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# NOVEL 7-AZAINDOLE DERIVATIVES AS POTENTIAL ANTIMICROBIAL AGENTS: SYNTHESIS, MOLECULAR DOCKING, AND PHARMACOKINETIC EVALUATION

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**ABSTRACT**

The present study contributes to the field of medicinal and heterocyclic chemistry by introducing a series of structurally novel 7-azaindole derivatives with demonstrated antimicrobial potential. The integration of an efficient synthetic strategy with biological evaluation and molecular docking provides a comprehensive framework for identifying promising lead compounds. Notably, the correlation observed between docking interactions and in vitro antimicrobial activity offers valuable insights into structure activity relationships, which can guide the rational design of more potent analogues. From a broader perspective, this research addresses the growing challenge of antimicrobial resistance by exploring new chemical scaffolds with potential therapeutic relevance. The inclusion of pharmacokinetic (ADMET) profiling further strengthens the study by evaluating drug likeness and highlighting compounds with favourable absorption and distribution characteristics, thereby reducing the risk of late-stage failure in drug development. The findings of this work are expected to influence future studies by encouraging the exploration of 7-azaindole-based hybrids as viable antimicrobial agents and by demonstrating the effectiveness of combining synthetic chemistry with computational and biological approaches. Practically, the identified lead molecules may serve as starting points for further optimisation and development into clinically relevant drugs. Overall, this study underscores the importance of interdisciplinary strategies in accelerating the discovery of new antimicrobial agents and contributes to ongoing efforts to combat drug-resistant microbial infections.

**Keywords:** 7-Azaindole, Click Chemistry, ADMET Analysis, Antimicrobial, Molecular Docking, Drug Likeness.
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## INTRODUCTION

A comprehensive review of recent studies highlights the significance of indole-based heterocyclic frameworks, particularly nitrogen containing heterocycles, in medicinal chemistry.[1] Among these, azaindoles are recognized as biologically active compounds, with their core structure acting as a versatile and attractive scaffold for drug development.[2] When there are multiple reactive sites within the azaindole framework enables diverse functionalization, facilitating extensive structural modification and optimization. The current study is aligned with Sustainable Development Goal 3 (SDG 3: Good Health and Well-being), which emphasizes the importance of ensuring healthy lives and promoting wellbeing for all. One of the major global health challenges addressed under this goal is the rapid emergence of antimicrobial resistance, which limits the effectiveness of existing therapeutic agents. In this context, the development of novel bioactive molecules with improved efficacy and safety profiles is of significant importance. The design and synthesis of 7-azaindole based derivatives, combined with their biological and computational evaluation, contribute to ongoing efforts to discover new antimicrobial agents. Thus, this research supports global initiatives aimed at combating infectious diseases and improving public health outcomes. Indole and its synthetic Derivatives display a broad spectrum of biological properties, particularly notable for their antibacterial effects[3], antimicrobial activity[4], and antioxidant activity properties.[5] Notably, heterocycles containing the 1,2,4-triazole moiety have demonstrated enhanced biological activity. Several anticancer agents incorporating 1,2,4-triazole show improved potency when conjugated with indole units. Furthermore, therapeutically approved pharmaceuticals that incorporate the 1,2,4-triazole moiety, such as letrozole (used in breast cancer therapy), ribavirin (an antiviral agent), and fluconazole (an antifungal drug), exhibit substantial pharmacological efficacy.[6] The thermal azide alkyne cycloaddition reaction originally reported by Huisgen was significantly advanced by Sharpless and Meldal through the introduction of a Cu(I) catalyst, which improved regioselectivity and reaction


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efficiency. This transformation, commonly mentioned to the "click chemistry" or copper catalyzed and azide alkyne cycloaddition (CuAAC), has been widely known as a result of its simplicity, reliability, and broad applicability in medicinal chemistry[7]. The discovery of new anticancer therapeutics remains a critical challenge for medicinal chemists. Among nitrogen containing heterocycles, 1,2,3-triazoles have attracted considerable attention due to their wide-ranging biological activities. Various compounds featuring the 1,2,3-triazole scaffold, including cefatrizine and carboxyamidotriazole, have been explored for their potential applications in cancer chemotherapy.[8] In addition to anticancer properties, 1,2,3-triazole derivatives have demonstrated notable antibacterial[9] and antifungal activities.[10] Molecular docking has emerged as a reliable, cost effective, and time efficient tool in modern drug discovery. Docking studies performed using the open-source software AutoDock Vina employ empirical scoring functions used to estimate the binding affinity of protein ligand complexes. Moreover, the SwissADME platform facilitates drug development by enabling the evaluation of physicochemical properties, ADME parameters, pharmacokinetics, drug likeness, and the compatibility of small compounds with medicinal chemistry.

## EXPERIMENTAL

### Material and Methods

Melting temperatures were found using an electrothermal apparatus using open capillary tubes and were discovered to be consistent. Thin layer chromatography (TLC) was carried out on Merck Silica Gel 60 $F_{254}$ precoated plates. Derivatives were visualized under UV light range at 254–365 nm or by exposure to iodine vapour. Infrared spectra (IR) were noted using the reduced total reflectance (ATR) technique on a Bruker ALPHA II Compact FT-IR spectrometer. $^1$H NMR ranges were acquired in DMSO-$d_6$ on a Bruker Ascend 400 MHz mass spectrometer. Mass spectra were obtained on a Waters Acquity QDa Ultra Mass Spectrometer using a direct injection probe. All substances were obtained from Loba, SRL, Merck, Spectrochem, Combi Blocks, and CDH and utilised without additional purification. Reactions took place under standard atmospheric conditions.

