中央研究院
生物醫學科學研究所
Institute of Biomedical Sciences
Academia Sinica

128 Academia Road, Section 2,
Nan Kang, Taipei 115
Taiwan
TEL: 886-2-27899000
Fax: 886-2-27853569
886-2-27829710

October 1st, 2018
Dr. Vicky Jain
Department of Chemistry,
Marwadi University,
Gujarat, India

Dear Dr. Vicky Jain:

I am writing this letter to inform you that the Institute of Biomedical Sciences (IBMS), Academia Sinica, would like to offer you a Postdoctoral Research Fellow position to work in my laboratory.

Your main research work is to design and synthesis of 1,2-bis(hygroxymethyl)benzo[*g*]pyrrolo[2,1-*a*]phthalazine hybrids with dual function of anti-angiogensis and DNA cross-linking. Our preliminary results showed that these agents possess potent anticancer activity in in vitro and in vivo models. We have to synthesize a series of analogs for evaluating their antitumor activity. I am sure it will be an exciting research area for you to learn the research and development of new drug.

Your salary of the first year will be around $NT 58,350/month (about $US 1,900/month), 13.5 month payments per year. The health insurance and pension will be also included. However, the institute will not provide you apartment and air-ticket fee.

I hope this letter will help you to get a visiting visa to Taiwan.

Sincerely yours,

Te-Chang Lee, Ph.D.
Distinguished Research Fellow
Institute of Biomedical Sciences
Academia Sinica
Tel: +886-2-2652-3055
Fax: +886-2782-9142
e-mail: bmtcl@ibms.sinica.edu.tw

Marwadi University

Date: 30th October, 2018

To,
Visa Officer,
Taipei Economic and Cultural Center in India,
New Delhi

TO WHOMSOEVER IT MAY CONCERN

This is to certify that Dr. Vicky Jain is presently working as Head and Assistant Professor at Department of Chemistry, Marwadi University, Rajkot-Morbi Highway, Gauridad, Rajkot, Gujarat. He joined Marwadi University on 20th July, 2016.

Dr. Jain has been invited to Academia Sinica, Taipei, Taiwan as a Post-doctoral researcher for the period of 1 year.

He has been granted leave for the period from 28th November . The travel expense and the local expense will be covered by Ministry of Science and Technology, Taiwan.

The institute has no objection to these visits and any assistance offered to Dr. Vicky Jain will be appreciated. His passport details are as follows:

Passport No. **K7747563**
Date of Issue : 11-10-2012
Date of Expiry : 10-10-2022

After his visit he will be returning to the Marwadi University to fulfil his regular responsibilities.

We shall be grateful if the necessary visa is issued to Dr. Vicky Jain for this visit.

Thanking you,

Yours Faithfully,

MARWADI UNIVERSITY * RAJKOT *

Mr. Naresh Jadeja
Registrar, Marwadi University,
Rajkot – Morbi Highway, Gauridad,
Rajkot 360 003
Gujarat INDIA

一葉蘭
Taiwan pleione

中華民國
REPUBLIC OF CHINA (TAIWAN)

USED VISA

姓名/Surname, Given Name

JAIN, VICKY DEVENDRA

護照號碼/Passport Number	出生日期/Date of Birth	簽證類別/Visa Type	性別/Sex
K7747563	06 JAN 1989	RESIDENT	M
簽發日期/Issue Date	入境限期/EnterBefore	停留期限/Duration of Stay	
14 DEC 2018	** *** ****	***	
簽發地點/Issued At	入境次數/Entries	簽證號碼/Visa Number	
TAIPEI	SINGLE	107TPE007123	

註記/Remarks

TR/A-中央研究院生物醫學科學研究所聘僱
APPLY FOR ARC AT LOCAL SERVICE CENTER OF NATIONAL IMMIGRATION AGENCY WITHIN 15 DAYS

00118652C

VRTWNJAIN<<VICKY<DEVENDRA<<<<<<<<<<<<<<<<<<<<<

K7747563<3IND8901066M<<<<<<0107TPE007123<<<<

M. B. TRAVEL & TRADE LINKS

JAGNATH TEMPLE CHOWK,DR. YAGNIK ROAD,
RAJKOT - 360 001.
Tel : 0281 - 2467162 / 93773 90090
email : travel@mbintl.net
GSTIN : 24ABGPV6535N1Z1 ST:GJ

