FIG. 1A

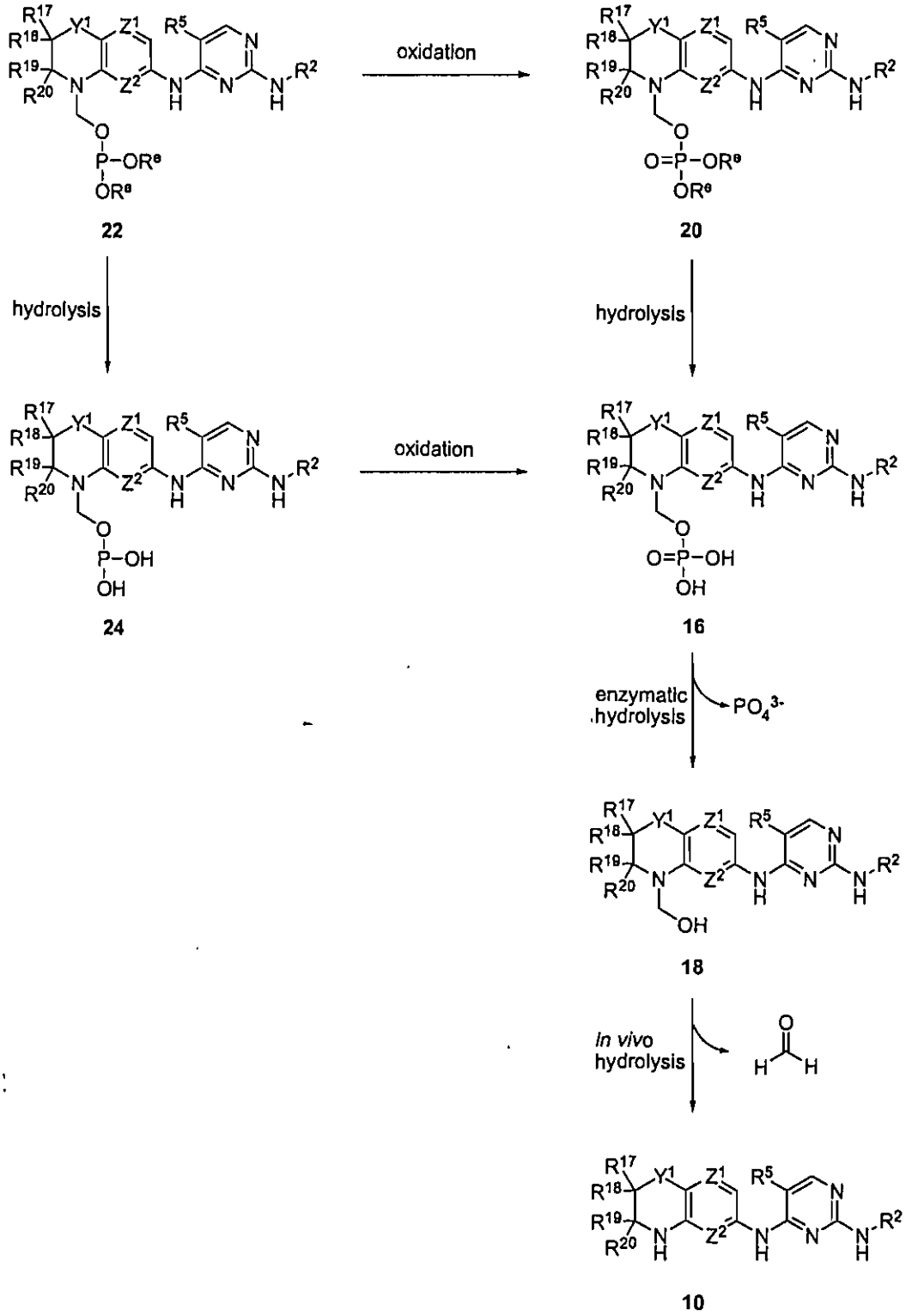

oxidation
22
20
hydrolysis
hydrolysis
oxidation
24
16
enzymatic hydrolysis
PO_4^{3-}
18
In vivo hydrolysis
10

