Linkage with University of KwaZulu-Natal, Westville Campus, Durban-4000, South Africa

- **Two M. Pharm Students Mr. Chirag Gohil and Ms. Kirtiben Patel, visited UKZN Durban for their research work**

STUDENT EXCHANGE PROGRAM

Mr. Chirag Gohil students of SDPC Visited to University of Kwazulu Natal, South Africa.

Outer World Connection

UNIVERSITY OF KWAZULU-NATAL

MR CHIRAGKUMAR GOHIL

Mumbai - Nairobi - Johannesburg - Durban

E-ticket number	706-8923323196-97
Issuing Airline:	KQ
Ticket status: e-ticket processed 16FEB15	

Durban - Johannesburg - Nairobi - Mumbai

E-ticket number	706-8924628008
Issuing Airline:	KQ
Endorsments/Restrictions	NONENDO/NONTRANSFERABLE RESTRICTIONS APPLY
Ticket status: e-ticket processed 13MAR15	

MS KIRTIBEN PATEL

Mumbai - Nairobi - Johannesburg - Durban

E-ticket number	706-8923323198-99
Issuing Airline:	KQ
Ticket status: e-ticket processed 16FEB15	

Durban - Johannesburg - Nairobi - Mumbai

E-ticket number	706-8924628009
Issuing Airline:	KQ
Endorsments/Restrictions	NONENDO/NONTRANSFERABLE RESTRICTIONS APPLY
Ticket status: e-ticket processed 13MAR15	

SHREE SAHKAR EDUCATION TRUST'S
Shree Dhanvantary Pharmacy College
(Approved by AICTE & PCI - New Delhi and Affiliated to G.T.U.)

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

Date: 13th April 2015

TO WHOM IT MAY CONCERN

This Letter is to confirm that Mr. Chiragkumar Jagdishchandra Gohil (Passport No. M2186361) from Republic of India, is an exchange student in the Discipline of Pharmaceutical Chemistry, University of KwaZulu-Natal (UKZN), Durban, South Africa, Undertaking research on Development of Anticancer Drugs under my supervision.
During the period of 01 month, From 3rd March 2015 to 3rd April 2015

Dr. R Karpoormath B. Pharm, M.Pharm, PhD

Synthetic and Medicinal Chemistry Research Group (SMCRG)
Department of Pharmaceutical Chemistry
Discipline of Pharmaceutical Sciences
College of Health Science
University of KwaZulu-Natal (Westville Campus)
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E-mail: karpoormath@ukzn.ac.za

1910 - 2010
100 YEARS OF ACADEMIC EXCELLENCE
IN KWAZULU-NATAL

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

Date: 13th April 2015

TO WHOM IT MAY CONCERN

This letter is to confirm that Miss. Kirtiben Narendrabhai Patel (Passport No. M3552476) from Republic of India is a Exchange student in The Discipline Pharmaceutical Chemistry, University of KwaZulu-Natal (UKZN), Durban-South Africa, undertaking research on Anticancer Drugs under my supervision. During a period of 1 Month, From 3rd March 2015 to 3rd April 2015.

Yours sincerely,

Dr. R Karpoormath B. Pharm, M.Pharm, PhD

Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

Synthetic and Medicinal Chemistry Research Group (SMCRG)
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1910 - 2010
100 YEARS OF ACADEMIC EXCELLENCE IN KWAZULU-NATAL

- **Indian-South Africa Joint Proposal**

PROJECT APPLIED WITH INTERNATIONAL UNIVERSITY

India-South Africa Joint proposals

Proposal Title: "*Investigations of Peptide Based CNT Guided Delivery Device For Cancer Therapy*"

UNIVERSITY OF KWAZULU-NATAL

Department of Science & Technology, Government of India

सत्यमेव जयते

- **Research Collaboration outcomes in form of research paper.**

Full Paper

Synthesis, *In Vitro* Evaluation, and Molecular Docking Studies of Azetidinones and Thiazolidinones of 2-Amino-5-cyclopropyl-1,3,4-thiadiazole as Antibacterial Agents

