SYNTHESIS, INSILICO STUDIES AND ANTIBACTERIAL ACTIVITY OF 2, 4, 5-TRIPHENYL IMIDAZOLE DERIVATIVES

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ABSTRACT

Imidazole is a five membered heterocyclic aromatic organic compound it is further classified as an alkaloid Imidazole refers to the parent compound C3H4N2, whereas imidazoles are a class of heterocycles with similar ring structure but varying substituents. This ring system is present in important biological building blocks such as histidine and the related hormone histamine. Imidazole can act as a base and as a week acid. Imidazole exists in two tautomeric forms with the hydrogen atom moving between the two nitrogen's. Many drugs contain an imidazole ring, such as antifungal drugs and nitro imidazole.

Keywords: Heterocycles, Imidazole, Antifungal agents, Lipophilicity, Cell permeability.

INTRODUCTION

This research deals with the investigation carried out by writer in the laboratory on the synthesis, In silico studies, Antibacterial activity of 2, 4, 5 tri phenyl Imidazole derivatives. Before discussing the experimental procedures adopted and the results obtained, a brief introduction to therapeutic agents based on this ring and related moiety and in particular literature survey on the investigations carried out by earlier workers on the synthesis and evaluation of the heterocyclic compounds based on the above ring moiety would be presented in this chapter [1]. In the past, almost all the medicines used were from the plants, the plants being man's only chemist for ages. As the science and technology developed his curiosity came down to the molecular level of the drug moieties. A new approach to drug discovery and drug development has been developed for synthesis of new compounds, based largely on modification of structures of known activity, by a more logical approach, which is termed as 'Structure – based drug design'. Most of the drugs of natural origin contain heterocyclic rings. Those cyclic compounds which in addition to carbon, contain at least one atom of another element (hetero atom) in the ring, are called heterocyclic compounds or simply heterocyclic [2]. The common heteroatom present in the carbon rings are O, N, and S. The heterocyclic compounds having the lesser common atoms such as Phosphorus, Tin, Boron, Silicon, Bromine etc., have been a subject of much investigation in recent years.

In Silico Studies

Computational evaluation of ADMET (absorption, distribution, metabolism and toxicity) properties play pivotal role in the current drug development process so as to minimize clinical failures.

ADMET Parameters

The first systematic guidelines in medicinal chemistry were introduced by Lipinski et al. the so-called Lipinski rule of five (RO5) which stipulates limits for certain parameters which were expected to impart on the compound favorable properties such as suitable lipophilicity for desired levels of absorption, solubility, cell permeability, and brain barrier penetration (Table.1).

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Open-source molecular modelling resources have been widely used to study ADME profile of ligand molecules such as Caco2 permeability, Maden Darby Canine Kidney (MDCK) cell permeability, skin permeability and help in selecting molecules with desirable properties and to eliminate compounds with undesirable properties such as poor ADME [3].

ADME descriptors which can be calculated by using in silico tool PreADMET are listed below and also given figure:

Caco-2 (human colon adenocarcinoma) permeability

Caco-2 cell model has been recommended as a reliable in vitro model for the prediction of oral drug absorption. Caco-2 cells are derived from human colon adenocarcinoma and possess multiple drug transport pathways through the intestinal epithelium.

MDCK (Madin-Darby canine kidney) cell permeability:

MDCK cell model has been recommended as a reliable in vitro model for the prediction of oral drug absorption and it serves as an experimental and computational screening model for the prediction of intestinal drug absorption.

HIA (Human Intestinal Absorption)

Predicting human intestinal absorption of drugs is very important for identifying potential drug candidate.

