CFC-222, A New Fluoroquinolone

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Abstract

CFC-222 is a novel fluoroqinolone antibacterial agent synthesized and under development by the Cheil Jedang Corporation, Korea. CFC-222 exerts the antibacterial activity by inhibition of bacterial DNA gyrase leading to bactericidal action.

In in vitro and in vivo preclinical testing, CFC-222 has been shown to possess a broad spectrum of antibacterial activity. In particular CFC-222 is very potent against Gram-positive bacteria such as *Staphylococcus* spp., *Streptococcus* spp. (in particular penicillin G-resistant and -susceptible *S. pneumoniae*) and *Enterococcus* spp. when compared to other quinolones (ciprofloxacin, ofloxacin or lomefloxacin). CFC-222 also showed potent activity against the methicillin resistant clinical isolates of *S. aureus* (MRSA). Against Gram-negative bacteria (*E. coli*, *Pseudomonas* and *Sarcina*) the activity of CFC-222 was slightly weaker than that of ciprofloxacin, but was more potent than that of ofloxacin or lomefloxacin. In urinary systemic infections caused by both Gram-positive and -negative bacteria, CFC-222 demonstrated a potent therapeutic efficacy in particular against Gram-positive bacteria *S. aureus*, *S. pyrogens* 203 and *S. pneumonia* Type III.

In preclinical pharmacokinetic studies, CFC-222 was characterized by dose dependency with no evidence of accumulation on repeated dosing, sex difference or food effects. The maximum plasma concentration (C_{max}) occurred 2-4 hours after oral administration, with an elimination half-life of between 3-6 hours. In tissue distribution studies, CFC-222 was concentrated in the lungs, liver and kidneys. In these organs concentrations of CFC-222 were 3-7 times higher than in the plasma. The extent of protein binding of CFC-222 was comparable to that seen with other quinolones (37-55%). CFC-222 is mainly excreted through feces (>70%) as the parent compound and the remainder via the urine. The major metabolite was the glucuronide conjugate. In the preclinical toxicity tests to date CFC-222 revealed a profile similar to that seen with other quinolones. In particular CFC-222 did not cause any signs of renal toxicity, central nervous system toxicity or hemolysis even at high doses.

In normal, healthy male volunteers CFC-222 was safe and well tolerated at single doses of 25, 50, 100, 200 and 400 mg p.o. CFC-222 was well absorbed with maximum plasma concentrations being achieved within two hours for the majority of subjects. The C_{max} was 1.35 μg/ml for the 200 mg dose and 2.92 μg/ml for the 200 mg dose. Pharmacokinetic analysis revealed linear relationships for C_{max} and AUC with increasing doses of CFC-222. The elimination half-life ($t_{1/2}$) ranged from 13.8 hours for the 400 mg dose to 18.7 hours for the 100 mg dose but was invariant to dose, suggesting a once daily dosing would be possible.

In conclusion, CFC-222 is the promising new drug candidate for the treatment of respiratory tract and urinary tract infections.

CFC-222
A NEW FLUOROQUINOLONE

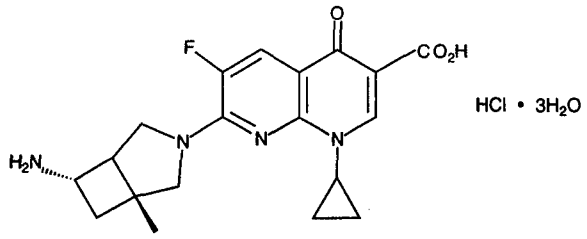
1997. 4

CHEIL JEDANG CORPORATION
Research and Development Center

CFC-222

1. Introduction to the molecule
2. *In vitro* efficacy
3. *In vivo* efficacy in animal models
4. Preclinical safety profile
5. Pharmacokinetics and safety in men
6. Summary