IATA APPROVED AGENT
Original for Recipient

T A X I N V O I C E

To : JAIN/VICKY MR [WI]

Invoice No : 1000124

Invoice Dt : 23/10/2018

Place of Supply : Gujarat

Refr. :
Page No. : 1

Airline : AIR INDIA - DOMESTIC

Passenger's Name	Ticket No.	Type	Class	Sector(s)	Flight Details	Basic	PSF	Taxes	Total
JAIN/VICKY MR	98 5777 990233	A	G	RAJ/BOM	AI0656 28/11/2018 OK	4,999	556		5,555
						4,999	556		5,555

Add 9% CGST (22.50) + 9% SGST (22.50) on Taxable Value 0 : 45

SAC 9985

Rupees Five Thousand Six Hundred Only

Total 5,600

For M. B. TRAVEL & TRADE LINKS

M. B. TRAVEL & TRADE LINKS RAJKOT

Terms Of Payment

CASH : Payment should be made directly to the cashier in our office. Company's printed official receipt duly signed by the cashier must always be obtained against payment made in cash or cheque as it will be considered as the only valid document for such payment.

CHEQUE : All cheques or demand drafts in payment of bills should be drawn in favour of M. B. TRAVEL & TRADE LINKS and should be crossed 'A/C PAYEE ONLY'.

OUTSTANDING : Interest @24% per annum will be charged on bills not paid within seven days.

RECEIPTS : Only our official receipt form duly signed by our cashier will be considered valid.

PAN NO. : ABGPV6535N

S.O.S. : Subject To RAJKOT Jurisdiction Only

M. B. TRAVEL & TRADE LINKS

JAGNATH TEMPLE CHOWK,DR. YAGNIK ROAD,
RAJKOT - 360 001.
Tel : 0281 - 2467162 / 93773 90090
email : travel@mbintl.net
GSTIN : 24ABGPV6535N1ZI ST:GJ

IATA APPROVED AGENT

TAX INVOICE

Original for Recipient

To : JAIN/VICKY MR [WI]

Invoice No : 1100109

Invoice Dt : 18/10/2018

Place of Supply : Gujarat

Refr. :
Page No. : 1

Airline : JET AIRWAYS : INTERNATIONAL

Passenger's Name	Ticket No.	Type	Class	Sector(s)	Flight Details	Basic	Taxes	Total
JAIN/VICKY MR	589 2948 762504	A	K	BOM/BKK TPE CI/HKG CI/BOM 9W	9W0062 29/11/2018 OK	24,699	6,824 13,230	44,753
						24,699	6,824 13,230	44,753

Add 9% CGST (123.50) + 9% SGST (123.50) on Taxable Value 0 : 247

SAC 9985

Rupees Forty Five Thousand Only

Total 45,000

For M. B. TRAVEL & TRADE LINKS

M. B. TRAVEL & TRADE LINKS RAJKOT

Terms Of Payment

CASH : Payment should be made directly to the cashier in our office. Company's printed Official receipt duly signed by the cashier must always be obtained against payment made in cash or cheque as it will be considered as the only valid document for such payment.

CHEQUE : All cheques or demand drafts in payment of bills should be drawn in favour of M. B. TRAVEL & TRADE LINKS and should be crossed 'A/C PAYEE ONLY'.

OUTSTANDING : Interest @24% per annum will be charged on bills not paid within seven days.

RECEIPTS : Only our official receipt form duly signed by our cashier will be considered valid.

