

FIG. 1

Amino acid residues constituting hPPAR δ ligand binding pocket

MEQPQEEAPEVREEEEKEEVAEAGAPELNGGPQHAPSSSYTDLSRSSPPSLDQLQM

GCDGASGSLNMECRVCGDKASGFHYGVHACEGCKGFFRRTIRMKLEYEKERSCKIQKK

NRNKCQYCRFQKCLALGMSHNAIRFGRMPEAEKRKL VAGLTANEGSQYNPQVADLKAFSK

HIYNAYLKNFNMTKKKARSILTGKASHTAPFV $\dot{\text{I}}$ HD $\dot{\text{I}}$ ETLWQA $\dot{\text{E}}$ KGLV $\dot{\text{W}}$ KQLVNGLPPYKE

ISVHV $\dot{\text{F}}$ YRC $\dot{\text{Q}}$ CT $\dot{\text{T}}$ V $\dot{\text{E}}$ TVR $\dot{\text{E}}$ LT $\dot{\text{E}}$ FAKSI $\dot{\text{P}}$ SFSSLFLNDQVTLLKYGV $\dot{\text{H}}$ EA $\dot{\text{I}}$ FAMLAS $\dot{\text{I}}$ VNK

DGLLV $\dot{\text{A}}$ NGSGF $\dot{\text{V}}$ TRE $\dot{\text{F}}$ LSLRKPFS $\dot{\text{D}}$ $\dot{\text{I}}$ EPKF $\dot{\text{E}}$ FAVKFNALEDDSDLALFIAA $\dot{\text{I}}$ ILCGD

RPGLMNVPRVEA $\dot{\text{I}}$ QDTILRALEFHLQANHPDAQYLFPKLLQKMADLRQLVTE $\dot{\text{H}}$ AQM $\dot{\text{M}}$ QRI

KKTETETSLHPL $\dot{\text{L}}$ QE $\dot{\text{I}}$ YKDMY

➡ Ligand binding domain

- Amino acid residue constituting interior surface of ligand binding domain
- Amino acid residue forming hydrogen bonding with metformin guanidine group