**General synthesis of 1-(prop-2-yn-1-yl)-1H-pyrrolo[2,3-b] pyridine-3-carbaldehyde (3)**

1*H*-pyrrolo[2,3-b] pyridine-3-carbaldehyde (1 mmol) was mixed in anhydrous DMF (10 mL) in an RBF, subsequently accompanied by the inclusion of $K_2CO_3$ (2 mmol) as a base. Propargyl bromide (1.2 mmol) was subsequently added slowly addition to the mixture under constant mixing, slowly at ambient temperature (25–30°C). The reaction combination was stirred for 4-6 hours, and the advancement was tracked with the help of thin-layer chromatography (TLC). After finishing, the reaction mixture was poured into the ice water to precipitate the product, which was gathered through filtration, washed with water, and dried under vacuum.

**General Synthesis of (Z)-2-((1-(prop-2-yn-1-yl)-1H-pyrrolo[2,3-b] pyridin-3-yl) methylene) hydrazine-1-carbothioamide (5)**

In to the RBF, 1-(prop-2-yn-1-yl)-1H-pyrrolo[2,3-b] pyridine-3-carbaldehyde (1 mmol) was added to the methanol solvent (10 mL), melted as well as acetic acid (2 mL) and added as a catalyst. Thiosemicarbazide (1.2 mmol) was then introduced to the solution, and the reaction mixture was agitated at reflux (90°C) for 3 hours. The reaction development was observed using thin layer chromatography (TLC). Once complete, the solvent was removed using a vacuum once the reaction had finished, and the solid formed crystals from the methanol to provide a pure product.

**General Synthesis of (Z)-2-(4-((3-((2-carbamothioylhydrazineylidene) methyl)-1H-pyrrolo[2,3-b] pyridin-1-yl) methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (7)**

In a round-bottom flask, (Z)-2-((1-(prop-2-yn-1-yl)-1H-indol-3-yl) methylene) hydrazine-1-carbothioamide (1 mmol) and 2-azido-N-phenylacetamide (1.2 mmol) were solved in a blend of DMF and water (v/v = 9:1). Copper sulfate ($CuSO_4$, 0.1 mmol) and sodium ascorbate (0.2 mmol) were addition as catalysts into the reaction mixture. The response was agitated at room temperature (25–30°C) for 6–8 hours, and the progress was monitored by thin-layer chromatography (TLC). After the completion. The solvent was evaporated under reduced pressure, and the residue was treated with water.

## Analytical Discussion

**(Z)-*N*-(4-bromophenyl)-2-(4-((3-((2-carbamothioylhydrazineylidene) methyl)-1*H*-pyrrolo[2,3-b] pyridin-1-yl) methyl)-1*H*-1,2,3-triazol-1-yl) acetamide (7a)**

(AA) IR Spectrum, ν, $cm^{-1}$: 1288.54 (C–O), 1681.22 (C=C), 3436.31 (NH). $^1$H NMR Spectrum, δ, ppm: 11.28 s (1H), 10.59 s (1H,), 8.73 d (1H, *J* = 7.8 Hz), 8.38 d (1H, *J* = 4.6 Hz), 8.28 s (1H), 8.16 – 8.07 m (3H), 7.69 s (1H), 7.51 t (4H, *J* = 6.3 Hz), 7.23 dd (1H, *J* = 7.8, 4.6 Hz), 5.60 s (2H), 5.30 s (2H).$^{13}$C NMR spectrum (101 MHz), DMSO-$d_6$, $\delta_C$, ppm: 164.84, 148.10, 144.51, 140.69, 138.20, 133.86, 132.21, 131.80, 125.69, 121.60, 117.90, 117.16, 115.87, 110.06, 52.66. Mass spectrum: m/z 512.39 $[M + H]^+$. Found, %: C, 48.88; H, 3.54; N, 24.61. $C_{20}H_{18}BrN_9OS$. Calculated, %: C, 48.92; H, 3.75; N, 24.88.

**(Z)-2-(4-((3-((2-carbamothioylhydrazineylidene) methyl)-1*H*-pyrrolo[2,3-b] pyridin-1-yl) methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(p-tolyl) acetamide (7b)**

(AA) IR Spectrum, ν, $cm^{-1}$: 1280.53 (C–O), 1613.57 (C=C), 3259.89 (NH). $^1$H NMR Spectrum, δ, ppm: 11.29 (s, 1H), 10.35 (s, 1H), 8.73 (d, *J* = 7.7 Hz, 1H), 8.38 (d, *J* = 4.0 Hz, 1H), 8.28 (s, 1H), 8.14 (s, 1H), 8.10 (s, 2H), 7.73 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.23 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.59 (s, 2H), 5.27 (s, 2H), 2.25 (s, 3H). $^{13}$C NMR spectrum (101 MHz), DMSO-$d_6$, $\delta_C$, ppm: 164.31, 148.12, 144.52, 140.90, 136.33, 133.93, 133.21, 131.80, 129.74, 119.66, 117.90, 117.17, 110.03, 52.64, 20.91. Mass spectrum: m/z 447.52 $[M + H]^+$. Found, %: C, 56.36; H, 4.73; N, 28.17. $C_{21}H_{21}N_9OS$. Calculated, %: C, 56.40; H, 4.78; N, 28.25.