PPB (Plasma Protein Binding)

Generally, unbound drug is available for diffusion or transport across the cell membranes and also for interaction with a pharmacological target [4]. As a result, the degree of plasma protein binding of a drug influences not only the drug's action but also its disposition and efficacy (Ganugapati J et al., 2014).The ranges of these descriptors used for in silico prioritization of molecules are shown in Table.2

Skin Permeability

It is important to predict the skin permeability rate as it is a crucial parameter for the transdermal delivery of drugs. Pre ADMET predicts in vitro skin permeability and the result value is given as logKp. KP (cm/hour) is defined as:

$$KP= Km*D/h$$

Where Km is distribution coefficient between stratum corneum and vehicle, and D is average diffusion coefficient (cm2 /h), and h is thickness of skin (cm) [5]

BBB (Blood Brain Barrier) Penetration

Blood-Brain Barrier (BBB) penetration is represented as BB = [Brain]/ [Blood], where [Brain] and [Blood] are the steady-state concentration of radiolabeled compounds in brain and peripheral blood. Predicting BBB penetration means predicting whether compounds pass the blood-brain barrier. This is crucial in pharmaceutical sphere because CNS-active compounds must pass across BBB and CNS inactive compounds mustn't pass in order to avoid of CNS side effects. The Boiled- Egg is known to be a straightforward interpretation and efficient translation to passive penetration through gastro-intestinal wall and BBB in molecular design.[6.

Metabolism

Cytochrome P450 is a family of isozymes responsible for the biotransformation of several drugs. Drug metabolism via the cytochrome P450 system has emerged as an important determinant in the occurrence of several drug interactions that can result in drug toxicities, reduced pharmacological effect and adverse drug reactions. Recognizing whether the drugs involved act as enzyme substrates, inducers, or inhibitors can prevent clinically significant interactions.

HERG

Human-ether-a-go-go-related channel (HERG) is a voltage gated K+ channel expressed not only in heart but also in brain, smooth muscle cells, endocrine cells, and in tumor cell lines. As the physiological role of HERG channels is regulation of ventricular and atrial myocyte cardiac action potential repolarization, HERG channel blockade may cause Long QT syndrome (LQTS), arrhythmia and Torsade de Pointes (TDP), which sometimes may result in sudden death. Several important drugs belonging to antiarrhythmic, antihistamines, antifungals, antipsychotics and antitussives have been withdrawn from the market due to HERG-related cardiotoxicity.

Structural alerts

PAINS (for pan assay interference compounds, a.k.a. frequent hitters or promiscuous compounds) are molecules containing substructures showing potent response in assays irrespective of the protein target. In Swiss ADME, it is possible to have a chemical description of the problematic fragments found in a given molecule. Swiss ADME is implemented for both PAINS and Brenk filters (Alves V et al., 2016).compounds with high BBB permeation and the white, for compounds with high HIA absorption. The outside grey region stands for molecules with low absorption and limited brain penetration.

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METHODOLOGY

Organic chemists are frequently facing the problem of characterizing and ultimately elucidating the structure of organic compounds. The worker in the field of natural products has the prospects of isolating such compounds from the sources in a pure state and then determining their structure. On the other hand, the synthetic organic chemist encounters new or unexpected compounds in the course of investigations into the applicability of new reagents or techniques or as byproducts of established reactions. All reactions were carried out under prescribed laboratory conditions. All the reactions requiring anhydrous conditions were conducted in well dried apparatus [10].

The solvents and reagents used in the synthetic work were of laboratory reagent grade and were purified by distillation and crystallization techniques wherever necessary and their melting points were checked with the available literature. The final products were purified by recrystallization. The IR spectra of the compounds were recorded on (FTIR) [11].

Procedure
Synthesis of Compound I

A solution of Benzil (5.25 gr. 0.025M), Ammonium acetate (10 gr. 0.129M) and Benzaldehyde (1.91 gr 0.018 M) in Glacial acetic acid (50 ml) was heated under reflux for 1-2 hours. The reaction mixture was allowed to stand to attain room temperature. The solid that appeared after the addition of water (150ml) was filtered. The filtrate was neutralized with Ammonium hydroxide to give solid and was filtered. The solid mass is obtained from first and second crop was washed well with toluene, dried in vacuum and recrystallized from aqueous Ethanol [12].

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Synthesis of Compound III

A solution of Benzil (5.25 gr. 0.025M), Ammonium acetate (10 gr. 0.129M) and Anisaldehyde (1.91 gr 0.018 M) in Glacial acetic acid (50 ml) was heated under reflux for 1-2 hours. The reaction mixture was allowed to stand to attain room temperature. The solid that appeared after the addition of water (150ml) was filtered. The filtrate was neutralized with Ammonium hydroxide to give solid and was filtered. The solid mass is obtained from first and second crop was washed well with toluene, dried in vacuum and recrystallized from aqueous Ethanol.