Harun Patel[1], Lishu Mishra[2], Malleshappa Noolvi[3], Rajshekhar Karpoormath[1], and Swaranjit Singh Cameotra[4]

[1] Faculty-Medicinal Chemistry, Department of Pharmaceutical Chemistry, University of KwaZulu-Natal (Westville Campus), Durban, South Africa
[2] Department of Pharmaceutical Chemistry, ASBASJS Memorial College of Pharmacy, Bela (Ropar), Punjab, India
[3] Department of Pharmaceutical Chemistry, Shree Dhanvantary Pharmacy College, Kim (Surat), Gujrat, India
[4] Environmental Biotechnology and Microbial Biochemistry, Institute of Microbial Technology, Chandigarh, India

In an attempt to find a new class of antimicrobial agents, a series of novel azetidin-2-ones **3a–e** and thiazolidin-4-ones **4a–e** of 2-amino-5-cyclopropyl-1,3,4-thiadiazole were synthesized. The synthesized compounds were confirmed by melting point, IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. The β-lactam derivative (**3e**) was found to be the most potent compound of the series displaying excellent antibacterial activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* with MIC values of 15.60, 31.50, 62.50, and 125 μg/mL, respectively, as compared to the positive control drug ampicillin. Molecular docking studies and determination of the leakage of UV_{260}- and UV_{280}-absorbing material (nucleic acid material and protein) confirmed that the synthesized compounds inhibit cell wall synthesis by inhibiting PTB (transpeptidase enzyme). Lipinski's rule and *in silico* ADME pharmacokinetic parameters are within the acceptable range defined for human use, thereby indicating their potential as a drug-like molecules.

Keywords: Azetidin-2-ones / Molecular docking / Thiazolidin-4-ones

Received: April 28, 2014; Revised: May 27, 2014; Accepted: May 28, 2014

DOI 10.1002/ardp.201400140

Introduction

Azetidin-2-one, a four membered β-lactam skeleton, has been recognized as a useful building block for the synthesis of a large number of organic molecules by exploiting its ring strain [1]. It is an essential part of the penicillin skeleton and a substructure found in β-lactamase inhibitors such as clavulanic acid or sulbactam [2]. Penams, cephems, monobactams, penems, carbapenems, and triems are several structural variants of β-lactam antibiotics, which have been developed based on penicillin structure as novel approaches to antibacterial therapy [3]. β-Lactam comes to be a generic descriptor for penicillin family. The ring ultimately proved to be the main component of the pharmacophore. The molecular mode of action of the β-lactam antibiotic is selective and irreversible inhibition of enzyme transpeptidases, which are also known as penicillin binding proteins (PBPs), responsible for the developing peptidoglycan layer involved in the biosynthesis of cell walls [4, 5]. These mechanism-based inhibitors prevent the construction of cell wall and eventually lead to cell lysis and death. Moreover, due to their β-lactamase inhibitory action, 2-azetidinone-based heterocycles represent an attractive target of contemporary organic synthesis [6]. On the other hand, 4-thiazolidinone ring system contains sulfur and nitrogen heterogeneous at position 1 and 3, respectively, and ketogroup at four positions.

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European Journal of Medicinal Chemistry 93 (2015) 599–613

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Design, synthesis and evaluation of small molecule imidazo[2,1-*b*][1,3,4]thiadiazoles as inhibitors of transforming growth factor-β type-I receptor kinase (ALK5)

Harun M. Patel [a], Baljeet Sing [b], Varun Bhardwaj [c], Mahesh Palkar [a], Mahamadhanif S. Shaikh [a], Rajesh Rane [a], Wesam S. Alwan [a], Andanappa K. Gadad [d], Malleshappa N. Noolvi [e, *], Rajshekhar Karpoormath [a, **]

