feature

Expansion of chemical space for collaborative lead generation and drug discovery: the European Lead Factory Perspective

Anna Karawajczyk[1], Fabrizio Giordanetto[1], Jorg Benningshof[2], Daniel Hamza[3], Tuomo Kalliokoski[4], Kees Pouwer[5], Remy Morgentin[6], Adam Nelson[7,8], Gerhard Müller[2], Alexander Piechot[1] and Dimitrios Tzalis[1,*], dtzalis@taros.de

High-throughput screening (HTS) represents a major cornerstone of drug discovery. The availability of an innovative, relevant and high-quality compound collection to be screened often dictates the final fate of a drug discovery campaign. Given that the chemical space to be sampled in research programs is practically infinite and sparsely populated, significant efforts and resources need to be invested in the generation and maintenance of a competitive compound collection. The European Lead Factory (ELF) project is addressing this challenge by leveraging the diverse experience and know-how of academic groups and small and medium enterprises (SMEs) engaged in synthetic and/or medicinal chemistry. Here, we describe the novelty, diversity, structural complexity, physicochemical characteristics and overall attractiveness of this first batch of ELF compounds for HTS purposes.

Introduction

The continuing discovery and development of novel, safe and effective medicines is expected by contemporary society. Nevertheless, the intellectual, technical and financial challenges associated with it are enormous. Despite the approval of 41 new therapeutics during 2014 (a significant 17-year high) [1], the ability of the pharmaceutical industry to rise to these formidable challenges is periodically questioned and tentative solutions are constantly suggested [2–7]. As a result, the field of drug research has seen significant changes over the past decades and a stronger emphasis on precompetitive, open-source models is evident [8]. One such approach, the European Lead Factory (ELF) a project of the Innovative Medicine Initiative, has recently created a collaborative lead generation platform to boost the early phases of drug discovery [9]. The state-of-the-art high-throughput screening (HTS) infrastructure and the industrial-quality Joint European Compound Collection of the ELF are made available at no cost to European research investigators, with a milestone payment system applied to any exploitation projects targeting commercialization (https://www.europeanlead-factory.eu/#). As part of the ELF open-source model, seven pharmaceutical companies (Bayer, AstraZeneca, UCB, Lundbeck, Sanofi, Merck, J&J) have contributed a total of 321,000 compounds from their proprietary collections [10]. This initial set is now being complemented with up to an additional 200,000 compounds [here termed the Public Compound Collection (PCC)] in a collaborative effort involving a unique blend of chemistry expertise from ten academic groups and six small and medium enterprises (SMEs) (Table 1) building the ELF Chemistry Consortium.

The goal of the PCC compounds is to populate new, biologically relevant chemical spaces that are typically not addressed in traditional screening collections from chemical vendors or corporate collections. This newly designed collection is based on proposals for libraries of compounds that are submitted by academic and

http://dx.doi.org/10.1016/j.drudis.2015.09.009

TABLE 1

Chemistry-focused academic groups and SMEs participating to the ELF

	Country	Website
Academic Institution (principal investigator)		
Max Planck Institute of Molecular Physiology (Herbert Waldmann and Kamal Kumar)	Germany	http://www.mpi-dortmund.mpg.de/74682/Kumar
Netherlands Cancer Institute (Huib Ovaa)	The Netherlands	http://www.nki.nl/divisions/cell-biology-ii/ovaa-h-group/
Technical University of Denmark (Mads Clausen)	Denmark	http://www.kemi.dtu.dk/english/Research/OrganicChemistry/Kemisk_Biologi/MadsHClausenIntro
University of Duisburg-Essen (Markus Kaiser)	Germany	https://www.uni-due.de/zmb/members/kaiser/overview.shtml
University of Groeningen (Alexander Dömling)	The Netherlands	http://www.rug.nl/staff/a.s.s.domling/
University of Leeds (Adam Nelson and Steve Mardsen)	UK	http://www.chem.leeds.ac.uk/People/Nelson.html; http://www.chem.leeds.ac.uk/People/Marsden.html
University of Leiden (Mario van der Stelt)	The Netherlands	http://biosyn.lic.leidenuniv.nl/people/vanderstelt
University of Nijmegen (Floris Rutjes)	The Netherlands	http://www.soc.science.ru.nl/index.php/people?view=member&id=1
University of Nottingham (Robert Stockman and Chris Moody)	UK	http://www.nottingham.ac.uk/chemistry/people/robert.stockman; http://www.nottingham.ac.uk/Chemistry/People/c.j.moody
VU University of Amsterdam (Romano Orru)	The Netherlands	http://www.chem.vu.nl/en/research/division-organic-chemistry/staff/orru/index.asp
SME		
Edelris	France	http://www.edelris.com
Lead Discovery Center	Germany	http://www.lead-discovery.de
Mercachem	The Netherlands	http://www.mercachem.com
Sygnature Discovery	UK	http://www.sygnaturediscovery.com
Syncom	The Netherlands	http://www.syncom.nl
Taros	Germany	http://www.taros-discovery.com

