The most common linkers in bioactive molecules and their bioisosteric replacement network

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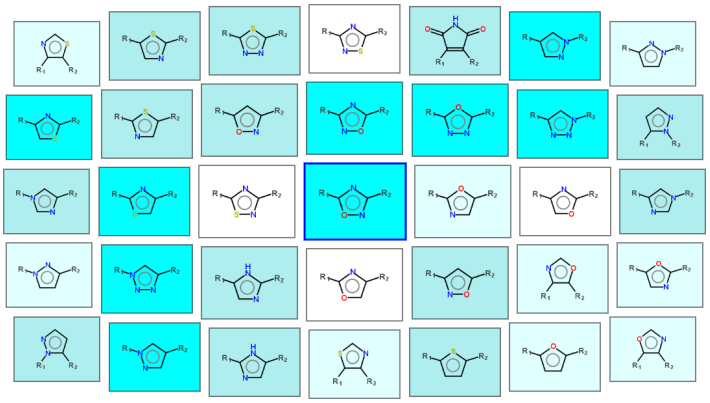
Abstract



Structures of the large majority of bioactive molecules are composed of several rings that are decorated by substituents and connected by linkers. While numerous cheminformatics studies focusing on rings and substituents are available, practically nothing has been published about the third important structural constituent of bioactive molecules - the linkers. The current study attempts to fill this gap. The most common linkers present in bioactive molecules are identified, their properties analyzed and a method for linker similarity search introduced. The bioisosteric replacement network of linkers is generated based on a large corpus of structure-activity data from medicinal chemistry literature.The results are presented in a graphical form and the underlying data are also made available for download. This analysis is intended to help medicinal chemists to better understand the role of linkers in bioactive molecules and to select an optimal set of linkers in their future project.

Keywords
cheminformatics, bioisosteric design, substructure analysis, linkers, medicinal chemistry

1. Introduction

The linkers, sometimes also called spacers, i.e. sets of atoms connecting 2 parts of a molecule together, play an important role in many areas of synthetic and medicinal chemistry. Many common linkers, for example amides, esters or amines are created by well established standard reactions used very often in medicinal chemistry (see more detailed discussion later). Some oxygen-containing linkers, like ethers, ketones or esters are used in synthesis of natural product-like molecules.[1,2] In fragment-based drug discovery tailored linkers are used to connect two fragments that have been identified to bind to the target protein.[3] This strategy is particularly important for more challenging targets with extended binding sites.[4] The selection of linkers is also important in connecting the reactive part of the molecule with the actual binding part in several so-called new modalities strategies,[5,6] including covalent drug discovery, bisubstrate inhibitors, targeted protein degradation and stabilization or antibody-drug conjugates.[7] Identification of an optimal collection of bifunctional building blocks, forming the central linkers of synthesized molecules, plays a crucial role in the design of combinatorial libraries and more recently of DNA-encoded libraries.[8] All these examples show that a good knowledge about linkers, their properties and selection strategies is indeed crucially needed in the drug discovery process.

While numerous studies are available about rings[9,10] and substituents[11,12] present in bioactive molecules, essentially nothing has been published about their third important structural constituent - the linkers. The present analysis attempts to fill this gap. We hope that the results will help medicinal chemists to better understand the roles of linkers commonly present in bioactive molecules and easily navigate their bioisosteric replacement network.

2. Methodology

2.1. Generation of the linker database

In medicinal chemistry the term linker is generally used to describe a part of the molecule that connects its other two parts together. This is a very broad description and for the purpose of this study we will use a more restricted definition of the linker. First of all, only the moieties that connect 2 ring systems are considered to be linkers, so the R atoms shown in the linker depictions below are ring atoms. We also introduced limits on the linker size, to restrict the linker space to only more common systems. The maximum size of linkers processed in this study was set to 8 non-hydrogen atoms and the maximal topological length (i.e. the number of bonds separating the 2 R atoms) limited to 5, which corresponds for example to a 1,4-substituted phenyl ring. Additionally, atoms in such longer linkers could be only part of a ring or a multiple bonded functional group, preventing many less-interesting linkers consisting of long flexible chains. Another restriction was that the linkers cannot contain side chains with 2 or more atoms. These rules were applied to extract linkers from 2 large molecular databases - ChEMBL[13] and ZINC.[14] ChEMBL is an indispensable resource for medicinal chemists and cheminformaticians alike, containing in its 31st release information about 2.3 million molecules, 15 thousand targets and 19.8 million bioactivity data points extracted from 85 thousand documents, mostly articles in medicinal chemistry journals. ZINC is a popular database containing offerings from a large number of commercial vendors. We extracted linkers from the "on the shelf" subset of the ZINC database, containing about 12 million molecules and representing well the commercially available drug-like chemical space.

Despite the rather strict limitations on the linker size and the structural features described above, the database analysis provided 926 linkers from the ChEMBL database and 1467 from the ZINC collection, yielding altogether 1686 unique linkers that formed the basis of the current study. Structures of the 40 most frequent linkers present in the bioactive molecules in the ChEMBL database are shown in Figure 1. As mentioned previously, these linkers connect together 2 rings. The types of these rings are, however, very diverse, including aliphatic and aromatic rings, pure carbon cycles and heterocycles. Also the connecting atom may be carbon or a heteroatom (mostly nitrogen). To illustrate this the most common ring environments for the 8 common liners are shown in Figure 2. This environment can provide information on how the particular linkers were synthetically accessed.

