2012-13

Rajnibhai V. Patel
PharmInnova Award
Best M. Pharm Thesis

RUNNER-UP

Runner-Up

Ms. Silpa P. Sankar

Research Guide

Mrs. CICI Mathew

Subject:
Pharmaceutical Chemistry

Thesis Title :
In-silico design, synthesis & Pharmacological screening of 1,3-Benz-oxazole-5-carbo Hydrazide derivatives

College:
College of Pharmaceutical Science, Medical College, Thiruvananthapuram

Chemical synthesis of new Benzoxazole derivatives as probable treatment for Tuberculosis and Inflammation

Outcome of Research

A chemical moiety called Benzoxazole is reported to have various biological properties like antibacterial, antifungal, anticancer, anti-inflammatory activities, etc. This study was conducted to enhance these biological properties by synthesizing various derivatives of Benzoxazole, using affordable and less toxic methods. Biological properties of various derivatives were compared with that of the standard drugs like gentamicin, clotrimazole, etc. Noticeable results were obtained with 1,3 benzoxasole-5 carbohydrazide derivatives, which are recommended as an economic option with enhanced anti-cancer (colon-cancer and breast cancer), anti-inflammatory and anti-tubercular properties.

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ABSTRACT

Benzoxazole produces versatile activities when attachment (aromatic/hetrocyclic ring etc.) with suitable linkage comes at 5th position. Hence we planned to attach aromatic aldehyde with free groups to benzoxazole ring at 5th position with –NH-N= linkage which results in Shiff's base formation.

1,3 benzoxazole -5-carbohydrazide derivatives with different aldehydes with free groups (–OH, -OCH3,-NO2,-Cl) on –NH=N- linkage at the 5th position scaffold inhibits HSP-90 protein; results in cytosolic vacuolization. And di- and tri-valent metal ions particularly Mg2+ ions helps benzoxazole derivatives to form complexes with double stranded DNA. These are reasons for anti-cancer property of benzoxazole derivatives. Studies are there about capability of benzoxazole derivatives to inhibit enzyme mycobacterium tuberculosis Enoyl-ACP reductase (Inh A, Rv1484); which prevents mycolic acid production; results in anti-tuberculosis property. With specific groups and Shiff's base on the 5th position enhances the enzymatic activity in both anti-tubercular and anti-inflammatory activity screening

Thesis was conducted in following stages

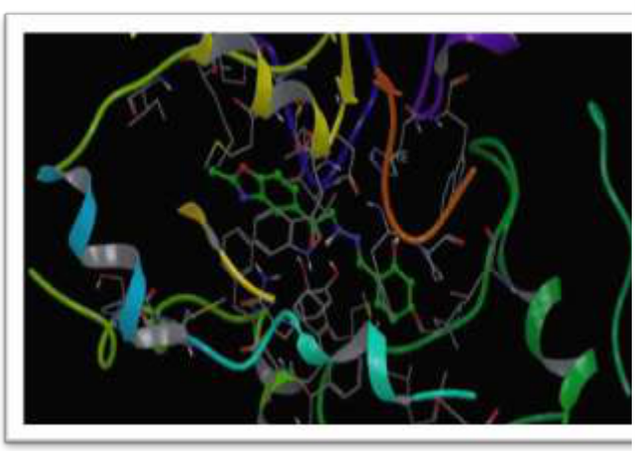
- In-silico design
  - Modelled 28 analogues
  - Evaluated molecular descriptors, drug-likeness, ADME prediction
  - Docked with specific receptors, analysed receptor-ligand complex, identified amino-acids
- Synthesise
  - Analogues were selected based on docking score, Lipinki's rule of five, PASS value>0.5.
    (Avoided unnecessary synthesis)
  - Prepared scheme and synthesised derivatives
  - Confirmed structure using spectral analysis
- Biological evaluation
  - From twelve synthesised analogues eight were selected based on best structural similarities with known biological active compounds
  - Following biological evaluations were done

Test	Methods
Acute-toxicity	Fix-dose method (OECD guideline-423)
Cytotoxicity	MTT-Assay
Anti-tubercular	Alamar blue-assay (REMA)
Anti-inflammatory	Carrageenan Induced Rat Paw Oedema
Anti-microbial	Agar diffusion Cup-Plate
Anthelmintic	One-way ANOVA followed by Dunnett's test.

