ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

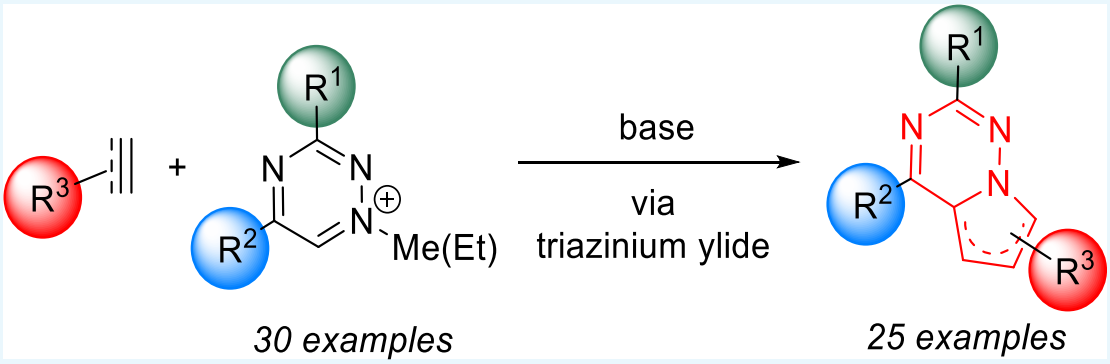
Regio- and Diastereoselective 1,3-Dipolar Cycloadditions of 1,2,4-Triazin-1-ium Ylides: a Straightforward Synthetic Route to Polysubstituted Pyrrolo[2,1-*f*][1,2,4]triazines

Juraj Galeta, Veronika Šlachtová, Martin Dračínský, and Milan Vrabel*

Cite This: *ACS Omega* 2022, 7, 21233−21238

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A synthetic strategy to pyrrolo[2,1-*f*][1,2,4]triazines is reported. We show that various synthetically easily accessible 1,2,4-triazines can be efficiently alkylated under mild conditions to provide the corresponding 1-alkyl-1,2,4-triazinium salts. These bench-stable salts serve as precursors to triazinium ylides, which react in 1,3-dipolar cycloadditions with electron-poor dipolarophiles to yield polysubstituted pyrrolotriazines in a single step.

INTRODUCTION

The bridgehead pyrrolo[2,1-*f*][1,2,4]triazine heterocycle is a privileged scaffold found in numerous pharmaceutically important substances. The biological activities of compounds containing the pyrrolotriazine core include inhibition of kinases, anticancer activities, and potent antiviral effects.[1−8]

The first synthesis of the heterocycle based on addition/fragmentation of 1,2,4-triazines (hereafter denoted as triazines) with dimethyl acetylenedicarboxylate (DMAD) was reported by Neuenhoeffer in 1977.[9] Two years later, Migliara and co-workers reported synthesis of the pyrrolotriazine core via an acid-mediated cyclization of semicarbazone onto a pendant α-ketoester, followed by a base-promoted cyclization and decarboxylation.[10] These pioneering studies paved the way for later re-emergence of the heterocycle as a 'purine-like' scaffold introduced into a series of C-nucleoside analogues.[11−13] The discovery that C-4-substituted pyrrolotriazines are potent ATP-competitive kinase inhibitors[14] further fueled the research interest in these compounds and led to numerous candidates in late stages of clinical development and to approved drugs (Figure 1).[1,7,15−20]

A typical synthetic route leading to pyrrolotriazines follows a number of steps depicted in Scheme 1A. Variations in these steps and late-stage modification of the heterocycle by, for example, cross-coupling reactions can provide access to diverse derivatives with a wide range of potential biological activities.[21−23]

Despite the pharmacological importance of pyrrolotriazines reflected in numerous literature reports and patent applications, virtually no alternative synthetic procedures to the scaffold exist. Even the most recent examples exploit reactions that have been originally developed decades ago.[24] To the best of our knowledge, the only alternative route to pyrrolotriazines, briefly examined in the early 90s, was based on cycloadditions of 1-alkyl-1,2,4-triazinium ylides generated in situ from the respective triazinium precursors under basic conditions.[25] Despite its great synthetic potential, this methodology has remained largely unexplored and neglected.

Herein, we show that various, previously unknown pyrrolotriazines can be prepared in a single step from readily accessible 1-alkyl-1,2,4-triazinium salts via 1,3-dipolar cycloaddition (DCA) of the in situ generated triazinium ylides with electron-poor dipolarophiles (Scheme 1B).

