Form Approved Through 09/30/2007 OMB No. 0925-0001

Department of Health and Human Services
Public Health Services

Grant Progress Report

Review Group	Type	Activity	Grant Number

Total Project Period
From: Through:

Requested Budget Period
From: Through:

1. TITLE OF PROJECT
Synthesis and analysis of potential anticancer protein kinase blockers

2a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Name and address, street, city, state, zip code)
Nesterov, Vladimir
New Mexico Highlands University
Ivan Hilton Science Building #237
Las Vegas, NM 87701

3. APPLICANT ORGANIZATION (Name and address, street, city, state, zip code)
New Mexico Highlands University
PO Box 9000
Las Vegas, NM 87701

2b. E-MAIL ADDRESS
vnesterov@nmhu.edu

4. ENTITY IDENTIFICATION NUMBER

2c. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Natural Sciences

2d. MAJOR SUBDIVISION
Chemistry

5. TITLE AND ADDRESS OF ADMINISTRATIVE OFFICIAL
New Mexico Highlands University
PO Box 9000
Las Vegas, NM 87701

E-MAIL:

6. HUMAN SUBJECTS
☒ No ☐ Yes

6a. Research Exempt
☒ No ☐ Yes

6b. Human Subjects Assurance No.

If Exempt ("Yes" in 6a):
Exemption No.

6c. NIH-Defined Phase III Clinical Trial ☒ No ☐ Yes

If Not Exempt ("No" in 6a):
IRB approval date
☐ Full IRB or
☐ Expedited Review

7. VERTEBRATE ANIMALS
☒ No
☐ Yes

7a. If "Yes," IACUC approval Date

7b. Animal Welfare Assurance No.

8. COSTS REQUESTED FOR NEXT BUDGET PERIOD

8a. DIRECT $	8b. TOTAL $

9. INVENTIONS AND PATENTS
☒ No ☐ Yes If "Yes," ☐ Previously Reported ☒ Not Previously Reported

10. PERFORMANCE SITE(S) *(Organizations and addresses)*
NMHU

11a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR *(Item 2a)*
TEL
FAX

11b. ADMINISTRATIVE OFFICIAL NAME *(Item 5)*
TEL
FAX

11c. NAME AND TITLE OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION *(Item 14)*
NAME Rodolfo Martinez
TITLE Program Director
TEL 505-454-3155 FAX 505-426-2036
E-MAIL rudy@nmhu.edu

12. Corrections to Page 1 Face Page

13. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 11c. *(In ink. "Per" signature not acceptable.)*

DATE

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Nesterov, Vladimir N.	Research Professor
eRA COMMONS USER NAME	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Lugansk State University, Ukraine	M.S.	1981	Chemistry and Biology
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Science, Moscow, Russia	Ph.D.	1988	Organic Chemistry

A. Positions and Honors.

Positions and Employment

1988-1990 – Senior Researcher	Lugansk State University	Ukraine
1990-1994 – Senior Lecturer	Lugansk State University	Ukraine
1994-1998 - Postdoctoral Training	A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow	Russia
1999 – present - Research Professor	New Mexico Highlands University	USA

Other experience and professional memberships

1989 - Member, International Union of Crystallography.
2000 - Member, International Society of Optical Engineering (SPIE).

B. Selected peer-reviewed publications (in chronological order).

(Publications selected from over 180 peer-reviewed publications)

1. Shestopalov, A.M., Bogomolova, O.P., Rodinovskaya, L.A., Litvinov, V.P., Bujnicki, B., Mikolayczyk, M., Nesterov, V.N., Struchkov, Yu.T. Stereoselective synthesis and atropoisomerism in 4-pyridyl-3-(1-pyridinio)-3,4-trans-1,2,3,4-tetrahydropyridines and their transformation products. *Heteroatom Chemistry*. 1993; 4. No 6: 593-602.
2. Samet, A.V., Shestopalov, A.M., Nesterov, V.N., Semenov, V.V. An improved stereoselective synthesis of 5-acyl-2-amino-4-aryl-3-cyano-4,5-dihydrothiophenes. *Synthesis*. 1997; N 6: 623-624.
3. Nasakin, O.E., Sheverdov, V.P., Moiseeva, I.V., Lyshchikov, A.N., Ershov, O.V., Nesterov, V.N. The synthesis of 3-amidino-2-aminopyridine-4-carboxylates. *Tetrahedron Lett*. 1997; 4455-4456.
4. Samet, A.V., Shestopalov, A.M., Nesterov, V.N., Semenov, V.V. Reactions of sulfur ylides with α,β-unsaturated thioamides: synthesis of dihydrothiophenes and cyclopropanes. *Izv. Akad. nauk, Ser. Khim.* (*Russ. Chem. Bull.*) 1998; No 1: 127-132.
5. Kislyi, V.P., Nesterov, V.N., Semenov, V.V. Heterocycles with a β-nitroenamine fragment 3. Synthesis of 3-amino-2-nitrothieno[2,3-b]pyridines. Crystal and molecular structure of 3-amino-4-methyl-2-nitro-6-trifluoro-methylthieno[2,3-b]pyridine. *Izv. Akad. nauk, Ser. Khim.* (*Russ. Chem. Bull.*) 1999; No 6: 1150-1153.
6. Selivanova, I.A., Tyukavkina, N.A., Kolesnik, Yu.A., Nesterov, V.N., Kuleshova, L.N., Khutoryanskii, V.A., Bazhenov, B.N., Saibotalov, M.Yu. Study of the crystalline structure of dihydroquercetin. *Pharm. Chem. J.* (*Khim. Farm. Zh.*) 2000; 33(4): 222-224.

7. Timofeeva, T.V., Nesterov, V.N., Dolgushin, F.M., Zubavichus, Y.V., Goldshtein, J.T., Sammeth, D.M., Clark, R.D., Penn, B., Antipin, M.Yu. One-pot polymorphism of nonlinear optical materials. First example of organic polytypes. *Crystal Engineering*, 2000; 3: 263-288.
8. Golubev, A.S., Pasternak, P.V., Shidlovskii, A.F., Savel`eva, L.N., Averkiev, B.B., Nesterov, V.N., Antipin, M.YU., Peregudov A.S., Chkanikov N.D. Synthesis and some heterocyclisation reactions of CF_2H- and CF_2C_l-substituted 1,1-dicyanoethylenes. *J. Fluor. Chem.* 2002; 114(1): 63-74.
9. Shestopalov, A.M., Emelianova, Yu.M., Nesterov, V.N. One-step synthesis of substituted 2-amino-4H-chromenes and 2-amino-4H-benzo[f]chromenes. Molecular and crystal structure of 2-amino-3-cyano-6-hydroxy-4-phenyl-4H-benzo[f]chromene. *Russ. Chem. Bull.* 2002; 51: 2238-2243.
10. Timofeeva, T.V., Nesterov, V.N., Clark, R.D., Penn, B., Fraizer, D., Antipin, M.Yu. Systematic study of polymorphism in crystalline non-linear optical materials. *J. Mol. Struct.*, 2003; 647: 181-202.
11. Nesterov, V.N., Timofeeva, T.V., Sarkisov, S.S., Leyderman, A., Lee, C.Y.-C., Antipin, M.Yu. 3,5-Bis(4'-diethylaminophenylidene)-1-methyl-4-piperidone and 3,5-bis(4'-diethylaminocinnamylidene)-1-methyl-4-piperidone: prospective bio-photonic materials. *Acta Crystallogr.* 2003; C59: o605-o608.
12. Shestopalov, A., Rodinovskaya, L., Shestopalov, A., Zlotin, S., Nesterov, V. A convenient one-pot synthesis of substituted 1,1-dicyanocyclopropanes from sulfonium salts, malononitrile, and carbonyl compounds. *Synlett.* 2003; 15: 2309-2312.
13. Antipin, M.Yu, Nesterov, V.N., Jiang, S., Borbulevych, O.Ya., Sammeth, D.M., Sevostianova, E.V., Timofeeva, T.V. X-Ray crystal structures, molecular mechanics and quantum chemical calculations, and calculations of the nonlinear optical polarizabilities in the series of monohalogen substituted derivatives of dicyanovinylbenzene. *J. Mol. Struct.* 2003; 650: 1-20.
14. Rodinovskaya , L.A., Gromova, A. V., Shestopalov, A.M., Nesterov, V.N. Synthesis of 6-amino-4-aryl-5-cyano-3-(3-cyanopyridin-2-ylthiomethyl)-2,4-dihydropyrano[2,3-*c*]pyrazoles and their hydrogenated analogs. Molecular structure of 6-amino-5-cyano-3-(3-cyano-4,6-dimethylpyridin-2-ylthiomethyl)-4-(2-nitrophenyl)-2,4-dihydropyrano[2,3-*c*]pyrazole. *Russ. Chem. Bull.* 2003; 52: 2207-2213.
15. Nesterov, V.V., Antipin, M.Yu., Nesterov, V.N., Moore, C.E., Cardelino, B.H., Timofeeva, T.V. Thermally stable heterocyclic imines as new potential NLO materials. *J. Phys. Chem. B.* 2004; 108: 8531-8539.
16. Nesterov, V.V., Antipin, M.Yu., Nesterov, V.N., Penn, B.G., Frazier, D.O., Timofeeva, T.V. Thermally stable imines as new potential nonlinear optical materials. *Crystal Growth & Design.* 2004; 4: 521-531.
17. Nesterov, V.N., Wiedenfeld, D., Nesterova, S.V., Minton. M. 2-Amino-4-(1-naphthyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile and 2-amino-7,7-dimethyl-4-(1-naphthyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile. *Acta Crystallogr.* 2004; C60: o334-o337.
18. Wiedenfeld, D., Minton. M., Nesterov, V.N., Glass, D.R., Montoya, C.L. Unexpected Dimeric Products from the Amidomethylation of Pentasubstituted Benzenes. *Tetrahedron Lett.* 2004; 45: 21, 4023-4026.
19. Nesterov, V.N., Nesterov, V.V. Polymorphism and solvolysis of 2-cyano-3-[4-(diethylamino)phenyl]-prop-2-enethioamide. *Acta Crystallogr.*, 2004; C60: o781-o785.
20. Nesterov, V.N. 3,5-Bis(4-methoxybenzylidene)-1-methyl-4-piperidone and 3,5-bis(4-methoxybenzylidene)-1-methyl-4-oxopiperidinium chloride: potential biophotonic materials. *Acta Crystallogr.*, 2004; C60: o806-o809.
21. Timofeeva, T.V., Kinnibrugh, T., Borbulevych, O.Ya., Averkiev, B., Nesterov, V.N., Sloan, A., Antipin, M.Yu. Vanishing polymorphism of (2E)-2-cyano-3-[4-(diethylamino)phenyl]prop-2-enethioamide: X-ray structural study and polymorph prediction. *Crystal Growth & Design.* 2004; 4: 265-1276.
22. Wiedenfeld, D.J., Minton. M.A., Glass, D.R., Nesterov, V.N., Nsamenang, K.D., Han, D. A general synthesis of quinone ammonium salts. *Synthesis,* 2005; 10: 1611-1618.
23. Dontsova, N.E., Nesterov, V.N., Shestopalov, A.M., Litvinov, V.P. Synthesis of substituted 1,2-di(alkylsulfonyl)indolizines. Molecular and crystal structure of 3-(4-fluorobenzoyl)-6-methyl-1,2-di(propylsulfonyl)indolizine. *Russ. Chem. Bull.* 2005; 5: 1205–1209.
24. Nesterov, V.N., Kislyi, V.P., Sabutis, J.L., Nesterov, V.V., Wiedenfeld, D.J., Semenov, V.V. 2-Amino-4-(2-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile and 2-amino-4-(2-methoxyphenyl)-7,7-dimethyl-3-nitro-4,6,7,8-tetrahydro-5H-chromen-5-one hemihydrate. *Acta Crystallogr.* 2005; C61: o741-o744.
25. Nesterov, V.N., Wiedenfeld, D.J., Nesterova, S.V., Hastings, L.F. 5-Acetyl-2-amino-6-methyl-4-phenyl-4H-pyran-3-carbonitrile, 2-amino-5-benzoyl-6-methyl-4-phenyl-4H-pyran-3-carbonitrile acetonitrile solvate. *Acta Crystallogr.* 2006; C62: o806-o809.
26. Nesterov, V.V., Antipin, M.Yu., Nesterov, V.N., Timofeeva, T.V. New potential NLO crystalline materials: chiral derivatives of (2S)-2-(methoxymethyl)pyrrolidine. *J. Mol. Struct.* 2007; 831: 18-25.

