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A facile one-pot parallel synthesis of 3-amino-1,2,4 – triazoles

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KEYWORDS: 1,2,4,-triazole, thiourea, 2,2,2-trifluoroethylthiocarbamate, ring closure, S-alkylation.

ABSTRACT. A 1,2,4-triazole motif is present in numerous commercialized and investigational bioactive molecules. Despite its importance for medicinal chemistry, there is a lack of convenient combinatorial approaches towards this molecular core. Herein, we present a synthetic strategy suitable for the quick preparation of a library of structurally diverse 1,2,4-triazoles in a one-pot setting. The key steps include the formation of thioureas followed by S-alkylation using 1,3-propanesultone and consecutive ring closure leading to the desired 1,2,4,-triazoles. Parallel synthesis yields thousands of 1,2,4-triazoles in a cost- and time-efficient manner from commercially available chemicals.

Introduction. Accessing combinatorial libraries of potentially bioactive molecules in a cost-efficient manner remains among the practical challenges in the modern drug discovery.[1] Supported by the growing potential of computational methods, optimization of existing and elaboration of new synthetic strategies leading to new drug-like molecules has become indispensable in medicinal chemistry. In the early stages, the efficiency of drug discovery often relies on the ability to identify the active compounds from an enormously large yet virtual or readily available pool of structures.[2] Despite the existence of well-established guidelines to deliver these chemical structures, such as Lipinski's "rule of five" or similar criteria for fragment-oriented hit identification projects, a thorough exploration of the chemical space remains a daunting challenge.[3,4] In this regard, a myriad of structurally and functionally diverse molecules which are synthetically undemanding remains unexplored solely because of the availability issue. This obstacle often occurs because of tedious and unreliable synthetic

protocols which can influence the pace of drug discovery process. Therefore, increasing the diversity and modularity of chemical synthesis can help to overcome these limitations and provide medicinal chemists with an enhanced capacity to detect and evolve the compounds of interest. Furthermore, a newly developed method should meet certain important criteria, such as safety of chemical synthesis, the possibility of automation, and economic feasibility.

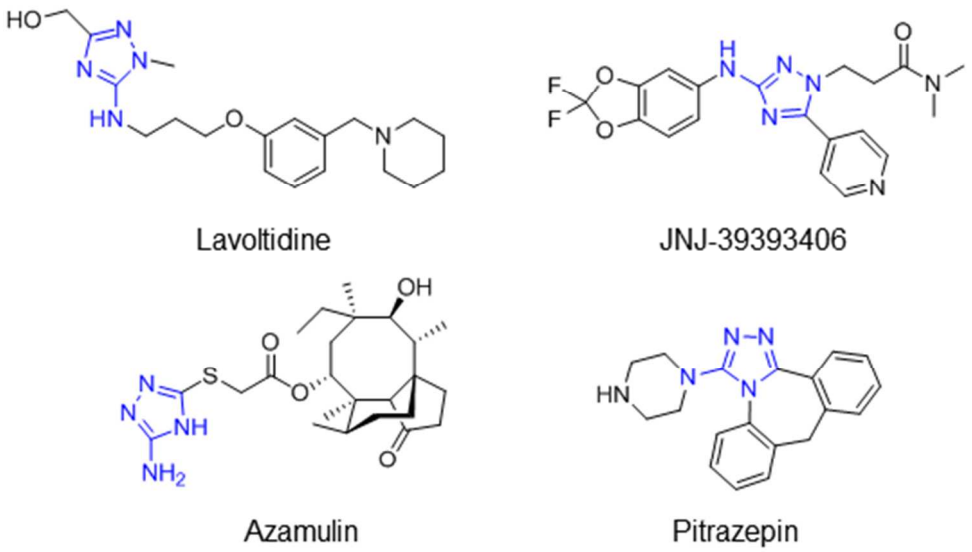


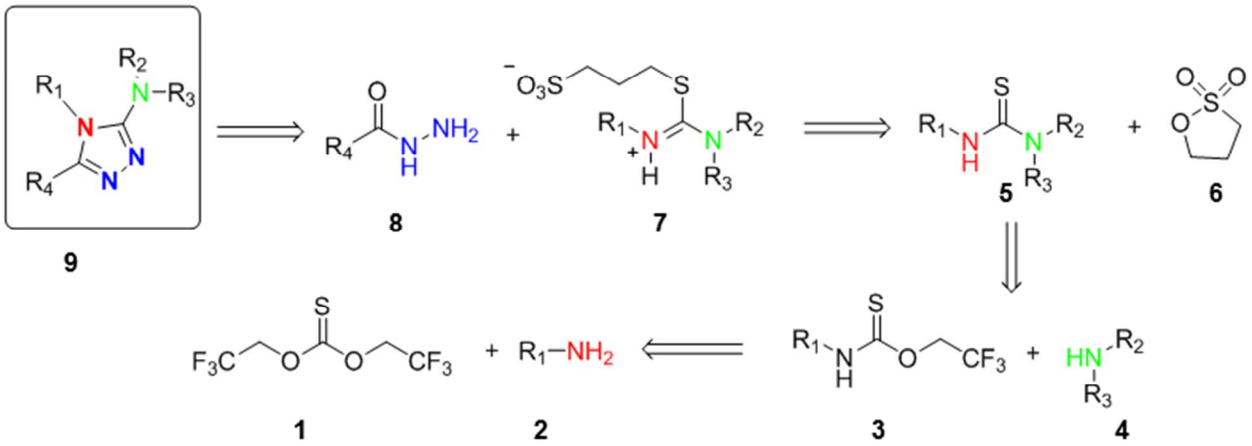
Figure 1. Representative bioactive molecules containing an aminotriazole motif.

