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Synthesis, Characterization and in Vitro Evaluation of MRSA Inhibitors by Designing of Ligand Based Approach (QSAR)

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ABSTRACT

In present investigation, we have design, synthesize and evaluate methicillin-resistant staphylococcus aureus (MRSA) inhibitors. It appears interesting result of MRSA inhibitors. Newly synthesized compounds have been characterized and studied their antimicrobial activity especially MRSA gram positive bacterium. The compounds were found to exhibit good to comparable activity with respect to standards.

Keywords: QSAR, Thiabendazole derivative, MRSA, Pharmacological activities.

I. INTRODUCTION

As MRSA (Methicllin Resistant Staphylococcus Aureus) becomes increasingly resistant to common antibiotics, the search for new compound to fight the infection is ever more urgent. Staphylococcus aureus continues to be a dangerous pathogen for both community-acquired as well as hospital-associated infections. S. aureus resistant to methicillin were reported soon after its introduction in October 1960. S. aureus is an important human pathogen that contributes significantly to morbidity and mortality in society.Methicillin resistant S. aureus (MRSA) is now endemic in India. The incidence of MRSA varies from 25 per cent in western part of India 2 to 50 per cent in South India. Community acquired MRSA (CA-MRSA) has been increasingly reported from India.The traditional way to discover new drugs has been to screen a large number of synthetic chemical compounds or natural products for desirable effects. Although this approach for the development of new anti-bacterial agents has been successful in the past but is not an ideal approach for a number of reasons. The major drawback of the screening process is the requirement of an appropriate screening procedure. Although drugs are ultimately developed in the clinic, it is usually inappropriate to put the chemicals of unknown efficacy directly into humans.

Quantitative structure activity relationship (QSAR) searches information relating chemical structure to biological and other activities by developing a QSAR model. Using such an approach one could predict the activities of newly designed compounds before a decision is being made whether these compounds should be really synthesized and tested. By considering above facts, we have decided to design, synthesize and evaluate methicillin-resistant staphylococcus aureus (MRSA) inhibitors.

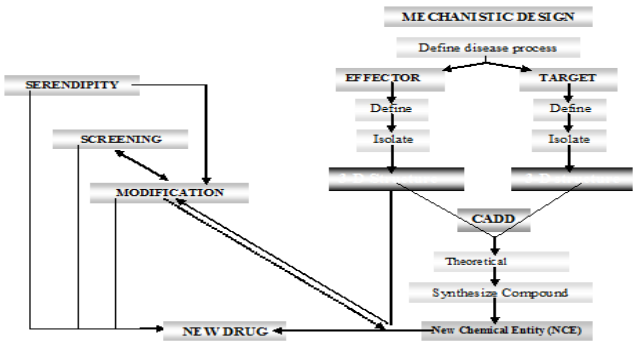
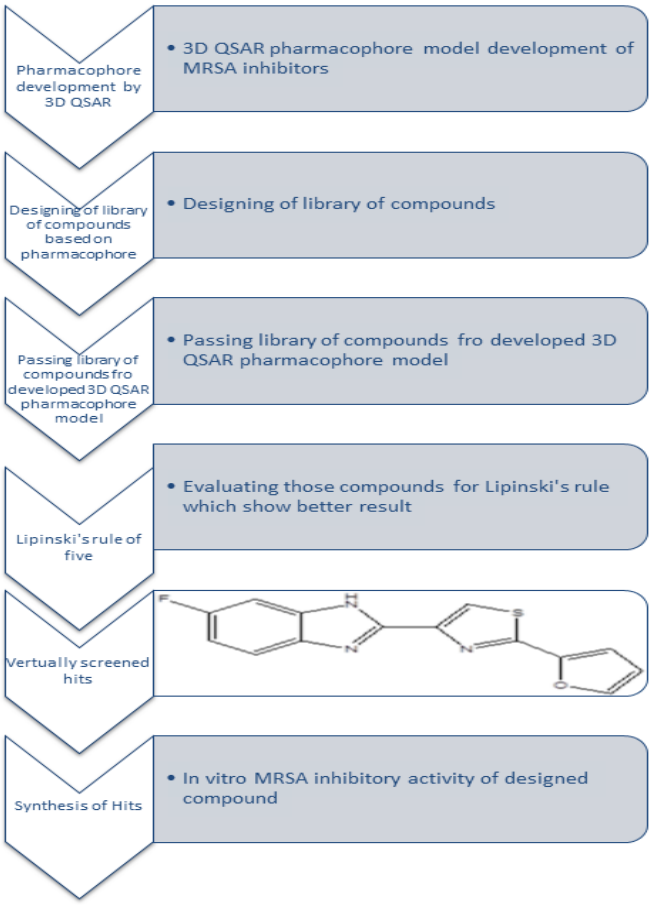
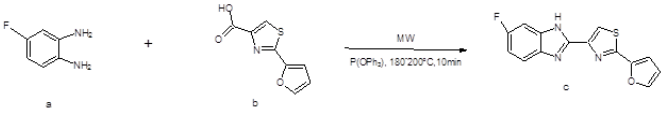


