CORE STRATEGY TO DESIGN OF G9a-TARGETED LIBRARY

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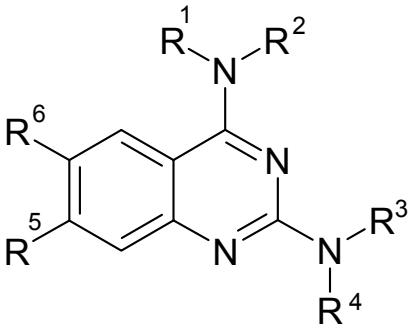
Currently, only one scaffold has been well described as highly potent inhibitors of G9a



- comprehensive SAR is available for these compounds in [Feng Liu et al. Protein Lysine Methyltransferase G9a Inhibitors: Design, Synthesis, and Structure Activity Relationships of 2,4-Diamino-7-aminoalkoxy-quinazolines. J Med Chem. 2010, 53, 5844–5857]
-29 compounds were well characterized and evaluated *in vitro*
- crystallographic data was obtained for several compounds

Our approach includes:

Current strategy

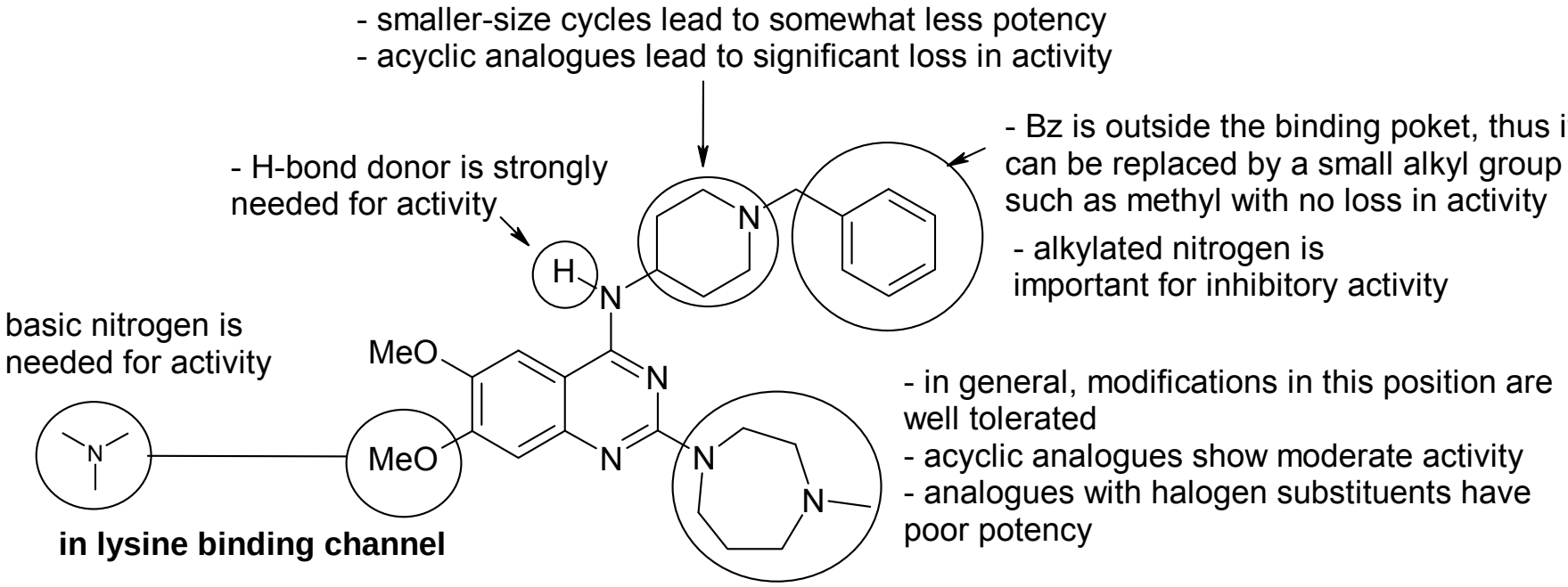
- generate close isosteric analogues with reliable topology
- keep the revealed crucial binding points
- apply 2D-similarity approach toward active compounds
- include the “targeted diversity” set, e.g. tyrosine kinase inhibitors

Further evaluation:

- 3D-molecular docking approach
- 3D-pharmacophore modeling/searching

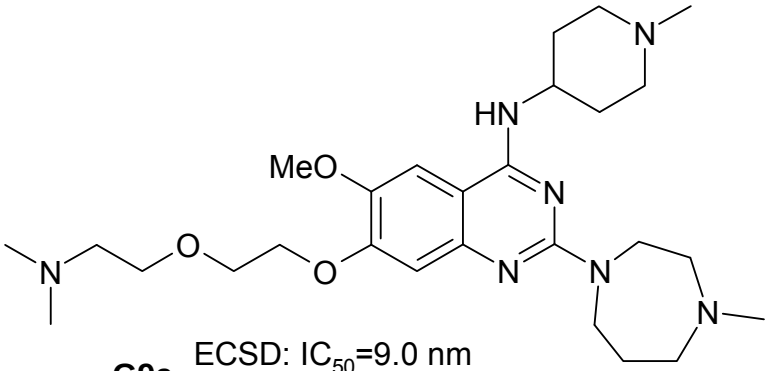
Highlighted among active compounds

the bulk of compounds from this series occupied the histone peptide binding site



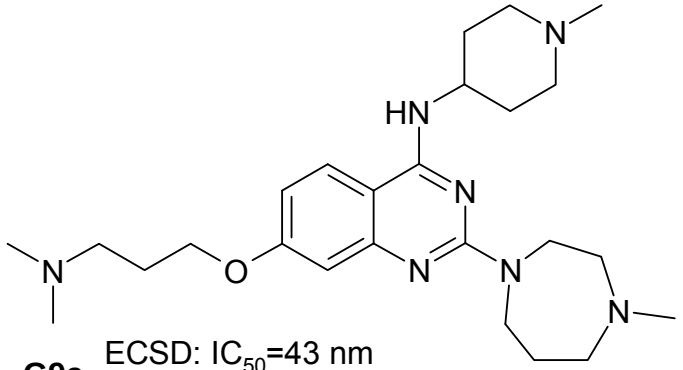
- 7-dimethylaminopropoxy chain significantly increases the activity
- there is space at the end of the channel to accommodate a longer chain or larger amino group
- 2-5-carbon chain, have similar high potency; 6-carbon chain is significantly less potent
- compounds with terminal N-methylamino, N,N-diethylamino, and N-methyl-N-propylamino groups are as potent as the core 7-N,N-dimethylamino active analogue
- primary amino group and several cyclic analogues including pyrrolidine, piperidine are also quite acceptable, exept morpholine; increasing the size of the amino capping group from dimethylamino to pyrrolidine led to > 5-fold potency decrease
- amide group is about 100-fold less potent compared to its amine analog
- replacing the 5-carbon chain with an ethoxyethyl chain resulted in compound with IC_{50}=6 nM (CLOT) and 9 nM (ECSD), the most potent G9a inhibitor to date. However, methylamine moiety in this position decreases the potency; conformationally constrained analog with shorter (piperidin-3-yl)methoxy group is significantly less potent

Most potent compounds form the series



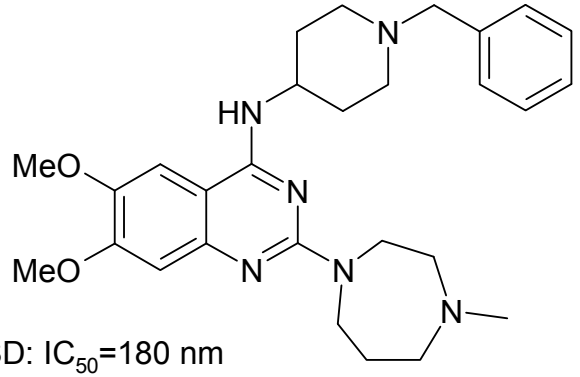
G9a ECSD: IC_{50}=9.0 nm
CLOT: IC_{50}=6.0 nm