FIG. 1B

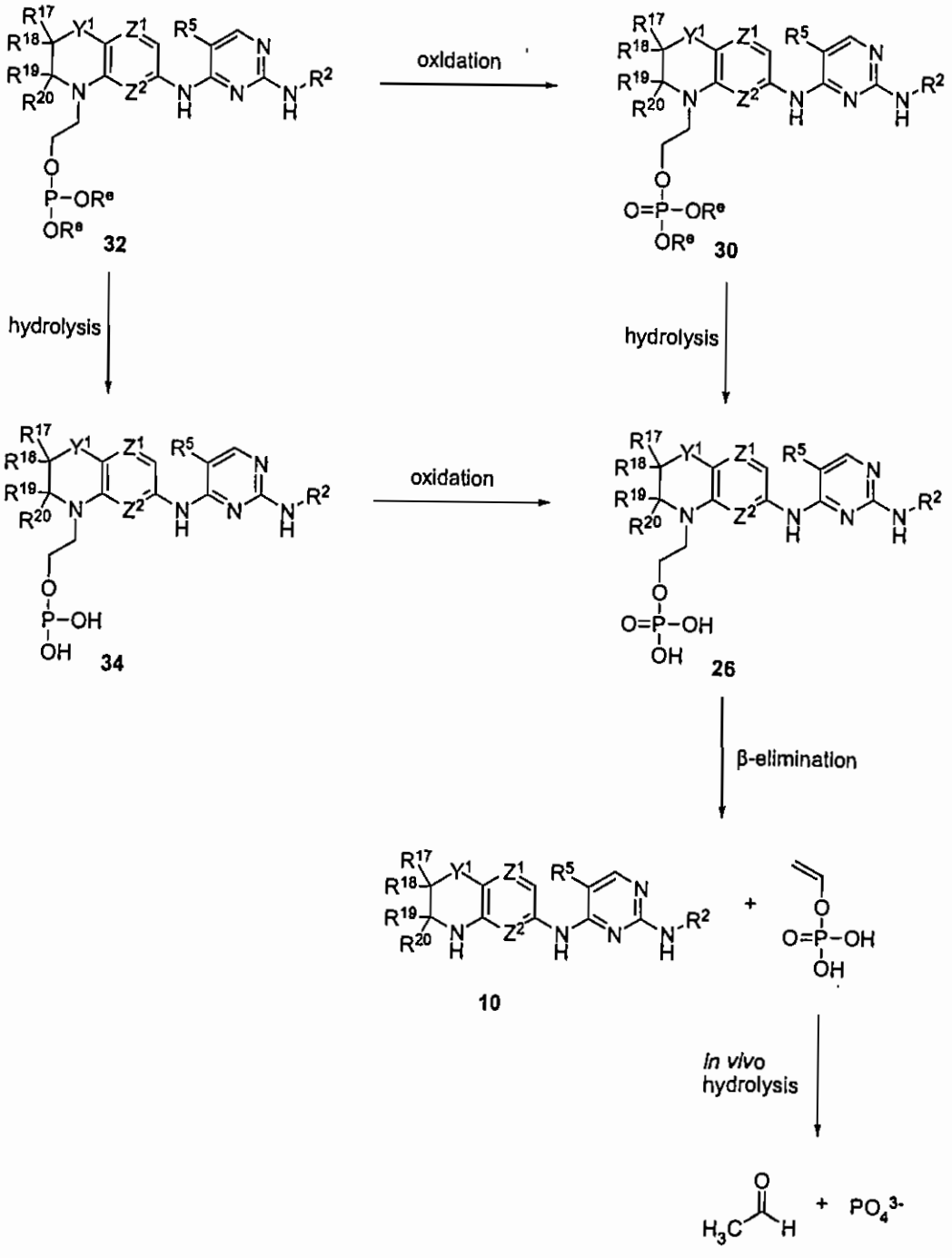

oxidation
hydrolysis
hydrolysis
oxidation
β-elimination
in vivo
hydrolysis
32
30
34
26
10