2.2. Calculation of linker properties

To process the linkers computationally and to develop a procedure for similarity calculation, it is of course necessary to characterize the likers numerically by a suitable set of calculated descriptors. A very large number of descriptors can be used, but it is of advantage that the descriptors should have clear physical meaning and be fast to calculate to enable processing of a large number of molecules. For this study we selected a set of simple topological descriptors including the number of non-hydrogen atoms, the topological length (number of bonds separating the 2 R atoms) and the number of heteroatoms in the linker, where the oxygen and nitrogen atoms contributed by 1 and other heteroatoms (not counting halogenes) by 0.5. Very important linker characteristics are their electronic properties, i.e. donating or accepting power at the linker ends. These were characterized by the calculated Hammett sigma constants. The methodology to calculate these parameters is fully described in[15] with the web tool allowing their calculations on-line being also available,[16] therefore here only a brief description is provided. To both ends of the linker phenyl groups were added, then the geometry of the system was fully optimized and atomic charges on both phenyls calculated using the xtb quantum chemical package.[17] These charges were used to calculate the Hammett sigma parameters using the model derived previously for a training set of substituents with experimentally known Hammett sigma constants. Since for the unsymmetrical linkers one needs to consider both possible linker orientations (the most common example being amide and inverse amide) the final database of linkers with calculated properties used for the follow-up studies contained 2972 entries. This dataset may be downloaded as Supporting Information.

2.3. Identification of the bioisosteric linkers

In order to identify the bioisosteric linkers, i.e. the linker pairs that after their exchange preserve bioactivity of the parent molecule, a large-scale cheminformatic analysis of the bioactivity data from ChEMBL was performed. The SAR information used for this analysis was extracted from compound series published in medicinal chemistry journals. A series had to contain at least 3 molecules reported in the same publication with bioactivity less than 10 μM on the same target measured by the same methodology (i.e. the same ChEMBL assay id). All targets, with exception of the known non-specific anti-targets (the hERG potassium ion channel and binding to Cytochromes P450), were considered. This analysis provided 60454 series with the average size of 16 molecules. The sets of analogous linkers were extracted from these series. All molecules in a series were pairwise compared and in the case that the 2 molecules differed only in central linkers with the rests on both sides being identical, this linker pair was collected. Only the replacements reported in at least 2 literature sources were retained, singletons were not considered. At the end the final data set used for the analysis contained 11600 unique replacements.

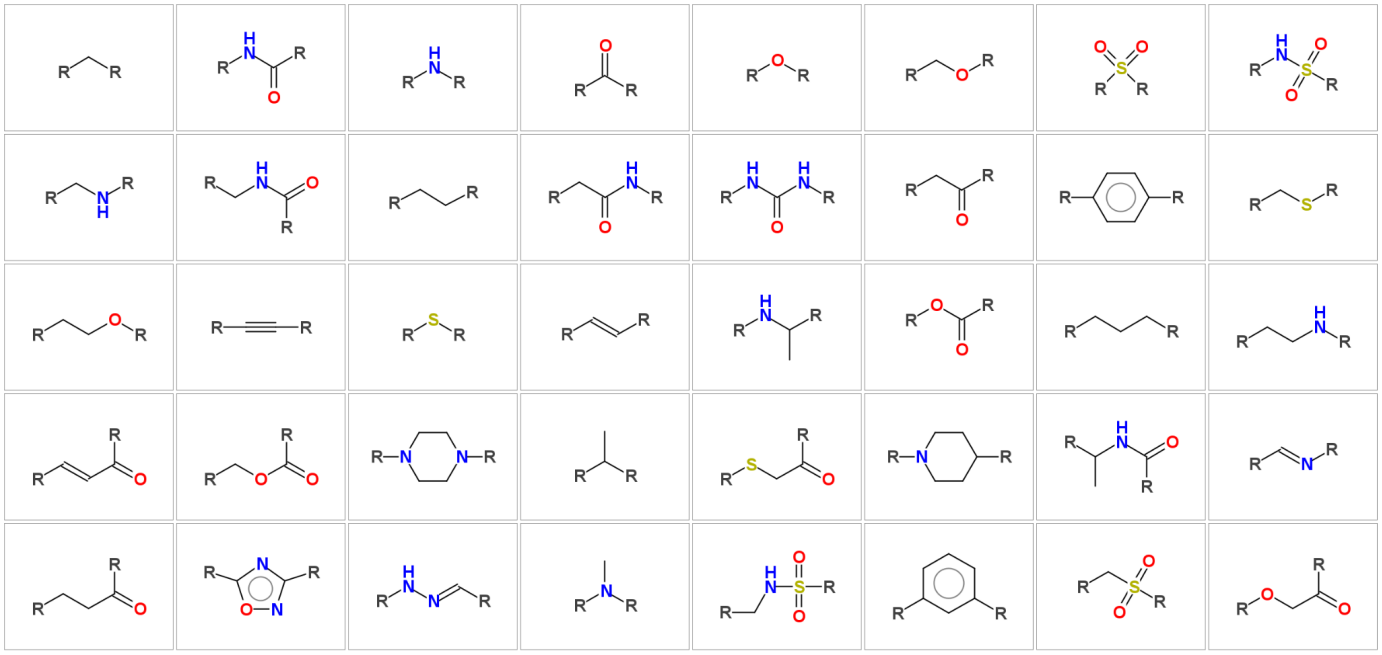


Figure 1. The most common linkers present in bioactive molecules.

