16:31:48 OCA PAD INITIATION - PROJECT HEADER INFORMATION 05/20/91

Active

Project #: G-33-628 Cost share #: Rev #: 0
Center # : 10/24-6-R7194-0A0 Center shr #: OCA file #:
Work type : RES
Contract#: STD AGREEMENT DATED 5/1/91 Mod #: Document : AGR
Prime #: Contract entity: GTRC

Subprojects ? : N CFDA: N/A
Main project #: PE #: N/A

Project unit: CHEMISTRY Unit code: 02.010.136
Project director(s):
POWERS J C CHEMISTRY (404)894-4038

Sponsor/division names: CETUS CORPORATION / EMERYVILLE, CA
Sponsor/division codes: 202 / 104

Award period: 910401 to 920430 (performance) 920430 (reports)

Sponsor amount	New this change	Total to date
Contract value	27,399.00	27,399.00
Funded	27,399.00	27,399.00
Cost sharing amount		0.00

Does subcontracting plan apply ?: N

Title: SYNTHESIS OF CONVERTASE INHIBITORS

PROJECT ADMINISTRATION DATA

OCA contact: E. Faith Gleason 894-4820

Sponsor technical contact

DR. DALE ANDO
(415)420-3300

CETUS CORPORATION
1400 53RD STREET
EMERYVILLE, CA 94306

Sponsor issuing office

GAYE ENGLER
(415)420-3300

CETUS CORPORATION
1400 53RD STREET
EMERYVILLE, CA 94306

Security class (U,C,S,TS) : U ONR resident rep. is ACO (Y/N): N
Defense priority rating : N/A N/A supplemental sheet
Equipment title vests with: Sponsor GIT
NOT APPLICABLE.
Administrative comments -
* INITIATION.

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

Closeout Notice Date 08/26/92

Project No. G-33-628_____ Center No. 10/24-6-R7194-0A0_

Project Director POWERS J C_____ School/Lab CHEMISTRY_____

Sponsor CETUS CORPORATION/EMERYVILLE, CA_____

Contract/Grant No. STD AGREEMENT DATED 5/1/91____ Contract Entity GTRC

Prime Contract No. _____

Title SYNTHESIS OF CONVERTASE INHIBITORS_____

Effective Completion Date 920430 (Performance) 920430 (Reports)

Closeout Actions Required:	Y/N	Date Submitted
Final Invoice or Copy of Final Invoice	Y	_____
Final Report of Inventions and/or Subcontracts	N	_____
Government Property Inventory & Related Certificate	N	_____
Classified Material Certificate	N	_____
Release and Assignment	N	_____
Other _____	N	_____

Comments_____

_____

Subproject Under Main Project No. _____

Continues Project No. _____

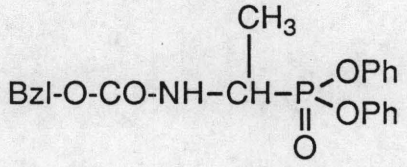
Distribution Required:

Project Director	Y
Administrative Network Representative	Y
GTRI Accounting/Grants and Contracts	Y
Procurement/Supply Services	Y
Research Property Managment	Y
Research Security Services	N
Reports Coordinator (OCA)	Y
GTRC	Y
Project File	Y
Other _____	N
_____	N

Chiron/Cetius Research Project on Convertase Inhibitors
Progress Report-June 21, 1992
by James C. Powers

