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Synthesis of [1,2,4]-triazolo[1,5-*a*]pyrimidines by Dimroth rearrangement of [1,2,4]-triazolo[4,3-*a*]pyrimidines: A theoretical and NMR study

Antonio Salgado [a,*], Carmen Varela [a], Ana María García Collazo [a], Fernando García [b], Paolo Pevarello [a], Ibon Alkorta [c], José Elguero [c]

[a] Department of Medicinal Chemistry, Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández Almagro, 3, E-28029 Madrid, Spain
[b] Department of Proteomics, Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández Almagro, 3, E-28029 Madrid, Spain
[c] Instituto de Química Médica, CSIC, Juan de la Cierva, 3, E-28006 Madrid, Spain

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ABSTRACT

Novel [1,2,4]-triazolo-[1,5-*a*]pyrimidine derivatives were prepared by oxidative cyclization of suitable *N*-benzylidene-*N'*-pyrimidin-2-yl hydrazine precursors, followed by a Dimroth rearrangement. Reaction of 6-bromo-[1,2,4]-triazolo-[4,3-*a*]pyrimidines with aliphatic amines under microwave irradiation gave the unexpected 5-amino compounds from an ANRORC-type mechanism. Full NMR and HRMS characterization was done for all the obtained compounds. DFT calculations of absolute shielding permitted to predict ^{1}H, ^{13}C and ^{15}N chemical shifts, which were in good agreement with the experimental ones. Theoretical studies at the B3LYP/6-311++G(d,p) level corroborated that [1,2,4]-triazolo-[1,5-*a*]pyrimidines were more stable than their [4,3-*a*] counterparts.

1. Introduction

Although there is almost no heterocycle devoid of biological properties, the [1,2,4]-triazolo-[1,5-*a*]pyrimidine ring (**I**, Fig. 1) [1–6] is particularly interesting because its closeness to purines (**II**) [7].

Compounds **I** have found wide application as ligands in coordination chemistry [8–11] and also in agriculture and in medicinal chemistry. Since the Fischer review contains much information till 2008 [5], we will report here only 2009 and 2010 references. Two very important herbicides, Flumetsulam and Metosulam, belong to the class of sulam herbicides showing acetohydroxyacid synthase inhibitor properties [12–14]. Other [1,2,4]-triazolo[1,5-*a*]pyrimidines with antiparasitic [15], antimicrobial [16] and anticancer [17,18] activities are well documented. Essramycin is the first antibiotic with a [1,2,4]-triazolo[1,5-*a*]pyrimidine skeleton [19,20].

We will report in this paper the synthesis and the characterization by NMR and theoretical calculations of a series of new [1,2,4]-triazolo[1,5-*a*]pyrimidines. Although the procedure we have used is said to afford [1,2,4]-triazolo[4,3-*a*]pyrimidines, our NMR and theoretical study will prove that a formal Dimroth rearrangement has also occurred and the isolated products belong to the [1,5-*a*] series. This kind of rearrangement has been described previously [21–24].

2. Results and discussion

2.1. Synthesis

There are several ways to prepare [1,2,4]-triazolo[1,5-*a*]pyrimidines [2]. We have used the method represented in Scheme 1 for a general case.

The first step is the formation of hydrazone **IV** that cyclizes with oxidation to [1,2,4]-triazolo[4,3-*a*]pyrimidine **V** and, in some cases depending on the experimental conditions, this last compound rearranges to [1,2,4]-triazolo[1,5-*a*]pyrimidines **VI**. The accepted mechanism of Dimroth rearrangement involves covalent hydration (**VII**), ring opening (**VIII**), 1,2,4-triazole rotation (**IX**), ring closure (**X**) and dehydration to **VI**.

The fact that [4,3-*a*] isomer **XI** transforms into the [1,5-*a*] one **XII** is related to the stability of the addition products of 1,2,4-triazole on carbonyl compounds: the addition occurs by the lone pair of one of the sp^2 nitrogen atoms (Scheme 2). Always, the 1-substituted isomer **XIV** is much more stable than the 4-substituted one **XIII** [25,26], for the same reasons that in 1,2,4-triazoles the 1H-tautomer **XVI** is much more stable than the 4H one **XV** [27].

The syntheses carried out in this work are shown in Scheme 3 starting from 2-chloro-5-bromopyrimidine (**1**) we prepared hydrazine **2** which was condensed with substituted benzaldehydes to afford hydrazones **3**. The cyclization of hydrazones **3a–d** to [1,2,4]-triazolo[4,3-*a*]pyrimidines **4a–d** was accomplished with $IPh(OAc)_2$

* Corresponding author.
E-mail address: asalgado@cnio.es (A. Salgado).

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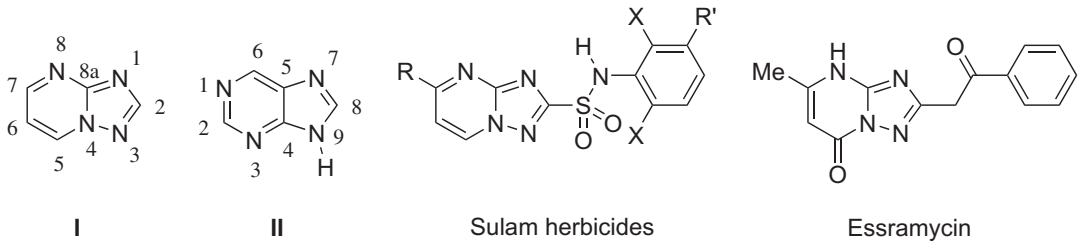
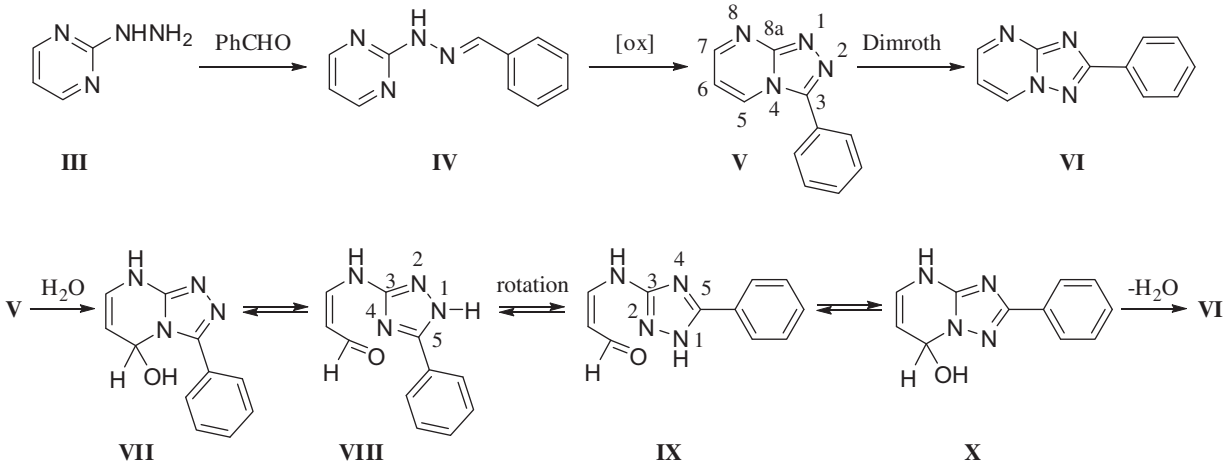
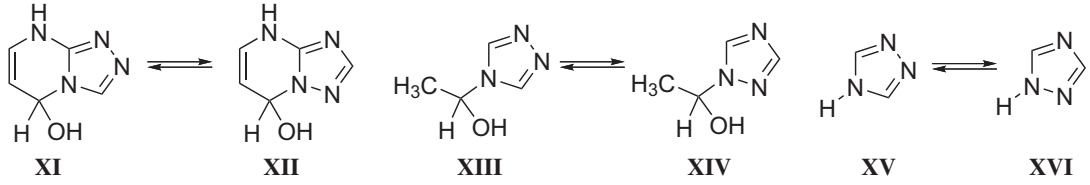


Fig. 1. Structure of the [1,2,4]-triazolo[1,5-*a*]pyrimidine ring system (**I**).



Scheme 1. The synthesis of [1,2,4]-triazolo[1,5-*a*]pyrimidines **VI** from 2-hydrazinopyrimidine (**III**) and the accepted mechanism of the Dimroth rearrangement.



