2,6-Bis-alkyl/aryltriazolylpurine derivatives **6a−d**, **6f**, and **6h−i** were synthesized according to literature procedures.[29,35] Reactions and purity of the synthesized compounds were monitored by TLC or/and HPLC. For TLC, Silica gel 60 F_{254} aluminum plates precoated with a 0.25 mm layer of silica gel (Merck) were used. Visualization was accomplished by UV light.

Column chromatography was performed using silica gel 60 (0.040−0.063 mm) (Merck). Yields refer to chromatographically and spectroscopically homogeneous materials (with purity ≥95%).

NMR spectra were recorded on a Bruker Avance 500 spectrometer. ^{1}H NMR spectra were recorded at 500 MHz, with internal references from residual nondeuterated solvents (δ = 7.26 for $CDCl_3$, δ = 2.50 for DMSO-d_6, δ = 2.04 for CD_3COOD). ^{13}C NMR spectra were recorded at 125.7 MHz with internal references from solvent carbon signals (δ = 77.1 for $CDCl_3$ and δ = 39.5 for DMSO-d_6, δ = 20.0 for CD_3COOD). ^{19}F NMR spectra were recorded at 470.5 MHz with no internal reference. ^{77}Se NMR spectra were recorded at 95.4 MHz, with an internal standard of diphenyl diselenide. Coupling constants are reported in Hz, and chemical shifts of signals are given in ppm, and standard abbreviations are used for multiplicity assignments.

IR spectra were recorded on a PerkinElmer Spectrum BX spectrophotometer and are reported in cm^{-1}.

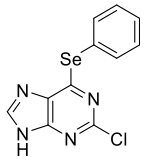
For HPLC analyses, an Agilent Technologies 1200 Series system was used (XBridge C_{18} column, 4.6 × 150 mm, particle size 3.5 μm). Eluent A: 0.1% aq TFA/CH_3CN (95:5, v/v), eluent B: CH_3CN. Gradient: 30−95% B 5 min, 95% B 5 min, 95−30% B 2 min. Flow rate: 1 mL/min. Wavelength of detection was set to 260 nm.

HRMS analysis was performed on an Agilent 1290 Infinity series UPLC system connected to an Agilent 6230 TOF LC/MS mass spectrometer; column Extend C_{18} RRHD 2.1 × 50 mm, 1.8 μm. Eluents: formic acid in CH_3CN (0.1%) and aq 0.1% formic acid. High-resolution accurate mass measurements for compounds **6e** and **6g** were performed by employing an Orbitrap Exploris 120 mass spectrometer (Thermo Fischer Scientific) operating in Full Scan mode at the 120,000 resolutions.

General Procedures and Characterization of Products. *Synthesis of 2-Chloro-6-selanyl-9(7)H-purine Derivatives* ***2****. Method A for* R^2SeH *Generation.* To a solution of diselenide (0.5−0.7 mmol, 0.5−0.7 equiv) in *i*-PrOH (10 mL), hypophosphorous acid (50% solution in H_2O, 0.5 mL) was added. The solution was stirred under argon at 40 °C until the yellow color disappeared (1−1.5 h). The mixture was placed in an ice bath and cooled to +5 °C; after that, the solution of 2,6-dichloro-9(7)*H*-purine derivative **1** (1 mmol, 1 equiv) in *i*-PrOH (5 mL) was added under stirring. The mixture was stirred in an ice bath for 2 h; after that, it was allowed to warm to room temperature and stirred until the reaction was completed (control by HPLC). The desired products **2** were isolated by precipitation or by column chromatography after the evaporation of the reaction mixture. For the synthesis of compound **2c**, $NaBH_4$ was used instead of H_3PO_2.

Method B for R^2SeH *Generation.* A solution of 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloro-9*H*-purine (**1d**) (223 mg, 0.5 mmol) in benzene was added to a solution of phenylselenol in benzene (10 mL), obtained from diphenyl diselenide (156 mg, 0.5 mmol), zinc powder (65 mg, 1 mmol), and 0.2 M HCl/H_2O (8 mL) in benzene (8 mL). Anhydrous K_2CO_3 (276 mg, 2.0 mmol) was added. The reaction mixture was stirred overnight at r.t. and for 12 h at 50−60 °C (HPLC control). After completion, the reaction mixture was cooled and washed with NH_4Cl/H_2O (5 mL) and H_2O (5 mL), and the benzene solution was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Silica gel column chromatography of the residue (toluene/EtOAc, 2:1), containing mainly the desired product **2f**, 4-substituted 1,2,3-triazole, and Ph_2Se_2, provided 2-chloro-6-selanylpurine **2f**.

*2-Chloro-6-(phenylselanyl)-9H-purine (****2a****).*



Compound **2a** was synthesized according to Method A. Diphenyl diselenide (156 mg, 0.5 mmol), *i*-PrOH (10 mL), hypophosphorous acid (50% in H_2O, 0.5 mL), and a solution of 2,6-dichloro-9*H*-purine (**1a**) (189 mg, 1 mmol) in *i*-PrOH (5 mL). Reaction conditions: 2 h at +5 °C, overnight at r.t. The suspension was cooled to 5−10 °C, filtered, precipitate washed with *i*-PrOH (2 × 1 mL), and dried in vacuum. Yield: 155 mg, 50%. Colorless solid. R_f = 0.31 (toluene/MeCN 3:1). mp 226−229 °C. IR ν (cm^{-1}): 3101, 3052, 2933, 2766, 2694, 2659, 1588, 1557, 1476, 1440, 1396, 1360, 1339. ^{1}H NMR (500 MHz, CD_3COOD): δ 8.66 (s, 1H, H−C(8)), 7.84 (d, 2H, ^3J = 7.1 Hz, 2 × H−C(Ph)), 7.59 (t, 1H, ^3J = 7.1 Hz, H−C(Ph)), 7.55 (t, 2H, ^3J = 7.1 Hz, 2 × H−C(Ph)). ^{13}C NMR (125.7 MHz, CD_3COOD): δ 163.1, 155.0, 151.4, 146.1, 138.2,

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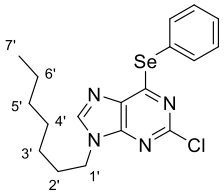
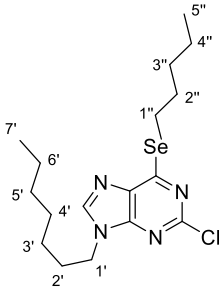
132.1, 131.1, 131.0, 125.8. ^{77}Se NMR (95.4 MHz, CD_3COOD): δ 456.4. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{11}H_8ClN_4Se$, 310.9595; found, 310.9595.

*2-Chloro-9-heptyl-6-(phenylselanyl)-9H-purine (**2b**).*



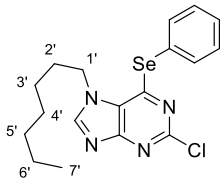
Compound **2b** was synthesized according to Method A. Diphenyl diselenide (218 mg, 0.7 mmol), *i*-PrOH (10 mL), H_3PO_2 (50% in H_2O, 0.5 mL), and a solution of 2,6-dichloro-9-heptyl-9*H*-purine (**1b**) (287 mg, 1 mmol) in *i*-PrOH (5 mL). Reaction conditions: 1.5 h in an ice bath, 4 h at r.t. The mixture was evaporated and purified by column chromatography (toluene/EtOAc, 0−10%). Yield: 240 mg, 59%. Colorless solid. R_f = 0.61 (toluene/MeCN 9:1). mp 50−52 °C. IR ν (cm^{-1}): 3071, 2991, 2913, 2638, 2566, 2484, 1590, 1518, 1488, 1475, 1440, 1386. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (s, 1H, H−C(8)), 7.74 (d, 2H, ^3J = 6.7 Hz, 2 × H−C(Ph)), 7.47−7.39 (m, 3H, 3 × H−C(Ph)), 4.19 (t, 2H, ^3J = 7.2 Hz, H_2−C(1′)), 1.87 (quintet, 2H, ^3J = 7.2 Hz, H_2−C(2′)), 1.33−1.24 (m, 8H, 4 × ($-CH_2-$)), 0.87 (t, 3H, ^3J = 6.9 Hz, H_3−C(7′)). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 161.8, 153.9, 150.0, 143.8, 136.4, 132.7, 129.4, 129.4, 124.8, 44.3, 31.7, 30.0, 28.8, 26.7, 22.6, 14.1. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 443.0. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{18}H_{22}ClN_4Se$, 409.0691; found, 409.0687.