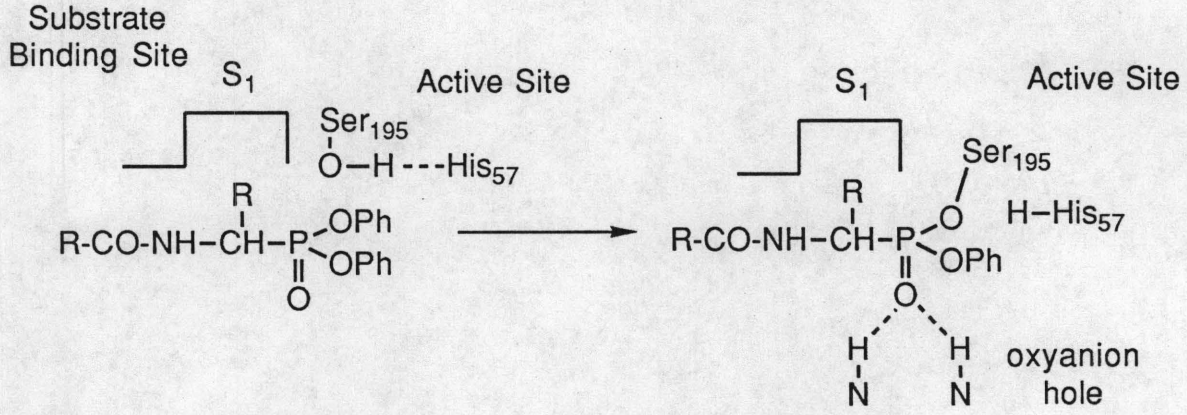
Peptide Phosphonate Inhibitors

The diesters of α-aminoalkylphosphonic acids are analogs of natural α-amino acids and are designated by the generally accepted three letter abbreviations for the amino acid followed by the superscript P. For example diphenyl α-(N-benzyloxycarbonylamino)ethylphosphonate which is related to alanine is abbreviated as Cbz-Ala^{P}(OPh)$_2$.



Complete Structure of Cbz-Ala^{P}(OPh)$_2$

The mechanism of inhibition of serine proteases involves phosphonylation of the active site serine residue to form a stable phosphonyl derivatives.



Properties of Peptide Phosophonates

Stable in plasma for > 3 days
Inhibited derivatives very stable
Highly specific
Irreversible inhibitors
Sequence can be tailored to a specific serine protease

October 1991

Provided Cetus with the following phosphonates for testing.

2.4 g Boc-Val-Pro-Val^{P}(OPh)$_2$
2.7 g Boc-Ala-Pro-Val^{P}(OPh)$_2$
1.1 g Boc-Ala-Gln-Ala^{P}(OPh)$_2$
1.2 g Boc-Ala-Gln-Ala^{P}(OPh)$_2$ (different crystallization batch)
0.5 g Boc-Leu-Ala-Gln-Ala^{P}(OPh)$_2$.

March 1992

Provided Cetus with small samples of the following phosphonates for testing.

Boc-Val-Pro-Val^{P}(OPh-4-Cl)$_2$
TFA salt of Val-Pro-Val^{P}(OPh-4-Cl)$_2$
HCl salt of Val-Pro-Val^{P}(OPh-4-Cl)$_2$
Z-Val-Pro-Val^{P}(OPh-4-Cl)$_2$
and several other simple derivatives as negative controls

These 4-chlorophenoxy derivatives should be more reactive than the corresponding phenoxy compounds.

March 1992

Provided Cetius with

1 g of Boc-Ala-Pro-Val^{P}(OPh)$_2$

Other Derivatives Synthesized (Spring 1992)

4-chlorophenoxy derivatives

Z-Val^{P}(OPh-4-Cl)$_2$
Z-Pro-Val^{P}(OPh-4-Cl)$_2$

3-chlorophenoxy derivatives

Z-Val^{P}(OPh-3-Cl)$_2$
Z-Pro-Val^{P}(OPh-3-Cl)$_2$
Pro-Val^{P}(OPh-3-Cl)$_2$
Z-Val-Pro-Val^{P}(OPh-3-Cl)$_2$
Val-Pro-Val^{P}(OPh-3-Cl)$_2$
Boc-Val-Pro-Val^{P}(OPh-3-Cl)$_2$

phenylphosphinic acid analogs

Z-Val^{P}(OPh)(Ph)
Val^{P}(OPh)(Ph)
Z-Pro-Val^{P}(OPh)(Ph)
Pro-Val^{P}(OPh)(Ph)
Z-Val-Pro-Val^{P}(OPh)(Ph)
Val-Pro-Val^{P}(OPh)(Ph)

Histidine Phosphonate Derivatives (April, May, and June 1992)

The route will involve synthesis of Im-CH_2-CHO (Im = imidazole). This will be converted Z-His^{P}(OPh)$_2$ and then eventually to Boc-Val-Pro-His^{P}(OPh)$_2$.

At present three separate routes for the synthesis of imidazole 4-acetaldehyde have been tried. They involved starting with histidine, histamine, imidazole ethanol, or imidazole acetic acid. We have been unable to obtain a significant yield of aldehyde. We are now planning alternate routes which involve addition/construction of the imidazole ring after the phosphonate is formed.