Frequent Hitters (FF) Set

Medicinal and Computational Chemistry Dept., ChemDiv, Inc., 6605 Nancy Ridge Drive, San Diego, CA 92121 USA, Service: +1 877 ChemDiv, Tel: +1 858-794-4860, Fax: +1 858-794-4931, Email: ChemDiv@chemdiv.com

High throughput screening (HTS) is a key discipline undertaken by pharmaceutical companies as part of successful drug discovery. It is inevitable that hits from HTS campaigns comprise predominantly false positives among the real hits-if there are any. Compounds can be regarded as false positives for a number of reasons, for example, those that interfere in binding interactions by forming aggregates, those that are protein-reactive, or those that directly interfere in assay signaling. Aggregate formation and related behavior can be minimized by the inclusion of surfactant in the primary screening protocol. However, a bit of compounds can be classified as real hits with a "*magic shotgun*" activity, but poor selectivity. Untargeted covalent bonding can be observed in the case of Michael acceptors (1,4-Michael addition), 2- or 5-unsubstituted furans and thiophenes (after CYP-mediated S-oxidation), alkynes (porphyrin acylation), hydroxamic acids, etc. In general, all the compounds with "abnormal" activity can be elicited by the use of well publicized functional group filters. However, it is clear that much about the nature of protein-reactive compounds remains to be known. With respect to the third cause of false positives, interference in assay signaling, it is not always clear which compounds might interfere with the primary screening assay technology until they are purchased and tested in an appropriately designed counter screen for assay interference. Using the reference base of the collected core structure motifs that were previously revealed in literature (Fig. 1) as the most frequent points presented in a wide variety of frequent hitters (Fig. 2), we screened in batch sub-structural mode (*in silico*) for such molecules across our stock (more that 1.5 mil compounds). As a result, more than 10K compounds (Fig. 3) were classified as potentially frequent hitters. For these compounds a promiscuous activity is actually predicted.

