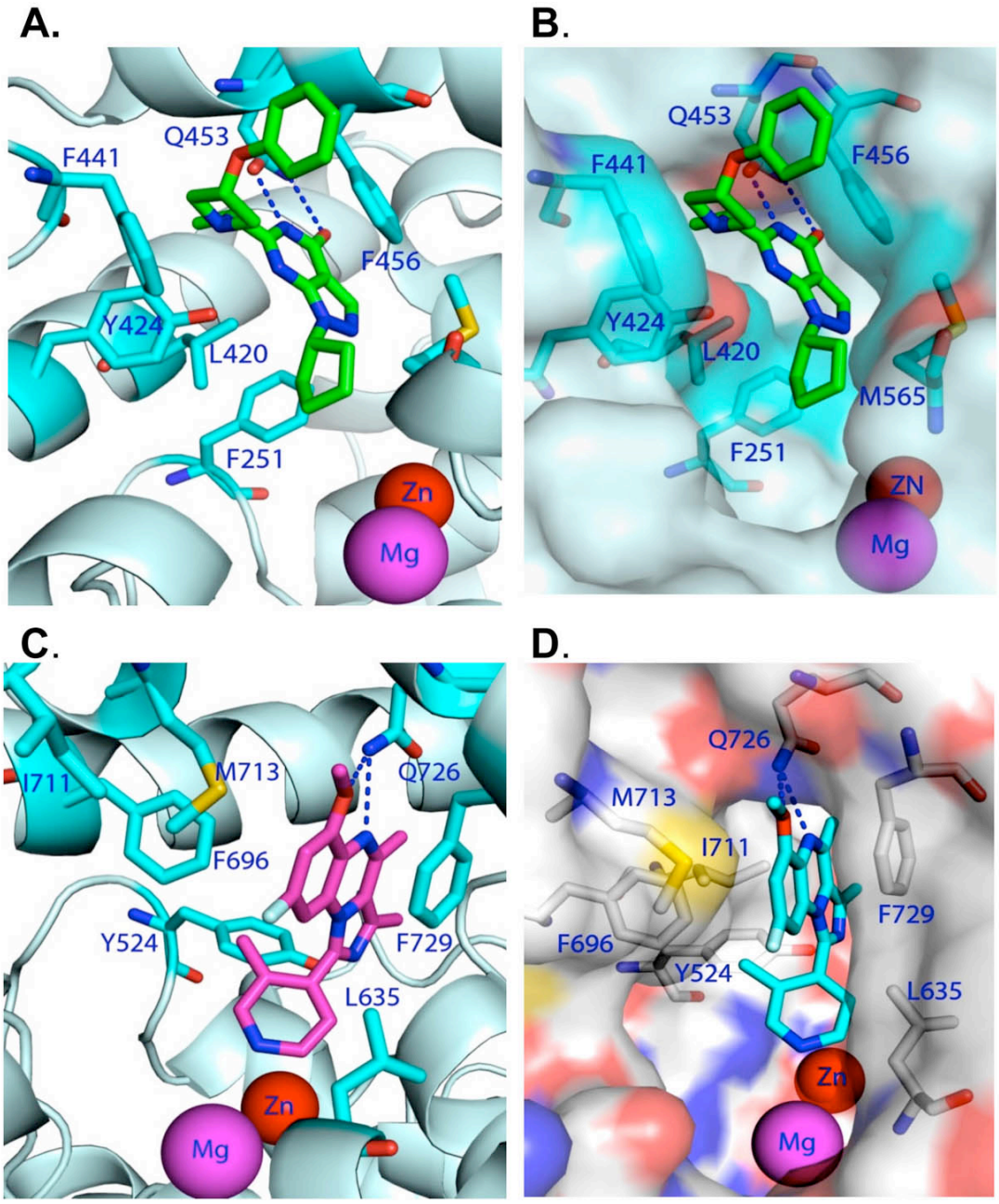
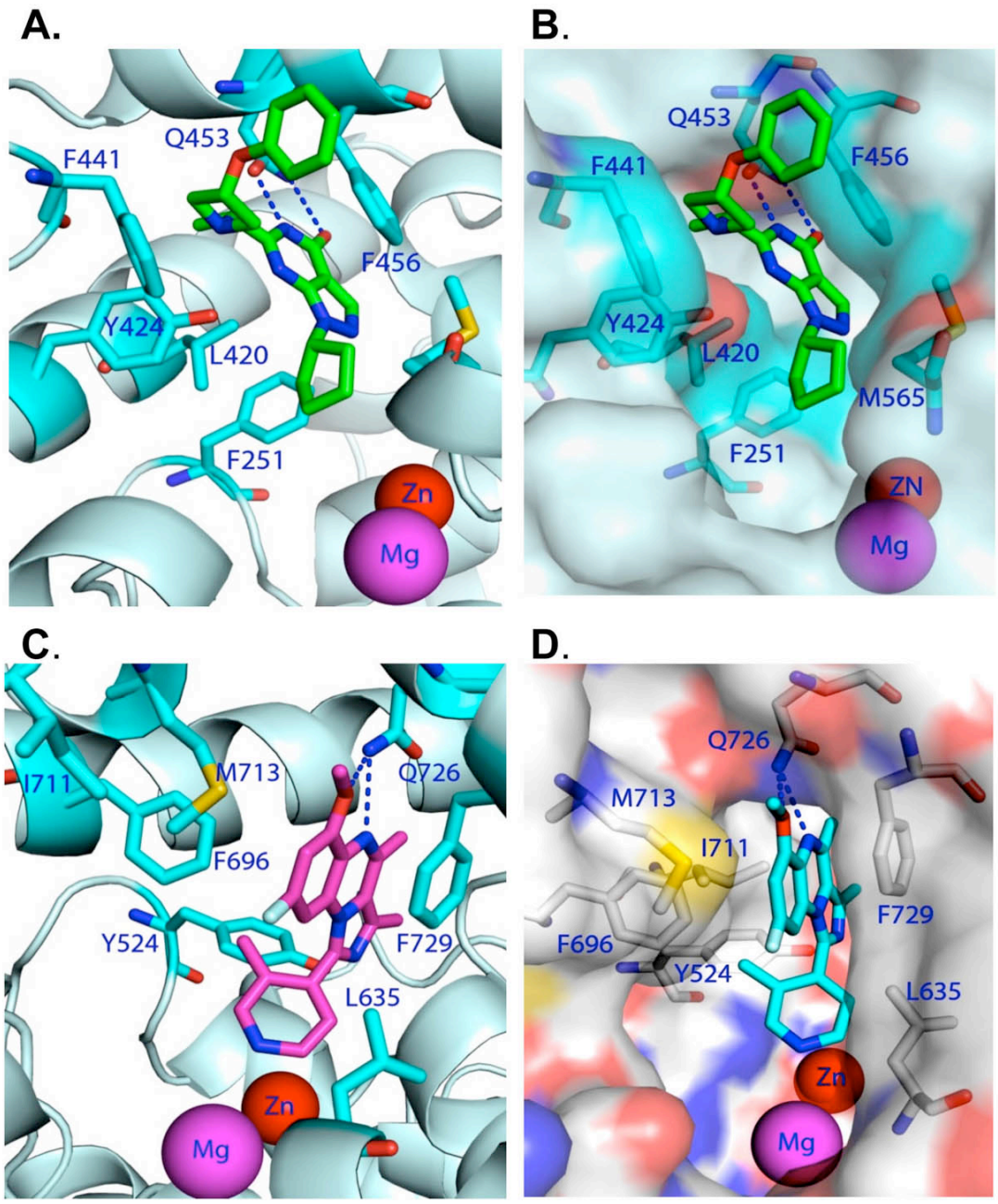
Supplementary information 2 | Application of structure-based drug design to generate selective PDE 9A (A, B) and PDE10A inhibitors. Stacking against the conserved phenylalanine and hydrogen bonding with the invariant glutamine are two characteristics of most PDE inhibitors, as shown in the examples of the binding of 6-amino-pyrazolopyrimidinone-derived PDE9[1,2] **(A, B)** and pyrazoloquinoline-derived PDE10[3,4,5] **(C, D)** inhibitors in the active site pockets. Dotted lines represent hydrogen bonds. **(A,C)** Ribbon diagram of the inhibitor (yellow sticks).Dotted lines represent hydrogen bonds. **(B,D)** Surface model of the inhibitor binding.



1. Meng, F. *et al*. Structure-based discovery of highly selective phosphodiesterase-9A inhibitors and implications for inhibitor design. *J. Med. Chem.* **55**, 8549-8558 (2012).