*2-Chloro-9-heptyl-6-(n-pentylselanyl)-9H-purine (**2c**).*



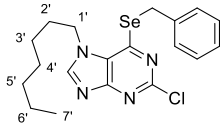
Compound **2c** was synthesized according to Method A. Dipentyl diselenide (0.61 g, 2.02 mmol, 1.0 equiv) in *i*-PrOH (5 mL), $NaBH_4$ (0.15 g, 4.04 mmol, 2.0 equiv), and 9-heptyl-2,6-dichloro-9*H*-purine (**1b**) (0.29 g, 1.01 mmol, 0.50 equiv) in *i*-PrOH (12 mL). Reaction conditions: 24 h at 60 °C. Column chromatography using a Büchi Pure C810 system (DCM/MeCN, gradient 0 → 3%). Yield: 0.27 g, 66%. Yellow oil. R_f = 0.49 (toluene/MeCN = 10/1). IR ν (cm^{-1}): 2953, 2926, 2855, 1552, 1337, 1223, 1139, 945, 855. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.92 (s, 1H, H−C(8)), 4.19 (t, 2H, ^3J = 7.1 Hz, H_2−C(1′)), 3.41 (t, 2H, ^3J = 7.2 Hz, H_2−C(1″)), 1.90−1.83 (m, 4H, H_2−C(2′), H_2−C(2″)), 1.46 (quintet, 2H, ^3J = 7.1 Hz, H_2−C(3″)), 1.41−1.36 (m, 2H, H_2−C(4″)), 1.35−1.19 (m, 8H, 4 × ($-CH_2-$)), 0.92 (t, 3H, ^3J = 7.1 Hz, H_3−C(5″)), 0.87 (t, 3H, ^3J = 6.5 Hz, H_3−C(7′)). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) 162.4, 153.8, 149.4, 143.3, 133.4, 44.3, 32.1, 31.7, 30.0, 29.9, 28.8, 26.7, 25.6, 22.6, 22.3, 14.1, 14.1. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ (ppm) 330.6. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{17}H_{28}ClN_4Se$, 403.1160; found, 403.1174.

*2-Chloro-7-heptyl-6-(phenylselanyl)-7H-purine (**2d**).*



Compound **2d** was synthesized according to Method A. Diphenyl diselenide (218 mg, 0.7 mmol), *i*-PrOH (10 mL), 50% H_3PO_2 (0.5 mL), and a solution of 2,6-dichloro-7-heptyl-7*H*-purine (**1c**) (287 mg, 1 mmol) in *i*-PrOH (5 mL). Reaction conditions: 1.5 h in an ice bath, 4 h at r.t. The suspension was cooled to 5−10 °C and filtered and then precipitate washed with *i*-PrOH (2 × 1 mL) and dried in vacuum. Yield: 245 mg, 60%. Colorless solid. R_f = 0.54 (toluene/MeCN 3:1). mp 126−127 °C. IR ν (cm^{-1}): 3089, 2952, 2927, 2852, 1745, 1572, 1530, 1477, 1387. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (s, 1H, H−C(8)), 7.68 (d, 2H, ^3J = 7.1 Hz, 2 × H−C(Ph)), 7.50−7.46 (t, 1H, ^3J = 7.1 Hz, H−C(Ph)), 7.44 (t, 2H, ^3J = 7.1 Hz, 2 × H−C(Ph)), 4.41 (t, 2H, ^3J = 7.4 Hz, H_2−C(1′)), 1.97 (quintet, 2H, ^3J = 7.4 Hz, H_2−C(2′)), 1.43−1.36 (m, 4H, 2 × ($-CH_2-$)), 1.33−1.28 (m, 4H, 2 × ($-CH_2-$)), 0.89 (t, 3H, ^3J = 6.9 Hz, H_3−C(3′)). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 160.7, 154.1, 151.8, 148.8, 136.2, 129.8, 129.72, 124.7, 124.5, 48.2, 32.2, 31.7, 28.8, 26.5, 22.6, 14.1. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 445.8. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{18}H_{22}ClN_4Se$, 409.0961; found, 409.0686.

*6-(Benzylselanyl)-2-chloro-7-heptyl-7H-purine (**2e**).*



Compound **2e** was synthesized according to Method A. Dibenzyl diselenide (240 mg, 0.7 mmol), *i*-PrOH (10 mL), 50% H_3PO_2 (1.0 mL), and a solution of 2,6-dichloro-7-heptyl-7*H*-purine (**1c**) (287 mg, 1 mmol) in *i*-PrOH (8 mL). Reaction conditions: 2 h at r.t. and 6 h at 50−60 °C. After evaporation of the reaction mixture, the residue was purified by column chromatography (toluene/MeCN, 0−30%). Yield: 200 mg, 49%. Colorless solid. R_f = 0.58 (toluene/MeCN 3:1). mp 86−87 °C. IR ν (cm^{-1}): 3248, 3087, 3028, 2949, 2927, 2854, 1736, 1690, 1573, 1528, 1479, 1455, 1396. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (s, 1H, H−C(8)), 7.46 (d, 2H, ^3J = 7.4 Hz, 2 × H−C(Ph)), 7.32 (t, 2H, ^3J = 7.4 Hz, 2 × H−C(Ph)), 7.24 (t, 1H, ^3J = 7.4 Hz, H−C(Ph)), 4.72 (s, 2H, ($-CH_2-$)), 4.28 (t, 2H, ^3J = 7.4 Hz, H_2−C(1′)), 1.85 (quintet, 2H, ^3J = 7.4 Hz, H_2−C(2′)), 1.34−1.23 (m, 8H, 4 × ($-CH_2-$)), 0.86 (t, 3H, ^3J = 6.7 Hz, H_3−C(7′)). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 160.3, 154.0, 152.2, 148.3, 137.5, 129.6, 128.9, 127.7, 124.6, 48.0, 32.2, 31.7, 30.5, 28.8, 26.4, 22.6, 14.1. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 403.9. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{19}H_{24}ClN_4Se$, 423.0847; found, 423.0846.

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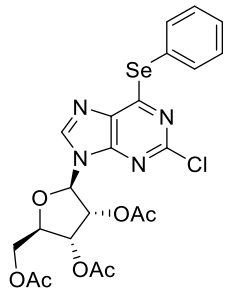
*9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-2-chloro-6-(phenylselanyl)-9H-purine (**2f**).*



Compound **2f** was synthesized according to Method B. Colorless solid. Yield: 160 mg, 84%. R_f = 0.59 (toluene/MeCN 3:1). mp 63−66 °C. IR ν (cm^{-1}): 3053, 2939, 1744, 1554, 1479, 1439, 1366. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (s, 1H, H−C(8)), 7.73 (d, 2H, ^3J = 7.1 Hz, 2 × H−C(Ph)), 7.48−7.41 (m, 3H, 3 × H−C(Ph)), 6.19 (d, 1H, ^3J = 5.6 Hz, H−C(1′)), 5.79 (dd, 1H, ^3J = 5.5, 5.3 Hz, H−C(2′)), 5.58 (dd, 1H, ^3J = 5.3, 4.6 Hz, H−C(3′), 4.47−4.43 (m, 1H, H−C(4′)), 4.41−4.38 (m, 2H, H_2−C(5′)), 2.16, 2.14, 2.08 (3s, 9H, 3 × Ac). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.4, 169.7, 169.5, 163.0, 154.4, 149.5, 141.8, 136.5, 133.2, 129.53, 129.51, 124.5, 86.2, 80.8, 73.3, 70.8, 63.1, 20.9, 20.7, 20.5. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 450.4. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{22}H_{22}ClN_4O_7Se$, 569.0337; found, 569.0307.

*Reaction Conditions for Transformation **2** → **3** (Scheme 1, Table 2). Reaction of 2-Chloro-9-heptyl-6-(phenylselanyl)-9H-purine (**2b**) with NaN_3 in i-PrOH (Entry 1, Table 2).* 2-Chloro-9-heptyl-6-(phenylselanyl)-9*H*-purine (**2b**) (0.020 g, 1.0 equiv) and NaN_3 (0.010 g, 3.5 equiv) solution in *i*-PrOH (7 mL) was stirred under argon at 50 °C. After several days of stirring, a slight degradation of the starting material was observed.

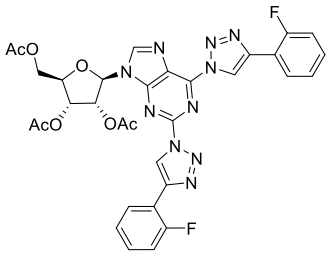
*Reaction of 2-Chloro-9-heptyl-6-(phenylselanyl)-9H-purine (**2b**) with NaN_3 in Toluene (Entry 2, Table 2).* 2-Chloro-9-heptyl-6-(phenylselanyl)-9*H*-purine (**2b**) (0.020 g, 1.0 equiv) and NaN_3 (0.010 g, 3.5 equiv) solution in toluene (2 mL) was stirred under argon at 50 °C. H_2O (1 mL) was added to dissolve NaN_3. In 24 h of stirring, a slight degradation of the starting material was observed.

*Reaction of 2-Chloro-9-heptyl-6-(phenylselanyl)-9H-purine (**2b**) with NaN_3 in DMF (Entry 3, Table 2).* 2-Chloro-9-heptyl-6-(phenylselanyl)-9*H*-purine (**2b**) (0.020 g, 1.0 equiv) and NaN_3 (0.010 g, 3.5 equiv) solution in DMF (2 mL) was stirred under argon at 50 °C. After 48 h, 30% formation of 2,6-diazido-9-heptyl-9*H*-purine (**5**) was observed by HPLC.

*Reaction of 2-Chloro-9-heptyl-6-(n-pentylselanyl)-9H-purine (**2c**) with NaN_3 in DMF (Entry 4, Table 2).* 2-Chloro-9-heptyl-6-(*n*-pentylselanyl)-9*H*-purine (**2c**) (0.020 g, 1.0 equiv) and NaN_3 (0.010 g, 3.5 equiv) solution in DMF (2 mL) was stirred under argon at 50 °C. H_2O (0.7 mL) was added to dissolve NaN_3. In 72 h of stirring, a slight degradation of the starting material was observed.