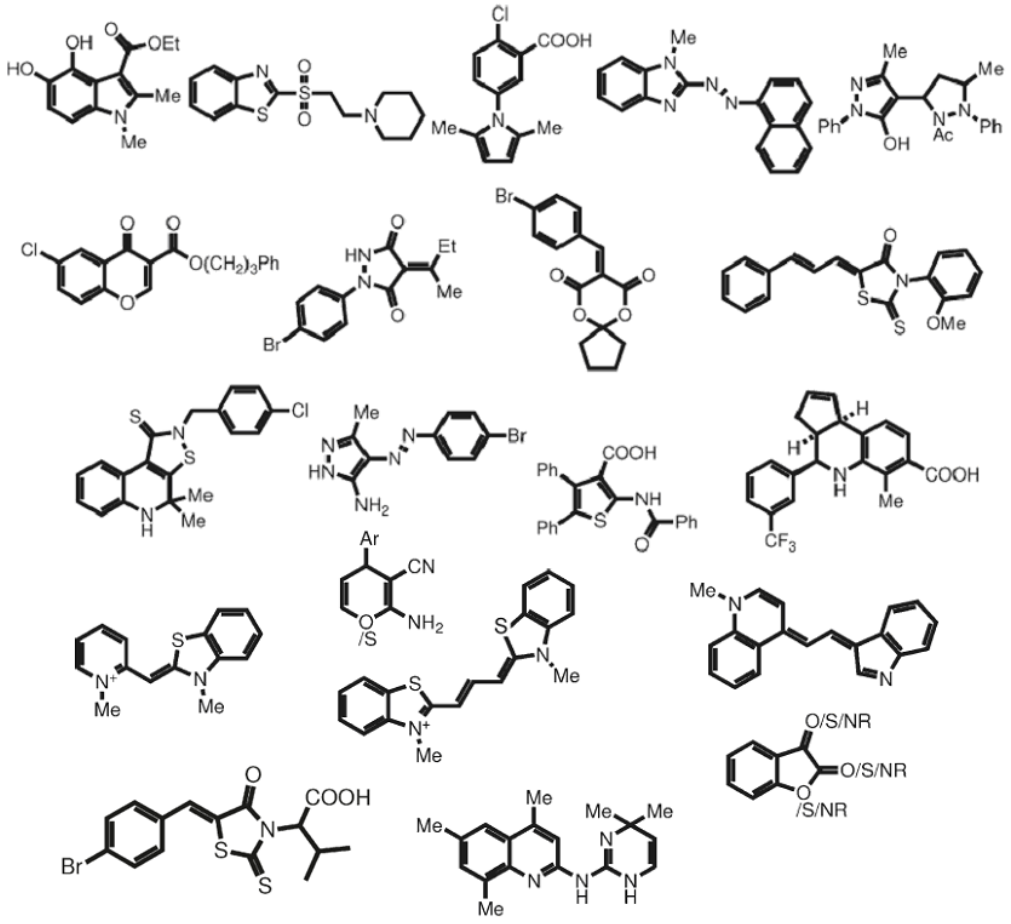

Fig. 1. Examples of promiscuous FF compounds that have been revealed during various biological trials.