Received: April 12, 2022
Accepted: June 1, 2022
Published: June 10, 2022

© 2022 The Authors. Published by American Chemical Society

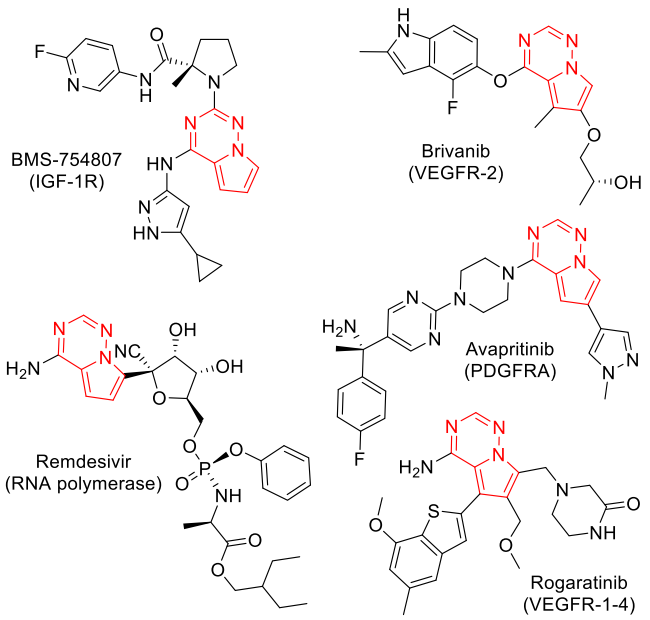
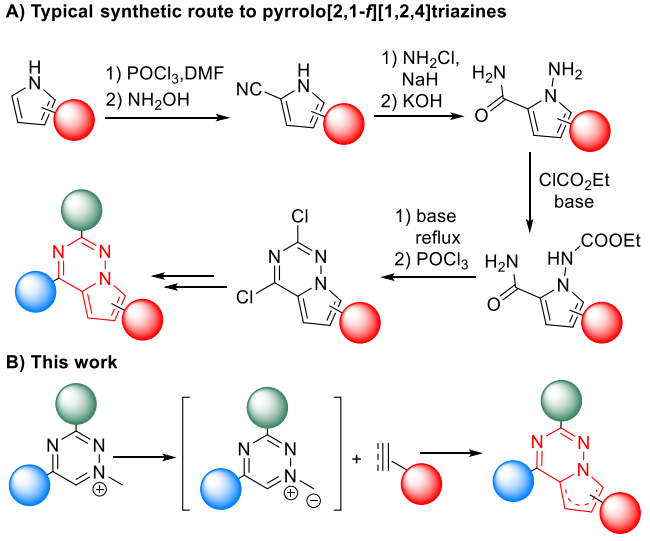


Figure 1. Examples of biologically active pyrrolo[2,1-*f*][1,2,4]-triazines (and their respective targets).

Scheme 1. (A) Example of a Typical Synthetic Route to Pyrrolo[2,1-*f*][1,2,4]triazines. (B) Single-Step Construction of Pyrrolotriazines via 1,3-Dipolar Cycloadditions



RESULTS AND DISCUSSION

Substituted 1,2,4-triazines are synthetically readily accessible heterocycles. Depending on the substitution pattern, their preparation typically includes a single and usually high-yielding condensation step starting from various commercial glyoxal hydrates and *S*-alkyl isothiosemicarbazides in the presence of sodium bicarbonate. More recent synthetic routes include regioselective reactions of *N*-tosyl hydrazones with aziridines,[26] carbene N−H insertion of hydrazides,[27] O−H insertion of rhodium-azavinylcarbenes,[28] Zn-catalyzed hydrohydrazination of propargylamides,[29] cycloaddition of tetrazines,[30] or domino annulation reactions.[31] There are numerous possibilities to further derivatize and decorate the basic heterocyclic core. For example, simple 3-substituted triazines are susceptible to an easy nucleophilic attack at position 5 followed by position 6.[32,33] The *S*-alkyl substituents can be utilized in cross-coupling reactions[33,34] or after oxidation, used in nucleophilic substitutions.[35,36] Therefore, the substrate scope of the starting triazines is immense, opening an easy access to diverse 1-alkyl-1,2,4-triazinium salts.

The first goal of our study was to optimize the alkylation of the triazine core. For this purpose, we used 3-phenyltriazine **1a**[34] and the commercial 3-methylthiotriazine and explored different alkylating agents and reaction conditions (Table S1). These experiments revealed that the alkylation with benzyl bromide and dimethyl sulfate is sluggish, while methyl iodide proved unreactive. In contrast, the use of Meerwein's salt ($Me_3O^+BF_4^-$) led to clean formation of the *N*1-alkylated product.[25] Due to difficulties in handling this sensitive compound, we decided to explore triflates as more convenient alkylating agents. To our delight, the alkylation with methyl or ethyl triflate was successful. Interestingly, the simple 3-aryltriazines are alkylated exclusively at position 1, while electronically richer derivatives, such as the commercial 3-methylthiotriazine, led under the same conditions to the formation of products alkylated at both, *N*1 and *N*2, as determined by heteronuclear multiple bond correlation nuclear magnetic resonance (NMR) experiments.

The observed differences in the preferred position for the alkylation can be explained, at least in part, by differences in the electrostatic potential of differently substituted triazines in combination with steric effects of the substituent at position 3 (Figure S1).

We also studied the influence of various solvents on the alkylation reaction. Anhydrous toluene was found superior over other solvents with the minor *N*2 isomer being formed in 15% yield using the methyl triflate and in only 10% using the ethyl triflate. We found that the two *N*-alkylated isomers can be separated by reversed phase column chromatography. However, the *N*2 isomer does not interfere with the subsequent DCA step and can be easily removed during purification of the final cycloaddition product. Therefore, we used the crude mixture of the triazinium isomers in all subsequent experiments. Under the optimized conditions, we next prepared a series of triazinium triflates **2a-o-Me(Et)** in excellent yields (Scheme 2).