industrial chemists (from either within or outside the consortium) adhering to strict quality workflows in terms of design, chemistry validation and production. Here, we describe the initial batch of PCC screening compounds delivered by the ELF Chemistry Consortium during the first 18 months of chemistry activities. These compounds are compared to the Maybridge Screening Collection (http://www.maybridge.com/portal/alias__Rainbow/lang__en/tabID__146/DesktopDefault.aspx), the collection of the Molecular Library Program (MLP) of the National Institutes of Health (NIH) [11] and compounds curated in the ChEMBL database [12]. The Maybridge collection was chosen as a representative screening library from commercial sources because of its diversity-based character and previous use in screening collections comparisons [13]. The MLP library was selected because of the similar collaborative nature of the MLP and ELF programs, and the ChEMBL database because of the medicinal chemistry relevance of the compounds curated therein.

ELF library workflow

Library proposals submitted to the ELF Chemistry Consortium using a specifically designed web-tool (https://www.europeanleadfactory.eu/proposals/chemical-scaffolds/submit-your-library-design-proposal/) are reviewed by a Library Selection Committee (LSC) comprising eight experienced synthetic and medicinal chemists from pharmaceutical companies, SMEs, academic groups and screening centers adhering to the ELF project. Each proposal is assessed against six specific criteria, as summarized in Box 1. The novelty requirements need to be met by all libraries to maximize coverage of novel chemical space. Deviations from the defaults of other parameters (e.g. molecular properties or structural filters) are considered by the LSC especially when a strong design concept (e.g. natural product inspiration or target class focus) is provided. The LSC final assessment is then fed back to the library proposer to guide the refinement of future submissions.

The accepted library proposals are then evaluated experimentally by academic and industrial ELF consortium partners to verify whether the intended libraries can be effectively produced within the ELF project timeline and budget. These library validation activities define optimal conditions for crucial synthetic and purification steps, and provide experimental proof of their scalability and robustness to diversity. The chemical stability of intermediates and final compounds is also monitored throughout the course of library validation activities. The experimental documentation is reviewed by a Validation Committee that ensures selected libraries are meeting the practical requirements for production.

Successfully validated ELF libraries are then further refined before production to maximize their diversity, optimize properties, and ensure novelty against public and commercial compound sources and the growing number of PCC compounds (http://www.int-conf-chem-structures.org/fileadmin/user_upload/ICCS_2014/posters/P22-Kalliokoski.pdf). The validated synthetic protocol is then executed to standard industrial specifications. Library compounds

BOX 1

ELF library proposals parameters and measures.

Novelty: no matches against the existing JECL collection, previously accepted JECL libraries, a collation of commercial vendor sources (http://www.int-conf-chem-structures.org/fileadmin/user_upload/ICCS_2014/posters/P22-Kalliokoski.pdf), and additional chemistry-oriented repositories based on the patent literature [14].
Molecular properties: contemporary drug-like properties [15].
Diversity potential: number of diversification points (at least two) and their practical exploitation.
Structural features: absence of chemical liabilities as defined by a collection of substructure filters contributed by the pharmaceutical companies participating in the ELF [10].
Synthetic tractability: cost of goods, atom economy, length and efficiency of the synthetic route, and associated purification and diversification steps.
Innovation: original library design (structural and synthetic levels) rationale and concept.