**(Z)-2-(4-((3-((2-carbamothioylhydrazineylidene) methyl)-1*H*-pyrrolo[2,3-b] pyridin-1-yl) methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-fluorophenyl) acetamide (7c)**

(AA) IR Spectrum, ν, $cm^{-1}$: 1297.10 (C–O), 1615.62 (C=C), 3437.02 (NH). $^1$H NMR Spectrum, δ, ppm: 11.30 (s, 1H), 10.50 (s, 1H), 8.73 (d, *J* = 7.8 Hz, 1H), 8.42 – 8.35 (m, 1H), 8.29 (s, 1H), 8.15 (s, 1H), 8.11 (s, 2H), 7.76 (s, 1H), 7.57 (dd, *J* = 9.0, 5.0 Hz, 2H), 7.27 – 7.10 (m, 3H), 5.60 (s, 2H), 5.28 (s, 2H). $^{13}$C NMR spectrum (101 MHz), DMSO-$d_6$, $\delta_C$, ppm: 164.54, 148.12, 144.53, 135.25, 134.00, 131.81, 121.48, 117.93, 115.98, 52.59. Mass spectrum: m/z 451.48 $[M + H]^+$. Found, %: C, 53.21; H, 4.02; N, 27.92. $C_{20}H_{18}FN_9OS$. Calculated, %: C, 53.28; H, 4.06; N, 27.95.

**(Z)-2-(4-((3-((2-carbamothioylhydrazineylidene) methyl)-1*H*-pyrrolo[2,3-b] pyridin-1-yl) methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-chlorophenyl) acetamide (7d)**

(AA) IR Spectrum, ν, $cm^{-1}$: 1295.44 (C–O), 1691.35 (C=C), 3439.82 (NH). $^1$H NMR Spectrum, δ, ppm: 11.28 (s, 1H), 10.65 (s, 1H), 8.72 (d, *J* = 7.8 Hz, 1H), 8.41 – 8.34 (m, 1H), 8.29 (s, 1H), 7.82 (s, 1H), 7.75 (s, 1H), 7.69 (s, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 5.60 (s, 2H), 5.32 (s, 2H). $^{13}$C NMR spectrum (101 MHz), DMSO-$d_6$, $\delta_C$, ppm: 185.79, 165.08, 148.11, 145.28, 144.52, 140.94, 140.74, 133.87, 133.66, 131.79, 131.11, 123.99, 119.18, 117.90, 117.17, 110.06, 52.66. Mass spectrum: m/z 467.93 $[M + H]^+$. Found, %: C, 51.34; H, 3.88; N, 26.94. $C_{20}H_{18}ClN_9OS$. Calculated, %: C, 51.37; H, 3.90; N, 26.96.

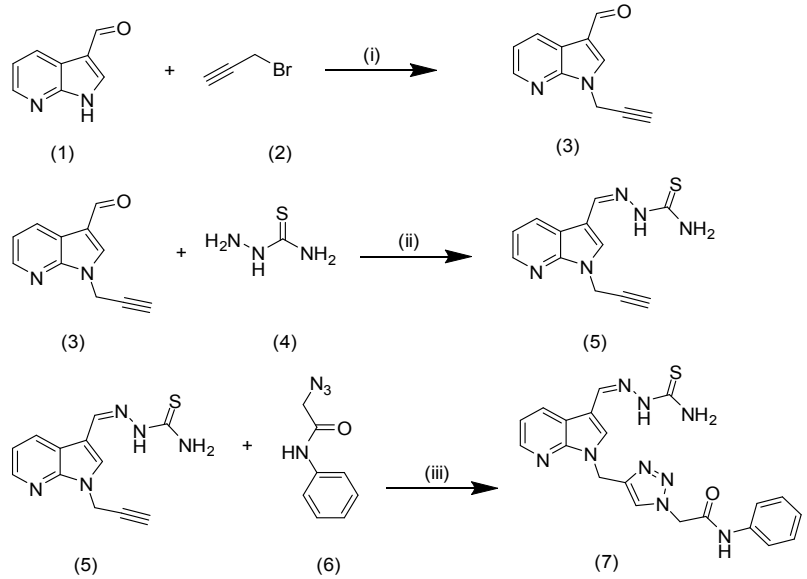
**(Z)-2-(4-((3-((2-carbamothioylhydrazineylidene) methyl)-1*H*-pyrrolo[2,3-b] pyridin-1-yl) methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-methoxyphenyl) acetamide (7e)**

(AA) IR Spectrum, ν, $cm^{-1}$: 1286.28 (C–O), 1666.56 (C=C), 3434.82 (NH). $^1$H NMR Spectrum, δ, ppm: 11.28 (s, 1H), 10.31 (s, 1H), 8.73 (d, *J* = 7.9 Hz, 1H), 8.42 – 8.35 (m, 1H), 8.29 (s, 1H), 8.17 – 8.07 (m, 3H), 7.69 (s, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.23 (dd, *J* = 7.9, 4.6 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.60 (s, 2H), 5.26 (s, 2H), 3.71 (s, 3H). $^{13}$C NMR spectrum (101 MHz), DMSO-$d_6$, $\delta_C$, ppm: 164.06, 155.99, 148.11, 144.51, 140.65, 133.85, 131.93, 131.79, 121.23, 117.89, 117.17, 114.47, 110.07, 55.62, 52.60. Mass spectrum: m/z 463.52 $[M + H]^+$. Found, %: C, 54.42; H, 4.57; N, 27.20. $C_{21}H_{21}N_9O_2S$. Calculated, %: C, 54.47; H, 4.59; N, 27.25.

## RESULTS AND DISCUSSION

The objective of this research was to employ click chemistry for the creation and development of innovative 7-azaindole hybrid derivatives to assess their antibacterial properties. The incorporation of propionic acid and amide linkages in the target molecules is illustrated in Scheme-1. Earlier studies have indicated that 1,2,3-triazole derivatives bearing amide functionalities show a broad spectrum of biological

activities[11]. Accordingly, N-propargylation and the 7-azaindole structure was conducted by employing propargyl bromide as a reagent and potassium carbonate ($K_2CO_3$) in dimethylformamide (DMF) at Ambient temperature, affording the corresponding terminal alkyne intermediate in 92% yield.