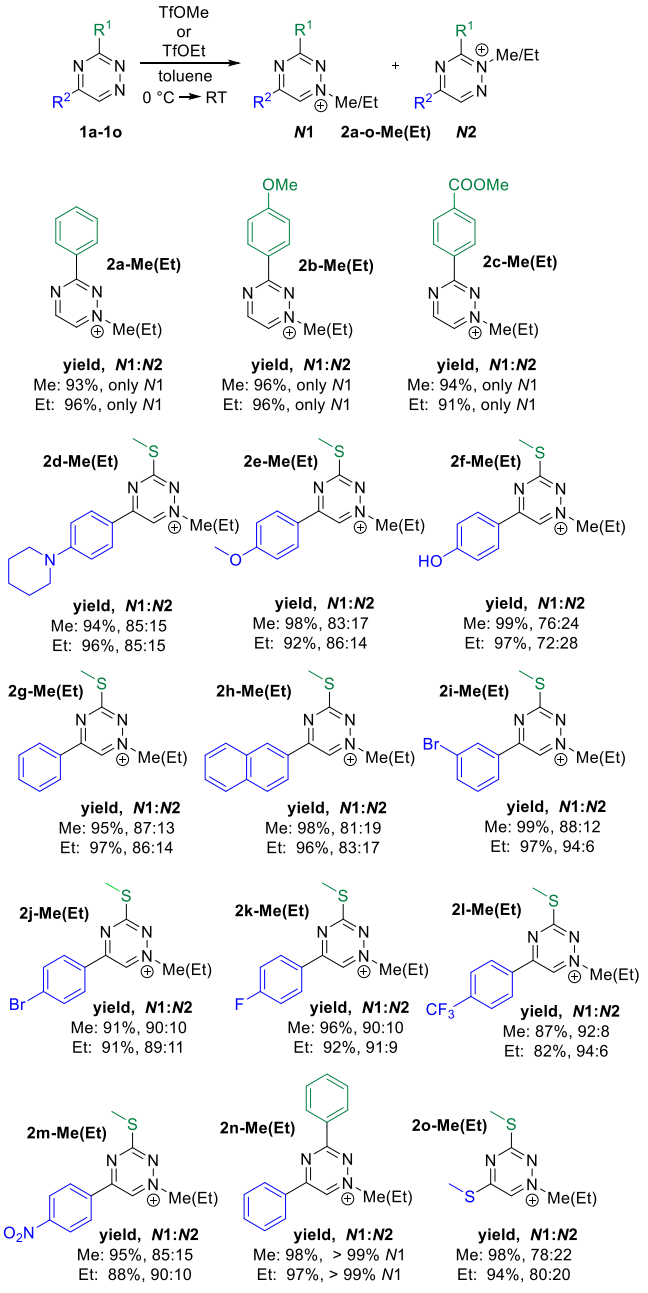
The alkylation is basically quantitative, and the formed triazinium salt simply precipitates from the reaction mixture in most cases. The reaction can be conveniently performed on a larger scale (hundreds of milligrams), and the 1-alkyltriazinium triflates are surprisingly stable when stored in the crystalline form and even in solution (Figure S2).

With the set of triaziniums in hand, we proceeded to optimize the 1,3-dipolar cycloaddition reaction using DMAD as the dipolarophile and 3-phenyltriazinium methyl triflates **2a-Me** and **2b-Me** as model substrates. We experimented with different bases, solvents, temperatures, and orders of reagent addition. Unfortunately, all these efforts led only to decomposition of the starting materials and formation of the cycloaddition product in less than 10% yield in the best case.

In contrast to these initial results, we found that the cycloaddition of compounds bearing additional substituents at position 5 is viable. In this case, the reaction with DMAD performed in tetrahydrofuran (THF) in the presence of *N*,*N*-diisopropylethylamine (DIPEA) afforded the desired cycloaddition products **3d-m-H(Me)** in good to very good yields (up to 84%). The reaction proceeded smoothly, and a wide range of triaziniums bearing various aryl substituents at

