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HASIL PENILAIAN SEJAWAT SEBIDANG ATAU PEER REVIEW
KARYA ILMIAH : JURNAL ILMIAH

Judul Artikel Ilmiah : Insufficient Implementation of Tuberculosis Screening and Prophylaxis in Child Contacts: a Situational Analysis

Penulis Artikel Ilmiah : J KROTZEK-SEAH, AB HIMAWAN, A RONDAGS, JF METSEMAKERS, TRI NUR KRISTINA

Status Pengusul : Penulis pertama/**penulis anggota/ penulis korespondensi**

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Nilai Total = (100%)	30	22,00
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KOMENTAR/ULASAN PEER REVIEW

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Ruang Lingkup dan Kedalaman Pembahasan	: Pembahasan dilakukan berdasarkan temuan yang menarik, dan merujuk paper-paper sebelumnya yang related.
Kecukupan & Kemutakhiran Data & Metodologi	: Merupakan crosssectional study dengan responden adalah penderita TB sebanyak 75 penderita menggunakan metode: qualitative dan quantitative yang dijelaskan secara derail dalam metode. Ethical consideration: lengkap
Kelengkapan Unsur dan Kualitas Penerbit	: PJMHS is scopus indexed journal Q4. Published quarterly by Medical and Dental College, Lahore, Pakistan. Manuscript submission melalui electronic email nayyar_salam@yahoo.com (bukan Editor in Chief: Khaled Javed Abid/Asadullah Malik). Partners majority conference dari negara-negara Asia. Terdapat ketidak sesuaian dengan journal bereputasi, dari cara submission dan journal ini di manage bukan oleh Editor in Chief. Dalam sekali terbitan, diterbitkan >500 paper.

Semarang, 3-8-2020
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3D QSAR Studies of 2-Arylpyrimidines and S-Triazines as Selective PDE4B Inhibitors

ANAND GAURAV, DHARMENDRA KUMAR

ABSTRACT

Background: Phosphodiesterase 4B (PDE4B) has emerged as important target for design of anti-inflammatory drugs for respiratory tract. Several selective PDE4B inhibitors are under various stages of development, among them 2-arylpyrimidines and s-triazines have been identified as inhibitors with high degree of selectivity for PDE4B. However, the structural features responsible for the PDE4B selectivity of these molecules have not been identified and explored so far.

Method: 3D QSAR studies were performed for the series of 2-arylpyrimidines and s-triazines using Accelrys Discovery Studio 3.5. The IC_{50} values were transformed to PDE4B selectivity by taking the ratio of IC_{50} values i.e. $PDE4D(IC_{50})/PDE4B(IC_{50})$ for all the molecules in the series, and used as the dependent variable. The dataset was divided into training and test set of 45 and 10 compounds respectively and 3D QSAR was performed using the default parameters. Test set prediction and Fischer statistic was used for validation of the developed model.

Results: Statistically robust and predictive 3D QSAR models with high r^2_{cv} value of 0.9794 were obtained. The contour maps revealed the sterically and electronically favourable and unfavourable regions around the 2-arylpyrimidines and s-triazines scaffolds.

Conclusion: 3D QSAR model for 2-arylpyrimidines and s-triazines as selective PDE4B inhibitors were developed and validated. The models were highly predictive and provided vital structural information for the design of newer and more selective PDE4B inhibitors having the 2-arylpyrimidine and s-triazines scaffold. The results of the present study will be followed up by the design, synthesis and experimental evaluation of newer selective PDE4B inhibitors.

Keywords: Cyclic Nucleotide Phosphodiesterases, Type 4B; 3D Quantitative Structure-Activity Relationship; Fischer statistic; 2-arylpyrimidines; s-triazines

INTRODUCTION

Prevalence of Inflammatory diseases of respiratory tract i.e., asthma and COPD has increased in recent years, with more than 200 million people affected by it worldwide. Most of the mortality related to these inflammatory disorders occurs in low- and low middle income countries¹.

Phosphodiesterase 4 (PDE4) is a major family of enzymes that selectively hydrolyze 3',5'-cyclic adenosine monophosphate (cAMP) and are involved in regulating the release of anti-inflammatory and pro-inflammatory cytokines within cells^{2,3,4}. Even though PDE4s are widely expressed in immune and inflammatory cells, levels of different PDE4 subtypes (PDE4A, PDE4B, PDE4C and PDE4D) vary in a specific cell. PDE4B is abundant in monocytes and neutrophils, while PDE4A is expressed to very low levels and PDE4C is absent in inflammatory cells^{5,6,7,8,9}. This makes PDE4B an interesting and

promising targets for anti-inflammatory drugs meant to be used in respiratory inflammatory diseases such as asthma and chronic obstructive pulmonary disease (COPD). Inhibition of PDE4 has been shown to suppress a diverse spectrum of inflammatory responses *in vitro* and *in vivo*.¹⁰⁻¹³ More importantly, many PDE4 inhibitors in development are efficacious in animal models of various inflammatory disorders, such as asthma, COPD, psoriasis, inflammatory bowel diseases, and rheumatoid arthritis^{11,14,15}, as well as in clinical trials for asthma and COPD^{16,17,18}. However the development of PDE4 inhibitors has been slowed down due to narrow therapeutic window of most of the compounds. A major reason for their poor clinical results is the consequence of dosing limitation caused by side effects such as nausea and emesis.¹⁹ Recent findings in PDE4 knockout mice suggest that an inhibitor with PDE4B selectivity should retain many beneficial anti-inflammatory effects without the unwanted side effects^{20,21}.