GLP ECSD: IC_{50}=15 nm
CLOT: IC_{50}=23 nm



G9a ECSD: IC_{50}=43 nm
CLOT: IC_{50}=57 nm

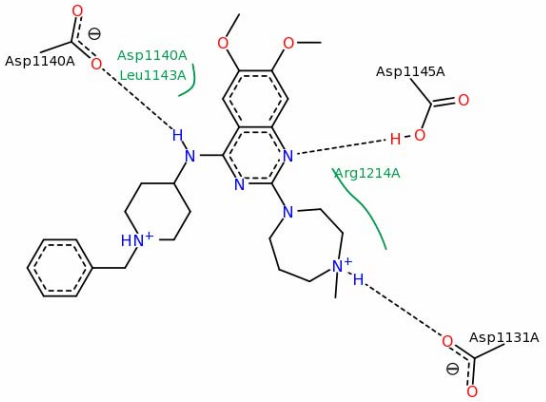
GLP ECSD: IC_{50}=50 nm
CLOT: IC_{50}=58 nm

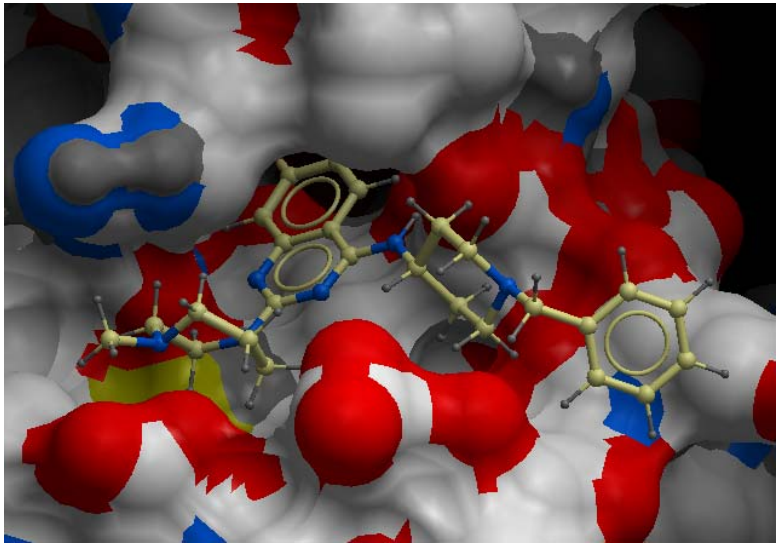


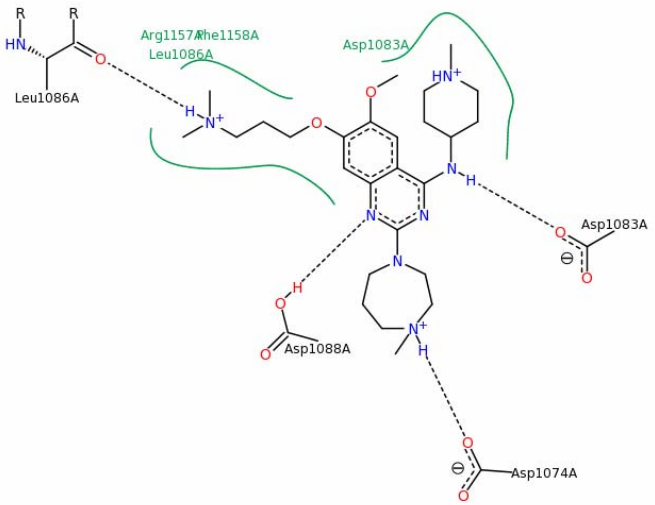
G9a ECSD: IC_{50}=180 nm
CLOT: IC_{50}=250 nm

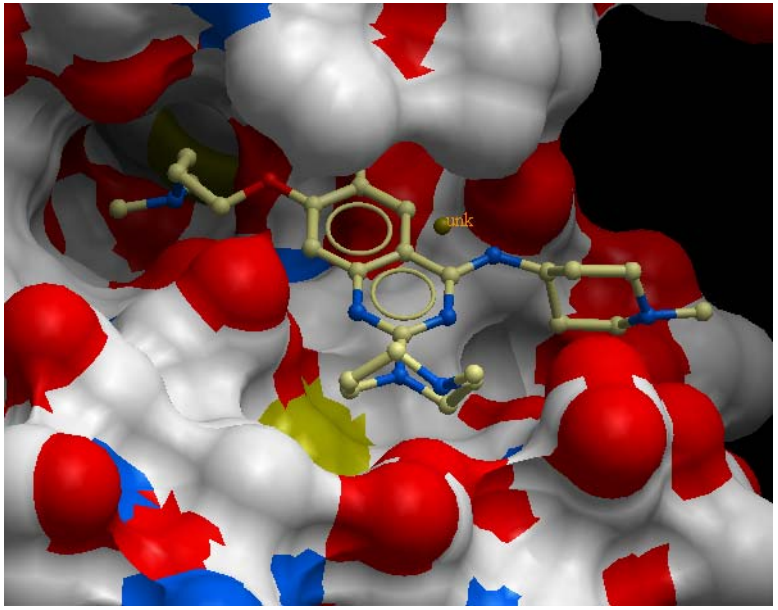
GLP ECSD: IC_{50}=34 nm
CLOT: IC_{50}=27 nm

