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Mini-Review

Advances in the Exploration of the Epigenetic Relevant Chemical Space

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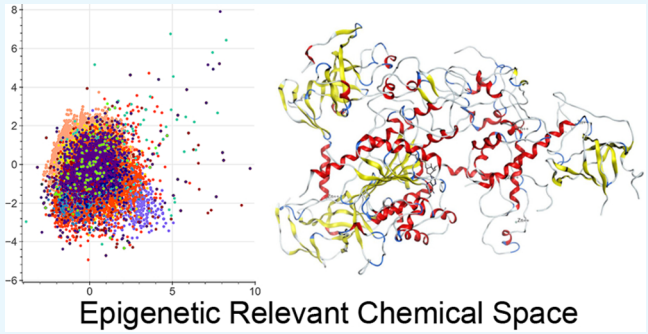
ABSTRACT: Epigenetic drug discovery is a promising avenue to find therapeutic agents for treating several diseases and developing novel chemical probes for research. In order to identify hit and lead compounds, the chemical space has been explored and screened, generating valuable bioactivity information that can be used for multiple purposes such as prediction of the activity of existing chemicals, e.g., small molecules, guiding the design or optimization of compounds, and expanding the epigenetic relevant chemical space. Herein, we review the chemical spaces explored for epigenetic drug discovery and discuss the advances in using structure−activity relationships stored in public chemogenomic databases. We also review current efforts to chart and identify novel regions of the epigenetic relevant chemical space. In particular, we discuss the development and accessibility of two significant types of compound libraries focused on epigenetic targets: commercially available libraries for screening and targeted chemical libraries using de novo design. In this mini-review, we emphasize inhibitors of DNA methyltransferases.



1. INTRODUCTION

Epigenetics has a central role in understanding the inheritance, development, and progression of diseases. Modulation and, in particular, inhibition of epigenetic targets was considered as an approach for cancer treatment. Several conditions are currently associated with the misregulation of epigenetic targets, such as depressive disorders, multiple sclerosis, diabetes, or Alzheimer's disease.[1] Epigenetic target inhibitors are attractive not only for drug development but also as chemical tools to understand the underlying mechanisms of epigenetic regulation.[2] Currently, there are 10 Food and Drug Administration (FDA)-approved drugs related to epigenetic targets, and there are several others under clinical development.[3] Likewise, there are several chemical probes focused on epigenetic targets. Figure 1 shows the chemical structures of representative epigenetic drugs.

DNA methyltransferases (DNMTs) are major epigenetic targets with therapeutic relevance (Figure 1). The enzyme family of DNMTs promotes the covalent addition of a methyl group from *S*-adenosyl-L-methionine (SAM) to the 5-carbon of cytosine, mainly within CpG dinucleotides, yielding *S*-adenosyl-L-homocysteine (SAH). Alterations in the functions of DNMT1, DNMT3A, and DNMT3B are related to tumorigenesis and other diseases.[4] Several reviews have been published regarding the status of the DNMTs inhibitors proposed so far.[5] Figure 2 shows chemical structures of representative DNMT inhibitors and compounds associated with a demethylating activity.

Identifying inhibitors of epigenetic targets, including DNMTs, is an active area of research. Screening compound libraries and optimization of hit and lead compounds, from either synthetic or natural sources, has led to the population of the so-called epigenetic relevant chemical space (ERCS).[6] More and more chemical libraries have been tested biologically, and the information has been deposited in public libraries such as ChEMBL and other chemogenomic databases as reviewed recently.[1] Consequently, the structure−activity relationships (SAR), or, more specifically, the structure−epigenetic activity relationships (SEAR), have increased, paving the way for developing predictive models. Although several drug discovery strategies are being successfully implemented and developed to augment the epigenetic relevant chemical space, some approaches have been used on a limited basis. Examples are de novo design and assembly of focused libraries from commercial sources for acquisition and experimental screening.

Herein, we review advances on the application of SEAR available in public chemogenomics databases. We also discuss techniques to chart novel and unexplored regions of chemical space to identify potential hits, e.g., augment the ERCS. In particular, we discuss avenues to design or test focused chemical

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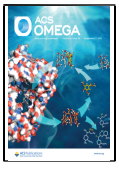

