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# Greener Synthesis, In-Silico and Theoretical Analysis of Hydrazides as Potential Antituberculosis Agents (Part 1) †

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**Abstract:** Since several decades, our healthcare burden has been increased due to tremendous cases of multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) infections especially in tropical countries. In present study, we have synthesized ten hydrazides with the use of greener **Chitosan-derived** catalyst. This catalyst accomplished the said condensation reaction within **15–30 min** at room temperature conditions. All our synthesized compounds showed stronger affinities against *mycobacterium tb* and bacterial targets, especially towards 1d7u than the standard drug ciprofloxacin. One of our compounds retained with lower toxicity (electrophilicity index (ω) **3.1304**), low chemical hardness (η: **2.1740**), and high softness (S: **0.4600**). In the realm of development of more potent, effective, safer antituberculosis agents with effective greener synthesis; our current study would provide more insights on potent analogues containing hydrazine motifs in them.

**Keywords:** hydrazide-hydrazones; antituberculosis activity; in-silico analysis; tuberculosis; synthesis; molecular modelling

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## 1. Introduction

The antimicrobial resistance is a severe global healthcare threat, which is hampering the quality of human life [1–4]. Searching for the potent, safe and effective agents is still a difficult task for medicinal chemists all over the world. Tuberculosis (TB) remains a major global healthcare threat as reported in W.H.O in 2019 [4]. Hydrazide–hydrazones motifs were reported for their wider pharmacological potentials like anticonvulsant, anticancer, antiviral, etc. [4]. Considering stronger antimicrobial potentials of Hydrazide–hydrazones having azomethine group (–NH–N=CH–), we decided to synthesis newer hydrazides using a greener catalyst, *Chitosan hydrochloride* and tested (3a–3j) theoretically for their antimicrobial potentials using several computational approaches [5]. These attempts would also enlighten on probable anti-TB mechanisms of previously (in-vitro) tested hydrazides [6,7]. Moreover, recently our group has also reported anti-TB potentials of varieties of potent Hydrazide–hydrazone derivatives.

## 2. Materials and Methods

All the necessary chemicals required for Schemes 1 and 2 (Figure 1) were procured from Sigma-Aldrich and Merck. Raw chitosan (MW = 50,000–190,000 Dalton) was purchased from Sigma-Aldrich. All compounds were synthesized according to the previous literature and characterized once again using various spectroscopic techniques, like proton magnetic resonance (1H-NMR), FT-IR (Infrared spectroscopy), etc. Exhaustive details

on catalyst characterization and methods are provided in the supporting information and data is coherent with the previous literature.