Recently, the derivatives of 1,2,4-triazoles drew our attention due to the high abundance of bioactive molecules containing this structural motif.[5,6] This five-membered ring is also a promising bioisosteric replacement of a cis-amide bond, further extending the scope of potential applications.[7] Not surprisingly, the 3-amino-1,2,4-triazole core is present in many experimental and investigational compounds – some examples are shown in Figure 1.[8,9]

Over the years, numerous synthetic approaches towards 1,2,4-triazoles have been reported in literature.[10–16] Considerable efforts were directed to adopt these methods to solid phase chemistry.[17–20] However, the majority of the attempts are practically ill-suited for the generation of large libraries due to the inherent shortcomings. The major practical problems emerge from

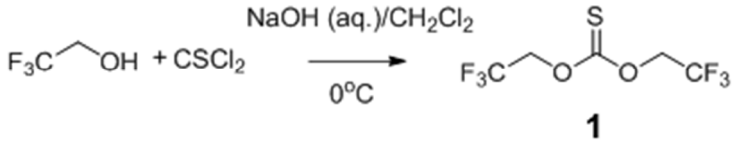
applying high temperatures, microwave irradiation, the formation of volatile and harmful chemicals, low purity and low yields of final products. In this regard, there is an existing demand for more convenient and efficient synthetic pathways which could match an ever-growing number of biological targets currently present in the research pipelines.

Recognizing the importance of further exploring the utility of 1,2,4- triazoles, we aimed to develop a method suitable for the preparation of a diverse library of drug-like compounds containing a 3-amino-1,2,4- triazole core. Herein, we propose an easy, one-pot synthetic route towards millions of the substituted aminotriazoles performed in a parallel synthesis setting. Briefly, the key steps include the formation of an asymmetrically substituted thiourea from bis(2,2,2-trifluoroethyl) thiocarbonate , followed by alkylation of the thiourea with 1,3-propanesultone and the ring closure in the aminotriazole motif upon addition of corresponding hydrazides (Scheme 1). The identity and purity of the formed 3-amino-1,2,4- triazole derivatives were confirmed by ^{1}H, ^{13}C NMR, and LC-MS.



Scheme 1. Synthetic route towards a library of triazoles **9**.

Results and discussion. A general method of synthesis of the substituted 3-amino-1,2,4-triazoles is reported in this work. To prove its efficiency for the synthetic purposes, a representative library of drug-like molecules containing the aminotriazole core (compounds **9**, Scheme 1) was successfully prepared in a one-pot setting using parallel synthesis. The final library of separated and characterized products includes 146 compounds (73% success rate) with different substituents (R_1-R_4) at variable positions. Importantly, the method yields a set of triazoles containing diverse moieties – aliphatic, aromatic and heteroaromatic – exclusively from the commercially available reagents. This aspect is of high importance in generating screening libraries with an increased diversity in a time- and cost-effective manner, avoiding the need of synthesizing commercially irrelevant and often unstable intermediate chemicals.



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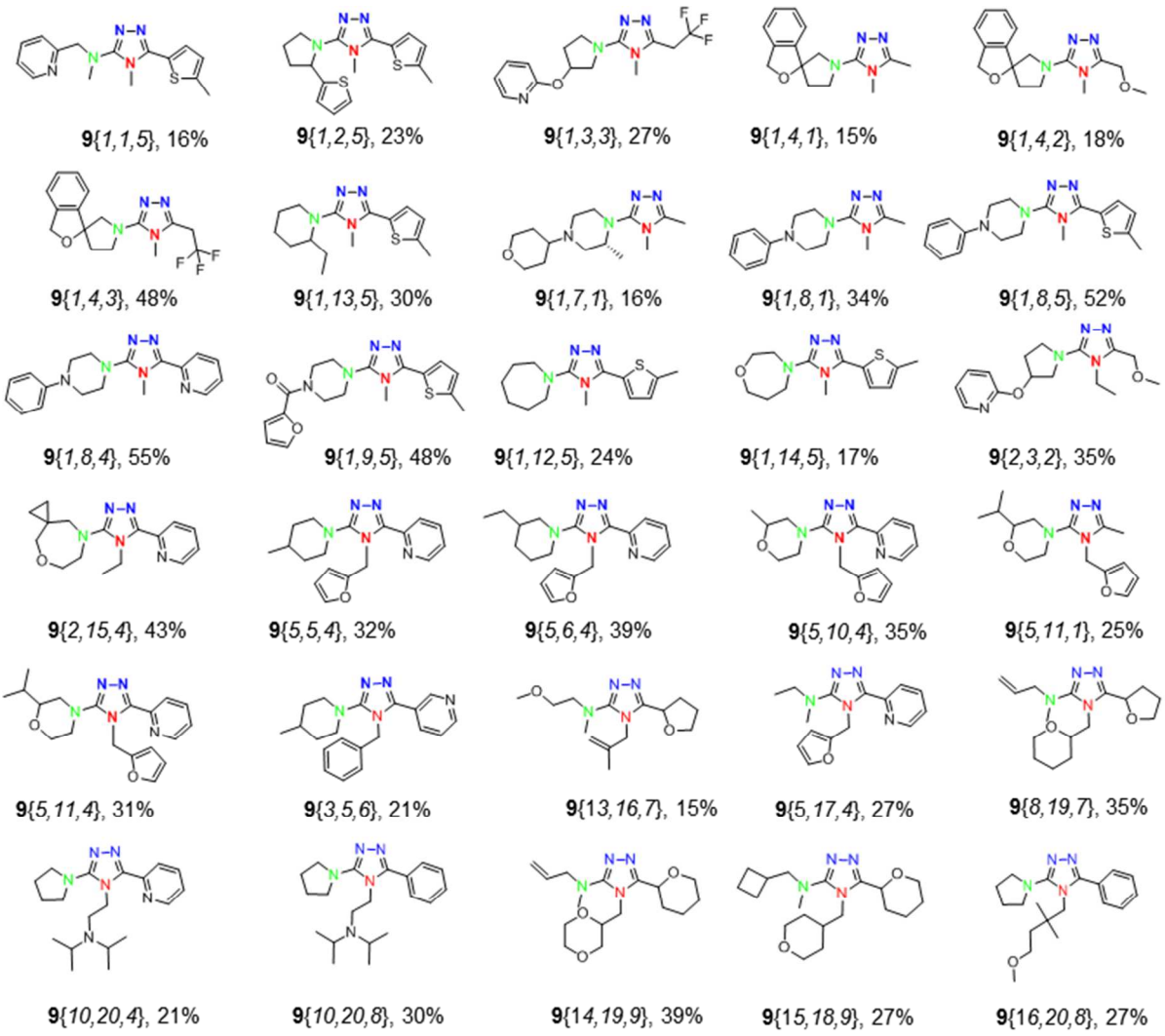
Scheme 2. Synthesis of bis(2,2,2-trifluoroethyl) thiocarbonate.

