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SYNTHESIS AND BIOLOGICAL EVALUATION OF IMIDAZOLE DERIVATIVES AS ANTIBACTERIAL AGENTS

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ABSTRACT

Imidazole has become an important synthon in the development of new drugs. The unique structural feature of the imidazole (1, 3-diazole) ring with a desirable electron-rich characteristic is beneficial for imidazole derivatives to readily bind with various enzymes and receptors in biological systems through diverse weak interactions, thereby exhibiting broad bioactivities. The derivatives of 1, 3-diazole show different biological activities such as antibacterial, antimycobacterial, anti-inflammatory, antitumor, antidiabetic, anti-allergic, antipyretic, antiviral, antioxidant, anti-amoebic, antihelmintic, antifungal, and ulcerogenic activities, etc. The present study, 2,4,5-triphenyl imidazole derivatives were synthesized using benzil, substituted aldehydes, ammonium acetate, and triethylammonium acetate. The synthesized compounds were characterized using mass spectroscopy and evaluated for antibacterial activity. The antibacterial report shows that compounds 1a *and 1b show a maximum zone of inhibition* against *Bacillus subtilis*.

Keywords: 2,4,5-triphenyl imidazole derivatives, bioactivity score, antibacterial activity

INTRODUCTION

In chemistry, a one-pot synthesis is a strategy to improve the efficiency of a chemical reaction whereby a reactant is subjected to successive chemical reactions in just one reactor. This is much desired by chemists because avoiding a lengthy separation process and purification of the intermediate chemical compounds can save time and resources while increasing chemical yield **[1]**.

One-pot synthesis, also known as multicomponent synthesis, is a chemical synthesis technique in which multiple chemical reactions take place in a single reaction vessel, usually in a heating or cooling step. This strategy has become increasingly popular due to its simplicity, efficiency, and cost-effectiveness, as it reduces the number of synthetic steps required for the production of complex molecules.

One-pot synthesis is used for a variety of applications, including the synthesis of organic molecules, inorganic nanoparticles, and biological materials. The strategy enables researchers to streamline the synthesis of molecules that previously required multiple reaction steps, often leading to higher yields, fewer byproducts, and shorter reaction times.

The one-pot synthesis strategy is widely used in pharmaceuticals, which has helped reduce time and cost in the drug discovery process. It has also enabled the production of structurally complex natural products and other biologically active molecules that may have potential applications in a variety of fields, including medicine, materials science, and chemical engineering.

Overall, one-pot synthesis is a powerful tool that has revolutionized the way chemists approach complex molecular synthesis. With its versatility and efficiency, it has become an indispensable technique in modern organic synthesis, allowing researchers to develop new, high-yield, and sustainable synthetic routes.

Imidazole

Imidazole is a planer five-membered heterocyclic ring with 3C and 2N atoms and in-ring N is present in 1st and 3rd positions. The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine, and nucleic acid. Being a polar and ionizable aromatic compound, it improves the pharmacokinetic characteristics of lead molecules and is thus used as a remedy to optimize the solubility and bioavailability parameters of proposed poorly soluble lead molecules. Imidazole derivatives have occupied a unique place in the field of medicinal chemistry. The incorporation of the imidazole nucleus is an important synthetic strategy in drug discovery. The high therapeutic properties of imidazole-related drugs have encouraged medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened the scope of remedying various dispositions in clinical medicines. Numerous methods for the synthesis of imidazole and also their various structure reactions offer enormous scope in the field of medicinal chemistry **[2-4]**. This study aims to synthesize and evaluate novel imidazole derivatives as antibacterial agents.