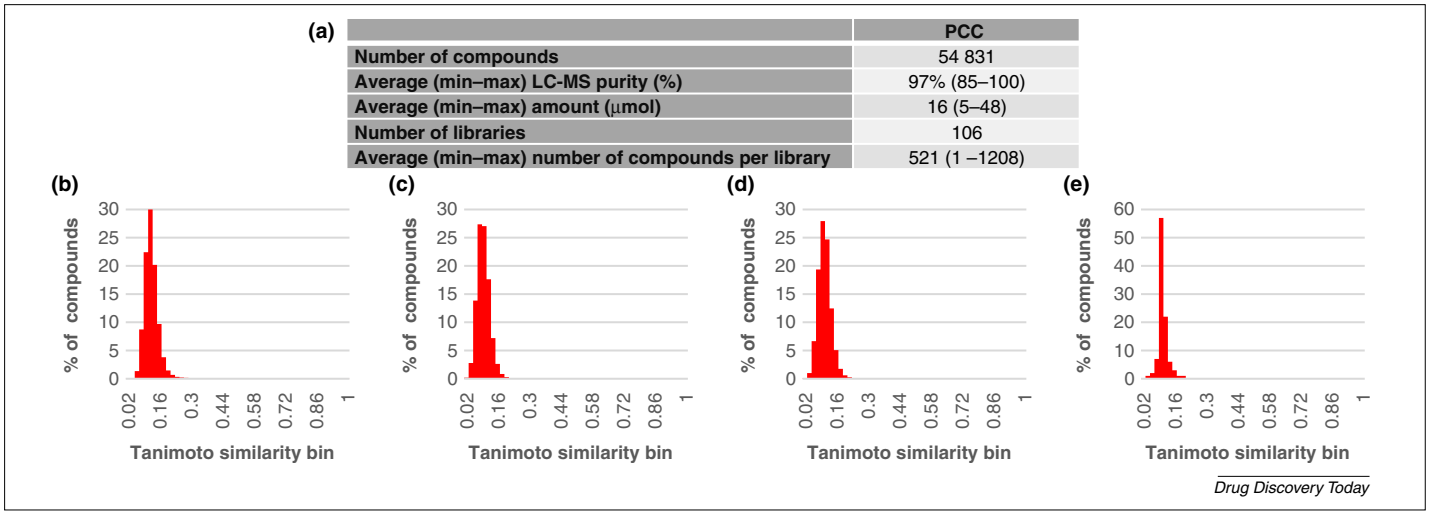

FIGURE 1

Evaluation of inter-and intra-collection similarity. **(a)** Compound and library level descriptive statistics for the Public Compound Collection (PCC) library. Frequency histograms of nearest neighbor molecular similarities, as measured by Tanimoto coefficients based on extended connectivity fingerprints (ECFP6) for: **(b)** PCC compounds, **(c)** PCC and Maybridge compounds, **(d)** PCC and Molecular Library Program (MLP) compounds and **(e)** PCC and ChEMBL compounds.

meeting the Joint European Compound Library (JECL) quality criteria for purity (LC–MS purity >85%) and quantity (>5 μmol) are then added to the JECL and plated for the ELF HTS. The ELF compound management groups routinely perform standard sample analyses to monitor compound purity, solubility and structural identity, and ensure adequate sample quality for biological screening purposes. The synthesized amounts have been defined so that each sample is available to all HTS campaigns and relevant follow-up activities during the course of the ELF project, without the need for its resynthesis. Additionally, each principal investigator who receives a qualified hit-list at the end of an ELF HTS and hit evaluation campaign could access the relevant physical samples and associated synthetic procedures for the compounds in the qualified hit-list to jump-start additional research efforts. Each hit compound appearing on such qualified hit-lists will be automatically removed from the JECL collection, as a way to protect the intellectual property of the principal investigator.

Data sharing across the various ELF chemistry consortium partners, from the original library enumeration performed by the Lead Discovery Center, to experimental validation procedures from academic and SME groups, to the shipment of the final compounds to the screening centers from each SME, is facilitated by Tarosgate, a chemistry management solution especially designed for the ELF project.

Compound-level analysis

A total of 54,831 final compounds has been successfully delivered to the ELF compound management facilities and distributed to the ELF screening centers, with an average LC–MS purity of 97% and average 16 mmol amount, as detailed in Fig. 1. Industrial and academic chemists have designed and validated libraries that contributed 57% and 43% of these compounds, respectively. Overlap analysis of the screening collections considered here reveals the PCC set to be unique, with no duplicate structures identified in the Maybridge collection, the MLP or ChEMBL.

Compounds in the PCC set are also structurally dissimilar to each other, as summarized in Fig. 1. Here, the average Tanimoto coefficient based on extended connectivity fingerprints (ECFP6) is 0.17. As a reference, compounds in the diversity-based Maybridge library have a maximum Tanimoto coefficient of 0.2 when using the same ECFP6 metric. Furthermore, the PCC compounds are significantly dissimilar from existing compounds in the other collections considered in the present study. Intercollection similarity is less than 0.2 for the PCC set compounds when compared with MPL-NIH, Maybridge and the ChEMBL database, as described in Fig. 1.

The distributions of molecular descriptors commonly used in medicinal chemistry are shown in Fig. 2 for the PCC set, the Maybridge screening collection, the MLP library and the ChEMBL compound bank. Overall, all libraries share typical Lipinski rule-of-five [14] attributes. Here, the PCC library displays the highest polarity and molecular weight. In total, 85% of the PCC compounds have *c* log *P* values less than 4 compared with 80% for MLP, 62% for Maybridge and 67% for ChEMBL compounds. In addition, 58% of the PCC compounds have a molecular mass greater than 400 Da (MLP, 30%; Maybridge, 21%, ChEMBL, 46%). The major differences between the libraries emerge when the number of chiral centers and the fraction of sp^3 hybridized carbon atoms (Fsp^3) are considered. 85% of the PCC compounds are chiral with 62% of them having two or more chiral centers (*cf.* Maybridge, 3%; MLP, 9% and ChEMBL, 22%). PCC compounds also have an increased 3D character, with 68% displaying Fsp^3 greater than 0.4 (*cf.* Maybridge, 15%; MLP, 29% and ChEMBL, 34%). This translates as a marked difference at a molecular-shape level. When the 3D conformations of the final compounds were analyzed using the molecular principal moments of inertia (PMI) [15] and plane of best fit (PBF) [16] methods (see the supplementary material online), PCC compounds demonstrated a significantly less flat and more globular ('sphere-like') shape compared with compounds in any of the databases evaluated in the present study (Fig. 2).

