A REVIEW OF SYNTHESIS, BIOLOGICAL ACTIVITY, & DOCKING STUDIES OF ANTI-TUBERCULAR AGENTS


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Abstract

The World Health Organization suggests treating tuberculosis with a 6-month course of isoniazid (INH), rifampicin (RMP), ethambutol, and pyrazinamide. The anti-TB activity of a number of novel styryl-1,2,4- oxadiazoles against the MTB H37Ra strain was assessed. These compounds were motivated by the molecular structure of cinnamic acid. There is a substantial correlation between the antibacterial activity and the location of the pyridine substituent on the thiosemicarbazide skeleton. A total of thirty-three ligands were docked against the two proteins AftaA and EmbA during the primary protein-ligand docking process, which was carried out using iGemDock. The following study included eight anti-tuberculosis medications as a control group: rifampicin, isoniazid, bedaquiline, delamanid, ethionamide, ethambutol, Gemifloxacin, and thioacetazone.

Keywords:
Inononizid (INH), rifampicin (RMP), Bedaquiline, ligand docking, lapazine, Building Evidence to Advance Treatment of TB (BEAT).

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Introduction

Tuberculosis (TB) continues to be a major cause of death globally and a critical global health concern. Despite efforts to lessen its effects, tuberculosis (TB) still causes about 10 million new cases and 1.6 million deaths yearly: co-infections, particularly those linked to HIV, further compound this burden. Between 2015 and 2017, there was a 3.9% decrease in the number of new cases of TB; 457,560 of these cases were multidrug-resistant TB (MDR-TB), and 558,000 cases were rifampicin-resistant TB (RR-TB). Therefore, tuberculosis (TB) presents a challenge to researchers looking for effective medications that can minimize side effects or the emergence of drug resistance while controlling the growth of the bacillus Mycobacterium tuberculosis [1]. An increase in mycobacterial resistance to aminoglycosides, quinolones, isoniazid, and rifampicin has resulted in extensively drug-resistant tuberculosis—the diverse populations of active mycobacteria [2]. The most active component in the search was generated from Brazilian plant extracts and natural product-derived phenazines, which are active against M. tuberculosis and have been known since the nineteenth century. Lapachol, a naturally occurring naphthoquinone that is readily derived from the Tabebuia species, can be used to create magazine, a benzo[a]phenazine. Lapachol can be processed into lapazine in two processes, yielding a quantitative yield overall. Its biological activities have garnered a lot of attention, but in vivo investigations of acute (LD50) and chronic toxicity in Balb/c mice have been limited by its low solubility. By encapsulating the medication in biodegradable nanoparticles (NPs) for drug delivery, shielding the medication from physiological circumstances, and focusing on its delivery, this restriction can be reduced [3]. As a TB treatment, the WHO advises a six-month course of treatment consisting of isoniazid (INH), rifampicin (RMP), ethambutol, and pyrazinamide. Treatment for cases of resistance can last up to 28 months and involve
second-line medications such aminoglycosides, D-cycloserine, linezolid, and fluoroquinolones, among others. The lengthy conventional regimen, high treatment termination rates, side effects, toxicity, drug-drug interactions, and ineffectiveness against latent mycobacteria are just a few of the drawbacks of the present treatment.[4]. Bedaquiline interacts with human ATP synthase very little and is very selective for MTB F1 F0 ATP synthase [5]. Even though M. tuberculosis induces a strong reaction, it has the ability to thwart the body’s attempts to eradicate it, even in cases where the underlying illness is successfully managed. The increasing number of strains of M. tuberculosis that are resistant to both isoniazid and rifampicin (first-line therapy), with or without protection from different medications, has led to the need for the discovery of drugs with novel mechanisms of action [6]. Because 1,2,4-oxadiazole derivatives are easily structurally modified, they may play a major role in the development of new anti-TB agents. The anti-TB activity of a number of novel steryl-1,2,4-oxadiazoles, which were modelled after the chemical structure of dinamic acid, was assessed against the MTB H37Ra strain.[7].

