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Original article

Pharmacophoric model building for antitubercular activity of the individual Schiff bases of small combinatorial library

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ABSTRACT

Synthesis and evaluation of anti-TB activity of individual compounds of Schiff bases combinatorial library were done against *Mycobacterium tuberculosis* $H_{37}Rv$ at a single concentration of 6.25 μg/mL according to the protocol of TAACF. Compounds **2C** and **3D** produced 99% inhibitory activity on the investigated organism, while the other tested compounds showed lower activity ranging from 35 to 84%. It was found that there are no relation between the anti-TB activity of the tested compounds and their lipophilicity expressed by *C* log *P* of these compounds. A 3D pharmacophoric model has been generated by Molecular Operating Environment (MOE) using a training set of 10 reported anti-TB compounds and testing the synthesized compounds (**1A**, **1B**, **1D**, **1E**, **2C**, **3A**, **3C**, **3D**, **3E** and **4A**–**4E**). The generated pharmacophoric features include, **F1**: hydrogen bond donors (Don), **F2**: aromatic rings (Aro), **F3**: hydrogen bond acceptors (Acc)/metal ligator (ML), **F4**: Aro/hydrophobic (Hyd). In all hit set, it was found that the amidic nitrogen CONH–N=C fitted the region of the Don, **F1**, while the amidic carbonyl group fitted the region of the Acc/ML, **F3**. The distances bridging **F1** to **F2**, **F3** and **F4** were essential for anti-TB activity in the developed pharmacophore model, as it was confirmed from model validation procedure.

1. Introduction

More than a decade since the World Health Organization declared Tuberculosis (TB) "a global health emergency" [1]. However, TB remains one of the world's greatest health problems whose morbidity and mortality are increasing. The appalling extent of infection by *Mycobacterium tuberculosis*, the exclusively human pathogen, covers one of every three people, a total of 2 billions persons worldwide. About 8 million people develop active TB, more than 2 million die of this disease each year, and over 95% of those are in developing countries [2]. Over the years, the organism has acquired resistance to nearly all first-line antitubercular drugs such as isoniazid, rifampin, ethionamide, etc., posing serious problems in treating the infection clinically. The problem of clinical treatment has become more acute especially in immuno-compromised AIDS patients where the rise in TB incidence and consequent deaths over the past two decades has escalated by more than 12% [3]. Thus, the increasing global health threat of TB is due to both the synergistic pathology of coinfection with the human immunodeficiency virus (HIV), and the continued evolution of multi-drug resistant (MDR) strains. Historically, drugs for treating TB have been available for over half a century. Nevertheless, in spite of major advances that have been made in the drug discovery process no new drugs have been introduced in the clinic since the discovery of rifampin [4]. As a result, there is a dire need to develop novel, faster acting chemotherapeutics with lower toxicity. Consequently, today, it is clear that vigorous and widespread research on drug design will be necessary to recapture lost ground and to make new advances.

Accordingly, as a contribution to the anti-TB drug development using combinatorial library synthesis, design and synthesis of a small mixture-based Schiff base library for anti-TB screening activity was undertaken [5]. The design of Schiff base combinatorial library was based on the hypothesis that hydrazone derivatives undergo hydrolysis to their parent hydrazides and the corresponding carbonyl compounds and their activity are related to the hydrazide type [6]. This article aimed to find pharmacophoric model for the synthesized Schiff bases from the structural features and the evaluated anti-TB activity using "Molecular Operating Environment" (MOE) software.