Synthesis of Compound IV

A solution of Benzil (5.25 gr. 0.025M), Ammonium acetate (10 gr. 0.129M) and Vanillin 4-hydroxy-3-methoxybenzaldehyde (1.91 gr 0.018 M) in Glacial acetic acid (50 ml) was heated under reflux for 1-2 hours. The reaction mixture was allowed to stand to attain room temperature. The solid that appeared after the addition of water (150ml) was filtered. The filtrate was neutralized with Ammonium hydroxide to give solid and was filtered. The solid mass is obtained from first and second crop was washed well with toluene, dried in vacuum and recrystallized from aqueous Ethanol.

Synthesis of Compound V

A solution of Benzil (5.25 gr. 0.025M), Ammonium acetate (10 gr. 0.129M) and (1.91 gr 0.018 M) P-amino benzaldehyde in Glacial acetic acid (50 ml) was heated under reflux for 1-2 hours. The reaction mixture was allowed to stand to attain room temperature. The solid that appeared after the addition of water (150ml) was filtered. The filtrate was neutralized with Ammonium hydroxide to give solid and was filtered. The solid mass is obtained from first and second crop was washed well with

toluene, dried in vacuum and recrystallized from aqueous Ethanol.

Synthesis of Compound VI

A solution of Benzil (5.25 gr. 0.025M), Ammonium acetate (10 gr. 0.129M) and P-dimethyl amino benzaldehyde (1.91 gr 0.018 M) in Glacial acetic acid (50 ml) was heated under reflux for 1-2 hours. The reaction mixture was allowed to stand to attain room temperature. The solid that appeared after the addition of water (150ml) was filtered. The filtrate was neutralized with Ammonium hydroxide to give solid and was filtered. The solid mass is obtained from first and second crop was washed well with toluene, dried in vacuum and recrystallized from aqueous Ethanol.

ANTI BACTERIAL ACTIVITY
Principle and Interpretation:

Nutrient Agar is a basic culture medium used for maintenance or to check purity of subcultures prior to biochemical or serological tests from water and Dairy. This medium may be used as slants or plates for routine work with non-fastidious organisms. Nutrient Agar, pH 6.8 has relatively simple formulation which provides the necessary nutrients for the growth of many microorganisms which are not very fastidious. Many bacteria have the optimum pH growth range of 6.6 to 7.0. [14]Wetmore and Gochenour maintained cultures of Malleomyces and Pseudomonas on Nutrient Agar to which glycerol was added. Greenberg and Cooper employed this medium in cultivation of Staphylococci for the preparation of vaccines and antigens. Nutrient Agar has relatively simple formulation which provides the necessary nutrients for the growth of many microorganisms which are not very fastidious. Beef extract contains vitamins, organic nitrogen compounds, salts and little carbohydrates. Peptic digest of animal tissue provide amino acids and long chain peptides for the organisms [15]

Bacteriological media come on a wide range of types. Nutrient Agar is a complex medium because it contains ingredients with contain unknown amounts or types of nutrients. Nutrient Agar contains Beef Extract (0.3%), Peptone (0.5%) and Agar (1.5%) in water. Beef extract is the commercially prepared dehydrated form of autolysed beef and is supplied in the form of a paste. Peptone is casein (milk protein) that has been digested with the enzyme pepsin. Peptone is dehydrated and supplied as a powder. Peptone and Beef Extract contain a mixture of amino acids and peptides. Beef Extract also contains water soluble digest products of all other macromolecules (nucleic acids, fats, polysaccharides) as well as vitamins and trace minerals. Although we know and can define Beef Extract in these terms, each batch cannot be chemically defined. There are many media ingredients which are complex: yeast extract, tryptone, and others. The advantage of complex media is that they support the growth of a wide range of microbe's g chain peptides for the organisms [16].