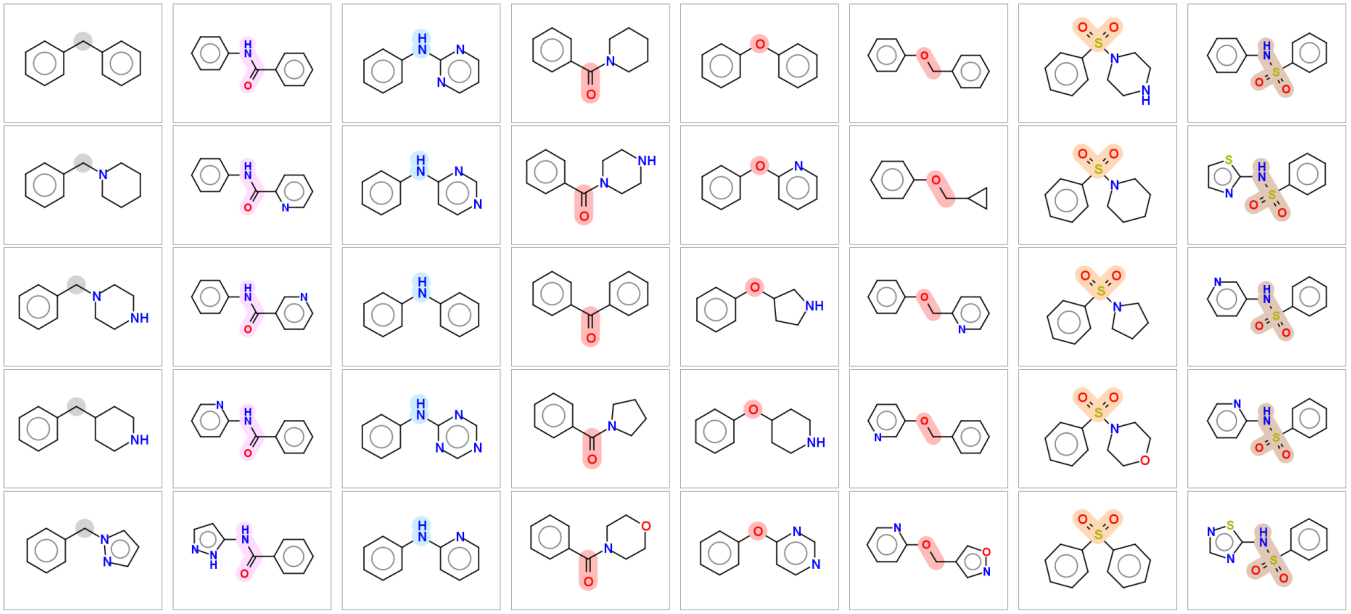


Figure 2. The most frequent ring substituents for the 8 most common linkers.

3. Results and discussion

3.1. Linkers in bioactive molecules

The most common linker connecting two rings present in bioactive molecules is a simple methylene group. This linker is readily synthetically accessible by a Stille or Negishi coupling or the reaction of a Grignard reagent from aryl bromides or of the corresponding lithium bromide intermediate with aryl- or heteroaryl aldehydes to furnish carbinols which are subsequently hydrogenated (reduced) to provide the diarylmethanes[18] or by a Suzuki-coupling of benzylic bromides with aryl or heteroaryl boronic acids.[19] Also hydrocarbon linkers containing a carbon-carbon double or triple bond are common. The acetylene moiety is relatively easily introduced using a Sonogashira coupling, which is the 2nd most frequently used carbon-carbon forming reaction after the Suzuki coupling.[20] The acetylene is a privileged structural motif for targeting many important proteins,[21] for example as a linker incorporated very successfully in kinase inhibitors.[22,23] A range of synthetic strategies are available for the preparation of derivatives incorporating alkene linkers. Forming a C=C bond is frequently achieved by reduction of acetylenes with Lindlar`s catalyst or through Wittig olefination by the reaction of phosphonate esters with aldehydes in the presence of NaH. Alternatively alkenes are synthetically easily accessible with a palladium-catalyzed cross coupling by a Heck reaction.[24]

The second most common linker is an amide, the functionality that is also incorporated in 3 other spacer moieties shown in Figure 1. Several studies have shown that amide coupling is indeed the most popular reaction used in medicinal chemistry projects as well as in patents.[25,26] This very reliable and well established reaction can rely on a large number of amide coupling reagents and a large number and diversity of commercially available carboxylic acid and amine building blocks which enable the synthesis of a vast number of products. The same applies also for the closely related linkers - ureas and sulfonamides. The popularity of sulfonamide linkers in medicinal chemistry has been growing in recent years.[27]

Oxygen-containing linkers are typical spacers present in natural products[28] and therefore this type of tether is often used in the synthesis of pseudo-natural products.[1,2] Ether linkers are generally accessed via palladium coupling of phenols[29,30] or can also be synthesized in a metal free manner using diaryliodonium salt.[31] While esters are generally obtained via standard esterification or transesterification, however, they can also be obtained through nickel activation of amides.[32] Diaryl ketones are often synthesized via aryl Grignard addition to Weinreb amides, but in the last years there is an emergence of metal catalyzed reactions such as Palladium CH activation of aldehydes,[33] Ni or Pd-catalyzed Suzuki of amides. (Weires, Baker, and Garg 2016) The nitrogen containing linkers in the list are prepared by several reactions that belong to the essential medicinal chemistry toolbox - e.g. reductive aminations, SN2 reactions, Buchwald-Hartwig and Chan-Lam couplings and several others.[20,25]

There are only 3 aromatic rings among the most common linkers shown in Figure 1. The 1,3- and 1,4-substituted phenyl rings and the 1,2,4-oxadiazole as a single representative of aromatic heterocycles (although many interesting 5-membered heterocycles follow just after the top 40 linkers). These will be discussed in the following section.

