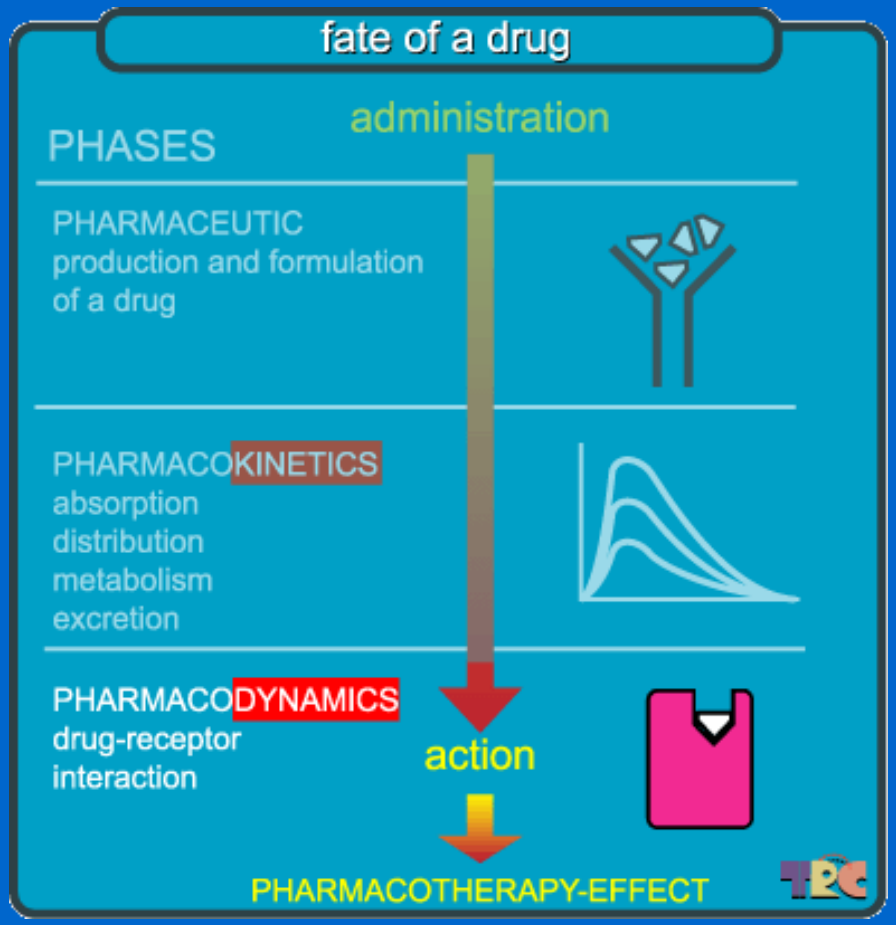
# Φαρμακευτικά φυτά και εφαρμογές τους στη σύγχρονη ιατρική

Εργαστήριο Φαρμακολογίας
Μονάδα Φαρμακοκινητικής

Περικλής Παππάς
Αναπληρωτής Καθηγητής
Εργαστήριο Φαρμακολογίας

# Φαρμακολογία



# ομάδες αντινεοπλασματικών φαρμάκων

- Αλκυλιωτικοί παράγοντες
- Ενώσεις λευκόχρυσου
- Αντιμεταβολίτες
- Κυτταροτοξικά αντιβιοτικά
- **Φυτικά προϊόντα**
- Άλλα χημειοθεραπευτικά
- Μη χημειοθεραπευτικά φάρμακα
  (ορμόνες, MABs, ραδιοϊσότοπα, κ.ά.)

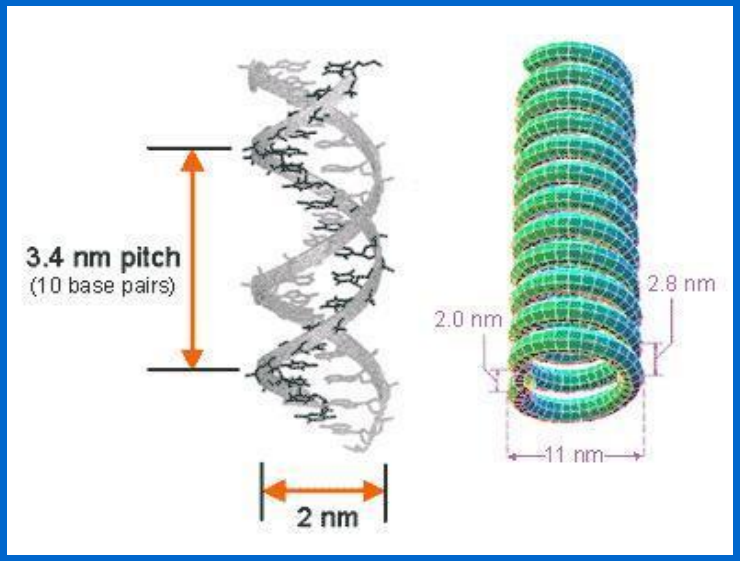
# ΟΜΑΔΕΣ ΦΑΡΜΑΚΩΝ

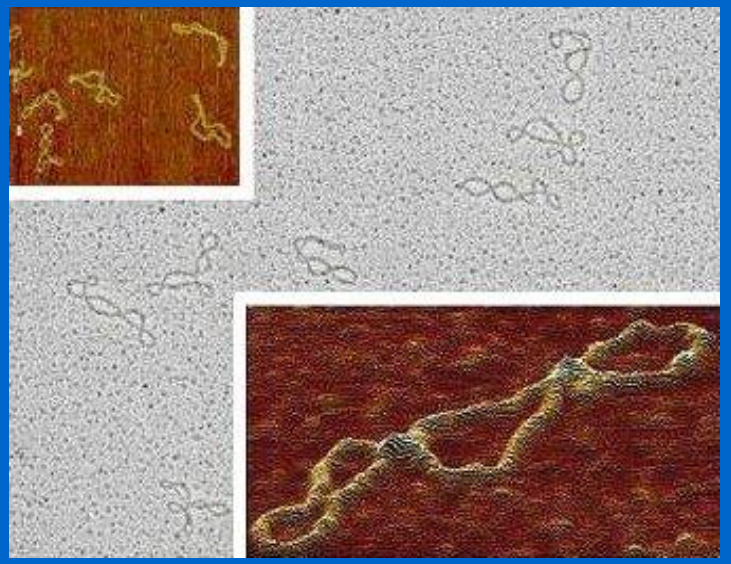
- Φυτικά προϊόντα

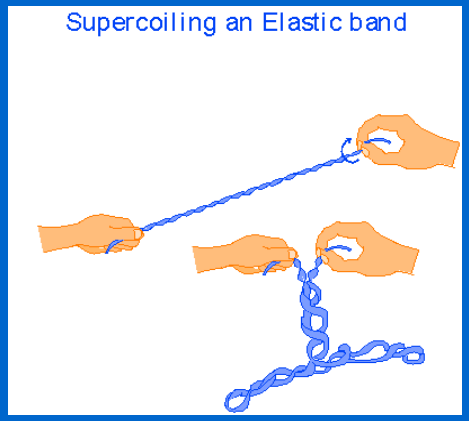
  Αλκαλοειδή του φυτού *Camptotheca acuminata*

  (Ιρινοτεκάνη, Τοποτεκάνη)


