

FIG. 1A

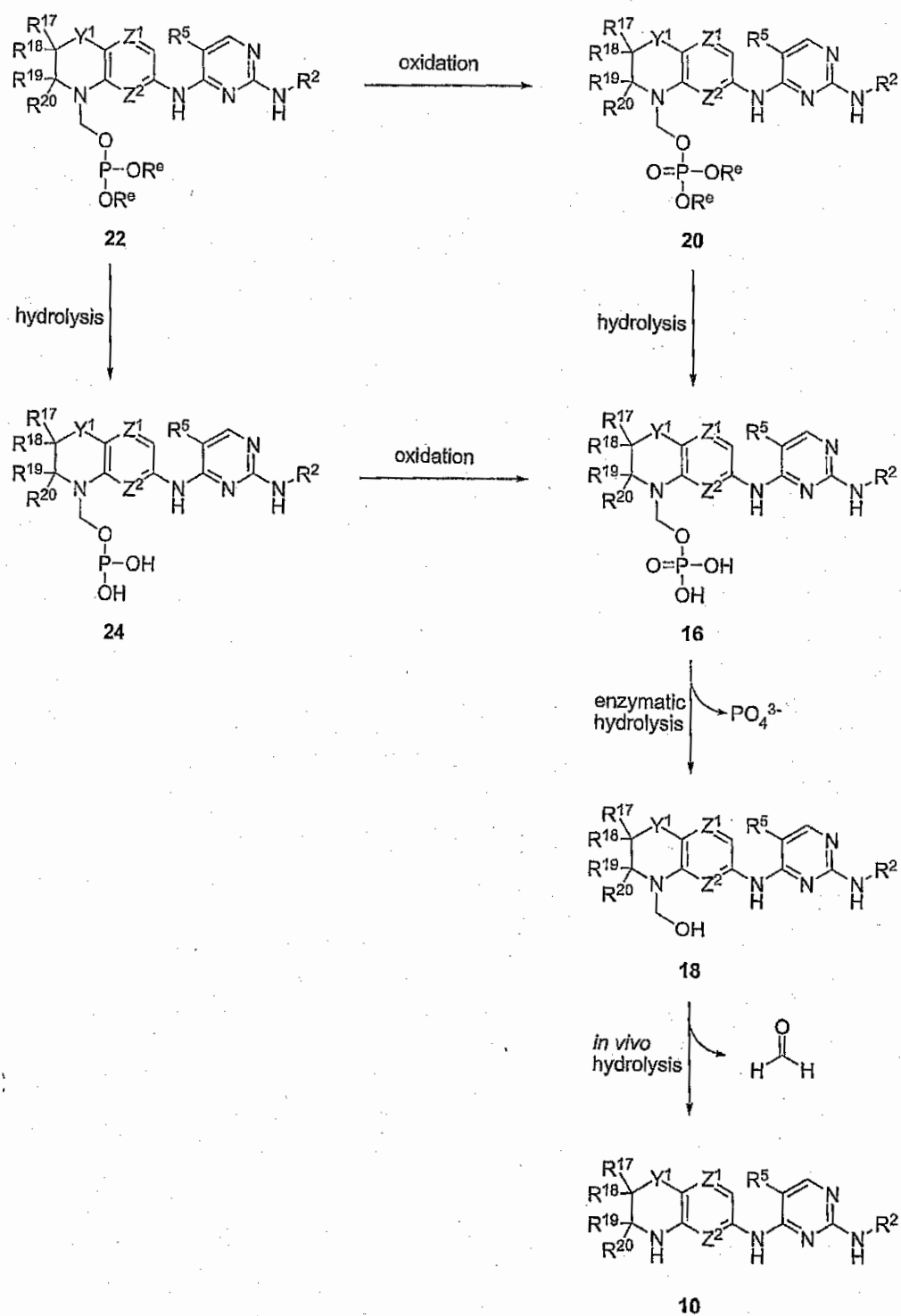


FIG. 1B

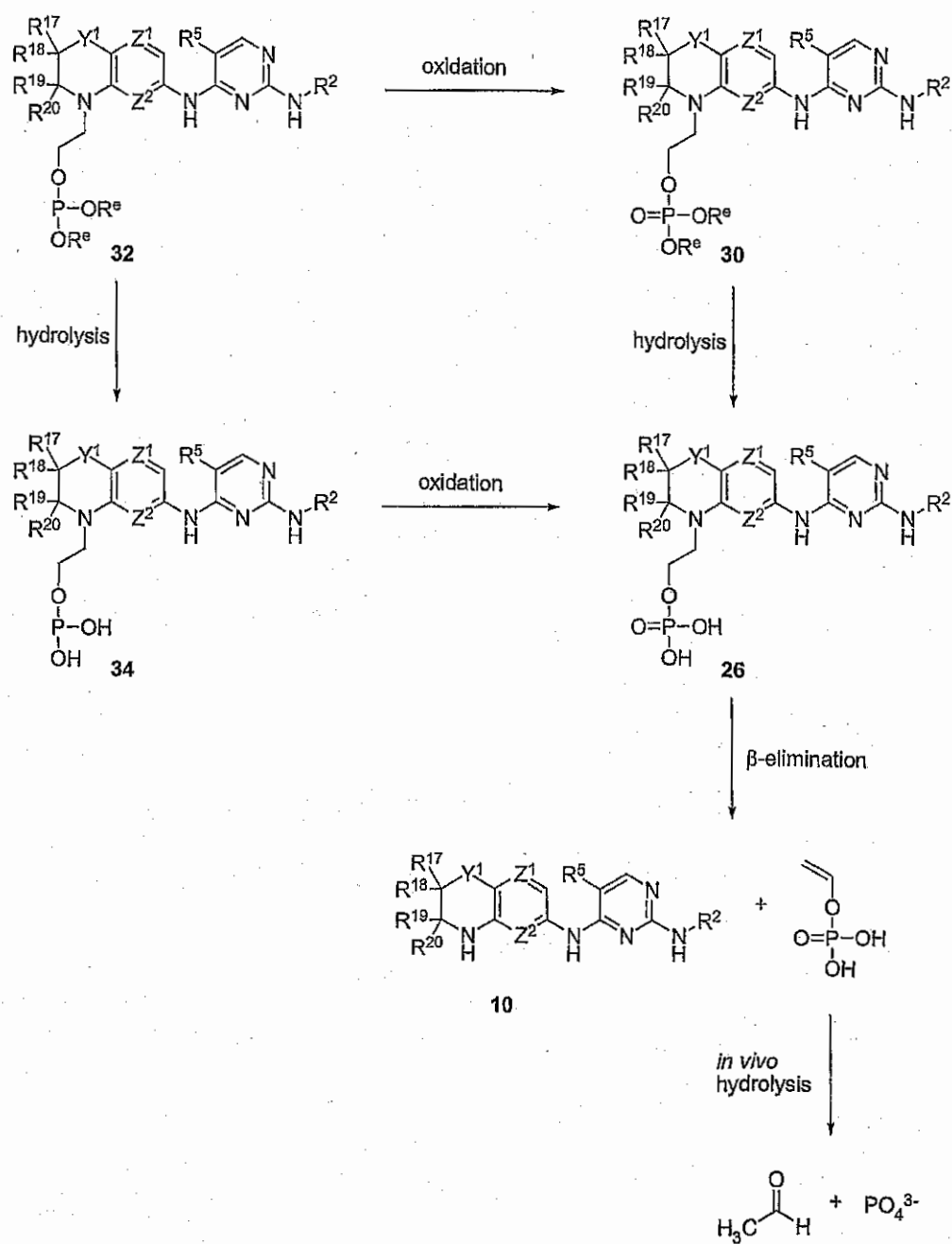


FIG. 2

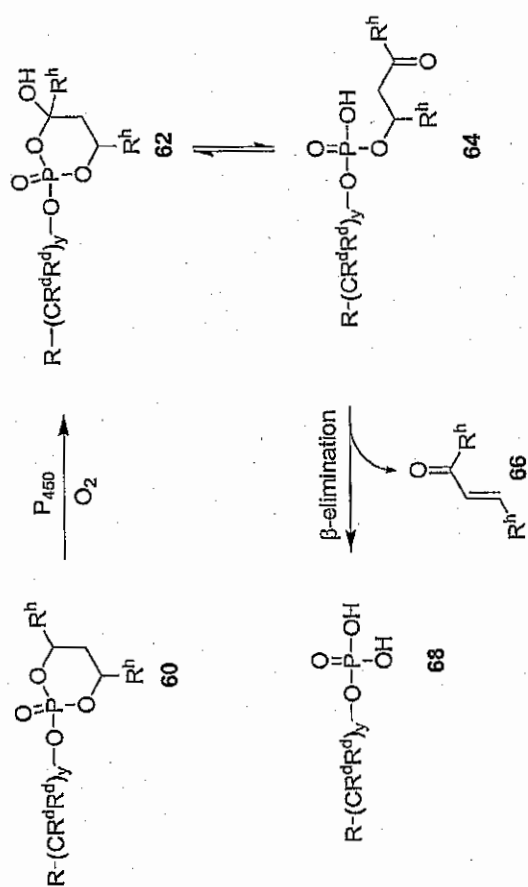


