Simple and Expedient Access to Novel Fluorinated Thiazolo- and Oxazolo[3,2-a]pyrimidin-7-one Derivatives and Their Functionalization via Palladium-Catalyzed Reactions

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Abstract: An efficient, versatile, and one-pot method for the preparation of novel fluorinated thiazolo- and oxazolo[3,2-a]pyrimidin-7-ones is described from 2-aminothiazoles or 2-amino-oxazoles and fluorinated alkynoates. This transformation, performed under transition-metal-free conditions, offers new fluorinated cyclized products with good to excellent yields. Moreover, the functionalization of these N-fused scaffolds via the Suzuki-Miyaura and Sonogashira cross-coupling reactions led to the synthesis of highly diverse thiazolo- and oxazolo[3,2-a]pyrimidin-7-ones.

Keywords: thiazolo[3,2-a]pyrimidin-7-ones; oxazolo[3,2-a]pyrimidin-7-ones; fluorinated alkynes; regioselective; one-pot reaction; Suzuki-Miyaura; Sonogashira coupling

1. Introduction

Thiazolo[3,2-a]pyrimidines are an important class of heterocyclic compounds that have aroused intensive research interest from chemists due to their wide range of biological properties, including antipsychotic [1], anticancer [2,3], anti-inflammatory [4-7], antimicrobial [8,9], antiviral [10,11] and anti-HIV activities [12]. Additionally, many compounds containing the oxazolo[3,2-a]pyrimidine framework are known for their pharmacological potential as anti-inflammatory [13], antihypertensive [14], and anti-leukemia agents [15]. It should be noted that some examples of structural analogues of thiazolo- and oxazolo[3,2-a]pyrimidinones, are used in clinical medicine, such as Ritalserin and Setoperone, which are antipsychotics [16], and SAR218645, which is an mGluR2 positive allosteric modulator that has been shown to be effective in treating some aspects of cognitive dysfunction in schizophrenia (Figure 1) [17].

In recent years, fluorinated heterocycles have acquired a crucial role in the pharmacological and agrochemical industries due to their wide range of biological properties [18,19]. In addition, fluorinated compounds are present in about 20% of drugs [20-22]. In general, the introduction of fluorine atoms or fluoroalkyl (perfluoroalkyl) groups into heterocyclic compounds increases lipophilicity, stability, solubility, reactivity, and biological properties [23-27]. Accordingly, the combination of two pharmacophoric entities such as the thiazolo- or oxazolo[3,2-a]pyrimidin-7-one scaffold and perfluoroalkyl groups could be an effective method to enhance the biological activity of these heterocycles.

Classically, Thiazolo and oxazolo[3,2-a]pyrimidin-7-one derivatives have been synthesized by reactions of the corresponding 2-aminoazoles with a symmetric alkyl such as dialkyl acetylenedicarboxylates [28-36] (Figure 2a), or an asymmetric alkyl such as
ethyl propiolate derivatives [37–40] (Figure 2b). However, despite their relevance, these procedures have several drawbacks such as a lack of generality, poor regioselectivity, the use of expensive reagents or less available reagents, as well as unsatisfactory yields.

![Figure 1](image-url) Examples of thiazolo- and oxazolo[3,2-a]pyrimidinone structural analogues used in clinical medicine.

**Previous work:** [3+3] cyclocondensation

(a) 

\[
\begin{align*}
R^1 & \quad R^2 = \text{Me, Et} \\
X & = \text{S, O} \\
\text{R}^2 \text{O}_2 \text{C} & \equiv \text{CO}_2 \text{R}^2 \\
R^2 \text{OH (or Toluene), reflux or THF, ultrasound, rt} & \rightarrow \\
\end{align*}
\]

(b) 

\[
\begin{align*}
R^1 & \quad R^2 = \text{H, Me, Ph} \\
X & = \text{S, O} \\
\Delta, \text{free solvent or EtOH, reflux} & \rightarrow \\
\end{align*}
\]

**This work:**

(c) 

\[
\begin{align*}
R & \quad \text{MeOH, reflux} \\
X & = \text{S, O} \\
\text{R}_0 & \equiv \text{CF}_3, \text{C}_2\text{F}_5, \text{CF}_3\text{Ar} \\
\text{R}_0 & \equiv \text{CO}_2\text{Et} \\
\text{MeOH, reflux} & \rightarrow \\
\end{align*}
\]

![Figure 2](image-url) Convergent approach for the synthesis of thiazolo- and oxazolo[3,2-a]pyrimidinone derivatives. (a) from symmetric alkyne[28–36]; (b) from asymmetric alkyne [37–40]; (c) extension to fluorinated ethyl propiolate derivatives.

Despite the numerous approaches described in the literature for the synthesis of non-fluorinated thiazolo- or oxazolo[3,2-a]pyrimidin-7-one derivatives, the incorporation of fluorinated groups into these scaffolds has never been reported to date. Thus, the development of a simple and efficient method using readily available starting materials to access new fluorinated thiazolo- and oxazolo[3,2-a]pyrimidin-7-one derivatives is highly desired.

Continuing our interest in the development of efficient methods for the synthesis of new fluorinated heterocyclic compounds with possible biological properties [41–47], we report here a simple and regioselective synthesis of a novel series of fluorinated thiazolo and oxazolo[3,2-a]pyrimidin-7-one derivatives, by [3+3] cyclocondensation of 2-aminothiazoles or 2-amino-oxazoles with fluorinated alkynoates (Figure 2c). This simple synthetic strategy,
which relies on the use of easily prepared fluorinated alkynoates [48] and of commercially available 2-aminothiazoles and oxazoles, represents a highly efficient one-step route and regioselective access to fluorinated thiazolo- and oxazolo[3,2-a]pyrimidin-7-ones.

2. Results and Discussion

In order to find the optimal reaction conditions for the synthesis of the target compounds, 2-aminothiazole, 1a, and ethyl 4,4,4-trifluorobut-2-ynoate, 2a, were selected as model substrates for the development of this condensation/heterocyclisation reaction by varying different conditions (solvents, temperature, and catalyst). The reaction conditions investigated leading to thiazolo[3,2-a]pyrimidin-7-one 3a are summarized in Table 1.

Table 1. Optimization of the reaction conditions.

| Entry | Catalyst | Solvent   | T (°C) | Convers. (%) a | Yield (%) b |
|-------|----------|-----------|--------|----------------|-------------|
| 1     | None     | toluene   | 70     | 20             | 5           |
| 2     | None     | DCE       | 70     | 50             | 31          |
| 3     | None     | THF       | 70     | 70             | 54          |
| 4     | None     | 1,4-dioxane | 70     | 85             | 62          |
| 5     | None     | MeCN      | 70     | 75             | 51          |
| 6     | None     | DMF       | 70     | 88             | 56          |
| 7     | None     | DMSO      | 70     | 90             | 50          |
| 8     | None     | H2O       | 70     | 45             | 28          |
| 9     | None     | EtOH      | 70     | 100            | 72          |
| 10    | None     | MeOH      | 70     | 100            | 88          |
| 11    | None     | MeOH      | 100    | 100            | 77          |
| 12    | None     | MeOH      | 25     | 30             | 15 c        |
| 13    | AgSO2CF3 | MeOH      | 70     | 100            | 65          |
| 14    | Ag2CO3   | MeOH      | 70     | 100            | 61          |
| 15    | AgOAc    | MeOH      | 70     | 100            | 58          |
| 16    | Cu(OAc)2 | MeOH      | 70     | 100            | 70          |
| 17    | Pd(OAc)2 | MeOH      | 70     | 100            | 50          |
| 18    | ZnCl2    | MeOH      | 70     | 100            | 68          |
| 19    | CuBr     | MeOH      | 70     | 100            | 67          |

a The conversion rate was calculated from the crude 1H NMR spectrum. b Isolated yield. c The reaction was kept under stirring for 72 h.

