European Journal of Medicinal Chemistry 208 (2020) 112767

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Synthesis of ticagrelor analogues belonging to 1,2,3-triazolo[4,5-*d*] pyrimidines and study of their antiplatelet and antibacterial activity

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ARTICLE INFO

Article history:
Received 27 May 2020
Received in revised form
13 August 2020
Accepted 15 August 2020
Available online 23 August 2020

Keywords:
Ticagrelor
Antiplatelet agents
Antibiotics
1,2,3-triazolo[4,5-*d*]pyrimidines
8-Azapurines

ABSTRACT

Based on the recent observation that the antiplatelet agent ticagrelor and one of its metabolite exert bactericidal activity against gram-positive bacteria, a series of 1,2,3-triazolo[4,5-*d*]pyrimidines structurally related to ticagrelor were synthesized and examined as putative antiplatelet and antibacterial agents. The aim was to assess the possibility of dissociating the two biological properties and to find novel 1,2,3-triazolo[4,5-*d*]pyrimidines expressing antiplatelet activity and devoid of *in vitro* antibacterial activity. The new compounds synthesized were known metabolites of ticagrelor as well as structurally simplified analogues. Some of them were found to express antiplatelet activity and to lose the antibacterial activity, supporting the view that the two activities were not necessarily linked.

1. Introduction

Ticagrelor (**1**; Fig. 1) is an orally active antiplatelet drug belonging to 1,2,3-triazolo[4,5-*d*]pyrimidines (8-azapurines), which acts by reversibly inhibiting the platelet P2Y12 receptor for ADP in a noncompetitive manner [1,2]. This drug used in human medicine was developed to improve the efficacy and circumvent the limitations of the first-generation P2Y12 inhibitors [3,4]. Although ticagrelor doesn't need to be metabolized to be active *in vivo*, this drug is known to be extensively metabolized via cytochrome P450 3A4 and 3A5 to form a main metabolite known as AR-C124910, representing approximately one third of ticagrelor in the circulation [5]. Ticagrelor and its main metabolite inhibit P2Y12 receptors with equivalent potency [5]. Recently, we observed that ticagrelor and its active metabolite AR-124910 also exert *in vitro* bactericidal activity against Gram-positive strains, including antibiotic-resistant strains, such as *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Enterococcus faecalis* [6]. As a result, ticagrelor might prove superior to other P2Y12 inhibitors in patients with cardiovascular disease at risk for gram-positive bacterial infections such as infective endocarditis [6]. Another well-known additional benefit of ticagrelor compared to other clinically used P2Y12 inhibitors is also its ability to exert anti-inflammatory activity, notably by decreasing inflammatory cytokines such as interleukin 6 and tumor necrosis factor alpha as well as platelet-leukocyte aggregates or by acting directly on endothelial cells, independently of the P2Y12 receptor [7–11].

N^7-substituted 7-amino-5-alkylsulfanyl-1,2,3-triazolo[4,5-*d*]pyrimidines, among which the antiplatelet agent ticagrelor, are relatively poorly described in the literature. Besides examples of P2Y12 receptor antagonists structurally related to ticagrelor [1,12], recent publications also reported compounds of this chemical class expressing antiproliferative activity [i.e. compound **2** [13]; compound **3** [14]; compound **4** [15]; compound **5** [16]; i.e. compound **6**, identified as a lysine specific demethylase 1 (LSD1) inhibitor [17]; Fig. 1]. No indication of antibacterial activity was reported for compounds of this class until the recent discovery of the antibiotic effect of ticagrelor on several Gram-positive bacterial strains.

The present work aims at establishing structure-activity relationships in order to identify the structural elements responsible, on the one hand, for the antiplatelet activity, and, on the other hand, for the antibacterial activity of ticagrelor analogues i.e. some

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https://doi.org/10.1016/j.ejmech.2020.112767
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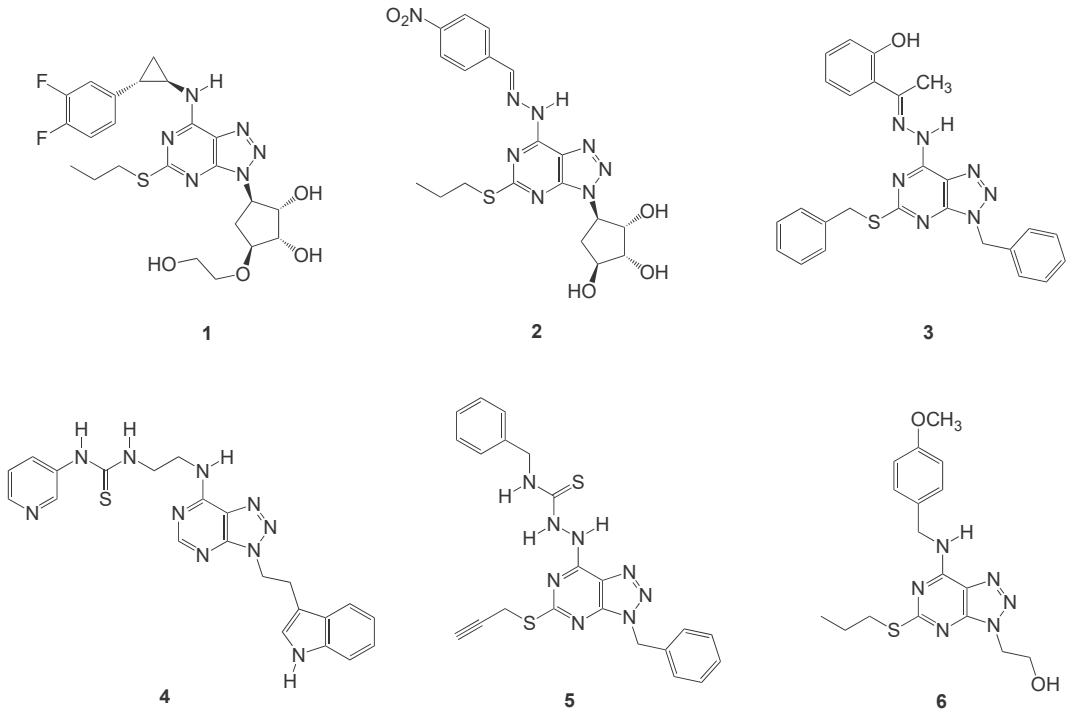


Fig. 1. Examples of N^7-substituted 7-amino-5-alkylsulfanyl-1,2,3-triazolo[4,5-*d*]pyrimidines described in the literature (**1**: ticagrelor).

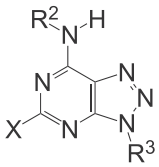
of its metabolites as well as simplified structures (general formula, see **7**; Fig. 2).

2. Results and discussion

2.1. Chemistry

The synthesis of the target compounds (**7**; Fig. 2) is described in Scheme 1. Several steps were adaptations of previously described processes [12]. Starting from thiobarbituric acid (**8**), alkylation in aqueous alkaline medium using an appropriate alkyl halide led to the 2-alkylsulfanyl-substituted derivatives of general formula **9**, which in turn were converted into the corresponding 5-nitro-substituted derivatives **10** after reaction with nitric acid in glacial acetic acid. The latter compounds reacted with phosphorus oxychloride in the presence of 2,6-lutidine to provide the corresponding 4,6-dichloro-substituted compounds **11b**. These intermediates **11b**, as well as the commercially available 2,4,6-trichloro-substituted analogue **11a**, were easily converted into the corresponding 5-amino-substituted compounds **12a** and **12b** after reduction in the presence of iron powder in a mixture of acetic acid and methanol. The appropriate primary amine [R^3-NH_2: methylamine, ethylamine, cyclopentylamine, (3a*R*,4*S*,6*R*,6a*S*)-6-amino-2,2-dimethyltetrahydrocyclopenta[*d*][1,3]dioxol-4-ol and 2-(((3a*R*,4*S*,6*R*,6a*S*)-6-amino-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)oxy)ethanol] was introduced at the 3-position of intermediates **12a-b** after nucleophilic substitution in methanol of one chlorine atom linked to the ortho position of the amine function. Ring closure reaction occurred after diazotization in the presence of sodium nitrite and acetic acid to provide the triazolo[4,5-*d*]pyrimidine intermediates **14a-c**. Due to the increased sensitivity of the 7-position of triazolo[4,5-*d*]pyrimidines to nucleophilic substitution as a probable result of the vicinity of the triazole ring, the chlorine atom at this position was easily substituted with the appropriate alkyl/aralkylamine [R^2-NH_2; cyclopropylamine, 3,4-difluorophenethylamine, (1*R*,2*S*)-2-phenylcyclopropylamine or (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropylamine] in acetonitrile in the presence of triethylamine, leading to intermediates **15a-c**. Strong nucleophiles such as thiols were able to displace the last chlorine atom linked at the 5-position of the triazolo[4,5-*d*]pyrimidine ring system giving access to compounds of general formula **7**. The final compounds bearing a polyhydroxypentane group (compounds **7h-t**) at the 3-position were obtained after removal of the acetonide protecting group under strong acidic conditions.

An interesting observation was made with the target compounds bearing an aralkylamino group at the 7-position of the 1,2,3-triazolo[4,5-*d*]pyrimidine core structure. The ^{1}H NMR spectral data of these drugs recorded in DMSO-d_6 always revealed the presence of two groups of signals. This was particularly evident for the N-H proton linked at the 7-position of the triazolopyrimidine ring and for the C-H proton linked at the first carbon atom of the cyclopropyl ring of (3,4-difluorophenyl)cyclopropylamino-substituted compounds (Table 2). Such an observation is in accordance with the existence of an equilibrium between two



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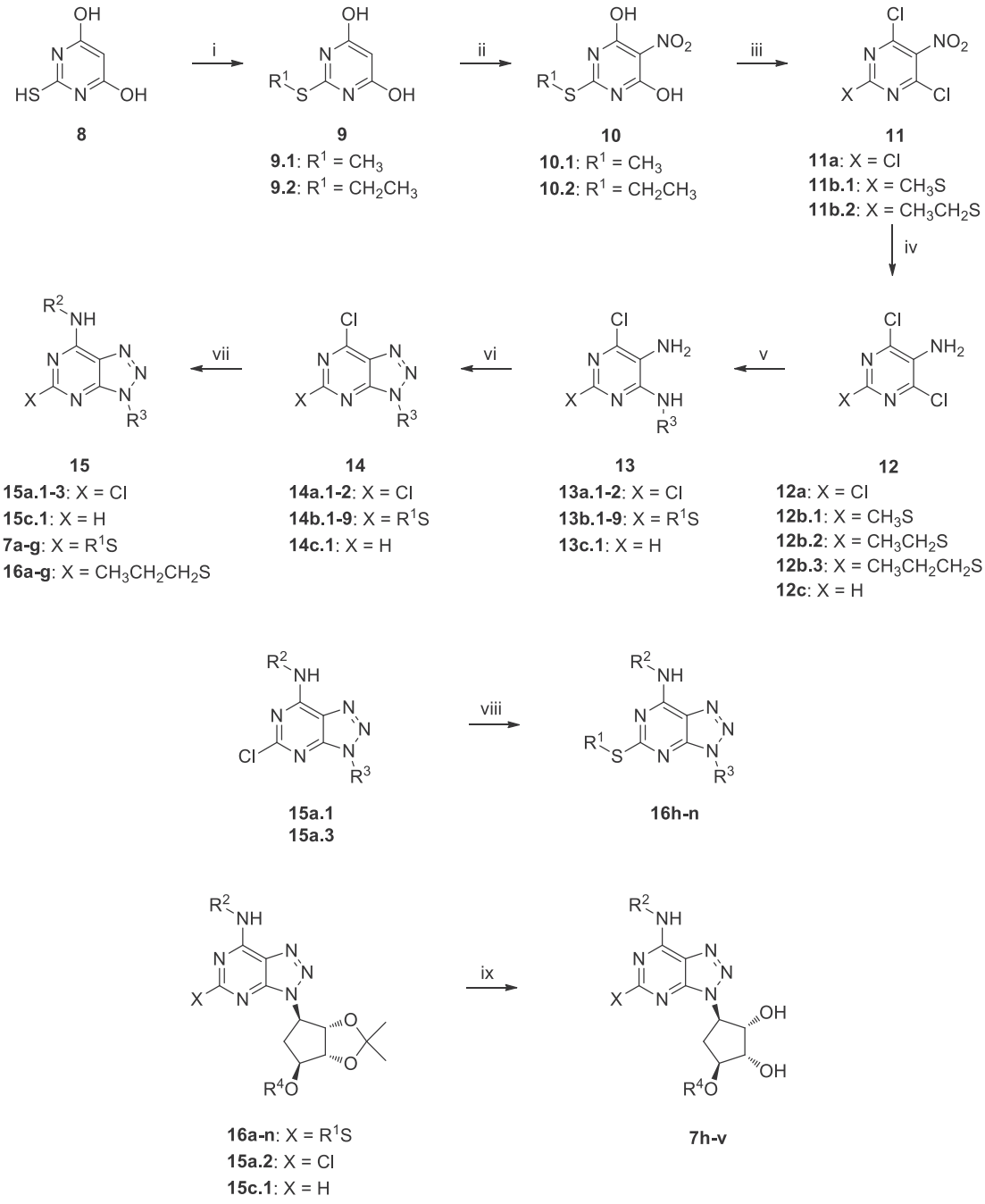
X = R^1S: **7a-t**

X = H: **7u**

X = Cl: **7v**

Fig. 2. General formula of the newly synthesized compounds.



Scheme 1. Synthesis of Ticagrelor Analogues Belonging to 1,2,3-Triazolo[4,5-*d*]pyrimidines.
Reagents and conditions: (i) R^1X, KOH, water, 80 °C, sealed tube, 2 h; (ii) nitric acid, acetic acid, 0 °C to r.t., 1 h; (iii) $POCl_3$, 2,6-lutidine, 0 °C–80 °C, 2 h; (iv) iron powder, acetic acid, methanol, r.t., 2 h; (v) R^3NH_2, methanol, 110 °C, sealed tube, 1 h; (vi) $NaNO_2$, acetic acid, 0 °C to r.t., 2 h; (vii) R^2NH_2, TEA, acetonitrile, 80 °C, 1–4 h; (viii) R^1SH, K_2CO_3, acetonitrile, 60–110 °C, 3 h; (ix) HCl, methanol, r.t., 30 min.

conformational isomers resulting from the rotation around the C^8-$N^{1'}$ bond (Fig. 3) (also reported for azaadenine derivatives [18]), the former isomers being the two preferred conformations assuming an optimal delocalization of electrons in the planar "amidine" system (numbering N^7-C^8-$N^{1'}$ in Fig. 3). In accordance with the planarity of the system, and for steric reasons, conformer B is expected to be the major form (estimation from NMR data in DMSO-d_6 at r.t.: 80% of conformer B *versus* 20% of conformer A). The preference of the B conformation for ticagrelor (and for related analogues) is confirmed by crystallographic data obtained with the antiplatelet agent (alone or in co-crystalisation) revealing the presence of conformer B in the crystal lattices [19–21]. The planarity of the "amidine" system was also confirmed from the crystallographic data obtained with ticagrelor alone providing a torsion angle C^9-C^8-$N^{1'}$-$C^{1'}$ of 178.6°, thus not far fom the planarity (180.0°) [20].

The attribution of the chemical shifts reported in Table 2 is deduced from the influence of the proximity of the N^1 nitrogen atom, which is expected to induce a greater deshielding of the C-H proton in the case of conformer A, and a greater deshielding of the N-H proton in the case of conformer B.

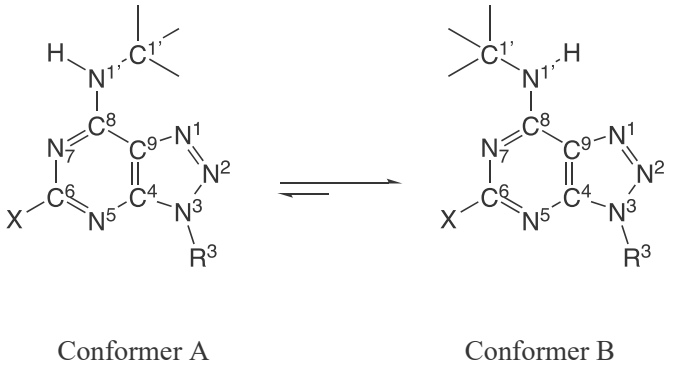


Fig. 3. Conformational isomerism resulting from the rotation around the C^8-$N^{1'}$ bond of N^7-substituted 7-amino-1,2,3-triazolo[4,5-*d*]pyrimidines.

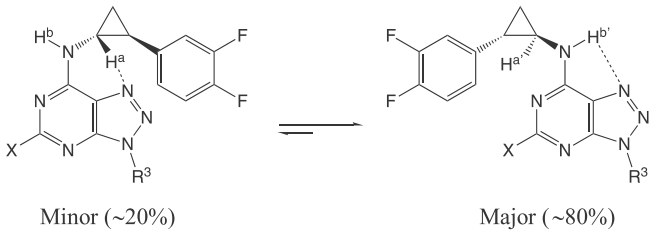
2.2. Biological evaluation

Table 1 reports the biological results (antiplatelet and antibacterial activity) obtained with ticagrelor (**1**), several of its metabolites (**7i**, **7n-t**) and simplified analogues of ticagrelor bearing a short alkyl group at the 3-position and/or a short alkylsulfanyl group at the 5-position and/or a simplified aralkylamino group at the 7-position (**7a-h**, **7j-m**, **7u-v**). The aim was to examine the antiplatelet *versus* antibacterial activity of other known ticagrelor metabolites as well as a series of original simplified analogues.

The antiplatelet activity of the tested molecules was analyzed by light transmission aggregometry upon platelet stimulation with ADP in citrated platelet-rich-plasma using a drug concentration equal to ticagrelor IC_{50} (1.8 μM) (Fig. 4). The antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA, ATCC BAA-1556) was determined by the broth microdilution method as recommended by EUCAST guidelines.

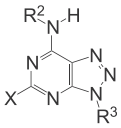
Only ticagrelor (**1**) and its main metabolite AR-C124910 (**7i**) showed antibacterial activity against MRSA. The other compounds revealed absence of activity against bacteria up to a concentration

Table 2
^{1}H NMR Chemical Shifts (in ppm) Attributed to the C-H Proton (H^a or $H^{a'}$) Linked to the First Cyclopropyl Carbon Atom and to the N-H Proton (H^b or $H^{b'}$) at the 7-Position of the 1,2,3-Triazolo[4,5-*d*]pyrimidine Ring.



Cmpd	-X	-R^3	C-H		N-H	
			H^a	$H^{a'}$	H^b	$H^{b'}$
7a	-SCH_3	-CH_3	3.76	3.15	8.96	9.34
7d	-SCH_2CH_3	-CH_2CH_3	3.77	3.16	8.96	9.37
7i	-$SCH_2CH_2CH_3$	-$C_5H_6(OH)_3$	3.78	3.16	8.93	9.35
1	-$SCH_2CH_2CH_3$	-$C_5H_6(OH)_2OCH_2CH_2OH$	3.79	3.16	8.94	9.36
7u	-H	-$C_5H_6(OH)_3$	3.82	3.29	9.04	9.34
7v	-Cl	-$C_5H_6(OH)_3$	3.82	3.14	9.53	9.81

Table 1
Antiplatelet activity of 1,2,3-triazolo[4,5-*d*]pyrimidines structurally related to ticagrelor; antibacterial activity established on methicillin-resistant *S. aureus*.