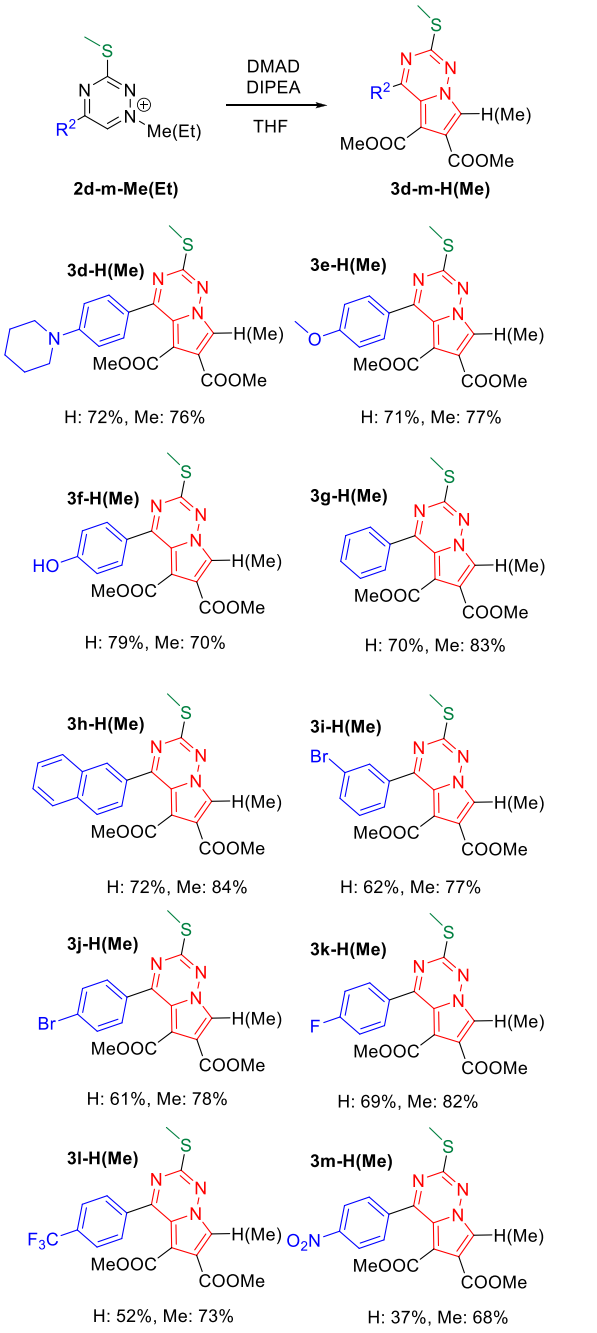
https://doi.org/10.1021/acsomega.2c02276
ACS Omega 2022, 7, 21233−21238

Scheme 2. Scope of Triazinium Compounds[a]



[a]Standard conditions: triazine **1a−1o** (2 mmol), triflate (2.4 mmol), anhydrous toluene (20 mL), 0 °C to RT, under argon. Note: all compounds are triflate salts.

Scheme 3. 1,3-Dipolar Cycloaddition of Triazinium Ylides with DMAD[a]



[a]Standard conditions: triazinium (0.5 mmol), DMAD (2 mmol), THF (10 mL), DIPEA (1.5 mmol), 0 °C to RT, 5 h.

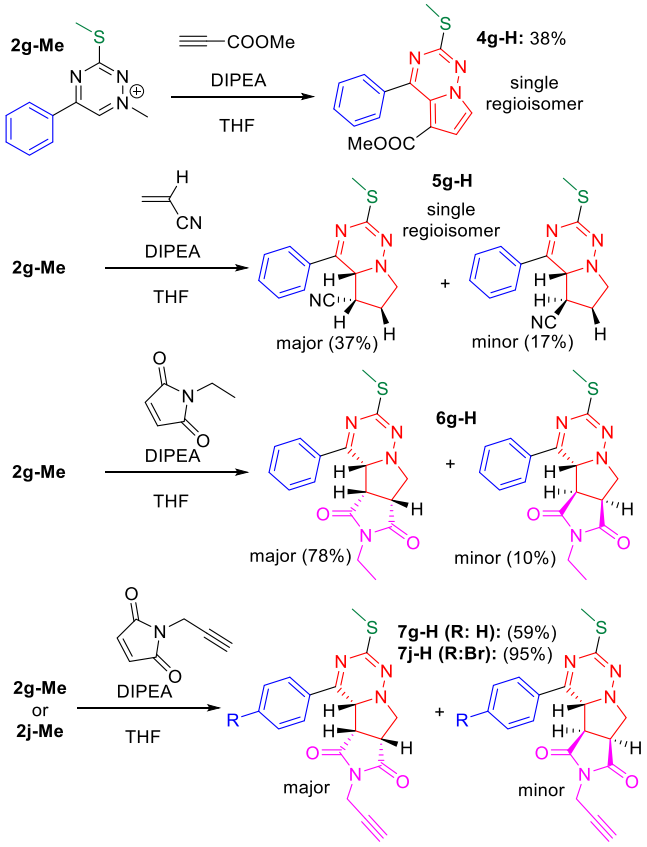
position 5 were tolerated (Scheme 3). In general, cycloadditions of ethyl triazinium ylides gave higher yields when compared to the methylated analogues. The final pyrrolotriazines form in the reaction as the fully oxidized products especially from the methyl triaziniums. If this was not the case, the dihydro intermediates were converted to the oxidized products by simply opening the reaction flask to the air. By following the reaction progress on high-performance liquid chromatography mass spectrometry, we observed that a small portion of the triazinium compounds undergoes dequaternization at the nitrogen atom to yield the starting triazine. Although the exact mechanism remains unclear, similar dealkylation of *N*-alkyl triazinium salts has been observed previously.[37] Interestingly, the pyrrolotriazines are fluorescent compounds when irradiated at 365 nm using a standard handheld UV lamp. This property could be potentially exploited in preparation of new fluorophores based on this heterocyclic core.