First, the reaction was carried out using a variety of solvents without any catalyst. The use of a non-polar solvent, such as toluene, gave only traces of the desired product 3a (Table 1, entry 1). The use of aprotic polar solvents such as DCE, THF, 1,4-dioxane, MeCN, DMF, and DMSO resulted in very low to moderate yields of 3a (Table 1, entries 2–7). Switching to a protic polar solvent such as H2O did not provide any improvement in the conversion of the starting material, and the expected product 3a was isolated with a yield not exceeding 28% (Table 1, entry 8), presumably due to the low solubility of the starting materials in water. In contrast, a significant improvement in the yield of target product 3a occurred, reaching 72%, when the reaction was performed with ethanol as the reaction solvent (Table 1, entry 9). To our delight, when the cyclocondensation reaction was run in MeOH as a solvent, the expected product was obtained with a good yield reaching 88% (Table 1, entry 10). Increasing the reaction temperature to 100 °C led to a decrease in the yield of compound 3a (Table 1, entry 11). At room temperature and under the same conditions, the reaction proceeded with a very low yield and incomplete conversion of 1a after 72 h (Table 1, entry 12). Further optimizations were undertaken using various catalysts, including Ag2SO3CF3, Ag2CO3, AgOAc, Cu(OAc)2, Pd(Oac)2, ZnCl2, and CuBr,
but did not improve the reaction yield and provided the cyclized product 3a with yields not exceeding 70% (Table 1, entries 13–19). The molecular structure of the new compound 3a was unambiguously confirmed by X-ray crystal analysis, as depicted in Figure 3 [49].

![Image of X-ray single-crystal structure of compound 3a.]

Figure 3. X-ray single-crystal structure of compound 3a.

With the optimized conditions in hand [1a (1 equiv), 2a (1.3 equiv), MeOH, 70 °C, 12 h], the substrate scope and limitation of the [3+3] cyclocondensation reaction were investigated using various 2-amino-thiazole or oxazole derivatives and fluorinated alkynes. The results are summarized in Scheme 1. As shown in Scheme 1, activated alkynes substituted with different fluorinated groups (CF₃, C₂F₅, CF₂Ar) reacted efficiently with 2-aminothiazole 1a to generate novel fluorinated thiazolo[3,2-a]pyrimidin-7-ones 3a-d with yields ranging from 65 to 88%. It is noteworthy that the presence of an electron-withdrawing atom such as bromine at the 4-position of 2-aminothiazole did not prevent the success of this condensation/lactamization reaction, providing the brominated cyclized products 3e-g with yields of 63%, 67%, and 62%, respectively. These brominated compounds could serve as key intermediates to access novel functionalized thiazolo[3,2-a]pyrimidin-7-ones.

![Scheme 1. Substrate scope studies.]

Scheme 1. Substrate scope studies.
The synthetic scope of this reaction was also successfully extended to benzo[d]thiazolo-2-amine derivatives to access new fluorinated tricyclic compounds 3h-i in good yields (61 and 60%, respectively). It should be noted that introducing a substituent such as a bromine atom on the aromatic ring of the benzo[d]thiazolo-2-amine had a negligible effect on the reactions, offering the possibility of diversifying the range of benzo[d]thiazolo[3,2-a]pyrimidin-7-ones.

To further extend the synthetic scope of this reaction, we sought to examine the reactivity of other 1,3-bis nucleophile reagents, such as 2-amino oxazole derivatives. Interestingly, 2-amino-oxazole derivatives were also efficiently cyclocondensed with fluorinated alkynoates (substituted with a CF₃, C₂F₅, or CF₂-Ar group) to give the expected products 3j-1 with a yield ranging from 60 to 68%. Continuing the evaluation of the cyclocondensation process, treatment of 2-aminobenzo-oxazole derivatives with ethyl 4,4,4-trifluorobutynoate under the same reaction conditions provided the corresponding oxazolo[3,2-a]pyrimidin-7-ones 3m and 3n with yields of 61% and 56%, respectively. Again, the presence of a chlorine atom on the aromatic ring had no significant influence on the efficiency of the reaction. It is noteworthy that ¹H, ¹⁹F, and ¹³C NMR spectrum analysis of the crude mixture of all examples confirmed that no trace of the second regioisomer is observed, showing full regioselectivity of the [3+3] cyclocondensation process. Thus, this synthetic process appears efficient and versatile for the regioselective synthesis of new thiazolo- and oxazolo[3,2-a]pyrimidin-7-ones 3a-n bearing fluoroalkyl groups.

Functionalization via the Palladium-catalyzed cross-coupling reaction of the C-Br bond at position 2 of compounds 3e-f will allow the preparation of a large library of novel thiazolo[3,2-a]pyrimidin-7-ones with a high structural diversity [50–52]. First, compounds 3e-f were subjected to Suzuki–Miyaura cross-coupling under known standard reaction conditions [53–55] using 1.2 equiv of boronic acid, 10 mol% of PdCl₂(PPh₃)₂, and 2 equiv of Na₂CO₃ in a 1,4-dioxane/water (4/1) mixture at 80 °C for 1 h. Under these conditions, these coupling reactions allowed complete conversion of the starting materials and efficient access to the new 2-arylated 5-fluorinated thiazolo[3,2-a]pyrimidin-7-ones 4a-l (Scheme 2).

![Scheme 2](image-url)

Scheme 2. Behavior of 2-bromo-5-fluoroalkylthiazolo[3,2-a]pyrimidin-7-ones in the Suzuki-Miyaura coupling.
As shown in Scheme 2, different boronic acids bearing electron-donating or electron-withdrawing groups on the aromatic ring provided the arylated products 4a-l in good to excellent yields. Notably, phenylboronic acid was successfully coupled with compound 3e leading to the arylation product 4a with a yield of 91%. Arylboronic acids bearing electron-donating groups, such as a methoxy group in the ortho, meta, or para-position, were readily coupled with 3e to provide the corresponding products 4b (82%), 4c (92%), and 4d (95%), respectively. It should be noted that a slight drop in yield was observed in the case of compound 4b, presumably due to the steric hindrance generated by the methoxy group on the ortho-position. As expected, the coupling reaction of compound 3f carrying a pentafluoroethyl group with p-methoxyphenylboronic acid led to the arylated product 4e with a moderate yield of 55%. This result seems to indicate that the nature of the fluoroalkyl group plays a significant role in the efficiency of this coupling reaction. Moreover, the coupling reactions of compound 3e with 1,4-dimethoxyboronic acid and 2,3-ethylenedioxyboronic acid were easily converted to the desired products 4f and 4g with yields of 98% and 60%, respectively. Interestingly, it is worth noting that the reaction was tolerant of the free amino group at the meta position of the phenylboronic acid, providing the corresponding compound 4h in a yield of 52%. Likewise, phenylboronic acid substituted at the para or meta position with an electron-withdrawing group such as CF3 yielded the expected products 4i (75%) and 4j (57%), respectively. Gratifyingly, the coupling reaction was extended to a heteroarylboronic acid such as 3-thiophenyl, providing the cross-coupling product 4l in excellent yield (95%).