FIG. 2

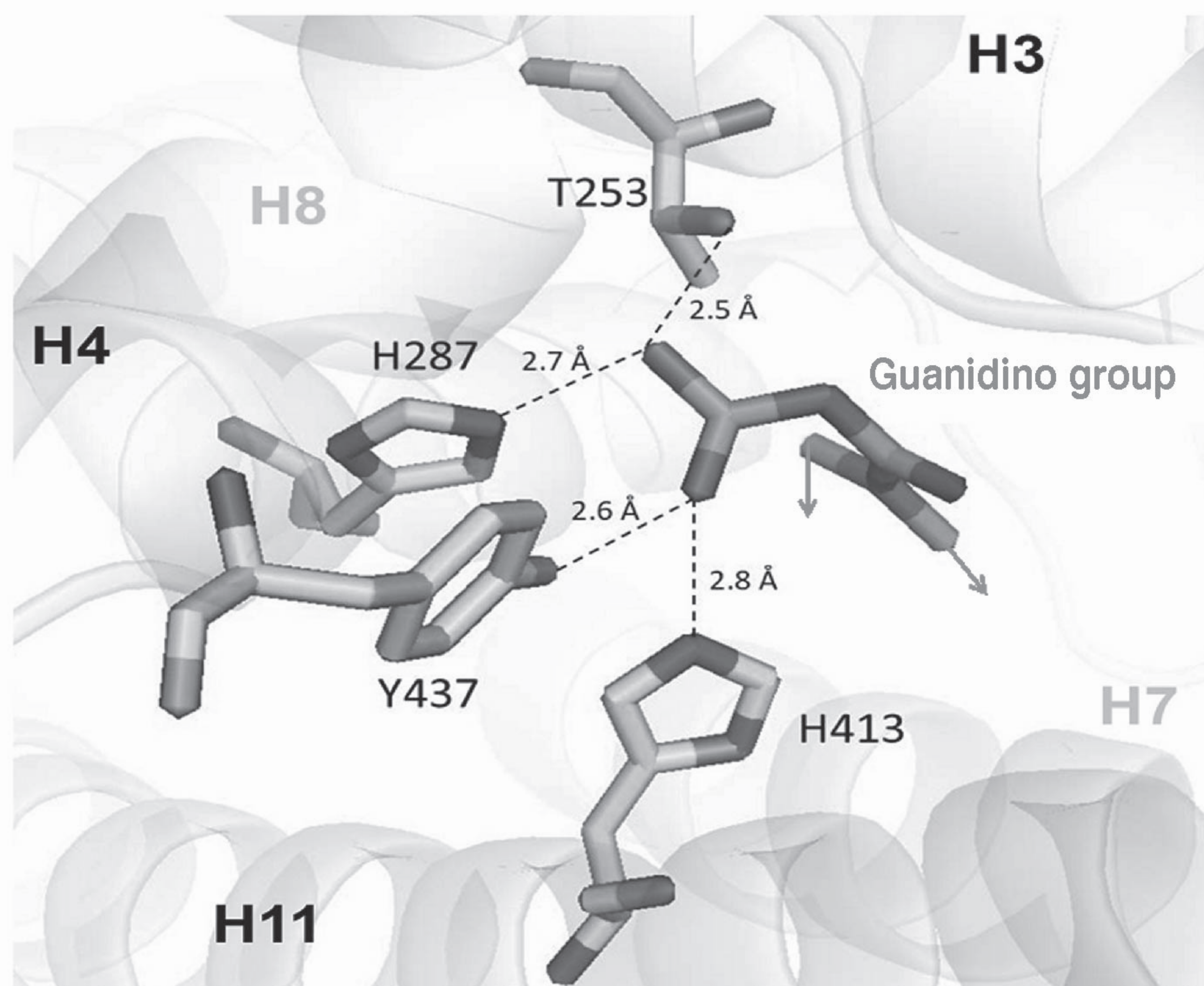


FIG. 3

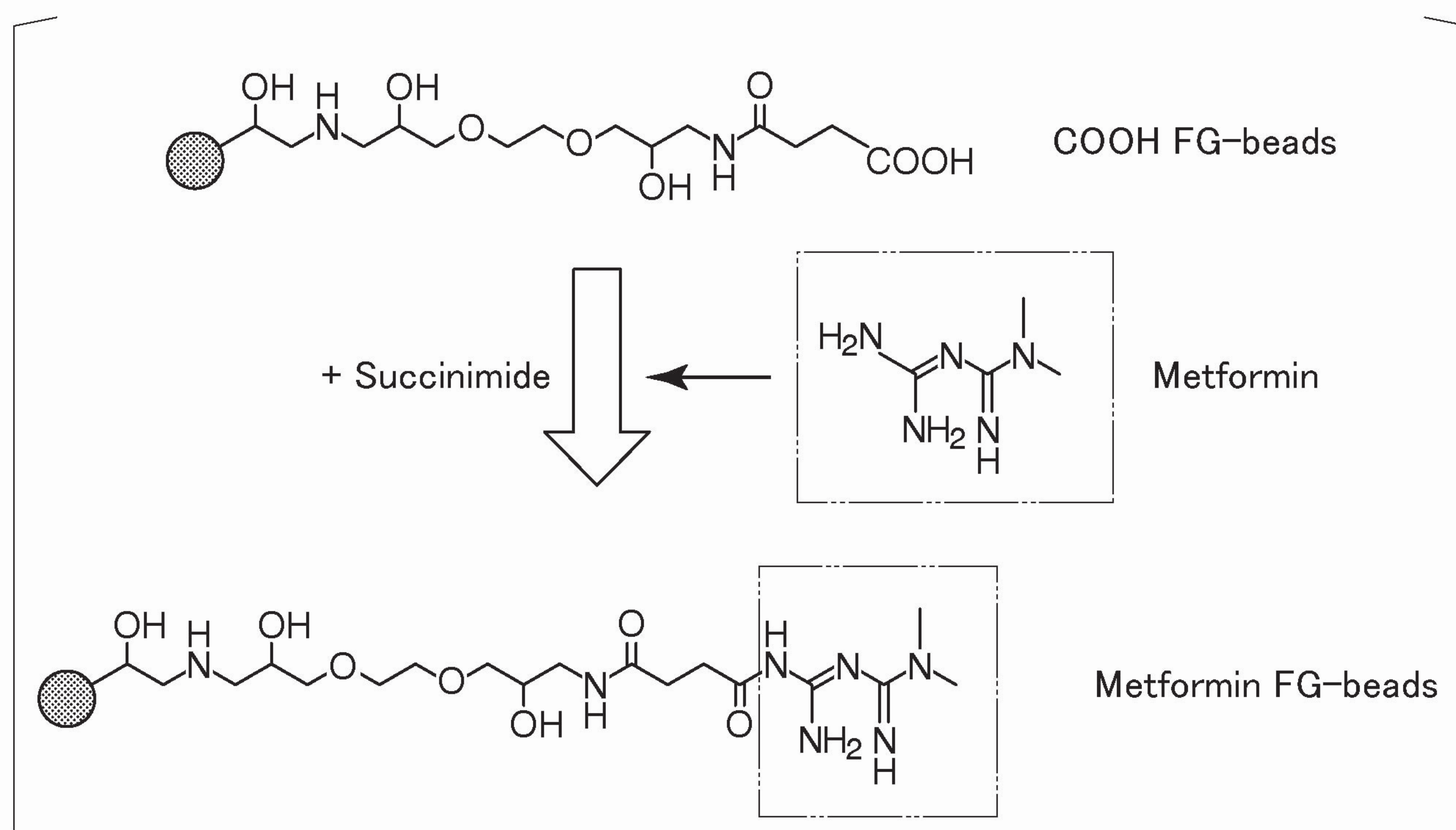


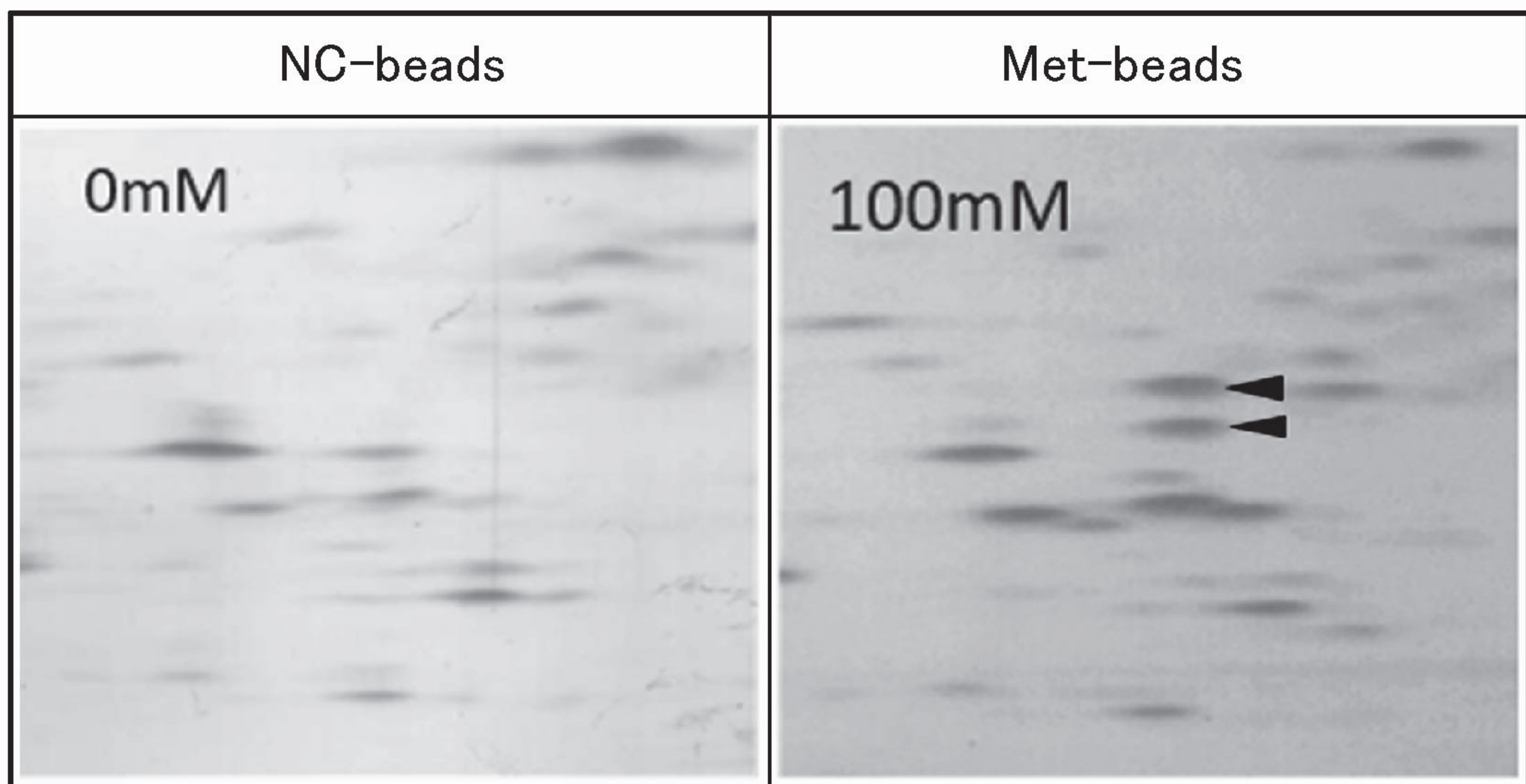
FIG. 4

FIG. 5

Protein sequence coverage: 26%

1 MEQPQEEAPE VREEEEKEEV AEAEGAPELN GGPQHALPSS SYTAIRFGRM
51 PEA EKRLVA GLTANEGSQY NPQVADLKAF SKHIYNAYLK NFNMTKKKAR
101 SILTGKASHT APFVIHD IET LWQAEKGLVW KQLVNGLP PY KEISVHV FYR
151 CQCTTVETVR ELTEFAKSIP SFSSLFLNDQ VTLLKYGVHE AIFAMLASIV
201 NKDGLLVANG SGFVTREFLR SLRKPFSDII EPKFEFAVKF NALEDDSDL
251 ALFIAAII LC GDRPGLMNVP RVEAIQDTIL RALEFHLQAN HPDAQYLFPK
301 LLQKMADLRQ LVTEHAQMMQ RIKKTETETS LHPLLQE IYK DMY