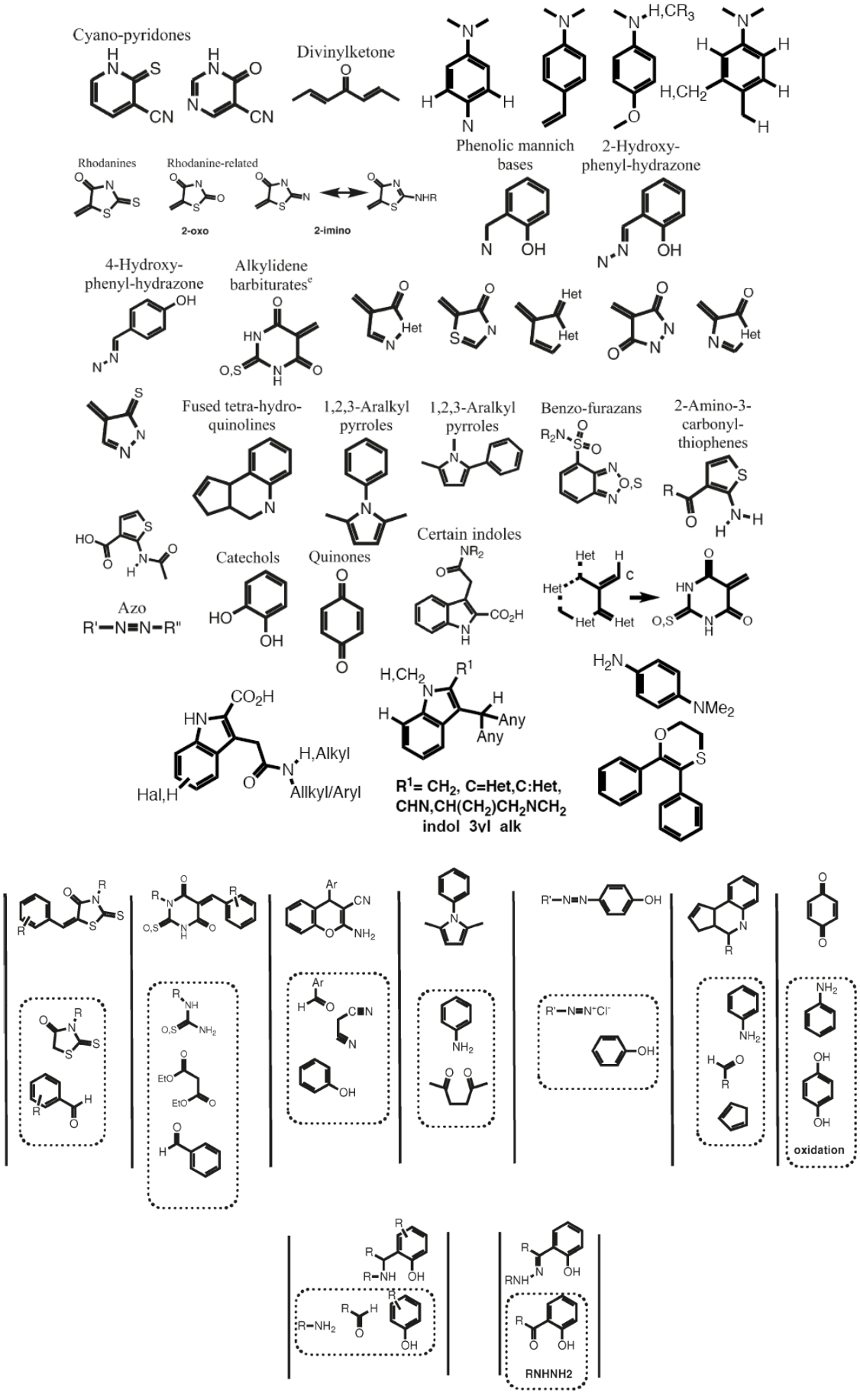

Fig. 2. Representative examples of sub-structures from our FF filter

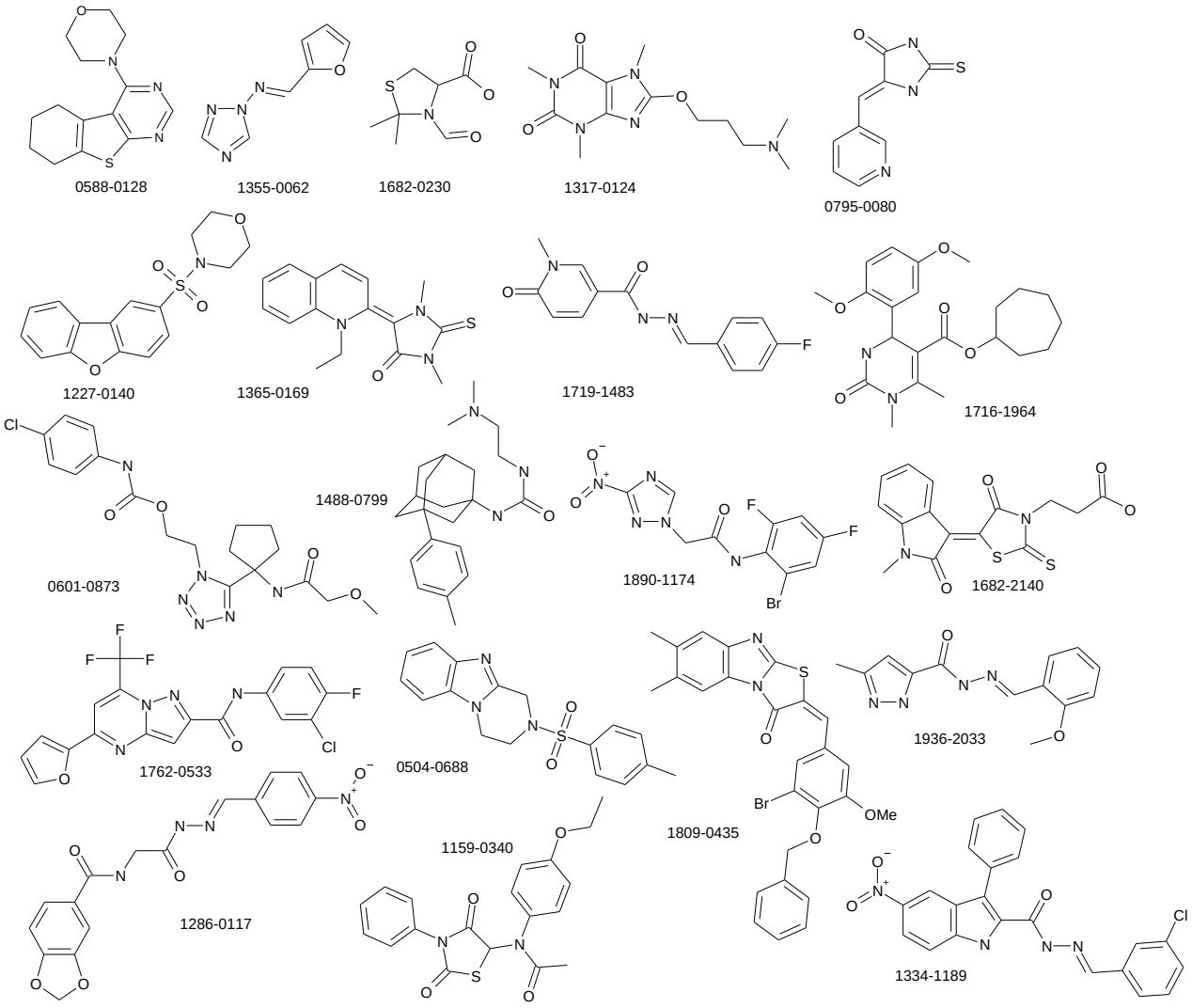

Fig. 3. Representative examples of compounds from FF set