Scheme-1: Preparation of the 7-azaindole Series 1,2,3-triazole Derivatives. *i*) $K_2CO_3$, DMF, RT; *ii*) AcOH, MeOH, Reflux 80℃; *iii*) $CuSO_4$, Sodium Ascorbate, DMF: $H_2O$, RT. R= 4-Br (a); 4-$CH_3$ (b); 4-F (c); 4-Cl (d); 4-$OCH_3$

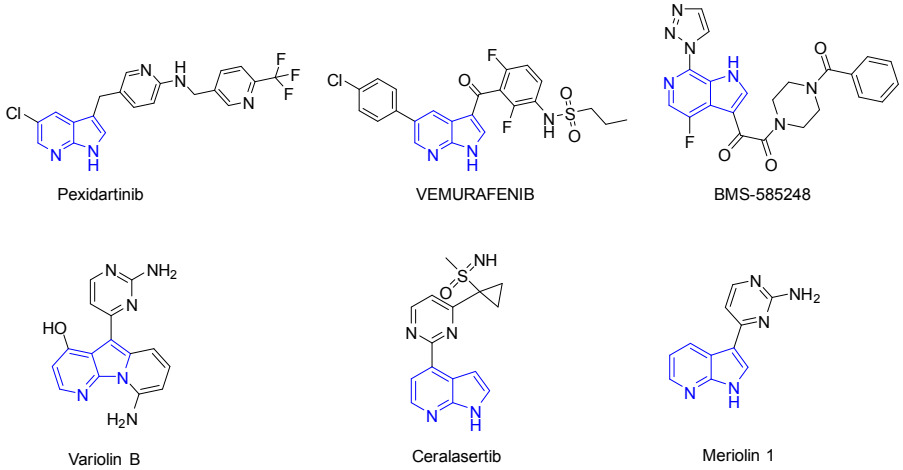



Fig.-1: Pharmaceutically Significant Drug Candidates Including 7-azaindole Structures

The generation of the synthesized structure of the compound was verified through spectroscopic characterization. In the $^1$H NMR spectrum, the NH hydrogen of the thiosemicarbazide moiety looked as a singlet at δ 11.28, while another NH proton associated with the N-phenylpropanamide group regarding the 7-azaindole ring was observed as a singlet at δ 10.59. The alkene proton resonated as a singlet in the range of δ 5.60–5.30. The aromatic protons of the fused 7-azaindole ring system appeared between δ 8.73 and 7.23. The IR spectrum displayed a characteristic N–H stretching vibration of the 7-azaindole ring at approximately 3142 cm$^{-1}$. In addition, the terminal alkyne exhibited C–H and C≡C stretching bands at around 3273 cm$^{-1}$ and 2995 cm$^{-1}$, respectively. The molecular ion peaks detected in the mass spectra validated the molecular weights of the synthesized compounds.[12] Notably, compound **7a** showed a prominent Compound ion peak at m/z 512.39, consistent with the proposed molecular formula $C_{20}H_{18}BrN_9OS$.

In this research, we set out to synthesise novel molecular hybrids by integrating 7-azaindole and 1,2,3-triazole units, as illustrated in Fig.-2, and evaluate their biological activity as part of our ongoing exploration of fresh heterocyclic substances with potential medical applications.

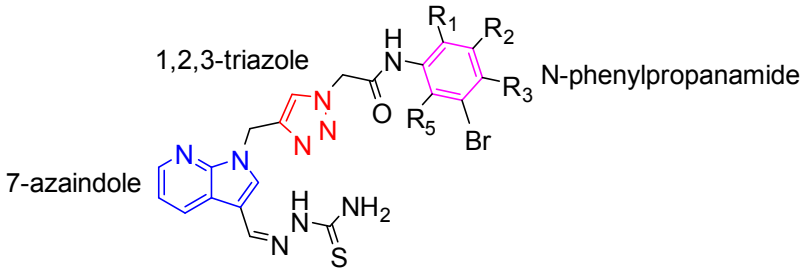



Fig.-2: Molecular Design Based on the Hybridization Strategy

Table-1: Optimization of Reaction Parameters

| S. No. | Solvent | Catalyst | Time (h) | Yield (%) | Purification |
|---|---|---|---|---|---|
| 1 | DMF: DMSO | CuCl | 6 | 22 | Yes |
| 2 | Ethanol: $H_2$ O | $CuSO_4$ , Sodium ascorbate | 10 | 33 | Yes |
| 3 | Acetonitrile: $H_2$ O | $CuCl_2$ | 11 | 39 | Yes |
| 4 | t-BuOH: Acetone | CuI | 16 | 42 | Yes |
| 5 | DMF: $CH_3$ CN | Cu $(OAc)_2$ , Sodium ascorbate | 21 | 48 | Yes |
| 6 | Ethanol: $CH_2$ $Cl_2$ | $CuSO_4$ , Sodium ascorbate | 27 | 63 | Yes |
| 7 | t-BuOH: $CH_3$ CN | $CuCl_2$ , Sodium ascorbate | 9 | 70 | Yes |
| 8 | DMF: DMSO | Cu $(OAc)_2$ , Sodium ascorbate | 7 | 84 | Yes |
| 9 | Methanol: $H_2$ O | $CuCl_2$ , Sodium ascorbate | 5 | 88 | Yes |
| 10 | Acetone: $H_2$ O | $CuSO_4$ , Sodium ascorbate | 8 | 91 | Yes |