_____ : Amino acid sequence identified by TOF–MF

FIG. 6

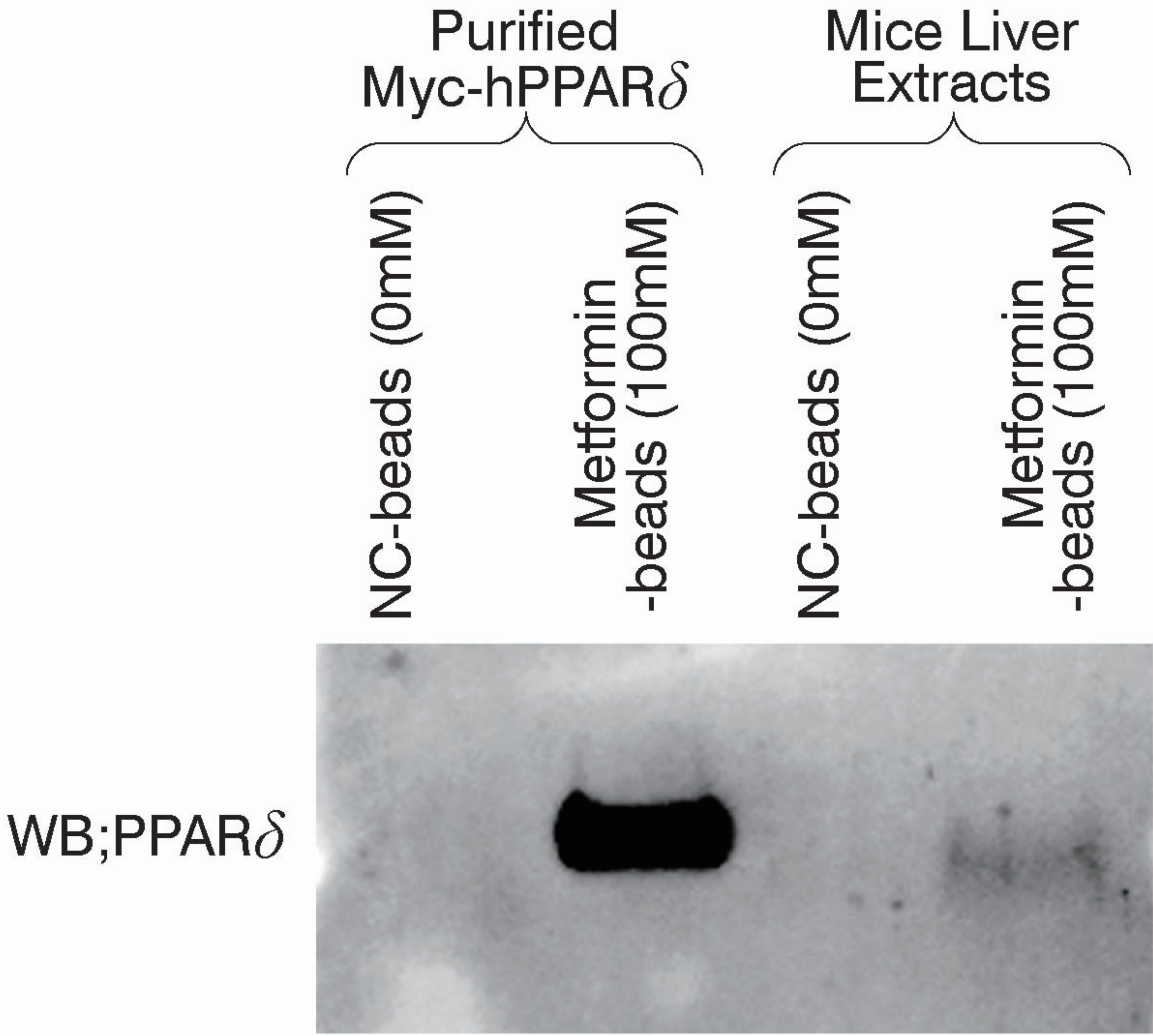


FIG. 7

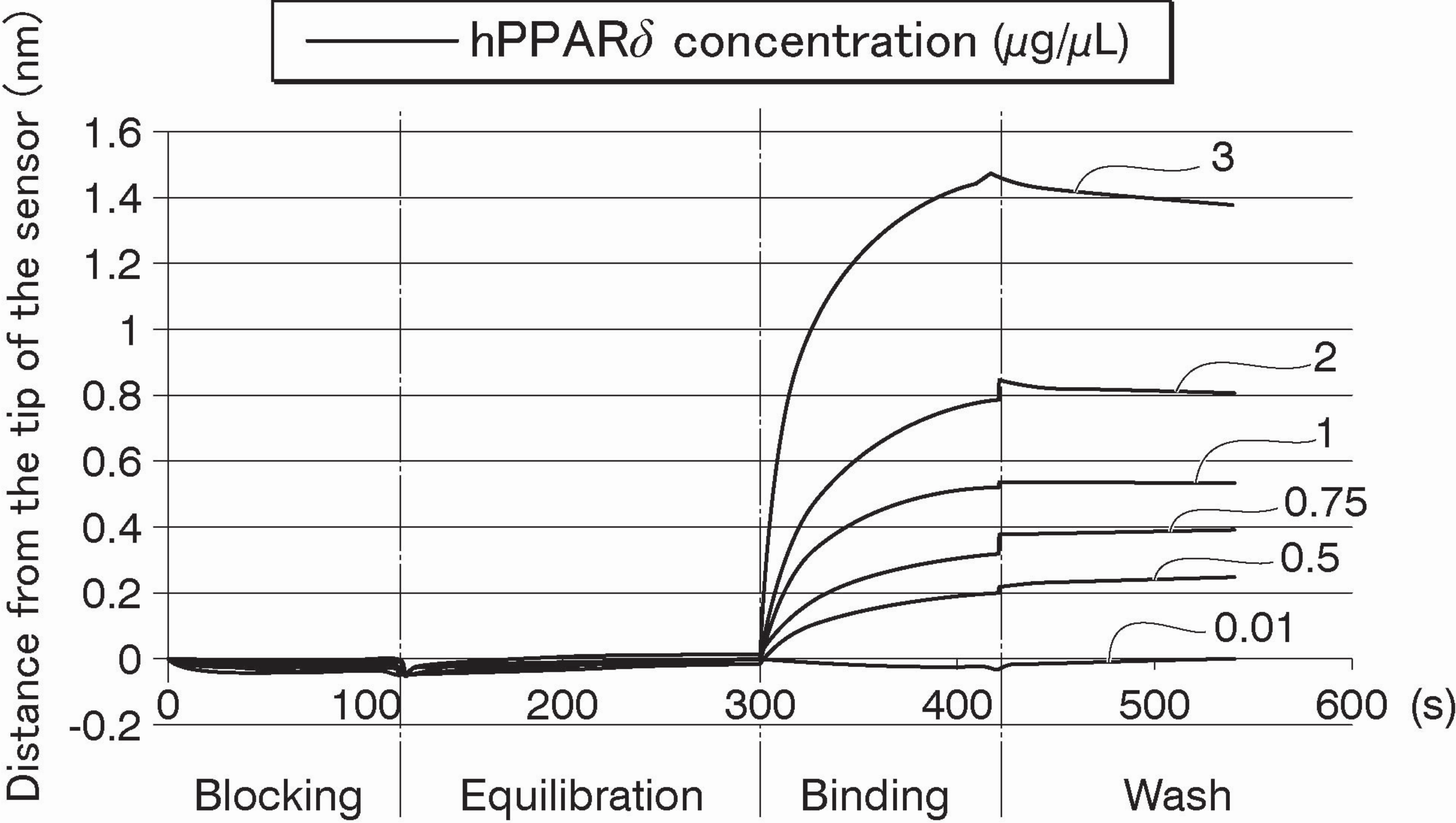


FIG. 8

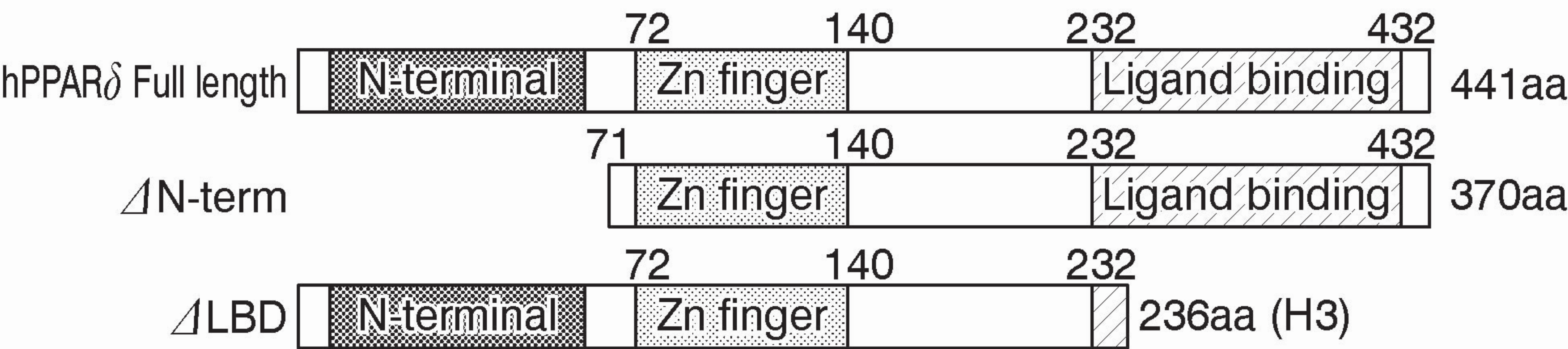


FIG. 9

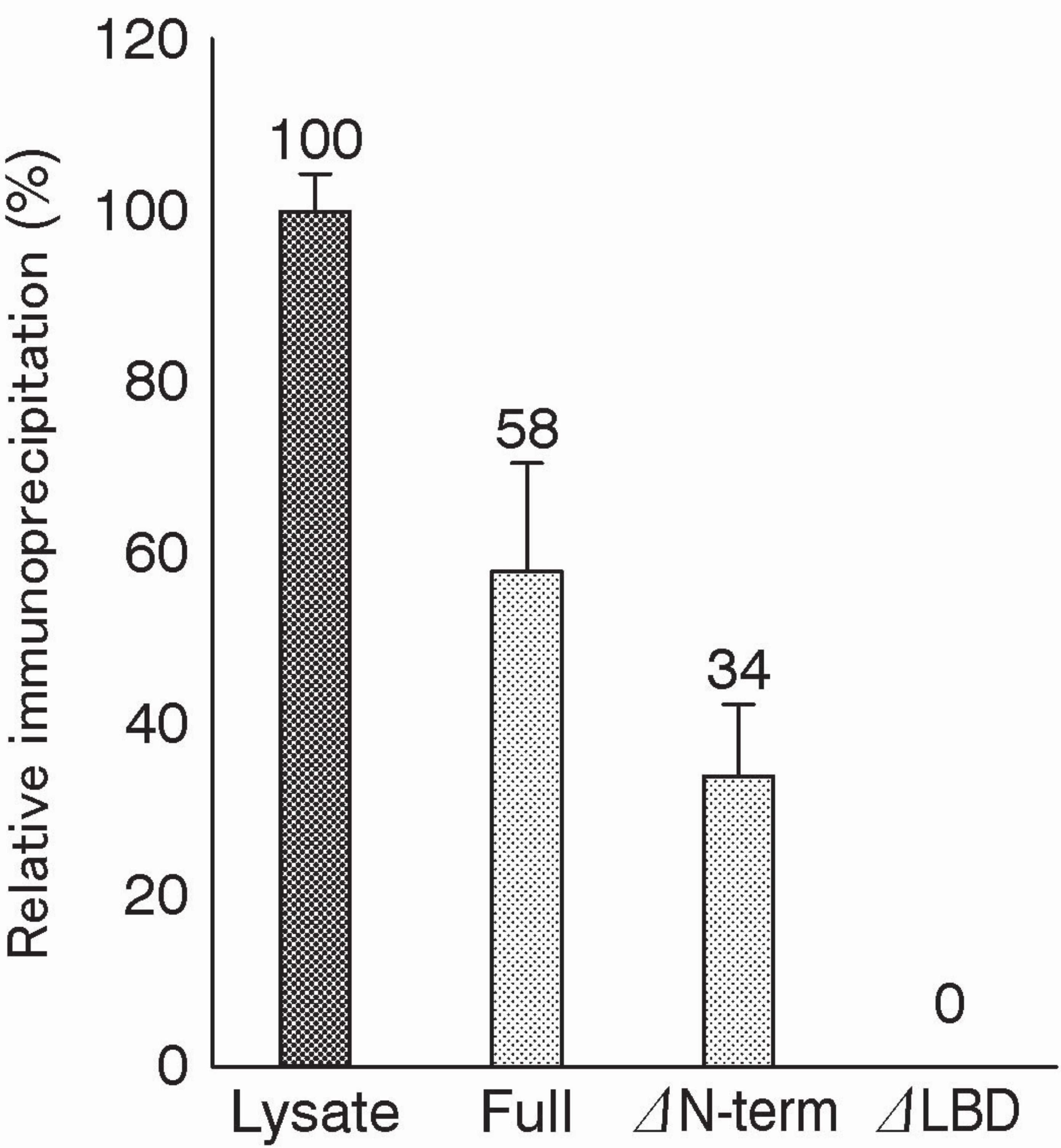


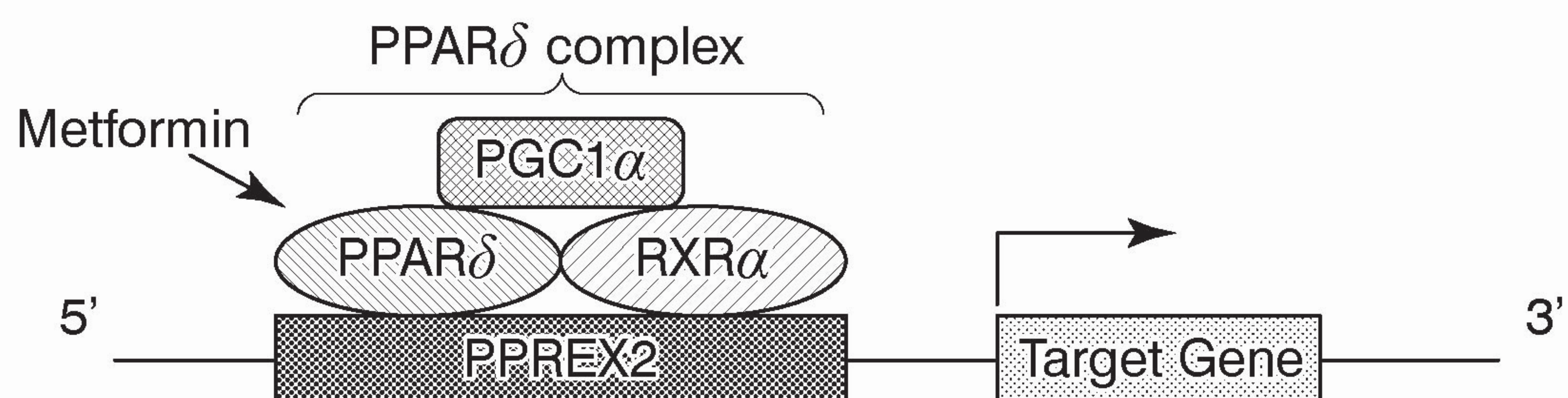
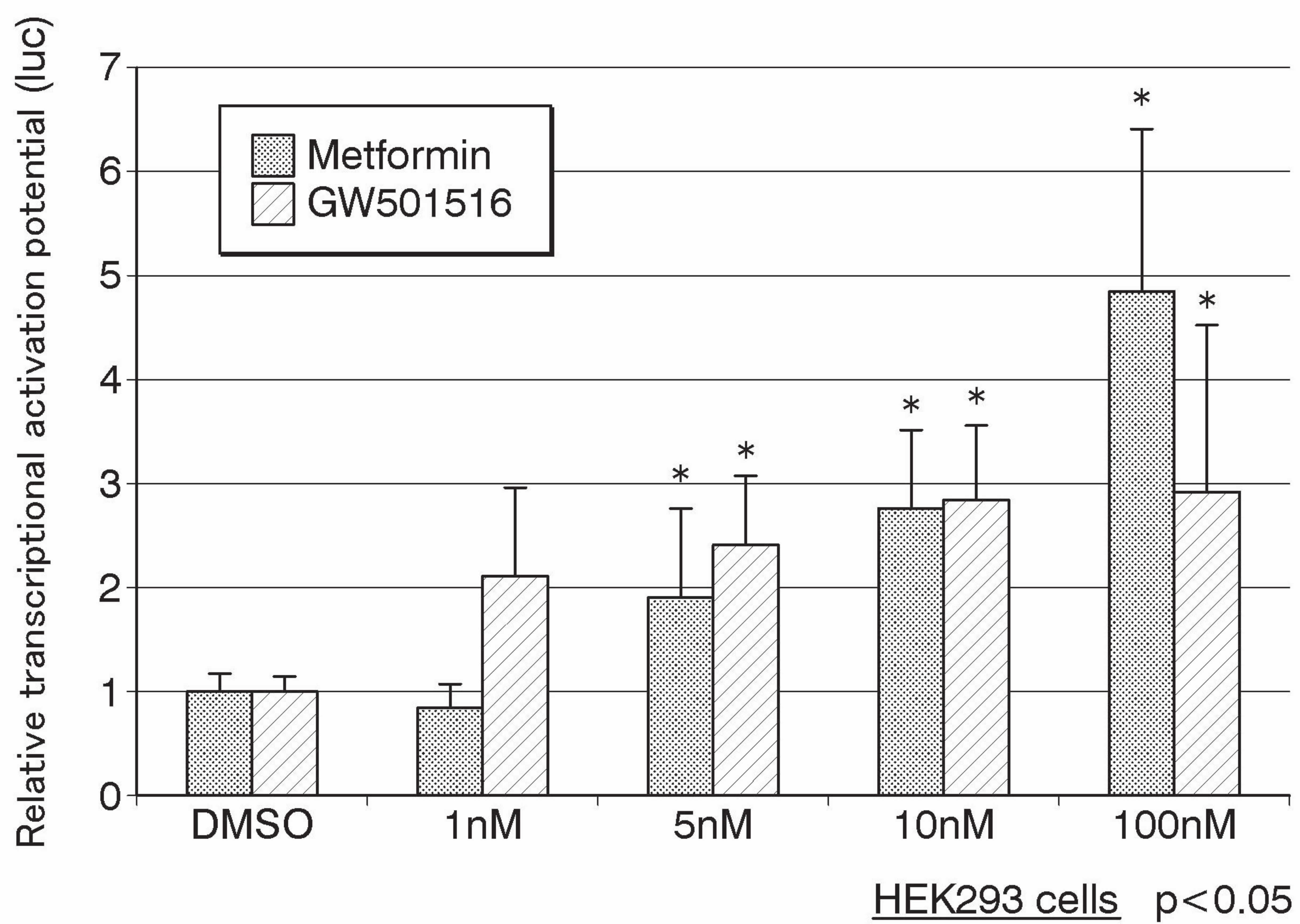
FIG. 10A*FIG. 10B*