# Περιέλιξη και υπερπεριέλιξη της διπλής έλικας



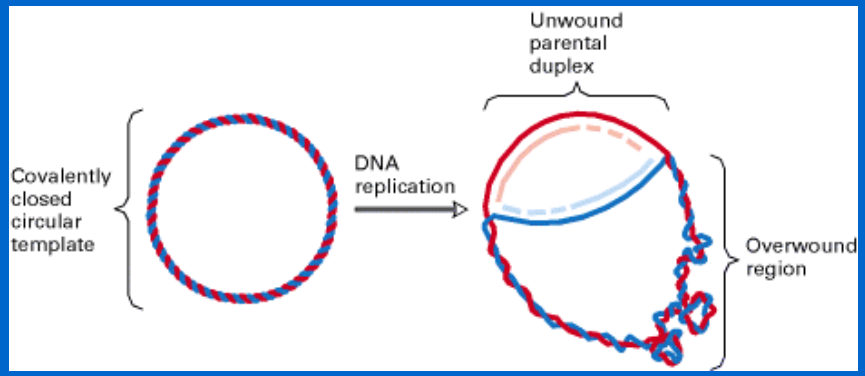





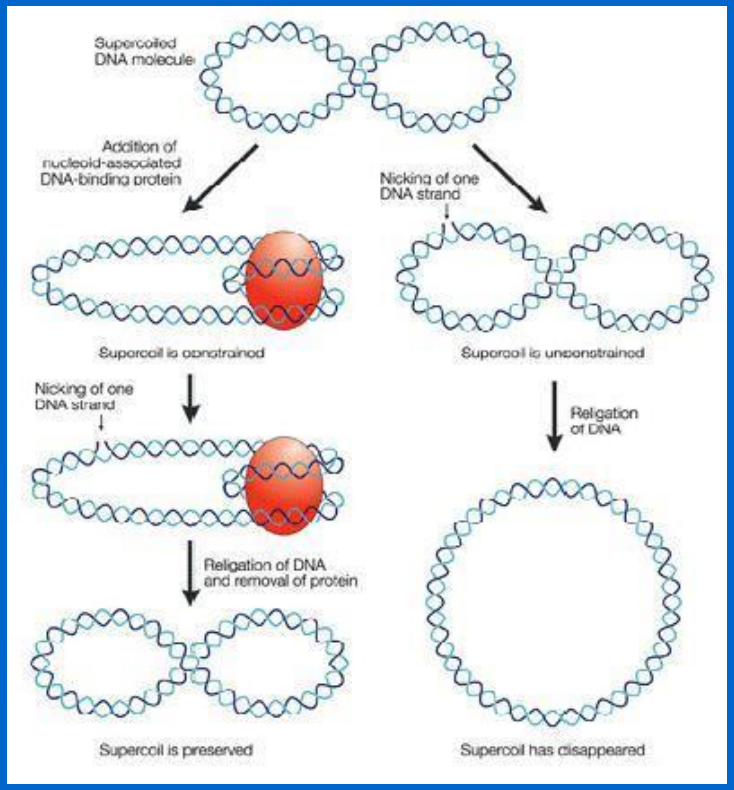

υπερέλικα

υπερσπείραμα

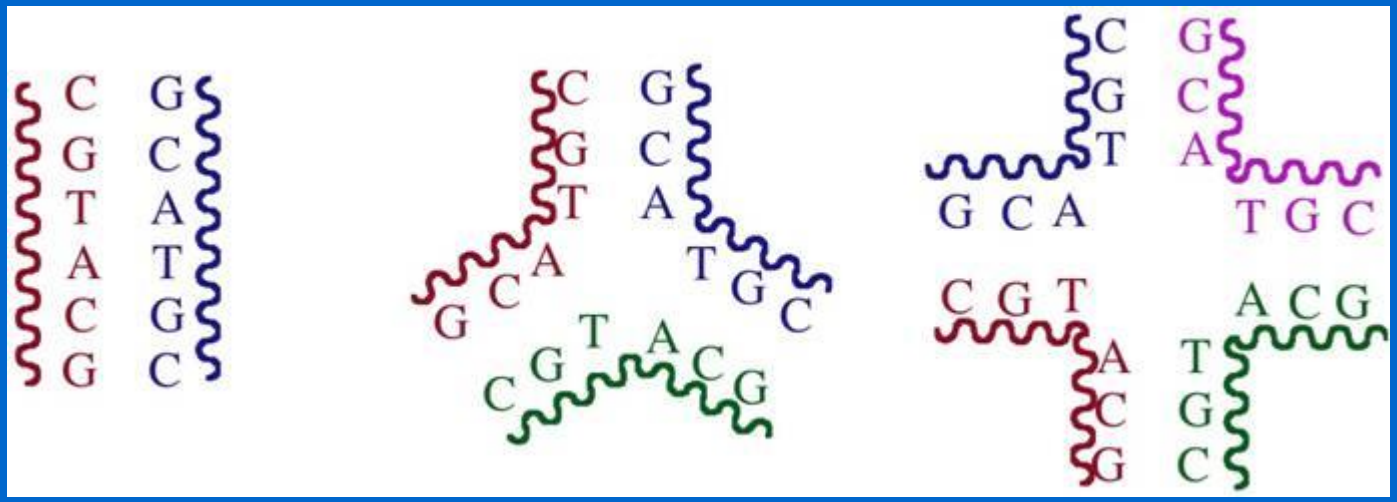
# Λειτουργία των τοποϊσομερασών Ι και ΙΙ



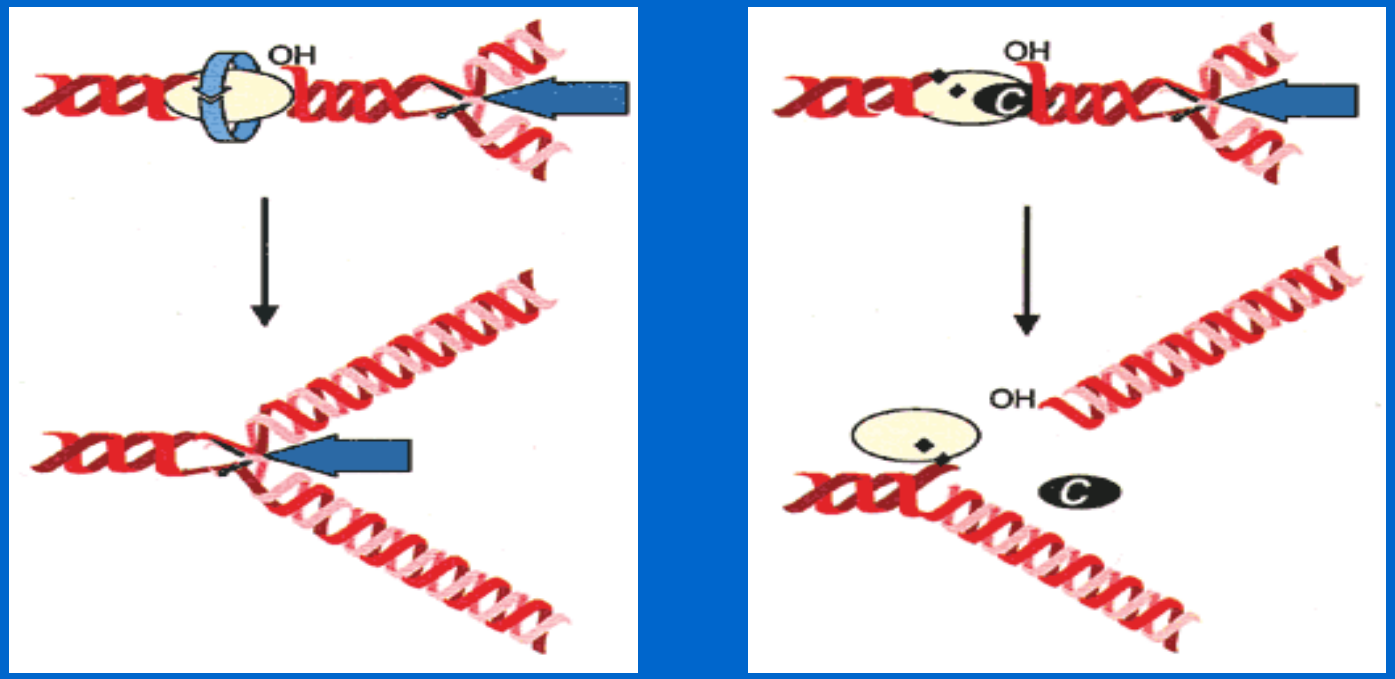

Απαραίτητα ένζυμα για την αποπεριέλιξη και τη διάνοιξη της διπλής αλυσίδας (μεταγραφή ή αναδιπλασιασμός του DNA )



Η αναστολή των τοποϊσομερασών καθιστά
το DNA εύθραυστο, ιδίως στα κομβικά σημεία με ‘παλινδρομική’ δομή:



# Αναστολή της τοποϊσομεράσης Ι από την ιρινοτεκάνη




Στο σημείο σύνδεσης με το ένζυμο, η διπλή έλικα είναι ασταθής και τελικώς σπάει

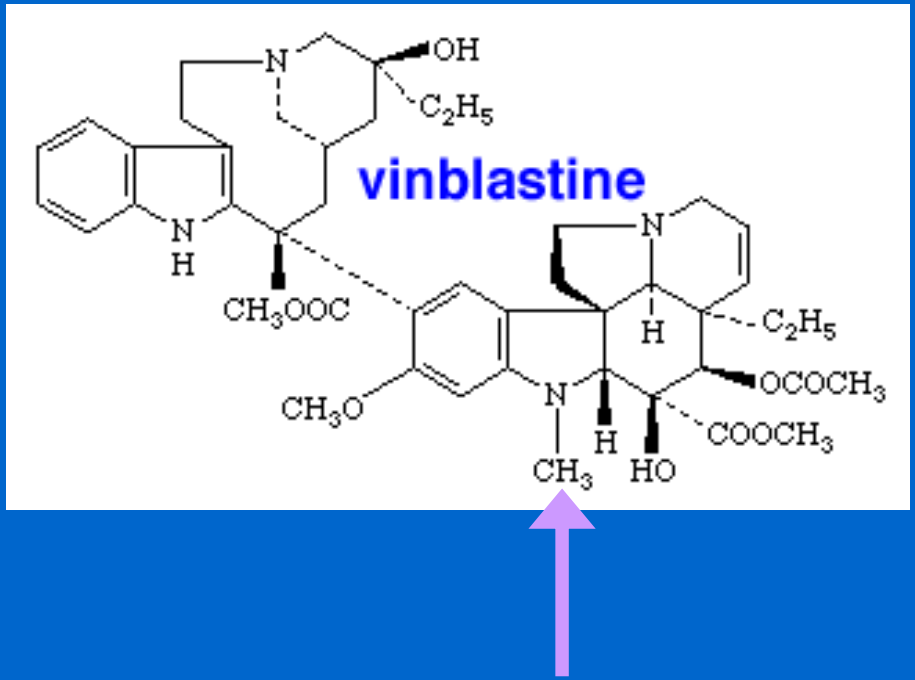
# ΟΜΑΔΕΣ ΦΑΡΜΑΚΩΝ

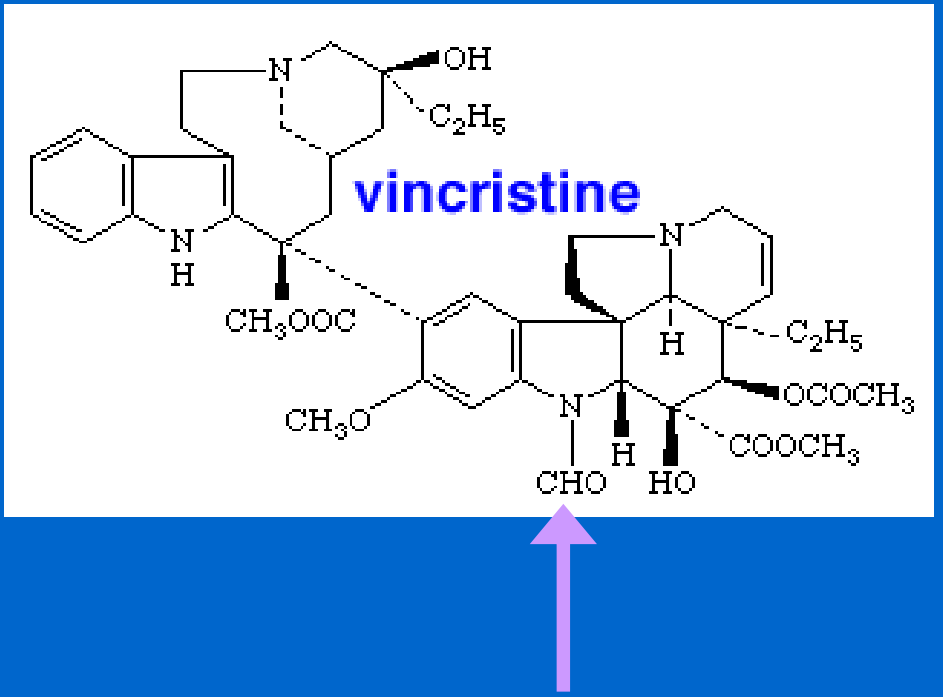
- Φυτικά προϊόντα

  Αλκαλοειδή του φυτού *Vinca rosea:*

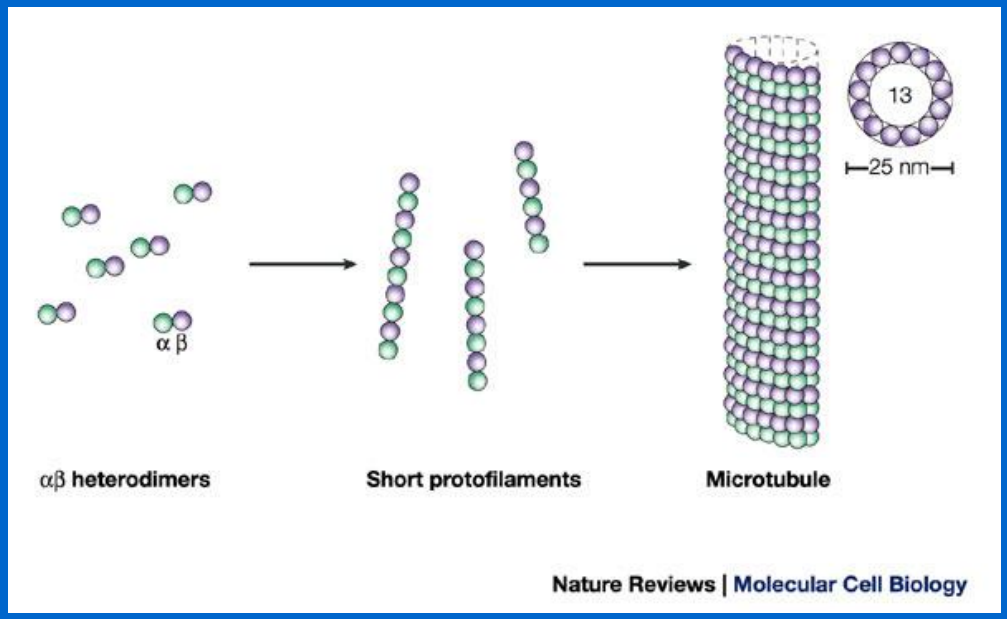
  Βινβλαστίνη, Βινκριστίνη, Βινδεσίνη, Βινορελβίνη

