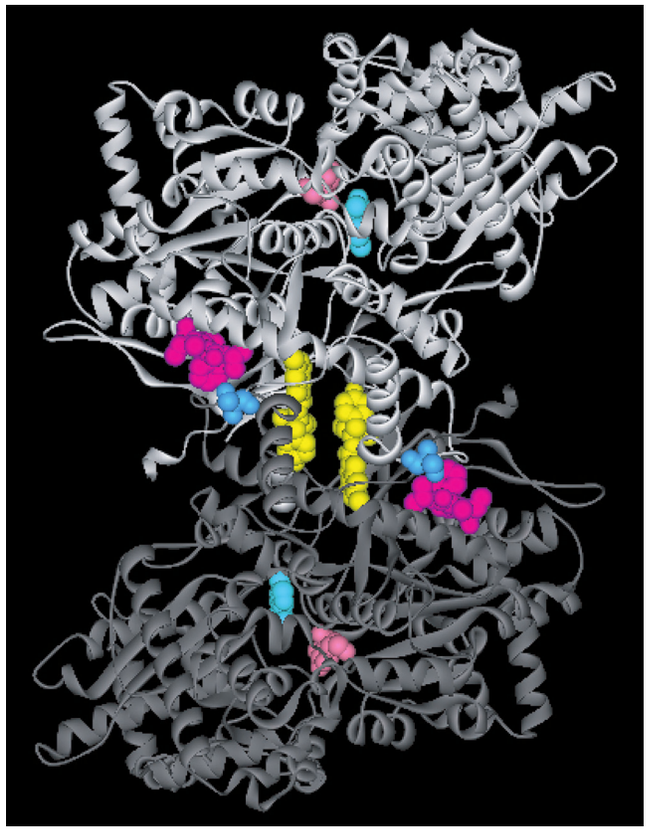
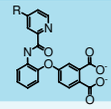


Figure 17.1. Regulatory sites of glycogen phosphorylase. The glycogen phosphorylase (PDB entry 3AMV) is shown in ribbon diagram with the two subunits colored in white and gray, respectively. To show all the regulatory sites in one picture, compounds that bind at different sites are copied from different PDB entries. In CPK models: Ser14 in blue at the phosphate recognition site; glucose in pink at the catalytic site; Bayer W1807 in magenta at the AMP allosteric site (PDB entry 3AMV); caffeine in cyan at the inhibitor site (PDB entry 1GFZ) and Pfizer CP320626 in yellow at the dimer interface site (PDB entry 1C50).

Additional characterization of the binding pocket by grid-based surface calculations[18] revealed a large unfilled hydrophobic region near the central phenyl ring, which provided an opportunity to potentially enhance binding of early leads by increasing the hydrophobic bulk in this region. A series of naphthyl compounds was designed and synthesized, and they displayed a significant improvement in potency.

Table 17.1. The activity of phenyl diacid compounds

	R	HLGPa (IC_{50} nM)	HMGPa (IC_{50} nM)
1a	$-NO_2$	3	25
1b	-Cl	17	181
1c	-OMe	20	200
1d	$-CF_3$	48	591
1e	-Et	56	433
1f	-Me	121	1090
1g	-H	1280	11790

STRUCTURE-BASED DESIGN OF GLYCOGEN PHOSPHORYLASE INHIBITORS

Prediction of putative binding pocket

The lead compounds are a series of phenyl diacids with activity on HLGPa ranging from 3 to 1280 nM with various substituents on the pyridine (Table 17.1). The most potent compound in the series incorporates a nitro group on the pyridine, compound **1a** [Figure 17.3(a)], with an IC_{50} of 3 nM for HLGPa and 25 nM for HMGPa (Table 17.1). Two hundred conformers of compound **1a** were generated using our implementation of the distance geometry approach, which incorporates the theory and algorithm as previously described.[19] The conformer set was energy minimized using a distance-dependent dielectric of $2r$ with the Merck Molecular Force Field (MMFF).[20–26] Of the 200 conformers generated and energy minimized, the energetically favored conformation of compound **1a** was found to be in a "V" shape [Figure 17.3(b)]. In this conformation, the NH group of the amide interacts with the nitrogen atom in

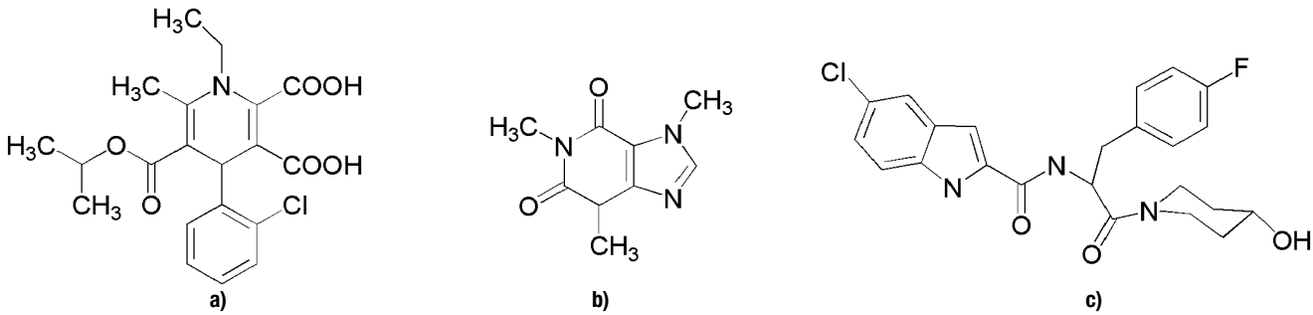


Figure 17.2. Examples of known GP inhibitors. **(a)** Bayer diacid compound W1807 ((-)(S)-3-isopropyl 4-(2-chlorophenyl)-1,4-dihydro-1-ethyl-2-methyl-pyridine-3,5,6-tricarboxylate) that binds at the AMP allosteric site (PDB entry 3AMV). **(b)** Caffeine that binds at the inhibitor site (PDB entry 1GFZ). **(c)** CP320626 (5-chloro-1H-indole-2-carboxylic acid [1-(4-fluorobenzyl)-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]amide) that binds at the dimer interface site (PDB entry 1C50).