Encouraged by these results, we decided to explore the possibility of using other dipolarophiles in the reaction (Scheme 4).

Hence, reaction of 1-methyl-5-phenyl-1,2,4-triazinium triflate **2g-Me** with methyl propiolate performed in THF using DIPEA as the base yielded after optimization the desired pyrrolotriazine **4g-H** as a single regioisomer in 38% yield. The

https://doi.org/10.1021/acsomega.2c02276
ACS Omega 2022, 7, 21233−21238

Scheme 4. Scope of Dipolarophiles

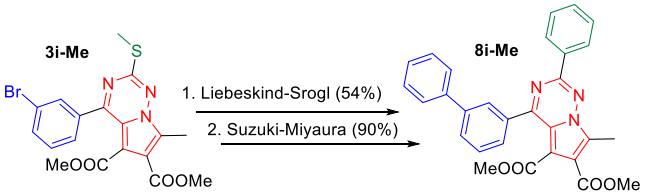


observed formation of the single regioisomer in the reaction is substantiated by the 5.0 kcal/mol lower energy of the corresponding transition state as evident from density functional theory (DFT) calculations (Figure S3). Even though the cycloaddition was in this case complicated by the competing reaction of the DIPEA base with the electron-poor triple bond,[38] this approach opens the possibility to generate additional pyrrolotriazines in a regioselective manner.

To further expand the scope of dipolarophiles, we performed the reaction with acrylonitrile, *N*-ethylmaleimide, and *N*-propargylmaleimide. The reaction with acrylonitrile yielded two diastereomers of a single regioisomer **5g-H** in a 2 to 1 ratio and in 54% overall yield. The reaction with maleimide proceeded smoothly and afforded two diastereomeric products **6g-H** in an 8 to 1 ratio and 88% overall yield. Based on DFT calculations, the transition state structure leading to the major product has lower calculated energy by 0.9 kcal/mol (Figure S4). Interestingly, only the minor isomer slowly oxidizes to the corresponding pyrrolotriazine. Cycloaddition experiments with *N*-propargylmaleimide and triaziniums **2g-Me** and **2j-Me** confirmed the diastereoselectivity of the transformation and yielded pyrrolotriazines **7g-H** and **7j-H** in 59% (significant dequarternization) and 95% overall yield, respectively.

Finally, to demonstrate the possibility of further derivatization of the pyrrolotriazine scaffold, we performed pilot coupling experiments with cycloadduct **3i-Me** (Scheme 5). The thiomethyl substituent at position 3 was successfully utilized in the Liebeskind–Srogl cross-coupling reaction with phenylboronic acid under standard conditions. The corresponding 3-phenyl pyrrolotriazine isolated in 54% yield was used in the next Suzuki–Miyaura cross-coupling reaction,

Scheme 5. Cross-Coupling Modifications[a]



[a]Conditions: 1. Phenylboronic acid (2.5 equiv), copper(I) thiophene-2-carboxylate (2.2 equiv), $Pd(PPh_3)_4$ (10 mol %), 1,4-dioxane, 95 °C. 2. Phenylboronic acid (2.0 equiv), $PdCl_2$(dppf)·DCM (10 mol %), K_2CO_3 (2.0 equiv), 1,4-dioxane/H_2O = 3/1, 100 °C.

which gave the desired heterocyclic product **8i-Me** in excellent 90% isolated yield.

CONCLUSIONS

In conclusion, we show that 1,3-dipolar cycloadditions of electron-poor dipolarophiles with triazinium ylides generated in situ from 1-alkyl-1,2,4-triazinium salts provide a facile access to various pyrrolo[2,1-*f*][1,2,4]triazines in a single step. The reaction gives differently substituted pyrrolotriazines in good yields, and the resulting compounds can be further elaborated by selective cross-coupling reactions. Our experimental data complemented by DFT calculations demonstrate that the reactions can be regio- and diastereoselective. We believe that the presented methodology will provide an efficient synthetic route to medicinally relevant pyrrolotriazines from readily available starting materials.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c02276.

General synthetic procedures, optimization details, ^{1}H, ^{13}C NMR and HRMS, and computational details (PDF)

AUTHOR INFORMATION

Corresponding Author

Milan Vrabel − *Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Prague 16000, Czech Republic*; orcid.org/0000-0001-6633-4351; Email: vrabel@uochb.cas.cz

Authors

Juraj Galeta − *Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Prague 16000, Czech Republic*

Veronika Šlachtová − *Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Prague 16000, Czech Republic*

Martin Dračínský − *Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Prague 16000, Czech Republic*; orcid.org/0000-0002-4495-0070

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c02276

Author Contributions

J.G. and V S. performed the synthetic work and isolated, purified, and characterized the compounds. M.D. performed all computational work and detailed NMR measurements of some

https://doi.org/10.1021/acsomega.2c02276
ACS Omega 2022, 7, 21233−21238

compounds. M.V. supervised the work. The manuscript was written through contributions of all authors, and all authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement no. 677465), by the Czech Science Foundation (20-30494L), and by the Academy of Sciences of the Czech Republic (RVO: 61388963). We also appreciate support from the IOCB fellowship for VS.