C. Research Support.

Ongoing Research Support

DoD – W911NF-05-1-0456 08/01/2005 – 07/31/2008 (20%)
Two –photon processes in new derivatives of piperidone and cyclohexanones.
Role: Co-P.I.

Completed Research Support

NIH – 1P20 MD001104 10/01/2004 – 05/15/2007 (25%)
Design, synthesis and structure-activity relationships of compounds with potential anticancer activities.
Role: Research professor

NIH – SCORE S06 GM 08066 01/01/2004 - 09/30/2004
Design, synthesis and structure-activity relationships of compounds with potential bio- activities.
Role: Research professor

AFOSR F49620-01-1-0561 08/01/2003 -12/31/2003
Subcontractor from the University of Puerto Rico at Mayaguez
Synthesis of organic compounds with potential two-photon properties (prospective bio-photonic materials) and investigation of their structure using different physical methods including X-ray analysis.
Role: Co-P.I.

NASA IRA "Alliance for Nonlinear Optics" 01/01/1999 - 03/15/2003
Synthesis of organic compounds with potential nonlinear optical properties and investigation of their structures using different physical methods including X-ray analysis.
Role: Co-P.I. since 2000-07/31/2003.

DESCRIPTION: See instructions. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project (i.e., relevance to the **mission of the agency**). Describe concisely the research design and methods for achieving these goals. Describe the rationale and techniques you will use to pursue these goals.

In addition, in two or three sentences, describe in plain, lay language the relevance of this research to **public** health. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

It has been shown that α,β-unsaturated malonic acid derivatives such as arylidenemalononitriles, arylidenecyanothio(oxo)acetamides and their dimers are compounds that inhibit protein kinases (PK). Protein kinases play an important role in cell growth. Increased PK activity is associated with the development of cancer, leukemia and other proliferative diseases. It is well known that such compounds with low molecular weight inhibit protein kinases (PK). In addition arylidenepiperidones and cyclohexanones, their analogs and various heterocyclic compounds are also obtainable from the compounds described above. We have synthesized several new compounds that have the potential possess anti-PK activity. They have been tested in vitro at the National Cancer Institute (NCI) and one of them has passed the in vivo Hollow Fiber Assay investigation. This compound was verified by the Developmental Therapeutics Program (NCI designated it NSC-726031 and selected it for hollow-fiber 6-cell-line testing in mice). Our goal is to design, synthesize and determine structure-activity relationships of several new compounds of the type described above. A second compound (NSC 736774-Y) was also selected for future testing in an in vivo. These compounds have also been referred to the Biological Evaluation Committee for Cancer Drugs (BEC/C). This is an interdisciplinary committee with expertise in cancer drug discovery and development. Thus, we propose to do additional research to synthesize several additional heterocyclic derivatives as potential anticancer compounds. Our current efforts will include an ongoing literature review, synthesis of selected compounds for our findings above and from the literature. We will then submit these new compounds to the NCI cancer drug discovery and Developmental Therapeutic Program. We will investigate through X-Ray structural analysis and other spectral methods all of the new compounds. We will build a library of these compounds to help predict structure-activity relationships on the basis of results from NCI, literature data and our structural information about these compounds. We will use all obtained results to develop synthetic pathways for numerous small molecules and heterocyclic compounds based on α,β-unsaturated malonic acid derivatives with anticancer activity.

Lay description: Protein kinases are enzymes critical to cell function. They are used at especially high rates by cancer cells. Thus drugs that inhibit protein kinase can reduce or stop cancer cell growth. This Principal Investigator, a synthetic chemist, makes new protein kinase inhibitors for testing by the National Cancer Institute as potential anticancer drugs. His work is an example of how scientists from all fields collaborate in the fight against cancer.

PERFORMANCE SITE(S) (organization, city, state)

New Mexico Highlands University, Department of Natural Sciences - Chemistry, Las Vegas, NM 87701

During Spring 2008 semester, I am going to continue our work with Tanya Ruiz (she is undergraduate student and minor in chemistry). We have already prepared some material and submitted to a Journal that has been accepted for publication [1]. I am going to invite to work with me the other undergraduate and graduate students. I am planning to synthesize with them several dozen heterocyclic compounds containing carbazole-substituted fragment that was in our active compounds. All such compounds we will submit to NIH for selection and investigation their properties as anti-cancer agents.

It is impossible to create new anticancer active materials/agents without knowing the correct molecular structure of the compounds studied. This information allows us to understand relations between the molecular structure and desirable properties of compounds. In turn, this knowledge helps in the synthesis of new compounds with even better characteristics. Therefore, in our project we will pay special attention to molecular structure characterizations of the synthesized compounds (we will intensively use NMR, IR, UV, GC/MS and others methods and equipment), especially those which might be appropriate models for understanding structure-(anticancer) property relations.

The work on the Project will be related to the X-ray analysis of the synthesized compounds, search for new structure-property/activity relations, and application of new approaches in the modern X-ray diffraction method to study the electronic structure of the compounds of interest. Today many labs are utilizing this technique to aid the discovery of small-molecule inhibitors and have applied crystallography to fragment-based drug discovery.

1. Nesterov, V.N., Sarkisov, S.S., Curley, M.J., Urbas, A., Ruiz, T. 3,5-Bis[4-(diethylamino)benzylidene]-1,1-dimethyl-4-oxopiperidinium iodide: a prospective biophotonic material. *Acta Cryst.* **2007**, E63, accepted.

Synthesis and Analysis of Potential Anticancer Protein Kinase Blockers

Project to the NIH by Nesterov, Vladimir N. (PI),

Research Professor at NMHU,

Department of Natural Sciences, NMHU, Las Vegas, NM, 87701-9000

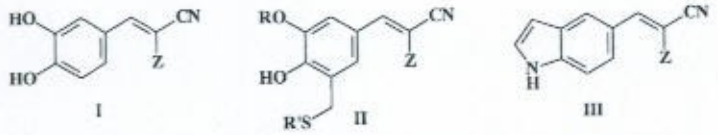
NM. Tel: (505)454-3464, E-mail: vnesterov@nmhu.edu

A. Specific aims and goal

Inhibition of cancer cell growth and progression is one of the most important goals of modern medicine. Despite encouraging progress in prevention and survival in the last decade, cancer remains the second leading cause of death in the United States [**1-4**]. For cancer researchers, much remains to be done.

Our goal is to synthesize and evaluate the biological activity of new α,β-unsaturated malonic acid derivatives and investigate how the presence of different substituents or functional groups influences their chemotherapeutic activity. It is well known that such compounds with low molecular weight (**Scheme 1**) are potent inhibitors of protein tyrosine kinases (PTKs) and many other kinases [**5- 36a**]. PTKs are a large family of enzymes which play a key role in cellular signal transduction leading to proliferation and differentiation [**5**]. Enhanced PTK activity is correlated with proliferative diseases such as cancers, leukemias, and psoriasis [**6-36a**]. According to literature data [**36b**], "the active sites of 491 human protein kinase domains are highly conserved, which makes the design of selective inhibitors a formidable challenge". Thus, huge effort is required to identify compounds that can selectively bind to one particular kinase out of the estimated 2000 highly homologous human protein kinases [**36c-e**]. Indeed, a work in this pathway is very hard but extremely important for human beings.

Scheme 1. General formulae of PTK inhibitors [**6 –34,36a**]:



Z = CN, $CONH_2$, $CSNH_2$, CONHR", CSNHR" (R" = Alk, Ar, ...); R = H, Alk; R' = Alk, Ar, ...

Objectives

Our specific objectives in pursuit of the above goal are to:

1. Design and develop synthetic methods for compounds belonging to the groups of α,β-unsaturated malonic acid derivatives (arylidenemalononitriles, arylidenecyanothio(oxo)acetamides, their dimers and derivatives), arylidenepiperidones and cyclohexanones, their analogs and different acyclic and heterocyclic compounds from all of them, possessing strong bio-activities and selective cancer cytotoxic activity. In our fragment-based drug discovery a major fragment in such compounds will be 3-(9-ethylcarbazole) that already gave us promising results as anticancer agent and prompted us to explore further carbazole derivatives. Such compounds are relatively stable, soluble in appropriate

solvents, have active hydrogen donor and acceptor groups and some of them will have chemically active groups that can form covalent bonds with target fragment in proteins.
2. Fully characterize the molecular structure of these compounds.
3. As we have previously, send them to NCI for screening as potential anti-cancer agents by the Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis.
4. Correlate structural and anticancer activity findings to direct future syntheses in our laboratory. Merging the most active fragments in one or several molecules or link them.

Background and significance

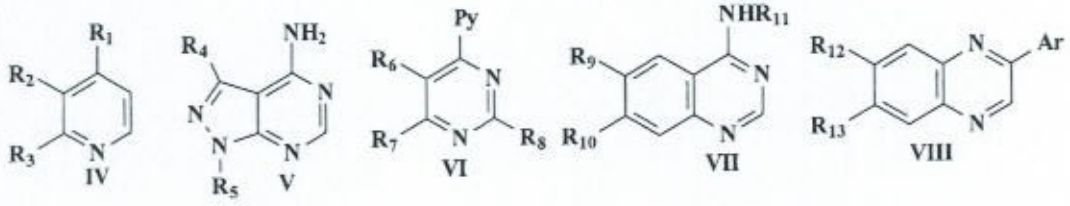
For the last fifteen years, hundreds of small molecules (**Scheme 1**) and heterocyclic derivatives from them (for instance, the cyano group was incorporated into a second ring, giving isoquinoline and quinoline derivatives) were synthesized and tested as anticancer agents [**6-36a**]. Many such compounds have progressively increasing affinity <over a 2500-fold range> toward the substrate site of epidermal growth factor receptor (EGFR) kinase domain [**6**]. EGFR is a family of proteins involved in the proliferation of normal and malignant cells and a marker for several human tumors: breast cancer, carcinoma of the neck and head, lung tumor, and glioma [**34**]. Such compounds inhibited EGFR kinase activity up to three orders of magnitude more than they inhibited insulin receptor kinase.

The first selective PTK inhibitors discovered were the benzylidenemalononitrile derivatives (**I-III, Scheme 1**), tyrphostins (the name of this class of antiproliferative compounds which act as protein tyrosine kinase blockers) which also block effectively EGFR [**6,31,36a**]. Moreover, they also effectively inhibited EGFR-dependent autophosphorylation of the insulin receptor [**6**].