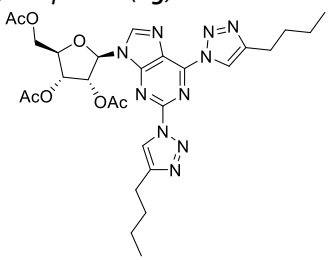
*Reaction of 2-Chloro-9-heptyl-6-(n-pentylselanyl)-9H-purine (**2c**) with NaN_3 in i-PrOH (Entry 5, Table 2).* 2-Chloro-9-heptyl-6-(*n*-pentylselanyl)-9*H*-purine (**2c**) (0.020 g, 1.0 equiv) and NaN_3 (0.010 g, 3.5 equiv) solution in *i*-PrOH (2 mL) was stirred under argon at 50 °C. H_2O (0.1 mL) was added to dissolve NaN_3. After 24 h, 9% formation of 2,6-diazido-9-heptyl-9*H*-purine (**5**) was observed by HPLC.

*Synthesis of 2,6-Bistriazolylpurine Derivatives **6e** and **6g**. 9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-2,6-bis(4-(2-fluorophenyl)-1H-triazol-1-yl)-9H-purine (**6e**).*



General procedure: Aqueous solution of acetic acid (10 wt %; 30 mL) was added to a stirred solution of 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-diazidopurine (3.0 g, 6.52 mmol, 1.0 equiv) and 2-fluorophenylacetylene (3.7 mL, ρ = 1.06 g/mL, 32.7 mmol, 5.0 equiv) in *t*-BuOH (90 mL) and acetone (15 mL). A solution of sodium ascorbate (0.12 g, 0.60 mmol, 9.2 mol %) in water (12 mL) and a solution of $CuSO_4{\cdot}5H_2O$ (0.09 g, 0.36 mmol, 5.5 mol %) in water (12 mL) were added, and the resulting reaction mixture was stirred at room temperature for 24 h (TLC control). Then the reaction mixture was cooled in an ice bath, and dry $NaHCO_3$ (2 g) was added to neutralize acetic acid. The resulting mixture was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (80 mL). The organic phase was washed with brine (3 × 80 mL), dried over anh. Na_2SO_4, and evaporated under reduced pressure. Solids were suspended in EtOH, filtered, and dried in vacuum. Product **6e** (2.56 g, 56%) was obtained as a pale green amorphous solid. R_f = 0.65 (toluene/MeCN = 3:1). IR ν (cm^{-1}): 1739, 1591, 1490, 1468, 1426, 1412, 1359, 1325, 1219, 1014, 996, 815, 753. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.40 (d, 1H, $^5J_{H-F}$ = 3.3 Hz H−C(triazole)), 9.09 (d, 1H, ^5J = 3.2 Hz, H−C (triazole)), 8.52 (s, 1H, H−C(8)), 8.47−8.37 (m, 2H, 2 × H−C(Ph)), 7.42−7.37 (m, 2H, 2 × H−C(Ph)), 7.35−7.30 (m, 2H, 2 × H−C(Ph)), 7.25−7.20 (m, 2H, 2 × H−C (Ar)), 6.46 (d, 1H, ^3J = 5.2 Hz, H−C(1′)), 5.92 (t, 1H, ^3J = 5.4 Hz, H−C(2′)), 5.69 (t, 1H, ^3J = 5.1 Hz, H−C(3′)), 4.59 (q, 1H, ^3J = 3.9 Hz, H−C(4′)), 4.52 (d, 2H, ^3J = 3.7 Hz, H−C(5′)), 2.22, 2.14, 2.13 (3s, 9H, 3 × Ac)). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) 170.3, 169.8, 169.7, 159.8 (D, $^1J_{C-F}$ = 249 Hz), 159.7 (D, $^1J_{C-F}$ = 249 Hz), 155.5, 149.0, 146.0, 145.2, 142.1 (D, $^3J_{C-F}$ = 2 Hz), 142.0 (D, $^3J_{C-F}$ = 2 Hz), 130.4 (D, $^3J_{C-F}$ = 9 Hz), 130.2 (D, $^3J_{C-F}$ = 8 Hz), 128.6 (D, $^3J_{C-F}$ = 3 Hz), 128.5 (D, $^3J_{C-F}$ = 3 Hz), 124.9 (2C) (assigned from HSQC and HMBC spectra), 123.0, 122.4 (D, $^4J_{C-F}$ = 14 Hz), 122.1 (D, $^4J_{C-F}$ = 13 Hz), 118.0 (D, $^2J_{C-F}$ = 13 Hz), 117.7 (D, $^2J_{C-F}$ = 13 Hz), 116.04 (D, $^2J_{C-F}$ = 22 Hz), 116.03 (D, $^2J_{C-F}$ = 21 Hz), 87.0, 81.2, 73.9, 70.9, 63.3, 20.9, 20.7, 20.6. ^{19}F NMR (470.5 MHz, $CDCl_3$): δ (ppm) −113.2, −113.5. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{32}H_{27}F_2N_{10}O_7$, 701.2032; found, 701.1996.

*9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-2,6-bis(4-butyl-1H-triazol-1-yl)-9H-purine (**6g**).*



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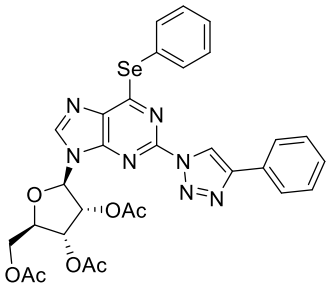
Compound **6g** was synthesized according to general procedure: 9-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-diazidopurine (2.3 g, 5.0 mmol, 1.0 equiv), *t*-BuOH (70 mL), acetone (12 mL), 1-hexyne (1.43 mL, ρ = 0.72 g/mL, 12.56 mmol, 2.5 equiv), aqueous solution of acetic acid (10 wt %; 23 mL), sodium ascorbate (0.092 g, 0.46 mmol, 9.2 mol %) in water (9 mL), and $CuSO_4 \cdot 5H_2O$ (0.069 g, 0.28 mmol, 5.6 mol %) in water (9 mL). Reaction conditions: 6 h at r.t. Silica gel column chromatography (toluene/EtOAc, gradient 50 → 100%) provided product **6g** (2.47 g, 79%) as a brown viscous solid. R_f = 0.70 (toluene/MeCN = 10/1). IR ν (cm^{-1}): 1748, 1611, 1588, 1457, 1369, 1215, 1032, 987, 809, 793. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.79 (s, 1H, H−C(8)), 8.52 (s, 1H, H−C(triazole)), 8.43 (s, 1H, H−C(triazole)), 6.38 (d, 1H, ^3J = 5.0 Hz, H−C(1′)), 5.91 (t, 1H, ^3J = 5.3 Hz, H−C(2′)), 5.71 (t, 1H, ^3J = 5.3 Hz, H−C(3′)), 4.55−4.52 (m, 1H, H−C(4′)), 4.51−4.40 (m, 2H, H_2−C(5′)), 2.91−2.82 (m, 4H, 2 × H_2−C), 2.19, 2.10, 2.08 (3s, 9H, 3 × Ac), 1.80−1.73 (m, 4H, 2 × H_2−C), 1.49−1.39 (m, 4H, 2 × H_2−C), 0.97 (t, 6H, ^3J = 7.4 Hz, 2 × H_3−C). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm): 170.3, 169.8, 169.7, 155.2, 149.6, 149.4, 149.2, 146.1, 145.0, 122.5, 121.0, 120.6, 87.0, 80.8, 73.7, 70.7, 63.1, 31.40, 31.37, 25.43, 25.41, 22.4 (2C) (assigned from HSQC and HMBC spectra), 20.8, 20.7, 20.5, 14.0, 13.9. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{28}H_{37}N_{10}O_7$, 625.2847; found, 625.2810.

General Procedures for the Synthesis of 6-Aryl(alkyl)-selanyl-2-triazolylpurine Derivatives (4a−m). *Method B for R³SeH Generation.* Diphenyl diselenide (0.5 mmol, 2 equiv) was dissolved in benzene (2 mL). 3.0 M HCl/H_2O (2 mL) was added, followed by zinc powder (2 mmol). The mixture was stirred under argon at room temperature until the color changed from yellow to colorless. An additional benzene (2 mL) was added, and the mixture was transferred to a separatory funnel, previously filled with argon. The benzene solution was allowed to flow through a layer of anhydrous Na_2SO_4 and was collected in a reaction flask under argon. The flask was placed in an oil bath, previously heated to 60 °C, and a solution of bis-triazole purine derivative **6** (0.25 mmol, 1 equiv) in benzene (5 mL) was added with a syringe, followed by anhydrous K_2CO_3 (1.0 mmol, 4 equiv). The mixture was stirred under argon at 60 °C, controlled by TLC or HPLC. After completion of the reaction, the reaction mixture was cooled and washed with NH_4Cl/H_2O (5 mL) and H_2O (5 mL); the benzene solution was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The silica gel column chromatography of the residue yielded the desired products **4d**, **4f**, **4h**, **4k**, as well as recovered diselenide and 4-substituted-1*H*-1,2,3-triazole.