Scaffold level analysis

The PCC compounds originate from a total of 106 library proposals, yielding an average size of library of 521 compounds (Fig. 1). Each library proposal is normally defined by a scaffold, that is, a molecular template that is chemically modified in a systematic fashion at given positions (diversity points). Of the 106 unique PCC scaffolds, 73 (69%) contain at least three diversity points that have been derivatized during library production (Fig. 3). Most PCC scaffolds tend to be compact (80% with molecular weight <200 Da) and polar (70% with TPSA of 40–80 $Å^2$).

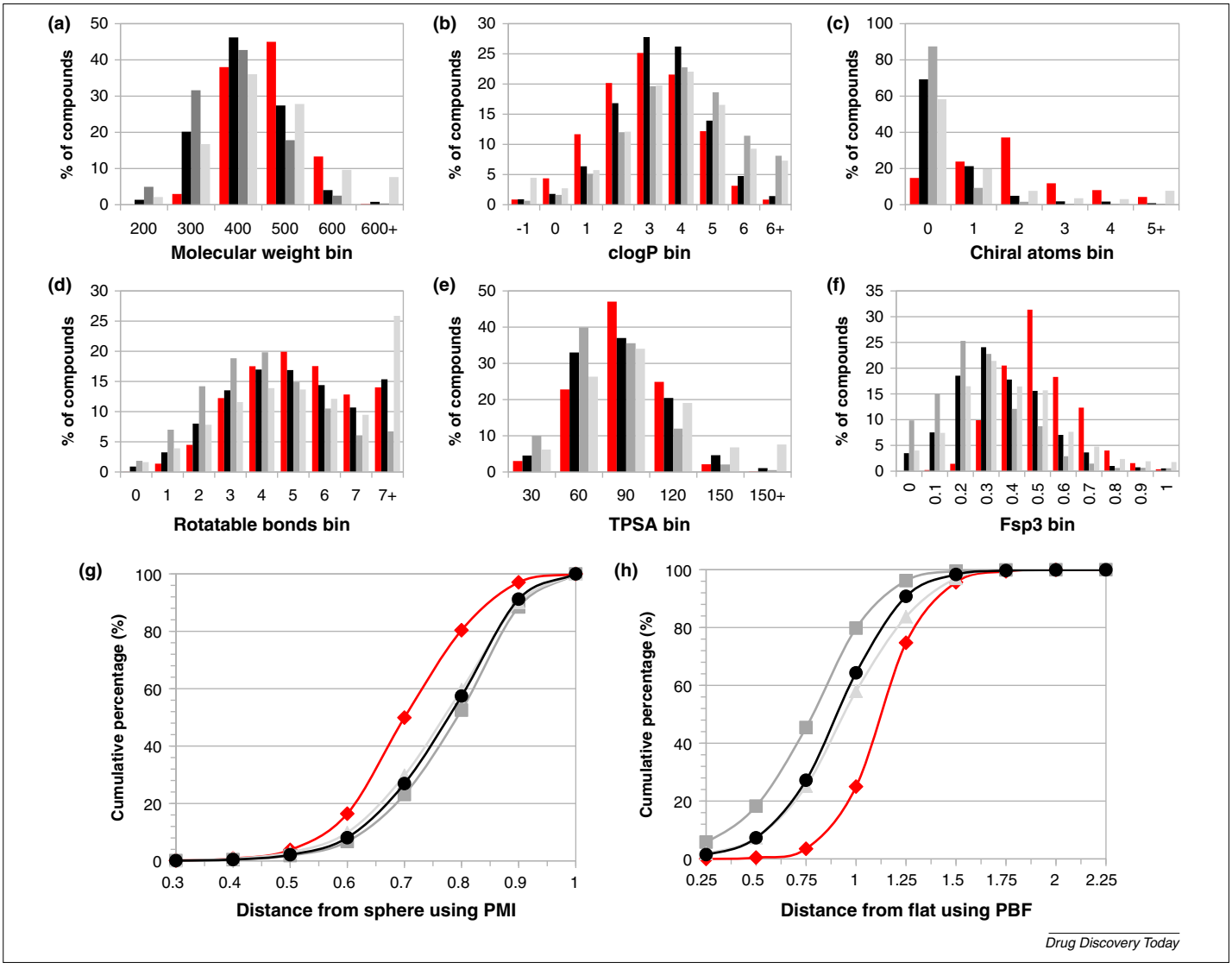

FIGURE 2

Comparitive inter-and intra-collection compound collection analysis. **(a)** Molecular weight, **(b)** calculated log *P* (*c* log *P*), **(c)** number of chiral centers, **(d)** number of rotatable bonds, **(e)** topological polar surface area (TPSA) and **(f)** fraction of sp^3-hybridized carbon atoms profiles for Public Compound Collection (PCC) (red bars), Molecular Library Program (MLP) (black bars), Maybridge (dark-gray bars) and ChEMBL (light-gray bars) compounds. Cumulative distributions of distances from canonical sphere **(g)** and flat **(h)** shapes using principal moments of inertia (PMI) and plane of best fit (PBF) descriptors, respectively, for PCC (red diamonds), MLP (black circles), Maybridge (dark-gray squares) and ChEMBL (light-gray triangles) compounds.

