

B I O S Y N

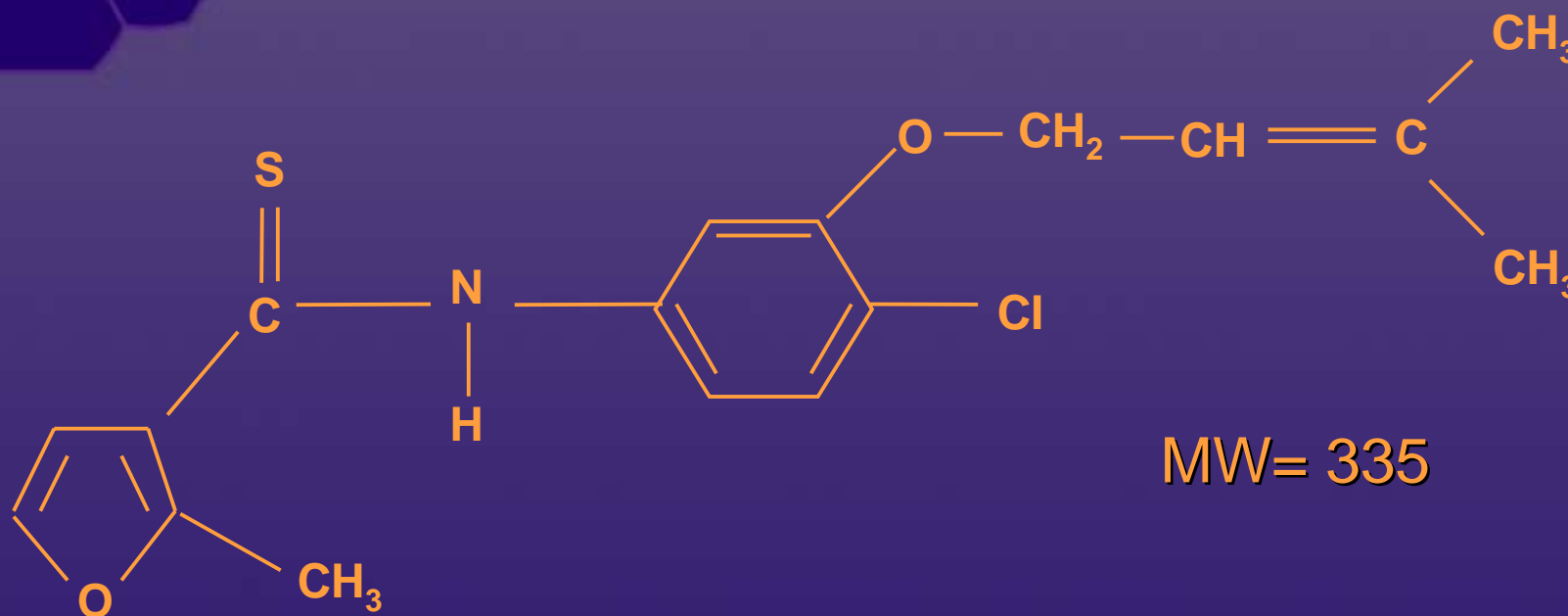
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Technology Platform: UC-781



MW= 335

- Developed by Crompton Corp. as a crop protection agent
- Carboxanilide class of compounds
- Licensed to Biosyn, Inc. for microbicide development in May, 2001

Characteristics of UC-781

- Potent HIV-1 inhibitor (nM range) with low cytotoxicity (TI >62,000)
- Active against HIV-1 infected cells
- Tight binding to RT at NNI site (1:1)
- Synergistic in combination with other RT inhibitors
- Active against HIV-1 RT inhibitor resistant isolates
- Hydrophobic molecule; low bioavailability
- “Memory Effect” protection of cells