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Cpd	-X	-R^2	-R^3	Antiplatelet activity (Fold-inhibition vs vehicle[a])	Antibacterial activity (MIC[b], μM)
7a	-SCH_3	-$CH(CH_2)CH$-$C_6H_3F_2$	-CH_3	0.94 ± 0.09	>200
7b	-SCH_3	-$CH(CH_2)CH$-$C_6H_3F_2$	-CH_2CH_3	0.87 ± 0.04	>200
7c	-SCH_2CH_3	-$CH(CH_2)CH$-$C_6H_3F_2$	-CH_3	0.97 ± 0.08	>200
7d	-SCH_2CH_3	-$CH(CH_2)CH$-$C_6H_3F_2$	-CH_2CH_3	0.91 ± 0.15	>200
7e	-$SCH_2CH_2CH_3$	-$CH(CH_2)CH$-$C_6H_3F_2$	-CH_3	1.08 ± 0.05	>200
7f	-$SCH_2CH_2CH_3$	-$CH(CH_2)CH$-$C_6H_3F_2$	-CH_2CH_3	0.97 ± 0.06	>200
7g	-$SCH_2CH_2CH_3$	-$CH(CH_2)CH$-$C_6H_3F_2$	-C_5H_9	1.00 ± 0.09	>200
7h	-$SCH_2CH_2CH_3$	H	-$C_5H_6(OH)_3$	1.10 ± 0.09	>200
7i	-$SCH_2CH_2CH_3$	-$CH(CH_2)CH$-$C_6H_3F_2$	-$C_5H_6(OH)_3$	4.80 ± 2.50#	25
7j	-$SCH_2CH_2CH_3$	H	-$C_5H_6(OH)_2OCH_2CH_2OH$	1.10 ± 0.13	>200
7k	-$SCH_2CH_2CH_3$	-$CH(CH_2)_2$	-$C_5H_6(OH)_2OCH_2CH_2OH$	2.60 ± 0.65	>200
7l	-$SCH_2CH_2CH_3$	-$CH(CH_2)CH$-C_6H_5	-$C_5H_6(OH)_2OCH_2CH_2OH$	3.10 ± 0.65#	>200
7m	-$SCH_2CH_2CH_3$	-CH_2CH_2-$C_6H_3F_2$	-$C_5H_6(OH)_2OCH_2CH_2OH$	1.10 ± 0.07	>200
1	-$SCH_2CH_2CH_3$	-$CH(CH_2)CH$-$C_6H_3F_2$	-$C_5H_6(OH)_2OCH_2CH_2OH$	4.30 ± 2.20#	25
7n	-$SCH_2CH(OH)CH_3$	H	-$C_5H_6(OH)_3$	1.00 ± 0.17	>200
7o	-$SCH_2CH_2CH_2OH$	H	-$C_5H_6(OH)_3$	1.00 ± 0.09	>200
7p	-$SCH_2CH_2CH_2OH$	-$CH(CH_2)CH$-$C_6H_3F_2$	-$C_5H_6(OH)_3$	2.70 ± 0.99*#	>200
7q	*R*−$SCH_2CH(OH)CH_3$	-$CH(CH_2)CH$-$C_6H_3F_2$	-$C_5H_6(OH)_3$	6.20 ± 3.70#	>200
7r	*S*-$SCH_2CH(OH)CH_3$	-$CH(CH_2)CH$-$C_6H_3F_2$	-$C_5H_6(OH)_3$	2.00 ± 0.72#	>200
7s	-$SCH_2CH(OH)CH_3$	-$CH(CH_2)CH$-$C_6H_3F_2$	-$C_5H_6(OH)_2OCH_2CH_2OH$	1.70 ± 0.24	>200
7t	-$SCH_2CH_2CH_2OH$	-$CH(CH_2)CH$-$C_6H_3F_2$	-$C_5H_6(OH)_2OCH_2CH_2OH$	1.00 ± 0.02	>200
7u	-H	-$CH(CH_2)CH$-$C_6H_3F_2$	-$C_5H_6(OH)_3$	1.00 ± 0.04	>200
7v	-Cl	-$CH(CH_2)CH$-$C_6H_3F_2$	-$C_5H_6(OH)_3$	1.10 ± 0.12	>200

[a] Vehicle: 1% DMSO.
[b] MIC: minimal inhibitory concentration. Antiplatelet activity is presented as fold-inhibition vs. vehicle of area under the curve values of ADP-induced platelet aggregation (mean ± S.D., n = 4−21). # indicates $P < 0.05$ vs. vehicle; * indicates $P < 0.05$ vs. antiplatelet activity of compound 1 (wilcoxon matched-pairs signed rank test).

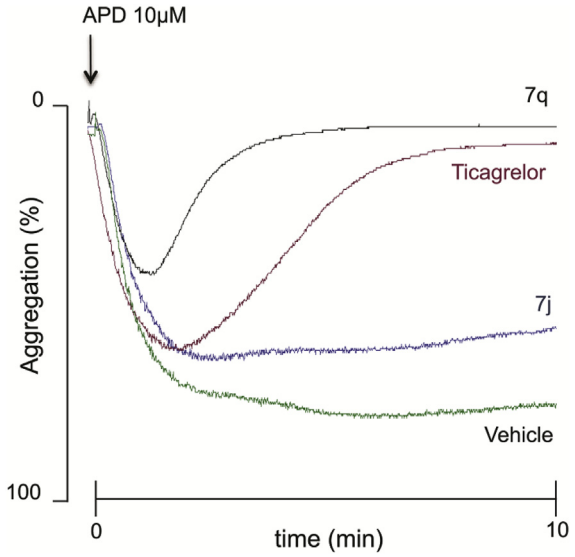

Fig. 4. Representative ADP-induced platelet aggregation curves performed in human citrated PRP after 10-min pre-incubation with the indicated molecules (1.8 μM) or vehicle (1% DMSO). The arrow depicts the time of agonist addition.

of 200 μM. On the contrary, five ticagrelor analogues (**7i**, **7l, 7p, 7q, 7r**), among which the active metabolite AR-C124910 (**7i**), displayed antiplatelet activity. The antiplatelet activity of molecules **7i**, **7l, 7q** and **7r** was similar to that of the reference compound **1** while it was weaker than the reference compound for molecule **7p** ($P = 0.016$).

Interestingly, the antiplatelet activity of the R-isomer **7q** was found to be more pronounced than that of its counterpart, the S-isomer **7r** ($P = 0.03$), both of them being possible metabolites of ticagrelor and resulting from the hydroxylation at the 2-position of the propylsulfanyl side chain of the active metabolite **7i** [22]. Hydroxylation at the 3-position of the same side chain of **7i** also provided another known metabolite [22], compound **7p**, which also showed antiplatelet activity.

The antiplatelet activity, but not the antibacterial activity, was maintained when the nature of the aralkylamino side chain at the 7-position was simplified. The ticagrelor analogue **7l** devoid of the two fluorine atoms at the 3,4-positions of the phenyl ring was equipotent to the reference compound **1**. The presence of a single cyclopropyl chain instead of a phenylcyclopropyl moiety (compound **7k**) was sufficient to maintain a marked antiplatelet activity. Surprisingly, the replacement of the cyclopropyl group of **1** with an ethylene moiety (compound **7m**) dramatically suppressed the antiplatelet activity. The absence of the aralkyl group on the nitrogen atom at the 7-position of **1** (providing compound **7j**) also generated the similar results.

3. Conclusion

A series of 1,2,3-triazolo[4,5-*d*]pyrimidines structurally related to ticagrelor were synthesized and examined as putative antiplatelet and antibacterial agents. Slight modifications of the structure of ticagrelor dramatically led to a loss of the antibacterial activity against methicillin-resistant *Staphylococcus aureus*, while the antiplatelet activity was maintained with some simplified ticagrelor analogues. Our results indicated that the antiplatelet and antibacterial activity of 1,2,3-triazolo[4,5-*d*]pyrimidines were not necessarily linked supporting the view that the observed effects involve distinct mechanisms and unrelated biological targets.

4. Experimental section

4.1. General procedures

Melting points were determined on a Stuart SMP3 capillary apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker instruments equipped with a TCI cryoprobe (Bruker Avance HD 500 MHz for ^{1}H; 125 MHz for ^{13}C/Bruker Avance III HD 700 MHz for ^{1}H; 176 MHz for ^{13}C) using deuterated dimethyl sulfoxide (DMSO-d_6) or deuterated chloroform ($CDCl_3$) as the solvent with tetramethylsilane (TMS) as an internal standard; chemical shifts are reported in δ values (ppm) relative to that of internal TMS. The abbreviations s = singlet, d = doublet, t = triplet, q = quadruplet, p = pentuplet, h = hexuplet, m = multiplet, dd = doublet of doublet, td = triplet of doublet, qd = quadruplet of doublet, dt = doublet of triplet, dq = doublet of quadruplet, tt = triplet of triplet, tq = triplet of quadruplet, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets and bs = broad singlet are used throughout. The compounds bearing an aralkylamino group at the 7-position shows existence of two isomeric forms, resulting in the duplication of several proton signals described as major and minor in the NMR data. Elemental analyses (C, H, N, S) were realized on a Thermo Scientific Flash EA 1112 elemental analyzer and were within ±0.4% of the theoretical values for carbon, hydrogen and nitrogen; a higher tolerance (±0.75%) was admitted for sulfur, considering its corresponding peak shape. This analytical method certified a purity of ≥95% for each tested compound. All reactions were routinely checked by TLC on silica gel Merck 60 F254.

4.2. Materials

2-Thiobarbituric acid **8**, 4,6-dichloro-2-(propylthio)pyrimidin-5-amine **12b.3** (R^1 = propyl), 4,6-dichloropyrimidin-5-amine **12c**, 2,4,6-trichloro-5-nitropyrimidine **11a**, (1*R*,2*S*)-2-(3,4- difluorophenyl)cyclopropanamine and 2-(((3a*R*,4*S*,6*R*,6a*S*)-6-amino-2,2-dimethyltetrahydro- 3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)oxy) ethanol were purchased from Fluorochem. (3a*R*,4*S*,6*R*,6a*S*)-6-Amino-2,2-dimethyltetrahydrocyclopenta[*d*][1,3]dioxol-4-ol was purchased from Spirochem. 3-mercapto-1-propanol and 1-mercaptopropan-2-ol were purchased from Aldrich. Both enantiomers of 1-mercaptopropan-2-ol were purchased from Chemspace.

4.3. 2-(Methylthio)pyrimidine-4,6-diol (*9.1*)

2-Thiobarbituric acid **8** (2,50 g, 17.4 mmol) was dissolved in KOH 10% (25 mL) and supplemented with methyl iodide (1.25 mL, 20.0 mmol). The reaction mixture was introduced in a sealed vessel and heated at 80 °C for 1 h. After cooling on an ice bath to 5 °C, the mixture was acidified by addition of hydrochloric acid 6 N and the resulting precipitate was filtered off and washed with diethyl ether to give **9.1** (2,10 g, 77% yield, m.p.: >300 °C). ^{1}H NMR (DMSO-d_6): δ 2.46 (s, 3H, SCH 3), 5.13 (s, 1H, C*H*), 11.71 (bs, 2H, O*H*). ^{13}C NMR (DMSO-d_6): δ 12.7, 85.5, 158.6, 163.5.

4.4. 2-(Ethylthio)pyrimidine-4,6-diol (*9.2*)

2-Thiobarbituric acid **8** (2.50 g, 17.4 mmol) was dissolved in KOH 10% (25 mL) and supplemented with ethyl iodide (1.63 mL, 20.0 mmol). The reaction mixture was introduced in a sealed vessel and heated at 80 °C for 1 h. After cooling on an ice bath to 5 °C, the mixture was acidified by addition of hydrochloric acid 6 N and the resulting precipitate was filtered off and washed with diethyl ether to give **9.2** (2.05 g, 69% yield, m.p.: >300 °C). ^{1}H NMR (DMSO-d_6):

δ 1.28 (t, $J = 7.3$ Hz, 3H, CH_3), 3.08 (q, $J = 7.3$ Hz, 2H, SCH 2), 5.12 (s, 1H, C*H*), 11.68 (bs, 2H, O*H*). ^{13}C NMR (DMSO-d_6): δ 14.6, 24.0, 85.6, 158.1, 162.8.

4.5. 2-(Methylthio)-5-nitropyrimidine-4,6-diol (**10.1**)

To 6 mL of acetic acid cooled at 5 °C on an ice bath were added fuming nitric acid (2.5 mL) and (**9.1**) (2.0 g, 12.6 mmol). After 1 h stirring at room temperature, the mixture was cooled at 5 °C on an ice bath, water (50 mL) was added and the resulting precipitate was filtered off to give **10.1** (1,72 g, 67% yield, m.p.: 220−221 °C (dec.)). ^{1}H NMR (DMSO-d_6) δ 2.56 (s, 3H, SCH 3). ^{13}C NMR (DMSO-d_6) δ 13.2, 117.4, 158.7, 164.6.

4.6. 2-(Ethylthio)-5-nitropyrimidine-4,6-diol (**10.2**)

To 6 mL of acetic acid cooled at 5 °C on an ice bath were added fuming nitric acid (2.5 mL) and (**9.2**) (1.80 g, 10.5 mmol). After 1 h stirring at room temperature, the mixture was cooled at 5 °C on an ice bath, water (50 mL) was added and the resulting precipitate was filtered off to give **10.2** (1.57 g, 69% yield, m.p.: 210−213 °C (dec.)). ^{1}H NMR (DMSO-d_6): δ 1.31 (t, $J = 7.3$ Hz, 3H, CH_3), 3.17 (q, $J = 7.3$ Hz, 2H, SCH 2). ^{13}C NMR (DMSO-d_6): δ 14.4, 24.7, 117.4, 158.9, 164.0.

4.7. 4,6-Dichloro-2-(methylthio)-5-nitropyrimidine (**11b.1**)

To a solution of (**10.1**) (1.5 g, 7.4 mmol) in $POCl_3$ (10 mL) cooled at 5 °C on an ice bath was added dropwise 2,6-lutidine (2.5 mL). After 2 h stirring at 80 °C, the mixture was poured on crushed ice and the resulting precipitate was filtered off to give **11b.1** (1.63 g, 92% yield, m.p.: 63−64 °C).^{1}H NMR (DMSO-d_6): δ 2.56 (s, 3H, SCH 3). ^{13}C NMR (DMSO-d_6): δ 13.5, 149.0, 154.5, 166.1.

4.8. 4,6-Dichloro-2-(ethylthio)-5-nitropyrimidine (**11b.2**)

To a solution of (**10.2**) (1.5 g, 6.9 mmol) in $POCl_3$ (10 mL) cooled at 5 °C on an ice bath was added dropwise 2,6-lutidine (2.5 mL). After 2 h stirring at 80 °C, the mixture was poured on crushed ice and extracted with ethyl acetate (3 × 50 mL). The organic layers were washed with water and with an aqueous saturated solution of sodium hydrogenocarbonate and ethyl acetate was evaporated to dryness under vacuum. The resulting oily residue **11b.2** (1.76 g, 85% yield) was used without further purification in the next step (**12b.2**). ^{1}H NMR (DMSO-d_6) δ 1.35 (t, $J = 7.3$ Hz, 3H, CH_3), 3.18 (q, $J = 7.3$ Hz, 2H, SCH 2). ^{13}C NMR (DMSO-d_6) δ 14.0, 25.3, 149.1, 154.5, 165.4.

4.9. 2,4,6-Trichloropyrimidin-5-amine (**12a**)

To a solution of 2,4,6-trichloro-5-nitropyrimidine **11a** (1.0 g, 4.38 mmol) in methanol (10 mL) and acetic acid (4 mL) was added iron powder (1.0 g, 17.9 mmol) under vigorous agitation. After 1 h at room temperature, the mixture was diluted with methanol (30 mL) and filtered. The precipitate was washed with methanol (30 mL) and the filtrate was then concentrated under reduced pressure. The residue was taken up with water (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, evaporated and purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **12a** as a white solid (0.77 g, 89% yield, m.p.: 107−109 °C). ^{1}H NMR ($CDCl_3$): δ 4.51 (bs, 2H, NH_2). ^{13}C NMR ($CDCl_3$): δ 134.7, 145.1, 145.4.

4.10. 4,6-Dichloro-2-(methylthio)pyrimidin-5-amine (**12b.1**)

To a solution of (**11b.1**) (1.0 g, 4.2 mmol) in methanol (10 mL) and acetic acid (4 mL) was added iron powder (1,07 g, 19.5 mmol). After 1 h stirring at room temperature, ethyl acetate (50 mL) was added and the suspension was filtered. The filtrate was washed with water and with an aqueous saturated solution of sodium hydrogenocarbonate and the organic layer was evaporated to dryness under vacuum. Water was added on the residue and the resulting precipitate was filtered off to give **12b.1** (0.83 g, 95% yield, m.p.: 105−108 °C). ^{1}H NMR (DMSO-d_6): δ 2.45 (s, 3H, SCH 3), 5.90 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6): δ 13.8, 133.4, 143.7, 154.4.

4.11. 4,6-Dichloro-2-(ethylthio)pyrimidin-5-amine (**12b.2**.)

To a solution of (**11b.2**) (1.0 g, 3.9 mmol) in methanol (10 mL) and acetic acid (4 mL) was added iron powder (1.07 g, 19.5 mmol). After 1 h stirring at room temperature, ethyl acetate (50 mL) was added and the suspension was filtered. The filtrate was washed with water and with an aqueous saturated solution of sodium hydrogenocarbonate and the organic layer was evaporated to dryness under vacuum. Water was added on the residue and the resulting precipitate was filtered off to give **12b.2** (0.76 g, 86% yield, m.p.: 48−50 °C). ^{1}H NMR (DMSO-d_6): δ 1.28 (t, $J = 7.3$ Hz, 3H, CH_3), 3.02 (q, $J = 7.3$ Hz, 2H, SCH 2), 5.90 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6): δ 14.3, 24.9, 133.5, 143.7, 153.8.

4.12. (3aR,4S,6R,6aS)-6-[(5-amino-6-chloropyrimidin-4-yl)amino]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (**13c.1**)

The mixture of 4,6-dichloropyrimidin-5-amine (1.0 g, 6.1 mmol), (3a*R*,4*S*,6*R*,6a*S*)-6-amino-2,2-dimethyltetrahydro cyclopenta[*d*][1,3]dioxol-4-ol (1.34 g, 7.8 mmol) and triethylamine (0.85 mL, 6.1 mmol) in acetonitrile (10 mL) was placed in a sealed vessel and heated overnight at 110 °C. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using 100% ethyl acetate to give **13c.1** as a white solid (1.43 g, 78% yield). ^{1}H NMR (DMSO-d_6): δ 1.21 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.70 (d, $J = 13.7$ Hz, 1H, 5′-*Ha*), 2.22 (m, 1H, 5′-*Hb*), 4.07 (m, 1H, 4′-*H*), 4.29 (t, $J = 5.9$ Hz, 1H, 6′-*H*), 4.41 (d, $J = 6.0$ Hz, 1H, 3a′-*H*), 4.51 (d, $J = 6.0$ Hz, 1H, 6a′-*H*), 4.97 (s, 2H, NH_2), 5.25 (d, $J = 3.1$ Hz, 1H, O*H*), 6.49 (d, $J = 7.2$ Hz, 1H, N*H*), 7.79 (s, 1H, 2-*H*). ^{13}C NMR (DMSO-d_6): δ 24.1, 26.5, 36.0, 57.0, 75.3, 84.4, 85.7, 109.7, 123.5, 137.6, 146.1, 151.7.

4.13. (3aR,4S,6R,6aS)-6-((5-amino-2,6-dichloropyrimidin-4-yl) amino)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (**13a.1**)

The mixture of 2,4,6-trichloropyrimidin-5-amine **12a** (1.0 g, 5.0 mmol), (3a*R*,4*S*,6*R*,6a*S*)-6- amino-2,2-dimethyltetrahydrocyclopenta[*d*][1,3]dioxol-4-ol (1.1 g, 6.4 mmol) and triethylamine (0.7 mL, 5.0 mmol) in acetonitrile (10 mL) was placed in a sealed vessel and heated overnight at 110 °C. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using 100% ethyl acetate to give 13a.1 as a white solid (1.48 g, 88% yield, m.p.: 105 °C (dec.)). ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.82 (d, $J = 14.5$ Hz, 1H, 5′-*Ha*), 2.17 (d, $J = 2.0$ Hz, 1H, O*H*), 2.36 (dt, $J = 14.5$ Hz/5.2 Hz, 1H, 5′-*Hb*), 3.28 (s, 2H, NH_2), 4.40 (d, $J = 2.0$ Hz, 1H, 4′-*H*), 4.54 (d, $J = 5.3$ Hz, 1H, 3a′-*H*), 4.57 (d, $J = 5.3$ Hz, 1H, 6a′-*H*), 4.71 (dd, $J = 8.4$ Hz/6.6 Hz, 1H, 6′-*H*), 6.11 (d, $J = 8.7$ Hz, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ 23.8, 26.2, 35.0, 57.0, 78.1, 85.2, 86.1, 110.6, 120.3, 142.8, 150.2, 155.1.

4.14. 2-(((3aR,4S,6R,6aS)-6-((5-amino-2,6-dichloropyrimidin-4-yl) amino)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl) oxy)ethanol (**13a.2**)

The mixture of 2,4,6-trichloropyrimidin-5-amine **12a** (1.0 g, 5.0 mmol), 2-(((3a*R*,4*S*,6*R*,6a*S*)-6-amino-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)oxy)ethanol (1.4 g, 6.4 mmol) and triethylamine (0.7 mL, 5.0 mmol) in acetonitrile (10 mL) was placed in a sealed vessel and heated overnight at 110 °C. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using 100% ethyl acetate to give 13a.2 as an oily residue (1.59 g, 83% yield). ^{1}H NMR (DMSO-d_6): δ 1.23 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.86 (d, J = 14.0 Hz, 1H, 5′-*Ha*), 2.22 (m, 1H, 5'-*Hb*), 3.51 (m, 4H, OCH_2CH_2OH), 3.90 (s, 1H, 4'-*H*), 4.30 (s, 1H, 6′-*H*), 4.50 (s, 1H, 6a′-*H*), 4.54 (s, 1H, 3a′-*H*), 5.04 (s, 1H, OCH$_2$-CH$_2$O*H*), 5.17 (s, 2H, NH_2), 6.83 (d, J = 6.7 Hz, 1H, N*H*). ^{13}C NMR (DMSO-d_6): δ 24.1, 26.3, 32.9, 56.6, 60.3, 70.3, 83.2, 83.5, 83.9, 110.2, 112.8, 136.5, 144.6, 152.7.

4.15. 6-Chloro-N^4-methyl-2-(methylthio)pyrimidine-4,5-diamine (**13b.1**)

4,6-Dichloro-2-(methylthio)pyrimidin-5-amine (**12b.1**) (0.5 g, 2.4 mmol) was dissolved in methanol (2 mL) and supplemented with a solution of methylamine 33% w/w in methanol (0.87 mL, 7.2 mmol). The reaction mixture was introduced in a sealed vessel and heated at 100 °C for 1 h. After concentration of the reaction mixture to dryness under vacuum, the residue was purified by silica gel column chromatography to give **13b.1** (0.4 g, 82% yield, m.p.: 141–143 °C). ^{1}H NMR (DMSO-d_6): δ 2.38 (s, 3H, SCH 3), 2.88 (d, J = 3.0 Hz, 3H, NHCH_3), 4.70 (s, 2H, NH_2), 7.01 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): δ 13.5, 27.8, 120.1, 137.2, 153.3, 155.9.