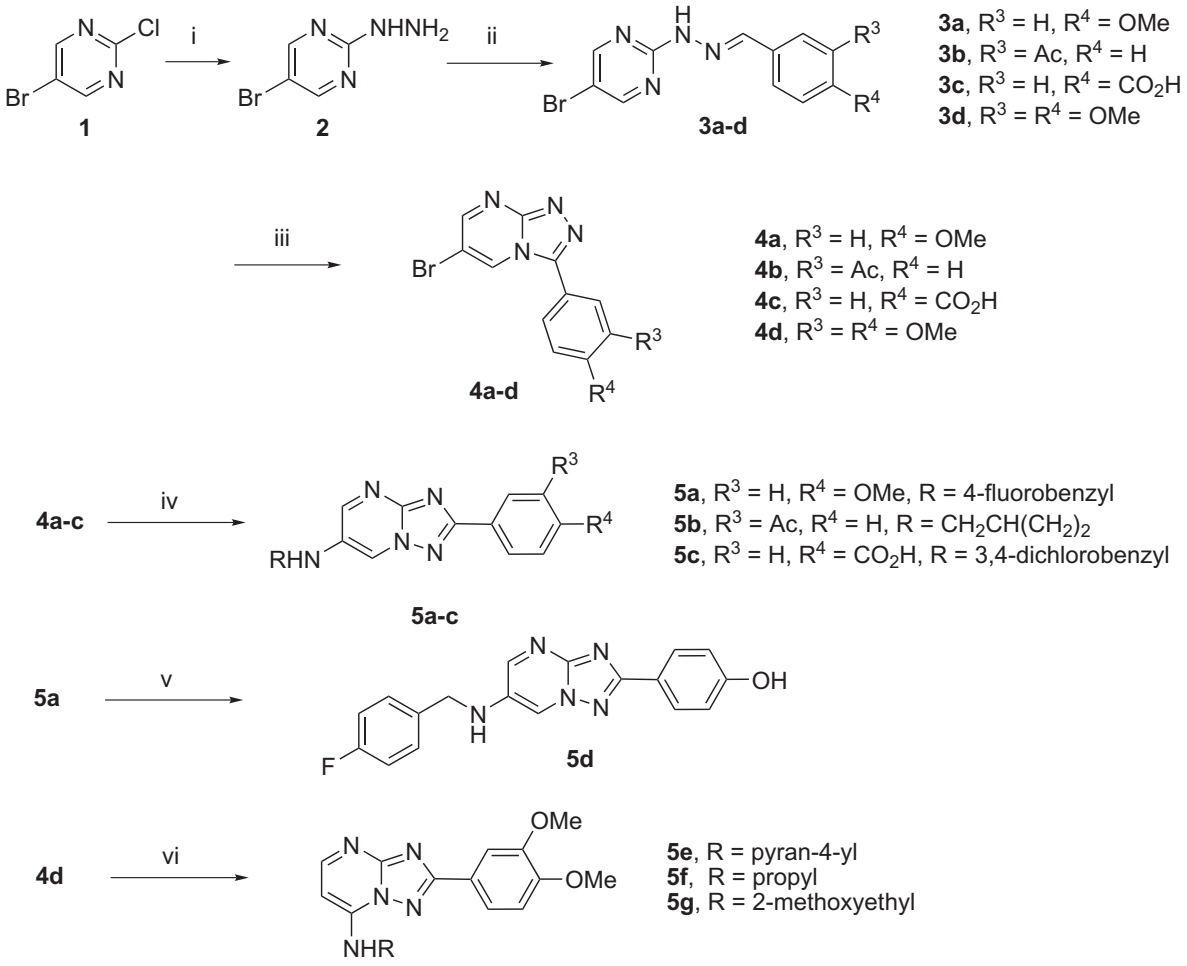
Scheme 2. Equilibria of isomers and tautomers in the [1,2,4]-triazole series.

[28]. Reaction of the 6-bromo[1,2,4]-triazolo[1,5-*a*]pyrimidines **4a–c** with alkyl amines gave compounds **5a–c**. Compound **5a** was demethylated by reaction with BBr_3 to yield the hydroxy derivative **5d**. Most remarkable is the transformation upon MW irradiation of the bromo derivative **4d** and an aliphatic amine into the 7-amino derivatives **5e–g**. The fact that the substitution took place in the adjacent position of the leaving group is known as the van der Plas' ANRORC process [29–31].

2.2. Experimental NMR results

The cyclization of hydrazones **3a–d** is said to give [1,2,4]-triazolo[4,3-*a*]pyrimidine derivatives [28]. Yet we have reported a similar reaction in which a [1,2,4]-triazolo[1,5-*a*]pyrimidine resulted without isolation of the [4,3-*a*] isomer [32]. In our hands, compounds **4a–d** were found to be [1,2,4]-triazolo[4,3-*a*]pyrimidines, as confirmed by their NMR data. For **4d**, the ^{13}C NMR spectrum gave a signal at 145.2 ppm, assigned at the triazole C-2 atom. The magnitude of this chemical shift is very characteristic of [1,2,4]-triazolo[4,3-*a*]pyrimidines. Moreover, a ^{15}N resonance at −197.7 ppm (N-4) was clearly "pyrrole-like" and quite similar in magnitude to that of other [1,2,4]-triazolo[4,3-*a*]pyrimidines. Additionally, in a 1D NOESY experiment, irradiation at 9.24 ppm (H-5) gave NOE response to H-2 and H-6 of the 3,4-dimethoxyphenyl at C-3 (7.46 and 7.47 ppm, respectively). All these indicated that **4d** belonged to the [1,2,4]-triazolo[4,3-*a*]pyrimidine series.

On the other hand, we found that compounds **5a–g** were [1,2,4]-triazolo[1,5-*a*]pyrimidines, as corroborated by their ^{1}H, ^{13}C and ^{15}N NMR and HRMS data. In particular, for **5a**, three ^{15}N signals at −104.0, −115.8 and −153.0 ppm were respectively assigned to N-8, N-3 and N-4. These measured chemical shifts were quite close in magnitude to those reported for other similar [1,2,4]-triazolo[1,5-*a*]pyrimidines [32], and thus signal assignment could be made by direct comparison. N-3 and N-8 are "pyrimidine-like" atoms, whereas N-4 is of the "pyrrole-like" class, coming to resonance at a higher field. As with other [1,2,4]-triazolo[1,5-*a*]pyrimidines, the measured δ ^{15}N value for N-4 is noticeably large if compared to a pure pyrrole compound, this being due to the presence of the adjacent N-3 atom. All ^{1}H and ^{13}C resonances were assigned on the basis of COSY, ^{1}H–^{13}C HSQC and HMBC results.



Scheme 3. Preparation of compounds **5a**–**g**.

Additionally, 1D NOESY experiments on **5a** irradiating at H-5 (8.36 ppm) did not show NOE interaction with the aryl substituent on the triazole moiety, as it would have been expected should **5a** have belonged to the [4,3-*a*] series. Furthermore, the large ^{13}C chemical shift of the C-2 atom (163.4 ppm) is very characteristic of [1,2,4]-triazolo[1,5-*a*]pyrimidines, as for the [4,3-*a*] counterparts the triazole carbon atom (C-3 in this case) is known to come to resonance at noticeably higher field. All these evidences supported the [1,2,4]-triazolo[1,5-a]pyrimidine structure of **5a**. The same conclusions were drawn for **5b**–**d**.

For compounds **5e**–**g**, the ^{1}H, ^{13}C and ^{15}N chemical shifts of the pyrimidine CH's were substantially different from those of **5a**–**d**. For **5g**, one of the pyrimidine CH's came to resonance at 8.31 ppm (^{1}H) and 153.6 ppm (^{13}C). These values were in accordance to an aromatic CH next to a nitrogen atom, such as C-7 in the [1,2,4]-triazolo[1,5-*a*]pyrimidine scaffold. Yet the other pyrimidine CH came to resonance at a remarkable high field (6.47 and 88.6 ppm), this in clear contrast to **5a**–**d**. Besides, and more relevant, the coupling constant for those two hydrogen atoms was far too large for a *meta* relationship, as seen with compounds **5a**–**d**. The encountered values (5.4 Hz for **5g**) were more consistent with an *ortho* relationship. Additionally, in a 1D NOESY experiment on **5g**, irradiation at 6.47 ppm showed NOE interaction with the vicinal pyrimidine hydrogen (8.31 ppm) and with the peripheral 2-methoxyethyl amino substituent (3.61 and 8.22 ppm). On the other hand, irradiation at the other pyrimidine hydrogen (8.31 ppm) only gave NOE with that at 6.47 ppm. It was thus deduced that compounds **5e**–**g** had the alkyl amino substituent at position C-5 rather than at C-6. The comparatively low chemical shift values for 6-CH was presumably due to the presence of an amino group linked to the vicinal carbon atom. Other differences with compounds **5a**–**d** accrued from the ^{1}H–^{15}N HMBC experiments. Three aromatic ^{15}N chemical shift values could be measured for compound **5g**, namely at −130.0, −148.6 and −170.4 ppm. On the basis of HMBC information, these signals were respectively assigned to N-8, N-3 and N-4. The fact that N-4, clearly a "pyrrole-like" nitrogen atom, was comparatively deshielded could be explained by the presence of the adjacent N-3, again supporting the [1,2,4]-triazolo[1,5-*a*]pyrimidine structure of **5g**. It is interesting to note that no NOE interaction was observed with the dimethoxyphenyl substituent upon irradiation at the 2-methoxyethyl amino group at C-5 (3.61 ppm), which further supported the [1,2,4]-triazolo[1,5-*a*]pyrimidine core of **5g**.

2.3. Theoretical calculations

2.3.1. Energies

The closely related [1,2,4]-triazolo[4,3-*c*]pyrimidine rearrangement to [1,2,4]-triazolo[1,5-*c*]pyrimidine has been studied theoretically at the B3LYP/6-31G(d,p) level [33]. Different mechanisms

Table 1
Total energy (hartree) and relative energy (kJ mol^{-1}) of the [1,2,4]-triazolo[1,5-*a*]pyrimidine, **5a–g**, and the (hypothetical) [1,2,4]-triazolo[4,3-*a*]pyrimidine isomers, **5a–g *bis***, calculated at the B3LYP/6-311++G(d,p) computational level.

	E_{total}		E_{total}	E_{rel}
5a	−1182.76734	**5a *bis***	−1182.74411	61.0
5b	−1007.25372	**5b *bis***	−1007.23010	62.0
5c	−2076.81820	**5c *bis***	−2076.79460	62.0
5d	−1143.45840	**5d *bis***	−1143.43480	62.0
5e	−1198.25572	**5e *bis***	−1198.23250	61.0
5f	−1045.58642	**5f *bis***	−1045.56315	61.1
5g	−1120.80942	**5g *bis***	−1120.78643	60.4

Table 2
Total energy (hartree) and relative energy (kJ mol^{-1}) of the [1,2,4]-triazolo[4,3-*a*]pyrimidine, **4a–d**, and their [1,2,4]-triazolo[1,5-*a*]pyrimidine counterparts, **4a–d *bis***, calculated at the B3LYP/6-311++G(d,p) computational level.

	E_{total}		E_{total}	E_{rel}
4a	−3331.21619	**4a *bis***	−3331.24031	63.34
4b	−3405.29446	**4b *bis***	−3405.31894	64.29
4c	−3369.34943	**4c *bis***	−3369.37137	57.60
4d	−3445.76584	**4d *bis***	−3445.79199	68.65

(neutral, acidic and basic), including solvent effects, were explored. The authors conclude that the Dimroth rearrangement occurs by an ANRORC mechanism. At the B3LYP/6-311++G(d,p) level, the three equilibriums of Scheme 2 correspond to the right side isomers (or tautomers) being more stable than the left ones: **XI** 48.4 kJ mol^{-1}, **XIII** 50.1 kJ mol^{-1} and **XV** 28.5 kJ mol^{-1}. The last value is close to that reported previously, 21 kJ mol^{-1}.