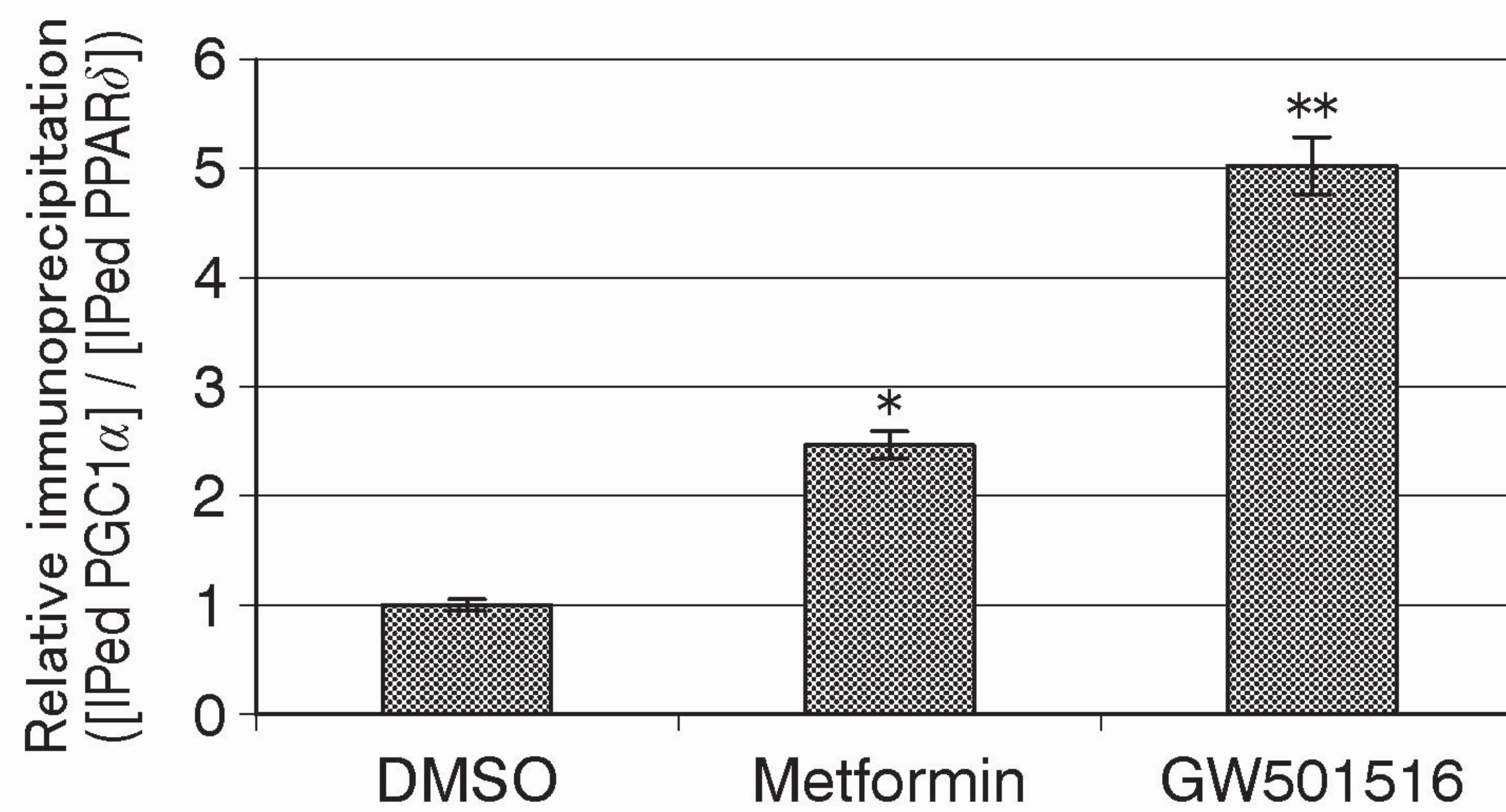
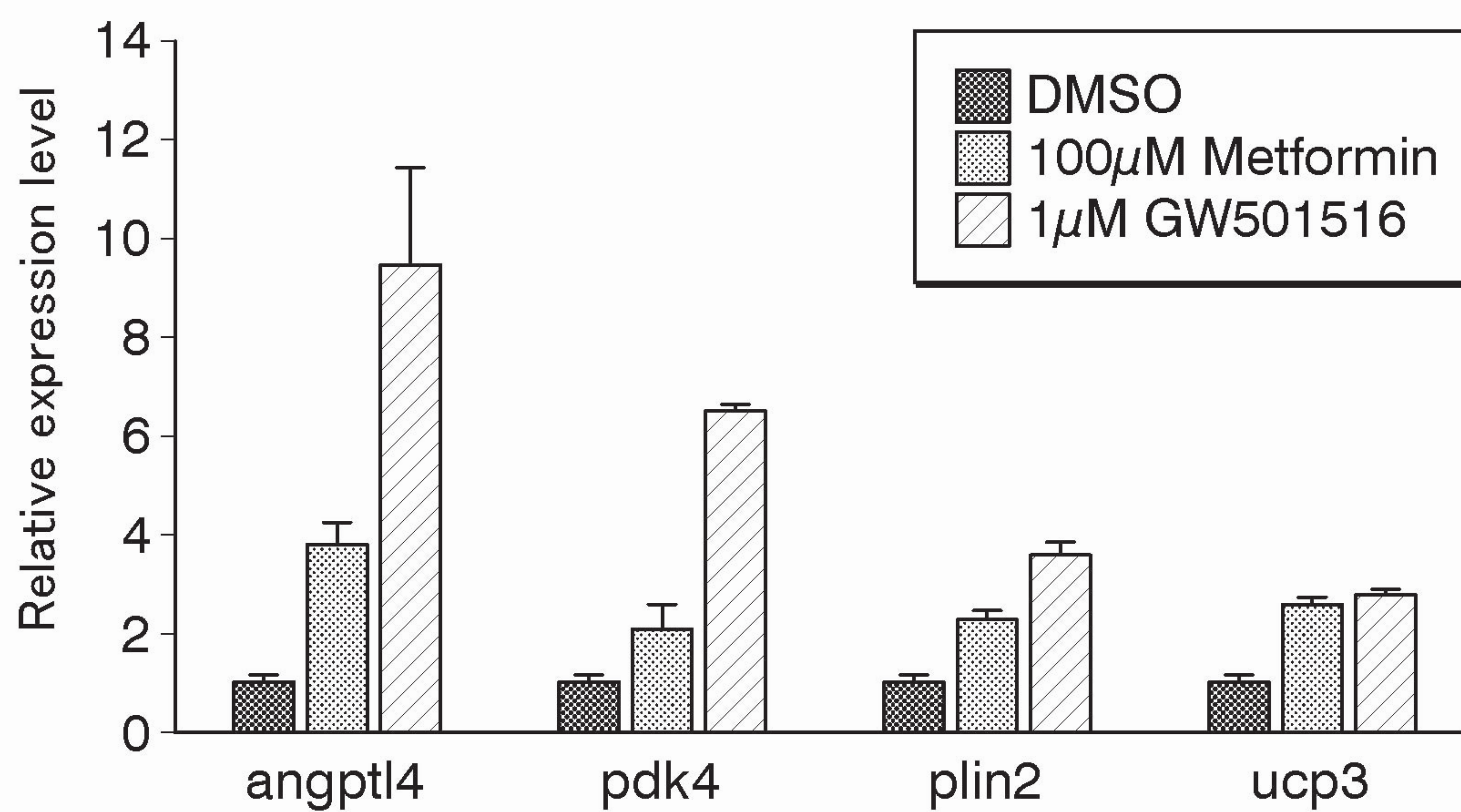
FIG. 11*FIG. 12*

