PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
https://doi.org/10.1080/10426507.2021.1966429

Synthesis of novel trifluoro methylated imidazothiadiazole derivatives via one-pot isocyanide-based three-component reaction under catalyst and solvent-free conditions

Maryam Sarchahi and Abbas Ali Esmaeili

Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran

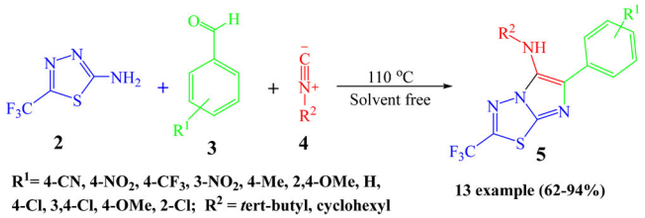
ABSTRACT

A catalyst and solvent-free synthesis of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives containing one trifluoromethyl (CF_3) group is reported via a three-component reaction between 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine, aromatic aldehydes, and isocyanides. This green reaction is characterized by operational simplicity and good-to-excellent yields of products. The structure of all products was deduced by ^{1}H NMR,^{13}C NMR, FT-IR, mass spectrometry, and elemental analysis.

ARTICLE HISTORY
Received 6 April 2021
Accepted 6 August 2021

KEYWORDS
Multicomponent domino reactions; imidazo[2,1-*b*][1,3,4]thiadiazole; catalyst-free isocyanide; solvent-free; green chemistry

GRAPHICAL ABSTRACT



Introduction

Organofluorine compounds have assumed an excellent position in modern medicine.[1,2] Interestingly, 20%–30% of modern pharmaceuticals contain a fluorine atom.[3] Among organofluorine compounds, trifluoromethyl-containing molecules have attracted much attention due to their biological activities, metabolic stability, high hydrophobicity, and lipophilicity.[4,5] The introduction of the trifluoromethyl (CF_3) group in drug molecules leads to improvement of their biological activities[6] and molecular properties such as pK_a, lipophilicity, chemical and metabolic stability, bioavailability, permeability, and protein-binding affinity are also enhanced.[3b,7–13]

There are many available procedures for the trifluoromethylation of organic compounds using electrophilic, nucleophilic, and radical sources. And the development of new trifluoromethylation methods using available abundant CF_3 sources is convenient and valuable in organic synthesis.[14–18]

Imidazo-fused scaffolds are one of the most important classes of heterocyclic systems and exhibit many biological and medicinal properties. The imidazo[2,1-*b*][1,3,4]thiadiazole core, as a rich source of the compounds of interest,[19] has been many applications in medicinal chemistry such as oncology,[20] infectiology,[21] central nervous system neurodegenerative diseases,[22] and cardiovascular diseases.[23] This bicyclic core, composed of imidazole and 1,3,4-thiadiazole moieties,[24] exhibits many biological activities such as antihyperlipidemic,[25] antibacterial,[26] antifungal,[27] antimicrobial,[28] anti-inflammatory,[29] antitubercular,[30] and anticancer[31] properties. In the design process of modern drugs, imidazo[2,1-*b*][1,3,4]thiadiazoles have played a selective inhibition role against some receptors and enzymes, so these compounds are used as a candidate for potential drugs.[32,33] Some drugs containing an imidazo[2,1-*b*][1,3,4]thiadiazole scaffold are presented in Figure 1, for example, 5,6-bis(4-methoxyphenyl)-2-(trifluoromethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (A) acts as an antitubercular, 5-formyl-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazole sulfonamide derivatives (B)[30] and 2-benzyl-6-(4′-fluorophenyl)-5-thiocyanato-imidazo[2,1-*b*][1,3,4]thiadiazole (C) as anti-cancer agents,[34] compound 5-phenyl-6-(4-sulfamoylphenyl)imidazo[2,1-*b*] [1,3,4]thiadiazole-2-sulfonamide (D) as an anti-inflammatory, and 6-(4-bromophenyl)-2-(3,4-dimethoxyphenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (E) as an antifungal.[35] In recent decades, methods to build bicyclic [5,5] nitrogen bridgehead-fused heterocycles have received much attention.[36]

The synthesis of heterocyclic compounds under solvent-free conditions is an important procedure from the

CONTACT Abbas Ali Esmaeili abesmaeili@um.ac.ir Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran.
Supplemental data for this article is available online at https://doi.org/10.1080/10426507.2021.1966429.

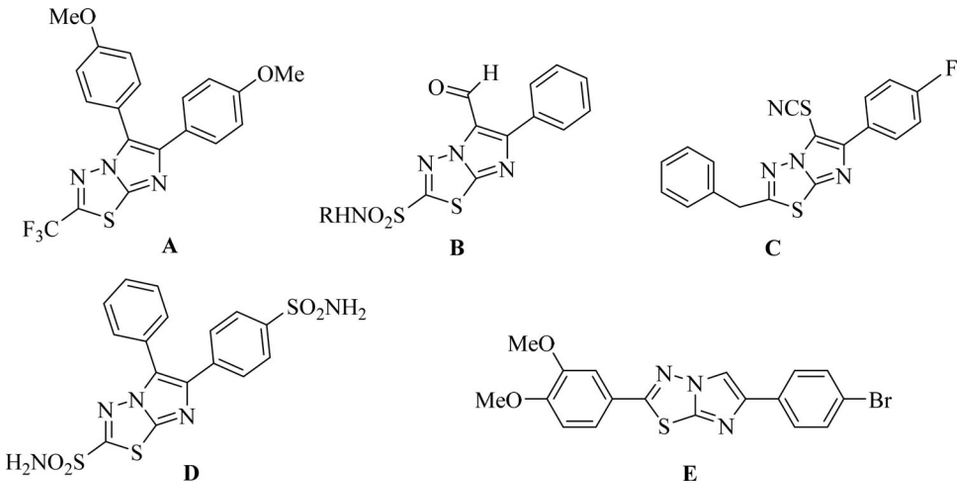
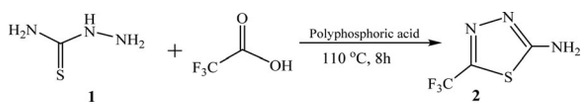
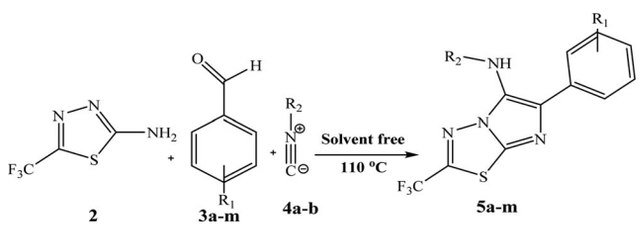


Figure 1. Drugs containing an imidazo[2,1-b][1,3,4]thiadiazole unit.