The initial attempt involved conducting the reaction at room temperature in the presence of both solvent and catalyst however product formation was not detected (Table-1, Entry 1). Subsequently a solvent system comprising DMF: DMSO was employed with CuCl as the catalyst. After 6 h, the reaction afforded a 22% yield, and the product was separated without additional purification (Table-1, Entry 2). In another trial, an ethanol: A combination of water and solvent was utilised. in the presence of CuSO4 and sodium ascorbate as the catalytic system.[13] The reaction proceeded for 10 h, giving a 33% yield without the need for purification (Table-1, Entry 3). When acetonitrile: water was employed as the solvent with $CuCl_2$ as the catalyst, the reaction required 11 h and resulted in a 39% yield; purification was necessary (Table-1, Entry 4). Using a tert-butanol: acetone solvent system with CuI as the catalyst, the reaction was finished in 16 h, affording a 42% yield, and the product required purification (Table 1, Entry 5). A further increase in yield (48%) was achieved using DMF: $CH_3CN$ as the solvent and Cu $(OAc)_2$ with sodium ascorbate as the catalyst after 21 h; purification was required (Table-1, Entry 6). When Ethanol: $CH_2Cl_2$ was working as the solvent system in the existence of $CuSO_4$ and sodium ascorbate, the reaction proceeded over 27 h and delivered a 63% yield, with purification of the product necessary (Table-1, Entry 7). A tert-butanol: $CH_3CN$ solvent mixture with $CuCl_2$ and sodium ascorbate significantly improved the reaction efficiency, affording a 70% yield within 9 h (Table-1, Entry 8). Further optimization using DMF: DMSO as the solvent system and Cu $(OAc)_2$ with sodium ascorbate reduced the reaction time to 7 h and increased the yield to 84%; purification was required (Table-1, Entry 9). The best outcomes were attained using methanol: water as the solvent when there is $CuCl_2$ and sodium ascorbate, where the reaction was completed within 5 h to afford an 88% yield (Table-1, Entry 10). Finally, acetone: water with $CuSO_4$ and sodium ascorbate provided the highest yield of 91% after 8 h, although purification was still necessary. Under the optimized reaction conditions, this protocol was subsequently applied to the combination of several unique indole derivatives, as summarized in Table-2.

The structural characterization of the recently created substances was established through comprehensive spectral analysis and elemental evaluation.[14] All compounds (7a–7e) were characterized using $^1H/^{13}C$ NMR, mass spectrometry, and infrared spectroscopy, along with the assessment of their physical properties and elemental composition. Structural confirmation was achieved by the appearance of two singlet signals matching the –NH protons in the range of δ 10.59–11.27 ppm, along with triplet signals attributed to methyl protons appearing between δ 2.5–4.2 and 2.9–4.6 ppm. The aromatic hydrogens

resonated within the δ 7.52–8.78 ppm region. The compound weights among the produced substances were further verified by the existence of characteristic molecular ion peaks in their respective mass spectra. For instance, compound 7a exhibited a structure ion peak at m/z 512.39, consistent with the calculated molecular formula $C_{20}H_{18}BrN_9OS$.

Table-2: The Physicochemical Properties of 7-azaindole Derivatives

| Compound | Structure formula | MW | Yield, % | MP, ℃ |
|---|---|---|---|---|
| 7a | $C_{20}H_{18}BrN_9OS$ | 512.39 | 88 | 240-243 |
| 7b | $C_{21}H_{21}N_9OS$ | 447.52 | 79 | 257-260 |
| 7c | $C_{20}H_{18}FN_9OS$ | 451.48 | 91 | 265-268 |
| 7d | $C_{20}H_{18}ClN_9OS$ | 467.94 | 78 | 249-252 |
| 7e | $C_{21}H_{21}N_9O_2S$ | 463.52 | 92 | 225-227 |

*MW- Molecule weight, Melting Point

Table-3: The physicochemical, Pharmacokinetic, and Medicinal Chemistry Profiles of the Synthesized Compounds

| Compound | Physicochemical properties | | | | | | pharmacokinetic | | Medicinal Chemistry | |
|---|---|---|---|---|---|---|---|---|---|---|
| | MW | HBA | HBD | TSPA | Log $P_{o/w}$ | Log *S* | GIA | Log K*p* | RoF (V) | SA |
| 7a | 512.39 | 5 | 3 | 160.13 | 2.83 | -3.91 | Low | -8.27 | No | 3.43 |
| 7b | 447.52 | 5 | 3 | 160.13 | 2.58 | -3.31 | Low | -8.10 | No | 3.50 |
| 7c | 451.48 | 6 | 3 | 160.13 | 2.49 | -3.16 | Low | -8.32 | No | 3.39 |
| 7d | 467.93 | 5 | 3 | 160.13 | 2.61 | -3.60 | Low | -8.04 | No | 3.39 |
| 7e | 463.52 | 6 | 3 | 169.36 | 2.86 | -3.08 | Low | -8.47 | No | 3.50 |
| Erythromycin | 502.60 | 10 | 2 | 137.82 | 1.77 | -2.37 | Low | -2.31 | No | 7.5 |

*MW Molecular weight, HBA H-bond acceptor, HBD H-bond donor, TPSA-topological polar surface area, Log Po/w-lipophilicity, Log S-water solubility, GIA- gastrointestinal absorption, Log Kp skin permeation, RoF (V)-Lipinski's rule of five, SA- synthetic accessibility.