Chemical Structure of CFC-222



In Vitro Activity of Fluoroquinolone Compounds Against Clinical Isolates

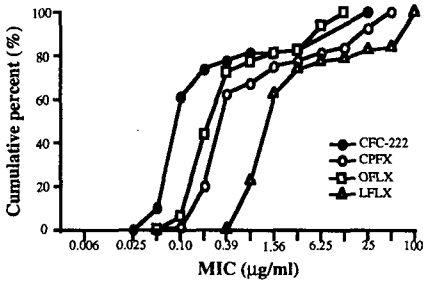
Microorganism (No. of strains)	Compound	MIC (μg/ml) 50%	90%
MSSA (144)	CFC-222	0.10	0.20
	CPFX	0.39	0.78
	OFLX	0.39	0.39
	LFLX	1.56	1.56
MRSA (80)	CFC-222	0.10	6.25
	CPFX	0.39	25
	OFLX	0.20	6.25
	LFLX	1.56	>50
S pneumoniae (123)	CFC-222	0.20	0.20
	CPFX	0.78	1.56
	OFLX	1.56	3.13
	LFLX	12.5	12.5
E. coli (90)	CFC-222	0.05	0.10
	CPFX	0.012	0.025
	OFLX	0.05	0.20
	LFLX	0.10	0.39
P. aeruginosa (146)	CFC-222	3.13	25
	CPFX	0.39	25
	OFLX	1.56	>50
	LFLX	3.13	>50

In Vitro Activity of Fluoroquinolone Compounds Against Clinical Isolates

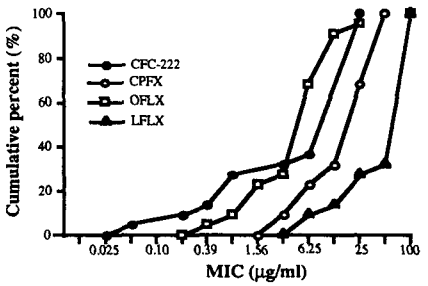
Microorganism (No. of strains)	Compound	MIC (μg/ml)	
		50%	90%
M. pneumoniae (33)	CFC-222	0.78	0.78
	CPFX	0.78	1.56
	OFLX	0.39	0.78
M. hominis (56)	CFC-222	0.39	1.56
	CPFX	0.78	6.25
	OFLX	0.78	6.25
U. urealyticum (124)	CFC-222	0.39	0.78
	CPFX	1.56	3.12
	OFLX	0.78	1.56
C. trachomatis (36)	CFC-222	0.15	0.3
	CPFX	0.6	1.2
	OFLX	0.6	0.6

In Vitro Activity of Quinolones Against Clinical Isolates

MRSA (n=80)

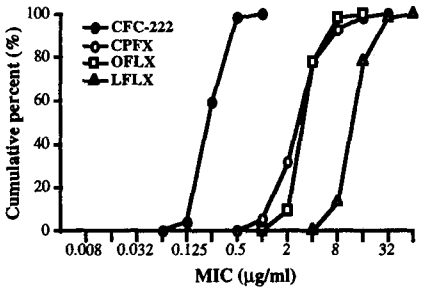


QRSA (n=22)

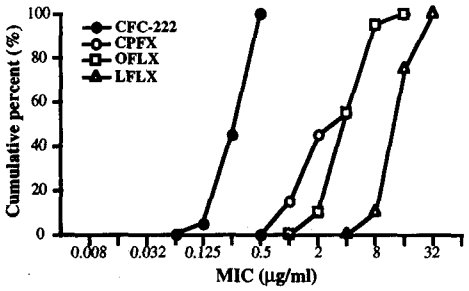


In Vitro Activity of Quinolones Against Clinical Isolates

PCG-Resistant *S. pneumoniae* (n=54)



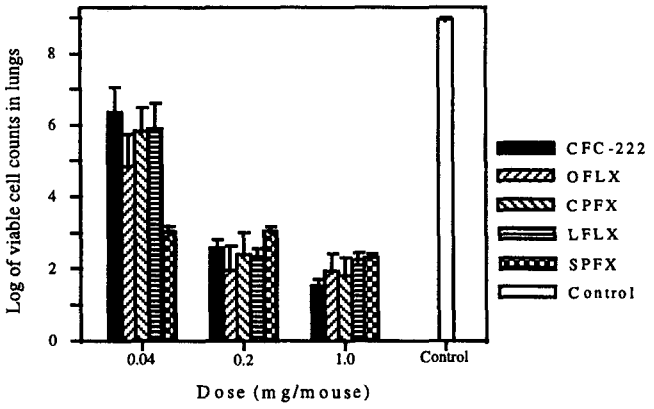
PCG-Susceptible *S. pneumoniae* (n=20)