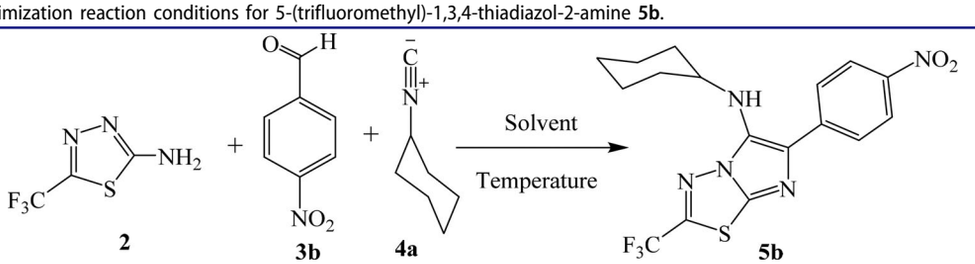


Scheme 1. Synthesis of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine.



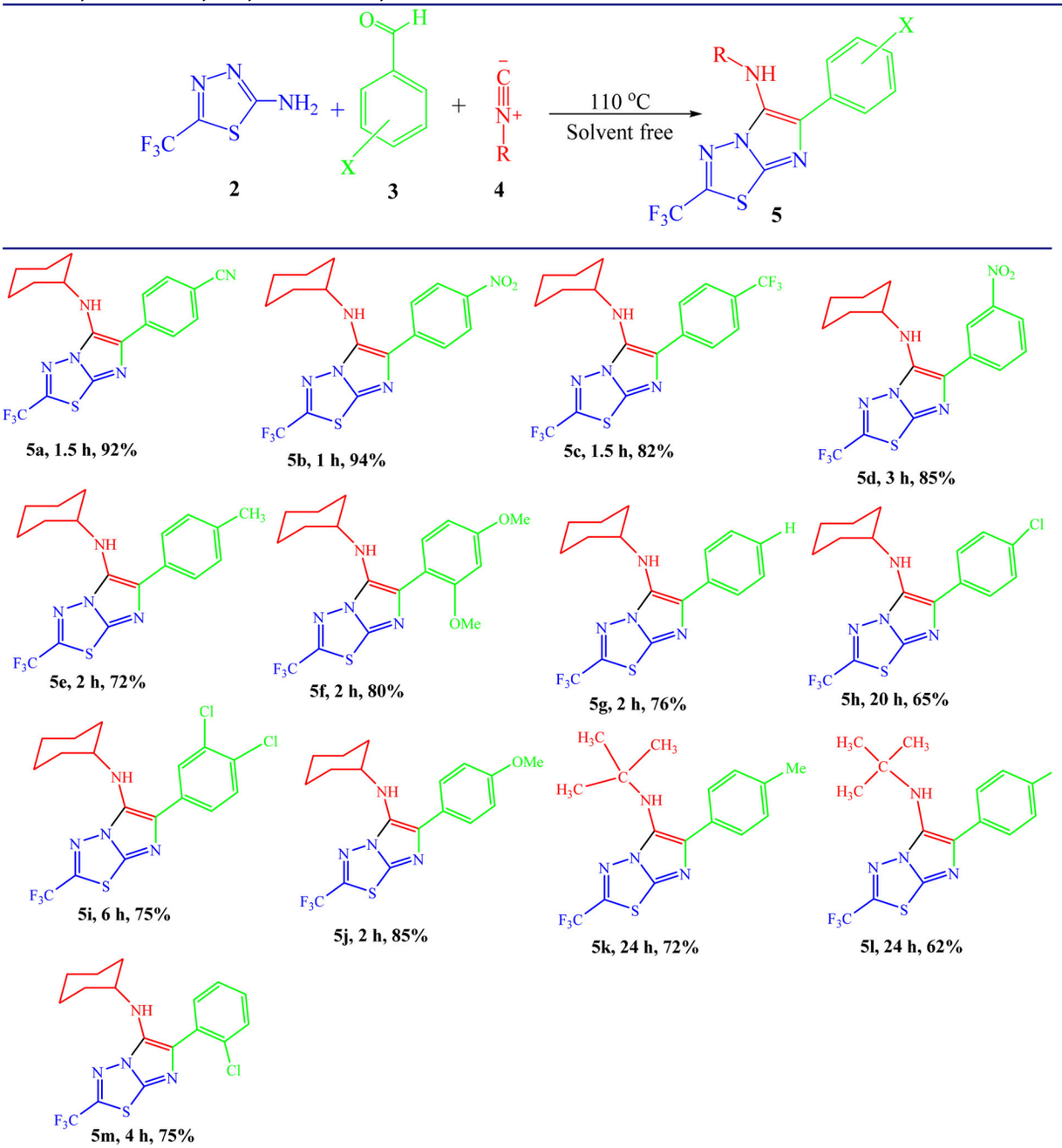
Scheme 2. Synthesis of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine.

Table 1. Optimization reaction conditions for 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine **5b**.



Entry	Solvent	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%)
1	CH_3CN	-	Reflux	24	60
2	EtOH	-	Reflux	24	62
3	EtOH/H_2O (1/1)	-	Reflux	24	55
4	PEG 400	-	110	24	72
5	EG	-	110	24	78
6	MeOH	-	Reflux	24	50
7	H_2O	-	Reflux	24	40
8	Neat	-	RT	24	Trace
9	Neat	-	70	24	30
10	Neat	-	90	1	80
11	Neat	-	110	1	94
12	Neat	-	130	1	94
13	Neat	KOH (5)	110	24	80
14	Neat	KOH (10)	110	24	80
15	Neat	K_2CO_3 (5)	110	24	70
16	Neat	Et_3N (5)	110	24	82
17	Neat	PTSA.1H_2O (5)	110	24	85
18	Neat	PTSA.1H_2O (10)	110	24	25
19	Neat	Lactic acid (5)	110	24	40
20	Neat	CH_3COOH (5)	110	24	Trace

Table 2. Synthesis of N-alkyl-6-aryl-2-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-amine 5.