FIG. 3

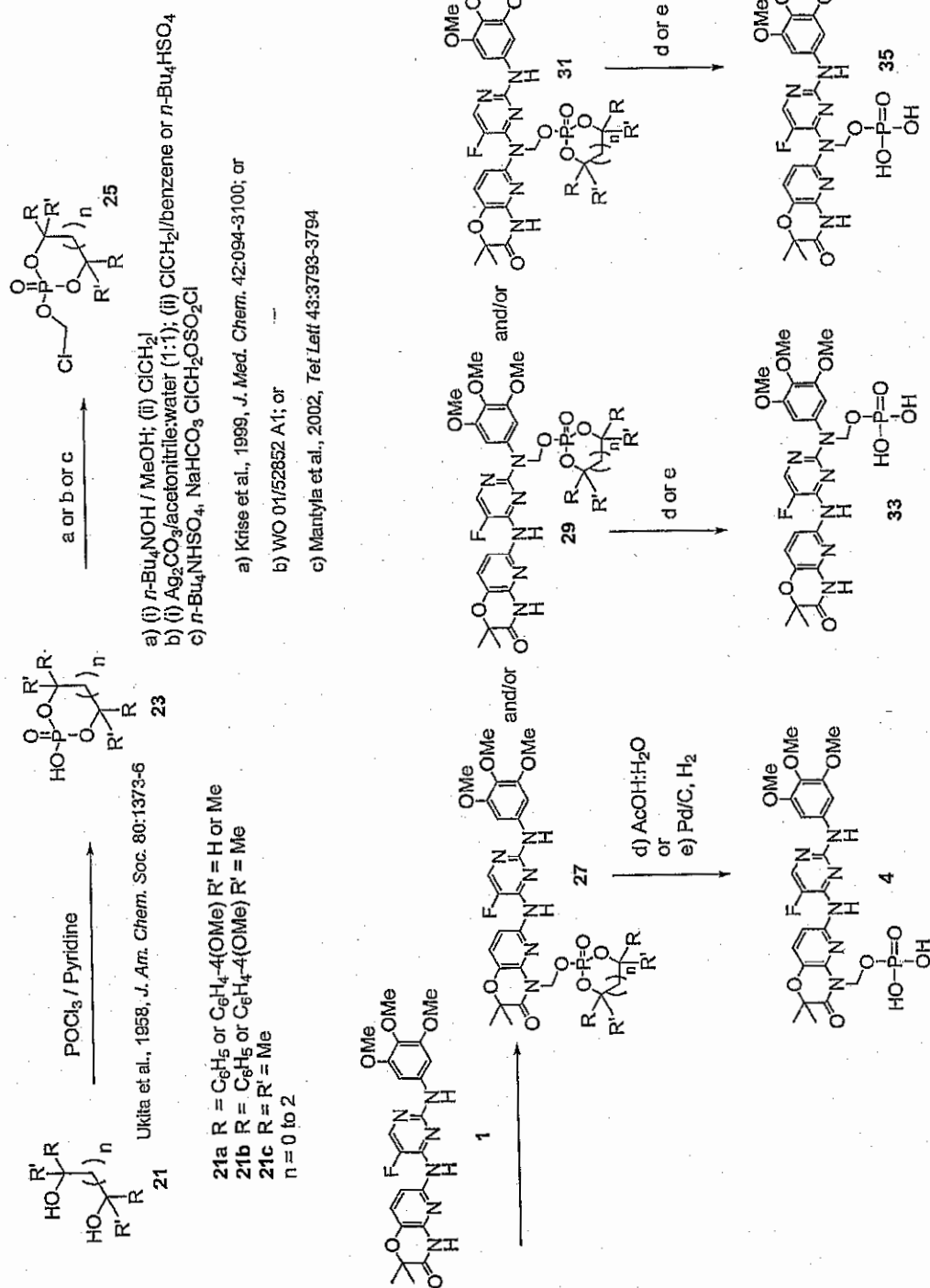


FIG. 4
Rat PK Profiles for Prodrug Compound 4

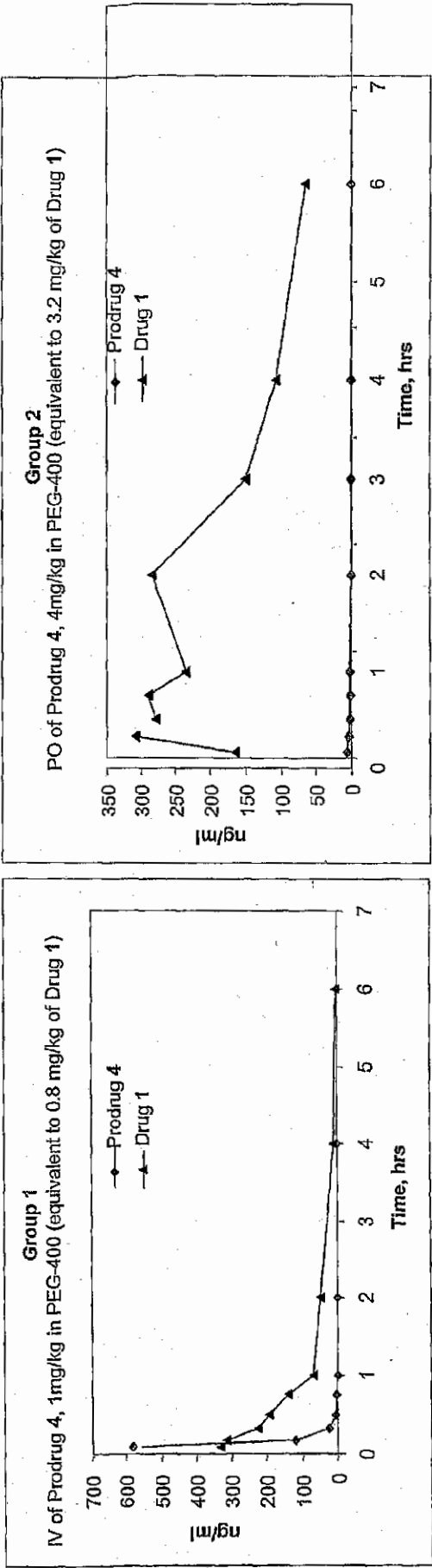


FIG. 5
PK Summary

Mode of Delivery	Analyte	Parameter	Value	Comments
IV	Prodrug 4	Clearance, ml/min/kg	93.1	AUC of 4 = 182
		T1/2, hr	0.2	AUC of 1 = 327
PO	Drug 1	%F	29.9	Total absorbed and converted to Drug 1
		Cmax, ng/ml	331	
	Prodrug 4	%F	0.3	
		Cmax, ng/ml	5.23	