FIG. 13

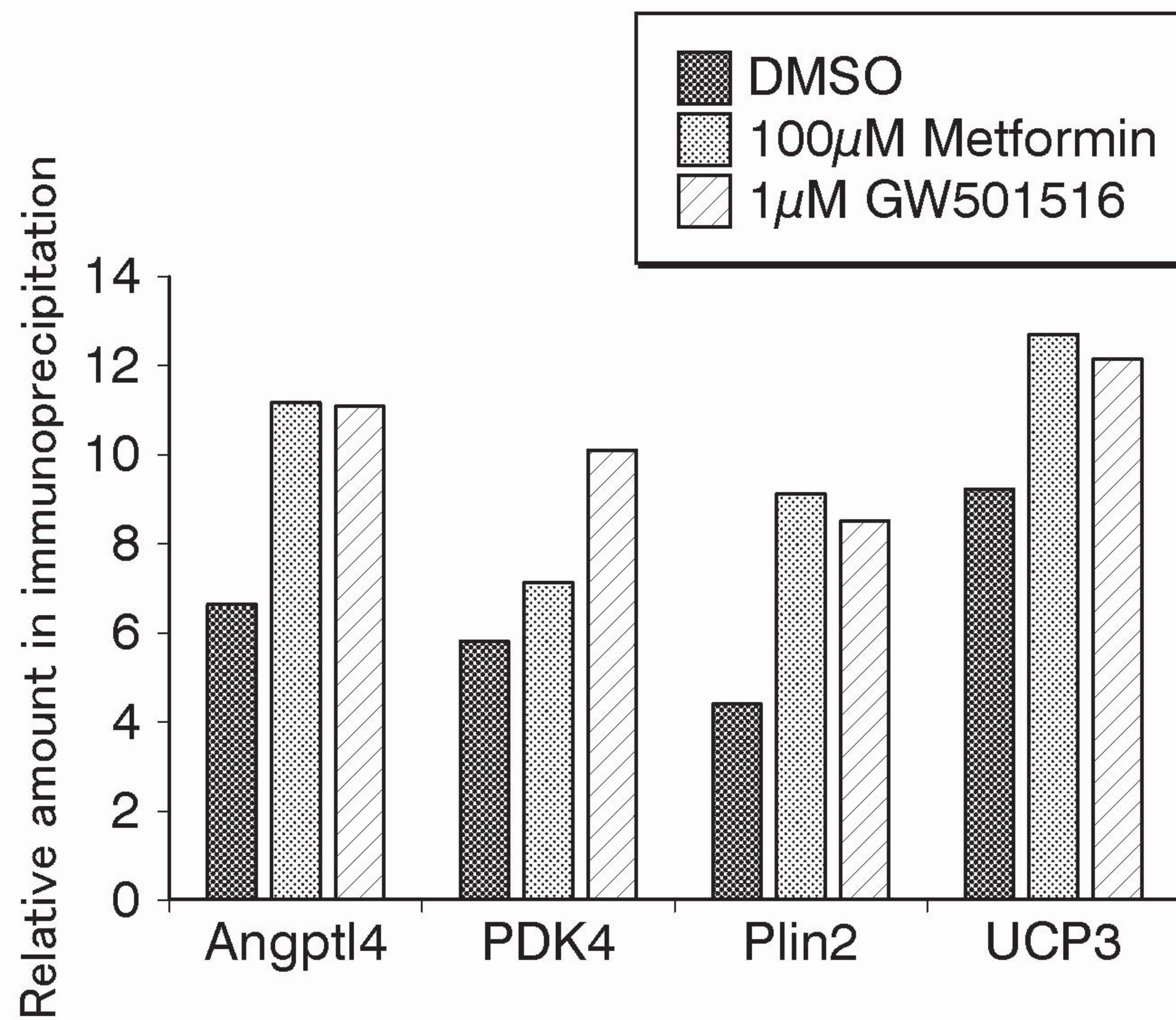


FIG. 14

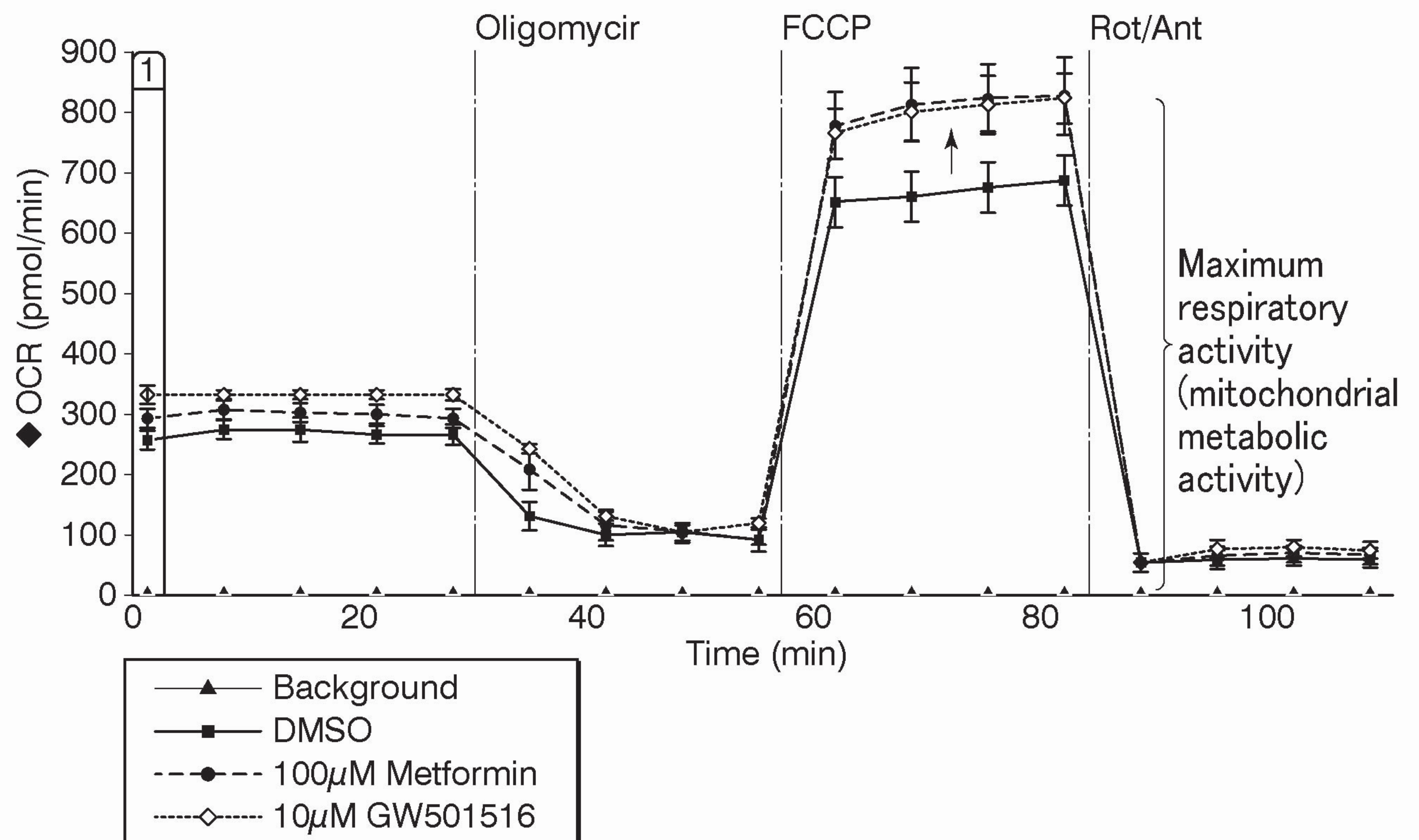


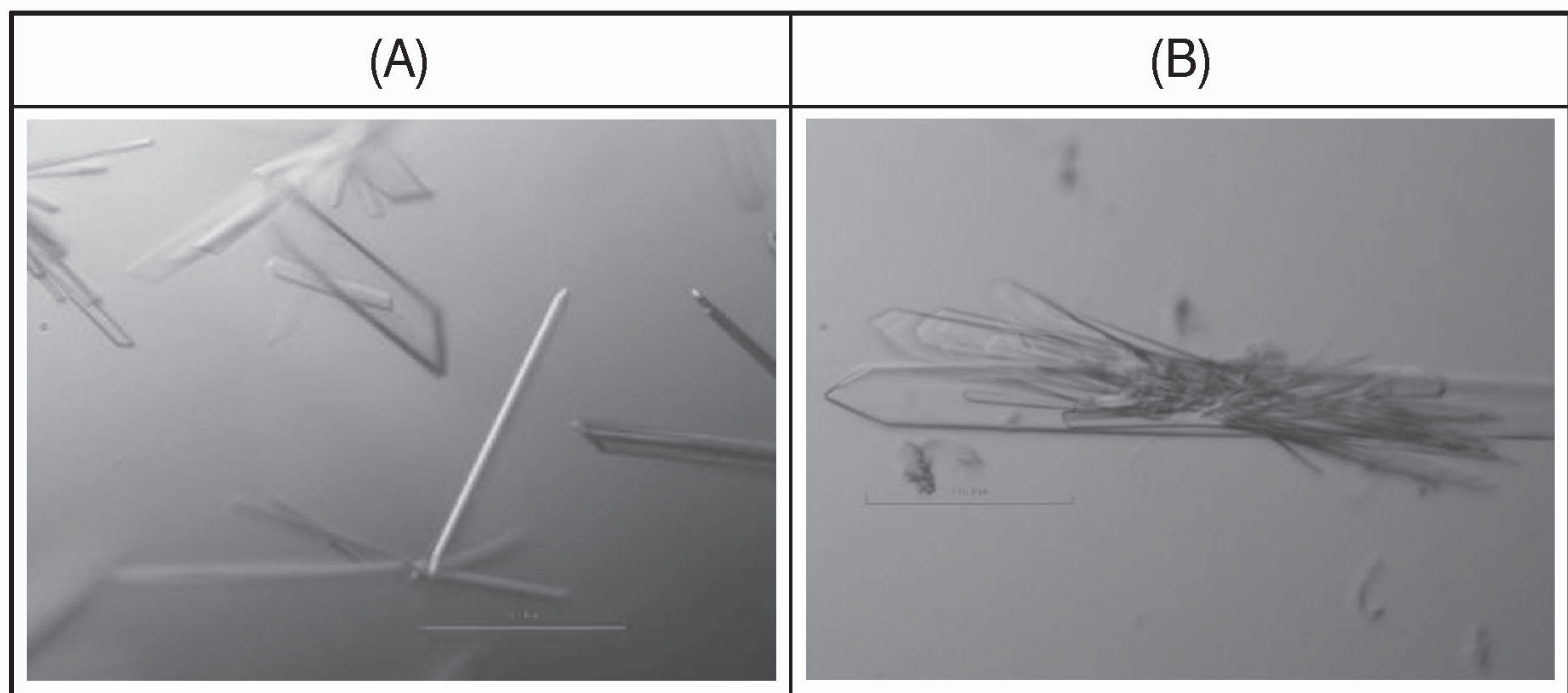
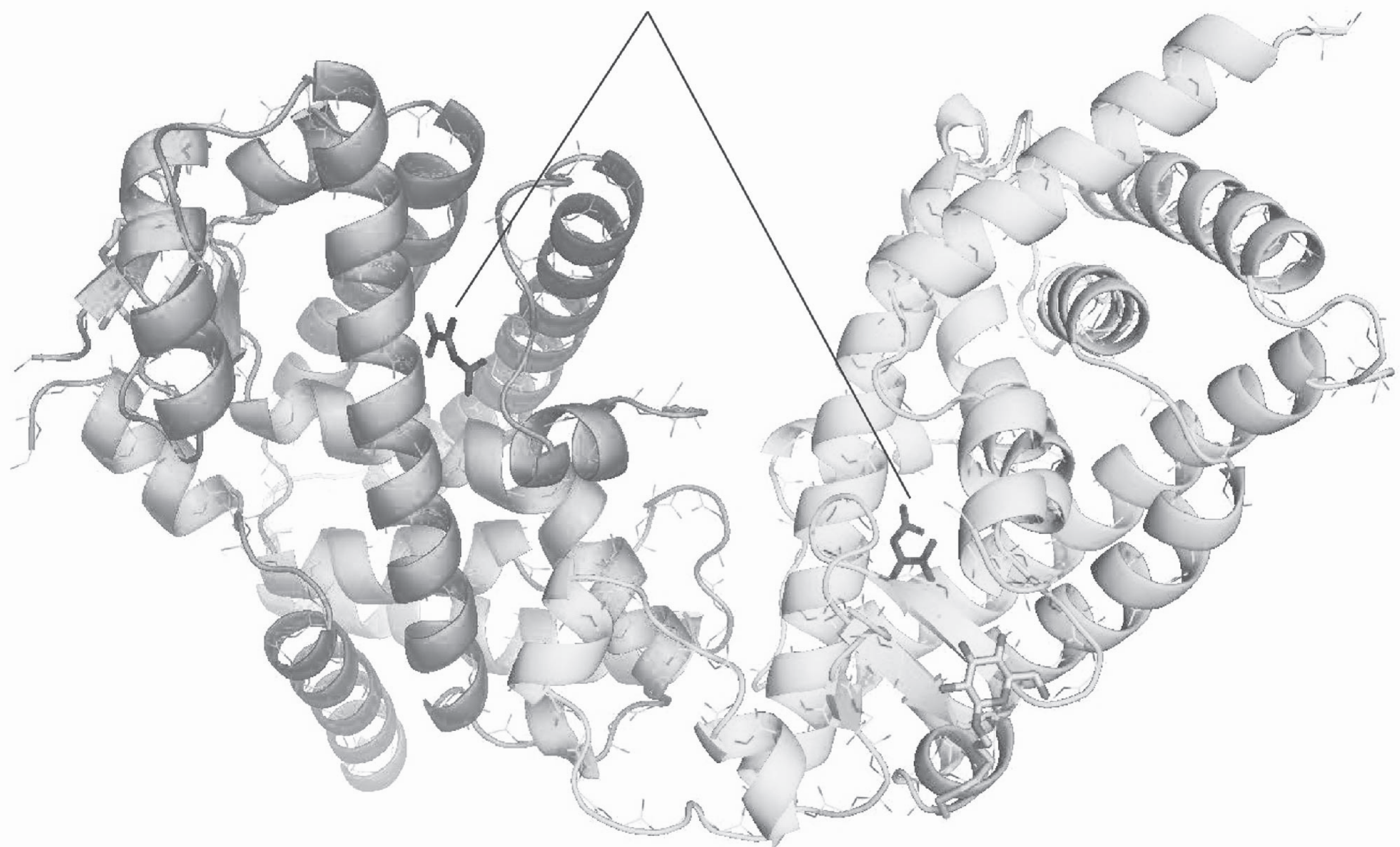
FIG. 15*FIG. 16***Metformin****Molecule A****Molecule B**