To showcase other practical applications of cross-coupling reactions and in order to introduce more molecular diversity at the C-2 position of the 2-bromo thiazolo[3,2-a]pyrimidin-7-ones 3e-f, we extended our work to Sonogashira cross-coupling reactions [56,57], which are a powerful method for the formation of new C–C bonds (Scheme 3). Alkynylated heterocycle compounds are, however, prevalent in many bioactive and natural products with a wide range of interesting biological activities [58–61]. In the context of synthetic transformations, these compounds allow a broad range of transformations, including click reactions, Michael addition, oxidations, and reductions [62–64].

![Scheme 3](image_url)

Scheme 3. Behavior of 2-bromo-5-(trifluoromethyl)thiazolo[3,2-a]pyrimidin-7-one 3e in the Sonogashira coupling.

To this end, the brominated compound 3e and a variety of available terminal alkynes were subjected to standard coupling conditions [alkyne (1.5 equiv), PdCl2(PPh3)2 (5 mol%), CuI (10 mol%), Et3N (2 equiv), DMF, 80 °C, 2 h]. The palladium-catalyzed alkynylation reactions of 3e proceeded successfully, providing the 2-alkynylated-5-trifluoromethyl
thiazolo[3,2-α]pyrimidin-7-ones 5a-h in good to excellent yields (55–92%) (Scheme 3). For example, phenylacetylethylene was cross-coupled to give the expected product 5a in a 68% yield.

Additionally, phenylacetylethylene substituted at the 4-position with an electron-donating group, such as methoxy, generated the coupled product 5b in a yield of 65%. Similarly, coupling with 4-chlorophenylacetylethylene provided the desired product 5c in 58% of yield, showing that an electron-withdrawing group at position 4 of the aromatic ring is also tolerated. We also briefly investigated the effect of the position of the fluorine atom on the aromatic ring on the efficiency of the coupling reaction. Overall, the electron-withdrawing atom fluor at the para or ortho position was tolerated to give rise to the alkynylated products 5d (85%) and 5e (68%), respectively, although a lower yield was observed when the fluorine atom was positioned in the ortho position, which is probably due to steric hindrance. Finally, when aliphatic alkynes, such as 1-hexyne and ethynylcyclohexane were subjected to the standard reaction conditions, the expected products 5g and 5h were obtained in yields of 75% and 55%, respectively.

As shown in Schemes 1–3, a wide variety of fluorinated thiazolo- and oxazolo[3,2-α]pyrimidin-7-ones were efficiently prepared with a large substrate scope and with good to excellent yields (34 examples). All products are new and have been fully characterized by 1H, 19F, and 13C NMR spectroscopy and HRMS.

Some synthesized derivatives were subjected to in vitro evaluation on human hMAO-A and hMAO-B by using p-tyramine as a nonspecific substrate. Screening of the compounds was done at 100 μM and 10 μM, and compounds with residual activities (RAs) below 50% at 100 μM were subjected to IC50 determination using a serial dilution of the inhibitors. The results expressed in IC50 showed that compound 3g selectively inhibited human monoamine oxidase A (hMAO-A) with an IC50 value of 54.08 μM (Table 2).

Table 2. In vitro hMAO inhibitors potencies of compound 3g.

| Product | IC50 ± SEM [μM] or RA b at 100/10 μM | hMAO-A | hMAO-B |
|---------|-------------------------------------|--------|--------|
| 3a      | 20/67                               | 20/67  | n.a.  |
| IC50    | 54.08 ± 10.45 μM                    |        |        |

a IC50 values are means ± standard error of the mean (SEM) of three independent experiments, each performed in duplicate. b RA, residual activity; c n.a., not active (RA at 100 μM ≥ 50%).

3. Materials and Methods

3.1. General Information

All reactions were performed under an inert atmosphere of argon in oven-dried glassware equipped with a magnetic stir bar. Solvents for reactions were obtained from Thermo Fisher Scientific in extra dry quality and stored under argon over activated 3 Å sieves. All reagents were purchased from Fluorochem and used as received without additional purification. Reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel 60 F254 plates. All products were visualized by exposure to UV light (longwave at 365 nm or shortwave at 254 nm). Column chromatography was performed using silica gel 60 (230–400 mesh, 0.040–0.063 mm). Eluents were distilled by the standard methods before each use. All new compounds were characterized by NMR spectroscopy (1H, 19F, and 13C), high-resolution mass spectroscopy (HRMS), and melting point (if solids). NMR spectra were recorded at 300 MHz for 1H, 282 MHz for 19F, and 75 MHz for 13C with a Bruker® 300 MHz NMR spectrometer. Proton and carbon magnetic resonance spectra (1H NMR and 13C NMR) were recorded using tetramethylsilane (TMS) as an external standard and CDCl3 (7.28 ppm for 1H NMR and 77.04 ppm for 13C NMR) or DMSO-d6 (2.50 ppm for 1H NMR and 40.0 ppm for 13C NMR) as internal standards. 19F spectra were unreferenced. Data for NMR are reported as follows: chemical shift (δ ppm),
multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet and br = broad resonance) and coupling constants \( J \) are reported in Hertz (Hz). All the NMR spectra were processed in MestReNova. HRMS experiments were performed on a hybrid tandem quadrupole/time-of-flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manchester, UK) operated in the positive mode.

3.2. General Procedure for the Synthesis of Thiazolo- and Oxazolo[3,2-a]pyrimidin-7-ones 3

To a flame-dried flask containing a magnetic stir bar under an inert atmosphere of argon was added to 2-aminothiazole or 2-amino-oxazole derivatives at 1 mmol (1.0 equiv) and dry methanol (4 mL). The solution was cooled to 0 °C followed by dropwise addition of fluorinated alkyne 1.3 mmol (1.3 equiv). The mixture was allowed to warm to room temperature and then heated at 70 °C for 12 h. The progress of the reaction was monitored by TLC (PE/EtOAc, 70/30). After cooling to room temperature, the solvent was evaporated in vacuo. The crude product was then triturated, rinsed, and washed with EtO. The resulting precipitate was collected via filtration to give the corresponding fluorinated substrates 3a-n as analytically pure solid without further purification. All compounds 3a-n were synthesized by adopting this procedure. \(^1\)H-NMR and \(^13\)C-NMR of compounds 3a-n are shown in Supplementary Materials.)

5-(Trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (3a).

Compound 3a was obtained as a white solid with a yield of 88%. m.p. 210–212 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.42 (d, \( J = 5.1, 1H \)), 7.14 (d, \( J = 5.1 \) Hz, 1H), 6.76 (s, 1H); \(^19\)F NMR (282 MHz, CDCl\(_3\)): \( \delta \) −67.95; \(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 166.9, 165.4, 135.3 (q, \( J = 37.4 \) Hz), 121.5 (q, \( J = 3.4 \) Hz), 119.1 (q, \( J = 274.5 \) Hz), 111.7 (q, \( J = 4.0 \) Hz), 111.6; HRMS (ESI) \( m/z \) [M+H]+ calcd for \( C_{22}H_{19}F_{2}N_{2}O_{2}S \): 356.9503; found: 356.9488.

