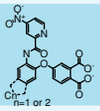
Table 17.2. Energy calculation on the designed compounds

	Fused ring	Bond	Interaction energy (kcal/mol)
Compound **1a**	no	No	−112.6
Design 1	5	Saturated	−117.6
Design 2	5	Unsaturated	−118.6
Design 3	6	Saturated	−117.5
Design 4	6	Unsaturated	−118.6

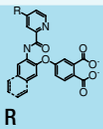
are listed in Table 17.3 for a head-to-head comparison with the parent phenyl compounds. Overall, the potency is improved by three- to fourteenfold for HLGP and seven- to nineteenfold for HMGP over the corresponding phenyl compounds. The enhancement in potency is consistent within the entire series and for both HLGP and HMGP. The naphthyl and phenyl series share a similar trend in potency change with different substitutions on the C ring: the unsubstituted compounds (i.e., compounds **1g** and **2g**) are least active while the potency increases over tenfold with hydrophobic substitutions on the meta position (e.g., compounds **1e** and **1f**, **2e** and **2f**); the compounds with a nitro group are most potent (i.e., compounds **1a** and **2a**). This indicates that the naphthyl and phenyl derivatives bind at the AMP allosteric site in a similar manner. The naphthyl series fills more space with the fused ring than the parent phenyl series, making more favorable interactions with the surrounding residues and thereby increasing their potency.[29]

COMPARISON OF THE DOCKING MODEL WITH X-RAY CRYSTAL STRUCTURES

At the time when we finished the design and synthesis of the naphthyl series, an x-ray crystal structure of RMGPb complexed with compound **1a** was solved in-house.[28] The predicted docking pose of compound **1a** was confirmed by the x-ray crystal structure. Compound **1a** is verified to be bound at the AMP allosteric site. Compared to the x-ray crystal structure, the docked compound **1a** occupies the same location and maintains all major interactions. The ring A and ring B are overlaid well with the diacid groups interacting with the positively charged arginines, Arg81, Arg309, and Arg310. The amide group next to ring B displays a different orientation, which causes the pyridines (ring C) to be poorly overlapped. However, the nitro group on ring C points to the same residue, Arg193, to form favorable interactions. The conformational difference in the amide and ring C region is accompanied by the substantial shift of the side-chain orientation of Arg193 in the binding pockets.

Later on, crystal structures of RMGPb complexed with similar diacid compounds were published by Kristiansen et al.[30] Our proposed binding mode for compound **1a** at the AMP allosteric site is similar to that of the compounds described therein.

Table 17.3. Comparison of activity of naphthyl and phenyl diacid compounds

		Phenyl			Naphthyl	
R		HLGPa (IC_{50} nM)	HMGPa (IC_{50} nM)		HLGPa (IC_{50} nM)	HMGPa (IC_{50} nM)
$-NO_2$	**1a**	3	25	**2a**	1	3
-Cl	**1b**	17	181	**2b**	2	12
-OMe	**1c**	20	200	**2c**	2	12
$-CF_3$	**1d**	48	591	**2d**	12	80
-Et	**1e**	56	433	**2e**	4	29
-Me	**1f**	121	1090	**2f**	10	57
-H	**1g**	1280	11790	**2g**	167	844

SUMMARY

In this chapter we describe modeling aided development of a new series of potent glycogen phosphorylase inhibitors. Due to the lack of suitable competition-based binding assays, superposition was used to predict the potential binding site for the lead compound **1a**. The overlay of compound **1a** onto the crystal structures of inhibitors that are known to bind at different sites in GP, together with analysis of nearby residues at each respective site, correctly determined the AMP allosteric site as the binding site for compound **1a**. By using the x-ray crystal structure of RMGP (PDB entry 3AMV), possible docking modes of compound **1a** were extensively explored by ICM calculations. A reasonable docking model was computationally determined and subsequently confirmed by in-house x-ray crystallography. Further analysis of the binding pocket of the docking model by grid-based surface calculation revealed a large unfilled region near the central phenyl ring of compound **1a**. Fused ring analogs were designed with the goal of increasing hydrophobic bulk in this unfilled region to improve binding. After evaluation of energetics and ease of synthesis for the fused ring analogs, a series of naphthyl compounds was synthesized. As predicted, this exercise resulted in a new series of GP inhibitors with significantly improved potency.

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