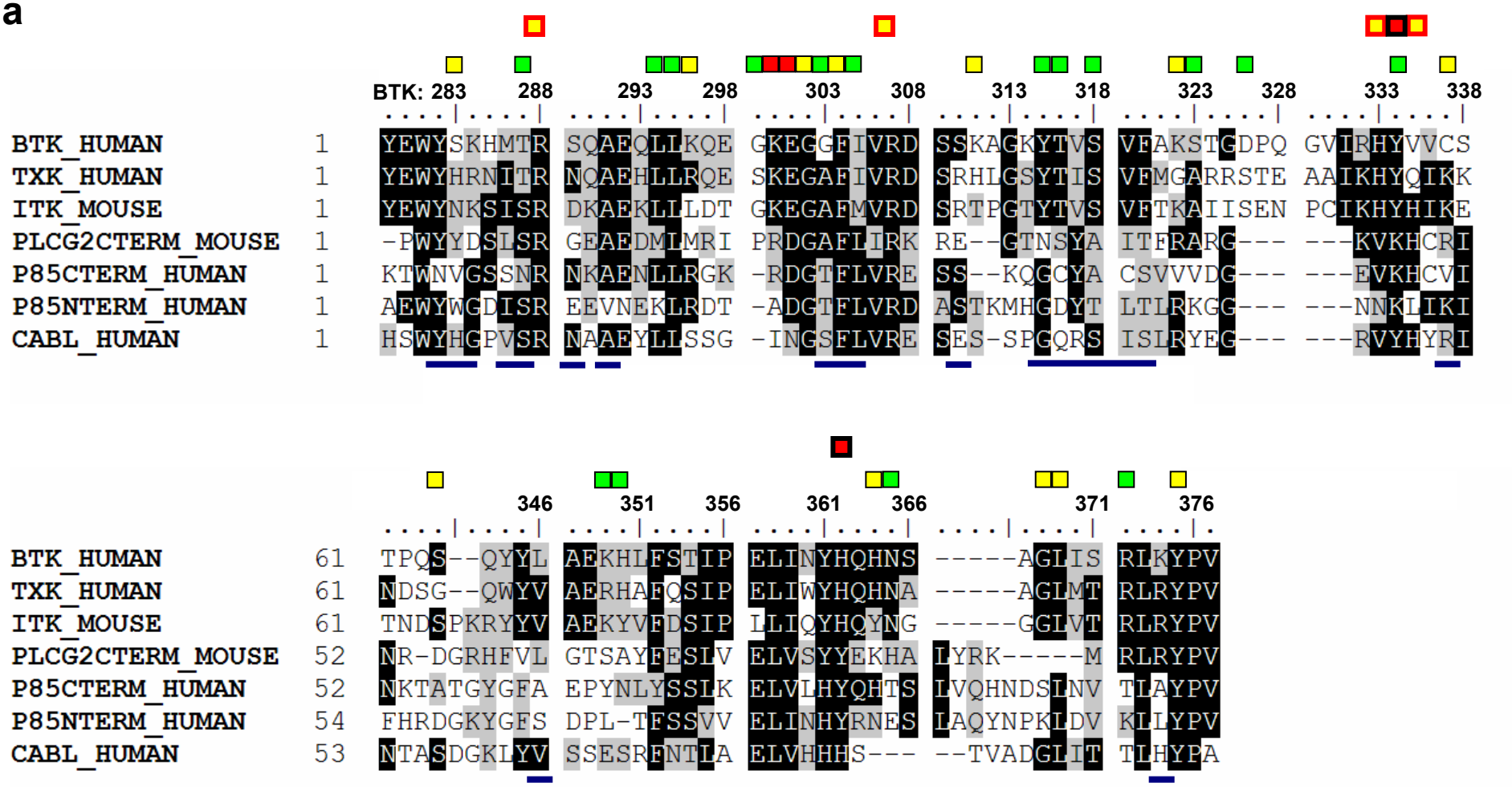