5-(Pentafluoroethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (3b).

Compound 3b was obtained as a yellow solid with a yield of 85%. m.p. 181–183 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.48 (d, \( J = 5.1 \) Hz, 1H), 7.00 (d, \( J = 5.1 \) Hz, 1H), 6.81 (s, 1H); \(^19\)F NMR (282 MHz, CDCl\(_3\)): \( \delta \) −82.43, −115.53; \(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 167.1, 164.9, 134.7 (t, \( J = 27.1 \) Hz), 122.3 (td, \( J = 7.1, 1.7 \) Hz), 118.0 (qt, \( J = 287.4, 36.1 \) Hz), 114.7 (t, \( J = 5.7 \) Hz), 111.0, 110.0 (tq, \( J = 258.8, 40.9 \) Hz); HRMS (ESI) \( m/z \) [M+H]+ calcd for \( C_{22}H_{19}F_{2}N_{2}O_{2}S \): 270.9959; found: 270.9954.

5-(4-Methoxyphenyl)difluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (3c).

Compound 3c was obtained as a yellow solid with a yield of 65%. m.p. 148–150 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.54 (dt, \( J = 5.1, 1.7 \) Hz, 1H), 7.48 (d, \( J = 8.8 \) Hz, 2H), 7.03 (d, \( J = 8.8 \) Hz, 2H), 7.87 (d, \( J = 5.1 \) Hz, 1H), 6.30 (s, 1H), 3.89 (s, 3H); \(^19\)F NMR (282 MHz, CDCl\(_3\)): \( \delta \) −93.40; \(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 166.8, 166.6, 162.3, 142.1 (t, \( J = 32.2 \) Hz), 127.7 (t, \( J = 5.6 \) Hz), 123.2 (t, \( J = 25.9 \) Hz), 123.1 (t, \( J = 5.3 \) Hz), 118.0 (t, \( J = 243.2 \) Hz), 114.6 (2C), 114.5 (d, \( J = 106.9 \) Hz), 113.0 (t, \( J = 4.9 \) Hz), 109.8, 55.6; HRMS (ESI) \( m/z \) [M+H]+ calcd for \( C_{14}H_{11}F_{2}S_{2}O_{2} \): 309.0504; found: 309.0496.

5-(4-Bromophenyl)difluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (3d).

Compound 3d was obtained as a yellow solid with a yield of 74%. m.p. 202–204 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.72 (d, \( J = 8.5 \) Hz, 2H), 7.55 (dt, \( J = 5.1, 1.8 \) Hz, 1H), 7.46 (d, \( J = 8.5 \) Hz, 2H), 6.92 (d, \( J = 5.1 \) Hz, 1H), 6.22 (s, 1H); \(^19\)F NMR (282 MHz, CDCl\(_3\)): \( \delta \) −94.91; \(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 166.9, 166.2, 141.3 (t, \( J = 31.1 \) Hz), 132.7 (3C), 130.3 (t, \( J = 25.9 \) Hz), 127.7 (t, \( J = 5.7 \) Hz), 126.9 (t, \( J = 2.1 \) Hz), 122.9 (t, \( J = 5.3 \) Hz), 117.7 (t, \( J = 244.1 \) Hz), 113.4 (t, \( J = 4.9 \) Hz), 110.1; HRMS (ESI) \( m/z \) [M+H]+ calcd for \( C_{13}H_{9}F_{2}Br_{2}N_{2}O_{2}S \): 356.9503; found: 356.9498.

2-Bromo-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (3e).

Compound 3e was obtained as a white solid with a yield of 63%. m.p. 184–186 °C; \(^1\)H NMR (300 MHz, DMSO-d6): \( \delta \) 8.19 (s, 1H), 6.81 (s, 1H); \(^19\)F NMR (282 MHz, DMSO-d6): \( \delta \) −67.10; \(^13\)C NMR (75 MHz, DMSO-d6): \( \delta \) = 166.9, 165.0, 135.0 (q, \( J = 37.0 \) Hz), 124.1 (q, \( J = 2.9 \) Hz), 119.3 (q, \( J = 274.5 \) Hz), 111.7 (q, \( J = 4.0 \) Hz), 101.0; HRMS (ESI) \( m/z \) [M+H]+ calcd for \( C_{7}H_{3}BrF_{3}N_{2}O_{2}S \): 298.9096; found: 298.9093.
2-Bromo-5-(pentafluoroethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (3f).

Compound 3f was obtained as a yellow solid with a yield of 67%. m.p. 171–173 °C; 1H NMR (300 MHz, CDCl3): δ 7.46 (s, 1H), 6.74 (s, 1H); 19F NMR (282 MHz, CDCl3): δ −82.37, −115.54; 13C NMR (75 MHz, CDCl3): δ 166.8, 164.1, 134.3 (t, J = 27.1 Hz), 122.3 (td, J = 7.2, 1.8 Hz), 171.7 (qt, J = 251.5, 36.0 Hz), 114.8 (t, J = 5.8 Hz), 109.8 (tq, J = 259.1, 41.0 Hz), 101.7; HRMS (ESI) m/z [M+H]+ calcd for C8H4BrF3N2O3: 348.9064; found: 348.9057.

2-Bromo-5-(4-bromophenyl)difuoromethyl]-7H-thiazolo[3,2-a]pyrimidin-7-one (3g).

Compound 3g was obtained as a beige solid with a yield of 62%. m.p. 218–220 °C; 1H NMR (300 MHz, CDCl3): δ 7.73 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 1.8 Hz, 1H), 7.45 (d, J = 8.7 Hz, 2H), 6.09 (s, 1H); 19F NMR (282 MHz, CDCl3): δ −94.89; 13C NMR (75 MHz, CDCl3): δ 166.6, 165.5, 141.0 (t, J = 31.1 Hz), 132.7 (3C), 129.9 (t, J = 25.6 Hz), 127.7 (t, J = 5.7 Hz), 127.1 (t, J = 2.2 Hz), 123.0 (t, J = 5.8 Hz), 117.7 (t, J = 244.3 Hz), 113.6 (t, J = 4.9 Hz), 100.9; HRMS (ESI) m/z [M+H]+ calcd for C13H7Br2F2N2O3: 434.8608; found: 434.8598.

4-(Trifluoromethyl)-2H-benzo[4,5]thiazolo[3,2-a]pyrimidin-2-one (3h).

Compound 3h was obtained as a yellow solid with a yield of 61%. m.p. 206–208 °C; 1H NMR (300 MHz, CDCl3): δ 7.90 (dd, J = 8.2, 1.8 Hz, 1H), 7.73 (dd, J = 7.5, 1.8 Hz, 1H), 7.54 (dd, J = 8.2, 7.5, 1.8 Hz, 1H), 7.53 (dd, J = 8.2, 7.5, 1.8 Hz, 1H), 6.94 (s, 1H); 19F NMR (282 MHz, CDCl3): δ −62.23; 13C NMR (75 MHz, CDCl3): δ 166.3, 165.0, 136.1 (q, J = 37.0 Hz), 134.1, 127.7 (q, J = 0.9 Hz), 127.1, 123.7, 123.2, 119.5 (q, J = 274.5 Hz), 115.5 (q, J = 8.2 Hz), 113.1 (q, J = 5.8 Hz); HRMS (ESI) m/z [M+H]+ calcd for C11H6F3N2O2: 271.0147; found: 271.0139.

