شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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التوثيق الإلكتروني والميكروفيلم

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HANAA ALY

كلية الصيدلة

كلية معتمدة

Molecular design and synthesis of small organic compounds based on optimization of selected scaffolds as targeted anticancer agents

Thesis

Presented by

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Msc. in Pharmaceutical Sciences

Ain Shams University

September 2014

Submitted for the partial fulfillment of the

PhD Degree

In Pharmaceutical Sciences (Pharmaceutical Chemistry)

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2021

Pre-requisite Predoctoral Courses and Exams

In addition, to the work presented in the thesis, the candidate has attended and passed the following Pre-requisite predoctoral courses:

- Pharmaceutical chemistry
- Drug design
- Stereochemistry
- Selected topics

Moreover, the candidate has passed a comprehensive exam in organic and Pharmaceutical chemistry and presented a research proposal with the title of “Molecular design and synthesis of novel acid ceramidase inhibitors as a challenging approach for treatment of melanoma”.

Acknowledgements

I am profoundly indebted to ***Professor Khaled Abouzid Mohamed Abouzid,*** *Professor of Pharmaceutical Chemistry, Ain shams university and dean of Faculty of Pharmacy, El sadat university, for suggesting the research point, scientific supervision, innovative ideas, fruitful opinion, invaluable advice, precious suggestions, continuous encouragement and untiring help. I am really sincerely and profoundly indebted to him for his priceless guidance, huge efforts and endless support during the whole work, and for following all the tiny details in every single step and also for making this thesis appear in its final form. He is a dedicated mentor and a role model.*

I owe my sincere appreciation and truthful gratitude to ***Professor Nahla Ahmed Hassan,*** *Professor of Pharmaceutical Chemistry, and head of Pharmaceutical Chemistry Department, MIU, for her continuous encouragement, tremendous support, endless motivation, and enthusiasm. I am heartily grateful to her indispensable opinion, real interest, trust, guidance, optimism, and positive energy throughout the whole work and especially in the practical part. She is a great mentor, role model and a very active professor indeed.*

I am truly thankful to ***Professor Rabah Ahmed Taha Serya****, Professor of Pharmaceutical Chemistry and head of Pharmaceutical Chemistry Department, Ainshams University, for her constant trust, precious guidance, continuous support, continuous encouragement, precious suggestions, and her help and kindness throughout the whole time.*

I owe my deepest appreciation to ***Dr Samar Ahmed Mowafy,*** *assistant professor of Pharmaceutical Chemistry, MIU, for her constant guidance, great effort, precious suggestions, continuous encouragement, and support, especially during writing the paper and thesis and making it appear in its final form. I would also like to thank her alot for bringing her whole experience to me and teaching me many concepts and for being such a great friend.*

I am very thankful for ***Dr. Eman el awady****, assistant professor of Pharmaceutical Chemistry, for her continuous friendly support, specifically in cooperating in sending my samples for biological testing and for giving me the opportunity to work with the hydrogenator at Ainshams university.*

Also, I would like to greatly thank ***Dr. Eman Zaghool,*** *assistant professor of pharmaceutical chemistry, for her friendly and amazing support, specially through bringing up her laboratory experience and advice.*

It is my great pleasure to thank all members of Pharmaceutical chemistry Department, Ain Shams University who supported me and helped me in my way and also I would like to thank all my colleagues in Misr International University who supported me and helped me in my way.

Dedication to my family,

I cannot forget to express my greatest appreciation and gratitude to my mother 'Mona Ali Hassan', father 'Mohamed Abdelatty', husband 'Ahmed Tarek Ghoneim', mother in law, and my siblings. Their continuous encouragement, full support, understanding, endless patience, continuous motivation, unconditional love, and their continuous prayers gave me the power and motivation to finish this work.

This work was published in **Journal of enzyme inhibition and medicinal chemistry** 2021, VOL. 36, NO. 1, 1290–1312.

https://doi.org/10.1080/14756366.2021.1933465

JOURNAL OF ENZYME INHIBITION AND MEDICINAL CHEMISTRY
2021, VOL. 36, NO. 1, 1290–1312
https://doi.org/10.1080/14756366.2021.1933465

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RESEARCH PAPER

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Molecular design, synthesis and *in vitro* biological evaluation of thienopyrimidine–hydroxamic acids as chimeric kinase HDAC inhibitors: a challenging approach to combat cancer

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ABSTRACT

A series of thieno[2,3-*d*]pyrimidine-based hydroxamic acid hybrids was designed and synthesised as multi-target anti-cancer agents, through incorporating the pharmacophore of EGFR, VEGFR2 into the inhibitory functionality of HDAC6. Three compounds **(12c, 15b and 20b)** were promising hits, whereas **(12c)** exhibited potent VEGFR2 inhibition (IC_{50}=185 nM), potent EGFR inhibition (IC_{50}=1.14 μM), and mild HDAC6 inhibition (23% inhibition). Moreover, compound **(15c)** was the most potent dual inhibitor among all the synthesised compounds, as it exhibited potent EGFR and VEGFR2 inhibition (IC_{50}=19 nM) and (IC_{50}=5.58 μM), respectively. While compounds **(20d)** and **(7c)** displayed nanomolar selective kinase inhibition with EGFR IC_{50}= 68 nM and VEGFR2 IC_{50}= 191 nM, respectively. All of the synthesised compounds were screened *in vitro* for their cytotoxic effect on 60 human NCI tumour cell lines. Additionally, molecular docking studies and ADMET studies were carried out to gain further insight into their binding mode and predict the pharmacokinetic properties of all the synthesised inhibitors.

ARTICLE HISTORY
Received 6 March 2021
Revised 13 May 2021
Accepted 14 May 2021

KEYWORDS
Thieno[2,3-d]pyrimidine; hydroxamic acid derivatives; chimeric HDAC-kinase inhibitors; multitarget therapy lead; ADMET study

Table of Contents

Table of contents

List of figures

List of tables

List of Abbreviations

A-loop: Activation loop

Anal.calc.: analytical calculations

Arg or R: Arginine

Asp: Aspartate

Asp-Phe-Gly: Aspartate-Phenyl alanine-Glycine

BCR-ABL: Breakpoint Cluster Region and Abelson proto-oncogene

BOC: tertiary butoxy carbonyl protecting group

BOP: benzotriazol-1-yloxy tris(dimethylamino) phosphonium hexafluorophosphate

BSA: Bovine serum albumin

BTK: Bruton's tyrosine kinase

c-FMS: Colony-stimulating factor-1 receptor

c-SRC: Cellular sarcoma (Schmidt-Ruppin A-2) viral oncogene

Cat.: Catalyst

CD: catalytic domain

CDI: Carbonyl diimidazole

C-Docker: CHARMm Docker

CHARMm: Chemistry at Harvard Macromolecular Mechanics

c-Kit: v-kit (Hardy-Zuckerman 4 feline) sarcoma viral oncogene

c-Myc: Cellular myelocytomosis gene

CNS: Central nervous system

CTLA-4: Cytotoxic T lymphocyte antigen-4

CYP2D6: Cytochrome P450 2D6

Cys or C: Cysteine

DCM: Dichloromethane

DCC: Dicyclo hexyl carbodiimide