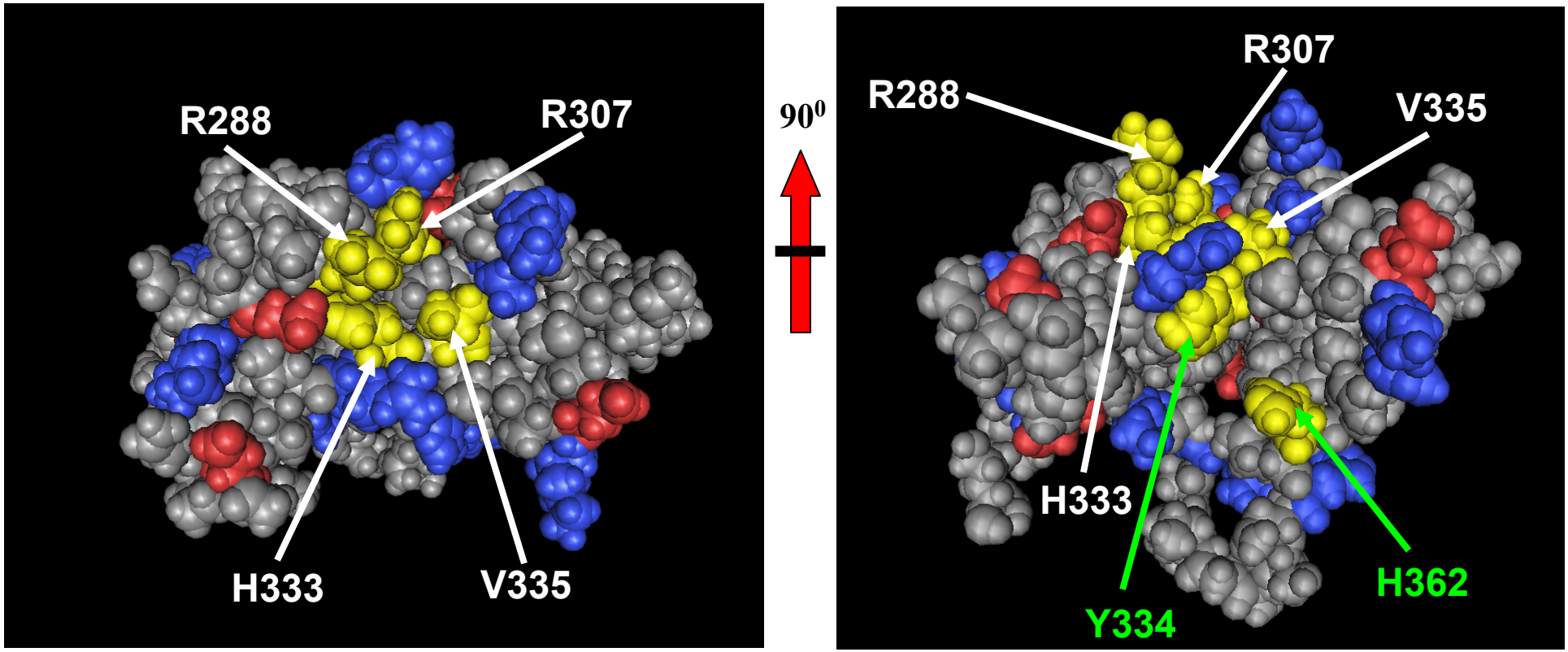
a