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[b] Department of Pharmaceutical Chemistry, ASBASJSM College of Pharmacy, Bela (Ropar) 140111, Punjab, India
[c] Department of Biotechnology, Bioinformatics and Pharmacy, Jaypee University of Information Technology, Waknaghat, Solan 173234, Himachal Pradesh, India
[d] School Pharmacy, Faculty of Medical Sciences, EWMS Complex, Mt. Hope, The University of the West Indies, Trinidad and Tobago, West Indies
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ARTICLE INFO

Article history:
Received 30 May 2014
Received in revised form
21 August 2014
Accepted 2 September 2014
Available online 3 September 2014

Keywords:
Synthesis imidazo [2,1-*b*][1,3,4]thiadiazole
ALK5
XP docking
Lipinski's rule

ABSTRACT

A new series of imidazo[2,1-*b*][1,3,4]thiadiazoles **5(a–g)**, **6(a–g)**, **9(a–i)** and **12(a–h)** were synthesized as transforming growth factor-β (TGF-β) type I receptor (also known as activin receptor-like kinase 5 or ALK5) inhibitors. These compounds were evaluated for their ALK5 inhibitory activity in an enzyme assay and their TGF-β -induced Smad2/3 phosphorylation inhibitory activity in a cell-based assay. Compound **6d**, 2-(5-((2-cyclopropyl-6-(4-fluorophenyl) imidazo [2,1-b][1,3,4]thiadiazol-5-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl) acetic acid, shows prominent ALK5 inhibition (IC_{50} = 0.0012 μM) and elective inhibition (91%) against the P38αkinase at10 μM. The binding mode of compound **6d** by XP docking studies shows that it fits well into the active site cavity of ALK5 by forming broad and tight interactions. Lipinski's rule and in silico ADME pharmacokinetic parameters are within the acceptable range defined for human use thereby indicating their potential as a drug-like molecules.

1. Introduction

Transforming growth factor-beta (TGF-β) is a ubiquitous cytokine that affects various biological processes such as regulation of cell proliferation, immune responses, growth, differentiation, angiogenesis, and apoptosis of different cell types [1]. TGF-β1 transduces signals through two highly conserved single transmembrane serine/threonine kinases, the type I and type II TGF-β receptors (TβR-I and TβR-II, respectively) [2]. TβR-II activates TβR-I upon formation of the ligand–receptor complex by hyperphosphorylating serine/threonine residues in the GS region of the TβR-I or activin-like kinase (ALK5), which creates a binding site for Smad proteins. The activated TβR-I in turn phosphorylates Smad2/Smad3 proteins at the C-terminal SSXS-motif thereby causing dissociation from the receptor and heteromeric complex formation with the Smad4 [3–5]. Smad complexes translocate to the nucleus, assemble with specific DNA-binding co-factors and co-modulators to finally activate transcription of an extracellular matrix component, and inhibitors of matrix-degrading proteases [6]. Therefore, it becomes evident that inhibition of ALK5 phosphorylation of Smad2/Smad3 could reduce TGF-β1-induced excessive accumulation of the extracellular matrix. Small molecules inhibitors of TGF-βR1 offer an attractive way to regulate the TGF-β pathway and can consequently find applications in the treatment of various diseases, especially, cancer [7]. Our on-going interest in the design and synthesis of novel anti-cancer agents [8–13], and recent reports by Hoelzemann and collaborators [14] suggesting the imidazo[2,1-*b*][1,3,4]thiadiazoles scaffold as a template to the design of inhibitors of ALK5; inspired us to synthesize and *in vitro* evaluated imidazo [2,1-*b*][1,3,4]thiadiazoles **5(a–g)**, **6(a–g)**, **9(a–i)** and **12(a–h)** for the ALK5 inhibitory activity in an enzyme assay and their TGF-β

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http://dx.doi.org/10.1016/j.ejmech.2014.09.002
0223-5234/

Linkage with R C Patel Institute of Pharmaceutical Education and Research, Shirpur

