▌ Organic & Supramolecular Chemistry

Synthesis of 1-(3-(1-substituted-1,2,3-triazol-4-yl)-1,2,4-triazol-5-yl)-tetrazoles by Sequential Assembly of Azole Fragments

Eugene Zviagin,*[a, b] Vyacheslav Saraev,[a] Dmytro Sysoiev,[c] Blanka Klepetářová,[c] Maryna Mazur,[a, d] Oleksii Zhelavskyi,[a, b] Yuliia Shliapkina,[a] Thomas J. J. Müller,[e] and Valentyn Chebanov*[a, d, e]

Only few efficient methods for the preparation of polyazoles containing three or four nitrogen atoms in each azole cycle exist. We have developed a novel synthetic strategy that allows the sequential assembly of 1,2,3-triazole, 1,2,4-triazole, and tetrazole fragments into a new stable polyazole. Along the novel strategy, some known procedures have been optimized to achieve better conversion, selectivity, and, in general, overall efficiency.

Introduction

Polyazoles have various applications in chemistry. For instance, triazoles and tetrazoles are effective high-energy materials, and studies on their detonation parameters are carried out continuously.[1] Modern synthetic approaches allow the preparation of such extraordinary molecules, as 4-pyrazolyl-1,2,3-triazole,[2] 1-diazidocarbamoyl-5-azidotetrazole (C_2N_{14}),[3] 3,3'-azo-5,5'-diazido-1,2,4-triazole $(C_4H_2N_{14})$,[4] 1,1'-azobistetrazole $(C_2H_2N_{10})$,[5] and their derivatives.[6] Polyazoles have also gained much interest in medicinal chemistry for bioimaging,[7] and they are known bioisosteres of amides, carboxylic acids, and esters.[8–11] 1,2,3-Triazoles,[8,12–15] 1,2,4-triazoles[16,17] and tetrazoles[11,18] are important fragments of numerous biologically active compounds and pharmaceutical agents. Such applications highlight the potential of nitrogen-containing compounds and draw attention to these molecules.

Besides, polyazoles are reported to form stable complexes with metals.[19–22] Such coordination compounds can be used for instance as catalysts in organic reactions,[23,24] stabilizers of sensitive explosives,[25] and other.[26–28] The complexation with metals is used for heavy metal sensing[29–31] and extraction.[32–34] Combination of two or more fragments of N-containing heterocycles in a single molecule should increase the complexation ability further,[35] and if immobilized on the surface of a solid carrier, extraction of metal ions from solutions for content monitoring and purification of water, particularly industrial waste waters, becomes an important use. Several research groups reported syntheses of poly(polyazoles) such as **I**,[36] or their precursors **IIa,b**[37] (Scheme 1) from the point of view of nitrogen gas sources.

In this work we focused on the synthesis of polyazoles, that can be grafted on the surface of a solid support, and the design and synthesis of molecule containing 1,2,3- and 1,2,4-triazoles and tetrazole. We chose metal-assisted azide-alkyne cycloaddition as the most common and reliable[38] method of 1,2,3-triazole formation. Among many possible procedures for the synthesis of 1,2,4-triazole we selected the reaction of aminoguanidine with acyl chlorides **III**. The addition-elimination product in basic medium (Scheme 2) cyclizes to give C-amino-1,2,4-triazole **IV**.[39] N-Substituted tetrazoles can be obtained from amines in a three-component reaction with orthoformic esters and sodium azide.[40]

[a] Dr. E. Zviagin, Dr. V. Saraev, M. Mazur, O. Zhelavskyi, Y. Shliapkina, Prof. Dr. V. Chebanov
Department of Organic and Bioorganic Chemistry
SSI "Institute for Single Crystals" NAS of Ukraine
60 Nauky ave., Kharkiv 61072, Ukraine
E-mail: chebanov@isc.kh.ua

[b] Dr. E. Zviagin, O. Zhelavskyi
Department of Chemistry
University of Michigan
930 N. University Ave, Ann Arbor, MI, 48109, United States of America
E-mail: ezviagin@umich.edu