Some of these tyrphostins have shown efficacy *in vivo* as antileukemic agents. For example, AG 490 (**I**, where **Z** is $CONHCH_2Ph$) is a Jak-2 inhibitor potent against recurrent pre-B acute lymphoblastic leukemia [**11,20,22**] and was also shown to effectively inhibit certain breast and prostate cancer metastases [**26**]. AG 1517 (SU 5271) is a potent EGFR kinase inhibitor currently in clinical trials for psoriasis [**22**]. SU 5416 is a potent kinase inhibitor of the vascular endothelial growth factor receptor and is currently in clinical trials as an anticancer agent by virtue of its strong anti-angiogenic activity [**22**]. AG 213 (**I**, where **Z** is $CSNH_2$) inhibits phosphorylation and phosphoinositide turnover [**26,36a**]. The selectivity and binding specificity of many PTKs render them non-toxic even in high concentrations [**26**]. These are only a small part of the data demonstrating the chemotherapeutic role of PTK inhibitors. Thus, it is critical to design, synthesize, and test new compounds that can bind receptors and inhibit PTK and other PK activity.

Heterocyclic compounds (**Scheme 2**) obtained from small molecules (**Scheme 1**) frequently possess even higher activity against PTKs and other kinases [**17,18,22,24,26,31,34-40a,b**]. This group of inhibitors consists of: pyridines, pyrazolopyrimidines, pyridopyrimidines, purines, quinazolines, quinaxolines and others derivatives (**Scheme 2**) [**34-43**].

Scheme 2. General formulae of heterocyclic PK inhibitors:



Thus, 4-anilido- substituted quinazolines (**VII**) potently inhibit EGFR kinase [**17**]. From this group of heterocyclic compounds, well known compounds include: STI 571/Gleevec/Glivec™

(pyridopyrimidine derivatives, **VI, Table 1**), which became the first signal transduction inhibitor and showed excellent efficacy in the clinic for early chronic myeloid leukemia (CML; approved in US as inhibitor of BCR-Abl kinase) [**35a**,**41-43**]; Iressa™ (derivatives from **VII, Table 1**) [**31**,**34**,**35a**,**b**], which was recently approved by the Federal Drug Administration (FDA) for treatment of lung cancer; Tarceva™ (also from **VII, Table 1**), and PP1/PP2 (pyrazolopyrimidine derivatives, **V**, **Table 1**) are potent Src family selective protein tyrosine kinase inhibitors [**35a**], an anti-EGFR agent (lung cancer) and numerous others [**31**,**34**,**35a**].

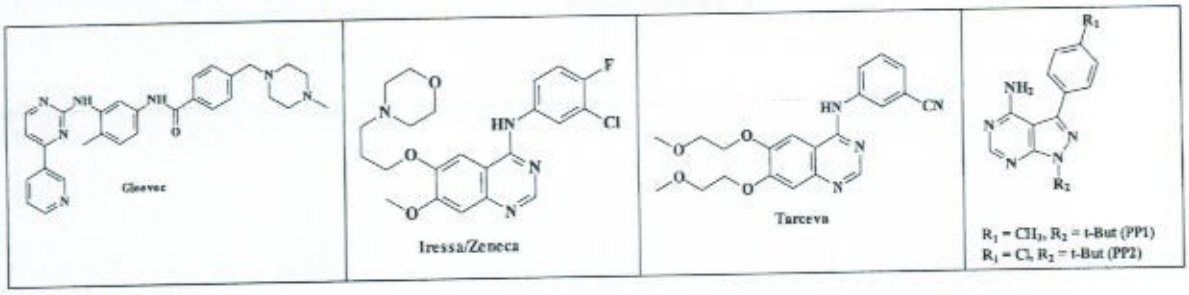
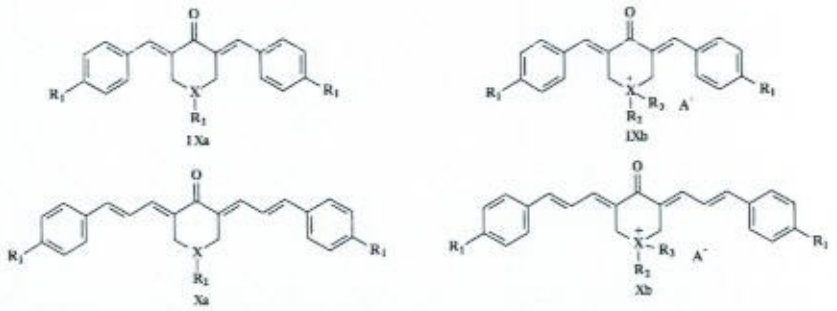


Table 1. Formulae of some compounds of the protein kinase inhibitors.

We will also synthesize many new related heterocyclic compounds, submit them to NCI for screening, and investigate which substituent and functional groups produce maximal chemotherapeutic bio-activity.

A final group of compounds of interest is arylidenepiperidone and cyclohexanone chromophores (**Scheme 3**):

Scheme 3. General formulae of arylidenepiperidone/cyclohexanone chromophores:

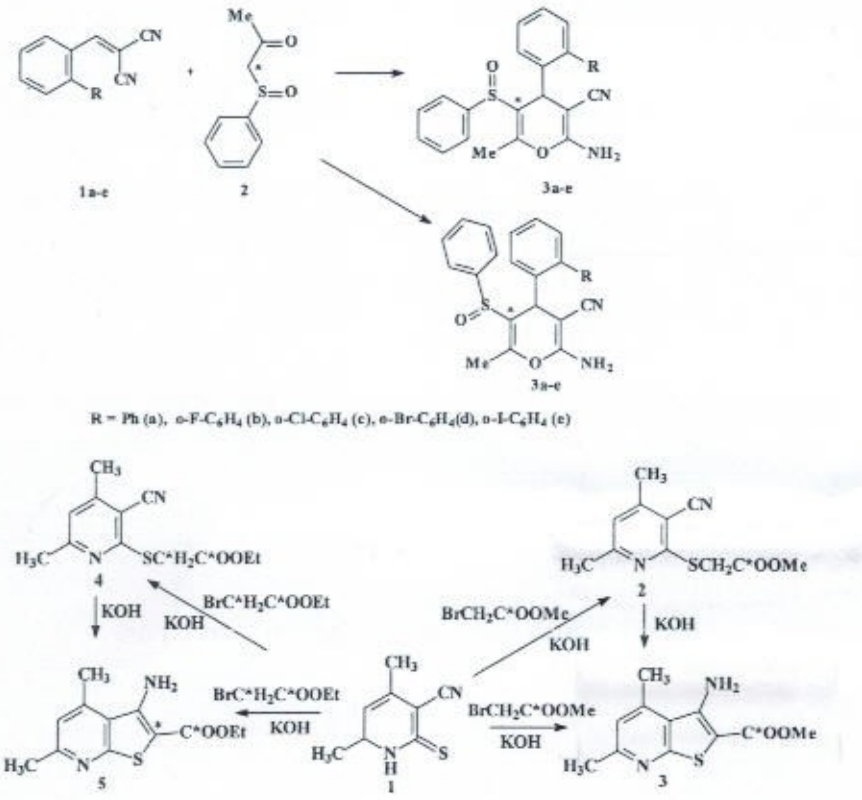


These compounds are also well known to have a cytotoxic effect, and are potential anticancer agents [**44-54a**]. The rational for further study of arylidenepiperidones centers on their effect against human leukemia cell lines such as P388 and lymphoid leukemia cells (L1210), where they have proven more cytotoxic than drugs currently in clinical use [**44-54a**]. We are planning to modify these compounds, introduce more effective functional groups and using them to synthesize different heterocyclic systems such as pyranopyridines that have already shown promising anticancer activities [**54b**] and others derivatives.

C. Preliminary studies

Our team will continue to collaborate with other groups at NMHU (Drs. R. Martinez, M. Helvenston and Sammeth) to perform molecular design, quantum calculations and molecular modeling. We have already begun to work with Dr Martinez group and synthesized several heterocyclic compounds containing one or two ^{13}C atoms and the structure of the products was thoroughly investigated by X-ray analysis and these results will be published soon (**Scheme 4**). In the future, we are planning to introduce in all our active compounds such labels which can improve an analysis of metabolic processes.

Scheme 4. Synthesis of compounds with one or two ^{13}C atoms

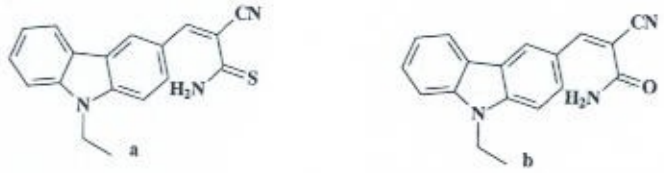


The PI of this project, has extensive experience in the field of design, synthesis, and structural and optical characterization of small molecules like α,β-unsaturated malonic acid derivatives (arylidenemalononitriles, arylidenecyanothio(oxo)acetamides, their dimers and derivatives; **Scheme 1**) arylidenepiperidones and cyclohexanones, their analogs (**Scheme 3**) and various heterocyclic compounds from all of them (**Scheme 2**). As discussed in section **B**, the potential bioactivity of these chemical groups against various cancers and proliferative diseases is high and warrants further study. Our laboratory has synthesized more than 3000 compounds (most of them by PI) and our main findings have been published in peer-reviewed journals [**55-94**]. Substituting a broad range of functional groups into the small organic molecule, we design and study has uncovered several potential applications.

This work began in 1999 at New Mexico Highlands University, a participant in the NASA-sponsored Alliance for Nonlinear Optics. From 2000 to 2003, Dr. Nesterov was co-PI of the project and its lead organic synthetic chemist. Work initially centering on the search for efficient two-photon absorbents for optical limiting led to the synthesis and characterization of many small organic molecules, including arylidenemalononitriles, arylidenecyanothio(oxo)acetamides and their

derivatives (**Scheme 1**), as well as arylidenepiperidones and cyclohexanones (**Scheme 3**). These compounds have been thoroughly investigated as non-linear optical materials [**95-112**] and as two-photon absorption and fluorescence compounds for potential phototherapeutic applications [**90,94,112**].

Most important to this proposal, in 2003–06 our group submitted approximately 70 compounds to the NCI Division of Cancer Treatment and Diagnosis/Developmental Therapeutics Program/Biological Testing Branch. In late 2003, based on positive cell line screening results, compound **1** [see **Scheme 5, (a)**], which NCI designated NSC-726031, was selected for hollow-fiber 6-cell-line testing in mice. In the hollow-fiber protocol, the efficacy of a compound, at two dosage levels, is tested against six human tumor cell lines *in vivo*. The cells are grown in 1-mm-diameter plastic fibers that are then implanted subcutaneously (SC) and intraperitoneally (IP) into mice. Scoring, based on a compound's ability to reduce cancer cell mass by 50%, is calculated on a 48-point scale, and compounds with a combined IP and SC score of 10 or greater are referred for further study (i.e., human xenograft assay) [**113**]. Approximately 20% of submitted compounds show sufficient anti-cancer activity in cell culture to be recommended for hollow fiber assay; of those, less than 5% go on to xenograft testing [**114a**]. In late 2006 the other our compound (see **Scheme 5, (b)**, NSC-736774-Y and related to the AG 490) also was selected by the NCI biological evaluation committee for performing hollow fiber 6-cell-line testing in mice and right now we are waiting results from it.



Scheme 5. Our active compounds: NSC-726031 (**a**) and NSC-736774-Y (**b**)

To date, approximately 1/2 (38 out of 70) of our submissions have been selected for bioactivity screening. One has shown significant anticancer activity: NSC-726031 had a combined IP + SC score of 4, and thus was not tested further [**113**]. We are, however encouraged by these preliminary results and will continue our research that involves synthesis of compounds related to NSC-726031 and NSC-736774-Y, including heterocyclic derivatives (**Schemes 6**), which we will submit to NCI for bioactivity testing.