Reaction conditions: **2** (1.3 mmol), **3** (1.0 mmol), **4** (1.0 mmol), at 110 °C and for synthesis of **5k** and **5 l**, use **2** (1.0 mmol), **3** (1.0 mmol), **4** (1.0 mmol), at 80 °C for 24 h.

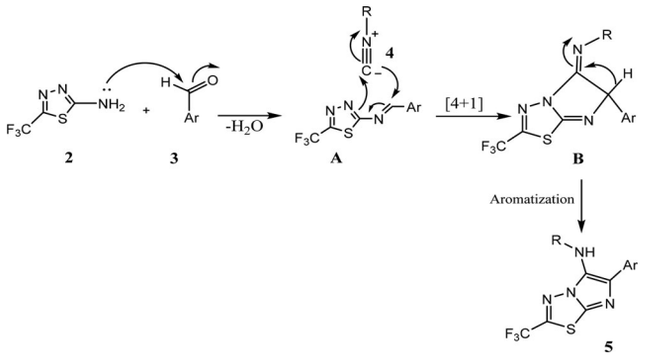
viewpoint of green chemistry. These approaches are safer, cleaner, and easier to perform than other procedures, and also, the amounts of hazardous chemicals used can reduce by these protocols.[37]

Recently, Wadhwa et al. reported the Groebke–Blackburn–Bienaymé (GBB) reaction of functionalized thiadiazole-2-amines, aldehydes, and isocyanide without any catalyst toward the construction of bicyclic imidazothiadiazoles under microwave irradiation.[38]

Due to the importance associated with trifluoromethyl-containing molecules in medicinal chemistry, and in our ongoing effort to the synthesis of new fused heterocyclic system,[39] herein, we would like to report a facile and efficient green synthesis of novel derivatives of imidazo[2,1-*b*][1,3,4]thiadiazole compounds containing CF_3 group. For this purpose, the first thiosemicarbazide was reacted with trifluoroacetic acid in the presence of polyphosphoric acid to synthesize 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (Scheme 1).[40] Subsequent reaction of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine **2** with aromatic aldehydes **3** and isocyanides **4** gave the final products **5** (Scheme 2).

Results and discussion

Initially, we started our investigation with the optimization of a model reaction, using 5-(trifluoromethyl)-1,3,4-



Scheme 3. Proposed mechanism for the formation of 5.

thiadiazol-2-amine (**2**) (1.3 mmol), 4-nitrobenzaldehyde (**3 b**) (1 mmol), and cyclohexyl isocyanide (**4a**) (1 mmol).

To develop the reaction conditions and increase the yield, the model reaction was conducted in various solvents. CH_3CN, EtOH, H_2O/EtOH (1: 1), polyethylene glycol (PEG 400), ethylene glycol, MeOH, and H_2O furnishing the products in 60%, 62%, 55%, 72%, 78%, 50%, and 40% yields, respectively (Table 1, entries 1–7). Also, the model reaction was examined at different temperatures under solvent-free conditions. Upon changing the temperature, the best result was found at 110 °C, and the desired product was formed in 94% yield within 1 h (Table 1, entries 8–12).

Finally, we performed the model reaction using Brønsted acids such as *p*-TSA.H_2O, lactic acid, CH_3COOH and as bases, for instance (KOH, K_2CO_3, Et_3N) under solvent-free conditions (Table 1, entries 13–20). As can be seen from the data listed in Table 1, the best result was obtained by heating the reaction mixture under solvent-free conditions at 110 °C to furnish *N*-cyclohexyl-6-(4-nitrophenyl)-2-(trifluoromethyl)imidazo[2,1-*b*][1,3,4]thiadiazol-5-amine (**4b**) in 94% yield (Table 1, entry 11).

With the established optimized conditions, we explored the reaction with a diverse range of aromatic aldehydes and isocyanides. 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (**2**) was examined in the reaction with aromatic aldehydes (**3a–m**) and isocyanides (**4a–b**), leading to the corresponding products **5a–m** in 62%–94% yield (Table 2).

Aromatic aldehydes containing electron-withdrawing groups such as 4-nitro, 4-cyano, 4-trifluoromethyl, 3-nitro, 4-Chloro, 2-chloro, and 3,4-dichloro exhibited good reactivities (65%–94%). Aromatic aldehydes with electron-donating substituents, for example, 4-methyl, 4-methoxy, and 2,4-dimethoxy, were also well accepted (72%–85%). Also, aliphatic aldehydes such as acetaldehyde, propionaldehyde, butyraldehyde, and capraldehyde (Hexanal) were examined, but unfortunately, trace amounts of the products were formed.

The structures of all compounds (**5a–m**) were deduced from their ^1H, ^{13}C NMR and I.R spectrosocopic data, mass spectrometry, and elemental analysis (Supplemental data). For example, the ^1H NMR spectrum of compound **5a** exhibited four multiplets arising from the cyclohexyl ring protons at δ 1.27, 1.63, 1.76, and 1.93 ppm. A multiplet appearing at δ 3.22 ppm was assigned to the CH-NH, a doublet at δ 3.39 ppm was also assigned to the N-H ($^2J_{NH}$ = 6.9 Hz), and four aromatic hydrogens exhibited two doublets at δ 7.71 ($^3J_{HH}$ = 8.1 Hz) and 8.21 ppm ($^3J_{HH}$ = 8.4 Hz). The ^{13}C NMR spectrum of **5a** displayed 13 distinct resonances and confirmed the suggested structure. The mass spectrum of **5a** demonstrated the molecular ion peak at M/Z = 391. The I.R. spectrum of **5a** showed absorptions bands at 3248, 2223, and 1699 cm^{-1} regions for N.H., C.N. (nitrile), and C = N. Spectroscopic data characterized all products (**5a–m**), and the results are presented in the Supplemental data.