Method C for R³SeH Generation. Anhydrous K_2CO_3 (0.5 mmol, 2 equiv) was added to a solution of 9-substituted-2,6-bis(1,2,3-triazol-1-yl)-9*H*-purine **6** (0.25 mmol, 1 equiv) in benzene (20 mL). The mixture was heated under argon to 50 °C, and commercial phenylselenol (0.5 mmol, 2 equiv) was added with a syringe under the level of solution. The mixture was stirred at 60 °C, controlled by TLC or HPLC. After completion of the reaction, the reaction mixture was cooled and washed with NH_4Cl/H_2O (5 mL) and H_2O (5 mL); the benzene solution was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The silica gel column chromatography of the residue, containing mainly the desired product, 4-substituted 1,2,3-triazole, and Ph_2Se_2, yielded the target products **4a**, **4b**, **4h**, and **4j**.

Method D for R³SeH Generation. Diselenide (1 mmol, 2 equiv) and sodium borohydride (2.0 mmol, 4 equiv) were placed in a round-bottom flask under argon. EtOAc (10 mL) was added, and the mixture was heated at 40 °C for 30−40 min until a white suspension was obtained. After cooling to room temperature, glacial acetic acid (0.58 mL, 10 mmol, 20 equiv) was added and the mixture was stirred for an additional 30 min. The solution of bis-triazolylpurine **6** (0.5 mmol, 1 equiv) in EtOAc (3 mL) was added, and the reaction mixture was stirred at 50−65 °C under argon, controlled by TLC or HPLC. After completion of the reaction, the reaction mixture was cooled and washed with H_2O (3 × 5 mL) and brine (5 mL) or NH_4Cl/H_2O (2 × 5 mL) and H_2O (2 × 5 mL); the organic solution was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The silica gel column chromatography of the residue yielded the target products **4**, as well as recovered diselenide and 4-substituted-1*H*-1,2,3-triazole.

*9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-6-(phenylselanyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-9H-purine (**4a**).*



Method C: 9-(2′,3′,5′-Tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-bis-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6a**) (166 mg, 0.25 mmol, 1 equiv), benzene (20 mL), anhydrous K_2CO_3 (69 mg, 0.5 mmol), and phenylselenol (78.5 mg, 52 μL, 0.50 mmol). Reaction conditions: 60 °C at 35 min. The reaction mixture contained the product **4a**, 4-phenyl-1*H*-1,2,3-triazole, and Ph_2Se_2. After column chromatography (toluene/MeCN, 0−10%), product **4a** was recrystallized from EtOH. Colorless solid. Yield: 100 mg, 59%.

Method D: 9-(2′,3′,5′-Tri-*O*-acetyl-*β*-D-ribofuranosyl)-2,6-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6a**) (665 mg, 1 mmol), diphenyl diselenide (640 mg, 2 mmol), $NaBH_4$ (160 mg, 4 mmol), AcOH (1.16 mL, 20 mmol), and EtOAc (20 mL). Reaction conditions: 12 h at 50 °C. Silica gel column chromatography (toluene/MeCN,10−25%). White foam after evaporation in vacuum. Yield: 400 mg, 60%. R_f = 0.52 (toluene/MeCN 3:1), mp 166−169 °C. IR ν (cm^{-1}): 3036, 2922, 2854, 1744, 1574, 1498, 1463, 1438, 1409, 1377, 1360. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (s, 1H, H−C(8)), 8.11 (s, 1H, H−C(triazole)), 7.84−7.78 (m, 4H, 2 × H−C(Ph), 2 × H−C(PhSe)), 7.61 (t, 1H, ^3J = 7.4 Hz, H−C(PhSe)), 7.54 (t, 2H, ^3J = 7.4 Hz, 2 × H−C(PhSe)), 7.46 (t, 2H, ^3J = 7.5 Hz, 2 × H−C(Ph)), 7.37 (t, 1H, ^3J = 7.5 Hz, H−C(Ph)), 6.37 (d, 1H, ^3J = 5.4 Hz, H−C(1′)), 5.82 (dd, 1H, ^3J = 5.5, 5.4 Hz), 5.69 (dd, 1H, ^3J = 5.5, 4.7 Hz, H−C(3′)), 4.53−4.45 (m, 3H, H−C(4′), H_2−C(5′)), 2.18, 2.11, 2.09 (3s, 9H, 3 × Ac). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.4, 169.8, 169.7, 163.1, 149.1, 148.7, 147.7, 142.4, 137.5, 133.4, 130.1, 129.7, 129.6, 129.0, 128.6, 125.9, 124.7, 119.0, 86.6, 80.9, 73.8, 71.0, 63.4, 20.9, 20.7, 20.6. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 463.0. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{30}H_{28}N_7O_7Se$, 678.1212; found, 678.1185.

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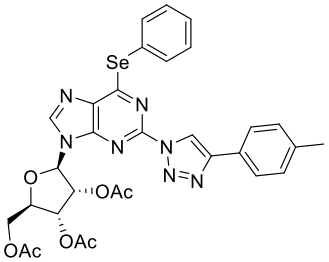
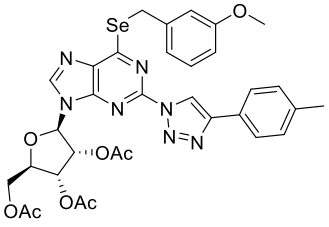
*9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-6-(phenylselanyl)-2-[4-(4-tolyl)-1H-1,2,3-triazol-1-yl]-9H-purine (**4b**).*



Method C: 9-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-bis-(4-tolyl-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6b**) (139 mg, 0.20 mmol, 1 equiv), benzene (20 mL), anhydrous K_2CO_3 (55 mg, 0.40 mmol), and phenylselenol (63 mg, 42 μL, 0.40 mmol). Reaction conditions: 60 °C at 1 h. After silica gel column chromatography (DCM/MeOH 50:1), product **4b** was recrystallized from EtOH. Colorless solid. Yield: 90 mg, 65%.

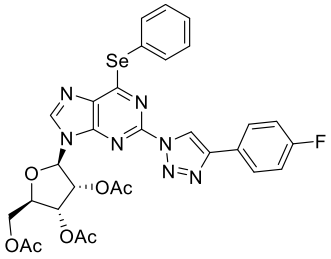
Method D: 9-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-bis(4-tolyl-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6b**) (173 mg, 0.25 mmol), diphenyl diselenide (156 mg, 0.5 mmol), $NaBH_4$ (38 mg, 1 mmol), acetic acid (0.24 mL, 4 mmol), and EtOAc (10 mL). Reaction conditions: 2 h at 60−65 °C. After silica gel column chromatography (toluene/MeCN 10/1 to 5/1), product **4b** was obtained as a colorless solid. Yield: 100 mg, 59%. R_f = 0.56 (toluene/MeCN 3:1). mp 172−173 °C. IR ν (cm^{-1}): 3110, 2917, 1749, 1571, 1493, 1460, 1436, 1395, 1360. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H, H−C(8)), 8.07 (s, 1H, H−C(triazole)), 7.80 (d, 2H, ^3J = 7.4 Hz, 2 × H−C(Ph)), 7.70 (d, 2H, ^3J = 8.0 Hz, 2 × H−C(Ar)), 7.60 (t, 1H, ^3J = 7.4 Hz, H−C(Ph)), 7.54 (t, 2H, ^3J = 7.4 Hz, 2 × H−C(Ph)), 7.27 (d, 2H, ^3J = 8.0 Hz, 2 × H−C(Ar)), 6.37 (d, 1H, ^3J = 5.3 Hz, H−C(1′)), 5.81 (dd, 1H, ^3J = 5.4, 5.3 Hz, H−C(2′)), 5.69 (dd, 1H, ^3J = 5.4, 4.6 Hz, H−C(3′)), 4.52−4.46 (m, 3H, H−C(4′), H_2−C(5′)), 2.40 (s, 3H, $-CH_3$), 2.18, 2.11, 2.09 (3s, 9H, 3 × Ac). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.4, 169.8, 169.7, 163.0, 149.1, 148.7, 147.8, 142.3, 138.5, 137.5, 133.3, 129.7 (2C) (observed with HSQC spectrum), 129.6, 127.3, 125.8, 124.7, 118.7, 86.6, 80.9, 73.9, 71.0, 63.4, 21.5, 20.9, 20.7, 20.6. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 462.7. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{31}H_{30}N_7O_7Se$ 692.1369; found, 692.1385.