Agar is purified from red algae in which it is an accessory polysaccharide (Poly galacturonic acid) of their cell walls. Agar is added to microbiological media only as a solidification agent. Agar for most purposes has no nutrient value. Agar is an excellent solidification agent because it dissolves at near boiling but solidifies at 45°C. Thus, one can prepare molten (liquid) agar at 45°C, mix cells with it, and then allow it to solidify thereby trapping living cells. Below 45°C agar is a solid and remains so as the temperature is raised melting only when >95°C is obtained [17].

Procedure

Weight accurately all the ingredients and dissolved in distilled water in a conical flask, make up to 1 liter. Adjust the pH to 7.2 to 7.5 by using 1N sodium hydroxide or 1N HCl. Close the flask by using sterile cotton, and auto clave the flask at 15 Psi for 15 min18. All the Petri dishes were sterilized in oven at 160°C for 1hour, Agar media, absorbent paper and test solutions were sterilized in autoclave at 121°C at 15psi then molten sterile agar was poured in sterile Petri dishes aseptically.[18] The agar was allowed to cool and the bacterial suspension was poured into the Petri dishes aseptically. Placing the absorbent paper was absorbed with solutions of the compound in the Petri dishes aseptically. Incubated the Petri dishes at 37°C for antimicrobial for 24 hrs and observed the Zone of inhibition [19].

INSILICO STUDIES
Pre ADMET (http://preadmet.bmdrc.org/)

PreADMET is a software package for prediction of various properties based on designed structure of chemical compounds. It supports friendly user interface and MS-Windows optimized software architecture, which easily provide useful numerical information related to absorption – distribution – metabolism – excretion (ADME) and toxicity of chemical compound, from the early step of drug discovery [20].

Characteristics

Using PreADMET for drug discovery and/or compound library design, you can perform following tasks:
- Sketch and edit 2D structure of chemical compound
- Edit additional data fields of chemical compound
- Collect structures and data fields of SD files
- Merge or separate SD/MOL files
- Visualize 3D structures of chemical compounds
- Integrate 2D -> 3D Conversion software (Corina (Mol-net), OMEGA (OpenEye), Vconf (VeraChem), Marvin (ChemAxon))

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- Calculate more than 2,000 descriptors, including both 2D and 3D descriptors.
- Predict solubility in pure water or buffer solution
- Screen drug candidates for similar drug group, by drug-like rule
- Predict properties related to ADME
- in vitro Caco-2 cell permeability, MDCK cell permeability
- In vivo blood-brain barrier penetration, BBB
- HIA or Human intestinal absorption

- In vitro skin permeability
- In vitro plasma protein binding
- Predict properties related to toxicity
- Mutagenicity from Ames test (in vitro)
- Carcinogenicity from mouse and rat (in vivo)
- Provide combinatorial library builder
- Design chemical compound library using ADME/Tox. Propertier.

Table 1. Lipinski rule of five (RO5) (Properties for drug likeness criteria)

S.NO	PROPERTIES	DRUG - LIKENESS
1.	Molecular weight (MW)	≤ 500
2.	Lipophilicity (C Log P)	≤ 5.0
3.	H-bond donor (Sum of NH and OH)	≤ 10.0
4.	H-bond acceptors (Sum of N and O	≤ 150
5.	Topological Polar surface area (TPSA)	≤ 10.0
6.	Number of rotatable bonds	≤ 0
7.	Number of Violations	≤ 0

Table.2 Ranges of ADME prediction values

	CaCO$_2$ cell Permeability	Maden Darby Canine Kidney (MDCK) cell permeability	Plasma Protein Binding (%PPB)	BBB Penetration	% HIA Absorption
Low/poor absorption	< 4	< 25	Strongly bound >90	CNS Active compounds (+) >1	0 – 20
Moderate High/well absorption	4 ~ 70 >70	25-500 >500	Weakly bound <90	CNS Active compounds (-) <1	20-70 70-100

Table 3. Ingredients

Ingredients	Quantity per 1000ml
Peptone	5 grams.
Sodium chloride	5 grams.
Beef extract	3 grams.
Agar agar	15 grams.
Distilled water	Up to 100ml

Table 4. Materials and methods for in silico studies

Property calculated	Online tool used	Website	Predicted Parameters	Reference
ADMET properties	Pre- ADMET & Swiss ADME	(http://preadmet.bmdrc.org/) & (http://www.swissadme.ch/)	MDCK, Caco2 Permeability, GI absorption, Skin permeability, BBB permeability, % PPB, Pgp substrate, hERG inhibition, presence of structural alerts and mutagenicity	(Zhao YH et al., 2002 & Marc G et al., 2018).