FIG. 2

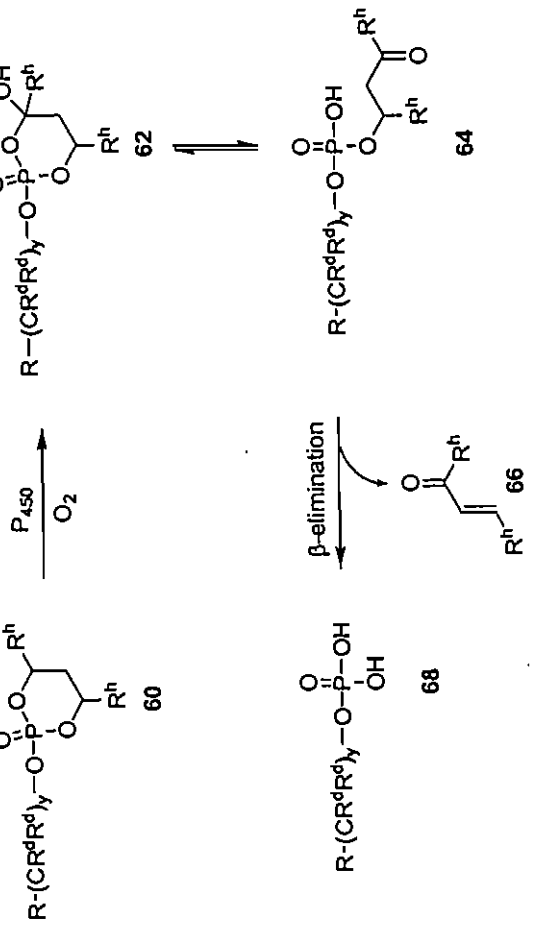


FIG. 3

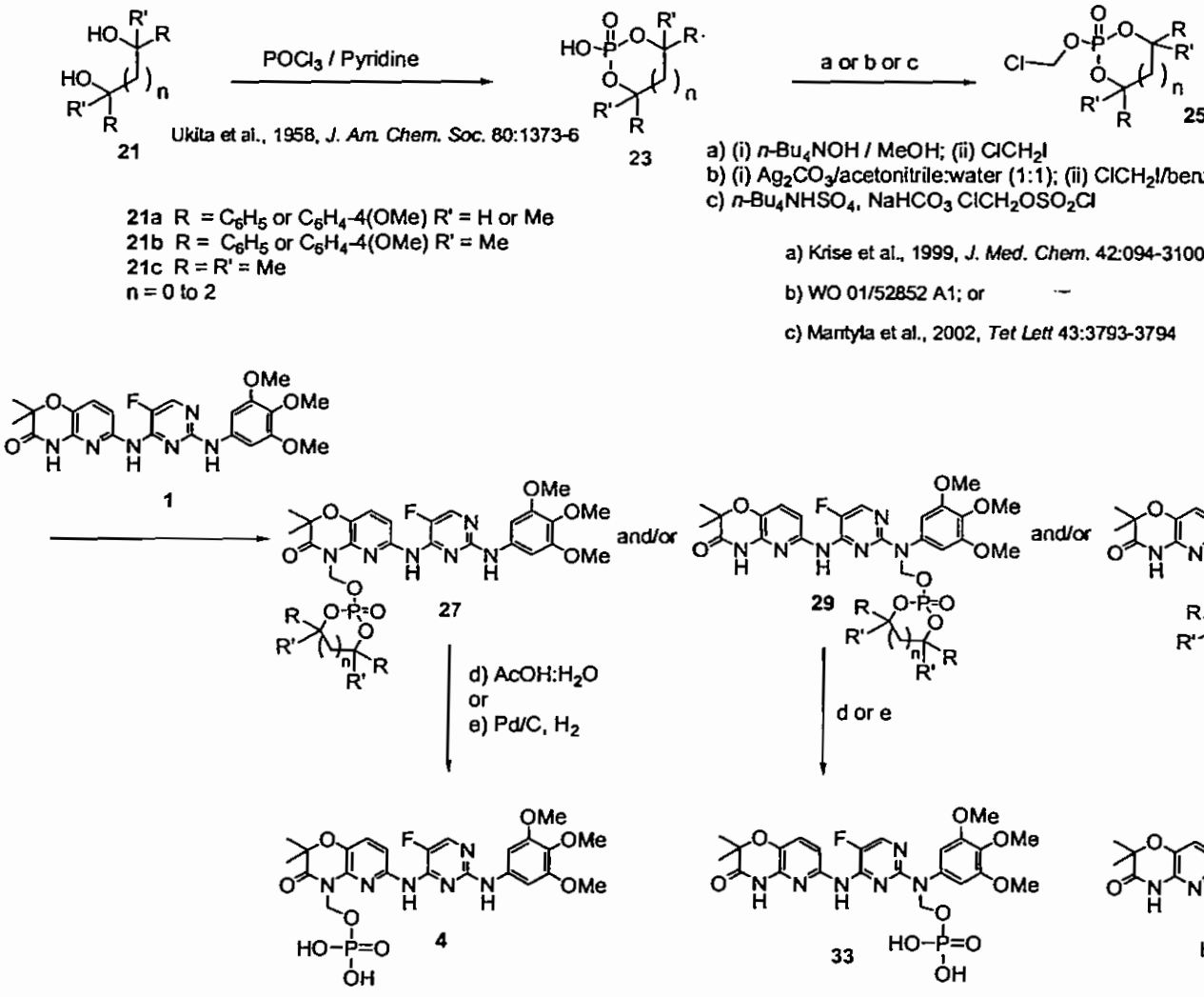
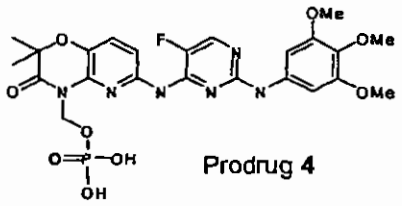
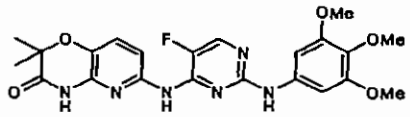