■ REFERENCES

(1) Dzierba Carolyn, D.; Dasgupta, B.; Macor John, E.; Bronson Joanne, J.; Rajamani, R.; Karageorge George, N. Pyrrolotriazine Kinase Inhibitors. WO 2015054358 A1, 2014/10/08, 2015.

(2) Kim In, W. O. O.; Yoo Ja, K.; Kim Ji, D.; Jun Sun, A. H.; Lee Jun, H. E. Pyrrolotriazine Derivatives As Kinase Inhibitor. WO 2018169373 A1, 2018/03/19, 2018.

(3) Liang, C.; Jia, M.; Tian, D.; Sun, H. A. N. Synthesis And Medical Application Of Pyrrolo-[2,1-*f*] [1,2,4] Triazine Mother Nucleus Compound. CN 106432249 A, 2016/09/30, 2017.

(4) Ott, G. R.; Favor, D. A. Pyrrolo[2,1-*f*][1,2,4] triazines: From C-nucleosides to kinases and back again, the remarkable journey of a versatile nitrogen heterocycle. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4238−4246.

(5) Yang, C.; Meng, L.; Chen, Y.; Wang, X.; Tan, C. U. N.; Li, J.; Ding, J.; Chen, Y. I. Pyrrolo[2,1-*f*[1,2,4]Triazine Compounds, Preparation Methods And Applications Thereof. U.S. Patent 9,724,352 B2, 2016/09/19, 2017.

(6) Tyndall, E. M.; Draffan, A. G.; Frey, B.; Pool, B.; Halim, R.; Jahangiri, S.; Bond, S.; Wirth, V.; Luttick, A.; Tilmanis, D.; Thomas, J.; Porter, K.; Tucker, S. P. Prodrugs of imidazotriazine and pyrrolotriazine C-nucleosides can increase anti-HCV activity and enhance nucleotide triphosphate concentrations in vitro. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 869−873.

(7) Mesaros, E. F.; Angeles, T. S.; Albom, M. S.; Wagner, J. C.; Aimone, L. D.; Wan, W.; Lu, L.; Huang, Z.; Olsen, M.; Kordwitz, E.; Haltiwanger, R. C.; Landis, A. J.; Cheng, M.; Ruggeri, B. A.; Ator, M. A.; Dorsey, B. D.; Ott, G. R. Piperidine-3,4-diol and piperidine-3-ol derivatives of pyrrolo[2,1-*f*][1,2,4]triazine as inhibitors of anaplastic lymphoma kinase. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1047−1052.

(8) Lim, J.; Altman, M. D.; Baker, J.; Brubaker, J. D.; Chen, H.; Chen, Y.; Kleinschek, M. A.; Li, C.; Liu, D.; Maclean, J. K. F.; Mulrooney, E. F.; Presland, J.; Rakhilina, L.; Smith, G. F.; Yang, R. Identification of N-(1H-pyrazol-4-yl)carboxamide inhibitors of interleukin-1 receptor associated kinase 4: Bicyclic core modifications. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5384−5388.

(9) Neunhoeffer, H.; Lehmann, B. Cycloadditionen mit Azabenzolen, XI. Cycloadditionen mit Methoxy- und Dialkylamino-1,2,4-triazinen. *Justus Liebigs Ann. Chem.* **1977**, *1977*, 1413−1420.

(10) Migliara, O.; Petruso, S.; Sprio, V. Synthesis of a new bridgehead nitrogen heterocyclic system. Pyrrolo [2,1-*f*]-[1,2,4]-triazine derivatives. *J. Heterocycl. Chem.* **1979**, *16*, 833−834.

(11) Maeba, I.; Hayashi, M.; Araki, A. C-Nucleosides A Synthesis of 2-Substituted 7-(β-D-Ribofuranosyl)pyrrolo[2,1-*f*]-[1,2,4]-triazines. A New Type of "Purine Like" C-Nucleoside. *Heterocycles* **1992**, *34*, 569−574.

(12) Patil, S. A.; Otter, B. A.; Klein, R. S. Synthesis of pyrrolo[2,1-*f*][1,2,4]triazine congeners of nucleic acid purines via the N-amination of 2-substituted pyrroles. *J. Heterocycl. Chem.* **1994**, *31*, 781−786.

(13) Patil, S. A.; Otter, B. A.; Klein, R. S. 4-aza-7,9-dideazaadenosine, a new cytotoxic synthetic C-nucleoside analogue of adenosine. *Tetrahedron Lett.* **1994**, *35*, 5339−5342.

(14) Hunt, J. T.; Mitt, T.; Borzilleri, R.; Gullo-Brown, J.; Fargnoli, J.; Fink, B.; Han, W.-C.; Mortillo, S.; Vite, G.; Wautlet, B.; Wong, T.; Yu, C.; Zheng, X.; Bhide, R. Discovery of the Pyrrolo[2,1-*f*][1,2,4]triazine Nucleus as a New Kinase Inhibitor Template. *J. Med. Chem.* **2004**, *47*, 4054−4059.

