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Antimycobacterial evaluation of novel hybrid arylidene thiazolidine-2,4-diones

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ABSTRACT

A series of novel hybrid heterocycles comprising arylidene thiazolidine-2,4-dione and 1-cyclopropyl-2-(2-fluorophenyl)ethanone were synthesized. These compounds were evaluated for their antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$ in High Throughput Screen. Most of the hybrid arylidene thiazolidine-2,4-diones displayed moderate to good activity with MIC of less than 50 μM. Compound **1m** exhibited maximum potency being 5.87 fold more active at EC_{50} and 6.26 fold more active at EC_{90} than the standard drug pyrimethamine.

Tuberculosis (TB) is a chronic bacterial infection caused by *Mycobacterium Tuberculosis* bacteria (MTB), which spreads through air and usually infects the lungs. TB can be treated by taking several drugs for a period of 6–9 months. Of the approved drugs, the first-line anti-TB agents that form the core of treatment regimen include isoniazid (INH), rifampin (RIF), ethambutol (EMB) and pyrazinamide (PZA). Regimens for treating TB disease have an initial phase of 2 months, followed by a choice of several options for the continuation phase of either 4 or 7 months. The initial empiric treatment of TB starts with a 4-drug regimen: isoniazid, rifampin, pyrazinamide and either ethambutol or streptomycin. Once the TB isolate is known to be fully susceptible, ethambutol (or streptomycin, if it is used as a fourth drug) can be discontinued.[1] After 2 months of therapy (for a fully susceptible isolate), pyrazinamide can be stopped. Isoniazid and rifampin are continued as daily or intermittent therapy for 4 more months. If isolated isoniazid resistance is documented, isoniazid is discontinued and treatment with rifampin, pyrazinamide and ethambutol is continued for the entire 6 months. The Directly Observed Therapy (DOT) is the most recommended for all patients. With DOT, patients on the above regimens can be switched to 2–3 times per week dosing after an initial 2 weeks of daily dosing.[2]

One of the most significant methods for the development of highly active compounds is the combination of active pharmacophores into a single unit.[3] The biological screening of such compounds may result in new lead compounds with better activity than the standard drugs. In this context, we envisage to investigate the antimycobacterial activity of novel hybrid thiazolidine-2,4-diones **1** (Fig. 1) that comprise 5-arylidene-thiazolidine-2,4-dione and 1-cyclopropyl-2-(2-fluorophenyl)ethanone unit. The latter is the key component of the platelet inhibitor prasugrel **2**.[4] Incidentally, thiazolidine-2,4-dione derivatives have been identified as the privileged class of organic heterocycles with profound biological activities. The well known drugs used for the treatment of type II diabetes mellitus troglitazone **3**[5] and pioglitazone **4**[6] comprise thiazolidine-2,4-dione moiety (Fig. 1). Troglitazone **3**[7] has been shown to exhibit anticancer activities through the inhibition of the Raf/MEK/ERK signaling pathway. Further, the 5-arylidene thiazolidine-2,4-dione derivatives have been identified as potent and highly selective inhibitors of the PIM kinase.[8] However, the antimycobacterial activity of these heterocyclic derivatives are still unknown. The above importance of 5-arylidene thiazolidine-2,4-diones and in view of our continued interest in the synthesis and biological evaluation of novel heterocycles,[9] we herein report the

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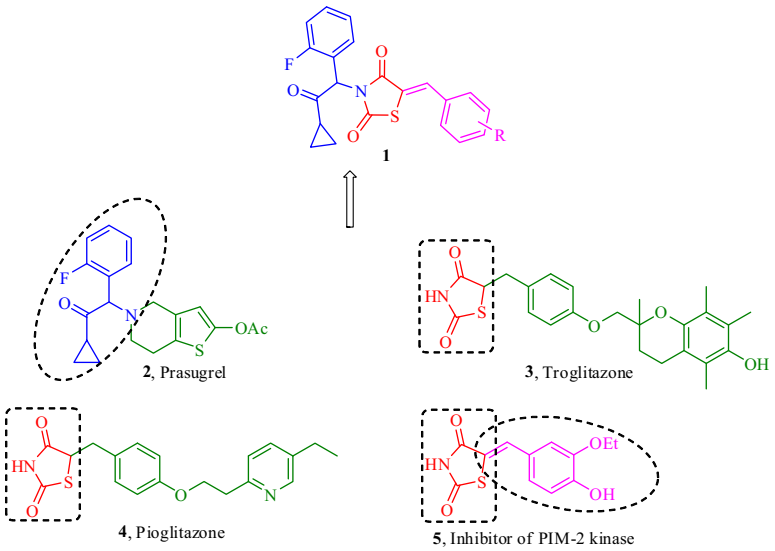