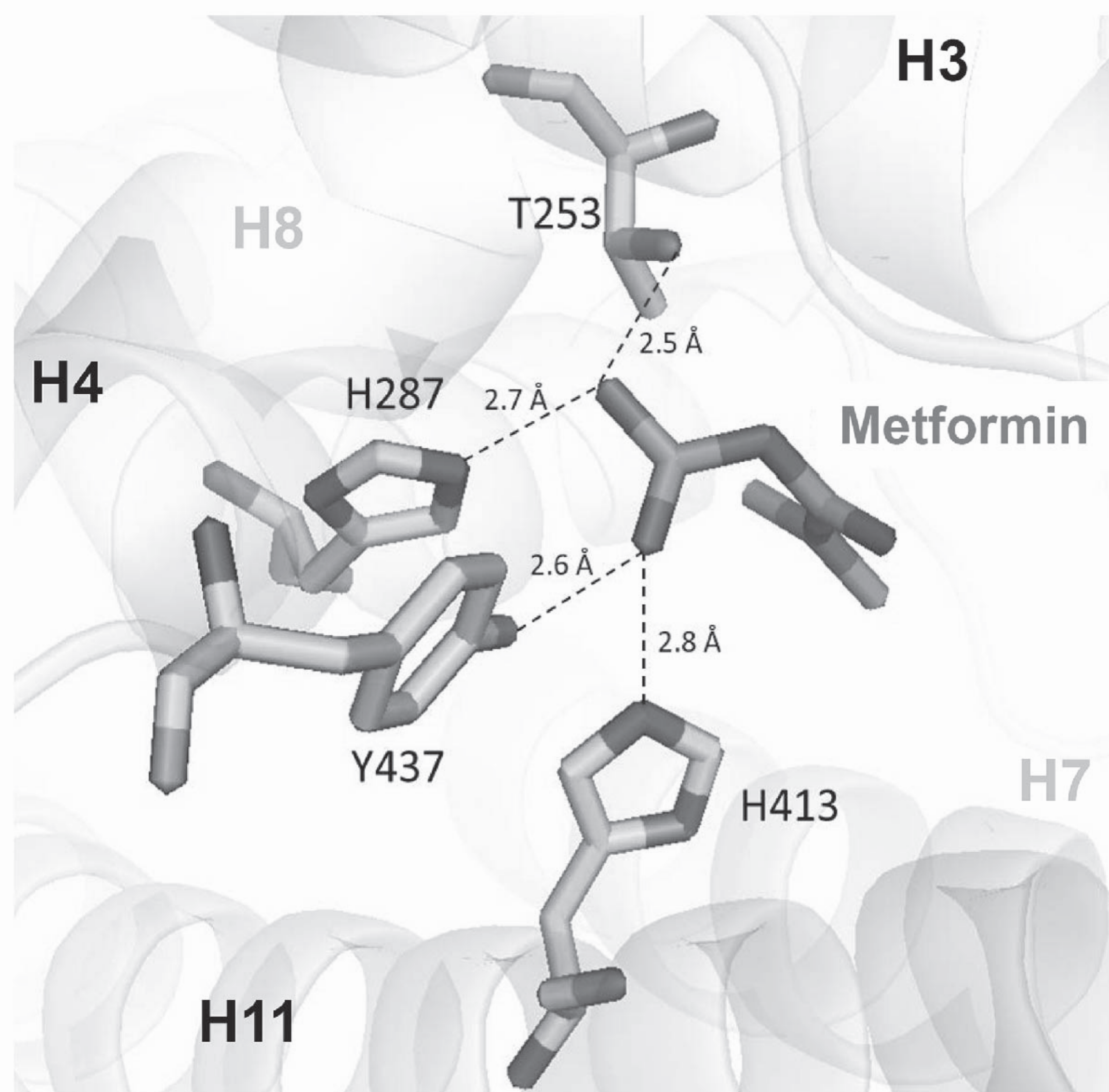
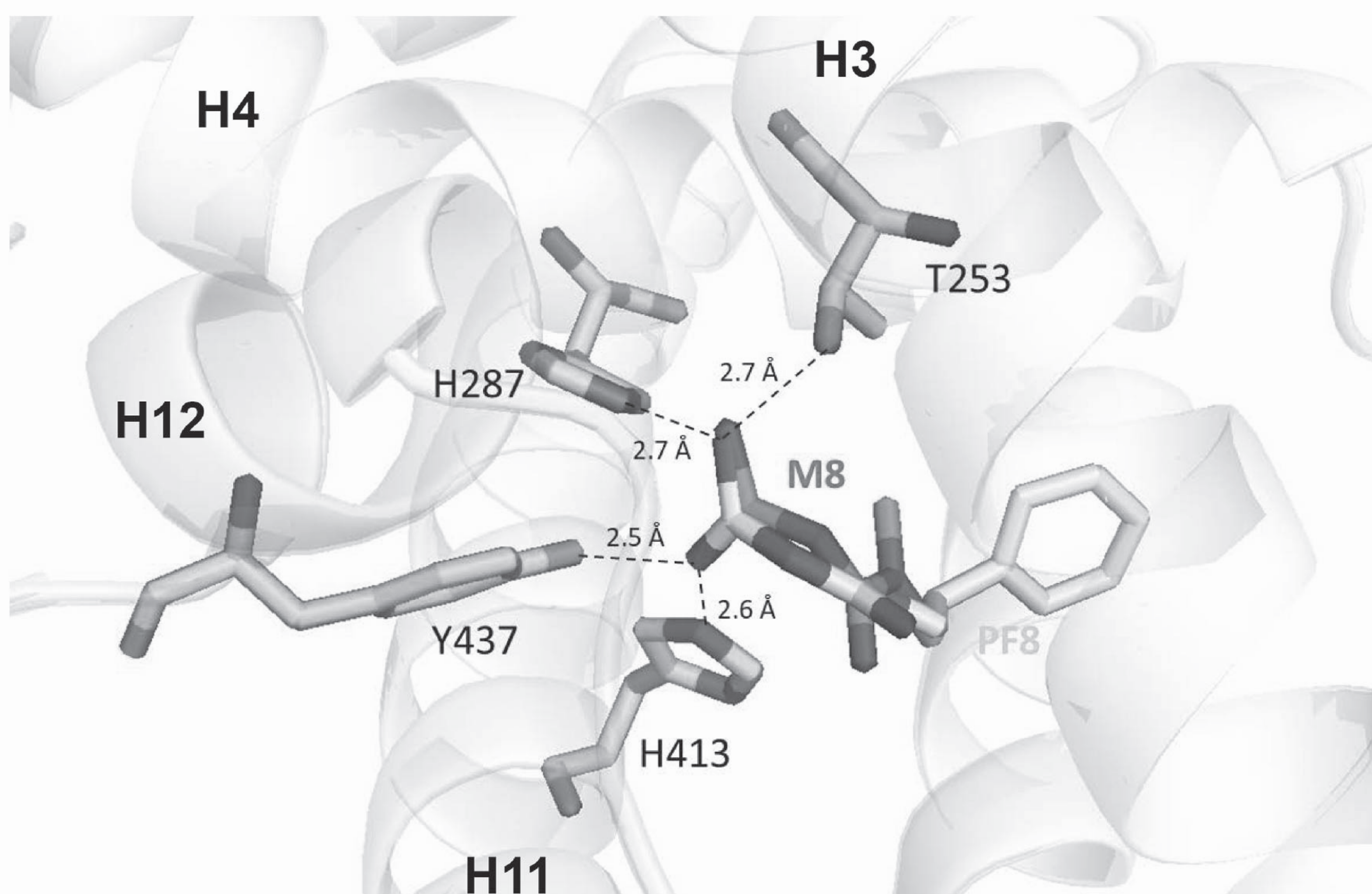
FIG. 17*FIG. 18*

