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Short communication

# Repurposing of a drug scaffold: Identification of novel sila analogues of rimonabant as potent antitubercular agents

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ABSTRACT

The structural similarity between an MmpL3 inhibitor BM212, and a cannabinoid receptor modulator rimonabant, prompted us to investigate the anti-tubercular activity of rimonabant and its analogues. Further optimization, particularly through incorporation of silicon into the scaffold, resulted in new compounds with significant improvement in anti-tubercular activity against *Mycobacterium tuberculosis* (H37Rv). The sila analogue **18a** was found to be the most potent antimycobacterial compound (MIC, 31 ng/mL) from this series with an excellent selectivity index.



## 1. Introduction

Drug discovery has become an increasingly tough endeavor. The average cost of bringing a drug into market is estimated to be about US$ 2600 million with a timeline of up to 15 years [1]. Identification of entirely novel compounds with unknown pharmacokinetic and safety profile poses more risk apart from being expensive and time consuming. The discovery of new indications for an existing drug termed “drug repurposing or drug reprofiling” is a lower risk strategy with increased probability of success within a short span of time. According to a recent report, 24 drugs had been remarketed for new uses and more than 15 are currently in the various developmental stages [2–4]. Also, molecules that failed in the clinic for a particular indication can be successfully repurposed for treatment of other conditions. Thalidomide, the most controversial drug of all time, is now used for pain relief in certain cancers and leprosy [5]. Pfizer’s blockbuster drug sildenafil citrate (Viagra®), which was originally intended for hypertension was serendipitously repurposed after the Phase I clinical trials for erectile dysfunction [6].

Tuberculosis (TB) is an infectious disease caused by various strains of mycobacteria; the most common one being *Mycobacterium tuberculosis* (Mtb). Almost one-third of the total world population is asymptomatically infected by Mtb and it is the second leading cause of death due to an infectious agent [7]. Medications are known to treat TB; however, the response rate is slow with development of antibiotic resistance posing a serious threat. In view of these challenges, there is a need to develop new drug candidates with novel mechanisms for treating tuberculosis. The pre-clinical candidate BM212, a 1,5-aryl substituted pyrrole was

*Abbrevations:* MIC, Minimum Inhibitory Concentration; ADME, absorption, distribution, metabolism, excretion; CB1, Cannabinoid receptor Type 1; Mtb, *Mycobacterium tuberculosis*; CNS, Central nervous system; TBAF, Tetrabutylammonium fluoride; INH, Isoniazid; DMPK, Drug metabolism and pharmacokinetics; PPB, Plasma protein binding; A549 cells, human alveolar adenocarcinoma cell line; HepG2 cells, human liver hepatocellular carcinoma cell line.

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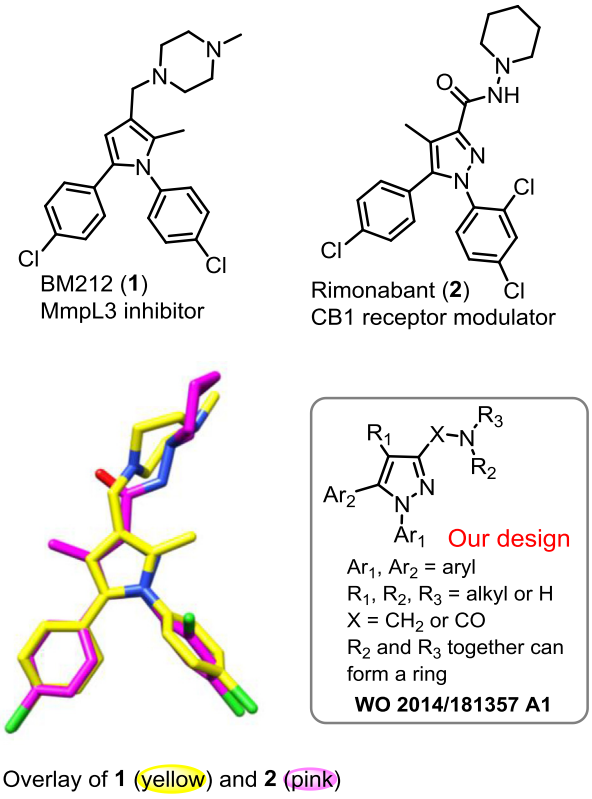