4.16. 6-Chloro-N^4-ethyl-2-(methylthio)pyrimidine-4,5-diamine (**13b.2**)

4,6-Dichloro-2-(methylthio)pyrimidin-5-amine (**12b.1**) (0.5 g, 2.4 mmol) was dissolved in a solution of ethylamine 2.0 M in methanol (3.6 mL, 7.2 mmol). The reaction mixture was introduced in a sealed vessel and heated at 100 °C for 1 h. After concentration of the reaction mixture to dryness under vacuum, the residue was purified by silica gel column chromatography to give **13b.2** (0.45 g, 86% yield, m.p.:120–122 °C). ^{1}H NMR (DMSO-d_6): δ 1.16 (t, J = 7.2 Hz, 3H, NHCH$_2$CH_3), 2.37 (s, 3H, SCH 3), 3.38 (qd, J = 7.2 Hz/ 5.3 Hz, 2H, NHCH_2CH$_3$), 4.76 (s, 2H, NH_2), 6.94 (t, J = 4.8 Hz, 1H, N*H*). ^{13}C NMR (DMSO-d_6): δ 13.5, 14.3, 35.7, 119.8, 137.2, 152.4, 155.7.

4.17. 6-Chloro-2-(ethylthio)-N^4-methylpyrimidine-4,5-diamine (**13b.3**)

4,6-Dichloro-2-(ethylthio)pyrimidin-5-amine (**12b.2**) (0.5 g, 2.2 mmol) was dissolved in methanol (2 mL) and supplemented with a solution of methylamine 33% w/w in methanol (0.80 mL, 6.6 mmol). The reaction mixture was introduced in a sealed vessel and heated at 100 °C for 1 h. After concentration of the reaction mixture to dryness under vacuum, the residue was purified by silica gel column chromatography to give **13b.3** (0.43 g, 87% yield, m.p.: 112–114 °C). ^{1}H NMR (DMSO-d_6): δ 1.27 (t, J = 7.2 Hz, 3H, SCH$_2$CH_3), 2.87 (d, J = 3.8 Hz, 3H, NHCH_3), 2.97 (q, J = 7.2 Hz, 2H, SCH_2CH$_3$), 4.70 (s, 2H, NH_2), 7.00 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): δ 14.9, 24.5, 27.8, 120.1, 137.2, 153.3, 155.4.

4.18. 6-Chloro-N^4-ethyl-2-(ethylthio)pyrimidine-4,5-diamine (**13b.4**)

4,6-Dichloro-2-(ethylthio)pyrimidin-5-amine (**12b.2**) (0.5 g, 2.2 mmol) was dissolved in a solution of ethylamine 2.0 M in methanol (3.3 mL, 6.6 mmol). The reaction mixture was introduced in a sealed vessel and heated at 100 °C for 1 h. After concentration of the reaction mixture to dryness under vacuum, the residue was purified by silica gel column chromatography to give **13b.4** (0.47 g, 91% yield, m.p.: 93–95 °C). ^{1}H NMR (DMSO-d_6): δ 1.16 (t, J = 7.2 Hz, 3H, NHCH$_2$CH_3), 1.27 (t, J = 7.2 Hz, 3H, SCH$_2$CH_3), 2.96 (q, J = 7.2 Hz, 2H, SCH_2CH$_3$), 3.38 (p, J = 6.1 Hz, 2H, NHCH_2CH$_3$), 4.74 (s, 2H, NH_2), 6.93 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): δ 14.4, 15.0, 24.5, 35.8, 119.9, 137.3, 152.6, 155.2.

4.19. 6-Chloro-N^4-methyl-2-(propylthio)pyrimidine-4,5-diamine (**13b.5**)

4,6-Dichloro-2-(propylthio)pyrimidin-5-amine **12b.3** (0.5 g, 2.1 mmol) was dissolved in methanol (2 mL) and supplemented with a solution of methylamine 33% w/w in methanol (0.76 mL, 6.3 mmol). The reaction mixture was introduced in a sealed vessel and heated at 100 °C for 1 h. After concentration of the reaction mixture to dryness under vacuum, the residue was purified by silica gel column chromatography to give **13b.5** (0.47 g, 96% yield, m.p.: 119–121 °C). ^{1}H NMR (DMSO-d_6): δ 0.95 (t, J = 7.4 Hz, 3H, SCH$_2$CH$_2$CH_3), 1.64 (h, J = 7.3 Hz, 2H, SCH$_2$CH_2CH$_3$), 2.87 (d, J = 4.5 Hz, 3H, NHCH_3), 2.96 (t, J = 7.2 Hz, 2H, SCH_2CH$_2$CH$_3$), 4.71 (s, 2H, NH_2), 7.01 (q, J = 4.4 Hz, 1H, N*H*CH$_3$). ^{13}C NMR (DMSO-d_6): δ 13.3, 22.6, 27.8, 32.1, 120.0, 137.1, 153.2, 155.4.

4.20. 6-Chloro-N^4-ethyl-2-(propylthio)pyrimidine-4,5-diamine (**13b.6**)

4,6-Dichloro-2-(propylthio)pyrimidin-5-amine **12b.3** (0.5 g, 2.1 mmol) was dissolved in a solution of ethylamine 2.0 M in methanol (3.2 mL, 6.4 mmol). The reaction mixture was introduced in a sealed vessel and heated at 100 °C for 1 h. After concentration of the reaction mixture to dryness under vacuum, the residue was purified by silica gel column chromatography to give **13b.6** (0.4 g, 77% yield, m.p.: 96–98 °C). ^{1}H NMR (DMSO-d_6): δ 0.95 (t, J = 7.4 Hz, 3H, SCH$_2$CH$_2$CH_3), 1.16 (t, J = 7.2 Hz, 3H, NHCH$_2$CH_3), 1.63 (h, J = 7.3 Hz, 2H, SCH$_2$CH_2CH$_3$), 2.94 (t, J = 7.2 Hz, 2H, SCH_2CH$_2$CH$_3$), 3.37 (m, 2H, NHCH_2CH$_3$), 4.75 (s, 2H, NH_2), 6.95 (t, J = 4.8 Hz, 1H, N*H*CH$_2$CH$_3$). ^{13}C NMR (DMSO-d_6): δ 13.3, 14.3, 22.7, 32.1, 35.7, 119.8, 137.3, 152.5, 155.3.

4.21. 6-Chloro-N^4-cyclopentyl-2-(propylthio)pyrimidine-4,5-diamine (**13b.7**)

4,6-Dichloro-2-(propylthio)pyrimidin-5-amine **12b.3** (0.5 g, 2.1 mmol) was dissolved in methanol (2 mL) and supplemented with cyclopentylamine (536.0 mg, 6.3 mmol). The reaction mixture was introduced in a sealed vessel and heated at 100 °C for 2 h. After concentration of the reaction mixture to dryness under vacuum, the residue was purified by silica gel column chromatography to give **13b.7** (0.57 g, 95% yield, oil). ^{1}H NMR (DMSO-d_6): δ 0.95 (t, J = 7.4 Hz, 3H, SCH$_2$CH$_2$CH_3), 1.49 (m, 2H, 2′-*Ha*/5′-*Ha*), 1.55 (m, 2H, 3′-*Ha*/4′-*Ha*), 1.64 (m, 2H, SCH$_2$CH_2CH$_3$), 1.70 (m, 2H, 3′-*Hb*/4′-*Hb*), 1.96 (m, 2H, 2′-*Hb*/5′-*Hb*), 2.94 (t, J = 7.2 Hz, 2H, SCH_2CH$_2$CH$_3$), 4.25 (h, J = 6.7 Hz, 1H, 1′-*H*), 4.83 (s, 2H, NH_2), 6.76 (d, J = 6.3 Hz, 1H, N*H*). ^{13}C NMR (DMSO-d_6): δ 13.3, 22.9, 23.5, 32.1, 32.2, 52.7, 119.9, 137.2, 152.0, 155.0.

*4.22. (3aR,4S,6R,6aS)-6-((5-amino-6-chloro-2-(propylthio) pyrimidin-4-yl)amino)-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3]dioxol-4-ol (**13b.8**)*

The mixture of 4,6-dichloro-2-(propylthio)pyrimidin-5-amine **12b.3** (1.0 g, 4.2 mmol), (3a*R*,4*S*,6*R*,6a*S*)-6-amino-2,2-dimethyltetrahydrocyclopenta[*d*][1,3]dioxol-4-ol (0.93 g, 5.4 mmol) and triethylamine (0.6 mL, 4.2 mmol) in acetonitrile (10 mL) was introduced in a sealed vessel and heated overnight at 110 °C. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using 100% ethyl acetate to give **13b.8** as a brown oil (1.40 g, 89% yield, oil). ^{1}H NMR ($CDCl_3$): δ 1.03 (t, J = 7.4 Hz, 3H, $SCH_2CH_2CH_3$), 1.26 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.76 (m, 2H, $SCH_2CH_2CH_3$), 1.83 (d, J = 14.5 Hz, 1H, 5′-*Ha*), 2.14 (s, 1H, O*H*), 2.36 (m, 1H, 5′-*Hb*), 3.01 (ddd, J = 13.4 Hz/8.3 Hz/6.4 Hz, 1H, S*CHa*), 3.09 (s, 2H, NH_2), 3.13 (ddd, J = 13.5 Hz/8.3 Hz/6.4 Hz, 1H, S*CHb*), 4.38 (s, 1H, 4′-*H*), 4.51 (dd, J = 5.4 Hz/1.7 Hz, 1H, 3a′-*H*), 4.57 (dd, J = 5.4 Hz/1.2 Hz, 1H, 6a′-*H*), 4.62 (t, J = 7.4 Hz, 1H, 6′-*H*), 5.93 (d, J = 8.4 Hz, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ 13.5, 23.2, 23.8, 26.2, 33.2, 35.0, 57.2, 78.1, 85.2, 86.2, 110.3, 117.2, 144.4, 154.5, 162.0.

*4.23. 2-(((3aR,4S,6R,6aS)-6-((5-amino-6-chloro-2-(propylthio) pyrimidin-4-yl)amino)-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3]dioxol-4-yl)oxy)ethanol (**13b.9**)*

The mixture of 4,6-dichloro-2-(propylthio)pyrimidin-5-amine **12b.3** (1.0 g, 4.2 mmol), 2-(((3a*R*,4*S*,6*R*,6a*S*)-6-amino-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)oxy) ethanol (1.17 g, 5.4 mmol) and triethylamine (0.6 mL, 4.2 mmol) in acetonitrile (10 mL) was introduced in a sealed vessel and heated overnight at 110 °C. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using 100% ethyl acetate to give **13b.9** (1.36 g, 77% yield, m.p.: 112−114 °C). ^{1}H NMR ($CDCl_3$) δ 1.03 (t, J = 7.4 Hz, 3H, $SCH_2CH_2CH_3$), 1.26 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.75 (m, 2H, $SCH_2CH_2CH_3$), 1.92 (d, J = 14.5 Hz, 1H, 5′-*Ha*), 2.28 (ddd, J = 14.5 Hz/5.9 Hz/4.4 Hz, 1H, 5′-*Hb*), 2.59 (bs, 1H, O*H*), 2.99 (ddd, J = 13.4 Hz/8.2 Hz/6.4 Hz, 1H, S*CHa*), 3.14 (ddd, J = 13.5 Hz/8.2 Hz/6.4 Hz, 1H, S*CHb*), 3.38 (bs, 2H, NH_2), 3.60 (ddd, J = 9.9 Hz/6.1 Hz/2.6 Hz, 1H, OC*Ha*), 3.70 (ddd, J = 9.9 Hz/5.8 Hz/2.5 Hz, 1H, OC*Hb*), 3.79 (m, 2H, OCH_2CH_2OH), 3.97 (d, J = 4.1 Hz, 1H, 4′-*H*), 4.53 (dd, J = 5.4 Hz/1.2 Hz, 1H, 3a′-*H*), 4.59 (m, 1H, 6′-*H*), 4.61 (dd, J = 5.5 Hz/1.8 Hz, 1H, 6a′-*H*), 6.17 (d, J = 8.4 Hz, 1H, N*H*). ^{13}C NMR ($CDCl_3$) δ 13.5, 23.2, 23.8, 26.2, 32.5, 33.2, 56.8, 61.9, 70.4, 82.8, 84.5, 85.3, 110.3, 116.9, 144.5, 154.4, 162.0.

*4.24. (3aR,4S,6R,6aS)-6-(7-chloro-3H-[1,2,3]triazolo[4,5-d] pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3] dioxol-4-ol (**14c.1**)*

To a solution of **13c.1** (1.0 g, 3.1 mmol) in acetic acid (10 mL) cooled on an ice bath was added $NaNO_2$ (275 mg, 4.0 mmol). The mixture was allowed to reach room temperature within 1 h and water (40 mL) was then added. The resulting mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated to give **14c.1** as an oily residue (0.95 g, 92% yield). ^{1}H NMR (DMSO-d_6) δ 1.23 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.59 (m, 2H, 5′-*H*), 4.17 (td, J = 6.1 Hz/2.6 Hz, 1H, 4′-*H*), 4.61 (dd, J = 6.8 Hz/2.6 Hz, 1H, 3a′-*H*), 5.20 (bs, 1H, O*H*), 5.25 (dd, J = 7.3 Hz/3.6 Hz, 1H, 6′-*H*), 5.42 (dd, J = 6.8 Hz/3.6 Hz, 1H, 6a′-*H*), 9.11 (s, 1H, 2-*H*). ^{13}C NMR (DMSO) δ 24.7, 26.9, 38.1, 62.1, 74.2, 82.3, 86.0, 112.1, 129.9, 148.4, 149.6, 155.3.

*4.25. (3aR,4S,6R,6aS)-6-(5,7-dichloro-3H-[1,2,3]triazolo[4,5-d] pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3] dioxol-4-ol (**14a.1**)*

To a solution of **13a.1** (1.0 g, 3.0 mmol) in acetic acid (10 mL) cooled on an ice bath was added $NaNO_2$ (275 mg, 4.0 mmol). The mixture was allowed to reach room temperature within 1 h and water (40 mL) was then added. The precipitate was filtered and washed with water to give **14a.1** as a white solid (0.61 g, 59% yield, decomposition at 280 °C). ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.41 (d, J = 15.2 Hz, 1H, 5′-*Ha*), 2.90 (ddd, J = 15.1 Hz/8.0 Hz/5.7 Hz, 1H, 5′-*Hb*), 3.23 (d, J = 5.2 Hz, 1H, O*H*), 4.46 (bs, 1H, 4′-*H*), 4.81 (d, J = 5.7 Hz, 1H, 3a′-*H*), 5.17 (d, J = 5.7 Hz, 1H, 6a′-*H*), 5.39 (d, J = 7.2 Hz, 1H, 6′-*H*). ^{13}C NMR ($CDCl_3$) δ 24.2, 26.6, 37.2, 64.7, 76.6, 84.9, 87.3, 112.0, 133.6, 150.8, 155.6, 157.9.

*4.26. 2-(((3aR,4S,6R,6aS)-6-(5,7-dichloro-3H-[1,2,3]triazolo[4,5-d] pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3] dioxol-4-yl)oxy)ethanol (**14a.2**)*

To a solution of **13a.2** (1.0 g, 2.6 mmol) in acetic acid (10 mL) cooled on an ice bath was added $NaNO_2$ (240 mg, 3.5 mmol). The mixture was allowed to reach room temperature within 1 h and water (40 mL) was then added. The resulting mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated to give **14a.2** as an oily residue (0.92 g, 89% yield). ^{1}H NMR (DMSO-d_6) δ 1.27 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.44 (m, 1H, 5′-*Ha*), 2.90 (dt, J = 13.1 Hz/6.0 Hz, 1H, 5′-*Hb*), 3.39−3.51 (m, 4H, OCH_2CH_2OH), 4.01 (m, 1H, 4′-*H*), 4.32 (bs, 12H, OCH_2CH_2OH/H_2O), 4.69 (dd, J = 7.2 Hz/2.9 Hz, 1H, 3a′-*H*), 5.01 (m, 1H, 6′-*H*), 5.17 (dd, J = 7.1 Hz/4.7 Hz, 1H, 6a′-*H*). ^{13}C NMR (DMSO-d_6) δ 24.7, 26.8, 35.8, 60.0, 61.8, 70.8, 82.0, 82.1, 83.7, 112.6, 129.3, 148.3, 155.4.

*4.27. 7-Chloro-3-methyl-5-(methylthio)-3H-[1,2,3]triazolo[4,5-d] pyrimidine (**14b.1**)*

To a solution of **13b.1** (1.0 g, 4.9 mmol) in acetic acid (10 mL) cooled on an ice bath was added $NaNO_2$ (450 mg, 6.5 mmol). The mixture was allowed to reach room temperature within 1 h and water (40 mL) was then added. The precipitate was filtered and washed with water to give **14b.1** as a beige solid (1.0 g, 95% yield). ^{1}H NMR (DMSO-d_6) δ 2.66 (s, 3H, SCH 3), 4.23 (s, 3H, NCH_3). ^{13}C NMR (DMSO-d_6) δ 14.2, 33.3, 131.2, 150.8, 151.7, 170.3.

*4.28. 7-Chloro-3-ethyl-5-(methylthio)-3H-[1,2,3]triazolo[4,5-d] pyrimidine (**14b.2**)*

To a solution of **13b.2** (1.0 g, 4.6 mmol) in acetic acid (10 mL) cooled on an ice bath was added $NaNO_2$ (415 mg, 6.0 mmol). The mixture was allowed to reach room temperature within 1 h and water (40 mL) was then added. The precipitate was filtered and washed with water to give **14b.2** as a beige solid (0.92 g, 87% yield). ^{1}H NMR (DMSO-d_6) δ 1.56 (t, J = 7.3 Hz, 3H, NCH_2CH_3), 2.65 (s, 3H, SCH 3), 4.66 (q, J = 7.3 Hz, 2H, NCH_2CH_3). ^{13}C NMR (DMSO-d_6) δ 14.2, 42.4, 131.4, 150.4, 151.7, 170.2.

*4.29. 7-Chloro-5-(ethylthio)-3-methyl-3H-[1,2,3]triazolo[4,5-d] pyrimidine (**14b.3**)*

To a solution of **13b.3** (1.0 g, 4.6 mmol) in acetic acid (10 mL) cooled on an ice bath was added $NaNO_2$ (415 mg, 6.0 mmol). The mixture was allowed to reach room temperature within 1 h and water (40 mL) was then added. The precipitate was filtered and washed with water to give **14b.3** as a beige solid (0.70 g, 87% yield).

^{1}H NMR (DMSO-d_6) δ 1.39 (t, J = 7.3 Hz, 3H, SCH$_2$C*H*$_3$), 3.25 (q, J = 7.3 Hz, 2H, SC*H*$_2$CH$_3$), 4.22 (s, 3H, NC*H*$_3$). ^{13}C NMR (DMSO-d_6) δ 14.0, 25.5, 33.3, 131.3, 150.8, 151.8, 169.7.

4.30. 7-Chloro-3-ethyl-5-(ethylthio)-3H-[1,2,3]triazolo[4,5-d] pyrimidine (**14b.4**)

To a solution of **13b.4** (1.0 g, 4.3 mmol) in acetic acid (10 mL) cooled on an ice bath was added $NaNO_2$ (395 mg, 5.7 mmol). The mixture was allowed to reach room temperature within 1 h and water (40 mL) was then added. The precipitate was filtered and washed with water to give **14b.4** as a beige solid (0.88 g, 87% yield). ^{1}H NMR (DMSO-d_6) δ 1.39 (t, J = 7.3 Hz, 3H, SCH$_2$C*H*$_3$), 1.56 (t, J = 7.3 Hz, 3H, NCH$_2$C*H*$_3$), 3.24 (q, J = 7.3 Hz, 2H, SC*H*$_2$CH$_3$), 4.66 (q, J = 7.3 Hz, 2H, NC*H*$_2$CH$_3$). ^{13}C NMR (DMSO-d_6) δ 13.9, 14.2, 25.5, 42.5, 131.5, 150.4, 151.8, 169.6.

4.31. 7-Chloro-3-methyl-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d] pyrimidine (**14b.5**)

To a solution of **13b.5** (1.0 g, 4.3 mmol) in acetic acid (10 mL) cooled on an ice bath was added $NaNO_2$ (395 mg, 5.7 mmol). The mixture was allowed to reach room temperature within 1 h and water (40 mL) was then added. The precipitate was filtered and washed with water to give **14b.5** as an orange solid (0.87 g, 84% yield). ^{1}H NMR (DMSO-d_6) δ 1.03 (t, J = 7.1 Hz, 3H, SCH$_2$CH$_2$C*H*$_3$), 1.76 (h, J = 7.0 Hz, 2H, SCH$_2$C*H*$_2$CH$_3$), 3.23 (t, J = 7.1 Hz, 2H, SC*H*$_2$CH$_2$CH$_3$), 4.22 (s, 3H, NC*H*$_3$). ^{13}C NMR (DMSO-d_6) δ 13.2, 21.7, 32.8, 33.2, 131.3, 150.8, 151.7, 169.8.

4.32. 7-Chloro-3-ethyl-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d] pyrimidine (**14b.6**)

To a solution of **13b.6** (1.0 g, 4.0 mmol) in acetic acid (10 mL) cooled on an ice bath was added $NaNO_2$ (375 mg, 5.4 mmol). The mixture was allowed to reach room temperature within 1 h and water (40 mL) was then added. The precipitate was filtered and washed with water to give **14b.6** as an orange solid (0.90 g, 86% yield). ^{1}H NMR (DMSO-d_6) δ 1.02 (t, J = 7.4 Hz, 3H, SCH$_2$CH$_2$C*H*$_3$), 1.56 (t, J = 7.3 Hz, 3H, NCH$_2$C*H*$_3$), 1.76 (h, J = 7.4 Hz, 2H, SCH$_2$C*H*$_2$CH$_3$), 3.24 (t, J = 7.2 Hz, 2H, SC*H*$_2$CH$_2$CH$_3$), 4.66 (q, J = 7.3 Hz, 2H, NC*H*$_2$CH$_3$). ^{13}C NMR (DMSO-d_6) δ 13.3, 14.2, 21.7, 32.9, 42.5, 131.5, 150.3, 151.8, 169.7.