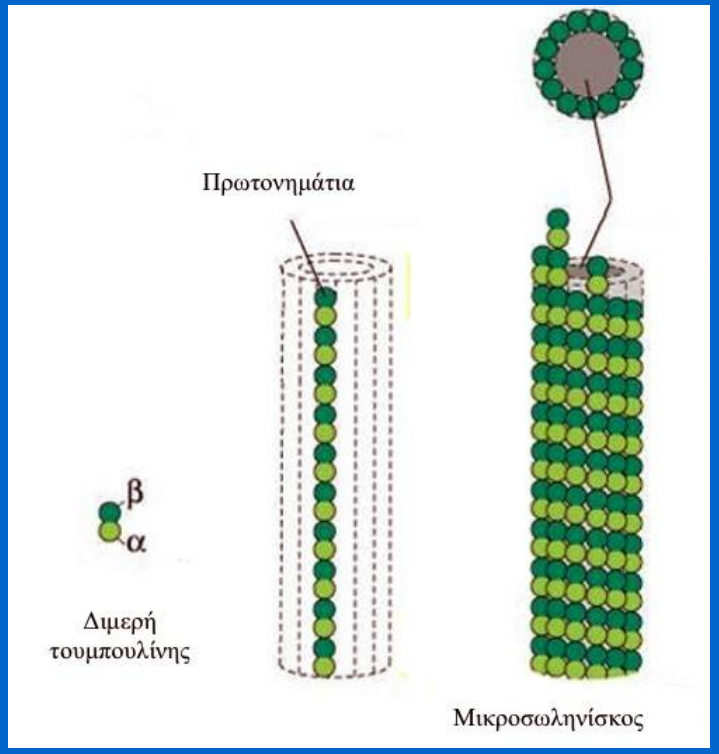
# Αλκαλοειδή του φυτού *Vinca rosea*



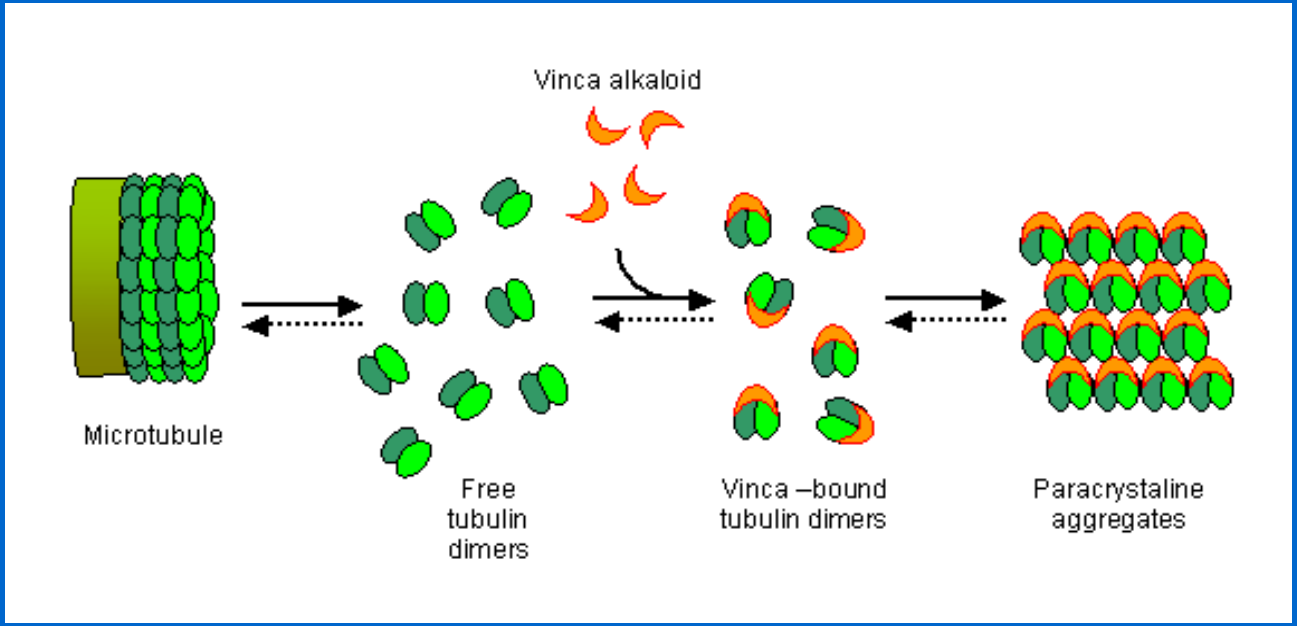



# Δομή των μικροσωληνίσκων



# Μηχανισμός δράσης αλκαλοειδών της *Vinca rosea*




Παρεμπόδιση του πολυμερισμού της τουμπουλίνης και της ενσωμάτωσής της στους μικροσωληνίσκους

# Κλινικές μελέτες



## A phase I-II and pharmacokinetic study of imatinib mesylate in combination with irinotecan in patients with relapsed or refractory small-cell lung cancer

Athanasios Karampeazis[1], Periklis Pappas[2], Anastasios Koutsopoulos[3], Athanasios Kotsakis[1], Sofia Agelaki[1], Nikolaos Vardakis[1], Martha Nikolaidou[2], Marios Marselos[2], Vassilis Georgoulias[1], Dimitris Mavroudis[1]

[1]Department of Medical Oncology, University General Hospital of Heraklion, Heraklion, Crete, Greece
[2]Department of Pharmacology, School of Medicine, University of Ioannina, Ioannina, Greece
[3]Department of Pathology, Democritus University of Thrace, Alexandroupolis, Greece

Correspondence:
Dimitris Mavroudis, MD, PhD,
Department of Medical Oncology,
University General Hospital of Heraklion,

**ABSTRACT**

**Background:** The purpose of this study was to determine the maximum tolerated doses (MTDs), the dose limiting toxicities (DLTs), the possible pharmacokinetic (PK) interactions, and to evaluate the clinical activity of the imatinib plus irinotecan combination in pre-treated patients with extensive stage SCLC.

**Patients & Methods:** Patients with refractory/relapsed SCLC were eligible. During the phase I part of the study, escalated doses of imatinib were administered daily in combination with irinotecan every 14 days. DLT and pharmacokinetic parameters of both drugs were determined during the first treatment cycle. During the phase II part of the study, the determined MTDs of the drugs were used to treat eligible patients.

**Results:** During the phase I part of the study (n=11 patients), the MTDs for imatinib and irinotecan were defined at 400 mg/day and 150 mg/m$^2$ every 2 weeks, respectively. Grade 4 neutropenia and treatment delay due to grade 3 neutropenia were the DLTs. PK analysis for imatinib, irinotecan and their major metabolites revealed no statistically significant drug

# Μεταφραστική έρευνα

## Cellular and molecular effects of metronomic vinorelbine and 4-*O*-deacetylvinorelbine on human umbilical vein endothelial cells

Eirini Biziota[a], Evangelos Briasoulis[b,c], Leonidas Mavroeidis[a,d], Marios Marselos[a], Adrian L. Harris[d] and Periklis Pappas[a,b]

Metronomic oral vinorelbine (VRL; Navelbine) was shown in clinical trials to yield sustainable antitumor activity possibly through antiangiogenic mechanisms. We investigated the effects of protracted low-dose VRL on human umbilical vein endothelial cells, compared with a conventional chemotherapy model. Human umbilical vein endothelial cell cultures were treated with different concentrations of VRL (0.001 nmol/l to 1 mmol/l) for 4, 24 and 96 h. The effects of different drug concentrations on cell growth, cell cycle, apoptosis and expression of the angiogenesis-modulating genes *interleukin-8, cyclooxygenase-2, CD36 and peroxisome proliferator-activated receptor γ* were assessed using the metronomic or conventional chemotherapy model. Apoptosis and cell-cycle effects were assessed by flow cytometry. Gene expression was measured at the transcript level by quantitative reverse transcriptase-PCR, protein expression by immunoblotting and levels of proteins secreted in the cell medium by enzyme-linked immunosorbent assay. Activation of the nuclear factor-κB dependent and *nuclear factor-κB*-related increase in proangiogenic *interleukin-8* and *cyclooxygenase-2* and a decrease in the thrombospondin-1 receptor CD36 and *peroxisome proliferator-activated receptor γ* at mRNA and protein levels. In contrast, the opposite was evident with protracted picomolar to low nanomolar concentrations (metronomic dosing). Our data provide experimental support for metronomic VRL by showing that a protracted low dose outperforms pulsed high-dose administration in inducing antiangiogenic effects in proliferating human endothelial cells. *Anti-Cancer Drugs* 00:000–000 

**Anti-Cancer Drugs** 2015, 00:000–000

**Keywords: human umbilical vein endothelial cell, interleukin-8, metronomic chemotherapy, nuclear factor-κB, peroxisome proliferator-activated receptor γ, vinorelbine**

[a]Department of Pharmacology, School of Medicine, [b]Interscience Molecular Laboratory, Cancer Biobank Center, [c]Department of Haematology, Division of Medicine, School of Life Sciences, Ioannina, Greece and [d]Molecular Oncology Laboratories, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital,

# Μεταφραστική έρευνα

INTERNATIONAL JOURNAL OF ONCOLOGY 47: 455-464, 2015

## Metronomic vinorelbine: Anti-angiogenic activity *in vitro* in normoxic and severe hypoxic conditions, and severe hypoxia-induced resistance to its anti-proliferative effect with reversal by Akt inhibition

L. MAVROEIDIS[1,4], H. SHELDON[1], E. BRIASOULIS[2,3], M. MARSELOS[4], P. PAPPAS[4] and A.L. HARRIS[1]

[1]Molecular Oncology Laboratories, Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DS, UK; [2]Department of Hematology, School of Medicine, [3]Interscience Molecular Oncology Laboratory, Cancer Biobank Center, [4]Department of Pharmacology, School of Medicine, University of Ioannina, University Campus, 45110 Ioannina, Greece

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**Abstract.** Metronomic chemotherapy is the protracted, dense administration of low sub-toxic doses of chemotherapy, to inhibit tumor angiogenesis. Vinorelbine is an orally bioavailable vinca alkaloid shown to be useable for metronomic administration. In clinical trials, metronomic vinorelbine has been demonstrated to generate sustainable antitumor efficacy at low nanomolar (nM) concentrations with negligible toxicity. We sought to determine whether the clinically relevant metronomic concentration of vinorelbine is anti-angiogenic *in vitro* anti-angiogenic basis of metronomic vinorelbine and we show that severe hypoxia mediates resistance to its anti-proliferative effect on endothelial cells. Akt warrants further investigation as a potential target to circumvent this hypoxic resistance.

