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Synthesis And Biological Evaluation Of Novel Azetidine Derivative

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Abstract:
We have synthesized of (3-(5-bromopyridin-2-yl) azetidin-3-yl) methanamine. The structure of the newly synthesized compound was confirmed by IR, 1H NMR, and Mass and chemical methods. The synthesized compound was evaluated for their antibacterial and antifungal activity which displayed acceptable results.

Key words: *Synthesis; 1-N-Boc-3-Cyano-azetidine biological activity*

1.Introduction

For many years, Four-membered nitrogen hetereocycles such as β-lactams (i.e. 2-azetidinones) and azetidines are useful substrates in organic chemistry for the design and preparation of biologically active compounds by the adequate functionalization in the different positions of the ring.

In addition, they are also versatile building blocks for the synthesis of other types of nitrogen-containing compounds with potential biological properties. β-lactams (i.e. 2-azetidinones) and azetidines have caught the attention of organic chemists and medical researchers. The azetidines are four-membered nitrogen heterocycles of great interest for fundamental research and useful for practical applications. On the other hand, the azetidine ring is present in natural products of interest. Medium-sized nitrogen-heterocycles are found in natural products with biological activity, however their preparation present some difficulties.

The enhanced prevalence of infectious diseases and the rapid emergence of multi-drug resistant strains has become a major concern in medicine worldwide and, therefore, the development of new potential drugs is one of the key issues and challenges for medicinal chemistry and related disciplines nowadays. Furthermore, the search for alternative drugs and pesticides with improved properties such as higher selectivity and lower toxicity has always been an important incentive for the synthesis of new organic compounds with potential biological activity.

The emergence and spread of antimicrobial resistance have become one of the most serious public health concerns across the world. Antimicrobial resistance refers to micro-organism that have developed the ability to inactivate, exclude or block the inhibitory or lethal mechanism of the antimicrobial agents [1]

Literature survey reveals scant mention of the above compounds with antimicrobial properties and hence more and more derivatives are worth tested for the possible medicinal applications.

The important and structural diversity of biologically active β-lactam antibiotics led to the development of many novel methods for the construction of appropriately substituted azetidine with attendant control of functional group and stereochemistry. Azetidine derivatives are reported to show a variety of antimicrobial [2-4], antitubercular [5], anticonvulsant [6], anti-inflammatory [8] and cardiovascular Activities [9].

Recently, Carreira and co-workers have designed novel azetidine-based azaspirocyclic frameworks as surrogates for piperazines, piperidines, morpholines and thiomorpholines with physicochemical and biochemical properties of potential druglike structures [10].

The challenge of synthesizing azetidine compounds has been attempted with some success by various other groups. [11-14] The synthesized in this series have been screened for anti-bacterial and anti-fungal activities.

These all activities showed that the minor change in the substitution pattern activities of azetidine derivatives has enhanced dramatically so our research group decide to synthesize a new azetidine derivative with several substitutions.