4.33. 7-Chloro-3-cyclopentyl-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidine (**14b.7**)

To a solution of **13b.7** (1.0 g, 3.5 mmol) in acetic acid (10 mL) cooled on an ice bath was added $NaNO_2$ (320 mg, 4.6 mmol). The mixture was allowed to reach room temperature within 1 h and water (40 mL) was then added. The precipitate was filtered and washed with water to give **14b.7** as an orange solid (0.70 g, 67% yield). ^{1}H NMR (DMSO-d_6) δ 1.03 (t, J = 7.3 Hz, 3H, SCH$_2$CH$_2$C*H*$_3$), 1.76 (m, 4H, 3′-*Ha*/4′-*Ha*/SCH$_2$C*H*$_2$CH$_3$), 1.93 (m, 2H, 3′-*Hb*/4′-*Hb*), 2.24 (m, 4H, 2′-*H*$_2$/5′-*H*$_2$), 3.21 (t, J = 7.1 Hz, 2H, SC*H*$_2$CH$_2$CH$_3$), 5.35 (p, J = 7.1 Hz, 1H, 1′-*H*). ^{13}C NMR (DMSO-d_6) δ 13.2, 21.8, 24.3, 31.8, 32.8, 59.7, 131.8, 150.1, 151.7, 169.3.

4.34. (3aR,4S,6R,6aS)-6-(7-chloro-5-(propylthio)-3H-[1,2,3] triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (**14b.8**)

To a solution of **13b.8** (1.0 g, 2.7 mmol) in acetic acid (10 mL) cooled on an ice bath was added $NaNO_2$ (250 mg, 3.6 mmol). The mixture was allowed to reach room temperature within 1 h and water (40 mL) was then added. The resulting mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated to give **14b.8** as an oily residue (0.88 g, 85% yield). ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 7.4 Hz, 3H, SCH$_2$CH$_2$C*H*$_3$), 1.33 (s, 3H, C*H*$_3$), 1.54 (s, 3H, C*H*$_3$), 1.83 (h, J = 7.3 Hz, 2H, SCH$_2$C*H*$_2$CH$_3$), 2.38 (d, J = 15.3 Hz, 1H, 5′-*Ha*), 2.90 (m, 1H, 5′-*Hb*), 3.24 (td, J = 7.1 Hz/1.7 Hz, 2H, SC*H*$_2$CH$_2$CH$_3$), 3.76 (d, J = 8.8 Hz, 1H, O*H*), 4.44 (m, 1H, 4′-*H*), 4.80 (d, J = 5.6 Hz, 1H, 3a′-*H*), 5.04 (d, J = 5.7 Hz, 1H, 6a′-*H*), 5.34 (d, J = 7.7 Hz, 1H, 6′-*H*). ^{13}C NMR ($CDCl_3$) δ 13.5, 22.1, 24.1, 26.6, 33.8, 37.0, 64.1, 76.7, 85.3, 87.6, 111.6, 132.0, 150.2, 153.7, 172.5.

4.35. 2-(((3aR,4S,6R,6aS)-6-(7-chloro-5-(propylthio)-3H-[1,2,3] triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)ethanol (**14b.9**)

To a solution of **13b.9** (1.0 g, 2.4 mmol) in acetic acid (10 mL) cooled on an ice bath was added $NaNO_2$ (225 mg, 3.2 mmol). The mixture was allowed to reach room temperature within 1 h and water (40 mL) was then added. The resulting mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated to give **14b.9** as an oily residue (0.96 g, 94% yield). ^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.4 Hz, 3H, SCH$_2$CH$_2$C*H*$_3$), 1.37 (s, 3H, C*H*$_3$), 1.55 (s, 3H, C*H*$_3$), 1.83 (h, J = 7.4 Hz, 2H, SCH$_2$C*H*$_2$CH$_3$), 2.14 (t, J = 6.0 Hz, 1H, O*H*), 2.54 (m, 1H, 5′-*Ha*), 2.70 (m, 1H, 5′-*Hb*), 3.21 (t, J = 7.2 Hz, 2H, SC*H*$_2$CH$_2$CH$_3$), 3.49–3.65 (m, 4H, OC*H*$_2$C*H*$_2$OH), 4.05 (m, 1H, 4′-*H*), 4.88 (d, J = 6.3 Hz, 1H, 3a′-*H*), 5.21 (td, J = 7.4 Hz/6.4 Hz/2.5 Hz, 1H, 6′-*H*), 5.53 (dd, J = 6.3 Hz/2.1 Hz, 1H, 6a′-*H*). ^{13}C NMR ($CDCl_3$) δ 13.6, 22.3, 24.5, 26.8, 33.9, 35.9, 61.8, 63.4, 70.7, 82.9, 83.6, 84.0, 112.4, 132.2, 150.7, 153.4, 171.8.

4.36. (3aR,4S,6R,6aS)-6-(7-(((1R,2S)-2-(3,4-difluorophenyl) cyclopropyl)amino)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (**15c.1**)

The mixture of **14c.1** (0.5 g, 1.6 mmol), (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanamine (0.41 g, 2.4 mmol) and triethylamine (0.29 mL, 2.05 mmol) in acetonitrile (10 mL) was left to react at room temperature for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **15c.1** as a white solid (0.67 g, 94% yield). ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 3H, C*H*$_3$), 1.37 (q, J = 6.0 Hz, 0.8H, 3′-*Ha* major), 1.42 (m, 0.2H, 3′-*Ha* minor), 1.47 (m, 3.2H, C*H*$_3$/3′-*Hb* minor), 1.54 (dt, J = 9.9 Hz/5.3 Hz, 0.8H, 3′-*Hb* major), 2.18 (ddd, J = 9.4 Hz/6.3 Hz/3.3 Hz, 0.8H, 2′-*H* major), 2.26 (m, 0.2H, 2′-*H* minor), 2.45–2.60 (m, 2H, 5‴-*H*), 3.28 (dd, J = 7.7 Hz/3.6 Hz, 0.8H, 1′-*H* major), 3.78 (m, 0.2H, 1′-*H* minor), 4.14 (m, 1H, 4‴-*H*), 4.57 (dd, J = 7.1 Hz/2.8 Hz, 1H, 3a‴-*H*), 5.08 (td, J = 7.9 Hz/4.4 Hz, 1H, 6‴-*H*), 5.22 (m, 0.2H, 6a‴-*H* minor), 5.29 (m, 1.8H, 6a‴-*H* major/O*H*), 7.03 (m, 0.2H, 2″-*H* minor), 7.09 (m, 0.8H, 6″-*H* major), 7.27–7.37 (m, 2H, 2″-*H*/5″-*H*), 8.32 (s, 0.2H, 2-*H* minor), 8.42 (s, 0.8H, 2-*H* minor), 9.01 (d, J = 3.7 Hz, 0.2H, N*H* minor), 9.34 (d, J = 4.0 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 15.2, 23.7, 24.7, 26.9, 33.9, 37.9, 62.1, 74.3, 82.2, 86.0, 112.0, 114.8, 117.1, 122.9, 124.6, 139.2, 146.8, 148.1, 148.4, 148.7, 150.3, 155.0, 156.4, 156.5.

4.37. (3aR,4S,6R,6aS)-6-(7-amino-5-chloro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3] dioxol-4-ol (**15a.1**)

The solution of **14a.1** (0.5 g, 1.45 mmol) in THF (10 mL) was saturated with ammonia gas in a sealed vessel and left to react at room temperature for 1 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **15a.1** as a white solid (0.45 g,

95% yield). ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.42 (m, 1H, 5′-*Ha*), 2.55 (m, 1H, 5′-*Hb*), 4.13 (m, 1H, 4′-*H*), 4.56 (dd, J = 7.0 Hz/3.0 Hz, 1H, 3a′-*H*), 4.98 (ddd, J = 8.6 Hz/7.0 Hz/4.2 Hz, 1H, 6′-*H*), 5.25 (m, 2H, O*H*/6a′-*H*), 8.64 (bs, 1H, N*Ha*), 8.96 (bs, 1H, N*Hb*). ^{13}C NMR (DMSO-d_6) δ 24.7, 26.8, 37.8, 61.9, 74.2, 82.1, 85.9, 112.0, 123.6, 150.0, 156.5, 157.6.

*4.38. (3aR,4S,6R,6aS)-6-(5-chloro-7-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (**15a.2**)*

The mixture of **14a.1** (0.5 g, 1.45 mmol), (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanamine (0.37 g, 2.2 mmol) and triethylamine (0.26 mL, 1.86 mmol) in acetonitrile (10 mL) was left to react at room temperature for 30 min. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **15a.2** as a white solid (0.59 g, 85% yield, decomposition at 85 °C). ^{1}H NMR (DMSO-d_6) δ 1.25 (s, 0.9H, CH_3 minor), 1.26 (s, 2.1H, CH_3 major), 1.41–1.50 (m, 5H, CH_3/3′-H_2), 2.23 (ddd, J = 9.7 Hz/6.6 Hz/3.3 Hz, 0.7H, 2′-*H* major), 2.29 (ddd, J = 9.5 Hz/6.5 Hz/3.2 Hz, 0.3H, 2′-*H* minor), 2.35–2.44 (m, 1H, 5‴-*Ha*), 2.56 (m, 1H, 5‴-*Hb*), 3.13 (dt, J = 7.7 Hz/3.9 Hz, 0., 1′-*H* major), 3.79 (m, 0.3H, 1′-*H* minor), 4.14 (m, 1H, 4‴-*H*), 4.54 (dd, J = 7.0 Hz/2.8 Hz, 0.3H, 3a‴-*H* minor), 4.57 (dd, J = 7.0 Hz/2.8 Hz, 0.7H, 3a‴-*H* major), 4.97 (td, J = 8.3 Hz/4.3 Hz, 0.3H, 6‴-*H* minor), 5.00 (td, J = 7.9 Hz/4.1 Hz, 0.7H, 6‴-*H* major), 5.21 (dd, J = 6.9 Hz/4.2 Hz, 0.3H, 6a‴-*H* minor), 5.23 (d, J = 4.6 Hz, 1H, O*H*), 5.27 (dd, J = 6.9 Hz/4.1 Hz, 0.7H, 6a‴-*H* major), 7.03 (bs, 0.3H, 6″-*H* minor), 7.14 (bs, 0.7H, 6″-*H* major), 7.25 (m, 0.3H, 2″-*H* minor), 7.31–7.37 (m, 1H, 5″-*H*), 7.40 (m, 0.7H, 2″-*H* major), 9.55 (bs, 0.3H, N*H* minor), 9.81 (bs, 0.7H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 14.5, 23.7, 24.7, 26.9, 33.6, 37.9, 62.2, 74.3, 82.2, 86.0, 112.0, 117.1, 123.4, 124.1, 138.6, 146.9, 148.4, 149.5, 150.4, 151.1, 155.4, 156.2, 156.8, 157.7.

*4.39. 2-(((3aR,4S,6R,6aS)-6-(5-chloro-7-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)ethanol (**15a.3**)*

The mixture of **14a.2** (0.5 g, 1.28 mmol), (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanamine (0.33 g, 1.9 mmol) and triethylamine (0.23 mL, 1.64 mmol) in acetonitrile (10 mL) was left to react at room temperature for 30 min. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **15a.3** as a yellowish solid (0.62 g, 92% yield). ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 0.9H, CH_3 minor), 1.27 (s, 2.1H, CH_3 major), 1.42–1.50 (m, 5H, CH_3/3′-H_2), 2.24 (ddd, J = 9.7 Hz/6.5 Hz/3.4 Hz, 0.7H, 2′-*H* major), 2.29 (ddd, J = 9.6 Hz/6.5 Hz/3.2 Hz, 0.3H, 2′-*H* minor), 2.5 (m, 1H, 5‴-*Ha*), 2.66 (m, 1H, 5‴-*Hb*), 3.14 (dt, J = 7.8 Hz/3.9 Hz, 0.7H, 1′-*H* major), 3.38–3.51 (m, 4H, OCH_2CH_2OH), 3.77 (m, 0.3H, 1′-*H* minor), 4.00 (m, 1H, 4‴-*H*), 4.56 (m, 1H, O*H*), 4.67 (dd, J = 7.3 Hz/3.1 Hz, 0.3H, 3a‴-*H* minor), 4.70 (dd, J = 7.3 Hz/3.1 Hz, 0.7H, 3a‴-*H* major), 5.01 (ddd, J = 10.1 Hz/6.8 Hz/5.0 Hz, 0.3H, 6‴-*H* minor), 5.04 (ddd, J = 9.7 Hz/6.8 Hz/4.7 Hz, 0.7H, 6‴-*H* major), 5.17 (dd, J = 7.3 Hz/4.8 Hz, 0.3H, 6a‴-*H* minor), 5.22 (dd, J = 7.3 Hz/4.6 Hz, 0.7H, 6a‴-*H* major), 7.03 (d, J = 8.3 Hz, 0.3H, 6″-*H* minor), 7.14 (d, J = 8.3 Hz, 0.7H, 6″-*H* major), 7.25 (ddd, J = 12.0 Hz/7.8 Hz/2.0 Hz, 0.3H, 2″-*H* minor), 7.31–7.37 (m, 1H, 5″-*H*), 7.40 (ddd, J = 12.0 Hz/7.8 Hz/2.0 Hz, 0.7H, 2″-*H* major), 9.56 (d, J = 4.9 Hz, 0.3H, N*H* minor), 9.83 (d, J = 3.4 Hz, 0.7H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 14.5, 23.7, 24.7, 26.8, 33.6, 35.5, 60.0, 61.7, 70.7, 81.9, 83.7, 112.5, 114.9, 115.6, 117.0, 123.4, 124.1, 138.6, 147.2, 148.6, 149.5, 150.0, 151.2, 155.4, 156.6, 156.9, 157.8.

*4.40. N-((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)-3-methyl-5-(methylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (**7a**)*

The mixture of **14b.1** (0.5 g, 2.3 mmol), (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanamine (0.59 g, 3.45 mmol) and triethylamine (0.42 mL, 2.95 mmol) in acetonitrile (10 mL) was left to react at room temperature for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **7a** as a white solid (0.69 g, 86% yield, m.p.: 213–216 °C). ^{1}H NMR (DMSO-d_6) δ 1.37 (q, J = 6.2 Hz, 0.8H, 3′-*Ha* major), 1.44 (m, 0.4H, 3′-*H* minor), 1.52 (m, 0.8H, 3′-*Hb* major), 2.14 (ddd, J = 9.5 Hz/6.3 Hz/3.3 Hz, 0.8H, 2′-*H* major), 2.23 (m, 0.2H, 2′-*H* minor), 2.34 (s, 2.4H, SCH 3 major), 2.52 (s, 0.6H, SCH 3 minor), 3.15 (m, 0.8H, 1′-*H* major), 3.76 (m, 0.2H, 1′-*H* minor), 4.04 (s, 0.6H, NCH_3 minor), 4.06 (s, 2.4H, NCH_3 major), 7.02 (m, 0.2H, 6″-*H* minor), 7.09 (m, 0.8H, 6″-*H* major), 7.22–7.36 (m, 2H, 2″-*H*/5″-*H*), 8.96 (d, J = 4.6 Hz, 0.2H, N*H* minor), 9.34 (d, J = 3.6 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 13.6, 15.0, 24.0, 33.0, 33.9, 115.0, 117.0, 122.6, 122.9, 139.2, 146.8, 148.4, 148.7, 148.9, 150.3, 153.9, 169.8. Anal. ($C_{15}H_{14}F_2N_6S$) theoretical: C, 51.71; H, 4.05; N, 24.12; S, 9.20. Found: C, 51.86; H, 4.27; N, 24.33, S, 9.13.

*4.41. N-((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)-3-ethyl-5-(methylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (**7b**)*

The mixture of **14b.2** (0.5 g, 2.2 mmol), (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanamine (0.56 g, 3.3 mmol) and triethylamine (0.4 mL, 2.8 mmol) in acetonitrile (10 mL) was left to react at room temperature for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **7b** as a white solid (0.58 g, 73% yield, m.p.: 164–165 °C). ^{1}H NMR (DMSO-d_6) δ 1.37 (q, J = 6.2 Hz, 1H, 3′-*Ha*), 1.49 (m, 4H, 3′-*Hb*/NCH_2CH_3), 2.13 (ddd, J = 9.4 Hz/6.3 Hz/3.3 Hz, 0.8H, 2′-*H* major), 2.25 (m, 0.2H, 2′-*H* minor), 2.33 (s, 2.4H, SCH 3 major), 2.52 (s, 0.6H, SCH 3 minor), 3.14 (m, 0.8H, 1′-*H* major), 3.78 (m, 0.2H, 1′-*H* minor), 4.49 (q, J = 7.3 Hz, 2H, NCH_2CH$_3$), 7.02 (m, 0.2H, 6″-*H* minor), 7.09 (m, 0.8H, 6″-*H* major), 7.22–7.36 (m, 2H, 2″-*H*/5″-*H*), 8.95 (d, J = 4.6 Hz, 0.2H, N*H* minor), 9.35 (d, J = 3.7 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 13.6, 14.5, 15.0, 24.0, 33.9, 41.3, 115.0, 117.0, 122.8, 123.0, 139.2, 146.8, 148.3, 148.7, 148.8, 150.3, 153.9, 169.8. Anal. ($C_{16}H_{16}F_2N_6S$) theoretical: C, 53.03; H, 4.45; N, 23.19; S, 8.85. Found: C, 52.94; H, 4.75; N, 23.30, S, 8.64.

*4.42. N-((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)-5-(ethylthio)-3-methyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (**7c**)*

The mixture of **14b.3** (0.5 g, 2.2 mmol), (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanamine (0.56 g, 3.3 mmol) and triethylamine (0.4 mL, 2.8 mmol) in acetonitrile (10 mL) was left to react at room temperature for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **7c** as a white solid (0.45 g, 58% yield, m.p.: 210–212 °C). ^{1}H NMR (DMSO-d_6) δ 1.09 (t, J = 7.3 Hz, 2.5 Hz, SCH$_2$CH_3 major), 1.35 (m, 1.4H, 3′-*Ha* major/SCH$_2$CH_3 minor), 1.44 (m, 0.4H, 3′-*H* minor), 1.56 (m, 0.8H, 3′-*Hb* major), 2.13 (ddd, J = 9.5 Hz/6.3 Hz/3.3 Hz, 0.8H, 2′-*H* major), 2.24 (m, 0.2H, 2′-*H* minor), 2.89 (m, 1.6H, SCH_2CH$_3$ major), 3.12 (m, 0.4H, SCH_2CH$_3$ minor), 3.17 (m, 0.8H, 1′-*H* major), 3.75 (m, 0.2H, 1′-*H* minor), 4.03 (s, 0.6H, NCH_3 minor), 4.05 (s, 2.4H, NCH_3 major), 7.01 (m, 0.2H, 6″-*H* minor), 7.07 (m, 0.8H, 6″-*H* major), 7.21–7.36 (m, 2H, 2″-*H*/5″-*H*), 8.96 (d, J = 4.7 Hz, 0.2H, N*H* minor), 9.36 (d, J = 3.8 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 14.6, 15.2, 24.0, 24.8, 32.4, 34.1, 114.7,

117.0, 122.7, 122.8, 139.4, 147.0, 148.4, 148.7, 149.4, 150.0, 153.9, 169.3. Anal. ($C_{16}H_{16}F_2N_6S$) theoretical: C, 53.03; H, 4.45; N, 23.19; S, 8.85. Found: C, 53.05; H, 4.65; N, 23.27, S, 8.41.

4.43. N-((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)-5-(ethylthio)-3-ethyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (**7d**)

The mixture of **14b.4** (0.5 g, 2.05 mmol), (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanamine (0.52 g, 3.1 mmol) and triethylamine (0.37 mL, 2.6 mmol) in acetonitrile (10 mL) was left to react at room temperature for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **7d** as a white solid (0.69 g, 90% yield, m.p.: 145–146.5 °C). ^{1}H NMR (DMSO-d_6) δ 1.09 (t, J = 7.3 Hz, 2.4H, SCH_2CH_3 major), 1.35 (m, 1.4H, 3′-*Ha* major/SCH_2CH_3 minor), 1.44 (m, 0.2H, 3′-*Ha* minor), 1.47 (t, J = 7.3 Hz, 3.2H, NCH_2CH_3/3′-*Hb* minor), 1.56 (m, 0.8H, 3′-*Hb* major), 2.12 (ddd, J = 9.5 Hz/6.3 Hz/3.3 Hz, 0.8H, 2′-*H* major), 2.24 (m, 0.2H, 2′-*H* minor), 2.88 (m, 1.6H, SCH_2CH_3 major), 3.11 (m, 0.4H, SCH_2CH_3 minor), 3.16 (m, 0.8H, 1′-*H* major), 3.77 (m, 0.2H, 1′-*H* minor), 4.48 (q, J = 7.3 Hz, 2H, NCH_2CH_3), 7.02 (m, 0.2H, 6″-*H* minor), 7.07 (m, 0.8H, 6″-*H* major), 7.23–7.36 (m, 2H, 2″-*H*/5″-*H*), 8.96 (d, J = 3.9 Hz, 0.2H, N*H* minor), 9.37 (s, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 14.5, 14.6, 15.2, 24.0, 24.8, 34.1, 41.3, 114.8, 117.0, 122.8, 122.9, 139.4, 147.0, 148.4, 148.7, 148.9, 150.0, 154.0, 169.2. Anal. ($C_{17}H_{18}F_2N_6S$) theoretical: C, 54.24; H, 4.82; N, 22.33; S, 8.52. Found: C, 54.25; H, 5.13; N, 22.48, S, 8.43.