MATERIALS AND METHODS

In-silico Studies

Molinspiration, web-based software was used to obtain parameters such as MiLogP, TPSA, and drug likeness scores. MiLogP is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors. MiLog P parameter is used to check good permeability across the cell membrane. The partition coefficient or Log P is an important parameter used in rational drug design to measure molecular hydrophobicity. The hydrophilic/lipophilic nature of drug molecules affects drug absorption, bioavailability, drug-receptor interactions, metabolism of molecules, as well as their toxicity. Molecular Polar Surface Area TPSA is calculated based on a sum of fragment contributions of O and N- and cantered polar fragments. Total polar surface area (TPSA) is closely related to the hydrogen bonding potential of a molecule and is a very good predictor of drug transport properties such as intestinal absorption, bioavailability, blood-brain barrier penetration, etc. The calculation of volume developed at Molinspiration is based on group contributors. The rotatable bonds measure molecular flexibility. It is a very good descriptor of the absorption and bioavailability of drugs. Through drug-likeness data of molecules, it can be checked molecular properties, and structure features with respect to known drugs **[5-6]**.

Bioavailability score

The bioactivity of the drug can be checked by calculating the activity score of the GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor, and enzyme inhibitor. All the parameters were checked with the help of software. Calculated drug-likeness scores of each compound were compared with the specific activity of other compounds and the results were compared with standard drugs. For organic molecules the probability is if the bioactivity score is (>0), then it is active, if (-5.0-0.0) then moderately active, if (< -5.0) then inactive **[7-9]**.

SYNTHESIS OF IMIDAZOLE DERIVATIVES

Step 1:

Preparation of Triethylammonium Acetate (TEAA)

To 50.5g (0.5 mol) of triethylamine in a 250 ml round-bottom flask equipped with a reflux condenser, a magnetic stir bar, and an addition funnel, added glacial acetic acid (30.0 g, 0.5 mol) was added dropwise with stirring at 80 0 C throughout 2 hrs. After the addition was complete, the reaction mixture was stirred for an additional 2 hrs at 80 ^{0} C to ensure the reaction had proceeded to completion. The reaction mixture was evaporated at 80 0 C until the weight of the residue remained constant.

Step 2:

Preparation of 2,4,5-Trisubstituted Imidazoles

A mixture of benzil or benzoin (1 mmol), the aldehyde (1 mmol), ammonium acetate (0.55 g, 7 mmol), and TEAA (0.1 ml) was stirred at 120^0C in an oil bath for the time shown in Table 2. After completion of the reaction as indicated by TLC (hexane-ethyl acetate, 8:2), the mixture was cooled to room temperature, hot 96% EtOH (1 ml) was added and the mixture was stirred for 2 min. It was then poured onto crushed ice and the solid products that separated were collected, washed with water, dried, and recrystallized from ethanol (96%, 6 ml) to afford the pure 2,4,5-trisubstituted imidazole derivatives **[10]**.

Synthesis of imidazole derivatives

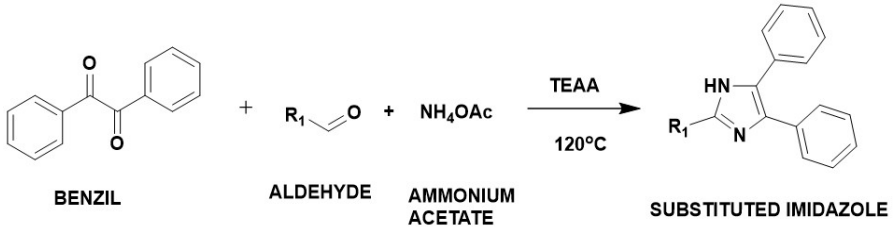

Table 1: Physical parameters of synthesized compounds

Compound Name	R_1	Molecular formula	% Yield (W/W)	Molecular weight	Melting point (ºC)	R_f value
1a	4-hydroxy benzene	$C_{21}H_{16}N_2O$	83.04	312.37	278-281	0.25
1b	3-hydroxy benzene	$C_{21}H_{16}N_2O$	83.04	312.37	160-165	0.9
1c	4-nitro benzene	$C_{21}H_{15}N_3O_2$	87	341.37	143-146	0.76
1d	3-nitro benzene	$C_{21}H_{15}N_3O_2$	87	341.37	240-243	0.44
1e	4-chloro benzene	$C_{21}H_{15}ClN_2$	89	330.82	198-201	0.90