*9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-6-[(3-methoxybenzyl)selanyl]-2-[4-(4-tolyl)-1H-1,2,3-triazol-1-yl]-9H-purine (**4c**).*



Compound **4c** was obtained according to method D from 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-bis(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6b**) (208 mg, 0.30 mmol), 1,2-bis(3-methoxybenzyl) diselenide (240 mg, 0.60 mmol), $NaBH_4$ (46 mg, 1,2 mmol), and acetic acid (0.40 mL) in EtOAc (8 mL). Reaction conditions: 4 h at 60−65 °C. HPLC showed 65% conversion. Silica gel column chromatography (toluene/EtOAc 10:1 to toluene/EtOAc 3:1) provided target product **4c**. Yield: 85 mg, 59% (brms). Yellow powder. R_f = 0.52 (toluene/MeCN 3:1). mp 87−90 °C. IR ν (cm^{-1}): 2927, 2857, 1745, 1570, 1516, 1502, 1490, 1457. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.91 (s, 1H, H−C(triazole)), 8.16 (s, 1H, H−C(8)), 7.92 (d, 2H, ^3J = 7.9 Hz, 2 × (Ar)), 7.29 (d, 2H, ^3J = 7.9 Hz, 2 × (Ar)), 7.21 (t, 1H, ^3J = 8.0 Hz, H−C(Bn)), 7.16−7.11 (m, 2H, 2 × H−C(Bn)), 6.77 (dd, 1H, ^3J = 8.0, 2.1 Hz, H−C(Bn)), 6.23 (d, 1H, ^3J = 4.3 Hz, H−C(1′)), 5.99 (dd, 1H, ^3J = 5.1, 4.3 Hz, H−C(2′)), 5.83 (dd, 1H, ^3J = 5.1, 5.5 Hz, H−C(3′)), 4.76 (s, 2H, $-CH_2-$), 4.52−4.45 (m, 2H, H−C(4′), H_a−C(5′)), 4.38 (dd, 1H, ^2J = 12.2 Hz, ^3J = 4.0 Hz, H_b−C(5′)), 3.74 (s, 3H, $-OCH_3$), 2.41 (s, 3H, $-CH_3$), 2.20, 2.13, 1.99 (3s, 9H, 3 × Ac). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.4, 169.9, 169.7, 163.3, 159.9, 148.9, 148.32, 148.25, 142.6, 139.6, 138.6, 134.0, 129.9, 129.7, 127.4, 126.1, 121.8, 118.6, 114.8, 113.4, 87.2, 80.3, 73.6, 70.5, 62.9, 55.4, 29.2, 21.5, 20.75, 20.73, 20.6. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 407.3. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{33}H_{34}N_7O_8Se$ 736.1632; found, 736.1613.

*9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-2-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]-6-(phenylselanyl)-9H-purine (**4d**).*



Method B: 9-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-bis-(4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6c**) (175 mg, 0.25 mmol, 1 equiv) in benzene (8 mL), diphenyl diselenide (310 mg, 1.0 mmol) and zinc powder (260 mg, 4.0 mmol) in benzene (8 mL), 3.0 M HCl/H_2O (4 mL), and K_2CO_3 (276 mg, 2.0 mmol). Reaction conditions: 1.5 h at 60 °C. The residue was suspended in hexane (10 mL) and filtered, and the precipitate was washed with hexane (3 × 3 mL). The hexane filtrate was evaporated to recover diphenyl diselenide. The silica gel column chromatography of the precipitate (toluene/EtOAc, 4:1 to 2:1) provided the target product **4d**. Colorless solid. Yield: 112 mg, 65%. R_f = 0.51 (toluene/MeCN 3:1), mp 190−191 °C.

Method D: Diphenyl diselenide (0.228 g, 0.73 mmol, 1.0 equiv), $NaBH_4$ (0.058 g, 1.53 mmol, 2.1 equiv), EtOAc (7 mL), AcOH (0.45 mL, 7.88 mmol, 10.8 equiv), and *p*-fluorophenyl-2,6-bistriazolylpurine derivative (**6c**) (0.196 g, 0.28 mmol, 0.38 equiv) in EtOAc (12 mL). Reaction conditions: 1.5 h at 60 °C and 24 h at r.t. Precipitated from toluene. Yield: 0.140 g, 62%. Colorless solid. R_f = 0.51 (toluene/MeCN = 3/1). IR ν (cm^{-1}): 3149, 3119, 2971, 1748, 1575, 1493, 1460, 1436, 1397. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (s, 1H, H−C(8)), 8.09 (s, 1H, H−C(triazole)), 7.82−7.76 (m, 4H, 2 × H−C(Ar), 2 × H−C(Ph)), 7.60 (t, 1H, ^3J = 7.4 Hz, H−C(Ph)), 7.54 (t, 2H, ^3J = 7.4 Hz, 2 × H−C(Ph)), 7.15 (t, 2H, ^3J = 8.6 Hz, 2 × H−C(Ar)), 6.35 (d, 1H, ^3J = 5.1 Hz, H−C(1′)), 5.84 (dd, 1H, ^3J = 5.3, 5.1 Hz, H−C(2′)), 5.71 (dd, 1H, ^3J = 5.3, 4.9 Hz, H−C(3′)), 4.53−4.44 (m, 3H, H−C(4′), H_2−C(5′)), 2.18, 2.10, 2.09 (3s, 9H, 3 × Ac). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.4, 169.8, 169.7, 163.1, 163.0 (D, $^1J_{C-F}$ = 248 Hz), 149.1, 148.6, 146.8, 142.5, 137.5, 133.4, 129.7, 129.6, 127.7 (D, $^3J_{C-F}$ = 8 Hz), 126.4 (D, $^4J_{C-F}$ = 3 Hz), 124.7, 118.8, 116.1 (D, $^2J_{C-F}$ = 22 Hz), 86.7, 80.9, 73.8, 71.0, 63.4, 20.9, 20.7, 20.6. ^{19}F NMR (470.5 MHz, $CDCl_3$): δ

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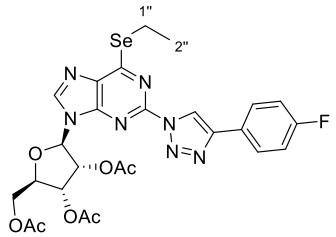
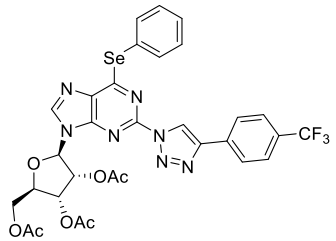
−113.0. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 463.1. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{30}H_{27}FN_7O_7Se$, 696.1118; found, 696.1113.

*9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-6-(ethylselanyl)-2-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]-9H-purine (**4e**).*



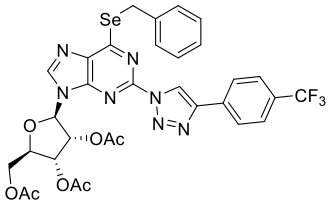
Compound **4e** was obtained according to method D from 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-bis(4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6c**) (175 mg, 0.25 mmol), diethyl diselenide (216 mg, 0.13 mL, 1.0 mmol), $NaBH_4$ (76 mg, 2.0 mmol), and acetic acid (0.58 mL) in EtOAc (10 mL). Reaction conditions: 25 h at 60−65 °C. Silica gel column chromatography (toluene/EtOAc 1:1). Yield: 131 mg, 80%. Colorless powder. R_f = 0.47 (Tol/MeCN 3:1). mp 174−175 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.92 (s, 1H, H−C(triazole)), 8.17 (s, 1H, H−C(8)), 8.01 (dd, 2H, ^3J = 8.6 Hz, $^4J_{H-F}$ = 5.4 Hz, 2 × H−C(Ar)), 7.16 (dd, 2H, ^3J = 8.6 Hz, $^3J_{H-F}$ = 8.5 Hz, 2 × H−C(Ar)), 6.24 (d, 1H, ^3J = 4.2 Hz, H−C(1′)), 5.99 (dd, 1H, ^3J = 4.9, 4.2 Hz, H−C(2′)), 5.84 (dd, 1H, ^3J = 5.6, 4.9 Hz), 4.52−4.45 (m, 2H, H−C(4′), H_a−C(5′)), 4.38 (dd, 1H, ^2J = 12.3 Hz, ^3J = 4.4 Hz, H_b-C(5′)), 3.53 (quartet, 2H, ^3J = 7.4 Hz, H_2−C(2″)), 2.19, 2.13, 2.00 (3s, 9H, 3 × Ac), 1.67 (t, 3H, ^3J = 7.4 Hz, H_3−C(2″)). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.4, 169.9, 169.7, 163.8, 163.1 (D, $^1J_{C-F}$ = 248 Hz), 148.8, 148.1, 147.2, 142.6, 134.4, 128.0 (D, $^3J_{C-F}$ = 8 Hz), 126.5 (D, $^4J_{C-F}$ = 3 Hz), 118.7, 116.1 (D, $^2J_{C-F}$ = 22 Hz), 87.2, 80.3, 73.6, 70.5, 62.9, 20.8, 20.7, 20.6, 20.0, 15.6. ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −113.0. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 374.5. IR ν (cm^{-1}): 2999, 2921, 1759, 1745, 1588, 1573, 1561, 1488, 1458. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{26}H_{27}FN_7O_7Se$, 648.1118; found, 648.1123.

