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Synthesis of Triazole Derivatives of 9-Ethyl-9H-carbazole and Dibenzo[b,d]furan and Evaluation of Their Antimycobacterial and Immunomodulatory Activity

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1,4-Disubstituted 1,2,3-triazole derivatives of 9-ethyl-9H-carbazole and dibenzo[b,d]furan were synthesized by the Huisgen's 1,3-dipolar cycloaddition reaction between azides and terminal alkynes. The synthesized derivatives **7d, 8a, 8b, 9e,** and **10c** exhibited good MIC values, especially against *Mycobacterium smegmatis* and these compounds were further evaluated for their immunomodulatory activity. Majority of the compounds exhibited no toxicity on splenocytes and macrophages and the compounds **8a** and **8b** are proved as induced proliferator. These compounds have shown decreased production of TNF-α from LPS stimulated RAW 264.7 cells and among all these compounds, **7d** has shown significant inhibition of TNF-α production. Molecular docking studies into the active site of mycobacterial DprE1 enzyme helped to establish a structural basis for inhibition of *Mycobacterium tuberculosis* and understand the type of ligand-protein interactions governing the binding affinity.

Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) is one of the deadliest disease. Patient with human immunodeficiency virus (HIV), if get co-infected with MTB is likely to develop active tuberculosis which increases the death risk by 20 fold.[1] Tuberculosis has occupied the second position for mortality rate and is responsible for infecting one-third population of the world.[2] In 2015, the number of people died due to TB is 1.8 million in which 0.4 million deaths were due to co-infection with HIV. In the same year, an estimated 480 000 people developed multidrug-resistant TB (MDR-TB). Eradicating TB globally by 2030 is one of the health target of newly adopted sustainable development goals of World Health Organization (WHO).[3] Therefore extensive research is undergoing to develop new drugs to combat this problem.

Most of the naturally occurring molecules lack the remarkable biological activity and also it requires a tedious procedure for their isolation. To overcome this problem, it is an urgent need to make their hybrid analogues or to synthesize new molecules with better activity. Lansine **I** and 3-formyl-6-methoxycarbazole **II** (Figure 1), the carbazole derivatives isolated from the stem bark of *Micromelum hirsutum* have shown MIC values of 14.3 μg/mL and 15.6 μg/mL respectively against *M. tuberculosis*.[4] Usnic acid **III** (Figure 1), a dibenzofuran derivative of the lichen secondary metabolite isolated from *Cladonia substellata*, exhibit antimycobacterial activity; but its development as a drug was restricted by weak potency.[5] Benzofurobenzopyran **IV** (Figure 1), a synthetic analogue derived from dibenzo[b,d]furan showed good inhibitory activity against *M. tuberculosis* but was found to be more cytotoxic.[6] Apart from these analogues, some of the recently synthesized analogues **V**,[7a] **VI**,[7b] **VII**,[7c] **VIII**,[7d] **IX**,[7e] **X**[7f] and **XI** (Figure 1) have shown remarkable anti-tubercular activity. Among them, benzofuran salicylic acid derivative **XI** (Figure 1) is a lead antitubercular agent currently in clinical evaluations.[8]

1,2,3-Triazole containing hybrid molecules are gaining importance in medicinal chemistry and their biological profiles are described in recent review articles.[9] The triazole derivatives exhibit versatile biological activities including anti-tubercular,[10] anti-bacterial, anti-HIV,[11] α-glycosidase[12] and anti-fungal.[13]

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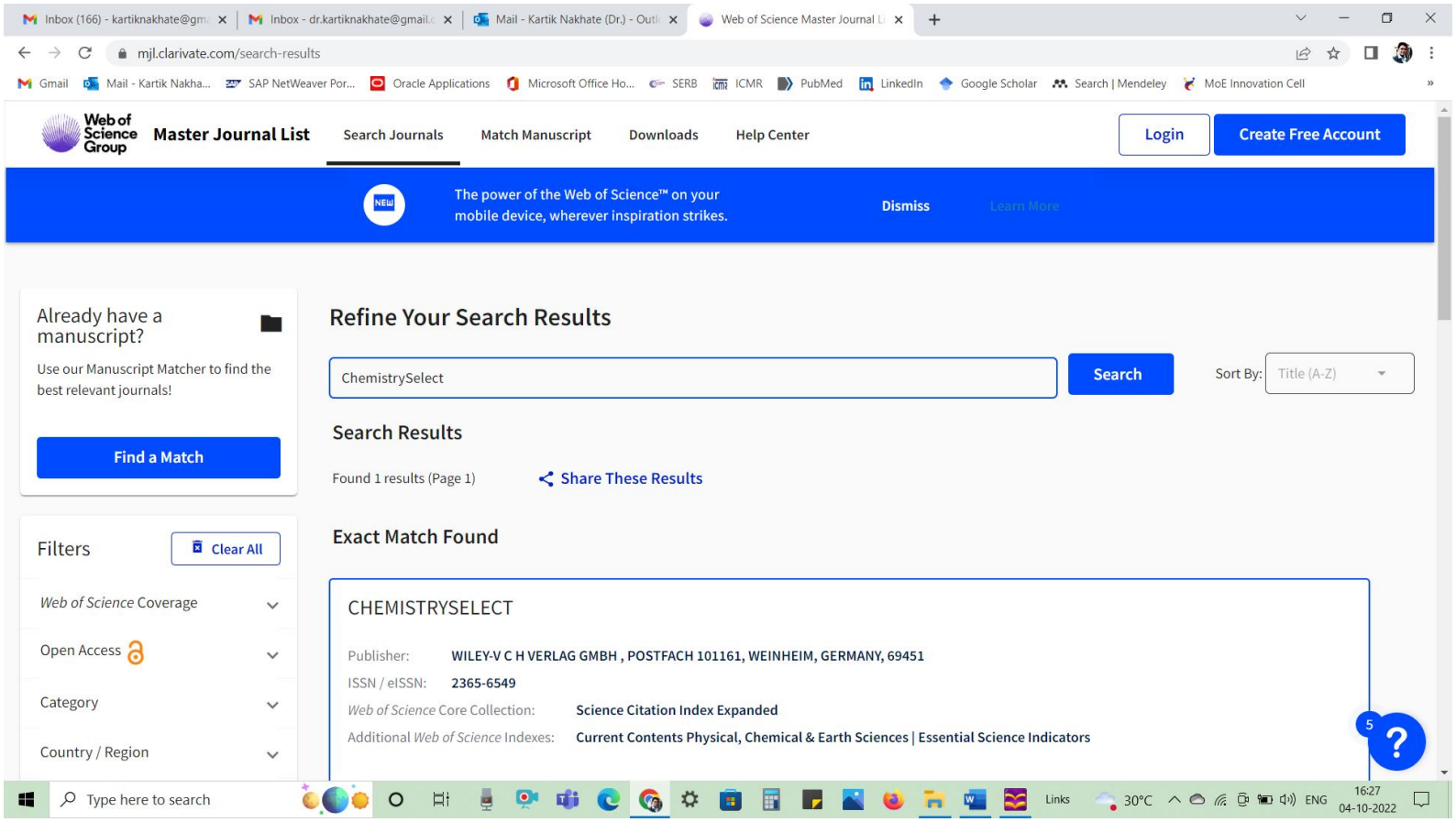
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