Although the reaction mechanism has not yet been established experimentally, the formation of the product can be rationalized as outlined in Scheme 3. Based on reported literature,[41] the initial step is forming imine A by the reaction of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine 2 aldehydes **3**. Next, the imine carbon is trapped by isocyanides **4** through [4 + 1] cycloaddition to produce nitrilium ion intermediate **B**; finally, aromatization leads to imidazo[2,1-*b*][1,3,4]thiadiazoles **5** (Scheme 3).

Conclusion

In conclusion, we have reported in the present investigation a green and efficient strategy for the synthesis of trifluoromethylated imidazo[2,1-*b*][1,3,4]thiadiazole derivatives *via* a simple one-pot three-component reaction between 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine, substituted benzaldehydes, and isocyanide in good-to-excellent yields under catalyst and solvent-free conditions. Operational simplicity, availability of the starting materials, good-to-excellent yields of products, simple workup, and easy purification are the main advantages of this reaction.

Experimental section

General

All chemicals and solvents were obtained from Merck companies and used without purification. Melting points were measured using Electrothermal 9100 apparatus. Infrared (IR) spectra of compounds are reported in cm^{-1} and were recorded on a Nicolet Avatar 370 FT-IR Therma instrument using KBr disks . ^1H, ^{13}C, and ^{19}F NMR spectra were acquired on Bruker DPX-300 Avance spectrometer at 300, 75.47, and 283 MHz, respectively. Chemical shifts are given in ppm, and $CDCl_3$ was used as the solvent. Mass spectra were determined on a Varian Meth ch-7 at 70 eV. Elemental analysis was performed using a Thermo Finnegan Flash EA 1112 series instrument. Plate chromatography was performed on silica gel (60 GF_{254}, E. Merck). Supplemental data contain sample ^1H and ^{13}C NMR, IR and mass spectra of the products 5 (Figures S 1 – S 56).

Typical procedure for synthesis of *N*-cyclohexyl-6-(4-nitrophenyl)-2-(trifluoromethyl)imidazo[2,1-*b*][1,3,4]thiadiazol-5-amine (5b)

In a vessel, 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine **2** (1.3 mmol) and substituted benzaldehyde **3b** (1 mmol) were

stirred under nitrogen at 110 °C for 30 min. The isocyanide 4a (1 mmol) was added to this mixture, and the reaction was stirred until the reaction was completed (controlled by TLC). Then, the mixture was cooled to room temperature and was purified through plate chromatography using silica gel and n-hexane-ethyl acetate (10:3) as eluent. to obtain the *N*-cyclohexyl-6-(4-nitrophenyl)-2-(trifluoromethyl)imidazo[2,1-*b*][1,3,4]thiadiazol-5-amine (**5 b**) (0.39 g, 94%) as a brown powder. For the synthesis of **5k** and **5l**, the model reaction was performed using *N*-*tert*-butyl isocyanide (1 mmol), aromatic aldehydes (1 mmol), and 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (1 mmol), at 80 °C for 24 h.

Conflicts of interest

There are no conflicts to declare.

Funding

The Research Council of the Ferdowsi University of Mashhad is acknowledged for financial support (Grant No. 3/52489).

ORCID

Maryam Sarchahi http://orcid.org/0000-0003-0698-9393
Abbas Ali Esmaeili http://orcid.org/0000-0002-1650-0224

References

[1] Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in Medicinal Chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320–330. DOI: 10.1039/B610213C.

[2] Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822–5880. DOI: 10.1021/acs.jmedchem.7b01788.

[3] (a) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359–4369. DOI: 10.1021/jm800219f. (b) Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011**, *54*, 2529–2591. DOI: 10.1021/jm1013693. (c) Wang, J.; Sánchez-Roselló, J. M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fuster, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs introduced to the Market in the Last Decade (2001–2011). *Chem. Rev.* **2014**, *114*, 2432–2506. DOI: 10.1021/cr4002879. (d) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. Data-Mining for Sulfur and Fluorine: An Evaluation of Pharmaceuticals to reveal Opportunities for Drug Design and Discovery: Miniperspective. *J. Med. Chem.* **2008**, *51*, 2842–4359. DOI: 10.1021/jm401375q.

[4] (a) O'Hagan, D. Fluorine in Health Care: Organofluorine Containing Blockbuster Drugs. *J. Fluorine Chem* **2010**, *131*, 1071–1081. DOI: 10.1016/j.jfluchem.2010.03.003. (b) Kirk, K. L. Fluorine in Medicinal Chemistry: Recent Therapeutic Applications of Small Fluorinated Molecules. *J. Fluorine Chem.* **2006**, *127*, 1013–1029. DOI: 10.1016/j.jfluchem.2006.06.007. (c) Bégué, J.-P.; Bonnet-Delpon, D. Recent Advances (1995–2005) in Fluorinated Pharmaceuticals Based on Natural Products. *J. Fluorine Chem.* **2006**, *127*, 992–1012. DOI: 10.1016/j.jfluchem.2006.05.006. (d) Jeschke, P. The Unique Role of Fluorine in the Design of Active Ingredients for Modern Crop Protection. *Chem. Bio. Chem.* **2004**, *5*, 570–589. DOI: 10.1002/cbic.200300833. (e) Yuan, C.; Li, S.; Xiao, J.; Cui, S.; Wang, G. Asymmetric Synthesis of Amino Phosphonic Acids and Trifluoromethylated Derivatives. *Phosphorus Sulfur Silicon Relat. Elem.* **2002**, *177*, 1731–1734. DOI: 10.1080/10426500212231. (f) Huang, X.; He, Y.; Ding, Y. The Novel Syntheses of α-Trifluoromethylated Ketones from β-Bromoenol Phosphates. *Phosphorus Sulfur Silicon Relat. Elem.* **2001**, *174*, 201–207. DOI: 10.1080/10426500108040244.

[5] (a) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, **2013**. (b) Gouverneur, V.; MüLler, K. *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*; Imperial College Press: London, **2012**. (c) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Blackwell: Oxford, **2009**.

[6] (a) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359–4369. DOI: 10.1021/jm800219f. (b) Wilson, R. M.; Danishefsky, S. J. On the Reach of Chemical Synthesis: Creation of a Mini-Pipeline from An Academic Laboratory. *Angew. Chem. Int. Ed. Engl.* **2010**, *49*, 6032–6056. DOI: 10.1002/anie.201000775. (c) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of Fluorine and Fluorine-Containing Functional Groups. *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 8214–8264. DOI: 10.1021/jm800219f.