[c] Dr. D. Sysoiev, Dr. B. Klepetářová
Institute of Organic Chemistry and Biochemistry
Czech Academy of Sciences
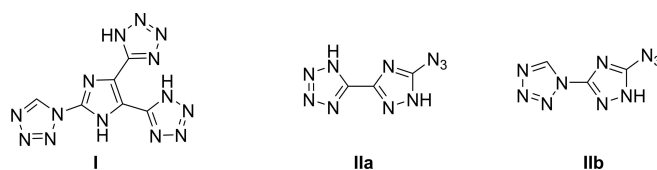Flemingovo nam. 2, 16610 Prague (Czech Republic)

[d] M. Mazur, Prof. Dr. V. Chebanov
Department of Chemistry
V. N. Karazin Kharkiv National University
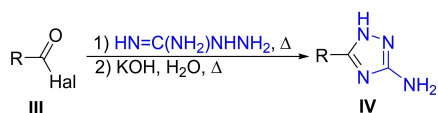4 Svobody sq., Kharkiv 61022, Ukraine

[e] Prof. Dr. T. J. J. Müller, Prof. Dr. V. Chebanov
Institut für Organische Chem. und Makromolekulare Chem
Heinrich-Heine-Universität Düsseldorf
Universitätsstraße 1, Düsseldorf, D-40225, Germany

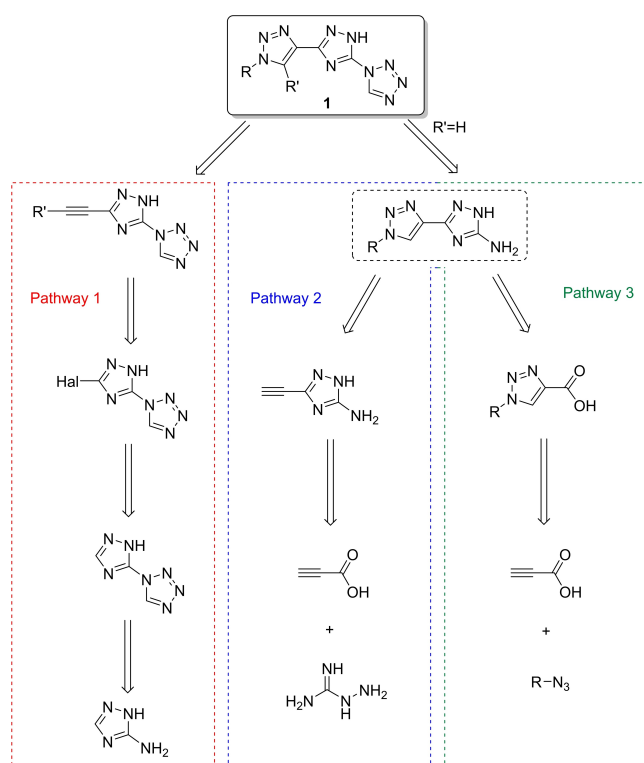Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.202102459

Scheme 1. Examples of N-rich heterocyclic systems.

ChemistrySelect

Full Papers
doi.org/10.1002/slct.202102459

Chemistry Europe
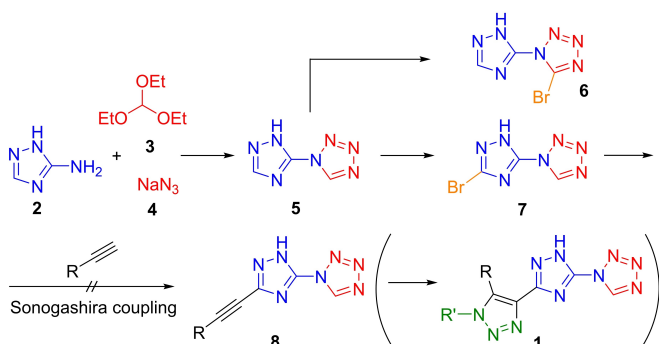European Chemical
Societies Publishing

Scheme 2. Preferred method of the preparation of amino-1,2,4-triazoles.