Table 5. IR Frequencies compound I

Compound	Types of vibration	Wave number (cm- 1)
I	Aromatic stretch (C-H) C=N stretch	3035.96 cm^{-1} 1597.06 cm^{-1}

Table 6. 2-(4,5-diphenyl-1H-imidazol-2-yl)phenol Table 7: IR Frequencies compound II.

Compound	Types of vibration	Wave number (cm- 1)
II	Aromatic stretch (C-H)C=N stretch O-H stretch	3061.03 cm^{-1} 1593.20 cm^{-1} 3429.43 $^{-1}$

RESULTS OF INSILICO STUDIES

Table 7. Absorption properties of title compounds

Compound Name	Molecular weight	CaCo2 Permeability	MDCK	G.I Absorption	TPSA	%ABS{109-0.345(TPSA)}	Skin Permeability (cm^2/h)
I	296.37	33.9926	13.6836	high	28.68	99.10	-2.142
II	312.37	43.9445	4.35245	high	48.91	92.12	-3.000
III	326.40	50.5376	8.57806	high	37.92	95.92	-2.288
IV	342.40	37.1127	38.316	high	58.15	90.53	-3.151
V	311.39	33.7169	1.69697	high	54.71	90.12	-2.916
VI	339.44	40.9599	0.131992	high	31.92	97.98	-2.003

Caco2- (Caco2 Cell Permeability); MDCK-(Maden Darby Canine Kidney cell permeability); SKIN- (Skin Permeability); GI (Gastrointestinal absorption); % ABS- Percentage of absorption.
CaCO2: LOW-Less than 4 MODERATE-4-70, HIGH- More than 70
MDCK: LOW-Less than 25, MODERATE-25-500, HIGH- More than 500.

Table 8. Distribution properties of title compounds

Compound Name	BBB Permeability	% Plasma protien Binding	P-gp substrate
I	Yes	93.11	Yes
II	Yes	100	Yes
III	Yes	99.47	Yes
IV	Yes	100	Yes
V	Yes	90.86	Yes
VI	Yes	88.86	Yes

BBB (Blood brain-barrier); PPB (Plasma protein binding); P-gp (P-glycoprotein)
Plasma protein binding: STRONGLY BOUND   : More than 90%,
WEAKLY BOUND   : Less than 90%.

Table 9. Metabolism properties of title compounds

Compound Name	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
I	Yes	Yes	Yes	No	Yes
Il	Yes	Yes	Yes	No	Yes
III	Yes	Yes	Yes	No	Yes
IV	No	Yes	Yes	No	Yes
V	Yes	Yes	Yes	No	Yes
VI	Yes	No	No	No	No

Table 10. Toxicity properties of title compounds

Compound Name	hERG INHIBITION	Presence of structural alerts "BRENK"	Mutagenisity [Ames test]
I	Low risk	Zero alert	Mutagen
II	Low risk	Zero alert	Mutagen
III	Low risk	Zero alert	Mutagen
IV	High risk	Zero alert	Mutagen

V	High risk	One alert- Anillin	Mutagen
VI	Medium risk	Zero alert	Mutagen

Table 11 Data for anti-bacterial activity of synthesized compounds

Compound No	Concentration in μg	Zone of inhibition in mm	
		Gram positive (Streptococus)	**Gram negative** (E.coli)
I	50	17	16
II	50	12	11
III	50	11	12
IV	50	18	19
V	50	12	13
VI	50	16	18
Standard	50	22	23
Solvent Control (DMSO)	-	-	-