[7] (a) Hagmann, W. K. The Many Roles for Fluorine in Medicinal chemistry. *J. Med. Chem.* **2008**, *51*, 4359–4369. DOI: 10.1021/jm800219f. (b) Muzalevskiy, V. M.; Shastin, A. V.; Balenkova, E. S.; Haufe, G.; Nenajdenko, V. G. Synthesis of Trifluoromethyl Pyrroles and Their Benzo Analogues. *Synthesis* **2009**, *23*, 3905–3929. DOI: 10.1055/s-0029-1217080. (c) Furuya, T.; Kamlet, A. S.; Ritter, T. Catalysis for Fluorination and Trifluoromethylation. *Nature* **2011**, *473*, 470–477. DOI: 10.1038/nature10108. (d) Kelly, C. B.; Mercadante, M. A.; Leadbeater, N. E. Trifluoromethyl Ketones: Properties, Preparation, and Application. *Chem. Commun. (Camb.)* **2013**, *49*, 11133–11148. DOI: 10.1039/c3cc46266h. (e) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. Recent Advances in the Trifluoromethylation Methodology and New CF3-Containing Drugs. *J. Fluorine Chem.* **2014**, *167*, 37–54. DOI: 10.1016/j.jfluchem.2014.06.026. (f) Bassetto, M.; Ferla, S.; Pertusati, F. Polyfluorinated Groups in Medicinal Chemistry. *Future Med. Chem.* **2015**, *7*, 527–546. DOI: 10.4155/fmc.15.5. (g) Gao, P.; Song, X. R.; Liu, X. Y.; Liang, Y. M. Recent Developments in the Trifluoromethylation of Alkynes. *Chemistry* **2015**, *21*, 7648–7661. DOI: 10.1002/chem.201406432. (h) Usachev, B. I. 6-(Trifluoromethyl)-2H-Pyran-2-Ones: Promising CF3-Bearing Conjugated Cyclic Diene and Electrophilic Building-Blocks. *J. Fluorine Chem.* **2015**, *175*, 36–46. DOI: 10.1016/j.jfluchem.2015.02.009. (i) Meyer, F. Trifluoromethyl nitrogen heterocycles: synthetic aspects and potential biological targets. *Chem. Commun. (Camb.)* **2016**, *52*, 3077–3094. DOI: 10.1021/jm800219f.

[8] He, X. H.; Ji, Y. L.; Peng, C.; Han, B. Organocatalytic Asymmetric Synthesis of Cyclic Compounds Bearing a Trifluoromethylated Stereogenic Center: recent Developments. *Adv. Synth. Catal.* **2019**, *361*, 1923–1957. DOI: 10.1002/adsc.201801647.

[9] Hiyama, H. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, **2000**.

[10] Ojima, I., Ed. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, **2009**.

[11] Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Germany, **2004**.

[12] Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking beyond Intuition. *Science* **2007**, *317*, 1881–1886. DOI: 10.1126/science.1131943.

[13] Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359–4369. DOI: 10.1021/jm800219f.

[14] (a) Ma, J. A.; Cahard, D. Strategies for Nucleophilic, Electrophilic, and Radical Trifluoromethylations. *J. Fluorine Chem.* **2007**, *128*, 975–996. DOI: 10.1016/j.jfluchem.2007.04.026.

(b) Furuya, T.; Kamlet, A. S.; Ritter, T. Catalysis for Fluorination and Trifluoromethylation. *Nature* **2011**, *473*, 470–477. DOI: 10.1038/nature10108. (c) Studer, A. A "Renaissance" in Radical Trifluoromethylation. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 8950–8958. DOI: 10.1002/anie.201202624. (d) Zhang, C. Application of Langlois' Reagent in Trifluoromethylation Reactions. *Adv. Synth. Catal.* **2014**, *356*, 2895–2906. DOI: 10.1002/adsc.201400370. (e) Zhang, C. Recent Advances in Trifluoromethylation of Organic Compounds Using Umemoto's Reagents. *Org. Biomol. Chem.* **2014**, *12*, 6580–6589. DOI: 10.1039/C4OB00671B. (f) Chu, L.; Qing, F. L. Oxidative Trifluoromethylation and Trifluoromethylthiolation Reactions Using (trifluoromethyl)trimethylsilane as a nucleophilic CF3 source. *Acc. Chem. Res.* **2014**, *47*, 1513–1522. DOI: 10.1021/ar4003202. (g) Liu, X.; Xu, C.; Wang, M.; Liu, Q. Trifluoromethyltrimethylsilane: Nucleophilic Trifluoromethylation and beyond. *Chem. Rev.* **2015**, *115*, 683–730. DOI: 10.1021/cr400473a. (h) Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. Carbon Trifluoromethylation Reactions of Hydrocarbon Derivatives and Heteroarenes. *Chem. Rev.* **2015**, *115*, 1847–1935. DOI: 10.1021/cr500368h.

[15] (a) Gelat, F.; Patra, A.; Pannecoucke, X.; Biju, A. T.; Poisson, T.; Besset, T. N-Heterocyclic Carbene-Catalyzed Synthesis of α-Trifluoromethyl Esters. *Org. Lett.* **2018**, *20*, 3897–3901. DOI: 10.1021/acs.orglett.8b01482. (b) Yang, W.; Ma, D.; Zhou, Y.; Dong, X.; Lin, Z.; Sun, J. NHC-Catalyzed Electrophilic Trifluoromethylation: Efficient Synthesis of γ-Trifluoromethyl α, β-Unsaturated Esters. *Angew. Chem.* **2018**, *130*, 12273–12277. DOI: 10.1002/ange.201806674. (c) Katayev, D.; Kajita, H.; Togni, A. Cover Picture: Magnesium-Catalyzed Electrophilic Trifluoromethylation: Facile Access to All-Carbon Quaternary Centers in Oxindoles. *Chem. Eur. J.* **2017**, *23*, 8322–8322. DOI: 10.1002/chem.201701336. (d) Katayev, D.; Matoušek, V.; Koller, R.; Togni, A. N-Heterocyclic Carbene-Catalyzed Synthesis of α-Trifluoromethyl Esters. *Org. Lett.* **2015**, 20, 3897–5901. DOI: 10.1021/acs.orglett.8b01482.

