بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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كلية الصيدلة
كلية معتمدة

Design, synthesis and biological evaluation of some novel benzenesulfonamide derivatives as potential carbonic anhydrase inhibitors

Thesis
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(Pharmaceutical Chemistry)

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بسم الله الرحمن الرحيم
وعلمك ما لم تكن تعلم
وكان فضل الله عليك عظيما

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Novel benzenesulfonamides aryl and arylsulfone conjugates adopting tail/dual tail approaches: Synthesis, carbonic anhydrase inhibitory activity and molecular modeling studies

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ABSTRACT

New series of benzenesulfonamide and benzoic acid derivatives were designed and synthesized using tail/dual tail approach to improve potency and selectivity as carbonic anhydrase inhibitors. The synthesized compounds evaluated as CAIs against isoforms hCA I, II, IV and IX with acetazolamide (**AAZ**) as standard inhibitor. The benzenesulfonamide derivatives **7a-d**, **8a-h**, **12a-c**, **13a** and **15a-c** showed moderate to potent inhibitory activity with selectivity toward isoform hCA II, especially, compound **13a** with (K_i = 7.6 nM), while the benzoic acid analogues **12d-f**, **13b** and **15d-f** didn't show any activity except compounds **12d,f** and **15e** that showed weak activity. Additionally, molecular docking was performed for compounds **7a**, **8a**, **8e**, **12a**, **13a** and **15a** on isoform hCA I, II to illustrate the possible interaction with the active site to justify the inhibitory activity.

1. Introduction

Carbonic anhydrases (CAs, EC 4.2.1.1) are pervasive metalloenzymes present in prokaryotes and eukaryotes [1]. 16 α-CA isozymes were identified in mammals with various catalytic activity and subcellular localization [2]. Up till now, 15 different isoenzymes of hCAs have been detected. Among these, 12 isoenzymes are catalytically active with different cellular localizations (I-III,VII, and XIII are cytosolic; IV, IX, XII, and XIV are membrane-bounded; VA and VB are mitochondrial; and VI is secreted in milk and saliva), while the CARPs VIII, X, and XI are catalytically inactive [3,4]. The Zn^{2+} active site is essential for acid-base homeostasis¯ by enzymatically catalyzing the conversion of carbon dioxide to carbonic acid [5,6]. Human CAs are involved in a vast range of physiopathological processes, including electrolytes secretion, pH and CO_2 homeostasis, biosynthetic reactions, bone resorption and oncogenesis, as a result, carbonic anhydrase suppressors are used for management of glaucoma, edema, epilepsy, obesity and tumors [7–14].

Sulphanilamide is one of the most classical classes acting as CAIs [15,16]. During last few years, many approaches was adopted to synthetize potent and selective carbonic anhydrase inhibitors as tail/dual tail approaches[16–18]. In tail approach, sulphanilamide was conjugated with different moieties to increase the interaction with hydrophobic or hydrophilic parts of the active site[19,20]. Compounds **I–V** (Fig. 1) were designed as CAIs depending on the last approach[21–24]. While dual tail approach depended on

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Besides the work presented in this thesis, the candidate successfully passed general and special postgraduate courses in Pharmaceutical Chemistry for one year during academic year **2018/2019** with the general grade: **Excellent (GPA 3.86)**

the following grades:

1) Biostatistics	Excellent
2) Instrumental Analysis	Excellent
3) Bioinformatics	Excellent
4) Scientific Writing & Research Ethics	Very Good
5) Pharmaceutical Chemistry	Very Good
6) Structural Elucidation of Chemical Entities	Excellent
7) Comprehensive Organic Chemistry	Excellent
8) Stereochemistry	Excellent
9) Methods of Drug Screening	Excellent
10) Computer Aided Drug Design	Excellent

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List of abbreviations:

AAZ	Acetazolamide
ACC	Acetyl-coa carboxylase
CSF	Cerebrospinal fluid
BT	Bicarbonate transporters
CA	Carbonic anhydrase
hCA	Human carbonic anhydrase
CAIs	Carbonic anhydrase inhibitors
GLUT	Glucose transporter
ECD	Extracellular domain
HIF	Hypoxia inducible factor
IC	Intracellular
IOP	Intraocular pressure
PC	Pyruvate carboxylase
PG	Proteoglycan
RCC	Human renal cell carcinoma
TM	Transmembrane region
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
NHE	NA+/H+ exchanger
MCT	Monocarboxylate transporter
ZBG	Zinc-binding group
CARP	Carbonic anhydrase related protein
DMF-DMA	Dimethylformamide dimethylacetal
Ki	Inhibition constant
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
DMSO	Dimethyl sulfoxide
PABA	Para amino benzoic acid
IC50	50% Inhibitory concentration

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Abstract

Title of thesis

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