**Fig. 1.** Design of diarylpyrazoles (rimonabant analogues) towards antitubercular agents.

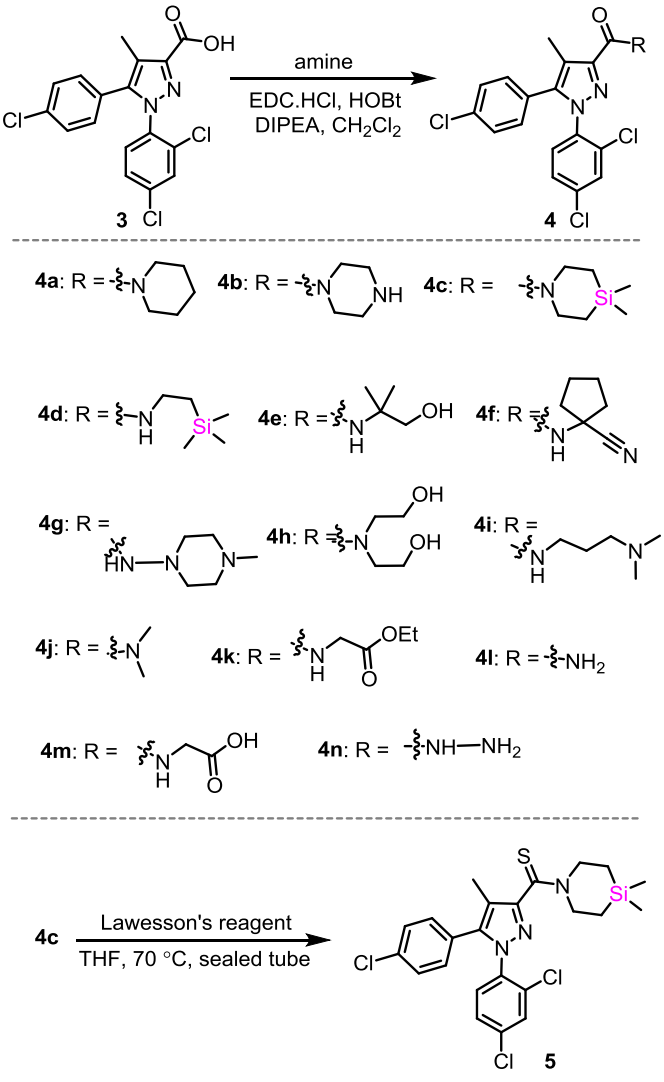
reported to be active against Mtb with a minimum inhibitory concentration (MIC) of 0.7–1.5 μg/mL [8]. BM212 belongs to the MmpL3 class of inhibitors and blocks the transport of mycolic acids that are essential for the development of cell wall of mycobacteria thereby inhibiting their growth [9]. MmpL3 is a relatively new therapeutic target and other lead compounds such as SQ109, AU-1235, NITD-304 are also known to act on this transporter protein [10–14]. To identify new antitubercular agents with novel scaffolds that have already been tested in humans, a scaffold hopping technique was adopted using BM212. Towards this direction, an anti-obesity drug rimonabant (**2**) [15] attracted our attention. An overlay of BM212 (**1**) and rimonabant (**2**) suggested close structural similarities between the two (see Fig. 1). Rimonabant acts by blocking the cannabinoid receptor-1 (CB1). This receptor is expressed mainly in the central and peripheral nervous system and is involved in controlling food consumption, mood, and anxiety related disorders [16,17]. An advantage with the rimonabant scaffold is that it can penetrate blood-brain-barrier (BBB) and may be useful in developing agents for the treatment of brain tuberculosis. The objective of the current study was to repurpose the rimonabant scaffold towards the development of agents active against Mtb [18].

## 2. Results and discussion

### 2.1. Synthesis

Initial screening of rimonabant demonstrated moderate potency (MIC = 25 μg/mL, Mtb) and gave us encouragement to synthesize more analogues. Analogues of rimonabant with varying structural features were synthesized and evaluated for their activity against Mtb. All the synthetic details are outlined in Schemes 1–5. Compound **3** was synthesized according to the literature protocol and was coupled with several amines to give a series of amides (**4a**–**4k**) [19]. Amide **4l** was prepared from the corresponding acid chloride employing procedures known in the literature [20]. The ester group in **4k** was hydrolyzed to obtain the acid **4m**. The hydrazide **4n** was obtained from the corresponding ester **6** and hydrazine hydrate [21]. Because of our group's continued interest in organosilicon molecules [22,23], we synthesized a few silicon analogues (**4c** and **4d**) as well. The bioisosteric replacement of carbon with silicon has gained attention in recent times [24–29]. The silaamide **4c** was converted to thioamide **5** by treating with Lawesson's reagent in THF (Scheme 1). Towards slightly more polar analogues, the known ester **6** was subjected to benzylic bromination using *N*-bromosuccinimide (NBS) and the bromo derivative was converted to alcohol in the presence of $AgNO_3$ and water. Hydroxylester **7** was hydrolyzed to obtain the acid **8** [30]. Carboxylic acid **8** was then coupled to the silicon amines **A** and **B** using EDC. HCl and HOBt to obtain amides **9a** and **9b**, respectively (Scheme 2). Alcohol **10** was prepared from ester **6** by following the literature procedures and was subjected to alkylation using benzyl bromide and NaH as base to obtain the ether **11** (Scheme 3) [31]. Alcohol was converted into its mesylate and displaced with various amines to generate a library of rimonabant amine analogues **12a**–**12g** (Scheme 3).

For the preparation of hydroxymethyl amine, the alcohol **7** was




**Scheme 1.** Syntheses of amides and thioamide.