Spectral Data of Synthesized Compounds
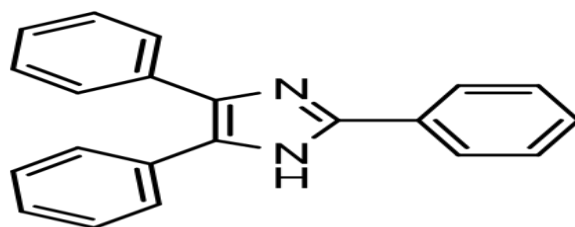
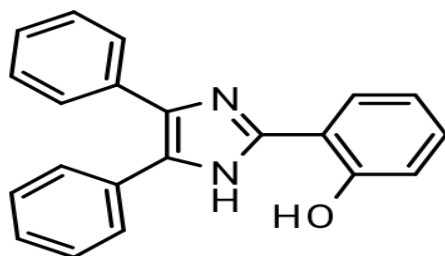2,4,5-triphenyl-1*H*-imidazole

I

Fourier Transform Infrared Spectroscopy data of Compound 1
Figure 1. IR frequency compound I
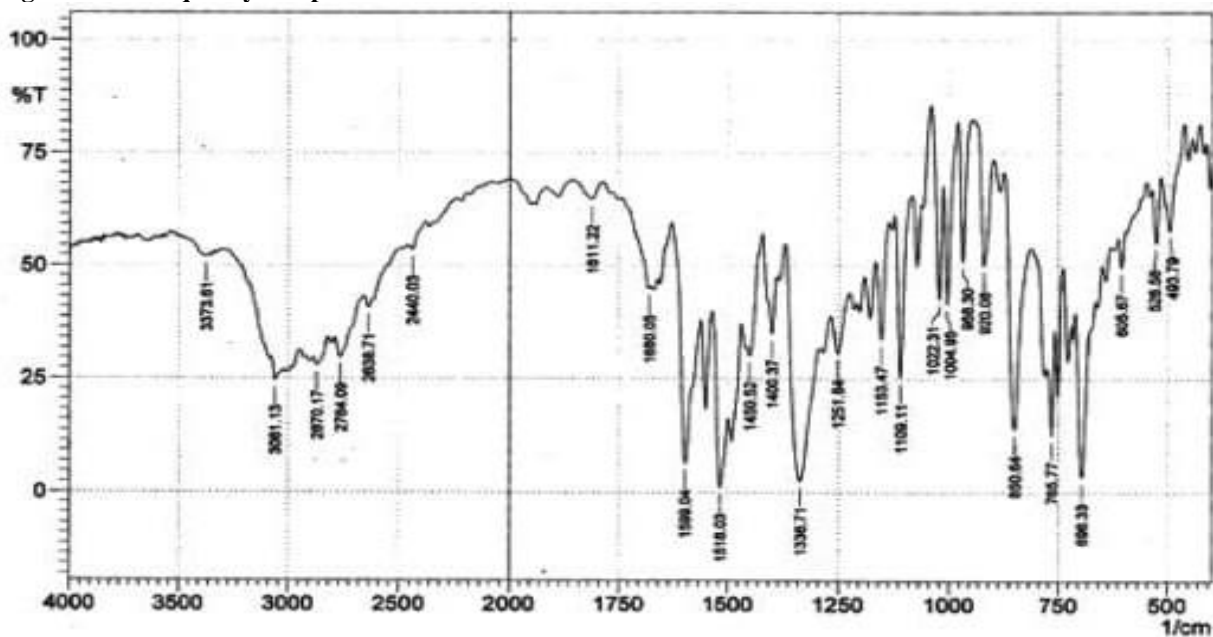
Fourier Transform Infrared Spectroscopy data of Compound II