Similar results are obtained for molecules **5a–g**, prepared here, being the [1,5-*a*] isomer more stable than the [4,3-*a*] between 60 and 62 kJ mol^{-1}, as shown in Table 1. The same is done for 6-bromo derivatives **4a–d** (Table 2). Again, the [1,5-*a*] isomers are more stable than the [4,3-*a*] counterparts between 57 and 69 kJ mol^{-1}.

2.3.2. Absolute shieldings

The optimized geometries and atom numbering of molecules **5a–g** are shown in Figs. 2–4. Absolute shieldings (σ) were calculated within GIAO methodologies. Predicted ^{1}H, ^{13}C and ^{15}N NMR chemical shifts were calculated from Eqs. (1)–(3), respectively.[34,35]

$$\delta^{1}\mathrm{H} = 31.0 - 0.97 \cdot \sigma(^{1}\mathrm{H}) \quad (\text{reference TMS, 0.00 ppm}) \tag{1}$$

$$\delta^{13}\mathrm{C} = 175.7 - 0.963 \cdot \sigma(^{13}\mathrm{C}) \quad (\text{reference TMS, 0.00 ppm}) \tag{2}$$

$$\delta^{15}\mathrm{N} = -152 - 0.946 \cdot \sigma(^{15}\mathrm{N}) \quad (\text{reference ext. neat } MeNO_2, 0.00\,\text{ppm}) \tag{3}$$

Theoretical and experimental chemical shifts for **5a–g** are shown in Tables 3–9. Theoretical data for the hypothetical [4,3-*a*] isomer of **5a** (**5a *bis***) are shown in Table 3 for comparison. It can be seen that calculated ^{13}C and ^{15}N chemical shifts for the [1,2,4]-triazolo[1,5-*a*]pyrimidine isomer geometry are very much alike to those measured, whereas large differences with calculated chemical shifts for **5a *bis*** are observed. For instance, the predicted chemical shift for C-2 is 165.2 ppm for the [1,5-*a*] isomer, and 143.9 ppm for C-3 of the [4,3-*a*], being the experimental value 163.4 ppm. Additionally, the theoretical ^{15}N chemical shifts for the [1,5-*a*] structure **5a** are −116.0, −154.4 and −96.0 ppm for N-3, N-4 and N-8, respectively, and −31.2 −56.2 and −87.3 ppm

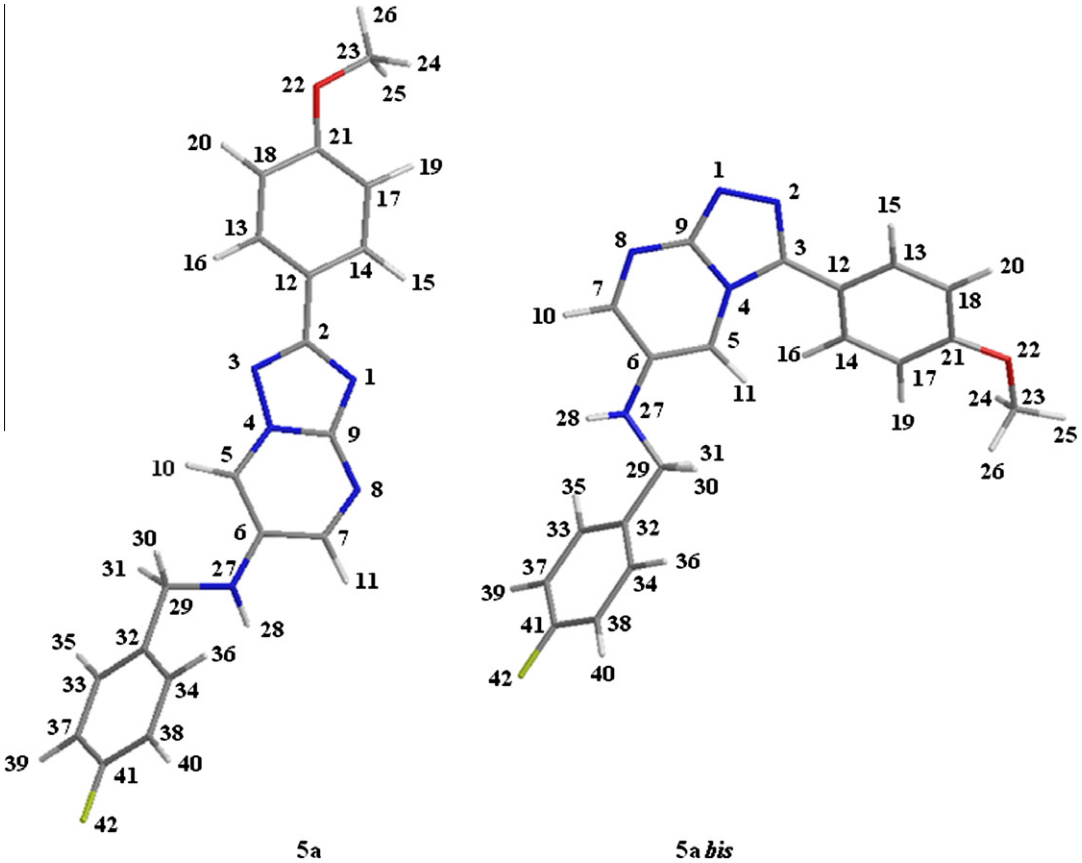


Fig. 2. Optimized geometries and atom numbering of compound **5a** and its tentative [4,3-*a*] counterpart **5a *bis***.

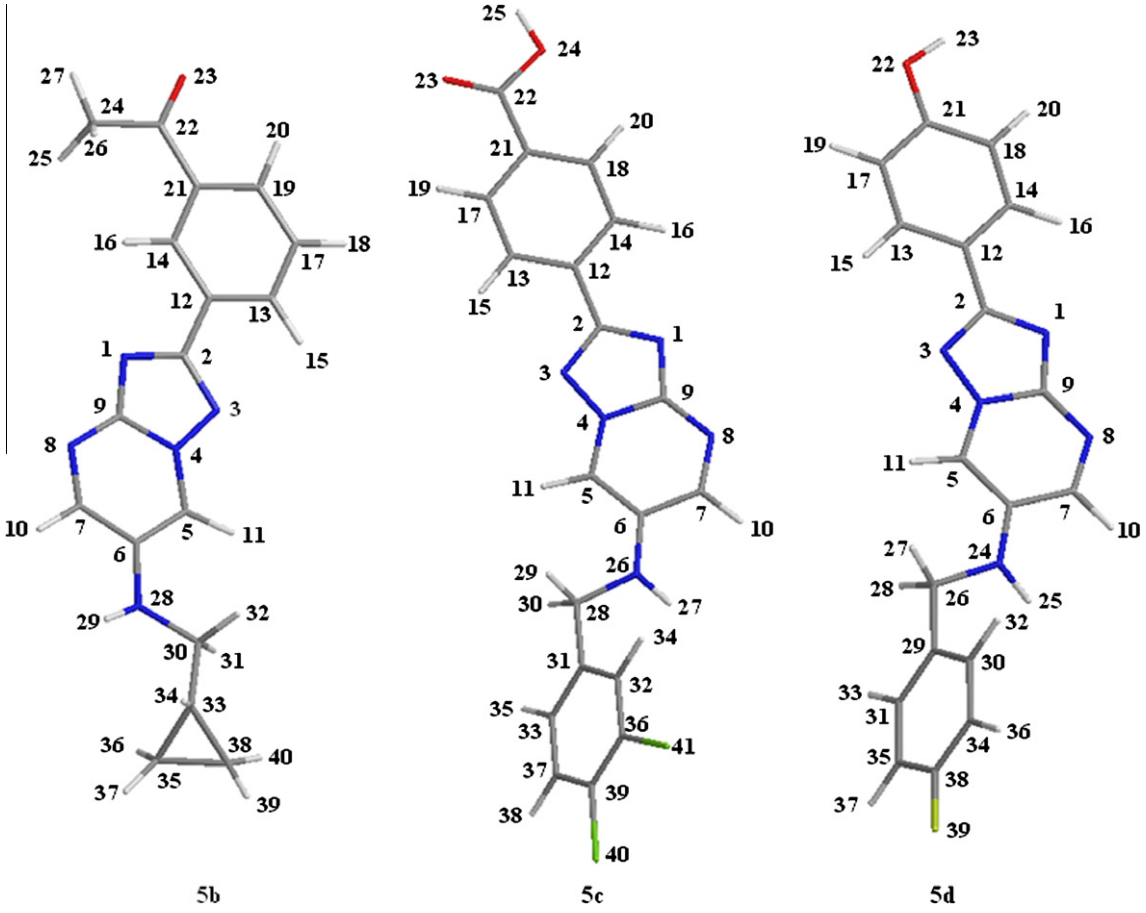


Fig. 3. Optimized geometries and atom numbering of compounds **5b–d**.

