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Synthesis of Diverse Nitrogen-Enriched Heterocyclic Scaffolds Using a Suite of Tunable One-Pot Multicomponent Reactions

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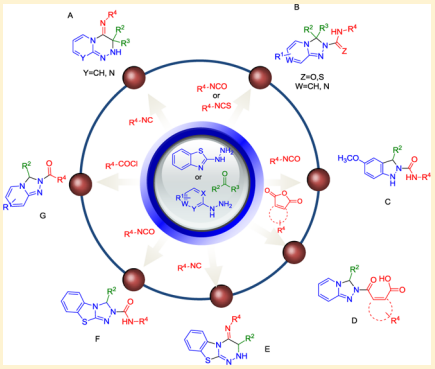
Supporting Information

ABSTRACT: Five elegant and switchable three-component reactions which enable access to a new series of nitrogen-containing heterocycles are reported. A novel one-step addition of an isocyanide to a hydrazine derived Schiff base affords unique six-membered pyridotriazine scaffolds (A and E). With slight modification of reaction conditions and replacement of the nucleophilic isocyanide moiety with different electrophiles (i.e., isocyanates, isothiocyanates, cyclic anhydrides, and acyl chlorides) five-membered triazolopyridine scaffolds (B, D, F, G) are generated in a single step. Furthermore, the use of phenyl hydrazine enables access to dihydroindazole-carboxamides, devoid of a bridge-head nitrogen (C). All protocols are robust and tolerate a diverse collection of reactants, and as such, it is expected that the new scaffolds and associated chemistry will garner high interest from medicinal chemists involved in either file enhancement or specific target-related drug discovery campaigns.

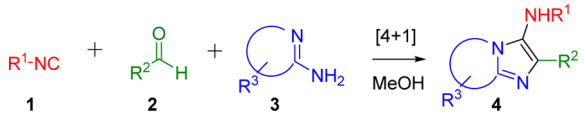


INTRODUCTION

Pyridotriazines are an important class of fused heterobicyclics with biological activity observed in antifungals,[1] anthelmintics,[2] antibacterials,[3] 5-hydroxytryptamine α-receptor antagonists,[4] hypotensives,[5] gastric acid secretase inhibitors[6] and kinase inhibitors for cell proliferative disorders.[7] However, reported syntheses of pyrido-triazine scaffolds usually require lengthy multistep efforts that hinder structure activity−relationship studies.[8] To circumvent this and initially access the unique pyrido[2,1-*c*][1,2,4]triazine scaffold **6**, inspiration was derived from the Groebke−Blackburn−Bienaymé three-component reaction (GBB-3CR),[10] a highly versatile example of an isocyanide based multicomponent reaction (IMCR).[9] Discovered in 1998, the typical GBB-3CR assembles an isocyanide **1**, aldehyde **2**, and α-amino-nitrogen containing heterocycle **3** via a [4 + 1] cycloaddition reaction to afford bicyclic 3-amino-imidazo-heterocycles with a bridge-head nitrogen **4** (Scheme 1).

As such, libraries derived from this methodology have inherent high skeletal diversity due to the plethora of α-amino-heterocycles compatible with the transformation, producing bicyclic rigid congeners where fine-tuning of preferable "lead" or "drug-like" physicochemical properties is readily achieved.

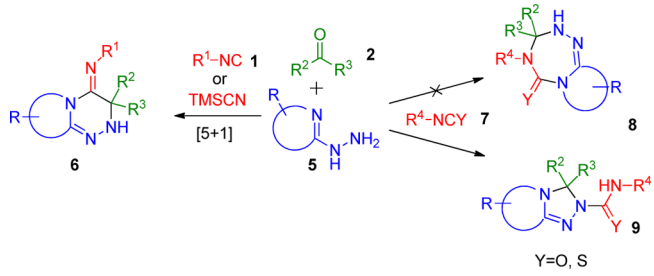
Scheme 1. Groebke−Blackburn−Bienaymé Reaction



Indeed, such efforts have produced numerous active ligands, exemplified by inhibitors of the cyclin-dependent kinase family (CDK),[11] modulators of G-protein coupled receptors implicated in Parkinson's disease,[12] and inhibitors of glycogen synthase kinase 3β (GSK3β) for oncology indications.[13]

Thus, given our ongoing interest in utilizing MCRs for the efficient production of medicinally relevant scaffolds,[14] it was envisioned that use of 2-hydrazinopyridines **5** would feasibly lead to fused 6,6-bicyclic pyrido[2,1-*c*][1,2,4]triazines **6** (Scheme 2) with enhanced fsp^3 character over GBB-derived scaffolds that possess a relatively planar architechture.[15] Although similar reactions have been performed with *p*-methoxyphenyl hydrazine[16] and 2-piconilic amine,[17] to the best of our knowledge the use of 2-hydrazinoazines in this

Scheme 2. Synthesis of Pyridotriazines 6 and Triazolopyridines 9



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context is unprecedented, affording a unique chemotype with a built-in H-bond donor−acceptor war-head that can be readily applied to engage target families that utilize nucleotide-based substrates or secondary messengers to elicit their biological function.[18] Replacement of the isonitrile **1** with electrophiles **7** (R^4NCY, Y=O or S) was postulated as a potential new route to enticing molecules with generic structure **8** via [5 + 2]-cycloaddition. However, intriguingly triazolopyridines of generic structure **9** were produced in a one-pot fashion (Scheme 2).

RESULTS AND DISCUSSION

Proof of concept studies for the synthesis of pyridotriazines **6a** were conducted with a model reaction (Scheme 3) screening a

Scheme 3. Pyridotriazine 6a Model Reaction

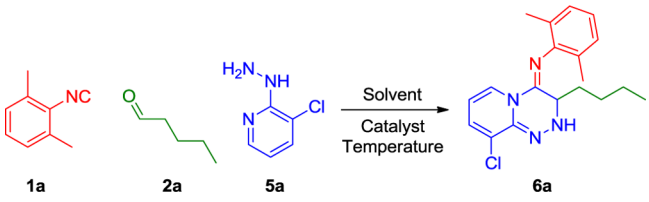


Table 1. Solvent and Catalyst Screening for the Preparation of Pyridotriazine 6a

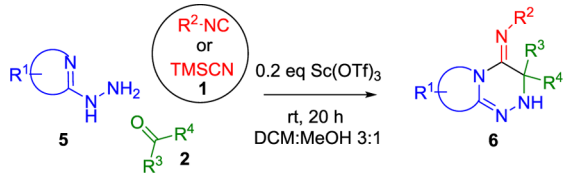
entry	solvent	catalyst (20 mol %)	yield[a] [%]
1	MeOH	$Sc(OTf)_3$	46
2	DCM	$Sc(OTf)_3$	51
3	DCM/MeOH (3:1)	$Sc(OTf)_3$	56
4	DCM/MeOH (3:1)	AcOH	5
5	DCM/MeOH (3:1)	TsOH	25
6	DCM/MeOH (3:1)	$HClO_4$	23
7	DCM/MeOH (3:1)	$ZnCl_2$	4
8	DCM/MeOH (3:1)	$Pd(OAc)_2$	0
9	DCM/MeOH (3:1)	CuI	0
10	DCM/MeOH (3:1)	$CaCl_2$	18
11	DCM/MeOH (3:1)	$ZrCl_4$	36
12[b]	DCM/MeOH (3:1)	$Sc(OTf)_3$	71
13[c]	DCM/MeOH (3:1)	$Sc(OTf)_3$	39

[a]Reactions were carried out on a 0.25 mmol scale at rt for 20 h. Reported % yields are "Area under the Curve" of desired product (A %) as judged by LC/MS at UV 254 nm. [b]1.3 equiv (**5a**) employed. [c]1.3 equiv (**5a**) employed and reaction irradiated with microwaves at 50 °C for 1 h.

variety of reaction conditions and catalysts (Table 1). Scandium triflate in dichloromethane/methanol (3:1) accompanied by a slight excess of the hydrazinoazine **5a** (entry 12) proved optimal, furnishing **6a** in 71% yield as judged by LC/MS at UV 254 nm. Brønsted acid catalysis proved unsatisfactory under the given reaction conditions (Table 1, entries 4−6), including perchloric acid often cited as the catalyst of choice for the GBB-3-component reaction.[10a] An additional attempt to accelerate the reaction via microwave irradiation witnessed a significant drop in product formation (Table 1, entry 13).

With the optimized reaction conditions in hand, the substrate scope of the transformation was explored. Thus, using five isocyanides, one isocyanide equivalent (TMSCN), eight aldehydes, four ketones, and four hydrazinoazines as a pool of reagents, a library of congeners of generic structure **6** was generated (Scheme 4, Figure 1). Encouragingly, products were

Scheme 4. Substrate Scope for Bicyclic Triazines 6



obtained in good to excellent isolated yields with both aliphatic aldehydes and ketones being well-tolerated, the latter generating spirocyclic products **6g** (90%) and **6h** (54%). Of note, the tricyclic product **6n** was also accessible from the corresponding benzothiazolo-hydrazine (39% yield). However, aromatic aldehydes performed poorly under the model conditions and attempts to facilitate reaction through heating to 140 °C proved fruitless (**6o**, **6p**). The only observed product through reaction monitoring via LC/MS was the Schiff base. Gratifyingly, however, both the use of an aqueous solution of formaldehyde (**6f**, 60% yield) and replacement of a classical isocyanide with TMSCN[20] (**6l**, 42% yield; **6m**, 55% yield) proved successful.