[16] (a) Musio, B.; Gala, E.; Ley, S. V. Real-Time Spectroscopic Analysis Enabling Quantitative and Safe Consumption of Fluoroform during Nucleophilic Trifluoromethylation in Flow. *ACS Sustainable Chem. Eng.* **2018**, *6*, 1489–1495. DOI: 10.1021/acssuschemeng.7b04012. (b) Pike, J. A.; Walton, J. W. Nucleophilic Trifluoromethylation of Electron-Deficient Arenes. *Chem. Commun. (Camb.)* **2017**, *53*, 9858–9861. DOI: 10.1039/c7cc05415g. (c) Prakash, G. K. S.; Wang, F.; Zhang, Z.; Haiges, R.; Rahm, M.; Christe, K. O.; Mathew, T.; Olah, G. A. Long-Lived Trifluoromethanide Anion: A Key Intermediate in Nucleophilic Trifluoromethylations. *Angew. Chem.* **2014**, *126*, 11759–11762. DOI: 10.1002/ange.201406505.

[17] (a) Zhou, S.; Song, T.; Chen, H.; Liu, Z.; Shen, H.; Li, C. Catalytic Radical Trifluoromethylalkynylation of Unactivated Alkenes. *Org. Lett.* **2017**, *19*, 698–701. DOI: 10.1021/acs.orglett.6b03870. (b) Wu, L.; Wang, F.; Wan, X.; Wang, D.; Chen, P.; Liu, G. Asymmetric Cu-Catalyzed Intermolecular Trifluoromethylarylation of Styrenes: enantioselective Arylation of Benzylic Radicals. *J. Am. Chem. Soc.* **2017**, *139*, 2904–2907. DOI: 10.1021/jacs.6b13299. (c) Wang, F.; Wang, D.; Zhou, Y.; Liang, L.; Lu, R.; Chen, P.; Lin, Z.; Liu, G. Divergent Synthesis of CF3 -Substituted Allenyl Nitriles by Ligand-Controlled Radical 1,2- and 1,4-Addition to 1,3-Enynes. *Angew. Chem. Int. Ed. Engl.* **2018**, *57*, 7140–7145. DOI: 10.1002/anie.201803668. (d) Chang, B.; Su, Y.; Huang, D.; Wang, K. H.; Zhang, W.; Shi, Y.; Zhang, X.; Hu, Y. Catalytic Radical Trifluoromethylalkynylation of Unactivated Alkenes. *Org. Lett.* **2017**, *19*, 698–4374. DOI: 10.1021/acs.orglett.6b03870.

[18] (a) Schareina, T.; Wu, X. F.; Zapf, A.; Cotté, A.; Gotta, M.; Beller, M. Towards a Practical and Efficient Copper-Catalyzed Trifluoromethylation of Aryl Halides. *Top. Catal.* **2012**, *55*, 426–431. DOI: 10.1007/s11244-012-9824-0. (b) Lishchynskyi, A.; Novikov, M. A.; Martin, E.; Escudero-Adán, E. C.; Novák, P.; Grushin, V. V. Trifluoromethylation of Aryl and Heteroaryl Halides with Fluoroform-Derived CuCF3: scope, Limitations, and Mechanistic Features. *J. Org. Chem.* **2013**, *78*, 11126–11146. DOI: 10.1021/jo401423h. (c) Lin, X.; Hou, C.; Li, H.; Weng, Z. Decarboxylative Trifluoromethylating Reagent [Cu(O2CCF3)(Phen)] and Difluoro Carbene Precursor [Cu(Phen)2][O2CCF2Cl]. *Chem. Eur. J.* **2016**, *22*, 2075–2084. DOI: 10.1002/chem.201504306. (d) Shi, G.; Shao, C.; Pan, S.; Yu, J.; Zhang, Y. Silver-Catalyzed C–H Trifluoromethylation of Arenes Using Trifluoroacetic Acid Trifluoromethylating Reagent. *Org. Lett.* **2015**, *17*, 38–41. DOI: 10.1021/ol503189j.

[19] (a) Terzioglu, N.; Gursoy, A. Synthesis and Anticancer Evaluation of Some New Hydrazone Derivatives of 2,6-Dimethylimidazo[2,1-b][1,3,4]Thiadiazole-5-Carbohydrazide. *Eur. J. Med. Chem.* **2003**, *38*, 781–786. DOI: 10.1016/S0223-5234(03)00138-7. (b) Khazi, I. A. M.; Gadad, A. K.; Lamani, R. S.; Bhongade, B. A. Chemistry of Imidazo[2,1-b][1,3,4]Thiadiazoles. *Tetrahedron* **2011**, *67*, 3289–3316. DOI: 10.1016/j.tet.2011.03.027. (c) Belavagi, N. S.; Sunagar, M. G.; Lamani, R. S.; Deshapande, N.; Khazi, I. A. M. Synthesis and Antimicrobial Activity of Novel Sulfides and Sulfones of Methylene-Bridged Benzisoxazolylimidazo[2,1-*b*][1,3,4]Thiadiazoles. *Phosphorus Sulfur Silicon Relat. Elem.* **2015**, *190*, 1580–1587. DOI: 10.1080/10426507.2015.1012196. (d) Sun, Y.; Fu, B. Q.; Ding, M. W. One-Pot Synthesis and Fungicidal Activities of Derivatives of Imidazo[2,1-*b*]-1,3,4-Thiadiazol-5(6H)-One. *Phosphorus Sulfur Silicon Relat. Elem.* **2006**, *181*, 1437–1443. DOI: 10.1080/10426500500328954.

[20] Romagnoli, R.; Baraldi, P. G.; Prencipe, F.; Balzarini, J.; Liekens, S.; Estévez, F. Design, Synthesis and Antiproliferative Activity of Novel Heterobivalent Hybrids Based on Imidazo[2,1-*b*][1,3,4]Thiadiazole and Imidazo[2,1-*b*][1,3]Thiazole Scaffolds. *Eur. J. Med. Chem.* **2015**, *101*, 205–217. DOI: 10.1016/j.ejmech.2015.06.042.