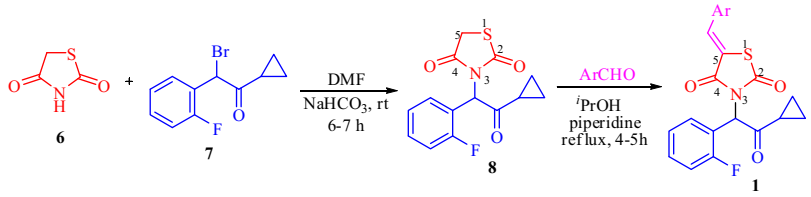
Figure 1. Design of the target molecule.

preliminary results of the antimycobacterial activity of novel 3-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-5-[(*Z*)-(aryl)methylidene]-1,3-thiazolane-2,4-diones **1**.

In the present investigation, the starting material 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone **7** was synthesized from the reaction of 2-bromo-2-(2-fluorophenyl)acetonitrile and cyclopropyl magnesium bromide solution, following a literature report.[10] Further, the reaction of **7** with thiazolidine-2,4-dione **6** in DMF in the presence of $NaHCO_3$ at ambient temperature afforded novel 3-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)thiazolidine-2,4-dione **8** in 93% yield (Scheme 1).[11] The structure of **8** is in complete agreement with its elemental analysis, mass, IR and NMR spectroscopy. The mass spectrum of **8** has a characteristic molecular ion peak at 292.0 (M^+). The IR spectrum of **8** shows strong absorptions at 1765, 1703 and 1687 cm^{-1} which are due to the three carbonyl groups. Further, in the ^1H NMR spectrum of **8** the diastereotopic 5-CH_2 protons appeared as doublets at 3.94 and 4.01 ppm with *J* value 17.7 Hz. The N–CH appeared as a singlet at 6.40 ppm whereas the cyclopropyl ring protons were observed as multiplets between 0.96 and 1.92 ppm. In the ^{13}C NMR of **8**, the carbonyls of the thiazolidine ring appeared at 170.4 and 170.5 ppm whilst the signal at 200.8 ppm is due to the carbonyl of the 1-cyclopropyl-2-(2-fluorophenyl)ethanone moiety.

In the next step, the synthesis of novel (*Z*)-5-benzylidene-3-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)thiazolidine-2,4-diones **1** via the Knoevenagel condensation of **8** with various aromatic aldehydes was performed (Scheme 1).[12] The reaction proceeded in isopropyl alcohol in the presence of piperidine as base under reflux condition affording **1a–q** in excellent yields (73–88%). A total of seventeen novel arylidene thiazolidine-2,4-dione hybrid heterocycles were synthesized (Table 1). The reaction occurred smoothly with aromatic aldehydes bearing electron-withdrawing or electron-donating group affording **1** in excellent yields. Further, the presence of sterically hindered groups in the aldehyde and bulky indoline, quinoxaline and benzo[*d*][1,3]dioxazole too had no adverse effects in the yield of the product. However, the reaction failed to occur with aliphatic aldehydes. The structure of all the arylidene thiazolidine-2,4-dione hybrid heterocycles **1a–q** were elucidated with the help of elemental analysis, mass, IR and NMR spectroscopic techniques. Moreover, the NMR spectra of **1** and thiazolidine-2,4-dione **8** were similar except for the presence of new signals in the ^1H and ^{13}C NMR spectra of **1** due to the aromatic ring and benzylidene protons and carbons. Further, the DEPT-135 spectrum of **1** reveals the absence of one 'CH_2' carbon and appearance of new signals due to aromatic 'C' and 'CH' carbons. The structure of **1** assigned from NMR spectroscopy was further solved from single crystal X-ray studies. The ORTEP diagram of **1f** reveals (*Z*)-configuration for the exocyclic alkene (Fig. 2).[13]

All the hybrid thiazolidine-2,4-diones **1a–q** and **8** were screened for their in vitro antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}R_V$ (MTB-$H_{37}Rv$) in a High Throughput Screen (HTS) using an assay adapted from the microdilution alamar Blue (AB) broth assay reported by Collins and Franzblau[14] and additionally an alternative method for end-point detection using the Promega reagent BacTiter-Glo™ Microbial Cell Viability (BTG). Five standard drugs were used as references together with the synthesized compound for the assay. Data were analyzed using the IDBS Activity Base software and the dose response result was analyzed using a four parameter logistic fit to the data (Excel Fit equation 205) with the maximum and minimum locked at 100 and 0. From these curves, EC_{50} and EC_{90} values were calculated. The MIC is the minimum concentration of the compound required to inhibit 90% of bacterial growth and MIC's of the compounds are given in Table 2 along with standard drugs for comparison.



Scheme 1. Synthesis of 1,3-thiazolane-2,4-diones **1**.