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Article

Microwave-Assisted Synthesis, Structure, and Preliminary Biological Evaluation of Novel 6-Methoxy-5,6-dihydro-5-azapurines

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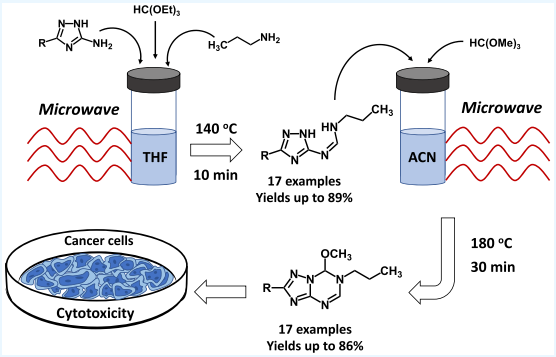
ABSTRACT: We herein disclose the microwave-assisted synthesis of previously unreported 6-methoxy-5,6-dihydro-5-azapurines, whose purine-like scaffold is promising for drug discovery. The method is simple, fast, and relies on easily accessible reagents such as trimethyl orthoformate, acetic acid, and aminotriazole-derived *N*,*N*′-disubstituted formamidines. The preliminary biological evaluation revealed that selected representatives of synthesized 6-methoxy-5,6-dihydro-5-azapurines dose-dependently reduce the viability of HepG2 and A549 cancer cells having little to no influence on five tested purinergic receptors.



INTRODUCTION

5-Azapurines or 1,2,4-triazolo[1,5-*a*][1,3,5]triazines are considered purine isosteres possessing an additional nitrogen atom in the fifth position of their bicyclic cores. The structural similarity of 5-azapurines to purines makes this scaffold promising for drug development, since the purine core is often found in developmental and clinically used drugs, such as acyclovir, mercaptopurine, diphylline, etc.[1−3] In particular, 5-azapurines are of great interest for the development of new thymidine phosphorylase inhibitors,[4] selective adenosine receptor ligands,[5−9] and antiproliferative agents[10] (e.g., compounds **1**−**3**, Figure 1). Apart from being useful in medicinal chemistry, 5-azapurines are also known as potential thermostable high-energy sources[11−14] as well as highly efficient thermally activated delayed fluorescence materials that are highly promising in the construction of new types of OLED-based displays.[15,16] Structurally related to 5-azapurines, substituted purines and purine-like compounds exhibiting 6-alkylamino or 6-alkoxy groups have also been described in the literature. These compounds are represented by, for example, alkylated nucleobases associated with mutagenesis and cancer[17−20] (e.g., **4** and **5**, Figure 1), as well as by more complex small molecules (e.g., **6**−**8**, Figure 1) exhibiting antiproliferative,[21] antiphosphodiesterase,[22] and anxiolytic[23] properties. In addition, alkylated 3,7-dihydropurine-2,6-diones (xanthines) known for their profound antagonistic activity toward adenosine receptors (e.g., **9** and **10**, Figure 1)[24−27] are also structurally related to 5-azapurines.

On the other hand, 5-azapurines containing the *s*-triazine core are structurally related to dihydrotriazines, e.g. **3**, **11** (cycloguanil), and **12**, a few known representatives of which exhibit antiproliferative and antifolate bioactivities (Figure 1).[10,28,29] Dihydrotriazines in general and 5,6-dihydro-5-azapurines, in particular, caught our attention because they feature an additional sp^3-hybridized C-atom in their triazine core that gives these compounds a certain three-dimensional complexity, potentially changing their physicochemical properties and increasing their drug-likeness.[30−35] Given that little is known about the synthesis and biological activity of 5,6-dihydro-5-azapurines, the development of new synthetic strategies toward this poorly studied class of compounds is of great interest and should allow for their further study as promising materials or drug candidates.

Synthetic approaches toward fully aromatic 5-azapurines are well-documented and often rely on 5-aminotriazole-derived formamidines, which are used as electrophilic intermediates (e.g., synthesis of **15** from **14**, Scheme 1).[36−40] In contrast, the synthesis of the 5,6-dihydro derivatives (e.g., **18**, Scheme 1) is less common and seemingly more challenging due to the tendency of the triazolotriazine core to aromatize. One example demonstrates that 6-alkylated 5,6-dihydro-5-azapurines **18** (Scheme 1) could be synthesized from amidines **17** and

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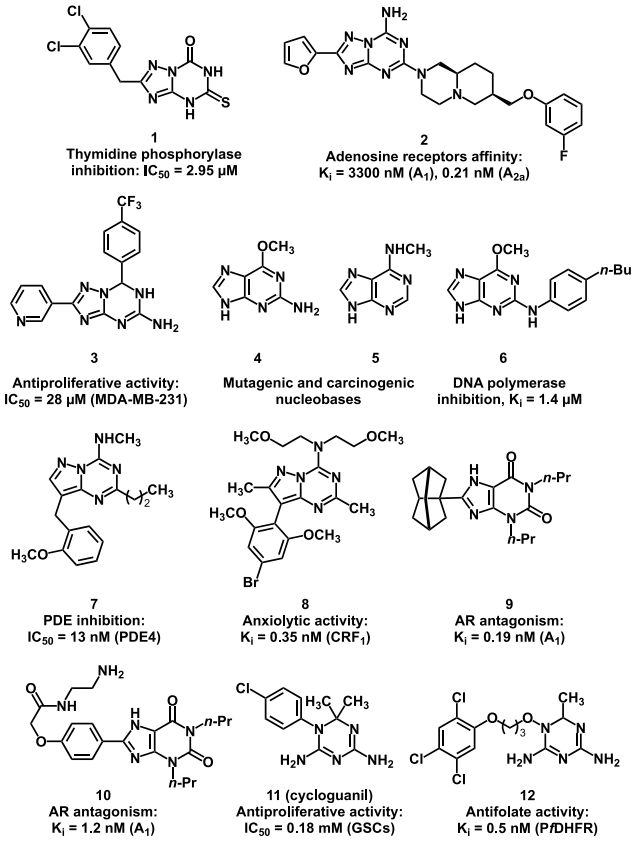
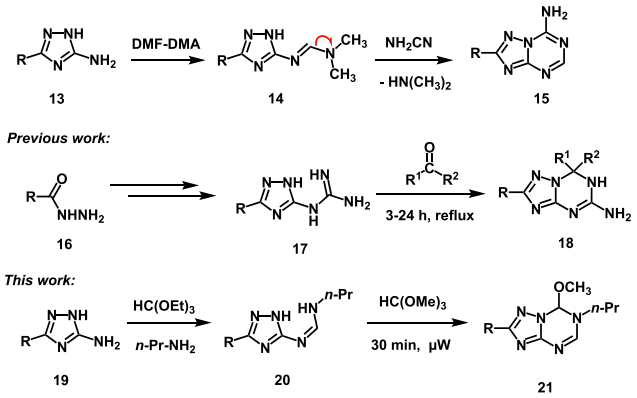


Figure 1. Exemplary structures of biologically active purines, 5-azapurines, and structurally related dihydrotriazines.

Scheme 1. Synthesis of 5-Azapurines and 5,6-Dihydro-5-azapurines



aldehydes or ketones; however, the reaction requires a prolonged reaction time (up to 24 h) under reflux conditions.[41]

In this work, we disclose a new microwave-assisted synthesis of a series of previously unreported 6-methoxy-5,6-dihydro-5-azapurines **21** (Scheme 1). The efficient synthesis of series **21** was possible due to the prior development of facile access to key intermediates formamidines **20** (Scheme 1). Additionally, we studied the cytotoxicity profile of synthesized previously unknown 6-methoxy-5,6-dihydro-5-azapurines **21** against two cancer cell lines and evaluated their affinity toward purinergic receptors.

RESULTS AND DISCUSSION

Synthesis of Aminotriazole-Based *N,N′*-Disubstituted Formamidines 20. The synthesis of 6-methoxy-5,6-dihydro-5-azapurines **21** required the synthesis of formamidines **20** as key intermediates (Scheme 1). We found that no efficient synthesis toward unsymmetrical aminotriazole-based *N,N′*-disubstituted formamidines **20** is known. Recently, we reported practical synthetic methods for 1,2,4-triazol-5-amines[42−45] that seemed to be suitable starting materials for formamidines **20**. Thereby, we initiated the development of an efficient and universal approach allowing access to desired *N,N′*-disubstituted formamidines **20.**

For this purpose, a model reaction between an alkyl orthoformate, aminotriazole **19a**, and *n*-propylamine was optimized to maximize the yield of formamidine **20a** (Table 1). The reaction was performed as a three-component one-pot procedure. At first, aminotriazole **19a** was treated with a triple excess of all reagents at 70 °C for 30 min in methanol, which resulted in a 4% yield only (entry 1, Table 1). The twofold temperature increase (140 °C) under microwave irradiation allowed us to achieve a 47% yield of **20a** (entry 2, Table 1), and the subsequent replacement of trimethyl orthoformate with triethyl orthoformate led to a further yield increase to 71% (entry 3, Table 1). Further attempts were undertaken to find a better solvent (entries 4−6, Table 1), revealing that THF and toluene give the best results with up to 92% yield, outperforming MeOH and ACN. It was interesting to check the influence of the amount of each component, as well as the minimum time required for the reaction. Thus, it was found that the presence of acetic acid is highly important, as its absence significantly reduced the yield of **20a** (36%, entry 7, Table 1). However, the amount of the acid could be reduced to 0.5 equiv without decreasing the reaction yield (95%, entry 8, Table 1). In turn, the triple excess of triethyl orthoformate and propylamine cannot be reduced without decreasing the yield (entries 8−10, Table 1).

It was interesting to observe that the reaction might be accomplished in 10 min, furnishing formamidine **20a** in a 95% yield (entry 11, Table 1), although without the excess of acetic acid this 10 min transformation was not as efficient (75%, entry 12, Table 1). The prolonged reaction time (entry 13, Table 1) did not serve any benefit, even resulting in a slight decomposition of the product. Additionally, performing the reaction at 100 °C decreased the yield more than half down to 44% (entry 14, Table 1). Finally, we were interested in attempting an extra procedure requiring no special equipment such as a microwave synthesizer because it may not be available in every laboratory. Since the high temperature appeared to be crucial, toluene was chosen as a solvent for the conventional synthesis. Under conventional heating in a sealed flask at 120 °C, the reaction required 4 h to achieve the high conversion of aminotriazole **19a** to formamidine **20a** (93%, entry 15, Table 1). No further attempts were undertaken to optimize this synthetic approach.

Hence, utilizing the optimized reaction conditions (entry 11, Table 1), a series of unsymmetrical *N,N′*-disubstituted formamidines **20a−q** were successfully synthesized (Scheme 2) and isolated with moderate (52−68% for **20c-f**, **20h**, and **20k-n**) to high yields (71−89% for **20a**, **20b**, **20g**, **20i**, **20j**, and **20o-q**). The efficacy and regioselectivity of this quick (10 min) microwave-assisted reaction is noteworthy considering the potential homoreactions possible for both aminotriazoles **19**

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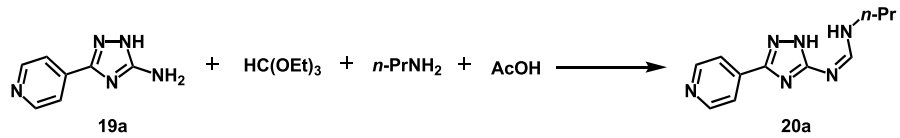
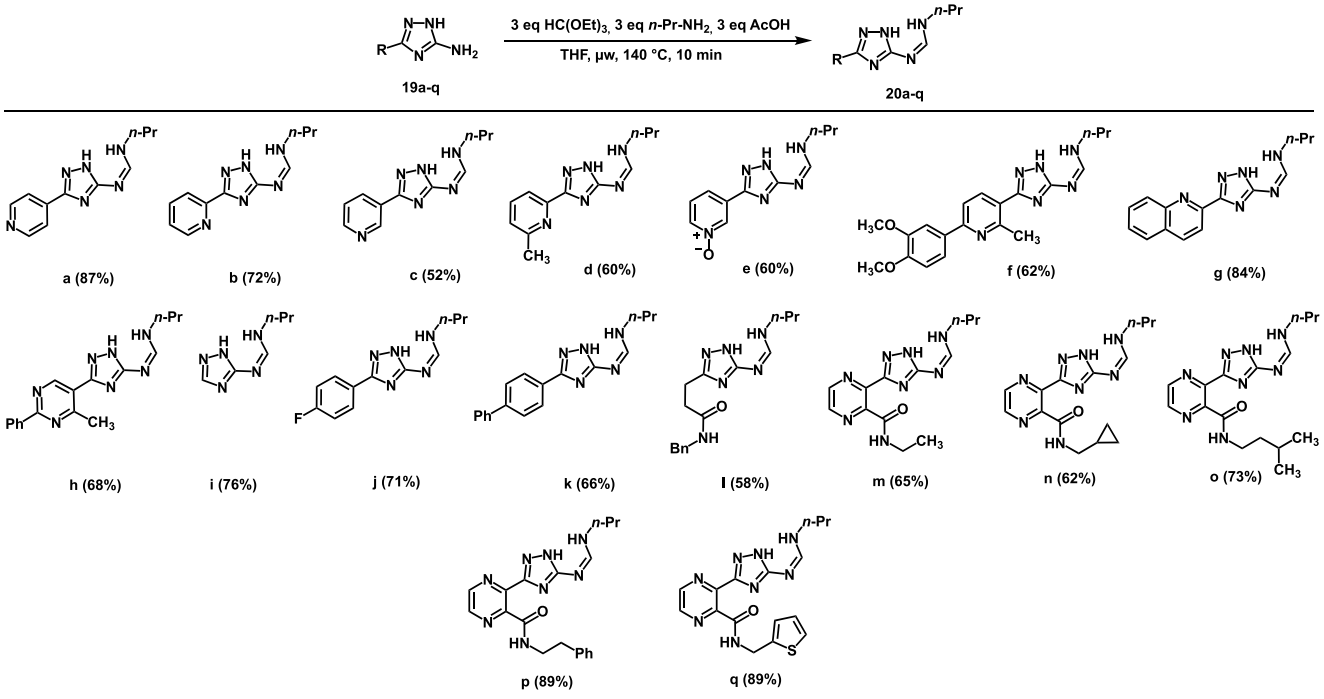
Table 1. Reaction Optimization toward Formamidine 20a[a]



no.	$HC(OEt)_3$ [equiv]	n-$PrNH_2$ [equiv]	AcOH [equiv]	solvent	T [°C]	time [min]	yield [%][b]
1	3.0[c]	3.0	3.0	MeOH	70[d]	30	4
2	3.0[c]	3.0	3.0	MeOH	140	30	47
3	3.0	3.0	3.0	MeOH	140	30	71
4	3.0	3.0	3.0	toluene	140	30	91
5	3.0	3.0	3.0	ACN	140	30	88
6	3.0	3.0	3.0	THF	140	30	92
7	3.0	3.0		THF	140	30	36
8	3.0	3.0	0.5	THF	140	30	95
9	1.0	1.0	1.0	THF	140	30	45
10	2.0	2.0	2.0	THF	140	30	85
11	**3.0**	**3.0**	**3.0**	**THF**	**140**	**10**	**95**
12	3.0	3.0	0.5	THF	140	10	75
13	3.0	3.0	3.0	THF	140	60	92
14	3.0	3.0	3.0	THF	100	30	44
15	3.0	3.0	3.0	toluene	120[e]	240	93

[a]Reaction conditions: 50 mg of **19a** (1.0 equiv, 310 μmol), alkyl orthoformate, n-propylamine, acetic acid, solvent (1 mL), and a microwave system CEM Discover. [b]HPLC analyzed yield. [c]Trimethyl orthoformate was used instead of triethyl orthoformate. [d]The reaction was performed in a sealed flask. [e]The reaction was performed with heating in a sealed flask at 120 °C.

