



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكرو فيلم

# بسم الله الرحمن الرحيم



**HANAA ALY**



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التوثيق الإلكتروني والميكروفيلم



# شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



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# جامعة عين شمس

## التوثيق الإلكتروني والميكروفيلم

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تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



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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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## **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”.

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RESEARCH PAPER



## 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  $\mu$ M), 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  $\mu$ M), 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.

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therapy lead; ADMET study



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## 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