M. B. TRAVEL & TRADE LINKS

JAGNATH TEMPLE CHOWK, DR. YAGNIK ROAD,
RAJKOT - 360 001.
Tel : 0281 - 2467162 / 93773 90090
email : travel@mbintl.net
GSTIN : 24ABGPV6535N1Z1 ST:GJ

IATA APPROVED AGENT
Original for Recipient

T A X I N V O I C E

To : JAIN/VICKY MR [WI]

Invoice No : 1250043

Invoice Dt : 03/11/2018

Place of Supply : Gujarat
Refr. : 20685
Page No. : 1

VISA CHARGES

Passengers Name	Particulars	Amount
JAIN/VICKY MR	TAIWAN VISA	6,153.00

Add 9.00% CGST (173.50) + 9.00% SGST (173.50): 347.00
SAC 9985

Rupees Six Thousand Five Hundred Only

Total 6,500

For M. B. TRAVEL & TRADE LINKS

TRAVEL & TRADE LINKS RAJKOT

Terms Of Payment

CASH : Payment should be made directly to the cashier in our office. Company's printed Official receipt duly signed by the cashier must always be obtained against payment made in cash or cheque as it will be considered as the only valid document for such payment.

CHEQUE : All cheques or demand drafts in payment of bills should be drawn in favour of M. B. TRAVEL & TRADE LINKS and should be crossed 'A/C PAYEE ONLY'.

OUTSTANDING : Interest @24% per annum will be charged on bills not paid within seven days.

RECEIPTS : Only our official receipt form duly signed by our cashier will be considered valid.

Service Tax Reg.-ABGPV6535NST001
PAN No. : ABGPV6535N

E.&O.E. Subject To RAJKOT Jurisdiction Only

Journal of Medicinal Chemistry

Article

Cite This: J. Med. Chem. 2019, 62, 2404−2418

pubs.acs.org/jmc

Design and Synthesis of 1,2-Bis(hydroxymethyl)pyrrolo[2,1-*a*]phthalazine Hybrids as Potent Anticancer Agents that Inhibit Angiogenesis and Induce DNA Interstrand Cross-links

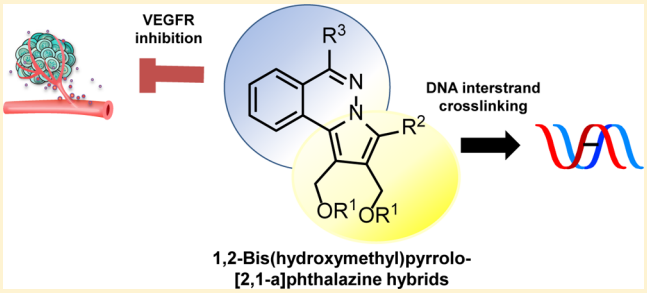
Sue-Ming Chang,[†,∥] Vicky Jain,[†,∥,⊥] Tai-Lin Chen,[†,∥] Anilkumar S. Patel,[†] Hima Bindu Pidugu,[†] Yi-Wen Lin,[†] Ming-Hsi Wu,[†,#] Jiao-Ren Huang,[‡] Han-Chung Wu,[‡] Anamik Shah,[§] Tsann-Long Su,*[,†] and Te-Chang Lee*[,†]

[†]Institute of Biomedical Sciences and [‡]Institute of Cellular and Organismic Biology, Academia Sinica, Taipei 11529, Taiwan

[§]Center of Excellence in Drug Discovery, Saurashtra University, Rajkot 360005, India

Supporting Information

ABSTRACT: Hybrid molecules are composed of two pharmacophores with different biological activities. Here, we conjugated phthalazine moieties (antiangiogenetic pharmacophore) and bis(hydroxymethyl)pyrrole moieties (DNA cross-linking agent) to form a series of bis(hydroxymethyl)pyrrolo-[2,1-*a*]phthalazine hybrids. These conjugates were cytotoxic to a variety of cancer cell lines by inducing DNA damage, arresting cell cycle progression at the G2/M phase, triggering apoptosis, and inhibiting vascular endothelial growth factor receptor 2 (VEGFR-2) in endothelial cells. Among them, compound **29d** encapsulated in a liposomal formulation (e.g., **29dL**) significantly suppressed the growth of small-cell lung cancer cell (H526) xenografts in mice. Based on immunohistochemical staining, the tumor xenografts in mice treated with **29dL** showed time-dependent decreases in the intensity of CD31, a marker of blood vessels, whereas the intensity of γ-H2AX, a marker of DNA damage, increased. The present data revealed that the conjugation of antiangiogenic and DNA-damaging agents can generate potential hybrid agents for cancer treatment.