- **Research Collaboration outcomes in form of research paper.**

RSC Advances

PAPER

Exploring the anti-breast cancer potential of flavonoid analogs†

Vanrajsinh Thakor,[a] Mayur Poddar,[a] Sumit Dey,[b] S. N. Manjula,[b] SubbaRao V. Madhunapantula,[c] Rahul Pawara,[d] Harun M. Patel*[d] and Malleshappa N. Noolvi*[a]

Cite this: *RSC Adv.*, 2016, 6, 79166

Received 3rd June 2016
Accepted 3rd August 2016

DOI: 10.1039/c6ra14428d

www.rsc.org/advances

In the course of our search for new antitumor agents for breast cancer, novel flavone derivatives were synthesized, characterized and examined for their antitumor activities against breast cancer cell lines. In initial screening, analogs **7a** [3-(5-amino-1,3,4-thiadiazol-2-yl)methoxy-2-phenyl-4*H*-chromen-4-one] and **7b** [3-(5-amino-1,3,4-thiadiazol-2-yl)methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one] were found to be effective against the estrogen receptor negative cell line (MDA-MB 453), which was followed by their evaluation in five dose assays. In addition, mechanistic studies of **7a** and **7b** were performed by cytometric analysis and electrophoretic studies and it was observed that apoptosis is a mechanism of cell death, confirmed morphologically by acridine orange/ethidium bromide double staining and TUNEL analysis. Further *in vivo* evaluation of the anti-tumor activity of compound **7a** and **7b** by Ehrlich Ascites Carcinoma (EAC) model and related studies confirms the anti-breast cancer potential of flavonoid analogs.

1. Introduction

Breast cancer is the most commonly diagnosed malignancy among women with more than one million new cases diagnosed per year throughout the world.[1,2] Despite advances in the early detection of breast cancer and the advent of novel targeted therapies, breast cancer still remains a significant public health problem due to the involvement of multiple aberrant and redundant signaling pathways in the tumorigenesis and the development of resistance to the existing therapeutic agents. The currently available breast cancer therapies achieve meaningful clinical results in only 30–40% of the patients.[3] The efficacy of current chemotherapeutics is low and undesirable side effects are still unacceptably high.[4] Hence, the development of novel, efficient, and less toxic anti-breast cancer agents remains an important and challenging goal of medicinal chemists worldwide.

The female hormone estrogen stimulates breast cell division leading to the increase in risk of permanent damage to DNA.[5] Compounds that can regulate the apoptosis of cancer cells are of a high medical significance.[6] Natural products (NPs) have played a valuable role in the drug discovery and development.[7–9] Newman and Cragg[10] reported that in the case of cancer around 79% of FDA-approved drugs during a period of 1981–2010 are either natural products or their based/mimicked-compounds. NPs are chosen through evolutionary process *via* lead optimization to interact with various enzymes/proteins and thus represent biologically relevant regions of the vast chemical space.[11–13] Flavopiridol, a semisynthetic flavones analog, acts as CDK9 inhibitor, is FDA-approved orphan drug for acute myeloid leukaemia. It has been reported that myricetin, (flavonoid compound) could decrease pancreatic cancer growth *via* induction of cell apoptosis.[14] LY294002 (flavonoid analogue) entered clinical trials as a potential antineoplastic agent.[15] Effects of phytoestrogens in cancer prevention have been reported for decades.[16–18] Since then many molecular mechanisms underlying these effects have been identified. Targets of phytoestrogens comprise steroid receptors, steroid metabolising enzymes, elements of signal transduction and apoptosis pathways, and even the DNA processing machinery.[18] Phytoestrogens include chalcones (A), flavones (B) and isoflavones (C) which are non-steroidal compounds possessing anti-estrogenic activity (Fig. 1).[19]

In light of these findings and in continuation of our research for novel anti-cancer agents[20–23] in the present study, new series of flavone derivatives has been synthesized and screened *in vitro* for cytotoxicity by sulphorhodamine B assay. Five dose assay in estrogen receptor negative cell line (MDA-MB 453) and determination of IC_{50} by SRB assay was also performed. In addition, mechanistic study was done with cytometric analysis and electrophoretic determination of apoptosis. Further *in vivo* activity

