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

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Contents

List of Tables	VII
List of Figures.....	VIII
List of Abbreviations	XI
Abstract.....	XIII
1. Introduction.....	1
1.1. Inflammation	1
1.2. The neurotransmitters and enzymes involved in inflammation:	2
1.3. Therapy for inflammation.....	6
1.3.1. Non-selective anti-inflammatory agents such as steroids and NSAIDS	7
1.3.2. Disease modifying anti-rheumatic drugs (DMARDs).....	11
1.3.3. Tumor necrosis factor – alpha (TNF- α) inhibitors	12
1.3.4. Target specific therapies	12
1.3.5. Very selective treatments that may be targeted towards certain tissue	14
1.4. Phosphodiesterases	15
1.5. PDE4 isoform:	22
1.5.1. Function of PDE4.....	22
1.5.2. Structural basis of PDEs catalysis and inhibition:	22
1.5.3. Role of PDE4 inhibitors:	24
1.5.4. Localization of PDE4 isoform	24
1.5.5. Mechanism of action of PDE4 isoform.....	25
1.5.6. PDE4 inhibitors	26
1.5.6.1. Non selective PDE4 inhibitors	26
1.5.6.2. Selective PDE4 inhibitors	27
1.5.6.2.1. First generation chemically synthesized PDE4 inhibitors	27
1.5.6.2.2. Second generation chemically synthesized PDE4 inhibitors	28

2. Rationale and Design	34
2.1 Design of selective PDE4B inhibitors	34
2.1.1. Identification of the key interactions with the binding site:	35
2.1.2. Exploration of the previous revealed SAR studies and bioisosteric modifications of the lead compound	37
2.1.2.1. Design of new target compounds as selective PDE4B “quinazoline scaffolds”	37
2.1.2.2. Design of new target compounds with phthalamidobenzimidazole moeity	42
2.2. Synthetic schemes	44
2.2.1. Scheme 1 for synthesis of compounds IIIa-e	45
2.2.2. Scheme 2 for synthesis of target compounds Vla-i	46
2.2.3. Scheme 3 for synthesis of target compounds IXa-h	47
2.2.4. Scheme 4 for synthesis of target compounds XVla-e	48
3. Results and discussion	49
3.1. Chemistry	49
3.2. Biological evaluation:	61
3.2.1. Effect of Test Compounds on carrageenan-induced rat paw edema model	62
3.2.2. The measurement of the effect of tested compounds on TNF- α level in the inflammatory exudates in the carrageenan-induced rat edema model	64
3.2.3. Examination of the effect of the prepared compounds on the gut mucosa “Ulcerogenisity test”	67
3.2.4. The measurement of the <i>invitro</i> activity of the prepared compounds via measurement of the enzyme inhibition over PDE4B enzyme	69
3.2.4.1. Interpretation of the results	69
4. Molecular Modeling	72
4.1. Docking using Discovery Studio Software 2.5	72

4.2. Molecular Modeling Simulation Study	73
4.3. Results and Interpretation	76
4.4. Molecular docking conclusion.....	91
Conclusion	92
5. Experimental	94
5.1 Chemistry	94
5.1.1 Materials & instrumentation	94
5.1.2. Synthesis.....	95
5.2. Biological evaluation.....	115
5.2.1. Chemicals	115
5.2.2. Animals	115
5.2.3. Measurement of paw volume in carrageenan-induced rat edema model.....	115
5.2.4. Statistical analysis	116
5.2.5. Determination of Rat TNF alpha concentration in the inflammatory exudates	116
5.2.5.1. Principle	116
5.2.5.2. Reagent preparation	117
5.2.5.3. Sample preparation.....	119
5.2.5.4. Procedure.....	119
5.2.6. Induction of gastric ulcer:	121
5.2.7. Measurement of the enzyme inhibition by the prepared compounds	121
5.2.7.1. Methodolgy	121
5.2.7.2 Materials and conditions of the assay	122
5.3. Molecular modeling.....	123
5.3.1. Loading the PDE4B enzyme from protein data bank (Pdb)	123
5.3.2. Preparation of the enzyme.....	123

5.3.3. Identifying the binding pocket	124
5.3.4. Display lead- protein interactions	124
5.3.5. Docking of lead compound	124
5.3.6. Displaying the docking scores	124
5.3.7. Validation of the lead compound docking and selection of proper binding pose	124
5.3.8. Docking of the test set.....	125
5.3.8.1.Loading the test-set molecules	125
5.3.8.2. Interactive docking	125
5.3.8.3. Displaying the docking scores	125
5.3.9. Displaying the binding pattern of tested compounds.....	126
 6. References.....	 127