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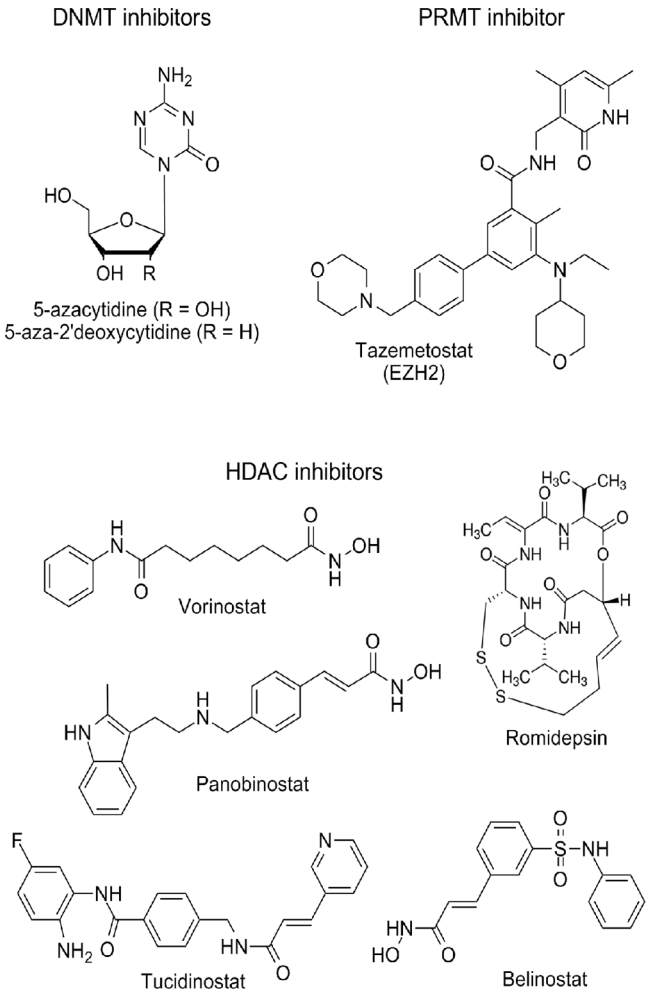

Figure 1. Chemical structures of representative epigenetic drugs.

libraries, use de novo design of molecules, or systematically explore the chemical space of large natural product databases. The mini-review is divided into five sections. After this introduction, section 2 presents trends in computational approaches toward epigenetic drug discovery. Section 3 discusses advances in the generation and use of the SAR from epigenetic databases. The following section addresses the opportunities to expand the ERCS. Finally, section 5 presents conclusions and future directions. In general, we emphasize DNMT inhibitors that have been the primary focus of our group's research.

2. TRENDS IN COMPUTER-AIDED DEVELOPMENT OF EPIGENETIC TARGETING COMPOUNDS

Different computational techniques followed by experimental validation have been used to chart the chemical space, searching for novel epigenetic targeting compounds. In addition, the significant increase in epigenetics-related data boosted computational methods applied to this field, giving rise to the subdiscipline "epi-informatics" that has progressed for more than 5 years.[1] Current trend in epi-informatics includes the generation and maintenance of target-compound databases, the structure-based design of multiepigenetic targets, the development of predictive models using machine learning, and molecular modeling (including docking and molecular dynamics simulations) of hit candidates and active molecules to understand better their activity at the molecular level. Other trends, such as de novo and fragment design, are further commented on in section 4.

Regarding DNMT inhibitors, Table 1 summarizes current trends for their design and discovery. The major techniques are docking-based and pharmacophore-based virtual screening, as previously pointed out.[7] Nevertheless, pharmacophore models have considered structure-based and ligand-based methods. These last included information from nucleoside analogues but also from non-nucleoside inhibitors. The most recent studies involved fragment-based design. The chemical structures of selected DNMT inhibitors developed recently are shown in Figure 2. One of the most notable developments is compound **4b**, with inhibitory activity in the low micromolar range (IC_{50} = 4.1 μM). This inhibitor also presents selectivity for DNMT1 versus DNMT3A/3B, as demonstrated experimentally.

3. ADVANCES ON STRUCTURE–EPIGENETIC ACTIVITY RELATIONSHIPS AND THEIR APPLICATIONS

As commented above, the screening of chemical libraries has expanded. A large amount of SEAR is the basis of computational chemogenomics and is a rich source to develop predictive models that help design and identify novel inhibitors.[1] In this area, a recent development is a free Web server to predict the epigenetic activity of small organic molecules across a panel of 55 epigenetic targets of therapeutic relevance. The server called Epigenetic Target Profiler (ETP)[13] is available at http://www.epigenetictargetprofiler.com/. It was developed based on extensively validated machine learning models trained on biological activity data deposited in ChEMBL.[14] ETP implements the best performing model for epigenetic target prediction, as identified from a systematic comparison of machine learning models built on molecular fingerprints of different designs. Full details of the development and implementation of ETP are described in detail elsewhere.[13,14] It is anticipated that ETP will help guide the identification of compounds with epigenetic activity.