The reaction mechanism is likely to involve a nonconcerted [5 + 1]-cycloaddition between isocyanides **1** and the corresponding Schiff base **I** to endow bicyclic product **6** (Scheme 5). Importantly, there are only a few reports involving such a process with isocyanides[21a,b] and none involve a 2-hydrazinopyridine moiety. Of note is that unlike a typical GBB-3CR product, the resultant chemotype **6c** (as confirmed by X-ray analysis, Figure S1, Supporting Information)[19] does not undergo imine−enamine tautomerization, presumably due to the stability of the nonaromatic imine form (**6**, Scheme 5) compared to the antiaromatic enamine form (**6′**, Scheme 5).

The successful development of a [5 + 1]-cycloaddition process to synthesize bicyclic-triazines **6** prompted us to pursue an analogous [5 + 2]-cycloaddition[21c] using isocyanates **7**, with the goal of producing novel seven-membered dihydropyrido-tetrazepinones **8** (Scheme 2). However, while exploring this transformation we serendipitously discovered a new highly efficient one-pot strategy to produce novel arrays of triazolopyridines **9** (Scheme 8, Figure 2), the strategy being in fact enticingly compatible with a variety of electrophilic reagents in one-pot fashion [Note: structure of **9c** was confirmed by X-ray diffraction, Figure S3, Supporting Information].[19] Interestingly, triazolopyridines are known to display a variety of biological activities including antifungal,[22] inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) as a potential treatment of type 2 diabetes,[23] and inhibition of phosphoinositide 3-kinase γ (PI3Kγ) for the prospective treatment of inflammatory diseases.[24a,b] Considering these and possibly undiscovered potential applications, optimal reaction conditions to access scaffold **9** were thus investigated via a "one-pot" model reaction (Scheme 6, Table 2). [Note: no preformation of Schiff base is necessary, and reagents may be added simultaneously]. The transformation was found to be favored in nonpolar solvents such as DCE and toluene (Table 2, entries 1, 3, 5−7), whereas in polar and/or protic solvents such as TFE and THF, product yields were diminished (Table 2, entries 2 and 4).

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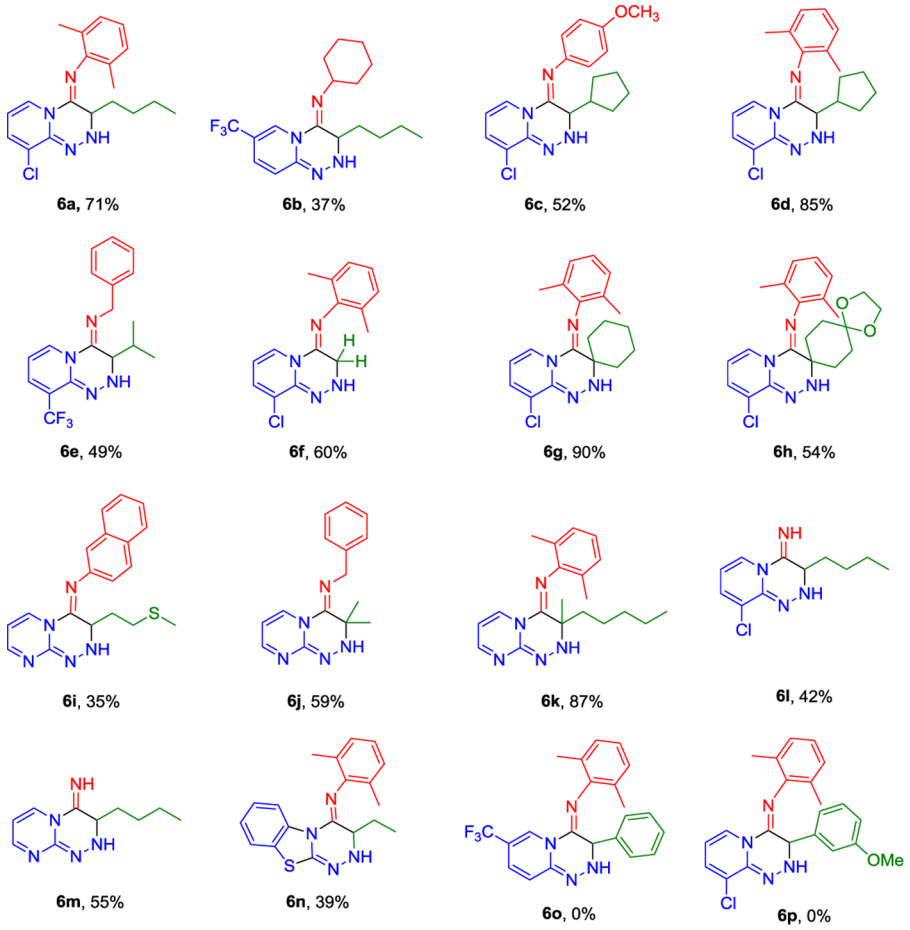
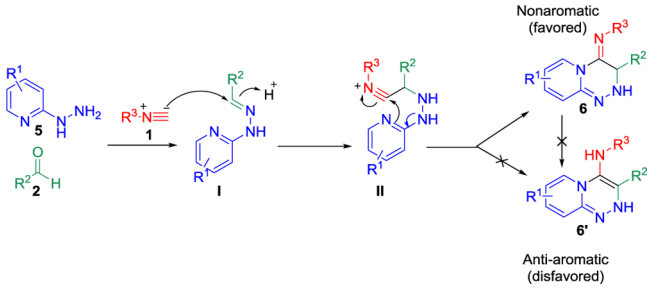


Figure 1. Synthesis of pyrido-, pyrimido-, and benzothiazolo-triazines via a novel one-pot 3-CR. Successful conversion with TMSCN required microwave irradiation (100 °C, 30 min).

Scheme 5. Proposed Mechanism for Pyridotriazine Formation



As expected, the use of desiccants slightly improved overall yields, probably attributable to a promotion of Schiff base formation and extension of the isocyanate half-life through removal of water. Optimal conditions proved to include calcium chloride in dichloroethane (DCE), while irradiating at 80 °C for 20 min (Table 2, entry 5, 77%). The reaction scope was subsequently studied, employing three aldehydes and ketones, six hydrazinoazines, and six isocyanates and isothiocyanates, to generate products **9a**–**9j** (Figure 2). In similar fashion to prior trends with the pyridotriazine scaffold **6**, aromatic aldehydes were found to be incompatible (**9k**, **9l**) whereas aliphatic aldehydes and ketones worked efficiently to furnish final products in isolated yields ranging from 36% to 91% (Figure 2). Replacing the isocyanate input with an isothiocyanate afforded triazolopyridine thioureas **9g**–**9i** albeit in moderate yields, requiring elevated temperatures and 5 equiv of isothiocyanate (Figure 2). Highly noteworthy was the successful use of tosyl-isocyanate affording **9j** containing an '*N*-acyl-sulfonamide-like' bioisostere of a carboxylic acid.[24c] Tricyclic scaffolds were also accessible as exemplified by **9f** (47%). Importantly, **9c** was synthesized on a larger scale (6.5 mmol of hydrazine–azine) with an acceptable isolated yield (61%).

A highly plausible mechanism for the transformation involves initial condensation of 2-hydrazinopyridine **5** and aldehyde **2** to produce imine **I** followed by intramolecular cyclization[25] to afford intermediate **III** which in turn undergoes an amidation reaction with **7** (Schemes 7 and 8).

Remarkably, the protocol was also amenable to the simple hydrazine **10**, resulting in the one-pot formation of the novel dihydroindazole-carboxamides **11a**–**d** (Scheme 9) with good overall isolated yields (Figure 3).

Encouraged by these results, we further investigated the compatibility of the one-pot reaction with other electrophiles. On replacement of an isocyanate with bromomaleic anhydride, the reaction proceeded smoothly and exclusively yielded the *E*-alkene isomer **14a** at room temperature (Scheme 10). A possible explanation for the high observed stereoselectivity is the hydrogen-bonding interaction between the proton of the carboxylic acid and the carbonyl of the amide moiety that confers stability, as observed by the X-ray structure of **14a** (Figure S5, Supporting Information).[19] Similarly, the use of

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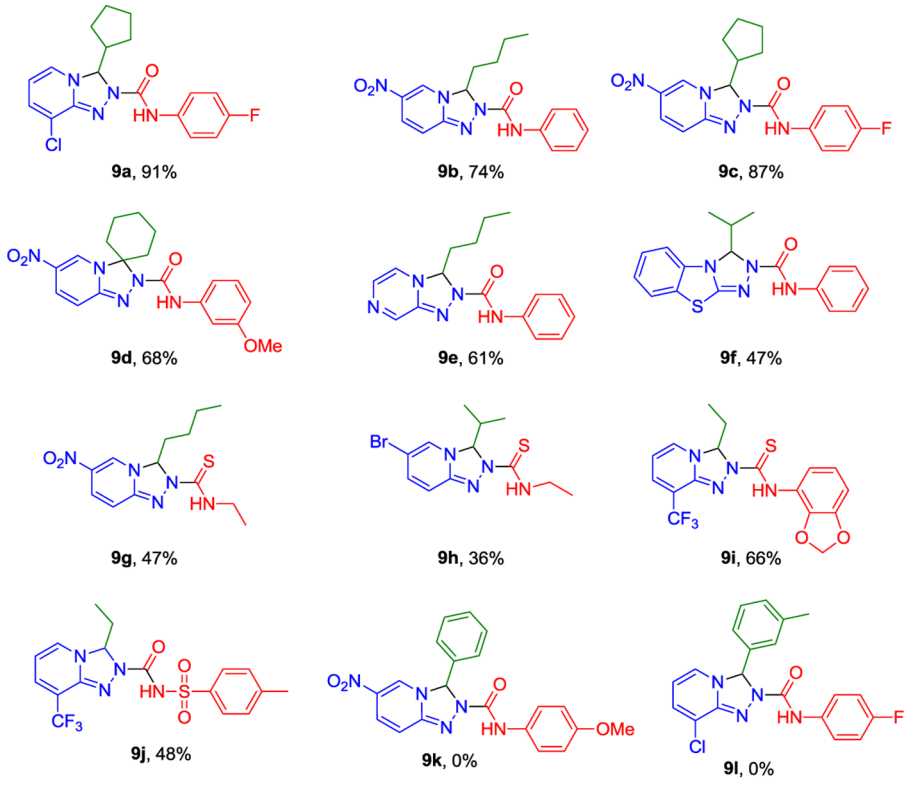


Figure 2. Exemplification of reaction scope. For **9a**–**9f**: 1 equiv of isocyanate was used with microwave irradiation at 80 °C for 20 min. For **9g**–**9i**: 5 equiv of isothiocyanate were used with microwave irradiation at 120 °C for 60 min. For **9j**: 1 equiv of tosyl isocyanate was used at room temperature with stirring for 30 min.

