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"Molecular Modeling and Synthesis of Certain Fused Heterocyclic Compounds having Potential Anti-inflammatory Activity"

By

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List of Abbreviations:

AC: Adenylate cyclase

Anal.Calcd: Analytical Calculated

A°: Angstrom

BBB: Blood brain barrier

°C: Celsius

CNS: Central nervous system

COPD: Chronic obstructive pulmonary disease

CADD: Computer Aided Drug Design

cAMP: Cyclic adenosine monophosphate

cGMP: Cyclic guanosine monophosphate

COX: Cyclooxygenase enzyme

ELISA: Enzyme-linked immunosorbent assay

EU: European Union

FDA: Food and Drug administration

FT-IR: Fourier transform Infra-red

g: Gram

GI: Gastrointestinal

HD: Huntington's Disease

hr: Hour

HRP: Horseradish peroxidase

IKK-β: Inhibitor of nuclear factor kappa-B kinase subunit beta

LOX: Lipooxygenase enzyme

LPS: Lipopolysaccharide

MAPK: Mitogen-activated protein kinases

MS: Mass spectroscopy

m.p: Melting point

µM: Micromole

µL: Microliter

mg: Milligrams

mL: Milliliters

min: Minute

nM: Nanomole

NADPH: Nicotinamide adenine dinucleotide phosphate

NO: Nitric oxide

NSAIDS: Non-steroidal anti-inflammatory drugs

NF-kβ: Nuclear factor kappa-light-chain-enhancer of activated B cells

NMR: Nuclear magnetic resonance

PDE: Phosphodiesterase enzyme

PG: Prostaglandins

pdb: Protein data bank

RA: Rheumatoid arthritis

ROS: Reactive oxygen species

r.t.: Room temperature

SAR: Structure activity relationship

S.c.: Subcutaneous

TMB: 3,3',5,5'- tetramethylbenzidine

2D: 2-Dimensional

3D: 3-Dimensional

TNF-α: Tumor necrosis factor alpha

UV: Ultraviolet

UCR: Upstream conserved region

Abstract

Inflammation is a protective body response that develops to get rid of any harmful agent together with the body's immunity. Non-steroidal anti-inflammatory drugs (NSAIDS), the most commonly used non-selective anti-inflammatory agents; exhibit several side effects upon prolonged use especially in treatment of chronic inflammatory diseases. Side effects maybe minimized by the use of selective inhibitors other than non-selective anti-inflammatory agents. Among the most commonly known targets in inflammation cascade is the PDE4 enzyme. The PDEs family consists of 11 isoforms but in our research our target was the PDE4 isoform and in particular PDE4B subtype due to its critical role in inflammation. Well established drugs acting on such target exhibited serious side effects as nausea, vomiting and diarrhea. In this research, the aim was to design and synthesize novel compounds with potential anti-inflammatory activity especially PDE4B inhibitory activity with minimal side effects.

The thesis included six parts:

1-Introduction

It includes definition of inflammation, and different inflammatory mediators secreted in the body during inflammation, one of which is tumor necrosis factor alpha (TNF-α) which is one of the most important cytokine, followed by brief note about PDE family and different PDE subtypes. Then, the role of PDE4 isoform in inflammation is clarified and in particular PDE4B subtype and finally examples from literature for different PDE4 inhibitors especially those acting at PDE4B subtypes.

2-Rationale and design

It emphasizes the design of novel organic compounds for synthesis **IIIa-e**, **VIa-i**, **IXa-h** and **XVIa-e** having potential anti-inflammatory activity against PDE4B enzyme. The design was done by bioisosteric modifications in different potent lead compounds after

structure activity relationship (SAR) study aiming to increase the selectivity towards PDE4B inhibition and to decrease the undesired side effects.

3- Results and Discussions

This part contains the theoretical discussions for the obtained results and divided into two parts:

- **Chemistry**

It includes a discussion of the different chemical methods for preparing the starting material and intermediates stated in the literature and the used procedures in this research.

- **Biological evaluation**

Among the novel synthesized target compounds **IIIa-e**, **VIa-i**, **IXa-h** and **XVIa-e**, the titled compounds **IIIb-e**, **VIc-h**, **IXa,b,d-g**, **XVIc,d,e** were tested for their anti-inflammatory activity against standard anti-inflammatory drug (indomethacin) via *invivo* assays as rat paw edema model and measurement of level of decrease in TNF-α levels by sandwiched ELISA technique. The titled compounds **IIIe, VIe, VIg, VIh, IXa, IXb, IXe, IXg** and **XVId** were subjected to the *invitro* assay by screening of the target compounds over PDE4B enzyme and comparison of the inhibitory activity of the tested compounds to that of reference compounds used during the experiment.

4 -Molecular Modeling:

The design of novel potential anti-inflammatory agents as PDE4B inhibitors was based on the molecular modeling simulation by direct molecular modeling docking study using the crystal structure of PDE4B enzyme obtained from protein data bank *(pdb.org).* The practical steps were carried using Discovery Studio Software 2.5, GOLD protocol. The results of PDE4B inhibitory activity obtained in in the *invitro* assay were interpreted and further correlated with the biological activity data.