Furthermore, the carbon atoms in the PCC scaffolds are mostly sp^3 hybridized ($Fsp^3 > 0.4$ for 86% of the PCC library cores) and two or more chiral atoms are present in 70% of their structures, as shown in Fig. 3. The structural similarity among scaffolds is also low, with average and maximum Tanimoto coefficients of 0.09 and 0.5, respectively (Fig. 3f).

Framework level analysis

Bemis–Murcko [17] scaffold analysis (see the supplementary material online) was then used to evaluate the 2D shape and topology of the PCC compounds. These are described by a total of 366 unique frameworks. Overlap analysis of the frameworks across the different compound sets studied here indicated that only 27% of the PCC frameworks ($N = 99$) are shared across the PCC, Maybridge, NIH and ChEMBL collections. Interestingly, 56% of the PCC frameworks ($N = 204$) are unique, as detailed in Fig. 4.

Discussion

After an initial preparatory phase dedicated to recruitment, infrastructure set-up, workflow evaluation and trust building, the ELF chemistry consortium is now fully operational and actively working toward the goal of synthesizing circa 200,000 novel, attractive compounds for biochemical HTS purposes by the end of 2017. As of March 2015, this had resulted in the successful synthesis, purification and delivery of 54,831 final compounds to the ELF screening centers. As described here, the delivered samples are well suited for HTS applications, being available in sufficient quantities to allow up to 240 HTS campaigns to be executed without sample depletion and in outstanding chemical purity, thus reducing the occurrence of screening false positives and greatly simplifying results interpretation, deconvolution and decision making during hit evaluation.

The PCC compounds originate from a library-based approach where congeneric series of compounds are obtained through derivatization of a common scaffold. Selection of diversity reagents in the ELF aims at ensuring a good balance between the availability of related

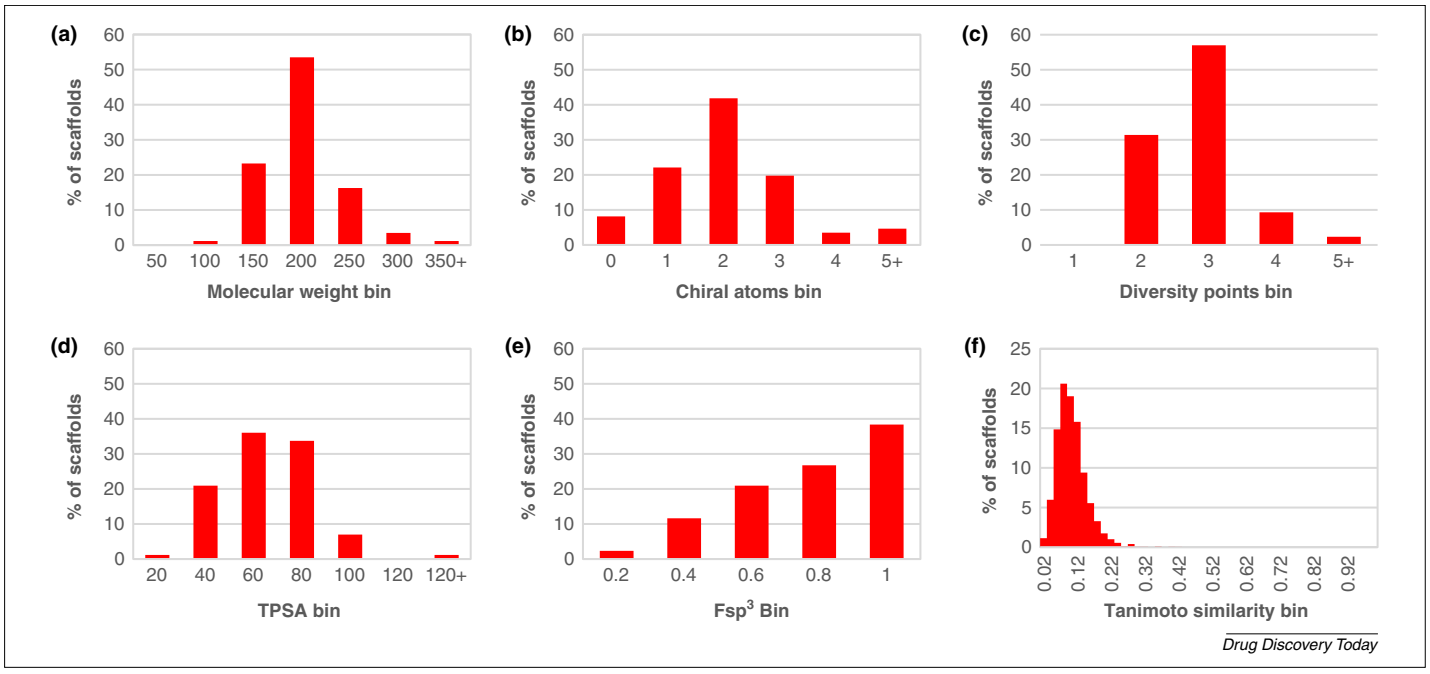

FIGURE 3

Phys. Chem. properties at the scaffold Level. **(a)** Molecular weight, **(b)** number of chiral atoms, **(c)** number of diversity points, **(d)** topological polar surface area (TPSA), **(e)** fraction of sp^3-hybridised carbon atoms and **(f)** ECFP6-based Tanimoto similarity profiles for Public Compound Collection (PCC) scaffolds ($N = 106$).