Scheme 6. Triazolopyridine-carboxamide 9b Model Reaction with Isocyanate 7a

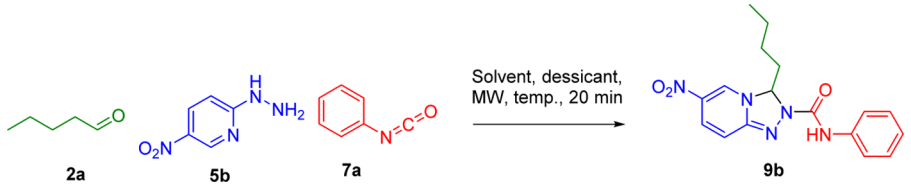
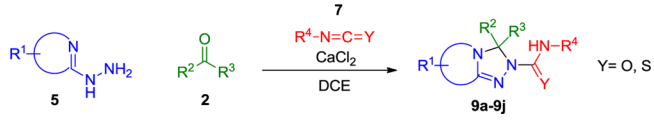


Table 2. Optimization of Reaction Conditions for the Synthesis of Triazolopyridines, 9

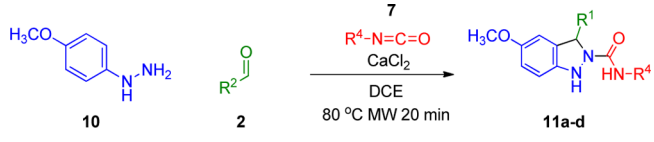
entry	solvent	desiccant	yield[a] [%]
1	DCE	–	65
2	TFE	–	13
3	toluene	–	54
4	THF	–	38
5	DCE	$CaCl_2$	77
6	DCE	$MgSO_4$	68
7	DCE	5 Å M.S.	66

[a]All reactions were carried out on a 0.25 mmol scale, irradiating with microwaves at 80 °C. Reported % yields are "Area under the Curve" of desired product (A%) as judged by LC/MS at UV 254 nm.

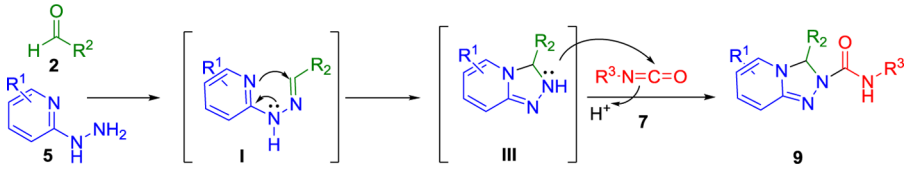
Scheme 8. Generic Reaction for Triazolo-carboxamide and Carbothiamide Synthesis



Scheme 9. Synthesis of Indazole-carboxamides



Scheme 7. Proposed Mechanism of Triazolopyridines Synthesis



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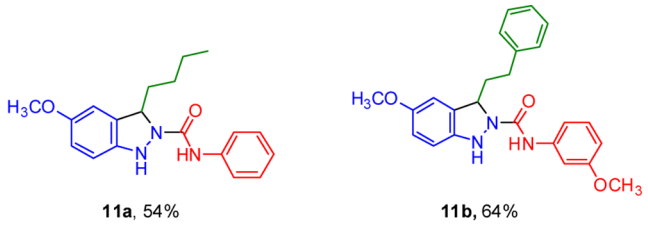


Figure 3. Collection of indazole carboxamides, **11a–11d**.

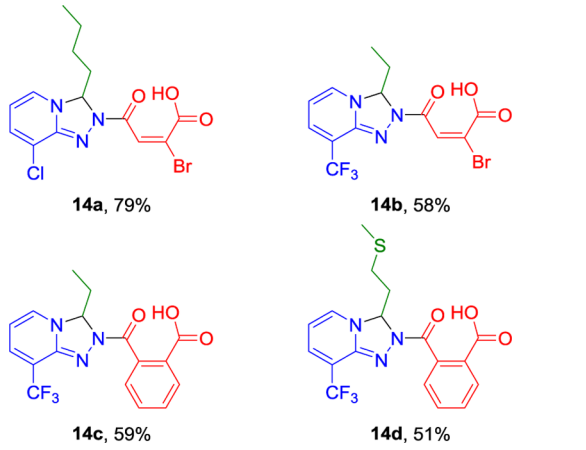


Figure 4. Small library of triazolopyridine-carboxylic acids, **14a–14d**.

phthalic anhydride as an electrophilic input rendered triazolopyridine-carboxylic acids **14c–d** (Figure 4) in good yields wherein the carboxylic acid moiety may be utilized for further diversification of the product.

Subsequently, the one-pot procedure involving condensation of benzoyl chloride **15a** with propanaldehyde **2b** and 2-hydrazino-5-nitro-pyridine **5b** was studied under different reaction conditions (Scheme 11). Surprisingly, use of base as an additive resulted in complex mixtures and the desired product was not observed by LC/MS (Table 3, entries 3–5). However, employing DCE as the solvent and microwave irradiation at 120 °C for 30 min proved highly satisfactory for the desired one-pot transformation (Table 3, entry 10). In this case, the use of calcium chloride as a desiccant did not improve yields (Table 3, entry 12).

Using these optimized reaction conditions, the scope of the transformation was further explored. Thus, employing three aldehydes, two hydrazino-pyridines, and six acyl chlorides (both aromatic and aliphatic), a small collection of compounds (**16a–f**) was prepared in moderate yields (Scheme 12, Figure 5).

CONCLUSIONS

In conclusion, a plethora of robust "one-pot" multicomponent synthetic strategies have been developed delivering novel scaffolds and representative sets with high skeletal diversity, namely pyridotriazines **6**, triazolopyridines **9**, **14**, and **16**, and dihydroindazoles **11**. Interestingly, a diverse set of triazolopyridines were generated employing various electrophiles (isocyanates, tosyl-isocyanates, isothiocyanates, cyclic anhydrides, and acyl chlorides) representative of a suite of "one-pot" three-component reactions where all reagents may be optimally added to the reaction mixture at the same time. The protocols are simple and straightforward and accommodate an assortment of miscellaneous reaction inputs delivering products with high atom economy. The majority of the starting materials are

Scheme 11. Model Reaction of 2-Hydrazino-pyridine 5b, Aldehyde 2b, and Acyl Chloride 15a

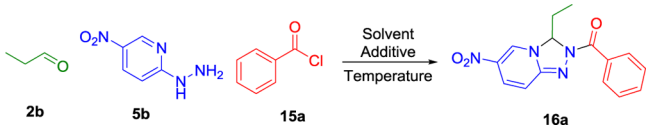
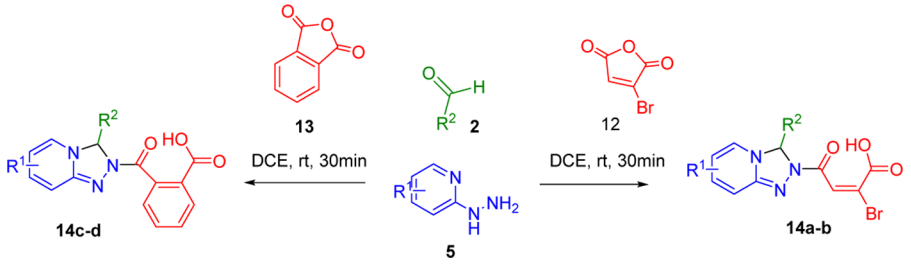


Table 3. Reaction Optimization for the Preparation of Acyl-triazolopyridine 16a

entry	solvent	temp (°C)	time (min)	additive	yield[a] [%]
1	DCE	rt, 30	30	–	nr
2	DCE	MW, 80	15	–	25
3	DCE	MW, 80	15	DIPEA	nd
4	DCE	MW, 80	15	DBU	nd
5	DCE	MW, 80	15	Na_2CO_3	nd
6	DCE	MW, 100	30	–	46
7	THF	MW, 100	30	–	21
8	dioxane	MW, 100	30	–	26
9	toluene	MW, 100	30	–	5
10	DCE	MW, 120	30	–	56
11	DCE	MW, 140	30	–	49
12	DCE	MW, 120	30	$CaCl_2$	51

[a]All reactions were carried out at 0.25 mmol scale. nr = no reaction, nd = not determined (complex mixture). Reported % yields are "Area under the Curve" of desired product (A%) as judged by LC/MS at UV 254 nm.