INTRODUCTION

Antiangiogenic therapy (AAT) is a strategy for treating cancer involving starving cancer cells to death.[1] Bevacizumab, a monoclonal antibody that neutralizes vascular endothelial growth factor A (VEGF-A),[2] is an FDA-approved drug used for the treatment of metastatic solid tumors.[1] Several receptor tyrosine kinase inhibitors, which inhibit vascular endothelial growth factor receptors (VEGFRs), are also approved for cancer treatment as AAT agents.[1] Unfortunately, the rapid appearance of resistance to AAT agents causes treatment failure and even promotes aggressiveness.[3,4] However, AAT is still a relevant and promising strategy for fighting highly aggressive cancers.[5] Therefore, the development of novel AAT agents is desirable. Recently, a large number of small-molecule VEGFR inhibitors with diverse chemical scaffolds have been synthesized and evaluated for their therapeutic potential in oncology.[6] Some of these compounds, such as sunitinib and sorafenib, were approved for the treatment of selected cancers.[7,8]

Several phthalazine derivatives exhibited potent angiogenesis inhibition and anticancer activities.[9−13] Vatalanib (**1**) (Figure 1), an anilinophthalazine derivative,[9,14,15] can inhibit all VEGFRs, but it shows especially high selectivity for VEGFR-2, which is the principle endothelial VEGF signaling receptor and primary mediator for tumor angiogenesis.[16] This agent has been included in several clinical trials on the treatment of metastatic colorectal cancer, pancreatic adenocarcinoma, and relapsed lymphoma.[17−19] Substitution of the bioactive pharmacophores at positions 1 and 4 of the phthalazine core, such as with compounds **2** and **3** (Figure 1), provided derivatives with an improved inhibitory activity toward VEGFR-2 and cancer cells.[10−12,20,21] The conjugation of phthalazine and a triazole ring was an alternative approach for generating phthalazine-based VEGFR-2 inhibitors (**4**) with enhanced anticancer activity (Figure 1).[13] Moreover, phthalazine-based compound exerted diverse pharmacological activities, such as AMG900 (**5**), which acts as a potent inhibitor of aurora kinase, and phthalazino[1,2-*b*]quinazolinones (**6**), which is a p53 activator (Figure 1).[22−24] These studies revealed important information for phthalazine-based drug development.

Received: October 30, 2018
Published: February 18, 2019

DOI: 10.1021/acs.jmedchem.8b01689
J. Med. Chem. 2019, 62, 2404−2418

European Journal of Medicinal Chemistry 202 (2020) 112516

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Research paper

Design, synthesis and antitumour evaluation of pyrrolo[1,2-*f*]-phenanthridine and dibenzo[*f*,*h*]pyrrolo[1,2-*b*]isoquinoline derivatives

Anilkumar S. Patel [a, b, 1], Vicky Jain [a, c, 1], Vaikar Navakanth Rao [a, d], Yi-Wen Lin [a], Anamik Shah [e], Kuo-Chu Lai [f], Tsann-Long Su [a, **], Te-Chang Lee [a, *]

[a] Institute of Biomedical Sciences, Academia Sinica, Taipei, 115, Taiwan
[b] Department of Chemistry, Atmiya University, Rajkot, Gujarat, India
[c] Department of Chemistry, Marwadi University, Rajkot, Gujarat, India
[d] PhD Program in Pharmacology and Toxicology, School of Medicine, Tzu Chi University, Hualien, 970, Taiwan
[e] Gujarat Vidyapith (Deemed University), Ahmedabad, Gujarat, India
[f] Department of Pharmacology, Tzu Chi University, Hualien, 970, Taiwan

ARTICLE INFO

Article history:
Received 15 February 2020
Received in revised form
18 May 2020
Accepted 29 May 2020
Available online 23 June 2020

Keywords:
Antitumour agents
bis(hydroxymethyl)pyrrolo[1,2-*f*]
phenanthridine
Cell cycle
Cytotoxicity
DNA cross-Linking
Apoptosis