Scheme 2. Synthesis of the Key Intermediates *N,N′*-Disubstituted Formamidines 20a−q



as well as propylamine to form undesired symmetrical formamidines.

Synthesis of 6-Methoxy-5,6-dihydro-5-azapurines 21. Having in hand reactive formamidines **20a−q**, we attempted their conversion into desired 6-methoxy-5,6-dihydro-5-azapurines **21**. For this purpose, in the model reaction, formamidine **20a** reacted with trimethyl orthoformate to form the cyclization product **21a** (Table 2). Initially, the reaction was performed neat at 150 °C for 30 min, assuming that a large excess of trimethyl orthoformate might shift the reaction equilibrium toward the product **21a**. Nevertheless, this attempt resulted only in a 37% yield of **21a** (entry 1, Table 2). Then, the amount of trimethyl orthoformate was decreased to 3 equiv, and three solvents, namely, ACN, THF, and toluene, were screened (entries 2−4, respectively), among which ACN furnished the desired product with the highest yield of 48%.

To explore the necessity of acetic acid, acid-free conditions were applied and were proved to be inefficient (1% yield, entry 5, Table 2). Decreasing the amount of acetic acid from 3 equiv to 1 equiv also resulted in a poor yield (19%, entry 6, Table 2).

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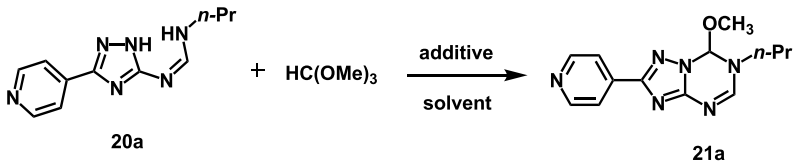
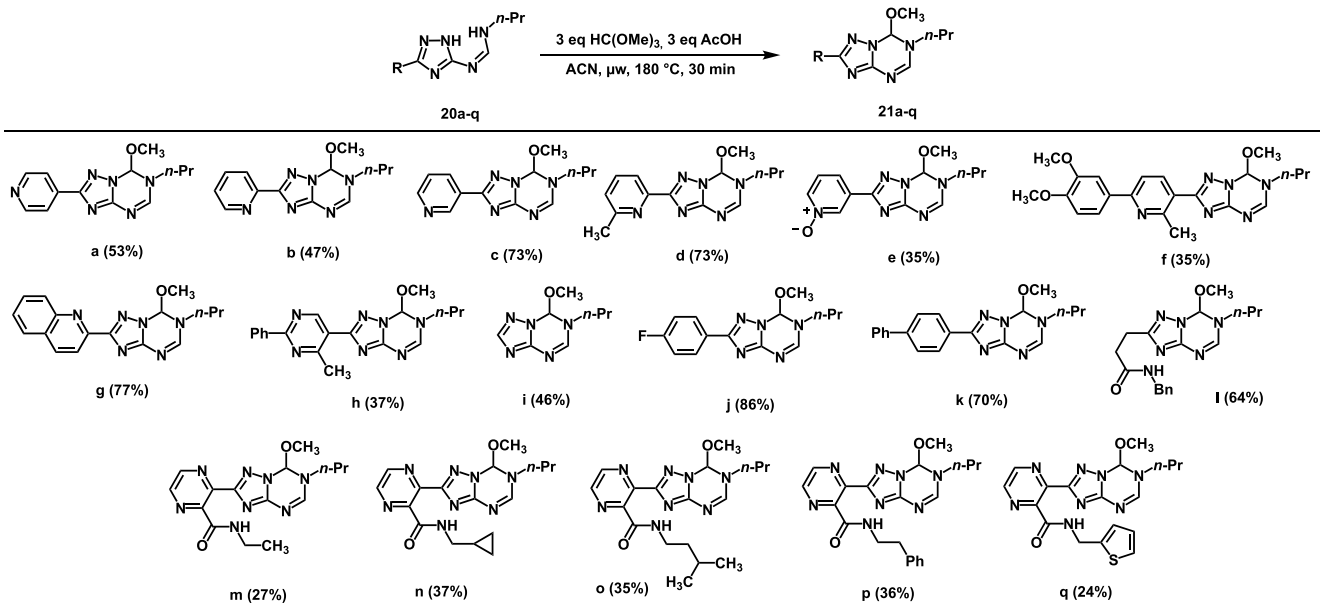
Table 2. Reaction Optimization toward 6-Methoxy-5,6-dihydro-5-azapurine 21a[a]



no.	$HC(OMe)_3$ [equiv]	additive	solvent	T [°C]	time [min]	yield [%][b]
1	42.0[c]	AcOH		150	30	37
2	3.0	AcOH	ACN	150	30	48
3	3.0	AcOH	THF	150	30	8
4	3.0	AcOH	toluene	150	30	29
5	3.0		ACN	150	30	1
6	3.0	AcOH[d]	ACN	150	30	19
7	10.0	AcOH	ACN	150	30	37
8	3.0	TFA	ACN	150	30	3
9	3.0	PTSA	ACN	150	30	0
10	3.0	HCO_2H	ACN	150	30	9
11	3.0	DIPEA	ACN	150	30	4
12	3.0	Et_3N	ACN	150	30	0
13	3.0	Cs_2CO_3	ACN	150	30	0
14	**3.0**	**AcOH**	**ACN**	**180**	**30**	**56**
15	3.0	AcOH	ACN	100	30	1
16	2.0	AcOH[e]	ACN	180	30	11
17	3.0	AcOH	ACN	180	40	35
18	3.0	AcOH	ACN	180	20	49

[a]Reaction conditions: 25 mg of **20a** (1.0 equiv, 109 μmol), trimethyl orthoformate, additive (3.0 equiv), solvent (1 mL), and a microwave system CEM Discover; [b]HPLC analyzed yield. [c]The reaction was performed neat. [d]1.0 equiv of AcOH was used. [e]2.0 equiv of AcOH was used.

Scheme 3. Synthesis of 6-Methoxy-5,6-dihydro-5-azapurines 21



Another attempt to shift the reaction equilibrium to the right with the large excess of the orthoester also resulted in a relatively low yield (37%, entry 7, Table 2). We also screened alternative acids such as TFA, formic acid, and PTSA (entries 8−10, respectively, Table 2) as well as bases DIPEA, Et_3N, and Cs_2CO_3 (entries 11−13, respectively, Table 2) in an attempt to improve the reaction yield. Nevertheless, acetic acid remained the best option ensuring the highest yield of 5,6-dihydro-5-azapurine **21a**. Increasing the temperature to 180 °C (entry 14, Table 2) further improved the reaction yield up to 56%, whereas lowering the temperature (100 °C, entry 15, Table 2) resulted in only traces of the product. An attempt to decrease the equivalents of the orthoester and acetic acid decreased the reaction yield (yield 11%, entry 16, Table 2). The reaction time of 30 min appeared to be optimal, as 20 min was not sufficient for efficient formation of product **21a** (yield 35%, entry 17, Table 2) and 40 min of reaction resulted in a partial decomposition of the product (yield 49%, entry 18, Table 2).

Applying optimized reaction conditions (entry 14, Table 2), a series of 6-methoxy-5,6-dihydro-5-azapurines **21a−q** were

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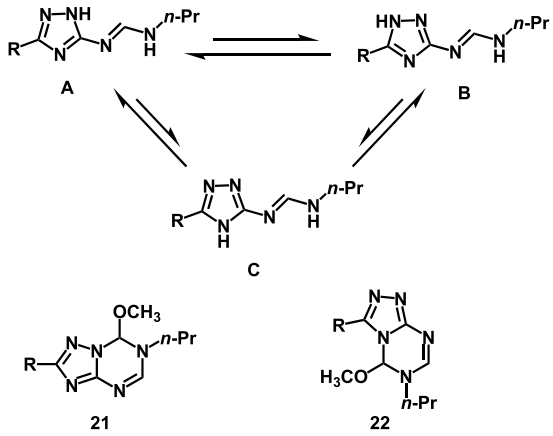
ACS Omega XXXX, XXX, XXX−XXX

synthesized (Scheme 3). Except for the model compound **21i**, having no substituent in the 8-position of its 5,6-dihydro-5-azapurine scaffold, all other synthesized compounds were 8-substituted. The scope of the substituents in the 8-position was represented by aromatic, heteroaromatic, and aliphatic residues (Scheme 3). Among them, 8-(hetero)aryl-substituted 5,6-dihydro-5-azapurines **17c**, **17d**, **17g**, **17j**, and **17k** were isolated with high yields between 70% and 86%. More complex substrates, e.g., comprising labile amide functional groups, where also successfully formed but isolated with lower yields (Scheme 3).

X-ray Crystal Structure of 6-Methoxy-5,6-dihydro-5-azapurines. It is reported that 1,2,4-triazol-5-amines exhibit annular tautomerism, existing in three main tautomeric forms A, B, and C (Scheme 4), of which forms A and B are typically

Scheme 4. Annular Tautomerism of 1,2,4-Triazol-5-amines (Tautomers A−C) and Two Cyclization Products 21 and 22 Potentially Arising from Tautomeric Forms A and C



prevalent.[38,46] Although tautomeric form C is most likely the least abundant form of formamidines **20**, its presence might complicate the subsequent cyclization step. Thus, instead of (or in addition to) the desired 5,6-dihydro-5-azapurines **21**, their regioisomers **22** could theoretically be formed (Scheme 4).

Therefore, to unambiguously confirm the structure of previously unreported 6-methoxy-5,6-dihydro-5-azapurines **21** and get insight into their three-dimensional properties, X-ray crystal structures of representative compounds **21c** and **21j** were recorded (Figure 2).

According to both crystal structures, the cyclization indeed took place and the ring closure occurred at the annular N^1-atom of tautomer A (Scheme 4, Figure 2) to form the desired 6-methoxy-5,6-dihydro-5-azapurine core. Data analysis also showed that crystals of both compounds are formed by (*R*)- and (*S*)-configured molecules, indicating that compounds **21** were synthesized as a mixture of enantiomers. In addition, other structure-specific characteristics of compounds **21c** and **21j** were noted. In particular, the X-ray crystal structures revealed that the pyridyl moiety of **21c** is nearly coplanar to the triazole ring (deviation from coplanarity ca. 7°), whereas the fluorophenyl ring of **21j** is not coplanar with respect to the triazole moiety, experiencing an offset of about 20° for molecule "A" and 11° for molecule "B". The dihydrotriazine ring of both compounds shows the tendency to adopt a half-chair conformation, although this conformation is less distorted in the case of compound **21c** (C4 distance from planarity of 0.18

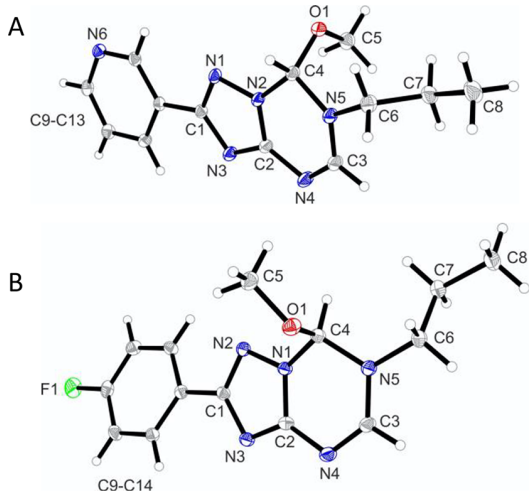


Figure 2. (A) X-ray crystal structure of **21c** displaying the thermal ellipsoids at the 30% probability level. (B) X-ray crystal structure of **21j** displaying the thermal ellipsoids at the 30% probability level. Only one molecule of two found in the asymmetric unit of compound **21j** is shown.

Å), which is probably due to the intermolecular interactions observed in its crystal structure (see the Supporting Information).

Cytotoxicity of 5,6-Dihydro-5-azapurines 21 to Cancer Cell Lines and Their Screening against Purinergic Receptors. As synthesized 5,6-dihydro-5-azapurines **21** share structural similarity with previously reported (aza)purines and dihydrotriazines exhibiting cytotoxic and antiproliferative activities,[10,29,47,48] it was interesting to evaluate their cytotoxicity profile against cancer cell lines. For this purpose, compounds **21a−q** were screened for their potential cytotoxicity toward human liver HepG2 cancer cell line as well as human lung adenocarcinoma cells A549 (Table 3). The initial screening revealed that compounds tested at 10 μM demonstrated low to moderate cytotoxicity against both cell lines compared to the positive control. Interestingly, compound **21f**, which contains one of the most bulky substituents in the 8-position of its 5,6-dihydro-5-azapurine scaffold, as well as derivative **21i**, which has no substituent in the 8-position, showed the most pronounced cytotoxic effects, similarly affecting both cancer cell lines (Table 3). We therefore studied multiple doses of compounds **21f** and **21i** to determine the IC_{50} values (Figure 3). Performed tests showed that **21f** reduced A549 and HepG2 cell viability with IC_{50} values of 9 and 7 μM, respectively, whereas **21i** showed an IC_{50} value of 12 μM against both cell lines (Figure 3).

Multiple studies have suggested that purinergic receptors are involved in the coordination of cell proliferation and cell apoptosis; thus, ligands modulating purinergic receptors find application as anticancer agents.[49−53] Considering that synthesized 5,6-dihydro-5-azapurines **21**, on the one hand, are structurally similar to adenosine receptor antagonists (Figure 1) and, on the other hand, influence cancer cell viability (Table 3, Figure 3), it was logical to test compounds **21** against human purinergic receptors. Therefore, compounds **21** were tested at 1 μM in radioligand displacement experiments against four subtypes of adenosine receptors, namely, A_1, A_{2A}, A_{2B}, and A_3, as previously reported (Figure S7 and Table S3, Supporting Information).[54] In addition, compounds were screened at 10 μM against P2X7R purinergic receptors in an YO-PRO-1 uptake

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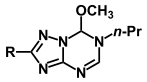
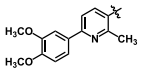
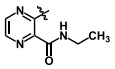
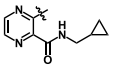
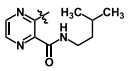
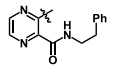
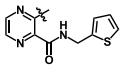
Table 3. Cytotoxicity Profile of Synthesized 6-Methoxy-5,6-dihydro-5-azapurines 21a−q[a]



Cmpd	R	Cell viability, % ± SD	
		HepG2 cells	A549 cells
21a		89 ± 10	83 ± 6*
21b		98 ± 2	86 ± 2**
21c		85 ± 15	70 ± 5**
21d		92 ± 13	80 ± 13
21e		83 ± 10	65 ± 14*
21f		59 ± 13**	52 ± 8***
21g		91 ± 12	81 ± 10*
21h		84 ± 13	80 ± 9*
21i		65 ± 5***	64 ± 3***
21j		98 ± 2	90 ± 5*
21k		91 ± 11	68 ± 6***
21l		96 ± 5	88 ± 10
21m		80 ± 15	61 ± 12**
21n		80 ± 11*	64 ± 7**
21o		88 ± 5*	69 ± 9**
21p		90 ± 9	85 ± 7*
21q		84 ± 8*	63 ± 10**
DMSO		98 ± 2	99 ± 2
Camptothecin		9 ± 1***	8 ± 1***

[a]Compounds were tested at 10 μM, camptothecin (5 μM) was used as a positive control, and DMSO (2%) was used as a negative control. Tests were performed in triplicate, and the mean ± SD is shown; *p < 0.05. **p < 0.01. ***p < 0.001 compared to DMSO.

assay[55] (Figure S8, Supporting Information). Performed experiments, however, revealed that synthesized 5,6-dihydro-5-azapurines **21** have little to no affinity/inhibitory activity toward these five purinergic receptors. This implies that the observed cytotoxic effects of compounds **21f** and **21i** against HepG2 and A549 cancer cells most likely are associated with cellular targets other than purinergic receptors.