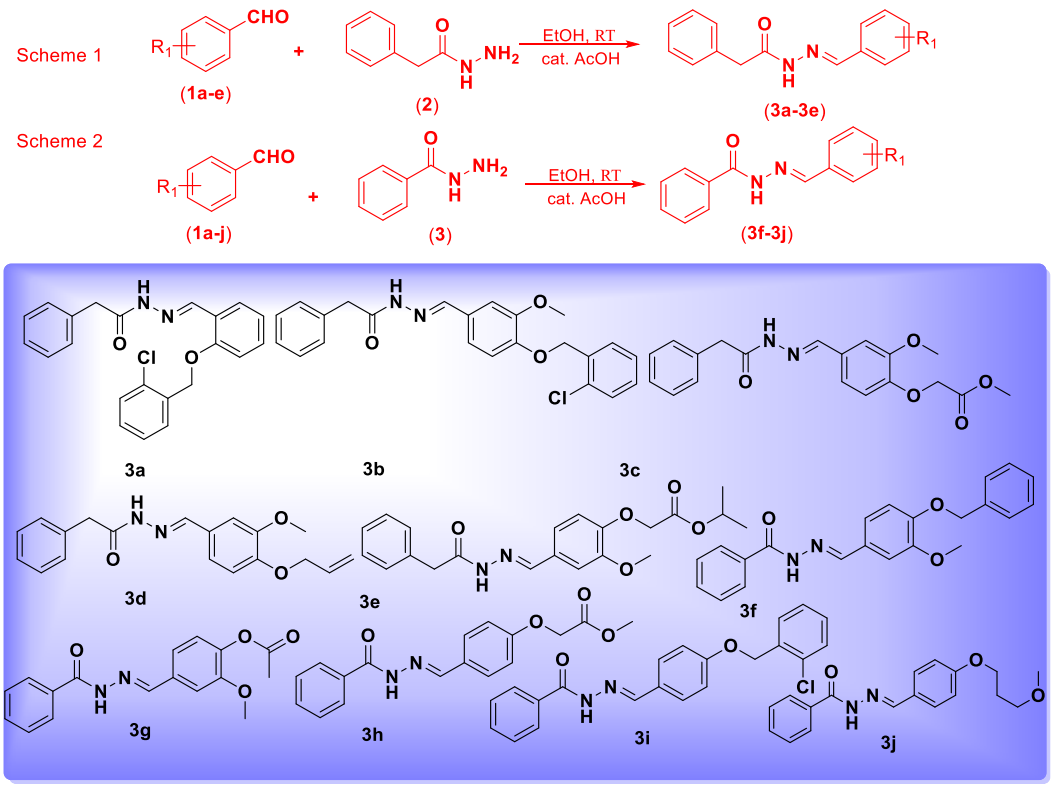


**Figure 1.** Schematic representation of synthesis schemes employed and studied hydrazide derivatives (3a–3j).

### *2.1. Preparation of Chitosan-HCl Catalyst*

We have synthesized newly chitosan-HCl catalyst by taking raw chitosan (1 g) and allowed it to dissolve in 75 $cm^3$ of 1% HCl. The stirring rate was maintained at 800 rpm along with frequent heating at 40 °C. Furthermore, the mixture was allowed to pass through cotton to filter undissolved mass. Finally, filtrate was collected and dried to get the catalyst [5].

### *2.2. Synthesis of Derivatives of Hydrazones (3a–3j)*

For the synthesis of hydrazides (3a–3j), we took equal amounts of phenyl acetohydrazine (**2**) (Scheme 1) or benzohydrazine (0.1 mmol, **3**, Scheme 2) and various substituted aldehydes (1a–1j) in round bottom flask containing catalytic amount of chitosan hydrochloride (20% *w*/*w*)/ethanol (Figure 1) [6,7]. This reaction mixture was stirred at room temperature until completion. Crude solid products obtained were then washed with cold alcohol and characterized. All reactions were completed within 15–20 min.

### *2.3. Molecular Docking and Theoretical Analysis*

Structures of all compounds were drawn using 'ChemDraw V. 12.1' and converted into 3D formats. The optimized structures were then docked using 'Glide' module from *Schrodinger, LLC, NY suite, 2021 [8]*. All 3D crystal structures for docking were downloaded from the protein database bank (PDB database, www.rcsb.org) [9]. Docking was carried out using known protocols (Table 1) [1,2]. The gas-phase structures of the synthesized compounds (shown in Figure 2) were optimized by means of density functional theory (DFT). The DFT calculation was performed by the hybrid B3LYP method, which is based on the idea of Becke and considers a mixture of the exact (HF) and DFT exchange

utilizing the B3 functional, together with the LYP correlation functional. The B3LYP calculations were performed in conjunction with the basis set 6-311++G** (Table 2) [1].

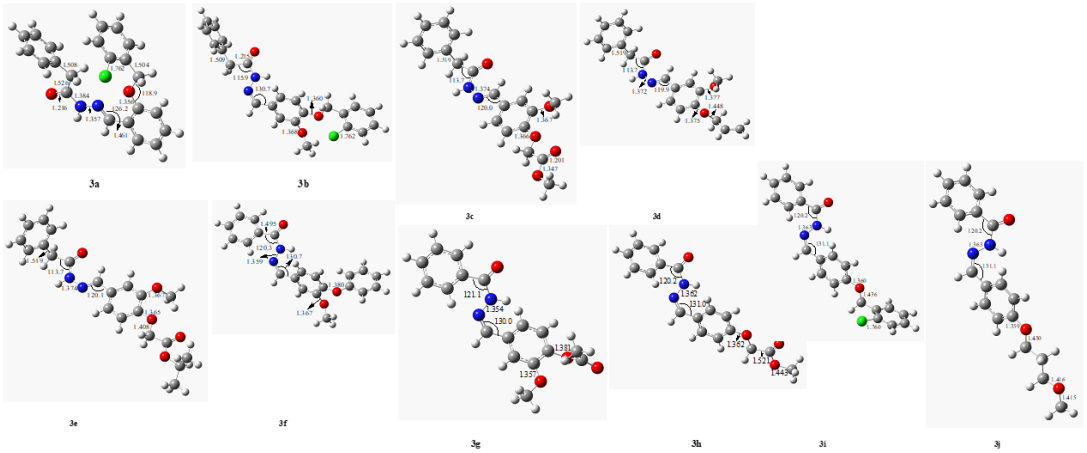

**Figure 2.** The B3LYP-optimized geometries of 3a~3j (bond lengths in Å and bond angles in).

**Table 1.** Glide docking score for the best docked molecule, **3e** along with interacted amino acid residues against various antimicrobial targets.