***In-vitro* anti-bacterial assay**

The anti-bacterial assay was performed on the synthesized products by the cup plate method, using staphylococcus and klebsiella as the specimen. The culture was prepared in a petri dish in sterile conditions. *E. coli* and *Bacillus subtilis* were inoculated in the culture medium and two concentrations of the sample (0.05gm/ml and 0.01gm/ml) were prepared. This was then placed in the culture medium by cup plate method and was incubated at 37 ℃ for 24 hours. The zone of restraint was estimated on the following day. The following table shows the result of the test conducted **[11]**.

RESULT AND DISCUSSION

Table 2: Physico-chemical parameters for Synthesised compounds

Compound name	miLogP	TPSA	natoms	nON	nOHNH	violati-ons	nrotb	MW
1a	4.18	48.91	24	3	2	0	3	312.37
1b	4.91	48.91	24	3	2	0	3	312.37
1c	5.35	74.51	26	5	1	1	4	341.37
1d	5.32	74.51	26	5	1	1	4	341.37
1e	6.07	28.68	24	2	1	1	3	330.82

miLogP – Partition coefficient, TPSA- topological polar surface area, MW- molecular weight, nrotb-Number of Rotatable Bonds, nON - No. of hydrogen bond acceptor, nOHNH-no. of hydrogen bond donor.

Table 3: Bioactivity score of imidazole derivatives

Compound name	GPCR ligand	Ion channel modulator	Kinase receptor inhibitor	Nuclear receptor ligand	Protease receptor inhibitor	Enzyme receptor inhibitor
1a	0.19	0.11	0.46	0.07	-0.32	0.25
1b	0.19	0.11	0.43	0.06	-0.30	0.24
1c	-0.02	0.00	0.21	-0.19	-0.43	0.06
1d	-0.01	-0.01	0.24	-0.18	-0.43	0.07
1e	0.15	0,06	0.37	-0.11	-0.36	0.15

>0 = drug is active to particular receptor, -5.0-0.0 =drug is moderately active to particular receptor, >-5.0 =drug is inactive to particular receptor

Table 4: Evaluation of anti-microbial activity using agar diffusion method (zone of inhibition)

Compound code	Concentration of drug	Zone of inhibition (mm) For *E. coli*	Zone of inhibition(mm) For *Bacillus subtilis*
1a	0.02g/ml	34mm	37mm
1b	0.02g/ml	33mm	35mm
1c	0.02g/ml	22mm	27mm
1d	0.02g/ml	24mm	19mm
1e	0.02g/ml	10mm	20mm
1f	0.02g/ml	12mm	14mm

The antibacterial report shows that compounds 1a and 1b show a maximum zone of inhibition against Bacillus subtilis.

SUMMARY AND CONCLUSION

The substituted imidazole derivatives 1a-1e were synthesized, and all the compounds are characterized by TLC and M.P. The physicochemical parameters of imidazole derivatives were assessed using Molinspiration. According to Lipinski's rule of five compounds, 1a and 1b derivatives exhibited no violations of Lipinski's rule of five and had favorable drug-likeness scores. The bioactivity of the drug is determined by calculating the bioactivity of the various receptors such as GPCR, ion channel receptor, protein kinase receptor inhibitor, nuclear receptor, and enzyme receptor inhibitor. The compound 1a and 1b shows good bioactivity scores against all the receptors. The antibacterial report shows that compound 1a shows a maximum zone of inhibition of 37 mm against Bacillus subtilis at 0.02g/ml concentration of drug and compound 1b shows a maximum zone of inhibition of 35 mm against Bacillus subtilis at 0.02g/ml concentration.

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