**Prediction of the ADMET Properties**

A lot of possible medication possibilities are rejected during the drug discovery process owing to unfavorable physicochemical and pharmacokinetic aspects. In the early stages of research, these limitations can be efficiently addressed through computational ADMET analyses of newly synthesized compounds. Table-3 summarizes the predicted ADMET parameters of the synthesized 7-azaindole derivatives (7a–7e), including hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), topological polar surface area (TPSA), lipophilicity (Log $P_o$/w), water solubility (Log S), gastrointestinal absorption (GIA), skin permeation coefficient (Log Kp), compliance with Lipinski's rule of five [RoF(v)], and synthetic accessibility (SA). As indicated by lipophilicity values (Log $P_o$/w) below 4 (ranging from 2.16 to 3.92) and water solubility values (Log S) greater than −6 (ranging from −3.07 to -5.74). Nearly all compounds complied with Lipinski's rule of five, suggesting good drug-like properties.[15] Furthermore, synthetic accessibility analysis was used to assess the structural complexity of the synthesized molecules. The results indicated that none of the 7-azaindole derivatives possessed a highly complex synthetic route with SA scores ranging from 3.39 to 3.73. All ADMET forecasts were made computationally utilising the SwissADME online platform.[16]

**Methodology for Conducting the Molecular Docking Study**

Designing the ligand structures was prepared with ChemSketch (version 2023.2.3) and investigations using molecular docking were carried out. with AutoDock Vina (version 1.5.7). The 3D structure of Mycobacterium synthase (PDB ID: 1EA1) was taken from the Protein Data Bank. (PDB). Before docking, heteroatoms were removed to eliminate any bound ligands currently in the receptor structure. There was water molecules found, followed by the addition of polar hydrogens and Kollman charges to the protein. The docking grid box was defined with dimensions of 40 × 40 × 40 Å along the x, y, and z axes, respectively. The coordinates of the grid centre were established at x = −17.295136, y = −2.725364, and z = 66.752636. A grid point spacing of 0.375 Å was applied, and the exhaustiveness parameter was set to

40 to ensure thorough conformational sampling. The predicted binding modes and protein ligand interactions were examined in more detail utilising Discovery Studio Visualizer (v21.1.0.20298).

**Computational Docking Studies**

Molecular docking studies of Escherichia *coli* cytochrome P450 14α-sterol demethylase were carried out with AutoDock Vina to find possible binding locations and assess the synthetic chemical's binding affinities.[17] The crystal structure of cytochrome P450 14α-sterol demethylase (PDB ID: 1EA1) was taken out of the Protein Data Bank. This enzyme was selected as the docking target owing to its crucial role in essential metabolic pathways in *E. coli*, making it a relevant target for antibacterial drug discovery. To validate the docking protocol, the ligand that is co-crystallised was extracted based on the crystal structure and redocked into the active site of the enzyme. The correctness and dependability of the docking methods[18] were confirmed when the redocked ligand was superimposed with the native ligand, resulting in a root mean square deviation (RMSD) value < 1.5Å. To guarantee stable conformations, all synthesised compound's 3D structures were optimised using energy reduction before docking.[19] For every freshly synthesised molecule, docking simulations were performed (7a–7e). The results revealed that the ligands interacted with key active site amino acid residues predominantly through hydrogen bonding interactions, including ARG A:326, ALA A:389, ALA A:256, THR A:260, CYS A:394, HIS A:392, LEU A:321, TYR A:76, MET A:79, PHE A:78, and MET A:433. An immediate list of the required energies, hydrogen bond interactions and active site residues is presented in Table-4. The synthesized compounds exhibited favorable binding energies ranging from −6.6 to −7.4 kJ/mol indicating strong interactions with the target enzyme. suggesting superior binding affinity.[20] Compound **7a** designed a hydrogen bond with ARG A:326, achieving a docking score of −9.4. Compound **7b** interacted with ARG A:326, GLN A:72, ARG A:96, and TYR A:76, resulting in a docking score of −9.6, while compound **7c** established a hydrogen bond with CYS A:394, with a score of −9.5. Compound **7d** formed hydrogen bonding interactions with GLN A:72 and showed a docking score of −8.7. Compound **7e** interacted with HIS A:392 and PHE A:387, achieving a docking score of −9.6. Overall, the docking results demonstrate strong and consistent interactions between the synthesise 7-azaindole derivatives and the dynamic place of cytochrome P450 14α-sterol demethylase, supporting their potential as promising antibacterial candidates.[21]

Table-4: Docking of 7-azaindole Molecules 7a–7o

| Compound | Binding energy, kJ/mol | Active site residues | No. of H-bonds |
|---|---|---|---|
| 7a | –9.4 | ARG A:326 | 1 |
| 7b | –9.6 | ARG A:326, GLN A:72, ARG A:96, TYR A:76 | 4 |
| 7c | –9.5 | CYS A:394 | 1 |
| 7d | –8.7 | GLN A:72 | 1 |
| 7e | –9.6 | HIS A:392, PHE A:387 | 2 |

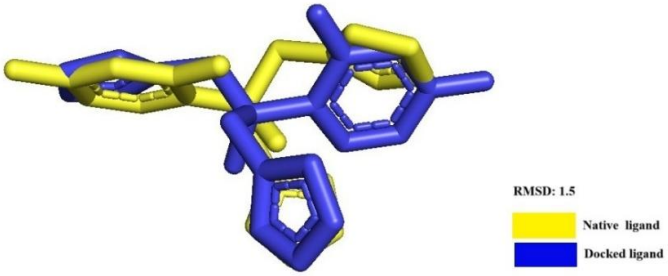



Fig.-3: Validation of the Molecular Docking Approach

**Evaluation of Biological Activity**

The synthesis of sulfadimidine derivatives 7a–7e was assessed for their antibacterial efficacy. against a panel of both Gram positive and Gram-negative bacterial strains, along with clinically significant fungal species. Aspergillus niger, Aspergillus clavatus, and Candida albicans were tested for antifungal activity, whereas Escherichia coli, Pseudomonas aeruginosa, Streptococcus pyogenes, and Staphylococcus aureus were evaluated for antibacterial activity.[22]