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[c]Department of Biochemistry, JSS Medical College, Mysore-570015, Karnataka, India
[d]Department of Pharmaceutical Chemistry, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, District Dhule-425 405, Maharashtra, India

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ra14428d

RSC Advances

REVIEW

Cite this: *RSC Adv.*, 2017, **7**, 28313

Small hybrid heteroaromatics: resourceful biological tools in cancer research

Vikrant Abbot,[a] Poonam Sharma,[a] Saurabh Dhiman,[a] Malleshappa N. Noolvi,[b] Harun M. Patel[c] and Varun Bhardwaj*[a]

Nowadays, hybrid drugs containing two or more covalently linked known potential pharmacophores are designed to simultaneously modulate multiple targets of multifactorial diseases to overcome the side effects associated with a single drug. In this review, an overview of the design strategies employed by various scientists over the past 20 years has been presented. The overview includes the synthesis of different chemical structure-based anticancer hybrids using molecular hybridization techniques. To tackle one of the world's most devastating diseases such as cancer, researchers have exploited the molecular hybridization (MH) technique to synthesize different anticancer hybrids, which include hybrids based on azole, camptothecin, chalcone, pyrrolobenzodiazepine (PBD), coumarin, colchicine, platinum, and some miscellaneous structures. The selection of two or more moieties for generating the hybrid drug is generally aided by the observed (or anticipated) synergistic or additive pharmacological activities of each single moiety. This eventually leads to the identification of novel and better active chemical entities with a superior profile as compared to the parent moieties. In addition to the design strategies, this review also highlights the structure–activity relationship (SAR), mechanism of action, and key features of the synthesized anticancer hybrids.

Received 3rd October 2016
Accepted 17th April 2017

DOI: 10.1039/c6ra24662a

rsc.li/rsc-advances

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[b]*Department of Pharmaceutical Chemistry, Shree Dhanvantary Pharmacy College, Kim, Surat, 3941110, Gujarat, India*

[c]*Department of Pharmaceutical Chemistry, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dhule, 425405, Maharashtra, India*

1. Introduction

Cancer is a cell cycle disease characterized by rapid, uncontrolled, and pathological proliferation of abnormal cells. It is one of the most formidable diseases in the world.[1,2] The most frequent forms of cancer are lung cancer, breast cancer, colorectal cancer, stomach cancer, and prostate cancer; among these, prostate cancer (male) and breast cancer (female)

Vikrant Abbot obtained his Bachelor's degree in Pharmacy from the Punjab Technical University in 2009. He started his professional career working as a Production Chemist at Comed Pharmaceuticals Ltd. Baddi for 2.5 years. Thereafter, he completed his Master's degree in Medicinal Chemistry from JUIT, Waknaghat in 2014. Then, he joined academics and is currently working as an Assistant Professor at ISF College of Pharmacy, Moga, Punjab. His present research interests include design and synthesis of small molecules with anticancer and antimicrobial profiles.

Poonam Sharma obtained her Master's in Philosophy in 2003 with a gold medal and completed her PhD in chemistry in 2006 from Himachal Pradesh University (India). She was awarded a UGC project fellowship for her PhD research. She was also awarded the Fast Track Young Scientist research project by DST in 2010. Presently, she is working as an Assistant Professor at the Jaypee University of Information Technology, Waknaghat, Solan (India). Her research revolves around physicochemical drug interactions, thermodynamics, heterocyclic bioactive analogs and topical drug delivery.

Linkage with SDPARC for training to the students and faculty.

Shree Dhanvantary Pharmaceutical Analysis and Research Centre, Kim

Certificate

This is to certify that

Mr. /Ms. Adat Jemishra

has worked in Instrumental, Microbiological, Chemical and Toxicological section of "Shree Dhanvantary Pharmaceutical Analysis & Research Centre, Kim" for a Period of one month. The Candidate during this period had a hand on experience of various instruments and analytical techniques.