Research design and methods

Problem 1: Design and synthesis of compounds as potential kinase inhibitors

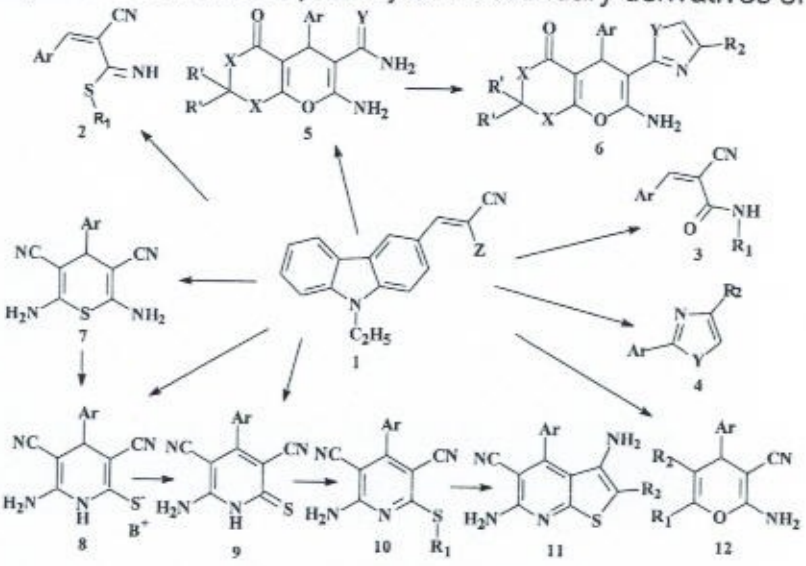
We will synthesize dozen analogs of compound **1** belonging to the well characterized class of PTK inhibitors [**6-36a,b**] depicted in **Scheme 1**, forming different heterocyclic derivatives (**Scheme 6**). This work provides a familiar starting point, as we have previously synthesized compound **1** (**Z** = $CSNH_2$), its **Z** = CN analog, and its thiazole derivative, compound **4** (**Y**=S, $\mathbf{R_2}$ = Ph). They were thoroughly investigated as potential non-linear optical materials [**104**]. They contain $\mathbf{Ar^1}$ [3-(9-ethylcarbazole) a framework or core (ring systems and a few functional groups) and different substituents connected with thio(oxo)amide groups, as an additional active side fragments. According to literature data [**6-36a,b,114b-i**], such substituents or small fragments have been found in known drug molecules and will play an important role in improving the anticancer activity of our compounds. Parallel to our major work with carbazole derivatives, we also plan to make similar investigations with 3-indole fragment,

as a core, that has already shown high potency as anticancer agent [**115a-d**] especially if it bears a halogen atom or a small size ether group at 5 of the indole moiety [**115d**].

Screening of the compounds in NCI, will help us to find out which substituent will contribute more to anticancer activity and shows us a way in which we should follow in our work with this type of compounds. It is necessary to mention that such fragment–based methods of drug discovery are useful in academia and industry, were successful in generating many new drugs with high potency, and improved pharmacokinetic properties [**115a**]. We are planning to use our efficient fragment, as a core, in most compounds that we will synthesize and make screening through NCI. Another word, we want to develop libraries of fragments around the core and identify the most potent one. After that we are planning to combine such potent fragments in one molecule.

From **1** and related compounds containing a carbazole core, we will synthesize acyclic, cyclic and heterocyclic derivatives belonging to structural **Scheme 1,2**. Moreover, there are several publications about carbazole derivatives which inhibit protein kinases [**35a,115a,116a,b**].

Scheme 6. General synthetic scheme for primary and secondary derivatives of compound **1**:



X = CH_2, O; Y = O, S; Z = CN, $COOR_1$, $CONH_2$, $CONHR_1$, $CSNH_2$, Ar,...; R_1 = Alk, cycloalkyl, CH_2COOH, CH_2COOR_1, CH_2CONH_2, CH_2CONHR_1, (CH_2)n-cycloalkyl(heterocycle), (CH_2)nAr, ...; R_2 = COOH, $COOR_1$, $CONH_2$, $CONHR_1$, COAr, $CO(CH_2)$nAr, ...; R' = H, CH_3, ...; Ar = carbazole.

It is well known that the presence in molecules of such R_3 and R_4 substituents increases their bio-activity [**117-125a,b**]. For instance, Gleevec™ (**Table 1**) contains a substituted piperazine fragment [**26,31,35a,43**]; ZD-1839 (Zeneca) and PD-183805 (both are EGFR kinase inhibitors) contain a morpholine substituent (**Table 1**) [**35a**].

Our purpose is to synthesize and evaluate the biological activity of compounds with different fragments and functional groups and find which substituents will maximize the inhibition of PTK and other kinases.

I. References

1. CDC National Center for Health Statistics *Fast Stats* website: http://www.cdc.gov/nchs/fastats/lcod.htm, accessed December 10, **2004**.
2. American Cancer Society: *Cancer Facts and Figures* **2004**. http://www.cancer.org/downloads/STT/CAFF_finalPWSecured.pdf, accessed December 10, 2004.
3. McLaughlin JK, Lipworth L: Epidemiologic aspects of renal cell cancer. Seminars in Oncology 21(2):115-123, **2000**.
4. Mortality Data from the National Vital Statistics System:

http://www.cdc.gov/nchs/about/major/dvs/mortdata.htm. Accessed September 10, **2004**.
5. Bishop, J.M. The molecular genetics of cancer. Science, **1987**, V335, pp. 305-308.
6. Yaish, P., Gazit, A., Gilon, C., Levitzki, A. Blocking of EGF-dependent cell proliferation by EGF receptor kinase inhibitors. Science, **1988**, V242, N.4880, pp. 933-935.
7. Gazit, A., Yaish, P., Gilon, C., Levitzki, A. Tyrphostins I: Synthesis and biological activity of protein tyrosine kinase inhibitors. J. Med. Chem., **1989**, V32, pp. 2344-2352.
8. Levitzki, A. Tyrphostins--potential antiproliferative agents and novel molecular tools. Biochem. Pharmacol., **1990**, V40, pp. 913-918.
9. Gazit, A., Osherov, N., Posner, I., Yaish, P., Paradosu, E., Gilon, C., Levitzki, A. Tyrphostins. 2. Heterocyclic and α-substituted benzylidenemalononitrile tyrphostins as potent inhibitors of EGF receptor and ErbB2/neu tyrosine kinases. J. Med. Chem., **1991**, V34, pp. 1896-1907.
10. Dvir, A., Milner, Y., Chomsky, O., Gilon, C., Gazit, A., Levitzki, A. The inhibition of EGF-dependent proliferation of keratinocytes by tyrphostin tyrosine blockers. J. Cell. Biol., **1991**, V113, pp. 857-865.
11. Anafi, M., Gazit, A., Gilon, C., Ben-Neriah, Y., Levitzki, A. Selective interactions of transforming and normal *abl* proteins with ATP, tyrosine-copolymer substrates, and tyrphostins. J. Biol. Chem., **1992**, V267, pp. 4518-4523.
12. Levitzki, A. Tyrphostins: tyrosine kinase blockers as novel antiproliferative agents and dissectors of signal transduction. Faseb. J., **1992**, V6, pp. 3275-3282.

13. Gazit, A., Osherov, N., Posner, I., Bar-Sinai, A., Gilon, C., Levitzki, A. Tyrphostins. 3. Structure-activity relationship studies of α-substituted benzylidenemalononitrile 5-S-aryltirphostins. J. Med. Chem., **1993**, V36, pp. 3556-3564.
14. Osherov, N., Gazit, A., Gilon, C., and Levitzki, A. (1993). Selective inhibition of the epidermal growth factor and HER2/neu receptors by tyrphostins. J. Biol. Chem., **1993**, V268, pp. 11134-1142.

15. Ben-Bassat, H., Vardi, D.V., Gazit, A., Klaus, S.N., Chaouat, M., Hartzstark, Z., Levitzki, A. Tyrphostins suppress the growth of psoriatic keratinocytes. Exp. Dermatol., **1995**, V4, pp. 82-88.
16. Levitzki, A., Gazit, A. Tyrosine kinase inhibition: an approach to drug development. Science, **1995**, V267, pp. 1782-1788.
17. Gazit, A., Chen, J., App, H., McMahon, G., Hirth, P., Chen, I., Levitzki, A. Tyrphostins. IV. Highly potent inhibitors of EGF receptor kinase. Structure-activity relationship study of 4-anilidoquinazolines. Bioorg. Med. Chem., **1996**, V4, pp. 1203-1207.
18. Gazit, A., App, H., McMahon, G., Chen, J., Levitzki, A., Bohmer, F.D. Tyrphostins. 5. Potent inhibitors of platelet-derived growth factor receptor tyrosine kinases: Structure-activity relationships in quinoxalines, quinolines, and indole tirphostins. J. Med. Chem., **1996**, V39, pp. 2170-2177.
19. Gazit, A., Osherov, N., Gilon, C., Levitzki, A. Tyrphostins. 6. Dimeric benzylidenemalononitrile tyrphostins: potent inhibitors of EGF receptor tyrosine kinases in vitro. J. Med. Chem., **1996**, V39, pp. 4905-4911.

20. Meydan, N., Grunberger, T., Dadi, H., Shahar, M., Arpaia, E., Lapidot, Z., Leeder, J. S., Freedman, M., Cohen, A., Gazit, A., Levitzki, A., and Roifman, C. M. Inhibition of acute lymphoblastic leukaemia by a Jak-2 inhibitor. Nature, **1996**, V379, 645-648.
21. Ben-Bassat, H., Rosenbaum-Mitrani, S., Hartzstark, Z., Levitzki, R., Chaouat, M., Shlomai, Z., Klein, B. Y., Kleinberger-Doron, N., Gazit, A., Tsvieli, R., and Levitzki, A. Tyrphostins that suppress the growth of human papilloma virus 16- immortalized human keratinocytes. J. Pharmacol. Exp. Ther., **1999**, V290, pp. 1442-1457.

22. Levitzki, A. Protein tyrosine kinase inhibitors as novel therapeutic agents. Pharmacol. Ther., **1999**, V82, pp. 231-239.

23. Ben-Bassat, H., Rosenbaum-Mitrani, S., Hartzstark, Z., Levitzki, R., Chaouat, M., Shlomai, Z., Klein, B. Y., Kleinberger-Doron, N., Gazit, A., Tsvieli, R., and Levitzki, A. Tyrphostins that suppress the growth of human papilloma virus 16- immortalized human keratinocytes. J. Pharmacol. Exp. Ther., **1999**, V290, pp. 1442-1457.

24. Thacher, S.M., Vasudevan, J., Tsang, K.-Y., Nagpal, S., Chandraratna, R.A.S. New dermatological agents for the treatment of psoriasis. J. Med. Chem., **2001**, V44, pp. 281-297.

25. Burdelya, L., Catlett-Falcone, R., Levitzki, A., Cheng, F., Mora, L. B., Sotomayor, E., Coppola, D., Sun, J., Sebti, S., Dalton, W. S., Jove, R., and Yu, H. Combination therapy with AG-490 and interleukin 12 achieves greater anti-tumor effects than either agent alone. Mol. Cancer Ther., **2002**, V1, pp. 893-899.

26. Levitzki, A. Tyrosine kinases as targets for cancer therapy. Eur. J. Cancer, **2002**, V38, Suppl., 5, S11-18.
27. Levitzki, A. Protein Kinase Inhibitors. In Encyclopedia of Cancer (USA: Elsevier Science), **2002**, pp. 475-480.
28. Ben-Bassat, H., Hartzstark, Z., Levitzki, R., Klein, B. Y., Shlomai, Z., Gazit, A., and Levitzki, A. Tyrosine kinase inhibitors suppress the growth of non-hodgkin B lymphomas. J. Pharmacol. Exp. Therap., **2002**, V303, pp.163-171.
29. Baars, S., Bachmann, A., Levitzki, A., Rosl, F. Tyrphostin AG555 inhibits bovine papillomavirus transcription by changing the ratio between E2 transactivator/repressor function. J. Biol. Chem., **2003**, V278, pp. 37306-37313.