8-Bromo-4-(trifluoromethyl)-2H-benzo[4,5]thiazolo[3,2-a]pyrimidin-2-one (3i).

Compound 3i was obtained as an orange solid with a yield of 60%. m.p. 232–234 °C; 1H NMR (300 MHz, CDCl3): δ 7.86 (d, J = 1.5 Hz, 1H), 7.75 (d, J = 9.5 Hz, 1H), 7.67 (dd, J = 9.5, 1.5 Hz, 1H), 6.96 (s, 1H); 19F NMR (282 MHz, CDCl3): δ −62.32; 13C NMR (75 MHz, CDCl3): δ 165.8, 164.6, 136.0 (q, J = 36.7 Hz), 133.1, 130.9, 125.8, 125.6, 120.5, 119.4 (q, J = 274.1 Hz), 116.7 (q, J = 8.3 Hz), 113.3 (q, J = 5.6 Hz); HRMS (ESI) m/z [M+H]+ calcd for C11H6BrF3N2O2: 348.9253; found: 348.9247.

5-(Trifluoromethyl)-7H-oxazolo[3,2-a]pyrimidin-7-one (3j).

Compound 3j was obtained as a white solid with a yield of 68%. m.p. 221–223 °C; 1H NMR (300 MHz, CDCl3): δ 7.56 (d, J = 2.0 Hz, 1H), 7.42–7.38 (m, 1H), 6.78 (s, 1H); 19F NMR (282 MHz, CDCl3): δ −68.13; 13C NMR (75 MHz, DMSO-d6): δ 168.2, 157.7, 156.3, 132.9 (q, J = 37.9 Hz), 119.4 (q, J = 273.6 Hz), 113.8 (q, J = 2.2 Hz), 111.6 (q, J = 3.5 Hz); HRMS (ESI) m/z [M+H]+ calcd for C5H4F3N2O2: 205.0219; found: 205.0215.

5-(Pentafluoroethyl)-7H-oxazolo[3,2-a]pyrimidin-7-one (3k).

Compound 3k was obtained as a white solid with a yield of 60%. m.p. 170–172 °C; 1H NMR (300 MHz, CDCl3): δ 7.52 (d, J = 2.1 Hz, 1H), 7.41 (br s, 1H), 6.79 (s, 1H); 19F NMR (282 MHz, CDCl3): δ −83.45, −117.31; 13C NMR (75 MHz, CDCl3): δ 167.3, 157.3, 134.6, 132.4 (t, J = 28.0 Hz), 118.0 (qt, J = 287.0, 36.2 Hz), 115.0 (t, J = 5.0 Hz), 113.0 (t, J = 4.4 Hz), 109.7 (tq, J = 258.5, 41.1 Hz); HRMS (ESI) m/z [M+H]+ calcd for C5H2F3N2O2: 255.0187; found: 255.0180.

5-(4-Bromophenyl) difluoromethyl]-7H-oxazolo[3,2-a]pyrimidin-7-one (3l).

Compound 3l was obtained as a white solid with a yield of 68%. m.p. 201–203 °C; 1H NMR (300 MHz, CDCl3): δ 7.72 (d, J = 8.5 Hz, 2H), 7.49–7.51 (m, 2H), 7.46 (d, J = 8.5 Hz, 2H), 6.13 (s, 1H); 19F NMR (282 MHz, CDCl3): δ −95.59; 13C NMR (75 MHz, CDCl3): δ 168.6, 157.5, 139.1 (t, J = 31.8 Hz), 134.3, 132.7 (3C), 129.8 (t, J = 25.6 Hz), 127.7 (t, J = 5.7 Hz), 127.0 (t, J = 2.2 Hz), 117.4 (t, J = 243.4 Hz), 113.5 (t, J = 4.7 Hz), 113.3 (t, J = 4.2 Hz); HRMS (ESI) m/z [M+H]+ calcd for C8H4BrF3N2O2: 340.9732; found: 340.9724.

4-(Trifluoromethyl)-2H-benzo[4,5]oxazolo[3,2-a]pyrimidin-2-one (3m).

Compound 3m was obtained as a white solid with a yield of 61%. m.p. 193–195 °C; 1H NMR (300 MHz, DMSO-d6): δ 7.40 (dt, J = 8.2, 1.3 Hz, 1H), 7.34 (td, J = 7.7, 1.3 Hz, 1H), 6.97 (dd, J = 8.2, 1.3 Hz, 1H), 6.90 (td, J = 7.7, 1.3 Hz, 1H), 6.56 (s, 1H); 19F NMR (282 MHz, DMSO-d6): δ −63.90; 13C NMR (75 MHz, DMSO-d6): δ 168.8, 158.3, 154.4, 140.7.
(q, J = 33.7 Hz), 132.1, 130.6, 122.0, 119.6 (q, J = 274.6 Hz), 119.4, 116.8, 109.2 (q, J = 4.5 Hz); HRMS (ESI) m/z [M+H]+ calcd for C11H8F3N2O2: 255.0303; found: 255.0296.

7-Chloro-4-(trifluoromethyl)-2H-benzo[4,5]oxazolo[3,2-a]pyrimidin-2-one (3n).

Compound 3n was obtained as a white solid with a yield of 56%. m.p. 249–251 °C; 1H NMR (300 MHz, MeOH-d4): δ 7.44 (q, J = 1.2 Hz, 1H), 7.39 (dd, J = 8.7, 2.7 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 6.62 (s, 1H); 19F NMR (282 MHz, MeOH-d4): δ −66.31; 13C NMR (75 MHz, MeOH-d4): δ 171.3, 158.7, 153.1, 141.7 (q, J = 34.6 Hz), 131.6, 129.5 (q, J = 1.0 Hz), 123.3, 122.4, 119.0 (q, J = 274.1 Hz), 117.1, 108.0 (q, J = 4.6 Hz); HRMS (ESI) m/z [M+H]+ calcd for C11H8F3N2O2: 288.9913; found: 288.9906.

3.3. General Procedure for Suzuki-Miyaura Cross-Coupling Reaction: Synthesis of 2-arylated 7H-thiazolo[3,2-a]pyrimidin-7-ones 4a-l

A sealed tube was charged with fluorinated 2-bromo-7H-thiazolo[3,2-a]pyrimidin-7-ones 3e-f 1 mmol (1.0 equiv), boronic acid 1.2 mmol (1.2 equiv), Na2CO3 2 mmol (2.0 equiv), and PdCl2(PPh3)2 (10 mol%). The sealed tube and contents were placed under a vacuum and back-filled with argon under a Schlenk line three times. The mixture of 1,4-dioxane/H2O (4/1) was then added under argon, and the reaction mixture was heated at 80 °C for 1 h. After the completion of the reaction as monitored by TLC analysis, the solvents were evaporated under reduced pressure, and the crude residue was purified by silica gel column chromatography to give the desired arylated 7H-thiazolo[3,2-a]pyrimidin-7-ones 4a-l. (1H-NMR and 13C-NMR of compounds 4a-l are shown in Supplementary Materials).

2-Phenyl-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (4a).