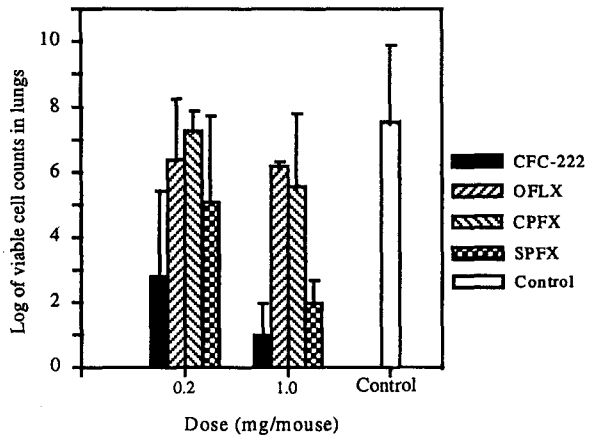
Protective Effects on Systemic Infection in Mice

Microorganism	Challenge dose (CFU/mouse)	Compound	MIC (μg/ml)	PD_{50} (mg/kg)
S. aureus Smith	8.7×10^6	CFC-222	0.10	0.40
		CPFX	0.20	2.33
		OFLX	0.39	2.08
		LFLX	0.78	4.64
E. coli C4002	1.4×10^6	CFC-222	0.20	0.71
		CPFX	0.05	0.65
		OFLX	0.10	1.37
		LFLX	0.39	1.67
K. pneumoniae C1040	1.5×10^6	CFC-222	0.20	0.59
		CPFX	0.05	0.34
		OFLX	0.20	1.23
		LFLX	0.39	1.02
P. aeruginosa GN11189	5.7×10^5	CFC-222	3.13	2.17
		CPFX	0.39	0.74
		OFLX	1.56	3.65
		LFLX	3.13	4.00

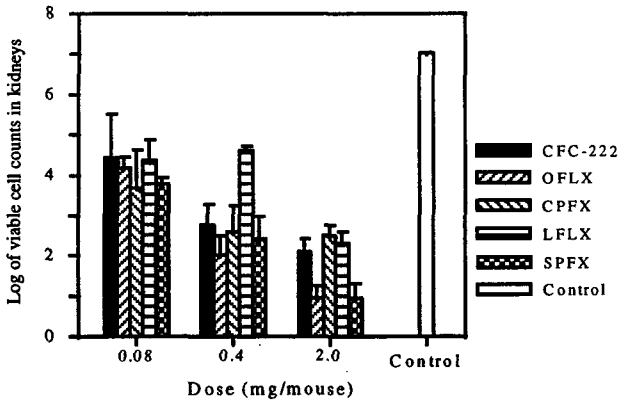
Therapeutic Effects on Mouse Nebulizer Infection Model (*K. pneumoniae* B-54)



Therapeutic Effects on Mouse Nasal Infection Model (*S. pneumoniae* Type III)



Therapeutic Effects on Mouse Urinary Tract Infection (*E. coli* 444)



Safety Pharmacology in Animals

- **CNS: No harmful effects observed in mice and rats**
- **CVS: No harmful effects observed in mice and rats**

Toxicity of CFC-222 in Rats and Dogs

- Acute Toxicity

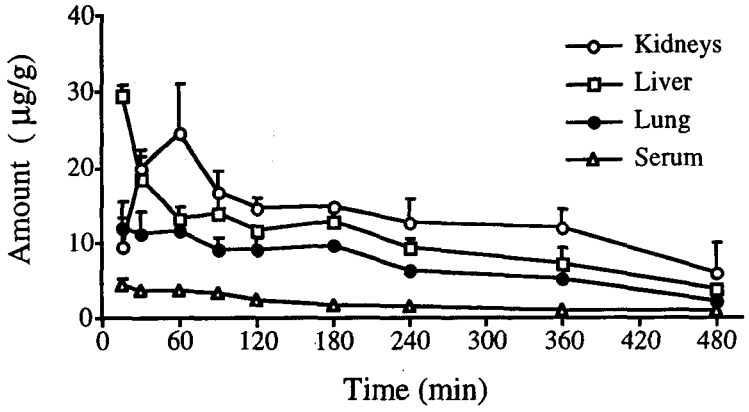
Animal	Administration route	LD_{50} (mg/kg)	
		Male	Female
Rat	*i.v.*	94	138
	p.o.	5300	4400
Dog	*i.v.*	>200	>100
	p.o.	>500	>500