4. OPPORTUNITIES TO EXPAND THE EPIGENETIC RELEVANT CHEMICAL SPACE

The number of synthetically viable organic compounds exceeds 166 billion molecules. However, as for many other targets of therapeutic relevance, just a tiny fraction of that chemical space has been screened, and there is a need to keep expanding the ERCS, balancing novelty with relevance in medicinal chemistry.

4.1. Focused Libraries Commercially Available for Screening. Recently, commercially available compound libraries focused on epigenetic targets[15] have emerged. Table 2 summarizes representative commercial libraries focused on epigenetic targets, including the number of compounds and the main targets. In total, there are over 53,000 compounds. Most of them are commercialized as epigenetic-focused libraries in general. However, few include subsets of compounds directed for specific targets such as histone-modifying enzymes and DNMTs like DNMT1 or DNMT3B.

Figure 3 shows a visual representation of the chemical space of the 11 compound libraries in Table 2. Before the visualization, the chemical structures of the compound data sets were curated using a standard and published protocol.[16] The principal component analysis was done based on six properties of pharmaceutical relevance: molecular weight, number of

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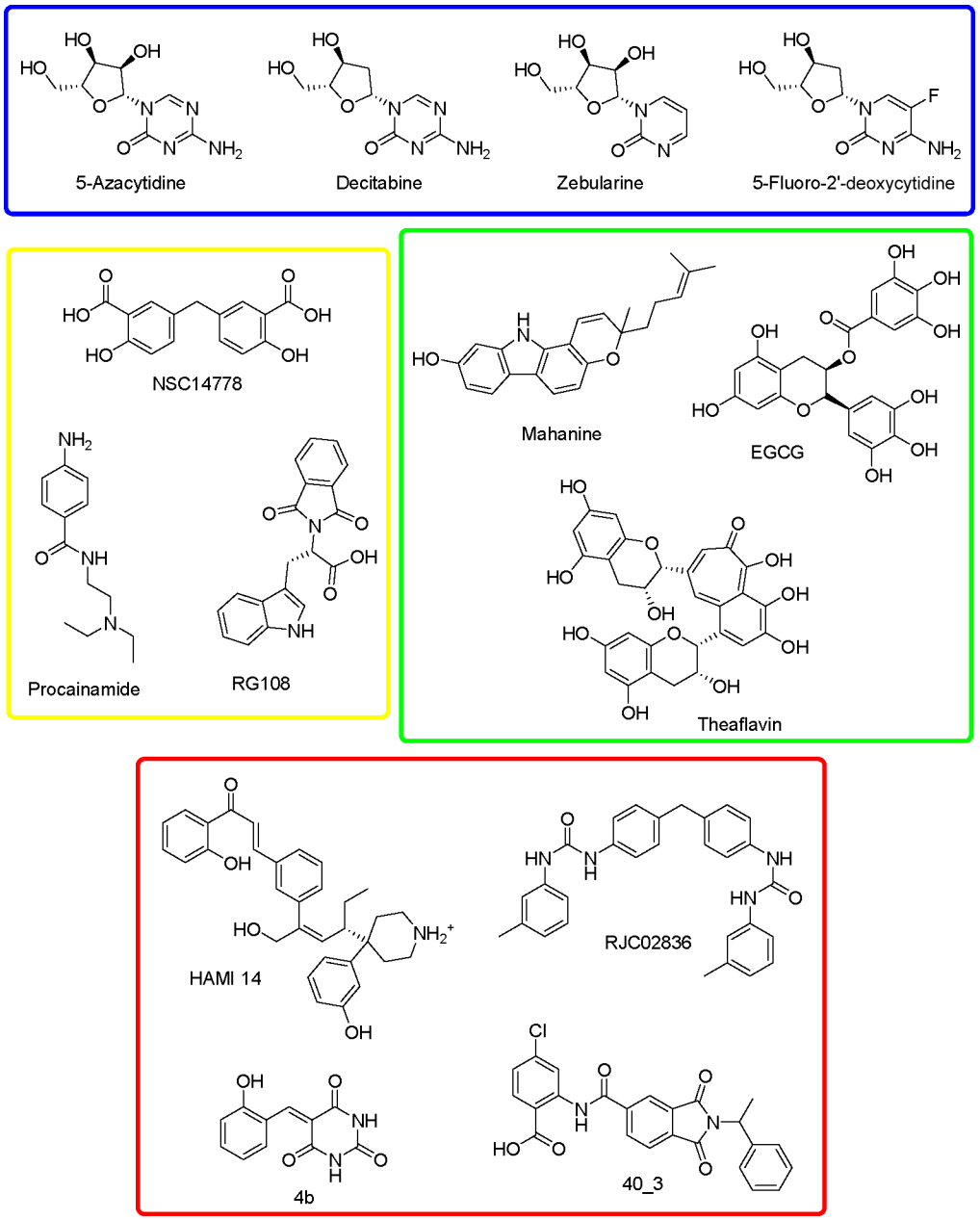

Figure 2. Chemical structures of nucleoside analogues, inhibitors of DNA methyltransferases, DNMTs (blue square). Molecular structures of DNMT inhibitors, identified and developed from different sources: organic synthesis (yellow), natural products (green), and virtual screening (red).

Table 1. Design and Discovery of DNMT Inhibitors

strategy	source	target	results[a]	ref
pharmacophore-based virtual screening and similarity searching	specs	DNMT3A (PDB ID: 4U7T)	compounds **40** and **40_3** with inhibitory activity (IC_{50} = 46.5 and 41 μM)	8
pharmacophore-based virtual screening	Maybridge	DNMT1 (PDB ID: 3PTA)	identification of three novel hits: **JFD01881**, **RJC02836**, and **RJC02837**	9
pharmacophore and docking-based virtual screening	in-house database	DNMT1 (PDB ID: 3SWR)	one derivative from an identified compound: **4b** (IC_{50} = 4.1 μM)	10
fragment-based design	natural products from PubChem	DNMT1 (PDB ID: 4WXX)	two proposals of lead compounds: **HAMI 9** and **HAMI 14**	11
fragment-based design and fragment merging with SAH	natural products' fragments from PubChem	DNMT1 (PDB ID: 3AV5, 3AV6, 3PTA, 3SWR, 4WXX)	most promising hit: **MAHI1**	11
fragment-based design	natural products' fragments from PubChem	DNMT1 (PDB ID: 3AV5)	potential drug lead: **C-7756**	12

[a]The chemical structures of selected compounds are shown in Figure 2.

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Table 2. Examples of Commercial Compound Libraries Focused on Epigenetic Targets for Screening

source	size (initial)	size (curated)[a]	brief description	website accessed June 2021
ApeXBio (DiscoveryProbe Epigenetics Compound Library)	328	310	small molecules with activity against different epigenetic targets; design approach not disclaimed	https://www.apexbt.com/discoveryprobetm-epigenetics-compound-library.html
Asinex (Epigenetic Library)	5391	5313	library focused on bromodomains and histone methyltransferase inhibitors; compounds designed by a combination of structure and ligand-based methods	http://www.asinex.com/
ChemDiv (Epigenetic Set)	30,431	27,543	library designed for modulation for all three classes of epi-targets; molecules were designed based on a combination of structure-based (based on X-ray and nuclear magnetic resonance) and ligand-based approaches	https://www.chemdiv.com/epigenetics-library/
Enamine (Epigenetics Library)	9352	9352	library designed with a combination of ligand and structure-based methods; compound optimization was made via pharmacophore profiling	https://enamine.net/hit-finding/focused-libraries/view-all/epigenetics-libraries
Life Chemicals (Epigenetics Screening Library)	7019	7011	derived with the use of similarity methods, this library is focused on methylation-related epi-enzymes	https://lifechemicals.com/screening-libraries/targeted-and-focused-screening-libraries/epigenetic-screening-libraries
MedChemExpress (Epigenetics Library)	700	650	library designed for modulation of several epi-targets; the targets and design approaches are not disclaimed	https://www.medchemexpress.com/virtual-screening/epigenetics-library.html
OTAVA DNMT1 (DNMTs Targeted Libraries)	466	399	drug-like compounds selected from virtual screening using docking and pharmacophore modeling	https://www.otavachemicals.com/targets/dnmt1-and-dnmt3b-targeted-libraries
OTAVA DNMT3b (DNMTs Targeted Libraries)	1261	1230	drug-like compounds selected from virtual screening using docking and pharmacophore modeling	https://www.otavachemicals.com/targets/dnmt1-and-dnmt3b-targeted-libraries
Targetmol (Epigenetics Compound Library)	932	859	a set of epi-regulators whose primary focus is lead optimization and HTS; design approach not disclaimed	https://www.targetmol.com/
TocrisScreen Epigenetics	101	99	collection of small molecules covering more than 40 epigenetic targets (including readers, writers, erasers, and transcriptional modulators); design approach not disclaimed	https://www.tocris.com/products/tocriscreen-epigenetics-library_6801
SelleckChem (Epigenetics Compound Library)	699	677	focused on experimental tests and for HTS validation, this library contains inhibitors for several epi-targets; design approach not disclaimed	https://www.selleckchem.com/screening/epigenetics-compound-library.html

[a]Data curation was done with a standard protocol described in ref 16 to conduct a comparative chemoinformatic profile of the compound libraries.

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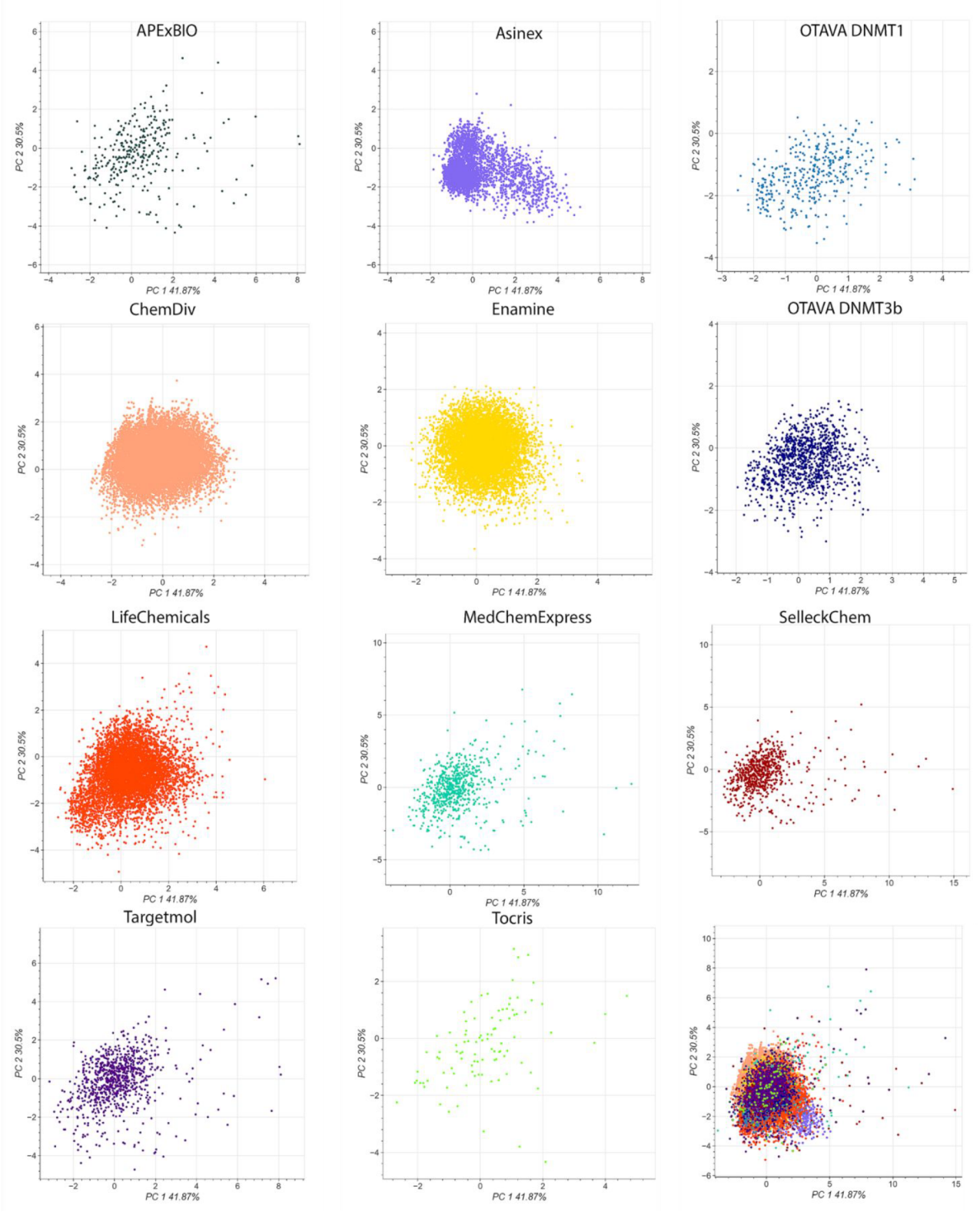

Figure 3. Visual representation of the chemical space of 11 compound libraries focused on epigenetic targets in Table 2. The visualization was done with a principal component analysis of six autoscaled properties of pharmaceutical relevance. Each compound library is plotted using the same coordinates. The plot on the bottom-right corner shows all 11 compound libraries plotted on the same graph. The percentage of variance recovered by each principal component is indicated along the *X*- and *Y*-axis.

rotatable bonds, number of hydrogen bond donors and acceptors atoms, topological polar surface area (TPSA), and octanol−water partition coefficient (LogP). The total variance captured by the first two principal components is 72%. The properties that contributed most to the first two principal components were TPSA and LogP. The visualization indicates that most libraries have comparable and drug-like properties, as designed and prefiltered by the chemical companies selling the

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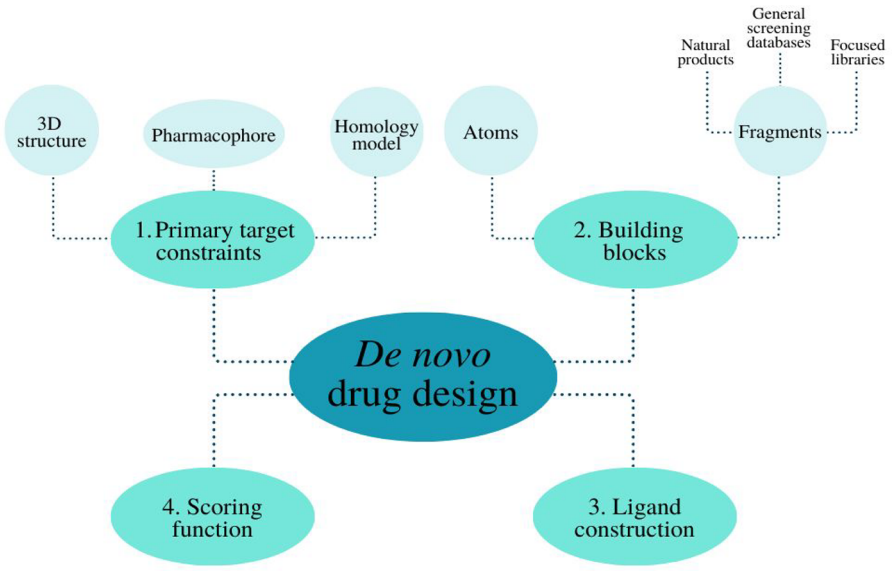

Figure 4. Schematic representation of major components involved in automated de novo drug design.

Table 3. De Novo Design Programs

		algorithm				
program	year	building blocks	ligand construction	search strategy	scoring function	refs
LUDI	1992	fragments	growing, linking	Breadth-first search	empirical	19,20
LEA3D	2005	fragments	growing, linking	genetic algorithm	user-defined fitness function	21
PhDD[a]	2010	fragments	linking	random	fit value (alignment with pharmacophore model)	22
eLEA3D[a]	2010	fragments	growing, linking	genetic algorithm	user-defined fitness function	23
DOGS	2012	fragments	reaction-based	deterministic process	similarity with reference ligand	24
DENOPTIM[a]	2019	fragments	graph-based	genetic algorithm	customizable fitness function	25
LigBuilder V3[a]	2020	fragments	growing, linking	genetic algorithm	empirical	26

[a]Free software for academic use.

libraries. Compounds in the Enamine collection populate a more constrained region of the chemical space compared with other libraries such as APExBIO and SelleckChem, covering broader areas of the property-based chemical space.

Recently, the need to include privileged substructures present in the collection of approved drugs for clinical use in the focused libraries for epigenetic drug discovery has been highlighted.[15]

4.2. De Novo Design. The main goal of de novo design is to generate new molecules with desired properties. Herein, we focus on the design of bioactive hits. A schematic summary of de novo design is presented in Figure 4. The method has four general stages. First of all, primary target constraints are established. These refer to the information related to ligand−receptor interaction.[17] Three-dimensional (3D) coordinates are needed to determine the constraints. The information could be obtained from the 3D structure of the target (X-ray or nuclear magnetic resonance), a homology model, or a pharmacophore model. The last one enables the use of known ligands to define primary target constraints, even if the 3D structure of the receptor is not available. Second, atoms or fragments could be the building blocks of the new molecules. Atom-based construction will likely give more diversity to the chemical space. However, proposed structures usually are synthetically challenging or unfeasible. In that sense, fragment-based approaches could overcome this disadvantage as they are typically larger and retain more chemical information. Fragments are drawn from sources like general screening databases, natural products, or focused libraries (vide supra). Once the building blocks are established, the algorithm continues to the ligand construction. This stage requires a seed atom or fragment. Techniques for molecular assembly include growing, linking, alignment-based, lattice-based, reaction-based, and graph-based methods.[18] Some software programs or algorithms also have strategies to address the issue of combinatorial search explosion, like breadth-first and depth-first search, Monte Carlo search combined with Metropolis criterion or evolutionary algorithms. Finally, the scoring function guides the ligand construction and defines the best candidate compounds. Functions could also consider the 3D structure of the target (structure-based) or information from known ligands (ligand-based). In general, structure-based methods are classified into force-field, knowledge-based, and empirical functions. Table 3 lists examples of de novo design programs. The description of the algorithm includes the selected building blocks, the technique for the ligand construction, the search strategy for the combinatorial problem, and the scoring function. Earlier de novo design programs considered atoms preferably as building blocks until synthetic tractability became an issue. Consequently, most recent programs typically consider fragments. Synthetic feasibility quantified with different approaches is also addressed. Current programs include fragment databases generated from already known drug-like compounds (LEA3D) or incorporate a new score to evaluate synthetic accessibility (PhDD). Current programs also incorporate genetic algorithms to optimize the searching (Table 3).

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Table 4. Epigenetic Target Profiling of Public Compound Libraries of Natural Products[a]

target	BIOFACQUIM (510)[b]	MEGx (3707)[b]	$NuBBE_{DB}$ (1995)[b]	Fungi (178)[b]	Marines (5371)[b]	Cyanobacteria (235)[b]	COCONUT (350,070)[b]
APEX1	433	3405	1614	139	4109	151	237,341
ATM	322	2812	1255	116	4233	203	258,867
AURKA	75	712	338	21	717	7	60,780
AURKB	137	850	535	44	1301	68	97,705
BRD2	310	2414	1143	119	3407	141	209,233
BRD4	117	1129	416	63	1515	141	100,391
BRPF1	0	15	19	0	12	0	2113
CARM1	38	294	171	4	403	31	64,177
CDK1	264	1519	871	81	2071	103	127,126
CDK2	44	401	177	20	894	37	40,350
CDK5	32	170	87	18	242	3	11,396
CDK7	3	16	5	1	90	3	7850
CHEK1	3	49	15	6	144	3	8989
CHUK	0	0	1	0	4	0	336
CREBBP	26	181	83	18	415	59	50,678
DAPK3	1	6	16	0	17	1	1559
DNMT1	0	0	0	0	0	0	3 (KNOWN)
DOT1L	0	4	0	0	5	15	3199
EHMT2	4	17	9	9	40	13	6828
EP300	132	1009	451	88	2080	98	119,920
EZH2	24	200	84	19	396	61	34,732
HDAC1	100	1236	352	57	1365	113	98,671
HDAC10	8	151	39	9	302	85	21,772
HDAC11	27	281	130	17	483	60	28,158
HDAC2	47	302	212	37	661	72	47,019
HDAC3	27	184	132	21	516	54	48,494
HDAC4	28	178	76	15	435	44	40,606
HDAC5	7	86	30	7	163	20	21,118
HDAC6	51	453	202	32	812	66	49,533
HDAC7	44	252	123	25	490	25	38,319
HDAC8	103	453	405	37	874	22	53,706
HDAC9	0	20	5	0	48	0	5223
JAK2	14	112	95	13	355	10	28,058
KAT2B	4	20	7	3	71	10	8507
KDM1A	55	244	223	16	410	72	47,451
KDM4A	1	15	9	0	13	0	2343
KDM4C	54	549	248	28	855	51	85,910
KDM4E	266	1654	818	77	1994	40	115,675
KDM5A	64	409	160	21	770	79	64,053
KDM6B	0	0	0	0	0	0	9
L3MBTL1	0	0	0	0	0	0	336
PARG	0	0	0	0	0	0	197
PARP1	144	1434	610	85	2469	171	168,852
PKN1	50	267	129	12	220	27	28,310
PRKAA1	15	11	16	0	28	0	3600
PRKCB	77	570	218	63	1432	51	56,473
PRKCD	182	1799	685	106	2700	87	112,135
PRKDC	107	820	352	39	1193	65	90,455
PRMT3	0	2	0	0	0	0	797
RPS6KA5	17	87	86	1	105	1	6038
SIRT1	5	52	27	4	108	13	8878
SIRT2	13	13	9	0	20	11	2190
SIRT3	0	0	0	0	0	0	72
TOP2A	3	2	5	0	16	0	1026
USP7	30	350	114	11	592	17	29,020

[a]Compounds classified as potentially active with the free server Epigenetic Target Profiler. [b]Number of compounds in each library.

In epigenetic drug discovery, de novo design has been applied to find new inhibitors of the (CREB (cAMP responsive element binding protein) binding protein) bromodomain, using the program LUDI (a structure-based approach).[27] In this example,

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the authors added new fragments to the core of the compound CPI-637. The search was guided with the information on crucial residues. As a result, structures with similar binding affinities to the original molecule were obtained. These results state the applicability of de novo design to aim the discovery of novel epigenetic drugs.

4.3. Profiling of Large Libraries of Natural Products. As with several other therapeutic targets, natural products are sources of compounds or starting points to inspire the development of active compounds with epigenetic targets. Natural products have been the sources of inhibitors of DNMTs and molecules with demethylating activity (Figure 2).[28] One of the most recent DNMT1 inhibitors identified from natural sources is theaflavin,[5] a polyphenol compound in black tea and previously identified as an inhibitor of DNMT3B. The importance of natural products as sources of epigenetic compounds, the increasing availability of large natural product databases in the public domain,[29] and overall significance of the emerging "natural products informatics" (e.g., rational application of informatics approaches to enhance natural product-based drug discovery) encourages the continued systematic virtual screening of natural products databases to identify compounds with potential epigenetic inhibitory activity, including DNMT inhibitors.

To illustrate this point, Table 4 summarizes the predicted classification of seven natural product libraries in the public domain. The predictions were made with the algorithms implemented in the free server ETP described in section 3. The natural product databases used in the epigenetic target prediction (e.g., epigenetic target fishing) were the same files previously curated and used in diversity profiling reported in detail elsewhere.[30] As discussed in those studies, the databases include a collection of 510 natural products isolated and characterized in Mexico (BIOFACQUIM), 3707 compounds from a screening library (MEGx), 1995 natural products from Brazil ($NUBBE_{DB}$), 178 fungi metabolites (Fungi), 5371 marine natural products, 235 cyanobacterial metabolites, and 350,070 molecules from the Collection of Open Natural Products (COCONUT). As discussed elsewhere, COCONUT is one of the largest public collections of natural products available today. Table 4 reports the number of compounds predicted as "active" (defined in ETP as molecules with at least IC_{50} = 10 μM) with confidence in the range quartiles 1−4.[14] The predictions were made with the consensus model Morgan::SVM−RDK::SVM as described elsewhere.[14] Results of the profiling indicated that three compounds (nucleoside analogues) in COCONUT had reported epigenetic activity with DNMT1 (including Vidaza and *S*-(5′-adenosyl)-L-homocysteine, Adohcy). However, there are no other compounds with predicted activity against DNMT1. Similar trends were predicted for other targets such as KDM6B, PARG, and SIRT3. Since the classification predicted with ETP is based on the experimental data deposited in ChEMBL, the low number of predicted active compounds can be related to the insufficient amount of information available in public (but this is expected to change when more screening data are deposited on public databases). In contrast, APEX1, followed by ATM and BRD2, were the epigenetic targets with the largest number of predicted active compounds per library (e.g., 60% of the compounds in COCONUT). The next logical step is to conduct additional computational studies to select the most promising compounds and experimentally test the activity of the natural products with the epigenetic target(s) of interest.

5. CONCLUSIONS AND FUTURE DIRECTIONS

The ERCS is expanding, as reflected by the increase in the number of SEAR. The ERCS' expansion is being driven by (1) novel and multiple compound libraries focused on epigenetic targets, ready for experimental testing, and (2) the growing interest to build de novo chemical libraries focused on epigenetic targets. The concurrent growth in the experimental screening information has encouraged the development of machine learning models, now implemented into a free Web server to predict small molecules epigenetic activity, including natural products, and guide the design of novel compounds. It is anticipated that as the increase of screening data continues, more predictive models will be developed. Perspectives in the field include augmenting the implementation of de novo design of compounds as candidate epi-drugs, experimental screening of the focused libraries already available for testing, and continuing epigenetic target profiling (e.g., inverse virtual screening) of natural product databases followed by testing of the computational hits and further refinement using other approaches such as structure-based virtual screening.

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Notes

The authors declare no competing financial interest.

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Diana L. Prado-Romero received her M.Sc. degree from the National Autonomous University of Mexico (UNAM) in 2020. She began her research at the School of Chemistry, UNAM, in 2017, focused on medicinal chemistry under the supervision of Dr. Rafael Castillo and Dr. Alicia Hernández-Campos. She is currently working to obtain her Ph.D. with Dr. Medina-Franco at DIFACQUIM. Her research interest is the design of novel inhibitors of DNA methyltransferases.

José L. Medina-Franco, Ph.D., FRSC, is a full professor in the Department of Pharmacy of the School of Chemistry at the National Autonomous University of Mexico (UNAM). He received his Ph.D. degree at UNAM. In 2005, Dr. Medina-Franco joined the University of Arizona as a postdoctoral fellow under the supervision of Prof. Gerald Maggiora, and he was named Assistant Member at the Torrey Pines Institute for Molecular Studies in Florida in August 2007. In 2013, he conducted research at the Mayo Clinic. In 2014, he joined UNAM and now is a Full-Time Research Professor. He leads the DIFACQUIM research group at UNAM. The research focus is on computer-aided drug design using chemoinformatics, machine learning, and molecular modeling with applications on epigenetic targets and natural products. In 2017, he was named Fellow of the Royal Society of Chemistry.

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■ ABBREVIATIONS

3D, three-dimensional; COCONUT, Collection of Open Natural Products; DNMTs, DNA methyltransferases; ERCS, epigenetic relevant chemical space; ETP, Epigenetic Target Profiler; FDA, Food and Drug Administration; HTS, high-throughput screening; LogP, octanol−water partition coefficient; SAH, *S*-adenosyl-L-homocysteine; SAM, *S*-adenosyl-L-methionine; SAR, structure−activity relationships; SEAR, structure−epigenetic activity relationships; TPSA, topological polar surface area

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