2. Results and discussion

2.1. Anti-TB activity of individual Schiff bases of the synthesized combinatorial library

Individual Schiff bases, **1A**–**5A**, **1B**–**5B**, **1C**–**5C**, **1D**–**5D** and **1E**–**5E**, of the synthesized combinatorial library, shown in Table 1, were

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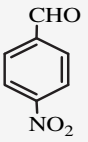
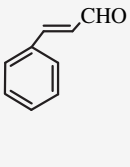
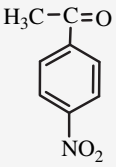
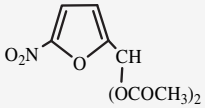
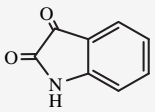
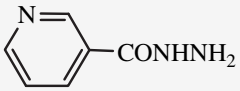
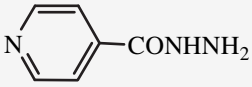
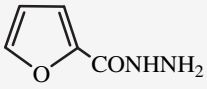
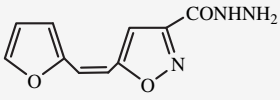
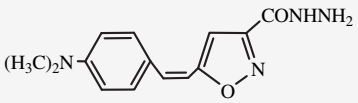
Table 1
The synthesized individual Schiff bases of the combinatorial library.

Building blocks		 A	 B	 C	 D	 E
	**1**	**1A**	**1B**	**1C**	**1D**	**1E**
	**2**	**2A**	**2B**	**2C**	**2D**	**2E**
	**3**	**3A**	**3B**	**3C**	**3D**	**3E**
	**4**	**4A**	**4B**	**4C**	**4D**	**4E**
	**5**	**5A**	**5B**	**5C**	**5D**	**5E**

synthesized in order to prove the validity of the technique used to evaluate anti-TB activity in mixtures. Synthesis of these targets was achieved by the classical method reported for hydrazide preparation. Simply by refluxing the convenient carbonyl derivative with the corresponding hydrazide derivative in ethanol in the presence of glacial acetic acid [5]. Anti-TB activity of these compounds was evaluated against *M. tuberculosis* $H_{37}Rv$ using Microplate Almar Blue assay (MABA) at a single concentration of 6.25 μg/mL according to the protocol of TAACF [7].

It is evident from the scattered data available in Table 2 that one cannot make a decision about which among the carbonyl carrier, **1**–**5**, or the hydrazine carrier, **A**–**E**, moieties maintained the upper hand in anti-TB activity. However, a general conclusion can be made about the SAR in this series of hydrazones. It is the integrated molecular structure features that are responsible for the elucidated activity irrespective of the building blocks corporated in individual molecules. As shown from the results two compounds were active, **2C** and **3D**, while the other tested compounds showed lower inhibition activity ranging from 35 to 84%.

Table 2
Anti-TB activity for some synthesized individual Schiff bases of the combinatorial library against *M. tuberculosis* $H_{37}Rv$.

Compd. no.	Inhibition %	Compd. no.	Inhibition %
2C	99	**1E**	57
3D	99	**1B**	54
1D	84	**1A**	51
4B	80	**3E**	41
4C	66	**4E**	39
3C	62	**4A**	37
4D	59	**3A**	35

2.2. Relation between lipophilicity and anti-TB

Correlation between lipophilicity and anti-TB activity was reported as lipophilicity of drug molecules may render them more capable of penetrating various biomembranes consequently improving their permeation properties toward microbial cell membrane [8–10].

Lipophilicity of the synthesized compounds expressed in the term of their *C* log *P* values, is shown in Table 3. Computation of the log *P* was based on the fragment method developed by Leo contained in a PC-software package [11]. It was found that there is no

Table 3
C log *P* values of the synthesized individual Schiff bases of the combinatorial library.

Compd. no.	*C* log *P*	Compd. no.	*C* log *P*	Compd. no.	*C* log *P*	Compd. no.	*C* log *P*	Compd. no.	*C* log *P*
1A	1.58	**2A**	1.58	**3A**	1.55	**4A**	2.57	**5A**	3.59
1B	3.56	**2B**	3.56	**3B**	3.49	**4B**	4.55	**5B**	5.57
1C	2.71	**2C**	2.71	**3C**	3.39	**4C**	3.66	**5C**	4.68
1D	0.76	**2D**	0.76	**3D**	0.69	**4D**	1.74	**5D**	2.76
1E	2.11	**2E**	2.11	**3E**	2.78	**4E**	3.05	**5E**	4.07