Scheme 10. Multicomponent Reaction of 2-Hydrazino-pyridine, Aldehydes, and Cyclic Anhydrides 12 and 13



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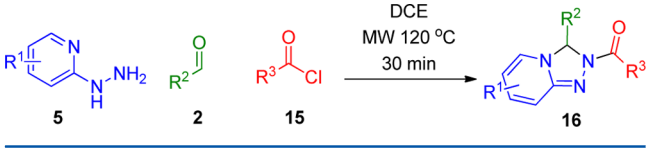
Scheme 12. Synthesis of Acyl-triazolopyridines 16



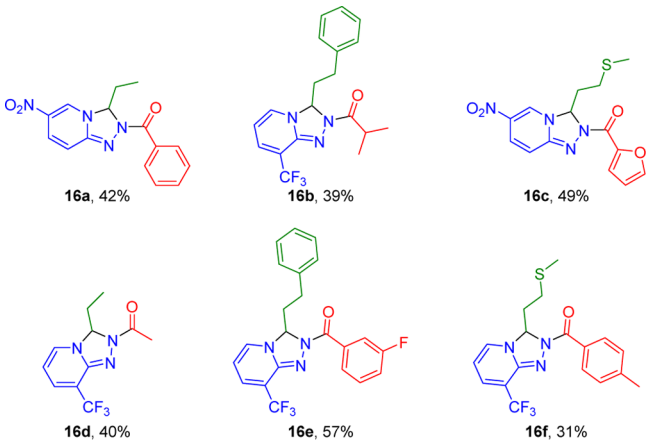


Figure 5. Small library of acyl-triazolopyridines **16a−16f**.

commercially available or can be prepared by well-known one- to two-step protocols.[26] The procedural simplicity, skeletal diversity, and high exploratory power associated with the chemistry presented herein render them suitable for high-throughput production of small molecules. Indeed, studies on the biological activity of these compounds against targets of interest are currently ongoing in our laboratory and results will be published in due course.

EXPERIMENTAL SECTION

General. All reagents and solvents were acquired from commercially available suppliers and used without further purification, unless specified. The products were purified using an automated flash chromatography apparatus. Low resolution mass spectra were obtained using positive ESI methods in a mass spectrometer. High resolution mass spectra were obtained using positive ESI methods for all compounds, except for **14b−d** for which negative ionization ESI methods were used and spectra were obtained with a Ion Cyclotron Resonance (ICR) spectrometer. ^{1}H and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively. The data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet). Coupling constants are reported in hertz (Hz) and were automatically generated using known NMR analyzer software. Melting points were obtained with open glass capillaries and are uncorrected. All microwave irradiation experiments were carried out in a Biotage Initiator, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 220 W maximum power using an external sensor of temperature. The reactions were either carried out in 5 mL microwave vials sealed with a Teflon septum through heating in the microwave cavity or stirring at room temperature. The scaled synthesis of **9c** was conducted in a 20 mL microwave vial.

General Procedure for the Synthesis of Pyrido/Pyrimido/Benzothiazolo-triazines 6a−6n. The corresponding 2-hydrazinyl-azine (1.3 equiv, 0.325 mmol), isocyanide (1.0 equiv, 0.25 mmol), aldehyde or ketone (1.0 equiv, 0.25 mmol), and scandium triflate (0.2 equiv, 0.05 mmol) were dissolved in a mixture of DCM/MeOH (3:1, 1 mL) and stirred at room temperature for 20 h. After reaction completion (monitored by TLC and LC/MS), the solvent was evaporated *in vacuo*, and the crude product was purified by flash chromatography (0−60% AcOEt/Hexane) to afford title compounds, **6a−6n**. For compounds **6i−k** and **6m** flash chromatography was performed using a more polar system (0−20% MeOH/DCM).

***(E)*-*N*-(3-Butyl-9-chloro-2*H*-pyrido[2,1-*c*][1,2,4]triazin-4(3*H*)-ylidene)-2,6-dimethylaniline (6a).** Yellow solid, 61 mg, 71% yield; mp 136−138 °C; R_f = 0.57 (silica gel, 20% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (d, J = 7.5 Hz, 1H), 7.03 (d, J = 7.4 Hz, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 6.7 Hz, 1H), 5.79 (t, J = 7.2 Hz, 1H), 5.61 (s, 1H), 3.49 (dd, J = 10.7, 2.8 Hz, 1H), 2.10 (d, J = 10.7 Hz, 6H), 1.61−1.50 (m, 1H), 1.26 (s, 2H), 1.06−1.04 (m, 3H), 0.73 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 148.4, 144.1, 138.0, 128.3, 128.0, 127.9, 127.0, 126.4, 125.9, 123.4, 110.0, 104.6, 48.7, 26.8, 25.6, 21.8, 18.2, 18.0, 13.6; $[M + H]^+$ = 343; HRMS (ESI) m/z calculated for $C_{19}H_{24}ClN_4$ $[M + H]^+$ = 343.16840; found 343.16852.

***(E)*-*N*-(3-Butyl-7-(trifluoromethyl)-2*H*-pyrido[2,1-*c*][1,2,4]-triazin-4(3*H*)-ylidene)cyclohexanamine (6b).** Yellow oil, 33 mg, 37% yield; R_f = 0.14 (silica gel, 20% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.36 (s, 1H), 6.47 (d, J = 9.9 Hz, 1H), 6.38 (d, J = 9.9 Hz, 1H), 5.30 (s, 1H), 4.11 (dd, J = 9.7, 3.8 Hz, 1H), 3.35 (t, J = 9.6 Hz, 1H), 1.86−1.25 (m, 16H), 0.93 (t, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 140.2, 128.5, 125.2, 123.3, 122.5, 122.3, 108.9, 56.6, 47.7, 34.3, 33.6, 29.7, 27.5, 25.5, 24.4 (d, J_{C-F} = 13.1 Hz), 22.3, 13.9; $[M + H]^+$ = 355; HRMS (ESI) m/z calculated for $C_{18}H_{26}F_3N_4$ $[M + H]^+$ = 355.21041; found 355.21055.

***(E)*-*N*-(9-Chloro-3-cyclopentyl-2*H*-pyrido[2,1-*c*][1,2,4]triazin-4(3*H*)-ylidene)-4-methoxyaniline (6c).** Orange solid, 46 mg, 52% yield; mp 154−155 °C, R_f = 0.12 (silica gel, 20% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.6 Hz, 1H), 6.91−6.82 (m, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.73−6.67 (m, 1H), 5.74 (m, 1H), 3.96 (d, J = 10.2 Hz, 1H), 3.81 (s, 3H), 1.93−1.79 (m, 1H), 1.68−1.65 (m, 2H), 1.48−1.37 (m, 6H), 1.12−1.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 151.3, 148.5, 147.0, 140.3, 138.2, 136.9, 127.0, 125.5, 121.7, 114.4, 104.3, 55.4, 52.4, 37.5, 29.5, 25.6, 24.9, 24.1; $[M + H]^+$ = 357; HRMS (ESI) m/z calculated for $C_{19}H_{22}ClN_4O$ $[M + H]^+$ = 357.14767; found 357.14771. Crystals for X-ray analysis were obtained by recrystallization using a mixture of Hexane/AcOEt (4:1).[19]

***(E)*-*N*-(9-Chloro-3-cyclopentyl-2*H*-pyrido[2,1-*c*][1,2,4]triazin-4(3*H*)-ylidene)-2,6-dimethylaniline (6d).** Yellow solid, 76 mg, 85% yield; mp 147−148 °C; R_f = 0.42 (silica gel, 20% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 6.6 Hz, 1H), 7.02 (d, J = 7.5 Hz, 2H), 6.97−6.86 (m, 1H), 6.74 (d, J = 6.7 Hz, 1H), 5.83−5.69 (m, 2H), 3.31 (d, J = 9.7 Hz, 1H), 2.15 (d, J = 15.6 Hz, 6H), 2.04 (d, J = 7.1 Hz, 1H), 1.85−1.69 (m, 1H), 1.49−1.37 (m, 5H), 1.10 (dd, J = 12.1, 8.5 Hz, 1H), 0.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 138.1, 129.5, 128.2, 127.9, 127.5, 126.7, 126.4, 125.6, 123.5, 104.4, 37.4, 29.7, 28.0, 25.0, 24.2, 18.7, 18.3, 18.2; $[M + H]^+$ = 355; HRMS (ESI) m/z calculated for $C_{20}H_{24}ClN_4$ $[M + H]^+$ = 355.16840; found 355.16846.

***(E)*-*N*-(3-Isopropyl-9-(trifluoromethyl)-2*H*-pyrido[2,1-*c*]-[1,2,4]triazin-4(3*H*)-ylidene)-1-phenylmethanamine (6e).** Orange solid, 43 mg, 49% yield; mp 171−172 °C; R_f = 0.33 (silica gel, 20% AcOEt/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.6 Hz, 1H), 7.35−7.26 (m, 6H), 6.94 (d, J = 6.5 Hz, 1H), 5.74−5.70 (m, 1H), 4.63 (dd, J = 38.2, 15.6 Hz, 2H), 3.84 (dd, J = 9.8, 1.7 Hz, 1H), 1.98 (ddt, J = 13.5, 9.8, 6.8 Hz, 1H), 1.06 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 139.3, 132.1, 129.2, 129.1, 128.5, 127.2, 126.9, 102.4, 53.0, 52.2, 25.5, 19.3, 18.6; $[M + H]^+$ = 349; HRMS (ESI) m/z calculated for $C_{18}H_{20}F_3N_4$ $[M + H]^+$ = 349.16346; found 349.16379.