Lipomannan’s biochemical precursor modulates the host immune response by acting as an immune modulator. It has been suggested by earlier research that AFB may be a useful new target for medication. We looked into and eliminated a few particular phytochemicals from the current study that might be viable drug candidates against Mycobacterium tuberculin’s possible therapeutic targets [8]. Clofazimine has anti-inflammatory, pro-oxidative, and antimycobacterial effects that are concentration-dependent [9]. Long chains of polysaccharides and residues from amino acids combine to form the peptidoglycan. A second-line treatment for tuberculosis is D-cycloserine [10]. The problem has been made more difficult by the rise of drug-resistant strains, specifically rifampicin- and multidrug-resistant tuberculosis (MDR- and RR-TB). Controlling the growth of Mycobacterium tuberculosis while limiting side effects and preventing the emergence of drug resistance are challenges faced by conventional treatments. Numerous compounds have been thoroughly investigated in research efforts for possible anti-TB activity. Certain compounds, like 5-nitrofuranyl derivatives and 1,3,4-oxadiazoles, have demonstrated promise by displaying a variety of pharmacological activities and, in certain cases, proving to be effective against tuberculosis. 1. Martínez R et al, 2019. synthesized N-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-(nitro heteroaryl)carboxamides 1a-e from methyl 4-chlorobenzoate. Methyl 4-chlorobenzoate synthesis for 20 hours, a solution containing 2 mmol of 4-chlorobenzoic acid and 1 mL of H2SO4 in 20 mL of anhydrous methanol was heated under reflux. Following the consumption of the starting material, which was observed through TLC, the mixture was extracted using AcOEt (3 x 100 mL) and neutralized using a saturated NaHCO3 solution (2 x 25 mL).

**Standard protocol for the synthesis of substances 1a–e**

Five, 0.51 mmol of 5-(4-chlorophenyl)-1,3,4-oxadiazol-2-amine was dissolved in fifteen millilitres of anhydrous THF was subjected to a 1.53 mmol NaH treatment. The mixture was then allowed to cool to 0°C in a nitrogen atmosphere, and acyl chloride 6a-e (0.51 mmol) was added. After 15 hours of stirring at room temperature, the mixture was quenched with 30 mL of a saturated NaHCO3 solution and extracted using 3 x 50 mL of AcOEt. After mixing, drying over anhydrous Na2 SO4, filtering, and concentrated under low pressure, the organic extracts were combined.

**Conclusions**

Using the hydrazide 2 as a common intermediate, two convergent pathways were used to synthesize compounds 1a–e. Three Mycobacterium tuberculosis cell lines were used to assess the anti-TB activities of compounds 1a–e. The findings imply that the distribution of electronic density throughout the ring connected to the amide group can be used to explain the anti-TB activity of compounds 1a–e. We are currently investigating the mechanism by which these novel compounds impede the growth of M. tuberculosis cells. 2. Pitucha M et al, 2019 was synthesized (A) 1-(pyridin-2-3,4-yl) carboxyl-4-substituted Thiourea (1–19) and (B) 1-(pyridin-4-ylacetyl)-4-substituted Thiourea (20–25).

(A) 15 milliliters of methanol were used to dissolve 0.01 mol of pyridine 2-, 3-, or 4-pyridine carboxylic acid hydrazide. Then, 0.01 mol of the suitable isothiocyanate was added. At reflux temperature, mixtures were heated for 0.5–1 hour. Following this, the mixture was allowed to cool, and the proper amount of thiosemicarbazide crystallized from the methanol. (B) For 24 hours, a solution of 0.01 mol of 4-pyridine acetic acid hydrazide and the corresponding 0.01 mol isothiocyanate in 10 mL of anhydrous diethyl ether was stored at room temperature. From the ethanol, the product was filtered off and crystallized.

**Antimycobacterial assay**

Four mycobacteria strains—M. phlei, M. smegmatis, M. limerick, and M. tuberculosis H37Ra—were employed. The studied substances’ stock solutions were made freshly in dimethyl sulfoxide (DMSO). The test chemical concentrations ranged from 500 to 1.95 µg/mL. Microorganisms stored on Lewenstein’s slants were scraped and then transferred to a vial containing Middlebrook 7H9 broth with ADC enrichment to create the inoculum for susceptibility testing. Diffusion well testing on Middlebrook 7H10 medium supplemented with OADC (oleic acid, bovine albumin fraction, dextrose, and catalase) was used to identify the zones of growth inhibition. The stock solution had a concentration of 5 mg/mL. For comparison, rifampicin was employed.

