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First synthesis of 7-amido-[1,2,4]triazolo[1,5-*a*]pyrimidines using halogen–metal exchange

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ABSTRACT

A new and efficient methodology for the preparation of novel 7-carboxyl-triazolopyrimidine derivatives via the halogen–metal exchange is described. In addition, we showed that this new method can be useful for the synthesis of amides, esters, and ketones by using different carbamoyl chlorides, isocyanides or acyl chlorides as electrophile.

1. Introduction

The [1,2,4]triazolo[1,5-*a*]pyrimidine heterobicycle constitutes a well-established scaffold in crop protection chemistry.[1] For instance, the herbicide family of [1,2,4]triazolo[1,5-*a*]pyrimidine sulfonanilides are potent inhibitors of acetohydroxyacid synthase (AHAS).[2] This class of compounds, which was discovered in the mid 1980s by Dow, is very effective for controlling various broadleaf and grass weed species at low doses while maintaining high levels of selectivity to agronomically important crop species. As an example, the triazolopyrimidine herbicide flumetsulam **1** has been developed for the use in corns and soybeans, whereas metosulam **2** is applied in corns and cereals (Fig. 1).

On the other hand, 7-amino-[1,2,4]triazolo[1,5-*a*]pyrimidines such as BAS600 **3**[3] are a new class of fungicides active against a broad range of different plant diseases.[4] Such compounds, which were discovered by Shell in the early 1990s,[5] have now been identified as promoters of tubulin polymerization with a paclitaxel-like mode of action. In addition, very similar molecules, such as TTI-237 **4**, were claimed as potent anti-cancer agents by Wyeth.[6] In the context of a program directed toward the synthesis of analogues of this class of fungicides with improved biological properties, we became interested in developing a synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidines having an amido group in position 7. In this article, we describe the first synthesis of such compounds.

Initial theoretical studies demonstrated that the route involving construction of the bicycle were long and were not considered.[7] Radical reactions starting with the derivative **7**[8] or **6** were tested and not successful. We tried also to apply the Minisci reaction[9] on **6** to introduce CH_2OH in position 7.[10] These experiments failed to provide any of the desired compound. We then turned our attention to the paths shown in Scheme 1.

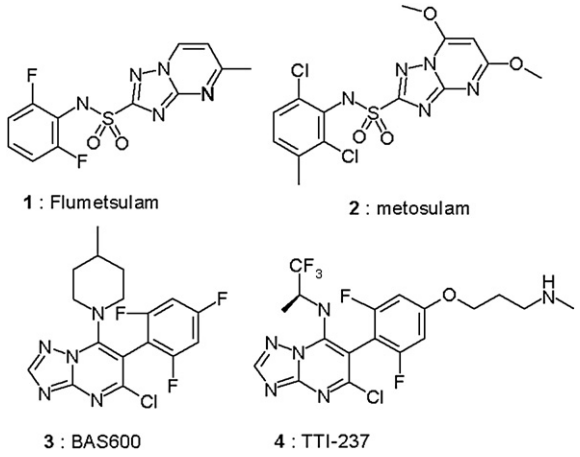

Figure 1. [1,2,4]Triazolo[1,5-*a*]pyrimidine herbicides, fungicides, and anti-cancer agents.

2. Results and discussion

2.1. Synthesis via the 5-chloro-6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carbonitrile

First, we tried the path A, in which the amide could be obtained via a cyanide derivative (Scheme 2).

