Table S1. List of interactions between AMPPNP and analogues **2**, **6**, **7**, **9**, **18**, **19** and **20** in their AMPPNP-like poses, with binding site residues within the catalytic site of the human NTPDase2 model.

Analogue	Base	Sugar	Phosphate chain
AMPPNP	π–π: Tyr350 π -cation: Arg394	Hbond: O3'—Arg245	d(Ca^{+2}—OP2)= 2.14Å d(Ca^{+2}—OP3)= 2.14Å Hbond: His50-ND1—OP1 Hbond: Ser49-OH—OP2 Hbond: Ser49-NH—OP2 Hbond: Ser48-OH—N(P) Hbond: Gly204-NH—N(P) Hbond: Thr122-OH—OP3 Hbond: Ser48-NH—OP3 Hbond: Ala205-NH—OP3
2	π–π: Tyr350 π -cation: Arg394 Hbond: Tyr398-OH—N1	Hbond: O2' —Ser49	d(Ca^{+2}—OP2)= 2.27Å d(Ca^{+2}—OP3)= 2.21Å Hbond: Ser49-NH—OP2 Hbond: Ser49-OH—OP2 Hbond: Thr122-OH—OP3 Hbond: Ser48-NH—OP3 Hbond: Ala205-NH—OP3 Hbond: Gly204-NH—OP3
6	π–π: Tyr350 π -cation: Arg394 Hbond: Tyr398-OH—N1	Hbond: O2'—Ser49 Hbond: O3'—Ser49	d(Ca^{+2}—OP2)= 2.45Å d(Ca^{+2}—OP3)= 2.24Å Hbond: Ser49- NH—OP2 Hbond: Ser49-OH—OP2 Hbond: Gly204-NH—OP2 Hbond: Thr122-OH—OP3 Hbond: Ser48-NH—OP3 Hbond: Ser206-NH—OP3 Hbond: Gly204-NH—OP3 Hbond: Ala205-NH—OP3
7	π–π: Tyr350 π -cation: Arg394		d(Ca^{+2}—OP2)= 2.39Å d(Ca^{+2}—OP3)= 2.16Å Hbond: Ser49- NH—OP2 Hbond: Ser49-OH—OP2 Hbond: Gly204-NH—OP2 Hbond: Ser48-NH—OP3 Hbond: Thr122-OH—OP3 Hbond: Gly204-NH—OP3 Hbond: Ala205-NH—OP3
9	π–π: Tyr350 π -cation: Arg394	Hbond: O5'—Ser48 Hbond: O4'—Ser49 Hbond: O5'—Gly204	d(Ca^{+2}—OP1)= 2.21Å Hbond: Ser48-NH— OP1 Hbond: Thr122-OH—OP1 Hbond: Ala205-NH—OP1 Hbond: Ser206-NH—OP1

18	π–π: Tyr350 π -cation: Arg394	Hbond: O2'—Arg394 Hbond: O2'—Arg245	d(Ca^{+2}—OP2)= 2.43Å d(Ca^{+2}—OP3)= 2.25Å Hbond: Ser49- NH—OP2 Hbond: Ser49-OH—OP2 Hbond: Ser48-NH—N(P) Hbond: Gly204-NH—N(P) Hbond: Thr122-OH—OP3 Hbond: Ser48-NH—OP3 Hbond: Ala205-NH—OP3
19	π -cation: Arg245 π -cation: Arg394	Hbond: O2'—Arg394 Hbond: O2'—Arg245 Hbond: O3'—Ser49 Hbond: O5'—Ser49 Hbond: O5'—Gly204	d(Ca^{+2}—OP1)= 3.06Å d(Ca^{+2}—OP2)= 2.21Å Hbond: Ser49- NH—OP1 Hbond: Ser49-OH—OP1 Hbond: Gly204-NH—OP1 Hbond: Thr122-OH—OP3 Hbond: Ser48-NH—OP3 Hbond: Gly204-NH—OP3 Hbond: Ala205-NH—OP3
20	π–π: Tyr350 π -cation: Arg245 π -cation: Arg394	Hbond: O2'—Arg394 Hbond: O2'—Arg245	d(Ca^{+2}—OP2)= 2.40Å d(Ca^{+2}—OP3)= 2.22Å Hbond: Ser49- NH—OP2 Hbond: Ser49-OH—OP2 Hbond: Thr122-OH—OP3 Hbond: Ser48-NH—OP3 Hbond: Gly204-NH—OP3 Hbond: Ala205-NH—OP3

Fig. S1

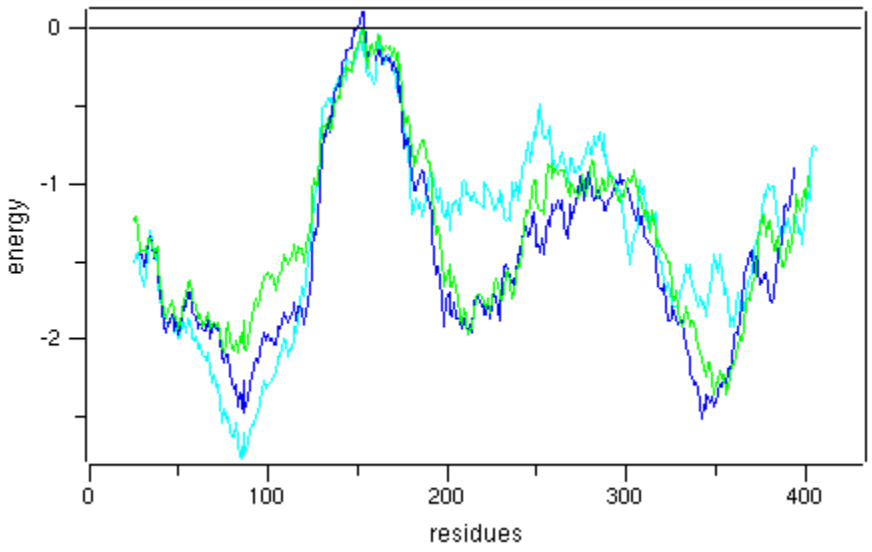

Figure S1. Model validation. Energy graphs (in Prosa units) for the NTPDase2 model (green), the NTPDase1 model (cyan) and the crystal structure of rat NTPDase2 (blue). Negative energy values are indicative of good structures. The figure clearly shows that both template and targets have similar Prosa profiles.