***(E)*-*N*-(9-Chloro-2*H*-pyrido[2,1-*c*][1,2,4]triazin-4(3*H*)-ylidene)-2,6-dimethylaniline (6f).** Brown solid, 43 mg, 60% yield; mp 109−111 °C; R_f = 0.39 (silica gel, 20% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.6 Hz, 1H), 7.00 (t, J = 19.2 Hz, 3H), 6.96−6.88 (m, 1H), 6.76 (dd, J = 6.8, 1.2 Hz, 1H), 5.80 (dd, J = 7.6, 6.8 Hz, 1H), 3.34 (s, 2H), 2.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 143.4, 136.8, 135.4, 128.4, 127.9, 125.1, 123.9, 114.7, 114.1, 110.0, 29.7, 18.0; $[M + H]^+$ = 287; HRMS (ESI) m/z calculated for $C_{15}H_{16}ClN_4$ $[M + H]^+$ = 287.10580; found 287.10572.

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(*E*)-*N*-(9′-Chlorospiro[cyclohexane-1,3′-pyrido[2,1-*c*][1,2,4]-triazin]-4′(2′*H*)-ylidene)-2,6-dimethylaniline (6g). Yellow solid, 80 mg, 90% yield; mp 185−187 °C; R_f = 0.71 (silica gel, 10% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 7.5 Hz, 2H), 6.88 (d, J = 7.3 Hz, 1H), 6.86 (s, 1H), 6.55 (d, J = 6.7 Hz, 1H), 5.65 (s, 1H), 5.36 (t, J = 7.1 Hz, 1H), 2.09 (s, 6H), 1.81−1.44 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 128.2, 128.1, 126.0, 125.8, 125.5, 122.8, 103.6, 103.5, 52.7, 29.9, 25.5, 21.8, 18.5, 18.4; $[M + H]^+$ = 355; HRMS (ESI) m/z calculated for $C_{20}H_{24}ClN_4$ $[M + H]^+$ = 355.16840; found 355.16846.

***N*-[(4″*E*)-9″-Chloro-dispiro[1,3-dioxolane-2,1′-cyclohexane-4′,3″-pyrido[2,1-*c*][1,2,4]triazin]-4′(2*H*)-ylidene]-2,6-dimethyl-aniline (6h).** Yellow solid, 56 mg, 54% yield; mp 194−196 °C; R_f = 0.42 (silica gel, 10% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 7.5 Hz, 2H), 6.89 (t, J = 7.5 Hz, 1H), 6.63 (s, 1H), 6.54 (d, J = 6.7 Hz, 1H), 5.55 (s, 1H), 5.37−5.28 (m, 1H), 3.96 (s, 4H), 2.10 (s, 6H), 2.09−2.02 (m, 2H), 1.94 (s, 2H), 1.81−1.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 143.3, 135.7, 128.1, 127.9, 126.0, 125.4, 123.2, 110.0, 108.1, 103.5, 64.4, 64.4, 51.7, 31.1, 29.7, 28.1, 18.5, 18.4; $[M + H]^+$ = 413; HRMS (ESI) m/z calcd for $C_{22}H_{26}ClN_4O_2$ $[M + H]^+$ = 413.17443; found 413.17428

(*E*)-*N*-(3-(2-(Methylthio)ethyl)-2*H*-pyrimido[2,1-*c*][1,2,4]-triazin-4(3*H*)-ylidene)naphthalen-2-amine (6i). Orange oil, 31 mg, 35% yield; R_f = 0.43 (silica gel, 10% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (dd, J = 4.4, 2.2 Hz, 1H), 8.45−8.29 (m, 3H), 7.83−7.69 (m, 4H), 7.44 (dd, J = 6.2, 3.2 Hz, 2H), 7.04 (dd, J = 6.5, 4.4 Hz, 1H), 4.71 (dd, J = 10.1, 5.3 Hz, 1H), 2.66−2.50 (m, 2H), 2.07 (dd, J = 13.5, 7.2 Hz, 1H), 2.00 (s, 3H), 1.56 (ddd, J = 14.1, 8.4, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.7, 158.6, 152.7, 148.2, 133.6, 133.3, 132.0, 129.1, 128.5, 127.8, 126.9, 126.6, 121.3, 113.8, 113.1, 50.9, 29.3, 15.5; $[M + H]^+$ = 350; HRMS (ESI) m/z calculated for $C_{19}H_{20}N_5S$ $[M + H]^+$ = 350.14339; found 350.14371.

(*E*)-*N*-(3,3-Dimethyl-2*H*-pyrimido[2,1-*c*][1,2,4]triazin-4(3*H*)-ylidene)-1-phenylmethanamine (6j). Yellow oil, 40 mg, 59% yield; R_f = 0.21 (silica gel, 10% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, J = 4.4, 2.1 Hz, 1H), 8.38 (dd, J = 6.6, 2.2 Hz, 1H), 7.49−6.98 (m, 7H), 4.84 (s, 2H), 1.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 162.8, 152.6, 146.3, 135.7, 128.8, 128.5, 128.0, 113.1, 51.9, 46.1, 21.6; $[M + H]^+$ = 268; HRMS (ESI) m/z calculated for $C_{15}H_{18}N_5$ $[M + H]^+$ = 268.15567; found 268.15590.

(*E*)-2,6-Dimethyl-*N*-(3-methyl-3-pentyl-2*H*-pyrimido[2,1-*c*]-[1,2,4]triazin-4(3*H*)-ylidene)aniline (6k). Orange solid, 73 mg, 87% yield; mp 118−120 °C; R_f = 0.32 (silica gel, 10% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.23 (d, J = 6.4 Hz, 1H), 7.84 (s, 1H), 7.11 (d, J = 7.5 Hz, 1H), 7.05 (d, J = 7.1 Hz, 2H), 6.98−6.92 (m, 1H), 2.23 (d, J = 30.3 Hz, 6H), 1.68 (s, 3H), 1.47−1.36 (m, 2H), 1.25 (dd, J = 11.0, 4.7 Hz, 6H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 162.6, 157.7, 155.1, 152.6, 152.6, 146.5, 138.9, 128.4, 121.7, 118.5, 55.1, 35.0, 31.6, 22.4, 22.3, 19.0, 13.8; $[M + H]^+$ = 338; HRMS (ESI) m/z calculated for $C_{20}H_{28}N_5$ $[M + H]^+$ = 338.23392; found 338.23388.

3-Butyl-9-chloro-2*H*-pyrido[2,1-*c*][1,2,4]triazin-4(3*H*)-imine (6l). Yellow oil, 25 mg, 42% yield; R_f = 0.63 (silica gel, 40% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 4.9, 1.1 Hz, 1H), 7.56−7.42 (m, 1H), 6.72 (dd, J = 7.6, 4.9 Hz, 1H), 6.55 (s, 1H), 5.04 (s, 1H), 4.03 (t, J = 7.0 Hz, 1H), 1.92−1.79 (m, 2H), 1.64−1.50 (m, 2H), 1.42 (dd, J = 14.6, 7.4 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 145.5, 136.9, 119.9, 115.8, 115.6, 53.1, 30.7, 27.6, 22.3, 13.8; $[M + H]^+$ = 239; HRMS (ESI) m/z calculated for $C_{11}H_{16}ClN_4$ $[M + H]^+$ = 239.10580; found 239.10581.

3-Butyl-2*H*-pyrimido[2,1-*c*][1,2,4]triazin-4(3*H*)-imine (6m). Yellow oil, 28 mg, 55% yield; R_f = 0.30 (silica gel, 10% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 4.8 Hz, 1H), 8.38 (d, J = 4.8 Hz, 1H), 7.26−7.22 (m, 1H), 7.06 (d, J = 3.9 Hz, 1H), 6.74−6.68 (m, 1H), 4.73 (t, J = 4.4 Hz, 1H), 2.47−2.36 (m, 1H), 1.87−1.80 (m, 1H), 1.62−1.49 (m, 2H), 1.45−1.37 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 146.9, 119.8, 113.1, 52.9, 30.8, 29.4, 27.7, 22.4, 13.9; $[M + H]^+$ = 206; HRMS (ESI) m/z calculated for $C_{10}H_{16}N_5$ $[M + H]^+$ = 206.13274; found 206.13271.

(*E*)-*N*-(3-Ethyl-2*H*-benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazin-4(3*H*)-ylidene)-2,6-dimethylaniline (6n). Beige solid, 33 mg, 39% yield; mp 135−136 °C; R_f = 0.30 (silica gel, 20% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89−8.70 (m, 1H), 7.33 (dd, J = 7.7, 1.4 Hz, 1H), 7.28−7.19 (m, 1H), 7.19−7.12 (m, 1H), 7.06 (d, J = 7.5 Hz, 2H), 6.95 (d, J = 7.5 Hz, 1H), 3.42 (dd, J = 10.8, 3.7 Hz, 1H), 2.16 (d, J = 6.5 Hz, 6H), 1.70 (ddd, J = 13.9, 10.8, 7.2 Hz, 1H), 1.26 (br s, 1H), 1.10 (ddd, J = 13.8, 7.4, 3.8 Hz, 1H), 0.78 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 144.6, 143.6, 137.9, 128.3, 128.2, 128.1, 126.6, 126.0, 124.6, 123.9, 123.4, 121.7, 117.4, 51.7, 20.3, 18.7, 18.4, 9.8; $[M + H]^+$ = 337; HRMS (ESI) m/z calculated for $C_{19}H_{21}N_4S$ $[M + H]^+$ = 337.14814; found 337.14847.