ABSTRACT

A series of 1,2-bis(hydroxymethyl)pyrrolo[1,2-*f*]phenanthridine derivatives and their alkyl (ethyl and isopropyl) carbamates and 12,13-bis(hydroxymethyl)-9,14-dihydro-dibenzo[*f*,*h*]pyrrolo[1,2-*b*]isoquinoline derivatives were synthesized for antiproliferative evaluation. The preliminary antitumour studies revealed that these two types of bis(hydroxymethyl) derivatives showed significant antitumour activities and were able to inhibit the growth of various human tumour cell lines *in vitro*. Several of the derivatives were demonstrated to cause DNA interstrand cross-links by an alkaline agarose gel shifting assay. These conjugates were cytotoxic to a variety of cancer cell lines by inducing DNA damage, delaying cell cycle progression in the G2/M phase and triggering apoptosis. Compound **21a**, dissolved in a vehicle suitable for intravenous administration, was selected for antitumour studies in animal models. We demonstrated that at a dose that did not cause body weight loss in mice, compound **21a** could significantly suppress the growth of tumour xenografts of human lung cancer H460 and colorectal cancer HCT-116 cells in nude mice. Our present results confirm the antitumour activities of these conjugates.

1. Introduction

Cancer is one of the major leading causes of death worldwide. The design of new antitumour agents is one of the most challenging tasks in the field of medicinal chemistry. Among anticancer agents, DNA alkylating agents have attracted attention and have been widely used as potential therapeutic agents for a long time. Notably, DNA-damaging therapeutic agents are widely used in combination therapy with targeted therapeutics as well as immunotherapeutics in clinical settings [1–4].

Naturally occurring mitomycin C (MMC, **1**, Fig. 1) is a clinically useful chemotherapeutic agent for treating various cancers [5]. Both MMC and synthetic indoloquinone EO9 (**2**) [6], which possess two reactive nucleophilic centres on its pyrrole, are capable of inducing DNA cross-linking via bioreductive activation [7]. Numerous pyrrolizine alkaloids [8–10] and their synthetic analogues bearing a bis(hydroxymethyl)pyrrolidine moiety, such as IPP (**3**) [11], are also capable of inducing DNA interstrand or intrastrand cross-linking (CL), giving them potent antitumour activities [12]. Numerous studies had shown that synthetic bis(hydroxymethyl or alkylcarbamate)pyrroles or pyrrolizines were able to generate an electrophilic centre on the pyrrole ring, and hence reacted with DNA to induce DNA interstrand cross-linking (ICL) via an electrophilic reaction (Fig. 2) [13,14]. Obviously, these agents do not require bioreductive activation to induce DNA CL.

To explore new bifunctional DNA alkylating agents, we previously synthesized 3*a*-azacyclopenta[*a*]indene derivatives (**4**) (wherein R^1 = H or CONH-alkyl; R^2 = alkyl or aryl), which contain a bis(hydroxymethyl)pyrrole alkylating pharmacophore and was viewed as a "benzologue" of IPP (**3**). Among these congeners, compound BO-1012 (**5**) exhibited significant *in vitro* cytotoxicity

* Corresponding author.
** Corresponding author.
E-mail addresses: tlsu@ibms.sinica.edu.tw (T.-L. Su), bmtcl@ibms.sinica.edu.tw (T.-C. Lee).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ejmech.2020.112516
0223-5234/

Journal of Medicinal Chemistry

pubs.acs.org/jmc

Article

Discovery of Oral Anticancer 1,2-Bis(hydroxymethyl)benzo[*g*]pyrrolo[2,1-*a*]phthalazine Hybrids That Inhibit Angiogenesis and Induce DNA Cross-Links