**Computational Details**

Protein Data Bank (PDB ID: 2BVC [17]) provided the crystal structure of Mycobacterium tuberculosis glutamine synthetase (MtGS) in association with magnesium, adenosine-5’-diphosphate (ADP), and L-methionine-s-sulfoximine phosphate (MSO-P). GOLD Suite v.5.5 was used to conduct docking investigations [18]. Four strains of Mycobacterium were evaluated in vitro against all recently acquired thiosemicarbazides: M. H37Ra, M. phlei, M.smegmatis, and M. timearek. The location of the pyridine substituent with respect to the thiosemicarbazide skeleton has a significant bearing on the antibacterial activity.
3. Silveira N et al., 2015 Lapachol was isolated and used as the starting point for the β-lapachone synthesis of lapazine, as suggested by previous research [15, 16]. In a 5:1 ratio, concentrated sulfuric acid was added to lapachol. Following the full solubilization of the naphthoquinone, the reaction medium was added to ice-cooled distilled water. This resulted in the formation of a red precipitate, which was then filtered using a Büchner filtration device under low pressure, cleaned with cold distilled water until it attained a neutral pH, and allowed to dry at room temperature. The previously outlined procedure was used to synthesise lapazine [15]. O-phenylenediamine, sodium acetate, and acetic acid were added to the β-lapachone in a 1:1:2.6 ratio. Acetic acid was then added and allowed to reflux for two hours. Following this, the reaction medium was put on ice and kept cold for the entire night. A Buchner filtration device was used to filter the material. After adjusting its pH to 6–7, it was desiccator-dried at room temperature.

As previously mentioned, the antimycobacterial activity of lapazine that was free and encapsulated in NPs was assessed. M. tuberculosis H37Rv strain.

Conclusion
The manufacture of lapazine yielded a nearly 99% pure product, indicating that the in vitro assessment of lapazine’s antimycobacterial effectiveness against susceptible and resistant strains of Mycobacterium TB was adequate. For the first time, an assessment of lapazine’s antimycobacterial activity at low concentrations in vitro was conducted on susceptible and resistant strains of Mycobacterium TB. Furthermore, the encapsulation of lapazine in the biocompatible polymers PCL and PLGA offered pertinent initial characteristics to develop a nanoparticulate system as a possible treatment for tuberculosis.

4. Dos Santos Fernandes GF et al., 2017
The antitubercular activity of twenty-two newly synthesised compounds containing N-oxide was assessed both in vitro and in vivo against Mtb. The most promising compounds were found to be the amide-furoxan series (4a–c), with SI values ranging from 2033.3 to 3204.7 and MIC90 values of about 0.40 μM against actively replicating Mtb. Compound 8 from the benzofuroxan series (8–17) showed very strong antitubercular action, with MIC90 values of 1.1 and 6.6 μM against Mtb that was actively growing and nonreplicating, respectively. Compound 8 also showed a lot of action in an infection model using macrophages.

5. Cristiane F. Da Costa et al., 2011
Equipment and Methods
NMR spectra were acquired in deuterated methanol, chloroform, or dimethyl sulfoxide using a Bruker Avance spectrometer operating at 400 or 500 MHz (1H) and 100 or 125 MHz (13C) and a Bruker Avance DRX300 spectrometer operating at 300 MHz (1H) and 75 MHz (13C). On silica gel plates, thin-layer chromatography was performed with mixes of chloroform and methanol as eluents. Column grade silica gel with a mesh size of 0.063–0.200 mm was used for column chromatographic purification. Using a 2Q electrospray spectrometer basic quadrupole, mass spectra (ESI) were acquired. A digital melting point instrument, the Microquimica MQAPF-301 (Microquimica, Santa Catarina, Brazil), was used to determine melting points.

Chemistry
The starting materials used were the amino acids L-phenylalanine 1a, L-leucine 1b, and L-alanine 1c. The protective groups t-butoxycarbonyl (BOC) and benzoylcarbonyl (Cbz) were added to the core structures of these compounds due to an innate instability shown in unprotected derivatives.