POCl3 / Pyridine
a or b or c
21
23
25
Ukita et al., 1958, J. Am. Chem. Soc. 80:1373-6
a) (i) n-Bu4NOH / MeOH; (ii) ClCH2I
b) (i) Ag2CO3/acetonitrile:water (1:1); (ii) ClCH2I/benzene or n-Bu4HSO4
c) n-Bu4NHSO4, NaHCO3 ClCH2OSO2Cl
21a R = C6H5 or C6H4-4(OMe) R' = H or Me
21b R = C6H5 or C6H4-4(OMe) R' = Me
21c R = R' = Me
n = 0 to 2
a) Krise et al., 1999, J. Med. Chem. 42:094-3100; or
b) WO 01/52852 A1; or
c) Mantyla et al., 2002, Tet Lett 43:3793-3794
1
27
29
31
and/or
and/or
d) AcOH:H2O
or
e) Pd/C, H2
d or e
d or e
4
33
35

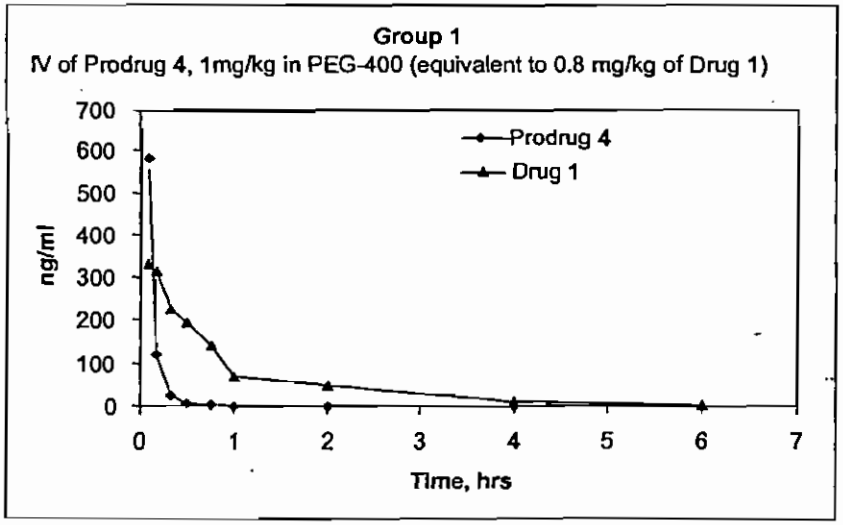
FIG. 4
Rat PK Profiles for Prodrug Compound **4**