CONCLUSIONS

In conclusion, we developed the first microwave-assisted synthesis of previously unreported 6-methoxy-5,6-dihydro-5-azapurines **21**. The method is simple and fast and relies on easily accessible reagents such as trimethyl orthoformate, acetic acid,

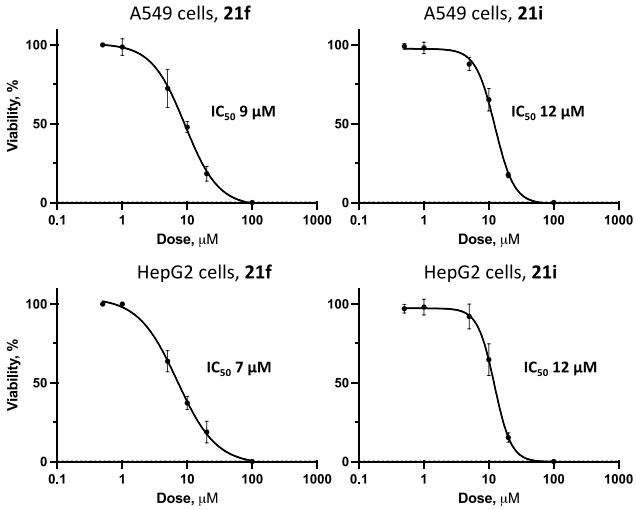


Figure 3. Sigmoidal curves obtained in the resazurin assay showing IC_{50} values for synthesized compounds **21f** and **21i** in HepG2 and A549 cancer cells. Each data point represents an average of three independent experiments with SD.

and formamidines **20**, which in turn are easily obtained from 1,2,4-triazol-5-amines. The robustness of this synthetic approach should allow the development of broad libraries of compounds **21**, whose purine-like scaffold is promising for drug discovery. To get the first insight into the biological properties of 5,6-dihydro-5-azapurines **21**, we studied their cytotoxicity profiles against two cancer cell-lines and evaluated their affinity at five purinergic receptors. It was found that selected representatives of this new series of compounds dose-dependently reduce the viability of HepG2 and A549 cancer cells while having little to no influence on the investigated purinergic receptors.

EXPERIMENTAL SECTION

Chemistry, General. Unless otherwise specified, for melting point (m.p.) measurements, an SMP3 (melting point apparatus, Stuart Scientific) instrument was used. Thin-layer chromatography (TLC) was performed with silica gel 60 F254 plates (Merck). Flash chromatography was performed with silica gel 60, 40−63 μm (Macherey-Nagel). For automatic flash column chromatography, an Isolera One (Biotage, Sweden) system was used; brackets include eluent and cartridge-type. ^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) were performed with an Agilent DD2 600 MHz spectrometer; chemical shifts (δ) are reported in ppm against TMS and calculated using the solvent residual peak of the undeuterated solvent. IR was performed with an IR Prestige-21 (Shimadzu) spectrometer. HRMS was performed with a MicrOTOF-QII (Bruker) instrument. The HPLC method to determine the purity of compounds, as well as the yields in method development procedures, is as follows: equipment 1, pump L-7100, degasser L-7614, autosampler L-7200, UV detector L-7400, interface D-7000, data transfer D-line, data acquisition HSMS software (LaChrom, Merck Hitachi); equipment 2, pump LPG-3400SD, degasser DG-1210, autosampler ACC-3000T, UV detector VWD-3400RS, interface Dionex UltiMate 3000, data acquisition Chromeleon 7 (Thermo Fisher Scientific); LiChrospher 60 RPselect B (5 μm) column, LiChroCART 250−4 mm cartridge; flow rate 1.0 mL/min; injection volume 5.0 μL; detection at λ = 210 nm; solvents A (demineralized water with 0.05% (v/v) trifluoroacetic acid)

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ACS Omega XXXX, XXX, XXX−XXX

and B (acetonitrile with 0.05% (v/v) trifluoroacetic acid); gradient elution (% A), 0−4 min 90%, 4−29 min gradient from 90 to 0%, 29−31 min 0%, 31−31.5 min gradient from 0 to 90%, and 31.5−40 min 90%.[42] The purity of compounds **21l−q** was analyzed without trifluoroacetic acid addition to solvents. The purity of all test compounds was greater than 95%.

General Procedure A. A mixture of respective 1,2,4-triazol-5-amine **19** (1.0 equiv), triethyl orthoformate (3.0 equiv), *n*-propylamine (3.0 equiv), and acetic acid (3.0 equiv) in THF (1−2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operated at maximal microwave power up to 180 W at 140 °C for 10 min. After cooling, the reaction mixture was concentrated under reduced pressure. The residue (**20a−c**, **20f**, **20g**, **20j−l**) was recrystallized from ACN (1 mL). After cooling in the fridge, a precipitate was filtered off, washed with cold ACN (1 mL), and dried in vacuo. In other cases, the residue was purified by flash column chromatography yielding formamidines **20**.

General Procedure B. A mixture of respective formamidine **20** (1.0 equiv), trimethyl orthoformate (3.0 equiv), and acetic acid (3.0 equiv) in ACN (1.3−2.7 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operated at maximal microwave power up to 180 W at 180 °C for 30 min. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography, yielding 6-methoxy-5,6-dihydro-5-azapurines **21**.

*N-Propyl-N′-(3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)-formamidine (**20a**).* According to general procedure A, a mixture of aminotriazole **19a** (100 mg, 620 μmol), triethyl orthoformate (310 μL, 1.86 mmol), *n*-propylamine (153 μL, 1.86 mmol), and acetic acid (107 μL, 1.86 mmol) in THF (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. The recrystallization of the crude yielded a colorless solid (124 mg, 540 μmol, 87%). m.p.: 212.3 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.91 (t, J = 7.4 Hz, 3H, 3-H$_{propyl}$), 1.53−1.60 (m, 2H, 2-H$_{propyl}$), 3.27 (dd, J = 12.8, 6.9 Hz, 2H, 1-H$_{propyl}$), 7.84 (dd, J = 4.5, 1.6 Hz, 2H, 3/5-H$_{pyridyl}$), 8.04 (d, J = 4.4 Hz, 1H, NH$_{formamidine}$), 8.46 (d, J = 4.5 Hz, 1H, CH), 8.61 (dd, J = 4.4, 1.6 Hz, 2H, 2/6-H$_{pyridyl}$), 13.22 (br s, 1H, NH$_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11.4 (1C, C-3$_{propyl}$), 21.5 (1C, C-2$_{propyl}$), 42.0 (1C, C-1$_{propyl}$), 119.7 (2C, C-3/5$_{pyridyl}$), 139.2 (1C, C-4$_{pyridyl}$), 150.0 (2C, C-2/6$_{pyridyl}$), 155.2 (1C, CH), 156.8 (1C, C-3$_{triazole}$), 162.0 (1C, C-5$_{triazole}$). IR (neat) ν [cm^{-1}] = 3661, 3217, 2978, 2886, 2832, 2160 2033, 1609, 1574, 1462, 1404, 1331, 1296, 1258, 1061, 833, 752, 706, 625. HRMS (APCI): m/z = 231.1353 calculated for [M + H]$^+$, found 231.1372.

*N-Propyl-N′-(3-(pyridin-2-yl)-1H-1,2,4-triazol-5-yl)-formamidine (**20b**).* According to general procedure A, a mixture of aminotriazole **19b** (100 mg, 620 μmol), triethyl orthoformate (310 μL, 1.86 mmol), *n*-propylamine (153 μL, 1.86 mmol), and acetic acid (107 μL, 1.86 mmol) in THF (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. The recrystallization of the crude yielded a colorless solid (103 mg, 449 μmol, 72%). m.p.: 207.7 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.92 (t, J = 7.4 Hz, 3H, 3-H$_{propyl}$), 1.53−1.61 (m, 2H, 2-H$_{propyl}$), 3.26 (dd, J = 12.9, 6.7 Hz, 2H, 1-H$_{propyl}$), 7.36 (s, 1H, 5-H$_{pyridyl}$), 7.84 (s, 1H, 4-H$_{pyridyl}$), 7.98 (d, J = 7.9 Hz, 1H, 3-H$_{pyridyl}$), 7.98 (br s, 1H, NH$_{formamidine}$), 8.46 (s, 1H, CH), 8.60 (d, J = 3.5 Hz, 1H, 6-H$_{pyridyl}$), 13.07 (br s, 1H, NH$_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11.4 (1C, C-3$_{propyl}$), 21.6 (1C, C-2$_{propyl}$), 42.0 (1C, C-1$_{propyl}$), 121.0 (1C, C-3$_{pyridyl}$), 123.3 (1C, C-5$_{pyridyl}$), 136.7 (1C, C-4$_{pyridyl}$), 149.2 (1C, C-6$_{pyridyl}$), 150.8 (1C, C-2$_{pyridyl}$), 154.9 (1C, CH), 159.0 (1C, C-3$_{triazole}$), 161.6 (1C, C-5$_{triazole}$). IR (neat) ν [cm^{-1}] = 3649, 3244, 3159, 3063, 2978, 2886, 2797, 2307, 2160, 2025, 1690, 1612, 1555, 1458, 1392, 1323, 1246, 1088, 1057, 953, 795, 741. HRMS (APCI): m/z = 231.1353 calculated for [M + H]$^+$, found 231.1357.

*N-Propyl-N′-(3-(pyridin-3-yl)-1H-1,2,4-triazol-5-yl)-formamidine (**20c**).* According to general procedure A, a mixture of aminotriazole **19c** (100 mg, 620 μmol), triethyl orthoformate (310 μL, 1.86 mmol), *n*-propylamine (153 μL, 1.86 mmol), and acetic acid (107 μL, 1.86 mmol) in THF (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. The recrystallization of the crude yielded a colorless solid (75 mg, 325 μmol, 52%). m.p.: 217.9 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.92 (t, J = 7.4 Hz, 3H, 3-H$_{propyl}$), 1.53−1.60 (m, 2H, 2-H$_{propyl}$), 3.27 (dd, J = 12.8, 6.9 Hz, 2H, 1-H$_{propyl}$), 7.44 (dd, J = 7.9, 4.8 Hz, 1H, 5-H$_{pyridyl}$), 8.01 (s, 1H, NH$_{formamidine}$), 8.22−8.26 (m, 1H, 4-H$_{pyridyl}$), 8.47 (d, J = 4.5 Hz, 1H, CH), 8.55 (dd, J = 4.8, 1.7 Hz, 1H, 6-H$_{pyridyl}$), 9.11 (dd, J = 2.2, 0.8 Hz, 1H, 2-H$_{pyridyl}$), 13.09 (br s, 1H, NH$_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11.4 (1C, C-3$_{propyl}$), 21.5 (1C, C-2$_{propyl}$), 42.0 (1C, C-1$_{propyl}$), 123.7 (1C, C-5$_{pyridyl}$), 128.0 (1C, C-3$_{pyridyl}$), 132.6 (1C, C-4$_{pyridyl}$), 146.6 (1C, C-2$_{pyridyl}$), 149.3 (1C, C-6$_{pyridyl}$), 155.1 (1C, CH), 156.5 (1C, C-3$_{triazole}$), 161.8 (1C, C-5$_{triazole}$). IR (neat) ν [cm^{-1}] = 3661, 3221, 3148, 2978, 2928, 2878, 2839, 2797, 2666, 2160, 2010, 1612, 1562, 1474, 1396, 1327, 1258, 980, 837, 752, 698, 633. HRMS (APCI): m/z = 231.1353 calculated for [M + H]$^+$, found 231.1364.

*N′-(3-(6-Methylpyridin-2-yl)-1H-1,2,4-triazol-5-yl)-N-propylformamidine (**20d**).* According to general procedure A, a mixture of aminotriazole **19d** (109 mg, 620 μmol), triethyl orthoformate (310 μL, 1.86 mmol), *n*-propylamine (153 μL, 1.86 mmol), and acetic acid (107 μL, 1.86 mmol) in THF (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (90 mg, 369 μmol, 60%). m.p.: 191.8 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.92 (t, J = 7.4 Hz, 3H, 3-H$_{propyl}$), 1.53−1.60 (m, 2H, 2-H$_{propyl}$), 2.50 (s, 3H, CH$_3$), 3.26 (dd, J = 12.8, 6.9 Hz, 2H, 1-H$_{propyl}$), 7.22 (d, J = 7.5 Hz, 1H, 5-H$_{pyridyl}$), 7.72 (t, J = 7.6 Hz, 1H, 4-H$_{pyridyl}$), 7.78 (d, J = 7.7 Hz, 1H, 3-H$_{pyridyl}$), 7.92 (br s, 1H, NH$_{formamidine}$), 8.46 (d, J = 4.0 Hz, 1H, CH), 13.07 (br s, 1H, NH$_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11.4 (1C, C-3$_{propyl}$), 21.6 (1C, C-2$_{propyl}$), 24.1 (1C, CH$_3$), 41.9 (1C, C-1$_{propyl}$), 118.2 (1C, C-3$_{pyridyl}$), 122.7 (1C, C-5$_{pyridyl}$), 136.8 (1C, C-4$_{pyridyl}$), 150.1 (1C, C-6$_{pyridyl}$), 154.8 (1C, CH), 157.5 (1C, C-2$_{pyridyl}$), 158.9 (1C, C-3$_{triazole}$), 162.3 (1C, C-5$_{triazole}$). IR (neat) ν [cm^{-1}] = 3229, 3051, 2967, 2924, 2874, 2785, 2164, 2033, 1971, 1616, 1570, 1504, 1412, 1377, 1335, 1308, 1254, 1188, 802, 756, 633. HRMS (APCI): m/z = 245.1509 calculated for [M + H]$^+$, found 245.1550.