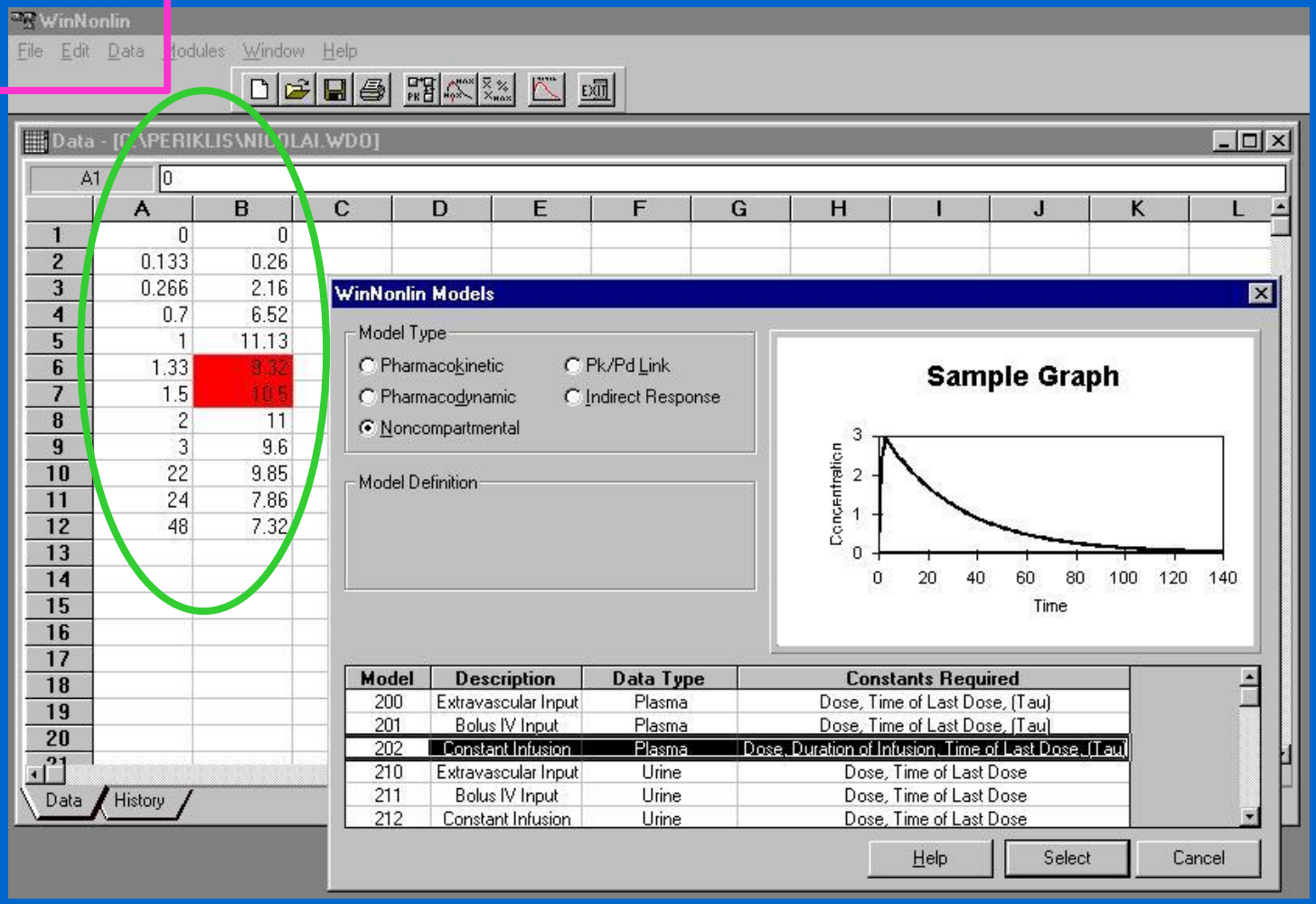
### Introduction

Metronomic chemotherapy is the chronic administration of low dose chemotherapy as opposed to the conventional

# Εργαστήριο Φαρμακολογίας
## Μονάδα Φαρμακοκινητικής

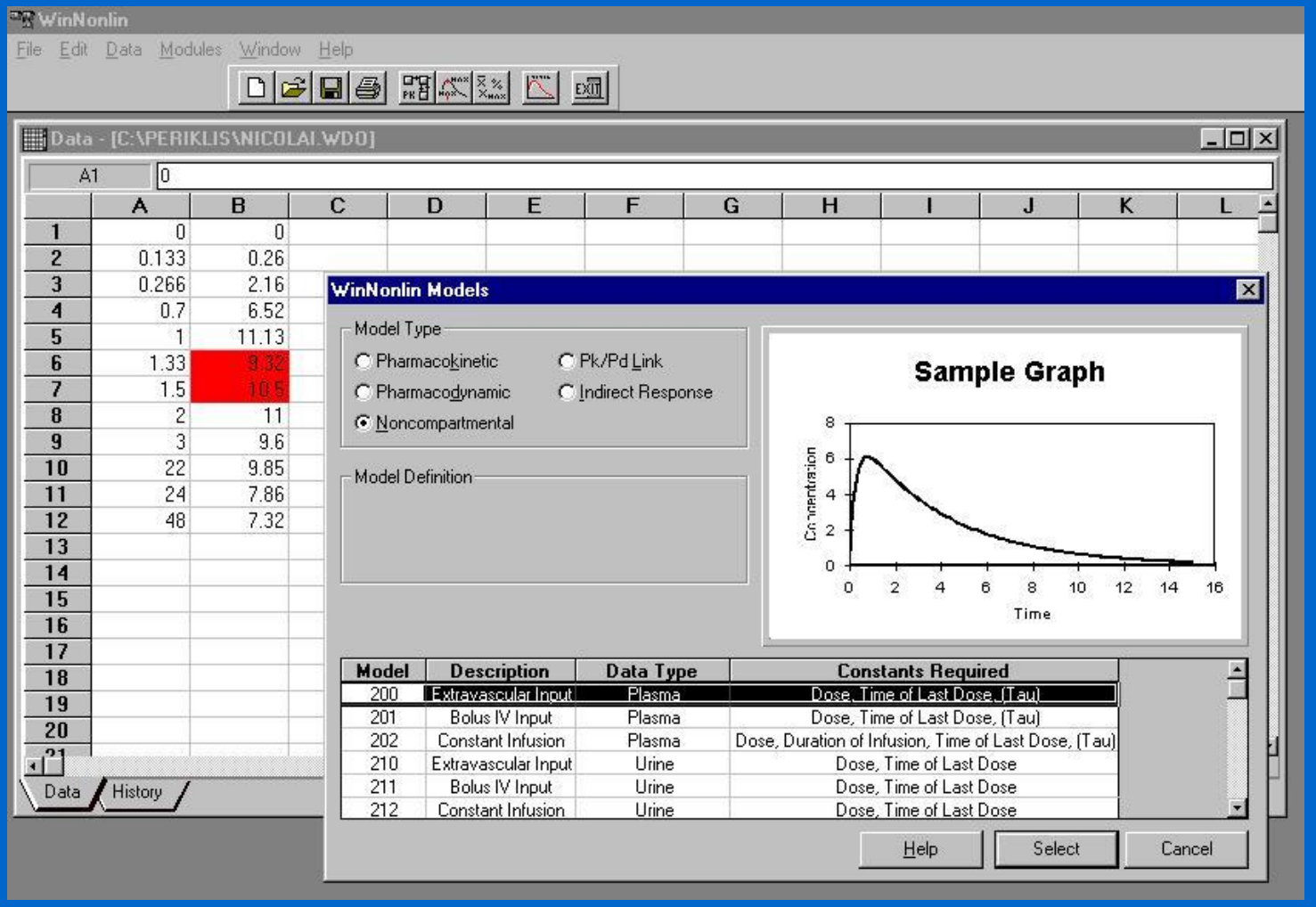
| πρωτόκολλο | συνεργασία |
|---|---|
| • Gemcitabine & Oxaliplatin | Ογκολογική Ηρακλείου |
| • Imatinib mesylate & renal disease | Ογκολογική Ιωαννίνων |
| • Gemcitabine & Oxaliplatin | Ογκολογική Ηρακλείου |
| • Oral Capecitabine & metabolites | Ογκολογική Ιωαννίνων<br>Τοξικολογία Ιωαννίνων |
| • p.l.Doxorubicin, Paclitaxel & Gemcitabine | Ογκολογική Ηρακλείου |
| • p.l.Doxorubicin, Paclitaxel & Oxaliplatin | Ογκολογική Ηρακλείου |
| • Lipoplatin & Gemcitabine | Πνευμονολογική Αλεξ/λης<br>Ογκολογική Ηρακλείου |
| • Metronomic Oral Vinorelbine | Ογκολογική Ιωαννίνων |
| • Paclitaxel, Gemcitabine & Oxaliplatin | Ογκολογική Ηρακλείου |
| • Sunitinib & SU012662 | Ογκολογική Θεσσαλονίκης |
| • Bleomycin | Πνευμονολογική Αλεξ/λης<br>Αιματολογική Ιωαννίνων |
| • Metronomic Oral Vinorelbine | Ογκολογική Ιωαννίνων |