[21] Alwan, W. S.; Karpoormath, R.; Palkar, M. B.; Patel, H. M.; Rane, R. A.; Shaikh, M. S.; Kajee, A.; Mlisana, K. P. Novel Imidazo[2,1-*b*]-1,3,4-Thiadiazoles as Promising Antifungal Agents against Clinical Isolate of Cryptococcus neoformans. *Eur. J. Med. Chem.* **2015**, *95*, 514–525. DOI: 10.1016/j.ejmech.2015.03.021.

[22] Patel, H. M.; Sing, B.; Bhardwaj, V.; Palkar, M.; Shaikh, M. S.; Rane, R.; Alwan, W. S.; Gadad, A. K.; Noolvi, M. N.; Karpoormath, R. Design, Synthesis and Evaluation of Small Molecule Imidazo[2,1-*b*][1,3,4]Thiadiazoles as Inhibitors of Transforming Growth Factor-β type-I Receptor Kinase (ALK5). *Eur. J. Med. Chem.* **2015**, *93*, 599–613. DOI: 10.1016/j.ejmech.2014.09.002.

[23] Place, M.; Copin, C.; Apotrosoaei, M.; Constantin, S.; Vasincu, I. M.; Profire, L.; Buron, F.; Routier, S. Synthesis of [1,3,4]Thiadiazolo[3',2':1,2]Imidazo[4,5-c]Quinolines including Pictet-Spengler Reaction and Exploration of Their C-2 Reactivity through SNAr. *J. Org. Chem.* **2017**, *82*, 13700–13707. DOI: 10.1021/acs.joc.7b02565.

[24] Hu, Y.; Li, C. Y.; Wang, X. M.; Yang, Y. H.; Zhu, H. L. 1,3,4-Thiadiazole: Synthesis, Reactions, and Applications in Medicinal, Agricultural, and Materials Chemistry. *Chem. Rev.* **2014**, *114*, 5572–5610. DOI: 10.1021/cr400131u.

[25] Patel, H. M.; Noolvi, M. N.; Goyal, A.; Thippeswamy, B. S. Thippeswamy, B. S. 2,5,6-Trisubstituted Imidazo[2,1-*b*][1,3,4]Thiadiazoles: Search for Antihyperlipidemic Agents. *Eur. J. Med. Chem.* **2013**, *65*, 119–133. DOI: 10.1016/j.ejmech.2013.04.020.

[26] Chandrakantha, B.; Isloor, A. M.; Shetty, P.; Fun, H. K.; Hegde, G. Synthesis and Biological Evaluation of Novel Substituted 1,3,4-thiadiazole and 2,6-di aryl substituted imidazo [2,1-b] [1,3,4] thiadiazole derivatives. *Eur. J. Med. Chem.* **2014**, *71*, 316–323. DOI: 10.1016/j.ejmech.2013.10.056.

[27] Gürsoy, E.; Dincel, E. D.; Naesens, L.; Güzeldemirci, N. U. Design and Synthesis of Novel Imidazo[2,1-*b*]Thiazole Derivatives as Potent Antiviral and Antimycobacterial Agents.

Bioorg. Chem. **2020**, *95*, 103496. DOI: 10.1016/j.bioorg.2019.103496.

[28] Lamani, R. S.; Shetty, N. S.; Kamble, R. R.; Khazi, I. A. M. Synthesis and Antimicrobial Studies of Novel Methylene Bridged Benzisoxazolyl imidazo[2,1-b][1,3,4]Thiadiazole Derivatives. *Eur. J. Med. Chem.* **2009**, *44*, 2828–2833. DOI: 10.1016/j.ejmech.2008.12.019.

[29] Gadad, A. K.; Palkar, M. B.; Anand, K.; Noolvi, M. N.; Boreddy, T. S.; Wagwade, J. Synthesis and Biological Evaluation of 2-Trifluoromethyl/Sulfonamido-5,6-Diaryl Substituted Imidazo[2,1-*b*]-1,3,4-Thiadiazoles: A Novel Class of Cyclooxygenase-2 Inhibitors. *Bioorg. Med. Chem.* **2008**, *16*, 276–283. DOI: 10.1016/j.bmc.2007.09.038.

[30] Ramprasad, J.; Nayak, N.; Dalimba, U.; Yogeeswari, P.; Sriram, D.; Peethambar, S. K.; Achur, R.; Kumar, H. S. S. Synthesis and Biological Evaluation of New Imidazo[2,1-*b*][1,3,4]Thiadiazole-Benzimidazole Derivatives. *Eur. J. Med. Chem.* **2015**, *95*, 49–63. DOI: 10.1016/j.ejmech.2015.03.024.

[31] Fascio, M. L.; Errea, M. I.; D'Accorso, N. B. Imidazothiazole and Related Heterocyclic Systems. Synthesis, Chemical and Biological Properties. *Eur. J. Med. Chem.* **2015**, *90*, 666–683. DOI: 10.1016/j.ejmech.2014.12.012.

[32] Gadad, A. K.; Noolvi, M. N.; Karpoormath, R. V. Synthesis and Anti-Tubercular Activity of A Series of 2-Sulfonamido/Trifluoromethyl-6-Substituted Imidazo[2,1-b]-1,3,4-Thiadiazole Derivatives. *Bioorg. Med. Chem.* **2004**, *12*, 5651–5659. DOI: 10.1016/j.bmc.2004.07.060.

[33] Kolavi, G.; Hegde, V.; Khazi, I. a.; Gadad, P. Synthesis and Evaluation of Antitubercular Activity of Imidazo[2,1-*b*][1,3,4]Thiadiazole Derivatives. *Bioorg. Med. Chem.* **2006**, *14*, 3069–3080. DOI: 10.1016/j.bmc.2005.12.020.

[34] Karki, S. S.; Panjamurthy, K.; Kumar, S.; Nambiar, M.; Ramareddy, S. A.; Chiruvella, K. K.; Raghavan, S. C. Synthesis and Biological Evaluation of Novel 2-Aralkyl-5-Substituted-6-(4'-Fluorophenyl)-Imidazo[2,1-b][1,3,4]Thiadiazole Derivatives as Potent Anticancer Agents. *Eur. J. Med. Chem.* **2011**, *46*, 2109–2116. DOI: 10.1016/j.ejmech.2011.02.064.