FIG. 19

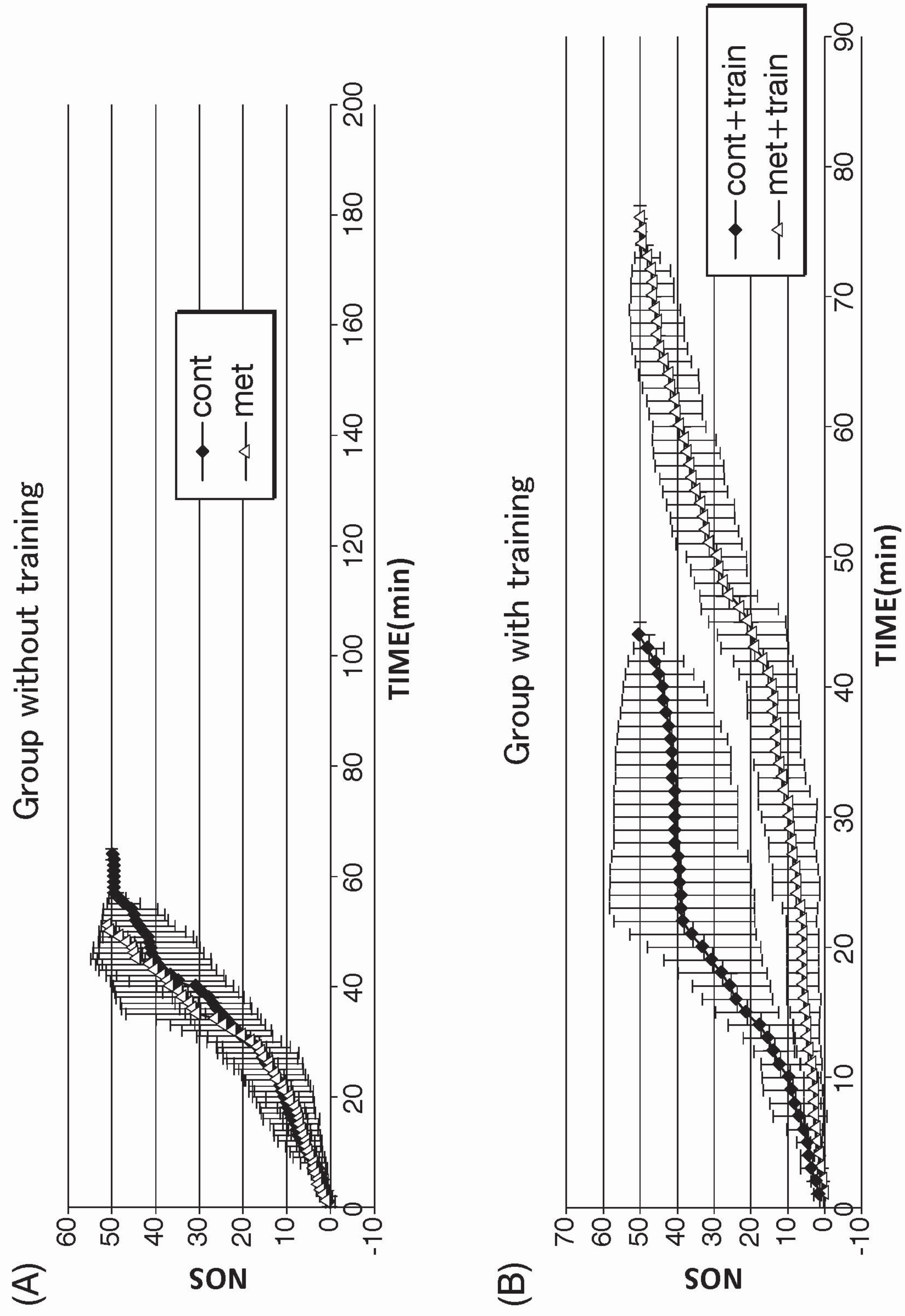


FIG. 20

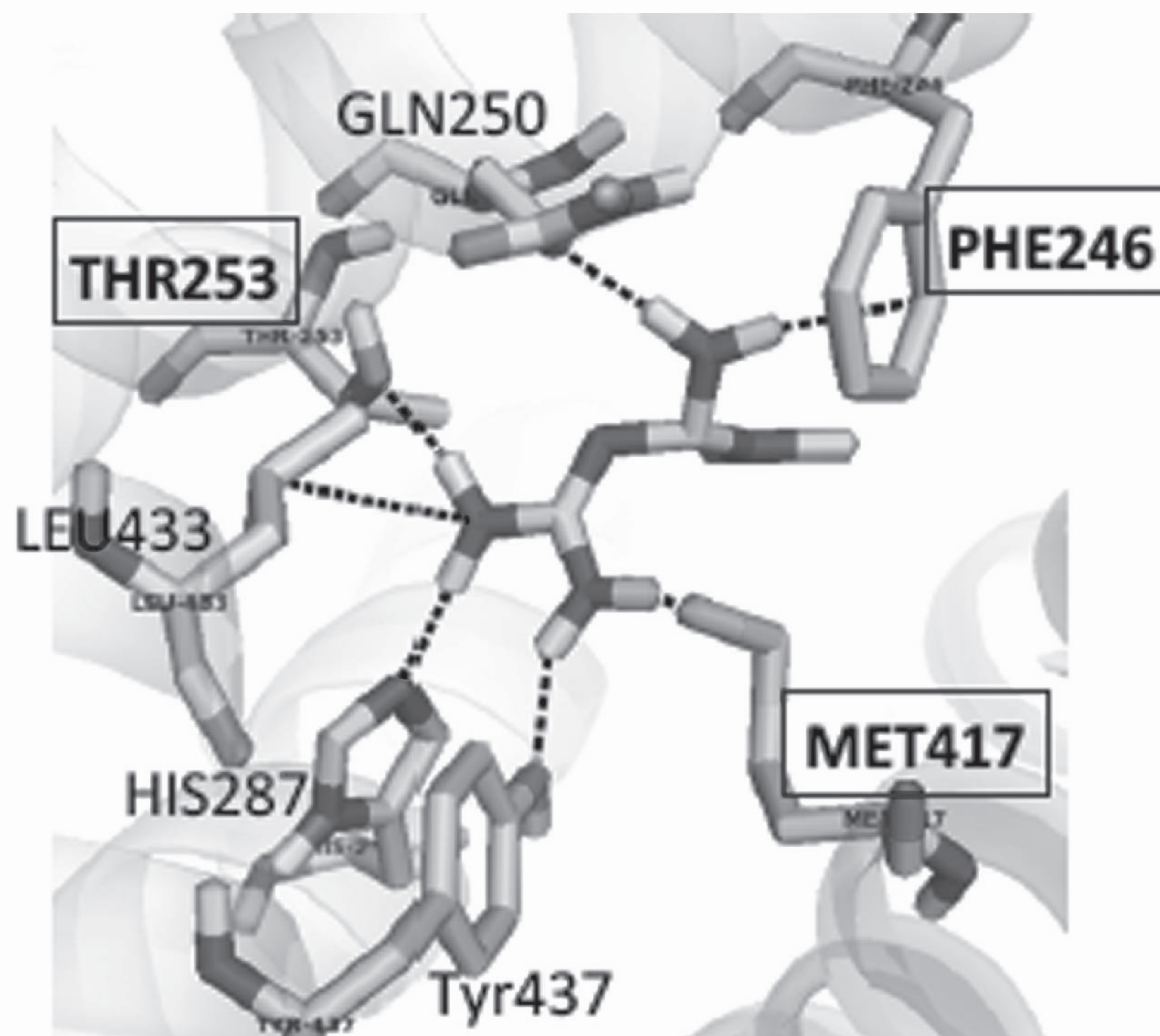


FIG. 21

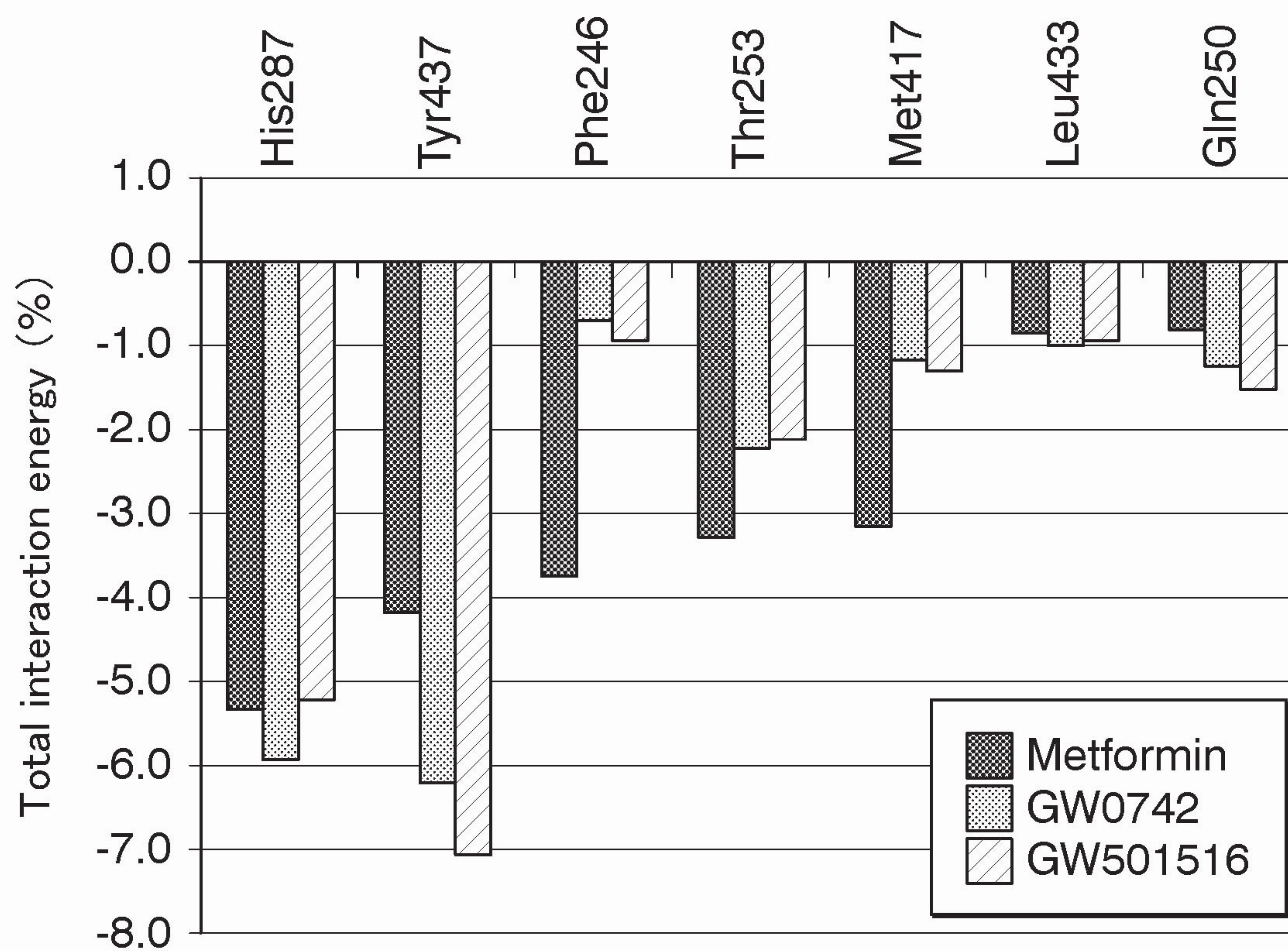


FIG. 22

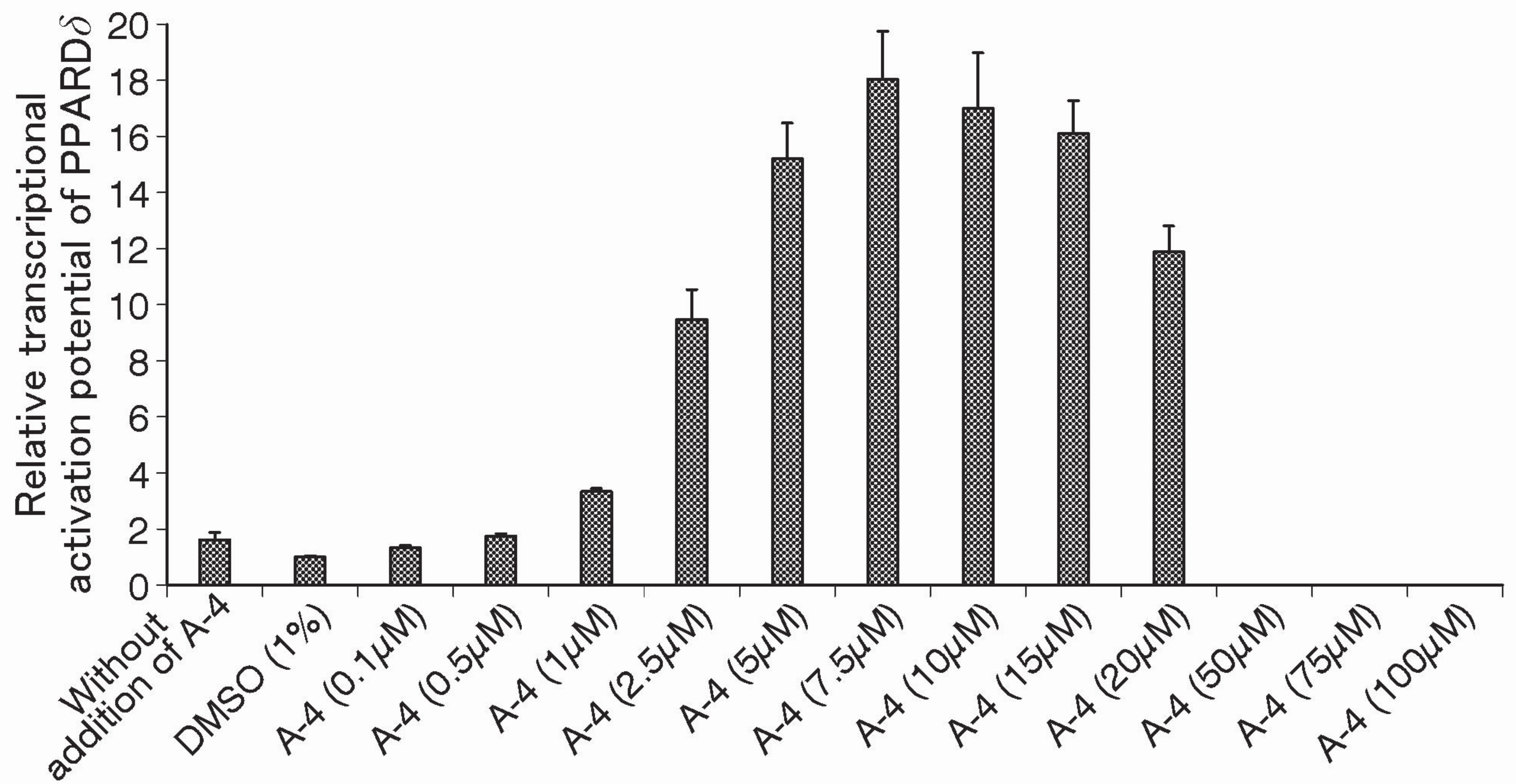