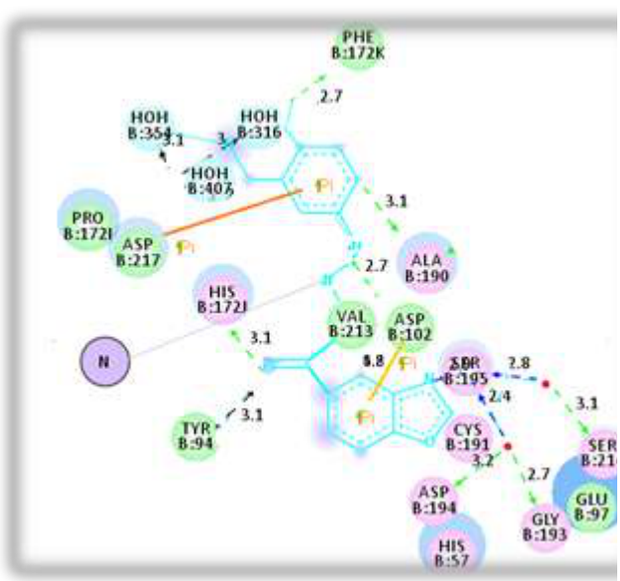
- Results were compared with standard drugs.

- QSAR analysis
  - Correlated biological activities with molecular descriptors
  - Established mathematical equation (Multiple regression analysis).

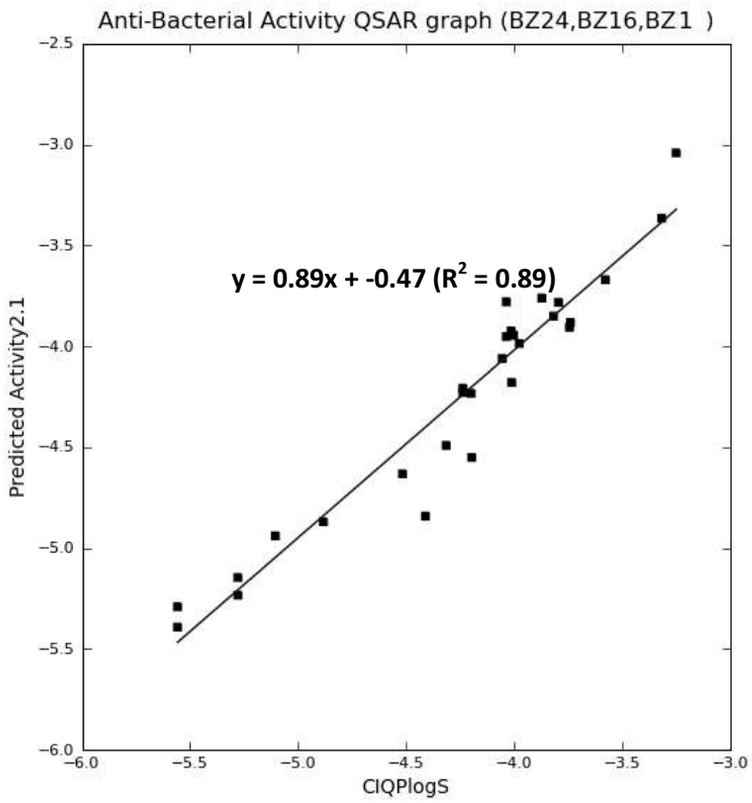
To sum up, 1,3-benzoxazole-5-carbohydrazide derivative with aldehyde at 5th position having functional groups at 3rdand 4thposition are more biologically active.



Docking:BZ24-3Q3S



Receptor-Ligand complex



Advanced studies in this work and encouraging results in the anti-cancer study reveals a fine tuned benzoxazole derivative can be a drug for specific cancer. It also has anti-inflammatory activity which helps to prevent inflammation caused by the cancerous cell especially in colon cancer. Different studies reveal that colon cancer produced large amount of prostaglandins, this can be regulated by benzoxazole derivatives. Since production method used in thesis study is cheap, a further research for finer tuning may give cheaper and effective targeted drug therapy for cancer.