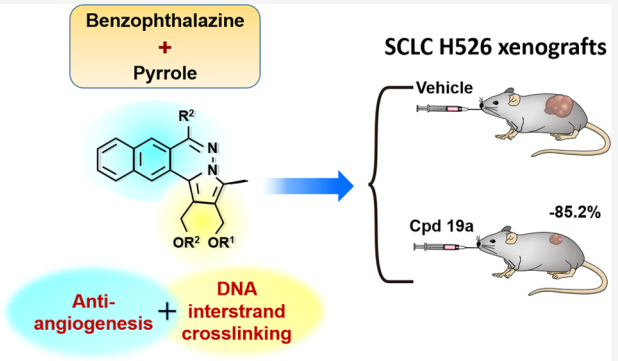
Tai-Lin Chen, Anilkumar S. Patel, Vicky Jain, Ramajayam Kuppusamy, Yi-Wen Lin, Ming-Hon Hou, Tsann-Long Su,* and Te-Chang Lee*

Cite This: *J. Med. Chem.* 2021, 64, 12469−12486

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Designing hybrid molecules with dual functions is one approach to improve the therapeutic efficacy of combination treatment. We have previously conjugated phthalazine and bis(hydroxymethyl)pyrrole pharmacophores to form hybrids bearing antiangiogenesis and DNA interstrand cross-linking activities. To improve the bioavailability, we adopted a benzology approach to design and synthesize a new series of 1,2-bis(hydroxymethyl)benzo[*g*]pyrrolo[2,1-*a*]phthalazines. These new hybrids retained the dual functions and could be formulated into vehicles for intravenous and oral administration. Among them, we demonstrated that compound **19a** with dimethylamine at the C6 position markedly suppressed the tumor growth of human small cell lung cancer cell line H526, squamous lung cancer cell line H520, and renal cancer cell line 786-O in nude mice, implying that compound **19a** is a broad-spectrum anticancer agent. Our results implicated that the conjugation of antiangiogenic and DNA cross-linking is likely to be a helpful approach to improving the efficacy of combination therapy.



INTRODUCTION

Designing hybrid molecules, which possess multiple modes of action in one molecule, is a promising strategy to discover new chemical entities with marked anticancer activity.[1,2] Since hybrid compounds are designed by conjugating two or more different bioactive moieties, they may possess certain advantages that are features of combination therapy, such as enhancement of efficacy by targeting different pathways in a characteristically synergistic or additive manner, reducing adverse effects, and overcoming drug resistance.[3,4]

Several reviews have reported that pharmacophores such as quinolone, triazole, and indoles are promising moieties for emerging novel hybrid molecules with potential for clinical application.[5−7] During the past several years, we focused on developing antitumor hybrid molecules by coupling a bis(hydroxymethyl)pyrrole moiety (**1**, Figure 1) with other active pharmacophores to generate potent anticancer agents with dual modes of action.[8−13] The scaffold of the bis(hydroxymethyl)pyrrole moiety contains two adjacent hydroxymethyl groups, in which the hydroxyl groups serve as leaving groups, leading to the formation of an electrophilic center at the N-atom of the pyrrole ring. The electrophilic center probably targets DNA and hence induces DNA interstrand cross-links (ICLs).[9,14] Among these hybrids, indolizino[6,7-*b*]indoles (**2**, Figure 1) comprising bis(hydroxylmethyl)pyrrole and *β*-carbolines (**3**, Topo I/II inhibiting moiety) have a broad spectrum of antitumor activity, and in particular, they potently suppressed the tumor growth of non-small-cell lung cancer (NSCLC).[11,12] Furthermore, compound **2a** was shown to have no cross-resistance to vinblastine and gefitinib. Compound **2a**, either alone or in combination with gefitinib (epidermal growth factor receptor (EGFR) inhibitor) or cisplatin (DNA cross-linker), was more potent than irinotecan or cisplatin in suppressing tumor growth in mice bearing NSCLC H460, PC9 (tyrosine kinase inhibitor (TKI)-sensitive NSCLC), and PC9/gef B4 (TKI-resistant NSCLC) xenografts.[11]

The phthalazine scaffold features a nitrogen-containing heterocycle that displays a variety of pharmacological activities.[15] A large number of biologically active compounds containing phthalazine as the pharmacophore have been reported in the literature.[15,16] Many of them were shown to inhibit vascular endothelial growth factor receptor-2 (VEGFR-2) and hence act as antiangiogenic agents.[17−19] More recently, we synthesized a new series of hybrids, namely, 1,2-

Received: October 2, 2020
Published: August 30, 2021