Experimental general procedures for the synthesis of methyl ester derivatives of L-amino acid
A solution of 200 mmol thiouyl chloride in 100 mL of methanol at 0°C was agitated, and 40 mmol of suitable L-amino acid was added. After 24 hours of stirring the reaction mixture at room temperature, the solvent was eliminated, yielding a quantitative yield of 2a–c.

General procedures for the synthesis of tert-butoxycarbonylamino derivatives
20 (13.5 mmol) was added to a reaction mixture that contained the proper methyl ester derivatives 2a–c (9 mmol) and triethylamine (10.8 mmol) in anhydrous THF (20 mL) at room temperature. After being shaken for 24 hours at room temperature and quenched with 40 millilitres of water, the reaction mixture was extracted using ethyl acetate. After being dried over anhydrous sodium sulphate, the mixed organic phases were concentrated at lower pressure. By using column chromatography on silica gel (hexane:ethyl acetate 7:3), the residue was purified and 3a–c were obtained in 65–75% yield.

Benzoxyl carbonylamino derivative synthesis general procedures 4a–b
Dropwise additions of benzyl chloroformate (14 mmol) were made to a reaction mixture containing the corresponding methyl ester derivative 2a–b (9 mmol), water (50 mL), diethyl ether (40 mL), and sodium bicarbonate (50 mmol) at 0°C. The reaction mixture was quenched with pyridine (8 mL) after 2 hours at 0°C and 1 hour at room temperature. Water was then added to solubilize all of the salts (40 mL). The organic layer was dried (MgSO4), filtered, concentrated, and cleaned with HCl (2.5 N). After chromatographing the residue on silica gel (hexane:ethyl acetate 8:2), 4a–b were obtained in 63–75% yield.

Biological assessment
Using the microplate Alamar Blue assay, the antimycobacterial activity of compounds 5a–c, 6a–b, 7a–b, 8a–j, 9a–d, and 10a–c have been evaluated against Mycobacterium tuberculosis ATCC 27294. This technology exhibits good correlation with proportional and BACTEC radiometric methods, is safe, and uses a thermally stable reagent. Here is a description of the method: To reduce the amount of medium evaporation in the test wells during incubation, 200 mL of sterile deionized water was supplied to each outer perimeter well of 96 sterile-well plates (falcon, 3072; Becton Dickinson, Lincoln Park, NJ, USA). A well’s blue colour was understood as representing no bacterial growth, whereas a pink colour indicated growth. The lowest pharmacological concentration that prevented a colour change was known as the minimum inhibitory concentration (MIC), a colour change from blue to pink.
Results and Discussion
The produced compounds' antitubercular efficacy in vitro compound 7a, an L-phenylalanine derivative synthesized with N-acyl hydrazine, was the only intermediate product that demonstrated activity against M. tuberculosis. For the synthesis of compounds 8a–b and 9a–b, respectively, the starting ingredients were compounds 5a and 6a. Heteroaromatic aldehydes and unprotected hydrazine 7a did not react, according to observations. Even yet, the intended molecule 10a was rendered ineffective against M. tuberculosis by the successful coupling process between 7a and p-nitrobenzaldehyde. With a minimum inhibitory concentration (MIC) of 50 µg/mL, derivative 8b, which was made from 5-nitrothiophene-carboxaldehyde, demonstrated moderate activity among the N-BOC-protected compounds 8a and 8b. Out of all the compounds synthesised in this investigation, the 5-nitrofurane derivative 9a showed the highest activity and was more potent when compared to the other compounds. Its MIC was 12.5 µg/mL.

Conclusion
The synthesis and biologic assessment of seventeen N-acylhydrazone derivatives of various amino acids, including L-phenylalanine, L-leucine, and L-alanine, are summarised in this paper. The stability of the synthesised derivatives required the protection of these amino acids with BOC and Cbz. The compounds’ evaluation against M. tuberculosis produced encouraging results, with a minimum inhibitory concentration (MIC) ranging from 12.5 to 50 µg/mL. The most promising of those was 9a, which showed greater potency when compared to the tuberculostatic medication D-cycloserine (20 µg/mL).