30. George, J., Biner, S., Keren, P., Barshack, I., Goldberg, I., Sherez, J., Levitzki, A., Keren, G., Roth, A. Tyrphostin AG-556 reduces myocardial infarct size and improves cardiac performance in the rat. Exp. Mol. Pathol., **2003**, V74, pp. 314-318.

31. Levitzki, A. Protein kinase inhibitors as a therapeutic modality. Acc. Chem. Res., **2003**, V36, pp. 462-469.
32. Blum, G., Gazit, A. & Levitzki, A. Development of new IGF-1 receptor kinase inhibitors using catechol mimics. J. Biol. Chem., **2003**, V278, pp. 40442-40454.
33. Shir, A., Friedrich, I., and Levitzki, A. Tumor specific activation of PKR as a non-toxic modality of cancer treatment. Semin. Cancer Biol., **2003**, V13, pp. 309-314.
34. Shaul, M., Abourbeh, G., Jacobson, O., Rozen, Y., Laky, D., Levitzki, A., and Mishani, E. Novel iodine-124 labeled EGFR inhibitors as potential PET agents for molecular imaging in cancer. Bioorg. Med. Chem., **2004**, V12, pp. 3421-3429.
35a. Sawyer, T.K., Bohacek, R.S., Metcalf III, C.A., Shakespeare, W.C., Wang, Y., Sundaramoorthi, R., Keenan, T., Narula, S., Weigele, M., Dalgarno, D.C. Novel protein kinase inhibitors: SMART drug design technology. Structure-guided drug discovery (A supplement to BioTechniques), **2003**, 6, pp. 2-15.

35b. Barker, A.J., Gibson, K.H., Grundy, W., Godfrey, A.A., Barlow, J.J., Healy, M.P., Woodburn, J.R., Ashton, S.E., Curry, B.J., Scarlett, L., Henthorn, L., Richards, L. Studies leading to the identification of ZD1839 (Iressa™): an orally active, selective epidermal growth factor receptor tyrosine inhibitor targeted to the treatment of cancer. Bioorg. Med. Chem. Let., **2001**, V14, pp.1911-1914.

36a. Lyall, R.M., Zilberstein, A., Gazit, A., Gilon, C., Levitzki, A., Schlessinger, J.
Tyrphostins inhibit epidermal growth factor (EGF)-receptor tyrosine kinase activity in living cells and EGF-stimulated cell proliferation. J. Biol. Chem., **1989**, pp. 14503-14509.

36b. Cohen, M.S., Zhang, C., Shokat, K.M., Taunton, J. Structural bioinformatics-based design of selective, irreversible kinase inhibitors. Science, **2005**, V308, pp. 1318-1321.

36c. Liu, Y., Bishop, A., Witucki, L., Kraybill, B., Shimizu, E., Tsien, J., Ubersax, J., Blethrow, J., Morgan, D.O., Shokat, K.M. Structural basis for selective inhibition of Src family kinases by PP1. Chem. & Biol., **1999**, V6, pp. 671-678.

36d. Zhu, X., Kim, J.L., Newcomb, J.R., Rose, P.E., Stover, D.R., Toledo, L.M., Zhao, H., Morgenstern, K.A. Structural analysis of the lymphocyte0specific kinase Lck in complex with non-selective and Src family selective kinase inhibitors. Structure, **1999**, V7, pp. 651-661.

36e. Schindler, T., Sicheri, F., Pico, A., Gazit, A., Levitzki, A., Kuriyan, J. Crystal structure of Hck in complex with a Src family-selective tyrosine kinase inhibitor. Mol. Cell, V3, pp. 639-648.

37. Cappelli, A., Giuliani, G., Mohr, G.P., Gallelli, A., Anzini, M., Vomero, S., Cupello, A., Scarrone, S., Matarrese, M., Moresco, R.M., Fazio, F., Finetti, F., Morbidelli, L., Ziche, M. A non-peptide NK_1 receptor agonist showing subpicomolar affinity. J. Med. Chem., **2004**, V47, pp. 1315-1318.

38. Gangjee, A., Lin, X., Queener, S.F. Design, synthesis, and biological evaluation of 2,4-diamino-5-methyl-6-substituted-pyrrolo[2,3-d]pyrimidines as dihydrofolate reductase inhibitors. J. Med. Chem., **2004**, V47, pp. 3689-3692.

39. Beukers, M.W., Chang, L.C.W., Künsel, J.K.F.D., Mulder-Krieger, T., Spanjersberg, R.F., Brussee, J., IJzerman, A.P. New, non-adenosine, high-potency agonists for the human adenosine A_{2B} receptor with an improved selectivity profile compared to the reference agonist N-ethylcarboxamidoadenosine. J. Med. Chem., **2004**, V47, pp. 3707-3709.

40a. Gellibert, F., Woolven, J, Fouchet, M.H., Mathews, N., Goodland, H., Lovegrove, V., Laroze, A., Nguyen, V.L., Sautet, S., Wang, R., Janson, C., Smith, W., Krysa, G., Boullay, V., Gouville, A.C., Huet, S., Hartley, D. Identification of 1,5-naphthyridine derivatives as a novel series of potent and selective TGF-β type I receptor Inhibitors. J. Med. Chem., **2004**, V47, pp. 4494-4506.

40b. Hauser, D.R.J., Scior, T., Domeyer, D.M., Kammerer, B., Laufer, S.A. Synthesis, biological testing, and binding mode prediction of 6,9-diarylpurin-8-ones as p38 MAP kinase inhibitors. J. Med. Chem., **2007**, V50, pp. 2060-2066.

41. Druker, B.J., Lydon, N.B. Lessons learned from the development of an abl tyrosine kinase inhibitor for chronic myelogenous leukemia. J. Clin. Invest., **2000**, V105, pp. 3-7.

42. Druker, B.J. Perspectives on the development of a molecularly targeted agent. Cancer Cell. **2002**, V1, pp. 31-36.

43. Shah, N.P., Tran, C, Lee, F.Y., Chen, P., Norris, D., Sawyers, C.L. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science, **2004**, V305, pp. 399-401.

44. Jia, Z., Quail, J.W., Arora, V.K. & Dimmock, J.R. Structures of 3,5-bis(benzylidene)-4-piperidone hydrochloride (I) and its N-methyl analog (II).

Acta Crystallogr., **1988**, C44, pp. 2114-2117.

45. Jia, Z., Quail, J.W., Arora, V.K. & Dimmock, J.R. Structures of 2,6-bis(benzylidene)cyclohexanone (III) and 3,5-bis(4-dimethylaminobenzylidene)-1-methyl-4-piperidone (IV). Acta Crystallogr., **1989**, C45, pp. 285-289.

46. Jia, Z., Quail, J.W., Arora, V.K. & Dimmock, J.R. Structures of 3,5-bis(benzylidene)-1-methyl-4-piperidone methobromide hemiethanol solvate. Acta Crystallogr., **1989**, C45, pp. 1117-1118.

47. Jia, Z., Quail, J.W., Arora, V.K. & Dimmock, J.R. Structures of 3,5-bis(4-dimethylaminobenzylidene)-1-methyl-4-piperidone methoiodide. Acta Crystallogr., **1989**, C45, pp. 1119-1120.
48. Dimmock, J.R., Arora, V.K., Duffy, M.J., Reid, R.S., Allen, T.M., Kao, G.Y. Evaluation of some N-acyl analogues of 3,5-bis(arylidene-4-piperidones) for cytotoxic activity. Drug Design and Discovery, **1992**, V8, pp. 291-299.
49. Dimmock, J.R., Arora, V.K., Quail, J.W., Pugazhenthi, U., Allen, T.M., Kao, G.Y., Clercq, E. D. Cytotoxic evaluation of some 3,5-diaryllidene-4-piperidones and related quaternary ammonium compounds and analogs. J. Pharm. Sciences. **1994**, V83, pp. 1124-1130.
50. Dimmock, J.R., Arora, V.K., Chen, M., Allen, T.M., Kao, G.Y. Cytotoxic evaluation of some N-acyl and N-acyloxy analogues of 3,5-bis(arylidene 4-piperidones. Drug Design and Discovery, **1994**, V12, pp. 19-28.
51. Dimmock, J.R., Vashishtha, S.C., Quail, J.W., Pugazhenthi, U., Zimpel, Z., Sudom, A.M., Allen, T.M., Kao, G.Y., Balzarini, J., Clercq, E.D. 4-(b-Arylvinyl)-3-(b-arylvinylketo)-1-ethyl-4-piperiinols and related compounds: a novel class of cytotoxic and anticancer agents. J. Med. Chem., **1998**, V41, pp. 4012-4020.
52. Dimmock, J.R., Kandepu, N.M, Nazarali, A.J., Kowalchuck, T.P., Motaganahalli, N.L., Quail, J.W., Wilson, J., Mykytuk, P.A, Audette, G.F., Perjejesi, P., Allen, T.M., Santos, C.L., Szydlowski, J., Clercq, E.D., Balzarini, J. Conformational and quantitavive structure-activity relationship study of cytotoxic 2-arylidenebenzocycloalkanones. J. Med. Chem., **1999**, V42, pp. 1358-1366.
53. Dimmock, J.R., Padmanilayam, M.P., Puthucode, R.N., Nazarali, A.J., Motaganahalli, N.L., Zello, G.A., Quail, J.W., Oloo, E.O., Kraatz, H.B., Prisciak, J.S., Allen, T.M., Santos, C.L., Balzarini, J., Clercq, E.D., Manavathu, E.K. A conformational and structure-activity relationship study of cytotoxic 3,5-bis(arylidene)-4-piperidones and related N-Acryloyl analogues. J. Med. Chem., **2001**, V44, pp. 586-593.
54a. Dimmock, J.R., Zello, G.A., Oloo, E.O., Quali, J.W., Kraatz, H.-B., Perjesi, P., Aradi, F., Takacs-Novak, K., Allen, T.M., Santos, C.L., Balzarini, J., De Clercq, E., Stables, J.P. Correlations between cytotoxicity and topography of some 2-arylidenebenzocycloalkanoines determined by X-Ray crystallography. J. Med. Chem., **2002**, V45, pp. 3103-3111.
54b. Pikul S., Ohler, N.E., Ciszewski, G., Laufersweiler, M.C., Almstead, N.G., De, B., Natchus, M.G., Hsieh, L.C., Janusz, M.J., Peng, S.X., Branch, T.M., King, S.L., Taiwo, Y.O., Mieling, G.E. Potent and selective carboxylic acid-based inhibitors of matrix metalloproteinases. J. Med. Chem., **2001**, V44, pp. 2499-2502.
55. Nesterov, V.N., Shklover, V.E., Struchkov, Yu.T., Sharanin, Yu.A., Shestopalov, A.M., Rodinovskaya, L.A. Structure of morpholinium 5-acetyl-3-cyano-1,4-dihydro-6-methyl-4-(2-nitrophenyl)-2-pyridine thiolate. Acta Crystallogr., **1985**, C41, pp. 1191-1194.
56. Litvinov, V.P., Sharanin, Yu.A., Rodinovskaya, L.A., Nesterov, V.N., Shklover, V.E., Struchkov, Yu.T. Condensed pyridines. 8. 5,6-Pentamethylene-3-cyanopyridine-2(1H)-thione and selenone in the synthesis of 3-aminothieno-and selenolo[2,3-b]pyridines. Crystal structure of 3-amino-2-benzoyl-5,6-pentamethyleneselenolo[2,3-b]pyridine. J. Chem. Scripta, **1989**, V. 29, pp. 327-332.
57. Nesterov, V.N., Shklover, V.E., Struchkov, Yu.T., Sharanin, Yu.A., Aitov, I.A., Shestopalov, A.M. Crystal Structure of 3-benzoyl-1,1,2-tricyano-3-(1-pyridinio)-2-propenide-1. Acta Crystallogr., **1991**, C47, pp. 109-112.
58. Nesterov, V.N., Shklover, V.E., Struchkov, Yu.T., Sharanin, Yu.A.,Shestopalov, A.M., Demerkov, A.S. Crystal structure of 2-benzoyl-2-(1-pyridinio)-1-phenylaminoethylene-1-thiolate. Acta Crystallogr., **1991**, C47, pp. 1927-1929.
59. Antonov, D.M., Belenkii, L.L., Bogdanov, V.S., Dudinov, A.A.,Krayushkin, M.M., Nesterov, V.N., Struchkov, Yu.T., Ugrak, B.I. Synthesis of heterocycles on the basis of products of polyhaloalkane