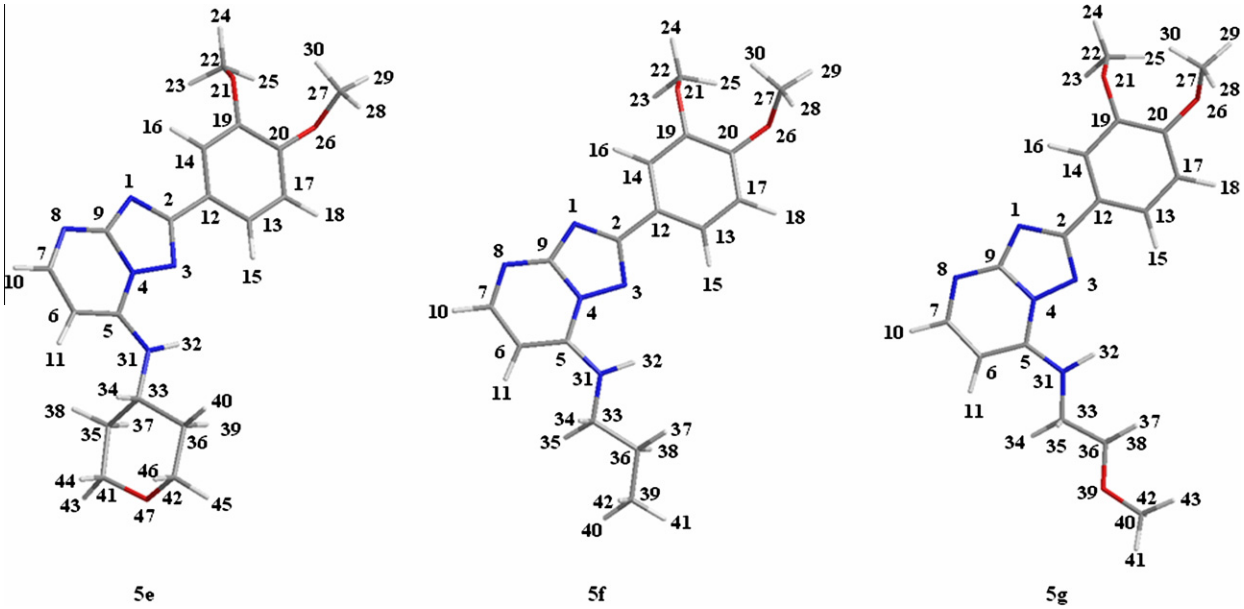


Fig. 4. Optimized geometries and atom numbering of compounds **5e–g**.

for the [4,3-*a*] counterpart (**5a *bis***). Again, the measured ^{15}N chemical shifts (−115.8, −153.0 and −104.0 ppm) corroborated the [1,2,4]-triazolo[1,5-*a*] pyrimidine structure of **5a**. Then, as shown in Tables 4–6, concordance between theoretical and experimental NMR data supported the structure of molecules **5b–d**. It is interesting to note that, according to our theoretical data, the steric repulsion between H-5 and H-2 of the phenyl substituent in the hypothetical [4,3-*a*] derivatives (**5a *bis*** to **5d *bis***) would force a

Table 3
Measured chemical shifts of compound **5a**, and absolute shieldings and calculated chemical shifts for the [1,5-*a*] and the (hypothetical) [4,3-*a*] structures.

Atom number	Atom position	Calc. shielding	δ (calc.)	Atom number	Atom position	Calc. shielding	δ (calc.)	δ (exp.)
Predicted for [1,2,4]-triazolo[1,5-*a*]pyrimidine scaffold				Predicted for [1,2,4]-triazolo[4,3-*a*]pyrimidine scaffold				
1	N-1	0.73	−152.7	1	N-1	−100.95	−56.2	−153
2	C-2	10.9	165.2	2	N-2	−127.25	−31.2	163.4
3	N-3	−37.9	−116.0	3	C-3	33.02	143.9	−115.8
4	N-4	2.58	−154.4	4	N-4	59.39	−208.4	n.d.
5	C-5	66.25	111.9	5	C-5	75.13	103.3	114.2
6	C-6	43.78	133.5	6	C-6	43.99	133.3	135.5
7	C-7	33.9	143.1	7	C-7	34.42	142.6	148.2
8	N-8	−58.96	−96.0	8	N-8	−68.21	−87.3	−104
9	C-8a	24.4	152.2	9	C-8a	24.99	151.6	150.5
10	H-7	23.63	8.1	10	H-7	23.71	8.0	8.57
11	H-5	23.94	7.8	11	H-5	24.21	7.6	8.36
12	Ph C-1	52.63	125.0	12	Ph C-1	55.79	122.0	123.8
13	Ph C-2	50.14	127.4	13	Ph C-2	45.06	132.3	128.1
14	Ph C-6	47.23	130.2	14	Ph C-6	53.39	124.3	128.1
15	Ph H-6	23.08	8.6	15	Ph H-6	23.62	8.1	8.05
16	Ph H-4	23.36	8.3	16	Ph H-4	24.26	7.5	8.05
17	Ph C-5	71.53	106.8	17	Ph C-5	58.43	119.4	114.5
18	Ph C-3	61.05	116.9	18	Ph C-3	72.36	106.0	114.5
19	Ph H-5	25.22	6.5	19	Ph H-5	24.54	7.2	7.06
20	Ph H-3	24.83	6.9	20	Ph H-3	25.18	6.6	7.06
21	Ph C-4	14.07	162.2	21	Ph C-4	15.28	161.0	160.9
22	$\underline{O}CH_3$	216.15		22	$\underline{O}CH_3$	215.85		
23	$O\underline{C}H_3$	126.89	53.5	23	$O\underline{C}H_3$	127.21	53.2	55.7
24	$OC\underline{H}_3$	28.22	3.6	24	$OC\underline{H}_3$	28.23	3.6	3.82
25	$OC\underline{H}_3$	28.22	3.6	25	$OC\underline{H}_3$	28.25	3.6	3.82
26	$OC\underline{H}_3$	27.83	4.0	26	$OC\underline{H}_3$	27.78	4.1	3.82
27	C-6-$\underline{N}$H	172.3	-315.5	27	C-6-$\underline{N}$H	170.28	−313.6	−281.4
28	C-6-N$\underline{H}$	28.99	2.9	28	C-6-N$\underline{H}$	28.93	2.9	
29	$NH\underline{C}H_2$	131.37	49.2	29	$NH\underline{C}H_2$	131.42	49.1	46.2
30	$NHC\underline{H}_2$	27.66	4.2	30	$NHC\underline{H}_2$	27.69	4.1	4.31
31	$NHC\underline{H}_2$	28.18	3.7	31	$NHC\underline{H}_2$	28.36	3.5	4.31
32	Bn C-1	43.28	134.0	32	Bn C-1	43.8	133.5	134.9
33	Bn C-2	46.15	131.3	33	Bn C-2	46.25	131.2	129.6
34	Bn C-6	46.82	130.6	34	Bn C-6	47.26	130.2	129.6
35	Bn H-2	24.14	7.6	35	Bn H-2	24.09	7.6	7.49
36	Bn H-6	24.44	7.3	36	Bn H-6	24.47	7.3	7.49
37	Bn C-3	61.51	116.5	37	Bn C-3	61.5	116.5	115.2
38	Bn C-5	62.68	115.3	38	Bn C-5	62.76	115.3	115.2
39	Bn H-3	24.63	7.1	39	Bn H-3	24.68	7.1	7.19
40	Bn H-5	24.72	7.0	40	Bn H-5	24.81	6.9	7.19
41	Bn C-4	10.66	165.4	41	Bn C-4	10.06	166.0	161.5
42	F	285.88		42	F	285.72		

ca. 30° rotation of the phenyl ring located in position C-3 of the triazolopyrimidine scaffold. On the other hand, in the compounds of the [1,5-*a*] series (**5a**–**d**) the two aromatic systems are coplanar.

The same agreement between theoretical and experimental data was also seen in the 5-amino derivatives **5e**–**g** (Tables 7–9), again proving that the proposed structures are correct. It should be taken into account that experimental chemical shifts correspond to the average of many conformers existing in the liquid state, whereas calculations are done for a unique (frozen) geometry. This fact could also contribute to the observed minor differences between calculated and measured data. It must be added that the position of substitution has little effect on the geometry of the pyridine ring, as the largest bond distance differences were found between the C6–C7 atoms, being their value 1.43 Å for **5a**–**d** and 1.41 Å for **5e**–**g**.

We also calculated theoretical chemical shifts for the bromoderivative **4d** and for its hypothetical [1,5-*a*] isomer **4d *bis*** (Table 10). Their optimized geometries and atom numbering are shown in Fig. 5. High agreement between measured ^{13}C and ^{15}N chemical shifts and those predicted for the [4,3-*a*] isomer was met, thus supporting the [1,2,4]-triazolo[4,3-*a*]pyrimidine structure of **4d**. It must be said, however, that a large disagreement between the theoretical and the experimental chemical shifts of C-6 was seen (calc. 124.9 ppm, exp. 105.8 ppm). Such data disparity has been reported to occur with carbon atoms with a bromine atom attached to them [36].

3. Conclusion

The structures of novel 5-amino and 6-amino-[1,2,4]-triazolo[1,5-*a*]pyrimidines were fully corroborated by their NMR and MS data. Distinctive ^{13}C and ^{15}N signal patterns were seen for each class of compounds. The preparation of the 5-substituted derivatives **5e**–**g** under microwave irradiation was rationalized by an ANRORC-type mechanism. The experimental NMR chemical shifts of compounds **5a**–**g** were in good agreement with those predicted from GIAO calculations.

4. Experimental

4.1. General

NMR spectra were recorded in a Bruker AVANCE 700 spectrometer or in a Bruker AVANCE II 300 spectrometer, respectively fitted with a QXI 700 MHz S4 probe (operating at 700.13 MHz, 176.05 MHz or 70.94 MHz as the ^{1}H, ^{13}C and ^{15}N frequencies)

Table 4
Absolute shieldings, calculated and measured chemical shifts of compound **5b**.