General Procedure for the Synthesis of Triazolo Azines Carboxamides 9a−9f. To a stirring solution of 2-hydrazinyl-azine (1.0 equiv, 0.25 mmol) dissolved in DCE (1 mL) were added the aldehyde or ketone (1.0 equiv, 0.25 mmol) and the isocyanate (1.0 equiv, 0.25 mmol), followed by the addition of calcium chloride (0.1 equiv). The reaction was heated via microwave irradiation for 20 min at 80 °C. Upon reaction completion (monitored by LC/MS and TLC), the solvent was evaporated *in vacuo* and the crude product was separated with an automated flash chromatography system (using a gradient of 0−30% AcOEt/Hexane) to obtain title compounds, **9a−9f**.

Procedure for the Synthesis of Triazolo-azine Carboxamide 9c (Scaled Version). To a stirring solution of 2-hydrazinyl-5-nitropyridine (1.0 equiv, 6.5 mmol, 1.0 g) dissolved in DCE (15 mL) were added cyclopentantecarboxaldehyde (1.0 equiv, 6.5 mmol, 0.693 mL) and 4-fluorophenyl isocyanate (1.0 equiv, 6.5 mmol, 0.738 mL). The reaction was heated via microwave irradiation for 20 min at 80 °C. Upon reaction completion (monitored by LC/MS and TLC), the solvent was evaporated *in vacuo* and the crude product was separated with an automated flash chromatography system (using a gradient of 0−30% AcOEt/Hexane) to obtain compound **9c** (61% yield, 1.47 g).

8-Chloro-3-cyclopentyl-*N*-(4-fluorophenyl)-[1,2,4]triazolo-[4,3-*a*]pyridine-2(3*H*)-carboxamide (9a). Orange solid, 82 mg, 91% yield; mp 157−159 °C; R_f = 0.24 (silica gel, 25% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.55−7.35 (m, 2H), 7.05−6.96 (m, 4H), 6.39 (d, J = 4.4 Hz, 1H), 5.81 (t, J = 6.9 Hz, 1H), 2.48−2.35 (m, 1H), 1.78−1.47 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 157.5, 154.3, 148.5, 134.4, 133.9, 129.3, 120.9, 117.1, 115.5, 115.3, 104.2, 79.6, 47.0, 27.4, 26.4, 25.4, 24.8; $[M + H]^+$ = 361; HRMS (ESI) m/z calculated for $C_{18}H_{19}ClFN_4O$ $[M + H]^+$ = 361.12259; found 361.12258.

3-Butyl-6-nitro-*N*-phenyl-[1,2,4]triazolo[4,3-*a*]pyridine-2(3*H*)-carboxamide (9b). Brown solid, 63 mg, 74% yield; mp 149−151 °C; R_f = 0.51 (silica gel, 25% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 2.0 Hz, 1H), 7.76 (d, J = 23.5 Hz, 1H), 7.58−7.52 (m, 1H), 7.47 (dd, J = 11.5, 3.8 Hz, 2H), 7.32 (d, J = 7.5 Hz, 2H), 7.06 (td, J = 7.5, 1.0 Hz, 1H), 6.34 (dd, J = 7.8, 4.3 Hz, 1H), 2.27 (m, 1H), 2.01−1.88 (m, 1H), 1.54−1.19 (m, 5H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 145.5, 137.9, 134.0, 134.0, 131.0, 129.0, 128.9, 123.4, 119.1, 111.3, 34.7, 23.9, 22.2, 13.9; $[M + H]^+$ = 342; HRMS (ESI) m/z calculated for $C_{17}H_{20}N_5O_3$ $[M + H]^+$ = 342.15607; found 342.15616.

3-Cyclopentyl-*N*-(4-fluorophenyl)-6-nitro-[1,2,4]triazolo[4,3-*a*]pyridine-2(3*H*)-carboxamide (9c). Orange solid, 81 mg, 87% yield; mp 154−155 °C; R_f = 0.48 (silica gel, 25% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 2.1 Hz, 1H), 7.76 (s, 1H), 7.59 (dd, J = 10.3, 2.1 Hz, 1H), 7.47−7.37 (m, 2H), 7.06−6.96 (m, 2H), 6.39 (dd, J = 7.3, 5.5 Hz, 2H), 2.52−2.39 (m, 1H), 1.72−1.59 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 157.7, 153.2, 146.7, 134.3, 129.1, 120.9, 115.7, 115.5, 111.1, 110.0, 78.3, 47.3, 27.2, 26.1, 25.2, 24.7; $[M + H]^+$ = 372; HRMS (ESI) m/z calculated for $C_{18}H_{19}FN_5O_3$ $[M + H]^+$ = 372.14664; found 372.14662. Crystals for X-ray analysis were obtained from a mixture of hexane/DCM (4:1) via slow solvent evaporation.[19]

***N*-(3-Methoxyphenyl)-6-nitro-2*H*-spiro[[1,2,4]triazolo[4,3-*a*]-pyridine-3,1′-cyclohexane]-2-carboxamide (9d).** Brown solid, 65 mg, 68% yield; mp 183−185 °C ; R_f = 0.37 (silica gel, 25% AcOEt/

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Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 1.9 Hz, 1H), 7.91 (s, 1H), 7.48 (dd, J = 10.3, 2.1 Hz, 1H), 7.21−7.15 (m, 2H), 6.96 (m, 1H), 6.61 (m, 1H), 6.30 (d, J = 10.3 Hz, 1H), 3.81 (s, 3H), 3.09 (td, J = 14.1, 5.4 Hz, 2H), 2.21 (d, J = 14.7 Hz, 2H), 2.07−1.87 (m, 3H), 1.73−1.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 150.2, 142.7, 139.4, 135.3, 130.4, 129.6, 128.2, 128.2, 111.4, 109.1, 104.8, 85.5, 55.3, 33.3, 23.1, 21.8; $[M + H]^+$ = 384; HRMS (ESI) m/z calculated for $C_{19}H_{22}N_5O_4$ $[M + H]^+$ = 384.16663; found 384.16655.

3-Butyl-*N*-phenyl-[1,2,4]triazolo[4,3-*a*]pyrazine-2(3*H*)-carboxamide (9e). Orange solid, 45 mg, 61% yield; mp 153−155 °C ; R_f = 0.33 (silica gel, 25% AcOEt/Hexane); ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.01 (s, 1H), 7.75 (s, 1H), 7.48 (d, J = 8.6 Hz, 2H), 7.30 (s, 1H), 7.04 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 4.7 Hz, 1H), 6.68 (d, J = 4.0 Hz, 1H), 6.30 (t, J = 3.7 Hz, 1H), 1.47−1.19 (m, 7H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 143.3, 142.4, 142.4, 138.2, 129.0, 123.1, 122.1, 119.0, 34.3, 24.2, 22.3, 14.0; $[M + H]^+$ = 298; HRMS (ESI) m/z calculated for $C_{16}H_{20}N_5O$ $[M + H]^+$ = 298.16624; found 298.16632.

3-Isopropyl-*N*-phenylbenzo[4,5]thiazolo[2,3-*c*][1,2,4]-triazole-2(3*H*)-carboxamide (9f). Brown solid, 40 mg, 47% yield; mp 155−157 °C; R_f = 0.25 (silica gel, 20% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1H), 8.56 (d, J = 4.7 Hz, 1H), 7.82−7.76 (m, 2H), 7.61−7.59 (m, 1H), 7.39−7.29 (m, 5H), 7.14 (d, J = 0.7 Hz, 1H), 1.29−1.27 (m, 6H), 1.17−1.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 150.5, 149.9, 137.9, 132.5, 129.4, 129.2, 126.3, 124.3, 124.0, 121.3, 121.1, 120.6, 33.0, 31.6, 19.9, 19.4; $[M + H]^+$ = 339; HRMS (ESI) m/z calculated for $C_{18}H_{19}N_4OS$ $[M + H]^+$ = 339.12013; found 339.12019.

General Procedure for the Synthesis of Triazolo-azines Carbothiamides 9g−9i. To a stirring solution of 2-hydrazinyl-pyridine (1.0 equiv, 0.25 mmol) in DCE (1 mL) were added the aldehyde (1.0 equiv, 0.25 mmol) and the isothiocyanate (5.0 equiv, 1.25 mmol), followed by the addition of calcium chloride (0.1 equiv). The reaction was heated by microwave irradiation for 60 min at 120 °C. Upon reaction completion (monitored by LC/MS and TLC), the solvent was evaporated *in vacuo* and the crude product was purified with an automated flash chromatography purification system (using a gradient of 0−30% AcOEt/Hexane) to obtain title compounds, **9g−9i**.

3-Butyl-*N*-ethyl-6-nitro-[1,2,4]triazolo[4,3-*a*]pyridine-2(3*H*)-carbothioamide (9g). Brown oil, 36 mg, 47% yield; R_f = 0.57 (silica gel, 25% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.20 (m, 1H), 7.62 (ddd, J = 10.3, 2.2, 0.8 Hz, 1H), 6.99 (s, 1H), 6.83−6.66 (m, 1H), 6.36 (d, J = 10.3 Hz, 1H), 3.74−3.60 (m, 2H), 2.71 (m, J, 1H), 1.37 (m, 4H), 1.25 (dd, J = 7.2, 0.6 Hz, 3H), 1.00−0.93 (m, 1H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 146.4, 133.6, 131.2, 129.6, 111.0, 79.3, 39.3, 34.3, 23.8, 22.2, 14.5, 13.9; $[M + H]^+$ = 310; HRMS (ESI) m/z calculated for $C_{13}H_{20}N_5O_2S$ $[M + H]^+$ = 310.13322; found 310.13315.