Prodrug **4**



Drug **1**



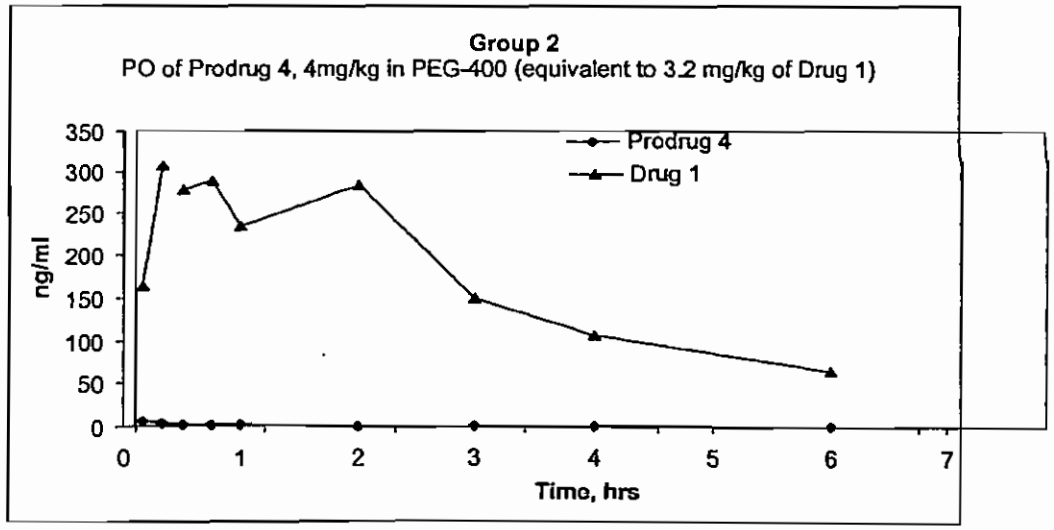


FIG. 5

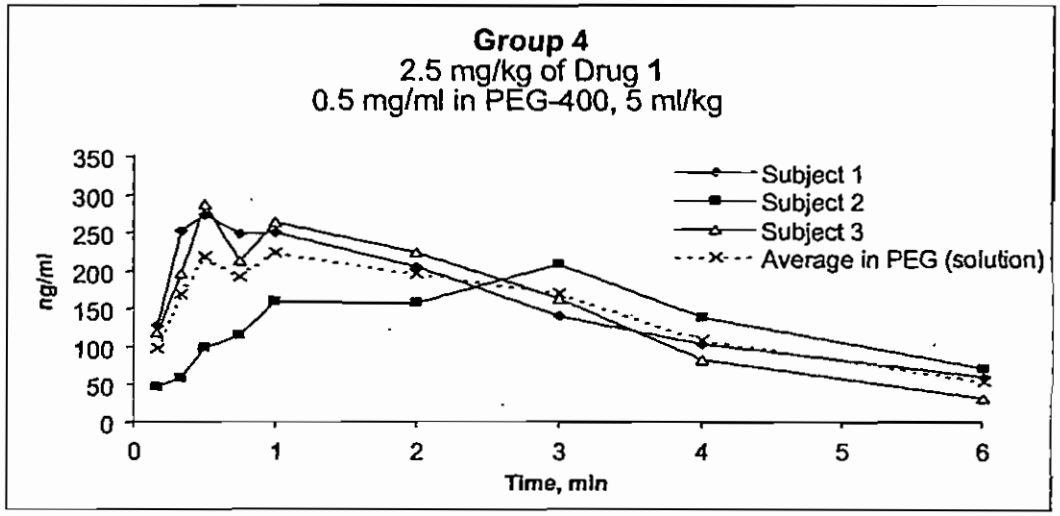
PK Summary

Mode of Delivery	Analyte	Parameter	Value	Comments
IV	Prodrug **4**	Clearance, ml/min/kg	93.1	AUC of **4** = 182 AUC of **1** = 327
		T1/2, hr	0.2	
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



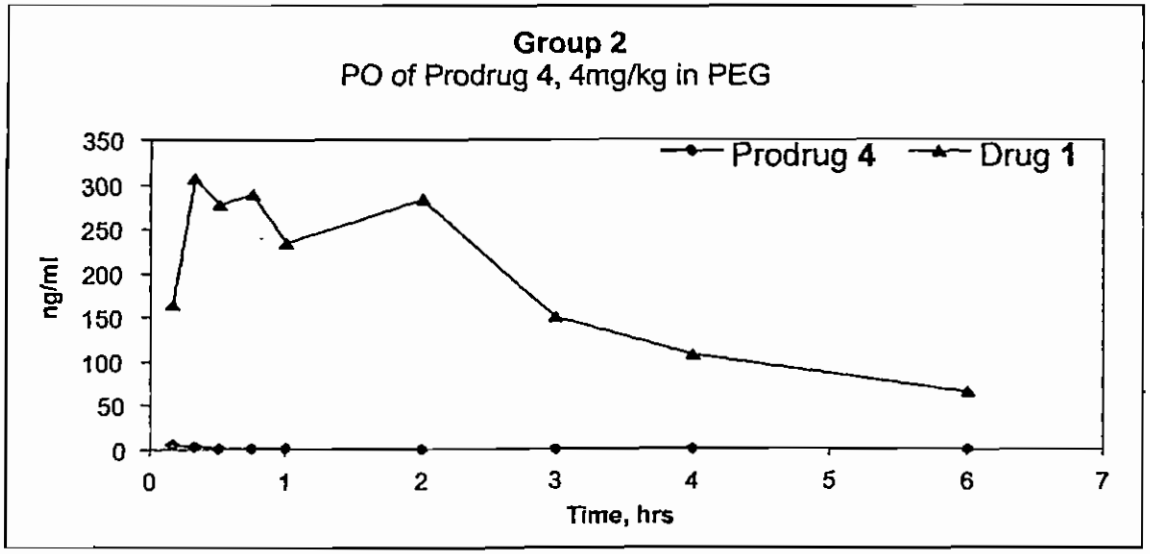
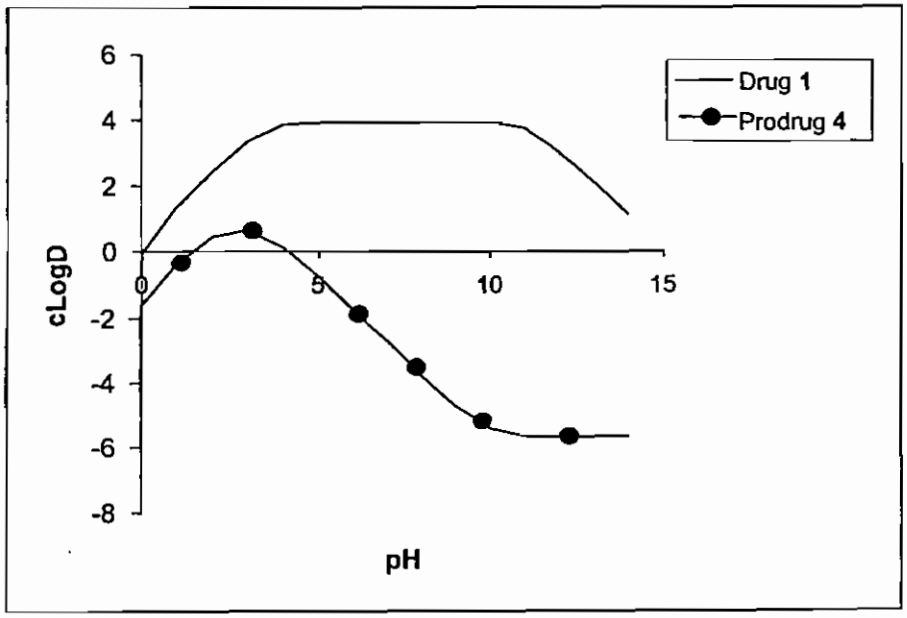