Director

Linkage with IMTECH-CSIR, collaborative research proposal applied to CSIR

Enclosed please find a proposal from Dr. Swaranjit Singh entitled ***"Development of Biosurfactants and Gemini surfactant (Synthetic) based delivery systems for cancer therapy"*** for undertaking collaborative research with Dr. M.N. Noolvi as Principal investigator from Shree Dhanvantary Pharmacy College, Surat, Gujarat. Director has accorded approval to undertake the aforesaid project.

IMTECH has to give an undertaking that it is willing to collaborate in the above project before submission to funding agency and for this a forwarding letter has to be signed by Director which is enclosed.

(Rajendra Soni)
Head
Project & Technology Management Group

ATTESTED
Principal
Shree Dhanvantary Pharmacy College
Kim, SURAT. (Gujarat)

Dr. Swaranjit Singh

Received on 28/5/15

This laboratory is willing to collaborate in a CSIR Scheme entitled: "***Development of Biosurfactants and Gemini surfactant (Synthetic) Based Delivery Systems for Cancer Therapy***" to be carried out between **Dr. M.N. Noolvi,** Professor and PG Coordinator at Shree Dhanvantary Pharmacy College, Kim, Surat, Gujarat as a principal investigator and **Dr. Swaranjit Singh Cameotra,** Professor Acsir, Senior Principal Scientist, IMTECH, Chandigarh, Punjab as a collaborating principal investigator from CSIR laboratory.

I recommend this scheme for funding and it will be an important collaboration between the institution and CSIR laboratory.

forwarded

05-05-2015

Forwarded by

Director
IMTECH

ATTESTED

Principal
Shree Dhanvantary Pharmacy College
Kim, SURAT. (Gujarat)

29/4/15

Linkage with Soniya Education Trusts College of Pharmacy, Dharwad, Karnataka

- **Research Collaboration outcomes in form of research paper.**

Chapter contents | Book contents

Outline

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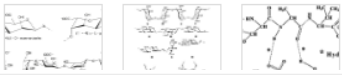
Figures (14)



ACADEMIC PRESS

Natural Polysaccharides in Drug Delivery and Biomedical Applications
2019, Pages 59-100

Chapter 3 - Sodium alginate in drug delivery and biomedical areas

Kiran Chaturvedi [1], Kuntal Ganguly [1], Uttam A. More [2], Kakarla Raghava Reddy [3], Tanavi Dugge [4], Balaram Naik [4], Tejraj M. Aminabhavi [1], Malleshappa N. Noolvi [2]

[1] Department of Pharmaceutical Engineering and Polymer Science, SET's College of Pharmacy, Dharwad, India
[2] Department of Pharmaceutical Chemistry, Shree Dhanvantary Pharmacy College, Kim, Surat, India
[3] School of Chemical and Biomolecular Engineering, The University of Sydney, Sydney, NSW, Australia
[4] Shri Dharmasthala Manjunath Dental College, Dharwad, India

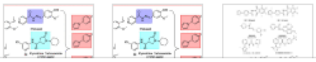
Available online 26 July 2019.

Show less

Outline

Show full outline

Figures (8)



ELSEVIER

Bioorganic Chemistry
Volume 75, December 2017, Pages 181-200

Short communication

Chemical synthesis and in *silico* molecular modeling of novel pyrrolyl benzohydrazide derivatives: Their biological evaluation against enoyl ACP reductase (InhA) and *Mycobacterium tuberculosis*

Shrinivas D. Joshi [a], Uttam A. More [a, b], Sheshagiri R. Dixit [a], Sunil V. Balmi [a], Basavaraj G. Kulkarni [a], Geeta Ullagaddi [a], Christian Lherbet [c, d], Tejraj M. Aminabhavi [a]

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https://www.sciencedirect.com/science/article/abs/pii/S0045206817304704#! d 24 June 2017, Revised 9 September 2017, Accepted 11 September 2017, Available online 12 September