4.44. N-((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)-3-methyl-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (**7e**)

The mixture of **14b.5** (0.5 g, 2.05 mmol), (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanamine (0.52 g, 3.1 mmol) and triethylamine (0.37 mL, 2.6 mmol) in acetonitrile (10 mL) was heated at 50 °C for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **7e** as a white solid (0.53 g, 69% yield, m.p.: 185–187 °C). ^{1}H NMR (DMSO-d_6) δ 0.80 (t, J = 7.4 Hz, 2.4H, $SCH_2CH_2CH_3$ major), 1.00 (t, J = 7.3 Hz, 0.6H, $SCH_2CH_2CH_3$ minor), 1.37 (m, 0.8H, 3′-*Ha* major), 1.43 (m, 0.2H, 3′-*Ha* minor), 1.49 (m, 1.8H, 3′-*Hb* minor/$SCH_2CH_2CH_3$ major), 1.56 (m, 0.8H, 3′-*Hb* major), 1.70 (h, J = 7.3 Hz, 0.4H, $SCH_2CH_2CH_3$ minor), 2.13 (ddd, J = 9.5 Hz/6.3 Hz/3.2 Hz, 0.8H, 2′-*H* major), 2.23 (m, 0.2H, 2′-*H* minor), 2.88 (m, 1.6H, $SCH_2CH_2CH_3$ major), 3.11 (t, J = 7.2 Hz, 0.4H, $SCH_2CH_2CH_3$ minor), 3.17 (m, 0.8H, 1′-*H* major), 3.75 (m, 0.2H, 1′-*H* minor), 4.03 (s, 0.6H, NCH_3 minor), 4.05 (s, 2.4H, NCH_3 major), 7.02 (m, 0.2H, 6″-*H* minor), 7.07 (m, 0.8H, 6″-*H* major), 7.22–7.37 (m, 2H, 2″-*H*/5″-*H*), 8.96 (s, 0.2H, N*H* minor), 9.36 (s, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 12.9, 15.1, 22.2, 24.0, 32.3, 32.4, 34.2, 117.0, 122.6, 122.7, 139.4, 146.7, 148.4, 148.7, 149.3, 150.3, 153.8, 169.3. Anal. ($C_{17}H_{18}F_2N_6S$) theoretical: C, 54.24; H, 4.82; N, 22.33; S, 8.52. Found: C, 54.25; H, 4.87; N, 22.38, S, 7.89.

4.45. N-((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)-3-ethyl-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (**7f**)

The mixture of **14b.6** (0.5 g, 1.95 mmol), (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanamine (0.50 g, 2.95 mmol) and triethylamine (0.35 mL, 2.5 mmol) in acetonitrile (10 mL) was heated at 50 °C for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **7f** as a white solid (0.45 g, 59% yield, m.p.: 136–138 °C). ^{1}H NMR (DMSO-d_6) δ 0.81 (t, J = 7.4 Hz, 2.4H, $SCH_2CH_2CH_3$ major), 0.99 (t, J = 7.3 Hz, 0.6H, $SCH_2CH_2CH_3$ minor), 1.37 (m, 0.8H, 3′-*Ha* major), 1.41 (m, 0.2H, 3′-*Ha* minor), 1.49 (m, 4.8H, 3′-*Hb* minor/$SCH_2CH_2CH_3$ major/NCH_2CH_3), 1.56 (m, 0.8H, 3′-*Hb* major), 1.70 (h, J = 7.1 Hz, 0.4H, $SCH_2CH_2CH_3$ minor), 2.13 (ddd, J = 9.5 Hz/6.3 Hz/3.3 Hz, 0.8H, 2′-*H* major), 2.25 (ddd, J = 9.1 Hz/6.2 Hz/3.2 Hz, 0.2H, 2′-*H* minor), 2.88 (m, 1.6H, $SCH_2CH_2CH_3$ major), 3.10 (t, J = 7.0 Hz, 0.4H, $SCH_2CH_2CH_3$ minor), 3.16 (m, 0.8H, 1′-*H* major), 3.76 (m, 0.2H, 1′-*H* minor), 4.48 (q, J = 7.3 Hz, 2H, NCH_2CH_3), 7.02 (m, 0.2H, 2″-*H* minor), 7.07 (m, 0.8H, 6″-*H* major), 7.23–7.36 (m, 2H, 2″-*H*/5″-*H*), 8.94 (d, J = 4.0 Hz, 0.2H, N*H* minor), 9.35 (s, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 13.0, 14.5, 15.0, 22.3, 24.0, 32.3, 34.1, 41.3, 114.8, 117.0, 122.8, 122.9, 139.4, 147.0, 148.4, 148.7, 148.8, 150.1, 153.9, 169.6. Anal. ($C_{18}H_{20}F_2N_6S$) theoretical: C, 55.37; H, 5.16; N, 21.52; S, 8.21. Found: C, 55.30; H, 5.41; N, 21.64, S, 8.03.

4.46. 3-Cyclopentyl-N-((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (**7g**)

The mixture of **14b.7** (0.5 g, 1.67 mmol), (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanamine (0.42 g, 2.5 mmol) and triethylamine (0.3 mL, 2.1 mmol) in acetonitrile (10 mL) was heated at 50 °C for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **7g** as a white solid (0.53 g, 74% yield, m.p.: 113.5–115 °C). ^{1}H NMR (DMSO-d_6) δ 0.82 (t, J = 7.2 Hz, 2.4H, $SCH_2CH_2CH_3$ major), 0.99 (t, J = 7.3 Hz, 0.6H, $SCH_2CH_2CH_3$ minor), 1.38 (m, 1H, 3′-*Ha*), 1.44–1.55 (m, 2.6H, 3′-*Hb*/$SCH_2CH_2CH_3$ major), 1.72 (m, 2.4H, $SCH_2CH_2CH_3$ minor/3‴-*Ha*/4‴-*Ha*), 1.90 (m, 2H, 3‴-*Hb*/4‴-*Hb*), 2.12–2.19 (m, 5H, 2′-*H*/2‴-H_2/5‴-H_2), 2.89 (m, 1.6H, $SCH_2CH_2CH_3$ major), 3.10 (m, 0.4H, $SCH_2CH_2CH_3$ minor), 3.14 (m, 0.8H, 1′-*H* major), 3.78 (m, 0.2H, 1′-*H* minor), 5.15 (p, J = 7.2 Hz, 1H, 1‴-*H*), 7.02 (m, 0.2H, 6″-*H* minor), 7.08 (m, 0.8H, 6″-*H* major), 7.22–7.37 (m, 2H, 2″-*H*/5″-*H*), 8.94 (bs, 0.2H, N*H* minor), 9.33 (bs, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 13.0, 15.0, 22.3, 24.0, 24.2, 31.8, 32.3, 34.0, 58.3, 114.8, 117.0, 122.8, 123.1, 139.3, 146.8, 148.4, 148.6, 148.7, 150.3, 153.9, 169.0. Anal. ($C_{21}H_{24}F_2N_6S$) theoretical: C, 58.59; H, 5.62; N, 19.52; S, 7.45. Found: C, 58.44; H, 5.62; N, 19.71, S, 7.49.

4.47. (3aR,4S,6R,6aS)-6-(7-amino-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (**16a**)

The solution of **14b.8** (0.5 g, 1.3 mmol) in THF (10 mL) was saturated with ammonia gas in a sealed vessel and left to react at room temperature for 1 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16a** as a white solid (0.38 g, 79% yield). ^{1}H NMR (DMSO-d_6) δ 1.00 (t, J = 7.4 Hz, 3H, $SCH_2CH_2CH_3$), 1.26 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.71 (h, J = 7.3 Hz, 2H, $SCH_2CH_2CH_3$), 2.47 (m, 1H, 5′-*Ha*), 2.56 (m, 1H, 5′-*Hb*), 3.08 (m, 2H, $SCH_2CH_2CH_3$), 4.13 (m, 1H, 4′-*H*), 4.54 (dd, J = 7.0 Hz/3.0 Hz, 1H, 3a′-*H*), 4.99 (ddd, J = 9.1 Hz/7.0 Hz/4.4 Hz, 1H, 6′-*H*), 5.25 (dd, J = 7.0 Hz/4.4 Hz, 1H, 6a′-*H*), 5.28 (d, J = 4.7 Hz, 1H, O*H*), 8.09 (bs, 1H, N*Ha*), 8.43 (bs, 1H, N*Hb*). ^{13}C NMR (DMSO-d_6) δ 13.4, 22.6, 24.7, 26.9, 32.2, 37.7, 61.9, 74.2, 82.1, 86.1, 111.9, 122.8, 149.4, 155.1, 169.3.

4.48. (3aR,4S,6R,6aS)-6-(7-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (**16b**)

The mixture of **14b.8** (0.5 g, 1.3 mmol), (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanamine (0.33 g, 1.95 mmol) and triethylamine (0.23 mL, 1.6 mmol) in acetonitrile (10 mL) was heated at 80 °C for 2 h. After evaporation of the solvent, the residue was

purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16b** as a white solid (0.62 g, 92% yield). ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 7.3 Hz, 2.4H, $SCH_2CH_2CH_3$ major), 1.00 (t, J = 7.3 Hz, 0.6H, $SCH_2CH_2CH_3$ minor), 1.26 (s, 3H, CH_3), 1.38 (m, 1H, 3′-*Ha*), 1.47 (s, 3H, CH_3), 1.53 (m, 2.6H, 3′-*Hb*/$SCH_2CH_2CH_3$ major), 1.71 (h, J = 7.1 Hz, 0.4H, $SCH_2CH_2CH_3$ minor), 2.13 (m, 0.8H, 2′-*H* major), 2.25 (m, 0.2H, 2′-*H* minor), 2.45 (m, 1H, 5‴-*Ha*), 2.54 (m, 1H, 5‴-*Hb*), 2.88 (dt, J = 13.6 Hz/7.2 Hz, 0.8H, SC*Ha* major), 2.94 (dt, J = 14.2 Hz/7.2 Hz, 0.8H, SC*Hb* major), 3.09 (m, 0.4H, SCH 2 minor), 3.15 (m, 0.8H, 1′-*H* major), 3.75 (m, 0.2H, 1′-*H* minor), 4.13 (m, 1H, 4‴-*H*), 4.55 (m, 1H, 3a‴-*H*), 4.98 (m, 1H, 6‴-*H*), 5.21 (m, 0.2H, 6a‴-*H* minor), 5.25 (m, 1.8H, 6a‴-*H* major/O*H*), 7.02 (bs, 0.2H, 6″-*H* minor), 7.07 (bs, 0.8H, 6″-*H* major), 7.22–7.36 (m, 2H, 2″-*H*/5″-*H*), 8.99 (d, J = 4.7 Hz, 0.2H, N*H* minor), 9.38 (d, J = 4.0 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 13.1, 15.0, 22.4, 24.1, 24.8, 27.0, 32.4, 34.1, 37.9, 61.9, 74.3, 82.2, 86.2, 112.0, 114.9, 117.1, 122.9, 123.2, 139.4, 146.9, 148.5, 148.8, 149.1, 150.4, 154.0, 169.4.

4.49. 2-(((3aR,4S,6R,6aS)-6-(7-amino-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)ethanol (**16c**)

The solution of **14b.9** (0.5 g, 1.16 mmol) in THF (10 mL) was saturated with ammonia gas in a sealed vessel and left to react at room temperature for 1 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16c** as a white solid (0.36 g, 75% yield). ^{1}H NMR (DMSO-d_6) δ 1.00 (t, J = 7.3 Hz, 3H, $SCH_2CH_2CH_3$), 1.27 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.71 (h, J = 7.2 Hz, 2H, $SCH_2CH_2CH_3$), 2.56 (dt, J = 13.0 Hz/9.7 Hz, 1H, 5′-*Ha*), 2.67 (dt, J = 13.0 Hz/6.6 Hz, 1H, 5′-*Hb*), 3.08 (m, 2H, $SCH_2CH_2CH_3$), 3.40–3.51 (m, 4H, OCH_2CH_2OH), 4.01 (m, 1H, 4′-*H*), 4.56 (t, J = 5.2 Hz, 1H, O*H*), 4.67 (dd, J = 7.3 Hz/3.1 Hz, 1H, 3a′-*H*), 5.02 (m, 1H, 6′-*H*), 5.22 (dd, J = 7.2 Hz/4.9 Hz, 1H, 6a′-*H*), 8.10 (bs, 1H, N*Ha*), 8.44 (bs, 1H, N*Hb*). ^{13}C NMR (DMSO-d_6) δ 13.4, 22.6, 24.8, 26.9, 32.2, 35.3, 60.0, 61.4, 70.7, 81.9, 82.0, 83.8, 112.4, 122.8, 149.4, 155.1, 169.4.

4.50. 2-(((3aR,4S,6R,6aS)-6-(7-(Cyclopropylamino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)ethanol (**16d**)

The mixture of **14b.9** (0.5 g, 1.16 mmol), cyclopropylamine (0.12 g, 1.74 mmol) and triethylamine (0.21 mL, 1.45 mmol) in acetonitrile (10 mL) was heated at 80 °C for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16d** as a white solid (0.48 g, 91% yield). ^{1}H NMR (DMSO-d_6) δ 0.68 (m, 2H, 2′-*Ha*/3′-*Ha*), 0.76 (m, 1.4H, 2′-*Hb* major/3′-*Hb* major), 0.87 (m, 0.6H, 2′-*Hb* minor/3′-*Hb* minor), 1.00 (t, J = 7.3 Hz, 3H, $SCH_2CH_2CH_3$), 1.26 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.73 (m, 2H, $SCH_2CH_2CH_3$), 2.54 (m, 1H, 5″-*Ha*), 2.65 (m, 1H, 5″-*Hb*), 3.05 (m, 0.7H, 1′-*H* major), 3.10 (m, 2H, $SCH_2CH_2CH_3$), 3.39–3.51 (m, 4.3H, 1′-*H* minor/OCH_2CH_2OH), 4.00 (m, 1H, 4″-*H*), 4.57 (bs, 1H, O*H*), 4.67 (dd, J = 7.3 Hz/3.2 Hz, 1H, 6a″-*H*), 5.01 (m, 1H, 6″-*H*), 5.20 (m, 1H, 3a″-*H*), 8.83 (d, J = 4.1 Hz, 0.3H, N*H* minor), 9.11 (d, J = 4.3 Hz, 0.7H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 5.9, 7.5, 13.6, 22.7, 23.7, 24.7, 26.9, 32.5, 35.4, 60.0, 61.3, 70.7, 81.8, 82.0, 83.7, 112.5, 148.9, 154.1, 169.4.

4.51. 2-(((3aR,4S,6R,6aS)-2,2-dimethyl-6-(7-(((1R,2S)-2-phenylcyclopropyl)amino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)ethanol (**16e**)

The mixture of **14b.9** (0.5 g, 1.16 mmol), (1*R*,2*S*)-2-phenylcyclopropanamine hydrochloride (0.3 g, 1.74 mmol) and triethylamine (0.21 mL, 1.45 mmol) in acetonitrile (10 mL) was heated at 80 °C for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16e** as a white solid (0.54 g, 88% yield). ^{1}H NMR (DMSO-d_6) δ 0.83 (t, J = 7.3 Hz, 2.4H, $SCH_2CH_2CH_3$ major), 1.00 (m, 0.6H, $SCH_2CH_2CH_3$ minor), 1.27 (s, 3H, CH_3), 1.33 (m, 1H, 3′-*Ha*), 1.40 (m, 0.2H, 3′-*Hb* minor), 1.50 (m, 5.4H, CH_3/3′-*Hb* major/$SCH_2CH_2CH_3$ major), 1.71 (h, J = 7.1 Hz, 0.4H, $SCH_2CH_2CH_3$ minor), 2.14 (m, 0.8H, 2′-*H* major), 2.26 (m, 0.2H, 2′-*H* minor), 2.51 (m, 1H, 5‴-*Ha*), 2.66 (m, 1H, 5‴-*Hb*), 2.91 (m, 1.6H, $SCH_2CH_2CH_3$ major), 3.09 (m, 0.4H, $SCH_2CH_2CH_3$ minor), 3.20 (m, 0.8H, 1′-*H* major), 3.39–3.50 (m, 4H, OCH_2CH_2OH), 3.82 (m, 0.2H, 1′-*H* minor), 4.00 (m, 1H, 4‴-*H*), 4.57 (t, J = 4.6 Hz, 1H, O*H*), 4.67 (m, z, 1H, 6a‴-*H*), 5.01 (m, 1H, 6‴-*H*), 5,20 (m, 1H, 3a‴-*H*), 7.19 (m, 3H, 2″-*H*/4″-*H*/6″-*H*), 7.29 (t, J = 7.5 Hz, 2H, 3″-*H*/5″-*H*), 8.99 (d, J = 4.4 Hz, 0.2H, N*H* minor), 9.37 (d, J = 3.6 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 13.1, 15.0, 22.4, 24.4, 24.8, 26.9, 32.5, 33.8, 35.4, 60.1, 61.4, 70.7, 81.9, 82.0, 83.7, 122.5, 125.7, 126.0, 128.2, 141.2, 149.1, 153.9, 169.5.

4.52. 2-(((3aR,4S,6R,6aS)-6-(7-((3,4-difluorophenethyl)amino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)ethanol (**16f**)

The mixture of **14b.9** (0.5 g, 1.16 mmol), 2-(3,4-difluorophenyl) ethanamine (0.27 g, 1.74 mmol) and triethylamine (0.21 mL, 1.45 mmol) in acetonitrile (10 mL) was heated at 80 °C for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16f** as a white solid (0.53 g, 83% yield). ^{1}H NMR (DMSO-d_6) δ 0.99 (t, J = 7.1 Hz, 3H, $SCH_2CH_2CH_3$), 1.26 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.70 (h, J = 7.3 Hz, 2H, $SCH_2CH_2CH_3$), 2.50 (m, 1H, 5‴-*Ha*), 2.65 (m, 1H, 5‴-*Hb*), 2.95 (m, 2H, 2′-H_2), 3.07 (m, 2H, $SCH_2CH_2CH_3$), 3.40–3.51 (m, 4H, OCH_2CH_2OH), 3.73 (q, J = 6.8 Hz, 1.6H, 1′-H_2 major), 4.00 (m, 1H, 4‴-*H*), 4.10 (q, J = 6.9 Hz, 0.4H, 1′-H_2 minor), 4.58 (t, J = 5.0 Hz, 1H, O*H*), 4.67 (dd, J = 7.3 Hz/3.2 Hz, 1H, 3a‴-*H*), 5.01 (m, 1H, 6‴-*H*), 5.19 (m, 0.2H, 6a‴-*H*), 7.07 (m, 0.8H, 6″-*H* major), 7.15 (m, 0.2H, 6″-*H* minor), 7.29–7.41 (m, 2H, 2″-*H*/5″-*H*), 8.74 (t, J = 6.3 Hz, 0.2H, N*H* minor), 9.09 (d, J = 5.6 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 13.3, 22.7, 24.7, 26.9, 32.4, 33.5, 35.4, 41.1, 60.0, 61.3, 70.7, 81.8, 83.7, 112.5, 117.0, 117.6, 123.0, 125.4, 137.1, 147.0, 148.2, 149.0, 149.1, 150.4, 153.0, 169.4.

4.53. 2-(((3aR,4S,6R,6aS)-6-(7-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)ethanol (**16g**)

The mixture of **14b.9** (0.5 g, 1.16 mmol), (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanamine (0.3 g, 1.74 mmol) and triethylamine (0.21 mL, 1.45 mmol) in acetonitrile (10 mL) was heated at 80 °C for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16g** as a white solid (0.56 g, 86% yield). ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 7.4 Hz, 2.4H, $SCH_2CH_2CH_3$ major), 1.00 (t, J = 7.3 Hz, 0.6H, $SCH_2CH_2CH_3$ minor), 1.26 (s, 3H, CH_3), 1.38 (m, 1H, 3′-*Ha*), 1.48 (s, 3H, CH_3), 1.53 (m, 2.6H, 3′-*Hb*/$SCH_2CH_2CH_3$ major), 1.71 (h, J = 7.2 Hz, 0.4H, $SCH_2CH_2CH_3$ minor), 2.13 (m, 0.8H, 2′-*H* major), 2.24 (m, 0.2H, 2′-*H* minor), 2.50 (m, 1H, 5‴-*Ha*), 2.65 (m, 1H, 5‴-*Hb*), 2.89 (m, 0.8H, SC*Ha* major), 2.93 (m, 0.8H, SC*Hb* major), 3.08 (m, 0.4H, SCH 2 minor), 3.15 (m, 0.8H, 1′-*H* major), 3.39–3.51 (m, 4H, OCH_2CH_2OH), 3.75 (m, 0.2H, 1′-*H* minor), 4.01 (m, 1H, 4‴-*H*), 4.56 (t, J = 5.2 Hz, 1H, O*H*), 4.64 (dd, J = 7.3 Hz/3.2 Hz, 0.2H, 3a‴-*H* minor), 4.68 (dd, J = 7.3 Hz/3.2 Hz, 0.8H, 3a‴-*H* major),

5.01 (m, 1H, 6‴-*H*), 5.17 (m, 0.2H, 6a‴-*H* minor), 5.21 (m, 0.8H, 6a‴-*H* major), 7.02 (bs, 0.2H, 6″-*H* minor), 7.08 (bs, 0.8H, 6″-*H* major), 7.22–7.37 (m, 2H, 2″-*H*/5″-*H*), 9.00 (d, $J = 4.7$ Hz, 0.2H, N*H* minor), 9.39 (d, $J = 3.9$ Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 13.1, 15.0, 22.4, 24.0, 24.8, 26.9, 32.4, 34.0, 35.5, 59.8, 60.0, 61.4, 70.7, 81.9, 83.7, 112.5, 114.9, 117.0, 122.9, 123.1, 139.3, 146.9, 148.5, 148.8, 149.1, 150.5, 153.9, 169.5.