addition to unsaturated system.3. Structure and stereochemistry of substituted N-furylformamidines. J. Khim. geterotsiklic soedinen. (Chem. of Heterocyclic Comp.), **1992**, pp. 1451-1460.
60. Nesterov, V.N., Khoroshilov, G.E., Struchkov, Yu.T., Sharanin, Yu.A. Synthesis and structure of novel 2-amino-1,3-dicyano-4-cyclopropyl-6-aryl-1,3-cyclohexadiens. Izv. Akad. nauk, Ser. Khim. (Russ. Chem. Bull.), **1993**, pp. 355-358.
61. Shestopalov, A.M., Bogomolova, O.P., Rodinovskaya, L.A.,Litvinov, V.P., Bujnicki, B., Mikolayczyk, M., Nesterov, V.N., Struchkov, Yu.T. Stereoselective Synthesis and atropoisomerism in 4-pyridyl-3-(1-pyridinio)-3,4-trans-1,2,3,4-tetrahydropyridines and their transformation products. Heteroatom Chemistry, **1993**, V4, pp. 593-602.
62. Yurovskaya, M.A., Khamlova, I.G., Nesterov, V.N., Shishkin, O.V., Struchkov, Yu.T. Regioorientation of side chain reactions of activated alkyl pyridines with electrophiles. J. Khim. geterotsiklic soedinen. (Chem. of Heterocyclic Comp.), **1995**, pp. 1543-1550.
63. Nesterov, V.N., Dyachenko, V.D., Sharanin, Yu.A., Struchkov, Yu.T. Synthesis and crystal structure of 5-amino-4,6-dicyan-3-dicyanomethylene-1,8,8-trimethyl-2-azabicyclo[2.2.2]oct-5-ene. Izv. Akad. nauk, Ser. Khim. (Russ. Chem. Bull.), **1996**, pp. 169-172.
64. Nesterov, V.N., Aitov, I.A., Sharanin, Yu.A., Struchkov, Yu.T. Synthesis, molecular and crystal structure of 1-allyl-4-[indan-1,3-dione-2-ylidene)-2-cyanoethylidene]-1,4-dihydroquinoline. Izv. Akad. Nauk. Ser. Khim. (Russ. Chem. Bull.), **1996**, pp. 173-176.
65. Aitov, I.A., Nesterov, V.N., Sharanin, Yu.A., Struchkov, Yu.T. Synthesis and structure of 1-[1-(4-R-benzoyl)-2- ethoxyvinyl]-2-dicyanomethylene-1,2-dihydropyridines. Izv. Akad. Nauk. Ser. Khim. (Russ. Chem. Bull.), **1996**, pp. 434-436.
66. Nesterov, V.N., Dyachenko, V.D., Sharanin, Yu.A., Struchkov, Yu.T.
Synthesis and structure of 7-allylseleno-5-amino-2-methyl-4-(2-furyl)-3-ethoxycarbonyl-8-cyano-1,4-dihydro-1,6- naphthyridine. Izv. Akad. Nauk. Ser. Khim. (Russ. Chem. Bull.), **1996**, pp. 437-440.
67. Ivanov, V.L., Artemov, V.A., Rodinovskaya, L.A., Shestopalov, A.M., Nesterov, V.N., Struchkov, Yu.T., Litvinov, V.P. New approaches to synthesis of functionally substituted pyrido-[3',2':4,5]thieno[3,2-b]pyridines; structure of obtained products. J. Khim. geterotsiklic soedinen. (Chem. of Heterocyclic Comp.), **1996**, pp. 115-121.
68. Ivanov, V.L., Artemov, V.A., Shestopalov, A.M., Nesterov, V.N.,Struchkov Yu.T., Litvinov V.P. 2-Bromo-1-phenylethylidenemalononitrile in synthesis of functionally substituted thieno[3,2-b]pyridines and thiazolo[4,5-b]pyridines. J. Khim. geterotsiklic soedinen. (Chem. of Heterocyclic Comp.), **1996**, pp. 413-419.
69. Nesterov, V.N., Dontsova, N.E., Shestopalov, A.M., Struchkov, Yu.T., Litvinov, V.P. Synthesis, molecular and crystal structure of 3-benzoyl-1,2-di(ethylsulfonyl)-indolizine. J. Khim. geterotsiklic soedinen. (Chem. of Heterocyclic Comp.), **1996**, pp. 950-954.
70. Samet, A.V., Shestopalov, A.M., Nesterov, V.N., Semenov, V.V. An improved stereoselective synthesis of 5-acyl-2-amino-4-aryl-3-cyano-4,5-dihydrothiophenes. Synthesis, **1997**, pp. 623-624.
71. Nasakin, O.E., Sheverdov, V.P., Moiseeva, I.V., Lyshchikov, A.N., Ershov, O.V., Nesterov, V.N. The synthesis of 3-amidino-2-aminopyridine-4-carboxylates. Tetrahedron Lett. **1997**, pp. 4455-4456.
72. Samet, A.V., Shestopalov, A.M., Nesterov, V.N., Semenov, V.V. Reactions of sulfur ylides with α,β-unsaturated thioamides: synthesis of dihydrothiophenes and cyclopropanes. Izv. Akad. nauk, Ser. Khim. (Russ. Chem. Bull.), **1998**, pp. 127-132.
73. Kislyi, V.P., Nesterov, V.N., Shestopalov, A.M., Semenov, V.V.
Heterocycles with the β-nitroenamine fragment 1. Synthesis of 2-amino-3- nitropyrans from nitroacetonitrile. Crystal and molecular structure of 2-amino-4-(4-fluorophenyl)-7,7-dimethyl-3-nitro-5,6,7,8-tetrahydrochromen-5(4H)-one
Izv. Akad. nauk, Ser. Khim. (Russ. Chem. Bull.), **1999**, pp. 1142-1145.
74. Kislyi, V.P., Nesterov, V.N., Shestopalov, A.M., Semenov, V.V. Heterocycles with a β-nitroenamine fragment 2. Synthesis of 2-amino-3-nitropyrano[3,2-c]pyrans and 2-amino-3-

nitropyrano[3,2-c]chromenes from nitroacetonitrile. Izv. Akad. nauk, Ser. Khim. (Russ. Chem. Bull.), **1999**, pp. 1146-1149.

75. Kislyi, V.P., Nesterov, V.N., Semenov, V.V. Heterocycles with a β-nitroenamine fragment 3. Synthesis of 3-amino-2-nitrothieno[2,3-b]pyridines. Crystal and molecular structure of 3-amino-4-methyl-2-nitro-6-trifluoromethylthieno[2,3-b]pyridine. Izv. Akad. nauk, Ser. Khim. (Russ. Chem. Bull.), **1999**, pp. 1150-1153.
76. Samet, A.V., Nesterov, V.N., Shestopalov, A.M., Semenov, V.V. Structures of products of the reaction of dimethylsulfonium phenacylide with benzylidenecyanoacetamide. Russ. Chem. Bull., **1999**, V48, pp. 1310-1317.
77. Nesterov, V.N., Antipin, M.Yu., Timofeeva, T.V., Clark, R.D. Trans,trans-2-cyano-5-(4-methoxyphenyl)penta-2,4-dienethioamide. Acta Crystallogr., **2000**, C56, pp. 88-89.
78. Nesterov, V.N., Kislyi, V.P., Timofeeva, T.V., Antipin, M.Yu., Semenov, V.V. Trans-1-cyano-2-(2-methoxyphenyl)-1-nitroethylene. Acta Crystallogr., **2000**, C56, pp. e107-e108.
79. Nesterov, V.N., Viltchinskaia, E.A. 6-Amino-5,5,7-tricyano-3,3a,4,5-tetrahydro-2H-indene-4-spirocyclopentane. Acta Crystallogr., **2000**, C56, pp. 872-873.
80. Selivanova, I.A., Tyukavkina, N.A., Kolesnik, Yu.A., Nesterov, V.N., Kuleshova, L.N., Khutoryanskii, V.A., Bazhenov, B.N., Saibotalov, M.Yu. Study of the crystalline structure of dihydroquercetin. Pharm. Chem. J. (Khim. Farm. Zh.) **2000**. 33(4), pp. 222-224.
81. Nesterov, V.N., Viltchinskaia, E.A. 5-Acetyl-2-amino-6-methyl-4-(3-nitrophenyl)-4H-pyran-3-carbonitrile and 2-amino-5-ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-4H-pyran-3-carbonitrile. Acta Crystallogr., **2001**, C57, pp. 616-618.
82. Golubev, A.S., Pasternak, P.V., Shidlovskii, A.F., Savel`eva, L.N., Averkiev, B.B., Nesterov, V.N., Antipin, M.YU., Peregudov A.S., Chkanikov N.D.
Synthesis and some heterocyclisation reactions of CF_2H- and CF_2C_l-substituted 1,1-dicyanoethylenes. J. Fluor. Chem., **2002**, 114(1), pp. 63-74.
83. Lichitsky, B.V., Kozhinov, D. V., Nesterov, V.N., Vorontsova, L. G., Starikova,Z.A., Dudinov, A.A., Krayushkin, M.M. Reactions of cyclic enehydrazino ketones with arylidenemalononitriles. Synthesis of 11-aryl-1-oxo-2,3,4,5,10b,11-hexahydro-1H-indolo[2,3-b]quinoline-10b-carbonitriles. Russ. Chem. Bull., **2002**, V51, pp. 1862-1868.
84. Shestopalov, A.M., Emelianova, Yu.M., Nesterov, V.N. One-step synthesis of substituted 2-amino-4H-chromenes and 2-amino-4H-benzo[f]chromenes. Molecular and crystal structure of 2-amino-3-cyano-6-hydroxy-4-phenyl-4H-benzo[f]chromene. Russ. Chem. Bull. **2002**, 51, pp. 2238-2243.
85. Nesterov, V.N., Viltchinskaia, E.A. and Nesterova, S.V. [(2-Methoxyanilino)methylene]malononitrile. Acta Crystallogr., **2003**, E59, pp. o625-o627.
86. Shestopalov, A., Rodinovskaya, L., Shestopalov, A., Zlotin, S., Nesterov, V. A convenient one-pot synthesis of substituted 1,1-dicyanocyclopropanes from sulfonium salts, malononitrile, and carbonyl compounds. Synlett., **2003**, 15, pp. 2309-2312.
87. Shestopalov, A.M., Naumov, O.A., Nesterov, V.N. One-step synthesis of 5-acetyl-2-amino-4-aryl-3-cyano-4H-pyrano[3,2-b]indoles. Molecular and crystal structure of 5-acetyl-2-amino-4-(4"-chloro-3"-nitrophenyl)-3-cyano-4H-pyrano[3,2-b]indole. Russ. Chem. Bull., **2003**, V52, pp. 179-186.
88. Shestopalov, A.M., Emelianova, Yu.M., Nesterov, V.N. One-step synthesis of substituted 2-amino-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyrans. Molecular and crystal structure of 2-amino-3-(2-methoxyethoxycarbonyl)-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran. Russ. Chem. Bull., **2003**, V52, pp. 1164-1171.
89. Rodinovskaya, L.A., Gromova, A. V., Shestopalov, A.M., Nesterov, V.N.
Synthesis of 6-amino-4-aryl-5-cyano-3-(3-cyanopyridin-2-ylthiomethyl)-2,4-dihydropyrano[2,3-*c*]pyrazoles and their hydrogenated analogs. Molecular structure of 6-amino-5-cyano-3-(3-cyano-4,6-

dimethylpyridin-2-ylthiomethyl)-4-(2-nitrophenyl)-2,4-dihydropyrano[2,3-*c*]pyrazole. Russ. Chem. Bull., **2003**, V52, pp. 2207-2213.