Table 1. A representative set of the substituted 3-amino-1,2,4- triazoles and overall yields of separated materials.



The structures of representative triazoles **9** and their overall yields are shown in Table 1; a full list and further characterization of these compounds can be found in the Supporting Information (SI). The 3-amino-1,2,4- triazoles **9** were prepared on a hundred milligram scale in four steps starting from bis(2,2,2-trifluoroethyl) thiocarbonate **1**. The latter compound is a stable yet reactive thiocarbonate ester; it is readily accessible in one step from thiophosgene and trifluoroethanol via fractional distillation (Scheme 2).[21] Based on our previous findings, the usage of the trifluoroethyl substituents as leaving groups enables to achieve suitable profiles of kinetics and selectivity of the stepwise aminolysis reaction in the case of carbonate esters.[22,23] A

similar approach applied to thiocarbonate esters gives an excellent starting material for the reliable utilization in synthetic projects which require the formation of thiocarbamates or thioureas either as target or intermediate compounds. Indeed, compared to volatile and toxic thiophosgene or its analogs, compound **1** is an easy-to-handle reagent that interacts consistently with a wide range of amines. The formation of asymmetrical thiourea derivatives **5** occurs via consecutive couplings of bis(2,2,2-trifluoroethyl) thiocarbonate with corresponding amines, although under different conditions (Scheme 3). Importantly, all amines tested in this project were randomly selected from our database. The first coupling step involves the reaction of **1** (1.5 eqv.) with a primary amine **2** (Figure 2). In general, the formation of an intermediate thiocarbamate **3** occurs at 75°C in acetonitrile in 2 h and the conversion can be easily monitored by ^{1}H NMR or LC-MS. All volatile components present in the mixture, including remaining **1** and 2,2,2-trifluoroethylethanol, are conveniently removed at this stage by evaporation under reduced pressure, yielding crude compound **3**. The purity of the intermediate **3** was sufficient for utilization in the next step. Our results demonstrate that compounds **2** applicable for the scheme mostly represent nucleophilic amines, whereas introducing anilines or hetarylamines in a one-pot protocol led to unsuccessful experiments. Some of the used derivatives **2** are presented in Figure 2, capturing the major chemotypes tested in this project. The following stage – formation of a thiourea **5** – is accomplished via coupling of **3** and a secondary amine **4** in the presence of DBU. This transformation proceeds successfully after heating the mixture in acetonitrile at 100°C for 16 h in a sealed vial. At this stage, the secondary aliphatic amines **4** were selected to ensure a regioselective ring closure reaction into **9** at later stages. Using primary amines will lead to a mixture of final products **9** which is not compliant with the requirements for parallel synthesis.

Noteworthy, the stepwise coupling of amines and bis(2,2,2-trifluoroethyl) thiocarbonate represents a valid strategy of achieving large libraries of asymmetrical thiourea derivatives which not only serve as the precursors for triazole synthesis but also form an independent class of bioactive molecules on their own. With regard to thioureas, one of the competitive advantages of the current protocol over other methods reported in literature resides in total reliance on commercial compounds. This statement is further supported by a wide selection of structurally and functionally diverse amines which abound in many catalogs, including ours (Figure 2, 3).

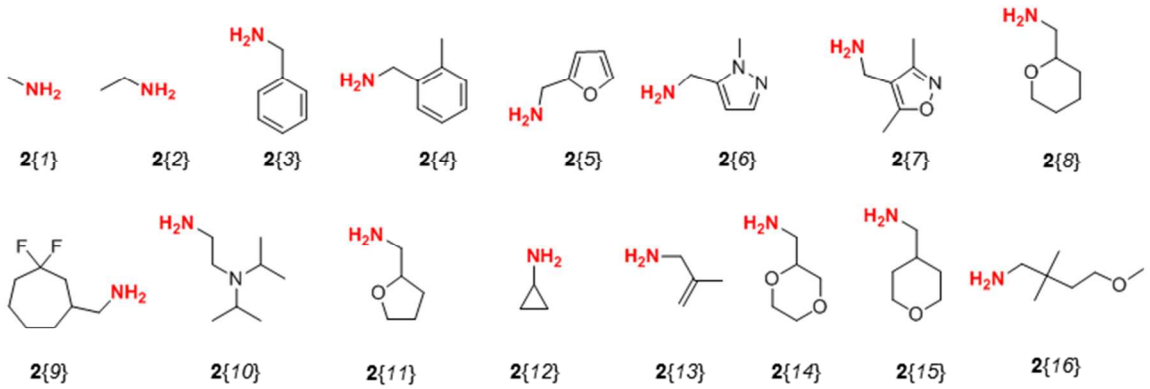


Figure 2. Amines **2**.