*3-(5-(((Propylamino)methylene)amino)-1H-1,2,4-triazol-3-yl)pyridine 1-Oxide (**20e**).* According to general procedure A, a mixture of aminotriazole **19e** (110 mg, 620 μmol), triethyl orthoformate (310 μL, 1.86 mmol), *n*-propylamine (153 μL, 1.86 mmol), and acetic acid (107 μL, 1.86 mmol) in THF (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. Flash column chromatography (DCM/MeOH = 100/0 → 85/15) yielded a colorless solid (92 mg, 374 μmol, 60%). m.p.: 200.3 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.91 (t, J = 7.4 Hz, 3H, 3-H$_{propyl}$), 1.53−1.59 (m, 2H,

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ACS Omega XXXX, XXX, XXX−XXX

2-H_{propyl}), 3.26 (dd, J = 12.8, 6.9 Hz, 2H, 1-H_{propyl}), 7.47 (dd, J = 8.0, 6.4 Hz, 1H, 5-$H_{pyridyl}$), 7.79 (ddd, J = 8.0, 1.5, 1.0 Hz, 1H, 4-$H_{pyridyl}$), 8.09 (dd, J = 9.9, 5.0 Hz, 1H, $NH_{formamidine}$), 8.21 (ddd, J = 6.4, 1.8, 1.0 Hz, 1H, 6-$H_{pyridyl}$), 8.44 (d, J = 4.6 Hz, 1H, CH), 8.54 (t, J = 1.6 Hz, 1H, 2-$H_{pyridyl}$), 13.25 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11.4 (1C, C-3_{propyl}), 21.5 (1C, C-2_{propyl}), 42.0 (1C, C-1_{propyl}), 121.7 (1C, C-$4_{pyridyl}$), 126.7 (1C, C-$5_{pyridyl}$), 131.4 (1C, C-$3_{pyridyl}$), 135.2 (1C, C-$2_{pyridyl}$), 138.3 (1C, C-$6_{pyridyl}$), 154.6 (1C, C-$3_{triazole}$), 155.3 (1C, CH), 162.1 (1C, C-$5_{triazole}$). IR (neat) ν [cm^{-1}] = 3229, 3063, 2967, 2882, 2824, 2801, 2658, 2156, 1975, 1612, 1470, 1400, 1285, 1231, 1103, 810, 756, 675, 629. HRMS (APCI): m/z = 264.0880 calculated for $[M + H]^+$, found 247.1302.

*N′-(3-(6-(3,4-Dimethoxyphenyl)-2-methylpyridin-3-yl)-1H-1,2,4-triazol-5-yl)-N-propylformamidine (**20f**).* According to general procedure A, a mixture of aminotriazole **19f** (97 mg, 310 μmol), triethyl orthoformate (155 μL, 930 μmol), *n*-propylamine (77 μL, 930 μmol), and acetic acid (53 μL, 930 μmol) in THF (1 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. The recrystallization of the crude yielded a colorless solid (73 mg, 192 μmol, 62%). m.p.: 192.8 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.92 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.54−1.61 (m, 2H, 2-H_{propyl}), 2.86 (s, 3H, CH_3), 3.28 (dd, J = 12.8, 6.8 Hz, 2H, 1-H_{propyl}), 3.82 (s, 3H, 4-OCH_3), 3.87 (s, 3H, 3-OCH_3), 7.06 (d, J = 8.5 Hz, 1H, 5-$H_{dimethoxyphenyl}$), 7.69 (dd, J = 8.4, 2.1 Hz, 1H, 6-$H_{dimethoxyphenyl}$), 7.74 (d, J = 2.0 Hz, 1H, 2-$H_{dimethoxyphenyl}$), 7.82 (d, J = 8.3 Hz, 1H, 5-$H_{methylpyridyl}$), 7.97 (d, J = 4.6 Hz, 1H, $NH_{formamidine}$), 8.27 (d, J = 8.2 Hz, 1H, 4-$H_{methylpyridyl}$), 8.48 (d, J = 4.5 Hz, 1H, CH), 13.07 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11. Four (1C, C-3_{propyl}), 21.5 (1C, C-2_{propyl}), 25.4 (1C, CH_3), 42.0 (1C, C-1_{propyl}), 55.5 (2C, 3/4-OCH_3), 109.8 (1C, C-$2_{dimethoxyphenyl}$), 111.7 (1C, C-$5_{dimethoxyphenyl}$), 116.6 (1C, C-$5_{methylpyridyl}$), 119.2 (1C, C-$6_{dimethoxyphenyl}$), 124.5 (1C, C-$3_{methylpyridyl}$), 131.1 (1C, C-$1_{dimethoxyphenyl}$), 136.8 (1C, C-$4_{methylpyridyl}$), 148.9 (1C, C-$3_{dimethoxyphenyl}$), 149.8 (1C, C-$4_{dimethoxyphenyl}$), 153.9 (1C, C-$6_{methylpyridyl}$), 155.0 (1C, CH), 155.1 (1C, C-$2_{methylpyridyl}$), 157.9 (1C, C-$3_{triazole}$), 161.2 (1C, C-$5_{triazole}$). IR (neat) ν [cm^{-1}] = 3665, 3298, 3156, 3071, 3040, 2978, 2909, 2835, 2797, 1581, 1512, 1462, 1381, 1296, 1273, 1246, 1227, 1142, 1084, 1026, 810, 648. HRMS (APCI): m/z = 381.2034 calculated for $[M + H]^+$, found 381.2129.

*N-Propyl-N′-(3-(quinolin-2-yl)-1H-1,2,4-triazol-5-yl)-formamidine (**20g**).* According to general procedure A, a mixture of aminotriazole **19g** (131 mg, 620 μmol), triethyl orthoformate (310 μL, 1.86 mmol), *n*-propylamine (153 μL, 1.86 mmol), and acetic acid (107 μL, 1.86 mmol) in THF (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. The recrystallization of the crude yielded a light beige solid (147 mg, 523 μmol, 84%). m.p.: 221.0 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.93 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.55−1.62 (m, 2H, 2-H_{propyl}), 3.29 (dd, J = 12.8, 6.9 Hz, 2H, 1-H_{propyl}), 7.62−7.58 (m, 1H, 7-$H_{quinolinyl}$), 7.80−7.76 (m, 1H, 6-$H_{quinolinyl}$), 7.98 (d, J = 7.4 Hz, 1H, 8z-$H_{quinolinyl}$), 8.02 (br s, 1H, $NH_{formamidine}$), 8.07 (d, J = 8.2 Hz, 1H, 5-$H_{quinolinyl}$), 8.17 (d, J = 8.6 Hz, 1H, 4-$H_{quinolinyl}$), 8.40 (d, J = 8.6 Hz, 1H, 3-$H_{quinolinyl}$), 8.54 (d, J = 4.3 Hz, 1H, CH), 13.26 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11.4 (1C, C-3_{propyl}), 21.6 (1C, C-2_{propyl}), 42.0 (1C, C-1_{propyl}), 119.4 (1C, C-$4_{quinolinyl}$), 126.5 (1C, C-$7_{quinolinyl}$), 127.4 (1C, C-$2_{quinolinyl}$), 127.9 (1C, C-$8_{quinolinyl}$), 129.0 (1C, C-$5_{quinolinyl}$), 129.8 (1C, C-$6_{quinolinyl}$), 136.5 (1C, C-$3_{quinolinyl}$), 147.4 (1C, C-$4a_{quinolinyl}$), 150.6 (1C, C-$3_{triazole}$), 155.1 (1C, CH), 160.9 (1C, C-$5_{triazole}$). IR (neat) ν [cm^{-1}] = 3653, 3210, 3152, 3044, 2978, 2928, 2886, 2797, 2662, 2160, 2025, 1975, 1697, 1558, 1450, 1404, 1342, 1292, 1250, 1107, 1061, 999, 837, 764, 721, 644. HRMS (APCI): m/z = 281.1509 calculated for $[M + H]^+$, found 281.1520.

*N′-(3-(4-Methyl-2-phenylpyrimidin-5-yl)-1H-1,2,4-triazol-5-yl)-N-propylformamidine (**20h**).* According to general procedure A, a mixture of aminotriazole **19h** (78 mg, 310 μmol), triethyl orthoformate (155 μL, 930 μmol), *n*-propylamine (77 μL, 930 μmol), and acetic acid (53 μL, 930 μmol) in THF (1 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. The recrystallization of the crude yielded a colorless solid (68 mg, 212 μmol, 68%). m.p.: 179.2 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.93 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.55−1.61 (m, 2H, 2-H_{propyl}), 2.89 (s, 3H, CH_3), 3.28 (dd, J = 12.8, 6.9 Hz, 2H, 1-H_{propyl}), 7.53 (tt, J = 2.7, 1.8 Hz, 3H, 3/4/5-H_{phenyl}), 8.05 (dd, J = 10.2, 5.2 Hz, 1H, $NH_{formamidine}$), 8.43−8.46 (m, 2H, 2/6-H_{phenyl}), 8.49 (d, J = 4.5 Hz, 1H, CH), 9.26 (s, 1H, 6-$H_{pyrimidinyl}$), 13.19 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11. Four (1C, C-3_{propyl}), 21.5 (1C, C-2_{propyl}), 24.6 (1C, C−CH_3), 42.0 (1C, C-1_{propyl}), 122.7 (1C, C-$5_{pyrimidinyl}$), 127.7 (2C, C-2/6_{phenyl}), 128.6 (2C, C-3/5_{phenyl}), 130.7 (1C, C-4_{phenyl}), 136.9 (1C, C-1_{phenyl}), 155.3 (1C, CH), 155.6 (1C, C-$4_{pyrimidinyl}$), 156.1 (1C, C-$6_{pyrimidinyl}$), 161.5 (1C, C-$2_{pyrimidinyl}$), 161.5 (1C, C-$5_{triazole}$), 164.2 (1C, C-$3_{triazole}$). IR (neat) ν [cm^{-1}] = 3642, 3159, 3063, 2970, 2932, 2882, 2801, 1570, 1539, 1393, 1304, 1242, 814, 760, 687, 629. HRMS (APCI): m/z = 322.1775 calculated for $[M + H]^+$, found 322.1848.

*N-Propyl-N′-(1H-1,2,4-triazol-5-yl)formamidine (**20i**).* According to general procedure A, a mixture of aminotriazole **19i** (52 mg, 620 μmol), triethyl orthoformate (310 μL, 1.86 mmol), *n*-propylamine (153 μL, 1.86 mmol), and acetic acid (107 μL, 1.86 mmol) in THF (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. Flash column chromatography (EA/MeOH = 100/0 → 85/15) yielded a colorless solid (72 mg, 469 μmol, 76%). m.p.: 111.2 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.90 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.50−1.57 (m, 2H, 2-H_{propyl}), 3.22 (dd, J = 12.8, 6.9 Hz, 2H, 1-H_{propyl}), 7.53 (br s, 1H, H-$3_{triazole}$), 7.83 (br s, 1H, $NH_{formamidine}$), 8.35 (d, J = 4.4 Hz, 1H, CH), 12.80 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11.4 (1C, C-3_{propyl}), 21.5 (1C, C-2_{propyl}), 41.9 (1C, C-1_{propyl}), 149.4 (1C, C-$3_{triazole}$), 154.6 (1C, CH), 160.9 (1C, C-$5_{triazole}$). IR (neat) ν [cm^{-1}] = 3240, 2959, 2874, 1609, 1543, 1489, 1408, 1315, 1250, 1088, 1049, 964, 926, 756, 652. HRMS (APCI): m/z = 154.1087 calculated for $[M + H]^+$, found 154.1088.

*N′-(3-(4-Fluorophenyl)-1H-1,2,4-triazol-5-yl)-N-propylformamidine (**20j**).* According to general procedure A, a mixture of aminotriazole **19j** (111 mg, 620 μmol), triethyl orthoformate (310 μL, 1.86 mmol), *n*-propylamine (153 μL, 1.86 mmol), and acetic acid (107 μL, 1.86 mmol) in THF (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. The recrystallization of the crude yielded a colorless solid (109 mg, 440 μmol, 71%). m.p.: 157.6 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.91 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.52−1.60 (m, 2H, 2-H_{propyl}), 3.26 (dd, J = 12.8, 6.9 Hz, 2H, 1-H_{propyl}), 7.21−7.25 (m, 2H, 3/5-$H_{fluorophenyl}$), 7.93−7.99 (m, 3H, 2/6-$H_{fluorophenyl}$/$NH_{formamidine}$), 8.44 (d, J = 4.5 Hz, 1H, CH), 12.92 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11.4 (1C, C-3_{propyl}), 21.5 (1C, C-2_{propyl}), 42.0 (1C, C-1_{propyl}), 115.3 (d, J = 21.5 Hz, 2C, C-3/$5_{fluorophenyl}$), 127.4 (d, J = 8.3 Hz, 2C, C-2/$6_{fluorophenyl}$), 154.9 (1C, CH), 157.7 (1C, C-

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ACS Omega XXXX, XXX, XXX−XXX

$4_{fluorophenyl}$), 161.4 (1C, C-$1_{fluorophenyl}$), 161.7 (1C, C-$5_{triazole}$), 163.0 (1C, C-$3_{triazole}$). IR (neat) ν [cm^{-1}] = 3202, 3156, 3021, 2974, 2936, 2882, 2801, 2654, 1608, 1555, 1474, 1339, 1288, 1215, 1150, 1096, 1053, 810, 760. HRMS (APCI): m/z = 248.1306 calculated for $[M + H]^+$, found 248.1305.

*N′-(3-([1,1′-Biphenyl]-4-yl)-1H-1,2,4-triazol-5-yl)-N-propylformamidine (**20k**).* According to general procedure A, a mixture of aminotriazole **19k** (73 mg, 310 μmol), triethyl orthoformate (155 μL, 930 μmol), *n*-propylamine (77 μL, 930 μmol), and acetic acid (53 μL, 930 μmol) in THF (1 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. The recrystallization of the crude yielded a light beige solid (62 mg, 203 μmol, 66%). m.p.: 194.4 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.92 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.54−1.61 (m, 2H, 2-H_{propyl}), 3.27 (dd, J = 12.8, 6.9 Hz, 2H, 1-H_{propyl}), 7.35−7.39 (m, 1H, 4-H_{phenyl}), 7.46−7.50 (m, 2H, 3/5-H_{phenyl}), 7.69−7.74 (m, 4H, 3/5-$H_{phenylene}$/2/6-H_{phenyl}), 7.95 (br s, 1H, $NH_{formamidine}$), 8.01−8.04 (m, 2H, 2/6-$H_{phenylene}$),8.48 (d, J = 4.4 Hz, 1H, CH), 12.97 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11.4 (1C, C-3_{propyl}), 21.6 (1C, C-2_{propyl}), 42.0 (1C, C-1_{propyl}), 126.0 (2C, C-2/$6_{phenylene}$), 126.5 (2C, C-3/5_{phenyl}), 126.7 (2C, C-3/$5_{phenylene}$), 127.5 (1C, C-4_{phenyl}), 128.9 (2C, C-2/6_{phenyl}), 131.4 (1C, C-$1_{phenylene}$), 139.7 (1C, C-1_{phenyl}), 139.9 (1C, C-$4_{phenylene}$), 154.9 (1C, CH), 158.3 (1C, C-$3_{triazole}$), 161.6 (1C, C-$5_{triazole}$). IR (neat) ν [cm^{-1}] = 3206, 3156, 3024, 2963, 2874, 2797, 2662, 1609, 1558, 1470, 1400, 1292, 1254, 1150, 1057, 976, 849, 748, 687. HRMS (APCI): m/z = 306.1713 calculated for $[M + H]^+$, found 306.1689.