Our group has previously reported preparation of a material based on the chosen polyazole skeleton, covalently bound to Merrifield resin. This functionalized polymer showed excellent extraction rates for europium(III) and copper(II) when added to a sample of spring water.[41] Here we discuss our initial synthetic studies towards the backbone, broad and deep investigations for the optimization of the synthetic steps, and also identifica-

tion procedures for the monomeric target molecules and their intermediates.

Results and Discussion
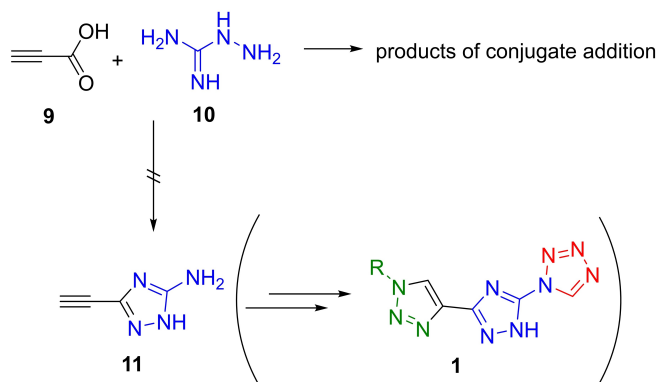
Synthetic approaches

From the variety of possible structures, we chose the one having three different types of azole rings-1-(3-(1,2,3-triazol-4-yl)-1,2,4-triazol-5-yl)-tetrazoles **1**, that can be accessed via several retrosynthetic pathways. Some prospective approaches to the target are summarized in Scheme 3.

Pathway 1 (Scheme 4) implies tetrazolation of 3-amino-1,2,4-triazole **2** using a procedure provided by Gaponik group,[42] followed by selective bromination of the triazole cycle, which was not previously described. However, it was found that standard bromination conditions, e.g. Br_2/base in water or organic solvent as well as using pyridinium bromide perbromide $PyHBr_3$, led to a mixture of two different mono- (**6**, **7**) and dibromination products or to decomposition of **5**. Only a solution of N-bromosuccinimide in CCl_4 under external ice-water cooling was able to selectively produce the targeted bromotriazole **7**, while bromotetrazole **6** was obtained as the major product under basic conditions in ice-cold $CHCl_3$ upon dropwise addition of a Br_2/$CHCl_3$ solution.
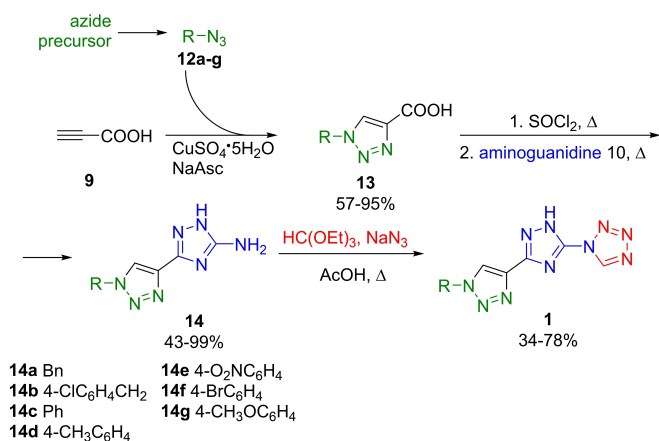
Installation of the alkyne in **7** via Sonogashira cross coupling was attempted,[43] that requires palladium-based catalysts by default. Surprisingly, in our case various reaction procedures and using such Pd(0) and Pd(II) catalysts as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2(dppf)$ and $PdCl_2(Me_2NPhP(t-Bu)_2)_2$ gave no target product, and only provided full recovery of starting material. Presumably, the main reason for such outcome is the deactivation of palladium catalysts due to the complexation of **2**. Although a new approach requires exploring, the complexation properties of the constituting precursor already indicated a favorable complexation profile for metal-complexing sorbents.