Atom number	Atom position	Calc. shielding	δ (calc.)	δ (exp.)
1	N-1	−0.82	−151.2	n.d.
2	C-2	12.31	163.8	162
3	N-3	−40.64	−113.4	−112.6
4	N-4	1.71	−153.6	−152.1
5	C-5	67.63	110.6	113.9
6	C-6	43.25	134.1	137
7	C-7	34.11	142.9	149.4
8	N-8	−60.17	−94.9	−102.7
9	C-8a	25.17	151.5	151.3
10	H-7	23.6	8.1	8.6
11	H-5	24.11	7.6	8.43
12	Ph C-1	44.88	132.5	132
13	Ph C-6	47.24	130.2	130.9
14	Ph C-2	47.83	129.6	126
15	Ph H-6	23.15	8.5	8.36
16	Ph H-2	22.55	9.1	8.67
17	Ph C-5	50.52	127.0	129.6
18	Ph H-5	24.28	7.4	7.68
19	Ph C-4	48.06	129.4	129.7
20	Ph H-4	23.26	8.4	8.06
21	Ph C-3	41.03	136.2	137.6
22	$\underline{C}OCH_3$	−19.39	194.4	198.2
23	$CO\underline{C}H_3$	−298.49		
24	$CO\underline{C}H_3$	155.34	26.1	27.3
25	$COC\underline{H}_3$	29.03	2.8	2.66
26	$COC\underline{H}_3$	29.03	2.8	2.66
27	$COC\underline{H}_3$	29.69	2.2	2.66
28	C-6-$\underline{N}$H	179.58	−322.4	−318.6
29	C-6-N$\underline{H}$	28.69	3.2	
30	NH–$\underline{C}H_2$	130.96	49.6	48.2
31	NH–$C\underline{H}_2$	29.84	2.1	2.92
32	NH–$C\underline{H}_2$	28.45	3.4	2.92
33	$\underline{C}H$	169.22	12.7	10.2
34	$C\underline{H}$	31.01	0.9	1.12
35	$(\underline{C}H_2)_2$	176.84	5.4	3.9
36	$(C\underline{H}_2)_2$	31.01	0.9	0.53
37	$(C\underline{H}_2)_2$	31.55	0.4	0.27
38	$(\underline{C}H_2)_2$	178.1	4.2	3.9
39	$(C\underline{H}_2)_2$	31.33	0.6	0.53
40	$(C\underline{H}_2)_2$	31.64	0.3	0.27

Table 5
Absolute shieldings, calculated and measured chemical shifts of compound **5c**.

Atom number	Atom position	Calc. shielding	δ (calc.)	δ (exp.)
1	N-1	−5.55	−146.7	n.d.
2	C-2	11.69	164.4	162
3	N-3	−43.8	−110.4	n.d.
4	N-4	2.05	−153.9	−151.9
5	C-5	66.04	112.1	114.3
6	C-6	43.18	134.1	136.2
7	C-7	32.78	144.1	148.5
8	N-8	−62.34	−92.8	−101.8
9	C-8a	24.74	151.9	151.3
10	H-7	23.52	8.2	8.64
11	H-5	23.96	7.8	8.42
12	Ph C-1	40.07	137.1	135.2
13	Ph C-2	52.29	125.3	126.7
14	Ph C-6	49.69	127.8	126.7
15	Ph H-2	23.21	8.5	8.23
16	Ph H-6	23.03	8.7	8.23
17	Ph C-3	46.2	131.2	130.2
18	Ph C-5	46.66	130.8	130.2
19	Ph H-3	23.41	8.3	8.06
20	Ph H-5	23.53	8.2	8.06
21	Ph C-4	48.93	128.6	132.4
22	$\underline{C}OOH$	12.08	164.1	167.6
23	$CO\underline{O}H$	−72.75		
24	$COO\underline{H}$	126.22		
25	$COO\underline{H}$	26.24	5.5	13.1
26	C-6-$\underline{N}$H	173.17	−316.3	−321.4
27	C-6-N$\underline{H}$	28.9	3.0	6.99
28	$NH\underline{C}H_2$	131.87	48.7	45.7
29	$NHC\underline{H}_2$	27.7	4.1	4.37
30	$NHC\underline{H}_2$	28.29	3.6	4.37
31	Bn C-1	40.26	136.9	140.1
32	Bn C-2	46.31	131.1	129.9
33	Bn C-6	50.63	126.9	128.4
34	Bn H-2	24.09	7.6	7.73
35	Bn H-6	24.7	7.0	7.44
36	Bn C-3	34.21	142.8	130.1
37	Bn C-5	47.07	130.4	131
38	Bn H-5	24.43	7.3	7.64
39	Bn C-4	34.84	142.1	131.2
40	Bn 4-Cl	678.58		
41	Bn 3-Cl	675.1		

and with a QNP 300 MHz S2 probe (operating at 300.13 MHz or 75.47 MHz as the ^{1}H and ^{13}C frequencies). All spectra were recorded at 25 °C. Chemical shifts are given as referred to external TMS (^{1}H and ^{13}C, 0.00 ppm) or external neat $MeNO_2$ (^{15}N, 0.00 ppm). The ^{1}H 90° hard pulse was calculated for every sample. No loss of signal resolution due to tentative aggregation effects was observed in the concentration range used here. A standard Bruker *hmbcgplpndqf* pulse sequence was used for the ^{1}H–^{13}C and ^{1}H–^{15}N HMBC experiments. The spectral sizes for the ^{1}H–^{13}C HMBC experiments were 8389.26 Hz (11.98 ppm) × 39062.50 Hz (221.86 ppm) with 128 increments in f_1 and 16 transients per increment (total experiment time 45 min). Delays were adjusted for one-bond ($^1J_{HC}$) couplings of 145 Hz and multiple-bond ($^nJ_{HC}$) couplings of 10 Hz. The ^{1}H–^{15}N HMBC experiments were done in duplicate, with delays adjusted for one-bond ($^1J_{HN}$) couplings of 90 Hz and multiple-bond ($^nJ_{HN}$) couplings of either 8 Hz or 3 Hz. In both cases the spectral sizes were 8389.26 Hz (11.98 ppm) × 39062.50 Hz (550.4 ppm) with 512 increments in f_1 and 32 transients per increment (total experiment time 6 h 28 min). All HMBC spectra were presented in magnitude mode. All NMR data were processed with the MestReNova software (version 6.1.1-6384, Mestrelab Research S. L., Santiago de Compostela, Spain). ESI+ high resolution mass spectra (HRMS) were obtained with a Bruker Daltonics maXis UHR-TOF system. 5-Bromo-2-chloro pyrimidine was purchased from AK Scientific Inc. (Mountain View, CA, USA) and was used as supplied. All other reagents and solvents were of analytical grade and were used as supplied.

4.2. 5-Bromo-2-hydrazinopyrimidine (2)

5-Bromo-2-chloropyrimidine (**1**, 2.0 g, 10.34 mmol, 1.0 eq) was suspended in abs. EtOH (15 mL) at RT, and hydrazine hydrate (1.51 mL, 31.02 mmol, 3 eq) was added in one portion. The white suspension was refluxed (95 °C) for 1.5 h, cooled to RT and the solvent was evaporated. Column chromatography (silica, 5–20% MeOH in dichloromethane) afforded 5-bromo-2-hydrazino-pyrimidine (**2**, 1.36 g, 70%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.40 (s, 2H), 4.19 (s, 2H).

4.3. (E)-2-(4-Methoxybenzylidene)-1-(5-bromopyrimidin-2-yl)hydrazine (3a)

5-Bromo-2-hydrazinopyrimidine (**2**, 0.18 g, 0.95 mmol, 1.0 eq) and 4-methoxybenzaldehyde (0.12 mL, 1.00 mmol, 1.05 eq) were suspended in abs. EtOH (5 mL), and stirred for 2 h at RT. Solvent evaporation and column chromatography (silica, 0–10% MeOH in dichloromethane) gave (*E*)-2-(4-methoxybenzylidene)-1-(5-bromopyrimidin-2-yl)hydrazine (**3a**, 240 mg, 82%) as a beige solid.

Table 6
Absolute shieldings, calculated and measured chemical shifts of compound **5d**.

Atom number	Atom position	Calc. shielding	δ (calc.)	δ (exp.)
1	N-1	0.86	−152.8	n.d.
2	C-2	11.18	164.9	163.1
3	N-3	−37.72	−116.2	−116
4	N-4	2.62	−154.5	−152.6
5	C-5	66.31	111.8	114.5
6	C-6	43.69	133.6	135.3
7	C-7	33.87	143.1	148.5
8	N-8	−59.12	−95.9	−103.4
9	C-8a	24.49	152.1	151.1
10	H-7	23.62	8.1	8.54
11	H-5	23.95	7.8	8.34
12	Ph C-1	52.57	125.1	122.1
13	Ph C-2	49.31	128.2	128.2
14	Ph C-6	47.05	130.4	128.2
15	Ph H-2	23.34	8.4	7.94
16	Ph H-6	23.19	8.5	7.94
17	Ph C-3	63.8	114.3	115.9
18	Ph C-5	66.75	111.4	115.9
19	Ph H-3	24.82	6.9	6.87
20	Ph H-5	25.35	6.4	6.87
21	Ph C-4	17.54	158.8	159.6
22	Ph 4-OH	202.46		
23	Ph 4-OH	27.98	3.9	
24	C-6-NH	172.14	−315.4	−320.8
25	C-6-NH	28.99	2.9	
26	NHCH$_2$	131.39	49.2	46.3
27	NHCH$_2$	27.67	4.2	4.3
28	NHCH$_2$	28.19	3.7	4.3
29	Bn C-1	43.34	134.0	134.6
30	Bn C-2	46.1	131.3	129.9
31	Bn C-6	46.79	130.6	129.9
32	Bn H-2	24.15	7.6	7.48
33	Bn H-6	24.44	7.3	7.48
34	Bn C-3	61.48	116.5	115.8
35	Bn C-5	62.64	115.4	115.8
36	Bn H-3	24.63	7.1	7.19
37	Bn H-5	24.71	7.0	7.19
38	Bn C-4	10.64	165.5	161.6
39	F	285.81		

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.47 (s, 2H), 7.97 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H).