The highly conserved catalytic domain of PDE4 isozymes makes the generation of inhibitors with PDE4 subtype selectivity a challenging task. However, residues in regulatory domain such as control region 3 (CR3) vary among subfamilies, which has proved to be responsible for PDE4B selectivity.²²

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The Prostatic Inflammation Effect on Clinical Examination of patients Whom Undergone Prostate Transurethral Resection (TURP) due to benign Prostatic Hyperplasia

SULTAN MOHAMMAD TAREEN¹, ABDUL SABOOR SOOMRO², MUHAMMAD MEHRAIZ KHAN³

ABSTRACT

Aim: To examine asymptomatic inflammatory prostatitis affects on patients clinical consequences experiencing transurethral resection of the prostate because of prostatic hyperplasia (BPH).

Method: This retrospective study was carried out during 1st July 2016 to 31st December 2017 at Bolan Medical Complex Hospital, Quetta and included 950 patients during this period. Before and one year after surgery, pathological results and clinical parameters were compared. The patients with lower urinary tract due to benign prostatic hyperplasia admit to urology clinic, over the fifty years of age, without past urologic surgery was included in this study. The patients having +ve urine results, chronic pelvic pain symptoms resulted in accordance with NIH rating, bladder stone, neurological disease, prostate cancer and urethral stenosis were excluded.

Results: Six hundred and five patients were identified with only benign prostatic hyperplasia and remaining 345 patients were identified with both benign prostatic hyperplasia (BPH) and prostatic inflammation (category-IV). Between two groups there was found no statistical significance among limitation/variables comprising prostate volume, post evacuate remnant (p value = >0.05) and age. Prostate inflammation's patients presenting lower Qmax values and higher pre-operative prostate score as compared to patients had not found inflammation before prostate transurethral resection.

Conclusion: In benign prostatic hyperplasia patients, prostate inflammation with no symptoms can cause to deteriorate lower urinary tract symptoms and rate of urinary flow

Keywords: Prostatic Inflammation, Prostate Pathology, Benign Prostatic Hyperplasia (BPH),

INTRODUCTION

Hyperplasia in glands and stroma is explained as benign prostatic hyperplasia (BPH), and it is mostly found in male population having age above than fifty years.¹ BPH is distinguished by lower urinary tract symptoms (LUTS). Lower urinary tract symptoms resulted due to numerous disorders but the major reason found is benign prostatic enlargement and about fifty percent of male population having ages >50 years, believe to experience lower urinary tract symptoms²⁻⁴.

Benign prostatic hyperplasia/lower urinary tract symptoms are probably causes to heavy load on health care systems, this condition pathogenesis are still unknown largely. There are several factors probably involved in development as well as prostate enlargement progression. There are many studies histopathological and epidemiological have indicate the role of prostate inflammation in benign prostatic hyperplasia and lower urinary tract symptoms pathogenesis.⁵ Prostate inflammation histological evidences examined in patients having benign prostatic hyperplasia which did not have prostatitis symptoms. Without symptoms prostate is confirmed in NIH (national institute of health) prostatitis grouping, type-IV, and has been noticed in forty three% to 98% of surgically extracted prostatic tissues detached for benign prostatic hyperplasia.⁶ Nickel et al⁷ proposed a standard classification system of chronic pelvic pain

syndrome and chronic prostatitis can be used in prostate biopsies for examination of prostatic inflammation, prostatectomy specimens or transurethral extracted prostatic tissues. The objective of current research was to emulate the prostatic inflammation effect on clinical parameters of outcomes of patients who undergo prostate TURP because of benign prostatic hyperplasia.

MATERIAL AND METHODS

The patients were examined who undergo transurethral resection of prostate due to benign prostatic hyperplasia retrospectively during the period from 1st July 2016 to 31st December 2017 at Bolan Medical Complex Hospital, Quetta. A total 950 patients along with histopathological results and clinical information were included in the study after scanning data of patients. Lower urinary tract patients due to benign prostatic hyperplasia admit to urology clinic, over the fifty years of age, without past urologic surgery were included in this study and those patients were excluded from study whose urine culture was positive, chronic pelvic pain syndrome diagnosed in accordance with National Institute of Health classifications group/type-III), bladder stone, neurological disease, prostate cancer. According to these criteria after screening medical data, 605 patients defined as benign prostatic hyperplasia. Among these patients, 161(16.95%) patients undergo catheterization because of severe urinary retention, and 345(36.36%) patients had prostatic inflammation (prostatitis category-IV). With the help of digital rectal examination transrectal guided ultrasound and micturition symptoms the benign prostatic hyperplasia was diagnosed. Before transurethral resection all patients received at least three months alpha blocker therapy except those patients with

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