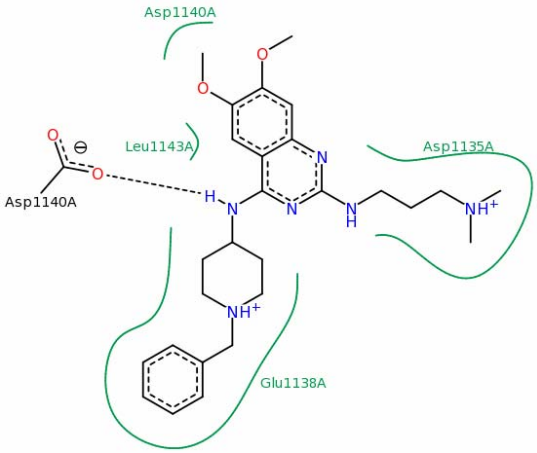
Representative examples of available crystallographic data







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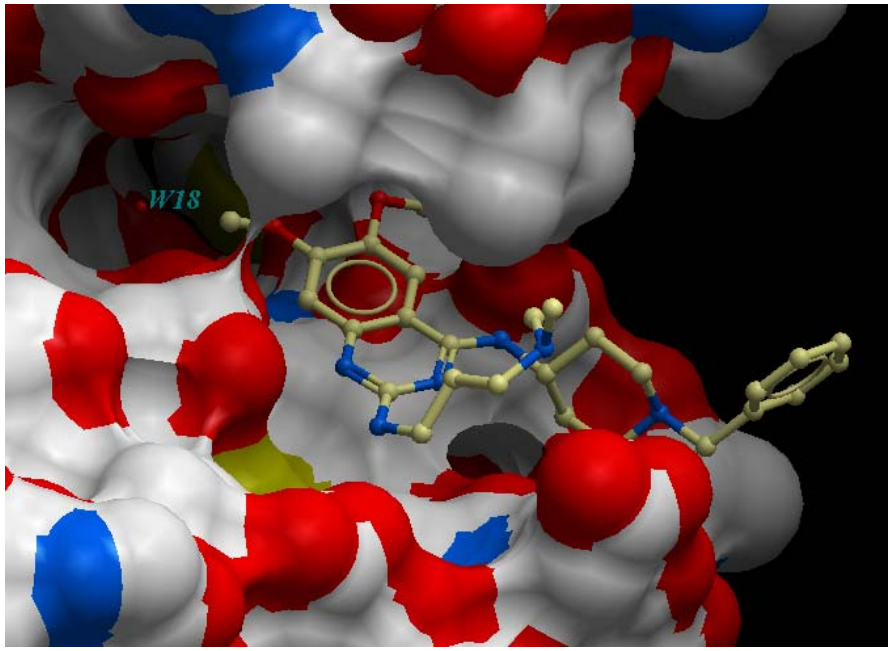
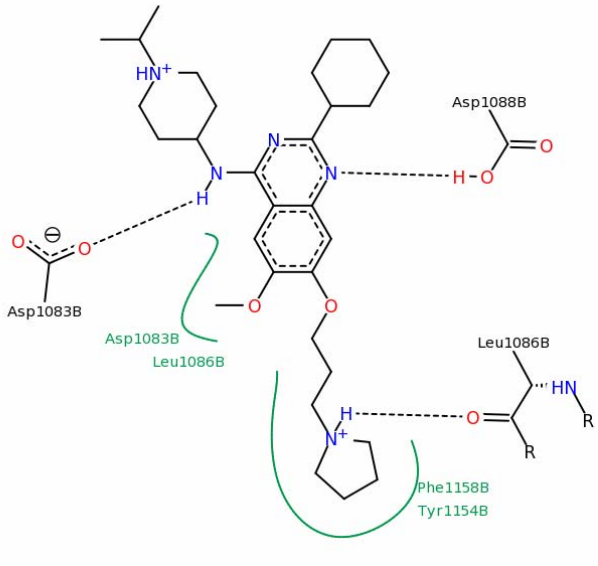
Asp1135A
Asp1140A
Glu1138A