90. Nesterov, V.N., Timofeeva, T.V., Sarkisov, S.S., Leyderman, A., Lee, Y.-C., Antipin, M.Yu 3,5-Bis[4-(diethylamino)benzylidene]-1-methyl-4-piperidone and 3,5-Bis[4-(diethylamino)cinnamylidene]-1-methyl-4-piperidone: prospective biophotonic materials. Acta Crystallogr., **2003**, C59, pp. o605-o608.

91. Nesterov, V.N., Wiedenfeld, D., Nesterova, S.V., Minton. M. 2-Amino-4-(1-naphthyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile and 2-amino-7,7-dimethyl-4-(1-naphthyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile.
Acta Crystallogr., **2004**, C60, pp. o334-o337.

92a. Nesterova, S.V., Wiedenfeld, D.J., Nesterov, V.N. 5-Acetyl-2-amino-6-methyl-4-(1-naphthyl)-4H-pyran-3-carbonitrile, methyl 6-amino-5-cyano-2-methyl-4-(1-naphthyl)-4H-pyran-3-carboxylate and tert-butyl 6-amino-5-cyano-2-methyl-4-(1-naphthyl)-4H-pyran-3-carboxylate. Acta Crystallogr., **2004**, C60, pp. o559-o563.

92b. Nesterov, V.N., Wiedenfeld, D.J., Nesterova, S.V., Daniels, L.M. Synthesis and X-ray structural investigations of 2-amino-7-methyl-4-(1-naphthyl)-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile and 2-amino-4-(1-naphthyl)-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile.
J. Chem. Crystallogr., **2005**, V35, pp. 917-922.

92c. Nesterov, V.N., Kislyi, V.P., Sabutis, J.L., Nesterov, V.V., Wiedenfeld, D.J., Semenov, V.V. 2-Amino-4-(2-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile and 2-amino-4-(2-methoxyphenyl)-7,7-dimethyl-3-nitro-4,6,7,8-tetrahydro-5H-chromen-5-one hemihydrate.
Acta Crystallogr., **2005**, C61, o741-o744.

92d. Nesterov, V.N., Wiedenfeld, D.J., Nesterova, S.V., Hastings, L.F.
5-Acetyl-2-amino-6-methyl-4-phenyl-4H-pyran-3-carbonitrile and 2-amino-5-benzoyl-6-methyl-4-phenyl-4H-pyran-3-carbonitrile acetonitrile solvate. Acta Crystallogr., **2006**, C62, o705-708.

93a. Nesterov, V.N., Nesterov, V.V. Polymorphism and solvolysis of 2-cyano-3-[4-(diethylamino)phenyl]-prop-2-enethioamide. Acta Crystallogr., **2004**, C60, pp. o781-o785.

93b. Nesterov, V.N., Sarkisov, S.S., Curley, M.J., Urbas, A. An orthorhombic polymorph of 3,5-bis(4'-dimethylaminophenylidene)-1-methyl-piperidone. Acta Crystallogr. **2007**, E63, pp. o.1785-o1787.

94. Nesterov, V.N. 3,5-Bis(4-methoxybenzylidene)-1-methyl-4-piperidone and 3,5-bis(4-methoxybenzylidene)-1-methyl-4-oxopiperidinium chloride: potential biophotonic materials. Acta Crystallogr., **2004**, C60, pp. o806-o809.

95. Nesterov, V.N., Timofeeva, T.V., Duerksen, G., Clark, R.D. Structure and nonlinear optical properties of phenylazo compounds. Structural characterization of 3-amino-3-morpholinyl-2-(o-nitrophenylazo)-propenonitrile and o-nitro-phenylhydrazonomalononitrile. J. Mol. Struct., **1998**, V 444, pp. 135-146.

96. Antipin, M.Yu., Timofeeva, T.V., Clark, R.D., Nesterov, V.N., Sanghadasa, M., Barr, T.A., Penn, B., Romero, L., Romero, M. Molecular crystal structure and nonlinear optical properties in the series of dicyanovinylbenzene and its derivatives. J. Phys. Chem. A, **1998**, V 102, pp. 7222-7232.

97. Antipin, M.Yu., Clark, R.D., Nesterov, V.N., Sanghadasa, M., Timofeeva, T.V., Lyssenko, K.A. Molecular design and nonlinear optical properties in the series of substituted dicyanovinylaromatics. J. Mol. Cryst. Liq. Cryst., **1998**, V 313, pp. 85-94.

98. Timofeeva, T.V., Nesterov, V.N., Antipin, M.Yu., Clark, R.D., Sanghadasa, M., Cardelino, B.H., Moore, C.E., Frazier, D.O. Molecular modeling and experimental study of non-linear optical compounds: monosubstituted derivatives of dicyanovinylbenzene. J. Mol. Srtuct., **2000**, V 519, pp. 225-241.

99. Nesterov, V.N., Deng, X., Timofeeva, T.V., Antipin, M.Yu., Clark, R.D., Frazier, D.O., Penn, B. Structural characterization of monomers for nonlinear optical polymers. X-ray analysis and molecular mechanics calculations of 2-(4-methacryloxy-3-methoxyphenyl)-1,1-dicyanoethylene, 2-(3-

methacryloxy-4-methoxyphenyl)-1,1-dicyanoethylene, and 2-(2-methacryloxy-3-methoxyphenyl)-1,1-dicyanoethylene. J.Mol. Struct., **2000**, V523, pp. 309-318.
100. Nesterov, V.N., Timofeeva, T.V., Borbulevych, O.Ya., Antipin, M.Yu., Clark, R.D. A combinatorial chemistry approach to new materials for nonlinear optics. I. Structures of five Schiff bases. Acta Crystallogr., **2000**, C56, pp. 971-975.
101. Nesterov, V.N., Timofeeva, T.V., Antipin, M.Yu., Clark, R.D. Combinatorial chemistry approach to new materials for nonlinear optics. II. Structures of 4-dimethylaminocinnamaldehyde and molecular complex of 4-methoxycinnamaldehyde with 2,4-dinitroaniline. Acta Crystallogr., **2000**, C56, pp. 976-978.
102. Timofeeva, T.V., Nesterov, V.N., Dolgushin, F.M., Zubavichus, Ya.V., Goldshtein, J.T., Sammeth, D.M., Clark, R.D., Penn, B., Antipin, M.Yu. One-pot polymorphism of nonlinear optical materials. First example of organic polytypes. Crystal Engin., **2001**, pp. 263-288.
103. Wang, Zh., Nesterov, V.N., Borbulevych, O.Ya., Clark, R.D., Antipin, M.Yu., Timofeeva, T.V. Indole- and carbazole-substituted pyridinium iodide salts: a rare case of conformational isomerism in crystals. Acta Crystallogr., **2001**, C57, pp. 1343-1348.
104. Nesterov, V.N., Montoya, N.G., Antipin, M. Yu., Sanghadasa, M., Clark, R.D., Timofeeva, T.V. Three polar derivatives of N-ethylcarbazole: materials for optical application. Acta Crystallogr., **2002**, C58, pp. 72-75.
105. Huang, X., Kuhn, G.H., Nesterov, V.N., Averkiev, B.B., Penn, B., Antipin, M.Yu., Timofeeva, T.V. (E)-(4-Hydroxyphenyl) (4-nitrophenyl)diazene, (E)-(4-methoxyphenyl) (4-nitrophenyl)diazene, (E)-[4-(6-bromohexyloxy)phenyl] (4-cyanophenyl)diazene. Acta Crystallogr., **2002**, C58, pp. 624-628.
106. Timofeeva, T.V., Nesterov, V.N., Clark, R.D., Penn, B., Fraizer, D., Antipin, M.Yu. Systematic study of polymorphism in crystalline non-linear optical materials. J. Mol. Struct., **2003**, V647, pp. 181-202.
107. Antipin, M.Yu, Nesterov, V.N., Jiang, S., Borbulevych, O.Ya., Sammeth, D.M., Sevostianova, E.V., Timofeeva, T.V. X-Ray crystal structures, molecular mechanics and quantum chemical calculations, and calculations of the nonlinear optical polarizabilities in the series of monohalogen substituted derivatives of dicyanovinylbenzene. J. Mol. Struct., **2003**, V650, pp. 1-20.
108. Nesterov, V.V., Antipin, M.Yu., Nesterov, V.N., Moore, C.E., Cardelino, B.H., Timofeeva, T.V. Thermally stable heterocyclic imines as new potential NLO materials. J. Phys. Chem. B, **2004**, V108, pp. 8531-8539.
109. Nesterov, V.V., Antipin, M.Yu., Nesterov, V.N., Penn, B.G., Frazier, D.O., Timofeeva, T.V. Thermally stable imines as new potential nonlinear optical materials. Crystal Growth & Design. **2004**, V4, 3, pp. 521-531.
110a. Timofeeva, T.V., Kinnibrugh, T., Borbulevych, O.Ya., Averkiev, B., Nesterov, V.N., Sloan, A., Antipin, M.Yu. Vanishing polymorphism of (2E)-2-cyano-3-[4-(diethylamino)phenyl]prop-2-enethioamide: X-ray structural study and polymorph prediction. Crystal Growth & Design. **2004**, V4, 6, pp. 1265-1276.
110b. Nesterov, V.N., Sarkisov, S.S., Curley, M.J., Urbas, A. An orthorhombic polymorph of 3,5-bis(4'-dimethylaminophenylidene)-1-methyl-piperidone. Acta Crystallogr. **2007**, E63, o.1785-o1787.
111. Helvenston, M.C., Nesterov, V.N., Jenkins, H.J. Synthesis and X-ray structural analysis of (2Z)-3-(4-hydroxyphenyl)-2-pyridin-4-ylacrylonitrile and (2Z)-3-(3,5- di-tert-butyl-4-hydroxyphenyl)-2-pyridin-4-ylacrylonitrile. J. Chem. Crystallogr., **2005**, V35, pp. 113-118.
112. Sarkisov, S.S., Peterson, B. H., Curley, M. J., Nesterov, V.N., Timofeeva, T., Antipin, M., Radovanova, E. I., Leyderman, A., Fleitz, P. Two-photon absorption and fluorescence of new derivatives of cyclohexanone and piperidone. J. Nonlinear Optical Physics and Materials (JNOPM). **2005**, V14, pp. 21-40.
113. NCI Division of Cancer Treatment and Diagnosis/Developmental Therapeutics Program/Biological Testing Branch. Mar. **2004**, correspondence.