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 8/2) to afford 4a as a beige solid with a yield of 91%. m.p. 216–218 °C; 1H NMR (300 MHz, CDCl3): δ 7.54–7.49 (m, 6H), 6.82 (s, 1H); 19F NMR (282 MHz, CDCl3): δ −67.81; 13C NMR (75 MHz, CDCl3): δ 165.7, 165.1, 135.2 (q, J = 37.3 Hz), 130.5, 129.6 (2C), 129.2, 128.3, 126.3 (2C), 119.1 (q, J = 274.5 Hz), 115.2 (q, J = 3.3 Hz), 111.8 (q, J = 4.1 Hz); HRMS (ESI) m/z [M+H]+ calcd for C13H12F3N2OS: 297.0304; found: 297.0300.

2-(2-Methoxyphenyl)-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (4b).

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 7/3) to afford 4b as a white solid with a yield of 82%. m.p. 227–229 °C; 1H NMR (300 MHz, CDCl3): δ 7.85 (q, J = 1.5 Hz, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.45 (td, J = 7.3, 1.5 Hz, 2H) 7.12–7.05 (m, 2H), 6.81 (s, 1H), 4.00 (s, 3H); 19F NMR (282 MHz, CDCl3): δ −67.91; 13C NMR (75 MHz, CDCl3): δ 165.7, 165.4, 156.4, 135.0 (q, J = 37.1 Hz), 131.3, 128.1, 125.1, 121.5, 119.2 (q, J = 274.4 Hz), 117.8 (q, J = 3.5 Hz), 117.2, 111.8 (q, J = 4.1 Hz), 111.7, 55.8; HRMS (ESI) m/z [M+H]+ calcd for C14H10F3N2O2S: 327.0410; found: 327.0404.

2-(3-Methoxyphenyl)-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (4c).

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 7/3) to afford 4c as a white solid with a yield of 92%. m.p. 193–195 °C; 1H NMR (300 MHz, CDCl3): δ 7.49 (q, J = 1.5 Hz, 1H), 7.43 (td, J = 7.7, 0.9 Hz, 1H), 7.11 (dt, J = 7.7, 0.9 Hz, 1H), 7.04–7.01 (m, 2H), 6.82 (s, 1H), 3.90 (s, 3H); 19F NMR (282 MHz, CDCl3): δ −67.80; 13C NMR (75 MHz, CDCl3): δ 165.6, 165.1, 160.4, 135.2 (q, J = 37.2 Hz), 130.8, 129.5, 129.0, 119.1 (q, J = 274.5 Hz), 118.7, 115.5, 115.4 (q, J = 3.5 Hz), 112.4, 111.9 (q, J = 3.9 Hz), 55.6; HRMS (ESI) m/z [M+H]+ calcd for C14H10F3N2O2S: 327.0405; found: 327.0405.

2-(4-Methoxyphenyl)-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (4d).

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 7/3) to afford 4d as a beige solid with a yield of 95%. m.p. 181–183 °C; 1H NMR (300 MHz, CDCl3): δ 7.45 (d, J = 9 Hz, 2H), 7.39 (q, J = 1.5 Hz, 1H), 7.02 (d, J = 9 Hz, 2H), 6.81 (s, 1H), 3.89 (s, 3H); 19F NMR (282 MHz, CDCl3): δ −67.87; 13C NMR (75 MHz, CDCl3): δ 165.5, 165.1, 161.3, 135.1 (q, J = 37.0 Hz), 128.5, 127.7 (2C), 120.6, 119.2 (q, J = 274.7 Hz), 115.0 (2C), 114.0 (q, J = 3.2 Hz), 111.7 (q, J = 4.0 Hz), 55.5; HRMS (ESI) m/z [M+H]+ calcd for C14H10F3N2O2S: 327.0410; found: 327.0405.

2-(4-Methoxyphenyl)-5-(pentafluoroethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (4e).
The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 8/2) to afford 4e as a beige solid with a yield of 55%. m.p. 201–203 °C; 1H NMR (300 MHz, CDCl3): δ 7.46 (s, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 6.79 (s, 1H), 6.64–6.57 (m, 2H), 6.39 (s, 3H), 5.97 (s, 3H); 13C NMR (75 MHz, CDCl3): δ 166.1, 164.8, 161.3, 134.5 (t, J = 26.9 Hz), 128.6, 127.7 (2C), 120.6, 118.1 (qt, J = 287.5, 36.1 Hz), 115.0 (2C), 114.9 (td, J = 7.1, 1.7 Hz), 114.6 (t, J = 5.9 Hz), 101.1 (qt, J = 258.6 Hz, J = 40.9 Hz), 55.5; HRMS (ESI) m/z [M+H]+ calculated for C17H10F3N2O2S: 377.0378; found: 377.0372.

2-(2,4-Dimethoxyphenyl)-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (4f)

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 7/3) to afford 4f as a solid beige with a yield of 98%. m.p. 260–262 °C; 1H NMR (300 MHz, CDCl3): δ 7.73 (q, J = 1.5 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 6.79 (s, 1H), 6.64–6.57 (m, 2H), 3.97 (s, 3H), 3.89 (s, 3H); 19F NMR (282 MHz, CDCl3): δ −82.28, −115.50; 13C NMR (75 MHz, CDCl3): δ 166.1, 164.8, 161.3, 134.5 (t, J = 26.9 Hz), 128.6, 127.7 (2C), 120.6, 118.1 (qt, J = 287.5, 36.1 Hz), 115.0 (2C), 114.9 (td, J = 7.1, 1.7 Hz), 114.6 (t, J = 5.9 Hz), 101.1 (qt, J = 258.6 Hz, J = 40.9 Hz), 55.5; HRMS (ESI) m/z [M+H]+ calculated for C17H10F3N2O2S: 377.0378; found: 377.0372.

2-(2,3-Dimethoxyphenyl)-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (4g)

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 7/3) to afford 4g as a solid white with a yield of 60%. m.p. 258–260 °C; 1H NMR (300 MHz, CDCl3): δ 7.73 (q, J = 1.5 Hz, 1H), 7.23 (d, J = 2.3 Hz, 1H), 7.18 (dd, J = 8.4, 2.3 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.90 (s, 1H), 4.32 (s, 4H); 19F NMR (282 MHz, MeOD-d4): δ −69.44; 13C NMR (75 MHz, CDCl3): δ 165.5, 165.2, 154.5, 144.3, 135.1 (q, J = 37.3 Hz), 128.9, 121.4, 119.6, 119.1 (q, J = 274.6 Hz), 118.5, 115.2, 114.3 (q, J = 3.3 Hz), 111.7 (q, J = 4.0 Hz), 64.5, 64.4; HRMS (ESI) m/z [M+H]+ calculated for C17H16F3N2O2S: 355.0359; found: 355.0354.

2-(3-Aminophenyl)-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (4h)

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 5/5) as a beige solid with a yield of 52%. m.p. 253–255 °C; 1H NMR (300 MHz, MeOD-d4): δ 7.93 (s, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.62 (dd, J = 8.0, 1.6 Hz, 1H), 6.65 (dd, J = 8.0, 1.6 Hz, 1H), 6.59 (s, 2H), 5.39 (s, 2H); 19F NMR (282 MHz, MeOD-d4): δ −66.88; 13C NMR (75 MHz, MeOD-d4): δ 165.7, 165.2, 150.0, 135.1 (q, J = 36.9 Hz), 130.4, 129.2, 128.1, 119.5 (q, J = 274.6 Hz), 116.9 (q, J = 2.4 Hz), 115.8, 114.0, 111.8 (q, J = 3.8 Hz), 111.4; HRMS (ESI) m/z [M+H]+ calculated for C19H14F3N3O2S: 332.0340; found: 321.0336.

