Journal of Molecular Graphics and Modelling 80 (2018) 282–292

Contents lists available at ScienceDirect

Journal of Molecular Graphics and Modelling

journal homepage: www.elsevier.com/locate/JMGM

Computational assessment of thioether isosteres

Robert D. Barrows[a], Kristin M. Blacklock[a], Paul R. Rablen[b], Sagar D. Khare[a], Spencer Knapp[a,*]

[a] Department of Chemistry & Chemical Biology, Rutgers The State University of New Jersey, 610 Taylor Rd., Piscataway, NJ 08854 USA
[b] Department of Chemistry & Biochemistry, Swarthmore College, 500 College Ave., Swarthmore, PA 19081 USA

ARTICLE INFO

Article history:
Received 20 November 2017
Received in revised form 25 January 2018
Accepted 29 January 2018
Available online 1 February 2018

Keywords:
Conformation
Sulfur hole
AMBER
Rosetta
Cytochrome P450

ABSTRACT

Replacement of the sulfur atom in biologically active diaryl and heteroaryl thioethers (Ar–S–Ar', HAr–S–Ar, and HAr–S–HAr') with any of several one-atom or two-atom linkers can be expected to reduce the susceptibility of the analogue to metabolic oxidation, a well-documented problem for thioethers intended for medicinal chemistry applications. Ab initio calculations indicate how well various proposed thioether isosteric groups, including some new and unusual ones, may perform structurally and electronically in replacing the bridging sulfur atom. Four of these are calculationally evaluated as proposed substructures in Axitinib analogues. The predicted binding behavior of the latter within two different previously crystallographically characterized protein-Axitinib binding sites (VEGFR2 kinase and ABL1 T315I gatekeeper mutant kinase), and an assessment of their suitability and anticipated shortcomings, are presented.

1. Introduction

An important tactic in medicinal chemistry is the replacement of one synthesized substructure with a "bioisostere" [1,2] that matches the original in most respects, but offers improved performance in others. As one example, tetrazol-5-yl has been used as a carboxyl (—CO_2H) equivalent to take advantage of its similar size and hydrogen bonding properties, but its resistance to some, if not all, unwanted metabolic conversions. [3,4] Similarly, suggestions for bioisosteric groups have been compiled for replacing various other commonly occurring linkers, functionalities, and substituents in medicinal chemistry, such as phenyl, carboxamide, ester, ether, hydroxyl, methoxyl, alkyl, and halogen.

Thioethers, especially Ar–S–Ar', HAr–S–Ar, and HAr–S–HAr' (Ar = aryl; HAr = heteroaryl) systems, occur commonly among bioactive compounds, "hit" and "lead" nominees, and drug candidates. Chart 1 displays a representative variety of thioethers **A**–**Q** gathered from the medicinal chemistry literature and the Protein Data Bank (PDB) [5–29]. A search of the latter turned up 148 examples of structures in which a bound thioether of the form Ar–S–Ar', HAr–S–Ar, or HAr–S–HAr' is found. Additional examples of alkyl thioethers (e.g., Ar–S-alkyl) are also available, and some of these will display similar properties, but for the present purpose only the aromatic thioethers will be considered. To summarize the 148 protein structure examples: the sulfur atom in bound aryl/heteroaryl thioethers does not play a role as a hydrogen bond acceptor, but rather as a hydrophobic structural element. According to PDB Poseview [30,31] representations, often the sulfur atom is buried deep within a hydrophobic pocket lined by protein side chains such as those from phenylalanine and leucine. Therefore, the important aspects for a potential thioether bioisostere to mimic include the unique structural features (Chart 1), as well as the relatively small size and lipophilicity of the sulfur atom itself. An additional aspect of covalent sulfur, the "sulfur hole effect," is discussed in Section 2.3.

Oxidation at the sulfur atom, often under the action of cytochrome P450 isoforms and, to a lesser extent, flavin containing monoxygenases, is a commonly observed metabolic process that can detract from the biological effectiveness of the intended thioether [32,33]. Among the Chart 1 thioethers, several (**A**, **E**, **G**, **I**, and **O**) are explicitly described as undergoing metabolic oxidation to the corresponding sulfoxide [—S(O)—] or sulfone [—$S(O_2)$—]; in other cases (**B**, **C**, **F**, **J**, **K**, **L**, and **P**), unspecified rapid metabolism or clearance of the thioether is reported. For some examples, the corresponding sulfoxide or sulfone is described as being less active than the sulfide (**A**, **C**, and **D**), although for three (**I**, **J**, and **N**) the sulfoxide or sulfone does possess activity. For several (**A**, **C**, **D**, **H**, **M**, and **P**), attempted isosteric replacement of the sulfur atom by —O—, —CH_2—, or other group is described, but the resulting analogue is less active. For **P** specifically, replacement of —S— by, variously,

* Corresponding author.
E-mail address: spencer.knapp@rutgers.edu (S. Knapp).