*9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-2-[4-(4-trifluoromethylphenyl)-1H-1,2,3-triazol-1-yl]-6-(phenylselanyl)-9H-purine (**4f**).*



Compound **4f** was obtained according to Method B: 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-bis(4-(4-trifluoromethylphenyl)-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6d**) (200 mg, 0.25 mmol, 1 equiv) in benzene (8 mL), diphenyl diselenide (310 mg, 1.0 mmol), zinc powder (260 mg, 4.0 mmol) in benzene (8 mL), 3.0 M HCl/H_2O (4 mL), and K_2CO_3 (276 mg, 2.0 mmol). Reaction conditions: 1.5 h at 60 °C (HPLC control). The residue was suspended in hexane (10 mL), filtered, washed with hot hexane (3 × 4 mL), and dried in vacuum. White powder. Yield: 120 mg, 64%. R_f = 0.51 (toluene/MeCN 3:1). mp 190−191 °C. IR ν (cm^{-1}): 2933, 2861, 1748, 1623, 1571, 1493, 1460, 1440, 1361. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H, H−C(8)), 8.23 (s, 1H, H−C(triazole)), 7.94 (d, 2H, ^3J = 7.9 Hz, 2 × H−C(Ar)), 7.81 (d, 2H, ^3J = 7.3 Hz, 2 × H−C(Ph)), 7.72 (d, 2H, ^3J = 7.9 Hz, 2 × H−C(Ar)), 7.61 (t, 1H, ^3J = 7.3 Hz, H−C(Ph)), 7.55 (t, 2H, ^3J = 7.3 Hz, 2 × H−C(Ph)), 6.34 (d, 1H, ^3J = 4.2 Hz, H−C(1′)), 5.85 (dd, 1H, ^3J = 5.0, 4.2 Hz, H−C(2′)), 5.72 (dd, 1H, ^3J = 5.0, 4.8 Hz, H−C(3′)), 4.55−4.43 (m, 3H, H−C(4′), H_2−C(5′)), 2.19, 2.10, 2.09 (3s, 9H, 3 × Ac). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.4, 169.8, 169.7, 163.3, 149.0, 148.5, 146.3, 142.7, 137.5, 133.59, 133.57, 130.4 (Q, $^2J_{C-F}$ = 32 Hz), 129.7, 129.6, 126.1 (2C) (signal determined by HSQC spectrum), 126.0, 124.7, 124.2 (Q, $^1J_{C-F}$ = 272 Hz), 119.9, 86.9, 80.8, 73.8, 70.9, 63.3, 20.9, 20.7, 20.6. ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −62.6. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 464.3. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{31}H_{27}F_3N_7O_7Se$, 746.1084; found, 746.1078.

*9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-6-(benzylselanyl)-2-[4-(4-trifluoromethylphenyl)-1H-1,2,3-triazol-1-yl]-9H-purine (**4g**).*



Compound **4g** was obtained according to method D: 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-bis(4-(4-trifluoromethylphenyl)-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6d**) (320 mg, 0.4 mmol), dibenzyl diselenide (340 mg, 1 mmol), $NaBH_4$ (76 mg, 2 mmol), and acetic acid (0.58 mL) in 10 mL EtOAc. Reaction conditions: 3 h at 60−65 °C. Silica gel column chromatography (toluene/MeCN 5:1 to toluene/MeCN 2:1). White powder. Yield: 303 mg, 82%. R_f = 0.64 (tol/MeCN 3:1). mp 145−146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.10 (s, 1H, H−C(triazole)), 8.18 (d, 2H, ^3J = 8.1 Hz, 2 × H−C(Ar)), 8.16 (s, 1H, H−C(8)), 7.73 (d, 2H, ^3J = 8.1 Hz, 2 × H−C(Ar)), 7.57 (d, 2H, ^3J = 7.5 Hz, 2 × H−C(Ph)), 7.30 (t, 2H, ^3J = 7.5 Hz, 2 × H−C(Ph)), 7.23 (t, 1H, ^3J = 7.5 Hz, H−C(Ph)), 6.19 (d, 1H, ^3J = 4.1 Hz, H−C(1′)), 6.07 (dd, 1H, ^3J = 5.0, 4.1 Hz, H−C(2′)), 5.90 (dd, 1H, ^3J = 5.0, 5.4 Hz, H−C(3′)), 4.80 (s, 2H, −CH_2−), 4.52−4.45 (m, 2H, H−C(4′), H_a−C(5′)), 4.35 (dd, 1H, ^2J = 12.2 Hz, ^3J = 4.3 Hz, H_b−C(5′)), 2.21, 2.15, 1.95 (3s, 9H, 3 × Ac). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.4, 170.0, 169.7, 163.6, 148.6, 148.1, 146.8, 143.0, 138.0, 134.2, 133.7, 130.4 (Q, $^2J_{C-F}$ = 32 Hz), 129.5, 128.8, 127.5, 126.4, 126.0 (Q, $^3J_{C-F}$ = 8 Hz), 124.2 (Q, $^1J_{C-F}$ = 272 Hz), 120.0, 87.6, 80.0, 73.5, 70.3, 62.8, 29.2, 20.73, 20.67, 20.6. ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −62.6. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 409.5. IR ν (cm^{-1}): 2942, 1744, 1622, 1576, 1491, 1461, 1417, 1387. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{32}H_{29}F_3N_7O_7Se$, 760.1243; found, 760.1266.

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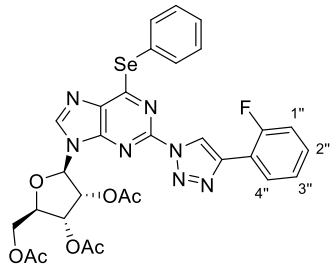
*9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-2-[4-(2-fluorophenyl)-1H-1,2,3-triazol-1-yl]-6-(phenylselanyl)-9H-purine (**4h**).*

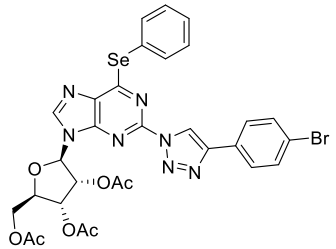


Method C: 9-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-bis-[4-(2-fluorophenyl)-1*H*-1,2,3-triazol-1-yl]-9*H*-purine (**6e**) (140 mg, 0.20 mol), phenylselenol (63 mg, 43 μL, 0.4 mmol), and K_2CO_3 (55 mg, 0.4 mmol) in benzene (20 mL). Reaction conditions: 2 h at 60 °C. Silica gel column chromatography (toluene/EtOAc 3:1). Yield: 82 mg, 59%.

Method B: EtOAC was used as a solvent instead of benzene. 9-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-bis-[4-(2-fluorophenyl)-1*H*-1,2,3-triazol-1-yl]-9*H*-purine (**6e**) (175 mg, 0.25 mg), diphenyl diselenide (156 mg, 0.5 mmol), Zn (130 mg, 2 mmol), 3 M HCl/H_2O (3 mL), and K_2CO_3 (69 mg, 0.5 mmol) in EtOAc (8 mL). Reaction conditions: 3 h at 60 °C. Silica gel column chromatography (toluene/EtOAc 3:1 to 1:1). Yield: 110 mg, 63%. Colorless powder. R_f = 0.53 (toluene/MeCN 3:1). mp 151−153 °C. IR ν (cm^{-1}): 2945, 1745, 1572, 1490, 1464, 1439, 1407, 1357. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (t, 1H, ^3J = 7.5 Hz, H−C(4″)), 8.28 (d, 1H, $^5J_{H-F}$ = 3.8 Hz, H−C(triazole)), 8.27 (s, 1H, H−C(8)), 7.79 (d, 2H, ^3J = 7.4 Hz, 2 × H−C(Ph)), 7.61 (t, 1H, ^3J = 7.4 Hz, H−C(Ph)), 7.54 (t, 2H, ^3J = 7.4 Hz, 2 × H−C(Ph)), 7.37−7.32 (m, H−C(2″), 7.28−7.26 (m, 1H, H−C(3″)), 7.19 (t, 1H, 9.5 Hz, H−C(1″)), 6.39 (d, 1H, ^3J = 5.5 Hz, H−C(1′)), 5.79 (dd, 1H, ^3J = 5.5, 5.2 Hz, H−C(2′)), 5.67 (dd, 1H, ^3J = 5.2, 4.3 Hz, H−C(3′)), 4.54−4.49 (m, 3H, H−C(4′), H_2−C(5′)), 2.18, 2.13, 2.08 (3s, 9H, 3 × Ac).

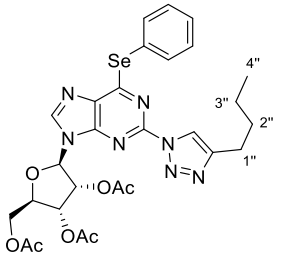
^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.3, 169.7, 169.6, 163.0, 159.4 (D, $^1J_{C-F}$ = 250 Hz), 149.0, 148.6, 142.1, 141.13 (D, $^3J_{C-F}$ = 2 Hz), 137.2, 133.3, 130.0, 129.6 (D, $^3J_{C-F}$ = 8 Hz), 129.5, 128.1 (D, $^3J_{C-F}$ = 3 Hz), 124.6 (D, $^4J_{C-F}$ = 3 Hz), 124.1, 122.0 (D, $^4J_{C-F}$ = 14 Hz), 118.1 (D, $^2J_{C-F}$ = 13 Hz), 115.8 (D, $^2J_{C-F}$ = 21 Hz), 86.4, 81.0, 73.8, 71.0, 63.4, 20.8, 20.6, 20.4. ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −113.6. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 461.3. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{30}H_{27}FN_7O_7Se$, 694.0973; found, 694.0970.