The preparation of **9** from **7** was briefly described. [11] In our hands, the introduction of a cyanide in position 7 was not easily obtained via simple addition of MCN. In order to solve this problem,

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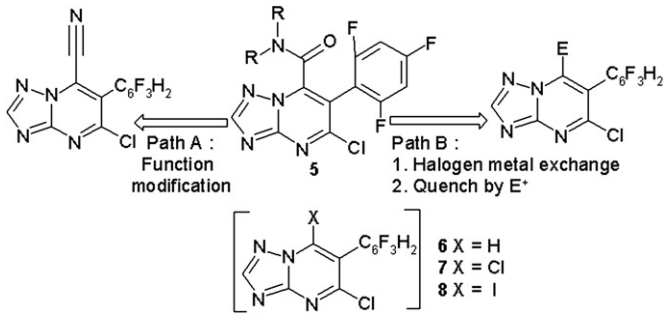
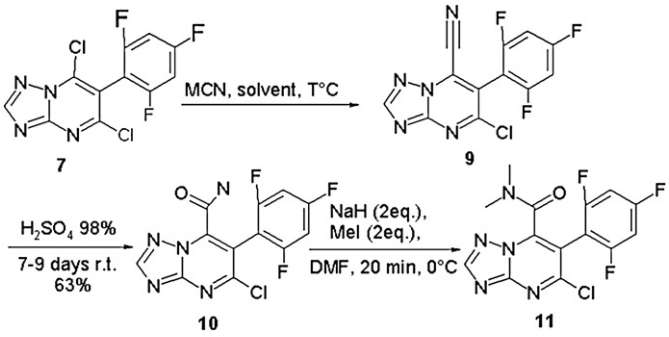


Scheme 1. Different approaches used to prepare the amide in position 7.



Scheme 2. Preparation of amide in position 7 via cyanide derivative.

we investigated the experimental conditions for this transformation, the result is shown in the Table 1.

We were surprised not to observe the formation of **9** with standard conditions (entries 1–4),[12] only degradation products were obtained. The same result was observed at 80 °C with or without catalyst (entries 5 and 6). At 0 °C, the reaction was very slow and we didn't observe the formation of the product. Traces of **9** were detected after 2 weeks of reaction at 25 °C by LC–MS (entry 7). Finally, the best conditions found without catalyst were at 40 °C after 7 days (entry 9). Based on this result, we tried to increase the yield of the reaction by using a catalyst. The presence of DMAP has positive effect on the yield (entry 10). The use of a crown ether (18-C-6-O), which is known to accelerate this type of reaction[13] affords **9** with only 31% of yield (entry 11). Finally, the best result was obtained with the use of sodium tolylsulfinate as catalyst (entry 12).[14] It is well known that in this kind of reaction, the rate-determining step is not the leaving group departure but the nucleophilic attack. The positive effect of the catalyst, in this case, is due to the replacement of the chlorine, which is a worse electron withdrawing group than the tosylsulfinate.

Several conditions tested to transform the cyanide group into an acid or directly into esters or amides failed.[15] It seems that the corresponding carboxylate is unstable and is converted in low yield into the reduced compound **6**. Only the reaction of **9** in pure H_2SO_4 gave the desired compound **10** in 63% yield. The reaction of **10** with a mixture of MeI (2 equiv)/NaH (2 equiv) in DMSO[16] gave the corresponding amide **11** in 28% yield. All attempts to prepare monoalkylated amine from **10** were unsuccessful.[17] Cross-coupling reactions were also tried on **7**, but we only isolated the reduced compound **6** in low yields or in complex mixtures.[18] An alternative approach to prepare these amides is the direct functionalization of **7** in amide or ester via halogen–metal exchange reaction.

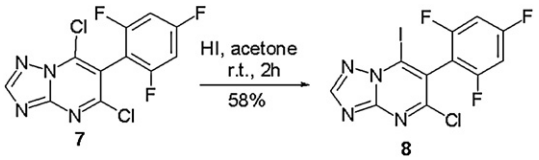
Table 1
Optimization of the cyanation reaction

Entry[a]	T (°C)	MCN	Solvent	Yield of **9** (%)
1	120	KCN	DMF	—
2	110	CuCN	NMP	—
3	100	KCN	NMP	—
4	80	KCN	DMF	—[b]
5	80	KCN	DMF	—
6	80	KCN+$MePhSO_2Na$	DMF	—
7	rt	KCN+$MePhSO_2Na$	DMF	—[c]
8	rt	KCN	DMF	—
9	40	KCN	DMF	23[d]
10	40	KCN+DMAP	DMF	25[d]
11	40	KCN+18-C-6-O	DMF	31[d]
12	40	KCN+$MePhSO_2Na$	DMF	53[d]

[a] Reaction: c=0.5 M, 1 equiv of MCN, 1 mmol scale.
[b] Eight percent of the compound corresponding to the replacement of the Cl in **7** by Me_2N was isolated.
[c] Traces in LC–MS after 2 weeks.
[d] 7 days.