Chandrasekaran Padmapriyadarsini.et.al, 2022
Between April 2019 and January 2021, participants in the prospective open-label, single-group cohort research known as BEAT-India (Building Evidence to Advance Treatment of TB) were recruited from five sites in India. All collaborating institutes’ institutional ethics committees approved the study before it could begin, and each study participant provided informed written consent. Participants in the trial had to be adults with pulmonary MDR-TB/FQ+ or/and MDR-TBSLI+ with two positive sputum smears or at least one culture-positive with negative sputum smears obtained within six weeks of the screening date. The WHO advised that the critical concentrations for the drug susceptibility test of CFZ, LZD, and BDQ be 1 µg/mL, and for DLM to be 0.06 µg/mL. As specified in the protocol, sputum, blood investigations, and chest X-rays (CXR) were performed during the course of treatment and the posttreatment follow-up period. The safety and tolerability of the regimen were evaluated using DAIDS criteria. Based on the 16th-week mycobacterial growth indicator tube (MGIT) sputum culture, the decision was made at week 24 to cease treatment. If two successive sputum cultures obtained at least four weeks apart were negative and there was clinical and radiological improvement at the conclusion of treatment, the treatment outcome was considered favourable.

Statistical Analysis
A 50% cure rate compared to a 30% cure rate under programmatic management of DR-TB was assumed by the new combination of the BEAT-India research regimen. Based on this assumption, the estimated sample size was 127, and the population risk difference was within 10% of the actual value with 95% confidence. In order to account for a 20% loss from death and a 10% loss from study withdrawal, a total sample size of 165 people was needed. All analyses were conducted using IBM SPSS software, version 25.0 (IBM Corporation). Patients with a sputum culture that was negative for inclusion, as well as those who were FQ sensitive and/or resistant to any trial medication, were excluded from the metasediment-to-treat analysis (mITT). Time-to-culture conversion was calculated using the Cox proportional hazards model in a standard time-to-event study.

Results
Qualities of the Patient
For a variety of reasons, 122 potential volunteers were ruled out of the trial, leaving 165 eligible individuals recruited. CONSORT checklist for BEAT-India research participants. Most patients had severe illness affecting both lungs and were classified as MDR-TBFQ+ in the lungs. Based on the degree of lung zone involvement and WHO body mass index (BMI) cut-offs, patients were further categorised. Every patient had previously taken antitubercular (TB) drugs; the most frequently prescribed ones were pyrazinamide, FQ, isoniazid, ethambutol, and SLI. Patients had baseline MGIT DST resistance: 1 patient had resistance to BDQ, LZD, and CFZ; 1 patient had resistance to BDQ and DLM; 1 patient had resistance to LZD and CFZ; and 1 patient had resistance to LZD alone.

Effectiveness Analysis
Seven patients received a 36-week extension of treatment after their initial 24-week course was interrupted due to sputum culture positivity in the sixteenth week. Due to medication resistance observed in the baseline study, culture negativity, or FQ and SLI sensitivity, twelve individuals were eliminated. Seventy-eight individuals out of 157 have had their cultures transformed by the eighth week of treatment. All of the given factors contributed to time to culture conversion (hazard ratio >1.0) according to the Cox proportional hazards model, although none of them were statistically significant. Mycobacterium TB (Mt) bacilli load and illness extent were found to be predictive of the time to culture conversion using the AFT model. By the time the treatment ended, every patient had significantly improved radiologically and gained at least 3.0 kg of body weight.

Safety Analysis
Due to COVID-19 infection, three individuals experienced severe dyspnea during the course of treatment, which required hospitalisation. The course of treatment was stopped for six of the thirteen individuals who had poor results. In patients with grade 3 or 4 severities, linezolid was temporarily withheld for 7-14 days, and symptoms were appropriately treated. The seventh week of treatment saw the first LZD dose reduction or interruption for neuropathy, and the ninth week saw the first LZD dose interruption for anaemia. In 45 patients, linezolid was reintroduced at a lower dose of 300 mg when their symptoms improved. Forty of those who received a lower dose of LZD were cured by the time the treatment concluded.