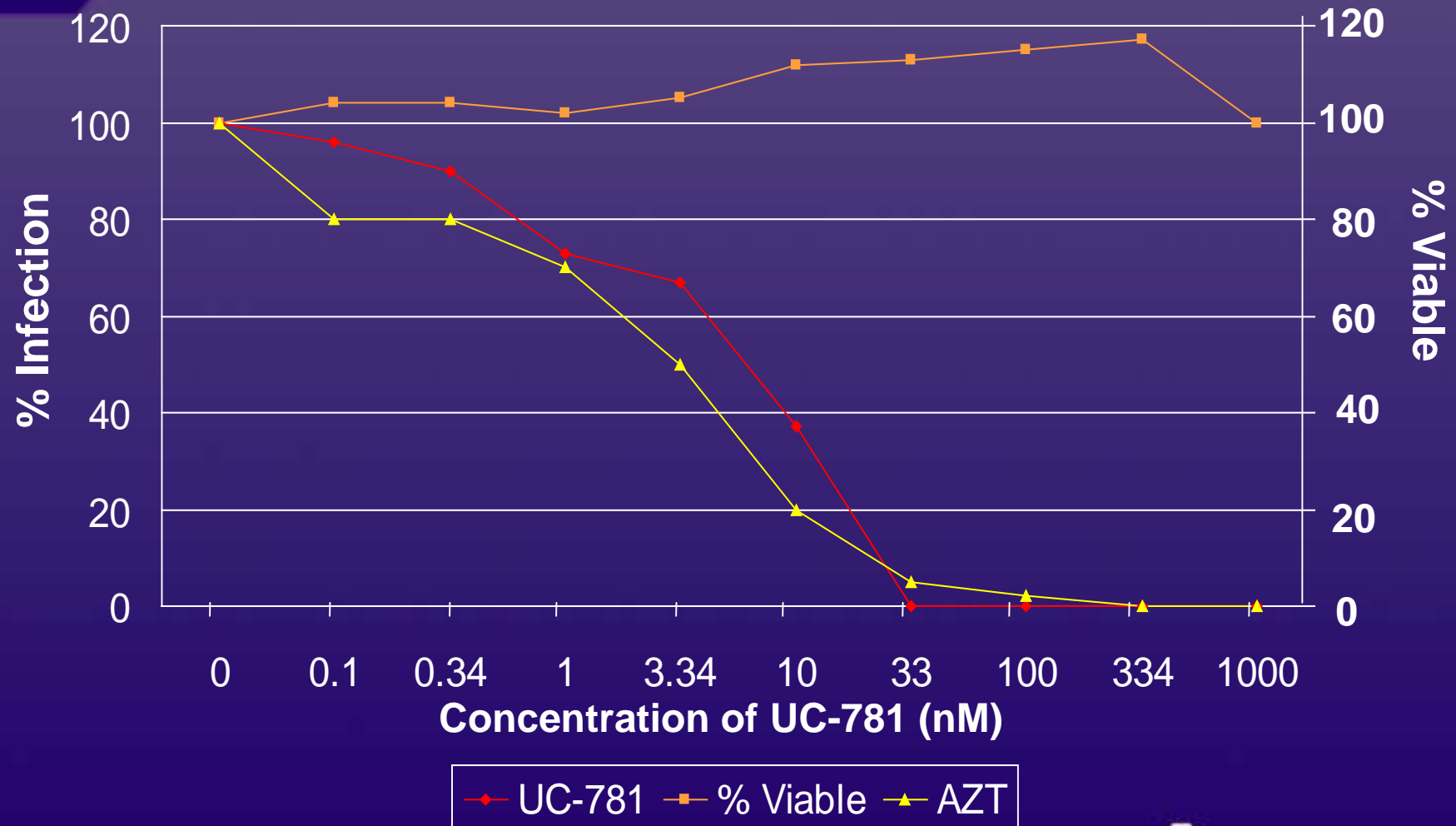
UC-781 Activity Against non-Clade B Isolates of HIV-1

- **Purpose:** To determine the IC_{50} of UC-781 against non-clade B isolates of HIV-1.
 - Highly relevant to the world wide utility of UC-781 as a microbicide
- **Method:** Attempted infection of PBMC with clades A through G and 3 type O isolates in the presence of 4-fold dilutions of UC-781 ranging from 0.1 nM to $>1.0 \mu\text{M}$
- **Endpoints:** RT activity and p24 content for HIV-infection; MTS dye reduction for cell viability
 - Calculated IC_{50} , TC_{50} and TI of UC-781 with each clade.
 - Conducted AZT treated control.