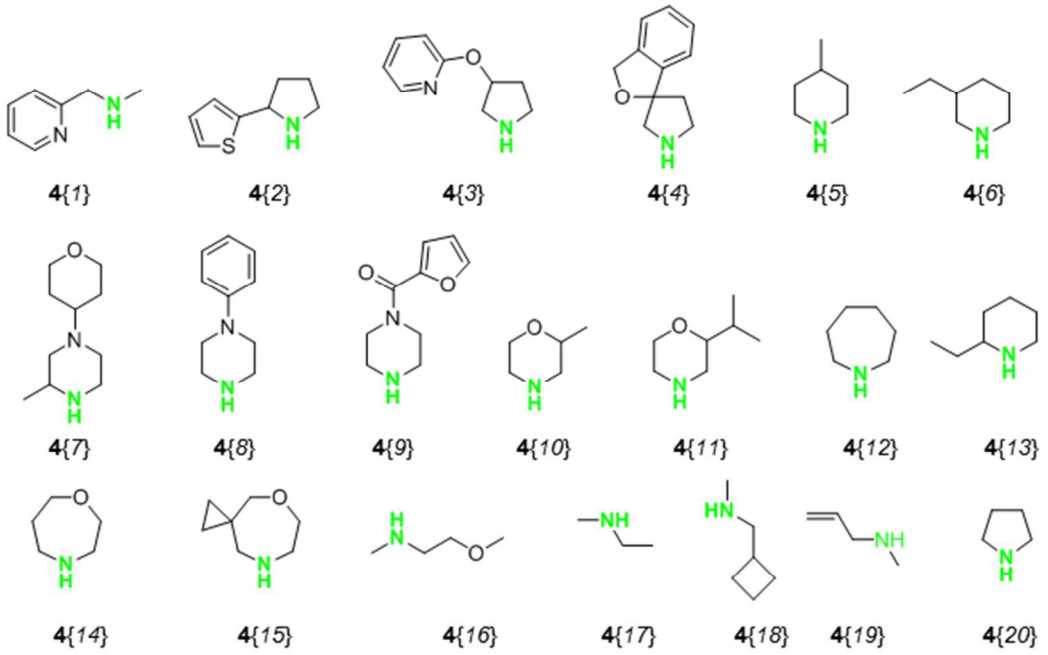
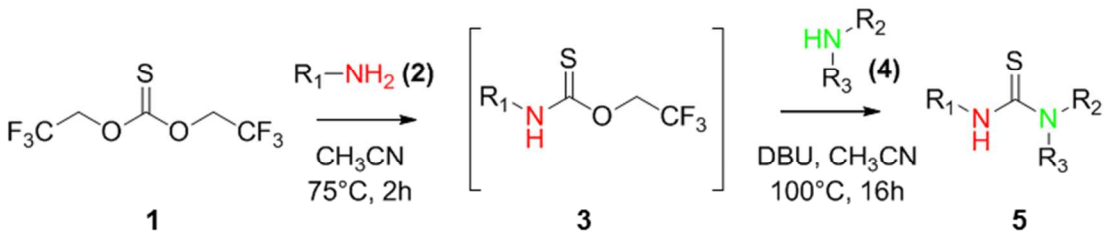
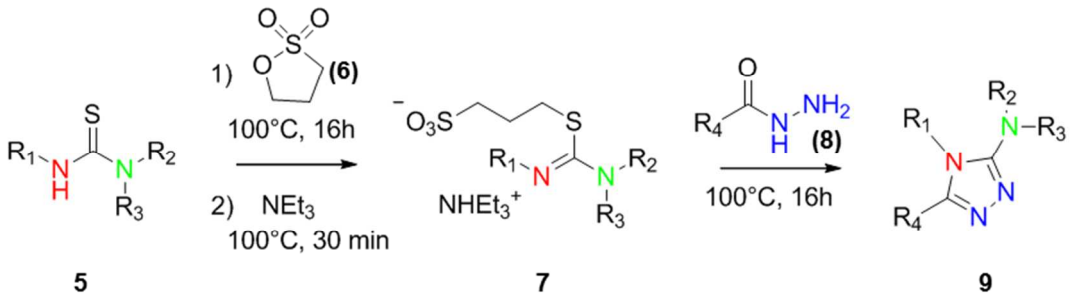


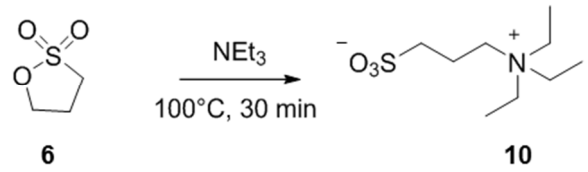
Figure 3. Amines **4**.



Scheme 3. Synthesis of the unsymmetrical thioureas **5**.



Scheme 4. Synthesis of 1,2,4-aminotriazoles **10** from thioureas **5**.



Scheme 5. Removal of **6** via reaction with triethylamine.

The next step includes conversion of the crude thioureas **5** into isothioureas **7** (Scheme 4). Adding a two-fold excess of a mild alkylating agent, 1,3-propanesultone **6**, leads to the formation of an isothiourea moiety which later serves as a suitable leaving group during the final ring closure reaction to yield **9**. At this stage, the usage of **6** was substantiated by advantageous safety and purification parameter profiles, such as non-volatile nature and polarity of all sulfonate

derivatives which are formed upon ring opening of **6**. The S-alkylation reaction leading to **7** requires heating the mixture of **5** and **6** to 100°C for 16 h. An excess of **6** and acidic sulfonate **7** was routinely quenched by adding triethylamine and equilibrating the reaction at 100°C for 30 min (Scheme 5). Finally, the derivatives **7** were easily converted into target 3-amino-1,2,4-triazoles **9** by treating them with an equimolar amount of hydrazides **8** at 100°C for 16 h. A diverse set of hydrazides was tested and successfully used in this reaction. The process proceeds smoothly with various aliphatic, aromatic and heteroaromatic hydrazide derivatives (Figure 4). The final reaction mixture was then evaporated, re-dissolved in chloroform and washed with water to remove the excess of remaining sulfonates. Importantly, the usage of polar sulfonates was crucial to increase the efficiency of the final purification compared to other alkylating agents which were tested for the S-alkylation reaction. The target products **9** were successfully purified by reverse-phase HPLC on C_{18} columns.