Considering the abovementioned results we envision an alternative approach to assemble triazolyltriazolyltetrazole **1** from 5-amino-3-ethynyl-1,2,4-triazole **11**, and then by means of CuAAC (copper-catalyzed alkyne-azide cycloaddition) and tri-component tetrazole formation converting it to target poly-azole (Scheme 5). Nonetheless the reaction of propiolic acid **9** and aminoguanidine **10** yielded only an inseparable mixture of several substances. The NMR spectra of this mixture showed no peaks of desirable triazole **11**, instead degradation and conjugate addition products as well as reactants were observed.

Therefore, a CuAAC reaction of propiolic acid **9** with organic azides **12** was chosen as a method to prepare 1,2,3-triazole-4-carboxylic acids **13**, which overrides the problem of conjugate addition. Further functionalization allowed us to obtain a series of aminotriazoles **14** and then target tetrazoles **1**. In this sequence, visualized in Scheme 6, most steps need more careful consideration.

Scheme 3. Discussed retrosynthetic approaches for the synthesis of **1**.

Scheme 4. Pathway 1 breakdown.

ChemistrySelect

Full Papers
doi.org/10.1002/slct.202102459

Chemistry Europe
European Chemical
Societies Publishing

Scheme 5. Details of proposed Pathway 2.

Scheme 6. Selected synthetic strategy to assembly the target polyazole **1**

Table 1. Survey of catalytic systems for CuAAC reaction of azides **12** and propiolic acid **9**.			
Cu^I generation approach	Direct introduction of Cu^I	In situ reduction	Comproportio-nation
Catalytic precursors	CuI	CuSO$_4$/sodium ascorbate	Cu/Cu(OTf)$_2$
Conditions	DIPEA, AcOH, DCM	t-BuOH, H$_2$O	CH$_3$CN
Results	Low yield, high purity	High yield, moderate purity	Low yield, low purity

as nitro- and carboxyl groups were found to react sluggishly with propiolic acid even after continuous stirring and heating. After 24 h of stirring the reaction mixture of azide **12 e** and acid **9** at 60 °C the ^{1}H NMR spectrum of isolated precipitate showed 25 % conversion of **12 e** to **13 e**. In this case application of ultrasonication was advantageous: the same reaction mixture subjected to ultrasound irradiation yielded the desired triazole-carboxylic acid **13 e** after only 3 hours. The traces of initial azide can be easily removed by washing with acetone. The role of ultrasound here is most probably improving mass transfer, and also local overheating and pressure increase caused by the cavitation effect.[47]

The heterocyclization of aminoguanidine with carboxylic acids **13** proceeded smoothly in 43–99 % yield. The low solubility of aminotriazoles **14** in most solvents allowed only limited series of target tetrazoles **1**.
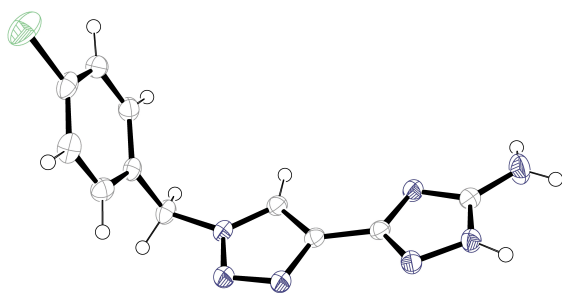
The yields of all intermediates and final compounds are summarized for the series in Table 2.

Identification and initial purity analysis of tetrazoles **1** and their precursors by routine NMR spectroscopy and mass spectrometry proved challenging due to their low solubility and signal broadening. Therefore, in addition we applied high-performance liquid chromatography as a reliable method for reaction and purity monitoring.