W18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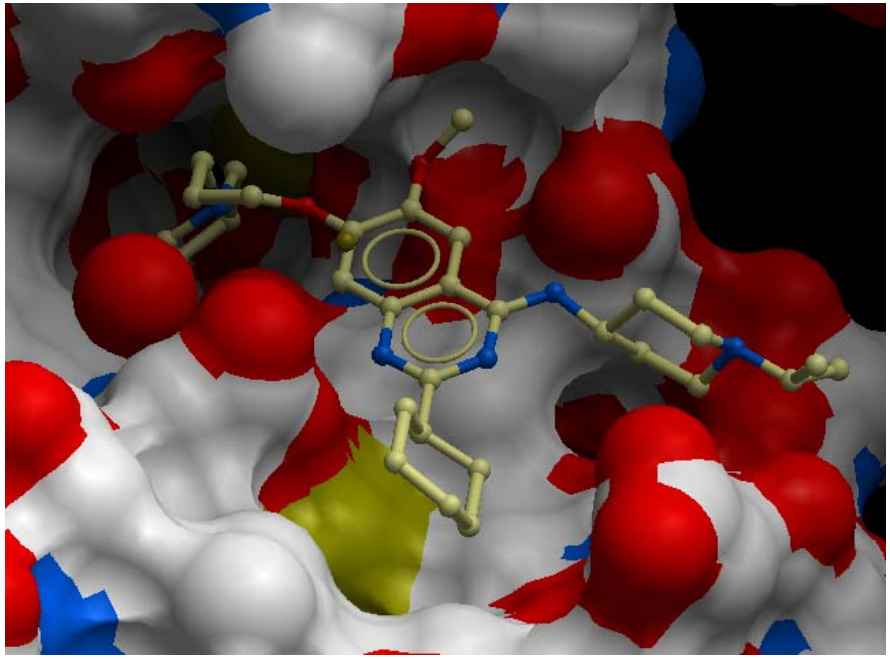
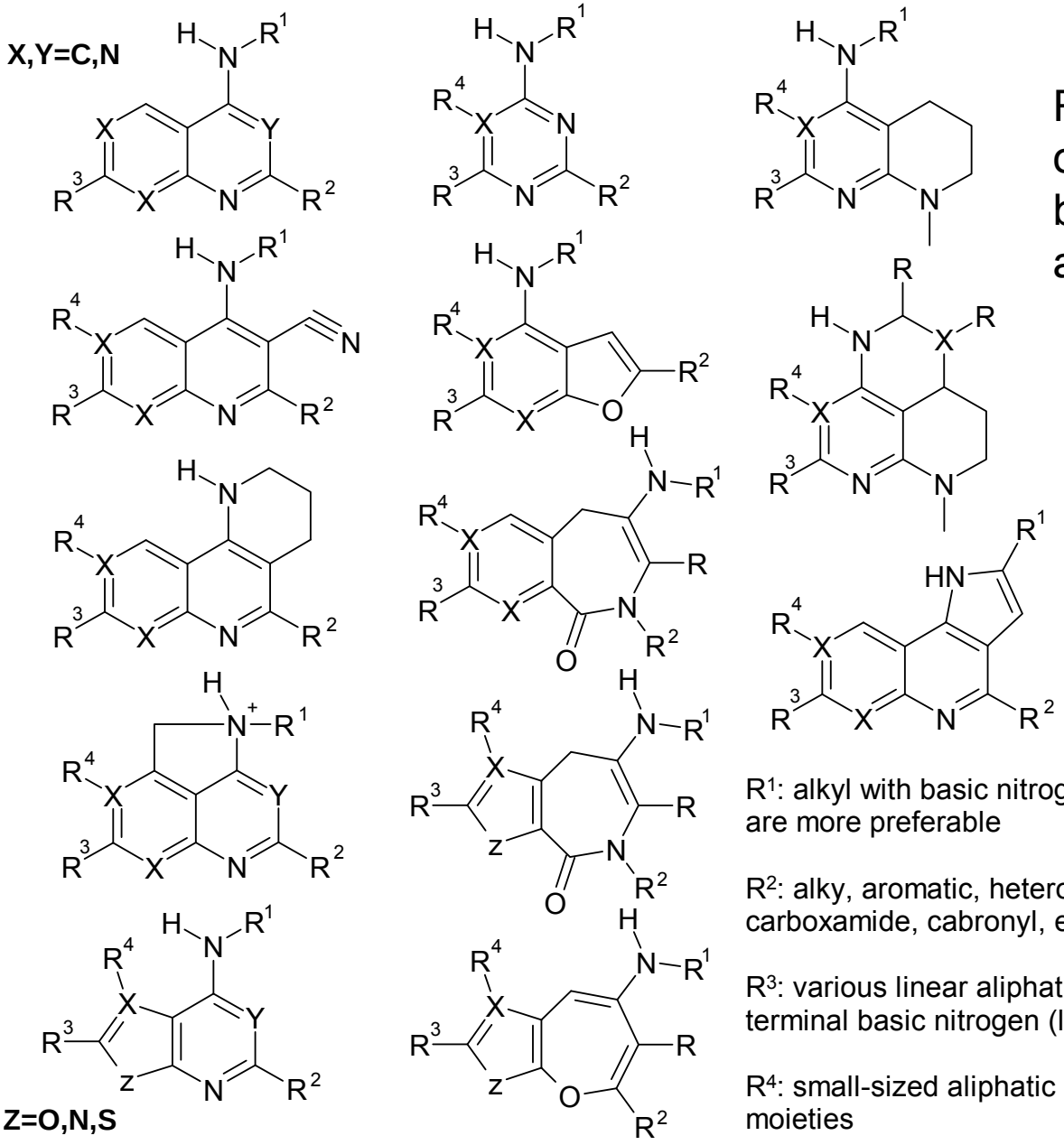
Asp1083B
Asp1083B
Leu1086B
Leu1086B
Phe1158B
Tyr1154B