2. Claffey, M. M. *et al*. Application of structure-based drug design and parallel chemistry to identify selective, brain-penetrant, in vivo active PDE 9A inhibitors. *J. Med. Chem.* **55**, 9055-9068 (2012).
3. Ho, G. D. *et al*. The SAR development of dihydroimidazoisoquinoline derivatives as phosphodiesterase 10A inhibitors for the treatment of schizophrenia. *Bioorg. Med. Chem. Lett.* **22**, 2585-2589 (2012).
4. Malamas, M., Ni, Y. & Erdei, J. Highly potent, selective, and orally active phosphodiesterase 10A inhibitors. *J. Med. Chem.* **54**, 7621-7638 (2011).
5. Verhoest, P. R. *et al*. Discovery of a novel class of phosphodiesterase 10A inhibitors and identification of clinical candidate 2-[4-(1-methyl-4-pyridin-4-yl-1H-pyrazol-3-yl)-phenoxymethyl]-quinoline (PF-2545920) for the treatment of schizophrenia. *J. Med. Chem.* **52**, 5188-5196 (2009).


A.
Q453
F441
F456
Y424
L420
F251
Zn
Mg
B.
Q453
F441
F456
Y424
L420
M565
F251
ZN
Mg
C.
I711
M713
Q726
F696
Y524
F729
L635
Zn
Mg
D.
Q726
M713
I711
F729
F696
Y524
L635
Zn
Mg