FIG. 6

Comparison of Drug Exposure – Prodrug 4 vs Drug 1 in PEG-400

Compound	Dose (Drug 1 mg/kg)	AUC/dose
Drug 1	2.5	345
Prodrug 4	3.2	316

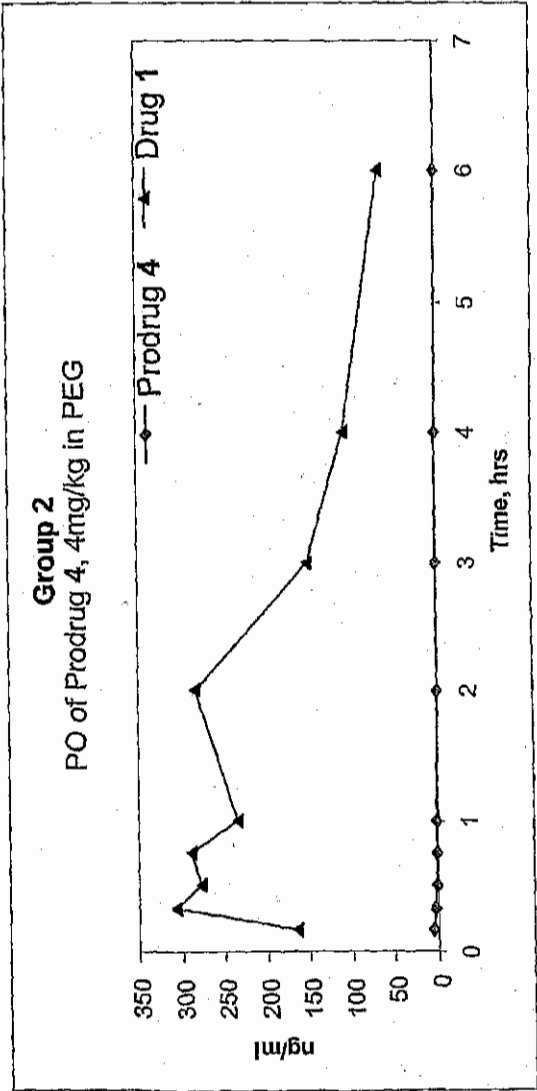
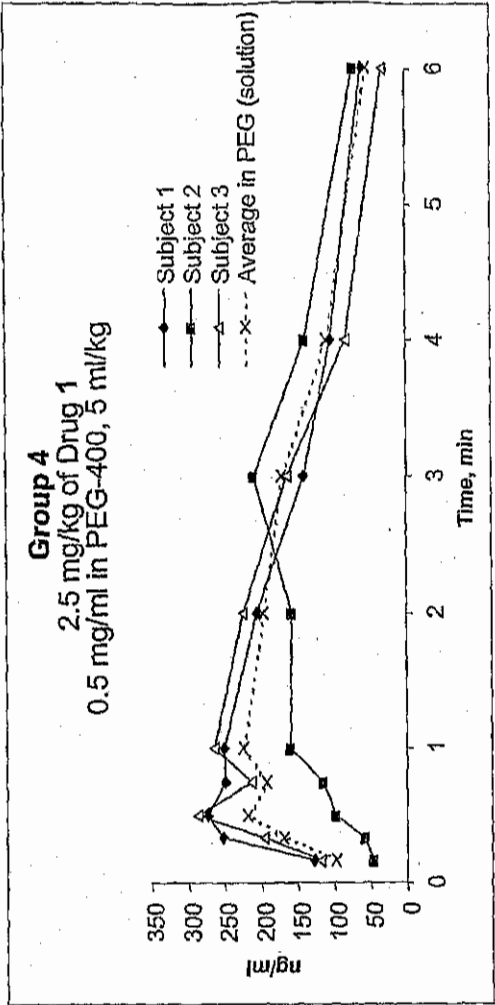
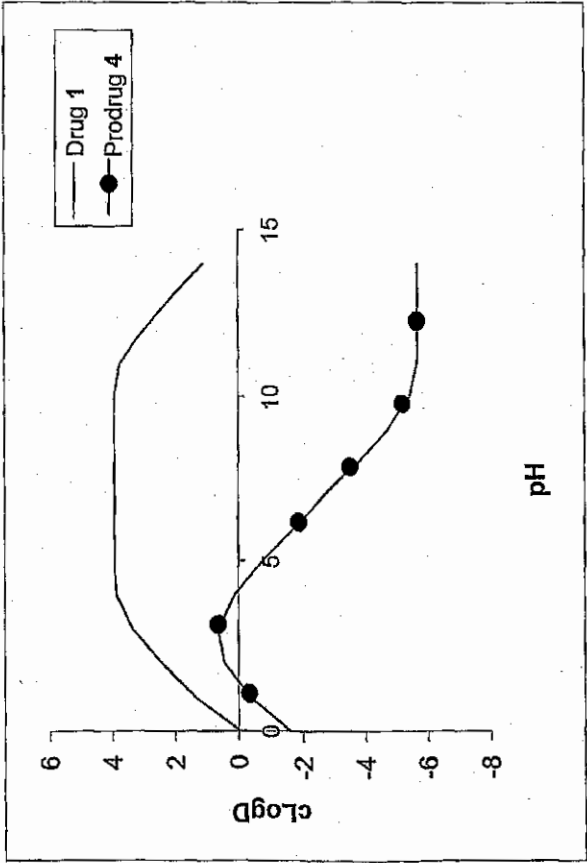


FIG. 7
cLogD vs pH (Pallas) and Measured Solubility

- Solubility (Prodrug 4) in Phosphate buffer (pH = 7.5, 100 mM)
- Conditions:
 - 0.4mg in 80 ul buffer (5 mg/ml).
 - Insoluble material removed by centrifugation at 2 and 24hrs.
 - LC/MS/MS analysis.