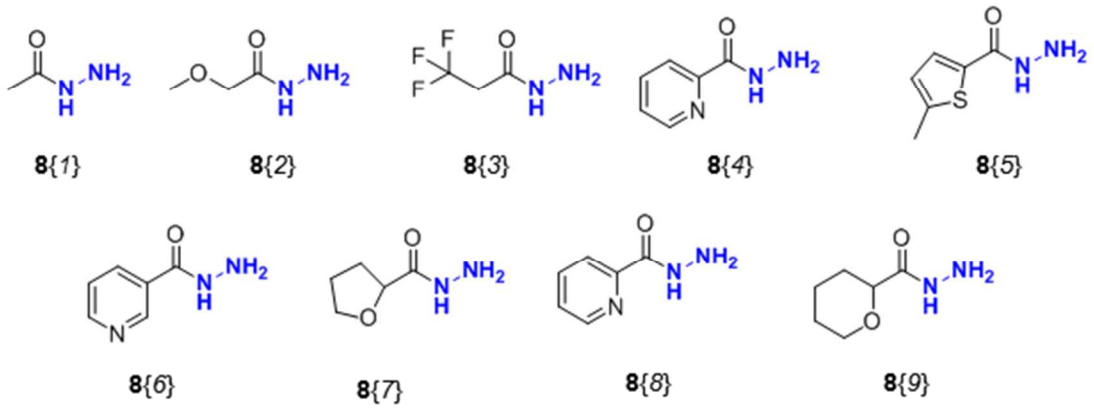


Figure 4. Hydrazides **8**.

Expanding chemical space with synthetically feasible compounds. Virtual high-throughput screening (vHTS) has eclipsed the classical HTS on the primary stages of drug discovery

projects.[24] Indeed, vHTS is not limited to off-the-shelf compounds: all theoretically possible structures are screened. But an important challenge in vHTS is the availability of the hits from virtual screens. More than 10 years ago, we have introduced REAL database[25,26] (REAL – readily accessible) to answer this question. High synthetic feasibility of compounds in the database is achieved through the following criteria applied during the enumeration:

- only qualified reagents available in at least 10 g amount are included;
- only well-validated parallel chemistry protocols are utilized.

The REAL compounds are additionally filtered based on the physicochemical criteria (Lipinski[27] and Veber[28] rules) to represent the medicinal chemistry-relevant molecules.

We found that a substituted 1,2,4-triazole motif, including 3-amino-1,2,4- triazoles, is underrepresented in public and commercial domains: a search by substructure revealed 172,714 and 400,567 matches in the public[29] and the commercial[30] databases, respectively (Figure 5). Our synthetic approach allows to significantly increase the current offer: application of the REAL criteria afforded 5,070,919 (REAL triazoles) substituted 3-amino-1,2,4-triazoles.

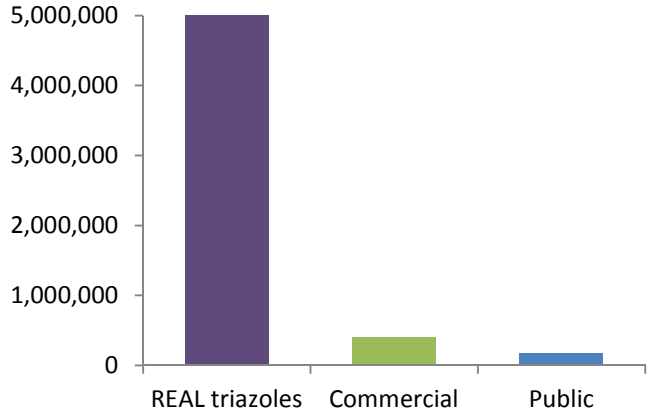


Figure 5. Substituted 1,2,4-triazoles in commercial, public, and REAL databases.

The REAL triazoles comprise mostly lead-like molecules (4,484,635 compounds, 88%) with no toxic motifs, 99% compounds passed PAINS[31], NIH[32] and ZINC[33] filters (Figure S1 in SI).

On the scaffold level, the REAL triazoles comprise 42,027 Bemis-Murcko frameworks most of which have more than one representative molecule (only 17% singletons) that is much higher than those in the public and the commercial databases (Figure S2 in SI). This feature makes REAL triazoles a tool for follow up libraries and lead optimization projects.

Conclusions. Herein, we report a convenient synthetic approach affording a library of molecules containing a potentially bioactive 1,2,4-aminotriazole structural motif cost- and time-efficiently. The proposed synthetic route leads to the target molecules with high overall yields and minimal purification efforts, compliant with the current requirements of combinatorial chemistry. The one-pot protocol is straightforward and includes the use of only commercially available chemicals. The modularity of this method enables the generation of triazole derivatives with a desired set of physicochemical properties and substitution scaffolds. The method distinguishes itself from the existing protocols since it excludes the formation of volatile and toxic chemicals, making it appropriate for the parallel synthesis setting. The REAL triazoles enumerated based on our approach significantly expand the current availability offer.

Experimental procedures.

General protocol of 1,2,4-aminotriazole synthesis. Compounds **1** (1.5 mmol) and **2** (1 mmol) were mixed in a sealable vial containing 0.7 mL of acetonitrile. After sealing, the vial was heated to 75°C for 2 h. The reaction mixture was evaporated under high vacuum, and compound **4** (1

mmol) was added to the remaining material. After sealing, the mixture was heated to 100°C for 16 h yielding **5** of sufficient for the next step purity. The mixture containing product **5** was cooled to an ambient temperature, followed by the addition of 2 mmol of sultone **6**. The content of the vial was sealed again and equilibrated at 100°C for 16 h. Upon cooling, a portion of NEt_3 (3 mmol) was added to the reaction mixture. The sealed vial was heated to 100°C for 30 min. Finally, compound **9** (1 mmol) was added to the pre-cooled mixture, and the reaction yielding crude **10** was completed upon heating the system to 100°C for 16 h. The obtained reaction mixture was evaporated and consecutively dissolved in 3 mL of chloroform. The organic layer was washed with water (2x4 mL). The remaining organic phase was evaporated and subjected to the HPLC purification on a C_{18}-column using methanol-water mixture as an eluent. The purification step yielded **10** with a purity at least 95%.