Linkage with Central Leather Research Institute (CSIR), Chennai, applied research proposal

Collaboration letter

We are pleased to collaborate in a CSIR research Scheme entitled: "Design of Biosurfactants and Gemini surfactant (Synthetic) Based Drug Delivery System for Cancer Therapy" to be carried out by Dr. M.N. Noolvi, Professor at Shree Dhanvantary Pharmacy College, Kim, Surat, Gujarat as a principal investigator. I, Dr. M. Surianarayanan, Principal Scientist, Cell for Industrial Safety and Risk Analysis, Chemical engineering Department, Central Leather Research Institute (CSIR), Adyar, Chennai agree to work with him as a collaborating principal investigator from CSIR laboratory. We request to support this scheme for funding as it will be an important collaboration between the mentioned institution and CSIR laboratory.

16/8/2016
Dr. M. Surianarayanan

Forwarded by Director, CLRI, Chennai

5/10/16
डॉ. बी. चंद्रसेकरन
Dr. B. Chandrasekaran
निदेशक Director
सीएसआईआर - केन्द्रीय चर्म अनुसंधान संस्थान
CSIR - Central Leather Research Institute
अडयार, चेन्नई Adyar, Chennai - 600 020

SHREE SAHKAR EDUCATION TRUST'S
Shree Dhanvantary Pharmacy College
(Approved by AICTE & PCI - New Delhi and Affiliated to G.T.U.)

Ref No: SET/ 9311/2016 Date: 07/09/2016

To,
Director,
CSIR-CLRI, Chennai,

Dear Sir,

Subject: Consent for signing MOU/Agreement for sharing the outcome of research project reg.,

With respect to subject cited above, at the outset, I thank project evaluation committee for considering our research proposal entitled: "Design of Biosurfactants and Gemini surfactant (Synthetic) Based Drug Delivery Systems for Cancer Therapy" in collaboration with **Dr. M. Surianarayanan**, (Principal Scientist, Cell for Industrial Safety and Risk Analysis, Chemical engineering Department, Central Leather Research Institute (CSIR), Adyar, Chennai-600020, India).

Further, as per the requirement of CLRI- Project evaluation committee, herewith, I am sending my consent for signing MOU/Agreement with CLRI, CSIR-Chennai to share the outcome and results of our proposed project, once it is funded by CSIR-New Delhi.

Thanking you,

Yours sincerely,

Dr. Malleshappa N. Noolvi,
Principal Investigator,

Forwarded by Principal
ATTESTED

Principal
Shree Dhanvantary Pharmacy College
Kim, Dist SURAT

Linkage with Lamar University, Beaumont, Texas, USA

- **Research Collaboration outcomes in form of research paper.**

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Mini-Reviews in Medicinal Chemistry, 2018, *18*, 000-000 1

REVIEW ARTICLE

Aromatase Inhibitors Evolution as Potential Class of Drugs in the Treatment of Postmenopausal Breast Cancer Women

Stephen Paul Avvaru[1], Malleshappa N. Noolvi[1,*], Tejraj M. Aminbhavi[1], Sudipta Chkraborty[2], Ashutosh Dash[2] and Shyam S. Shukla[3]

[1]*Department of Pharmaceutical Chemistry, Shree Dhanvantary Pharmacy College, Kim, Surat, 394110, India;* [2]*Radiopharmaceuticals Division, Bhabha Atomic Research Centre, India;* [3]*Department of Chemistry and Biochemistry, Lamar University, Beaumont, Texas 77710, USA*

ARTICLE HISTORY

Received: September 06, 2016
Revised: December 15, 2016
Accepted: February 06, 2017

