Drugs and PAINs: A DrugBank analysis of pan-assay interference compounds

Ion George Nicolae Daniel, George Mihai Nitulescu

Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, Bucharest, Romania

Background:

Many successful drugs have been developed in the pharmaceutical industry starting from hits discovered by High-throughput Screening (HTS) methods, through various types of assays testing thousands of compounds against targets of interest in the therapeutic field. Unfortunately, several chemical motifs have been found to confer non-specificity against different targets, rendering compounds with such substructures to determine false-positive results in screening assays. These structures, widely known as PAINS (Pan-assay interference compounds), are often avoided by medicinal chemists when selecting hits from HTS assays, for toxicity- and potency-related reasons (Baell & Holloway, 2010). However, several drugs classifiable as PAINS have already been approved, with many more being present in the drug development stages.

Objectives:

The present work aims to investigate the frequency of use and utility of PAINs among the currently approved or in-development drugs by analyzing different types of PAINs comprised in the DrugBank chemical database, in order to better understand the impact of a pan-assay interference.

Methods and materials:

DrugBank version 5.0, containing 10631 structures, has been analyzed using OSIRIS DataWarrior 4.4.4 software, filtering for PAIN substructures indicated by Baell & Holloway. Selected compounds representing PAINs set were managed and analyzed using DataWarrior, Microsoft Excel and SPSS Statistics, regarding approval status, pharmacology, targets,etc.

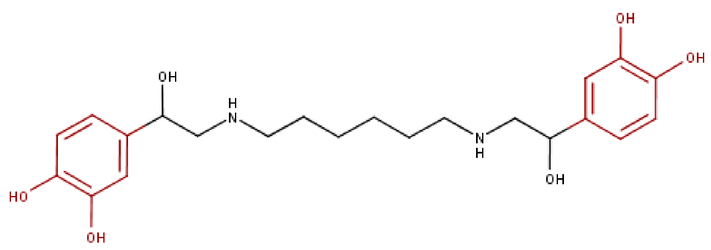
Results:

From **10631 compounds** extracted from DrugBank, **198 substances** were identified as being PAINS. **12 types** of problematic substructures have been identified in DrugBank, the most common structures to be found as PAINs being substances containing **catechols, quinones, rhodanine-related groups, hydrazones** and **phenolic Mannich bases**.

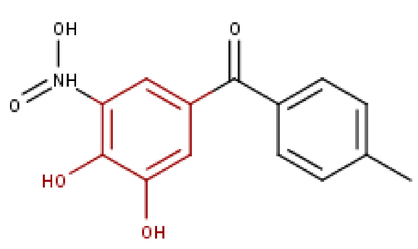
Table 1 – Descriptives of PAINs extracted from DrugBank – multiple categories possible

Compound status	Number of PAINs
Approved	38
Investigational	61
Experimental	123
Withdrawn	3

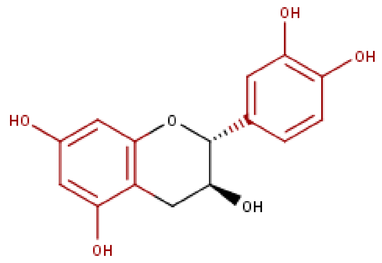
Figure 1 – Withdrawn drugs identified as PAINs



Hexoprenaline

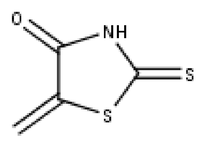
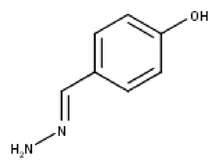
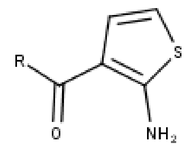
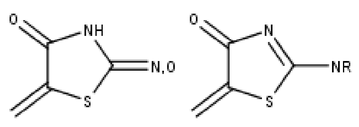
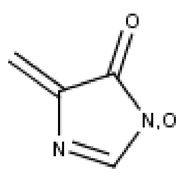
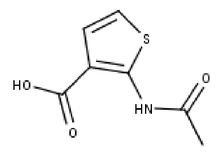
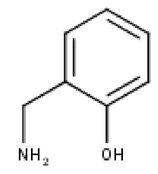
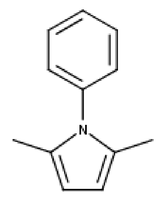
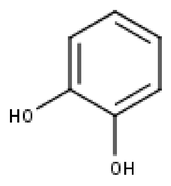
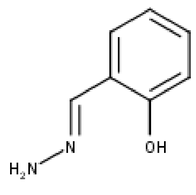
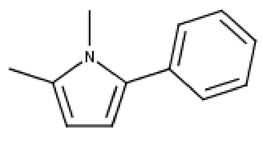
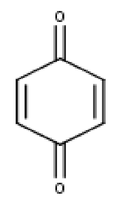


Cianidanol



Tolcapone

Table 2 – Types of PAINs structures identified in DrugBank database

PAIN type	Structure	Count	PAIN type	Structure	Count	PAIN type	Structure	Count
Rhodanine		3	4-Hydroxy-phenyl-hydrazone		15	2-Amino-3-carbonyl-thiophenes_A		1
Rhodanine-related		14	Ene_five_het_G		12	2-Amino-3-carbonyl-thiophenes_B		4
Phenolic Mannich bases		16	1-Aryl-2,5-alkylpyrrole		2	Catechols		95
2-Hydroxy-phenyl-hydrazone		18	2-Aryl-1,5-alkylpyrrole		6	Quinones		28

Conclusion:

Although selectivity of a compound labeled as a PAIN is indeed deficient, these problematic compounds seem not to be as problematic as originally predicted in terms of toxicity and pharmacological profile, as numerous substances found to be PAINs are successfully used in current therapy.

5th International Electronic Conference on Medicinal Chemistry
1-30 November 2019

sponsors: MDPI pharmaceuticals