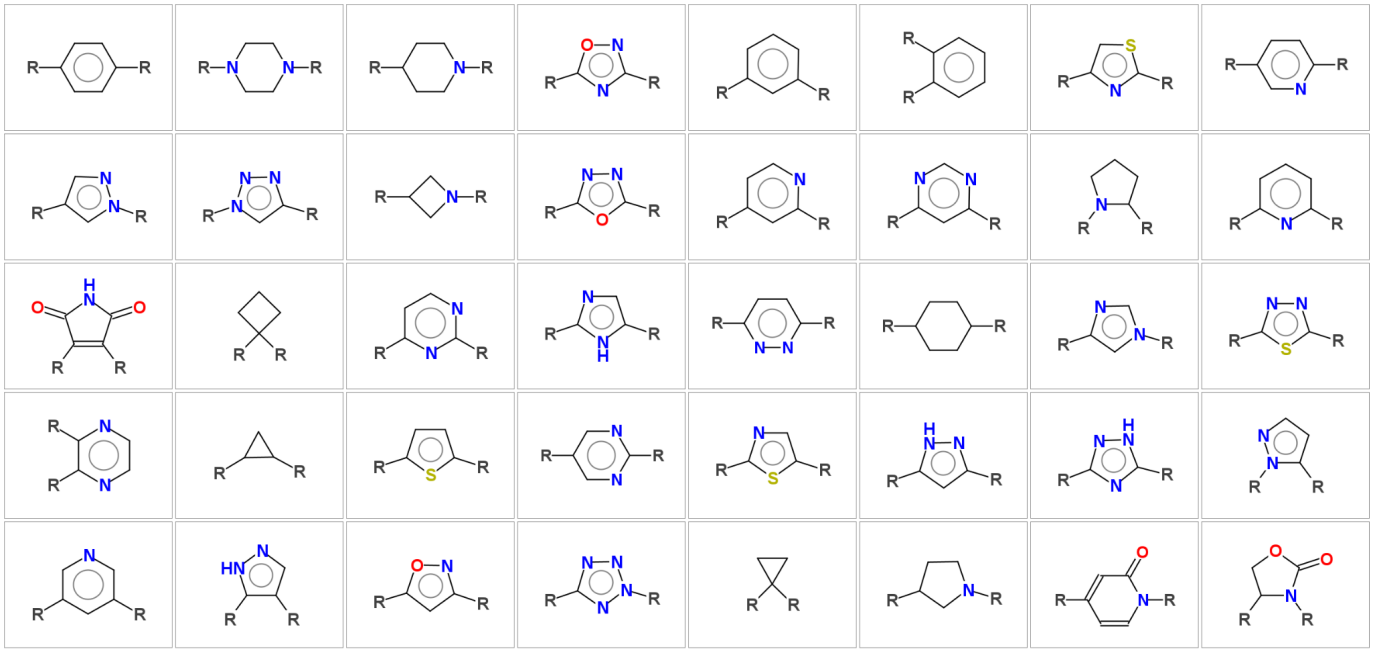


Figure 3. The most common ring linkers present in bioactive molecules.

Ring linkers are particularly important in medicinal chemistry. Rings provide several advantages compared to flexible linear linkers, particularly higher conformational rigidity and a predictable molecular shape. The most common cyclic spacers present in bioactive molecules (considering the size restriction introduced in the methodology part) are shown in Figure 3. 30 out of the 40 ring linkers shown here are aromatic. This is not surprising, aromatic rings are easily introduced synthetically and a very large number of available building blocks of this type can accommodate practically any pharmacophore requirements. Substituted phenyl and heteroaryl rings allow exploration of different vectors without introducing stereocenters. On the other hand, one needs to be cautious, because a larger number of aromatic rings in a molecule negatively impacts the properties and the developability of compounds.[34] The phenyl ring with 3 types of connectivity (1,4-, 1,3- and 1,2-) is the most common aromatic ring linker. It is an ideal linker from the synthetic point of view due to availability of a very large and diverse collection of substituted benzene-based building blocks and the straightforward synthesis of aryl-aryl systems via Suzuki coupling. The disadvantage of phenyl ring is its high hydrophobicity, which negatively affects molecular properties like solubility, plasma protein binding and metabolic stability which makes identification of phenyl bioisosteres highly relevant.[35] The nitrogen-containing 6-membered aromatic heterocycles (pyridine, pyrimidine and pyrazine) share the above mentioned advantages of benzene derivatives, while providing better properties.[36] Another advantage of electron rich nitrogen heterocycles is that they can act as substrates for the SnAr reaction, which is frequently used in the synthesis of bioactive molecules. 5-membered aromatic heterocycles are represented with 17 members in the list of common ring linkers, which clearly demonstrates their usefulness as building blocks for synthesis of bioactive molecules. The importance of oxadiazoles, oxazoles and isoxazoles in medicinal chemistry is discussed in several reviews.[37–39] The pyrazole, also a very important constituent of bioactive molecules[40,41] is presented in the list by 4 different substitution patterns. The high frequency of triazole linkers may be explained by its easy synthesis by click reaction, a very versatile synthetic method enabling the preparation of very diverse molecules by mild conditions.[42]

The most common aliphatic ring linkers are cyclic amines - piperazine, piperidine, pyrrolidine and azetidine - classical medicinal chemistry building blocks.[20] Also few aliphatic hydrocarbons, including cyclobutane and 2 connection forms of cyclopropane are in the list of the most common ring linkers. This type of small aliphatic rings have been increasingly exploited in medicinal chemistry as a means to introduce 3-dimensionality into the molecule, for their beneficial physicochemical properties and applications as functional group bioisosteres.[43]