*4.54. (3aR,4S,6R,6aS)-6-(7-amino-5-((2-hydroxypropyl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (**16h**)*

The mixture of **15a.1** (0.3 g, 0.92 mmol), 1-mercaptopropan-2-ol (0.12 mL, 1.38 mmol) and K_2CO_3 (0.19 g, 1.38 mmol) in acetonitrile (3 mL) was heated in a sealed vessel at 100 °C for 1 h. After evaporation of the solvent, the residue was taken up with water (25 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, evaporated and purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16h** as an oily residue (0.27 g, 77% yield). ^{1}H NMR (DMSO-d_6) δ 1.18 (d, $J = 6.2$ Hz, 3H, CHOHC*H*$_3$), 1.26 (s, 3H, C*H*$_3$), 1.47 (s, 3H, C*H*$_3$), 2.46 (m, 1H, 5′-*Ha*), 2.57 (m, 1H, 5′-*Hb*), 3.10 (ddd, $J = 13.4$ Hz/6.6 Hz/4.3 Hz, 1H, SC*Ha*), 3.22 (dt, $J = 13.3$ Hz/5.4 Hz, 1H, SC*Hb*), 3.89 (ddt, $J = 11.6$ Hz/8.6 Hz/4.1 Hz, 1H, C*H*OHCH$_3$), 4.13 (m, 1H, 4′-*H*), 4.55 (m, 1H, 3a′-*H*), 4.86 (dd, $J = 4.9$ Hz/1.4 Hz, 1H, 4′-O*H*), 4.98 (ddd, $J = 9.0$ Hz/7.0 Hz/4.3 Hz, 1H, 6′-*H*), 5.25 (m, 1H, 6a′-*H*), 5.27 (d, $J = 4.8$ Hz, 1H, CHO*H*CH$_3$), 8.10 (bs, 1H, N*Ha*), 8.43 (bs, 1H, N*Hb*). ^{13}C NMR (DMSO-d_6) δ 22.7, 24.8, 26.9, 37.8, 47.8, 61.8, 65.4, 74.2, 82.1, 86.1, 111.9, 122.8, 149.3, 155.1, 169.5.

*4.55. (3aR,4S,6R,6aS)-6-(7-amino-5-((3-hydroxypropyl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (**16i**)*

The mixture of **15a.1** (0.3 g, 0.92 mmol), 3-mercapto-1-propanol (0.12 mL, 1.38 mmol) and K_2CO_3 (0.19 g, 1.38 mmol) in acetonitrile (3 mL) was heated in a sealed vessel at 100 °C for 1 h. After evaporation of the solvent, the residue was taken up with water (25 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, evaporated and purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16i** as an oily residue (0.25 g, 71% yield). ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 3H, C*H*$_3$), 1.47 (s, 3H, C*H*$_3$), 1.84 (m, 2H, SCH$_2$C*H*$_2$CH$_2$OH), 2.48 (m, 1H, 5′-*Ha*), 2.55 (m, 1H, 5′-*Hb*), 3.14 (t, $J = 7.2$ Hz, 2H, SCH 2), 3.52 (t, $J = 6.2$ Hz, 1H, C*H*$_2$OH), 4.13 (m, 1H, 4′-*H*), 4.55 (m, 2H, 3a′-*H*/CH$_2$O*H*), 4.98 (ddd, $J = 9.1$ Hz/7.0 Hz/4.4 Hz, 1H, 6′-*H*), 5.26 (m, 2H, 6a′-*H*/4′-O*H*), 8.09 (bs, 1H, N*Ha*), 8.43 (bs, 1H, N*Hb*). ^{13}C NMR (DMSO-d_6) δ 24.7, 26.9, 27.2, 32.3, 37.7, 59.5, 61.9, 74.2, 82.0, 86.1, 111.9, 122.8, 149.4, 155.1, 169.3.

*4.56. (3aR,4S,6R,6aS)-6-(7-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)-5-((3-hydroxypropyl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (**16j**)*

The mixture of **15a.2** (0.3 g, 0.63 mmol), 3-mercapto-1-propanol (0.08 mL, 0.96 mmol) and K_2CO_3 (0.13 g, 0.96 mmol) in acetonitrile (3 mL) was heated in a sealed vessel at 100 °C for 1 h. After evaporation of the solvent, the residue was taken up with water (25 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, evaporated and purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16j** as a white solid (0.24 g, 72% yield). ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 3H, C*H*$_3$), 1.38 (q, $J = 6.3$ Hz, 1H, 3′-*Ha*), 1.47 (s, 3H, C*H*$_3$), 1.52 (dt, $J = 9.9$ Hz/5.4 Hz, 1H, 3′-*Hb*), 1.70 (p, $J = 6.6$ Hz, 1.6H, SCH$_2$C*H*$_2$CH$_2$OH major), 1.84 (p, $J = 6.7$ Hz, 0.4H, SCH$_2$C*H*$_2$CH$_2$OH minor), 2.14 (m, 0.8H, 2′-*H* major), 2.25 (m, 0.2H, 2′-*H* minor), 2.44 (m, 1H, 5‴-*Ha*), 2.54 (m, 1H, 5‴-*Hb*), 2.97 (dt, $J = 13.8$ Hz/7.1 Hz, 0.8H, SC*Ha* major), 3.03 (dt, $J = 13.9$ Hz/7.0 Hz, 0.8H, SC*Hb* major), 3.16 (m, 1.2H, SCH 2 minor/1′-*H* major), 3.40 (q, $J = 6.0$ Hz, 1.6H, C*H*$_2$OH major), 3.53 (q, $J = 5.6$ Hz, 0.4H, C*H*$_2$OH minor), 3.76 (m, 0.2H, 1′-*H* minor), 4.13 (m, 1H, 4‴-*H*), 4.49 (t, $J = 5.1$ Hz, 0.8H, CH$_2$O*H* major), 4.55 (m, 1.2H, CH$_2$O*H* minor/3a‴-*H*), 4.98 (m, 1H, 6‴-*H*), 5.22 (m, 0.2H, 6a‴-*H* minor), 5.26 (m, 1.8H, 6a‴-*H* major/4‴-O*H*), 7.02 (bs, 0.2H, 6″-*H* minor), 7.08 (bs, 0.8H, 6″-*H* major), 7.22–7.36 (m, 2H, 2″-*H*/5″-*H*), 8.99 (d, $J = 4.6$ Hz, 0.2H, N*H* minor), 9.37 (d, $J = 3.9$ Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 15.0, 23.9, 24.7, 26.9, 27.3, 32.2, 33.9, 37.8, 59.3, 61.9, 74.3, 82.1, 86.1, 111.9, 115.0, 117.0, 122.9, 123.2, 139.2, 146.9, 148.4, 149.0, 150.4, 154.0, 169.4.

*4.57. (3aR,4S,6R,6aS)-6-(7-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)-5-(((R)-2-hydroxypropyl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (**16k**)*

The mixture of **15a.2** (0.3 g, 0.63 mmol), (R)-1-mercaptopropan-2-ol (0.08 mL, 0.96 mmol) and K_2CO_3 (0.13 g, 0.96 mmol) in acetonitrile (3 mL) was heated in a sealed vessel at 100 °C for 1 h. After evaporation of the solvent, the residue was taken up with water (25 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, evaporated and purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16k** as a white solid (0.25 g, 75% yield). ^{1}H NMR (DMSO-d_6) δ 1.01 (d, $J = 6.1$ Hz, 2.4H, CHOHC*H*$_3$ major), 1.18 (d, $J = 6.0$ Hz, 0.6H, CHOHC*H*$_3$ minor), 1.26 (s, 3H, C*H*$_3$), 1.38 (m, 1H, 3′-*Ha*), 1.47 (s, 3H, C*H*$_3$), 1.53 (m, 1H, 3′-*Hb*), 2.13 (m, 0.8H, 2′-*H* major), 2.24 (m, 0.2H, 2′-*H* minor), 2.43 (m, 1H, 5‴-*Ha*), 2.55 (m, 1H, 5‴-*Hb*), 2.88 (dd, $J = 13.4$ Hz/7.0 Hz, 0.8H, SC*Ha* major), 3.10–3.18 (m, 1.8H, SC*Ha* minor/SC*Hb* major/1′-*H* major), 3.23 (dd, $J = 13.3$ Hz/5.2 Hz, 0.2H, SC*Hb* minor), 3.78 (m, 1H, C*H*OHCH$_3$ major/1′-*H* minor), 3.90 (m, 0.2H, C*H*OHCH$_3$ minor), 4.14 (bs, 1H, 4‴-*H*), 4.56 (m, 1H, 3a‴-*H*), 4.79 (d, $J = 4.8$ Hz, 0.8H, CHO*H*CH$_3$ major), 4.87 (d, $J = 4.2$ Hz, 0.2H, CHO*H*CH$_3$ minor), 4.99 (m, 1H, 6‴-*H*), 5.22 (m, 0.2H, 6a‴-*H* minor), 5.26 (m, 1.8H, 6a‴-*H* major/4‴-O*H*), 7.02 (bs, 0.2H, 6″-*H* minor), 7.09 (bs, 0.8H, 6″-*H* major), 7.22–7.36 (m, 2H, 2″-*H*/5″-*H*), 9.00 (d, $J = 4.8$ Hz, 0.2H, *N*H minor), 9.37 (d, $J = 4.0$ Hz, 0.8H, *N*H major). ^{13}C NMR (DMSO-d_6) δ 15.0, 22.5, 24.0, 24.7, 26.9, 33.9, 37.8, 39.3, 61.8, 65.1, 74.3, 82.1, 86.1, 111.9, 114.9, 117.1, 123.0, 123.1, 139.2, 144.5, 146.8, 148.5, 149.0, 150.3, 153.9, 155.4, 169.6.

*4.58. (3aR,4S,6R,6aS)-6-(7-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)-5-(((S)-2-hydroxypropyl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (**16l**)*

The mixture of **15a.2** (0.3 g, 0.63 mmol), (S)-1-mercaptopropan-2-ol (0.08 mL, 0.96 mmol) and K_2CO_3 (0.13 g, 0.96 mmol) in acetonitrile (3 mL) was heated in a sealed vessel at 100 °C for 1 h. After evaporation of the solvent, the residue was taken up with water (25 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, evaporated and purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16l** as a white solid (0.28 g, 84% yield). ^{1}H NMR (DMSO-d_6) δ 1.01 (d, $J = 6.1$ Hz, 2.4H, CHOHC*H*$_3$ major), 1.18 (d, $J = 6.0$ Hz, 0.6H, CHOHC*H*$_3$ minor), 1.25 (s, 3H, C*H*$_3$), 1.37 (m, 0.8H, 3′-*Ha* major), 1.40 (m, 0.2H, 3′-*Ha* minor), 1.47 (s, 3.2H, 3′-*Hb* minor/C*H*$_3$), 1.51 (m, 0.8H, 3′-*Hb* major), 2.14 (m, 0.8H, 2′-*H* major), 2.24 (m, 0.2H, 2′-*H* minor), 2.43 (m, 1H, 4‴-*Ha*), 2.55 (m, 1H, 4‴-*Hb*), 3.06 (m, 1.6H, SCH 2 major), 3.12 (m, 0.2H, SC*Ha* minor), 3.17

(m, 0.8H, 1′-*H* major), 3.23 (dd, *J* = 13.5 Hz/5.1 Hz, 0.2H, SC*Hb* minor), 3.77 (m, 1H, C*H*OHCH$_3$ major/1′-*H* minor), 3.88 (m, 0.2H, C*H*OHCH$_3$ minor), 4.13 (bs, 1H, 4‴-*H*), 4.56 (m, 1H, 3a‴-*H*), 4.79 (d, *J* = 4.8 Hz, 0.8H, CHO*H*CH$_3$ major), 4.86 (d, *J* = 4.8 Hz, 0.2H, CHO*H*CH$_3$ minor), 4.99 (m, 1H, 6‴-*H*), 5.20 (m, 0.2H, 6a‴-*H* minor), 5.25 (m, 1.8H, 6a‴-*H* major/4‴-O*H*), 7.02 (m, 0.2H, 6″-*H* minor), 7.08 (m, 0.8H, 6″-*H* major), 7.23−7.35 (m, 2H, 2″-*H*/5″-*H*), 8.99 (d, *J* = 4.2 Hz, 0.2H, N*H* minor), 9.36 (d, *J* = 3.1 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 15.0, 22.6, 23.9, 24.7, 26.9, 33.8, 37.8, 39.2, 61.8, 65.2, 74.3, 82.1, 86.1, 111.9, 115.0, 117.0, 123.0, 123.1, 139.1, 147.2, 148.5, 148.6, 148.9, 150.1, 150.3, 153.8, 155.4, 169.6.

*4.59. 1-((7-(((1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl)amino)-3-((3aS,4R,6S,6aR)-6-(2-hydroxyethoxy)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)thio)propan-2-ol (**16m**)*

The mixture of **15a.3** (0.3 g, 0.57 mmol), 1-mercaptopropan-2-ol (0.07 mL, 0.87 mmol) and K_2CO_3 (0.12 g, 0.87 mmol) in acetonitrile (3 mL) was heated in a sealed vessel at 100 °C for 3 h. After evaporation of the solvent, the residue was taken up with water (25 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, evaporated and purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16m** as a white solid (0.25 g, 74% yield). ^{1}H NMR (DMSO-d_6) δ 1.01 (d, *J* = 6.1 Hz, 1.2H, CHOHC*H*$_3$ major *R* or *S*), 1.05 (d, *J* = 6.1 Hz, 1.2H, CHOHC*H*$_3$ major *R* or *S*), 1.18 (m, 0.6H, CHOHC*H*$_3$ minor), 1.27 (s, 3H, C*H*$_3$), 1.38 (m, 1H, 3′-*Ha*), 1.49 (s, 3H, C*H*$_3$), 1.52 (m, 1H, 3′-*Hb*), 2.14 (m, 1H, 2′-*H* major), 2.25 (m, 1H, 2′-*H* minor), 2.50 (m, 1H, 5‴-*Ha*), 2.66 (m, 1H, 5‴-*Hb*), 2.88 (dd, *J* = 13.5 Hz/7.0 Hz, 0.4H, SC*Ha* major *R* or *S*), 3.02 (dd, *J* = 13.4 Hz/6.8 Hz, 0.4H, SC*Ha* major *R* or *S*), 3.08−3.17 (m, 2H, SC*Ha* minor/SC*Hb*/1′-*H* major), 3.40−3.50 (m, 4H, OC*H*$_2$C*H*$_2$OH), 3.76 (m, 1H, C*H*OH major/1′-*H* minor), 3.88 (m, 0.2H, C*H*OH minor), 4.00 (m, 1H, 4‴-*H*), 4.56 (t, *J* = 4.5 Hz, 1H, OCH$_2$CH$_2$O*H*), 4.67 (m, 1H, 3a‴-*H*), 4.79 (m, 0.8H, CHO*H* major), 4.85 (m, 0.2H, CHO*H* minor), 5.02 (m, 1H, 6‴-*H*), 5.17 (m, 0.2H, 6a‴-*H* minor), 5.22 (m, 0.8H, 6a‴-*H* major), 7.02 (bs, 0.2H, 6″-*H* minor), 7.09 (bs, 1H, 6″-*H* major), 7.22−7.36 (m, 2H, 2″-*H*/5″-*H*), 9.00 (d, *J* = 4.5 Hz, 0.2H, N*H* minor), 9.37 (m, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 15.0, 22.5, 22.6, 23.9, 24.8, 26.9, 33.8, 35.5, 39.2, 60.0, 61.4, 65.1, 70.7, 81.9, 82.0, 83.7, 112.5, 115.0, 117.1, 123.0, 123.1, 139.2, 146.9, 148.5, 148.7, 149.0, 150.4, 153.9, 169.7.

*4.60. 3-((7-(((1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl)amino)-3-((3aS,4R,6S,6aR)-6-(2-hydroxyethoxy)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)thio)propan-1-ol (**16n**)*

The mixture of **15a.3** (0.3 g, 0.57 mmol), 3-mercapto-1-propanol (0.07 mL, 0.87 mmol) and K_2CO_3 (0.12 g, 0.87 mmol) in acetonitrile (3 mL) was heated in a sealed vessel at 100 °C for 1 h. After evaporation of the solvent, the residue was taken up with water (25 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, evaporated and purified by column chromatography on silica gel using hexane/ethyl acetate gradient to give **16n** as a white solid (0.22 g, 65% yield). ^{1}H NMR (DMSO-d_6) δ 1.27 (s, 3H, C*H*$_3$), 1.37 (q, *J* = 6.2 Hz, 1H, 3′-*Ha*), 1.49 (s, 3H, C*H*$_3$), 1.52 (dt, *J* = 10.4 Hz/5.5 Hz, 1H, 3′-*Hb*), 1.70 (p, *J* = 6.7 Hz, 1.6H, SCH$_2$C*H*$_2$CH$_2$OH major), 1.84 (p, *J* = 6.7 Hz, 0.4H, SCH$_2$C*H*$_2$CH$_2$OH minor), 2.15 (ddd, *J* = 9.5 Hz/6.4 Hz/3.3 Hz, 0.8H, 2′-*H* major), 2.24 (m, 0.2H, 2′-*H* minor), 2.51 (m, 1H, 5‴-*Ha*), 2.66 (m, 1H, 5‴-*Hb*), 3.00 (m, 1.6H, SC*H*$_2$CH$_2$CH$_2$OH major), 3.16 (m, 1.2H, SC*H*$_2$CH$_2$CH$_2$OH minor/1′-*H* major), 3.38−3.54 (m, 6H, SCH$_2$CH$_2$C*H*$_2$OH/OC*H*$_2$CH$_2$OH), 3.74 (m, 0.2H, 1′-*H* minor), 4.00 (m, 1H, 4‴-*H*), 4.50 (t, *J* = 5.1 Hz, 0.8H, SCH$_2$CH$_2$CH$_2$O*H* major), 4.55 (t, *J* = 5.2 Hz, 0.2H, SCH$_2$CH$_2$CH$_2$O*H* minor), 4.58 (t, *J* = 5.1 Hz, 1H, OCH$_2$CH$_2$O*H*), 4.67 (m, 1H, 3a‴-*H*), 5.02 (m, 1H, 6‴-*H*), 5.18 (m, 0.2H, 6a‴-*H* minor), 5.22 (dd, *J* = 7.2 Hz/4.9 Hz, 0.8H, 6a‴-*H* major), 7.02 (m, 0.2H, 6″-*H* minor), 7.08 (m, 0.8H, 6″-*H* major), 7.22−7.36 (m, 2H, 2″-*H*/5″-*H*), 8.99 (d, *J* = 4.6 Hz, 0.2H, N*H* minor), 9.37 (d, *J* = 3.8 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 15.1, 23.9, 24.8, 26.9, 27.4, 32.3, 33.9, 35.5, 59.3, 60.1, 61.5, 70.7, 81.9, 82.1, 83.7, 112.5, 115.0, 117.1, 123.0, 123.2, 139.2, 146.9, 148.4, 148.8, 149.1, 150.4, 154.0, 169.5.

*4.61. (1S,2R,3S,4R)-4-(7-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)cyclopentane-1,2,3-triol (**7u**)*

To a solution of **15c.1** (0.15 g, 0.34 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate 100% to give **7u** as a white solid (0.12 g, 88% yield, m.p.: 148−152 °C). ^{1}H NMR (DMSO-d_6) δ 1.37 (m, 0.8H, 3′-*Ha* major), 1.41 (m, 0.2H, 3′-*Ha* minor), 1.49 (m, 0.2H, 3′-*Hb* minor), 1.54 (m, 0.8H, 3′-*Hb* major), 1.94 (m, 1H, 5‴-*Ha*), 2.19 (m, 0.8H, 2′-*H* major), 2.26 (m, 0.2H, 2′-*H* minor), 2.63 (m, 1H, 5‴-*Hb*), 3.29 (m, 0.8H, 1′-*H* major), 3.80 (m, 1H, 3‴-*H*), 3.82 (m, 0.2H, 1′-*H* minor), 3.94 (m, 1H, 1‴-*H*), 4.67 (m, 1H, 2‴-*H*), 4.93 (d, *J* = 3.6 Hz, 1H, 3‴-O*H*), 5.06 (m, 2H, 2‴-O*H*, 4‴-*H*), 5.16 (d, *J* = 5.2 Hz, 1H, 1‴-O*H*), 7.05 (m, 0.2H, 6″-*H* minor), 7.09 (m, 0.8H, 6″-*H* major), 7.27−7.36 (m, 2H, 2″-*H*/5″-*H*), 8.30 (s, 0.2H, 2-*H* minor), 8.40 (s, 0.8H, 2-*H* major), 8.95 (s, 0.2H, N*H* minor), 9.29 (d, *J* = 4.0 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 15.3, 23.7, 33.9, 36.1, 59.8, 61.2, 73.3, 74.9, 76.8, 114.9, 117.2, 123.0, 124.6, 139.3, 147.1, 148.4, 148.5, 148.7, 150.1, 154.8, 156.1, 156.2. Anal. ($C_{18}H_{18}F_2N_6O_3.H_2O$) theoretical: C, 51.18; H, 4.77; N, 19.90. Found: C, 51.23; H, 4.74; N, 19.60.