2.2. Synthesis via halogen–metal exchange reaction

Our first attempt to generate an organometallic species in position 7, from **7** via a halogen–metal exchange reaction failed. In order to solve this problem, we turned our attention onto the synthesis of **8**. The reaction of **7** with HI in acetone gave **8** in 58% yield (Scheme 3).[19] However, cross-coupling reactions with **8** were not successful.



Scheme 3. Iodination of **7**.

For the metal–halogen exchange, we used either *t*-BuLi or *i*-PrMgCl in THF. The influence of the experimental conditions of this halogen metal exchange[20] was analysed by quenching the reaction with $ClCO_2Me$. Detailed investigations of these reactions showed that the reaction is strongly dependent on the temperature, the reaction time, and the solubility of the starting material.

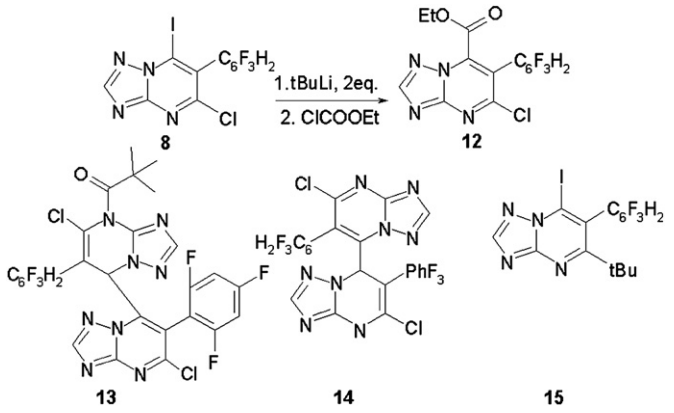
The results obtained by using the *t*-BuLi in THF to realize the halogen–metal exchange reaction is disclosed in Table 2 (Scheme 4).

At −78 °C, the halogen–metal exchange reaction failed, probably due to the poor solubility of the starting material at this temperature (entry 1). The first assays at higher temperatures were done, but after 1 h at −60 °C or −50 °C only complex mixtures were obtained and only few percents of the dimeric compound **14** were isolated. The first improvement for this halogen–metal exchange reaction came from the decreasing the reaction time from 1 h to 30 min before quenching. In this case, we isolated for the first time 4% of the desired **12** (entry 4). On decreasing the reaction time to 5 min, **12** was obtained in 12% yield (entry 5). Attempts to decrease the concentration afforded only side product **13** or **15** in less than

Table 2
Optimization of the halogen–metal exchange reaction with *t*-BuLi

Entry[a]	T (°C)	Reaction time	[c]	Solvent	*t*-BuLi (equiv)	Yield (%)
1	−78	1 h	0.2	THF	2	—[a]
2	−60	1 h	0.2	THF	2	—
3	−50	1 h	0.2	THF	2	—
4	−50	30 min	0.2	THF	2	4
5	−50	<5 min	0.2	THF	2	12
6	−50	<1 min	0.4	THF	2	—[b]
7	−60	<1 min	0.2	THF/DME	2	18
8	−78	<1 min	0.2	THF/HMPT	2	28

[a] Starting material.
[b] Seven percent of **15** and traces of **13**.



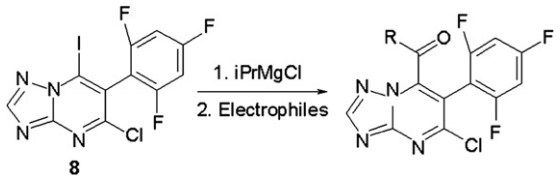
Scheme 4. Halogen–metal exchange reaction on **8** with *t*-BuLi.