| Sr. No. | Target (PDB Id) | Residues with Contribution Energy (kcal/mol) |
|---|---|---|
| 1 | 1ai9 (*candida albicans* dihydrofolate reductase) | LYS 57, ALA 115, THR 58, ARG 56 **(−7.2)** |
| 2 | 1d7u (2,2-dialkylglycine decarboxylase) | ARG406, LYS 272, ASN 394, SER 271, TRP 138 **(−9.746)** |
| 3 | 2x22 (enoyl acyl carrier enzyme) | ALA191, PRO 193, THR 196, MET 199, ILE 202, TRP 222 (−8.32) |
| 4 | 2xcs (*S. aureus* Gyrase complex) | **DG E:10, DC E:11, DG F:10, DC F:11 (−5.47)** |
| 5 | 3ivx (*mycobacterial* pantothenate synthase) | GLN 72, TYR 82, LYS 160, HIS 47, THR 186, VAL 184, VAL 187, ALA 49 **(−9.23)** |

**Table 2.** Calculated quantum chemical descriptors.

| Comp.Id | EHOMO (eV) | ELUMO (eV) | Gap, D (Debye) | μ (eV) | η (eV) | S (eV-1) | ω (eV) |
|---|---|---|---|---|---|---|---|
| **3a** | −6.0906 | −1.6796 | 4.7314 | 3.8851 | 2.2055 | 0.4534 | 3.4219 |
| **3b** | −6.2155 | −1.5537 | 5.8692 | 3.8846 | 2.3309 | 0.4290 | 3.2369 |
| **3c** | −5.8994 | −1.5409 | 5.1159 | 3.7201 | 2.1793 | 0.4589 | 3.1753 |
| **3d** | −6.1532 | −1.6587 | 1.7175 | 3.9059 | 2.2473 | 0.4450 | 3.3944 |
| **3e** | −5.8632 | −1.5153 | 5.3443 | 3.6893 | **2.1740** | **0.4600** | **3.1304** |
| **3f** | −6.5476 | −1.8888 | 3.7701 | 4.2182 | 2.3294 | 0.4293 | 3.8192 |
| **3g** | −6.6409 | −2.0006 | 5.4182 | 4.3207 | 2.3202 | 0.4310 | 4.0231 |
| **3h** | −6.3164 | −1.6927 | 6.3137 | 4.0045 | 2.3119 | 0.4326 | 3.4682 |
| **3i** | −6.2147 | −1.6233 | 5.2590 | 3.9190 | 2.29568 | 0.4356 | 3.3451 |
| **3j** | −6.2198 | −1.6279 | 6.1410 | 3.9239 | 2.2960 | 0.4355 | 3.3530 |

## 3. Results and Discussion

### *3.1. Docking Studies*

All our synthesized compounds, 3a–3j were allowed to dock into the binding pockets of various antimicrobial targets such as the common antibacterial target 2,2-dialkylglycine decarboxylase (pdb id:1d7u), *candida albicans* dihydrofolate reductase (pdb id:1ai9), *M. tuberculosis* InhA (pdb id:2x22) and crystal structure of pantothenate synthetase (pdb id:3ivx), etc (Figure 3) [1]. The docking protocol was validated by redocking all in-bound ligands into active binding pockets of respective crystal structures. The average RMSD value was retained to be around 2 Å. Our molecular docking analysis suggested that compound 3e had highest XP Gscore of −9.746 kcal/mol for the common antibacterial target (pdb id:1d7u) indicating stronger antibacterial potentials. Compound 3e was interacted with *ASN394, ARG 406, LYS 272, SER 54, SER 215* amino acid residues from target 1d7u. The detailed binding scores (kcal/mol) and interacting residues for the best docked molecule 3e are provided in Table 1.