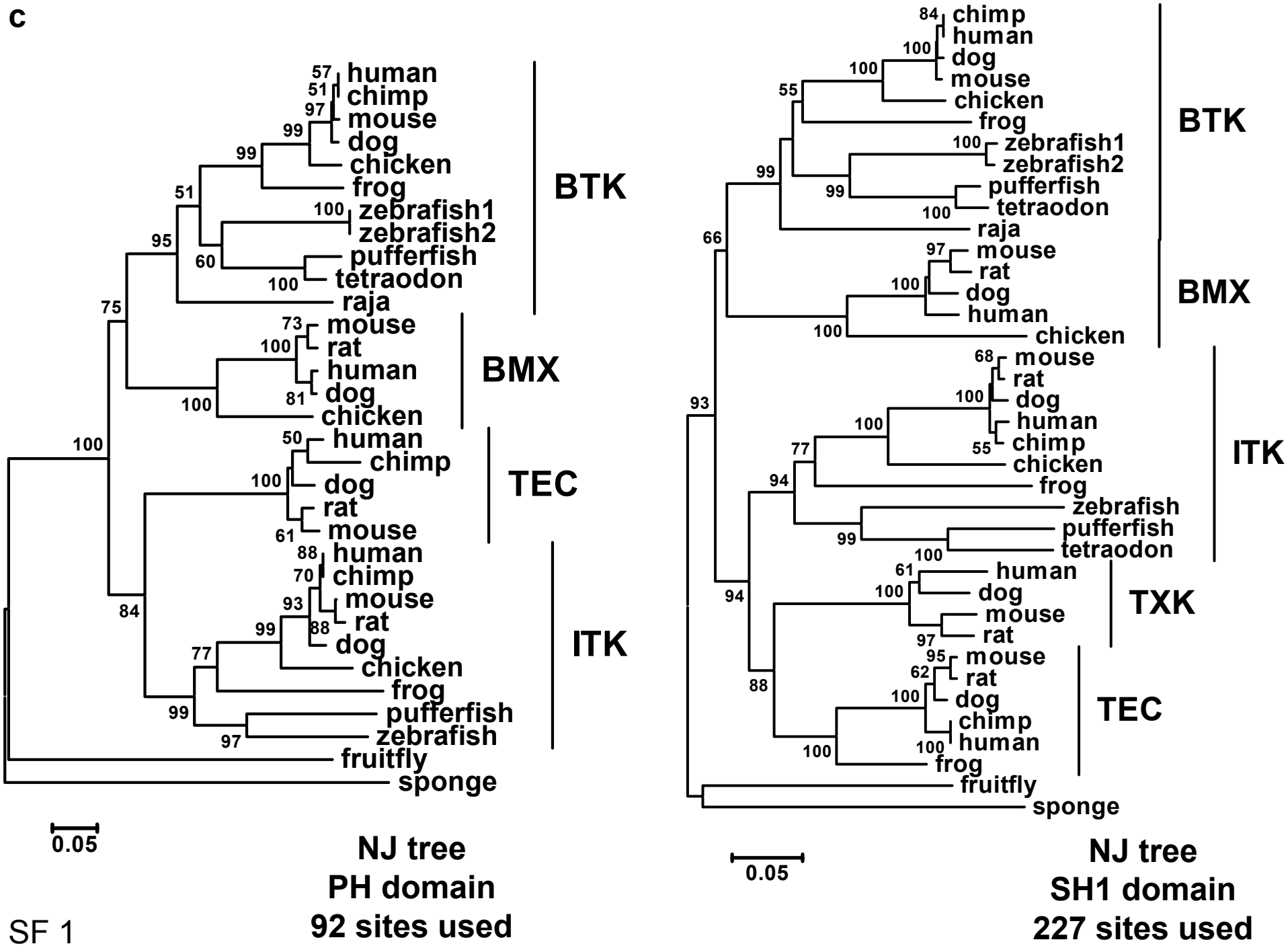


Supplemental Figure 1

b



SF 1


c
human
chimp
mouse
dog
chicken
frog
zebrafish1
zebrafish2
pufferfish
tetraodon
raja
mouse
rat
human
dog
chicken
human
chimp
dog
rat
mouse
human
chimp
mouse
rat
dog
chicken
frog
pufferfish
zebrafish
fruitfly
sponge
BTK
BMX
TEC
ITK
0.05
NJ tree
PH domain
92 sites used
chimp
human
dog
mouse
chicken
frog
zebrafish1
zebrafish2
pufferfish
tetraodon
raja
mouse
rat
dog
human
chicken
mouse
rat
dog
human
chimp
chicken
frog
zebrafish
pufferfish
tetraodon
human
dog
mouse
rat
mouse
rat
dog
chimp
human
frog
fruitfly
sponge
BTK
BMX
ITK
TXK
TEC
0.05
NJ tree
SH1 domain
227 sites used

SF 1

Supplemental Figure 1: (a) Multiple sequence alignment (MSA) of 7 structurally resolved SH2 domains which bind lipid. This MSA is annotated for the P-Tyrosine and Hydrophobic residues and those positions identified by GDDA-BLAST (in main text Figure 2a). In addition, positions in c-Abl which move in response to lipid-binding are plotted. **(b)** Structure of BTK SH2 annotated for the 4 P-Tyrosine (White) and 2 Hydrophobic (green) positions (PDB: 2GE9). **(c)** *Left*: Neighbor-joining tree of the PH domain in TEC, TXK, BMX, and BTK sequences from various taxa. This tree is rooted by the fruitfly and sponge TEC sequences. TXK does not have a PH domain and therefore has been excluded from these measures. *Right*: as above except the Neighbor-joining tree was constructed with only the SH1 domain (Kinase). These results are not due to the reduced number of sites utilized since trees generated from PH domain only (92 sites) or SH1 domain only (227 sites) retain the full-length topology and have significant support. Taken together, this suggests that the SH3-SH2 module is evolving more rapidly than the other domains in the protein. The clades have been colored with respect to their lipid specificity *in vitro*.