List of Tables

Table 1 : Different sub-types of PDEs and their clinical significance.....	16
Table 2 : Residues lining the active site of PDE4B & PDE4D isoforms	35
Table 3: The essential aminoacids residues to be interacted for inhibiton.	36
Table 4: The effect of tested compounds on rat paw volume in carrageenan-induced rat edema model	63
Table 5: The effect of tested compounds on TNF- α level in the inflammatory exudates in carrageenan-induced rat edema model	65
Table 6: Ulcer scores obtained from synthesized target compounds IIIe , VIe , IXb and XVIId in comparison to indomethacin as a reference compound.....	67
Table 7: The effect of synthesized target compounds IIIe , VIe , VIg , VIIh , IXa , IXb , IXe and IXg on PDE4B <i>invitro</i> activity at 10 μ M.....	70
Table 8: The effect of IXb , IXe and IXg tested compounds on PDE4B <i>invitro</i> activity at 50 μ M	70
Table 9: The results of screened compound XVIId at concentration of 50 μ M over PDE4B enzyme	71
Table 10: The Goldscore.Fitness & 2D-diagram of each target compound inside the binding site of PDE4B using GOLD.....	77
Table 11: The best target compounds according to GoldFitness Score and biological evaluation tests	93
Table 12: Reagents preparation for (TNF- α) kits for rats provided by RayBio®	117
Table 13: Assay conditions for screening compounds over PDE4B enzyme.....	122

List of Figures

Figure 1: Inflammation process after injury	1
Figure 2: A sketch diagram showing causes of inflammation and different inflammatory diseases and disorders	3
Figure 3: Sites of release of chemical mediators and neurotransmitters during inflammation	4
Figure 4 : Regulatory effects of cAMP on the release of different inflammatory mediators	6
Figure 5: The role of NSAIDs in inhibition of inflammation.....	11
Figure 6: Different chronic inflammatory diseases use anti-TNF alpha marketed drugs in treatment.....	12
Figure 7: Targets for selective inhibitors during inflammation.....	13
Figure 8: Map for PDE4 different isoforms.....	23
Figure 9: Structures of the different PDE families constituting the PDE superfamily.....	24
Figure 10: The role of PDE4 in different cell types during inflammation	25
Figure 11: PDE4 inhibitor effect on inflammation in COPD	26
Figure 12: (A) Cilomilast (36) co-crystallized with PDE4B active site , (B) Cilomilast (36) co-crystallized at PDE4D active site	36
Figure 13: The binding site of PDE4B together with compound 43 obtained from (pdb.org) showing the essential interactions with key amino acids in the binding site	38

Figure 14: Binding mode of quinoline based compound 41 after docking at PDE4B binding site showing hydrogen bonding of trifluoromethyl moiety with Gln443	38
Figure 15: 2D interaction diagram of docked quinazoline based reference compound 46 showing interaction with essential amino acid residues at the active site of PDE4B enzyme	39
Figure 16: Design of proposed target compounds IIIa-e (scheme 1) based on molecular modifications of reference compound 46	41
Figure 17: Design of proposed target compounds VIa-i (scheme 2) and compounds IXa-h (scheme 3) based on hybridization between reference compounds 41 and 43	42
Figure 18: The design of proposed target compounds XVIa-e (scheme 4) based on structure similarity with apremilast (35) and ibudilast (37) for PDE4B inhibitory activity	43
Figure 19: Synthetic approaches for 4-quinazolinone preparation via Pathway A and Pathway B	50
Figure 20: Synthetic approach for preparation of 4-substituted quinazoline starting from 2-amino benzonitrile derivatives (Pathway C) and steps of 4-anilinoquinazoline synthesis from anthranilic acid derivatives (Pathway D)	51
Figure 21: Formation of benzimidazole from o-phenylenediamine and formic acid	57
Figure 22: Formation of 2-H benzimidazole from 2-nitro amines	58
Figure 23: Mechanism of benzimidazole derivatives formation from orthophenylenediamine and aryl aldehydes	58
Figure 24: The effect of tested compounds on TNF- α level in the inflammatory exudates in carrageenan-induced edema model	66

Figure 25: Histological section showing stomach mucosa in different animal groups using digital video camera mounted at light microscope (A-F)	68
Figure 26 : Alignment of the lead compound 43 co-crystallized with the X-ray structure before (orange) and after (blue) docking at PDE4B active site (Code: 3GWT).....	73
Figure 27: (A): Alignment of the lead compound 43 co-crystallized with the X-ray structure before (orange) and after (blue) docking at PDE4B active site with 3D representation, (B): 2D diagram showing the binding of lead compound 43 with amino acids at the active site of PDE4B after docking using GOLD.....	75
Figure 28: The binding site of PDE4B together with rolipram (18) showing the essential interactions with key amino acids in the binding site	76
Figure 29: 3D diagram of compound IXb at PDE4B active site showing interaction of different groups with essential amino acids for inhibitory activity.....	89
Figure 30: 3D diagram of compound IXa at PDE4B active site showing interaction of different groups with essential amino acids for inhibitory activity.....	89
Figure 31: 3D diagram of compound IXe at PDE4B active site showing interaction of different groups with essential amino acids for inhibitory activity.....	90
Figure 32: 3D diagram of compound IXg at PDE4B active site showing interaction of different groups with essential amino acids for inhibitory activity.....	91
Figure 33: A schematic diagram for determination of TNF alpha by enzyme linked immune-sorbent assay (ELISA).....	117
Figure 34: Serial dilutions preparation for standard during reagent preparation in the ELISA assay.....	119
Figure 35: Standard calibration curve of TNF alpha at 450nm	120

List of Abbreviations:

AC: Adenylate cyclase

Anal.Calcd: Analytical Calculated

Å : 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

List of Abbreviations

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-κβ: 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 **XVIId** 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.