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Evaluation of substituted methyl cyclohexanone hybrids for anti-tubercular, anti-bacterial and anti-fungal activity: Facile syntheses under catalysis by ionic liquids

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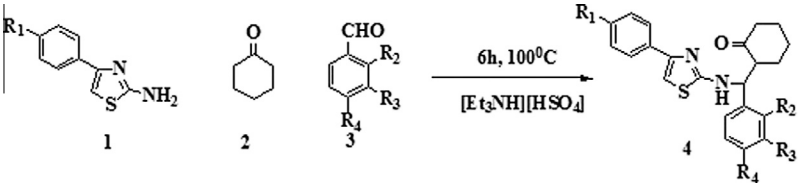
HIGHLIGHTS

- Designed and synthesized unique and versatile scaffolds.
- Reactions within dual nature ionic liquids.
- Activity against *M. tuberculosis* strains.

GRAPHICAL ABSTRACT

A broad range biological evaluation and facile one pot Mannich type syntheses of *rac*-(2*S*)-2-[(*R*)-(4-substituted phenyl){[4-(4-substituted phenyl)-1,3-thiazol-2-yl]amino}methyl]cyclo hexanone derivatives in Bronsted acidic quaternary ammonium sulfated ionic liquids serving as dual solvents and catalysts were investigated.



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Bronsted acidic quaternary ammonium ionic liquids

ABSTRACT

An library of unresolved racemic Mannich bases incorporating two stereogenic carbon centers was evaluated for antibacterial activity against clinically isolated Gram-positive bacteria i.e. *Staphylococcus aureus*, Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* and for antifungal activity against *Candida albicans* strains. Additionally, the susceptibility of microorganisms to Mannich bases prompted us to evaluate the potential for anti-tubercular activity against clinically isolated *Mycobacterium tuberculosis* and virulent *H37Rv* strains. All compounds showed potent activity against *M. tuberculosis* strains at MIC ranging from 50 μg/mL to 6.25 μg/mL of concentration. Facile one pot Mannich type syntheses of *rac*-(2*S*)-2-[(*R*)-[(4-substituted phenyl){[4-(4-substituted phenyl)-1,3-thiazol-2-yl]amino}methyl]cyclo hexanone derivatives were achieved by reactions of various 2-amino-4-aryl-thiazoles, appropriately substituted aromatic aldehydes and cyclohexanone in Bronsted acidic quaternary ammonium sulfated ionic liquids serving as dual solvents and catalysts.

Introduction

Tuberculosis, a disease that has haunted mankind for several thousand years is caused by the bacterium *Mycobacterium tuberculosis*. The WHO estimates that one third of the worlds population is infected with the bacterium. In 2006, more than 9 million people developed active tuberculosis resulting in the death of

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around 2 million people [1]. These numbers have progressively risen during the last decade, mainly due to the increased number of HIV patients that are co-infected with latent tuberculosis leading to a yearly risk of 10% to develop active TB [2]. For treatment of tuberculosis, a cocktail of antituberculat such as isoniazid and rifampicin complemented with pyrazinamide and ethambutol, is used, four antituberculat are used in the first two months followed by two antituberculat for four additional months [3,4]. These drugs target different cellular mechanisms thus minimizing the risk of cross resistance. Today, many *M. tuberculosis* strains are resistant to several of the commonly used antibiotics. Multi drug resistant tuberculosis strains (MDR) are resistant to isoniazid and rifampicin. The extremely drug resistant strains (XDR) are resistant to isoniazid, rifampicin, any fluoroquinolones and at least one of the three second line injectable antituberculat (Amikacin, Kanamycin, or Capreomycin) [5].

Mycobacterium, meaning fungus-bacterium refers to the fungus-like growth of the organisms on the surface of liquid cultures. The *M. tuberculosis* cell envelope differs substantially from the wall structures of both Gram-negative and Gram-positive bacteria. This unique cell wall structure accounts for its unusual low permeability and resistance towards common antibiotics. The main structural elements consists of a cross-linked network of PG (peptidoglycan) in which some of the muramic acids residues are replaced with complex polysaccharides like AG (arabinogalactan). The AG is attached to PG thorough a unique linker unit, and acylated at its distal end to PG with mycolic acids. The entire complex, abbreviated as the mAGP (mycolylarabinogalactan-peptido glycan) is essential for viability in *M. tuberculosis* and other mycobacteria. The drug-resistance mechanisms, the immunobiology of cell wall components to elucidate host-pathogen interactions and the discovery of new drug targets for the treatment of TB are well documented [6,7].

The knowledge of the mechanism of mycobacterial resistance to a drug could suggest plausible new products to specifically overcome this mechanism [8]: effective alternatives with high specific regimens possessing synergistic susceptibility towards microorganisms i.e. Gram-negative and Gram-positive bacterial as well as fungal strains are urgently needed.