Figure 1. Flow diagrams showing the potential interactions that occur in the process of discovering new chemical entity.

II. EXPERIMENTAL SECTION





4-fluorobenzene-1,2-diamine (a, 1.0 equiv) with 2-(furan-2-yl)-1,3-thiazole-4-carboxylic acid (b, 1.0 equiv) in the presence of P(OPh)3 (1.2 equiv) in pyridine under microwave irradiation at 180-200 ^{0}C for 10 min. successfully form 6-fluoro-2-[2-(furan-2-yl)-1,3-thiazol-4-yl]-*1H*-benzimidazole (c).

The conversions are determined by TLC. The purities of the isolated products were determined by LC–MS and melting point. In addition, the formation of title compounds was also confirmed by recording their respective mass spectra, which were in agreement with their expected molecular weights.

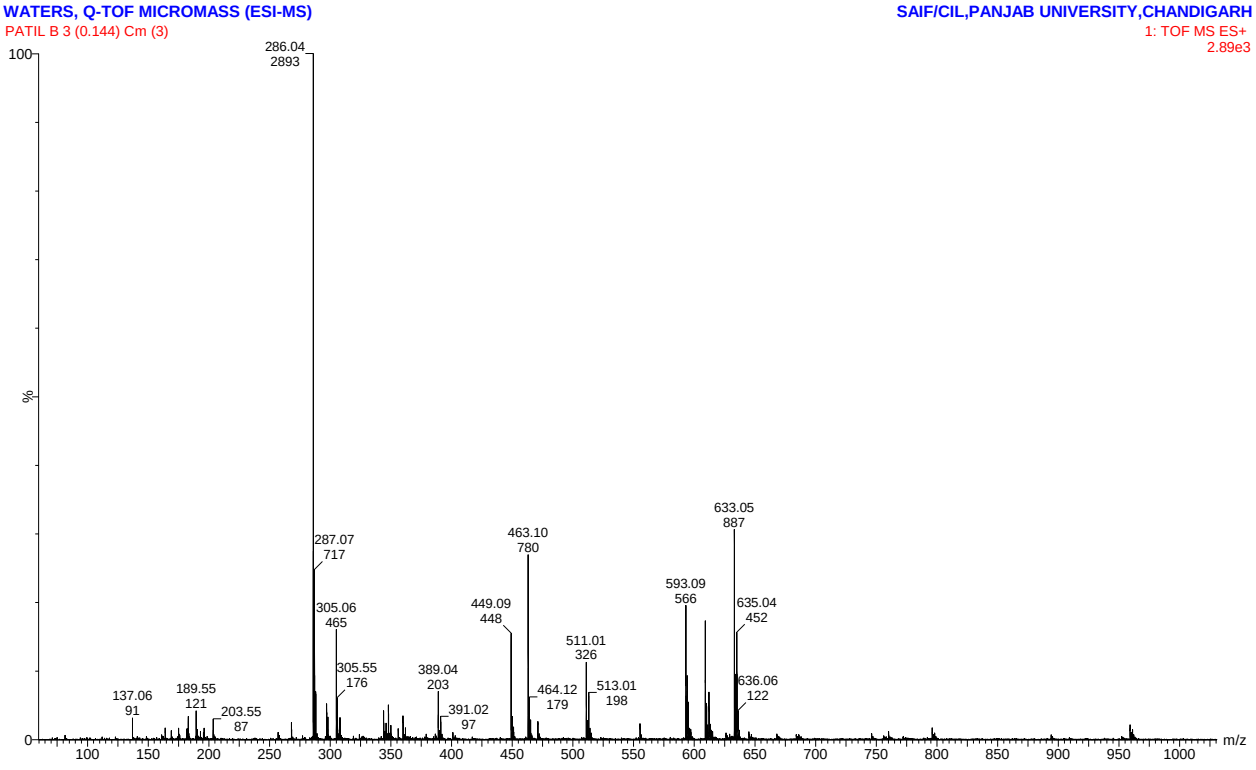
Physical properties of compound-

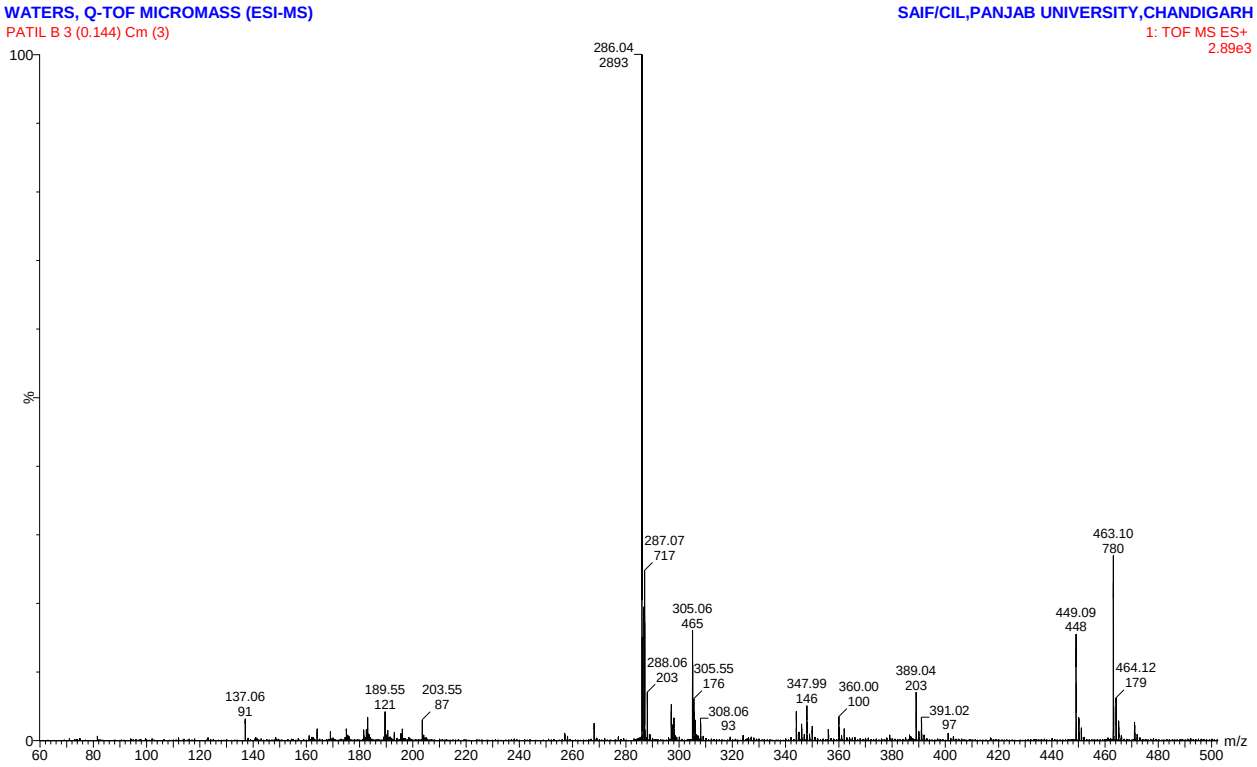
Melting point of compound 'C' = 528^{0}C