4.4. (E)-2-(3-Acetylbenzylidene)-1-(5-bromopyrimidin-2-yl)hydrazine (3b)

5-Bromo-2-hydrazinopyrimidine (**2**, 0.35 g, 1.85 mmol, 1.0 eq) and 3-acetylbenzaldehyde (0.288 g, 1.94 mmol, 1.05 eq) suspended in abs. EtOH (7 mL) and stirred at RT for 4 h. The yellow suspension was evaporated. Column chromatography (silica, 0–10% MeOH in dichloromethane) afforded (*E*)-2-(3-acetylbenzylidene)-1-(5-bromopyrimidin-2-yl)hydrazine (**3b**, 472 mg, 80%) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.64–8.60 (m, 3H), 8.21 (d, J = 10.4 Hz, 2H), 7.99–7.87 (m, 2H), 7.57 (t, J = 7.7 Hz, 1H), 2.62 (s, 3H).

4.5. (E)-2-(4-Carboxybenzylidene)-1-(5-bromopyrimidin-2-yl)hydrazine (3c)

5-Bromo-2-hydrazino-pyrimidine (**2**, 0.35 g, 1.85 mmol, 1.0 eq) and 4-carboxybenzaldehyde (0.292 g, 1.94 mmol, 1.05 eq) were suspended in abs. EtOH (7 mL), and stirred for 5 h at RT. (*E*)-2-(4-carboxybenzylidene)-1-(5-bromopyrimidin-2-yl)hydrazine (**3c**, assumed 100%) was obtained after solvent evaporation and was used without further treatment. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.87 (s, 2H), 8.68 (s, 2H), 8.46 (s, 1H), 8.21 (m, 3H), 8.03 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 8.2 Hz, 2H).

Table 7
Absolute shieldings, calculated and measured chemical shifts of compound **5e**.

Atom number	Atom position	Calc. shielding	δ (calc.)	δ (exp.)
1	N-1	0.66	−152.6	−154.4
2	C-2	12.3	163.9	163.2
3	N-3	−13.75	−139.0	n.d.
4	N-4	22.6	−173.4	−170
5	C-5	32.73	144.2	147.7
6	C-6	94.3	84.9	89.1
7	C-7	25.38	151.3	152.8
8	N-8	−19.61	−133.4	n.d.
9	C-8a	20.94	155.5	156.4
10	H-7	23.48	8.2	8.33
11	H-6	26.13	5.7	6.6
12	Ph C-1	47.68	129.8	124.1
13	Ph C-6	54.9	122.8	120.4
14	Ph C-2	51.07	126.5	110.4
15	Ph H-6	23.71	8.0	7.84
16	Ph H-2	23.3	8.4	7.77
17	Ph C-5	54.51	123.2	112.0
18	Ph H-5	24.71	7.0	7.12
19	Ph C-3	20.82	155.7	149.2
20	Ph C-4	18.94	157.5	151.1
21	Ph 3-OCH$_3$	257.01		
22	Ph 3-OCH$_3$	121.48	58.7	56.1
23	Ph 3-OCH$_3$	28.27	3.6	3.88
24	Ph 3-OCH$_3$	27.84	4.0	3.88
25	Ph 3-OCH$_3$	27.5	4.3	3.88
26	Ph 4-OCH$_3$	251.85		
27	Ph 4-OCH$_3$	121.47	58.7	56.0
28	Ph 4-OCH$_3$	28.46	3.4	3.84
29	Ph 4-OCH$_3$	27.97	3.9	3.84
30	Ph 4-OCH$_3$	27.14	4.7	3.84
31	C-6-NH	148.14	−292.6	n.d.
32	C-6-NH	26.35		
33	NHCH	130.24	50.3	49.2
34	NHCH	28.59	3.3	3.88
35	CHCH$_2$	146.01	35.1	32.2
36	CHCH$_2$	146.77	34.4	32.2
37	CHCH$_2$	30.36	1.6	1.86
38	CHCH$_2$	29.81	2.1	1.86
39	CHCH$_2$	30.21	1.7	1.86
40	CHCH$_2$	30.14	1.8	1.86
41	CH$_2$O	114.87	65.1	66.8
42	CH$_2$O	113.4	66.5	66.8
43	CH$_2$O	27.96	3.9	3.88
44	CH$_2$O	28.49	3.4	3.46
45	CH$_2$O	27.9	3.9	3.88
46	CH$_2$O	28.42	3.4	3.46
47	CH$_2$O	268.7		

4.6. (E)-2-(3,4-Dimethoxybenzylidene)-1-(5-bromopyrimidin-2-yl)hydrazine (3d)

5-Bromo-2-hydrazino-pyrimidine (**2**, 3.25 g, 17.19 mmol, 1.0 eq) and 3,4-dimethoxy-benzaldehyde (3.0 g, 18.05 mmol, 1.05 eq) were suspended in abs. EtOH (50 mL), stirred at RT for 5 h and then refluxed for 2 h. Evaporation of the solvent gave (*E*)-2-(3,4-dimethoxybenzylidene)-1-(5-bromopyrimidin-2-yl)hydrazine (**3d**, 5.9 g, assumed 100%) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.33 (s, 1H), 8.56 (d, J = 0.8 Hz, 1H), 8.08 (s, 1H), 7.26 (s, 1H), 7.14 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 8.2 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H).

4.7. 6-Bromo-2-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyrimidine (4a)

To compound **3a** (0.24 g, 0.78 mmol, 1.0 eq, dissolved in 5 mL dichloromethane), iodobenzene diacetate (0.252 g, 0.78 mmol,

Table 8
Absolute shieldings, calculated and measured chemical shifts of compound **5f**.

Atom number	Atom position	Calc. shielding	δ (calc.)	δ (exp.)
1	N-1	0.91	−152.86	n.d.
2	C-2	12.25	163.90	163.2
3	N-3	−14.18	−138.54	−149.4
4	N-4	23.01	−173.84	−170.5
5	C-5	32.01	144.87	148.4
6	C-6	94.11	85.07	88.7
7	C-7	25.3	151.34	154.4
8	N-8	−19.52	−133.48	−129.9
9	C-8a	21.06	155.42	156.6
10	H-7	23.48	8.22	8.3
11	H-6	26.18	5.61	6.42
12	Ph C-1	47.51	129.95	124.1
13	Ph C-6	54.78	122.95	120.2
14	Ph C-2	51.31	126.29	110.4
15	Ph H-6	23.71	8.00	7.82
16	Ph H-2	23.27	8.43	7.76
17	Ph C-5	54.62	123.10	112.2
18	Ph H-5	24.71	7.03	7.12
19	Ph C-3	21	155.48	149.0
20	Ph C-4	19.47	156.95	150.9
21	Ph 3-$\underline{O}CH_3$	257.16		
22	Ph 3-O$\underline{C}H_3$	121.01	59.17	56.0
23	Ph 3-OC$\underline{H}_3$	28.33	3.52	3.87
24	Ph 3-OC$\underline{H}_3$	27.92	3.92	3.87
25	Ph 3-OC$\underline{H}_3$	27.67	4.16	3.87
26	Ph 4-$\underline{O}CH_3$	251.23		
27	Ph 4-O$\underline{C}H_3$	121.71	58.49	56.0
28	Ph 4-OC$\underline{H}_3$	28.47	3.38	3.83
29	Ph 4-OCH_3	28	3.84	3.83
30	Ph 4-OC$\underline{H}_3$	27.22	4.60	3.83
31	C-6-$\underline{N}H$	162.64	−306.35	−293
32	C-6-N$\underline{H}$	26.42		
33	NH$\underline{C}H_2$	135.53	45.18	43.8
34	NHC$\underline{H}_2$	28.8	3.06	3.38
35	NHC$\underline{H}_2$	28.84	3.03	3.38
36	$\underline{C}H_2CH_3$	156.47	25.02	21.9
37	C$\underline{H}_2CH_3$	30.03	1.87	1.67
38	C$\underline{H}_2CH_3$	30.05	1.85	1.67
39	$CH_2\underline{C}H_3$	170.7	11.32	11.7
40	$CH_2C\underline{H}_3$	30.86	1.07	0.94
41	$CH_2C\underline{H}_3$	30.6	1.32	0.94
42	$CH_2C\underline{H}_3$	30.84	1.09	0.94

Table 9
Absolute shieldings, calculated and measured chemical shifts of compound **5g**.

Atom number	Atom position	Calc. shielding	δ (calc.)	δ (exp.)
1	N-1	0.94	−152.89	n.d.
2	C-2	12.28	163.87	163.4
3	N-3	−13.45	−139.24	−148.6
4	N-4	22.19	−173.06	−170.4
5	C-5	31.39	145.47	148.5
6	C-6	93.46	85.70	89.1
7	C-7	25.04	151.59	153.9
8	N-8	−20.68	−132.37	−130
9	C-8a	21.19	155.29	156.6
10	H-7	23.43	8.27	8.31
11	H-6	26.04	5.74	6.48
12	Ph C-1	47.58	129.88	123.7
13	Ph C-6	54.91	122.82	120.3
14	Ph C-2	51.05	126.54	110.5
15	Ph H-6	23.73	7.98	7.82
16	Ph H-2	23.31	8.39	7.76
17	Ph C-5	54.52	123.20	112.0
18	Ph H-5	24.69	7.05	7.13
19	Ph C-3	20.62	155.84	149.2
20	Ph C-4	19.01	157.39	151.0
21	Ph 3-$\underline{O}CH_3$	257.24		
22	Ph 3-O$\underline{C}H_3$	121.33	58.86	56.0
23	Ph 3-OC$\underline{H}_3$	28.29	3.56	3.88
24	Ph 3-OC$\underline{H}_3$	27.85	3.99	3.88
25	Ph 3-OC$\underline{H}_3$	27.52	4.31	3.88
26	Ph 4-$\underline{O}CH_3$	251.94		
27	Ph 4-O$\underline{C}H_3$	121.67	58.53	56.0
28	Ph 4-OC$\underline{H}_3$	28.44	3.41	3.84
29	Ph 4-OC$\underline{H}_3$	27.94	3.90	3.84
30	Ph 4-OC$\underline{H}_3$	27.14	4.67	3.84
31	C-6-$\underline{N}H$	170.58	−313.88	−297.7
32	C-6-N$\underline{H}$	26.59		
33	NH$\underline{C}H_2$	138.69	42.14	41.9
34	NHC$\underline{H}_2$	28.32	3.53	3.61
35	NHC$\underline{H}_2$	28.48	3.37	3.61
36	$\underline{C}H_2OCH_3$	109.13	70.61	70.4
37	C$\underline{H}_2OCH_3$	28.18	3.67	3.6
38	C$\underline{H}_2OCH_3$	28.26	3.59	3.6
39	$CH_2\underline{O}CH_3$	298.99		
40	$CH_2O\underline{C}H_3$	122.46	57.77	57.8
41	$CH_2OC\underline{H}_3$	28.13	3.71	3.28
42	$CH_2OC\underline{H}_3$	28.59	3.27	3.28
43	$CH_2OC\underline{H}_3$	28.58	3.28	3.28

1.0 eq) was added in one portion. The mixture was stirred for 15 h at RT and the solvent was evaporated. The residue was triturated with Et_2O (4 mL) and filtered to give 6-bromo-2-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-*a*]pyrimidine (**4a**, 190 mg, 80%) as a beige solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.20 (d, J = 1.9 Hz, 1H), 8.78 (d, J = 1.9 Hz, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.76, 155.08, 152.01, 145.07, 132.57, 129.73, 117.95, 114.65, 105.72, 55.39.