10% of yield. We were surprised to isolate these compounds because the addition of *t*-BuLi to pyrimidines is not described and only one example was found in the literature with *t*-BuMgBr.[21] The product **13** is more surprising and is probably coming from the over reaction of the anionic **14** with $ClCO_2Me$. Finally, the use of a mixture of solvents to solubilize our starting material (THF/DME 1:1 or HMPT/THF 1:10) gave the desired compound in a moderate 28% yield (entries 7 and 8).[22]

The same type of study was done by using Knochel's method (Scheme 5, Table 3).[23]

Table 4
Preparation of amides, ester, and ketone by using halogen–metal exchange reaction

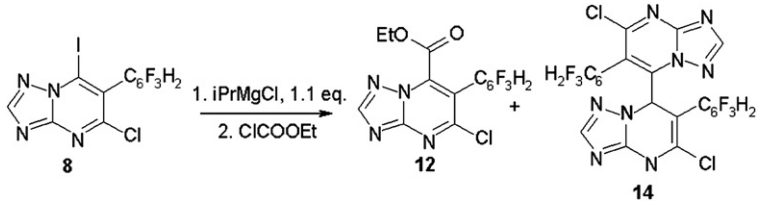
Compound	R=	Yield (%)
11	Me_2N–	33
16	$Allyl_2N$–	35
17	–N–$(CH_2)_4$–	26
18	–N–$(CH_2)_2$–O–$(CH_2)_2$–	32
19	MeNH	23
20	Me	16



Scheme 6. Preparation of derivatives from **8**.

3. Conclusion

In summary, we have developed the first method for the preparation of new 7-carboxyl-triazolopryimidines derivatives via the halogen–metal exchange reaction on a electron deficient heterocyclic structure. The prepared compounds are currently been tested to evaluate their biological activity.



Scheme 5. Halogen exchange reaction on **8** with *i*-PrMgCl.

The halogen–metal exchange reaction using *i*-PrMgCl is highly temperature and time dependent. The optimal temperature that we found is around −25 °C. At higher temperature, we observed only degradation of the starting material and at lower temperature the desired product was not obtained or only in traces (entries 1–5). As previously, the quench must be done as soon as possible after the addition of the Grignard reagent (entries 6 and 7). Finally, we noted that a higher dilution affords only the product corresponding to the addition of the *i*-Pr in position 4 (entry 8). The best result was obtained by treating **8** with 1.1 equiv of *i*-PrMgCl in THF at −25 °C and quenching with an excess of $ClCO_2Et$ (entry 7, 33%).

Finally, we applied the best experimental conditions found with *i*-PrMgCl to prepare amides, ester, and ketone using as electrophile different carbamoyl chlorides, isocyanides or acyl chlorides (Table 4, Scheme 6 and see Section 4).

Table 3
Optimization of the halogen–metal exchange reaction with *i*-PrMgCl

Entry[a]	*T* (°C)	Reaction time	[*c*]	*i*-PrMgCl (equiv)	Yield (%)
1	rt	1 h	0.2	1	—
2	0	30 min	0.2	1	—
3	−20	1 h	0.2	1	—
4	−40	30 min	0.2	1	—[b]
5	−50	<5 min	0.2	1	—[b]
6	−25	<5 min	0.2	1	12
7	−25	1 min	0.2	1	33
8	−25	1 min	0.4	1	—

[a] All reactions were done in THF.
[b] The starting material was recovered.

4. Experimental

4.1. General experimental information

All experiments sensitive to air and/or to moisture were carried out under an argon atmosphere in dried glassware assembled under a stream of argon. Nuclear magnetic resonance spectra were recorded on Brucker Ultrashield Avance (^1H, 400 MHz; ^{13}C, 100 MHz) spectrometers. Solvents and reagents were purchased from commercial source and used without further purification. THF is purchased anhydrous from Aldrich Chemical Co. and used without further purification.