6-Bromo-*N*-ethyl-3-isopropyl-[1,2,4]triazolo[4,3-*a*]pyridine-2(3*H*)-carbothioamide (9h). Orange solid, 30 mg, 36% yield; mp 122−123 °C; R_f = 0.28 (silica gel, 20% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09−7.04 (m, 1H), 6.92 (dd, J = 9.9, 1.9 Hz, 2H), 6.53 (d, J = 2.0 Hz, 1H), 6.31 (d, J = 9.9 Hz, 1H), 3.66 (qd, J = 7.3, 5.6 Hz, 2H), 2.92−2.81 (m, 1H), 1.25 (d, J = 7.2 Hz, 3H), 1.10 (d, J = 7.3 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 139.2, 131.1, 113.1, 96.6, 83.3, 39.3, 33.5, 29.8, 18.4, 14.8, 14.7; $[M + H]^+$ = 329; HRMS (ESI) m/z calculated for $C_{12}H_{18}BrN_4S$ $[M + H]^+$ = 329.04299; found 329.04395.

***N*-(Benzo[*d*][1,3]dioxol-4-yl)-3-ethyl-8-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine-2(3*H*)-carbothioamide (9i).** Orange oil, 65 mg, 66% yield; R_f = 0.12 (silica gel, 20% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (m, 1H), 7.40−7.30 (m, 1H), 7.15 (q, J = 5.4 Hz, 2H), 6.89−6.71 (m, 3H), 5.97 (s, 2H), 2.76 (qd, J = 7.4, 3.9 Hz, 1H), 2.03−1.92 (m, 1H), 1.26 (t, J = 7.1 Hz, 1H), 1.00−0.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 147.4, 145.6, 136.0, 134.0, 132.5, 118.7, 107.8, 107.5, 103.7, 101.4, 79.3, 26.9, 6.1; $[M + H]^+$ = 397; HRMS (ESI) m/z calculated for $C_{17}H_{16}F_3N_4O_2S$ $[M + H]^+$ = 397.09406; found 397.09461.

General Procedure for the Synthesis of *N*-Tosyl Triazolo-pyridine-carboxamide 9j. To a stirring solution of 2-hydrazinyl-pyridine (1.0 equiv, 0.25 mmol) in DCE (1 mL) were added the aldehyde (1.0 equiv, 0.25 mmol) and tosyl isocyanate (1.0 equiv, 0.25 mmol), followed by the addition of calcium chloride (0.1 equiv). The reaction was stirred at room temperature for 30 min. Upon reaction completion (monitored by LC/MS and TLC), the solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography with an automated flash chromatography system (using a gradient of 0−60% AcOEt/Hexane) to obtain the title compound **9j**.

3-Ethyl-*N*-tosyl-8-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]-pyridine-2(3*H*)-carboxamide (9j). Orange solid, 50 mg, 48% yield; mp 136−138 °C; R_f = 0.47 (silica gel, 60% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (br. s, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.27−7.24 (m, 1H), 7.04−6.98 (m, 1H), 6.10 (t, J = 3.4 Hz, 1H), 5.88 (t, J = 6.8 Hz, 1H), 2.42 (s, 3H), 2.17 (m, 1H), 1.83 (m, 1H), 0.85 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 145.1, 144.7, 136.5, 135.9, 133.9, 129.6, 128.4, 122.9, 120.2, 113.4, 103.5, 76.6, 26.9, 21.8, 6.1; $[M + H]^+$ = 415; HRMS (ESI) m/z calculated for $C_{17}H_{18}F_3N_4O_3S$ $[M + H]^+$ = 415.10462; found 415.10526.

General Procedure for the Synthesis of Indazole-carboxamides 11a−d. To a stirring solution of 4-methoxyphenylhydrazine (1.0 equiv, 0.25 mmol) and aldehyde (1.0 equiv, 0.25 mmol) dissolved in DCE (1 mL) was added the isocyanate (1.0 equiv, 0.25 mmol), followed by the addition of calcium chloride (0.1 equiv), and the reaction was heated under microwave irradiation for 20 min at 80 °C. Upon reaction completion (monitored by LC/MS and TLC), the solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography with an automated flash chromatography system (using a gradient of 0−30% AcOEt/Hexane) to obtain the title compounds **11a−11d**.

3-Butyl-5-methoxy-*N*-phenyl-1*H*-indazole-2(3*H*)-carboxamide (11a). Orange oil, 44 mg, 54% yield; R_f = 0.45 (silica gel, 25% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.61−7.49 (m, 2H), 7.35−7.26 (m, 2H), 7.14−6.98 (m, 5H), 6.61 (t, J = 5.4 Hz, 1H), 3.83 (s, 3H), 2.35−2.14 (m, 2H), 1.56−1.38 (m, 2H), 1.40−1.26 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 152.9, 143.7, 143.6, 138.7, 131.0, 128.9, 128.0, 122.8, 119.0, 115.3, 55.5, 55.4, 32.2, 28.6, 22.3, 13.9; $[M + H]^+$ = 326; HRMS (ESI) m/z calculated for $C_{19}H_{24}N_3O_2$ $[M + H]^+$ = 326.18630; found 326.18621.

5-Methoxy-*N*-(3-methoxyphenyl)-3-phenethyl-1*H*-indazole-2(3*H*)-carboxamide (11b). Brown oil, 65 mg, 64% yield; R_f = 0.53 (silica gel, 40% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.42 (s, 1H), 7.28 (d, J = 7.5 Hz, 2H), 7.23−7.12 (m, 4H), 7.06 (d, J = 9.0 Hz, 2H), 6.99 (d, J = 9.0 Hz, 2H), 6.92 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 6.65 (t, J = 5.1 Hz, 1H), 6.60 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.84 (t, J = 7.6 Hz, 2H), 2.68−2.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.9, 152.9, 142.6, 140.6, 139.9, 130.9, 129.4, 128.5, 128.3, 127.8, 126.3, 115.4, 111.1, 109.4, 104.2, 55.5, 55.2, 34.0, 32.8; $[M + H]^+$ = 404; HRMS (ESI) m/z calculated for $C_{24}H_{26}N_3O_3$ $[M + H]^+$ = 404.19687; found 404.19776.

***N*-(3-Chlorophenyl)-3-ethyl-5-methoxy-1*H*-indazole-2(3*H*)-carboxamide (11c).** Beige solid, 33 mg, 40% yield; mp 146−147 °C; R_f = 0.34 (silica gel, 20% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.51 (d, J = 8.9 Hz, 2H), 7.25 (d, J = 8.9 Hz, 2H), 7.16−6.90 (m, 4H), 6.65 (t, J = 5.0 Hz, 1H), 3.83 (s, 3H), 2.30 (qd, J = 7.5, 5.0 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 153.0, 144.9, 137.5, 131.1, 129.0, 127.8, 127.7, 120.3, 115.5, 55.6, 26.0, 10.8; $[M + H]^+$ = 332; HRMS (ESI) m/z calculated for $C_{17}H_{19}ClN_3O_2$ $[M + H]^+$ = 332.11603; found 332.11637.

5-Methoxy-3-(2-(methylthio)ethyl)-*N*-(4-(trifluoromethoxy)-phenyl)-1*H*-indazole-2(3*H*)-carboxamide (11d). Beige solid, 71 mg, 66% yield; mp 133−135 °C; R_f = 0.22 (silica gel, 20% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.59 (d, J = 9.1 Hz, 2H), 7.21−6.86 (m, 5H), 6.66 (t, J = 4.8 Hz, 1H), 3.84 (s, 3H), 2.71 (td, J = 6.7, 1.1 Hz, 2H), 2.65−2.54 (m, 2H), 2.14 (s, 3H), 1.59 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 152.9, 144.5, 141.6,

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137.6, 131.0, 127.6, 121.9, 120.1, 115.6, 55.7, 32.2, 31.3, 16.0; $[M + H]^+$ = 428; HRMS (ESI) m/z calculated for $C_{19}H_{21}F_3N_3O_3S$ $[M + H]^+$ = 428.12502; found 428.12561.

General Procedure for the Synthesis of Triazolopyridine Carboxylic Acids 14a−d. To a stirring solution of the corresponding 2-hydrazinylpyridine (1.0 equiv, 0.25 mmol) in DCE (1 mL) were added the aldehyde (1.0 equiv, 0.25 mmol) and the corresponding cyclic anhydride (1.0 equiv, 0.25 mmol). The reaction was stirred for 30 min at room temperature. Upon reaction completion (monitored by LC/MS and TLC), the solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (using a gradient 0−20% AcOET/DCM) to obtain compounds of generic structure **14**.

(*E*)-2-Bromo-4-(3-butyl-8-chloro-[1,2,4]triazolo[4,3-*a*]-pyridin-2(3*H*)-yl)-4-oxobut-2-enoic Acid (14a). Orange crystals, 77 mg, 79% yield; mp 154−155 °C ; R_f = 0.28 (silica gel, 5% AcOEt/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.19 (dd, J = 7.1, 0.9 Hz, 1H), 7.07 (dd, J = 6.8, 0.9 Hz, 1H), 6.46 (t, J = 3.4 Hz, 1H), 6.06 (t, J = 7.0 Hz, 1H), 2.56−2.32 (m, 1H), 1.94 (m, 1H), 1.33 (m, 4H), 1.15 (m, 1H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 158.3, 150.5, 136.1, 128.6, 128.5, 117.4, 110.1, 106.5, 79.3, 31.7, 23.9, 22.2, 13.9; $[M + H]^+$ = 388; HRMS (ESI) m/z calculated for $C_{14}H_{16}BrClN_3O_3$ $[M + H]^+$ = 388.00581; found 388.00505. Single crystal structure for X-ray analysis was obtained from a mixture of AcOEt/Hexane (1:3) by means of slow evaporation.[19]

(*E*)-2-Bromo-4-(3-ethyl-8-(trifluoromethyl)-[1,2,4]triazolo-[4,3-*a*]pyridin-2(3*H*)-yl)-4-oxobut-2-enoic Acid (14b). Orange oil, 57 mg, 58% yield; R_f = 0.15 (silica gel, 5% AcOEt/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.45 (d, J = 6.8 Hz, 1H), 7.32 (d, J = 1.0 Hz, 1H), 6.41 (t, J = 3.3 Hz, 1H), 6.12 (t, J = 6.9 Hz, 1H), 2.51 (m, 1H), 2.06−1.93 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 158.4, 147.8, 137.3, 136.2, 134.1, 128.7, 120.1, 113.3, 104.9, 78.0, 25.0, 5.9; $[M + H]^+$ = 394; HRMS (ESI) m/z calculated for $C_{13}H_{10}BrF_3N_3O_3$ $[M - H]^-$ = 391.98630; found 391.98622.

