## **Supplementary Materials**

Investigation of PDE5/PDE6 and PDE5/PDE11 Selective Potent Tadalafil-like PDE5 Inhibitors Using Combination of Molecular Modeling Approaches, Molecular Fingerprint-Based Virtual Screening Protocols and Structure-based Pharmacophore Development

## Gülru Kayık<sup>1,2</sup>, Nurcan Ş. Tüzün<sup>1</sup>, Serdar Durdagi<sup>3,\*</sup>

<sup>1</sup>Department of Chemistry, Istanbul Technical University, Istanbul, Turkey

<sup>2</sup>Department of Pharmacy, University of Pisa, Via Bonanno, 6, 56126, Pisa, Italy

<sup>3</sup>Department of Biophysics, School of Medicine, Bahcesehir University, Istanbul, Turkey

\* E-mail: serdar.durdagi@med.bau.edu.tr

PDE5 E T R E L QS L AA A hPDE6 C E E E L AE I L QA	15 20 25 30 35 VVPSAQTLKITDFSFSDFELSDLET. ELPDADKYEINKFHFSDLPLTELEL	PDES hPDE11	EETRELOSLAAAVVPSAOTLKITDESESDEELSDLETAL CTIRM
45 50 PDE5 T I RMF TD L NL VQ hPDE6 G I QMYY E L K V VD	55 60 65 70 75 NFQMKHEVLCRWILSVKKNYRKNVA KFHIPQEALVRFMYSLSKGYRK IT	PDE5 hPDE11	FTDLNLVQNFQMKHEVLCRWILSVKKNYRKNVAYHNWRHAFNTAQ FMELGMVQKFKIDYETLCRWLLTVRKNYRM VLYHNWRHAFNVCQ
PDE5 WRHAFNTAQCMF hPDE6 WRHGFNVGQTMF	95 100 105 110 115 AALKAGKIONKLTDLEILALLIAAL SLLVTGKLKRYFTDLEALAMVTAAF	PDE5 hPDE11	CMFAALKAGKIONKLIDLEILALLIAALSHDLDHRGVNNSYTORS
PDE5 LDHRGVNNSYIQ hPDE6 IDHRGVNNLYQM	135 140 145 150 155 RSEHPLAQLYCHSIMEHHHFDQCLM KSQNPLAKLHGSSILERHHLEFGKT	PDE5 hPDE11	EHPLAQUYCHST MEHHHFDQCLMILNSPGNQTLSGLSTEEVKTT GSALAQUYGTSATLEHHHFNHAVMILQSEGHNIFANLSSKEYSDL
PDE5 SPGNQILSGLSI hPDE6 DESLNIFQNLNR	175 180 185 190 195 EEYKTTLKIIKQAILATDLALYIKR RQHEHAIHMMDIAIIATDLALYFKK	PDE5 hPDE11	103 100 195 200 205 210 215 220 223   LKTIKQATLATDLALYIKRRGEFFELIRKNOFNLEDPHOKELFLA   MQLLKQSILATDLTLYFERRTEFFELVSKGEYDWNIKNHRDIFRS
PDE5 hPDE6 FFELIRKN FQKIVDQSKTYE	215 220 225 230 235 OF NEED PHOKELFLAMLMT. SEQEWTQYMMLEQTRKEIVMAMMMT.	PDE5 hPDE11	MLMTACDLSAITK PWPIQQRIAELVATEFFDQGDRERKELNIEPT MLMTACDLGAVTK PWEISRQVAELVTSEFFEQGDRERLELKLTPS
PDE5 LSAITKPWPIQQ hPDE6 LSAITKPWEVQS6	255 260 265 270 275 RIAELVATEFFDQGDRERKELNLEP QVALLVAAEFWEQGDLERTVLQQNP	PDE5 hPDE11	275 240 245 240 255 400 455 510 155 DLMNREKKNK I PSMQYGF I DA I CLQL YEAL THVS EDC FPL LDGCR A I FDRNRKDEL PRLQL EW I DS I CMPL YQAL VK VNVK LK PML DS VA
PDE5 MNREKKNKIPSM hPDE6 MDRNKADELPKLC	295 300 305 310 315 QVGFIDALCLQLYEALTHVSEDCFP QVGFIDFVCTFVYKEFSRFHEEITPI	PDES hPDE11	120 123 218 135 348 146 156 155 260 KNRQKWQALAEQQ TNRSKWEELHQ
PDE5 GCRKNRQKWQAL hPDE6 GITNNRKEWKAL	AEQQ ADEY		

**Figure S1.** Aminoacid sequence alignments of PDE6 andPDE11 over PDE5 catalytic site residues. Alignment procedure was achieved with Blosum62 matrix via MOE software.



Figure S2. Ramachandran plots of the homology models of PDE6 and PDE11.



**Figure S3.** Contact Energy Profiles of the catalytic side residues that correspond to PDE5, PDE6 and PDE11. The x axis and y axis represent the aminoacid residues numbering and atom-atom contact pair energies in kcal/molunit, respectively.







**Figure S4**. 2D protein-ligand interaction diagrams of the selected compounds (Table 1) with the catalytic site residues of PDE5.