The compound **7** was prepared according to the procedure described in the BASF patents US 6,297,251, US 6,117,876, and WO 9846607.

4.2. Synthesis of 7-iodo-5-chloro-6-(2,4,6-trifluorophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (8)

Compound **7** (4.1 g) was solubilized in 100 mL of acetone, and then 50 mL of an aqueous solution of HI (55%) was added slowly at rt. After 2 h, **7** had disappeared completely and the solvents were removed under vacuum and the residue was purified on silica (cyclohexane/AcOEt 6:1) to give 7-iodo-5-chloro-6-(2,4,6-trifluorophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine **8** as a white powder (2.38 g, 58% yield). ^1H NMR (400 MHz; $CDCl_3$): δ 6.82 (t, J=6 Hz, 2H), 8.51 (s, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 101.3, 111.5, 121.4, 151.9 154.6, 156.0, 159.1, 161.6, 163.2, 166.5. ESP MS (positive ion spectrum) m/z: 410.

4.3. Synthesis of 7-cyano-5-chloro-6-(2,4,6-trifluorophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (9)

Compound **7** (1.55 g, 5 mmol) was solubilized in 30 mL of DMF, and then 232 mg (0.15 mmol, 0.3 equiv) of sodium tosylsulfinate and 357.5 mg (5.5 mmol, 1.1 equiv) of potassium cyanide were added to the mixture. After 7 days at 40 °C, **7** had disappeared, then DMF was removed under vacuum and the residue was purified on silica (cyclohexane/AcOEt 4:1) to give 821 mg of 7-cyano-5-chloro-6-(2,4,6-trifluorophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine **9** (53%) as a white powder. ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.90 (t, J=6 Hz, 2H), 8.52 (s, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 101.8, 107.7, 118.8, 122.2, 153.5, 156.3, 158.1, 159.4, 162.0, 163.9, 166.5. ESP MS (positive ion spectrum) m/z: 310.

4.4. Synthesis of 5-chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acid amide (10)

Compound **9** (620 mg, 2 mmol) was solubilized in 10 mL of pure H_2SO_4. After 9 days this solution was added slowly on 1 L of ice and neutralized by $NaHCO_3$. The aqueous phase was extracted three times with AcOEt. The combined organic layers were dried on anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified on silica (AcOEt/cyclohexane 2:1) to give as a white powder 412 mg of 5-chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acid amide **10** (63%). ^{1}H NMR (400 MHz; DMSO-d_6): δ 6.95 (t, J=6 Hz, 2H), 8.22 (br s, 1H), 8.44 (br s, 1H), 8.58 (s, 1H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 100.6, 108.9, 144.8, 153.5, 156.3, 156.5, 158.5, 159.0, 161.3, 162.3. ESP MS (positive ion spectrum) m/z: 327.

4.5. Synthesis of the 5-chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acid dimethylamide (11)

*4.5.1. Method A, dialkylation of **10***

Compound **10** (108 mg, 0.33 mmol) and 40 μL (0.66 mmol, 2 equiv) of MeI were solubilized in 1.0 mL of anhydrous DMF. Then, at 0 °C, 28 mg of NaH (0.66 mmol, 2 equiv, 55% in mineral oil) was added to the mixture. After 20 min, **10** has disappeared completely in LC–MS. The mixture is quenched with 10 mL on water. The aqueous phase was extracted three times with AcOEt. The combined organic layers were dried on anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified on reversed phase chromatography (Apparatus: Varian Prostar; injector: Gilson 215. Column Sunfire Prep C OBD, 10 μm, 19×150 mm; flow: 30 mL/min; grad: 80% MeCN/H_2O to 100% MeCN; wavelength: 254 nm) to give as a white powder 32.1 mg of 5-chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acid dimethylamide **11** (28%).