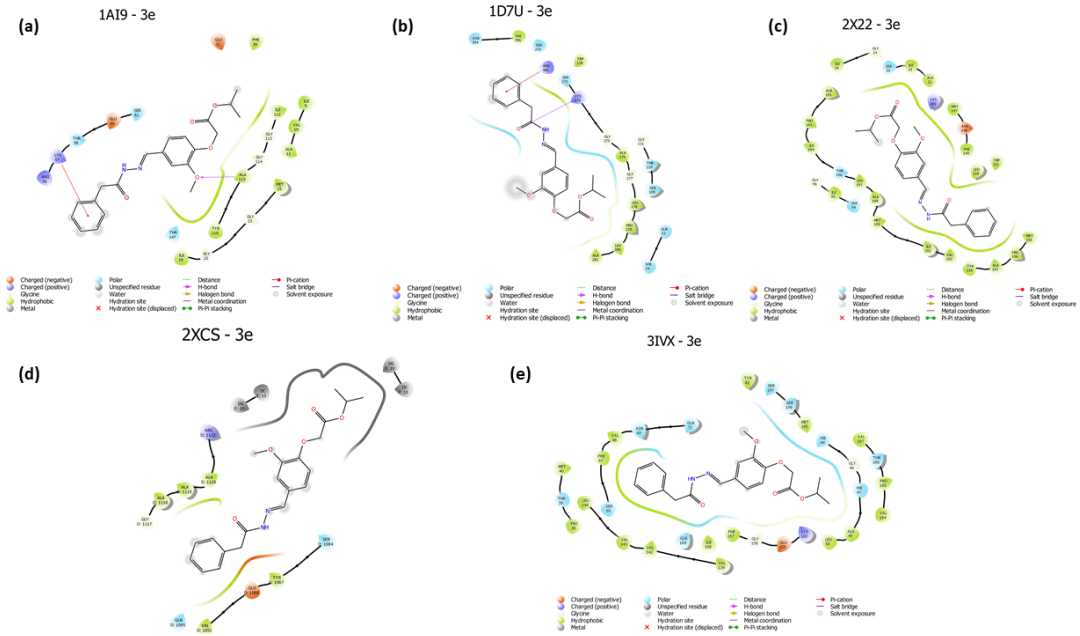


**Figure 3.** Docking interaction diagrams for best docked, 3e against various microbial targets, (**a**) 1ai9, (**b**) 1d7u, (**c**) 2x22, (**d**) 2xcs and (**e**) 3ivx.

### *3.2. Theoretical Analysis*

The B3LYP-converged geometries of the studied compounds were summarized in Figure 3. The energy of the highest-occupied molecular orbital ($E_{HOMO}$), the energy of the lowest-unoccupied molecular orbital ($E_{LUMO}$), dipole moment (D), and the qunatum chemical descriptors including the chemical potential (μ), chemical hardness (η), softness (S), and electrophilicity index (ω) calculated by known equations (Supporting Material) [1]. where I and A are the ionization energy and electron affinity of a species, respectively. Furthermore, the ionization energy (I) and the electron affinity (A) of a species could be calculated by applying the Koopmans' theory ($I = -E_{HOMO}$ and $A = -E_{LUMO}$) and the quantum chemical descriptors were calculated and summarized in Table 2. The stability and reactivity of molecules are significantly related to their chemical hardness and global softness [1]. A Smaller (greater) the value of hardness (softness) a molecule has, the more reactive it should be. From Table 2, it was observed that **3e** exhibited the lowest value of chemical hardness and highest value of global softness among the studied compounds, therefore, it is chemically more reactive and less stable than all other compounds. According to the previous relevant studies [10,11], the toxicity of a species seems to be correlated with its

electrophilicity index (ω). From Table 2, it was observed that **3e** showed the lowest value of electrophilicity index (ω) among the tested compounds, which indicates that it should have the lowest toxicity among all the studied compounds [11]. Figure 4 depicts HOMO and LUMO diagrams for best docked molecule 3e.

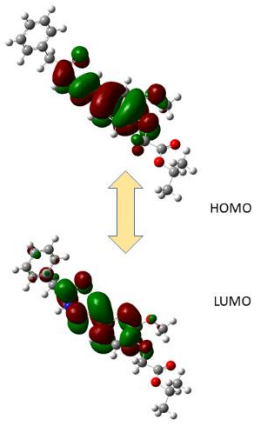


**Figure 4.** Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbitals (LUMO) of 3e.

## 4. Conclusions

In the current study, we have successfully synthesized various hydrazide derivatives (3a–3j) using a greener catalyst (chitosan HCl). The reaction was accompanied with minimal use of solvents and lesser workups. Considering the abundancy of raw unmodified chitosan, chitosan. HCl mediated reactions may strengthen newer aspects of greener reactions. Hydrazide-hydrazones are typically reported for their potent antimicrobial potentials. Currently synthesized analogues (3a–3j) were showed higher binding scores against common bacterial targets. Moreover, our DFT calculations depicted that compound 3e had better theoretical properties. Combining in-silico docking and DFT results, compound 3e may serve as future hit/lead molecule for the developments of potent antimicrobial agents.

**Supplementary Materials:** The following are available online at www.mdpi.com/xxx/s1.

**Author Contributions:** Conceptualization, S.N.M. and B.R.T.; methodology, B.R.T.; software, S.N.M., C.-H.L.; writing—review and editing, A.P., B.R.T., S.N.M., C.-H.L.; visualization, S.N.M. and A.P.; supervision, A.P. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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