3.2. Linker bioisosteric network

The collection of bioisosteric linker pairs generated as described in the methodology section above was used to develop a model for the estimation of linker similarity. In fact a formula for the linker distance (what is an opposite to similarity) was developed. The distance of 2 linkers was calculated as the sum of squared differences between their descriptors. The weights of the descriptor contributions were optimized to provide the best recovery of the 20 best known analogs for the 100 most common linkers, picked out of the whole dataset of 2972 linkers. The optimization procedure yielded the following weights of linker descriptors: difference in number of atoms 0.75, in topological length 0.19, in number of heteroatoms 0.41 and in the sigma parameters 3.23. During the optimization process we noticed that the similarity searching considering only the structural and physicochemical descriptors provides many hits, that although being closely similar in properties to the query, are quite exotic, present only few times or even only as singletons in the database. To get the result close to the bioisosteres reported in the literature also experimental factors like their stability or ease of synthesis apparently must be considered. The results improved considerably when also the frequency of the linkers in the ChEMBL and ZINC databases were taken into account. We used this frequency in the form of log10(percentage of molecules having this linker in the whole database) and the identified optimal weight for this parameter was -0.73.
The distance between linker L_x and the query linker L_q may be then calculated as:

$$\text{distance} = \sum (w_i * (L_q p_i - L_x p_i) ** 2) - 0.73 * \log10(\%\text{frequency } L_x) \quad \text{(Eq. 1)}$$

where $L_x p_i$ is the property i of linker L_x and the w_i is the weight (contribution) of the property p_i. The last parameter in the equation favors the more "common" replacements and reflects their easier synthetic accessibility, availability of building blocks, stability and similar experimental effects. It is up users to include also this weighting and get suggested bioisosteres close to those reported in the literature, or to perform similarity searches based on the property descriptors only and get a diverse set of hits closely similar in properties, but at the price of including also many exotic, and possibly unstable structures that would require more thorough manual filtering.

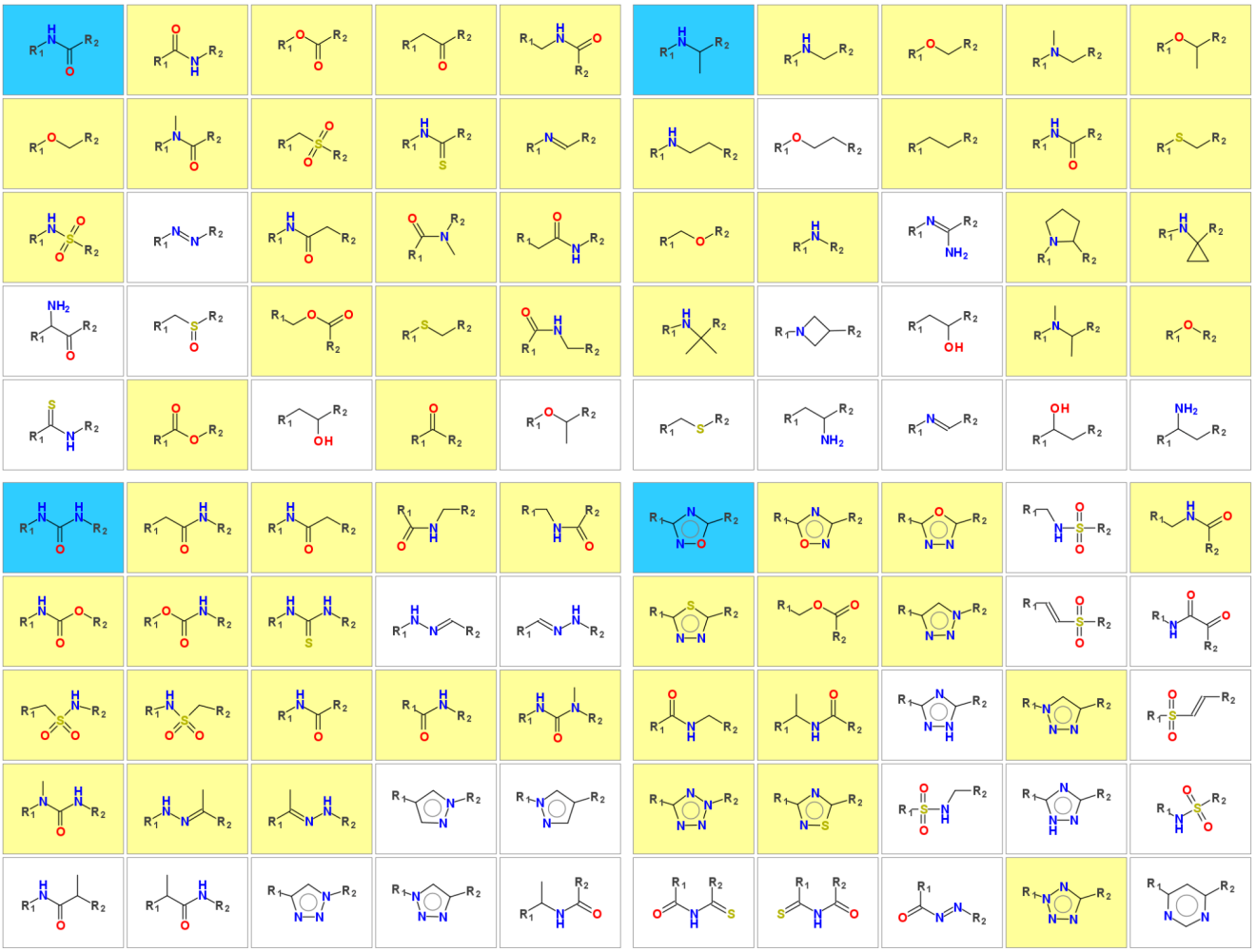


Figure 4. Example of linkers identified by the linker similarity search. The query linkers have blue background and the linkers that are among the 20 closest analogs based on the ChEMBL data are marked by yellow background.