# Εργαστήριο Φαρμακολογίας
## Μονάδα Φαρμακοκινητικής

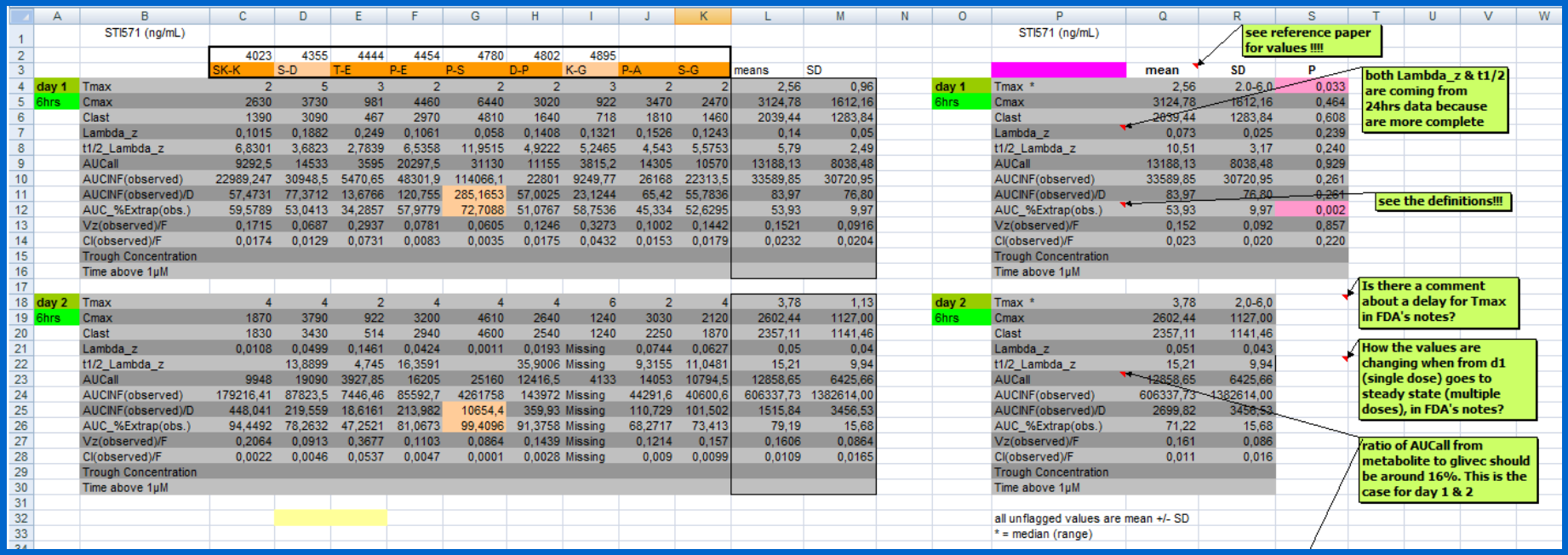


# Εργαστήριο Φαρμακολογίας

## Μονάδα Φαρμακοκινητικής



# Εργαστήριο Φαρμακολογίας
## Μονάδα Φαρμακοκινητικής



STI571 (ng/mL)

| | | | 4023 | 4355 | 4444 | 4454 | 4780 | 4802 | 4895 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | SK-K | S-D | T-E | P-E | P-S | D-P | K-G | P-A | S-G | means | SD |
| day 1 | 6hrs | Tmax | 2 | 5 | 3 | 2 | 2 | 2 | 3 | 2 | 2 | 2,56 | 0,96 |
| | | Cmax | 2630 | 3730 | 981 | 4460 | 6440 | 3020 | 922 | 3470 | 2470 | 3124,78 | 1612,16 |
| | | Clast | 1390 | 3090 | 467 | 2970 | 4810 | 1640 | 718 | 1810 | 1460 | 2039,44 | 1283,84 |
| | | Lambda_z | 0,1015 | 0,1882 | 0,249 | 0,1061 | 0,058 | 0,1408 | 0,1321 | 0,1526 | 0,1243 | 0,14 | 0,05 |
| | | t1/2_Lambda_z | 6,8301 | 3,6823 | 2,7839 | 6,5358 | 11,9515 | 4,9222 | 5,2465 | 4,543 | 5,5753 | 5,79 | 2,49 |
| | | AUCall | 9292,5 | 14533 | 3595 | 20297,5 | 31130 | 11155 | 3815,2 | 14305 | 10570 | 13188,13 | 8038,48 |
| | | AUCINF(observed) | 22989,247 | 30948,5 | 5470,65 | 48301,9 | 114066,1 | 22801 | 9249,77 | 26168 | 22313,5 | 33589,85 | 30720,95 |
| | | AUCINF(observed)/D | 57,4731 | 77,3712 | 13,6766 | 120,755 | 285,1653 | 57,0025 | 23,1244 | 65,42 | 55,7836 | 83,97 | 76,80 |
| | | AUC_%Extrap(obs.) | 59,5789 | 53,0413 | 34,2857 | 57,9779 | 72,7088 | 51,0767 | 58,7536 | 45,334 | 52,6295 | 53,93 | 9,97 |
| | | Vz(observed)/F | 0,1715 | 0,0687 | 0,2937 | 0,0781 | 0,0605 | 0,1246 | 0,3273 | 0,1002 | 0,1442 | 0,1521 | 0,0916 |
| | | Cl(observed)/F | 0,0174 | 0,0129 | 0,0731 | 0,0083 | 0,0035 | 0,0175 | 0,0432 | 0,0153 | 0,0179 | 0,0232 | 0,0204 |
| | | Trough Concentration | | | | | | | | | | | |
| | | Time above 1μM | | | | | | | | | | | |
| day 2 | 6hrs | Tmax | 4 | 4 | 2 | 4 | 4 | 4 | 6 | 2 | 4 | 3,78 | 1,13 |
| | | Cmax | 1870 | 3790 | 922 | 3200 | 4610 | 2640 | 1240 | 3030 | 2120 | 2602,44 | 1127,00 |
| | | Clast | 1830 | 3430 | 514 | 2940 | 4600 | 2540 | 1240 | 2250 | 1870 | 2357,11 | 1141,46 |
| | | Lambda_z | 0,0108 | 0,0499 | 0,1461 | 0,0424 | 0,0011 | 0,0193 | Missing | 0,0744 | 0,0627 | 0,05 | 0,04 |
| | | t1/2_Lambda_z | | 13,8899 | 4,745 | 16,3591 | | 35,9006 | Missing | 9,3155 | 11,0481 | 15,21 | 9,94 |
| | | AUCall | 9948 | 19090 | 3927,85 | 16205 | 25160 | 12416,5 | 4133 | 14053 | 10794,5 | 12858,65 | 6425,66 |
| | | AUCINF(observed) | 179216,41 | 87823,5 | 7446,46 | 85592,7 | 4261758 | 143972 | Missing | 44291,6 | 40600,6 | 606337,73 | 1382614,00 |
| | | AUCINF(observed)/D | 448,041 | 219,559 | 18,6161 | 213,982 | 10654,4 | 359,93 | Missing | 110,729 | 101,502 | 1515,84 | 3456,53 |
| | | AUC_%Extrap(obs.) | 94,4492 | 78,2632 | 47,2521 | 81,0673 | 99,4096 | 91,3758 | Missing | 68,2717 | 73,413 | 79,19 | 15,68 |
| | | Vz(observed)/F | 0,2064 | 0,0913 | 0,3677 | 0,1103 | 0,0864 | 0,1439 | Missing | 0,1214 | 0,157 | 0,1606 | 0,0864 |
| | | Cl(observed)/F | 0,0022 | 0,0046 | 0,0537 | 0,0047 | 0,0001 | 0,0028 | Missing | 0,009 | 0,0099 | 0,0109 | 0,0165 |
| | | Trough Concentration | | | | | | | | | | | |
| | | Time above 1μM | | | | | | | | | | | |

STI571 (ng/mL)

| | | | mean | SD | P |
|---|---|---|---|---|---|
| day 1 | 6hrs | Tmax * | 2,56 | 2,0-6,0 | 0,033 |
| | | Cmax | 3124,78 | 1612,16 | 0,464 |
| | | Clast | 2039,44 | 1283,84 | 0,608 |
| | | Lambda_z | 0,073 | 0,025 | 0,239 |
| | | t1/2_Lambda_z | 10,51 | 3,17 | 0,240 |
| | | AUCall | 13188,13 | 8038,48 | 0,929 |
| | | AUCINF(observed) | 33589,85 | 30720,95 | 0,261 |
| | | AUCINF(observed)/D | 83,97 | 76,80 | 0,261 |
| | | AUC_%Extrap(obs.) | 53,93 | 9,97 | 0,002 |
| | | Vz(observed)/F | 0,152 | 0,092 | 0,857 |
| | | Cl(observed)/F | 0,023 | 0,020 | 0,220 |
| | | Trough Concentration | | | |
| | | Time above 1μM | | | |
| day 2 | 6hrs | Tmax * | 3,78 | 2,0-6,0 | |
| | | Cmax | 2602,44 | 1127,00 | |
| | | Clast | 2357,11 | 1141,46 | |
| | | Lambda_z | 0,051 | 0,043 | |
| | | t1/2_Lambda_z | 15,21 | 9,94 | |
| | | AUCall | 12858,65 | 6425,66 | |
| | | AUCINF(observed) | 606337,73 | 1382614,00 | |
| | | AUCINF(observed)/D | 2699,82 | 3456,53 | |
| | | AUC_%Extrap(obs.) | 71,22 | 15,68 | |
| | | Vz(observed)/F | 0,161 | 0,086 | |
| | | Cl(observed)/F | 0,011 | 0,016 | |
| | | Trough Concentration | | | |
| | | Time above 1μM | | | |

all unflagged values are mean +/- SD
* = median (range)



Karampeazis A, Pappas P, et al. FCO 2 (3), 18-27. 2012.