(15) Borzilleri, R. M.; Cai, Z.-w.; Ellis, C.; Fargnoli, J.; Fura, A.; Gerhardt, T.; Goyal, B.; Hunt, J. T.; Mortillo, S.; Qian, L.; Tokarski, J.; Vyas, V.; Wautlet, B.; Zheng, X.; Bhide, R. S. Synthesis and SAR of 4-(3-hydroxyphenylamino)pyrrolo[2,1-*f*][1,2,4]triazine based VEGFR-2 kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1429−1433.

(16) Cai, Z.-w.; Wei, D.; Borzilleri, R. M.; Qian, L.; Kamath, A.; Mortillo, S.; Wautlet, B.; Henley, B. J.; Jeyaseelan, R.; Tokarski, J.; Hunt, J. T.; Bhide, R. S.; Fargnoli, J.; Lombardo, L. J. Synthesis, SAR, and Evaluation of 4-[2,4-Difluoro-5-(cyclopropylcarbamoyl)-phenylamino]pyrrolo[2,1-*f*][1,2,4]triazine-based VEGFR-2 kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1354−1358.

(17) Gavai, A. V.; Fink, B. E.; Fairfax, D. J.; Martin, G. S.; Rossiter, L. M.; Holst, C. L.; Kim, S.-H.; Leavitt, K. J.; Mastalerz, H.; Han, W.-C.; Norris, D.; Goyal, B.; Swaminathan, S.; Patel, B.; Mathur, A.; Vyas, D. M.; Tokarski, J. S.; Yu, C.; Oppenheimer, S.; Zhang, H.; Marathe, P.; Fargnoli, J.; Lee, F. Y.; Wong, T. W.; Vite, G. D. Discovery and Preclinical Evaluation of [4-[[1-(3-fluorophenyl)methyl]-1H-indazol-5-ylamino]-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl]carbamic Acid, (3S)-3-Morpholinylmethyl Ester (BMS-599626), a Selective and Orally Efficacious Inhibitor of Human Epidermal Growth Factor Receptor 1 and 2 Kinases. *J. Med. Chem.* **2009**, *52*, 6527−6530.

(18) Schroeder, G. M.; Chen, X.-T.; Williams, D. K.; Nirschl, D. S.; Cai, Z.-W.; Wei, D.; Tokarski, J. S.; An, Y.; Sack, J.; Chen, Z.; Huynh, T.; Vaccaro, W.; Poss, M.; Wautlet, B.; Gullo-Brown, J.; Kellar, K.; Manne, V.; Hunt, J. T.; Wong, T. W.; Lombardo, L. J.; Fargnoli, J.; Borzilleri, R. M. Identification of pyrrolo[2,1-*f*][1,2,4]triazine-based inhibitors of Met kinase. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1945−1951.

(19) Thieu, T.; Sclafani, J. A.; Levy, D. V.; McLean, A.; Breslin, H. J.; Ott, G. R.; Bakale, R. P.; Dorsey, B. D. Discovery and Process Synthesis of Novel 2,7-Pyrrolo[2,1-*f*][1,2,4]triazines. *Org. Lett.* **2011**, *13*, 4204−4207.

(20) Hodous Brian, L.; Wilson Kevin, J.; Zhang, Y. Compositions Useful For Treating Disorders Related To Kit And Pdfgr. U.S. Patent 20,170,022,206 A1, 2016/07/22, 2017.

(21) Cascioferro, S.; Parrino, B.; Spanò, V.; Carbone, A.; Montalbano, A.; Barraja, P.; Diana, P.; Cirrincione, G. An overview on the recent developments of 1,2,4-triazine derivatives as anticancer compounds. *Eur. J. Med. Chem.* **2017**, *142*, 328−375.

(22) Xin, M.; Zhang, L.; Tang, F.; Tu, C.; Wen, J.; Zhao, X.; Liu, Z.; Cheng, L.; Shen, H. Design, synthesis, and evaluation of pyrrolo[2,1-f][1,2,4]triazine derivatives as novel hedgehog signaling pathway inhibitors. *Bioorg. Med. Chem.* **2014**, *22*, 1429−1440.

(23) Song, Y. n.; Zhan, P.; Zhang, Q.; Liu, X. Privileged scaffolds or promiscuous binders: a glance of pyrrolo[2,1-f][1,2,4]triazines and related bridgehead nitrogen heterocycles in medicinal chemistry. *Curr. Pharm. Des.* **2013**, *19*, 1528−1548.

(24) Paymode, D. J.; Cardoso, F. S. P.; Agrawal, T.; Tomlin, J. W.; Cook, D. W.; Burns, J. M.; Stringham, R. W.; Sieber, J. D.; Gupton, B. F.; Snead, D. R. Expanding Access to Remdesivir via an Improved Pyrrolotriazine Synthesis: Supply Centered Synthesis. *Org. Lett.* **2020**, *22*, 7656−7661.

(25) Chupakhin, O. N.; Rudakov, B. V.; Alexeev, S. G.; Shorshnev, S. V.; Charushin, V. N. 1-Alkyl-1,2,4-triazinium Ylides as 1,3-Dipoles in a Cycloaddition Reaction with Diethyl Acetylenedicarboxylate. *Mendeleev Commun.* **1992**, *2*, 85−86.