114a. Camel, Richard, NCI Division of Cancer Treatment and Diagnosis/Developmental Therapeutics Program/Biological Testing Branch. Sept. **2004**, personal communication.
114b. Peifer, C., Krasowski, A., Hammerle, N., Kohlbacher, O., Dannhardt, G., Totzke, F., Schachtele C., Laufer, S. Profile and molecular modeling of 3-(indole-3-yl)-4-(3,4,5-trimethoxyphenyl)-1H-pyrrole-2,5-dione (1) as a highly selective VEGF-R2/3 inhibitors. J. Med. Chem., **2006**, V50, pp. 7549-7553.
114c. Boschelli, D.H., Wu, B., Ye, F., Wang, Y., Golas, J.M., Lucas, J., Boschelli, F.Synthesis and Src kinase inhibitory activity of a series of 4[(2,4-dichloro-5-methoxyphenyl)amino]-7-furyl-3-quinolinecarbonitriles. J. Med. Chem., **2006**, V50, pp. 7868-7876.
114d. Duan, J.-X., Cai, X., Meng, F., Lan, L., Hart, C., Matteucci, M. Potent antitubulin tumor cell cytotoxins based on 3-aroyl indazoles. J. Med. Chem., **2007**, V50, pp. 1001-1006.
114e. Zhang, Q., Peng, Y., Wang, X.I., Keenan, S.M., Arora, S., Welsh, W.J. Highly potent triazole-based polymerization inhibitors. J. Med. Chem., **2007**, V50, pp. 749-754.
114f. Hodous, B.L., Geuns-Meyer, S.D., Hughes, P.E., Albrecht, B.K., Bellon, S., Bready, J., Caenepeel, S., Cee, V.J., Chaffee, S.C., Coxon, A., Emery, M., Fretland, J., Gallant P., Gu, Y., Hoffman, D., Johnson, R.E., Kendall, R., Kim, J.L., Long, A.M., Morrison, M., Oliver, P.R., Patel, V.F., Polverino, A., Rose, P., Tempest, P., Wang, L., Whittington, D.A., Zhao, H. Evolution of a highly selective and potent 2-(pyridine-2-yl)-1,3,5-triazine Tie-2 kinase inhibitor. J. Med. Chem., **2007**, V50, pp. 611-626.
114g. Cee, V.J., Albrecht, B.K., Geuns-Meyer, S., Hughes, P., Bellon, S., Bready, J., Caenepeel, S., Chaffee, S.C., Coxon, A., Emery, M., Fretland, J., Gallant, P., Gu, Y., Hodous, B.L., Hoffman, D., Johnson, R,E., Kendall, R., Kim, J.L., Long, A.M., McGowan, D., Morrison, M., Olivieri, P.R., Patel, V.F., Polverino, A., Powers, D., Rose, P., Wang, L., Zhao, H. Alkynylpyrimidine amide derivatives as potent, selective, and orally active inhibitors of Tie-2 kinase. J. Med. Chem., **2007**, V50, pp. 627-640.
114h. Soliva, R., Gelpi, J.L., Almansa, C., Virgili, M., Orozco, M. Dissection of the recognition properties of p38 MAP kinase. Determination of the binding mode of a new pyridinyl-heterocycle inhibitor family. J. Med. Chem., **2007**, V50, pp. 283-293.
114i. Romagnoli, R., Baraldi, P.G., Carrion, M.D., Cara, C.L., Preti, D., Fruttarolo, F., Pavani, M.G., Tabrizi, A., Tolomeo, M., Grimaudo, S., Di Cristina, A., Balzarini, J., Hadfield, J., Brancale, A., Hamel, E. Synthesis and biological evaluation of 2- and 3-aminobenzo[b]thiophene derivatives as antimitotic agents and inhibitors of tubulin polymerization. J. Med. Chem., **2007**, V50, pp. 2273-2277.
115a. Erlanson, D.A., McDowell, R.S., O'Brien, T. Fragment-based drug discovery. J. Med. Chem., **2004**, V47, pp. 3463-3482.
115b. De Martino, G., Regina, G., Coluccia, A., Edler, M.C., Barbera, M.C., Brancale, A., Wilcox, E., Hamel, E., Artico, M., Silvestri, R. Arylthioindoles, potent inhibitors of tubulin polymerization. J. Med. Chem., 2004, V47, pp. 6120-6123.
115c. Gill, A.L., Frederickson, M., Cleasby, A., Woodhead, S.J., Carr, M.G., Woodhead, A.J., Walker, M.T., Congreve, M.S., Devine, L.A., Tisi, D., O'Reilly, M., Seavers, L.C.A., Davis, D.J., Curry, J., Anthony, R., Padova, A., Murray, C.W., Carr, R.A.E., Jhoti, H. Identification of novel p38α MAP kinase inhibitors using fragment-based lead generastion. J. Med. Chem., **2005**, V48, pp. 414-426.
115d. La Regina, G., Edler, M.C., Brancale, A., Kandil, S., Coluccia, A., Piscitelli, F., Hamel, E., De Mertino, G., Matesanz, R., Diaz, J.F., Scovassi, A.I., Prosperi, E., Lavecchia, A., Novellino, E., Artico, M., Silvestri, R. . Arylthioindole inhibitors of tubulin polymerization. 3. Biological evaluation, structure-activity relationships and molecular modeling studies. J. Med. Chem., **2007**, V50. Published on Web 05/12/2007.
116a. Balasubramanian, B.N., Laurent, D.R.St., Saulnier, M.G., Long, B.H., Bachand, C., Beaulieu, F., Clarke, W., Deshpande, M., Eummer, J., Fairchild, C.R., Frennesson, D.B., Kramer, R., Lee, F.Y., Mahler, M., Martel, A., Narasimhulu, B., Russell, J., Ruediger, E., Solomon, C., Stoffan, K.M., Wong, H., Zimmermann, K., Vyas, D.M. Design and synthesis of a fluoroindolocarbazole series as selective topoisomerase I active agents. Discovery of water-soluble 3,9-difluoro-12,13-dihydro-13-[6-amino-β-

D-glucopyranosyl]-5H,13H-benzo[b]thienyl[2,3-b]pyrrolo[3,4-c]carbazole-5,7(6H)-dione (BMS-251873) with curative antitumor activity against prostate carcinoma xenograft tumor model. J. Med. Chem., **2004**, V47, pp. 1609-1612.

116b. Leslie, C.P., Di Fabio, R., Bonetti, F., Borriello, M., Braggio, S., Dal Forno, G., Donati, D., Falchi, A., Ghirlanda, D., Giovannini, R., Pavone, F., Pecunioso, A., Pentassuglia, G., Pizzi, D.A., Rumboldt, G., Stasi, L. Novel carbazole derivatives as NPY Y1 antagonists. Bioorg. Med. Chem. Let., **2007**, V17, pp. 1043-1046.

117. Xia, Y., Yang, Z.Yu., Xia, P., Hackl, T., Hamel, E., Mauger, A., Wu, J.H., Lee, K.H. Antitumor agents. 211. Fluorinated 2-phenyl-4-quinolone derivatives as antimitotic antitumor agents. J. Med. Chem., **2001**, V44, pp. 3932-3936.

118. Orus, L., Silanes, S.P., Oficialdegui, A.M., Martinez-Esparza, J., Castillo, J.C.D., Mourelle, M., Langer, T., Guccione, S., Donzella, G., Krovat, E.M., Poptodorov, K., Lasheras, B., Ballaz, S., Hervias, I., Tordera, R., Rio, J.D., Monge, A. Synthesis and molecular modeling of new 1-aryl-3-[4-arylpiperazin-1-yl]-1-propane derivatives with high affinity at the serotonin transfer and at 5-HT1a receptors. J. Med. Chem., **2002**, V45, pp. 4128-4139.

119. Ryckebush, A., Deprez-Poulain, R., Maes, L., Debreu-Fontaine, M.A., Mouray, E., Grellier, P., Sergheraert, C. Synthesis and in vitro and in vivo antimalarial activity of N-(7-chloro-4-quinolyl)-1,4-bis(3-aminopropyl)piperazine derivatives. J. Med. Chem., **2003**, V46, pp. 542-557.

120. Strekowski, L., Say, M., Henary, M., Ruiz, P., Manzel, L., Macfarlane, D.E., Bojarski, A. Synthesis and activity of substituted 2-phenylquinolin-4-amines, antagonists of immunostimulatory CpG-oligodeoxynucleotides. J. Med. Chem., **2003**, V46, pp. 1242-1249.

121. Bell., I.M. Inhibitors of farnesyltransferase: a rational approach to cancer.chemotherapy? J. Med. Chem., **2004**, V47, pp. 1869-1877.

122. Guillon, J., Grellier, P., Labaied, M., Sonnet, P., Leger, J.M., Deprez-Poulain, R., Forfar-Bares, I., Dallemagne, P., Lemaitre, N., Pehourcq, F., Rochette, J., Sergheraert, C., Jarry, C. Synthesis antimalarial activity, and molecular modeling of new pyrrolo[1,2-a]quinoxalines, bispyrrolo[1,2-a]quinoxalines, bispyrido[3,2-e]pyrrolo[1,2-a]pyrazines, and bispyrrolo[1,2-a]thieno[3,2-e]pyrazines. J. Med. Chem., **2004**, V47, pp. 1997-2009.

123. Stewart, A.O., Cowart, M.D., Moreland, R.B., Latshaw, S.P., Matulenko, M.A., Bhatia, P.A., Wang, X., Daanen, J.F., Nelson, S.L., Terranova, M.A., Namovic, M.T., Donnelly-Roberts, D.L., Miller, L.N., Nakane, M., Sullivan, J.P., Brioni, J.D. J. Med. Chem., **2004**, V47, pp. 2348-2355.

124. Zaragoza, F., Stephensen, H., Knudsen, S.M., Pridal, L., Wulff, B.S., Rimvall, K. 1-Alkyl-4-acylpiperazines as a new class of imidazole free histamine H_3 receptor antagonists. J. Med. Chem., **2004**, V47, pp. 2833-2838.

125a. Tagat, J.R., McCombie, S.W., Nazareno, D., Labroli, M.A., Xiao, Y., Steensma, R.W., Strizki, J.M., Baroudy, B.M., Cox, K., Lachowicz, J., Varty, G., Watkins, R. Piperazine based CCR5 antagonists as HIV-1 inhibitors. IV. Discovery of 1-[4,6-dimethyl-5-pyrimidinyl)carbonyl]-4-[4-{2-methoxy-1(R)-4-(trifluoromethyl)-phenyl}ethyl-3(S)-methyl-1-piperazinyl]-4-methylpiperidine (Sch-417690/Sch-D), a potent, highly selective, and orally bioavailable CCR5 antagonist. J. Med. Chem., **2004**, V47, pp. 2405-2408.

125b. Dawson, M.I., Xia, Z., Liu, G., Fontana, J.A., Farhana, L., Patel, B.B., Arumugarajah, S., Bhuiyan, M., Zhang, X.-K., Han, Y.-H., Stallcup, W.B., Fukushi, J., Mustelim, T., Tautz, L., Su, Y., Harris, D.L., Waleh, N., Hobbs, P.D., Jong, L., Chao, W., Schiff, L.J., Sani, B.P. An adamantyl-substituted retinoid-derived molecule that inhibits cancer cell growth and angiogenesis by inducing apoptosis and binds to small heterodimer partner nuclear receptor: effects of modifying its carboxylate group on apoptosis, proliferation, and protein-tyrosine phosphate activity. J. Med. Chem., **2007**, V50. Published on Web 05/10/2007.

New Mexico
HIGHLANDS
University

Box 9000
Las Vegas, New Mexico 87701
Telephone: 505 425-7511

MEMORANDUM OF UNDERSTANDING

Between Dr. Vladimir Nesterov and the Department of Chemistry

The Department of Chemistry and Dr. Vladimir Nesterov agree that the Department shall provide Dr. Nesterov, if approved by the RIMI Advisory Board, a 25% FTE award for a Research Fellowship in Spring 2008.

Dr. Vladimir Nesterov

Agreed to by:

Merritt Helvenston, Ph.D.
Chair, Department of Chemistry