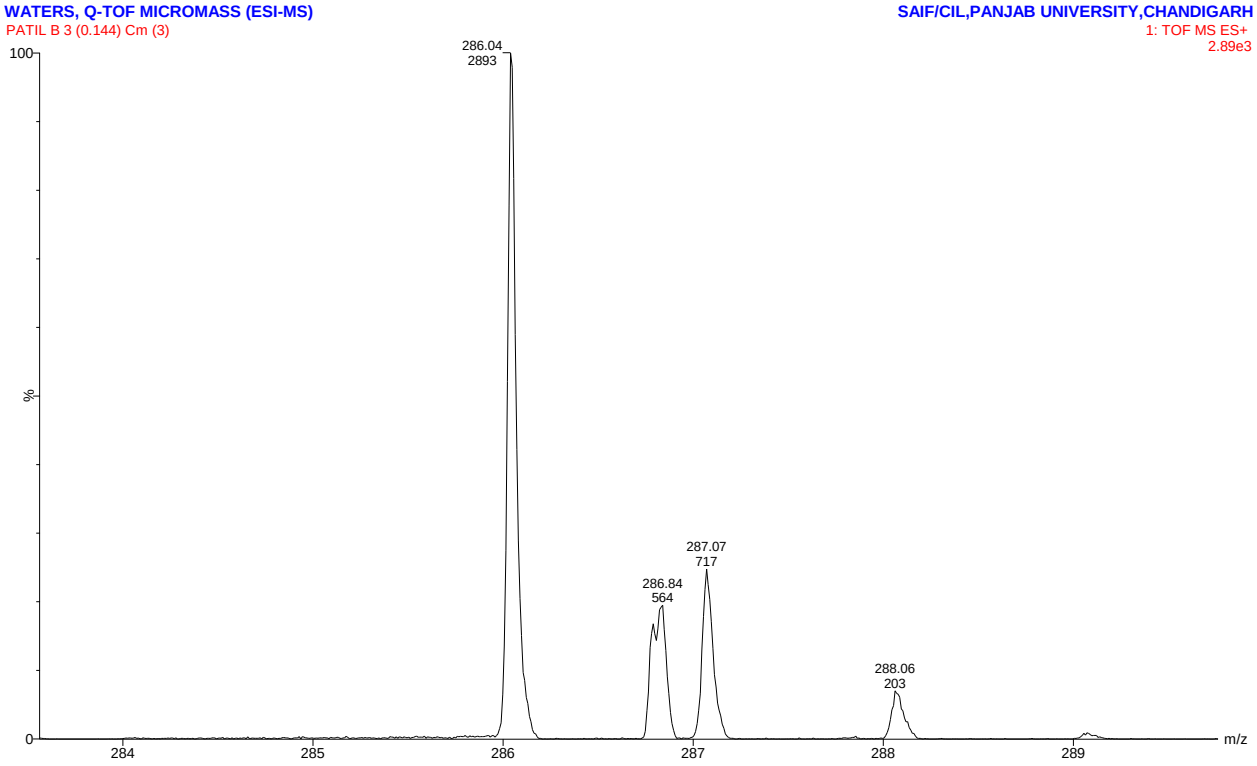
Spectral data of compound-

Mass of compound-

Synthesis of screen hits-




WATERS, Q-TOF MICROMASS (ESI-MS)
PATIL B 3 (0.144) Cm (3)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
1: TOF MS ES+
2.89e3
100
%
0
286.04
2893
287.07
717
305.06
465
288.06
203
305.55
176
137.06
91
189.55
121
203.55
87
308.06
93
347.99
146
360.00
100
389.04
203
391.02
97
449.09
448
463.10
780
464.12
179
60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500
m/z


WATERS, Q-TOF MICROMASS (ESI-MS)
PATIL B 3 (0.144) Cm (3)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
1: TOF MS ES+
2.89e3
100
%
0
286.04
2893
287.07
717
286.84
564
288.06
203
284 285 286 287 288 289
m/z