Extensive experiments showed that the optimal mobile phases were gradients of A (H$_2$O + 0.1 % H$_3$PO$_4$) and B (CH$_3$OH) with its variation on time- 20 % of methanol in 0–15 min interval, 95 % in 15–21 min interval and again 20 % after 21 min. Retention times increased in order of aminotriazoles **14** < acids **13** < decarboxylated triazoles **13′** < tetrazoles **1** independent on phenyl ring substituents, which allowed us to analyze the reaction mixtures, conversion level and purity of the reaction products.

Synthesis of target triazolyltriazolyltetrazoles 1

It should be noted that the substituent on the phenyl ring of the azide is a crucial factor for the ease of isolation of the products from the reaction mixture. Thus, the azides with electron-withdrawing groups are air-stable, have high melting points and low solubility in water and their isolation comes down to simple filtration. Halogen-derived phenyl azide **12 f** has a melting point close to room temperature and should be filtered and washed with ice-cold water. Interestingly enough, the color of 4-bromophenyl azide **12 f** is reported as "green", "yellow" and "brown" in different publications,[44,45] but we established that freshly obtained it is a white compound which should be stored in cold: even at room temperature it quickly changes to green and then to brown.

For the CuAAC of azides (**12**) and propiolic acid (**9**), the three most common catalytic systems for the in situ generation of Cu^I were tested on several azide substrates (Table 1). Based on the results, we selected the CuSO$_4$/ascorbate system as the most promising and used EDTA solutions to extract the main impurity- Cu^{II} ions.

Despite some of the records in recent literature,[46] phenyl azides bearing such electron-withdrawing functionalities such

Table 2. Reaction yields of preparation of compounds **12–14** and **1**.				
	R,	12, yield, %	13, yield, %	14, yield, %	1, yield, %
a	C$_6$H$_5$CH$_2$	87	78	92	34
b	4-ClC$_6$H$_4$CH$_2$	99	94	43	78
c	C$_6$H$_5$	92	73	74	34
d	4-CH$_3$C$_6$H$_4$	93	95	84	62
e	4-O$_2$NC$_6$H$_4$	94	75	mixture	–
f	4-BrC$_6$H$_4$	91	93	99	63
g	4-CH$_3$OC$_6$H$_4$	96	57	65	64

ChemistrySelect

Full Papers
doi.org/10.1002/slct.202102459

Chemistry Europe
European Chemical
Societies Publishing

Figure 1. ORTEP[48] diagram of aminotriazole **14 b**, displacement ellipsoids shown with 50 % probability.

Structural assignments were supported by ^{1}H-^{15}N HMBC NMR experiments (Figures **SI**–**7**, **SI**–**18** and **SI**–**21** in Supplementary Information) where the connectivity of the benzyl fragment with the triazole and the correlation of the tetrazole proton with its nitrogen atoms were shown. Moreover, we were able to grow single crystals of aminotriazole **14 b** from its DMF solution covered with a water layer (3:1 per vol) in a glass vial. X-Ray diffraction data confirmed the connectivity of 1,2,3- and 1,2,4-triazole rings (Figure 1).

Supporting Information Summary

Supporting information contains experimental procedures, detailed characterization data, including ^{1}H, ^{13}C, ^{13}C APT, ^{1}H-^{15}N HMBC spectra. Deposition Number 2083793 (for 14 b) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Center and Fachinformationszentrum Karlsruhe Access Strurctures service.

Conclusion

In the present work, we have developed a novel synthetic strategy to obtain a new stable polyazole - 1-(3-(1-substituted-1,2,3-triazol-4-yl)-1,2,4-triazol-5-yl)tetrazole - by sequential construction of 1,2,3-triazole, 1,2,4-triazole and tetrazole cycles. It consisted in obtaining the 1,2,3-triazole fragment by the reaction of an organic azide with propargylic acid; synthesizing the 1,2,4-triazole cycle by acylation of aminoguanidine with triazole carboxylic acid obtained in the first step; introducing the tetrazole fragment by exocyclic amino group modification. The CuAAC efficiency was shown to be improved by ultra-sonication.

Conflict of Interest

The authors declare no conflict of interest.