Bioisosteric morphing



Representative examples of straight and non-trivial bioisosteric analogues of active compounds

Put the accent on:

- heterocyclic diversity
- side-chain variations

R^1: alkyl with basic nitrogen, cyclic analogues are more preferable

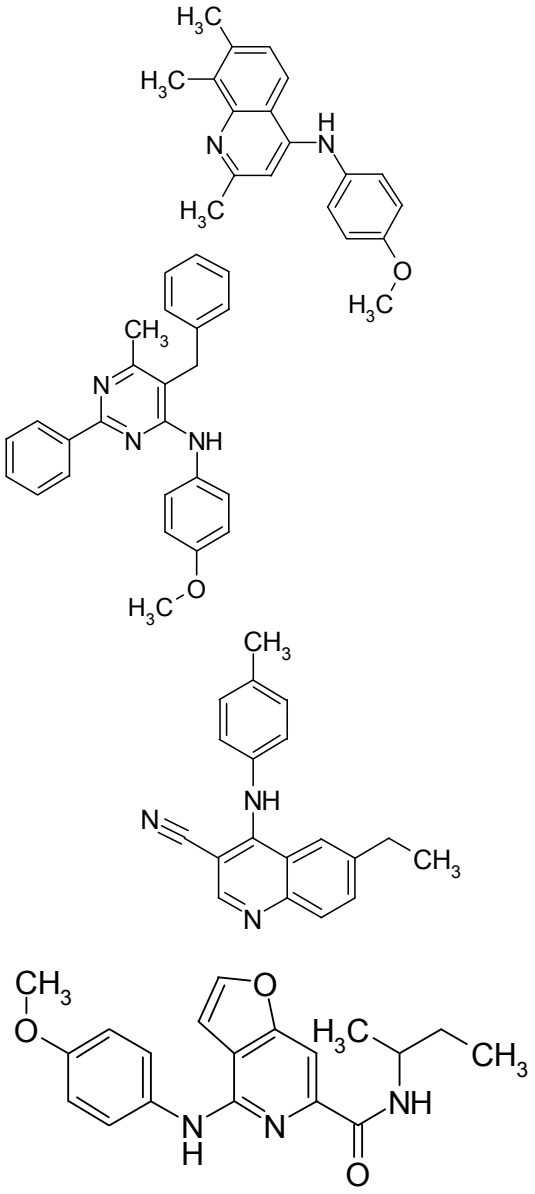
R^2: alky, aromatic, heteroaromatic, carboxamide, cabronyl, etc.