- Thirteen-week toxicity of CFC-222 in rat and dog comparable to other quinolone compounds

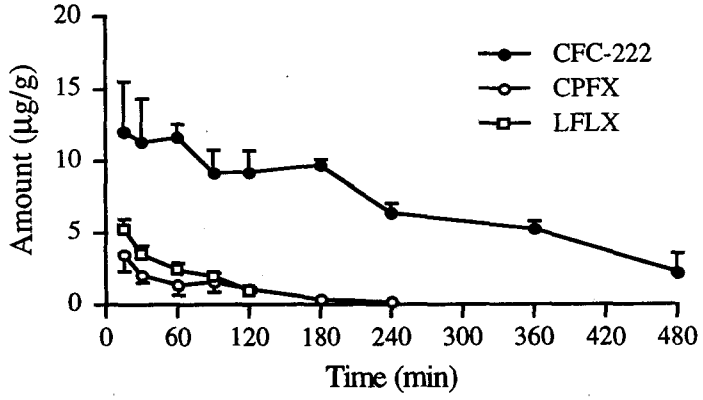
Mutagenicity Studies with CFC-222

Mutagenicity	Result
Reverse mutation test	No mutagenic pontential
Chromosome aberration test in CHL cells	Comparable to other quinolone
Micronucleus test in mice	No mutagenic potential
In vivo UDS	No mutagenic potential
In vivo chromosome aberration test	Not clatogenic

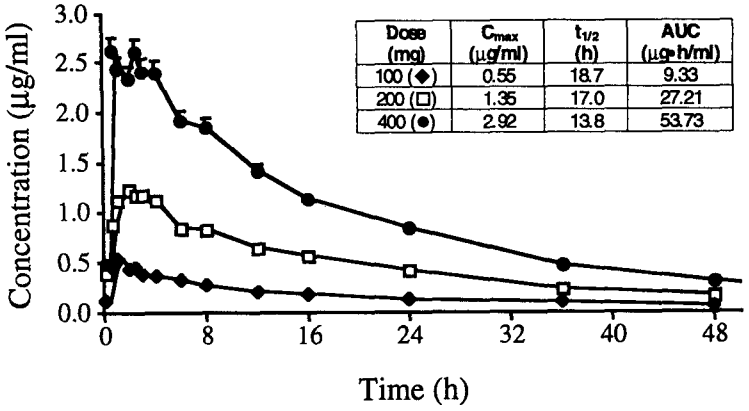
Penetration of CFC-222 into Mouse Tissues (20 mg/kg, p.o.)



Levels of Fluoroquinolones in Mouse Lungs after a 20 mg/kg Single Oral Dose



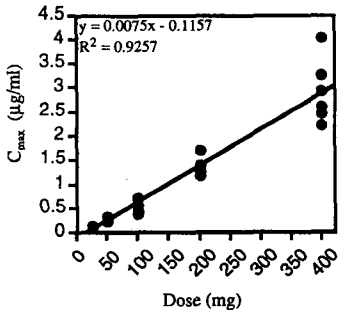
Pharmacokinetics in Men (Single, p.o.)



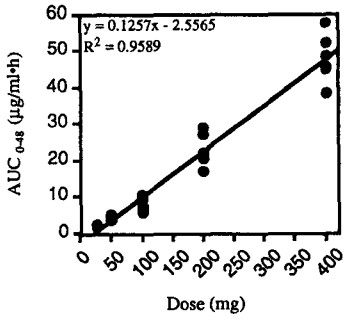
Dose (mg)	C_{max} (μg/ml)	$t_{1/2}$ (h)	AUC (μg·h/ml)
100 (◆)	0.55	18.7	9.33
200 (□)	1.35	17.0	27.21
400 (●)	2.92	13.8	53.73

Dose Proportionality of CFC-222 in Healthy Male Subjects (Single-dose, p.o.)