# Εργαστήριο Φαρμακολογίας
## Μονάδα Φαρμακοκινητικής

| | | STI571 (ng/mL) | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 4023 | 4355 | 4444 | 4454 | 4780 | 4802 | 4895 | | | | | | | | | |
| | | | SK-K | S-D | T-E | P-E | P-S | D-P | K-G | P-A | S-G | means | SD | | | | | |
| day 1 | | Tmax | 2 | 5 | 3 | 2 | 2 | 2 | 3 | 2 | 2 | 2,56 | 0,96 | | day 1 | Tmax * | 2,56 | 2.0-6.0 | 0,033 |
| 6hrs | | Cmax | 2630 | 3730 | 981 | 4460 | 6440 | 3020 | 922 | 3470 | 2470 | 3124,78 | 1612,16 | | 6hrs | Cmax | 3124,78 | 1612,16 | 0,464 |
| | | Clast | 1390 | 3090 | 467 | 2970 | 4810 | 1640 | 718 | 1810 | 1460 | 2039,44 | 1283,84 | | | Clast | 2039,44 | 1283,84 | 0,608 |
| | | Lambda_z | 0,1015 | 0,1882 | 0,249 | 0,1061 | 0,058 | 0,1408 | 0,1321 | 0,1526 | 0,1243 | 0,14 | 0,05 | | | Lambda_z | 0,14 | 0,05 | 0,003 |
| | | t1/2_Lambda_z | 6,8301 | 3,6823 | 2,7839 | 6,5358 | 11,9515 | 4,9222 | 5,2465 | 4,543 | 5,5753 | 5,79 | 2,49 | | | t1/2_Lambda_z | 5,79 | 2,49 | 0,218 |
| | | AUCall | 9292,5 | 14533 | 3595 | 20297,5 | 31130 | 11155 | 3815,2 | 14305 | 10570 | 13188,13 | 8038,48 | | | AUCall | 13188,13 | 8038,48 | 0,929 |
| | | AUCINF(observed) | 22989,247 | 30948,5 | 5470,65 | 48301,9 | 114066,1 | 22801 | 9249,77 | 26168 | 22313,5 | 33589,85 | 30720,95 | | | AUCINF(observed) | 33589,85 | 30720,95 | 0,261 |
| | | AUCINF(observed)/D | 57,4731 | 77,3712 | 13,6766 | 120,755 | 285,1653 | 57,0025 | 23,1244 | 65,42 | 55,7836 | 83,97 | 76,80 | | | AUCINF(observed)/D | 83,97 | 76,80 | 0,261 |
| | | AUC_%Extrap(obs.) | 59,5789 | 53,0413 | 34,2857 | 57,9779 | 72,7088 | 51,0767 | 58,7536 | 45,334 | 52,6295 | 53,93 | 9,97 | | | AUC_%Extrap(obs.) | 53,93 | 9,97 | 0,002 |
| | | Vz(observed)/F | 0,1715 | 0,0687 | 0,2937 | 0,0781 | 0,0605 | 0,1246 | 0,3273 | 0,1002 | 0,1442 | 0,15 | 0,09 | | | Vz(observed)/F | 0,15 | 0,09 | 0,857 |
| | | Cl(observed)/F | 0,0174 | 0,0129 | 0,0731 | 0,0083 | 0,0035 | 0,0175 | 0,0432 | 0,0153 | 0,0179 | 0,02 | 0,02 | | | Cl(observed)/F | 0,02 | 0,02 | 0,220 |
| | | Trough Concentration | | | | | | | | | | | | | | Trough Concentration | | | |
| | | Time above 1μM | | | | | | | | | | | | | | Time above 1μM | | | |
| | | | | | | | | | | | | | | | | | | | |
| day 2 | | Tmax | 4 | 4 | 2 | 4 | 4 | 4 | 6 | 2 | 4 | 3,78 | 1,13 | | day 2 | Tmax * | 3,78 | 2,0-6,0 | |
| 6hrs | | Cmax | 1870 | 3790 | 922 | 3200 | 4610 | 2640 | 1240 | 3030 | 2120 | 2602,44 | 1127,00 | | 6hrs | Cmax | 2602,44 | 1127,00 | |
| | | Clast | 1830 | 3430 | 514 | 2940 | 4600 | 2540 | 1240 | 2250 | 1870 | 2357,11 | 1141,46 | | | Clast | 2357,11 | 1141,46 | |
| | | Lambda_z | 0,0108 | 0,0499 | 0,1461 | 0,0424 | 0,0011 | 0,0193 | Missing | 0,0744 | 0,0627 | 0,05 | 0,04 | | | Lambda_z | 0,05 | 0,04 | |
| | | t1/2_Lambda_z | 64,1136 | 13,8899 | 4,745 | 16,3591 | 638,3883 | 35,9006 | Missing | 9,3155 | 11,0481 | 99,22 | 204,60 | | | t1/2_Lambda_z | 99,22 | 204,60 | |
| | | AUCall | 9948 | 19090 | 3927,85 | 16205 | 25160 | 12416,5 | 4133 | 14053 | 10794,5 | 12858,65 | 6425,66 | | | AUCall | 12858,65 | 6425,66 | |
| | | AUCINF(observed) | 179216,41 | 87823,5 | 7446,46 | 85592,7 | 4261758 | 143972 | Missing | 44291,6 | 40600,6 | 606337,73 | 1382614,00 | | | AUCINF(observed) | 606337,73 | 1382614,00 | |
| | | AUCINF(observed)/D | 448,041 | 219,559 | 18,6161 | 213,982 | 10654,4 | 359,93 | Missing | 110,729 | 101,502 | 1515,84 | 3456,53 | | | AUCINF(observed)/D | 2699,82 | 3456,53 | |
| | | AUC_%Extrap(obs.) | 94,4492 | 78,2632 | 47,2521 | 81,0673 | 99,4096 | 91,3758 | Missing | 68,2717 | 73,413 | 79,19 | 15,68 | | | AUC_%Extrap(obs.) | 71,22 | 15,68 | |
| | | Vz(observed)/F | 0,2064 | 0,0913 | 0,3677 | 0,1103 | 0,0864 | 0,1439 | Missing | 0,1214 | 0,157 | 0,16 | 0,09 | | | Vz(observed)/F | 0,16 | 0,09 | |
| | | Cl(observed)/F | 0,0022 | 0,0046 | 0,0537 | 0,0047 | 0,0001 | 0,0028 | Missing | 0,009 | 0,0099 | 0,01 | 0,02 | | | Cl(observed)/F | 0,01 | 0,02 | |
| | | Trough Concentration | | | | | | | | | | | | | | Trough Concentration | | | |
| | | Time above 1μM | | | | | | | | | | | | | | Time above 1μM | | | |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | all unflagged values are mean +/- SD | | | |
| | | | | | | | | | | | | | | | | * = median (range) | | | |

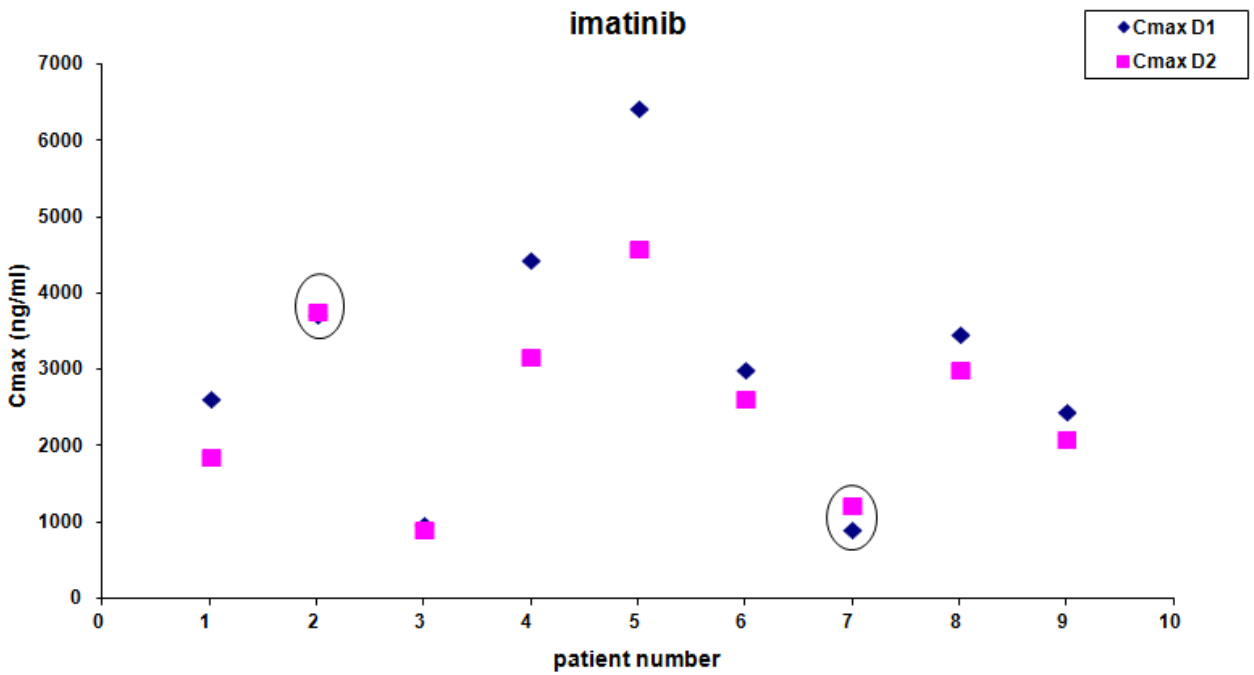
Karampeazis A, Pappas P, et al. FCO 2 (3), 18-27. 2012.