5-(Trifluoromethyl)-2-(3-(trifluoromethyl)phenyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (4i)

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 6/4) to afford 4i as a white solid with a yield of 75%. m.p. 241–243 °C; 1H NMR (300 MHz, MeOD-d4): δ 8.26 (q, J = 1.5 Hz, 1H), 8.09 (s, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H), 6.81 (s, 1H); 19F NMR (282 MHz, MeOD-d4): δ = −64.29, −69.33; 13C NMR (75 MHz, MeOD-d4): δ = 165.9, 165.2, 135.3 (q, J = 37.0 Hz), 131.0, 130.9, 130.6 (q, J = 32.2 Hz), 130.2, 126.5 (q, J = 3.8 Hz), 125.6, 124.3 (q, J = 272.8 Hz), 123.4 (q, J = 3.7 Hz), 119.8 (q, J = 2.7 Hz), 119.4 (q, J = 274.5 Hz), 112.1 (q, J = 4.1 Hz); HRMS (ESI) m/z [M+H]+ calculated for C19H14F3N3O2S: 365.0178; found: 365.0174.

5-(Trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (4j)

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 6/4) to afford 4j as a white solid with a yield of 57%. m.p. 262–264 °C; 1H NMR (300 MHz, MeOD-d4): δ 8.22 (q, J = 1.5 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 6.95 (s, 1H); 19F NMR (282 MHz, MeOD-d4): δ = −64.46, −69.32; 13C NMR (75 MHz, MeOD-d4): δ = 166.0, 165.2, 135.3 (q, J = 37.0 Hz), 133.1 (q, J = 1.4 Hz), 130.0 (q, J = 32.3 Hz), 127.6 (2C), 126.6 (q, J = 3.8 Hz, 2C), 125.5, 124.4 (q, J = 272.1 Hz), 120.1 (q, J = 3.0 Hz), 119.4 (q, J = 274.6 Hz), 112.1 (q, J = 3.9 Hz); HRMS (ESI) m/z [M+H]+ calculated for C19H14F3N3O2S: 365.0178; found: 365.0172.

Ethyl 4-(7-oxo-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-2-yl)benzoate (4k)
The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 7/3) to afford 4k as a white solid with a yield of 60%. m.p. 254–256 °C; 1H NMR (300 MHz, CDCl3): δ 8.18 (d, J = 8.5 Hz, 2H); 7.60 (q, J = 1.5 Hz, 1H); 7.59 (d, J = 8.5 Hz, 2H); 6.84 (s, 1H); 4.44 (q, J = 7.2 Hz, 2H); 1.44 (t, J = 7.2 Hz, 3H); 19F NMR (282 MHz, CDCl3): δ −67.70; 13C NMR (75 MHz, DMSO-d6): δ 165.9, 165.5, 165.2, 135.2 (q, J = 37.1 Hz), 133.9, 130.9, 130.4 (2C), 127 (2C), 125.9, 119.9 (q, J = 3.2 Hz), 119.4 (q, J = 274.7 Hz), 112.2 (q, J = 4.0 Hz), 61.5, 14.6; HRMS (ESI) m/z [M+H+] calcd for C16H11F3N2O5S: 369.0442; found: 369.0437.

2-(Thiophen-3-yl)-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (4l). The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 5/5) to afford 4l as a white solid with a yield of 95%. m.p. 222–224 °C; 1H NMR (300 MHz, MeOH-d4): δ 8.00 (q, J = 1.5 Hz, 1H); 7.90 (dd, J = 2.9, 1.3 Hz, 1H); 7.63 (dd, J = 5.2, 2.9 Hz, 1H); 7.55 (dd, J = 5.2, 1.3 Hz, 1H); 6.91 (s, 1H); 19F NMR (282 MHz, MeOH-d4): δ −69.44; 13C NMR (75 MHz, MeOH-d4): δ 167.1, 166.4, 136.2 (q, J = 37.4 Hz), 129.1, 127.8, 125.1, 124.6, 124.4, 119.1 (q, J = 273.9 Hz), 116.7 (q, J = 3.2 Hz), 110.9 (q, J = 4.1 Hz); HRMS (ESI) m/z [M+H+] calcd for C16H11F3N2O5S: 369.0442; found: 369.0437.

3.4. General Procedure for Sonogashira Cross-Coupling Reaction: Synthesis of 2-alkynylated 5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-ones 5a-h

Then, 2-Bromo-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one 3e (1 mmol, 1 equiv), alkyne 1.5 mmol (1.5 equiv), CuI (10 mol%), Et3N 2 mmol (2 equiv), and PdCl2(PPh3)2 (5 mol%) were added in an oven-dried 10 mL sealed tube. The reaction tube was placed under a vacuum and backfilled with argon three times. Then anhydrous DMF (4.0 mL) was added to the tube via a microsyringe, and the reaction mixture was refluxed at 80 °C for 2 h. Upon the consumption of the starting material, 3e (determined by TLC), the solvent was evaporated under reduced pressure, and the crude residue was purified by silica gel column chromatography to give the desired alkynylated 5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-ones 5a-h. (1H-NMR and 13C-NMR of compounds 5a-h are shown in Supplementary Materials.)

2-(Phenylethynyl)-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (5a).

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 8/2) to afford 5a as a beige solid with a yield of 68%. m.p. 181–183 °C; 1H NMR (300 MHz, CDCl3): δ 7.56 (q, J = 1.4 Hz, 1H); 7.57–7.51 (m, 3H); 7.47–7.39 (m, 3H); 6.81 (s, 1H); 19F NMR (282 MHz, CDCl3): δ −67.91; 13C NMR (75 MHz, CDCl3): δ 165.1, 164.9, 134.9 (q, J = 37.8 Hz), 131.8 (2C), 130.1, 128.7 (2C), 123.3 (q, J = 3.3 Hz), 120.7, 119.0 (q, J = 274.5 Hz), 111.9 (q, J = 3.6 Hz), 110.1, 99.7, 76.0; HRMS (ESI) m/z [M+H+] calcd for C15H14F3N2O2S: 321.0304; found: 321.0300.

2-(4-Methoxyphenyl)ethynyl-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (5b).

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 8/2) to afford 5b as a beige solid with a yield of 65%. m.p. 213–215 °C; 1H NMR (300 MHz, CDCl3): δ 7.49 (d, J = 8.9 Hz, 2H); 7.46 (q, J = 1.5 Hz, 1H); 6.94 (d, J = 8.9 Hz, 2H); 6.80 (s, 1H); 3.87 (s, 1H); 19F NMR (282 MHz, CDCl3): δ −67.95; 13C NMR (75 MHz, CDCl3): δ 165.1, 164.9, 161.1, 134.8 (q, J = 37.4 Hz), 133.5 (2C), 122.7 (q, J = 3.4 Hz), 119.0 (q, J = 274.4 Hz), 114.4 (2C), 112.6, 111.8 (q, J = 3.4 Hz), 110.5, 100.1, 75.0, 55.4; HRMS (ESI) m/z [M+H+] calcd for C16H16F3N2O2S: 351.0416; found: 351.0416.

2-(4-Chlorophenyl)ethynyl-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (5c).