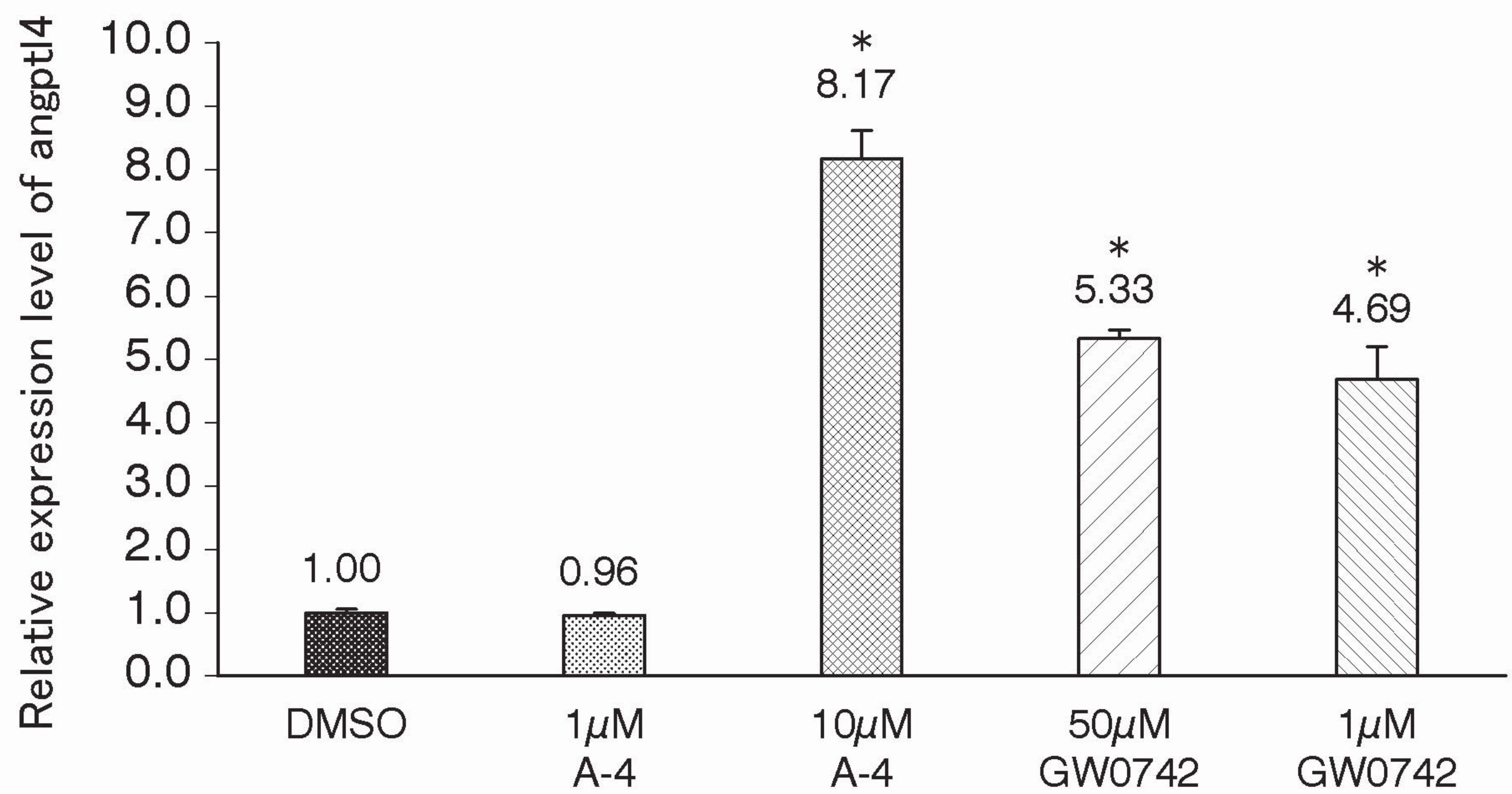
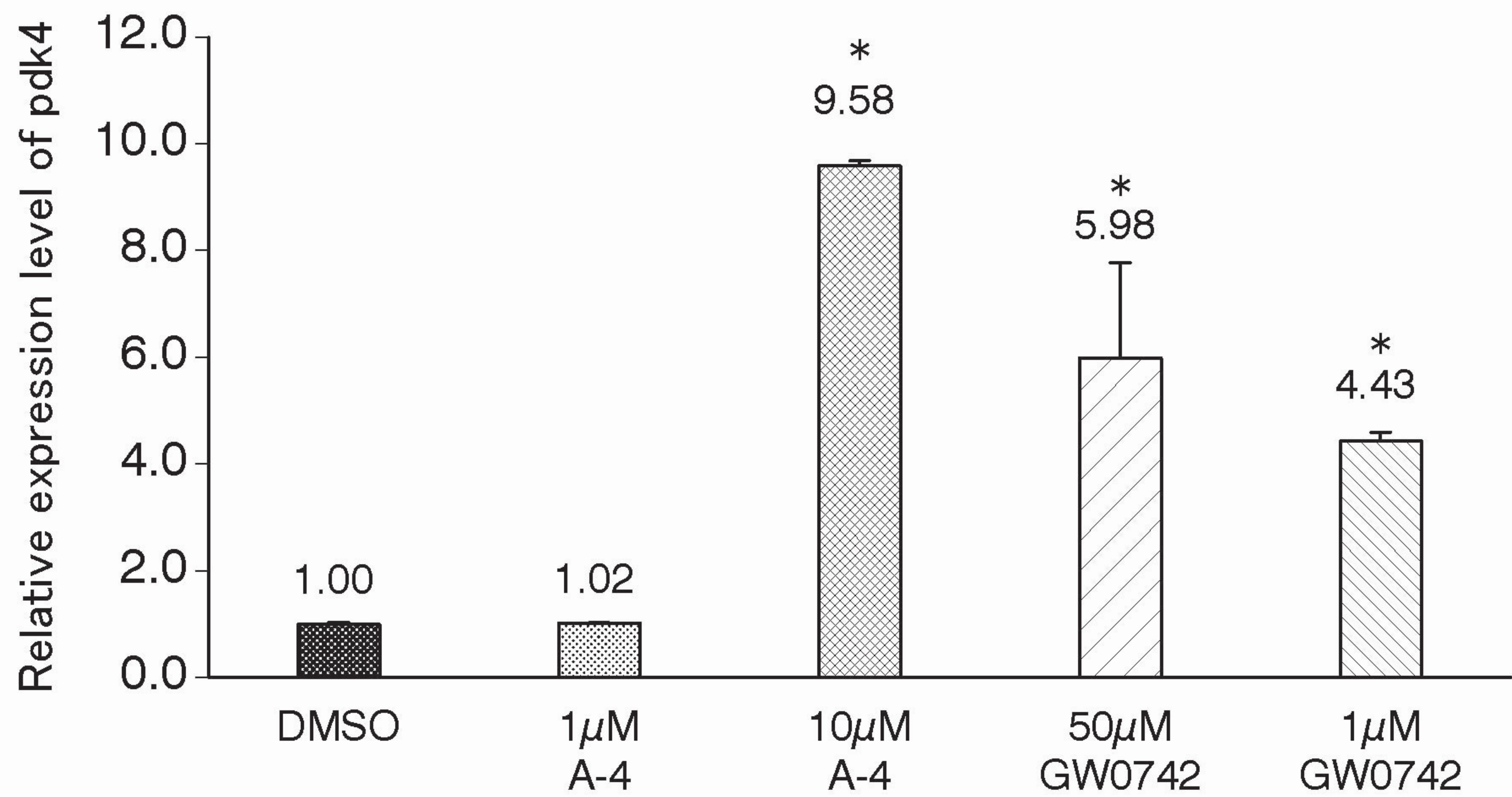


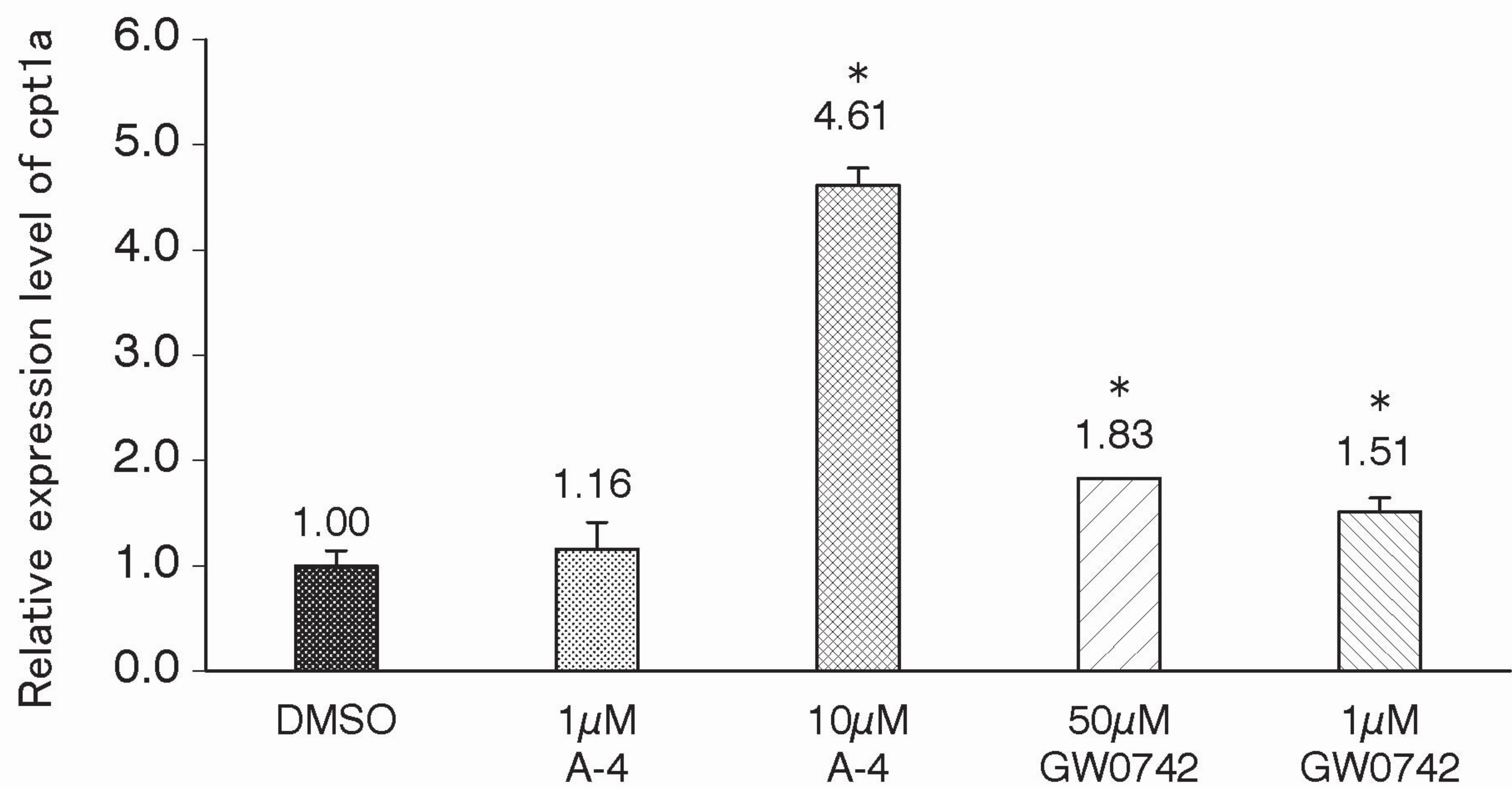
FIG. 23A



n=3
* p<0.05

FIG. 23B

n=3
* p<0.05

FIG. 23C

n=3
* p<0.05