# Εργαστήριο Φαρμακολογίας
## Μονάδα Φαρμακοκινητικής

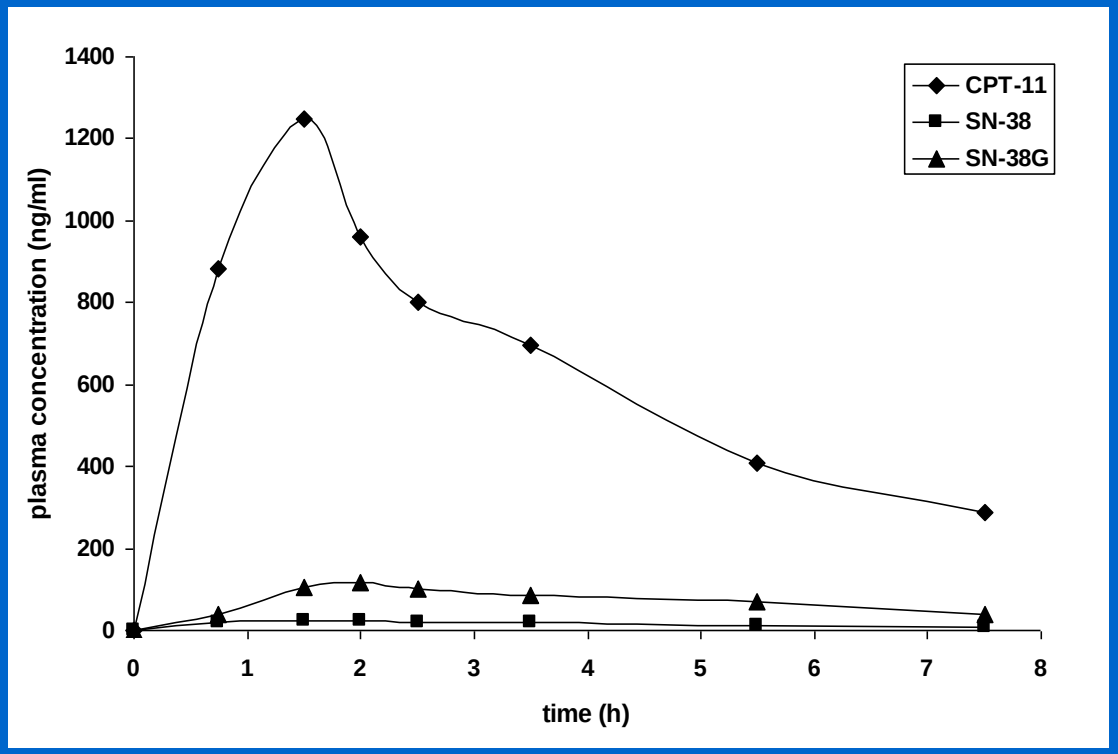
| | A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | | II | IV | V | III | IV | VI | VII | VI | II | IV | VII | III | V | VII | VIII | I | | |
| 11 | *dox* | 12 | 12 | 14 | 12 | 12 | 14 | 14 | 14 | 12 | 12 | 14 | 12 | 14 | 14 | 16 | 10 | | |
| 12 | *pac* | 100 | 110 | 110 | 100 | 110 | 110 | 120 | 110 | 100 | 110 | 120 | 100 | 110 | 120 | 120 | 100 | | |
| 13 | *oxa* | 50 | 60 | 60 | 60 | 60 | 70 | 70 | 70 | 50 | 60 | 70 | 60 | 60 | 70 | 70 | 50 | | |
| 14 | | | | 14mg/m2 | | | 14mg/m2 | 14mg/m2 | 14mg/m2 | | | 14mg/m2 | | 14mg/m2 | 14mg/m2 | 16mg/m2 | | means | SD |
| 15 | Dosing_time | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 16 | Rsq | 0,9812 | 0,9817 | 0,8076 | 0,948 | 0,9957 | 0,9944 | 0,937 | 0,9972 | 0,9941 | 0,634 | 0,8882 | 0,9563 | 0,9317 | 0,9948 | 0,9504 | 0,8712 | | |
| 17 | Rsq(adjusted) | 0,9749 | 0,9726 | 0,7435 | 0,9307 | 0,9943 | 0,9916 | 0,916 | 0,9944 | 0,9911 | 0,512 | 0,8509 | 0,9344 | 0,9089 | 0,9931 | 0,9256 | 0,8068 | | |
| 18 | Corr(x:y) | -0,9905 | -0,9908 | -0,8987 | -0,9737 | -0,9979 | -0,9972 | -0,968 | -0,9986 | -0,997 | -0,7962 | -0,9424 | -0,9779 | -0,9652 | -0,9974 | -0,9749 | -0,9334 | | |
| 19 | Tmax | 1 | 1 | 1 | 1 | 1 | 6 | 1 | 24 | 1 | 1 | 1 | 6 | 1 | 1 | 1 | 1 | 3,0625 | 5,65098 |
| 20 | Cmax | 5,02 | 7,487 | 8,704 | 7,003 | 7,399 | 6,513 | 8,404 | 2,373 | 3,591 | 5,897 | 4,584 | 2,773 | 8,774 | 8,335 | 7,524 | 3,469 | 6,11563 | 2,12924 |
| 21 | No._points_Lambda_z | 5 | 4 | 5 | 5 | 5 | 4 | 5 | 3 | 4 | 5 | 5 | 4 | 5 | 5 | 4 | 4 | | |
| 22 | Tlast | 168 | 72 | 168 | 168 | 168 | 168 | 168 | 168 | 72 | 168 | 168 | 168 | 168 | 168 | 72 | 168 | 150 | 37,47 |
| 23 | Clast | 0,012 | 0,355 | 2,524 | 0,366 | 0,117 | 0,833 | 2,393 | 0,296 | 0,274 | 0,927 | 0,328 | 0,396 | 1,592 | 0,653 | 1,241 | 0,592 | 0,80619 | 0,74177 |
| 24 | AUClast | 04,874 | 161,794 | 668,846 | 264,575 | 292,275 | 463,955 | 825,991 | 202,013 | 92,513 | 298,273 | 172,13 | 179,271 | 594,365 | 495,115 | 273,937 | 197,767 | 330,481 | 209,561 |
| 25 | Lambda_z | 0,0351 | 0,0426 | 0,0059 | 0,0167 | 0,0246 | 0,0124 | 0,0067 | 0,0143 | 0,0358 | 0,0083 | 0,0141 | 0,0111 | 0,0098 | 0,0153 | 0,0237 | 0,0089 | 0,01783 | 0,01097 |
| 26 | Lambda_z_lower | 1 | 1 | 1 | 1 | 1 | 6 | 1 | 24 | 1 | 1 | 1 | 6 | 1 | 1 | 1 | 1 | | |
| 27 | Lambda_z_upper | 168 | 72 | 168 | 168 | 168 | 168 | 168 | 168 | 72 | 168 | 168 | 168 | 168 | 168 | 72 | 168 | | |
| 28 | t1/2_Lambda_z | 9,7692 | 16,2706 | 117,486 | 41,6044 | 28,17 | 55,9758 | 103,606 | 48,44 | 19,3627 | 83,0971 | 49,2838 | 62,4381 | 70,4519 | 45,3531 | 29,1894 | 78,0594 | 54,2849 | 29,1768 |
| 29 | AUCall | 04,874 | 161,794 | 668,846 | 264,575 | 292,275 | 463,955 | 825,991 | 202,013 | 92,513 | 298,273 | 172,13 | 179,271 | 594,365 | 495,115 | 273,937 | 197,767 | 330,481 | 209,561 |
| 30 | AUCINF(observed) | 05,216 | 170,127 | 1096,66 | 286,543 | 297,03 | 531,224 | 1183,68 | 222,698 | 100,167 | 409,405 | 195,451 | 214,942 | 756,177 | 537,841 | 326,197 | 264,436 | 418,612 | 320,309 |
| 31 | AUCINF(observed)/D | 8,768 | 14,1773 | 78,3325 | 23,8786 | 24,7525 | 37,9446 | 84,5484 | 15,907 | 8,3473 | 34,1171 | 13,9608 | 17,9118 | 54,0126 | 38,4172 | 20,3873 | 22,0363 | | |
| 32 | AUC_%Extrap(obs.) | 0,3253 | 4,8981 | 39,0104 | 7,6666 | 1,6008 | 12,6632 | 30,2183 | 9,2887 | 7,6413 | 27,1448 | 11,932 | 16,5958 | 21,3987 | 7,944 | 16,0211 | 25,2117 | | |
| 33 | Vz(observed) | 3,2528 | 1,6557 | 2,1638 | 2,5137 | 1,6419 | 2,1283 | 1,7679 | 4,3933 | 3,3466 | 3,5139 | 5,0929 | 5,029 | 1,8818 | 1,7032 | 2,0656 | 5,1105 | 2,95381 | 1,27419 |
| 34 | Cl(observed) | 0,1141 | 0,0705 | 0,0128 | 0,0419 | 0,0404 | 0,0264 | 0,0118 | 0,0629 | 0,1198 | 0,0293 | 0,0716 | 0,0558 | 0,0185 | 0,026 | 0,0491 | 0,0454 | 0,04977 | 0,03127 |
| 35 | AUCINF(predicted) | 05,149 | 169,447 | 1081,05 | 283,216 | 296,815 | 529,23 | 1204,03 | 222,268 | 99,8607 | 402,226 | 192,211 | 212,706 | 743,47 | 535,617 | 328,803 | 261,413 | 416,719 | 320,884 |
| 36 | AUCINF(predicted)/D | 8,7624 | 14,1206 | 77,218 | 23,6013 | 24,7345 | 37,8022 | 86,0019 | 15,8763 | 8,3217 | 33,5188 | 13,7294 | 17,7255 | 53,105 | 38,2683 | 20,5502 | 21,7844 | | |
| 37 | AUC_%Extrap(pred.) | 0,2614 | 4,5166 | 38,1301 | 6,5818 | 1,5294 | 12,3341 | 31,3976 | 9,1133 | 7,3579 | 25,8445 | 10,4474 | 15,7192 | 20,0553 | 7,5618 | 16,6867 | 24,3469 | | |
| 38 | Vz(predicted) | 3,2549 | 1,6624 | 2,195 | 2,5432 | 1,6431 | 2,1363 | 1,738 | 4,4018 | 3,3568 | 3,5766 | 5,1788 | 5,0819 | 1,914 | 1,7102 | 2,0492 | 5,1696 | | |
| 39 | Cl(predicted) | 0,1141 | 0,0708 | 0,013 | 0,0424 | 0,0404 | 0,0265 | 0,0116 | 0,063 | 0,1202 | 0,0298 | 0,0728 | 0,0564 | 0,0188 | 0,0261 | 0,0487 | 0,0459 | | |
| 40 | AUMClast | 296,79 | 2549,97 | 46527,2 | 11272,3 | 9790,35 | 23760,1 | 54059,7 | 10001,5 | 1700,3 | 19571,8 | 8522,56 | 9609,73 | 34513,7 | 22466,9 | 6443,34 | 10177,1 | | |
| 41 | AUMCINF(observed) | 364,05 | 3345,56 | 190912 | 16281,5 | 10782,4 | 40493,8 | 167615 | 14922,3 | 2465,21 | 51565 | 14098,7 | 18815,8 | 78144,7 | 32440,5 | 12406,8 | 28885,4 | | |
| 42 | AUMC_%Extrap(obs.) | 2,8451 | 23,7804 | 75,6289 | 30,7664 | 9,2009 | 41,3242 | 67,7478 | 32,9762 | 31,028 | 62,0443 | 39,5508 | 48,9272 | 55,8336 | 30,7444 | 48,0662 | 64,7673 | | |
| 43 | AUMCINF(predicted) | 350,82 | 3280,65 | 185646 | 15522,8 | 10737,5 | 39997,8 | 174075 | 14820 | 2434,59 | 49498,2 | 13324 | 18238,8 | 74718,5 | 31921,4 | 12704,2 | 28037,1 | | |
| 44 | AUMC_%Extrap(pred.) | 2,2981 | 22,2723 | 74,9376 | 27,3822 | 8,8208 | 40,5966 | 68,9447 | 32,5138 | 30,1606 | 60,4595 | 36,0358 | 47,3116 | 53,8084 | 29,618 | 49,2819 | 63,7014 | | |
| 45 | MRTlast | 1,9005 | 15,7606 | 69,5635 | 42,6052 | 33,497 | 51,212 | 65,4483 | 49,5093 | 18,379 | 65,6173 | 49,5124 | 53,6046 | 58,0682 | 45,3772 | 23,5212 | 51,46 | | |
| 46 | MRTINF(observed) | 2,4685 | 19,6651 | 174,086 | 56,8205 | 36,3008 | 76,2274 | 141,606 | 67,0068 | 24,6109 | 125,951 | 72,1342 | 87,5388 | 103,342 | 60,3162 | 38,0347 | 109,234 | | |
| 47 | Vss(observed) | 2,5626 | 1,3871 | 2,2224 | 2,3796 | 1,4666 | 2,0089 | 1,6748 | 4,2124 | 2,9484 | 3,6917 | 5,1669 | 4,8872 | 1,9133 | 1,57 | 1,8656 | 4,957 | | |
| 48 | MRTINF(predicted) | 22,357 | 19,3609 | 171,727 | 54,809 | 36,1757 | 75,5773 | 144,578 | 66,6764 | 24,3798 | 123,061 | 69,3194 | 85,7464 | 100,5 | 59,5974 | 38,6377 | 107,252 | | |
| 49 | Vss(predicted) | 2,5515 | 1,3711 | 2,2239 | 2,3223 | 1,4626 | 1,9993 | 1,6811 | 4,1997 | 2,9297 | 3,6714 | 5,049 | 4,8375 | 1,8925 | 1,5578 | 1,8802 | 4,9234 | | |