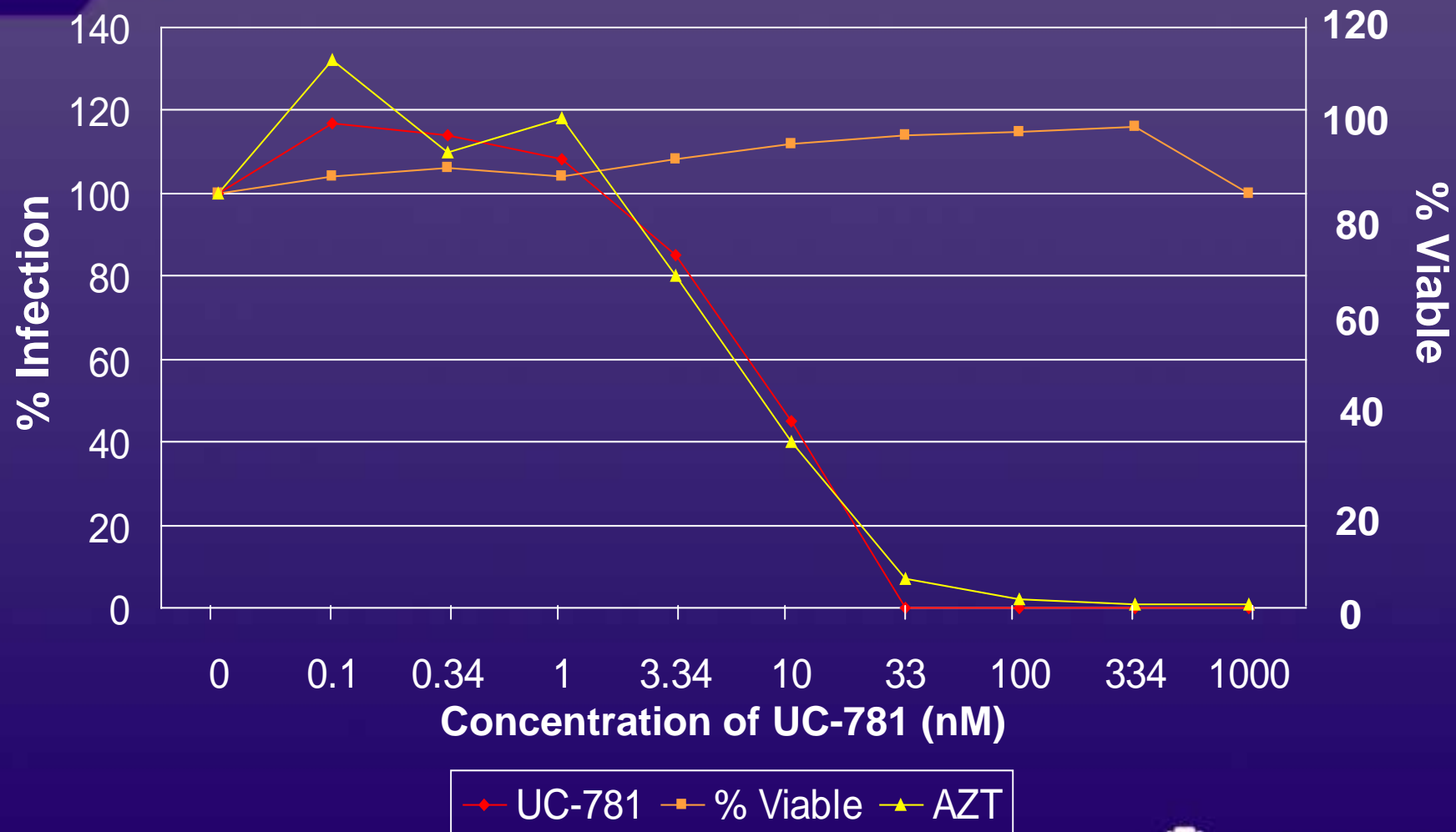
Non-Clade B Isolates Tested:

Isolate	Clade
•RW/92/016	A
•91US056	B
•WeJo	B
•BR/92/025	C
•UC/92/046	D
•CMU02	E
•BR/93/020	F
•JV 1083	G
•BCF01	O
•BCF02	O
•BCF03	O

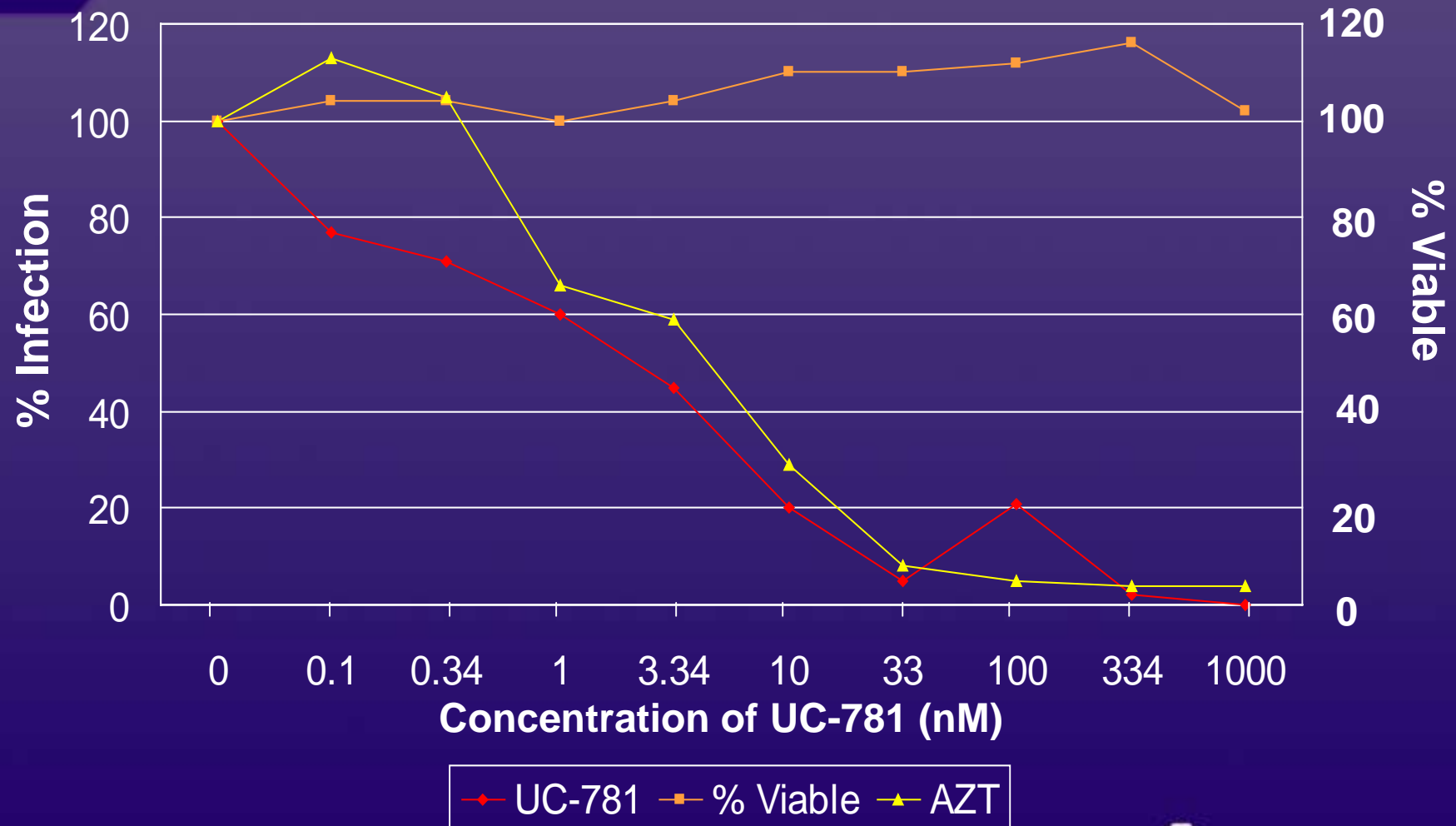
UC-781 vs. CMU02 (Clade E): RT Activity Endpoint