[35] Khalafy, J.; Etivand, N.; Khalillou, N. An Efficient Synthesis of Imidazo[2,1-*b*][1,3,4]Thiadiazol-7-Ium Hydroxides by a One-Pot, Three-Component Reaction in Water. *Heterocycl. Commun.* **2018**, *24*, 297–302. DOI: 10.1515/hc-2018-0117.

[36] (a) Goswami, B. N.; Kataky, J. C. S.; Baruah, J. N. J. Synthesis and Biological Activity of Bridgehead Nitrogen Heterocycles. *J. Heterocycl. Chem.* **1986**, *23*, 1439–1442. DOI: 10.1002/jhet.5570230538. (b) Leung-Toung, R.; Tam, T. F.; Zhao, Y.; Simpson, C. D.; Li, W.; Desilets, D.; Karimian, K. J. Synthesis of 3-Substituted Bicyclic Imidazo[1,2-d][1,2,4]Thiadiazoles and Tricyclic Benzo[4,5]Imidazo[1,2-d][1,2,4]Thiadiazoles. *J. Org. Chem.* **2005**, *70*, 6230–6241. DOI: 10.1021/jo0507486. (c) Mathew, V.; Keshavayya, J.; Vaidya, V. P. Heterocyclic System Containing Bridgehead Nitrogen Atom: synthesis and Pharmacological Activities of Some Substituted 1,2,4-Triazolo[3,4-b]-1,3,4-Thiadiazoles. *Eur. J. Med. Chem.* **2006**, *41*, 1048–1058. DOI: 10.1016/j.ejmech.2006.03.018.

[37] (a) Kiasat, A. R.; Kazemi, F.; Jardi, M. F. M. Solvent-Free Conversion of Oxiranes to Thiiranes with Thiourea. *Phosphorus, Sulfur, Silicon* **2004**, *179*, 1841–1844. DOI: 10.1080/10426500490466599. (b) Ghafuri, H.; Paravand, F.; Rashidizadeh, A. Nano Fe_3O_4@ZrO_2/SO_4^{2-}: A Highly Efficient Catalyst for the Protection and Deprotection of Hydroxyl Groups Using HMDS under Solvent-Free Conditions. *Phosphorus Sulfur Silicon Relat. Elem.* **2017**, *192*, 129–135. DOI: 10.1080/10426507.2016.1236104. (c) Bardajee, G. R.; Afsari, H. S.; Sadraei, S.; Taimoory, S. OH-/Silica-Mediated One-Pot Synthesis of Dithiocarbamates under Solvent-Free Conditions. *Phosphorus Sulfur Silicon Relat. Elem.* **2012**, *187*, 871–878. DOI: 10.1080/10426500490466599.

[38] Krasavin, M.; Tsirulnikov, S.; Nikulnikov, M.; Kysil, V.; Ivachtchenko, A. Poorly Reactive 5-Piperazin-1-*yl*-1,3,4-Thiadiazol-2-Amines Rendered as Valid Substrates for Groebke–Blackburn Type Multicomponent Reaction with Aldehydes and Isocyanides Using TMSCl as a Promoter. *Tetrahedron Lett.* **2008**, *49*, 5241–5243. DOI: 10.1016/j.tetlet.2008.06.113.

[39] (a) Tabibi, T.; Esmaeili, A. A.; Mague, J. T. An Efficient Diastereoselective Synthesis of Novel Fused 5-*H*-Furo[2,3-*d*]Thiazolo[3,2-*a*]Pyrimidin-5-Ones via One-Pot Three-Component Reaction. *Mol. Divers* **2021**, *3*, 1–8. DOI: 10.1007/s11030-020-10173-4. (b) Zangouei, M.; Esmaeili, A. A.; Mague, J. T. One-Pot Three Component Isocyanide-Based Reaction: Synthesis of Novel Tetracyclic Fused Furo[2′,3′:4,5]Pyrimido[2,1-b][1,3]Benzothiazole. *Tetrahedron* **2017**, *73*, 2894– 2900. DOI: 10.1016/j.tet.2017.03.082. (c) Zangouei, M.; Esmaeili, A. A.; Mague, J. T. An Unexpected Diastereoselective Synthesis of Novel Substituted Pyridines via One-Pot, Four-Component Reaction. *Synlett* **2016**, *27*, 1669–1673. DOI: 10.1055/s-0035-1561429. (d) Jannati, S.; Esmaeili, A. A. Synthesis of Novel Spiro[Benzo[4,5]Thiazolo[3,2-a]Chromeno[2,3-d]Pyrimidine-14, 3′-Indoline]-1, 2′,13(2H)-Triones via Three Component Reaction. *Tetrahedron* **2018**, *74*, 2967–2972. DOI: 10.1016/j.tet.2018.04.092. (e) Esmaeilinezhad, M.; Esmaeili, A. A.; Jannati, S. Facile Construction of Novel Fused Chromeno[2,3-d]Thiazolo[3,2-a]Pyrimidine Derivatives in Biocompatible Ionic Liquid under Solvent-Free Conditions. *J. Chem. Res.* **2018**, *42*, 618–622. DOI: 10.3184/174751918X15423512867751. (f) Zangouei, M.; Esmaeili, A. A.; Habibi, A.; Fakhari, A. R. Efficient Synthesis of Novel Tricyclic Fused Pyranothiazolopyrimidine Derivatives via Isocyanide-Based Three-Component Reactions. *Tetrahedron* **2014**, *70*, 8619–8623. DOI: 10.1016/j.tet.2014.09.048.

[40] Li, K.; Chen, W. A New Convenient Way to Synthesize 1,3,4-Thiadiazol-2-*yl* Urea Derivatives under Microwave Irradiation. *Heteroatom Chem.* **2008**, *19*, 621–629. DOI: 10.1002/hc.20489.

[41] Wadhwa, P.; Kaur, T.; Sharma, A. The First Catalyst and Solvent-Free Synthesis of 2-Arylimidazo[2,1-*b*][1,3,4]Thiadiazoles: A Comparative Assessment of Greenness. *RSC Adv.* **2015**, *5*, 44353–44360. DOI: 10.1039/C5RA06747B.