ASSOCIATED CONTENT

Supporting Information. Supporting information contains data on the abundance of 3,4,5-trisubstituted triazoles in different databases, a list of synthesized molecules with corresponding NMR (^{1}H and ^{13}C) and LC-MS information.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. [&] These authors (A.V.B., O.S., A.V.Z.) contributed equally.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Macarron, R.; Banks, M. N.; Bojanic, D.; Burns, D. J.; Cirovic, D. A.; Garyantes, T.; Green, D. V. S.; Hertzberg, R. P.; Janzen, W. P.; Paslay, J. W.; Impact of High-Throughput Screening in Biomedical Research. *Nat. Rev. Drug Discov.* **2011**, *10*, 188–195.

(2) Swinney, D. C.; Anthony, J. How Were New Medicines Discovered? *Nat. Rev. Drug Discov.* **2011**, *10* (7), 507–519.

(3) Hann, M. M.; Oprea, T. I. Pursuing the Leadlikeness Concept in Pharmaceutical Research. *Curr. Opin. Chem. Biol.* **2004**, *8* (3), 255–263.

(4) Lipinski, C. A. Lead- and Drug-like Compounds: The Rule-of-Five Revolution. *Drug Discov. Today Technol.* **2004**, *1* (4), 337–341.

(5) Zhou, C.-H.; Wang, Y. Recent Researches in Triazole Compounds as Medicinal Drugs. *Curr. Med. Chem.* **2012**, *19*, 239–280.

(6) Küçükgüzel, G.; Çikla-Süzgün, P. Recent Advances Bioactive 1,2,4-Triazole-3-Thiones. *Eur. J. Med. Chem.* **2015**, *97* (1), 830–870.

(7) Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Csöregh, I.; Hesselink, W.; Hacksell, U. Synthesis of 1,2,4-Oxadiazole-, 1,3,4-Oxadiazole-, and 1,2,4-Triazole-Derived Dipeptidomimetics. *J. Org. Chem.* **1995**, *60* (10), 3112–3120.

(8) Demange, L.; Boeglin, D.; Moulin, A.; Mousseaux, D.; Ryan, J.; Bergé, G.; Gagne, D.; Heitz, A.; Perrissoud, D.; Locatelli, V.; et al. Synthesis and Pharmacological in Vitro and in Vivo Evaluations of Novel Triazole Derivatives as Ligands of the Ghrelin Receptor. 1. *J. Med. Chem.* **2007**, *50* (8), 1939–1957.

(9) Bayrak, H.; Demirbas, A.; Demirbas, N.; Karaoglu, S. A. Synthesis of Some New 1,2,4-Triazoles Starting from Isonicotinic Acid Hydrazide and Evaluation of Their Antimicrobial Activities. *Eur. J. Med. Chem.* **2009**, *44* (11), 4362–4366.

(10) Maddila, S.; Pagadala, R.; Jonnalagadda, S. B. 1 , 2 , 4-Triazoles : A Review of Synthetic Approaches and the Biological Activity. *Lett. Org. Chem.* **2013**, *10*, 693–714.

(11) Holm, S. C.; Straub, B. F. Synthesis of N-Substituted 1,2,4-Triazoles. a Review. *Org. Prep. Proced. Int.* **2011**, *43* (4), 319–347.

(12) Sathish Kumar, S.; Kavitha, H. P. Synthesis and Biological Applications of Triazole Derivatives – A Review. *Mini. Rev. Org. Chem.* **2013**, *10*, 40–65.

(13) Cao, X.; Wang, W.; Wang, S.; Bao, L. Asymmetric Synthesis of Novel Triazole Derivatives and Their in Vitro Antiviral Activity and Mechanism of Action. *Eur. J. Med. Chem.* **2017**, *139*, 718–725.

(14) Meng, J.; Kung, P. P. Rapid, Microwave-Assisted Synthesis of N1-Substituted 3-Amino-

1,2,4-Triazoles. *Tetrahedron Lett.* **2009**, *50* (15), 1667–1670.

(15) Guin, S.; Rout, S. K.; Khatun, N.; Ghosh, T.; Patel, B. K. Tandem Synthesis of [1,2,4]-Triazoles Mediated by Iodine - A Regioselective Approach. *Tetrahedron* **2012**, *68* (25), 5066–5074.

(16) Shen, J.; Zhang, H. Synthesis of 1-Substituted 3-Amino-1H-1,2,4-Triazoles from Ethyl N-(5-Phenyl-1,2,4-Oxadiazol-3-Yl)formimidate. *Tetrahedron* **2015**, *71* (36), 6164–6169.

(17) Makara, G. M.; Ma, Y.; Margarida, L. Solid-Phase Synthesis of 3-Alkylamino-1,2,4-Triazoles. *Org. Lett.* **2002**, *4* (10), 1751–1754.

(18) Boeglin, D.; Cantel, S.; Heitz, A.; Martinez, J.; Fehrentz, J. A. Solution and Solid-Supported Synthesis of 3,4,5-Trisubstituted 1,2,4-Triazole-Based Peptidomimetics. *Org. Lett.* **2003**, *5* (23), 4465–4468.

(19) Samanta, S. K.; Yli-Kauhaluoma, J. Polymer-Supported 1,3-Oxazolium-5-Olates: Synthesis of 1,2,4-Triazoles. *J. Comb. Chem.* **2005**, *7* (1), 142–146.

(20) Noël, R.; Song, X.; Jiang, R.; Chalmers, M. J.; Griffin, P. R.; Kamenecka, T. M. Efficient Methodology for the Synthesis of 3-Amino-1,2,4-Triazoles. *J. Org. Chem.* **2009**, *74* (19), 7595–7597.

(21) Gilligan, W. H. Synthesis of 2-Fluoro- and 2-Nitro-Substituted Thionocarbonates. *J. Chem. Eng. Data* **1983**, *28* (1), 131–132.

(22) Bogolubsky, A. V.; Moroz, Y. S.; Mykhailiuk, P. K.; Granat, D. S.; Pipko, S. E.; Konovets, A. I.; Doroschuk, R.; Tolmachev, A. Bis(2,2,2-Trifluoroethyl) Carbonate as a

Condensing Agent in One-Pot Parallel Synthesis of Unsymmetrical Aliphatic Ureas. *ACS Comb. Sci.* **2014**, *16* (6), 303–308.

(23) Bogolubsky, A. V.; Moroz, Y. S.; Mykhailiuk, P. K.; Pipko, S. E.; Zhemera, A. V.; Konovets, A. I.; Stepaniuk, O. O.; Myronchuk, I. S.; Dmytriv, Y. V.; Doroschuk, R. A.; et al. 2,2,2-Trifluoroethyl Chlorooxoacetate-Universal Reagent for One-Pot Parallel Synthesis of N1-Aryl-N2-Alkyl-Substituted Oxamides. *ACS Comb. Sci.* **2015**, *17* (10), 615–622.

(24) Irwin, J. J.; Shoichet, B. K. Docking Screens for Novel Ligands Conferring New Biology. *J. Med. Chem.* **2016**, *59* (9), 4103–4120.

(25) Shivanyuk, A. N.; Ryabukhin, S. V.; Bogolyubsky, A. V.; Mykytenko, D. M.; Chupryna, A. A.; Heilman, W.; Kostyuk, A. N.; Tolmachev, A. Enamine Real Database: Making Chemical Diversity Real. *Chim. Oggi* **2007**, *25* (6), 58–59.

(26) Tolmachev, A.; Bogolubsky, A. V.; Pipko, S. E.; Grishchenko, A. V.; Ushakov, D. V.; Zhemera, A. V.; Viniychuk, O. O.; Konovets, A. I.; Zaporozhets, O. A.; Mykhailiuk, P. K.; et al. Expanding Synthesizable Space of Disubstituted 1,2,4-Oxadiazoles. *ACS Comb. Sci.* **2016**, *18* (10), 616–624.

(27) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Adv. Drug Deliv. Rev.* **1997**, *23* (1–3), 3–25.

(28) Veber, D. F.; Johnson, S. R.; Cheng, H. Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med.*

Chem. **2002**, *45* (12), 2615–2623.

(29) PubChem.

(30) Chemspace.

(31) Baell, J. B.; Holloway, G. A. New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays. *J. Med. Chem.* **2010**, *53* (7), 2719–2740.

(32) Doveston, R. G.; Tosatti, P.; Dow, M.; Foley, D. J.; Li, H. Y.; Campbell, A. J.; House, D.; Churcher, I.; Marsden, S. P.; Nelson, A. A Unified Lead-Oriented Synthesis of over Fifty Molecular Scaffolds. *Org. Biomol. Chem.* **2015**, *13* (3), 859–865.

(33) ZINC filters.

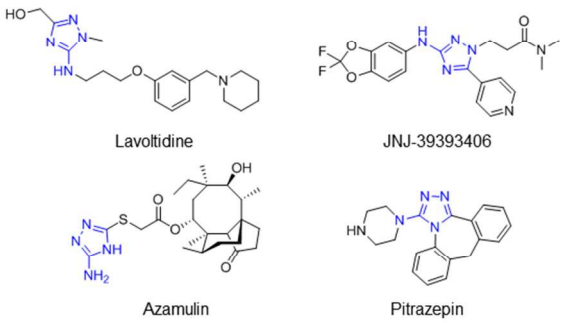


Figure 1

254x190mm (96 x 96 DPI)

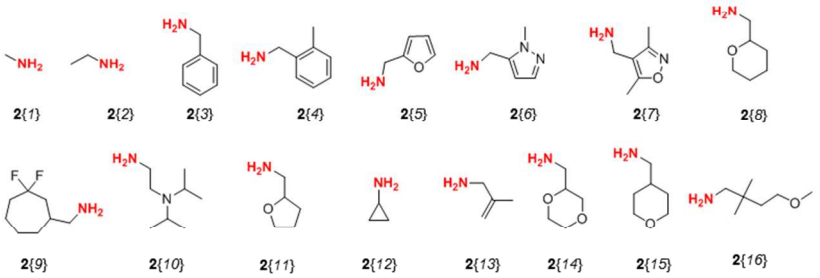


Figure 2

254x190mm (96 x 96 DPI)

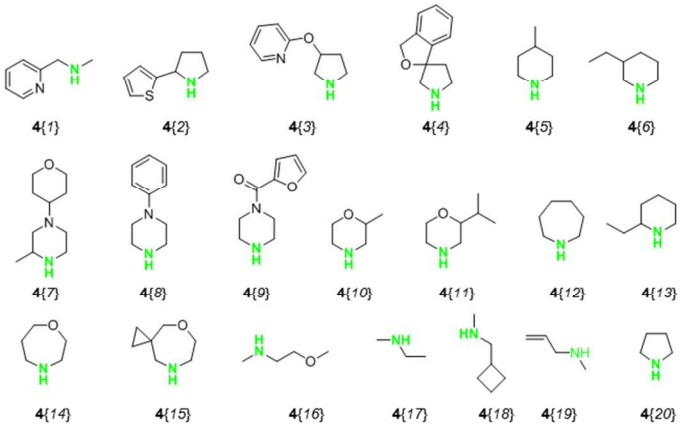


Figure 3

254x190mm (96 x 96 DPI)

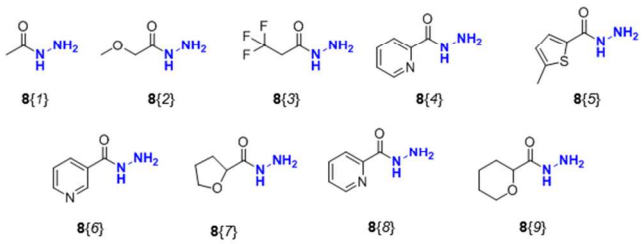


Figure 4

254x190mm (96 x 96 DPI)