*N-Benzyl-3-(5-(((propylamino)methylene)amino)-1H-1,2,4-triazol-3-yl)propanamide (**20l**).* According to general procedure A, a mixture of aminotriazole **19l** (73 mg, 310 μmol), triethyl orthoformate (155 μL, 930 μmol), *n*-propylamine (77 μL, 930 μmol), and acetic acid (53 μL, 930 μmol) in THF (1 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. The recrystallization of the crude yielded a colorless solid (56 mg, 178 μmol, 57%). m.p.: 151.5 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.90 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.50−1.57 (m, 2H, 2-H_{propyl}), 2.49−2.53 (m, 2H, $COCH_2\underline{CH_2}$), 2.72 (dd, J = 8.8, 6.8 Hz, 1H, $CO\underline{CH_2}CH_2$), 2.89 (s, 3H, CH_3), 3.22 (dd, J = 12.7, 6.9 Hz, 2H, 1-H_{propyl}), 4.26 (d, J = 5.9 Hz, 2H, $\underline{CH_2}$NHCO), 7.19−7.24 (m, 3H, 3/4/5-H_{phenyl}), 7.27−7.32 (m, 2H, 2/6-H_{phenyl}), 7.77 (s, 1H, $NH_{formamidine}$), 8.32 (d, J = 4.3 Hz, 1H, CH), 8.36 (t, J = 5.9 Hz, 1H, NHCO), 12.41 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11. Four (1C, C-3_{propyl}), 21.5 (1C, C-2_{propyl}), 24.3 (1C, $CO\underline{CH_2}CH_2$), 33.6 (1C, $COCH_2\underline{CH_2}$), 41.9 (1C, C-1_{propyl}), 41.90 (1C, $CH_{2\text{-}benzyl}$), 126.6 (1C, C-4_{benzyl}), 127.0 (2C, C-3/5_{benzyl}), 128.2 (2C, C-2/6_{benzyl}), 139.6 (1C, C-1_{benzyl}), 154.4 (1C, CH), 159.7 (1C, C-$3_{triazole}$), 161.2 (1C, C-$5_{triazole}$), 171.32 (1C, CO). IR (neat) ν [cm^{-1}] = 3645, 3298, 3163, 3063, 2978, 2928, 2805, 1643, 1616, 1551, 1404, 1350, 1227, 1157, 1072, 806, 733, 698. HRMS (APCI): m/z = 315.1928 calculated for $[M + H]^+$, found 315.1920.

*N-Ethyl-3-(5-(((propylamino)methylene)amino)-1H-1,2,4-triazol-3-yl)pyrazine-2-carboxamide (**20m**).* According to general procedure A, a mixture of aminotriazole **19m** (72 mg, 310 μmol), triethyl orthoformate (155 μL, 930 μmol), *n*-propylamine (77 μL, 930 μmol), and acetic acid (53 μL, 930 μmol) in THF (1 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (61 mg, 202 μmol, 65%). m.p.: 194.4 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.91 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.09 (t, J = 7.2 Hz, 3H, 2-H_{ethyl}), 1.52−1.60 (m, 2H, 2-H_{propyl}), 3.20−3.28 (m, 4H, 1-H_{ethyl}/1-H_{propyl}), 8.01 (br s, 1H, $NH_{formamidine}$), 8.41 (m, 2H, CH/NHCO), 8.60 (d, J = 2.4 Hz, 1H, 6-$H_{pyrazinyl}$), 8.73 (d, J = 2.5 Hz, 1H, 5-$H_{pyrazinyl}$), 13.15 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11. Four (1C, C-3_{propyl}), 14.3 (1C, C-2_{ethyl}), 21.5 (1C, C-2_{propyl}), 33.7 (1C, (C-1_{ethyl}), 42.0 (1C, C-1_{propyl}), 142.4 (1C, C-$6_{pyrazinyl}$), 143.7 (1C, C-$3_{pyrazinyl}$), 144.1 (1C, C-$5_{pyrazinyl}$), 149.1 (1C, C-$2_{pyrazinyl}$), 155.0 (1C, CH), 161.2 (1C, C-$5_{triazole}$), 166.0 (1C, CO). C-$3_{triazole}$ is invisible due to tautomerism. IR (neat) ν [cm^{-1}] = 3661, 2978, 2886, 2160, 2033, 1975, 1620, 1528, 1454, 1381, 1250, 1153, 1088, 957, 756. HRMS (APCI): m/z = 303.1676 calculated for $[M + H]^+$, found 303.1658.

*N-(Cyclopropylmethyl)-3-(5-(((propylamino)methylene)-amino)-1H-1,2,4-triazol-3-yl)pyrazine-2-carboxamide (**20n**).* According to general procedure A, a mixture of aminotriazole **19n** (81 mg, 310 μmol), triethyl orthoformate (155 μL, 930 μmol), *n*-propylamine (77 μL, 930 μmol), and acetic acid (53 μL, 930 μmol) in THF (1 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (63 mg, 192 μmol, 62%). m.p.: 118.5 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.18−0.22 (m, 2H, $(CH_2)_{cyclopropyl}$), 0.39−0.43 (m, 2H, $(CH_2)_{cyclopropyl}$), 0.91 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 0.93−1.0 (m, 1H, $CH_{cyclopropyl}$), 1.52−1.60 (m, 2H, 2-H_{propyl}), 3.10 (t, J = 6.2 Hz, 2H, $\underline{CH_2}$NHCO), 3.26 (dd, J = 12.8, 6.8 Hz, 2H, 1-H_{propyl}), 8.00 (br s, 1H, $NH_{formamidine}$), 8.40 (d, J = 4.4 Hz, 1H, CH), 8.50 (t, J = 5.7 Hz, 1H, NHCO), 8.61 (d, J = 2.4 Hz, 1H, 6-$H_{pyrazinyl}$), 8.73 (d, J = 3.8 Hz, 1H, 5-$H_{pyrazinyl}$), 13.14 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 3.2 (2C, C-2/$3_{cyclopropyl}$), 10.5 (1C, C-$1_{cyclopropyl}$), 11.4 (1C, C-3_{propyl}), 21.5 (1C, C-2_{propyl}), 42.0 (1C, C-1_{propyl}), 43.1 (1C, $\underline{CH_2}$NHCO), 142.4 (1C, C-$6_{pyrazinyl}$), 144.1 (1C, C-$5_{pyrazinyl}$), 149.1 (1C, C-$2_{pyrazinyl}$), 155.0 (1C, CH), 161.4 (1C, C-$5_{triazole}$), 166.1 (1C, CO). C-$3_{pyrazinyl}$ and C-$3_{triazole}$ are invisible due to tautomerism. IR (neat) ν [cm^{-1}] = 3661, 3237, 3063, 2978, 2886, 2160, 2037, 1979, 1620, 1528, 1458, 1381, 1254, 1157, 1096, 988, 957, 829, 756. HRMS (APCI): m/z = 329.1833 calculated for $[M + H]^+$, found 329.1819.

*N-Isopentyl-3-(5-(((propylamino)methylene)amino)-1H-1,2,4-triazol-3-yl)pyrazine-2-carboxamide (**20o**).* According to general procedure A, a mixture of aminotriazole **19o** (85 mg, 310 μmol), triethyl orthoformate (155 μL, 930 μmol), *n*-propylamine (77 μL, 930 μmol), and acetic acid (53 μL, 930 μmol) in THF (1 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (79 mg, 228 μmol, 73%). m.p.: 181.6 °C (decomposed). ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.87 (d, J = 6.6 Hz, 6H, $CH(\underline{CH_3})_2$), 0.91 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.36 (dd, J = 14.5, 7.0 Hz, 2H, $CONHCH_2\underline{CH_2}$), 1.53−1.60 (m, 2H, 2-H_{propyl}), 1.56−1.64 (m, 1H, $\underline{CH}(CH_3)_2$), 3.20 (dd, J = 14.0, 6.3 Hz, 2H, $CONH\underline{CH_2}CH_2$), 3.26 (dd, J = 12.8, 6.8 Hz, 2H, 1-H_{propyl}), 8.00 (br s, 1H, $NH_{formamidine}$), 8.36 (t, J = 5.7 Hz, 1H, NHCO), 8.40 (d, J = 4.4 Hz, 1H, CH), 8.60 (d, J = 2.4 Hz, 1H, 6-$H_{pyrazinyl}$), 8.72 (d, J = 2.5 Hz, 1H, 5-$H_{pyrazinyl}$), 13.15 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11.4 (1C, C-3_{propyl}), 21.5 (1C, C-2_{propyl}), 22.4 (2C, $CH(\underline{CH_3})_2$), 25.1 (1C, $\underline{CH}(CH_3)_2$), 37.1 (1C, $CONH\underline{CH_2}CH_2$), 37.6 (1C, $CONHCH_2\underline{CH_2}$), 42.0 (1C, C-1_{propyl}), 142.4 (1C, C-$6_{pyrazinyl}$), 143.8 (1C, C-$3_{pyrazinyl}$), 144.0

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ACS Omega XXXX, XXX, XXX−XXX

(1C, C-$5_{pyrazinyl}$), 149.2 (1C, C-$2_{pyrazinyl}$), 155.0 (1C, CH), 156.7 (1C, C-$3_{triazole}$), 161.3 (1C, C-$5_{triazole}$), 166.0 (1C, CO). IR (neat) ν [cm^{-1}] = 3657, 3217, 2978, 2886, 2160, 2021, 1979, 1647, 1616, 1528, 1450, 1385, 1304, 1153, 957, 883, 752, 706. HRMS (APCI): m/z = 345.2146 calculated for $[M + H]^+$, found 345.2148.

*N-Phenethyl-3-(5-(((propylamino)methylene)amino)-1H-1,2,4-triazol-3-yl)pyrazine-2-carboxamide (**20p**).* According to general procedure A, a mixture of aminotriazole **19p** (96 mg, 310 μmol), triethyl orthoformate (155 μL, 930 μmol), *n*-propylamine (77 μL, 930 μmol), and acetic acid (53 μL, 930 μmol) in THF (1 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (104 mg, 275 μmol, 89%). m.p.: 100.8 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.89 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.51−1.58 (m, 2H, 2-H_{propyl}), 2.78−2.82 (m, 2H, CONHCH$_2$CH$_2$), 3.25 (dd, J = 12.8, 6.9 Hz, 2H, 1-H_{propyl}), 3.42 (dt, J = 7.7, 6.0 Hz, 2H, CONHCH$_2$CH$_2$), 7.18−7.22 (m, 1H, 4-H_{phenyl}), 7.23−7.26 (m, 2H, 2/6-H_{phenyl}), 7.27−7.31 (m, 2H, 3/5-H_{phenyl}), 7.99 (br s, 1H, $NH_{formamidine}$), 8.42 (d, J = 4.5 Hz, 1H, CH), 8.57 (t, J = 5.7 Hz, 1H, NHCO), 8.61 (d, J = 2.4 Hz, 1H, 6-$H_{pyrazinyl}$), 8.74 (d, J = 2.5 Hz, 1H, 5-$H_{pyrazinyl}$), 13.18 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11.4 (1C, C-3_{propyl}), 21.5 (1C, C-2_{propyl}), 34.8 (1C, CONHCH$_2$CH$_2$), 40.6 (1C, CONHCH$_2$CH$_2$), 42.0 (1C, C-1_{propyl}), 126.0 (1C, C-4_{phenyl}), 128.3 (2C, C-3/5_{phenyl}), 128.6 (2C, C-2/6_{phenyl}), 139.5 (1C, C-1_{phenyl}), 142.4 (1C, C-$6_{pyrazinyl}$), 143.7 (1C, C-$3_{pyrazinyl}$), 144.1 (1C, C-$5_{pyrazinyl}$), 149.0 (1C, C-$2_{pyrazinyl}$), 155.0 (1C, CH), 161.4 (1C, C-$5_{triazole}$), 166.2 (1C, CO). C-$3_{triazole}$ is invisible due to tautomerism. IR (neat) ν [cm^{-1}] = 3244, 3063, 2967, 2928, 2874, 2160, 2021, 1975, 1620, 1528, 1450, 1308, 1157, 988, 864, 748, 698. HRMS (APCI): m/z = 379.1989 calculated for $[M + H]^+$, found 379.2001.

*3-(5-(((Propylamino)methylene)amino)-1H-1,2,4-triazol-3-yl)-N-(thiophen-2-ylmethyl)pyrazine-2-carboxamide (**20q**).* According to general procedure A, a mixture of aminotriazole **19q** (94 mg, 310 μmol), triethyl orthoformate (155 μL, 930 μmol), *n*-propylamine (77 μL, 930 μmol), and acetic acid (53 μL, 930 μmol) in THF (1 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a light yellow solid (102 mg, 275 μmol, 89%). m.p.: 201.6 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (in ppm) = 0.92 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.54−1.61 (m, 2H, 2-H_{propyl}), 3.27 (dd, J = 12.7, 6.9 Hz, 2H, 1-H_{propyl}), 4.58 (d, J = 5.9 Hz, 2H, CONHCH$_2$), 6.97 (dd, J = 5.1, 3.4 Hz, 1H, 4-$H_{thiophenyl}$), 7.06−7.07 (m, 1H, 3-$H_{thiophenyl}$), 7.39 (dd, J = 5.1, 1.3 Hz, 1H, 5-$H_{thiophenyl}$), 7.98 (d, J = 4.5 Hz, 1H, $NH_{formamidine}$), 8.40 (d, J = 4.5 Hz, 1H, CH), 8.62 (d, J = 2.5 Hz, 1H, 6-$H_{pyrazinyl}$), 8.75 (d, J = 2.5 Hz, 1H, 5-$H_{pyrazinyl}$), 9.07 (t, J = 5.9 Hz, 1H, NHCO), 12.84 (br s, 1H, $NH_{triazole}$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (in ppm) = 11.4 (1C, C-3_{propyl}), 21.5 (1C, C-2_{propyl}), 37.6 (1C, CONHCH$_2$), 42.0 (1C, C-1_{propyl}), 125.0 (1C, C-$5_{thiophenyl}$), 125.6 (1C, C-$3_{thiophenyl}$), 126.6 (1C, C-$4_{thiophenyl}$), 141.6 (1C, C-$2_{thiophenyl}$), 142.4 (1C, C-$6_{pyrazinyl}$), 143.6 (1C, C-$3_{pyrazinyl}$), 144.3 (1C, C-$5_{pyrazinyl}$), 148.6 (1C, C-$2_{pyrazinyl}$), 155.1 (1C, CH), 156.3 (1C, C-$3_{triazole}$), 161.6 (1C, C-$5_{triazole}$), 166.0 (1C, CO). IR (neat) ν [cm^{-1}] = 3653, 3225, 2978, 2886, 2160, 2037, 1975, 1647, 1616, 1520, 1450, 1385, 1300, 1219, 1153, 1092, 991, 849, 748, 698. HRMS (APCI): m/z = 371.1324 calculated for $[M + H]^+$, found 371.1373.