Syntheses of Azetidines and Azetidin-2-ones

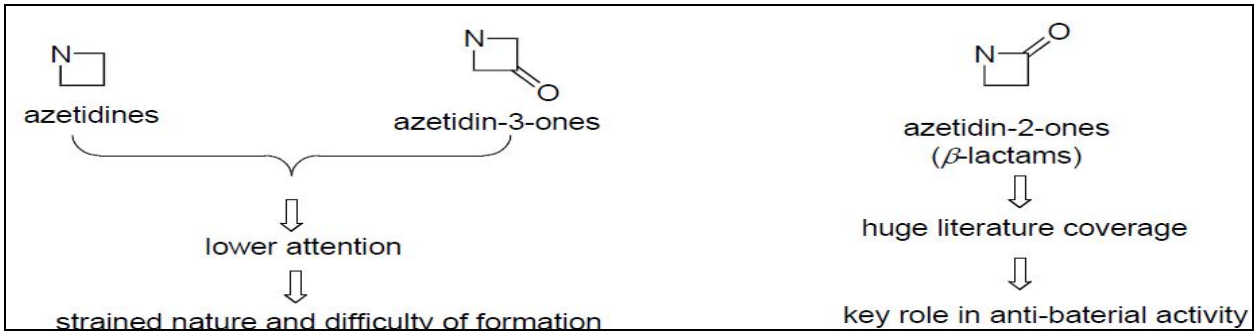

Figure 1

2.Experimental Section

Synthesis of (3-(5-bromopyridin-2-yl) azetidin-3-yl) methanamine

Step 1

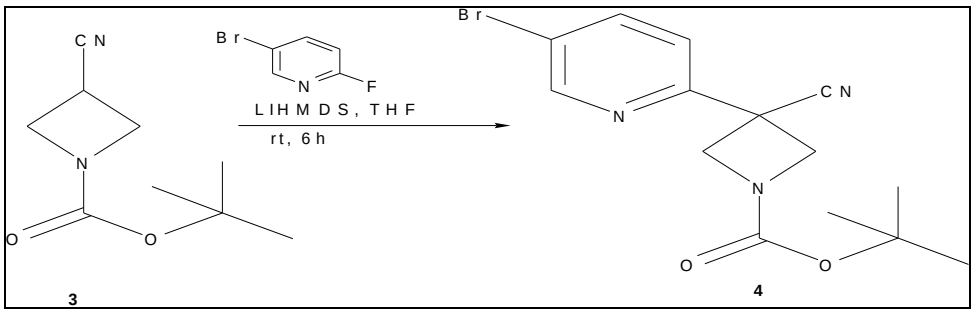

Figure 2

To a stirred solution of 1-N-Boc-3-Cyano-azetidine compound 3 (1.0 g, 5.49 mmol) in THF (40 ml) along with 2-Fluoro-5-Bromo-pyridine (1.05 g, 6.04 mmol) was added LiHMDS (11.0 ml, 10.98 mmol) at rate drop wise. stirred the reaction at RT for 1h.

After completion of the reaction by TLC, reaction mass was quenched into cold saturated ammonium chloride solution (10mL) and extracted with ethyl acetate (3x25 ml) trice. Combined organics was washed with brine , dried over sodium sulphate filtered and concentrated in vacuo to get crude, which was recrystalised in per-ether to get Compound 4 (3-(5-bromopyridin-2-yl)azetidine nitrile -white solid.(500 mg)

1H NMR (CDCl3, δ ppm: 1.56(9H, s), 4.50(4H, m), 7.45(1H,s), 7.91(1H,d), 8.79(1H, s)

LCMS purity: 84%, m/z, M+H, 338

Step 2

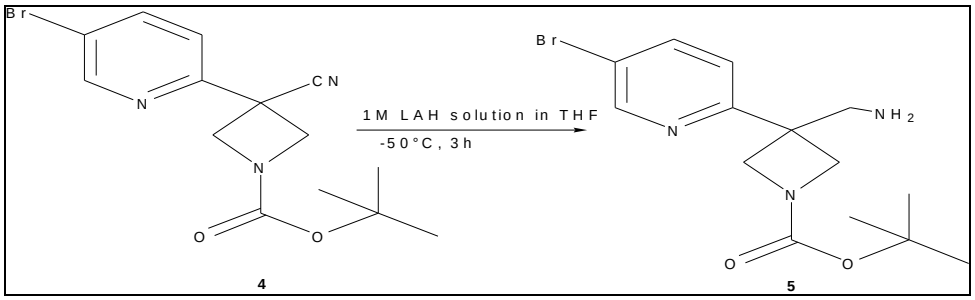

Figure 3

To a stirred 1M LAH (89mL, 89.02mmol) solution in THF(400mL) at -50°C under nitrogen was added compound 4 (3-(5-bromopyridin-2-yl)azetidine nitrile (30.0 g, 89.02mmol) by dissolving in THF(200mL)drop wise at -50°C for 3h. After consumption of the starting material the reaction mass was quenched with saturated sodium sulphate solution (100mL), and the solid formed was filtered and the cake was washed with THF (2X100mL) twice. Organic layer was dried over anhydrous $MgSO_4$ and concentrated to get crude. The crude was purified by flash column chromatography using 0 to 5% methanol in dichloromethane to afford pure (3-(5-bromopyridin-2-yl)azetidin-3-yl)methanamine product (20.0g, 66%) as light green viscous liquid.

1H NMR (CDCl3, δ ppm:1.45(9H,s), 3.20(2H, s), 4.01(2H,d), 4.20(2H, d), 7.15(1H,d), 7.81(1H, d), 861(1H,s)

LCMS purity: 91%, m/z, M+H, 342

3.Biological Activity

3.1.Antibacterial

The in vitro biological screening effects of the investigated compounds were tested against the bacteria Bacillus subtilis and E Coli. Paper discs of Whatman filter paper no. 1 were cut and sterilized in an autoclave. The paper discs were saturated with 1-4 µl of the compounds dissolved in DMSO solution. DMSO as negative control and was placed aseptically in the Petri dishes containing Nutrient agar media inoculated with the above mentioned two bacteria separately. The petridishes were incubated at 370C and the inhibition zones were recorded after 24 h of incubation.