4.8. 6-Bromo-2-(3-acetylphenyl)-[1,2,4]triazolo[4,3-a]pyrimidine (4b)

Compound **3b** (0.59 g, 1.85 mmol, 1.0 eq) was suspended in dichloromethane (10 mL), and iodobenzene diacetate (0.595 g, 1.85 mmol, 1.0 eq) was added in one portion. The reaction mixture was stirred at RT for 20 min and the solvent was evaporated. The residue was triturated with diethyl ether (10 mL) and filtered to give 6-bromo-2-(3-acetylphenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine (**4b**, 500 mg, 80%) as a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76–8.67 (m, 2H), 8.42 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 7.7 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 2.72 (s, 3H).

4.9. 6-Bromo-2-(4-carboxyphenyl)-[1,2,4]triazolo[4,3-a]pyrimidine (4c)

Compound **3c** (0.4 g, 1.25 mmol, 1.0 eq) and iodobenzene diacetate (0.4 g, 1.25 mmol, 1.0 eq) were suspended in dichloromethane (10 mL) and stirred at RT for 4 days. Solvent evaporation and trituration with diethyl ether (10 mL) gave 6-bromo-2-(4-carboxyphenyl)-[1,2,4]triazolo[4,3-*a*]pyrimidine (**4c**, 360 mg, 91%) as a beige solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.21 (s, 1H), 9.37 (d, J = 2.2 Hz, 1H), 8.85 (d, J = 2.2 Hz, 1H), 8.32–7.91 (m, 4H).

4.10. 6-Bromo-2-(3,4-dimethoxyphenyl)-[1,2,4]triazolo[4,3-a]pyrimidine (4d)

Compound **3d** (5.9 g, 17.50 mmol, 1.0 eq) and iodobenzene diacetate (5.64 g, 17.50 mmol, 1.0 eq) were suspended in dichloromethane (50 mL). The reaction mixture was stirred for 1 h at RT and the solvent was evaporated. The residue was triturated with petroleum ether (15 mL) and filtered. The resulting dark orange solid was purified by column chromatography (silica, 2–15% MeOH in

Table 10
Measured chemical shifts of compound **4d**, and absolute shieldings and calculated chemical shifts for the (hypothetical) [1,5-*a*] and the [4,3-*a*] structures.

Atom number	Atom position	Calc. shielding	δ (calc.)	Atom number	Atom position	Calc. shielding	δ (calc.)	δ (exp.)
Predicted for [1,2,4]-triazolo[1,5-a]pyrimidine				*Predicted for [1,2,4]-triazolo[4,3-a]pyrimidine*				
1	C	22.0004	154.51	1	C	24.8177	151.80	152.03
2	N	−56.9111	−98.16	2	N	−66.6936	−88.91	−98.5
3	C	25.5077	151.14	3	C	27.9889	148.75	155.16
4	C	55.042	122.69	4	C	52.7038	124.95	105.76
5	C	44.5512	132.80	5	C	49.386	128.14	132.71
6	N	−3.7091	−148.49	6	N	51.5286	−200.75	−197.7
7	Br	2044.3337		7	Br	2037.3843		
8	N	−36.6435	−117.34	8	C	33.4134	143.52	145.23
9	C	7.9035	168.09	9	N	−130.6203	−28.43	n.d.
10	N	0.2463	−152.23	10	N	−99.7456	−57.64	−51.3
11	C	58.5271	119.34	11	C	50.6469	126.93	121.1
12	C	55.2783	122.47	12	C	57.2031	120.61	117.93
13	C	70.997	107.33	13	C	67.8124	110.40	112.01
14	C	23.9362	152.65	14	C	21.9826	154.53	150.54
15	C	26.1332	150.53	15	C	26.5614	150.12	149.08
16	C	68.2544	109.97	16	C	58.697	119.17	111.57
17	O	221.9033		17	O	224.8474		
18	C	127.9291	52.50	18	C	126.9326	53.46	55.72
19	O	228.2694		19	O	247.4952		
20	C	127.6883	52.74	20	C	122.5707	57.66	55.77
21	H	23.2897	8.41	21	H	23.4667	8.24	8.8
22	H	23.2076	8.49	22	H	23.236	8.46	9.24
23	H	23.729	7.98	23	H	23.8079	7.91	7.47
24	H	25.2658	6.49	24	H	24.8851	6.86	7.18
25	H	23.9152	7.80	25	H	24.5165	7.22	7.46
26	H	27.6808	4.15	26	H	27.6994	4.13	3.87
27	H	28.2438	3.60	27	H	28.0043	3.84	3.87
28	H	28.2432	3.60	28	H	28.1387	3.71	3.87
29	H	27.7423	4.09	29	H	28.015	3.83	3.87
30	H	28.1575	3.69	30	H	28.5926	3.27	3.87
31	H	28.1576	3.69	31	H	27.2273	4.59	3.87

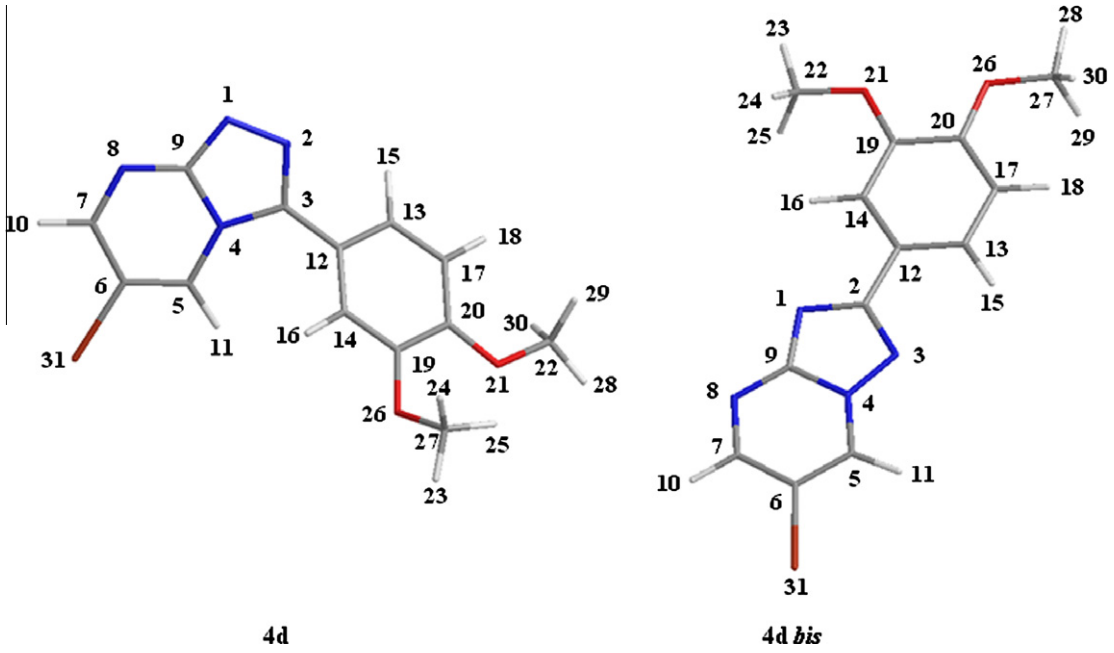


Fig. 5. Optimized geometries and atom numbering of compound **4d** and its tentative isomer **4d *bis***.

dichloromethane) to give 6-bromo-2-(3,4-dimethoxyphenyl)-[1,2,4]triazolo[4,3-*a*]pyrimidine (**4d**, 5.86 g, assumed 100%) as a yellow solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 9.24 (d, J = 2.2 Hz, 1H), 8.80 (d, J = 2.1 Hz, 1H), 7.47 (dd, J = 8.2, 1.8 Hz, 1H), 7.46 (d, J = 1.6 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 3.87 (s, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.16, 152.03, 150.54, 149.08, 145.23, 132.71, 121.10, 117.93, 112.00, 111.57, 105.76, 55.72, 55.67. ^{15}N NMR (70 MHz, DMSO-d_6): as in Table 10. HRMS (ESI+): $C_{13}H_{11}BrN_4O_2^+$ requires m/z 334.0065; $C_{13}H_{12}BrN_4O_2^+$ $(M+H)^+$ requires m/z 335.0138; found m/z 335.0147.