*9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-2-[4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl]-6-(phenylselanyl)-9H-purine (**4i**).*



Method D: 9-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-bis-[4-(4-bromophenyl)-1*H*-1,2,3-triazol-1-yl]-9*H*-purine (**6f**) (82 mg, 0.1 mmol), diphenyl diselenide (62.4 mg, 0.2 mmol), $NaBH_4$ (15.2 g, 0.4 mmol), and AcOH (0.12 mL) in EtOAc (6 mL). Reaction conditions: 18 h at 60 °C. After column chromatography (toluene/MeCN 3:1), the product was washed with hot ethanol (3 × 1 mL). Yield: 45 mg, 60%. Colorless solid. R_f = 0.47 (toluene/MeCN 3:1). mp 210−212 °C. IR ν (cm^{-1}): 3120, 2970, 1746, 1577, 1492, 1475, 1458, 1438, 1423, 1404. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H, H−C(8)), 8.13 (s, 1H, H−C(triazole)), 7.80 (d, 2H, ^3J = 7.3 Hz, 2 × H−C(Ph)), 7.68 (d, 2H, ^3J = 8.4 Hz, 2 × H−C(Ar)), 7.61−7.57 (m, 3H, 2 × H−C(Ar), H−C(Ph)), 7.53 (t, 2H, ^3J = 7.3 Hz, 2 × H−C(Ph)), 6.34 (d, 1H, ^3J = 5.1 Hz, H−C(1′)), 5.84 (dd, 1H, ^3J = 5.4, 5.1 Hz, H−C(2′)), 5.71 (dd, 1H, ^3J = 5.4, 5.0 Hz, H−C(3′)), 4.52−4.44 (m, 3H, H−C(4′), H_2−C(5′)), 2.18 (s, 3H, Ac), 2.09 (s, 6H, 2 × Ac). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.4, 169.8, 169.7, 163.2, 149.0, 148.6, 146.7, 142.6, 137.5, 133.5, 132.2, 129.7, 129.6, 129.1, 127.4, 124.7, 122.6, 119.2, 86.8, 80.9, 73.8, 71.0, 63.4, 20.9, 20.7, 20.6. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 464.0. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{30}H_{27}BrN_7O_7Se$ 756.0315; found, 756.0329.

*9-(2′,3′,5′-Tri-O-acetyl-β-D-ribofuranosyl)-2-(4-butyl-1H-1,2,3-triazol-1-yl)-6-(phenylselanyl)-9H-purine (**4j**).*



Method C: 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-bis-(4-butyl-1*H*-triazol-1-yl)-9*H*-purine (**6g**) (0.149 g, 0.24 mmol, 1.0 equiv), abs. toluene (19 mL), K_2CO_3 (0.066 g, 0.48 mmol, 2.0 equiv), and phenylselenol (0.05 mL, ρ = 1.48 g/mL, 0.48 mmol, 2.0 equiv). Reaction conditions: 90 min at 60 °C. HPLC showed 62% conversion. Silica gel column chromatography (Hex/EtOAc = 1/2). Yield: 47 mg, 48% (brms). Colorless solid. R_f = 0.49 (toluene/MeCN = 3/1).

Method D: 9-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-bis(4-butyl-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (156 mg, 0.25 mmol), diphenyl diselenide (160 mg, 0.50 mmol), $NaBH_4$ (38 mg, 1,0 mmol), and acetic acid (0.29 mL) in EtOAc (10 mL). Reaction conditions: 8 h at 60−65 °C. HPLC showed 62% conversion. Silica gel column chromatography (toluene/EtOAc 10:1 to toluene/EtOAc 3:1). Yield: 74 mg, 73% (brms). Off-white powder. R_f = 0.49 (toluene/MeCN 3:1). mp 80−83 °C. IR ν (cm^{-1}): 2958, 2931, 2858, 1745, 1571, 1493, 1459, 1439, 1365. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (s, 1H, H−C(8)), 7.75 (d, 2H, ^3J = 7.3 Hz, 2 × H−C(Ph)), 7.60 (s, 1H, H−C(triazole)), 7.53 (t, 1H, ^3J = 7.3 Hz, H−C(Ph)), 7.48 (t, 2H, ^3J = 7.3 Hz, 2 × H−C(Ph)), 6.39 (d, 1H, ^3J = 5.7 Hz, H−C(1′)), 5.77 (dd, 1H, ^3J = 5.7, 5.4 Hz, H−C(2′)), 5.63 (dd, 1H, ^3J = 5.4, 4.3 Hz, H−C(3′)), 4.51−4.43 (m, 3H, H−C(4′), H_2−C(5′)), 2.71 (t, 2H, ^3J = 7.4 Hz, H_2−C(1″)), 2.16, 2.11, 2.06 (3s, 9H, 3 × Ac), 1.61 (quintet, 2H, ^3J = 7.4 Hz, H_2−C(2″)), 1.37 (quintet, 2H, ^3J = 7.4 Hz, H_2−C(3″)), 0.95 (t, 3H, ^3J = 7.4 Hz, H_3−C(4″)). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.3, 169.8, 169.7, 162.7, 149.2, 148.9, 148.6, 142.1, 137.4, 133.1, 129.6, 129.5, 124.6, 120.3, 86.1, 81.0, 73.8, 71.1, 63.4, 31.0, 25.2, 22.2, 20.9, 20.7, 20.5, 14.0. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 460.5. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{28}H_{32}N_7O_7Se$ 658.1525; found, 658.1530.

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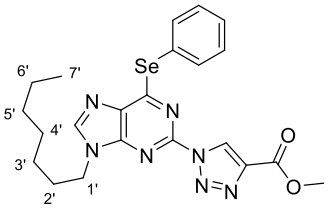
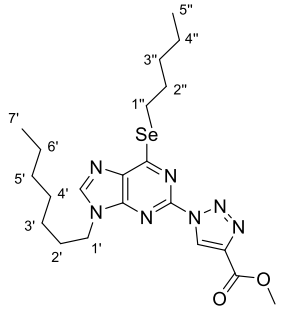
*9-Heptyl-2-(4-methoxycarbonyl-1H-1,2,3-triazol-1-yl)-6-(phenylselanyl)-9H-purine (**4k**).*



Method B: 9-Heptyl-2,6-bis(4-methoxycarbonyl-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6h**) (79 mg, 0.17 mmol) in benzene (3 mL), diphenyl diselenide (105 mg, 0.34 mmol), zinc powder (240 mg, 3.67 mmol), 2.9 M HCl/H_2O (5 mL) in benzene (5 mL), and K_2CO_3 (94 mg, 0.68 mmol). Reaction conditions: 1 h at 50−60 °C (HPLC control). Silica gel column chromatography (toluene/EtOAc 6:1 to 4:1). Yield: 72 mg, 86%. Colorless solid.

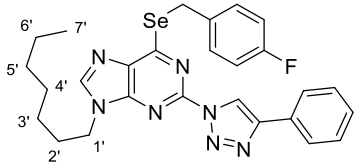
Method D: 9-Heptyl-2,6-bis(4-methoxycarbonyl-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6h**) (468 mg, 1 mmol), diphenyl diselenide (624 mg, 2 mmol), $NaBH_4$ (152 mg, 4 mmol), AcOH (1,2 mL, 2 mmol), and *i*-PrOH (40 mL). Reaction conditions: 1 h at 60−65 °C. The reaction mixture was evaporated, and the residue was suspended in ethanol (5 mL), filtered, and washed with cold ethanol (2 × 2 mL). Yield: 412 mg, 87%. Colorless solid. R_f = 0.52 (toluene/MeCN 4:1). mp 142−143 °C. IR ν (cm^{-1}): 2945, 2928, 2852, 1747, 1717, 1575, 1560, 1499, 1458, 1439, 1408. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (s, 1H, H−C(triazole)), 8.11 (s, 1H, H−C(8)), 7.77 (d, 2H, ^3J = 7.4 Hz, 2 × H−C(Ph)), 7.57 (t, 1H, ^3J = 7.4 Hz, H−C(Ph)), 7.51 (t, 2H, ^3J = 7.4 Hz, 2 × H−C(Ph)), 4.34 (t, 2H, ^3J = 7.2 Hz, H_2−C(1′)), 3.98 (s, 3H, −OCH_3), 1.95 (quintet, 2H, ^3J = 7.2 Hz, H_2−C(2′)), 1.37−1.24 (m, 8H, 4 × (−CH_2−)), 0.86 (t, 3H, ^3J = 6.8 Hz, H_3−C(7′)). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 162.4, 161.0, 149.4, 148.1, 144.9, 139.9, 137.3, 133.4, 129.9, 129.7, 127.4, 124.5, 52.5, 44.6, 31.7, 30.1, 28.8, 26.7, 22.6, 14.1. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 456.7. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{22}H_{26}N_7O_2Se$, 500.1309; found, 500.1326.

*9-Heptyl-2-(4-methoxycarbonyl-1H-1,2,3-triazol-1-yl)-6-(pentylselanyl)-9H-purine (**4l**).*



Method D: Dipentyl diselenide (0.128 g, 0.42 mmol, 1.0 equiv), $NaBH_4$ (0.032 g, 0.84 mmol, 2.0 equiv), EtOAc (5 mL), AcOH (0.24 mL, 4.20 mmol, 10.0 equiv), and 9-heptyl-2,6-bis(4-methoxycarbonyl-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6h**) (0.100 g, 0.21 mmol, 0.50 equiv) in EtOAc (10 mL). Reaction conditions: 12 h at 60 °C and 24 h at 80 °C. HPLC showed 52% conversion. Purification by column chromatography using a Büchi Pure C810 system (DCM/MeCN, gradient 0 → 3%) and by preparative HPLC. Yield: 40.0 mg, 74% (brms). Colorless amorphous solid. R_f = 0.45 (toluene/MeCN = 5/1). IR ν (cm^{-1}): 2951, 2928, 2854, 1727, 1579, 1458, 1354, 1258, 1154, 1026, 945, 858, 774. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 9.11 (s, 1H, H−C(triazole)), 8.08 (s, 1H, H−C(8)), 4.32 (t, 2H, ^3J = 7.4 Hz, H_2−C(1′)), 4.03 (s, 3H, −OCH_3), 3.48 (t, 2H ^3J = 7.4 Hz, H_2−C(1″)), 1.98−1.89 (m, 4H, H_2−C(2′), H_2−C(2″)), 1.50 (quintet, 2H ^3J = 7.7 Hz, H_2−C(3″)), 1.44−1.38 (m, 2H, H_2−C(4″)), 1.37−1.22 (m, 8H, 4 × (−CH_2−)), 0.92 (t, 3H, ^3J = 7.4 Hz, H_3−C(5″)), 0.87 (t, 3H, ^3J = 6.6 Hz, H_3−C(7″)). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm): 162.9, 161.2, 148.8, 148.2, 144.4, 140.1, 134.2, 127, 52.6, 44.5, 32.2, 31.7, 30.1, 29.9, 28.8, 26.7, 25.9, 22.6, 22.34, 14.14, 14.12. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ (ppm): 336.7. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{21}H_{32}N_7O_2Se$, 494.1778; found, 494.1795.