*7-Methoxy-6-propyl-2-(pyridin-4-yl)6,7-dihydro-[1,2,4]-triazolo[1,5-a][1,3,5]triazine (**21a**).* According to general procedure B, a mixture of formamidine **20a** (51 mg, 220 μmol), trimethyl orthoformate (72 μL, 660 μmol), and acetic acid (38 μL, 660 μmol) in ACN (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (32 mg, 117 μmol, 53%). m.p.: 141.8 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.03 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.74−1.86 (m, 2H, 2-H_{propyl}), 3.16 (s, 3H, OCH_3), 3.35−3.41 (m, 1H, 1-H_{propyl}), 3.60 (ddd, J = 14.1, 8.4, 5.7 Hz, 1H, 1-H_{propyl}), 6.87 (s, 1H, 2-$H_{triazine}$), 7.59 (s, 1H, 6-$H_{triazine}$), 8.02 (dd, J = 4.5, 1.6 Hz, 2H, 3/5-$H_{pyridyl}$), 8.69 (dd, J = 4.5, 1.6 Hz, 1H, 2/6-$H_{pyridyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.1 (1C, C-3_{propyl}), 21.8 (1C, C-2_{propyl}), 51.1 (1C, OCH_3), 51.5 (1C, C-1_{propyl}), 90.6 (1C, C-$2_{triazine}$), 120.8 (2C, C-3/$5_{pyridyl}$), 138.3 (1C, C-$4_{pyridyl}$), 150.4 (2C, C-2/$6_{pyridyl}$), 152.5 (1C, C-$6_{triazine}$), 154.2 (1C, C-$5_{triazole}$), 160.7 (1C, C-$3_{triazole}$). IR (neat) ν [cm^{-1}] = 2968, 1593, 1562, 1541, 1514, 1458, 1425, 1396, 1358, 1304, 1260, 1217, 1196, 1153, 1103, 1061, 991, 953, 897, 856, 837, 787, 762, 746, 727, 710, 669, 658. HRMS (APCI): m/z = 273.1458 calculated for $[M + H]^+$, found 273.1443. HPLC: t_R = 10.7 min, purity 100.0%.

*7-Methoxy-6-propyl-2-(pyridin-2-yl)-6,7-dihydro-[1,2,4]-triazolo[1,5-a][1,3,5]triazine (**21b**).* According to general procedure B, a mixture of formamidine **20b** (51 mg, 220 μmol), trimethyl orthoformate (72 μL, 660 μmol), and acetic acid (38 μL, 660 μmol) in ACN (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (28 mg, 103 μmol, 47%). m.p.: 78.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.00 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.72−1.84 (m, 2H, 2-H_{propyl}), 3.17 (s, 3H, OCH_3), 3.37 (ddd, J = 14.4, 8.4, 7.2 Hz, 1H, 1-H_{propyl}), 3.59 (ddd, J = 14.2, 8.4, 5.8 Hz, 1H, 1-H_{propyl}), 6.87 (s, 1H, 2-$H_{triazine}$), 7.32 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H, 5-$H_{pyridyl}$), 7.58 (s, 1H, 6-$H_{triazine}$), 7.79 (td, J = 7.7, 1.8 Hz, 1H, 4-$H_{pyridyl}$), 8.21 (dt, J = 7.9, 1.0 Hz, 1H, 3-$H_{pyridyl}$), 8.72 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H, 6-$H_{pyridyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.1 (1C, C-3_{propyl}), 21.9 (1C, C-2_{propyl}), 51.3 (1C, OCH_3), 51.5 (1C, C-1_{propyl}), 90.7 (1C, C-$2_{triazine}$), 122.3 (1C, C-$3_{pyridyl}$), 124.3 (1C, C-$5_{pyridyl}$), 136.9 (1C, C-$4_{pyridyl}$), 149.7 (1C, C-$2_{pyridyl}$), 150.0 (1C, C-$6_{pyridyl}$),152.4 (1C, C-$6_{triazine}$), 154.0 (1C, C-$5_{triazole}$), 162.1 (1C, C-$3_{triazole}$). IR (neat) ν [cm^{-1}] = 2965, 2936, 2876, 1584, 1537, 1468, 1447, 1412, 1377, 1350, 1281, 1250, 1213, 1190, 1144, 1063, 995, 959, 901, 802, 760, 745, 712, 675, 621. HRMS (APCI): m/z = 273.1458 calculated for $[M + H]^+$, found 273.1443. HPLC: t_R = 11.5 min, purity 100.0%.

*7-Methoxy-6-propyl-2-(pyridin-3-yl)-6,7-dihydro-[1,2,4]-triazolo[1,5-a][1,3,5]triazine (**21c**).* According to general procedure B, a mixture of formamidine **20c** (51 mg, 220 μmol), trimethyl orthoformate (72 μL, 660 μmol), and acetic acid (38 μL, 660 μmol) in ACN (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (43 mg, 159 μmol, 72%). m.p.: 166.9 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.02 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.73−1.86 (m, 2H, 2-H_{propyl}), 3.16 (s, 3H, OCH_3), 3.35−3.42 (m, 1H, 1-H_{propyl}), 3.60 (ddd, J = 14.1, 8.3, 5.7 Hz, 1H, 1-H_{propyl}), 6.87 (s, 1H, 2-$H_{triazine}$), 7.36 (ddd, J = 7.9,

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ACS Omega XXXX, XXX, XXX−XXX

4.8, 0.8 Hz, 1H, 5-$H_{pyridyl}$), 7.59 (s, 1H, 6-$H_{triazine}$), 8.42 (dt, J = 7.9, 2.0 Hz, 1H, 4-$H_{pyridyl}$), 8.64 (dd, J = 4.8, 1.7 Hz, 1H, 6-$H_{pyridyl}$), 9.38 (dd, J = 2.1, 0.7 Hz, 1H, 2-$H_{pyridyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.1 (1C, C-3_{propyl}), 21.8 (1C, C-2_{propyl}), 51.0 (1C, OCH_3), 51.4 (1C, C-1_{propyl}), 90.5 (1C, C-$2_{triazine}$), 123.5 (1C, C-$5_{pyridyl}$), 127.0 (1C, C-$3_{pyridyl}$), 134.0 (1C, C-$4_{pyridyl}$), 148.2 (1C, C-$2_{pyridyl}$), 150.6 (1C, C-$6_{pyridyl}$),152.4 (1C, C-$6_{triazine}$), 154.1 (1C, C-$5_{triazole}$), 160.6 (1C, C-$3_{triazole}$). IR (neat) ν [cm^{-1}] = 2980, 1593, 1535, 1456, 1445, 1423, 1393, 1371, 1348, 1310, 1254, 1211, 1188, 1144, 1099, 1067, 1020, 980, 964, 897, 833, 793, 764, 746, 712, 681, 621. HRMS (APCI): m/z = 273.1458 calculated for $[M + H]^+$, found 273.1441. HPLC: t_R = 10.9 min, purity 100.0%.

*7-Methoxy-2-(6-methylpyridin-2-yl)-6-propyl-6,7-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]triazine (**21d**).* According to general procedure B, a mixture of formamidine **20d** (54 mg, 220 μmol), trimethyl orthoformate (72 μL, 660 μmol), and acetic acid (38 μL, 660 μmol) in ACN (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (46 mg, 160 μmol, 73%). m.p.: 168.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 0.99 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.70−1.83 (m, 2H, 2-H_{propyl}), 2.66 (s, 3H, CH_3), 3.12 (s, 3H, OCH_3), 3.31−3.41 (m, 1H, 1-H_{propyl}), 3.58 (ddd, J = 14.1, 8.1, 5.9 Hz, 1H, 1-H_{propyl}), 6.92 (s, 1H, 2-$H_{triazine}$), 7.17−7.20 (m, 1H, 5-$H_{pyridyl}$), 7.58 (d, J = 0.7, 1H, 6-$H_{triazine}$), 7.67 (t, J = 7.8 Hz, 1H, 4-$H_{pyridyl}$), 8.03 (ddd, J = 7.8, 1.0, 0.5 Hz, 1H, 3-$H_{pyridyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.0 (1C, C-3_{propyl}), 21.9 (1C, C-2_{propyl}),24.3 (1C, CH_3), 50.7 (1C, OCH_3), 51.4 (1C, C-1_{propyl}), 90.4 (1C, C-$2_{triazine}$), 119.6 (1C, C-$3_{pyridyl}$), 124.1 (1C, C-$5_{pyridyl}$), 137.0 (1C, C-$4_{pyridyl}$), 149.1 (1C, C-$6_{pyridyl}$), 152.4 (1C, C-$6_{triazine}$), 154.0 (1C, C-$5_{triazole}$), 158.9 (1C, C-$2_{pyridyl}$), 162.4 (1C, C-$3_{triazole}$). IR (neat) ν [cm^{-1}] = 2961, 2943, 1585, 1537, 1395, 1373, 1346, 1300, 1211, 1163, 1107, 1088, 1059, 970, 908, 897, 866, 812, 797, 762, 748, 708, 658. HRMS (APCI): m/z = 287.1615 calculated for $[M + H]^+$, found 287.1598. HPLC: t_R = 11.8 min, purity 100.0%.

*3-(7-Methoxy-6-propyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]-[1,3,5]triazin-2-yl)pyridine 1-Oxide (**21e**).* According to general procedure B, a mixture of formamidine **20e** (54 mg, 220 μmol), trimethyl orthoformate (72 μL, 660 μmol), and acetic acid (38 μL, 660 μmol) in ACN (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (17 mg, 60 μmol, 28%). m.p.: 156.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.02 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.73−1.87 (m, 2H, 2-H_{propyl}), 3.20 (s, 3H, OCH_3), 3.36−3.42 (m, 1H, 1-H_{propyl}), 3.60 (ddd, J = 14.2, 8.3, 5.7 Hz, 1H, 1-H_{propyl}), 6.83 (s, 1H, 2-$H_{triazine}$), 7.34 (dd, J = 7.9, 6.5 Hz,1H, 5-$H_{pyridyl}$), 7.59 (s, 1H, 6-$H_{triazine}$), 8.00−8.04 (m, 1H, 4-$H_{pyridyl}$), 8.22−8.24 (m, 1H, 6-$H_{pyridyl}$), 8.99 (t, J = 1.6, 1H, 2-$H_{pyridyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.1 (1C, C-3_{propyl}), 21.8 (1C, C-2_{propyl}), 51.6 (1C, C-1_{propyl}), 51.8 (1C, OCH_3), 90.7 (1C, C-$2_{triazine}$), 124.0 (1C, C-$4_{pyridyl}$), 126.0 (1C, C-$5_{pyridyl}$), 130.8 (1C, C-$3_{pyridyl}$), 137.6 (1C, C-$2_{pyridyl}$), 139.7 (1C, C-$6_{pyridyl}$), 152.6 (1C, C-$6_{triazine}$), 154.2 (1C, C-$5_{triazole}$), 158.2 (1C, C-$3_{triazole}$). IR (neat) ν [cm^{-1}] = 2961, 2934, 1584, 1541, 1466, 1427, 1366, 1348, 1292, 1144, 1107, 1072, 1013, 970, 910, 897, 880, 856, 808, 795, 764, 737, 673. HRMS (APCI): m/z = 289.1408 calculated for $[M + H]^+$, found 289.1397. HPLC: t_R = 12.0 min, purity 100.0%.

*2-(6-(3,4-Dimethoxyphenyl)-2-methylpyridin-3-yl)-7-methoxy-6-propyl-6,7-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]-triazine (**21f**).* According to general procedure B, a mixture of formamidine **20f** (55 mg, 143 μmol), trimethyl orthoformate (47 μL, 430 μmol), and acetic acid (25 μL, 430 μmol) in ACN (1.3 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (Et_2O/MeOH = 1:0 → 9:1) yielded a colorless solid (21 mg, 50 μmol, 35%). m.p.: 188.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.03 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.76−1.86 (m, 2H, 2-H_{propyl}), 2.99 (s, 3H, CH_3), 3.21 (s, 3H, CHO$\underline{CH_3}$), 3.35−3.41 (m, 1H, 1-H_{propyl}), 3.61 (ddd, J = 14.1, 8.2, 5.8 Hz, 1H, 1-H_{propyl}), 3.94 (s, 3H, 4-OCH_3), 4.01 (s, 3H, 3-OCH_3), 6.87 (s, 1H, 2-$H_{triazine}$), 6.96 (d, J = 8.4 Hz, 1H, 5-$H_{dimethoxyphenyl}$), 7.59 (s, 1H, 6-$H_{triazine}$), 7.60 (dd, J = 9.1, 7.4 Hz, 2H, 5-$H_{pyridyl}$/6-$H_{dimethoxyphenyl}$), 7.73 (d, J = 2.0 Hz, 1H, 2-$H_{dimethoxyphenyl}$), 8.41 (d, J = 8.2 Hz, 1H, 4-$H_{pyridyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11. One (1C, C-3_{propyl}), 21.9 (1C, C-2_{propyl}), 25.6 (1C, CH_3), 51.4 (2C, C-1_{propyl}/CH$\underline{OCH_3}$), 56.1 (1C, 3-OCH_3), 56.1 (1C, 4-OCH_3), 90.6 (1C, C-$2_{triazine}$), 110.2 (1C, C-$2_{dimethoxyphenyl}$), 111.2 (1C, C-$5_{dimethoxyphenyl}$), 117.1 (1C, C-$5_{pyridyl}$), 119.8 (1C, C-$6_{dimethoxyphenyl}$), 123.6 (1C, C-$3_{pyridyl}$), 132.3 (1C, C-$1_{dimethoxyphenyl}$), 138.0 (1C, C-$4_{pyridyl}$), 149.4 (1C, C-$3_{dimethoxyphenyl}$), 150.2 (1C, C-$4_{dimethoxyphenyl}$), 152.2 (1C, C-$6_{triazine}$), 153.3 (1C, C-$5_{triazole}$), 156.4 (1C, C-$6_{pyridyl}$), 157.1 (1C, C-$2_{pyridyl}$), 162.1 (1C, C-$3_{triazole}$). IR (neat) ν [cm^{-1}] = 2963, 2934, 2837, 1584, 1539, 1512, 1445, 1408, 1364, 1321, 1298, 1271, 1225, 1169, 1142, 1090, 1059, 1022, 951, 881, 847, 808, 775, 766, 679. HRMS (APCI): m/z = 423.2139 calculated for $[M + H]^+$, found 423.2167. HPLC: t_R = 22.1 min, purity 96.0%.

*2-(7-Methoxy-6-propyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]-[1,3,5]triazin-2-yl)quinolone (**21g**).* According to general procedure B, a mixture of formamidine **20g** (62 mg, 220 μmol), trimethyl orthoformate (72 μL, 660 μmol), and acetic acid (38 μL, 660 μmol) in ACN (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (54 mg, 168 μmol, 77%). m.p.: 80.8 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.01 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.74−1.84 (m, 2H, 2-H_{propyl}), 3.17 (s, 3H, OCH_3), 3.35−3.42 (m, 1H, 1-H_{propyl}), 3.60 (ddd, J = 14.2, 8.3, 5.8 Hz, 1H, 1-H_{propyl}), 6.97 (s, 1H, 2-$H_{triazine}$), 7.55 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H, 6′-$H_{quinolinyl}$), 7.62 (s, 1H, 6-$H_{triazine}$), 7.72 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H, 7-$H_{quinolinyl}$), 7.83 (dd, J = 8.0, 0.8 Hz, 1H, 5-$H_{quinolinyl}$), 8.26 (d, J = 8.6 Hz, 1H, 4-$H_{quinolinyl}$), 8.32 (d, J = 8.4 Hz, 1H, 8-$H_{quinolinyl}$), 8.36 (d, J = 8.6 Hz, 1H, 3-$H_{quinolinyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.1 (1C, C-3_{propyl}), 21.9 (1C, C-2_{propyl}), 51.0 (1C, OCH_3), 51.5 (1C, C-1_{propyl}), 90.5 (1C, C-$2_{triazine}$), 120.0 (1C, C-$3_{quinolinyl}$), 127.1 (1C, C-$6_{quinolinyl}$), 127.6 (1C, C-$5_{quinolinyl}$), 128.5 (1C, C-$4a_{uinolinyl}$), 129.8 (1C, C-$7_{quinolinyl}$), 130.4 (1C, C-$8_{quinolinyl}$), 137.0 (1C, C-$4_{quinolinyl}$), 148.2 (1C, C-$8a_{quinolinyl}$), 149.7 (1C, C-$2_{quinolinyl}$), 152.5 (1C, C-$6_{triazine}$), 154.2 (1C, C-$5_{triazole}$), 162.4 (1C, C-$3_{triazole}$). IR (neat) ν [cm^{-1}] = 2965, 2932, 2876, 1585, 1537, 1489, 1454, 1431, 1418, 1315, 1250, 1211, 1190, 1144, 1107, 1065, 957, 941, 901, 839, 773, 733. HRMS (APCI): m/z = 323.1615 calculated for $[M + H]^+$, found 323.1589. HPLC: t_R = 17.1 min, purity 98.8%.