pairs of molecules to discern structure–activity relationships (SAR) during hit evaluation and wide sampling of chemical space. Accordingly, the PCC compounds have a low level of structural redundancy, as measured by nearest neighbor similarity, which is comparable to that observed in the Maybridge set, a diversity-based collection in the strictest sense. Importantly, this degree of structural dissimilarity at a final compound level is also observed at a scaffold level. All the library scaffolds synthesized thus far differ significantly from each other, and this further increases the structural diversity and chemical space coverage of the PCC set.

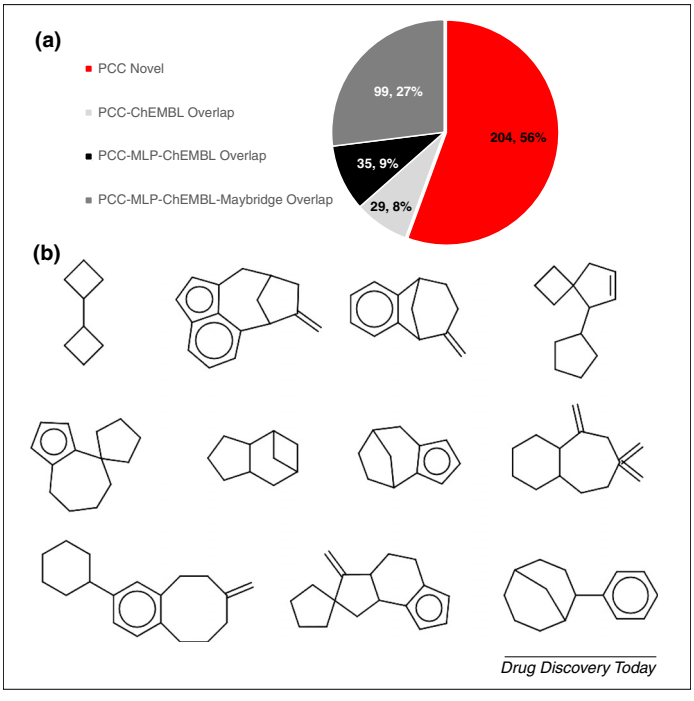

FIGURE 4

Bemis-Murcko Frameworks. **(a)** Number of Bemis–Murcko frameworks unique to the Public Compound Collection (PCC) and overlapping with the Maybridge, Molecular Library Program (MLP) and ChEMBL compound sets. **(b)** Representative selection of Bemis–Murcko frameworks unique to the PCC compounds. The Bemis–Murcko frameworks used in the current analysis do not regard atom types, and all heteroatoms have been mutated to carbons, to increase the focus on topological diversity rather than heteroatomic composition.

Although preferred extents of physicochemical properties in drug discovery applications are a matter of debate, these are monitored throughout the ELF process. As a result, the profile of the PCC compounds does not significantly deviate from commonly accepted properties trends in the field [14,18]. Here, a focus on maintaining a low lipophilicity character is evident because of its perceived importance in the subsequent hit development and lead optimization phases. This is especially important given that a significant portion (45%) of the PCC compounds have molecular weight of 400–500 Da. Some of these compounds are aiming at addressing challenging target classes (e.g. protein–protein interactions) with innovative chemotypes. Complex natural products have also been used as starting points for library design, thus intrinsically increasing the weight of the resulting compounds. In an effort to maximize the structural diversity of each library, the ELF consortium has been favoring designs with three or more diversification points, which has also yielded compounds with a modest increase in weight. Nevertheless, it is anticipated that reduced lipophilicity could also be beneficial in these higher molecular weight instances.

A distinctive characteristic of the synthesized PCC set is their high level of structural complexity and three-dimensionality, two features that are regarded as attractive in drug discovery application [19,20]. Given that most PCC compounds are chiral molecules with nonaromatic, nonplanar moieties and a strong propensity for a globular shape, their systematic screen against biological systems will prove useful in further understanding the general relevance of such compound characteristics, especially when confirmed hit rates, target class and developability considerations are taken into account. When comparing final compounds and scaffolds profiles, it is interesting to note that the polarity, structural complexity and 3D elements have been engineered in the scaffolds rather than deriving entirely from the subsequent chemical decoration. Given that the PCC scaffolds tend to be small, polar and chiral with a high 3D character, they provide versatile starting points and ample opportunities for further chemical exploration and growth during the hit-to-lead phase, based on the specific biological target and/or therapeutic area requirements.

