COMPUTATIONAL CHEMISTRY

Homing in on desired drug properties

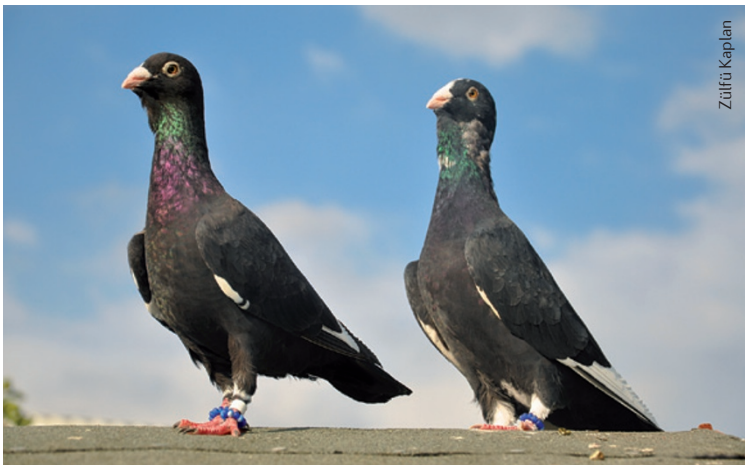
Drugs that have activity against more than one target protein may be beneficial in complex disorders such as cancer and neuropsychiatric disorders. However, designing polypharmacological drugs is challenging.

Writing in *Nature*, Hopkins and colleagues describe a new computational method that can be used to design drugs with specific properties, such as multitarget activity. The method uses automated learning of medicinal chemistry-based design tactics, applies these automated learning approaches to the generation of chemical structures and then prioritizes each compound relative to a predefined profile of objectives, including target selectivity.

First, the authors tested whether the method could be used to design compounds with new activities. The acetylcholinesterase inhibitor donepezil — which also has activity at the dopamine D4 receptor but low activity at the D2 receptor — was used as a starting compound. Based on this structure, the authors searched for a compound that had improved D2 receptor activity and penetrated the blood–brain barrier (BBB).

In the method, the desired multi-objective profile (in this case D2 receptor activity and BBB penetration) is defined *a priori* and then expressed as a point in multi-dimensional space (in this case two-dimensional space because of the two desired characteristics), termed 'the ideal achievement point'.

Chemical structures were computationally generated (based on the donepezil template) by a process of adaptive design and then ranked by the distance (in two-dimensional space) between the predicted properties for each structure and the ideal achievement point. Compounds were filtered for novelty, rule-of-five compliance and synthetic accessibility.



Zülfü Kaplan

Prioritized structures were selected for the next iterative cycle and the process was repeated until structures as close as possible to the objectives (that is, improved D2 receptor activity and BBB penetration) were identified.

This process resulted in a series of isoindoles, eight of which were then synthesized and experimentally tested. All of these compounds had substantial affinity at the D2 receptor and penetrated the BBB in mice.

Although not selected for in the method, the set of isoindole analogues was predicted to have activity at serotonin, adrenergic and other dopamine receptor subtypes.

So because α1-adrenergic receptor antagonists can induce hypotension, the authors next tried to reduce the activity of the isoindoles at this receptor while maintaining a polypharmacological profile (that is, modulation of 5-hydroxytryptamine 1A (5-HT_{1A}) receptors as well as D2, D3 and D4 receptors). This process resulted in a series of benzolactams, which represented a new chemical series. Several were synthesized and the predicted activity at the desired receptors was confirmed.

Together, these studies show that this method can be used to derive compounds that have desired target activities and properties while minimizing unwanted target activities.

The authors also showed that the method could be used to develop highly selective compounds. In particular, a potent, selective, BBB-penetrant D4 receptor ligand was derived (starting with the chemical structure of donepezil) that had *in vivo* activity and represented a new D4 receptor chemotype.

The authors suggest that, provided sufficient structure–activity data are available, this approach could be applicable to all drug–target classes.

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ORIGINAL RESEARCH PAPER Besnard, J. *et al.* Automated design of ligands to polypharmacological profiles. *Nature* **492**, 215–220 (2012)