Many carbonyl compounds like aryloxy cyclopropyl phenyl methanones [9], acetophenones [10], chalcones [11] and Mannich bases containing carbonyl compounds [12] have been exploited as potent anti-tubercular agents with their mode of action postulated to be the inhibition of initial steps in fatty acid biosynthesis. The cycloalkanones are found to be versatile antimicrobial agents possessing drug resistance reversal [13], cytotoxicity [14], and histone acetyl transferase [15] properties. Due to the unique biological and pharmacological activity, thiazoles have attracted considerable attention. Various substituted thiazoles have been synthesized and examined for their anti-tubercular, anti-fungal and anti-bacterial activities [16–21]. Demonstrations of in vitro activity against the virulent strain of *M. tuberculosis*, *H37Rv* is one of the simplest preliminary tests for a new antimycobacterial agent.

We designed and synthesized unique and versatile scaffolds containing thiazole, Mannich base and cyclohexanone moieties in the same molecular skeleton with potential therapeutic significance. Our present synthetic approach of these hybrid molecules comprised Mannich type C—C bond forming reactions within dual nature ionic liquids. Mannich-type reactions have been reported in imidazolium [22], pyridium [23], tert. ammonium [24] and phosphonium [25] based ionic liquids.

To the best of our knowledge, no study has been done hitherto, for the synthesis of thiazole based Mannich bases incorporating cyclohexanones, in Bronsted acidic quaternary ammonium sulfate ionic liquids functioning as solvent as well as catalyst. Design of synthetic methods for the efficient preparation of these heterocyclic compounds was necessary: we embarked on the synthesis, via aromatic aldehyde moieties, of compounds having a thiazole linked cyclohexanone, embedded in a joint molecular framework to improve the specificity and efficacy of these hybrid scaffolds against microorganisms. In this communication synthesis of four different ionic liquids of general type [amine][HSO_4] has been utilized for the comparative study of three component Mannich reaction of aldehyde, 2-amino thiazole and cyclohexanone. These ionic liquids are Bronsted acids, which can be easily synthesized from readily available cheap raw materials. These can be used both as a catalyst and environmentally benign solvent, thus eliminating the need for a volatile organic solvent used in traditional methodology. Use of these ionic liquids as a novel reaction media may also offer a convenient solution to both the solvent emission and catalyst recycling problem. Bronsted acidic quaternary ammonium sulfated ionic liquids served as efficient solvents and catalysts. Four different ionic liquids of general type [amine][HSO_4] [26] were selected. Ease of preparation, moisture resistance, air tolerance and ready availability of cheap raw materials made the use of these ionic liquids convenient. Thiazole based Mannich bases were screened as anti-bacterial, anti-fungal and anti-tubercular agents. All synthesized Mannich bases showed pronounced activity against Gram-negative *Pseudomonas* strains and moderate activity against Gram-positive *Staphylococcus aureus* and fungus, *Candida* strain. We also evaluated these compounds as anti-tubercular agents: All compounds exhibited excellent activity against clinically isolates of *M. tuberculosis* and *H37Rv* at concentration ranging from 50 μg/mL to 6.25 μg/mL.

Chemistry

Catalytic Mannich type reactions have been reported by several research groups to provide β-amino carbonyl compounds with the formation of Mannich bases. β-amino carbonyls are important synthons, whereas Mannich bases are effective prodrugs which enhance the hydrophilicity of the parent drugs [27]. We have synthesized *rac*-(2*S*)-2-[(*R*)-[(4-substituted phenyl){[4-(4-substituted phenyl)-1,3-thiazol-2-yl]amino}methyl]cyclohexanones **4a**–**u** by condensation of appropriate 2-amino-4-aryl thiazoles and aromatic aldehydes with cyclohexanone in Bronsted acidic tert. ammonium sulfated ionic liquids. Two unresolved stereogenic carbon centers led to racemic products with no optical activity. The effects of ionic liquids, triethylamine, n-tripropylamine, di-isopropyl amine, tri-n-butyl amine sulfate, control of temperature and variable time on the yield are reported in Table 1, (Scheme 1).

Biology

In vitro anti-bacterial and anti-fungal activities

The newly synthesized compounds **4a**–**u** were tested for their in vitro antimicrobial activity against clinical isolates of

Table 1
Optimization of isolated yields of **4a** in different Ionic liquids at 100 °C.

Entry	Solvent	Temp (°C)	% Isolated yield at time interval					mp (°C)
			6 h	12 h	24 h	36 h	48 h	
1	Triethylamine sulfate [Et_3NH][HSO_4]	100	90	90	90	90	90	217
2	n-Tripropylamine sulfate [n-Pr_3NH][HSO_4]	100	55	70	78	86	90	217
3	IsoPropylamine sulfate [iso-$PrNH_2$][HSO_4]	100	55	65	72	80	92	217
4	Tri-n-butylamine sulfate [tri-n-Bu_3NH][HSO_4]	100	56	60	75	82	88	217