[1] J. Ma, G. Zhang, H. Gu, J. Tang, B. Wang, H. Yang, G. Cheng, *New J. Chem.* **2019**, *43*, 8370–8375.
[2] P. Niesobski, F. Klukas, H. Berens, G. Makhloufi, C. Janiak, T. J. J. Müller, *J. Org. Chem.* **2018**, *83*, 4851–4858.
[3] T. M. Klapötke, F. A. Martin, J. Stierstorfer, *Angew. Chem. Int. Ed.* **2011**, *50*, 4227–4229; *Angew. Chem.* **2011**, *123*, 4313–4316.
[4] C. Lei, H. Yang, H. Xiong, G. Cheng, *Propellants Explos. Pyrotech.* **2020**, *45*, 416–421.
[5] T. M. Klapötke, D. G. Piercey, *Inorg. Chem.* **2011**, *50*, 2732–2734.
[6] L. Türker, *Def. Technol.* **2016**, *12*, 1–15.
[7] Kenry, B. Liu, *Trends Chem.* **2019**, *1*, 763–778.
[8] E. Bonandi, M. S. Christodoulou, G. Fumagalli, D. Perdicchia, G. Rastelli, D. Passarella, *Drug Discovery Today* **2017**, *22*, 1572–1581.
[9] W. H. Song, M. M. Liu, D. W. Zhong, Y. L. Zhu, M. Bosscher, L. Zhou, D. Y. Ye, Z. H. Yuan, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4528–4531.
[10] G. A. Patani, E. J. LaVoie, *Chem. Rev.* **1996**, *96*, 3147–3176.
[11] Y. Zou, L. Liu, J. Liu, G. Liu, *Future Med. Chem.* **2020**, *12*, 91–93.
[12] P. Prasher, M. Sharma, *MedChemComm* **2019**, *10*, 1302–1328.
[13] K. Bozorov, J. Zhao, H. A. Aisa, *Bioorg. Med. Chem.* **2019**, *27*, 3511–3531.
[14] D. Dheer, V. Singh, R. Shankar, *Bioorg. Chem.* **2017**, *71*, 30–54.
[15] A. Rani, G. Singh, A. Singh, U. Maqbool, G. Kaur, J. Singh, *RSC Adv.* **2020**, *10*, 5610–5635.
[16] S. Maddila, R. Pagadala, S. Jonnalagadda, *Lett. Org. Chem.* **2013**, *10*, 693–714.
[17] R. Sathyanarayana, B. Poojary, *J. Chin. Chem. Soc.* **2020**, jccs.201900304.
[18] E. A. Popova, R. E. Trifonov, V. A. Ostrovskii, *Russ. Chem. Rev.* **2019**, *88*, 644–676.
[19] M. Massi, S. Stagni, M. I. Ogden, *Coord. Chem. Rev.* **2018**, *375*, 164–172.
[20] G. Aromí, L. A. Barrios, O. Roubeau, P. Gamez, *Coord. Chem. Rev.* **2011**, *255*, 485–546.
[21] J. D. Crowley, D. A. McMorran in *Click Triazoles. Topics in Heterocyclic Chemistry, vol 28.* (eds. Košmrlj J.) Springer, Berlin, Heidelberg, **2012**, pp. 31–83.
[22] P. N. Gaponik, S. V. Voitekhovich, O. A. Ivashkevich, *Russ. Chem. Rev.* **2006**, *75*, 507–539.
[23] D. Huang, P. Zhao, D. Astruc, *Coord. Chem. Rev.* **2014**, *272*, 145–165.
[24] S. Neumann, M. Biewend, S. Rana, W. H. Binder, *Macromol. Rapid Commun.* **2020**, *41*, 1900359.
[25] J. Stierstorfer, M. H. H. Wurzenberger, M. Lommel, M. S. Gruhne, N. Szimhardt, *Angew. Chem. Int. Ed.* **2020**, 12367–12370.
[26] P. A. Scattergood, A. Sinopoli, P. I. P. Elliott, *Coord. Chem. Rev.* **2017**, *350*, 136–154.
[27] P. I. P. Elliott, *Organomet. Chem.* **2014**, *39*, 1–25.
[28] J. Lauko, P. H. J. Kouwer, A. E. Rowan, *J. Heterocycl. Chem.* **2017**, *54*, 1677–1699.
[29] Y. H. Lau, P. J. Rutledge, M. Watkinson, M. H. Todd, *Chem. Soc. Rev.* **2011**, *40*, 2848–2866.
[30] J. Zhang, C. Yu, S. Qian, G. Lu, J. Chen, *Dyes Pigm.* **2012**, *92*, 1370–1375.
[31] J. J. Bryant, U. H. F. Bunz, *Chem. Asian J.* **2013**, *8*, 1354–1367.
[32] E. A. Popova, R. E. Trifonov, V. A. Ostrovskii, *Arkivoc* **2012**, *I*, 45–65.
[33] Y. Chen, W. Zhao, H. Zhao, J. Dang, R. Jin, Q. Chen, *Chem. Phys.* **2020**, *529*, 110550.
[34] M. Lamanna, L. Leiton, I. N. Vega, B. L. Rivas, N. D'Accorso, *Adv. Mater. Sci.* **2017**, *2*, 1–6.
[35] Y. Zhang, Y. Chen, C. Wang, Y. Wei, *J. Hazard. Mater.* **2014**, *276*, 129–137.
[36] D. Srinivas, V. D. Ghule, K. Muralidharan, *RSC Adv.* **2014**, *4*, 7041–7051.
[37] D. Izsák, T. M. Klapötke, *Cent. Eur. J. Energ. Mater.* **2015**, *12*, 403–416.