DOI:
10.2174/1389557517666171101100902

Abstract: Aromatase inhibitors are class of drugs that inhibit aromatase, a rate limiting enzyme in the biosynthesis of estrogens from their corresponding androgens. Estrogens play a vital role in the development and growth of breast tumors especially in postmenopausal women apart from their important functions in cell homeostasis. The reduction of estrogen physiological concentration through aromatase inhibition is one of the most important therapeutic strategies against this cancer type. The third-generation aromatase inhibitors are now used as first-line therapy in the treatment of early and metastatic breast cancer in postmenopausal women. However the quest for new class of drugs still stays indispensable to evade the danger of conceivable rising resistances to existing drugs, toxicity and unwanted side effects due to chronic treatment. The current review deals with recent advances in understanding of aromatase, its mechanism and research in the development of various novel chemotypes as aromatase inhibitors. The new challenges and the fast changing trends in bringing rational approach in aromatase inhibitors to a different level like research in dual/multiple target enzyme inhibition strategies, radiolabeling of aromatase inhibitors as theranostic agents; the development of new computational models for complete understanding of aromatase enzyme and its substrate/ligand interactions will bring in holistic approach to comprehensive inhibition of aromatase and other relevant enzymes for effective treatment and monitoring of postmenopausal breast cancer.

Keywords: Aromatase inhibitors, estrogen, breast cancer, dual inhibitors, molecular modeling, radiolabeling.

1. INTRODUCTION

An estimated 1.67 million new breast cancer cases were diagnosed in 2012 which makes it the second most common cancer among women in the world [1]. Around 70-80 per cent of postmenopausal breast cancer patients are found to be estrogen-dependent breast cancer cases [2]. Endogenous estrogens affect the cellular roles of genes involved in cell division, protein expression, cell communication [3] and play a vital role in the development and growth of breast tumors [4]. Ovaries and placenta are the major sources of estrogen biosynthesis and to a lesser degree in testes, liver, adrenal glands, breasts and fat cells. Androgens are known to be precursors for the synthesis of Estrogens.

1.1. Aromatase

Estrogens are biosynthesized from their corresponding androgens by aromatase or estrogen synthetase (CYP19A1; EC 1.14.14.1) a rate-limiting enzyme [5]. It is a microsomal membrane-bound cytochrome p-450 monooxygenase complex comprising of aromatase cytochrome p-450 arom and NADPH-cytochrome p-450 reductase. Cytochrome p-450 arom is a heme protein that binds the steroid substrate, molecular oxygen and catalyses oxidation. The reductase is a flavoprotein, found ubiquitously in endoplasmic reticulum, and responsible for transferring reducing equivalents from NADPH to cytochrome p-450 arom [4, 6]. The gene CYP19 expresses cytochrome p-450 arom, and the gene is located on chromosome 15 in humans. The human CYP19 gene includes nine coding exons, 2-10. Tissue-specific regulation of the aromatase gene in various tissues is determined by tissue-specific promoters. In placenta, p-450 arom transcripts contain promoter 1.1 or 1.2. Ovarian transcripts comprise of promoter PII [7, 8]. Aromatase activity in human adipose and ovarian granulosa cells is associated to complex multifactorial regulation and changes in aromatase activity are correlated with changes in the levels of mRNA encoding p-450 arom [9].

Aromatase cytochrome P450 is the rate limiting enzyme that catalyzes androgens conversion to estrogens in vertebrates [10]. It is the hallmark androgenic specificity that is C19 steroids with 4-ene-3-one system that sets aromatase

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Certificate of Participation

This is to certify that

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a student of Pharmacy
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Located in Kim-Surat, Gujarat (hereinafter referred to as "Pharmacy College") which expression shall, unless it be repugnant to the context or meaning thereof, mean and include its successors-in-interest and permitted assigns, acting through its authorized representative,duly authorized to sign and execute this Agreement

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For the sake of brevity and convenience, the Pharmacy College, and **GREENKEM ORGANICS PRIVATE LTD** here in after be collectively referred to as the "**Parties**", and individually, as the "**Party**" as the context may require.

NOW THEREFORE, in consideration of the foregoing, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, accepted and agreed to, the Parties, intending to be legally bound, agree to the terms set forth below.