4.5.2. Method B

See typical procedure for the halogen exchange reaction on **8** and quench with *N*,*N*-dimethylcarbamyl chloride. ^{1}H NMR (400 MHz; $CDCl_3$): δ 2.81 (s, 3H), 3.01 (s, 3H), 6.78 (m, 2H), 8.50 (s, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 34.8, 37.0, 100.7, 101.8, 110.2, 143.8, 153.9, 157.4, 157.7, 158.0, 162.6, 163.0, 165.5. ESP MS (positive on spectrum) m/z: 356.

4.6. Typical procedure for the halogen exchange reaction on 8 and quench with an electrophile

Compound **8** (205 mg, 0.5 mmol) was dried three times at 100 °C under vacuum for 30 min. Anhydrous THF (2.5 mL) was added to the powder. The solution was cooled at −23 °C with a solid CO_2/CCl_4 bath. The temperature was controlled in situ with a thermometer. Then, 275 μL (1.1 equiv, 0.55 mmol) of *i*-PrMgCl (2 M in THF) was added as fast as possible on the mixture in order to keep the temperature below −20 °C. After the end of the addition of *i*-PrMgCl, 4 equiv of the electrophile was added rapidly to the mixture and the bath was removed rapidly and the ball was heated with a hair drier till the intern temperature was equal to 25 °C. After 30 min at rt, 10 mL of a saturated solution was added to the mixture. The aqueous phase was extracted three times with AcOEt. The combined organic layers were dried on anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified on silica to give as a white powder the amides or the esters.

*4.6.1. 5-Chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo-[1,5-a]pyrimidine-7-carboxylic acid ethyl ester (**12**)*

See typical procedure for the halogen exchange reaction on **8** and quench with ethyl chloroformate. ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.19 (t, J=6.5 Hz, 3H), 4.03 (q, J=7.0 Hz, 2H), 6.79 (q, J=6 Hz, 2H), 8.51 (s, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 19.2, 64.1, 100.9, 110.2, 139.8, 154.1, 157.2, 157.6, 158.0, 159.7, 162.1, 163.1. ESP MS (positive ion spectrum) m/z: 357.

*4.6.2. 1-[5,5′-Dichloro-6,6′-bis-(2,4,6-trifluoro-phenyl)-7H-[7,7′]bi[[1,2,4]triazolo[1,5-a]pyrimidinyl]-4-yl]-2,2-dimethyl-propan-1-one (**13**)*

^{1}H NMR (400 MHz; $CDCl_3$): δ 1.35 (s, 9H), 6.39 (s, 1H), 6.45 (t, J=6 Hz, 1H), 6.58 (t, J=6 Hz, 1H), 6.62 (t, J=6 Hz, 1H), 6.89 (t, J=6 Hz, 1H), 7.58 (s, 1H), 8.42 (s, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 26.9, 41.6, 59.0, 87.6, 101.9, 111.4, 132.2, 144.0, 149.6, 150.2, 154.3, 156.7, 157.2, 160.2, 163.4, 173.4. ESP MS (positive ion spectrum) m/z: 653.

*4.6.3. 5,5′-Dichloro-6,6′-bis-(2,4,6-trifluoro-phenyl)-4,7-dihydro-[7,7′]bi[[1,2,4]triazolo[1,5-a]pyrimidinyl] (**14**)*

^{1}H NMR (400 MHz; DMSO-d_6): δ 6.41 (s, 1H), 6.45 (t, J=6 Hz, 1H), 6.57 (t, J=6 Hz, 1H), 6.61 (t, J=6 Hz, 1H), 6.99 (t, J=6 Hz, 1H), 7.59 (s, 1H), 8.43 (s, 1H), 12.4 (br s, 1H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 59.0, 87.7, 100.8, 101.2, 111.4, 132.1, 144.0, 149.7, 150.2, 154.3, 156.7, 157.1. ESP MS (positive ion spectrum) m/z: 568.

*4.6.4. 5-tert-Butyl-7-iodo-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (**15**)*

^{1}H NMR (400 MHz; DMSO-d_6): δ 1.41 (s, 9H), 6.74 (t, J=6.5 Hz, 2H), 8.40 (s, 1H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 28.4, 39.6, 100.9, 115.2, 135.5, 154.5, 155.1, 156.3, 159.7, 162.1, 163.0, 165.5. ESP MS (positive ion spectrum) m/z: 433.

