Compound Optimization through Data Set-Dependent Chemical Transformations

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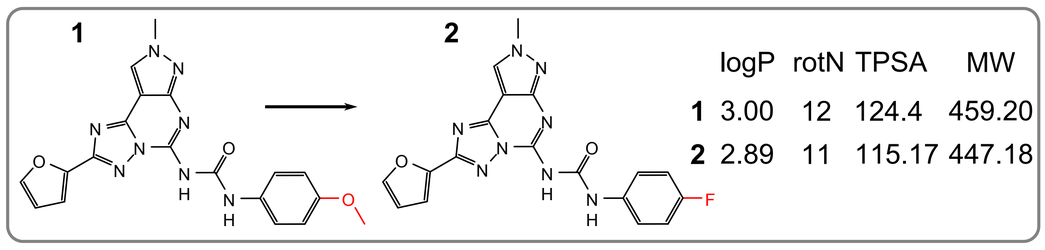
INTRODUCTION

Matched molecular pairs (MMPs) have been used previously as a source of chemical transformations to study their effect on molecular properties such as activity[1,2]. Compound optimization towards defined activity profiles has been successfully accomplished using prespecified chemical transformations[3]. In this work, MMPs retrieved from bioactive compounds were used to evaluate the effect of chemical transformations. These transformations were then utilized to optimize compounds and improve ADME-relevant properties.

MMP AND TRANSFORMATIONS

Bioactive molecules were collected and their molecular weight (MW), number of rotatable bonds (rotN), topological polar surface area (TPSA), and lipophilicity (logP) were calculated. These values were classified as unfavorable, intermediate, or favorable.

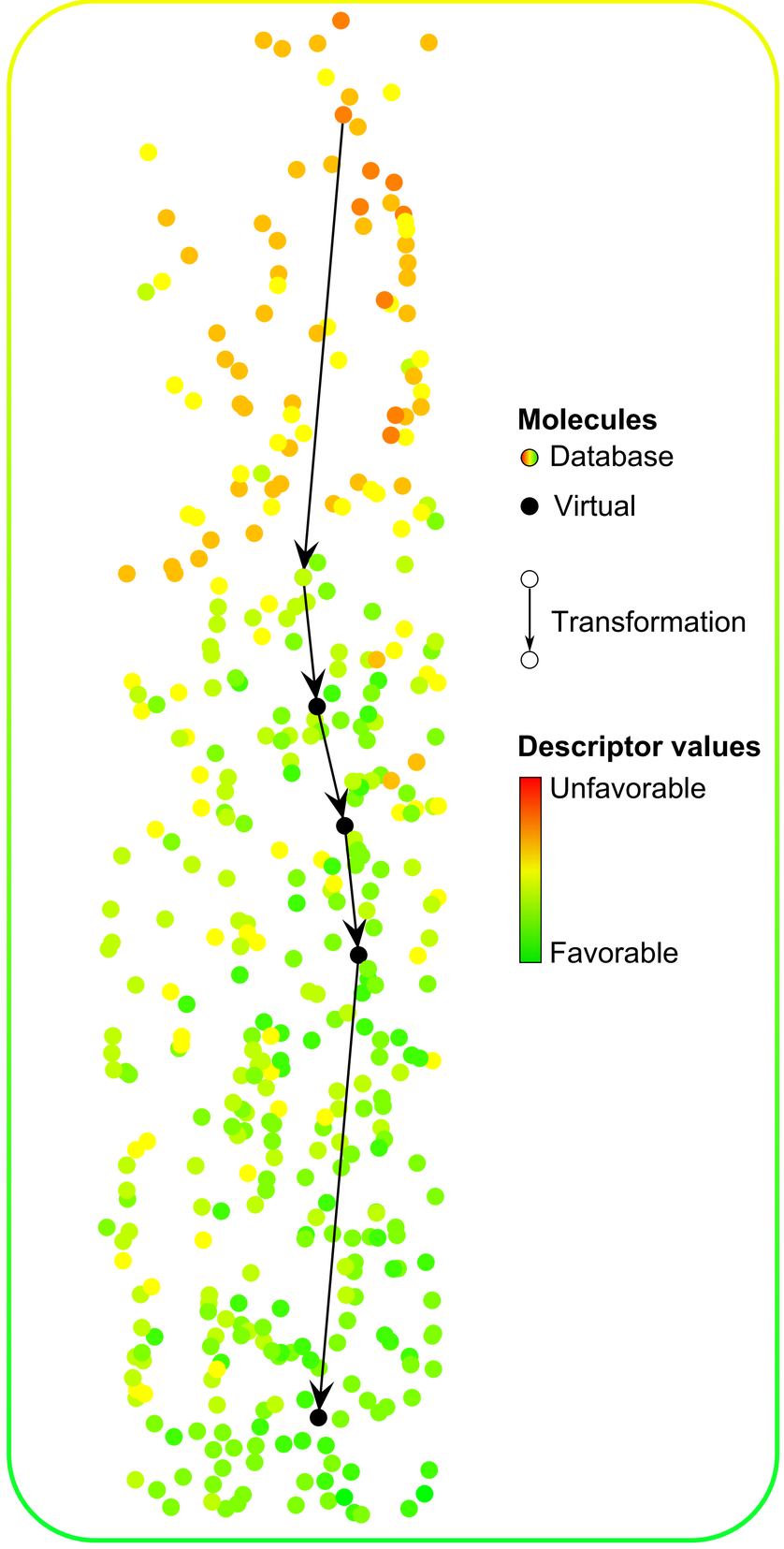
Size restricted MMPs were obtained for each data set and grouped into chemical transformations. The effect of the transformations were calculated from the MMPs. Molecules with unfavorable values were modified in a stepwise manner utilizing these transformations.