4.11. N-(4-Fluorobenzyl)-2-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-6-amine (5a)

Compound **4a** (170 mg, 0.56 mmol, 1 eq) and 4-fluorobenzylamine (0.7 mL, 6.12 mmol) were heated at 100 °C for 10 min. After

cooling down to RT, dichloromethane (10 mL) was added and excess 4-fluorobenzylamine hydrochloride was removed by filtration. The filtrate was evaporated and chromatographed (silica, 5–10% MeOH in dichloromethane). *N*-(4-fluorobenzyl)-2-(4-methoxy-phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-amine (**5a**, 36 mg, 19%) was obtained as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.36 (s, 1H), 8.05 (d, J = 7.7 Hz, 1H), 7.57–7.42 (m, 2H), 7.19 (t, J = 8.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 6.78 (t, J = 5.1 Hz, 1H), 4.31 (d, J = 5.4 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.5, 161.4 ($^1J_{C-F}$ = 242 Hz), 160.7, 150.60, 148.12, 135.61, 134.4 ($^4J_{C-F}$ = 2.6 Hz), 129.7 ($^3J_{C-F}$ = 8.3 Hz), 127.9, 123.4, 115.3 ($^2J_{C-F}$ = 20.9 Hz), 114.3, 114.0, 55.3, 45.9. ^{15}N NMR (70 MHz, DMSO-d_6): as in Table 3. HRMS (ESI+): $C_{19}H_{16}FN_5O^+$ requires m/z 349.1333; $C_{19}H_{17}FN_5O^+$ $(M+H^+)^+$ requires m/z 350.1411; found m/z 350.1435

4.12. N-(Cyclopropylmethyl)-2-(3-acetylphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-6-amine (5b)

Compound **4b** (500 mg, 1.58 mmol, 1 eq) and cyclopropanemethylamine (0.8 mL, 9.24 mmol) were stirred at RT for 30 min. Removal of excess amine by evaporation and purification by column chromatography (silica, 2–10% MeOH in dichloromethane) gave *N*-(cyclopropylmethyl)-2-(3-acetylphenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-amine (**5b**, 80 mg, 17%) as a pale yellow solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.60 (s, 1H), 8.43 (s, 1H), 8.36 (d, J = 7.7 Hz, 1H), 8.06 (d, J = 7.2 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 6.34 (s, 1H), 2.92 (d, J = 6.6 Hz, 2H), 2.66 (s, 3H), 1.12 (s, 1H), 0.53 (d, J = 7.2 Hz, 2H), 0.27 (d, J = 3.6 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 197.6, 161.4, 150.4, 148.7, 137.3, 136. 5, 131.4, 130.6, 129.5, 129.4, 125.6, 113.2, 47.7, 26.8, 10.0, 3.6. ^{15}N NMR (70 MHz, DMSO-d_6): as in Table 4. HRMS (ESI+): $C_{17}H_{17}N_5O^+$ requires m/z 307.1428; $C_{17}H_{18}N_5O^+$ $(M+H)^+$ requires m/z 308.1506; found m/z 308.1528.

4.13. N-(3,4-Dichlorobenzyl)-2-(4-carboxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-6-amine (5c)

Compound **4c** (360 mg, 1.13 mmol, 1 eq) and 3,4-dichlorobenzylamine (0.7 mL, 5.31 mmol) were heated at 100 °C for 1 h. Excess amine was removed by evaporation and residue was purified by column chromatography (silica, 5–15% MeOH in dichloromethane). *N*-(3,4-Dichlorobenzyl)-2-(4-carboxyphenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-amine (**5c**, 30 mg, 6%) was obtained as a yellow solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.63 (s, 1H), 8.43 (s, 1H), 8.23 (d, J = 6.6 Hz, 2H), 8.06 (d, J = 6.0 Hz, 2H), 7.73 (s, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.44 (d, J = 7.7 Hz, 1H), 6.99 (s, 1H), 4.37 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.9, 161.4, 150.6, 148.9, 139.6, 135.7, 134.774, 131.770, 131.1, 130.6, 129.9, 129.6, 129.6, 127.9, 126.3, 113.9, 45.2. ^{15}N NMR (70 MHz, DMSO-d_6): as in Table 5. HRMS (ESI+): $C_{19}H_{13}Cl_2N_5O_2^+$ requires m/z 413.0441; $C_{19}H_{14}Cl_2N_5O_2^+$ $(M+H)^+$ requires m/z 414.0519; found m/z 414.0534

4.14. N-(4-Fluorobenzyl)-2-(4-hydroxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-6-amine (5d)

Compound **5a** (110 mg, 0.32 mmol, 1.0 eq) was suspended in dichloromethane (4 mL) and boron tribromide (2.2 mL of a 1 M solution in dichloromethane, 2.2 mmol) was added dropwise at RT. The reaction mixture was stirred for 2.5 h at RT, MeOH (5 mL) was slowly added and the mixture was stirred for additional 30 min. The solvent was evaporated and the residue was purified by column chromatography (silica, 2–10% MeOH in dichloromethane). *N*-(4-Fluorobenzyl)-2-(4-hydroxyphenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-6-amine (**5d**, 38 mg, 36%) was obtained as a pale yellow solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 9.84 (s, 1H), 8.54 (s, 1H), 8.34 (s, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.48 (s, 2H), 7.19 (t, J = 8.3 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 6.75 (s, 1H), 4.30 (d, J = 5.4 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.9, 161.4 (1JC-F = 243 Hz), 159.1, 150.6, 147.8, 135.4, 134.4 ($^4J_{C-F}$ = 2.8 Hz), 129.7 ($^3J_{C-F}$ = 7.7 Hz), 127.9, 121.8, 115. 6, 115.2 ($^2J_{C-F}$ = 21.5 Hz), 114.0, 45.8. ^{15}N NMR (70 MHz, DMSO-d_6): as in Table 6. HRMS (ESI+): $C_{18}H_{14}FN_5O^+$ requires m/z 335.1177; $C_{18}H_{15}FN_5O^+$ $(M+H)^+$ requires m/z 336.1255; found m/z 336.1290.

4.15. N-(Tetrahydro-2H-pyran-4-yl)-2-(3,4-dimethoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-5-amine (5e)

Compound **4d** (200 mg, 0.60 mmol, 1.0 eq) and 4-aminotetrahydropyrane (241 mg, 2.39 mmol, 4 eq) were dissolved in TFE (1.5 mL) and the reaction mixture was irradiated under microwave conditions (200 W, 170 °C, 30 min). *N*-(Pyran-4-yl)-2-(3,4-dimethoxyphenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-amine (**5e**, 38 mg, 18%) was obtained as a white solid after purification by column chromatography (silica, 4–10% MeOH in dichloromethane). ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.33 (s, 1H), 8.22 (s, 1H), 7.84 (s, 1H), 7.77 (s, 1H), 7.12 (s, 1H), 6.60 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.46 (s, 2H), 1.86 (s, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.9, 156.0, 153.0, 150.7, 148.8, 147.0, 123.1, 120.1, 111.7, 110.1, 89.0, 66.0, 55.6, 55.5, 48.8, 31.7. ^{15}N NMR (70 MHz, DMSO-d_6): as in Table 7. HRMS (ESI+): $C_{18}H_{21}N_5O_3^+$ requires m/z 355.1639; $C_{18}H_{22}N_5O_3^+$ $(M+H)^+$ requires m/z 356.1717; found m/z 356.1779.

4.16. N-Propyl-2-(3,4-dimethoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-5-amine (5f)

Compound **4d** (300 mg, 0.90 mmol, 1.0 eq) and propylamine (0.294 mL, 3.58 mmol, 4 eq) were dissolved in TFE (2 mL). The reaction mixture was irradiated under microwave conditions (200 W, 170 °C, 30 min) and the solvent was removed by evaporation. The residue was purified by column chromatography (silica, 4–10% MeOH in dichloromethane). *N*-(Propyl)-2-(3,4-dimethoxyphenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-amine (**5f**, 33 mg, 12%) was obtained as a beige solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.30 (d, J = 5.4 Hz, 2H), 7.82 (d, J = 8.3 Hz, 1H), 7.76 (s, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.42 (d, J = 4.8 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.39 (d, J = 6.6 Hz, 2H), 1.67 (dd, J = 14.3, 7.2 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.9, 156.4, 153.6, 150.6, 148.8, 147.7, 123.4, 119.9, 111.7, 109.9, 88.3, 55.6, 55.5, 43.3, 21.7, 11.1. ^{15}N NMR (70 MHz, DMSO-d_6): as in Table 8. HRMS (ESI+): $C_{16}H_{19}N_5O_2^+$ requires m/z 313.1533; $C_{16}H_{20}N_5O_2^+$ $(M+H)^+$ requires m/z 314.1611; found m/z 314.1679.

4.17. N-(2-Methoxyethyl)-2-(3,4-dimethoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-5-amine (5g)

Compound **4d** (300 mg, 0.90 mmol, 1.0 eq) and 2-methoxyethylamine (0.31 mL, 3.58 mmol, 4 eq) were dissolved in TFE (2 mL). The mixture was irradiated under microwave conditions (200 W, 170 °C, 30 min). Column chromatography (silica, 4–10% MeOH in dichloromethane) gave *N*-(2-methoxyethyl)-2-(3,4-dimethoxyphenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-amine (**5g**, 95 mg, 32%) as a pale yellow solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.31 (d, J = 5.4 Hz, 1H), 8.21 (s, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.76 (s, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.47 (d, J = 5.4 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.61 (dd, J = 11.9, 4.2 Hz, 5H), 3.28 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.0, 156.3, 153.60, 150.6, 148.8, 147.8, 123.3, 119.9, 111.7, 109.9, 88.6, 70.1, 58.1, 55.6, 55.5, 41.5. ^{15}N NMR (70 MHz, DMSO-d_6): as in Table 9. HRMS (ESI+):

$C_{16}H_{19}N_5O_3^+$ requires m/z 329.1482; $C_{16}H_{20}N_5O_3^+$ $(M+H)^+$ requires m/z 330.1561; found m/z 330.1589.

4.18. Computational details

The geometries of all molecules have been fully optimized with the DFT B3LYP [37] computational method and the 6-31G(d) basis set [38]. Frequency calculations have been carried out at the same computational level to verify that the structures obtained correspond to energetic minima. A further optimization has been carried out at the B3LYP/6-311++G(d,p) level [39]. These geometries have been used for the calculations of the absolute chemical shieldings with the GIAO method [40] and the B3LYP/6-311++G(d,p) computational level. All the calculations have been carried out with the Gaussian-03 package [41].

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