FIG. 7

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**

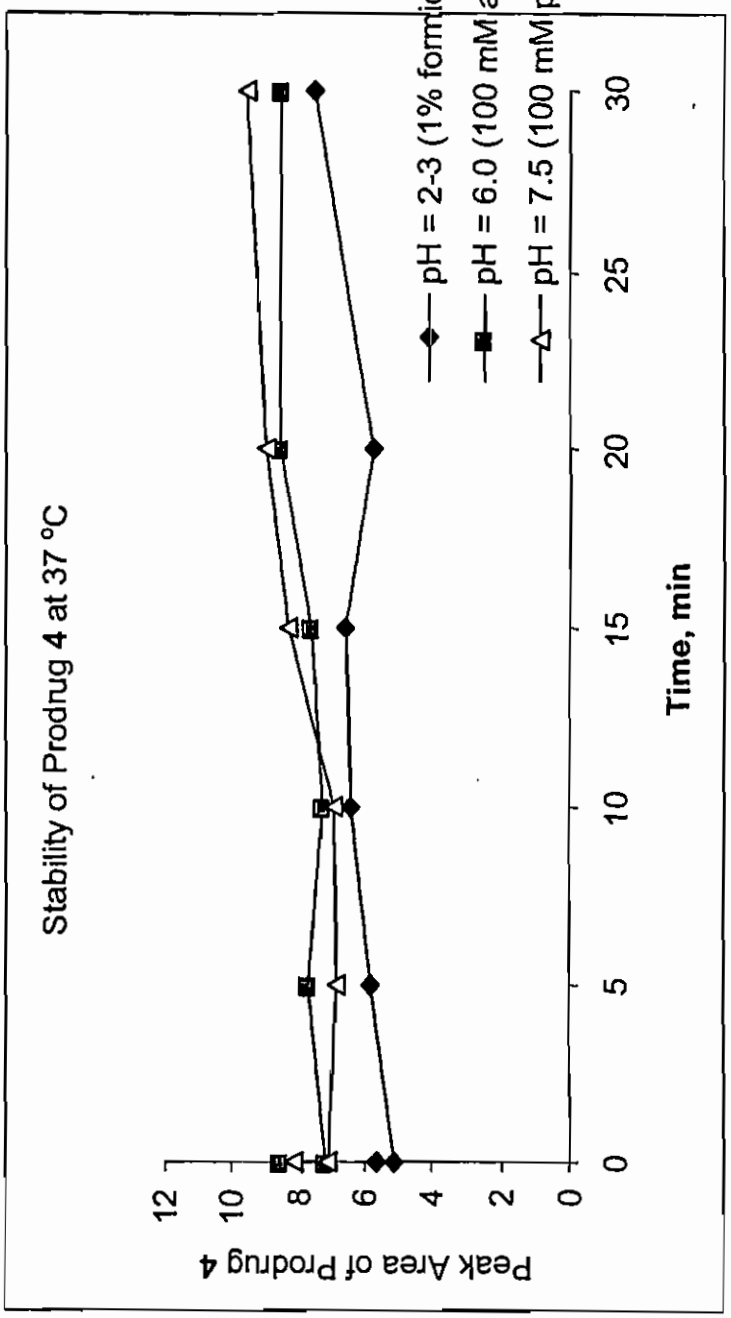
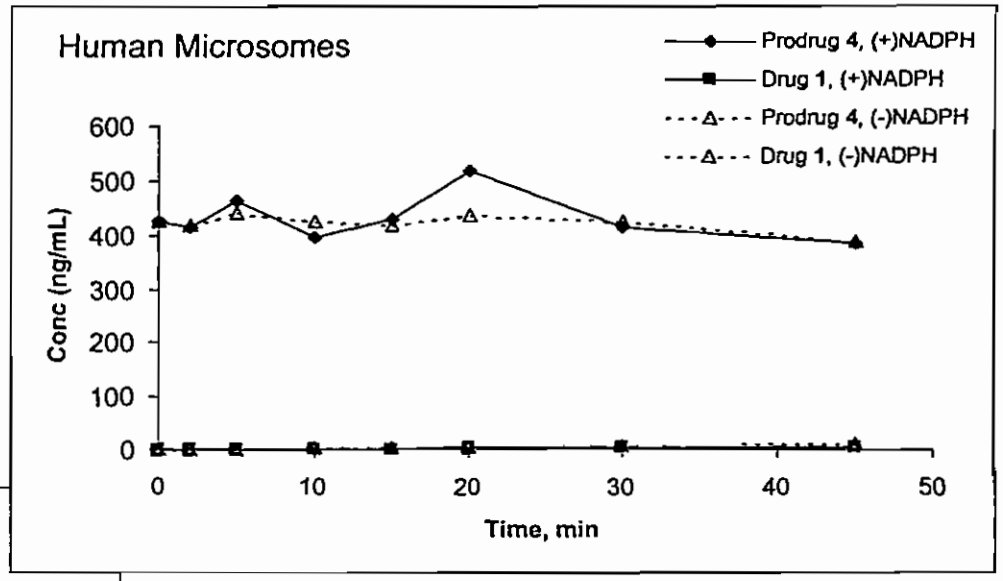


