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Side effect profile prediction - early addressing of big pharma's worst nightmare

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Adverse effects of drugs that are only identified after a compound enters the clinic seriously limit therapeutic potential and could result in withdrawal from the market. Two well-known examples in recent years were Rofecoxib (Vioxx®) and Cerivastatin (Baycol®, Lipobay®), but there are many other examples. Avoiding such adverse effects is therefore a key goal in drug discovery.

It is desirable to have a computational tool that predicts possible problems even before a compound has been synthesized. Bender et al. have shown a proof-of-principle for predicting adverse events based on chemical structure [1].

In the current study we present an advancement of this method. Approximately 200 marketed drugs were tested against 80 different targets in the Novartis Safety Profiling Panel and the IC50 values were determined. The well-documented adverse effects of these marketed drugs were stored in a database using standard MedDRA terminology.

For every side effect described by the MedDRA terminology and every target covered by the Safety Profiling Panel models were calculated and validated using both a Naïve Bayesian classifier and Linear Discriminant Analysis in conjunction with two chemical descriptors (Extended Connectivity Fingerprints and MDL Public Keys). We present results demonstrating correlations between chemical features and adverse effects on the one hand, and between targets and adverse effects on the other. Therefore the method can be used for predicting adverse events based on chemical structure alone. Furthermore, novel links between targets and adverse effects can be unraveled which are of interest in their own right, but which can also be applied to select targets for *in vitro* compound profiling.

References

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