2-(4,5-diphenyl-1*H*-imidazol-2-yl)phenol

II
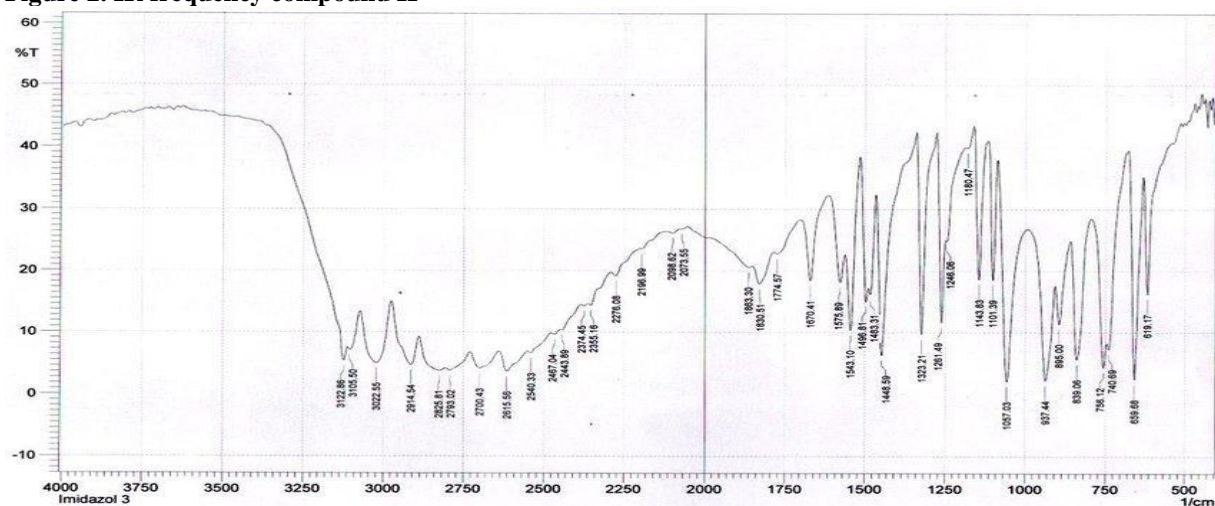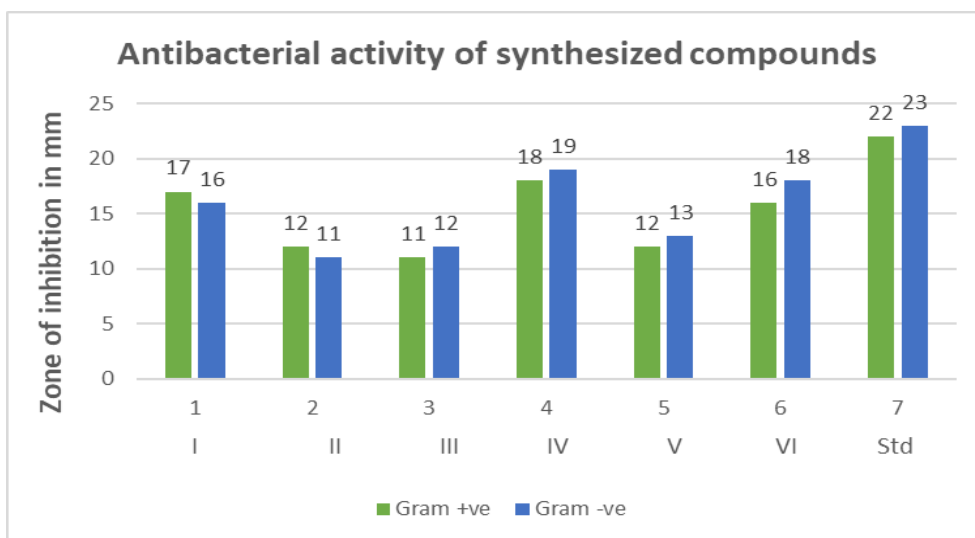
Figure 2. IR frequency compound II

Fig 25 Anti-bacterial activity for compound I, II, III, IV, V&VI & standard

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RESULTS AND DISCUSSION

Imidazole and its derivatives are also biologically very important heterocyclic systems and exhibit a wide range of biological activities like anthelmintics, anti-inflammatory, antimicrobial, anticancer, antibacterial, anti-fungal activities etc. Hence it was though that a Manich reaction on imidazole moiety, the resulting compound might possess enhanced biological activity.

In view of these facts, it was planned to synthesize Manich bases of Imidazole's. Of all imidazole derivatives, Manich bases at 1st position are less exploited. So, it is obvious to synthesize N- substituted derivatives. It is likely that the new derivatives with some modification in their chemical structure may result in some profound change in the pharmacological responses.