FIG. 9

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



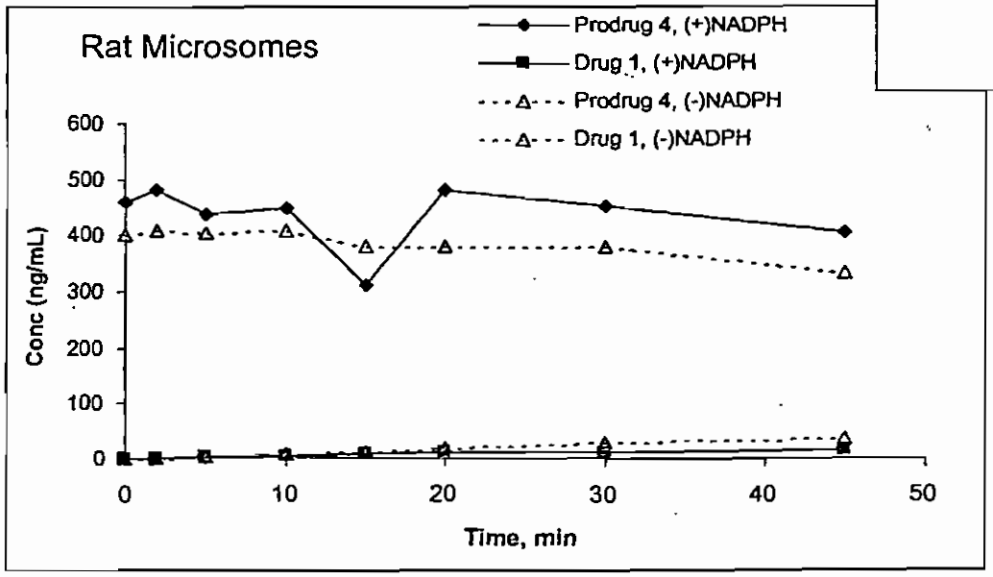
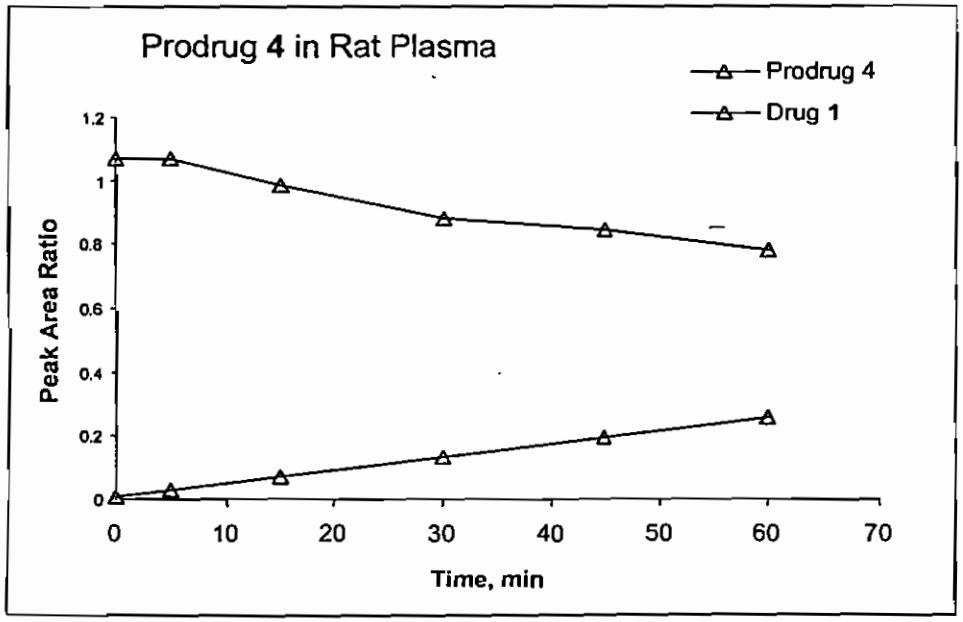