*6-[(4-Fluorobenzyl)selanyl]-9-heptyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-9H-purine (**4m**).*



Method D: 1,2-Bis(4-fluorobenzyl) diselenide (188 mg, 1 mmol), $NaBH_4$ (76 mg, 2 mmol), EtOAc (20 mL), glacial acetic acid (0.6 mL, 10 mmol), and 9-heptyl-2,6-bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)-9*H*-purine (**6i**) (252 mg, 0.5 mmol) in DMF (4 mL). Reaction conditions: 30−40 min at 40 °C and 4 h at 50−60 °C under argon. HPLC showed unreacted bis-triazole, but additional heating did not improve the conversion. HPLC showed 60% conversion. The reaction mixture was evaporated to remove EtOAc and then taken in 5 volumes of cold water. After 12−14 h at 4 °C, water was decanted from the thick yellow oil which was evaporated with MeCN (3 × 10 mL). Silica gel column chromatography (toluene/MeCN, 0−40%). Colorless solid. Yield: 120 mg, 73% (brms). R_f = 0.39 (toluene/MeCN 9:1). mp 126−127 °C. IR ν (cm^{-1}): 3165, 3102, 3060, 3036, 2953, 2928, 2855, 1574, 1508, 1495, 1461, 1444,1406, 1390, 1361, 1327. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.78 (s, 1H, H−C(triazole)), 8.03 (s, 1H, H−C(8)), 7.97 (d, 2H, ^3J = 7.6 Hz, 2 × H−C(Ph)), 7.55 (dd, 2H, ^3J = 8.3 Hz, $^4J_{H-F}$ = 5.5 Hz, 2 × H−C(Bn)), 7.48 (t, 2H, ^3J = 7.6 Hz, 2 × H−C(Ph)), 7.39 (t, 1H, ^3J = 7.6 Hz, H−C(Ph)), 6.98 (t, 2H, ^3J = 8.6 Hz, 2 × H−C(Bn)), 4.75 (s, 2H, −CH_2−), 4.31 (t, 2H, ^3J = 7.2 Hz, H_2−C(1′)), 1.95 (quintet, 2H, ^3J = 7.2 Hz, H_2−C(2′)), 1.39−1.25 (m, 8H, 4 × (−CH_2−)), 0.87 (t, 3H, ^3J = 6.8 Hz, H_3−C(7′)). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 162.1 (D, $^1J_{C-F}$ = 246 Hz), 161.7, 149.1, 148.7, 148.0, 144.2, 134.2 (D, $^4J_{C-F}$ = 3 Hz), 133.5, 131.2 (D, $^3J_{C-F}$ = 8 Hz), 130.2, 129.1, 128.7, 126.2, 118.7, 115.7 (D, $^2J_{C-F}$ = 22 Hz), 44.5, 31.7, 30.0, 28.8, 28.1, 26.7, 22.7, 14.1. ^{77}Se NMR (95.4 MHz, $CDCl_3$): δ 403.4. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{27}H_{29}FN_7Se$, 550.1630; found, 550.1645.

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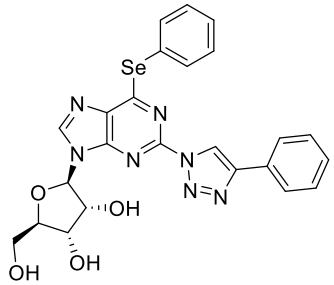
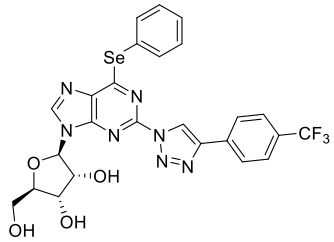
*Deprotection of Acetyl Protecting Groups from Ribosyl Moiety. 9-(β-D-Ribofuranosyl)-6-(phenylselanyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-9H-purine (**7a**).*



Suspension of compound **4a** (100 mg, 0.15 mmol) in NH_3/H_2O, 25% (8 mL), was stirred at r.t. under argon for 2 days (controlled by HPLC). After completion of the reaction, the mixture was placed in a freezer at −10 °C overnight. The suspension was filtered, and the precipitate was washed with cold water (3 × 1 mL) and dried in vacuum. Colorless solid. Yield: 50 mg, 62%. R_f = 0.11 (EtOAc); mp 230−235 °C. IR ν (cm^{-1}): 3343 (broad), 2927, 2885, 1571, 1491, 1477, 1460, 1445, 1404, 1359, 1330. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.91 (s, 1H, H−C(8)), 8.56 (s, 1H, H−C(triazole)), 7.85 (t, 4H, ^3J = 7.2 Hz, 4 × H−C(Ph)), 7.64−7.54 (m, 3H, 3 × H−C(Ph)), 7.52 (t, 2H, ^3J = 7.2 Hz, 2 × H−C(Ph)), 7.41 (t, 1H, ^3J = 7.2 Hz, H−C(Ph)), 6.09 (d, 1H, ^3J = 5.1 Hz, H−C(1′)), 5.61, 5.32, 5.05 (3s, 3H, 3 × HO), 4.69−4.64 (m, 1H, H−C(2′)), 4.27−4.22 (m, 1H, H−C(3′)), 4.04−3.99 (m, 1H, H−C(4′)), 3.73, 3.61 (2d, 2H, ^2J = 11.2 Hz, H_2−C(5′)). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 160.1, 149.1, 147.7, 146.5, 145.2, 136.6, 133.0, 129.6, 129.5, 129.4, 129.2, 128.6, 125.4, 124.5, 119.4, 87.8, 86.0, 73.9, 70.3, 61.2. ^{77}Se NMR (95.4 MHz, DMSO-d_6): δ 458.3. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{24}H_{22}N_7O_4Se$, 552.0895; found, 552.0918.

*9-(β-D-Ribofuranosyl)-2-[4-(4-trifluoromethylphenyl)-1H-1,2,3-triazol-1-yl]-6-(phenylselanyl)-9H-purine (**7b**).*



Suspension of **4f** (60 mg, 0.08 mmol) in NH_3/H_2O, 25% (3 mL), was stirred for 2 days at r.t. (controlled by HPLC). After completion of the reaction, the suspension was cooled and filtered. The precipitate was washed with water (4 × 2 mL) and dried in vacuum. White powder. Yield: 40 mg, 80%. R_f = 0.12 (EtOAc). mp 210−212 °C. IR ν (cm^{-1}): 3340 (broad), 2926, 2883, 1570, 1492, 1477, 1460, 1440, 1403, 1360, 1330. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.91 (s, 1H, H−C(8)), 8.78 (s, 1H, H−C(triazole)), 8.10 (d, 2H, ^3J = 8.2 Hz, 2 × H−C(Ph)), 7.89 (d, 2H, ^3J = 8.2 Hz, 2 × H−C(Ph)), 7.85 (d, 2H, ^3J = 7.4 Hz, 2 × H−C(Ph)), 7.65−7.54 (m, 3H, 3 × H−C(Ph)), 6.09 (d, 1H, ^3J = 5.5 Hz, H−C(1′)), 5.60 (d, 1H, ^3J = 5.7 Hz, HO−), 5.31 (d, 1H, ^3J = 5.0 Hz, HO−), 5.07−5.03 (m, 1H, HO−), 4.70−4.63 (m, 1H, H−C(2′)), 4.27−4.22 (m, 1H, H−C(3′)), 4.05−3.99 (m, 1H, H−C(4′)), 3.78−3.68 (m, 2H, H_2−C(5′)). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 160.1, 149.1, 147.6, 145.23, 145.18, 136.5, 133.6, 133.1, 129.54, 129.49, 128.6 (Q, ^2J = 32 Hz), 126.1 (Q, ^4J = 4 Hz), 126.0, 124.6, 124.1 (Q, ^1J = 272 Hz), 120.8, 87.7, 86.0, 73.9, 70.3, 61.2. ^{19}F NMR (470.5 MHz, DMSO-d_6): δ −61.1. ^{77}Se NMR (95.4 MHz, DMSO-d_6): δ 458.5. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{25}H_{21}F_3N_7O_4Se$, 620.0768; found, 620.0766.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c04994.

^{1}H-, ^{13}C-, ^{19}F-, and ^{77}Se-NMR spectra of compounds **2a−f**, **6e**, **6g**, **4a−m**, and **7a−b** (PDF)

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Notes

The authors declare no competing financial interest.

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