MMPs are combined into a chemical transformation

Id	logP	rotN	TPSA	MW	Transformation	Database id	pKi
1	3.11	16	122.10	538.30		[EM] 473440	9.15
2	3.00	13	112.87	494.28	[R1]COC>>[R1]	[EM] 480756	8.60
3	2.89	12	112.87	480.26	[R1]CC[R2]>>[R1]C[R2]	[NN] 473439	8.82
4	2.78	11	114.45	466.22	[R1]C>>[R1]	[NN] 480749	8.02
5	2.70	10	114.50	452.20	[R1]CO[R2]>>[R1]O[R2]	[NN] 245848	10.00
6	2.60	7	105.20	408.20	[R1]COC>>[R1]	[NN] 240030	8.89

Evolution of chemical properties among the optimization pathway shown left



Optimization pathway as seen in a PCA projection of the chemical space

RESULTS AND DISCUSSION

Frequent transformations, found in 10 or more MMPs, were selected for the optimization procedure. Compounds having unfavorable descriptor values were transformed. Exact matches (EM) or nearest neighbors (NN) of optimized compounds were retrieved from the database to assess potency changes during optimization.

In total, half of the tested compounds reached favorable chemical space. For many of these virtual compounds, identical or close matches were found in ChEMBL.

Data set		A2AR	CB2	D2R	MOR
Optimization candidate compounds		36	35	27	56
Did not reach favorable space		17	0	27	34
Reached favorable space	***No NN***	8	11	0	17
	NN	8	24	0	4
	Active NN	3	0	0	1

Results of all optimization procedures

1) Wassermann AM, Bajorath J. *J Chem Inf Model* 2010, **50**: 1248-1256.
2) Wassermann AM, Bajorath J. *Future Med Chem* 2011, **3**: 425-436.
3) Besnard J *et al*. *Nature* 2012, **492**: 215-220.

Images on this poster were adapted from de la Vega de León A, Bajorath J. *J Chem Inf Model* 2013, **53**: 1263-1271.