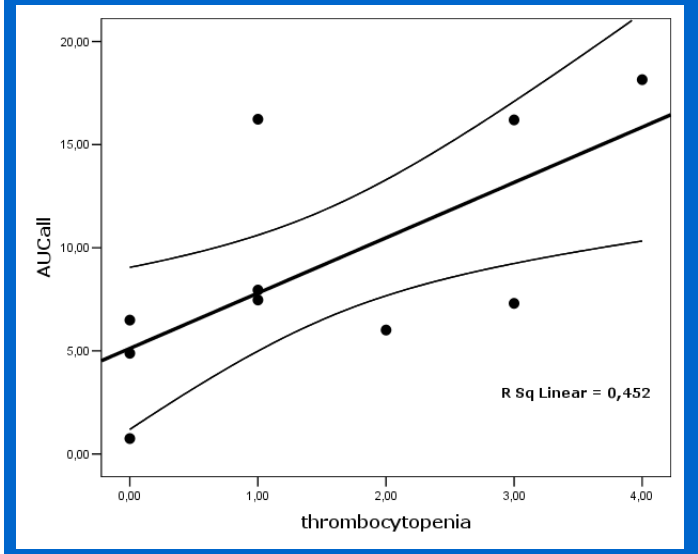
# Εργαστήριο Φαρμακολογίας
## Μονάδα Φαρμακοκινητικής

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| | SK-K | S-D | T-E | P-E | P-S | D-P | K-G | P-A | S-G |
| Cmax D1 | 2630 | 3730 | 981 | 4460 | 6440 | 3020 | 922 | 3470 | 2470 |
| Cmax D2 | 1870 | 3790 | 922 | 3200 | 4610 | 2640 | 1240 | 3030 | 2120 |



# Εργαστήριο Φαρμακολογίας
## Μονάδα Φαρμακοκινητικής



# Εργαστήριο Φαρμακολογίας
## Μονάδα Φαρμακοκινητικής

**UF**

| Conc (ng/ml) / Time (hr) | Κ-Σ 0000 50 mg/m2 | Κ-Μ 5142 50 mg/m2 | Φ-Α 1460 50 mg/m2 | Mean | SD |
|---|---|---|---|---|---|
| Tmax | 8 | 6 | 6 | 6,667 | 0,943 |
| Cmax | 75,3 | 52,7 | 114,6 | 80,867 | 25,575 |
| Tlast | 24 | 24 | 24 | 24,000 | 0,000 |
| Clast | 25,3 | 3,1 | 15,4 | 14,600 | 9,081 |
| AUClast | 1289 | 372,2 | 1445,3 | 1035,500 | 473,345 |
| Lambda_z | 0,0495 | 0,1108 | 0,053 | 0,071 | 0,028 |
| t1/2_Lambda_z | 14,002 | 6,2585 | 13,0897 | 11,117 | 3,455 |
| AUCall | 1289 | 372,2 | 1445,3 | 1035,500 | 473,345 |
| AUCINF(observe | 1800,0767 | 400,19 | 1736,1215 | 1312,129 | 645,367 |
| Vz(observed) | 0,5611 | 1,1281 | 0,5439 | 0,744 | 0,271 |
| Cl(observed) | 0,0278 | 0,1249 | 0,0288 | 0,061 | 0,046 |

**TOTAL**

| Conc (ng/ml) / Time (hr) | Κ-Σ 0000 50 mg/m2 | Κ-Μ 5142 50 mg/m2 | Φ-Α 1460 50 mg/m2 | Mean | SD |
|---|---|---|---|---|---|
| Tmax | 8 | 6 | 6 | 6,667 | 0,943 |
| Cmax | 646,4 | 981,4 | 1038,9 | 888,900 | 173,073 |
| Tlast | 24 | 24 | 24 | 24,000 | 0,000 |
| Clast | 477,2 | 537,6 | 555,5 | 523,433 | 33,499 |
| AUClast | 12817,6 | 15036,6 | 17729,5 | 15194,567 | 2008,383 |
| Lambda_z | 0,0051 | 0,0194 | 0,0194 | 0,015 | 0,007 |
| t1/2_Lambda_z | 134,9947 | 35,7668 | 35,7226 | 68,828 | 46,787 |
| AUCall | 12817,6 | 15036,6 | 17729,5 | 15194,567 | 2008,383 |
| AUCINF(observe | 105755,24 | 42777,067 | 46358,172 | 64963,493 | 28881,149 |
| Vz(observed) | 0,0921 | 0,0603 | 0,0556 | 0,069 | 0,016 |
| Cl(observed) | 0,0005 | 0,0012 | 0,0011 | 0,001 | 0,000 |

**UF**

| Conc (ng/ml) / Time (hr) | Λ-Ζ 6308 60mg/m2 | Κ-Ζ 5960 60 mg/m2 | Κ-Ζ 6320 60 mg/m2 | Λ-Β 5091 60 mg/m2 | Mean | SD |
|---|---|---|---|---|---|---|
| Tmax | 2 | 6 | 6 | 6 | 5,000 | 1,732 |
| Cmax | 77,3 | 99,5 | 117,4 | 134,6 | 107,200 | 21,261 |
| Tlast | 24 | 24 | 24 | 24 | 24,000 | 0,000 |
| Clast | 23,9 | 5,7 | 5,6 | 48,2 | 20,850 | 17,460 |
| AUClast | 859,6 | 1173 | 1588,1 | 2196,4 | 1454,275 | 500,353 |
| Lambda_z | 0,0478 | 0,1372 | 0,1364 | 0,0385 | 0,090 | 0,047 |
| t1/2_Lambda_z | 14,5 | 5,0504 | 5,0808 | 17,9927 | 10,656 | 5,725 |
| AUCall | 859,6 | 1173 | 1588,1 | 2196,4 | 1454,275 | 500,353 |
| AUCINF(observe | 1359,5653 | 1214,5311 | 1629,1483 | 3447,5748 | 1912,705 | 898,560 |
| Vz(observed) | 0,9232 | 0,3599 | 0,27 | 0,4518 | 0,501 | 0,252 |
| Cl(observed) | 0,0441 | 0,0494 | 0,0368 | 0,0174 | 0,037 | 0,012 |

**TOTAL**

| Conc (ng/ml) / Time (hr) | Λ-Ζ 6308 60mg/m2 | Κ-Ζ 5960 60 mg/m2 | Κ-Ζ 6320 60 mg/m2 | Λ-Β 5091 60 mg/m2 | Χ-Γ 0001 60 mg/m2 | Γ-Ν 7594 60 mg/m2 | Meanall | SD |
|---|---|---|---|---|---|---|---|---|
| Tmax | 6 | 8 | 6 | 6 | 2 | 2 | 5,000 | 2,236 |
| Cmax | 1379,9 | 887,7 | 935,3 | 768,6 | 635 | 822,7 | 904,867 | 232,746 |
| Tlast | 24 | 24 | 24 | 24 | 24 | 24 | 24,000 | 0,000 |
| Clast | 512,5 | 499,7 | 499,7 | 440 | 342,8 | 618,1 | 485,467 | 82,814 |
| AUClast | 18148,1 | 16625,5 | 16895,5 | 13450,2 | 11390,8 | 16671,5 | 15530,267 | 2333,835 |
| Lambda_z | 0,0074 | 0,0203 | 0,0214 | 0,0018 | 0,028 | 0,013 | 0,015 | 0,009 |
| t1/2_Lambda_z | 93,327 | 34,1254 | 32,3376 | 380,7122 | 24,7361 | 53,3299 | 103,095 | 126,192 |
| AUCall | 18148,1 | 16625,5 | 16895,5 | 13450,2 | 11390,8 | 16671,5 | 15530,267 | 2333,835 |
| AUCINF(observe | 87152,293 | 41226,975 | 40208,159 | 255120,88 | 23624,168 | 64227,405 | 85259,980 | 78598,368 |
| Vz(observed) | 0,0927 | 0,0717 | 0,0696 | 0,1292 | 0,0906 | 0,0719 | 0,088 | 0,021 |
| Cl(observed) | 0,0007 | 0,0015 | 0,0015 | 0,0002 | 0,0025 | 0,0009 | 0,001 | 0,001 |

**UF**

| Conc (ng/ml) / Time (hr) | Α-Α 8134 70mg/m2 | Ξ-Α 6424 70 mg/m2 | Ν-Ε 7987 70 mg/m2 | Β-Ε 8073 70 mg/m2 | Mean | SD |
|---|---|---|---|---|---|---|
| Tmax | 6 | 6 | 6 | 6 | 6,000 | 0,000 |
| Cmax | 85,1 | 94,7 | 94,7 | 159,5 | 108,500 | 29,705 |
| Tlast | 24 | 24 | 24 | 24 | 24,000 | 0,000 |
| Clast | 50,6 | 15,1 | 15,7 | 87,4 | 42,200 | 29,792 |
| AUClast | 1381,3 | 1131,5 | 1381,3 | 2759,6 | 1663,425 | 641,041 |
| Lambda_z | 0,0257 | 0,0512 | 0,0759 | 0,0179 | 0,043 | 0,023 |
| t1/2_Lambda_z | 26,9847 | 13,5496 | 9,1335 | 38,7352 | 22,101 | 11,639 |
| AUCall | 1381,3 | 1131,5 | 1381,3 | 2759,6 | 1663,425 | 641,041 |
| AUCINF(observe | 3351,1964 | 1426,6746 | 1588,1764 | 7643,7797 | 3502,457 | 2507,328 |
| Vz(observed) | 0,8132 | 0,9591 | 0,5808 | 0,5118 | 0,716 | 0,179 |
| Cl(observed) | 0,0209 | 0,0491 | 0,0441 | 0,0092 | 0,031 | 0,016 |

**TOTAL**

| Conc (ng/ml) / Time (hr) | Α-Α 8134 70mg/m2 | Ξ-Α 6424 70 mg/m2 | Ν-Ε 7987 70 mg/m2 | Β-Ε 8073 70 mg/m2 | Mean | SD |
|---|---|---|---|---|---|---|
| Tmax | 6 | 6 | 6 | 6 | 6,000 | 0,000 |
| Cmax | 917,5 | 854,2 | 788,3 | 1195,2 | 938,800 | 154,921 |
| Tlast | 24 | 24 | 24 | 24 | 24,000 | 0,000 |
| Clast | 197,7 | 375,6 | 290,1 | 706,2 | 392,400 | 191,785 |
| AUClast | 12783,9 | 13876,2 | 10787,7 | 21021,6 | 14617,350 | 3859,776 |
| Lambda_z | 0,0642 | 0,0322 | 0,0359 | 0,0075 | 0,035 | 0,020 |
| t1/2_Lambda_z | 10,8046 | 21,5241 | 19,2881 | 92,1641 | 35,945 | 32,703 |
| AUCall | 12783,9 | 13876,2 | 10787,7 | 21021,6 | 14617,350 | 3859,776 |
| AUCINF(observe | 15865,593 | 25539,617 | 18860,268 | 114921,31 | 43796,697 | 41212,872 |
| Vz(observed) | 0,0688 | 0,0851 | 0,1033 | 0,081 | 0,085 | 0,012 |
| Cl(observed) | 0,0044 | 0,0027 | 0,0037 | 0,0006 | 0,003 | 0,001 |

# Εργαστήριο Φαρμακολογίας

ΚΛΙΝΙΚΕΣ ΜΕΛΕΤΕΣ & Πρωτόκολλα μεταφραστικής έρευνας