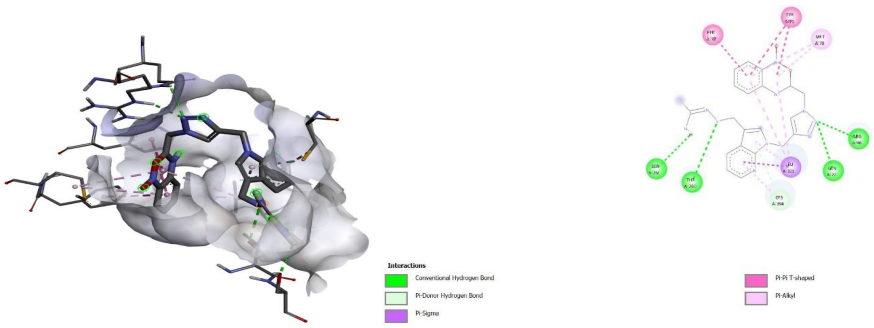



Fig.-4: Docking Position of 7b with E. coli Cytochrome P450 14 Alpha-Sterol Demethylase Synthase

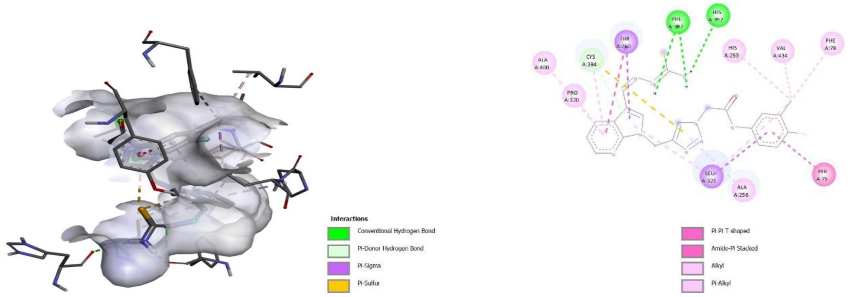



Fig.-5: Docking Position of 7e with E. coli Cytochrome P450 14 alpha-sterol Demethylase Synthase

Ciprofloxacin and fluconazole remained employed as reference standards for antibacterial and antifungal activity, respectively. Among the tested compounds, derivatives 7a-7e exhibited moderate to robust antimicrobial and antifungal activities with values of the minimum inhibitory concentration (MIC) falling between 64 and 128 µg/mL against all tested strains. Notably compound **7c** displayed a consistent inhibition profile, showing MIC values of 64 µg/mL against E. coli and S. aureus, and 128 µg/mL against P. aeruginosa and S. pyogenes, along with comparable antifungal activity. Similarly, compound **7c** demonstrated activity profiles comparable to those of **7b** across both bacterial and fungal strains. The findings of the antifungal screening showed that substance **7c** exhibited the most pronounced antifungal activity, effectively inhibiting Aspergillus niger, Aspergillus clavatus and Candida albicans at the lowest dosage of inhibition (MIC) values of 128 µg/mL. These findings suggest a potential structure activity relationship (SAR), in which specific functional groups within the sulfonamide triazole moiety may enhance membrane permeability or interfere with key fungal enzymatic pathways.[23] The reference drugs established superior antimicrobial potency with ciprofloxacin exhibiting antibacterial activity at MIC values ranging from 1 to 4 µg/mL, while fluconazole showed effective antifungal inhibition with MIC values between 2 and 4 µg/mL.[24] These results validate the reliability and reproducibility of the applied assay protocols.

Table-5: Biological Activity Studies

| Antibacterial Activity | | | | | Antifungal Activity | | |
|---|---|---|---|---|---|---|---|
| Compound | E. coli | P. aeruginosa | S. pyogenes | S. aureus | A. niger | A. clavatus | C. albicans |
| 7a | 32 | 64 | 16 | 32 | 64 | 32 | 64 |
| 7b | 16 | 32 | 8 | 16 | 32 | 16 | 32 |
| 7c | 64 | 128 | 32 | 64 | 128 | 64 | 128 |
| 7d | 8 | 16 | 4 | 8 | 16 | 8 | 16 |
| 7e | 16 | 32 | 8 | 16 | 32 | 16 | 32 |
| Ciprofloxacin | 2 | 4 | 1 | 2 | - | - | - |
| Fluconazole | - | - | - | - | 4 | 2 | 4 |

## CONCLUSION

This study reports that a newly developed series of 7-azaindole derivatives was successfully designed and synthesized, and their constructions were verified by comprehensive spectral analyses, including NMR, FT-IR, and mass spectrometry. All synthesized compounds were evaluated for their antibacterial and

antifungal activities. Several derivatives demonstrated moderate to strong antimicrobial action against bacteria that are Gram positive (*Staphylococcus aureus* and *Streptococcus pyogenes*), Gram negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*), as well as having antifungal properties against Aspergillus niger, *Aspergillus clavatus*, and *Candida albicans*. Compounds **7c** exhibited broad-spectrum antimicrobial activity with minimum inhibitory concentration (MIC) values ranging from 64 to 128 µg/mL. Moderate activity was observed for compound **7a** whereas derivatives presented the maximum potency, with MIC values as low as 2–8 µg/mL. Furthermore, molecular docking studies exposed that compounds **7b** and **7e** achieved the highest docking scores (−9.6) and exhibited strong binding affinities toward *E. coli* cytochrome P450 14α-sterol demethylase, supporting their observed biological activity.