With a large collection of linkers characterized by calculated properties and the procedure to estimate their similarity it is now possible to analyze the multidimensional bioisosteric replacement network. In Figure 5 the 150 most common linkers are placed in the 10 x 15 grid in such a manner, that the similarity between the neighboring linkers in the grid is maximized. The layout was obtained by an iterative optimization procedure where the initial position of linkers in the grid was selected based on the results of principal component analysis and then in a loop pairs of linkers were exchanged until no more improvement could be achieved. This procedure was repeated several times with different starting random seeds with the best result shown in Figure 5. This image illustrates the 2-dimensional bioisosteric linker replacement network. We believe that the depicted linker network is close to the way experienced medicinal chemists think, their many years of chemistry experience created a similar relationship between molecular substructures / linkers in their brains. The network depicted in Figure 5 is a generalization of such experience, since it was created using the bioactivity data from about 60 thousand publications summarizing results of more than 30 years of global medicinal chemistry research around the world.

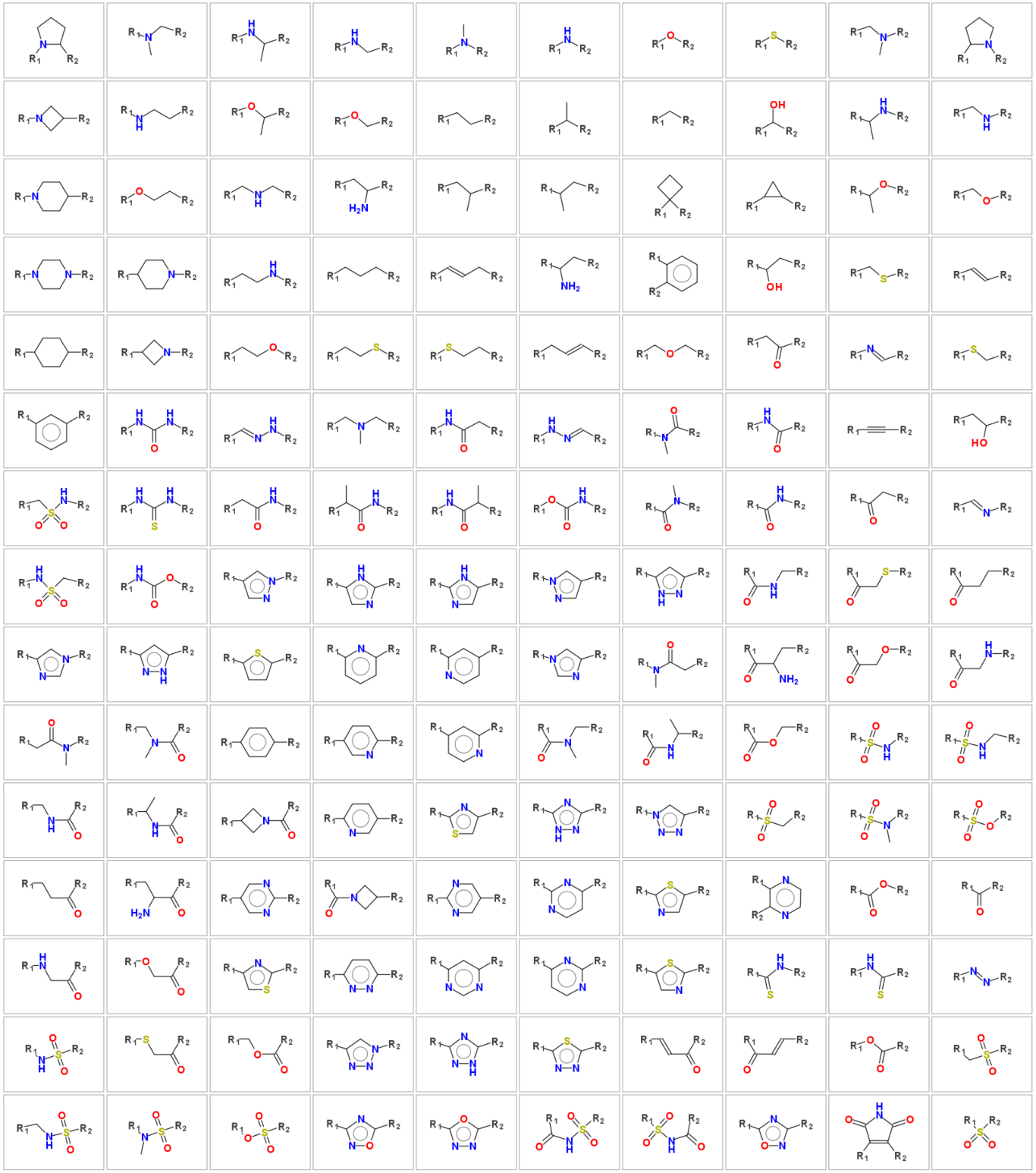


Figure 5. The bioisosteric replacement network of the 150 most common linkers.

