Journal of Organic and Pharmaceutical Chemistry

Advanced Research

OPEN ACCESS
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UDC 615: 54.057:547.833:577.113

O. V. Oksiuta[1,2], A. E. Pashenko[1,3,4], R. V. Smalii[3], D. M. Volochnyuk[1,3,4], S. V. Ryabukhin[1,3,4]

[1] Institute of Organic Chemistry of the National Academy of Sciences of Ukraine, 5 Academician Kukhar str., 02660 Kyiv, Ukraine
[2] Chemspace Ltd., 85 Winston Churchill str., 02094 Kyiv, Ukraine
[3] Enamine Ltd., 78 Winston Churchill str., 02094 Kyiv, Ukraine
[4] Taras Shevchenko National University of Kyiv, 60 Volodymyrska str., 01033 Kyiv, Ukraine

Heterocyclization *vs* Coupling Reactions: A DNA-Encoded Libraries Case

Abstract

Aim. DNA-encoded libraries technologies (DELT) are gradually becoming an important part of standard drug discovery toolbox. DELT is looking to find its place between classic low-molecular-weight drug candidates on the one hand, and high-molecular-weight antibodies and peptides on the other hand. On its natural path to overcoming the "childhood diseases" typical for every novel technology, DELT has reached a point where the chemical diversity of DNA-encoded libraries (DELs) becomes an important factor to look out for. In this paper, we aim to take a closer look at the chemical diversity of DELs in their present state and find the ways to improve it.

Results and discussion. We have identified the DEL-viable building blocks from the Enamine Ltd. stock collection, as well as from Chemspace Ltd. virtual collection, using the SMARTS set, which takes into account all the necessary structural restrictions. Using modern cheminformatics tools, such as Synt-On, we have analyzed the scaffold diversity of both stock and virtual core bi- and tri-functional building blocks (BBs) suitable for DNA-tolerant reactions. The identification of scaffolds from the most recently published on-DNA heterocyclization reactions and analysis of their inclusion into the existing BBs space have shown that novel DNA-tolerant heterocyclizations are extremely useful for expanding chemical diversity in DEL technologies.

Conclusions. The analysis performed allowed us to recognize which functional groups should be prioritized as the most impactful when the new BBs are designed. It is also made clear that the development of new DNA-tolerant reactions, including heterocyclizations, have a significant potential to further expand DEL molecular diversity.

Keywords: DNA-encoded libraries technology; orthogonal functional groups; coupling reactions; polyfunctional building blocks; heterocyclizations; chemoinformatics; scaffold diversity

О. В. Оксюта[1,2], А. Є. Пащенко[1,3,4], Р. В. Смалій[3], Д. М. Волочнюк[1,3,4], С. В. Рябухін[1,3,4]

[1] Інститут органічної хімії Національної академії наук України, вул. Академіка Кухаря, 5, м. Київ, 02660, Україна
[2] ТОВ «Кемспейс», вул. Вінстона Черчилля, 85, м. Київ, 02094, Україна
[3] НВП «Єнамін», вул. Вінстона Черчилля, 78, м. Київ, 02094, Україна
[4] Київський національний університет імені Тараса Шевченка, вул. Володимирська, 60, м. Київ, 01033, Україна

Гетероциклізація або реакції каплінгу: випадок ДНК-кодованих бібліотек

Анотація

Мета. Технології ДНК-кодованих бібліотек (DELT) поступово стають важливою частиною стандартного набору інструментів для пошуку нових лікарських субстанцій. Наразі DELT прагне знайти своє місце у просторі між класичними низькомолекулярними кандидатами у ліки з одного боку та високомолекулярними антитілами й пептидами з іншого. На своєму шляху до подолання «дитячих хвороб», характерних для кожної нової технології, DELT досягли того моменту, коли хімічна різноманітність ДНК-кодованих бібліотек (DEL) стає важливим фактором, на який варто звернути увагу. У цій статті ми прагнемо ближче розглянути хімічне різноманіття ДНК-кодованих бібліотек у їхньому поточному стані та знайти можливості для його покращення.

Результати та їх обговорення. Ми визначили DEL-життєздатні будівельні блоки з наявної колекції Enamine Ltd., а також із віртуальної колекції Chemspace Ltd., використовуючи набір SMARTS, який враховує всі необхідні структурні обмеження.

За допомогою таких сучасних інструментів хемоінформатики, як Synt-On, ми проаналізували різноманітність каркасів як уже синтезованих, так і віртуальних бі- та трифункціональних білдинг-блоків (BB), придатних для реакцій, у яких ДНК залишається інтактною. Ідентифікація молекулярних скафолдів, використовуваних у нещодавно опублікованих «on-DNA» реакціях гетероциклізації, та аналіз їх внесення до простору BB, який існує, засвідчили, що нові толерантні до ДНК гетероциклізації є надзвичайно корисними для розширення хімічної різноманітності в технологіях DEL.
Висновки. Виконаний аналіз дозволив нам визначити, яким функціональним групам варто віддати пріоритет як найбільш впливовим у процесі дизайну нових BB. Також стало зрозуміло, що розвиток нових толерантних до ДНК реакцій, зокрема й гетероциклізації, має значний потенціал для подальшого розширення молекулярного різноманіття DEL.
***Ключові слова*:** технологія ДНК-кодованих бібліотек; ортогональні функціональні групи; реакції каплінгу; поліфункціональні білдинг-блоки; гетероциклізації; хемоінформатика; разноманітність молекулярних каркасів

Citation: Oksiuta, O. V.; Pashenko, A. E.; Smalii, R. V.; Volochnyuk, D. M.; Ryabukhin, S. V. Heterocyclization *vs* Coupling Reactions: A DNA-Encoded Libraries Case. *Journal of Organic and Pharmaceutical Chemistry* **2023**, *21* (1), 3–19.
https://doi.org/10.24959/ophcj.23.275133
Supporting information: The links to source databases: Enamine Ltd. DEL-viable stock bi- and tri-functional core building blocks (freely available at https://cloud.chem-space.com/s/zk7QraSYsrcn7c4); ChemSpace tangible virtual DEL-viable bi- and tri-functional core building blocks (freely available at https://cloud.chem-space.com/s/ePmFyzNYj6bQbci). The set of SMARTS used for separating the abovementioned sub-sets is available free of charge at https://cloud.chem-space.com/s/3DbC7KZeKGK4ZaW.
Received: *14 January 2023*; **Revised:** *23 February 2023*; **Accepted:** *5 March 2023*

Funding: The authors received no specific funding for this work.
Conflict of interests: The authors have no conflict of interests to declare.

■ Introduction

DNA-Encoded Libraries Technology (DELT) was first proposed as an idea by *Brenner* and *Lerner* back in 1992 [1]. Since then it has become an actively developing tool for Drug Discovery, which allows to generate the multi-billion screening molecules collection in a single vial [2] and identify the hit molecules by decoding their unique DNA tags. The synthesis of DNA-encoded chemical libraries (DECLs) [3] is based on the split-and-pool strategy [4, 5], which is a common combinatorial chemistry approach topped with DNA fragments as chipping tags. The most general sequence for a DNA-encoded library synthesis is schematically presented in Figure 1. Building-blocks and the corresponding DNA tags are repeatedly connected to DNA primers from the opposing end (Figure 1).

The most common approach to screening the DNA-encoded libraries [6, 7] demands placing the protein target of interest (POI) on the solid support bed and exposing it to the action of the set of DNA-tagged molecules from the library (Figure 2). The binders remain connected to the protein, and the non-binding molecules are washed away (Figure 2). Then the binders (potential hits) are eluted, their chemical structures are disclosed using PCR sequencing of the coding DNA-tags, and the data obtained is analyzed. At the current stage of the DELT development, it is gradually beginning to expand into more complex biological assays, for instance cell-based assays [8–11], which is a positive sign indicating the flexibility and translation potential of DELT-based platforms.

It is notable that the size of libraries created using the DEL technology nowadays exceeds the size of the conventional high-throughput screening (HTS) combinatorial libraries by several orders of magnitude. The HTS libraries almost never exceed one million individual compounds, while 3- and 4-cycle DNA-encoded libraries with the input size of 1000 molecules on each cycle generate a billion and a trillion molecules, respectively.

The typical sequence for the four-cycle assemblies is given in Figure 3. It is worth mentioning that there are also several approaches to DNA-tagging, likewise double-strand [4, 12] and single-strand [13] technologies. However, this technical aspect is non-important for the current discussion. Although traditionally viewed as the major advantage, the gigantic size of the DELs also introduces several risks and drawbacks. First of all, chemical diversity of such libraries relies heavily on the pool of reactions available for the DNA-friendly environment [7, 14], as well as on the sufficient number of suitable and available bi- and tri-functional core building blocks (BBs) with orthogonal functional groups (FGs), and diverse monofunctional molecules (capping agents) [15–19]. Another important factor influencing the success of DEL-derived screening campaigns is the development of the readout methods [4, 20, 21] and statistical analysis of the hits [21–23].

ISSN 2308-8303 (Print) / 2518-1548 (Online)

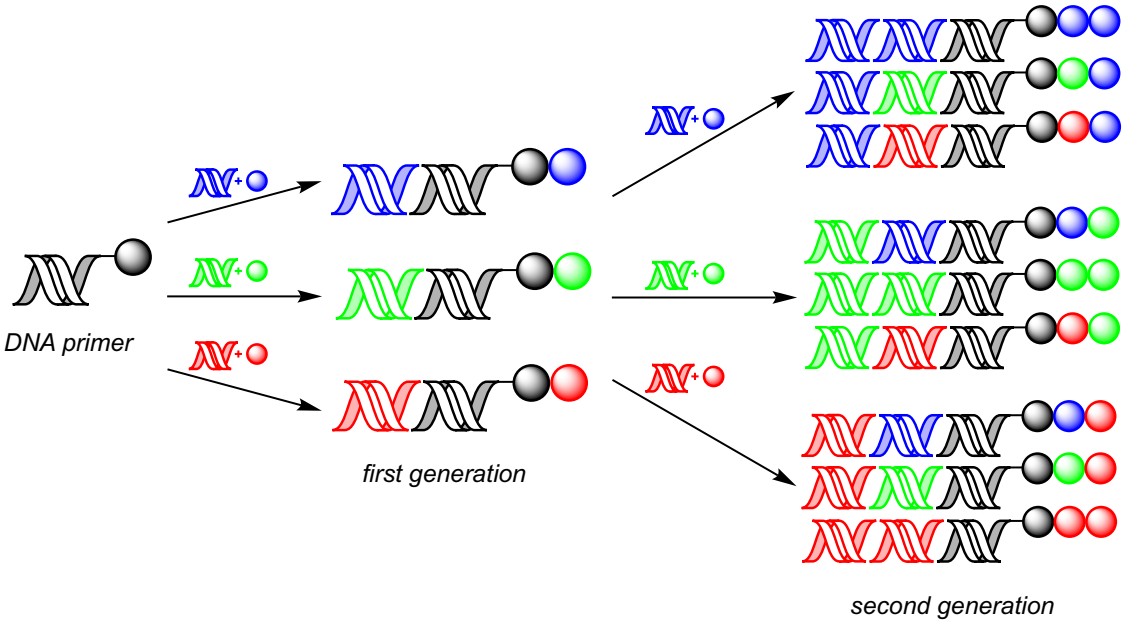


Figure 1. Schematic representation of the split-and-pool process for the DNA-encoded library synthesis