UC-781 vs. CMU02 (Clade E): p24 Antigen Detection Endpoint



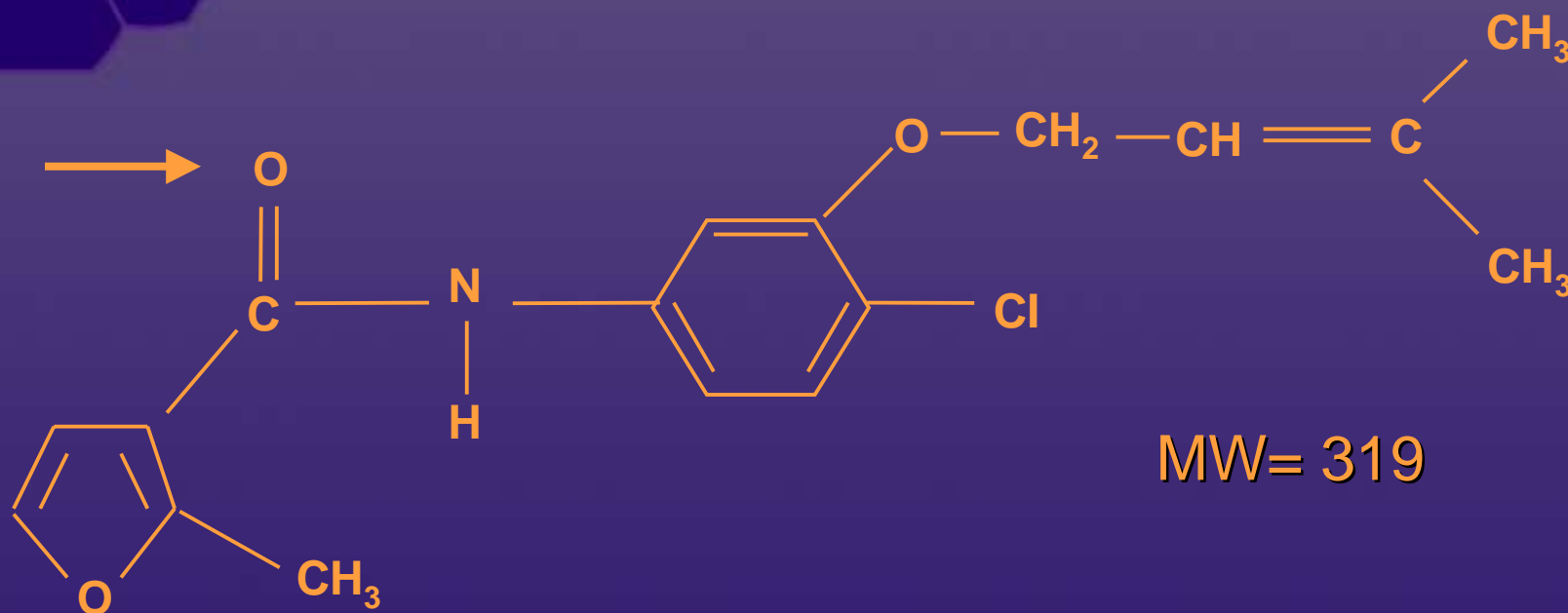
UC-781 vs. RW/92/016 (Clade A): p24 Antigen Detection Endpoint



Inhibition of HIV-1 Clinical Isolates by UC-781 (nM)

Virus (Clade)	<u>IC50</u>		<u>TC50</u>		<u>TI</u>	
	RT	p24	RT	p24	RT	p24
RW/92/016 (A)	1.5	2.7	>1000	>1000	>671	>370
WeJo (B)	3.8	6.1	>1000	>1000	>260	>163
91US056 (B)	4.5	8.8	>1000	>1000	>221	>114
BR/91/025 (C)	6.0	7.5	>1000	>1000	>168	>133
UG/92/046 (D)	7.6	12.8	>1000	>1000	>132	>78
CMU02 (E)	5.9	10.5	>1000	>1000	>169	>95
BR/93/0202 (F)	4.2	6.1	>1000	>1000	>240	>164
JV 1083 (G)	3.1	4.1	>1000	>1000	>325	>245

Molecular Structure: UC-22



- Carboxanilide class of compounds
- Final intermediate in UC-781 synthesis pathway.
- Significantly reduced activity against RT resistant strains of HIV-1

Inhibition of HIV-1 Clinical Isolates by UC-22 (nM)

Virus (clade)	IC50 (nM)	TI
RW/92/016 (A)	20	>250
91USO56 (B)	1.0	>5000
BR/92/025 (C)	4.0	>1250
UG/92/046 (D)	4.0	>1250
CMU02 (E)	4.0	>1250
BR/93/020 (F)	4.0	>1250
JV 1083 (G)	10.0	>500

UC-781 and AZT Activity Against HIV-1 Type O Isolates (nM)

Virus Strain	Antiviral Efficacy (IC ₅₀ , nM)	
	UC-781	AZT
BCF01(O Subtype)	6,000*	2.0
BCF02 (O Subtype)	5,500	1.0
BCF03 (O Subtype)	7,880	1.0
WeJo (B Subtype)	6.1	8.7

*Result from a second trial >10,000

NNRTI's and Type O:

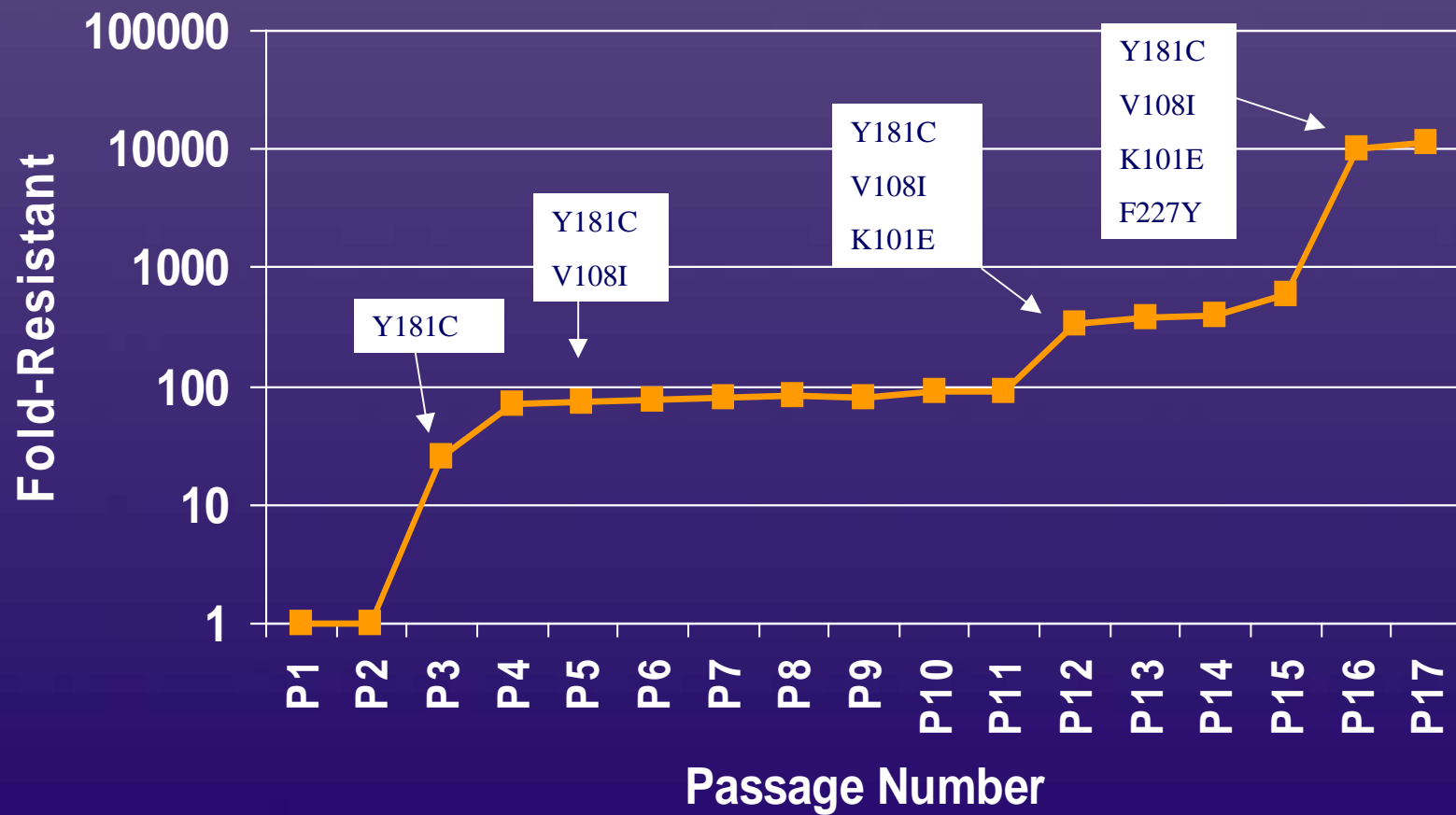
Drug	Antiviral Efficacy (IC ₅₀ , nM)			
	BCF01	BCF02	BCF03	M
UC-781	6,000	5,500	7,880	1-5
UC-22	>5,000	>5,000	>5,000	4-10
Nevirapine*	15,000	21,000	41,000	40
Delavirdine*	1,200	7,200	>20,000	20