Discussion
According to our research, individuals with MDR-TBFQ+/SLI+ and those with both FQ and SLI resistance have a 91%
Favourable outcome when using a totally oral, short-course regimen of BDQ and DLM with other medications. Our outcomes are similar to those of the NixTB experiment. Further proof of the effectiveness of one such combination that can be tested in the event that Pa is unavailable or contraindicated was produced by this study. Salvation therapy combining BDQ and DLM has demonstrated encouraging outcomes, with little impact on QTc interval and no arrhythmias. According to our experience, an ECG should be taken prior to starting treatment as well as 8, 16, 24, 32, or 40 weeks later. When administered to MDR-TB patients who had previously been exposed to FQ, the combination of BDQ and DLM has demonstrated encouraging outcomes. In nations where Pa and DLM are available, as well as in the early stages of the illness, this combination may also be taken into consideration.

**Conclusions**

This study shows that a short-course, all-oral regimen of BDQ and DLM combined with repurposed medications can effectively treat MDR-TB/FQ+. Additionally, in field situations, this combination makes it possible to detect and address AEs early on. Short-course regimens should be the norm of treatment and started early in the management of DR-TB, according to new research.

**Devvret et al., 2017**

**Material and methods**

The literature search helped identify the phytochemicals and possible therapeutic targets. For the docking study, the three-dimensional structures of the ligand and protein were necessary. Target protein homology modelling. None of the protein structural databases contained any information about the tertiary structure of any protein. The produced homology models were then verified using Rampage and the Ramachandran Plot.

**Ligand Preparation**

The Zinc and Pubchem databases were used to obtain the pharmacological and photochemical compounds. The Mol2 file was obtained from these databases, and since docking software accepts the.pdb format as an input, the compounds were subsequently translated to it using open Babel freeware. Following a scan of these compounds using Lipinski’s filter, the molecules that met the requirements of the Rule of Five were selected for further investigation. The ligand employed in this investigation possesses every characteristic of a medication. Ligand Docking and Virtual Screening By using molecular docking techniques, the strength of the connection or binding affinity between two molecules can be anticipated. AFB and EmbA are crucial components. iGEMDock, which employs the Generic Evolutionary Method and empirical scoring function for molecular docking, was used to conduct the primary docking analysis. Its graphical user interface is capable of virtual screening and pharmacological interaction recognition. After that, Autodock Vina was used to validate the docking simulation results, and Ligplot+ was used to display the interaction.

**Results and Discussion**

In the process of creating new drugs, molecular docking and de novo drug design have become indispensable techniques. The use of in-silico docking has drawn a lot of interest since it has shortened the cost and duration of the drug development process while boosting productivity. Mycobacterium tuberculosis is the causative agent of the pandemic disease tuberculosis. In the treatment of tuberculosis, bacteria that are extended drug resistant (XDR) and multidrug resistant (MDR) have emerged as a significant issue. Certain traditional medications have been shown to be ineffective against the tuberculosis pathogen. In the current investigation, we have chosen phytochemicals with previously established antimicrobial efficacy and conventional tuberculosis medications as a control group to examine the affinity ligand binding to the protein. The downloads of ligand molecules were made from the Zinc and PubChem databases. iGEMDock was used for primary protein ligand docking; a total of thirty-three ligands were docked against the two proteins, EmbA and AFB. The following study included eight anti-tuberculosis medications as a control group: rifampicin, isoniazid, bedaquiline, delamanid, ethionamide, ethambutol, gatifloxacin, and thiacetazone. Additionally, it displayed higher binding energy than both bedaquiline and delamanid, which are now undergoing clinical trials and have received provisional approval for the treatment of drug-resistant tuberculosis. Ultimately, the findings made it abundantly evident that Palmarin precisely interacts with the protein targets AFB and EmbA.

**Conclusion**

The management of tuberculosis is seriously threatened by extensively drug-resistant (XDR-TB) and multidrug-resistant (MDR-TB) tuberculosis. Numerous studies are being conducted to create anti-tuberculosis medications, but no new medications have been introduced to the market in the last thirty years. Drug development is a costly and time-consuming process in and of itself, but it can be made faster and more effective by applying computational techniques. De novo drug design and protein-ligand docking have grown in importance as methods to aid in the drug-designing process due to the quick increase in pharmacologically significant macromolecular structures becoming available. Two proteins, AFB and EmbA, were chosen for the current investigation, and a docking analysis was done on them. When compared to other phytochemicals and well-known anti-TB medications, the phytochemical compounds showed superior docking energy.

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All authors are contributed equally.

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