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Discovery of Potential Antitubercular Activity in 'Non-Antibiotics' Through Virtual Screening

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Editorial

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INTRODUCTION

Ligand based virtual screening is an extremely useful tool in identification of lead molecules, especially for less explored molecular targets [1]. Amongst many techniques available, 3D pharmacophore model based virtual screening methods are most successful [2]. Virtual screening of chemical libraries compiling known therapeutics has significantly helped in knowledge-based rational drug repositioning [3-6]. It has been recently recognized as an effective strategy to aid novel drug discovery for rare and neglected conditions [7-9].

3D Shape based screening method; Rapid Overlay of Chemical Structures (ROCS) found to be very successful in identification of chemically diverse compounds possessing similar bioactivity profile [10] and hence used for our study. ROCS uses descriptors, which compare molecules based on their molecular shapes, by assessing atom-centred overlapping Gaussians and calculating the maximal intersection of the volume between molecules [11]. In this method, a low energy 3D conformer of a compound is calculated and a shape is derived from the molecule's surface. During the screening process, this query shape is used to check fitment of 3D conformers present in test compound library. Molecules fitting the query shape are expected to interact with similar molecular targets. The overlap of two molecules is estimated with Gaussians, parameterized according to the volume of the available heavy atoms. Simultaneously, complementary properties in chemical functionalities are also calculated. ROCS's ComboScore (CS) is evaluated by measuring extent of overlap in both shape (Tanimoto score) and chemical functionality (Scaled Colour Tanimoto Score). The CS ranges from 0 to 2, and 2 represents identity.

Phenothiazine based antipsychotics were recently reported to possess clinically useful antitubercular activity against multi-drug/extremely drug resistant tuberculosis [12]. The mechanism proposed for antimycobacterial activity of this drug includes disruption of mycobacterial respiration process most probably via type II NADH: quinine oxido-reductase inhibition [13]. Another unusual mechanism proposed is the activation of host macrophages to effectively destroy dormant mycobacterium [14,15]. The later mechanism draws attention of the drug designers as it does not involve biochemistry of the pathogen and hence less chances for development of resistance [16]. The only problem with this therapy is the unwanted CNS activity, neuronal and cardiac toxicity, which makes continuous therapeutic drug monitoring mandatory. Inspired by these results, we have initiated a project successfully to search for anti-TB activity in "non-antibiotic" drug molecules using ligand based virtual screening tools.

CONCLUSION

In conclusion, the efficacy of ligand based virtual screening tools in identification of similar bio-actives in chemically diverse

libraries is very much useful. This technique extremely helps in conserving time and resources. It further impetus to evaluate approved drug molecules for their possible anti TB activity and clinical application. The observed pharmacophoric features may be used for designing newer anti TB agents with better bioactivity profile.

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