*Descamps et al., J. Virol. 71:8893, 1997

UC-781 Activity and RT Sequence

Position in Group M RT Gene	NNRTI Mutation	Amino Acid At Position			UC 781 Antiviral Efficacy (EC ₅₀ , nM)	Wild type HIV Outcome
		BCF01	BCF02	BCF03		
A98	G	G	G	G	6.0	S
L100	I	L	L	L	144	R (>5-fold)
K103	N	R	K	K	62	R (>5-fold)
V106	A	V	I	V	43	R (>5-fold)
V108	I	V	V	V	10	S
E138	K	E	E	E	15	S
Y181	C	C	C	C	52	R (>5 fold)
Y188	H/L/C	Y	Y	Y	30-150	R (<5-fold)
G190	A	G	G	G	--	--
P236	L	P	P	P	--	--
NL4-3 (Wild type)					6.0	

Selection of UC-781 Resistant Virus



Buckheit et al.

Summary:

- UC-781 and UC-22 are potent inhibitors of primary HIV-1 isolates clades A through G
 - World wide utility as a microbicide
- UC-781 has reduced activity against Type O isolates; UC-22 is not active
 - Consistent with other NNRTI
- The reduced activity against type O can not be completely accounted for by known NNRTI resistance mutations, nor by the resistance development pattern to UC-781
 - Other residues of relevance?

Activity and Stability Assessment of UC-781 Microbicide Formulations

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IC ₅₀ values (µg/ml of gel)	Pre-treat virus	Pre-treat cells	Leave In
Suspension Gel Placebo	8390.0	>100000.0	7.5
0.1% UC 781 in Suspension Gel	2.9	57.1	36.6
1% UC 781 in Suspension Gel	8.2	82.5	<0.38
0.1% UC 781 in Anionic Cream A	12.3	1.9	<0.38
1% UC 781 in Anionic Cream A	0.8	2.8	<0.38
0.1% UC 781 in Anionic Cream B	0.8	1.0	<0.38
0.1% UC 781 in Solution Gel	1.6	17	<0.38

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