*7-Methoxy-2-(4-methyl-2-phenylpyrimidin-5-yl)-6-propyl-6,7-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]triazine (**21h**).* According to general procedure B, a mixture of formamidine **20h** (46 mg, 143 μmol), trimethyl orthoformate (47 μL, 430 μmol),

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ACS Omega XXXX, XXX, XXX−XXX

and acetic acid (25 μL, 430 μmol) in ACN (1.3 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (Et_2O/MeOH = 1:0 → 9:1) yielded a colorless solid (19 mg, 53 μmol, 37%). m.p.: 110.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.04 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.75−1.88 (m, 2H, 2-H_{propyl}), 2.98 (s, 3H, CH_3), 3.23 (s, 3H, OCH_3), 3.37−3.43 (m, 1H, 1-H_{propyl}), 3.62 (ddd, J = 14.1, 8.3, 5.7 Hz, 1H, 1-H_{propyl}), 6.88 (s, 1H, 2-$H_{triazine}$), 7.48−7.52 (m, 3H, 3/4/5-H_{phenyl}), 7.60 (s, 1H, 6-$H_{triazine}$), 8.50−8.53 (m, 2H, 2/6-H_{phenyl}), 9.40 (s, 1H, 6-$H_{pyrimidinyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.2 (1C, C-3$_{propyl}$), 21.9 (1C, C-2$_{propyl}$), 25.1 (1C, CH_3), 51.5 (1C, C-1$_{propyl}$), 51.6 (1C, OCH_3), 90.7 (1C, C-2$_{triazine}$), 121.7 (1C, C-5$_{pyr3imidinyl}$), 128.6 (2C, C-2/6$_{phenyl}$), 128.7 (2C, C-3/5$_{phenyl}$), 130.8 (1C, C-4$_{phenyl}$), 137.7 (1C, C-1$_{phenyl}$), 152.3 (1C, C-6$_{triazine}$), 153.5 (1C, C-5$_{triazole}$), 157.4 (1C, C-6$_{pyrimidinyl}$), 159.9 (1C, C-4$_{pyrimidinyl}$), 163.9 (1C, C-2$_{pyrimidinyl}$), 165.8 (1C, C-3$_{triazole}$). IR (neat) ν [cm^{-1}] = 2961, 2936, 1585, 1551, 1522, 1433, 1406, 1358, 1327, 1310, 1250, 1206, 1152, 1113, 1061, 963, 897, 868, 766, 748, 729, 706, 691, 627. HRMS (APCI): m/z = 364.1880 calculated for $[M + H]^+$, found 364.1847. HPLC: t_R = 19.5 min, purity 95.9%.

*7-Methoxy-6-propyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]-[1,3,5]triazine (**21i**).* According to general procedure B, a mixture of formamidine **20i** (46 mg, 300 μmol), trimethyl orthoformate (99 μL, 901 μmol), and acetic acid (52 μL, 901 μmol) in ACN (2.7 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (Et_2O/MeOH = 1:0 → 9:1) yielded a colorless oil (27 mg, 139 μmol, 46%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.00 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.71−1.82 (m, 2H, 2-H_{propyl}), 3.09 (s, 3H, OCH_3), 3.35 (ddd, J = 14.3, 8.4, 7.3 Hz, 1H, 1-H_{propyl}), 3.57 (ddd, J = 14.2, 8.4, 5.7 Hz, 1H, 1-H_{propyl}), 6.82 (s, 1H, 2-$H_{triazine}$), 7.55 (s, 1H, 6-$H_{triazine}$), 7.93 (s, 1H, H-3$_{triazole}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.1 (1C, C-3$_{propyl}$), 21.8 (1C, C-2$_{propyl}$), 50.9 (1C, OCH_3), 51.4 (1C, C-1$_{propyl}$), 90.5 (1C, C-2$_{triazine}$), 152.1 (1C, C-6$_{triazine}$), 152.7 (1C, C-3$_{triazole}$), 153.3 (1C, C-5$_{triazole}$). IR (neat) ν [cm^{-1}] = 2965, 2936, 2878, 2835, 1585, 1537, 1470, 1414, 1375, 1263, 1248, 1211, 1179, 1132, 1061, 972, 953, 899, 851, 797, 781, 756, 689, 658. HRMS (APCI): m/z = 196.1193 calculated for $[M + H]^+$, found 196.1198. HPLC: t_R = 9.9 min, purity 97.7%.

*2-(4-Fluorophenyl)-7-methoxy-6-propyl-6,7-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]triazine (**21j**).* According to general procedure B, a mixture of formamidine **20j** (55 mg, 220 μmol), trimethyl orthoformate (72 μL, 660 μmol), and acetic acid (38 μL, 660 μmol) in ACN (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (Et_2O/MeOH = 100/0 → 95/5) yielded a colorless solid (55 mg, 190 μmol, 86%). m.p.: 108.7 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.00 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.71−1.84 (m, 2H, 2-H_{propyl}), 3.12 (s, 3H, OCH_3), 3.32−3.39 (m, 1H, 1-H_{propyl}), 3.57 (ddd, J = 14.2, 8.4, 5.7 Hz, 1H, 1-H_{propyl}), 6.85 (s, 1H, 2-$H_{triazine}$), 7.08−7.12 (m, 2H, 3/5-H_{phenyl}), 7.56 (s, 1H, 6-$H_{triazine}$), 8.12−8.16 (m, 2H, 2/6-H_{phenyl}). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.1 (1C, C-3$_{propyl}$), 21.8 (1C, C-2$_{propyl}$), 50.6 (1C, OCH_3), 51.4 (1C, C-1$_{propyl}$), 90.4 (1C, C-2$_{triazine}$), 115.6 (d, J = 21.7 Hz, 2C, C-3/5$_{phenyl}$), 127.2 (d, J = 3.1 Hz, 1C, C-1$_{phenyl}$), 128.7 (d, J = 8.5 Hz, 2C, C-2/6$_{phenyl}$), 152.2 (1C, C-6$_{triazine}$), 154.0 (1C, C-5$_{triazole}$), 162.0 (1C, C-3$_{triazole}$), 163.9 (d, J = 248.8 Hz, 1C, C-4$_{phenyl}$). IR (neat) ν [cm^{-1}] = 2070, 1589, 1539, 1470, 1431, 1414, 1369, 1333, 1217, 1190, 1150, 1119, 1086, 1053, 1001, 970, 943, 864, 843, 816, 781, 764, 741, 706, 623. HRMS (APCI): m/z = 290.1412 calculated for $[M + H]^+$, found 290.1420. HPLC: t_R = 17.2 min, purity 98.3%.

*2-([1,1′-Biphenyl]-4-yl)-7-methoxy-6-propyl-6,7-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]triazine (**21k**).* According to general procedure B, a mixture of formamidine **20k** (44 mg, 143 μmol), trimethyl orthoformate (47 μL, 430 μmol), and acetic acid (25 μL, 430 μmol) in ACN (1.3 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (Et_2O/MeOH = 1:0 → 9:1) yielded a colorless solid (35 mg, 99 μmol, 70%). m.p.: 124.3 °C (decomposition). ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.02 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.74−1.84 (m, 2H, 2-H_{propyl}), 3.14 (s, 3H, OCH_3), 3.33−3.40 (m, 1H, 1-H_{propyl}), 3.59 (ddd, J = 14.2, 8.4, 5.7 Hz, 1H, 1-H_{propyl}), 6.89 (s, 1H, 2-$H_{triazine}$), 7.34−7.38 (m, 1H, 4-H_{phenyl}), 7.43−7.47 (m, 2H, 3/5-H_{phenyl}), 7.58 (s, 1H, 6-$H_{triazine}$), 7.63−7.66 (m, 2H, 2/6-H_{phenyl}), 7.67−7.69 (m, 4H, 3/5-$H_{phenylene}$), 8.23−8.27 (m, 2H, 2/6-$H_{phenylene}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.1 (1C, C-3$_{propyl}$), 21.8 (1C, C-2$_{propyl}$), 50.6 (1C, OCH_3), 51.4 (1C, C-1$_{propyl}$), 90.4 (1C, C-2$_{triazine}$), 127.2 (2C, C-2/6$_{phenylene}$), 127.2 (2C, C-2/6$_{phenyl}$), 127.3 (2C, C-3/5$_{phenylene}$), 127.6 (1C, C-4$_{phenyl}$), 128.9 (2C, C-3/5$_{phenyl}$), 129.9 (1C, C-1$_{p\text{-}phenylene}$), 140.7 (1C, C-1$_{phenyl}$), 142.4 (1C, C-4$_{p\text{-}phenylene}$), 152.2 (1C, C-6$_{triazine}$), 154.0 (1C, C-5$_{triazole}$), 162.5 (1C, C-3$_{triazole}$). IR (neat) ν [cm^{-1}] = 2963, 2936, 2874, 1587, 1530, 1466, 1447, 1429, 1410, 1375, 1339, 1300, 1261, 1250, 1211, 1188, 1146, 1123, 1101, 1063, 1007, 957, 899, 851, 799, 754, 737, 696. HRMS (APCI): m/z = 348.1819 calculated for $[M + H]^+$, found 348.1788. HPLC: t_R = 20.2 min, purity 97.7%.

*N-Benzyl-3-(7-methoxy-6-propyl-6,7-dihydro-[1,2,4]-triazolo[1,5-a][1,3,5]triazin-2-yl)propanamide (**21l**).* According to general procedure B, a mixture of formamidine **20l** (45 mg, 143 μmol), trimethyl orthoformate (47 μL, 430 μmol), and acetic acid (25 μL, 430 μmol) in ACN (1.3 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (EA/MeOH = 1:0 → 9:1) yielded a colorless oil (33 mg, 91 μmol, 64%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 0.99 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.68−1.81 (m, 2H, 2-H_{propyl}), 2.74 (td, J = 7.2, 2.5 Hz, 2H, $\underline{CH_2}CH_2CO$), 3.02 (s, 3H, OCH_3), 3.09 (t, J = 7.4 Hz, 2H, $CH_2\underline{CH_2}CO$), 3.31 (ddd, J = 14.3, 8.4, 7.2 Hz, 1H, 1-H_{propyl}), 3.53 (ddd, J = 14.1, 8.4, 5.6 Hz, 1H, 1-H_{propyl}), 4.42 (d, J = 5.8 Hz, 2H, $(CH_2)_{benzyl}$), 6.56 (s, 1H, NH), 6.69 (s, 1H, 2-$H_{triazine}$), 7.16−7.25 (m, 3H, 2/4/6-H_{phenyl}), 7.26−7.30 (m, 2H, 3/5-H_{phenyl}), 7.48 (s, 1H, 6-$H_{triazine}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11. One (1C, C-3$_{propyl}$), 21.8 (1C, C-2$_{propyl}$), 24.8 (1C, $CH_2\underline{CH_2}CO$), 34.2 (1C, $\underline{CH_2}CH_2CO$), 43.6 (1C, $CH_{2benzyl}$), 50.8 (1C, C-1$_{propyl}$), 51.3 (1C, OCH_3), 90.2 (1C, C-2$_{triazine}$), 127.3 (1C, C-4$_{phenyl}$), 127.8 (2C, C-2/6$_{phenyl}$), 128.7 (2C, C-3/5$_{phenyl}$), 138.6 (1C, C-1$_{phenyl}$), 152.1 (1C, C-6$_{triazine}$), 153.5 (1C, C-5$_{triazole}$), 157.4 (1C, C-6$_{pyrimidinyl}$), 164.3 (1C, C-3$_{triazole}$), 172.1 (1C, CO). IR (neat) ν [cm^{-1}] = 3291, 2963, 2932, 1655, 1585, 1535, 1497, 1443, 1377, 1350, 1250, 1215, 1146, 1065, 1030, 957, 899, 795, 737, 698. HRMS (ESI): m/z = 357.2034 calculated for $[M + H]^+$, found 357.2062. HPLC: t_R = 14.9 min, purity 97.5%.

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*N-Ethyl-3-(7-methoxy-6-propyl-6,7-dihydro-[1,2,4]-triazolo[1,5-a][1,3,5]triazin-2-yl)pyrazine-2-carboxamide (**21m**).* According to general procedure B, a mixture of formamidine **20m** (67 mg, 220 μmol), trimethyl orthoformate (72 μL, 660 μmol), and acetic acid (38 μL, 660 μmol) in ACN (2 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (21 mg, 60 μmol, 27%). m.p.: 178.8 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.01 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.25 (t, J = 7.3 Hz, 3H, 2-H_{ethyl}), 1.72−1.85 (m, 2H, 2-H_{propyl}), 3.19 (s, 1H, OCH_3), 3.36 (ddd, J = 14.4, 8.5, 7.2 Hz, 1H, 1-H_{propyl}), 3.44−3.49 (m, 2H, 1-H_{ethyl}), 3.58 (ddd, J = 14.2, 8.5, 5.6 Hz, 1H, 1-H_{propyl}), 6.90 (s, 1H, 2-$H_{triazine}$), 7.32 (br s, 1H, NH), 7.57 (s, 1H, 6-$H_{triazine}$), 8.57 (d, J = 2.4 Hz, 1H, 6-$H_{pyrazinyl}$), 8.76 (d, J = 2.4 Hz, 1H, 5-$H_{pyrazinyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.1 (1C, C-3_{propyl}), 14.7 (1C, C-2_{ethyl}), 21.9 (1C, C-2_{propyl}), 34.8 (1C, C-1_{ethyl}), 51.2 (1C, OCH_3), 51.5 (1C, C-1_{propyl}), 90.7 (1C, C-$2_{triazine}$), 142.7 (1C, C-$6_{pyrazinyl}$), 145.2 (1C, C-$5_{pyrazinyl}$), 145.6 (1C, C-$3_{pyrazinyl}$), 146.6 (1C, C-$2_{pyrazinyl}$), 152.3 (1C, C-$6_{triazine}$), 153.6 (1C, C-$5_{triazole}$), 160.7 (1C, C-$3_{triazole}$), 163.8 (1C, CO). IR (neat) ν [cm^{-1}] = 3217, 2978, 2349, 1667, 1585, 1531, 1450, 1381, 1339, 1308, 1254, 1219, 1188, 1153, 1080, 968, 903, 856, 799, 760, 721, 667, 617. HRMS (ESI): m/z = 345.1782 calculated for $[M + H]^+$, found 345.1806. HPLC: t_R = 10.9 min, purity 100.0%.