Time, hrs	Solubility, mg/ml	
	replicate 1	replicate 2
2	5.04	4.94
24	5.09	5.03

FIG. 8
Chemical Stability of Prodrug 4

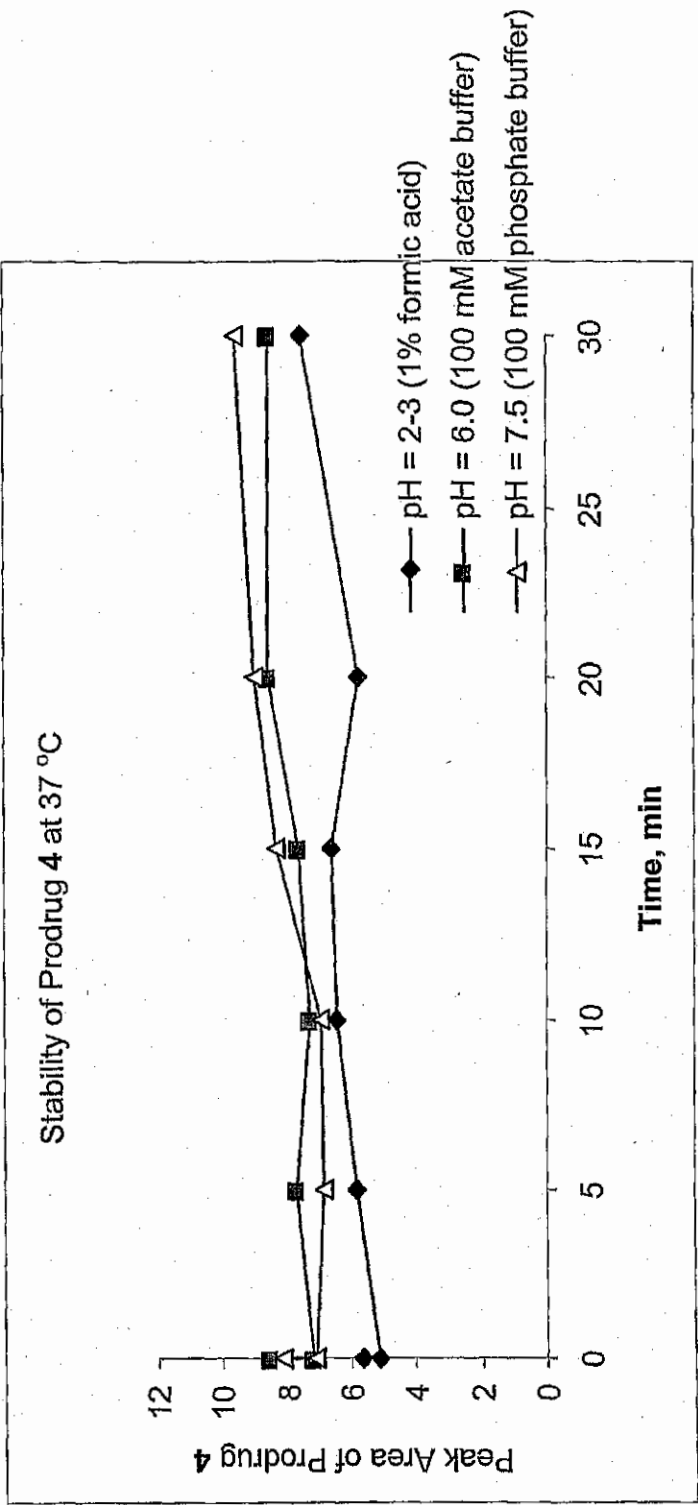


FIG. 9

Metabolic Stability: Microsomes

- p-nitrophenyl phosphate (PNP) is stable in microsomes and S9 fractions.
- PNP is a known substrate for both acid and alkaline phosphatase