*4.6.5. 5-Chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo-[1,5-a]pyrimidine-7-carboxylic acid diallylamide (**16**)*

See typical procedure for the halogen exchange reaction on **8** and quench with *N*,*N*-diallylcarbamyl chloride. ^{1}H NMR (400 MHz; $CDCl_3$): δ 3.52 (dd, J=6 and 12 Hz, 1H), 3.57 (dd, J=5 and 13 Hz, 1H), 3.75 (dd, J=6 and 12 Hz, 1H), 4.24 (dd, J=5 and 13 Hz, 1H), 4.95–5.16 (m, 4H), 5.93 (m, 1H), 5.62 (m, 1H), 6.79 (q, J=6 Hz, 1H), 8.51 (s, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 47.9, 50.7, 100.3, 101.6, 110.0, 118.8, 120.8, 130.4, 131.5, 143.6, 154.0, 157.3, 157.6, 157.7. ESP MS (positive ion spectrum) m/z: 408.

*4.6.6. [5-Chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo-[1,5-a]pyrimidin-7-yl]-pyrrolidin-1-yl-methanone (**17**)*

Method B: see typical procedure for the halogen exchange reaction on **8** and quench with 1-pyrrolidinylcarbonyl chloride. ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.72–1.95 (m, 4H), 3.10–3.40 (m, 3H), 3.60–3.70 (m, 1H), 6.70–6.85 (m, 3H), 8.50 (s, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 24.0, 25.6, 45.5, 46.4, 100.6, 101.6, 110.0, 144.1, 154.0, 156.1, 157.6, 161.0, 161.8, 163.0, 165.5. ESP MS (positive ion spectrum) m/z: 382.

4.6.7. [5-Chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo-[1,5-a]pyrimidin-7-yl]-morpholin-4-yl-methanone (**18**)

Method B: see typical procedure for the halogen exchange reaction on **8** and quench with 4-morpholinocarbonyl chloride. ^{1}H NMR (400 MHz; $CDCl_3$): δ 3.09 (m, 1H), 3.20 (m, 1H), 3.39 (t, J=3 Hz, 1H), 3.45–3.60 (m, 3H), 3.70–3.81 (m, 2H), 6.81 (q, J=7.0 Hz, 2H), 8.50 (s, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 42.4, 44.5, 46.6, 64.7, 66.3, 100.4, 101.8, 110.4, 143.0, 153.9, 156.6, 157.4, 157.8, 163.1. ESP MS (positive ion spectrum) m/z: 398.

4.6.8. 5-Chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo-[1,5-a]pyrimidine-7-carboxylic acid methylamide (**19**)

Method B: see typical procedure for the halogen exchange reaction on **8** and quench with methyl isocyanate. ^{1}H NMR (400 MHz; $CDCl_3$): δ 2.96 (d, J=3 Hz, 3H), 6.76 (t, J=6.5 Hz, 2H), 8.54 (s, 1H), 9.21 (br s, 1H), 9.24 (br s, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 27.0, 100.7, 107.5, 114.4, 138.8, 154.3, 156.3, 157.0, 158.9, 159.3, 161.3, 162.4, 165.0. ESP MS (positive ion spectrum) m/z: 342.

4.6.9. 1-[5-Chloro-6-(2,4,6-trifluoro-phenyl)-[1,2,4]triazolo [1,5-a]pyrimidin-7-yl]-ethanone (**20**)

Method B: see typical procedure for the halogen exchange reaction on **8** and quench with acetyl chloride. ^{1}H NMR (400 MHz; $CDCl_3$): δ 2.70 (s, 3H), 6.78 (t, J=6.5 Hz, 3H), 8.52 (s, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 29.9, 101.2, 109.4, 144.7, 154.2, 157.4, 157.8, 159.4, 161.9, 163.0, 165.5, 191.3. ESP MS (positive ion spectrum) m/z: 327.

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