4. Conclusions

The analysis of linkers present in bioactive molecules and their bioisosteric compatibility based on the data from medicinal chemistry literature allowed us to develop a method for linker similarity search and apply this method to create a linker bioisosteric network. The results, as well as the underlying data that are available for download are provided with the hope that they can help chemists to better understand the relationship between linkers, make rational decisions in selecting spacers in their project and ultimately make the quest for novel bioactive molecules slightly more efficient.

Data availability

The set of 2972 linkers with calculated properties used in this study is provided as Supporting Information.

References

1. Foley DJ, Waldmann H. Ketones as strategic building blocks for the synthesis of natural product-inspired compounds. *Chem Soc Rev*. 2022;51(10):4094-4120. doi:10.1039/D2CS00101B
2. Karageorgis G, Foley DJ, Laraia L, Waldmann H. Principle and design of pseudo-natural products. *Nat Chem*. 2020;12(3):227-235. doi:10.1038/s41557-019-0411-x
3. Erlanson DA, Fesik SW, Hubbard RE, Jahnke W, Jhoti H. Twenty years on: the impact of fragments on drug discovery. *Nat Rev Drug Discov*. 2016;15(9):605-619. doi:10.1038/nrd.2016.109
4. Ward RA, Brassington C, Breeze AL, et al. Design and Synthesis of Novel Lactate Dehydrogenase A Inhibitors by Fragment-Based Lead Generation. *J Med Chem*. 2012;55(7):3285-3306. doi:10.1021/jm201734r
5. Wu G, Zhao T, Kang D, et al. Overview of Recent Strategic Advances in Medicinal Chemistry. *J Med Chem*. 2019;62(21):9375-9414. doi:10.1021/acs.jmedchem.9b00359
6. Valeur E, Guéret SM, Adihou H, et al. New Modalities for Challenging Targets in Drug Discovery. *Angew Chem Int Ed*. 2017;56(35):10294-10323. doi:10.1002/anie.201611914
7. Yang X, Pan Z, Choudhury MR, et al. Making smart drugs smarter: The importance of linker chemistry in targeted drug delivery. *Med Res Rev*. 2020;40(6):2682-2713. doi:10.1002/med.21720
8. Goodnow RA, Dumelin CE, Keefe AD. DNA-encoded chemistry: enabling the deeper sampling of chemical space. *Nat Rev Drug Discov*. 2017;16(2):131-147. doi:10.1038/nrd.2016.213
9. Ertl P. Magic Rings: Navigation in the Ring Chemical Space Guided by the Bioactive Rings. *J Chem Inf Model*. 2022;62(9):2164-2170. doi:10.1021/acs.jcim.1c00761
10. Ertl P, Altmann E, Racine S, Lewis R. Ring replacement recommender: Ring modifications for improving biological activity. *Eur J Med Chem*. 2022;238:114483. doi:10.1016/j.ejmech.2022.114483
11. Takeuchi K, Kunimoto R, Bajorath J. Systematic mapping of R-group space enables the generation of an R-group replacement system for medicinal chemistry. *Eur J Med Chem*. 2021;225:113771. doi:10.1016/j.ejmech.2021.113771
12. Ertl P. Cheminformatics Analysis of Organic Substituents: Identification of the Most Common Substituents, Calculation of Substituent Properties, and Automatic Identification of Drug-like Bioisosteric Groups. *J Chem Inf Comput Sci*. 2003;43(2):374-380. doi:10.1021/ci0255782
13. Mendez D, Gaulton A, Bento AP, et al. ChEMBL: towards direct deposition of bioassay data. *Nucleic Acids Res*. 2019;47(D1):D930-D940. doi:10.1093/nar/gky1075
14. Irwin JJ, Tang KG, Young J, et al. ZINC20—A Free Ultralarge-Scale Chemical Database for Ligand Discovery. *J Chem Inf Model*. 2020;60(12):6065-6073. doi:10.1021/acs.jcim.0c00675
15. Ertl P. A Web Tool for Calculating Substituent Descriptors Compatible with Hammett Sigma Constants**. *Chemistry–Methods*. :e202200041. doi:10.1002/cmtd.202200041
16. Ertl P. Calculation of Substituent Properties. Accessed September 1, 2022. https://peter-ertl.com/molecular/substituents/sigmas.html
17. Bannwarth C, Ehlert S, Grimme S. GFN2-xTB—An Accurate and Broadly Parametrized Self-Consistent Tight-Binding Quantum Chemical Method with Multipole Electrostatics and Density-Dependent Dispersion Contributions. *J Chem Theory Comput*. 2019;15(3):1652-1671. doi:10.1021/acs.jctc.8b01176
18. Mondal S, Panda G. Synthetic methodologies of achiral diarylmethanols, diaryl and triarylmethanes (TRAMs) and medicinal properties of diaryl and triarylmethanes-an overview. *RSC Adv*. 2014;4(54):28317-28358. doi:10.1039/C4RA01341G
19. Burns MJ, Fairlamb IJS, Kapdi AR, Sehnal P, Taylor RJK. Simple Palladium(II) Precatalyst for Suzuki−Miyaura Couplings: Efficient Reactions of Benzylic, Aryl, Heteroaryl, and Vinyl Coupling Partners. *Org Lett*. 2007;9(26):5397-5400. doi:10.1021/ol702291r
20. Roughley SD, Jordan AM. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J Med Chem*. Published online 2011:29.
21. Talele TT. Acetylene Group, Friend or Foe in Medicinal Chemistry. *J Med Chem*. 2020;63(11):5625-5663. doi:10.1021/acs.jmedchem.9b01617
22. Liu X, Kung A, Malinoski B, Prakash GKS, Zhang C. Development of Alkyne-Containing Pyrazolopyrimidines To Overcome Drug Resistance of Bcr-Abl Kinase. *J Med Chem*. 2015;58(23):9228-9237. doi:10.1021/acs.jmedchem.5b01125
23. Kaitsiotou H, Keul M, Hardick J, et al. Inhibitors to Overcome Secondary Mutations in the Stem Cell Factor Receptor KIT. *J Med Chem*. 2017;60(21):8801-8815. doi:10.1021/acs.jmedchem.7b00841
24. Jagtap S. Heck Reaction—State of the Art. *Catalysts*. 2017;7(9):267. doi:10.3390/catal7090267
25. Brown DG, Boström J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone?: Miniperspective. *J Med Chem*. 2016;59(10):4443-4458. doi:10.1021/acs.jmedchem.5b01409
26. Schneider N, Lowe DM, Sayle RA, Tarselli MA, Landrum GA. Big Data from Pharmaceutical Patents: A Computational Analysis of Medicinal Chemists' Bread and Butter. *J Med Chem*. 2016;59(9):4385-4402. doi:10.1021/acs.jmedchem.6b00153
27. Ertl P, Altmann E, McKenna JM. The Most Common Functional Groups in Bioactive Molecules and How Their Popularity Has Evolved over Time. *J Med Chem*. Published online July 14, 2020. doi:10.1021/acs.jmedchem.0c00754
28. Wetzel S, Schuffenhauer A, Roggo S, Ertl P, Waldmann H. Cheminformatic Analysis of Natural Products and their Chemical Space. *Chimia*. 2007;61:355-360.
29. Aranyos A, Old DW, Kiyomori A, Wolfe JP, Sadighi JP, Buchwald SL. Novel Electron-Rich Bulky Phosphine Ligands