The enzyme CYP2C19 is found primarily in the liver, as are the previous enzymes we discussed (CYP1A2 and CYP2C9). CYP450 enzymes metabolize most medications, and the most important of these enzymes are CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

CYP1A2

Theophylline and tizanidine have drug interactions with CYP1A2 when potent CYP1A2 inhibitor fluvoxamine was given consecutively.

CYP2C19

Propranolol, Diazepam, Phenobarbital are metabolized by CYP2C19 enzyme. Isoniazid and fluoxetine are CYP2C19 inhibitors.

CYP2C9

Warfarin has drug interactions with CYP2C9 enzyme, whereas phenytoin toxicity was observed when it is given with CYP2C9 inhibitors simultaneously. Few CYP2C9 inhibitors include amiodarone, fluorouracil, metronidazole, miconazole.

CYP2D6

Fluoxetine, paroxetine, and quinidine, are potent inhibitors of CYP2D6. Thioridazine is a CYP2D6 substrate increased plasma concentrations can cause serious adverse effects.

CYP3A4

Carbamazepine administration leads to adverse reactions like vomiting when it is combinedly given with CYP3A4 inhibitors. Drugs, such as clarithromycin, itraconazole, and ketoconazole, are particularly potent inhibitors of CYP3A4.

Toxicity studies predicted that except IV and V remaining compounds are devoid of cardiotoxicity (hERG affinity is low).

Molecular descriptor calculations

A series of synthesized 2, 4, 5-triphenylimidazole derivatives were considered to calculate the molecular properties and presented in above tables. Results revealed that, all the compounds (I to VI) obeyed Lipinski rule of five, indicating that their oral bioavailability will be good. Molecular properties of synthesized derivatives include TPSA: 28.68-31.92; MW: 296.37-339.44; Gastro intestinal absorption was found to be good for all the derivatives. All the screened compounds (I to VI), crossed the blood brain barrier (BBB) indicating that these compounds may possess CNS activity. Regarding CYP inhibition, all the compounds showed no affinity toward CYP2D6 isoenzymes. Toxicity studies predicted that except IV and V remaining compounds are devoid of cardiotoxicity (hERG affinity is low). According to Brenk et al., aniline (compound V) containing derivative was indicated as structural alert.

Evaluation of Anti-Bacterial Activity

All the compounds were successfully showed anti-bacterial activity potent to weak activity. Compound IV showed more potent anti-bacterial activity against all bacterial strains i.e., zone of inhibition of 18mm and 19mm was observed against both gram positive and gram negative bacterial. Compound I and VI showed intermediate anti-bacterial activity and Compound II, III and V showed weak anti-bacterial activity when compared to standard i.e., Amoxycillin.

CONCLUSION

Imidazole moiety have been most frequently studied, many of its analogues are active against various pathological conditions. Imidazole is an entity which has interesting physical and chemical properties, in the present thesis focused on synthesis and their antibacterial activity which in turn may be exploited for different pharmacological activities.

The various Manich bases of 2,4,5-triphenylimidazole derivatives have been synthesized and evaluated for their anti-bacterial activity. These derivatives showed good responses when compared to the standard drug. It is concluded that the some of the Manich bases of 2,4,5-triphenylimidazoles are potent anti-bacterial agents against both gram positive and gram-negative bacteria.

All the 2,4,5 triphenyl imidazole derivatives are predicted, using Pre ADMET website. All the compounds have good oral bioavailability, strong bound to plasma protein also penetrate BBB, no affinity towards cyp2D6 isoenzyme. Except IV and V compounds I.e., vanillin and aniline substituted compounds, remaining all the four derivatives are devoid of cardiotoxicity (HERG affinity is low).

All the 2,4,5 triphenyl imidazole derivatives are synthesized and screened for their anti-bacterial activity

and compared with standard drugs (amoxycillin). Good anti-bacterial activity seen with compound IV when compared with other derivatives. I and VI compounds showed intermediate anti-bacterial activity and II, III and V showed weak anti-bacterial activity.

In future study, further detailed investigation should be done, the mechanism of action and toxicity studies should also be carried for the synthesized drugs.

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