2-(3-Ethyl-8-(trifluoromethyl)-2,3-dihydro-[1,2,4]triazolo-[4,3-*a*]pyridine-2-carbonyl)benzoic Acid (14c). Brown oil, 54 mg, 59% yield; R_f = 0.5 (silica gel, 10% AcOEt/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (br. s, 1H), 8.14 (m,1H), 8.07−7.78 (m, 3H), 7.62 (d, J = 7.0 Hz, 1H), 7.64−7.46 (m, 2H), 6.99 (t, J = 6.9 Hz, 1H), 3.17 (q, J = 7.6 Hz, 2H), 1.50 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 151.7, 136.2, 134.7, 131.7, 130.9, 129.8, 128.7, 125.8, 125.7, 124.1, 116.6, 112.5, 52.9, 29.8, 18.2, 11.0; $[M + H]^+$ = 366; HRMS (ESI) m/z calculated for $C_{17}H_{13}F_3N_3O_3$ $[M - H]^-$ = 364.09145; found 364.09153.

2-(3-(2-(Methylthio)ethyl)-8-(trifluoromethyl)-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyridine-2-carbonyl)benzoic Acid (14d). Orange oil, 52 mg, 51% yield; R_f = 0.22 (silica gel, 10% AcOEt/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−7.67 (m, 3H), 7.62−7.37 (m, 2H), 7.10 (m, 2H), 5.66 (t, J = 6.8 Hz, 1H), 2.74 (m, 1H), 2.65−2.41 (m, 2H), 2.34−2.23 (m, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 162.7, 145.6, 136.0, 134.6, 129.7, 128.2, 125.7, 124.0, 116.4, 114.2, 110.0, 75.5, 33.7, 31.6, 31.4, 27.6, 15.6; $[M + H]^+$ = 412; HRMS (ESI) m/z calculated for $C_{18}H_{15}F_3N_3O_3S$ $[M - H]^-$ = 410.07917; found 410.07967.

General Procedure for the Synthesis of Acyl-triazolo-pyridines 16a−f. To a stirring solution of the corresponding 2-hydrazinyl-pyridine (1.0 equiv, 0.25 mmol) and aldehyde (1.0 equiv, 0.25 mmol) dissolved in DCE (1 mL) was added acyl chloride (1.0 equiv, 0.25 mmol), and the reaction was heated via microwave irradiation for 30 min at 120 °C. After reaction completion (monitored by LC/MS and TLC), solvent was evaporated *in vacuo* and the crude product was purified with an automated flash chromatography system (using a gradient of 0−40% AcOEt/Hexane) to obtain compounds of generic structure **16**.

(3-Ethyl-6-nitro-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)-(phenyl)methanone (16a). Brown oil, 31 mg, 42% yield; R_f = 0.20 (silica gel, 40% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 2.1 Hz, 1H), 7.97 (dd, J = 8.4, 1.4 Hz, 2H), 7.66−7.33 (m, 4H), 6.60 (s, 1H), 6.37 (dd, J = 10.4, 0.5 Hz, 1H), 2.59 (ddd, J = 15.2, 7.5, 3.5 Hz, 1H), 2.22−1.93 (m, 1H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 146.8, 133.8, 133.0, 131.7, 129.8, 129.2, 128.1, 111.8, 77.9, 26.3, 6.1; $[M + H]^+$ = 299; HRMS (ESI) m/z calculated for $C_{15}H_{15}N_4O_3$ $[M + H]^+$ = 299.11387; found 299.11410.

2-Methyl-1-(3-phenethyl-8-(trifluoromethyl)-[1,2,4]triazolo-[4,3-*a*]pyridin-2(3*H*)-yl)propan-1-one (16b). Brown oil, 35 mg, 39% yield; R_f = 0.23 (silica gel, 40% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.01 (m, 6H), 6.84 (d, J = 6.9 Hz, 1H), 6.30 (t, J = 3.3 Hz, 1H), 5.63 (t, J = 6.8 Hz, 1H), 3.38−3.15 (m, 1H), 2.82−2.40 (m, 3H), 2.23−2.05 (m, 1H), 1.23 (d, J = 6.9 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 144.7, 140.4, 135.0, 135.1, 133.9, 129.0, 128.7, 128.6, 128.7, 126.3, 123.2, 102.4, 75.6, 34.5, 31.5, 28.7, 19.1, 18.2; $[M + H]^+$ = 364; HRMS (ESI) m/z calculated for $C_{19}H_{21}F_3N_3O$ $[M + H]^+$ = 364.16312; found 364.16318.

Furan-2-yl(3-(2-(methylthio)ethyl)-6-nitro-[1,2,4]triazolo-[4,3-*a*]pyridin-2(3*H*)-yl)methanone (16c). Red oil, 41 mg, 49% yield; R_f = 0.19 (silica gel, 40% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 2.1 Hz, 1H), 7.83−7.51 (m, 3H), 6.62 (t, J = 3.6 Hz, 1H), 6.55 (dd, J = 3.5, 1.7 Hz, 1H), 6.46 (d, J = 10.3 Hz, 1H), 2.83−2.58 (m, 2H), 2.61−2.45 (m, 1H), 2.36 (ddq, J = 11.3, 7.4, 4.4, 3.7 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 147.1, 145.9, 145.0, 133.9, 129.9, 119.5, 111.8, 111.7, 110.0, 76.4, 33.2, 27.5, 15.7; $[M + H]^+$ = 335; HRMS (ESI) m/z calculated for $C_{14}H_{15}N_4O_4S$ $[M + H]^+$ = 335.08085; found 335.08122.

1-(3-Ethyl-8-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)ethanone (16d). Red oil, 26 mg, 40% yield; R_f = 0.14 (silica gel, 40% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 6.8 Hz, 1H), 7.09−6.85 (m, 1H), 6.28 (t, J = 3.4 Hz, 1H), 5.79 (t, J = 6.8 Hz, 1H), 2.32 (m, 1H), 2.27 (s, 3H), 1.85 (ddd, J = 15.0, 7.5, 3.2 Hz, 1H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 135.3, 135.2, 134.1, 133.9, 123.2, 102.5, 76.5, 26.3, 21.2, 6.3; $[M + H]^+$ = 260; HRMS (ESI) m/z calculated for $C_{11}H_{13}F_3N_3O$ $[M + H]^+$ = 260.10052; found 260.10073.

(3-Fluorophenyl)(3-phenethyl-8-(trifluoromethyl)-[1,2,4]-triazolo[4,3-*a*]pyridin-2(3*H*)-yl)methanone (16e). Brown oil, 59 mg, 57% yield; R_f = 0.15 (silica gel, 40% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−7.83 (m, 2H), 7.38 (td, J = 8.1, 5.8 Hz, 1H), 7.33−7.07 (m, 7H), 6.94 (d, J = 6.5 Hz, 1H), 6.55 (t, J = 3.1 Hz, 1H), 5.73 (t, J = 6.8 Hz, 1H), 2.94−2.75 (m, 2H), 2.64 (m, 1H), 2.47−2.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 140.0, 139.9, 129.1, 128.6, 128.19, 128.17, 128.16, 126.3, 126.1, 118.3, 118.1, 117.6, 117.3, 113.1, 102.9, 76.7, 33.8, 28.6; $[M + H]^+$ = 416; HRMS (ESI) m/z calculated for $C_{22}H_{18}F_4N_3O$ $[M + H]^+$ = 416.13805; found 416.13867.

(3-(2-(Methylthio)ethyl)-8-(trifluoromethyl)-[1,2,4]triazolo-[4,3-*a*]pyridin-2(3*H*)-yl)(*p*-tolyl)methanone (16f). Brown oil, 30 mg, 31% yield; R_f = 0.13 (silica gel, 40% AcOEt/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.4 Hz, 3H), 7.21−6.97 (m, 1H), 6.60 (t, J = 3.6 Hz, 1H), 5.84 (t, J = 6.8 Hz, 1H), 2.84−2.61 (m, 1H), 2.59 (m, 1H), 2.60−2.47 (m, 1H), 2.39 (s, 3H), 2.33−2.20 (m, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 145.1, 141.9, 135.4, 135.3, 134.1, 130.5, 130.1, 128.5, 123.1, 120.4, 102.9, 76.1, 33.2, 27.8, 21.7, 15.8; $[M + H]^+$ = 382; HRMS (ESI) m/z calculated for $C_{18}H_{19}F_3N_3OS$ $[M + H]^+$ = 382.11954; found 382.12005.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for compounds of generic structure **6**, **9**, **11**, **14**, **16** and CIF files/ORTEP diagrams for compounds **6c**, **9c**, and **14a** (Figures S1, S3, and S5, respectively). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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