C_{max} vs. Dose



AUC_{0-48} vs. Dose



Pharmacokinetic Parameters of CFC-222 and Other Quinolones

	Dose (mg)	C_{max} (μg/ml)	t_{max} (h)	$t_{1/2}$ (h)	AUC (μg•h/ml)
CFC-222	50	0.285	1.0	15.0	4.56
	100	0.549	1.5	18.7	9.33
	200	1.351	2.5	17.0	27.21
	400	2.915	1.8	13.8	53.73
SPFX	200	0.7	4	20.8	18.75
	400	1.18	5	18.2	32.73
OFLX	200	2.19	1.28	5.56	14.6
	400	3.51	1.92	4.9	28.0
CPFX	200	1.18	0.69	4.11	4.18
	500	2.3	1.33	3.9	9.9

Tolerability of CFC-222 in Healthy Male Volunteers (n=6)

Dose	Adverse Events
Single dose p.o.	
50 mg	No drug-related AE
100 mg	One episode of mild headache, possibly drug-related
200 mg	No drug-related AE
400 mg	One episode of loose stool, possibly drug-related, Six subjects - Increase of serum creatinine (20%), drug-related
Multiple dose p.o.	
50 mg	One episode of dizziness and lightheadedness, possibly drug-related.
100 mg	One episode of headache and nausea, possibly drug-related
200 mg	No serious adverse events, minor elevations of plasma creatinine in some patients, further assessments of renal function (inulin clearance, urine NAG and RBP) were within normal ranges.

Summary

- **Broad-spectrum antimicrobial effects**
  - better than CPFX against Gram-positive bacteria
  - comparable to CPFX against Gram-negative bacteria
  - effective against Mycoplasma, Chlamydia
- **Excellent activity against PCG-resistant Pneumonococci**
- **Good bioavailability and penetration into tissues, esp. lungs**
- **Safe and effective in animal models**
  - No side-effects observed in CNS and CVS

Summary (continued)

- Well tolerated in Phase I Clinical Trials
- Once-a-day dosing possible: $T_{1/2}$ 17 h
- Dose proportionality: linear
- Renal Excretion 20%

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Education

Ph. D. in Biochemistry
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Advisor: Ronald T. Borchardt, Ph.D., Chairman, Dept. of Pharmaceutical Chemistry

B. A. in Pharmaceutics
March 1985, Seoul National University, Seoul, S. Korea

Research Experience

Development of CFC-222, a new antibacterial fluoroquinolone, Department of Pharmacology, Research and Development Center, Cheil Jedang Corporation (5/96-Present)

Expression of human cytochrome P-450 isoforms using baculovirus-insect cell gene expression system and their application to drug metabolism studies. Clinical Pharmacology Dept., Glaxo Research Institute (1/95-4/96)

Transport of pharmaceuticals using Caco-2 cells as an *in vitro* model of intestinal transport. Advisors: Dr. Poe-Hirr Hsyu, Clinical Pharmacology Dept., Glaxo Research Institute. (10/93-12/94)

Transport of pharmaceuticals using Caco-2 cells as an *in vitro* model of intestinal transport. Advisor: Dr. Ronald T. Borchardt (8/93-10/93)

Studies on the mechanism by which S-adenosylhomocysteine hydrolase inhibitors exert differential antiviral activity depending on the host cell line. Advisor: Dr. Ronald T. Borchardt (12/90-7/93).

Studies on the role of isozymes of S-adenosylhomocysteine hydrolase in the metabolism of S-adenosylhomocysteine and homocysteine. Advisor: Dr. Ronald T. Borchardt (6/88-10/90).

Purification of bovine liver S-adenosylhomocysteine hydrolase and screening of potent S-adenosylhomocysteine hydrolase inhibitors as broad spectrum antiviral agents. Advisor: Dr. Ronald T. Borchardt (6/88-8/91).

Internalization of Protease Nexin (PN) I in human fibroblast cells. Advisor: Dr. Joffre Baker (12/87-5/88)

Employment History

May 1996-Present Senior Scientist, Cheil Jedang Corporation, Research and Development Center, Department of Pharmacology, Korea

October 1993-April 1996 UNC/Glaxo Industry postdoctoral fellow, Glaxo Wellcome Research Institute, Dept. of Clinical Pharmacology, NC, U.S.A.

August 1993-October 1993 Postdoctoral fellow, University of Kansas, Dept. of Pharmaceutical Chemistry, KS, U. S. A.

March 1988-July 1993 Graduate Research Assistant, University of Kansas, Dept. of Pharmaceutical Chemistry, KS, U. S. A.