*N-(Cyclopropylmethyl)-3-(7-methoxy-6-propyl-6,7-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]triazin-2-yl)pyrazine-2-carboxamide (**21n**).* According to general procedure B, a mixture of formamidine **20n** (47 mg, 143 μmol), trimethyl orthoformate (47 μL, 430 μmol), and acetic acid (25 μL, 430 μmol) in ACN (1.3 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (20 mg, 53 μmol, 37%). m.p.: 163.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 0.25−0.28 (m, 2H, $(CH_2)_{cyclopropyl}$), 0.52−0.56 (m, 2H, $(CH_2)_{cyclopropyl}$), 1.01 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.04−1.10 (m, 1H, $CH_{cyclopropyl}$), 1.71−1.80 (m, 2H, 2-H_{propyl}), 3.18 (s, 3H, OCH_3), 3.29 (dd, J = 7.1, 5.7 Hz, 2H, $\underline{CH_2}$NHCO), 3.36 (ddd, J = 14.3, 8.5, 7.1 Hz, 1H, 1-H_{propyl}), 3.58 (ddd, J = 14.2, 8.5, 5.6 Hz, 1H, 1-H_{propyl}), 6.89 (s, 1H, 2-$H_{triazine}$), 7.43 (br s, 1H, NH), 7.57 (d, J = 0.6 Hz, 1H, 6-$H_{triazine}$), 8.59 (d, J = 2.4 Hz, 1H, 6-$H_{pyrazinyl}$), 8.77 (d, J = 2.4 Hz, 1H, 5-$H_{pyrazinyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 3.6 (1C, C-2/$3_{cyclopropyl}$), 3.6 (1C, C-2/$3_{cyclopropyl}$), 10.7 (1C, C-$1_{cyclopropyl}$), 11.1 (1C, C-3_{propyl}), 21.9 (1C, C-2_{propyl}), 44.7 (1C, $\underline{CH_2}$NHCO), 51.1(1C, OCH_3), 51.4 (1C, C-1_{propyl}), 90.6 (1C, C-$2_{triazine}$), 142.8 (1C, C-$6_{pyrazinyl}$), 145.2 (1C, C-$5_{pyrazinyl}$), 145.7 (1C, C-$3_{pyrazinyl}$), 146.6 (1C, C-$2_{pyrazinyl}$), 152.3 (1C, C-$6_{triazine}$), 153.6 (1C, C-$5_{triazole}$), 160.7 (1C, C-$3_{triazole}$), 163.8 (1C, CO). IR (neat) ν [cm^{-1}] = 3240, 3059, 2932, 1667, 1585, 1531, 1450, 1381, 1304, 1215, 1188, 1157, 1096, 1076, 968, 903, 856, 799, 760, 613. HRMS (ESI): m/z = 371.1938 calculated for $[M + H]^+$, found 371.1970. HPLC: t_R = 12.9 min, purity 97.5%.

*N-Isopentyl-3-(7-methoxy-6-propyl-6,7-dihydro-[1,2,4]-triazolo[1,5-a][1,3,5]triazin-2-yl)pyrazine-2-carboxamide (**21o**).* According to general procedure B, a mixture of formamidine **20o** (49 mg, 143 μmol), trimethyl orthoformate (47 μL, 430 μmol), and acetic acid (25 μL, 430 μmol) in ACN (1.3 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (20 mg, 50 μmol, 35%). m.p.: 179.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 0.92 (d, J = 6.6 Hz, 6H, $CH(\underline{CH_3})_2$), 1.01 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.51 (dd, J = 14.5, 7.4 Hz, 2H, $CONHCH_2\underline{CH_2}$), 1.64−1.71 (m, 2H, 2-H_{propyl}), 1.72−1.83 (m, 1H, $\underline{CH}(CH_3)_2$), 3.18 (s, 3H, OCH_3), 3.33−3.39 (m, 1H, 1-H_{propyl}), 3.39−3.46 (m, 2H, $CONH\underline{CH_2}CH_2$), 3.57 (ddd, J = 14.2, 8.5, 5.6 Hz, 1H, 1-H_{propyl}), 6.89 (s, 1H, 2-$H_{triazine}$), 7.32 (br s, 1H, NH), 7.67 (s, 1H, 6-$H_{triazine}$), 8.56 (d, J = 2.4 Hz, 1H, 6-$H_{pyrazinyl}$), 8.76 (d, J = 2.4 Hz, 1H, 5-$H_{pyrazinyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.1 (1C, C-3_{propyl}), 21.9 (1C, C-2_{propyl}), 22.6 (2C, $CH(\underline{CH_3})_2$), 26.0 (1C, $\underline{CH}(CH_3)_2$), 38.2 (1C, $CONHCH_2\underline{CH_2}$), 38.3 (1C, $CONH\underline{CH_2}CH_2$), 51.1 (1C, OCH_3), 51.4 (1C, C-1_{propyl}), 90.6 (1C, C-$2_{triazine}$), 142.7 (1C, C-$6_{pyrazinyl}$), 145.2 (1C, C-$5_{pyrazinyl}$), 145.7 (1C, C-$3_{pyrazinyl}$), 146.5 (1C, C-$2_{pyrazinyl}$), 152.3 (1C, C-$6_{triazine}$), 153.6 (1C, C-$5_{triazole}$), 160.7 (1C, C-$3_{triazole}$), 163.8 (1C, CO). IR (neat) ν [cm^{-1}] = 3217, 3055, 2955, 2874, 1667, 1589, 1531, 1450, 1381, 1342, 1308, 1219, 1188, 1157, 1096, 1076, 968, 903, 856, 799, 760. HRMS (ESI): m/z = 387.2257 calculated for $[M + H]^+$, found 387.2297. HPLC: t_R = 15.5 min, purity 100.0%.

*3-(7-Methoxy-6-propyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]-[1,3,5]triazin-2-yl)-N-phenethylpyrazine-2-carboxamide (**21p**).* According to general procedure B, a mixture of formamidine **20p** (54 mg, 143 μmol), trimethyl orthoformate (47 μL, 430 μmol), and acetic acid (25 μL, 430 μmol) in ACN (1.3 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (EA/MeOH = 1:0 → 9:1) yielded a colorless solid (22 mg, 51 μmol, 36%). m.p.: 157.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.02 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.72−1.85 (m, 2H, 2-H_{propyl}), 2.94 (t, J = 7.2 Hz, 2H, $CONHCH_2\underline{CH_2}$), 3.20 (s, 3H, OCH_3), 3.33−3.40 (m, 1H, 1-H_{propyl}), 3.59 (ddd, J = 14.2, 8.5, 5.6 Hz, 1H, 1-H_{propyl}), 3.69 (dd, J = 13.9, 6.7 Hz, 2H, $CONH\underline{CH_2}CH_2$), 6.91 (s, 1H, 2-$H_{triazine}$), 7.22 (t, J = 7.2 Hz, 1H, 4-H_{phenyl}), 7.24−7.28 (m, 2H, 2/6-H_{phenyl}), 7.30 (t, J = 7.4 Hz, 2H, 3/5-H_{phenyl}), 7.39 (br s, 1H, NH), 7.58 (s, 1H, 6-$H_{triazine}$), 8.55 (d, J = 2.4 Hz, 1H, 6-$H_{pyrazinyl}$), 8.77 (d, J = 2.4 Hz, 1H, 5-$H_{pyrazinyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.1 (1C, C-3_{propyl}), 21.9 (1C, C-2_{propyl}), 35.7 (1C, $CONHCH_2\underline{CH_2}$), 41.1 (1C, $CONH\underline{CH_2}CH_2$), 51.1 (1C, OCH_3), 51.5 (1C, C-1_{propyl}), 90.7 (1C, C-$2_{triazine}$), 126.6 (2C, C-4_{phenyl}), 128.7 (1C, C-3/C-5_{phenyl}), 129.0 (2C, C-2/C-6_{phenyl}), 139.0 (1C, C-1_{phenyl}), 142.8 (1C, C-$6_{pyrazinyl}$), 145.3 (1C, C-$5_{pyrazinyl}$), 145.7 (1C, C-$3_{pyrazinyl}$), 146.5 (1C, C-$2_{pyrazinyl}$), 152.3 (1C, C-$6_{triazine}$), 153.6 (1C, C-$5_{triazole}$), 160.7 (1C, C-$3_{triazole}$), 164.0 (1C, CO). IR (neat) ν [cm^{-1}] = 2963, 2936, 1663, 1585, 1535, 1450, 1373, 1342, 1304, 1250, 1215, 1188, 1150, 1103, 1065, 964, 903, 868, 748, 702. HRMS (ESI): m/z = 421.2100 calculated for $[M + H]^+$, found 421.2150. HPLC: t_R = 15.9 min, purity 100.0%.

*3-(7-Methoxy-6-propyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]-[1,3,5]triazin-2-yl)-N-(thiophen-2-ylmethyl)pyrazine-2-carboxamide (**21q**).* According to general procedure B, a mixture of formamidine **20q** (53 mg, 143 μmol), trimethyl orthoformate (47 μL, 430 μmol), and acetic acid (25 μL, 430 μmol) in ACN (1.3 mL) was irradiated in a 10 mL seamless pressure vial using a microwave system operating at maximal microwave power up to 180 W at 180 °C for 30 min. Flash column chromatography (DCM/MeOH = 1:0 → 9:1) yielded a colorless solid (14 mg, 34

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ACS Omega XXXX, XXX, XXX−XXX

μmol, 24%). m.p.: 148.4 °C (decomposition). ^{1}H NMR (600 MHz, $CDCl_3$) δ (in ppm) = 1.02 (t, J = 7.4 Hz, 3H, 3-H_{propyl}), 1.75−1.85 (m, 2H, 2-H_{propyl}), 3.19 (s, 3H, OCH_3), 3.37 (ddd, J = 14.3, 8.5, 7.1 Hz, 1H, 1-H_{propyl}), 3.54−3.63 (m, 1H, 1-H_{propyl}), 4.77−4.80 (m, 2H, CONH$\underline{CH_2}$), 6.90 (s, 1H, 2-$H_{triazine}$), 6.96 (dd, J = 5.1, 3.5 Hz, 1H, 4-$H_{thiophenyl}$), 7.05−7.07 (m, 1H, 3-$H_{thiophenyl}$), 7.22 (dt, J = 3.9, 1.9 Hz, 1H, 5-$H_{thiophenyl}$), 7.59 (d, J = 6.1 Hz, 1H, 6-$H_{triazine}$), 7.71 (d, J = 4.3 Hz, 1H, NH), 8.56 (dd, J = 5.9, 2.4 Hz, 1H, 6-$H_{pyrazinyl}$), 8.77−8.79 (m, 1H, 5-$H_{pyrazinyl}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ (in ppm) = 11.1 (1C, C-3_{propyl}), 21.9 (1C, C-2_{propyl}), 38.6 (1C, CONH$\underline{CH_2}$), 51.2 (1C, OCH_3), 51.5 (1C, C-1_{propyl}), 90.7 (1C, C-$2_{triazine}$), 125.4 (1C, C-$5_{thiophenyl}$), 126.5 (1C, C-$3_{thiophenyl}$), 127.1 (1C, C-$4_{thiophenyl}$), 140.3 (1C, C-$2_{thiophenyl}$), 142.8 (1C, C-$6_{pyrazinyl}$), 145.5 (1C, C-$5_{pyrazinyl}$), 145.9 (1C, C-$3_{pyrazinyl}$), 146.0 (1C, C-$2_{pyrazinyl}$), 152.4 (1C, C-$6_{triazine}$), 153.6 (1C, C-$5_{triazole}$), 160.6 (1C, C-$3_{triazole}$), 163.5 (1C, CO). IR (neat) ν [cm^{-1}] = 3271, 3044, 2967, 2932, 1667, 1585, 1535, 1447, 1373, 1342, 1296, 1250, 1215, 1184, 1150, 1099, 1065, 984, 961, 903, 853, 826, 748, 698. HRMS (ESI): m/z = 413.1508 calculated for $[M + H]^+$, found 413.1553. HPLC: t_R = 14.4 min, purity 96.7%.

X-ray Crystallography. Data sets for derivatives **21c** and **21j** were collected using a Bruker D8 Venture Photon III diffractometer. Software used: data collection, APEX4 ver. 2021.4.0;[56] cell refinement, SAINT ver. 8.40B;[56] data reduction, SAINT ver. 8.40B;[56] absorption correction, SADABS ver. 2016/2;[56] structure solution, SHELXT ver. 2018-3;[57] structure refinement, SHELXL ver. 2018-3;[58] and graphics, XP.[59] R-Values are given for observed reflections, and wR^2 values are given for all reflections. CCDC 2238380 (**21c**) and CCDC 2238381 (**21j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. The analysis of X-ray crystal structures of **21c** and **21j** are shown in the Supporting Information.

Cytotoxicity Studies. The cytotoxicity of the synthesized compounds was evaluated using a resazurin assay.[45] In 96-well plates, human liver carcinoma cells (HepG2, HB-8065) and lung adenocarcinoma cells (A549, CCL-185) were seeded (10,000 cells/well) and incubated for 24 h. After the medium was replaced by a serum-free medium, the cells were incubated for another 24 h. Test compounds were dissolved in DMSO, the final assay concentration of which was kept below 2%. The synthesized compounds were applied in a screening concentration of 10 μM and were incubated for 24 h. Camptothecin (CPT, 5 μM) was used as a positive control. This proceeded with the addition of the standard resazurin solution (10 μL) to the cells and incubation for 90 min at 37 °C. For the analysis of the reduction of resazurin to resorufin, the fluorescence was measured at λ = 590 nm with a microplate reader (Infinite M200PRO, Tecan, Mannendorf, Switzerland). In cytotoxicity tests, three triplicates from three independent passages ($n \geq 9$) for HepG2 and A549 cell lines were used. After subtraction of cell-free blank values, cellular viability was calculated as a test over control (T/C). The data are shown as the mean ± SD. For the IC_{50} calculation, compounds **21f** and **21i** were tested in a concentration range of 0.5−100 μM. GraphPad Prism software was used to make sigmoidal curves, and IC_{50} values were derived from the fitted curves. The concentration-dependent effects were evaluated by analysis of variance (one-way ANOVA) and the Tukey post hoc test (*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$).[45]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c00765.

^{1}H and ^{13}C NMR spectra of all synthesized compounds, X-ray crystal structure analysis of **21c** and **21j**, radioligand displacement assay at adenosine receptors for compounds **21a−q**; results of the YO-PRO-1 uptake assay at P2X7 receptors for compounds **21a−q** (PDF)

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Author Contributions

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

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

ACN, acetonitrile; APCI, atmospheric-pressure chemical ionization; ARs, adenosine receptors; DCM, dichloromethane; DIPEA, *N*, *N*-diisopropylethylamine; DMA, dimethylacetamide; DMF, dimethyformamide; DMSO, dimethyl sulfoxide; DNA, Deoxyribonucleic acid; EA, ethyl acetate; ESI, electrospray ionization; GSC, glioblastoma stem cells; HRMS, high-resolution mass spectrometry; MDA-MB-231, M.D. Anderson metastatic breast 231; OLED, organic light-emitting diode; PDE, phosphodiesterase; PfDHFR, *Plasmodium falciparum*

dihydrofolate reductase; PTSA, *p*-toluenesulfonic acid; SAR, structure−activity relationship; SD, standard deviation; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TLC, thin-layer chromatography

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