Facilitate the Palladium-Catalyzed Preparation of Diaryl Ethers. *J Am Chem Soc*. 1999;121(18):4369-4378. doi:10.1021/ja990324r
30. Shelby Q, Kataoka N, Mann G, Hartwig J. Unusual in Situ Ligand Modification to Generate a Catalyst for Room Temperature Aromatic C−O Bond Formation. *J Am Chem Soc*. 2000;122(43):10718-10719. doi:10.1021/ja002543e
31. Jalalian N, Petersen TB, Olofsson B. Metal-Free Arylation of Oxygen Nucleophiles with Diaryliodonium Salts. *Chem – Eur J*. 2012;18(44):14140-14149. doi:10.1002/chem.201201645
32. Hie L, Fine Nathel NF, Shah TK, et al. Conversion of amides to esters by the nickel-catalysed activation of amide C–N bonds. *Nature*. 2015;524(7563):79-83. doi:10.1038/nature14615
33. Wakaki T, Togo T, Yoshidome D, Kuninobu Y, Kanai M. Palladium-Catalyzed Synthesis of Diaryl Ketones from Aldehydes and (Hetero)Aryl Halides via C–H Bond Activation. *ACS Catal*. 2018;8(4):3123-3128. doi:10.1021/acscatal.8b00440
34. Ritchie TJ, Macdonald SJF, Young RJ, Pickett SD. The impact of aromatic ring count on compound developability: further insights by examining carbo- and hetero-aromatic and -aliphatic ring types. *Drug Discov Today*. 2011;16(3-4):164-171. doi:10.1016/j.drudis.2010.11.014
35. Subbaiah MAM, Meanwell NA. Bioisosteres of the Phenyl Ring: Recent Strategic Applications in Lead Optimization and Drug Design. *J Med Chem*. 2021;64(19):14046-14128. doi:10.1021/acs.jmedchem.1c01215
36. Chiacchio MA, Iannazzo D, Romeo R, Giofrè SV, Legnani L. Pyridine and Pyrimidine Derivatives as Privileged Scaffolds in Biologically Active Agents. *Curr Med Chem*. 2019;26(40):7166-7195. doi:10.2174/0929867325666180904125400
37. Boström J, Hogner A, Llinàs A, Wellner E, Plowright AT. Oxadiazoles in Medicinal Chemistry. *J Med Chem*. 2012;55(5):1817-1830. doi:10.1021/jm2013248
38. Lamberth C. Oxazole and Isoxazole Chemistry in Crop Protection. *J Heterocycl Chem*. 2018;55(9):2035-2045. doi:10.1002/jhet.3252
39. Zhang HZ, Zhao ZL, Zhou CH. Recent advance in oxazole-based medicinal chemistry. *Eur J Med Chem*. 2018;144:444-492. doi:10.1016/j.ejmech.2017.12.044
40. Ansari A, Ali A, Asif M, Shamsuzzaman. Review: biologically active pyrazole derivatives. *New J Chem*. 2017;41(1):16-41. doi:10.1039/C6NJ03181A
41. Khan MF, Alam MM, Verma G, Akhtar W, Akhter M, Shaquiquzzaman M. The therapeutic voyage of pyrazole and its analogs: A review. *Eur J Med Chem*. 2016;120:170-201. doi:10.1016/j.ejmech.2016.04.077
42. Jiang X, Hao X, Jing L, et al. Recent applications of click chemistry in drug discovery. *Expert Opin Drug Discov*. 2019;14(8):779-789. doi:10.1080/17460441.2019.1614910
43. Bauer MR, Fruscia PD, Lucas SCC, et al. Put a ring on it: application of small aliphatic rings in medicinal chemistry. *RSC Med Chem*. 2021;12(4):448-471. doi:10.1039/D0MD00370K