A strong focus of the ELF chemistry consortium is to populate areas of chemical space that are not directly accessible from commercial sources or the scientific literature. Thus, no structural overlap with the Maybridge, MLP or ChEMBL databases is observed. Importantly, the similarity of the PCC compounds to any of the collections analyzed here is also limited, highlighting the complementary nature of the PCC compounds in terms of chemical space distribution. The high novelty attribute of the PCC compounds is also apparent when structural shape and topology is considered. A large proportion of the PCC frameworks are absent in the compound collections analyzed here. Indeed, a significant number of unprecedented spiro, bridged and fused polycycles with different degrees of saturation, conjugation and substitution have been synthesized and expanded to a library format. This has been recently exemplified by several publications from the ELF chemistry groups detailing the associated design and validation aspects [21–38]. Given that most theoretical ring systems remain unexplored [39], the synthesis of novel rings represents one of the strategies embraced by the ELF chemistry consortium to expand the available chemical space.

Concluding remarks

Given that large-scale screening continues to be a practical and productive entry to successful drug discovery [40,41], the availability of a novel, high-quality screening collection cannot be emphasized enough [42]. During the past year and a half of work, the ELF Chemistry Consortium has implemented an innovative compound library factory based on a collaborative approach between chemistry-focused academic groups and SMEs. This has resulted in an effective pooling of complementary ideas, solutions and resources to carry out high-risk chemistry research to explore unprecedented areas of chemical space that are relevant to biological screening. These efforts have yielded diverse and distinctive compounds that will properly complement existing public and proprietary compound collections for HTS drug discovery applications. Building on intersectoral, complementary strengths and expertise, this offers a practical blueprint for future compound collection enhancement campaigns in the everlasting quest for novel chemical space.

Acknowledgements

We thank Wolf Heidler for support with the PMI calculations. The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115489, resources of which comprise financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies' in-kind contribution.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drudis.2015.09.009.

References

1 Mullard, A. (2015) 2014 FDA drug approvals. *Nat. Rev. Drug Discov.* 14, 77–81
2 Williams, M. (2011) Productivity shortfalls in drug discovery: contributions from the preclinical sciences? *J. Pharmacol. Exp. Ther.* 336, 3–8
3 Khanna, I. (2012) Drug discovery in pharmaceutical industry: productivity challenges and trends. *Drug Discov. Today* 17, 1088–1102
4 Pammolli, F. *et al.* (2011) The productivity crisis in pharmaceutical R&D. *Nat. Rev. Drug Discov.* 10, 428–438
5 Paul, S.M. *et al.* (2010) How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat. Rev. Drug Discov.* 9, 203–214
6 Cumming, J.G. *et al.* (2014) Potential strategies for increasing drug-discovery productivity. *Future Med. Chem.* 6, 515–527
7 Morgan, P. *et al.* (2012) Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. *Drug Discov. Today* 17, 419–424
8 Munos, B. (2010) Can open-source drug R&D repower pharmaceutical innovation? *Clin. Pharmacol. Ther.* 87, 534–536
9 Mullard, A. (2013) European Lead Factory opens for business. *Nat. Rev. Drug Discov.* 12, 173–175
10 Besnard, J. *et al.* (2015) The Joint European Compound Library: boosting precompetitive research. *Drug Discov. Today* 20, 181–186
11 McCarthy, A. (2010) The NIH Molecular Libraries Program: identifying chemical probes for new medicines. *Chem. Biol.* 17, 549–550
12 Bento, A.P. *et al.* (2014) The ChEMBL bioactivity database: an update. *Nucleic Acids Res.* 42, D1083–D1090
13 Clemons, P.A. *et al.* (2011) Quantifying structure and performance diversity for sets of small molecules comprising small-molecule screening collections. *Proc. Natl. Acad. Sci. U. S. A.* 108, 6817–6822
14 Lipinski, C.A. (2004) Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discov. Today Technol.* 1, 337–341
15 Sauer, W.H.B. and Schwarz, M.K. (2003) Molecular shape diversity of combinatorial libraries: a prerequisite for broad bioactivity. *J. Chem. Inf. Comput. Sci.* 43, 987–1003
16 Firth, N.C. *et al.* (2012) Plane of best fit: a novel method to characterize the three-dimensionality of molecules. *J. Chem. Inf. Model.* 52, 2516–2525
17 Bemis, G.W. and Murcko, M.A. (1996) The properties of known drugs. 1. Molecular frameworks. *J. Med. Chem.* 39, 2887–2893
18 Teague, S.J. *et al.* (1999) The design of leadlike combinatorial libraries. *Angew. Chem. Int. Ed Engl.* 38, 3743–3748
19 Lovering, F. *et al.* (2009) Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* 52, 6752–6756
20 Harvey, A.L. *et al.* (2015) The re-emergence of natural products for drug discovery in the genomics era. *Nat. Rev. Drug Discov.* 14, 111–129
21 Craven, P. *et al.* (2015) Design, synthesis and decoration of molecular scaffolds for exploitation in the production of alkaloid-like libraries. *Bioorg. Med. Chem.* 23, 2629–2635
22 Murali, A. *et al.* (2015) Branching cascades provide access to two amino-oxazoline compound libraries. *Bioorg. Med. Chem.* 23, 2656–2665
23 Sankar, M.G. *et al.* (2015) Stereoselective synthesis of a natural product inspired tetrahydroindolo[2,3-a]-quinolizine compound library. *Bioorg. Med. Chem.* 23, 2614–2620
24 Petersen, R. *et al.* (2015) Synthesis of hexahydropyrrolo[2,1-a]isoquinoline compound libraries through a Pictet–Spengler cyclization/metal-catalysed cross coupling/amidation sequence. *Bioorg. Med. Chem.* 23, 2646–2649
25 Padwal, J. *et al.* (2015) Cyclopentitol as a scaffold for a natural product-like compound library for drug discovery. *Bioorg. Med. Chem.* 23, 2650–2655
26 Van der Pijl, F. *et al.* (2015) Synthesis and functionalization of bicyclic N,O-acetal scaffolds from furfural. *Bioorg. Med. Chem.* 23, 2721–2729
27 Storr, T.E. *et al.* (2015) Combining two-directional synthesis and tandem reactions, Part 21: Exploitation of a dimeric macrocycle for chain terminus differentiation and synthesis of an sp^3-rich library. *Bioorg. Med. Chem.* 23, 2621–2628
28 Nortcliffe, A. and Moody, C.J. (2015) Seven-membered ring scaffolds for drug discovery: access to functionalised azepanes and oxepanes through diazocarbonyl chemistry. *Bioorg. Med. Chem.* 23, 2730–2735
29 Petersen, M.Å. *et al.* (2015) Synthesis of 1,4,5 trisubstituted γ-lactams via a 3-component cascade reaction. *Bioorg. Med. Chem.* 23, 2695–2698