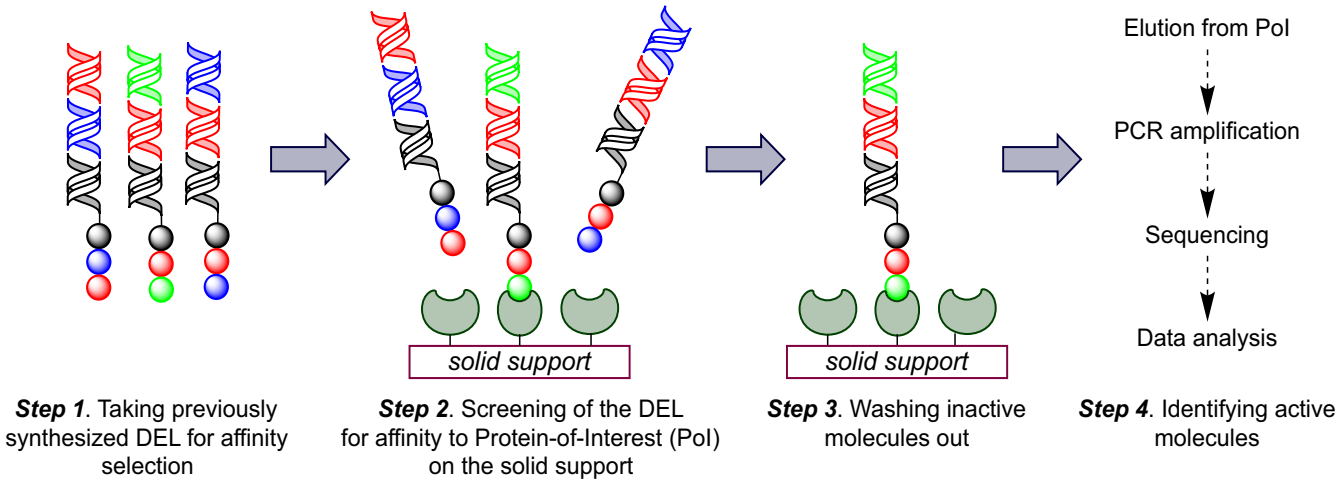


Figure 2. Workflow for identifying an active molecule from DEL

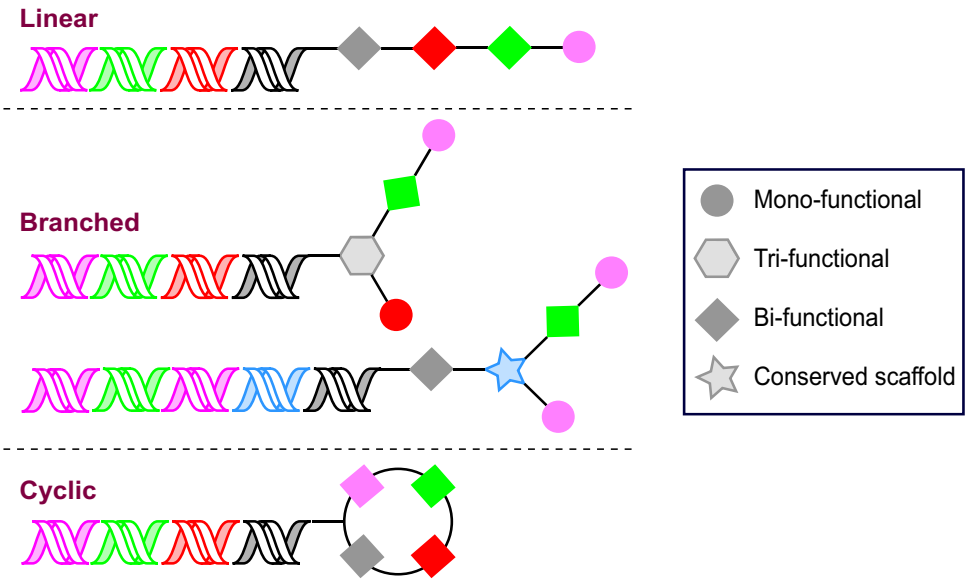


Figure 3. Typical DEL sequence for a 4-step cycle with examples of mono-, bi-, tri-functional BBs

As it is mentioned above, the main limitation for DELT is the demand to use only such chemical transformations, which leave DNA fragments intact. At the early stages of development, DELT was used as a platform for amide couplings only [24]; however, the overall advances in organic synthesis techniques enabled the application of a broad spectrum of chemical transformations in DNA-tolerant conditions, including classical C-C and C-N cross-couplings [25], metathesis [26, 27], click reactions [17, 28–33], photoredox reactions [34], and many others. Now that the vast majority of common transformations used in the cross-couplings has been successfully translated into on-DNA chemistry, and DELT is approaching the moment when the search for new chemotypes again becomes a limiting factor. In this connection, the cheminformatic algorithms, such as eDESIGNER [35], which helps to design libraries accounting both diversity and reaction applicability factors, have been developed and reported recently. Eventually, in the "maturation" [36] process DELT replicates the evolutionary route of traditional HTS-derived combinatorial chemistry [37, 38] and is on a track from amide coupling to more complex cross-coupling reactions [39] and, finally, to the on-DNA heterocycles formation. One can find a comprehensive review on DNA-tolerant couplings described in multiple review articles [3, 14, 39, 40], however, the works focused on the on-DNA heterocycles formation started to show up in the periodical press on a regular basis only recently. In this paper, we aim to give an overview on the diversity of DELT-suitable BBs for "traditional" cross-coupling reactions based on the catalogue of stock molecules provided by Enamine Ltd., and virtual set provided by Chemspace Ltd., and evaluate the potential contribution of the chemotypes emerging from the most recent discoveries in the field of on-DNA heterocyclizations.

■ Results and discussion

For the decomposition of the pool of stock (Enamine) building blocks we used the SMARTS set (see the experimental part for details) specially designed to account orthogonality of FGs in the multifunctional compounds, the absence of undesired functions (alkylators, moisture-sensitive groups, etc.), and find compatible mono-functional molecules or "capping agents" [19]. We distributed the molecules obtained according to the combination of functional and protective groups. In case of stock polyfunctional cores, 11 classes of bi-functional and 8 classes of tri-functional molecules were identified. We decided not to include capping agents to our analysis. This is the most widespread group having a decent overlap with "traditional" monofunctional BBs commonly used for combinatorial chemistry, and it hardly contributes much to the chemical diversity, in contrast with rather scarce suitable multifunctional core molecules. In case of stock BBs (Enamine), 26816 bi- and 1438 tri-functional "core" compounds were obtained (Figures 4 and 5, respectively).

We performed the same type of extraction using SMARTS and further analysis in Chemspace (virtual) database. Additionally, the Synt-On software package was used for this analysis [41, 42]. Using Synt-On, 43 848 442 molecules in 33 sub-classes of, bi- and 3 119 488 molecules in 25 sub-classes of tri-functional BBs were identified. Low-reactive BBs and those with non-orthogonal functional groups were removed. The molecules obtained were combined into broader classes as we did previously for stock compounds. This approach allows to evaluate which FGs and, consequently, which reactions contribute the most to the DEL-derived chemical space. Despite the insignificant shuffle in the "lower bracket" of the histogram for bi-functional molecules (Figure 6), the proportion between the most widespread chemotypes in virtual space remains close to the stock case (Figure 4). However, in case of tri-functional cores, the fraction of acids, which fulfill the selection criteria on the virtual side (Figure 7), is significantly smaller than in the stock (Figure 5). In all the remaining classes, the general trend for virtual structures correlates with the stock. This observation led to the conclusion that despite many reactions were optimized for DNA-friendly conditions, the chemical diversity of DELs remains to the most part to be limited to either amide- or ArX-amine cross-couplings.

Introducing heterocycle formation reactions is a beneficial way to expand the chemical space of combinatorial chemistry-derived molecules, which have proven itself in the HTS development [43, 44]. It is also true that with the development of organic synthesis many heterocyclic cores became readily available as scaffolds for classical combinatorial chemistry, as well as DEL-chemistry. Considering the growing number of publications focused on the on-DNA cycle formation we assumed that DELT is about to cross the same frontier as traditional combinatorial

ISSN 2308-8303 (Print) / 2518-1548 (Online)

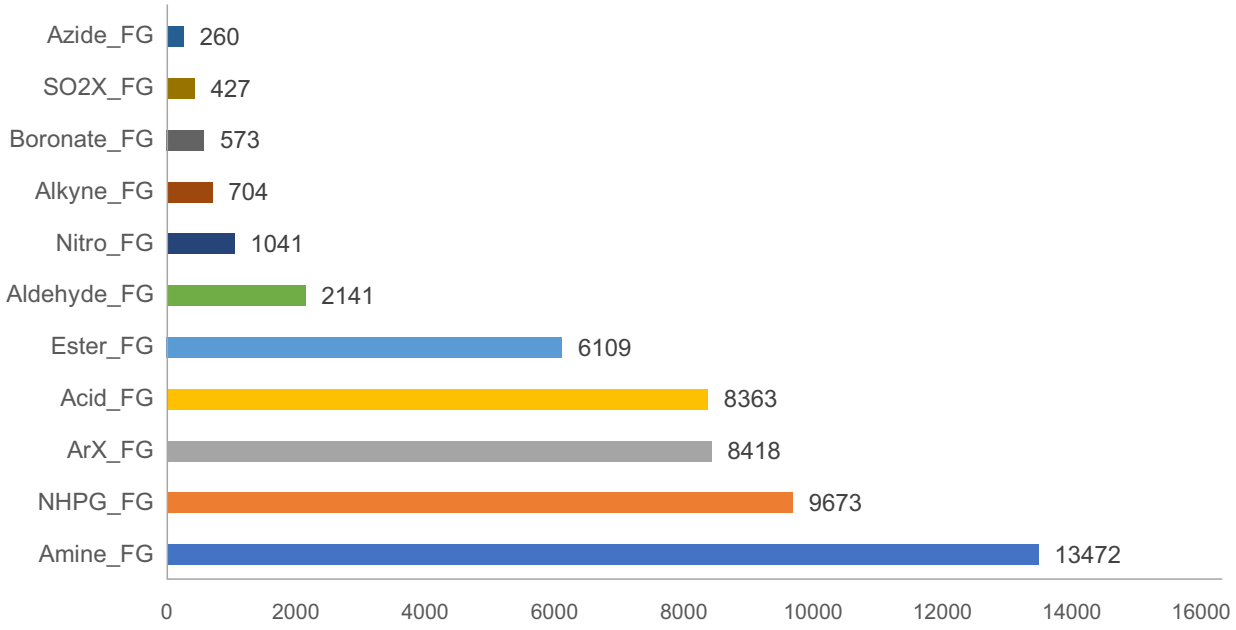


Figure 4. Enamine stock bifunctional DEL-viable BBs, 26816 molecules in 11 classes

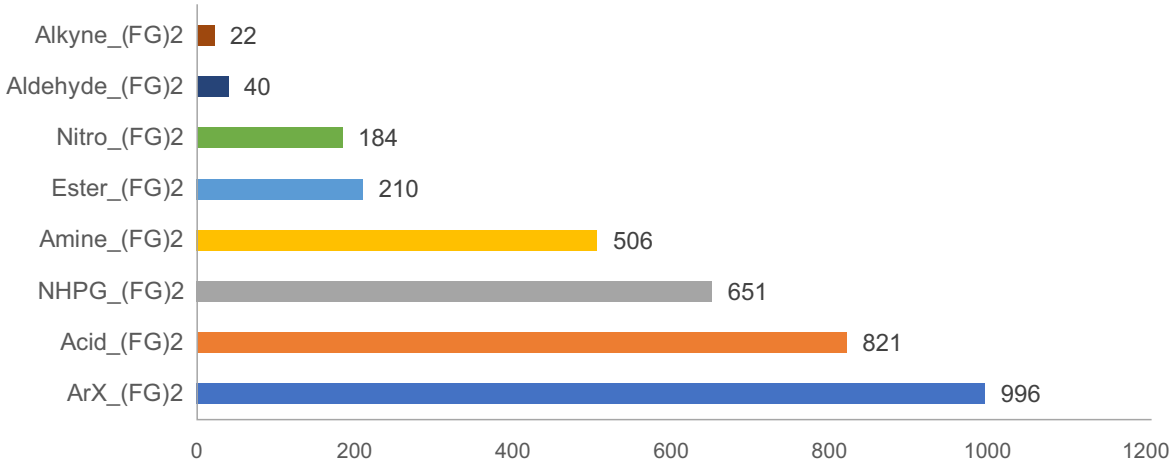


Figure 5. Enamine stock trifunctional DEL-viable BBs, 1438 molecules in 8 classes

chemistry did at the time when heterocyclizations became noticeable part of the combinatorial reaction toolkit. In order to have a closer look at this tendency, we studied the literature sources over the period from 2016 to 2020. We observed the growing number of such publications over time: a single one in 2015, and 14 in 2020. We also identified 26 distinct types of the on-DNA heterocycle formation reactions. They are summarized in Table 1.

With this in mind, we wanted to study in more detail if scaffolds from on-DNA heterocyclizations occur as scaffolds in cross-coupling based DEL builds. In other words, we wanted to look at the population of heterocyclization-derived scaffolds in the bi- and tri-functional core BBs subsets, and evaluate the potential contribution of heterocyclizations to the DELT-relevant chemical space diversity. We used Synt-On to identify scaffolds in both stock and virtual bi- and trifunctional BBs sets, as well as in heterocyclization reactions products in Table 1. The latter provided 30 separate heterocyclic scaffolds. The scaffold-inclusion analysis for the scaffolds from Table 1 relative to bifunctional cores subclasses (Table 2) and trifunctional core subclasses (Table 3) was performed. The structure of Tables 2 and 3 is as follows: entry (subclass) number in the first column; subclass abbreviation and an overall number of compounds in the subclass; "scaffolds in ref" shows how many times scaffolds from Table 1 are included "as is" or as substructures to the BBs subclass scaffolds; in the "molecules in ref" the number of molecules with "sub-class" scaffolds, which contain the exact structure of scaffolds from the heterocyclic set,

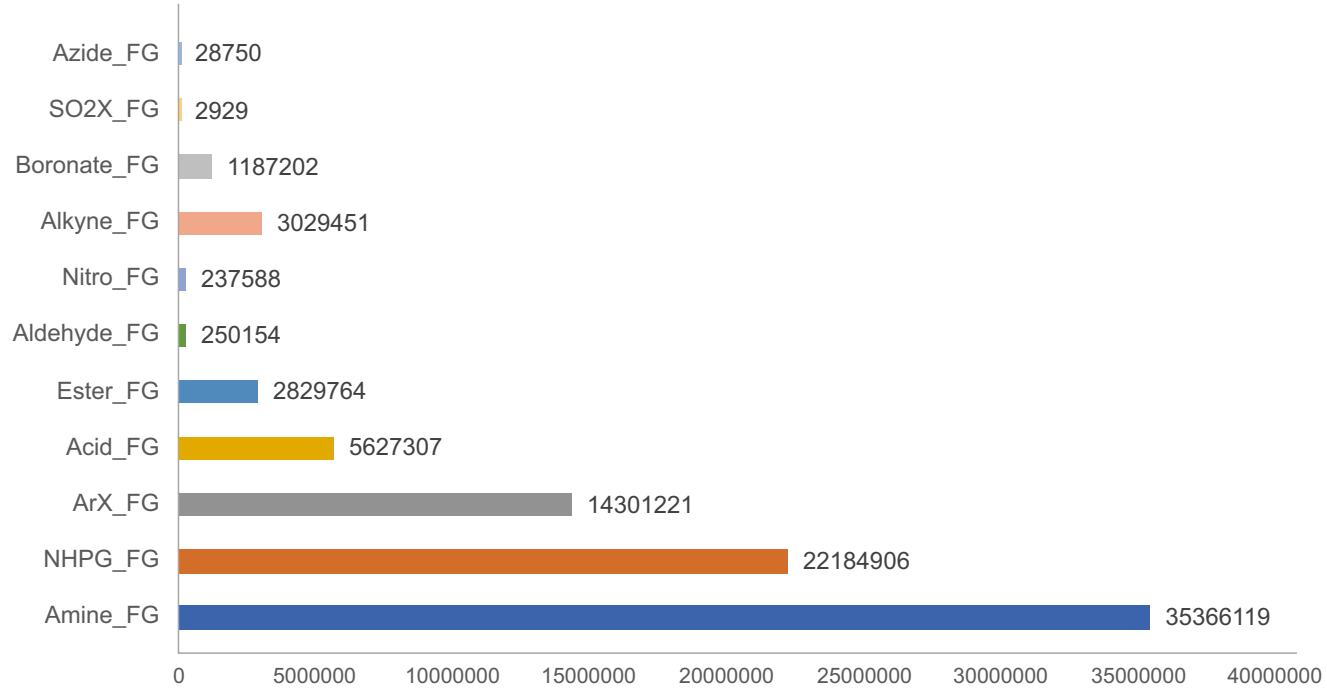


Figure 6. Chemspace "tangible" virtual bifunctional DEL-viable BBs, 43 848 442 molecules in 11 classes

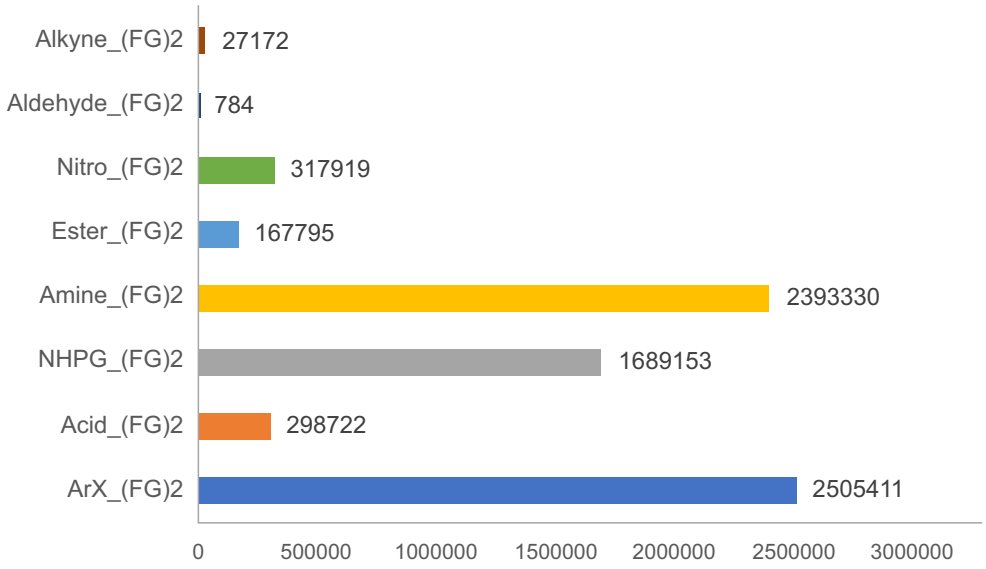


Figure 7. Chemspace "tangible" virtual trifunctional DEL-viable BBs, 3 119 488 molecules in 8 classes

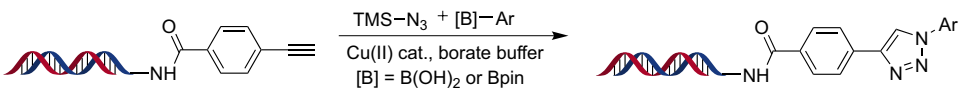
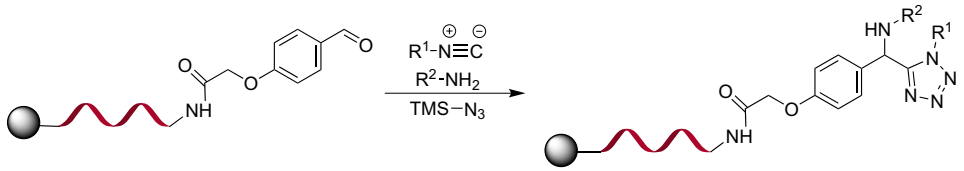
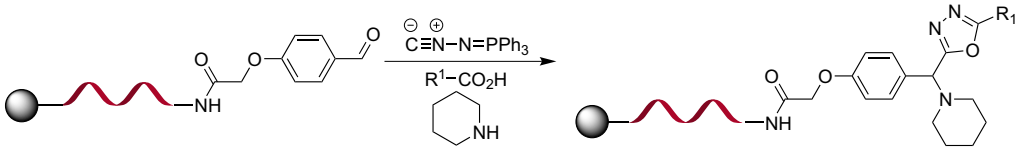
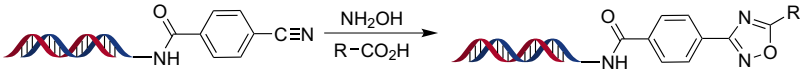
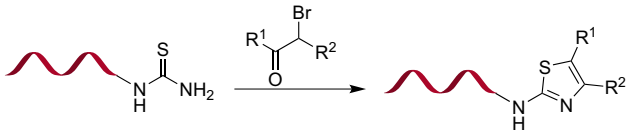
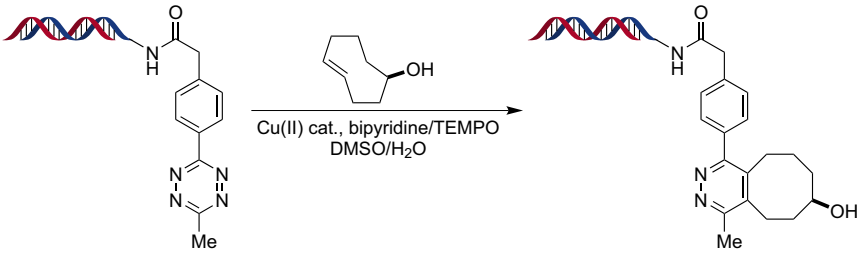
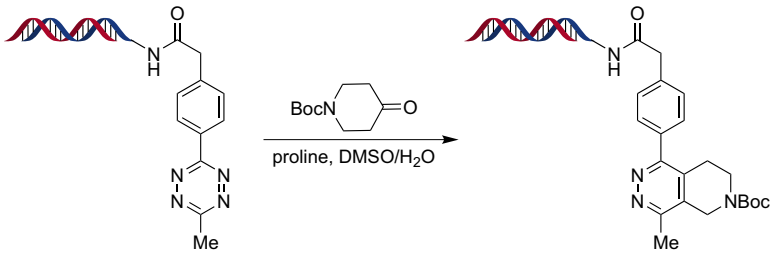
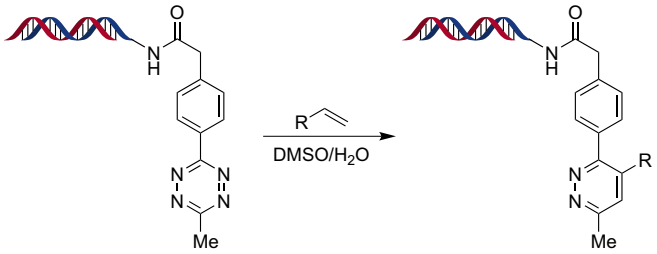
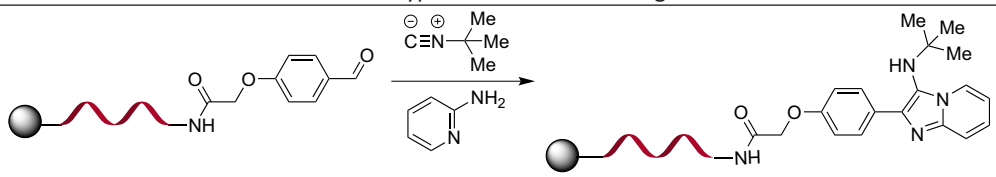
or contain those as substructures, is given; the "unique scaffolds" column contains data on how many scaffolds are represented in the subclass; the "unique molecules" shows exactly how many molecules contain "unique scaffolds".

To summarize the data obtained, we combined the results of our calculations into a single table (Table 4). The latter shows the inclusion of heterocyclization-derived scaffolds into the overall pool of bi- and tri-functional BBs, the stock (Enamine), as well as the virtual ones (Chemspace). The results of this analysis are not entirely expected: despite the fact that over the half of the core BBs chemotypes used in the heterocyclizations described in Table 1 remain in DEL-chemistry for a long time (functional aldehydes, amines, etc.), their use in the reaction types outside "traditional" cross-couplings immediately provide more than 30% of the scaffold diversity in the entire DELT chemical extraspace.

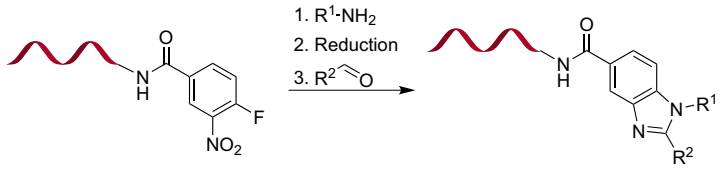
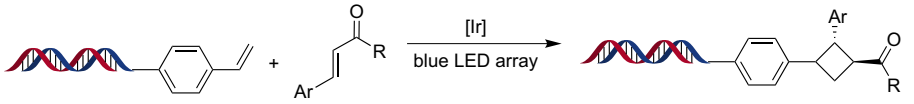
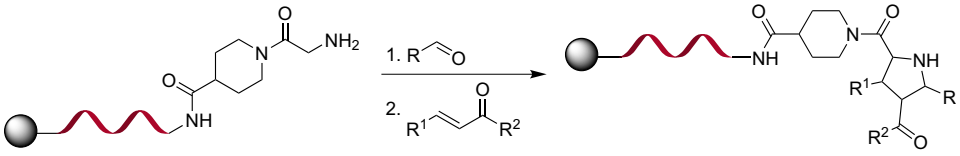
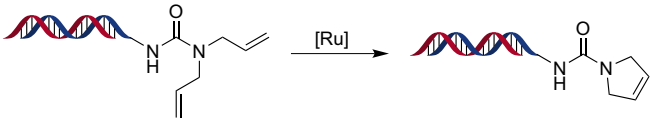
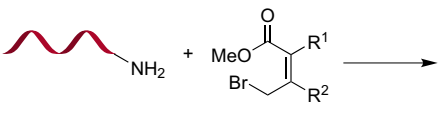
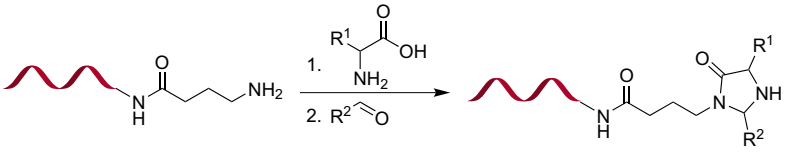
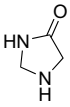
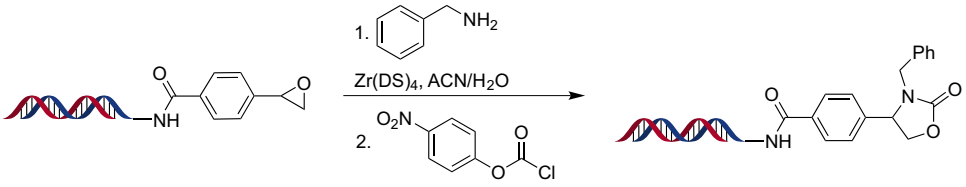
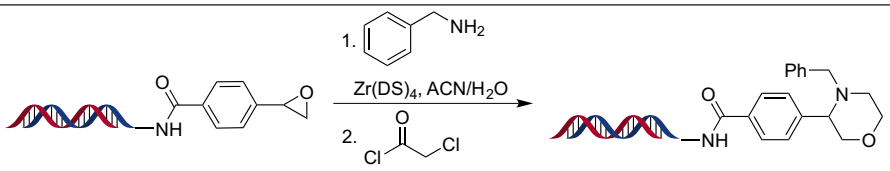
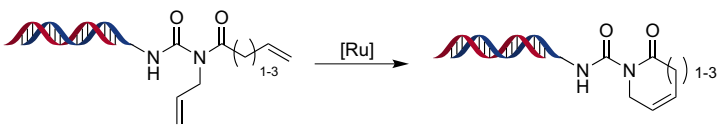
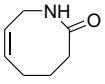
For better visualizing the outline from Table 4, we constructed diagrams showing the contribution of the heterocyclic scaffolds to bifunctional BBs space, both stock (Figure 8A) and virtual (Figure 8B). We did the same for stock and virtual trifunctional blocks (Figure 9A and 9B, respectively).

ISSN 2308-8303 (Print) / 2518-1548 (Online)

Table 1. Heterocyclization reactions on DNA from the first case study to 2020

#	Reaction	Scaffold/Code
1	2	3
Reaction type: 5-membered Aromatic Rings formation		
1. [31]		Scaf_01
2. [45]		Scaf_02
3. [45]		Scaf_03
4. [46]		Scaf_04
5. [47]		Scaf_05
Reaction type: 6-membered Aromatic Rings formation		
6. [32]		Scaf_06
7. [32]		Scaf_07
8. [32]		Scaf_08
Reaction type: Fused Aromatic Rings formation		
9. [48]		Scaf_09

Continuation of Table 1

1	2	3
10. [49]		 Scaf_10
Reaction type: Carbocyclic, 5 and 6-membered Non-Aromatic Rings formation		
11. [50]		 Scaf_11
12. [51]		 Scaf_12
13. [27]		 Scaf_13
14. [49]		 Scaf_14
15. [49]		 Scaf_15
16. [52]		 Scaf_16
17. [52]		 Scaf_17
18. [27]		 Scaf_18  Scaf_19  Scaf_20

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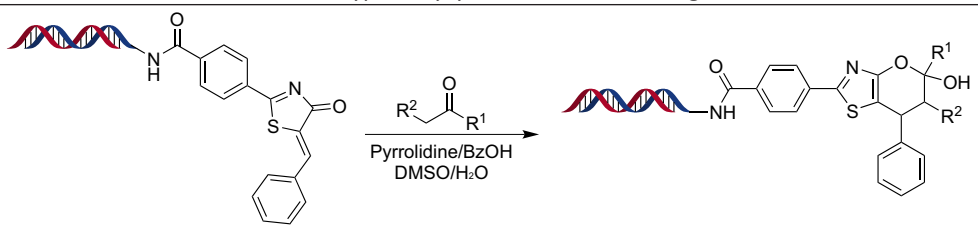
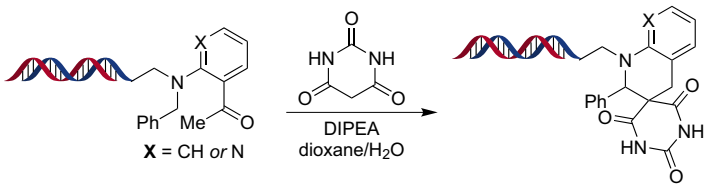
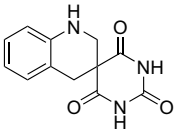
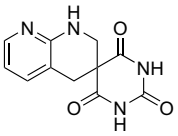
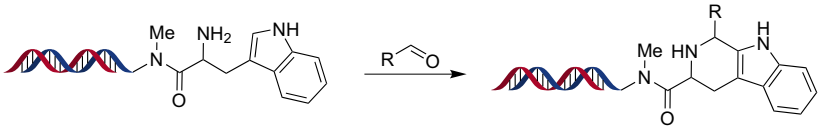
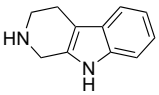
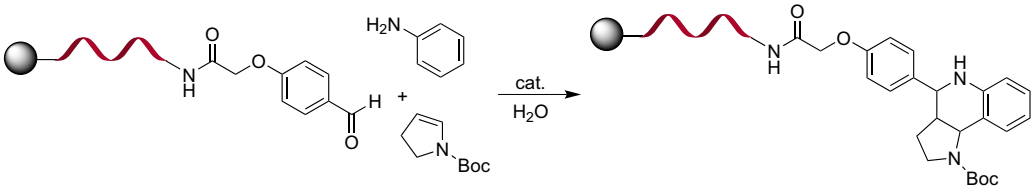
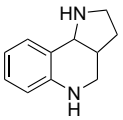
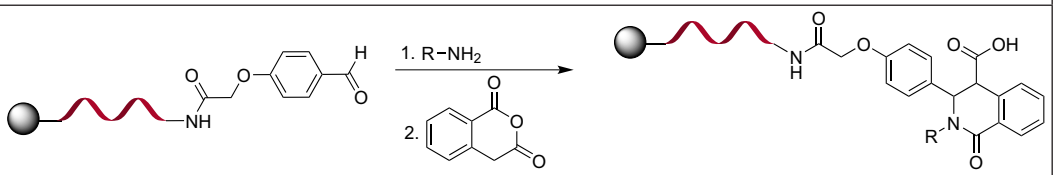
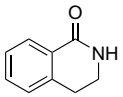
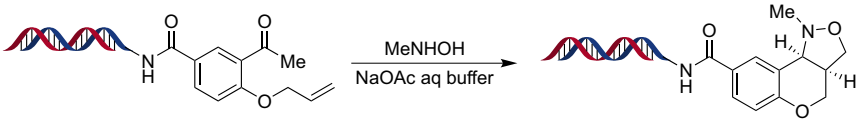
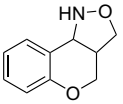
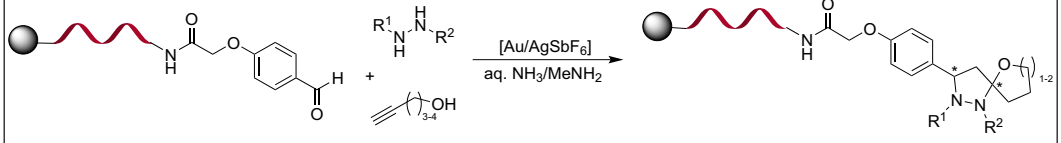
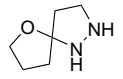
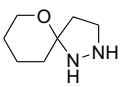
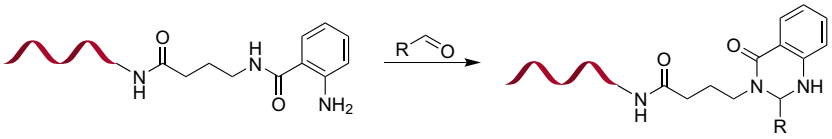
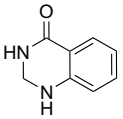
Continuation of Table 1

1	2	3
Reaction type: Polycyclic Non-Aromatic Rings formation		
19. [53]		 Scaf_21
20. [54]		 Scaf_22  Scaf_23
21. [55]		 Scaf_24
22. [56]		 Scaf_25
23. [51]		 Scaf_26
24. [57]		 Scaf_27
25. [58]		 Scaf_28  Scaf_29
26. [49]		 Scaf_30

Notes:

1. – DNA fragment (double-stranded), ds-DNA
2. – DNA fragment (single-stranded), ss-DNA
3. – ss-DNA fragment on a solid support

Table 2. The impact of heterocyclization-derived scaffolds to the bifunctional BBs chemical space

#	Sub-class	Scaffolds in ref	Molecules in ref	Unique scaffolds	Unique molecules
1	Acid_Aldehyde	6	12	55	331
2	Acid_Alkyne	6	10	25	141
3	Acid_ArX	79	234	311	2440
4	Acid_Azide	13	24	21	71
5	Acid_Ester	23	71	95	521
6	Acid_Nboc	257	806	349	1919
7	Acid_Ncbz	10	28	23	84
8	Acid_NCS	0	0	2	7
9	Acid_Nfmoc	179	437	247	1509
10	Acid_Nitro	29	46	119	781
11	Aldehyde_ArX	20	54	92	820
12	Aldehyde_Azide	0	0	6	8
13	Aldehyde_Ester	11	37	68	368
14	Aldehyde_Nboc	53	115	86	262
15	Aldehyde_Nitro	7	11	46	222
16	Aldehyde_SO2X	0	0	4	12
17	Amino_Alkyne	23	63	59	430
18	Amino_ArX	177	422	577	3352
19	Amino_Azide	7	16	21	54
20	Amino_Ester	267	878	523	4047
21	ArX_AlkyneCH	2	4	18	108
22	ArX_ArX	57	168	232	1227
23	Azide_ArX	4	8	11	80
24	Azide_SO2X	0	0	3	17
25	Diamines_Nbn	67	131	75	205
26	Diamines_Nboc	302	807	469	1761
27	Diamines_Ncbz	11	18	19	46
28	Diamines_Nfmoc	3	7	9	11
29	Ester_Isocyanates	1	2	6	31
30	Ester_SO2X	9	29	43	372
31	Functional tetrazine	0	0	2	8
32	Functional_Boronates	21	40	90	562
33	Functional_BF3K	8	12	18	51

Table 3. The impact of heterocyclization-derived scaffolds to the trifunctional BBs chemical space

#	Sub-class	Scaffolds in ref	Molecules in ref	Unique scaffolds	Unique molecules
1	2	3	4	5	6
1	1,3,5-Trisfunctionalised_benzenes	12	15	20	257
2	Acid_Aldehyde_AlkyneCH	0	0	1	1
3	Acid_Aldehyde_ArX	1	3	6	23
4	Acid_Aldehyde_Nitro	0	0	1	4
5	Acid_ArX_Ester	0	0	5	16
6	Acid_ArX_Nitro	0	0	9	71
7	Acid_Ester_Nitro	0	0	2	5
8	Amino_ArX_ArX	3	10	35	172
9	Amino_ArX_Nitro	0	0	13	102
10	ArX_ArX_ArX	3	4	27	93
11	ArX_ArX_Carboxy	9	27	27	201
12	Azide_ArX_Carboxy	0	0	0	0
13	NbocAA_AlkyneCH	1	2	4	16
14	NbocAA_ArX	4	6	18	69
15	NbocAA_Ester	4	10	4	30
16	NbocAA_Nitro	0	0	1	4

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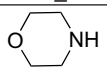
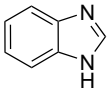
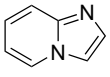
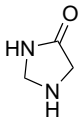
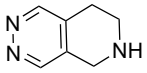
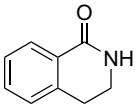
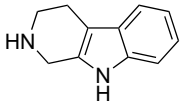
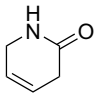
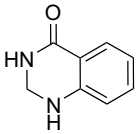
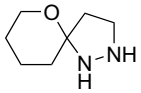
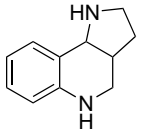
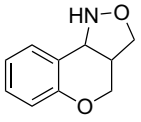
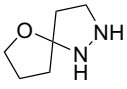
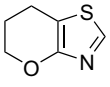
Continuation of Table 3

1	2	3	4	5	6
17	NbocArX_Amino	10	11	29	40
18	NbocEsterAA_Aldehyde	3	3	7	10
19	NbocEsterAA_Amino	23	41	24	57
20	NbocNCbzAA	2	2	4	8
21	NbocNfmocAA	21	34	23	75
22	NfmocAA_alkyneCH	1	1	3	7
23	NfmocAA_ArX	17	20	15	54
24	NfmocAA_Ester	1	4	5	27
25	NfmocAA_Nitro	0	0	1	3

Table 4. The overall quantity of bi- and tri-functional molecules containing the generated scaffolds (stock and virtual)

#	Scaffold (SMILES)	Scaffold Structure/Code	Bifunctional BBs		Trifunctional BBs	
			Stock	Virtual	Stock	Virtual
1	2	3	4	5	6	7
1	C1CCNC1	 Scaf_12	2078	7871461	109	485045
2	C1CCC1	 Scaf_11	1104	5941890	27	312303
3	S1C=CN=C1	 Scaf_05	648	1533087	15	75218
4	C1COCCN1	 Scaf_17	305	939622	3	51623
5	N1C=CN=N1	 Scaf_01	175	660222	2	53908
6	C1=CC=NN=C1	 Scaf_08	232	573015	33	52826
7	N1C=NC2=CC=CC=C12	 Scaf_10	69	175965	0	3524
8	O1C=NC=N1	 Scaf_04	39	156634	0	5888
9	N1C=NN=N1	 Scaf_02	29	103910	3	5056
10	C1NCC=C1	 Scaf_13	21	57571	0	4304
11	C1=CN2C=CC=CC2=N1	 Scaf_09	97	50346	5	1530

Continuation of Table 4

1	2	3	4	5	6	7
12	O=C1NCCO1	 Scaf_16	5	15795	0	756
13	O=C1CNCN1	 Scaf_15	5	4651	0	133
14	C1CC2=C(CN1)C=NN =C2	 Scaf_07	0	2694	0	16
15	O=C1NCCC2=CC=CC =C12	 Scaf_26	2	274	0	5
16	O=C1NCC=C1	 Scaf_14	2	253	0	11
17	C1CC2=C(CN1)NC1=C C=CC=C21	 Scaf_24	10	220	0	2
18	O=C1CC=CCN1	 Scaf_18	0	96	0	12
19	O=C1NCNC2=CC=CC =C12	 Scaf_30	0	11	0	0
20	C1CC2(CCCCO2)NN1	 Scaf_29	0	0	0	0
21	C1CC2CNC3=CC=CC =C3C2N1	 Scaf_25	0	0	0	0
22	C1ONC2C1COC1=CC =CC=C21	 Scaf_27	0	0	0	0
23	C1COC2(C1)CCNN2	 Scaf_28	0	0	0	0
24	C1COC2=C(C1)SC=N2	 Scaf_21	0	0	0	0

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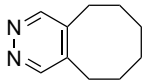
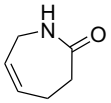
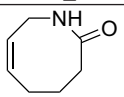
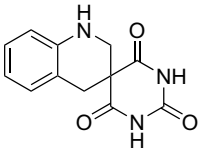
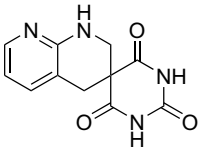
Continuation of Table 4

1	2	3	4	5	6	7
25	C1CCCC2=C(CC1)C =NN=C2	 Scaf_06	0	0	0	0
26	O1C=NN=C1	 Scaf_03	0	0	0	0
27	O=C1CCC=CCN1	 Scaf_19	0	0	0	0
28	O=C1CCCC=CCN1	 Scaf_20	0	0	0	0
29	O=C1NC(=O)C2(CNC3=CC =CC=C3C2)C(=O)N1	 Scaf_22	0	0	0	0
30	O=C1NC(=O)C2(CNC3=NC =CC=C3C2)C(=O)N1	 Scaf_23	0	0	0	0

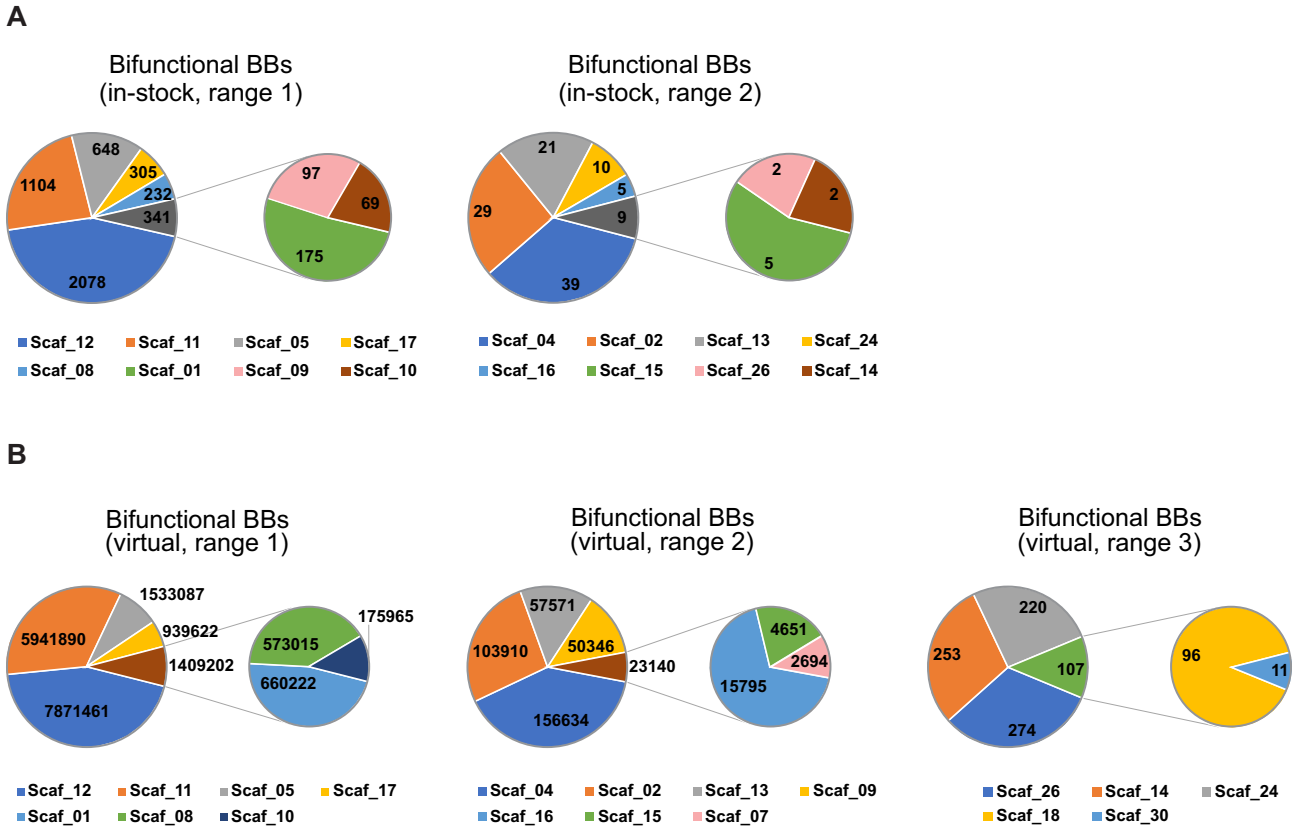


Figure 8. The visualized impact of the on-DNA heterocyclization reactions-derived scaffold to the existing chemical space of stock (**A**) and tangible virtual (**B**) bifunctional DEL-viable BBs

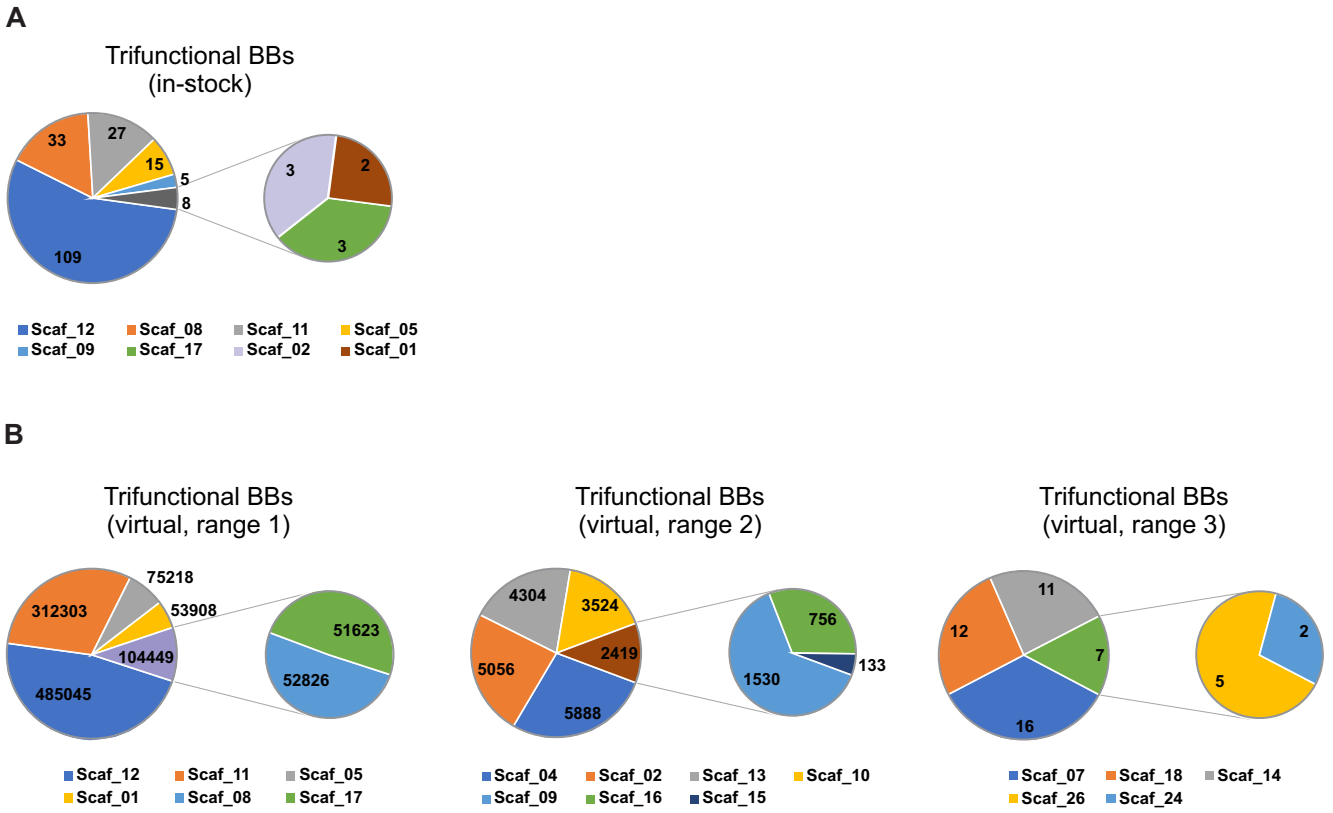


Figure 9. The visualized impact of the on-DNA heterocyclization reactions-derived scaffold to the existing chemical space of stock (**A**) and tangible virtual (**B**) trifunctional DEL-viable BBs

■ Conclusions

We have analyzed both stock and virtual chemical spaces of bi- and tri-functional DELT-viable building blocks using Enamine Ltd. stock collection (*ca.* 30000 molecules) and Chemspace Ltd. tangible set (over 43 million structures) as case studies. Despite seeming variability within both groups (bi- and tri-functional BBs), the compounds with functions suitable for classic cross-coupling reactions, such as amide couplings or ArX – NHR_2 couplings, namely acids, amines, protected amines and aryl halides, vastly outnumber other functional classes. The latter significantly limits both current and nearest-time potential chemical diversity of the DNA-encoded libraries composed on the basis of these types of BBs, especially on the background of the huge size of such libraries: literally what we get is massive numbers of chemically homogeneous molecules, and it extremely complicates readout at the stages of the biological testing. Considering the fact that in case of the cross-coupling approach to the DEL synthesis, the overwhelming majority of potentially useful transformations were already adapted for DNA-friendly conditions, one promising way to approach better diversity of DEL chemical space is to facilitate the synthesis of less common classes of bi- and tri-functional cores like those with sulfonyl halide, boronate, nitro- or aldehyde FGs. However, recent advances in on-DNA heterocyclizations introduced some new chemotypes to the field. Surprisingly, adding 30 scaffolds derived from 26 types of heterocyclizations, even with many of these scaffolds already being a part of the multifunctional cores space, has allowed to expand the general scaffold diversity of the chemical space observed by more than 30%. This finding clearly indicates that adapting the existing and/or finding new heterocyclizations suitable for DNA-friendly conditions, which first and foremost could feed on the existing pool of BBs, is another very potent way to expand the scaffold diversity in DELs.

■ Acknowledgments

The authors express their gratitude to Enamine Ltd. and Chemspace Ltd. for granting access to their data sets, and personally to Prof. Andrey A. Tolmachev for encouragement and comprehensive support in preparing the manuscript.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

References

1. Brenner, S.; Lerner, R. A. Encoded combinatorial chemistry. *Proceedings of the National Academy of Sciences* **1992,** *89* (12), 5381–5383. https://doi.org/10.1073/pnas.89.12.5381.
2. Goodnow, R. A., Jr.; Dumelin, C. E.; Keefe, A. D. DNA-encoded chemistry: enabling the deeper sampling of chemical space. *Nat. Rev. Drug Discov.* **2017,** *16* (2), 131–147. https://doi.org/10.1038/nrd.2016.213.
3. Satz, A. L.; Brunschweiger, A.; Flanagan, M. E.; Gloger, A.; Hansen, N. J. V.; Kuai, L.; Kunig, V. B. K.; Lu, X.; Madsen, D.; Marcaurelle, L. A.; Mulrooney, C.; O'Donovan, G.; Sakata, S.; Scheuermann, J. DNA-encoded chemical libraries. *Nature Reviews Methods Primers* **2022,** *2* (1). https://doi.org/10.1038/s43586-021-00084-5.
4. Mannocci, L.; Zhang, Y.; Scheuermann, J.; Leimbacher, M.; De Bellis, G.; Rizzi, E.; Dumelin, C.; Melkko, S.; Neri, D. High-throughput sequencing allows the identification of binding molecules isolated from DNA-encoded chemical libraries. *Proc. Natl. Acad. Sci. U. S. A.* **2008,** *105* (46), 17670–5. https://doi.org/10.1073/pnas.0805130105.
5. Liu, R.; Li, X.; Lam, K. S. Combinatorial chemistry in drug discovery. *Curr. Opin. Chem. Biol.* **2017,** *38*, 117–126. https://doi.org/10.1016/j.cbpa.2017.03.017.
6. Deng, H.; O'Keefe, H.; Davie, C. P.; Lind, K. E.; Acharya, R. A.; Franklin, G. J.; Larkin, J.; Matico, R.; Neeb, M.; Thompson, M. M.; Lohr, T.; Gross, J. W.; Centrella, P. A.; O'Donovan, G. K.; Bedard, K. L.; van Vloten, K.; Mataruse, S.; Skinner, S. R.; Belyanskaya, S. L.; Carpenter, T. Y.; Shearer, T. W.; Clark, M. A.; Cuozzo, J. W.; Arico-Muendel, C. C.; Morgan, B. A. Discovery of highly potent and selective small molecule ADAMTS-5 inhibitors that inhibit human cartilage degradation via encoded library technology (ELT). *J. Med. Chem.* **2012,** *55* (16), 7061–79. https://doi.org/10.1021/jm300449x.
7. Madsen, D.; Azevedo, C.; Micco, I.; Petersen, L. K.; Hansen, N. J. V. An overview of DNA-encoded libraries: A versatile tool for drug discovery. *Prog. Med. Chem.* **2020,** *59*, 181–249. https://doi.org/10.1016/bs.pmch.2020.03.001.
8. Petersen, L. K.; Christensen, A. B.; Andersen, J.; Folkesson, C. G.; Kristensen, O.; Andersen, C.; Alzu, A.; Slok, F. A.; Blakskjaer, P.; Madsen, D.; Azevedo, C.; Micco, I.; Hansen, N. J. V. Screening of DNA-Encoded Small Molecule Libraries inside a Living Cell. *J. Am. Chem. Soc.* **2021,** *143* (7), 2751–2756. https://doi.org/10.1021/jacs.0c09213.
9. Satz, A. L.; Kuai, L.; Peng, X. Selections and screenings of DNA-encoded chemical libraries against enzyme and cellular targets. *Bioorg. Med. Chem. Lett.* **2021,** *39*, 127851. https://doi.org/10.1016/j.bmcl.2021.127851.
10. Huang, Y.; Li, Y.; Li, X. Strategies for developing DNA-encoded libraries beyond binding assays. *Nat. Chem.* **2022,** *14* (2), 129–140. https://doi.org/10.1038/s41557-021-00877-x.
11. Roy, A.; Kodadek, T. DELs Inside Cells. *Trends in Pharmacological Sciences* **2020,** *41* (4), 225–227. https://doi.org/10.1016/j.tips.2020.01.007.
12. Bassi, G.; Favalli, N.; Oehler, S.; Martinelli, A.; Catalano, M.; Scheuermann, J.; Neri, D. Comparative evaluation of DNA-encoded chemical selections performed using DNA in single-stranded or double-stranded format. *Biochem. Biophys. Res. Commun.* **2020,** *533* (2), 223–229. https://doi.org/10.1016/j.bbrc.2020.04.035.
13. Li, X.; Liu, D. R. DNA-templated organic synthesis: nature's strategy for controlling chemical reactivity applied to synthetic molecules. *Angew. Chem. Int. Ed. Engl.* **2004,** *43* (37), 4848–70. https://doi.org/10.1002/anie.200400656.
14. Fair, R. J.; Walsh, R. T.; Hupp, C. D. The expanding reaction toolkit for DNA-encoded libraries. *Bioorg. Med. Chem. Lett.* **2021,** *51*, 128339. https://doi.org/10.1016/j.bmcl.2021.128339.
15. Clark, M. A.; Acharya, R. A.; Arico-Muendel, C. C.; Belyanskaya, S. L.; Benjamin, D. R.; Carlson, N. R.; Centrella, P. A.; Chiu, C. H.; Creaser, S. P.; Cuozzo, J. W.; Davie, C. P.; Ding, Y.; Franklin, G. J.; Franzen, K. D.; Gefter, M. L.; Hale, S. P.; Hansen, N. J.; Israel, D. I.; Jiang, J.; Kavarana, M. J.; Kelley, M. S.; Kollmann, C. S.; Li, F.; Lind, K.; Mataruse, S.; Medeiros, P. F.; Messer, J. A.; Myers, P.; O'Keefe, H.; Oliff, M. C.; Rise, C. E.; Satz, A. L.; Skinner, S. R.; Svendsen, J. L.; Tang, L.; van Vloten, K.; Wagner, R. W.; Yao, G.; Zhao, B.; Morgan, B. A. Design, synthesis and selection of DNA-encoded small-molecule libraries. *Nat. Chem. Biol.* **2009,** *5* (9), 647–54. https://doi.org/10.1038/nchembio.211.
16. Gerry, C. J.; Wawer, M. J.; Clemons, P. A.; Schreiber, S. L. DNA Barcoding a Complete Matrix of Stereoisomeric Small Molecules. *J. Am. Chem. Soc.* **2019,** *141* (26), 10225–10235. https://doi.org/10.1021/jacs.9b01203.
17. Fitzgerald, P. R.; Paegel, B. M. DNA-Encoded Chemistry: Drug Discovery from a Few Good Reactions. *Chem. Rev.* **2021,** *121* (12), 7155–7177. https://doi.org/10.1021/acs.chemrev.0c00789.
18. Song, M.; Hwang, G. T. DNA-Encoded Library Screening as Core Platform Technology in Drug Discovery: Its Synthetic Method Development and Applications in DEL Synthesis. *J. Med. Chem.* **2020,** *63* (13), 6578–6599. https://doi.org/10.1021/acs.jmedchem.9b01782.
19. Pikalyova, R.; Zabolotna, Y.; Volochnyuk, D. M.; Horvath, D.; Marcou, G.; Varnek, A. Exploration of the Chemical Space of DNA-encoded Libraries. *Molecular Informatics* **2022,** *41* (6). https://doi.org/10.1002/minf.202100289.
20. Shi, B.; Zhou, Y.; Huang, Y.; Zhang, J.; Li, X. Recent advances on the encoding and selection methods of DNA-encoded chemical library. *Bioorg. Med. Chem. Lett.* **2017,** *27* (3), 361–369. https://doi.org/10.1016/j.bmcl.2016.12.025.
21. Salamon, H.; Klika Skopic, M.; Jung, K.; Bugain, O.; Brunschweiger, A. Chemical Biology Probes from Advanced DNA-encoded Libraries. *ACS Chem. Biol.* **2016,** *11* (2), 296–307. https://doi.org/10.1021/acschembio.5b00981.
22. Zhu, H.; Foley, T. L.; Montgomery, J. I.; Stanton, R. V. Understanding Data Noise and Uncertainty through Analysis of Replicate Samples in DNA-Encoded Library Selection. *J. Chem. Inf. Model.* **2022,** *62* (9), 2239–2247. https://doi.org/10.1021/acs.jcim.1c00986.
23. Foley, T. L.; Burchett, W.; Chen, Q.; Flanagan, M. E.; Kapinos, B.; Li, X.; Montgomery, J. I.; Ratnayake, A. S.; Zhu, H.; Peakman, M. C. Selecting Approaches for Hit Identification and Increasing Options by Building the Efficient Discovery of Actionable Chemical Matter from DNA-Encoded Libraries. *SLAS Discov.* **2021,** *26* (2), 263–280. https://doi.org/10.1177/2472555220979589.
24. Needels, M. C.; Jones, D. G.; Tate, E. H.; Heinkel, G. L.; Kochersperger, L. M.; Dower, W. J.; Barrett, R. W.; Gallop, M. A. Generation and screening of an oligonucleotide-encoded synthetic peptide library. *Proc. Natl. Acad. Sci. U. S. A.* **1993,** *90* (22), 10700–4. https://doi.org/10.1073/pnas.90.22.10700.
25. de Pedro Beato, E.; Priego, J.; Gironda-Martinez, A.; Gonzalez, F.; Benavides, J.; Blas, J.; Martin-Ortega, M. D.; Toledo, M. A.; Ezquerra, J.; Torrado, A. Mild and Efficient Palladium-Mediated C-N Cross-Coupling Reaction between DNA-Conjugated Aryl Bromides and Aromatic Amines. *ACS Comb. Sci.* **2019,** *21* (2), 69–74. https://doi.org/10.1021/acscombsci.8b00142.
26. Monty, O. B. C.; Nyshadham, P.; Bohren, K. M.; Palaniappan, M.; Matzuk, M. M.; Young, D. W.; Simmons, N. Homogeneous and Functional Group Tolerant Ring-Closing Metathesis for DNA-Encoded Chemical Libraries. *ACS Comb. Sci.* **2020,** *22* (2), 80–88. https://doi.org/10.1021/acscombsci.9b00199.

27. Lu, X.; Fan, L.; Phelps, C. B.; Davie, C. P.; Donahue, C. P. Ruthenium Promoted On-DNA Ring-Closing Metathesis and Cross-Metathesis. *Bioconjug. Chem.* **2017,** *28* (6), 1625–1629. https://doi.org/10.1021/acs.bioconjchem.7b00292.
28. Devaraj, N. K.; Finn, M. G. Introduction: Click Chemistry. *Chem. Rev.* **2021,** *121* (12), 6697–6698. https://doi.org/10.1021/acs.chemrev.1c00469.
29. Reddavide, F. V.; Lin, W.; Lehnert, S.; Zhang, Y. DNA-Encoded Dynamic Combinatorial Chemical Libraries. *Angew. Chem. Int. Ed. Engl.* **2015,** *54* (27), 7924–8. https://doi.org/10.1002/anie.201501775.
30. An, Y.; Yan, H.; Dong, Z.; Satz, A. L. DNA-Compatible Click Reaction Employing In Situ Generated Azides from Boronic Acids. *Curr. Protoc.* **2021,** *1* (5), e125. https://doi.org/10.1002/cpz1.125.
31. Qu, Y.; Wen, H.; Ge, R.; Xu, Y.; Gao, H.; Shi, X.; Wang, J.; Cui, W.; Su, W.; Yang, H.; Kuai, L.; Satz, A. L.; Peng, X. Copper-Mediated DNA-Compatible One-Pot Click Reactions of Alkynes with Aryl Borates and TMS-N(3). *Org. Lett.* **2020,** *22* (11), 4146–4150. https://doi.org/10.1021/acs.orglett.0c01219.
32. Li, H.; Sun, Z.; Wu, W.; Wang, X.; Zhang, M.; Lu, X.; Zhong, W.; Dai, D. Inverse-Electron-Demand Diels-Alder Reactions for the Synthesis of Pyridazines on DNA. *Org. Lett.* **2018,** *20* (22), 7186–7191. https://doi.org/10.1021/acs.orglett.8b03114.
33. Sun, H.; Xue, Q.; Zhang, C.; Wu, H.; Feng, P. Derivatization based on tetrazine scaffolds: synthesis of tetrazine derivatives and their biomedical applications. *Organic Chemistry Frontiers* **2022,** *9* (2), 481–498. https://doi.org/10.1039/d1qo01324f.
34. Matsuo, B.; Granados, A.; Levitre, G.; Molander, G. A. Photochemical Methods Applied to DNA Encoded Library (DEL) Synthesis. *Acc. Chem. Res.* **2023,** *56* (3), 385–401. https://doi.org/10.1021/acs.accounts.2c00778.
35. Martín, A.; Nicolaou, C. A.; Toledo, M. A. Navigating the DNA encoded libraries chemical space. *Communications Chemistry* **2020,** *3* (1). https://doi.org/10.1038/s42004-020-00374-1.
36. Conole, D.; Hunter, J. H.; Waring, M. J. The maturation of DNA encoded libraries: opportunities for new users. *Future Med. Chem.* **2021,** *13* (2), 173–191. https://doi.org/10.4155/fmc-2020-0285.
37. Pereira, D. A.; Williams, J. A. Origin and evolution of high throughput screening. *Br. J. Pharmacol.* **2007,** *152* (1), 53–61. https://doi.org/10.1038/sj.bjp.0707373.
38. Volochnyuk, D. M.; Ryabukhin, S. V.; Moroz, Y. S.; Savych, O.; Chuprina, A.; Horvath, D.; Zabolotna, Y.; Varnek, A.; Judd, D. B. Evolution of commercially available compounds for HTS. *Drug Discov. Today* **2019,** *24* (2), 390–402. https://doi.org/10.1016/j.drudis.2018.10.016.
39. Buskes, M. J.; Blanco, M. J. Impact of Cross-Coupling Reactions in Drug Discovery and Development. *Molecules* **2020,** *25* (15). https://doi.org/10.3390/molecules25153493.
40. Shi, Y.; Wu, Y. R.; Yu, J. Q.; Zhang, W. N.; Zhuang, C. L. DNA-encoded libraries (DELs): a review of on-DNA chemistries and their output. *RSC Adv.* **2021,** *11* (4), 2359–2376. https://doi.org/10.1039/d0ra09889b.
41. Zabolotna, Y.; Volochnyuk, D. M.; Ryabukhin, S. V.; Gavrylenko, K.; Horvath, D.; Klimchuk, O.; Oksiuta, O.; Marcou, G.; Varnek, A. SynthI: A New Open-Source Tool for Synthon-Based Library Design. *J. Chem. Inf. Model.* **2022,** *62* (9), 2151–2163. https://doi.org/10.1021/acs.jcim.1c00754.
42. Zabolotna, Y.; Volochnyuk, D. M.; Ryabukhin, S. V.; Horvath, D.; Gavrilenko, K. S.; Marcou, G.; Moroz, Y. S.; Oksiuta, O.; Varnek, A. A Close-up Look at the Chemical Space of Commercially Available Building Blocks for Medicinal Chemistry. *J. Chem. Inf. Model.* **2022,** *62* (9), 2171–2185. https://doi.org/10.1021/acs.jcim.1c00811.
43. Verma, A.; Ram Yadav, M.; Giridhar, R.; Prajapati, N.; C. Tripathi, A.; K. Saraf, S. Nitrogen Containing Privileged Structures and their Solid Phase Combinatorial Synthesis. *Combinatorial Chemistry & High Throughput Screening* **2013,** *16* (5), 345–393.
44. Mishra, B. B.; Kumar, D.; Mishra, A.; Mohapatra, P. P.; Tiwari, V. K., Chapter 2 - Cyclo-Release Strategy in Solid-Phase Combinatorial Synthesis of Heterocyclic Skeletons. In *Advances in Heterocyclic Chemistry*, Katritzky, A. R., Ed. Academic Press: 2012; Vol. 107, pp 41–99.
45. Kunig, V. B. K.; Ehrt, C.; Domling, A.; Brunschweiger, A. Isocyanide Multicomponent Reactions on Solid-Phase-Coupled DNA Oligonucleotides for Encoded Library Synthesis. *Org. Lett.* **2019,** *21* (18), 7238–7243. https://doi.org/10.1021/acs.orglett.9b02448.
46. Du, H. C.; Bangs, M. C.; Simmons, N.; Matzuk, M. M. Multistep Synthesis of 1,2,4-Oxadiazoles via DNA-Conjugated Aryl Nitrile Substrates. *Bioconjug. Chem.* **2019,** *30* (5), 1304–1308. https://doi.org/10.1021/acs.bioconjchem.9b00188.
47. Potewar, T. M.; Ingale, S. A.; Srinivasan, K. V. Catalyst-free efficient synthesis of 2-aminothiazoles in water at ambient temperature. *Tetrahedron* **2008,** *64* (22), 5019–5022. https://doi.org/10.1016/j.tet.2008.03.082.
48. Shaaban, S.; Abdel-Wahab, B. F. Groebke-Blackburn-Bienayme multicomponent reaction: emerging chemistry for drug discovery. *Mol. Divers.* **2016,** *20* (1), 233–54. https://doi.org/10.1007/s11030-015-9602-6.
49. Satz, A. L.; Cai, J.; Chen, Y.; Goodnow, R.; Gruber, F.; Kowalczyk, A.; Petersen, A.; Naderi-Oboodi, G.; Orzechowski, L.; Strebel, Q. DNA Compatible Multistep Synthesis and Applications to DNA Encoded Libraries. *Bioconjug. Chem.* **2015,** *26* (8), 1623–32. https://doi.org/10.1021/acs.bioconjchem.5b00239.
50. Kolmel, D. K.; Ratnayake, A. S.; Flanagan, M. E.; Tsai, M. H.; Duan, C.; Song, C. Photocatalytic [2+2] Cycloaddition in DNA-Encoded Chemistry. *Org. Lett.* **2020,** *22* (8), 2908–2913. https://doi.org/10.1021/acs.orglett.0c00574.
51. Potowski, M.; Kunig, V. B. K.; Losch, F.; Brunschweiger, A. Synthesis of DNA-coupled isoquinolones and pyrrolidines by solid phase ytterbium- and silver-mediated imine chemistry. *MedChemComm* **2019,** *10* (7), 1082–1093. https://doi.org/10.1039/c9md00042a.
52. Fan, L.; Davie, C. P. Zirconium(IV)-Catalyzed Ring Opening of on-DNA Epoxides in Water. *Chembiochem* **2017,** *18* (9), 843–847. https://doi.org/10.1002/cbic.201600563.
53. Wu, W.; Sun, Z.; Wang, X.; Lu, X.; Dai, D. Construction of Thiazole-Fused Dihydropyrans via Formal [4+2] Cycloaddition Reaction on DNA. *Org. Lett.* **2020,** *22* (8), 3239–3244. https://doi.org/10.1021/acs.orglett.0c01016.
54. Tian, X.; Basarab, G. S.; Selmi, N.; Kogej, T.; Zhang, Y.; Clark, M.; Goodnow Jr, R. A. Development and design of the tertiary amino effect reaction for DNA-encoded library synthesis. *MedChemComm* **2016,** *7* (7), 1316–1322. https://doi.org/10.1039/c6md00088f.
55. Li, K.; Liu, X.; Liu, S.; An, Y.; Shen, Y.; Sun, Q.; Shi, X.; Su, W.; Cui, W.; Duan, Z.; Kuai, L.; Yang, H.; Satz, A. L.; Chen, K.; Jiang, H.; Zheng, M.; Peng, X.; Lu, X. Solution-Phase DNA-Compatible Pictet-Spengler Reaction Aided by Machine Learning Building Block Filtering. *iScience* **2020,** *23* (6), 101142. https://doi.org/10.1016/j.isci.2020.101142.
56. Skopic, M. K.; Gotte, K.; Gramse, C.; Dieter, M.; Pospich, S.; Raunser, S.; Weberskirch, R.; Brunschweiger, A. Micellar Bronsted Acid Mediated Synthesis of DNA-Tagged Heterocycles. *J. Am. Chem. Soc.* **2019,** *141* (26), 10546–10555. https://doi.org/10.1021/jacs.9b05696.
57. Gerry, C. J.; Yang, Z.; Stasi, M.; Schreiber, S. L. DNA-Compatible [3+2] Nitrone-Olefin Cycloaddition Suitable for DEL Syntheses. *Org. Lett.* **2019,** *21* (5), 1325–1330. https://doi.org/10.1021/acs.orglett.9b00017.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

58. Klika Skopic, M.; Willems, S.; Wagner, B.; Schieven, J.; Krause, N.; Brunschweiger, A. Exploration of a Au(I)-mediated three-component reaction for the synthesis of DNA-tagged highly substituted spiroheterocycles. *Org. Biomol. Chem.* **2017,** *15* (40), 8648–8654. https://doi.org/10.1039/c7ob02347b.

Information about the authors:
Oleksandr V. Oksiuta, Ph.D. Student of the Biologically Active Compounds Department, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine; Data Scientist at Chemspace Ltd.; https://orcid.org/0000-0003-3049-0373.
Alexander E. Pashenko, Ph.D. in Chemistry, Junior Researcher of the Department of Physicochemical Investigations, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine; https://orcid.org/0000-0001-6157-0785.
Radomyr V. Smalii, Ph.D. in Chemistry, Project Manager at Enamine Ltd.; https://orcid.org/0000-0003-0379-1138.
Dmitriy M. Volochnyuk (*corresponding author*), Dr.Sci. in Chemistry, Professor of the Supramolecular Chemistry Department, Institute of High Technologies, Taras Shevchenko National University of Kyiv; Head of the Biologically Active Compounds Department, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine; Senior Scientific Advisor, Enamine Ltd.; https://orcid.org/0000-0001-6519-1467; e-mail for correspondence: d.volochnyuk@gmail.com.
Sergey V. Ryabukhin (*corresponding author*), Dr.Sci. in Chemistry, Professor, Head of the Supramolecular Chemistry Department, Institute of High Technologies, Taras Shevchenko National University of Kyiv; Senior Scientific Advisor, Enamine Ltd.; Senior Researcher of the Department of Physicochemical Investigations, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine; https://orcid.org/0000-0003-4281-8268; e-mail for correspondence: s.v.ryabukhin@gmail.com.