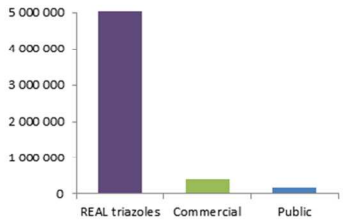
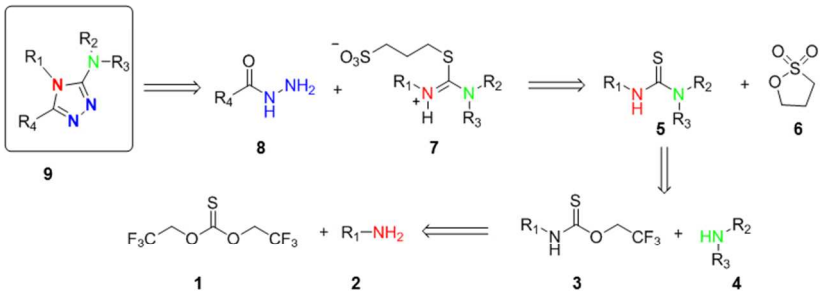


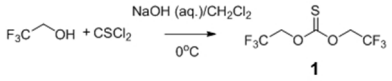
Figure 5

254x190mm (96 x 96 DPI)



Scheme 1

254x190mm (96 x 96 DPI)



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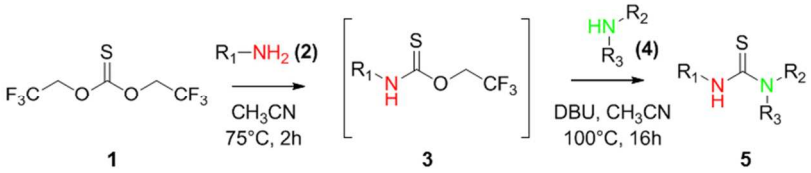
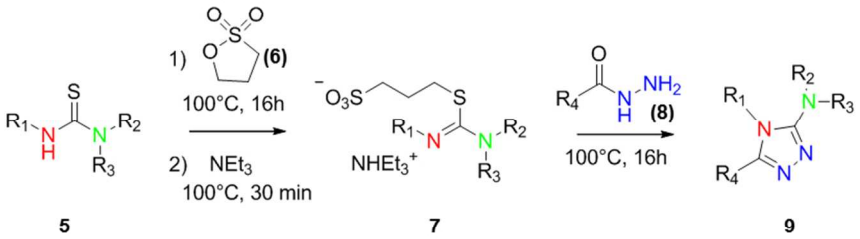
Scheme 2

254x190mm (96 x 96 DPI)



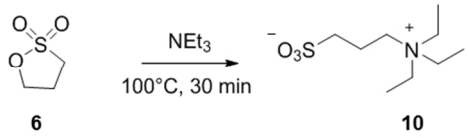
Scheme 3

254x190mm (96 x 96 DPI)



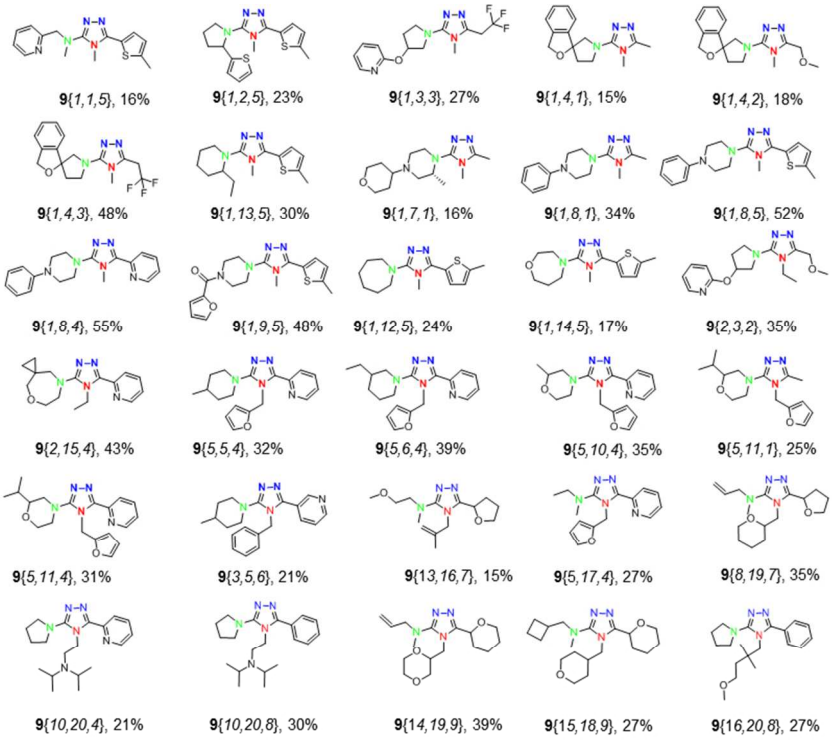
Scheme 4

254x190mm (96 x 96 DPI)

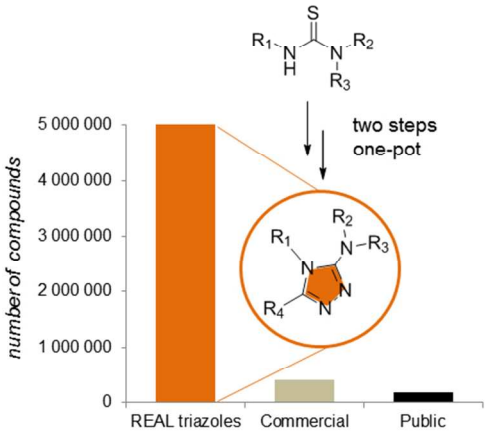


Scheme 5

254x190mm (96 x 96 DPI)



254x190mm (96 x 96 DPI)



TOC

254x190mm (96 x 96 DPI)