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## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-Being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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## REFERENCES

1. S. Narva, S. Chitti, B. R. Bala, M. Alvala, N. Jain, V. G. C. S. Kondapalli, *European Journal of Medicinal Chemistry*, **114**, 220(2016), https://doi.org/10.1016/j.ejmech.2016.02.059.
2. A. M. S. Krishna, H. B. Gandham, K. R. Valluru, N. S. K. Rao, G. Sridhar, V. R. Battula, *Chemistry Data Collections*, **34**, 100743(2021), https://doi.org/10.1016/j.cdc.2021.100743.
3. M. P. Giovannoni, N. Cantini, L. Crocetti, G. Guerrini, A. Iacovone, I. A. Schepetkin, C. Vergelli, A. I. Khlebnikov, M. T. Quinn, *Drug Development Research*, **80**, 617(2019), https://doi.org/10.1002/ddr.21539.
4. M. Kashetti, M. Krishna Vanga, K. Chevula, V. Kuchana, V. Manga, *ChemistrySelect*, **9**, e202403149 (2024), https://doi.org/10.1002/slct.202403149.
5. M. K. Vanga, R. Bhukya, V. Thumma, S. S. S. S. S. Ambadipudi, V. L. Nayak, S. B. Andugulapati, V. Manga, *RSC Medicinal Chemistry*, **15(5)**, 1709(2024), https://doi.org/10.1039/D4MD00015C.
6. A. F. Zahoor, S. Saeed, A. Rasul, R. Noreen, A. Irfan, S. Ahmad, S. Faisal, S. A. Al-Hussain, M. A. Saeed, M. T. Muhammed, Z. A. Muhammad, M. E. A. Zaki, *Biomedicines*, **11**, 3078(2023), https://doi.org/10.3390/biomedicines11113078.
7. K. Sharma, R. K. Tittal, K. Lal, R. S. Mathpati, D. Vikas Ghule, *New Journal of Chemistry*, **47(19)**, 9077(2023), https://doi.org/10.1039/D3NJ00223C.
8. V. Mallikanti, V. Thumma, K. C. Veeranki, S. Gali, J. Pochampally, *ChemistrySelect*, **7**, e202204020 (2022), https://doi.org/10.1002/slct.202204020.
9. V. K. Chaitanya, P. Jalapathi, M. R. Chandar, T. Vishnu, M. Veerabhadraiah, M. Raghavender, *Journal of the Iranian Chemical Society*, **20**, 995(2023), https://doi.org/10.1007/s13738-022-02737-y.
10. D. Veeranna, L. Ramdas, G. Ravi, S. Bujji, V. Thumma, J. Ramchander, *ChemistrySelect*, **7**, e202201758(2022), https://doi.org/10.1002/slct.202201758.

11. A. Chaouni-Benabdallah, C. Galtier, H. Allouchi, A. Kherbeche, O. Chavignon, J.-C. Teulade, M. Witvrouw, C. Pannecouque, R. Snoeck, G. Andrei, J. Balzarini, E. De Clercq, F. Fauvelle, C. Enguehard, A. Gueiffier, *Chemical and Pharmaceutical Bulletin*, **49**, 1631(2001), https://doi.org/10.1248/cpb.49.1631.
12. S. Tancredi, A. Chiolero, C. Wagner, M. L. Haller, P. Chocano-Bedoya, N. Ortega, N. Rodondi, L. Kaufmann, E. Lorthe, H. Baysson, S. Stringhini, *Infection*, **51(5)**, 1453(2023), https://doi.org/10.1007/s15010-023-02038-2.
13. S. V. Akolkar, A. A. Nagargoje, M. H. Shaikh, M. Z. A. Warshagha, J. N. Sangshetti, M. G. Damale, B. B. Shingate, *Archiv der Pharmazie*, **353**, 2000164(2020), https://doi.org/10.1002/ardp.202000164.
14. Z. Batool, S. Ullah, A. Khan, F. Siddique, S. Nadeem, A. Alshammari, N. A. Albekairi, R. Talib, A. Al-Harrasi, Z. Shafiq, *RSC Advances*, **14(39)**, 28524(2024),https://doi.org/10.1039/D4RA05015K.
15. B. Daydé-Cazals, B. Fauvel, M. Singer, C. Feneyrolles, B. Bestgen, F. Gassiot, A. Spenlinhauer, P. Warnault, N. Van Hijfte, N. Borjini, G. Chevé, A. Yasri, *Journal of Medicinal Chemistry*, **59**, 3886(2016), https://doi.org/10.1021/acs.jmedchem.6b00087.
16. R. García-Vázquez, E. P. Rebitski, L. Viejo, C. de los Ríos, M. Darder, E. M. García-Frutos, *Applied Clay Science*, **189**, 105541(2020), https://doi.org/10.1016/j.clay.2020.105541.
17. C. Gill, G. Jadhav, M. Shaikh, R. Kale, A. Ghawalkar, D. Nagargoje, M. Shiradkar, *Bioorganic and Medicinal Chemistry Letters*, **18**, 6244(2008), https://doi.org/10.1016/j.bmcl.2008.09.096.
18. T. Irie, M. Sawa, *Chemical and Pharmaceutical Bulletin*, **66**, 29(2018), https://doi.org/10.1248/cpb.c17-00380.
19. D. R. Motati, R. Amaradhi, T. Ganesh, *Organic Chemistry Frontiers*, **8(3)**, 466(2021), https://doi.org/10.1039/D0QO01079K.
20. M. Nagamani, T. Vishnu, P. Jalapathi, M. Srinivas, *Journal of the Iranian Chemical Society*, **19**, 1049(2022), https://doi.org/10.1007/s13738-021-02365-y.
21. A. A. E. T. N. Shareefa Ahmed Saleh Alzahrani, M. Mahboob, *Polycyclic Aromatic Compounds*, **43**, 3380(2023), https://doi.org/10.1080/10406638.2022.2069133.
22. K. Sharma, B. Lal, R. K. Tittal, K. Lal, L. Vats, D. Vikas Ghule, *ChemMedChem*, **19**, e202400451 (2024), https://doi.org/10.1002/cmdc.202400451.
23. R. Vadlakonda, R. Nerella, S. V. Srinivas, *Rasayan Journal of Chemistry*, **10**, 1316(2017), https://doi.org/10.7324/RJC.2017.1041914.
24. B. Zhang, *European Journal of Medicinal Chemistry*, **168**, 357(2019), https://doi.org/10.1016/j.ejmech.2019.02.055.

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