R^3: various linear aliphatic chains with terminal basic nitrogen (lysine binding cavity)

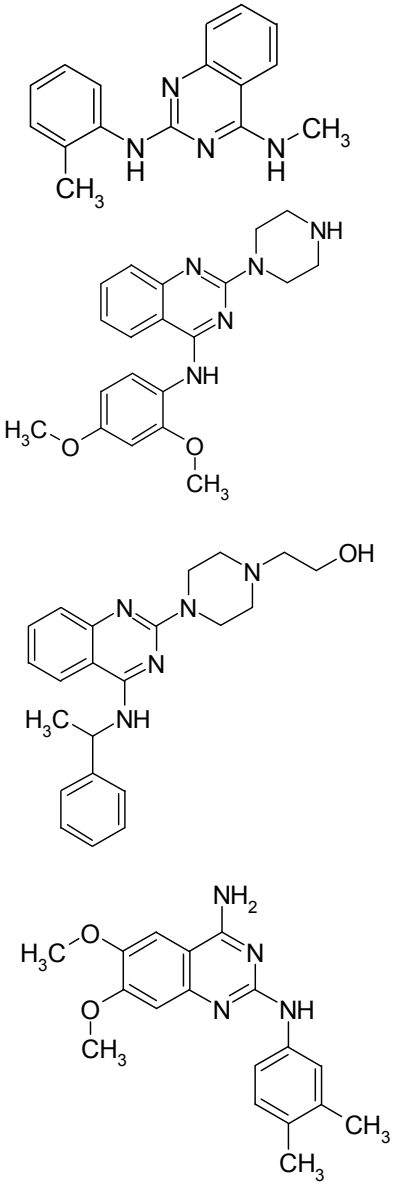
R^4: small-sized aliphatic and aromatic moieties

Representative examples of compounds from G9a-targeted library

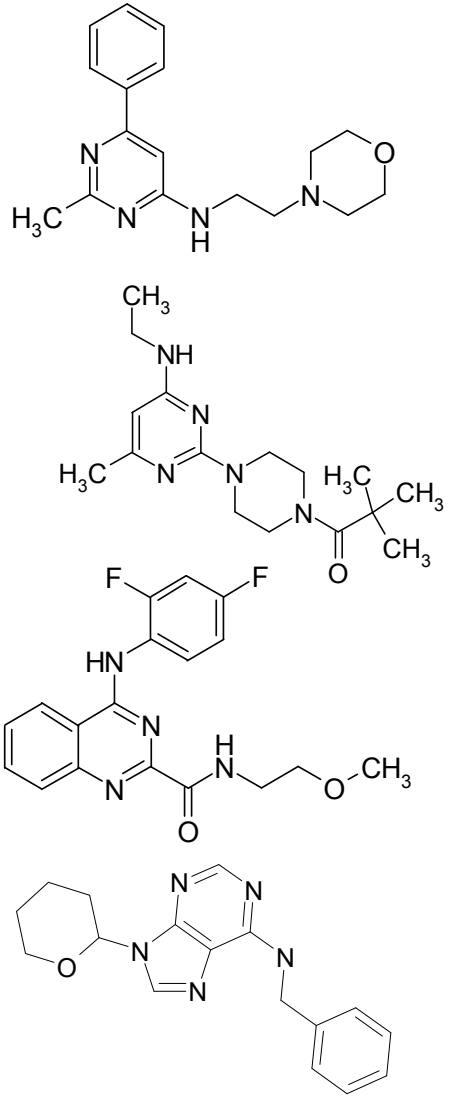
Bioisosteric morphing



2D-similarity



compounds from TK-targeted library



More than 14K cmpds in G9a-targeted library