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 8/2) to afford 5c as a yellow solid with a yield of 58%. m.p. 243–245 °C; 1H NMR (300 MHz, CDCl3): δ 7.51 (q, J = 1.5 Hz, 1H); 7.48 (d, J = 8.7 Hz, 2H); 7.41 (d, J = 8.7 Hz, 2H); 6.81 (s, 1H); 19F NMR (282 MHz, CDCl3): δ −67.90; 13C NMR (75 MHz, CDCl3): δ 165.1, 164.8, 136.5, 134.8 (q, J = 37.5 Hz), 133.0 (2C), 129.2 (2C), 123.5 (q, J = 3.3 Hz), 119.1, 119.0 (q, J = 274.7 Hz), 111.9 (q, J = 3.7 Hz), 109.7, 98.4, 76.9; HRMS (ESI) m/z [M+H+] calcd for C16H12ClF3N2O2S: 354.9914; found: 354.9910.

2-(4-Fluorophenyl)ethynyl-5-(trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (5d).
The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 8/2) to afford 5d as a yellow solid with a yield of 85%. m.p. 203–205 °C; 1H NMR (300 MHz, CDCl3): δ 7.59 (dd, J = 8.7, 5.3 Hz, 2H), 7.50 (q, J = 1.5 Hz, 1H), 7.12 (t, J = 8.7 Hz, 2H), 6.81 (s, 1H); 13C NMR (75 MHz, CDCl3): δ 165.1, 164.8, 163.6 (d, J = 253.0 Hz), 134.9 (q, J = 37.5 Hz), 134.0, 133.9, 123.4 (q, J = 3.2 Hz), 119.0 (q, J = 274.7 Hz), 116.8 (d, J = 3.6 Hz), 116.4, 116.1, 111.9 (q, J = 3.9 Hz), 109.9, 98.5, 75.8 (d, J = 1.4 Hz); HRMS (ESI) m/z [M+H]+ calcld for C13H7F2N2O2S: 339.0210; found: 339.0207.

2-[(2-Fluorophenyl)ethynyl]-5-( trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (5e).

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 8/2) to afford 5e as a yellow solid with a yield of 68%. m.p. 176–178 °C; 1H NMR (300 MHz, CDCl3): δ 7.56–7.51 (m, 2H), 7.50–7.42 (m, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.16 (d, J = 9.2 Hz, 1H), 6.82 (s, 1H); 13C NMR (75 MHz, CDCl3): δ 165.1, 164.8, 162.8 (d, J = 254.2 Hz), 134.4 (q, J = 37.6 Hz), 133.4, 132.0 (d, J = 8.2 Hz), 123.8 (d, J = 3.8 Hz), 119.0 (q, J = 274.7 Hz), 116.0 (d, J = 20.4 Hz), 111.9 (q, J = 3.9 Hz), 109.6 (d, J = 2.5 Hz), 109.4, 93.0, 80.7 (d, J = 3.3 Hz); HRMS (ESI) m/z [M+H]+ calcld for C13H7F2N2O2S: 339.0210; found: 339.0206.

2-(Pyridin-2-ylethynyl)-5-( trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (5f).

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 6/4) to afford 5f as a brown solid with a yield of 92%. m.p. 193–195 °C; 1H NMR (300 MHz, CDCl3): δ 8.70 (s, 1H), 7.80 (td, J = 7.8, 1.5 Hz, 1H), 7.60 (q, J = 1.5 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.40–7.38 (m, 1H), 6.82 (s, 1H); 13F NMR (282 MHz, CDCl3): δ −67.92; 13C NMR (75 MHz, CDCl3): δ 165.2, 164.8, 150.5, 141.2, 136.6, 134.9 (q, J = 37.9 Hz), 127.5, 124.9 (q, J = 3.4 Hz), 124.3 (q, J = 3.4 Hz), 118.9 (q, J = 274.7 Hz), 112.0 (q, J = 3.9 Hz), 109.0, 97.9, 75.5; HRMS (ESI) m/z [M+H]+ calcld for C14H7F2N3O2S: 322.0256; found: 322.0252.

2-(Cyclohexyethylthynyl)-5-( trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (5g).

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 9/1) to afford 5g as a beige solid with a yield of 75%. m.p. 146–148 °C; 1H NMR (300 MHz, CDCl3): δ 7.34 (q, J = 1.5 Hz, 1H), 6.77 (s, 1H), 2.68–2.60 (m, 1H), 1.90–1.87 (m, 2H), 1.79–1.71 (m, 2H), 1.62–1.48 (m, 3H), 1.44–1.34 (m, 3H); 13F NMR (282 MHz, CDCl3): δ −67.97; 13C NMR (75 MHz, CDCl3): δ 165.1, 134.4 (q, J = 37.4 Hz), 128.5, 122.6 (q, J = 3.3 Hz), 119.0 (q, J = 274.5 Hz), 111.7 (q, J = 4.0 Hz), 110.9, 106.3, 67.7, 31.9 (2C), 29.9, 25.6, 24.7 (2C); HRMS (ESI) m/z [M+H]+ calcld for C15H14F2N3O2S: 327.0773, found: 327.0769.

2-(Hex-1-yn-1-yl)-5-( trifluoromethyl)-7H-thiazolo[3,2-a]pyrimidin-7-one (5h).

The purification of the crude product by chromatography on silica gel is carried out using (PE/EtOAc: 9/1) to afford 5h as a yellow solid with a yield of 55%. m.p. 145–147 °C; 1H NMR (300 MHz, CDCl3): δ 7.34 (q, J = 1.5 Hz, 1H), 6.77 (s, 1H), 2.47 (t, J = 7.2 Hz, 2H), 1.66–1.57 (m, 2H), 1.53–1.41 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H); 13F NMR (282 MHz, CDCl3): δ −67.98; 13C NMR (75 MHz, CDCl3): δ 165.1, 135.3 (q, J = 37.3 Hz), 128.5, 122.7 (q, J = 3.4 Hz), 119.0 (q, J = 274.6 Hz), 111.7 (q, J = 3.8 Hz), 110.8, 102.6, 67.8, 30.0, 22.0, 19.4, 13.5; HRMS (ESI) m/z [M+H]+ calcld for C13H11F2N2O2S: 301.0617; found: 301.0614.

4. Conclusions

In conclusion, we have developed a simple and convenient method for straightforward access to an important range of fluorinated thiazolo[3,2-a]pyrimidin-7-ones and oxazolo[3,2-a]pyrimidin-7-ones. We first established a concise one-pot strategy for the synthesis of 5-fluoroalkylated thiazolo -and oxazolo[3,2-a]pyrimidin-7-ones by condensation of 2-amino thiazole or 2-amino oxazole derivatives with fluorinated ethyl propiolates. The synthesized 2-bromo-5-trifluoromethyl thiazolo[3,2-a]pyrimidin-7-ones were used as building blocks for the synthesis of a series of new 2-arylated and 2-alkynylated thiazolo[3,2-a]pyrimidin-7-ones containing a fluoroalkyl group. A preliminary biological evaluation carried out on a few synthesized compounds on human hMAO-A and hMAO-B showed that compound 3g exhibits a selective micromolar inhibition of hMAO-A, which is a promising target in...
the symptomatic treatment and potentially disease-modifying treatment of neurodegenerative disorders.

Further exploration of this strategy and further evaluation of the biological potential of the synthesized compounds are currently under investigation in our laboratory.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/article/10.3390/molecules20093013/s1, 1H-NMR and 13C-NMR of compounds 3a-n, 4a-l, and 5a-h.

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