[38] M. V. Murlykina, A. D. Morozova, I. M. Zviagin, Y. I. Sakhno, S. M. Desenko, V. A. Chebanov, *Front. Chem.* **2018**, *6*, 527.

[39] V. M. Chernyshev, E. V. Tarasova, A. V. Chernysheva, V. A. Taranushich, *Russ. J. Appl. Chem.* **2011**, *84*, 1890–1896.

[40] S. V. Voitekhovich, A. N. Vorob'ev, P. N. Gaponik, O. A. Ivashkevich, *Chem. Heterocycl. Compd.* **2005**, *41*, 999–1004.

[41] I. M. Zviagin, S. V. Khimchenko, T. A. Blank, I. B.-K. Shcherbakov, E. Y. Bryleva, Z. Y. Bunina, D. S. Sofronov, K. N. Belikov, V. A. Chebanov, *Funct. Mater.* **2018**, *25*, 619–624.

[42] P. N. Gaponik, V. P. Karavai, Y. V. Grigor'ev, *Chem. Heterocycl. Compd.* **1985**, *21*, 1255–1258.

[43] J. Wan, Y. Xia, Y. Liu, M. Wang, P. Rocchi, J. Yao, F. Qu, J. Neyts, J. L. Iovanna, L. Peng, *J. Med. Chem.* **2009**, *52*, 1144–1155.

[44] P. S. Gribanov, M. A. Topchiy, Y. D. Golenko, Y. I. Lichtenstein, A. V. Eshtukov, V. E. Terekhov, A. F. Asachenko, M. S. Nechaev, *Green Chem.* **2016**, *18*, 5984–5988.

[45] P. Sonzini, C. Damiano, D. Intrieri, G. Manca, E. Gallo, *Adv. Synth. Catal.* **2020**, *362*, 2961–2969.

[46] Q. K. Shen, H. Deng, S. Ben Wang, Y. S. Tian, Z. S. Quan, *Eur. J. Med. Chem.* **2019**, *173*, 15–31.

[47] G. Chatel, *Ultrason. Sonochem.* **2018**, *40*, 117–122.

[48] L. J. Farrugia, *J. Appl. Crystallogr.* **2012**, *45*, 849–854.