(26) Crespin, L.; Biancalana, L.; Morack, T.; Blakemore, D. C.; Ley, S. V. One-Pot Acid-Catalyzed Ring-Opening/Cyclization/Oxidation of Aziridines with N-Tosylhydrazones: Access to 1,2,4-Triazines. *Org. Lett.* **2017**, *19*, 1084−1087.

(27) Shi, B.; Lewis, W.; Campbell, I. B.; Moody, C. J. A Concise Route to Pyridines from Hydrazides by Metal Carbene N−H

https://doi.org/10.1021/acsomega.2c02276
ACS Omega 2022, 7, 21233−21238

Insertion, 1,2,4-Triazine Formation, and Diels−Alder Reaction. *Org. Lett.* **2009**, *11*, 3686−3688.
(28) Meng, J.; Wen, M.; Zhang, S.; Pan, P.; Yu, X.; Deng, W.-P. Unexpected O−H Insertion of Rhodium-Azavinylcarbenes with N-Acylhydrazones: Divergent Synthesis of 3,6-Disubstituted- and 3,5,6-Trisubstituted-1,2,4-Triazines. *J. Org. Chem.* **2017**, *82*, 1676−1687.
(29) Lukin, A.; Vedekhina, T.; Tovpeko, D.; Zhurilo, N.; Krasavin, M. Zn-catalyzed hydrohydrazination of propargylamides with $BocNHNH_2$: a novel entry into the 1,2,4-triazine core. *RSC Adv.* **2016**, *6*, 57956−57959.
(30) Zhu, Z.; Glinkerman, C. M.; Boger, D. L. Selective N1/N4 1,4-Cycloaddition of 1,2,4,5-Tetrazines Enabled by Solvent Hydrogen Bonding. *J. Am. Chem. Soc.* **2020**, *142*, 20778−20787.
(31) Tang, D.; Wang, J.; Wu, P.; Guo, X.; Li, J.-H.; Yang, S.; Chen, B.-H. Synthesis of 1,2,4-triazine derivatives via [4 + 2] domino annulation reactions in one pot. *RSC Adv.* **2016**, *6*, 12514−12518.
(32) Yamanaka, H; Konno, S.; Sagi, M.; Yoshida, N.; Yamanaka, H. Studies on as-Triazine Derivatives .X. Addition-Reaction of Phenylmagnesium Bromide with 1,2,4-Triazines. *Heterocycles* **1987**, *26*, 3111−3114.
(33) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. A General Approach to Selective Functionalization of 1,2,4-Triazines Using Organometallics in Palladium-Catalyzed Cross-Coupling and Addition Reactions. *Synthesis* **2004**, 2893−2899.
(34) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. Copper(I)-Promoted Palladium-Catalyzed Cross-Coupling of Unsaturated Tri-*n*-butylstannane with Heteroaromatic Thioether. *Org. Lett.* **2003**, *5*, 803−805.
(35) Finlay, M. R. V.; Anderton, M.; Bailey, A.; Boyd, S.; Brookfield, J.; Cairnduff, C.; Charles, M.; Cheasty, A.; Critchlow, S. E.; Culshaw, J.; Ekwuru, T.; Hollingsworth, I.; Jones, N.; Leroux, F.; Littleson, M.; McCarron, H.; McKelvie, J.; Mooney, L.; Nissink, J. W. M.; Perkins, D.; Powell, S.; Quesada, M. J.; Raubo, P.; Sabin, V.; Smith, J.; Smith, P. D.; Stark, A.; Ting, A.; Wang, P.; Wilson, Z.; Winter-Holt, J. J.; Wood, J. M.; Wrigley, G. L.; Yu, G.; Zhang, P. Discovery of a Thiadiazole−Pyridazine-Based Allosteric Glutaminase 1 Inhibitor Series That Demonstrates Oral Bioavailability and Activity in Tumor Xenograft Models. *J. Med. Chem.* **2019**, *62*, 6540−6560.
(36) Shi, D.-H.; Harjani, J. R.; Gable, R. W.; Baell, J. B. Synthesis of 3-(Alkylamino)-, 3-(Alkoxy)-, 3-(Aryloxy)-, 3-(Alkylthio)-, and 3-(Arylthio)-1,2,4-triazines by Using a Unified Route with 3-(Methylsulfonyl)-1,2,4-triazine. *Eur. J. Org. Chem.* **2016**, *2016*, 2842−2850.
(37) Chupakhin, O. N.; Rudakov, B. V.; McDermott, P.; Alexeev, S. G.; Charushin, V. N.; Hegarty, F. An Unusually Easy Oxidative Dequaternization of N-Alkyl-1,2,4-triazinium Salts. *Mendeleev Commun.* **1995**, *5*, 104−105.
(38) McCulloch, A. W.; McInnes, A. G. The Reaction of Propiolic Acid Esters with Tertiary Amines. Formation of Betaines. *Can. J. Chem.* **1974**, *52*, 3569−3576.

https://doi.org/10.1021/acsomega.2c02276
ACS Omega 2022, 7, 21233−21238