*4.62. (1S,2R,3S,4R)-4-(5-chloro-7-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)cyclopentane-1,2,3-triol (**7v**)*

To a solution of **15a.2** (0.15 g, 0.31 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate 100% to give **7v** as a white solid (0.11 g, 80% yield, m.p.: 195−200 °C). ^{1}H NMR (DMSO-d_6) δ 1.42−1.50 (m, 2H, 3′-*H*), 1.89 (m, 1H, 5‴-*Ha*), 2.18 (ddd, *J* = 9.6 Hz/6.5 Hz/3.3 Hz, 0.7H, 2′-*H* major), 2.29 (ddd, *J* = 9.6 Hz/6.4 Hz/3.2 Hz, 0.3H, 2′-*H* minor), 2.63 (m, 1H, 5‴-*Hb*), 3.14 (m, 0.7H, 1′-*H* major), 3.77 (m, 1H, 3‴-*H*), 3.82 (m, 0.3H, 1′-*H* minor), 3.94 (m, 1H, 1‴-*H*), 4.56 (m, 0.3H, 2‴-*H* minor), 4.61 (m, 0.7H, 2‴-*H* major), 4.96 (m, 2H, 3‴-O*H*/4‴-*H*), 5.05 (d, *J* = 6.4 Hz, 0.3H, 2‴-O*H* minor), 5.08 (d, *J* = 6.4 Hz, 0.7H, 2‴-O*H* major), 5.13 (d, *J* = 4.1 Hz, 0.3H, 1‴-O*H* minor), 5.15 (d, *J* = 4.0 Hz, 0.7H, 1‴-O*H* major), 7.04 (m, 0.3H, 6″-*H* minor), 7.14 (m, 0.7H, 6″-*H* major), 7.24−7.42 (m, 2H, 2″-*H*/5″-*H*), 9.53 (d, *J* = 5.0 Hz, 0.3H, N*H* minor), 9.81 (d, *J* = 3.9 Hz, 0.7H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 14.6, 23.7, 24.4, 33.6, 35.6, 36.1, 36.2, 61.0, 73.2, 75.1, 76.7, 114.9, 115.6, 117.1, 122.9, 123.5, 123.6, 124.0, 138.6, 147.2, 148.6, 150.0, 150.1, 151.7, 155.4, 156.6, 156.8, 157.6. Anal. ($C_{18}H_{17}ClF_2N_6O_3.H_2O$) theoretical: C, 47.32; H, 4.19; N, 18.40. Found: C, 47.51; H, 4.07; N, 18.08.

*4.63. (1S,2R,3S,4R)-4-(7-amino-5-(propylthio)-3H-[1,2,3]triazolo [4,5-d]pyrimidin-3-yl)cyclopentane-1,2,3-triol (**7h**)*

To a solution of **16a** (0.15 g, 0.41 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate/methanol gradient to give **7h** as a white solid (0.05 g, 37% yield, m.p.: 175–180 °C). ^{1}H NMR (DMSO-d_6) δ 0.99 (t, J = 7.3 Hz, 3H, $SCH_2CH_2CH_3$), 1.68 (h, J = 7.1 Hz, 2H, $SCH_2CH_2CH_3$), 1.99 (ddd, J = 13.5 Hz/9.1 Hz/4.4 Hz, 1H, 5′-*Ha*), 2.58 (ddd, J = 13.7 Hz/9.1 Hz/7.2 Hz, 1H, 5′-*Hb*), 3.08 (m, 2H, $SCH_2CH_2CH_3$), 3.78 (m, 1H, 2′-*H*), 3.93 (m, 1H, 1′-*H*), 4.68 (m, 1H, 3′-*H*), 4.96 (q, J = 9.0 Hz, 1H, 4′-*H*), 5.08 (bs, 3H, 1‴-O*H*/2‴-O*H*/3‴-O*H*), 8.05 (bs, 1H, N*Ha*), 8.40 (bs, 1H, N*Hb*). ^{13}C NMR ($CDCl_3$) δ 13.3, 22.5, 32.1, 35.8, 61.2, 73.2, 74.3, 76.8, 122.8, 149.6, 155.1, 169.0. Anal. ($C_{12}H_{18}N_6O_3S.H_2O$) theoretical: C, 41.85; H, 5.85; N, 24.40. Found: C, 41.83; H, 5.51; N, 24.18.

*4.64. (1S,2R,3S,4R)-4-(7-(((1R,2S)-2-(3,4-difluorophenyl) cyclopropyl)amino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d] pyrimidin-3-yl)cyclopentane-1,2,3-triol (**7i**)*

To a solution of **16b** (0.15 g, 0.29 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate 100% to give **7i** as a white solid (0.104 g, 75% yield, m.p.: 60–65 °C). ^{1}H NMR (DMSO-d_6) δ 0.81 (t, J = 7.4 Hz, 2.4H, $SCH_2CH_2CH_3$ major), 0.99 (t, J = 7.3 Hz, 0.6H, $SCH_2CH_2CH_3$ minor), 1.38 (dq, J = 13.8 Hz/6.4 Hz, 1H, 3′-*Ha*), 1.49 (tq, J = 13.6 Hz/6.9 Hz, 1.8H, $SCH_2CH_2CH_3$ major/3′-*Hb* minor), 1.56 (dt, J = 10.2 Hz/5.5 Hz, 0.8H, 3′-*Hb* major), 1.68 (h, J = 7.1 Hz, 0.4H, $SCH_2CH_2CH_3$ minor), 1.91 (ddd, J = 13.6 Hz/9.0 Hz/4.3 Hz, 1H, 5‴-*Ha*), 2.13 (ddd, J = 9.5 Hz/6.3 Hz/3.5 Hz, 0.8H, 2′-*H* major), 2.25 (m, 0.2H, 2′-*H* minor), 2.59 (ddd, J = 13.7 Hz/9.1 Hz/7.3 Hz, 1H, 5‴-*Hb*), 2.85 (dt, J = 13.6 Hz/7.2 Hz, 0.8H, SC*Ha* major), 2.95 (dt, J = 13.9 Hz/7.1 Hz, 0.8H, SC*Hb* major), 3.09 (m, 0.4H, SCH 2 minor), 3.16 (m, 0.8H, 1′-*H* major), 3.78 (m, 1.2H, 1′-*H* minor/2‴-*H*), 3.93 (dt, J = 6.7 Hz/3.3 Hz, 1H, 1‴-*H*), 4.65 (m, 1H, 3‴-*H*), 4.91 (d, J = 3.9 Hz, 1H, 2‴-O*H*), 4.95 (q, J = 9.0 Hz, 1H, 4‴-*H*), 4.99 (d, J = 6.5 Hz, 0.2H, 3‴-O*H* minor), 5.02 (d, J = 6.4 Hz, 0.8H, 3‴-O*H* major), 5.07 (d, J = 3.8 Hz, 0.2H, 1‴-O*H* minor), 5.10 (d, J = 4.1 Hz, 0.8H, 1‴-O*H* major), 7.03 (bs, 0.2H, 6″-*H* minor), 7.07 (bs, 0.8H, 6″-*H* major), 7.24–7.36 (m, 2H, 2″-*H*/5″-*H*), 8.93 (d, J = 4.7 Hz, 0.2H, N*H* minor), 9.35 (d, J = 4.0 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 13.0, 15.0, 22.3, 24.0, 32.3, 34.1, 36.0, 61.0, 73.2, 74.5, 76.8, 114.8, 117.0, 122.8, 123.1, 139.3, 147.1, 148.5, 149.4, 150.1, 153.9, 169.1. Anal. ($C_{21}H_{24}F_2N_6O_3S$) theoretical: C, 52.71; H, 5.06; N, 17.56; S, 6.70. Found: C, 52.31; H, 5.26; N, 17.50, S, 6.28.

*4.65. (1S,2S,3R,5S)-3-(7-amino-5-(propylthio)-3H-[1,2,3]triazolo [4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (**7j**)*

To a solution of **16c** (0.15 g, 0.37 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate/methanol gradient to give **7j** as a white solid (0.09 g, 66% yield, m.p.: 180–182 °C). ^{1}H NMR (DMSO-d_6) δ 0.99 (t, J = 7.3 Hz, 3H, $SCH_2CH_2CH_3$), 1.69 (h, J = 7.2 Hz, 2H, $SCH_2CH_2CH_3$), 2.06 (ddd, J = 14.3 Hz/9.8 Hz/5.0 Hz, 1H, 4′-*Ha*), 2.63 (m, 1H, 4′-*Hb*), 3.08 (m, 2H, $SCH_2CH_2CH_3$), 3.46–3.52 (m, 4H, OCH_2CH_2OH), 3.76 (t, J = 6.1 Hz, 1H, 5′-*H*), 3.94 (m, 1H, 1′-*H*), 4.60 (m, 2H, 2′-*H*/OCH_2-CH_2OH), 4.97 (q, J = 9.1 Hz, 1H, 3′-*H*), 5.06 (d, J = 3.9 Hz, 1H, 1′-O*H*), 5.13 (d, J = 6.4 Hz, 1H, 2′-O*H*), 8.07 (s, 1H, N*Ha*), 8.42 (s, 1H, N*Hb*). ^{13}C NMR (DMSO-d_6) δ 13.3, 22.4, 32.1, 33.1, 60.3, 60.7, 70.8, 73.7, 74.1, 81.7, 122.8, 149.6, 155.1, 169.0. Anal. ($C_{14}H_{22}N_6O_4S$) theoretical: C, 45.39; H, 5.99; N, 22.69; S, 8.66. Found: C, 45.66; H, 6.33; N, 22.53, S, 8.58.

*4.66. (1S,2S,3R,5S)-3-(7-(Cyclopropylamino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy) cyclopentane-1,2-diol (**7k**)*

To a solution of **16d** (0.15 g, 0.33 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate/methanol gradient to give **7k** as a white solid (0.09 g, 66% yield, m.p.: 156–158 °C). ^{1}H NMR (DMSO-d_6) δ 0.69 (m, 2H, 2′-*Ha*/3′-*Ha*), 0.76 (m, 1.4H, 2′-*Hb* major/3′-*Hb* major), 0.87 (m, 0.6H, 2′-*Hb* minor/3′-*Hb* minor), 0.99 (t, J = 7.3 Hz, 3H, $SCH_2CH_2CH_3$), 1.71 (m, 2H, $SCH_2CH_2CH_3$), 2.04 (ddd, J = 14.1 Hz/9.8 Hz/5.0 Hz, 1H, 4″-*Ha*), 2.65 (m, 1H, 4″-*Hb*), 3.05 (m, 0.7H, 1′-*H* major), 3.12 (m, 2H, $SCH_2CH_2CH_3$), 3.42–3.52 (m, 4.3H, 1′-*H* minor/OCH_2CH_2OH), 3.75 (m, 1H, 5″-*H*), 3.94 (m, 1H, 1″-*H*), 4.56 (m, 1H, 2″-*H*), 4.61 (m, 1H, OCH_2CH_2OH), 4.96 (m, 1H, 3″-*H*), 5.06 (bs, 1H, 1″-O*H*), 5.13 (bs, 1H, 2″-O*H*), 8.78 (d, J = 2.6 Hz, 0.3H, N*H* minor), 9.08 (d, J = 2.1 Hz, 0.7H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 5.9, 7.5, 13.3, 22.7, 23.7, 24.7, 26.1, 32.5, 33.2, 60.3, 61.5, 70.8, 73.6, 74.0, 74.3, 81.8, 123.1, 149.2, 154.1, 169.1. Anal. ($C_{17}H_{26}N_6O_4S$) theoretical: C, 49.74; H, 6.38; N, 20.47; S, 7.81. Found: C, 49.90; H, 6.44; N, 20.57, S, 7.10.

*4.67. (1S,2S,3R,5S)-3-(7-(((1R,2S)-2-phenylcyclopropyl)amino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol (**7l**)*

To a solution of **16e** (0.15 g, 0.28 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate 100% to give **7l** as a white solid (0.11 g, 79% yield, m.p.: 174–179 °C). ^{1}H NMR (DMSO-d_6) δ 0.80 (t, J = 7.4 Hz, 2.4H, $SCH_2CH_2CH_3$ major), 0.99 (t, J = 7.3 Hz, 0.6H, $SCH_2CH_2CH_3$ minor), 1.32 (m, 1H, 3′-*Ha*), 1.40 (m, 0.2H, 3′-*Hb* minor), 1.50 (m, 2.4H, 3′-*Hb* major/$SCH_2CH_2CH_3$ major), 1.69 (h, J = 7.1 Hz, 0.4H, $SCH_2CH_2CH_3$ minor), 2.04 (ddd, J = 14.1 Hz/9.7 Hz/5.0 Hz, 1H, 4‴-*Ha*), 2.12 (ddd, J = 9.5 Hz/6.3 Hz/3.3 Hz, 0.8H, 2′-*H* major), 2.26 (m, 0.2H, 2′-*H* minor), 2.63 (m, 1H, 4‴-*Hb*), 2.88 (m, 1.6H, $SCH_2CH_2CH_3$ major), 3.09 (m, 0.4H, $SCH_2CH_2CH_3$ minor), 3.20 (dq, J = 7.9 Hz/4.4 Hz, 0.8H, 1′-*H* major), 3.45–3.53 (m, 4H, OCH_2CH_2OH), 3.75 (m, 1H, 5‴-*H*), 3.85 (m, 0.2H, 1′-*H* minor), 3.93 (m, 1H, 1‴-*H*), 4.54 (m, 1H, 2‴-*H*), 4.61 (t, J = 5.0 Hz, 1H, OCH_2CH_2OH), 4.96 (q, J = 9.1 Hz,

1H, 3‴-*H*), 5.05 (d, *J* = 4.1 Hz, 1H, 1‴-O*H*), 5.12 (d, *J* = 6.4 Hz, 1H, 2‴-O*H*), 7.18 (m, 3H, 2″-*H*/4″-*H*/6″-*H*), 7.29 (t, *J* = 7.6 Hz, 2H, 3″-*H*/5″-*H*), 8.96 (d, *J* = 4.9 Hz, 0.2H, N*H* minor), 9.35 (d, *J* = 4.3 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 13.0, 15.0, 22.3, 24.5, 32.4, 33.2, 33.9, 60.3, 60.4, 70.8, 73.6, 74.4, 81.7, 123.1, 125.6, 125.9, 128.2, 141.2, 149.4, 153.8, 169.1. Anal. ($C_{23}H_{30}N_6O_4S$) theoretical: C, 56.77; H, 6.21; N, 17.27; S, 6.59. Found: C, 56.64; H, 6.20; N, 17.08, S, 6.26.

*4.68. (1S,2S,3R,5S)-3-(7-((3,4-difluorophenethyl)amino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (**7m**)*

To a solution of **16f** (0.15 g, 0.27 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate 100% to give **7m** as a white solid (0.10 g, 72% yield, m.p.: 137–142 °C). ^{1}H NMR (DMSO-d_6) δ 0.97 (t, *J* = 7.3 Hz, 3H, $SCH_2CH_2CH_3$), 1.69 (h, *J* = 6.9 Hz, 2H, $SCH_2CH_2CH_3$), 2.03 (ddd, *J* = 14.0 Hz/9.7 Hz/4.9 Hz, 1H, 4‴-*Ha*), 2.63 (m, 1H, 4‴-*Hb*), 2.94 (t, *J* = 7.1 Hz, 2H, 2′-H_2), 3.08 (m, 2H, $SCH_2CH_2CH_3$), 3.45–3.52 (m, 4H, OCH_2CH_2OH), 3.74 (m, 2.6H, 1′-H_2 major/5‴-*H*), 3.94 (m, 1H, 1‴-*H*), 4.10 (m, 0.4H, 1′-H_2 minor), 4.55 (m, 1H, 2‴-*H*), 4.61 (t, *J* = 5.0 Hz, 1H, OCH_2CH_2OH), 4.96 (q, *J* = 9.2 Hz, 1H, 3‴-*H*), 5.06 (d, *J* = 4.1 Hz, 1H, 1‴-O*H*), 5.12 (d, *J* = 6.4 Hz, 1H, 2‴-O*H*), 7.08 (m, 0.8H, 6″-*H* major), 7.17 (m, 0.2H, 6″-*H* minor), 7.30–7.42 (m, 2H, 2″-H/5″-H), 8.70 (t, *J* = 6.4 Hz, 0.2H, N*H* minor), 9.06 (d, *J* = 5.6 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 13.3, 22.6, 32.4, 33.2, 33.5, 41.1, 60.2, 60.5, 70.8, 73.6, 74.3, 81.7, 117.1, 117.5, 123.0, 125.4, 137.1, 147.1, 148.2, 148.9, 149.3, 150.1, 150.6, 153.0, 169.0. Anal. ($C_{22}H_{28}F_2N_6O_4S$) theoretical: C, 51.75; H, 5.53; N, 16.46; S, 6.28. Found: C, 51.35; H, 5.81; N, 16.86, S, 6.34.

*4.69. (1S,2S,3R,5S)-3-(7-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (**1**, ticagrelor)*

To a solution of **16g** (0.15 g, 0.27 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate 100% to give **1** as a white solid (0.115 g, 83% yield, m.p.: 135–138 °C). ^{1}H NMR (DMSO-d_6) δ 0.82 (t, *J* = 7.3 Hz, 2.4H, $SCH_2CH_2CH_3$ major), 0.99 (t, *J* = 7.3 Hz, 0.6H, $SCH_2CH_2CH_3$ minor), 1.37 (m, 1H, 3′-*Ha*), 1.46 (m, 0.2H, 3′-*Hb* minor), 1.50 (ddt, *J* = 11.5 Hz/7.1 Hz/4.4 Hz, 1.6H, $SCH_2CH_2CH_3$ major), 1.55 (dt, *J* = 10.3 Hz/5.4 Hz, 0.8H, 3′-*Hb* major), 1.69 (h, *J* = 6.9 Hz, 0.4H, $SCH_2CH_2CH_3$ minor), 2.03 (m, 1H, 4‴-*Ha*), 2.12 (m, 0.8H, 2′-*H* major), 2.25 (m, 0.2H, 2′-*H* minor), 2.63 (m, 1H, 4‴-*Hb*), 2.85 (dt, *J* = 13.6 Hz/7.2 Hz, 0.8H, S*CHa* major), 2.94 (dt, *J* = 13.9 Hz/7.1 Hz, 0.8H, S*CHb* major), 3.08 (m, 0.4H, SCH 2 minor), 3.16 (m, 0.8H, 1′-*H* major), 3.44–3.52 (m, 4H, OCH_2CH_2OH), 3.76 (t, *J* = 5.2 Hz, 1H, 5‴-*H*), 3.79 (m, 0.2H, 1′-*H* minor), 3.94 (m, 1H, 1‴-*H*), 4.56 (dt, *J* = 8.7 Hz/6.0 Hz, 1H, 2‴-*H*), 4.60 (t, *J* = 4.9 Hz, 1H, OCH_2CH_2OH), 4.96 (q, 9.1 Hz, 1H, 3‴-*H*), 5.05 (d, *J* = 4.0 Hz, 1H, 1‴-O*H*), 5.12 (m, 1H, 2‴-O*H*), 7.04 (bs, 0.2H, 6″-*H* minor), 7.07 (bs, 0.8H, 6″-*H* major), 7.23–7.37 (m, 2H, 2″-*H*/5″-*H*), 8.94 (d, *J* = 4.6 Hz, 0.2H, N*H* minor), 9.36 (d, *J* = 3.6 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 13.0, 15.0, 22.3, 24.0, 32.3, 33.2, 34.1, 60.3, 60.5, 70.8, 73.7, 74.3, 81.8, 114.8, 117.0, 122.8, 123.2, 139.3, 146.8, 148.4, 148.7, 149.4, 150.3, 150.8, 154.0, 169.2. Anal. ($C_{23}H_{28}F_2N_6O_4S$) theoretical: C, 52.86; H, 5.40; N, 16.08; S, 6.13. Found: C, 52.75; H, 5.75; N, 16.06, S, 6.26.

*4.70. (1S,2R,3S,4R)-4-(7-amino-5-((2-hydroxypropyl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)cyclopentane-1,2,3-triol (**7n**)*

To a solution of **16h** (0.15 g, 0.39 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate/methanol gradient to give **7n** as a white solid (0.07 g, 52% yield, m.p.: 177–180 °C). ^{1}H NMR (DMSO-d_6) δ 1.16 (d, *J* = 5.7 Hz, 3H, CH_3), 1.94 (ddt, *J* = 13.2 Hz/8.5 Hz/4.1 Hz, 1H, 5′-*Ha*), 2.57 (m, 1H, 5′-*Hb*), 3.17 (m, 2H, SCH 2), 3.78 (bs, 1H, 2′-*H*), 3.87 (m, 1H, SCH_2CHOH), 3.93 (m, 1H, 1′-*H*), 4.67 (m, 1H, 3′-*H*), 4.85 (d, *J* = 4.6 Hz, 0.5H, *S*-SCH_2CHOH), 4.87 (d, *J* = 4.8 Hz, 0.5H, *R*–SCH_2CHOH), 4.95–4.98 (m, 2H, 2′-O*H*/4′-*H*), 5.04 (bs, 1H, 3′-O*H*), 5.17 (d, *J* = 3.3 Hz, 1H, 1′-O*H*), 8.07 (s, 1H, N*Ha*), 8.42 (s, 1H, N*Hb*). ^{13}C NMR (DMSO-d_6) δ 22.6, 35.7, 38.8, 61.1, 65.4, 73.1, 74.3, 76.7, 122.8, 149.5, 155.1, 169.1. Anal. ($C_{12}H_{18}N_6O_4S$) theoretical: C, 42.10; H, 5.30; N, 24.55; S, 9.37. Found: C, 42.17; H, 5.56; N, 24.47, S, 9.39.