https://doi.org/10.1016/j.jmgm.2018.01.018
1093-3263/

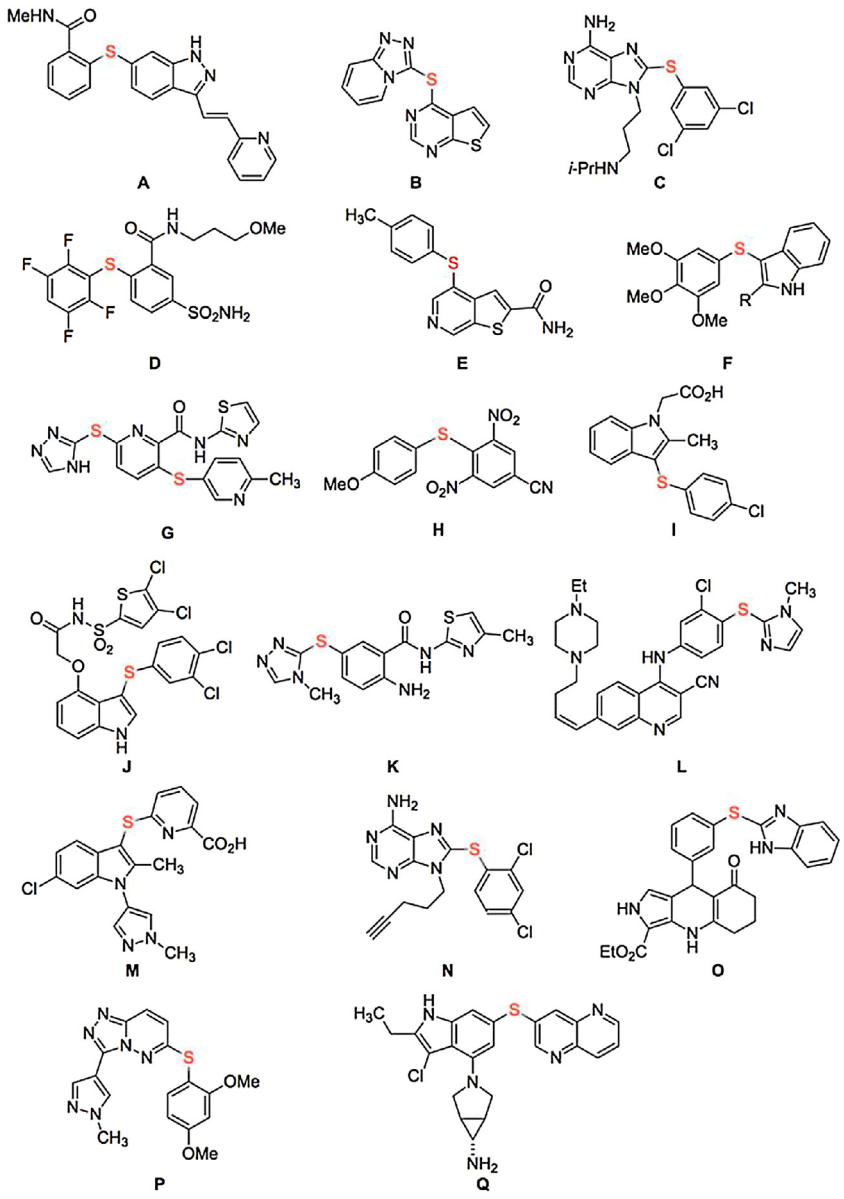

Chart 1. Representative aryl and heteroaryl thioethers from the medicinal chemistry literature. The bridging sulfur atoms are shown in red.

—O—, —NH—, —CH_2—, —CF_2—, —NMe—, or —CHOH— gave in each case a less active analogue. In some examples (**F**, **I**, **K**, **N**, **O**, and **Q**) the corresponding ether or other one atom bridge is only slightly worse or actually an improvement over the thioether.

The common occurrence of thioethers in medicinal chemistry is due in part to their ease of synthesis, as the S–Ar/HAr bond can be assembled in a variety of useful and efficient ways. 34–43 Additionally, sulfur as a bridging atom offers unique structural characteristics, as displayed in Fig. 1. Calculated values for bond lengths, angles, and interatomic distances are shown for Ph—S—Ph (**1**) and Ph—O—Ph (**2**). C(·) represents the ipso carbon. Thus, the divalent bridging sulfur atom, relative to —O—, features much longer bonds, a narrower central bond angle, and aromatic rings that are less co-planar. Interestingly, the C(para)—C(para) distances taken alone are a good match. Nevertheless, the positioning of the attached aromatic rings in **1** differs considerably from that in **2** and other commonly used one-atom bridged structures, including those with —NH—, or —CH_2—.

In this paper, we evaluate by *ab initio* calculation the structural characteristics of a variety of thioether isosteres, including several that feature two-atom bridges and one with a three-atom bridge, in comparison with diphenyl sulfide. We also examine the electrostatic charge characteristics of several bis(pyrid-4-yl) isosteres as stand-ins for bis(heteroaryl) sulfide systems. Finally, we simulate the incorporation of four isosteres of Axitinib into two crystallographically characterized protein binding sites, and comment on which aspects of the isosteres lead to favorable and unfavorable interactions.

2. Results and discussion

2.1. Calculated parameters for isosteres of diphenyl thioether and bis(pyridin-4-yl) thioether

A selection of 22 proposed thioether isosteres for diphenyl thioether (**3a**=**1**) is shown in Chart 2. Calculated geometrical parameters for the most stable conformation of these compounds (**4a**–**25a**), optimized by using the B3LYP/6-31G(d) procedure, are displayed in Table 1. The isosteres are arranged according to the increasing theoretical distortion energy required to geometrically