3.2.Bacillus Subtilis

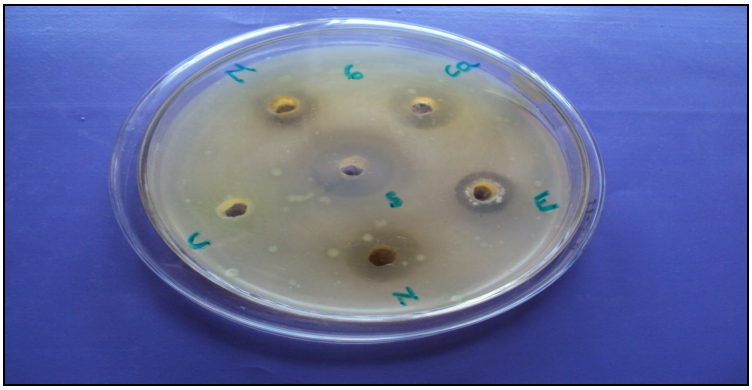

Figure 4

Ca: standard drug amoxicillin 5mg/ml DMSO
C:Control M: 1mg/ml S: 2mg/ml N: 3mg/ml E: 4mg/ml
E.Coli:

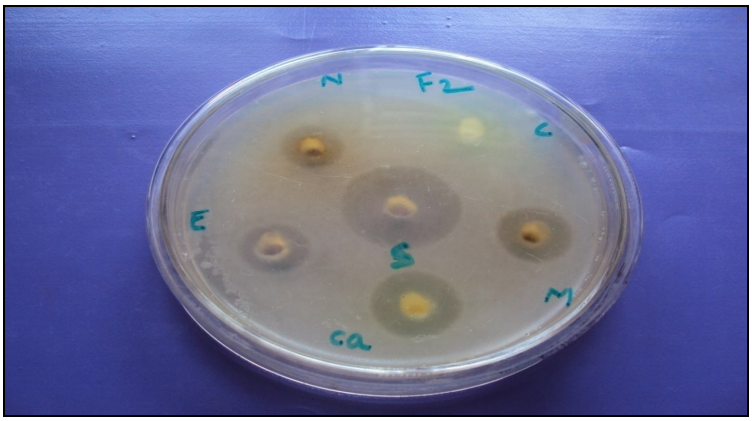

Figure 5

Ca: standard drug amoxicillin 5mg/ml DMSO
C: Control E: 1mg/ml N: 2mg/ml M: 3mg/ml S: 4mg/ml
Antifungal

The Schiff base complexes were screened for their antifungal activity against fungi viz. candida. Filter paper discs of 5 mm in size, prepared by using Whatman filter paper no. 1 (sterilized in an autoclave) was saturated with 10 µl of the compounds dissolved in DMSO solution . The fungal culture plates were inoculated and incubated at 25± 20C for 48 h. The plates were then observed and the diameters of the inhibition zones (in mm) were measured and tabulated.

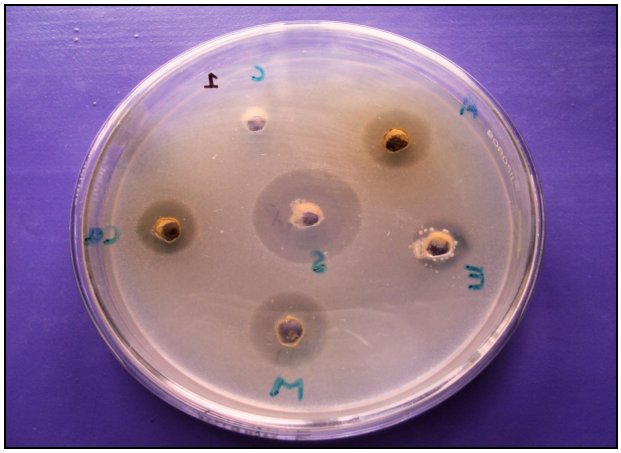

Figure 6

Ca: standard drug miconazole 5mg/ml DMSO
C: Control E: 1mg/ml M: 2mg/ml A: 3mg/ml S: 4mg/ml

4.Results and Discussion

The Main focus of this research work was to synthesize, characterize and evaluate antimicrobial activities of the newly synthesized Azetidine derivative, (3-(5-bromopyridin-2-yl)azetidin-3-yl)methanamine structures of synthesized compounds were confirmed and characterized with the help of analytical data's such as IR, 1H-NMR and Mass.

The synthesized compound shows NMR signals for different kinds of protons at their respective positions. The synthesized found to be more active than standard antibacterial drug amoxicillin against Bacillus subtilis and E.Coli..

The synthesized (3-(5-bromopyridin-2-yl) azetidin-3-yl) methanamine is found to be more active than standard antifungal drug Miconazole against candida.

5.Conclusion

The chemistry of β-lactams and azetidines is in a privilege position in chemistry, medicine and natural products disciplines due to their interesting biological activities. It is likely that in the near future, the synthesis of new β-lactam and azetidine derivatives and the preparation of novel nitrogen-containing structures, will be a challenge for synthetic organic chemists and an exciting opportunity for biological evaluations.

In summary, we have described the synthesis and antimicrobial activity of novel (3-(5-bromopyridin-2-yl)azetidin-3-yl)methanamine has shown good activity against the bacterial as well as fungal strains.

Hence,further study of a synthesized compound (3-(5-bromopyridin-2-yl)azetidin-3-yl)methanamine in antimicrobial and anti fungal activities may become fruitful.

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