FIG. 10

Plasma Stability (Rat) of Prodrug **4** and PNP



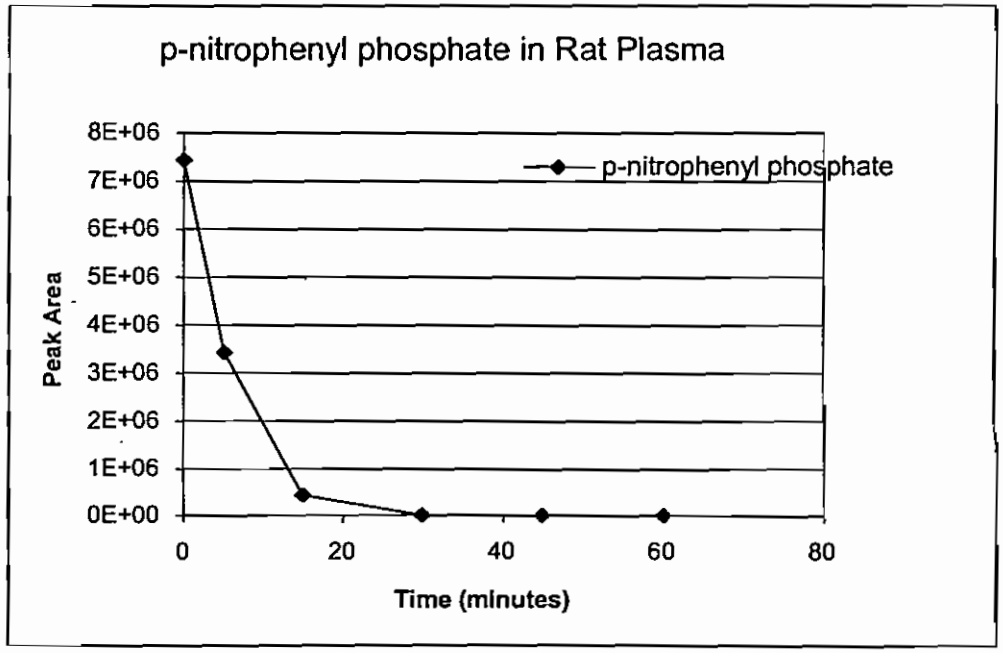
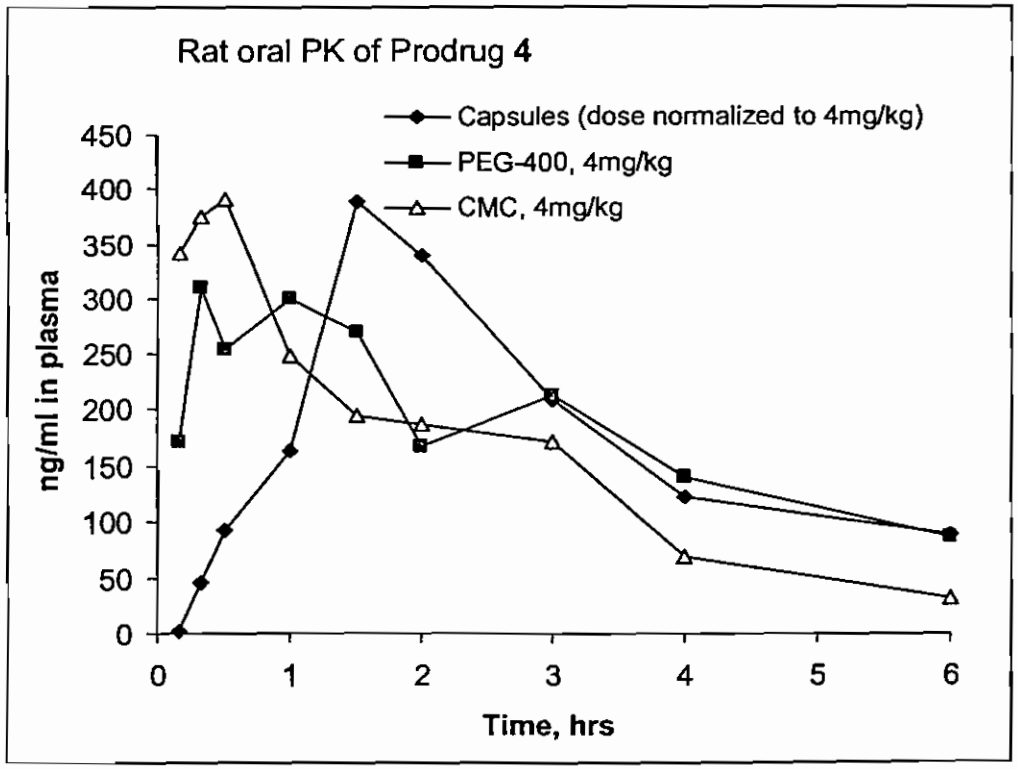


FIG. 11

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