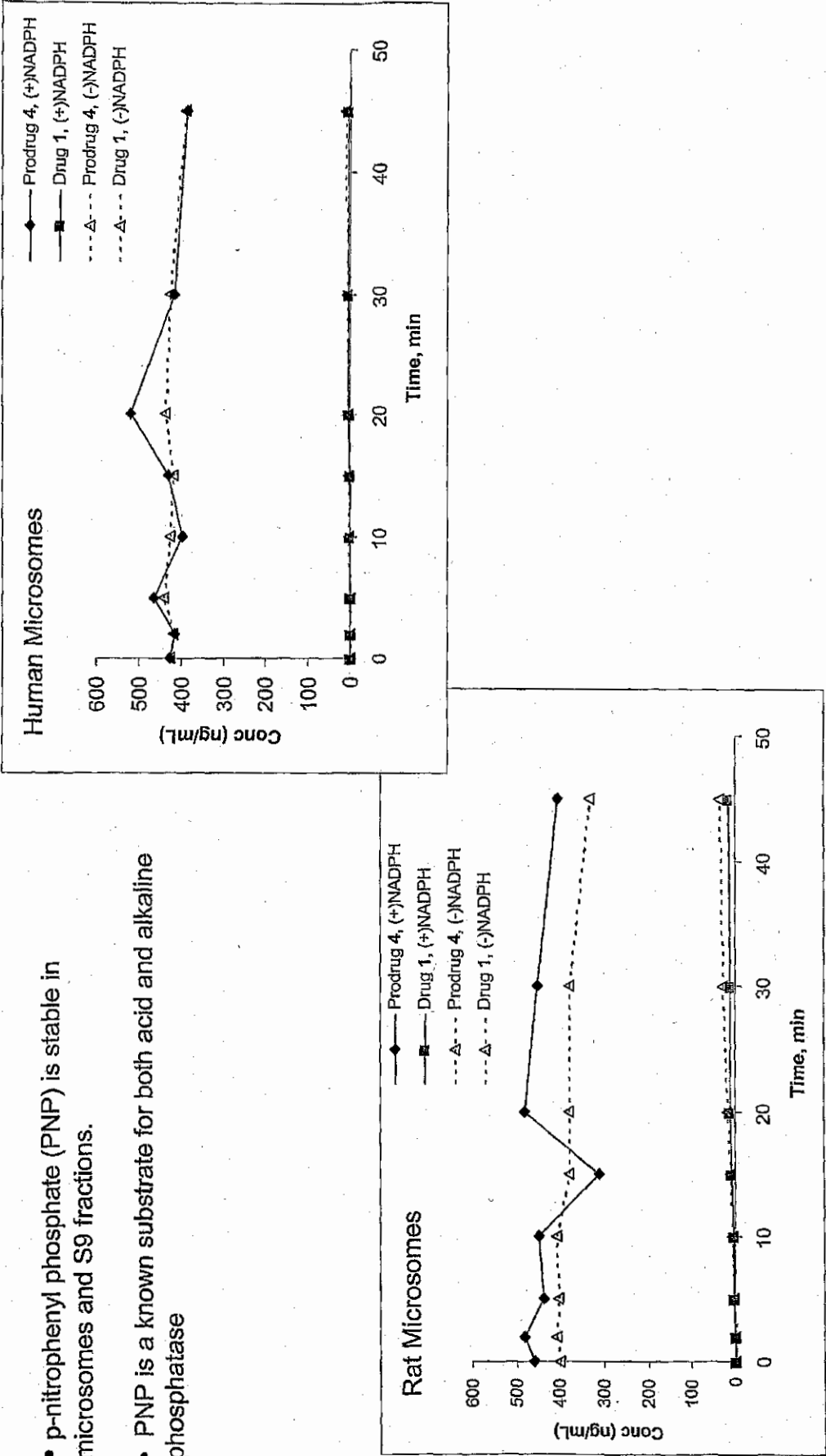


FIG. 10
Plasma Stability (Rat) of Prodrug 4 and PNP

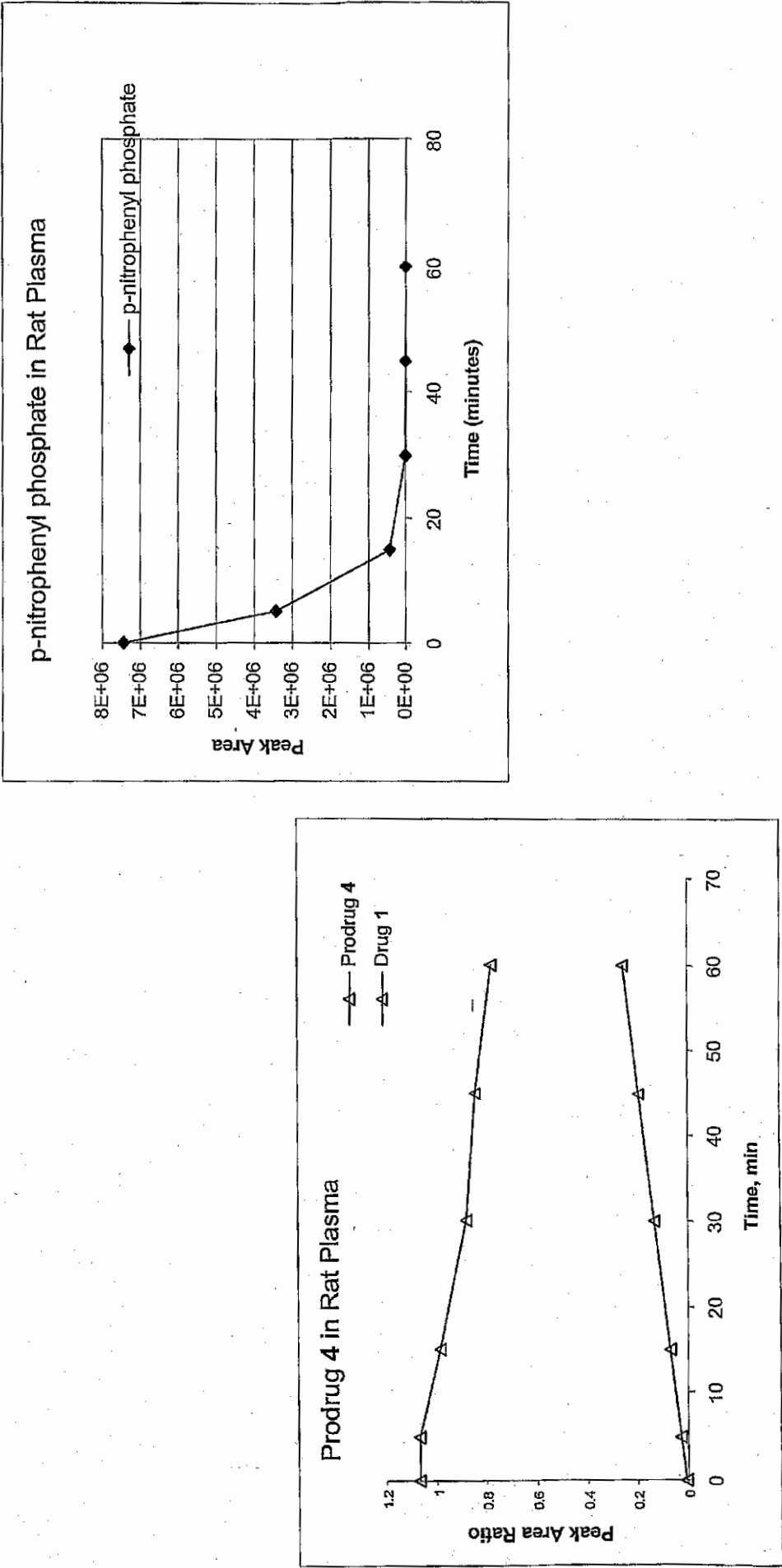
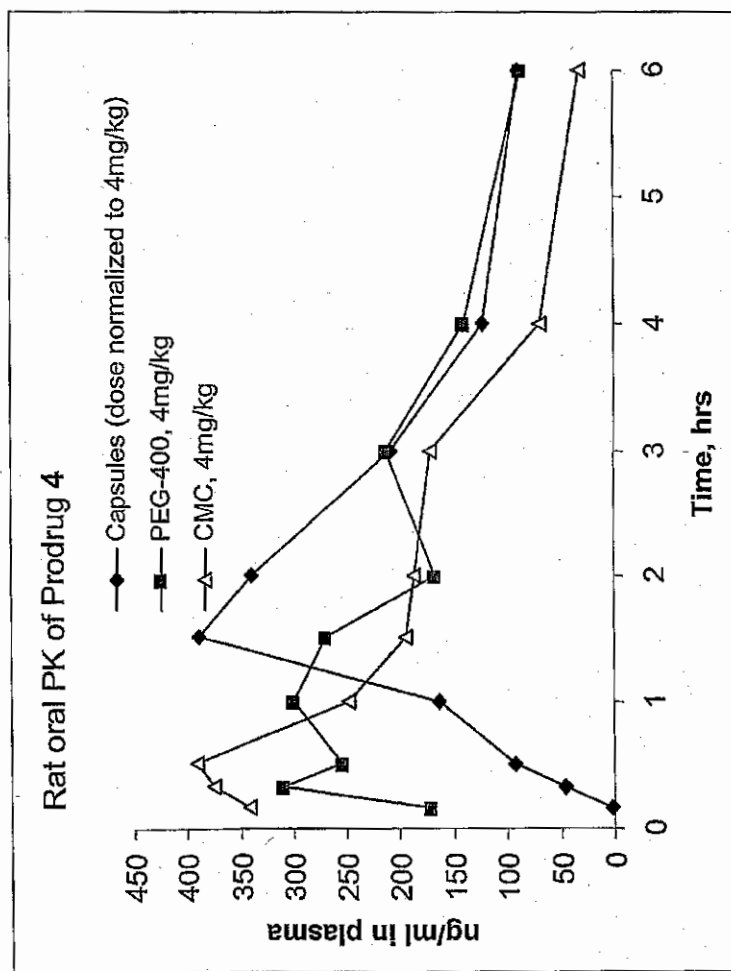


FIG. 11

Rat PK Study of Prodrug 4

- Oral Delivery:
 - Solutions: Carboxymethylcellulose (CMC) and PEG (0.8 mg/ml Prodrug 4), 5ml/kg
 - Powder: #9 Hard gelatin capsules (HGC), 5.7 – 6.9 mg Prodrug 4 /capsule



Vehicle	AUC	SD
PEG-400	914	79
CMC	1083	78.2
HGC	1049	292