March 1985-June 1987 Dept. of Development (documentation), Il-Yang Pharmaceutical Co., Seoul, S. Korea

Publications

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2) Sufrin, J. R., A. J. Spiess, D. L. Kramer, P. R. Libby, J. T. Miller, R. J. Bernacki, Y. Lee, R. T. Borchardt, and C. W. Porter (1991), Targeting 5'-Deoxy-5'-(methylthio)adenosine Phosphorylase by 5'-Haloalkyl Analogues of 5'-Deoxy-5'-(methylthio)adenosine, *J. Med. Chem.* **34**(8):2600-2606.

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4) Robins, M. J., V. Samano, W, Zhang, J. Balzarini, E. De Clercq, R. T. Borchardt, Y. Lee, and C.-S. Yuan (1992), Nucleic Acid Related Compounds. 74. Synthesis and Biological Activity of 2'(and 3')-Deoxy-2'(and 3')-methylenenucleoside Analogues That Function as Mechanism-Based Inhibitors of S-Adenosyl-L-homocysteine Hydrolase and/or Ribonucleotide Reductase, *J. Med. Chem.* **35**(12):2283-2293.

5) Robins, M. J., S. F. Wnuk, K. B. Mullah, N. K. Dalley, R. T. Borchardt, Y. Lee, and C.-S. Yuan (1993), Adenosine-Derived 5'-α-Fluoro Thioester, Sulfoxide, Sulfone, and Fluoromethylene Analogues. Inhibition of S-Adenosyl-L-homocysteine Hydrolase in Nucleosides as Antitumor and Antiviral Agents (C. K. Chu and D. C. Baker, Eds), Plenum Press, New York, N. Y., pp 115-126.

6) Ault-Riché, D. B., Y. Lee, M. Hasobe, C.-S. Yuan, M. S. Wolfe, D. R. Borcherding, and R. T. Borchardt (1993), Effects of 4'-Modified Analogs of Aristeromycin on the Metabolism of S-Adenosylhomocysteine in Murine L929 Cells, *Mol. Pharmacol.* 43:989-997.

7) Lee, Y. (1993), S-Adenosyl-L-homocysteine Hydrolase Isozymes: Their Role in Regulating Cellular Metabolism of S-Adenosyl-L-homocysteine and Homocysteine. Doctoral dissertation, University of Kansas, Lawrence, Kansas.

8) Robins, M. J., S. F. Wnuk, K. B. Mullah, N. K. Dalley, R. T. Borchardt, Y. Lee, and C.-S. Yuan (1994), Nucleic Acid Related Compounds. 80. Synthesis of 5'-*S*-(Alkyl and aryl)-5'-thioadenosines with Xenon Difluoride or (Diethylamino)sulfur Trifluoride, Hydrolysis in Aqueous Buffer, and Inhibition of *S*-Adenosyl-*L*-homocysteine Hydrolase by Derived "Adenosine 5'-aldehyde" Species, *J. Org. Chem.* 59:544-555.

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1) Lee, Y., M. Hasobe, D. B. Ault-Riché, J. G. McKee, and R. T. Borchardt (1990), The Role of S-Adenosylhomocysteine Hydrolase in the Formation of S-Adenosylhomocysteine in Mouse L929 Cells, *FASEB J.* **4**:A2049 (Abstract No. 2058).

2) Ault-Riché, D. B., Y. Lee, M. Hasobe, M. S. Wolfe, W. J. Bartlett, D. B. Borcherding, and R. T. Borchardt (1990), Effects of 4'-Modified Analogs of Aristeromycin and Neplanocin A on Metabolism of S-Adenosyl-L-homocysteine in Mouse L929 Cells, *FASEB J.* **4**:A2050 (Abstract No. 2064).

3) Robins, M. J., S. F. Wnuk, K. B. Mullah, N. K. Dalley, R. T. Borchardt, Y. Lee, and C.-S. Yuan (1992), Synthesis and Enzyme-Inhibitory Activity of Nucleotide a-Halo Thioesters, American Chemical Society meeting, San Francisco, CA.

4) Lee, Y and P.-H. Hsyu (1995) Carrier-mediated Transport of Sumatriptan, a Serotonin Receptor Type 1 Agonist, Across Caco-2 Cell Monolayers, *FASEB J.* **9**:A367 (Abstract No. 2128).