MRSA Activity of compound-

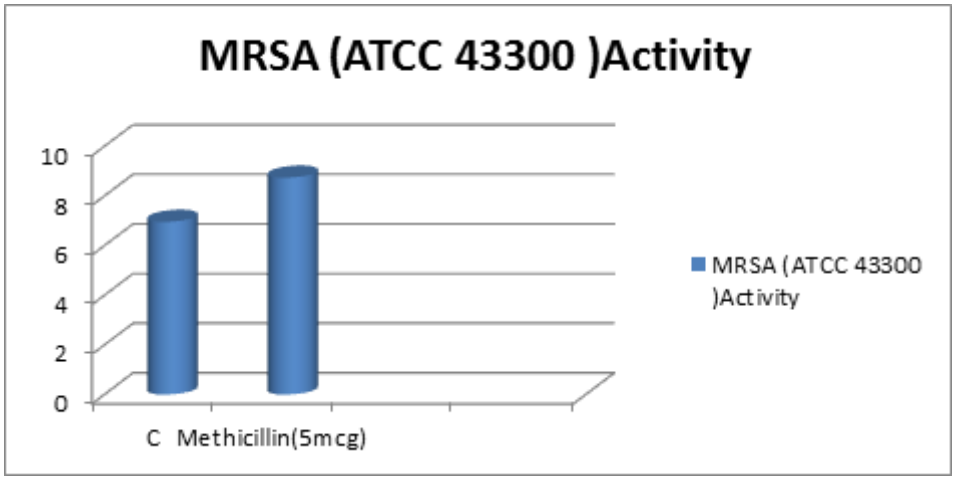
Method used- **Agar diffusion assay (Disc diffusion method, Disc size 6 mm)**[7]

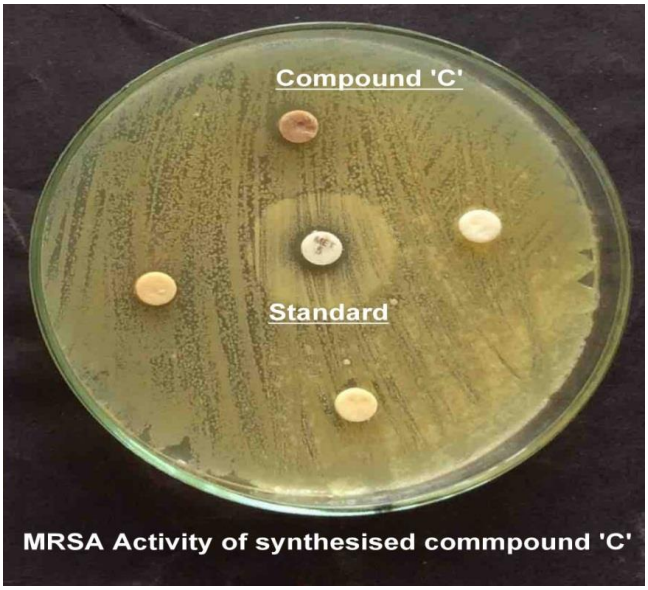
Concentration of compound- Stock solution [1000 microgram per ml] of each compound was prepared in DMSO. Assay carried out by taking concentration 100 microgram per disk.Hi-media antibiotics disk:Chloramphenicol (10 microgram/disk), Amphotericin-B (100 units/disk) moistened with waterare used as standard.

Media used-Microbiological media used for bacteria [Staphylococcus aureus (MRSA)] is Nutrient agar (Hi-media) Composition (gL-1): Sodium chloride, 5.0; Beef extract 10.0; Peptone 10.0 (pH 7.2)

Results of MRSA testing (Disc Diffusion Assay)

Compound	**Zone of inhibition in mm (conc. µg/ml) MRSA (ATCC43300)**
C	6.96
Methicillin(5mcg)	8.74





III. CONCLUSION

We conclude that rapid method of Quantitative structure activity relationship (QSAR) searches for methicillin-resistant Staphylococcus aureus (MRSA) inhibitors. We developed and evaluated the derivative 6-fluoro-2-[2-(furan-2-yl)-1,3-thiazol-4-yl]-1H-benzimidazole (c). A very good percentage of the MRSA were sensitive to synthesized compound C.

This research may pave the way for more effective MRSA drugs.

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