30 Nickel, S. *et al.* (2015) Synthesis of a hexahydropyrrolo indole (HPI) compound library. *Bioorg. Med. Chem.* 23, 2636–2645
31 Patil, P. *et al.* (2015) MCR synthesis of a tetracyclic tetrazole scaffold. *Bioorg. Med. Chem.* 23, 2699–2715
32 Ortega, R. *et al.* (2015) Design and synthesis of 1,1-disubstituted-1-silacycloalkane-based compound libraries. *Bioorg. Med. Chem.* 23, 2716–2720
33 Neochoritis, C.G. *et al.* (2015) Leuckart–Wallach route toward isocyanides and some applications. *ACS Comb. Sci.* http://dx.doi.org/10.1021/acscombsci.5b00066 (published online 10.08.15)
34 Neochoritis, C.G. *et al.* (2015) Efficient isocyanide-less isocyanide-based multicomponent reactions. *Org. Lett.* 17, 2002–2005
35 Foley, D.J. *et al.* (2015) A systematic approach to diverse, lead-like scaffolds from α,α-disubstituted amino acids. *Chem. Commun. Camb. Engl.* 51, 11174–11177
36 Doveston, R.G. *et al.* (2015) A unified lead-oriented synthesis of over fifty molecular scaffolds. *Org. Biomol. Chem.* 13, 859–865
37 Colomer, I. *et al.* (2015) Aminomethylhydroxylation of alkenes: exploitation in the synthesis of scaffolds for small molecule libraries. *Bioorg. Med. Chem.* 23, 2736–2740
38 Firth, J. *et al.* (2015) Exploitation of the Ugi–Joullié reaction in the synthesis of libraries of drug-like bicyclic hydantoins. *Synthesis* 47, 2391–2406
39 Lipkus, A.H. *et al.* (2008) Structural diversity of organic chemistry. A scaffold analysis of the CAS Registry. *J. Org. Chem.* 73, 4443–4451
40 Eder, J. *et al.* (2014) The discovery of first-in-class drugs: origins and evolution. *Nat. Rev. Drug Discov.* 13, 577–587
41 Moffat, J.G. *et al.* (2014) Phenotypic screening in cancer drug discovery: past, present and future. *Nat. Rev. Drug Discov.* 13, 588–602
42 Wigglesworth, M.J. *et al.* (2015) Increasing the delivery of next generation therapeutics from high throughput screening libraries. *Curr. Opin. Chem. Biol.* 26, 104–110

Anna Karawajczyk[1]
Fabrizio Giordanetto[1]
Jorg Benningshof[2]
Daniel Hamza[3]
Tuomo Kalliokoski[4]
Kees Pouwer[5]
Remy Morgentin[6]
Adam Nelson[7,8]
Gerhard Müller[2]
Alexander Piechot[1]
Dimitrios Tzalis[1,*]

[1]*Taros Chemicals GmbH & Co. KG, Emil-Figge-Str. 76a, 44227 Dortmund, Germany*
[2]*Mercachem, Kerkenbos 1013, 6546 BB Nijmegen, The Netherlands*
[3]*Sygnature Discovery, BioCity, Nottingham NG1 1GF, UK*
[4]*Lead Discovery Center GmbH, Otto-Hahn-Strabe 15, 44227 Dortmund, Germany*
[5]*Syncom BV, Kadijk 3, 9747 AT Groningen, The Netherlands*
[6]*Edelris, 115, Avenue Lacassagne, F-69003 Lyon, France*
[7]*School of Chemistry, University of Leeds, Leeds LS2 9JT, UK*
[8]*Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds LS2 9JT, UK*

**Corresponding author*: