15:29:40 OCA PAD AMENDMENT - PROJECT HEADER INFORMATION 03/19/92

Active

Project #: G-33-515 Cost share #: Rev #: 2
Center # : 10/11-6-P5066-3A0 Center shr #: OCA file #:
Work type : RES
Contract#: 5 F32 HL07994-03 Mod #: LTR DTD 3/6/92 Document : GRANT
Prime #: Contract entity: GTRC

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

Project unit: CHEMISTRY Unit code: 02.010.136
Project director(s):
SUDDATH F L JR CHEMISTRY (404)894-4028

Sponsor/division names: DHHS/PHS/NIH / NATL INSTITUTES OF HEALTH
Sponsor/division codes: 108 / 001

Award period: 910118 to 930102 (performance) 930402 (reports)

Sponsor amount	New this change	Total to date
Contract value	0.00	28,789.69
Funded	0.00	28,789.69
Cost sharing amount		0.00

Does subcontracting plan apply ?: N

Title: MOLECULAR MODELING OF INHIBITOR - PROTEASE COMPLEXES

PROJECT ADMINISTRATION DATA

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Security class (U,C,S,TS) : U ONR resident rep. is ACO (Y/N): N
Defense priority rating : N/A NIH supplemental sheet
Equipment title vests with: Sponsor GIT X
NONE PROPOSED.
Administrative comments -
ISSUED TO EXTEND TERMINATION DATE FROM 1/2/92 TO 1/2/93.

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

N
342
7 SR

Closeout Notice Date 09/03/92

Project No. G-33-515 Center No. 10/11-6-P5066-3A0

Project Director ~~SUDDATH F L JR~~ School/Lab CHEMISTRY

Sponsor DHHS/PHS/NIH/NATL INSTITUTES OF HEALTH

Contract/Grant No. 5 F32 HL07994-03 Contract Entity GTRC

Prime Contract No.

Title MOLECULAR MODELING OF INHIBITOR - PROTEASE COMPLEXES

Effective Completion Date 930102 (Performance) 930402 (Reports)

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

CommentsPATENT REPORT = DHHS 568, ATTACHED

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

~~NOTE: Final Patent Questionnaire sent to PDPI.~~

FINAL PROGRESS REPORT

Individual Postdoctoral National Research Service Award for R. Richard Plaskon
5 F32 HL07994-03 BI-4

Sponsored by F.L. Suddath

Much of the training goals and research aims of the fellowship were satisfied. However, inadequacies in the application of available computational methods to accomplish the research aims necessitated the development of novel uses for the available methods. The amount of time devoted to this effort prevented the use of molecular dynamics and allowed only two enzymes to be studied. Nonetheless, valuable experience in the molecular modeling (excluding molecular dynamics) of serine proteases and their interactions with inhibitors was obtained. The quantum mechanical (QM) calculations performed resulted in much experience in using the semiempirical QM package MOPAC (QCPE, Indiana University). Many papers were read and discussions held on the inhibition of serine proteases and computational procedures of possible use in modeling serine protease inhibition as well as protein-ligand interactions.

The research performed on porcine pancreatic elastase (PPE) resulted in the development of a method useful for the design of potent PPE inhibitors. The method produced results consistent with the potency of six 7-substituted 4-chloro-3-ethoxyisocoumarin inhibitors of PPE and led to the synthesis of the most potent inhibitor of this class of PPE inhibitors. This novel inhibitor is as potent as predicted by the method. The molecular mechanics program, CHARMm of the Polygen Corp. (Waltham, MA 02254), used for the method provides a set of atomic point charges necessary for the electrostatic portion of the calculations. Inclusion of these charges produced results inconsistent with inhibitor potency. Only with charges derived from a MOPAC calculation is the method useful for the prediction of inhibitor potency toward PPE. A portion of the results with PPE have been published in the journal Proteins and another portion submitted for publication in Archives of Biochemistry and Biophysics.

To determine if the method developed with PPE is suitable for the design of inhibitors for a medically important enzyme, inhibition of human leukocyte elastase (HLE) by 7-substituted 3-alkoxy-4-chloroisocoumarins was modeled. Unlike PPE, the x-ray structure of the native form of HLE is not known and only structures complexed with peptide and protein inhibitors are available. The inhibitors were removed and the method developed with PPE was performed. Results consistent with the potency of all three of the inhibitors tested were obtained. From these results, a fourth inhibitor is expected to be the best of the 7-substituted 4-chloro-3-ethoxyisocoumarin inhibitors of HLE. Publication of these results is planned.

Publications (Current and Future)

Plaskon, R.R., Kam, C.-M., Burgess, E.M., Powers, J.C., and Suddath, F.L. Michaelis Complexes of Porcine Pancreatic Elastase with 7-[(Alkylcarbamoyl)amino]-4-Chloro-3-Ethoxyisocoumarins: Translational Sampling of Inhibitor Position and Kinetic Measurements. (1992) *Proteins* **13**, 141-151.

Plaskon, R.R., Kam, C.-M., Kerrigan, J.E., Burgess, E.M., Powers, J.C., and Suddath, F.L. Inhibition of Porcine Pancreatic Elastase by 7-Substituted 4-Chloro-3-Ethoxyisocoumarins: Structural Characterisitics of Modeled Noncovalent Complexes Relate to the Measured Inhibition Kinetics. (1992) *Archives of Biochemistry and Biophysics*, submitted.

Plaskon, R.R., Kam, C.-M., Burgess, E.M., Powers, J.C., and Suddath, F.L. Modeled Structural Characteristics Relate to the Inhibition of Human Leukocyte Elastase by 7-Substituted 3-Alkoxy-4-Chloroisocoumarins. (1992) Planned.

Inventions and/or Patents

None

June 26, 1992

R. Richard Plaskon