*4.71. (1S,2R,3S,4R)-4-(7-amino-5-((3-hydroxypropyl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)cyclopentane-1,2,3-triol (**7o**)*

To a solution of **16i** (0.15 g, 0.33 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate/methanol gradient to give **7o** as a white solid (0.08 g, 59% yield, m.p.: 185–187 °C). ^{1}H NMR (DMSO-d_6) δ 1.82 (m, 2H, $SCH_2CH_2CH_2OH$), 1.94 (m, 1H, 5′-*Ha*), 2.59 (m, 1H, 5′-*Hb*), 3.14 (m, 2H, $SCH_2CH_2CH_2OH$), 3.52 ($SCH_2CH_2CH_2OH$), 3.79 (m, 1H, 2′-*H*), 3.94 (m, 1H, 1′-*H*), 4.52 (m, 1H, $SCH_2CH_2CH_2OH$), 4.67 (m, 1H, 3′-*H*), 4.91 (m, 1H, 2′-O*H*), 4.96 (d, *J* = 8.4 Hz, 1H, 4′-*H*), 5.02 (m, 1H, 3′-O*H*), 5.10 (m, 1H, 1′-O*H*), 8.04 (s, 1H, N*Ha*), 8.40 (s, 1H, N*Hb*). ^{13}C NMR (DMSO-d_6) δ 27.1, 32.2, 35.9, 59.4, 61.1, 73.1, 74.4, 76.7, 122.8, 149.6, 155.1, 169.0. Anal. ($C_{12}H_{18}N_6O_4S$) theoretical: C, 42.10; H, 5.30; N, 24.55; S, 9.37. Found: C, 42.46; H, 5.61; N, 24.36, S, 9.60.

*4.72. (1S,2R,3S,4R)-4-(7-(((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)-5-((3-hydroxypropyl)thio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)cyclopentane-1,2,3-triol (**7p**)*

To a solution of **16j** (0.15 g, 0.28 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate/methanol gradient to give **7p** as a white solid (0.11 g, 79% yield, m.p.: 147–149 °C). ^{1}H NMR (DMSO-d_6) δ 1.37 (q, *J* = 6.4 Hz, 0.8H, 3′-*Ha* major), 1.40 (q, *J* = 6.7 Hz, 0.2H, 3′-*Ha* minor), 1.46 (m, 0.2H, 3′-*Hb* minor), 1.52 (dt, *J* = 10.0 Hz/5.3 Hz, 0.8H, 3′-*Hb* major), 1.66 (p, *J* = 6.6 Hz, 1.6H, $SCH_2CH_2CH_2OH$ major), 1.81 (p, *J* = 6.3 Hz, 0.4H, $SCH_2CH_2CH_2OH$ minor), 1.91 (ddd, *J* = 13.3 Hz/

9.0 Hz/4.2 Hz, 1H, 5‴-*Ha*), 2.14 (m, 0.8H, 2′-*H* major), 2.25 (m, 0.2H, 2′-*H* minor), 2.59 (m, 1H, 5‴-*Hb*), 2.95 (dt, *J* = 13.7 Hz/7.1 Hz, 0.8H, SC*Ha* major), 3.02 (dt, *J* = 13.8 Hz/7.0 Hz, 0.8H, SC*Hb* major), 3.16 (m, 1.2H, SCH 2 minor/1′-*H* major), 3.38 (q, *J* = 5.9 Hz, 1.6H, $SCH_2CH_2CH_2OH$ major), 3.52 (q, *J* = 5.5 Hz, 0.4H, $SCH_2CH_2CH_2OH$ minor), 3.78 (m, 1.2H, 1′-*H* minor/2‴-*H*), 3.93 (m, 1H, 1‴-*H*), 4.47 (t, *J* = 5.1 Hz, 0.8H, $SCH_2CH_2CH_2OH$ major), 4.53 (t, *J* = 4.8 Hz, 0.2H, $SCH_2CH_2CH_2OH$ minor), 4.65 (m, 1H, 3‴-*H*), 4.92 (d, *J* = 3.8 Hz, 1H, 2‴-O*H*), 4.95 (q, *J* = 9.0 Hz, 1H, 4‴-*H*), 5.00 (d, *J* = 6.5 Hz, 0.2H, 3‴-O*H* minor), 5.02 (d, *J* = 6.4 Hz, 0.8H, 3‴-O*H* major), 5.09 (d, *J* = 3.8 Hz, 0.2H, 1‴-O*H* minor), 5.11 (d, *J* = 4.0 Hz, 0.8H, 1‴-O*H* major), 7.03 (bs, 0.2H, 6″-*H* minor), 7.07 (bs, 0.8H, 6″-*H* major), 7.24–7.35 (m, 2H, 2″-*H*/5″-*H*), 8.94 (d, *J* = 4.5 Hz, 0.2H, N*H* minor), 9.34 (d, *J* = 3.7 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 15.1, 23.9, 27.2, 32.2, 33.9, 36.0, 59.2, 61.0, 73.2, 74.5, 76.7, 114.8, 117.0, 122.8, 123.1, 139.2, 147.0, 148.4, 149.3, 150.0, 153.9, 169.1. Anal. ($C_{21}H_{24}F_2N_6O_4S$) theoretical: C, 51.00; H, 4.89; N, 16.99; S, 6.48. Found: C, 50.68; H, 4.93; N, 16.56, S, 6.34.

*4.73. (1S,2R,3S,4R)-4-(7-(((1R,2S)-2-(3,4-difluorophenyl) cyclopropyl)amino)-5-(((R)-2-hydroxypropyl)thio)-3H-[1,2,3] triazolo[4,5-d]pyrimidin-3-yl)cyclopentane-1,2,3-triol (**7q**)*

To a solution of **16k** (0.15 g, 0.28 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate/methanol gradient to give **7q** as a white solid (0.09 g, 65% yield, m.p.: 90 °C dec.). ^{1}H NMR (DMSO-d_6) δ 1.00 (d, *J* = 6.0 Hz, 2.4H, CH_3 major), 1.17 (d, *J* = 6.9 Hz, 0.6H, CH_3 minor), 1.38 (m, 1H, 3′-*Ha*), 1.46 (m, 0.2H, 3′-*Hb* minor), 1.53 (m, 0.8H, 3′-*Hb* major), 1.92 (ddd, *J* = 13.3 Hz/8.9 Hz/4.1 Hz, 1H, 5‴-*Ha*), 2.13 (m, 0.8H, 2′-*H* major), 2.25 (m, 0.2H, 2′-*H* minor), 2.60 (m, 1H, 5‴-*Hb*), 2.89 (dd, *J* = 13.4 Hz/6.8 Hz, 0.8H, SC*Ha* major), 3.14 (m, 1.8H, SC*Ha* minor/SC*Hb* major/1′-*H* major), 3.21 (dd, *J* = 13.5 Hz/5.2 Hz, 0.2H, SC*Hb* minor), 3.72–3.78 (m, 2H, SCH_2CHOH major/1′-*H* minor/2‴-*H*), 3.87 (m, 0.2H, SCH_2CHOH minor), 3.93 (m, 1H, 1‴-*H*), 4.66 (q, *J* = 6.3 Hz, 1H, 3‴-*H*), 4.80 (d, *J* = 4.8 Hz, 0.8H, SCH_2CHO*H* major), 4.87 (d, *J* = 4.5 Hz, 0.2H, SCH_2CHO*H* minor), 4.95 (d, *J* = 4.3 Hz, 1H, 2‴-O*H*), 4.98 (m, 1.2H, 4‴-*H*/3‴-O*H* minor), 5.04 (d, *J* = 6.4 Hz, 0.8H, 3‴-O*H* major), 5.17 (d, *J* = 3.7 Hz, 1H, 1‴-O*H*), 7.04 (bs, 0.2H, 6″-*H* minor), 7.09 (bs, 0.8H, 6″-*H* major), 7.24–7.37 (m, 2H, 2″-*H*/5″-*H*), 8.96 (d, *J* = 4.4 Hz, 0.2H, N*H* minor), 9.36 (d, *J* = 3.9 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 15.0, 22.4, 24.0, 33.9, 35.9, 39.6, 61.1, 65.2, 73.2, 74.5, 76.7, 114.9, 117.0, 122.9, 123.1, 139.2, 147.1, 148.4, 148.7, 149.2, 150.1, 153.9, 169.2. Anal. ($C_{21}H_{24}F_2N_6O_4S$) theoretical: C, 51.00; H, 4.89; N, 16.99; S, 6.48. Found: C, 50.77; H, 5.15; N, 16.64, S, 6.99.

*4.74. (1S,2R,3S,4R)-4-(7-(((1R,2S)-2-(3,4-difluorophenyl) cyclopropyl)amino)-5-(((S)-2-hydroxypropyl)thio)-3H-[1,2,3] triazolo[4,5-d]pyrimidin-3-yl)cyclopentane-1,2,3-triol (**7r**)*

To a solution of **16l** (0.15 g, 0.28 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate/methanol gradient to give **7r** as a white solid (0.10 g, 72% yield, m.p.: 90 °C dec.). ^{1}H NMR (DMSO-d_6) δ 1.02 (d, *J* = 6.1 Hz, 2.4H, CH_3 major), 1.17 (d, *J* = 6.0 Hz, 0.6H, CH_3 minor), 1.38 (m, 1H, 3′-*Ha*), 1.46 (m, 0.2H, 3′-*Hb* minor), 1.52 (m, 0.8H, 3′-*Hb* major), 1.92 (m, 1H, 5‴-*Ha*), 2.15 (m, 0.8H, 2′-*H* major), 2.25 (m, 0.2H, 2′-*H* minor), 2.60 (m, 1H, 5‴-*Hb*), 3.06 (m, 1.6H, SCH 2 major), 3.18 (m, 1.2H, 1′-*H* major/SCH 2 minor), 3.73–3.78 (m, 2H, SCH_2CHOH major/1′-*H* minor/2‴-*H*), 3.88 (m, 0.2H, SCH_2CHOH minor), 3.93 (m, 1H, 1‴-*H*), 4.66 (m, 1H, 3‴-*H*), 4.76 (d, *J* = 4.7 Hz, 0.8H, SCH_2CHO*H* major), 4.84 (d, 4.5 Hz, 0.2H, SCH_2CHO*H* minor), 4.93 (d, *J* = 3.8 Hz, 1H, 2‴-O*H*), 4.96 (q, *J* = 9.0 Hz, 1H, 4‴-*H*), 4.99 (d, *J* = 6.5 Hz, 0.2H, 3‴-O*H* minor), 5.02 (d, *J* = 6.4 Hz, 0.8H, 3‴-O*H* major), 5.16 (d, *J* = 4.0 Hz, 1H, 1‴-O*H*), 7.04 (bs, 0.2H, 6″-*H* minor), 7.09 (bs, 0.8H, 6″-*H* major), 7.24–7.35 (m, 2H, 2″-*H*/5″-*H*), 8.94 (d, *J* = 4.4 Hz, 0.2H, N*H* minor), 9.33 (d, *J* = 3.9 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 15.1, 22.4, 23.9, 33.8, 36.0, 39.1, 61.0, 65.2, 73.2, 74.5, 76.8, 114.9, 117.0, 122.9, 123.1, 139.2, 147.1, 148.7, 149.2, 153.8, 169.3. Anal. ($C_{21}H_{24}F_2N_6O_4S.H_2O$) theoretical: C, 49.21; H, 5.11; N, 16.40; S, 6.26. Found: C, 49.56; H, 5.05; N, 16.18, S, 5.99.

*4.75. (1S,2S,3R,5S)-3-(7-(((1R,2S)-2-(3,4-difluorophenyl) cyclopropyl)amino)-5-((2-hydroxypropyl)thio)-3H-[1,2,3]triazolo [4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (**7s**)*

To a solution of **16m** (0.15 g, 0.26 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate/methanol gradient to give **7s** as a white solid (0.12 g, 86% yield, m.p.: 148–153 °C). ^{1}H NMR (DMSO-d_6) δ 1.00 (d, *J* = 6.2 Hz, 1.2H, CH_3 major *R* or *S*), 1.02 (d, *J* = 6.2 Hz, 1.2H, CH_3 major *R* or *S*), 1.17 (d, *J* = 7.1 Hz, 0.6H, CH_3 minor), 1.38 (m, 1H, 3′-*Ha*), 1.47 (m, 0.2H, 3′-*Hb* minor), 1.53 (m, 0.8H, 3′-*Hb* major), 2.02 (ddt, *J* = 14.0 Hz/9.3 Hz/4.4 Hz, 1H, 4‴-*Ha*), 2.14 (m, 0.8H, 2′-*H* major), 2.25 (m, 0.2H, 2′-*H* minor), 2.64 (m, 1H, 4‴-*Hb*), 2.86 (dd, *J* = 13.4 Hz/7.0 Hz, 0.4H, SC*Ha* major *R* or *S*), 3.05 (d, *J* = 5.8 Hz, 1H, SC*Hb* major), 3.13–3.19 (m, 1.6H, SC*Ha* major *R* or *S*, SC*Ha* minor, SC*Hb* minor, 1′-*H*), 3.46–3.52 (m, 4H, OCH_2CH_2OH), 3.74 (m, 1.8H, SCH_2CHOH major/5‴-*H*), 3.88 (m, 0.2H, SCH_2CHOH minor), 3.95 (m, 1H, 1‴-*H*), 4.56 (m, 1H, 2‴-*H*), 4.61 (t, *J* = 4.9 Hz, OCH_2CH_2OH), 4.78 (m, 0.8H, SCH_2CHO*H* major), 4.86 (m, 0.8H, SCH_2CHO*H* minor), 4.96 (q, *J* = 8.7 Hz, 1H, 3‴-*H*), 5.06 (d, *J* = 3.8 Hz, 1H, 1‴-OH), 5.09–5.12 (m, 1H, 2‴-O*H*), 7.03 (m, 0.2H, 6″-*H* minor), 7.09 (m, 0.8H, 6″-*H*), 7.24–7.36 (m, 2H, 2″-*H*/5″-*H*), 8.96 (d, *J* = 4.5 Hz, 0.2H, N*H* minor), 9.35 (m, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 15.1, 22.5, 24.0, 33.3, 33.9, 35.7, 39.4, 60.3, 60.5, 65.2, 70.9, 73.7, 74.4, 81.8, 114.9, 117.0, 122.9, 123.1, 139.2, 147.1, 148.5, 148.7, 149.4, 150.1, 153.9, 169.4. Anal. ($C_{23}H_{28}F_2N_6O_5S$) theoretical: C, 51.29; H, 5.24; N, 15.60; S, 5.95. Found: C, 51.29; H, 5.49; N, 15.51, S, 5.85.

*4.76. (1S,2S,3R,5S)-3-(7-(((1R,2S)-2-(3,4-difluorophenyl) cyclopropyl)amino)-5-((3-hydroxypropyl)thio)-3H-[1,2,3]triazolo [4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (**7t**)*

To a solution of **16n** (0.15 g, 0.26 mmol) in MeOH (3 mL), was added HCl 12 N (1 mL). After 30 min at room temperature, methanol was evaporated under reduced pressure and the resulting residue was suspended in water (20 mL), neutralized with NaOH 10% and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica gel using ethyl acetate/methanol gradient to give **7t** as a white solid

(0.10 g, 72% yield, m.p.: 135–137.5 °C). ^{1}H NMR (DMSO-d_6) δ 1.38 (q, J = 6.1 Hz, 0.8H, 3′-*Ha* major), 1.40 (m, 0.2H, 3′-*Ha* minor), 1.46 (dt, J = 9.9 Hz/5.3 Hz, 0.2H, 3′-*Hb* minor), 1.53 (dt, J = 11.0 Hz/5.5 Hz, 0.8H, 3′-*Hb* major), 1.66 (p, J = 6.7 Hz, 1.6H, $SCH_2CH_2CH_2OH$ major), 1.81 (p, J = 6.6 Hz, 0.4H, $SCH_2CH_2CH_2OH$ minor), 2.02 (ddd, J = 14.0 Hz/9.7 Hz/5.0 Hz, 1H, 4‴-*Ha*), 2.14 (ddd, J = 9.5 Hz/6.4 Hz/3.3 Hz, 0.8H, 2′-*H* major), 2.25 (m, 0.2H, 2′-*H* minor), 2.64 (m, 1H, 4‴-*Hb*), 2.93–3.03 (m, 1.6H, $SCH_2CH_2CH_2OH$ major), 3.15–3.18 (m, 1.2H, $SCH_2CH_2CH_2OH$ minor/1′-*H* major), 3.38 (q, J = 6.1 Hz, 1.6H, $SCH_2CH_2CH_2OH$ major), 3.46–3.53 (m, 4.4H, $SCH_2CH_2CH_2OH$ minor/OCH_2CH_2OH), 3.76 (m, 1H, 5‴-*H*), 3.79 (m, 0.2H, 1′-*H* minor), 3.94 (m, 1H, 1‴-*H*), 4.47 (t, J = 5.2 Hz, 0.8H, $SCH_2CH_2CH_2OH$ major), 4.55 (m, 1.2H, $SCH_2CH_2CH_2OH$ minor/2‴-*H*), 4.61 (t, J = 5.2 Hz, 1H, OCH_2CH_2OH), 4.96 (q, J = 9.1 Hz, 1H, 3‴-*H*), 5.05 (d, J = 4.1 Hz, 1H, 1‴-O*H*), 5.09 (d, J = 6.5 Hz, 0.8H, 2‴-O*H* major), 5.12 (d, J = 6.4 Hz, 0.2H, 2‴-O*H* minor), 7.03 (m, 0.2H, 6″-*H* minor), 7.07 (m, 0.8H, 6″-*H* major), 7.24–7.35 (m, 2H, 2″-*H*/5″-*H*), 8.95 (d, J = 4.8 Hz, 0.2H, N*H* minor), 9.35 (d, J = 4.0 Hz, 0.8H, N*H* major). ^{13}C NMR (DMSO-d_6) δ 15.1, 23.9, 27.3, 32.1, 33.3, 33.9, 59.2, 60.3, 60.5, 70.9, 73.7, 74.4, 81.8, 115.0, 117.1, 122.8, 123.1, 139.2, 147.1, 148.4, 148.7, 149.4, 150.1, 153.9, 169.2. Anal. ($C_{23}H_{28}F_2N_6O_5S$) theoretical: C, 51.29; H, 5.24; N, 15.60; S, 5.95. Found: C, 50.89; H, 5.29; N, 15.51, S, 5.99.

4.77. Biological evaluation

4.77.1. Antiplatelet activity

4.77.1.1. Platelet rich plasma (PRP) preparation. Venous blood was obtained from healthy volunteers (between 20 and 40 years old) who had not taken any drugs or medications for at least 10 days. Procedures were approved by the institutional review committee of the Universtisty of Liege (Comité d'éthique hospital-facultaire universitaire de liege). Blood samples were collected into citrate tubes (3.2% citrate, Greiner-BioOne) and processed within 30 min after collection. Platelet-rich-plasma (PRP) was separated by centrifugation of anticoagulated whole blood at 100×*g* for 15 min at room temperature. Platelet count was measured using a hematology analyser (Cell-dyn 3700, Abbott). Platelet poor plasma (PPP) was obtained by centrifugation of whole blood at 800×*g* for 15 min. The platelet count in PRP was then adjusted to 250000/μl by diluting PRP with autologous PPP.

4.77.1.2. Platelet aggregation. Platelet aggregation assays were performed with PRP under stirring (1200 rpm) at 37 °C on a Chrono-Log Lumi-aggregometer (Kordia). PRP was pre-incubated with ticagrelor or its analogues (1.8 μM) for 10 min prior to stirring and addition of ADP (10 μM). Platelet aggregation was monitored for 10 min. The area under the curve (AUC) was recorded. Results were expressed as fold-inhibition vs. vehicle (1% DMSO). Data are presented as mean ± S.D. obtained from 4 to 21 healthy volunteers (age: 29 (3), median (IQR); 67% males). AUC values recorded in the presence of test molecules were compared to the values obtained with the vehicle control (1% DMSO) or with the reference molecule 1 (ticagrelor) by using the non-parametric Wilcoxon signed rank test for paired samples (Prism version 8.1.2). $P < 0.05$ was considered significant.

4.77.2. Antibacterial activity

A single colony of *S.aureus* (MRSA, BAA-1556) grown on a Brain Heart Infusion Agar plate was resupended and cultured in Brain Heart infusion broth medium (BHI) overnight (O/N) under aerobic conditions (37 °C, 190 rpm shaking). On the next day, the resulting inoculum was diluted 100 times in Mueller-Hinton broth (MHB) and incubated in aerobic conditions to reach a growth exponential phase. The resulting inoculum corresponding to about 5.10^5 colony forming units (CFU)/ml was further incubated in the presence or in the absence of different concentrations of the tested molecules. The vehicle was 1% DMSO. The bacterial growth in culture media was evaluated by measuring the optical density (OD) at 600 nm (OD_{600}) by use of a spectrophotometer. The Minimal Inhibitory Concentration (MIC) of each molecule tested was determined according to the EUCAST guidelines. The MIC represents the concentration at which there is no visible growth, *i.e* ΔOD at 600 nm is equal to zero wherein ΔOD is the difference between the resulting OD in the presence of the molecule and the OD of the blank (blank is the medium with 1% DMSO).

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

C. Oury is Research Director at the National Funds for Scientific Research, Belgium (F.R.S.-FNRS). The technical assistance of S. Counerotte is gratefully acknowledged. This work was supported by a European Research Council (ERC)-Consolidator grant (PV- COAT 647197).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmech.2020.112767.

Abbreviations

ADP	adenosine diphosphate
DMSO	dimethylsulfoxide
LSD1	lysine specific demethylase 1
MRSA	methicillin-resistant *Staphylococcus aureus*
NMR	nuclear magnetic resonance
TLC	thin layer chromatography
TMS	tetramethylsilane

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