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Design, synthesis and molecular docking of substituted 3-hydrazinyl-3-oxo-propanamides as anti-tubercular agents ☆

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ABSTRACT

Based on the anti-mycobacterial activity of various acid hydrazides, a series of substituted 3-hydrazinyl-3-oxo-propanamides has been designed. The target compounds have been synthesized from diethylmalonate using substituted amines and hydrazine hydrate in ethanol. Computational studies and anti-tubercular activity screenings were undertaken to test their inhibitory effect on protein kinase PknB from *Mycobacterium tuberculosis*. Binding poses of the compounds were energetically favorable and showed good interactions with active site residues. Designed molecules obey the Lipinski's rule of 5 and gave moderate to good drug likeness score. Among the sixteen compounds (**1**–**16**) taken for in silico and in vitro studies, 3 compounds (**11**, **12** and **15**) have shown good binding energies along with exhibiting good anti-tubercular activity and thus may be considered as a good inhibitors of PknB.

Mycobacterium tuberculosis (MTB) is considered to be the leading bacterial infection around the globe.[1] With an estimated 8.7 million new tuberculosis (TB) cases (13% co-infected with HIV) and 1.4 million fatalities each year,[2] MTB causes more human deaths than any other single infectious organism. The disease is one of India's most challenging public health problems and it accounts for nearly one-third of the global burden. Approximately 2 million people acquire TB every year in India.[3] Furthermore, MTB strains resistance is emerging at an alarming rate to all of the first line drugs (isoniazid, rifampicin, fluoroquinolone) and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).[4]

Isonicotinic acid hydrazide (isoniazid, INH, Fig. 1) belongs to the group of the first line antitubercular drugs which are in clinical practice for more than 50 years. After the discovery of INH, the full therapeutic possibilities of acid hydrazides were realized. Investigations of other heterocyclic hydrazides having mono-cyclic nuclei such as furan, thiophene, pyrrole and dicyclic nuclei such as quinoline and isoquinoline was stimulated due to the remarkable clinical value of INH.[5] A large number of such substances have been synthesized in pure form having differing ranges of curative effects. With a view to establish the structural requirements for antitubercular activity, Yale et al.[6] reported the synthesis of a number of hydrazides of the nicotinic acid hydrazide type.

A large number of hydrazides and their derivatives are reported to possess a wide array of biological activities like antifungal,[7] psychotropic,[7] antituberculous,[8–10] antiparasite,[7,11] bacteriostatic,[7,12–14] antiviral,[14] insecticidal[15] and anti-cancer[16] activities. Thus, these were found to be useful especially in the treatment of inflammatory and autoimmune diseases, osteoarthritis, respiratory diseases, tumors, cachexia, cardiovascular diseases, fever, hemorrhage and sepsis.[17]

Protein kinase B (PknB) plays an important role in mammalian cellular signaling. *Mycobacterium tuberculosis* PknB is an essential receptor-like protein kinase involved in cell growth control. The protein kinase B peptide contains two types of structural elements (VAL 95, ARG 97) and basic residue ring constituted of glycine rich residue. *M. tuberculosis* PknB is a *trans*-membrane Ser/Thr protein kinase (STPK) highly conserved in Gram-positive bacteria and apparently essential for mycobacterial viability.[18] It was previously shown that PknB is regulated by auto-phosphorylation and de-phosphorylation by the Ser/Thr protein phosphatase PstP[19,20]

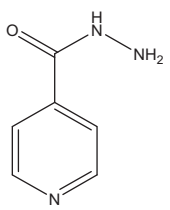

Figure 1. Structure of isoniazid.

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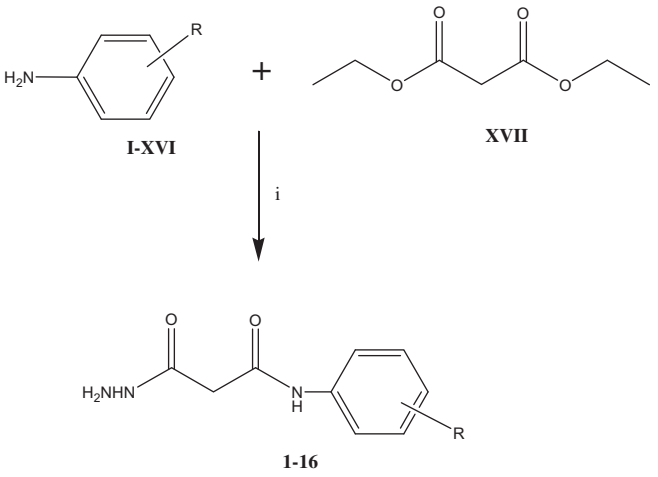
and work showed that PknB is predominantly expressed during exponential growth, where it's over expression causes morphological changes linked to defects in cell wall synthesis and cell division.[21]

Therefore, there is an urgent need to develop new drugs against MTB. To achieve this endeavor, we have synthesized some substituted malonamic acid hydrazides (**1–16**). The molecular docking studies of newly synthesized compounds were carried out. Oral bioavailability is a desirable property of compounds under investigation in the drug discovery process. Lipinski's rule-of-five is a simple model to forecast the absorption and intestinal permeability of a compound.[22,23] The designed molecules obey the Lipinski rule of five along with obeying some additional parameters.[24] Compounds which were found promising in the docking study were evaluated for their anti-mycobacterial activity by resazurin micro-titre assay (REMA) method[25] against *M. tuberculosis* H37Rv.



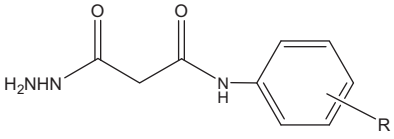
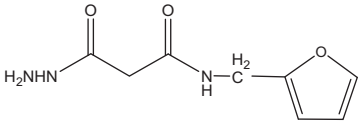
Scheme 1. Reagents and conditions: (i) [a] C_2H_2OH, reflux, 4 h. [b] $NH_2NH_2{\cdot}HCl$, reflux, 5 h.

All the compounds were prepared by Scheme 1. For synthesis, substituted amines (**I–XVI**) were first refluxed with ethanolic solution of diethyl malonate (**XVII**) for 4 h. Further refluxing with hydrazine hydrate for another 5 h gave compounds **1–16** (58–88% yield, Table 1, Scheme 1). All the compounds (**1–16**) were characterized spectroscopically. The base peak in ESI-MS was found at M^++1. In IR spectra, a strong band from 1538 to 1681 cm^{-1} indicated the presence of carbonyl of amide group. Bands from 2806 to 2969 indicated the presence of methylene group. In ^1H NMR spectra of compounds **1–16**, singlet peak between 3.52 and 3.32 ppm, indicated two protons of the methylene group (>CH_2). Broad singlet between 4.32 and 4.20 ppm was found indicating two protons attached to nitrogen atom (–NH–NH_2). Peaks between 8.91 and 6.60 ppm indicated the presence of protons of aromatic ring of respective compounds. Two broad singlets between 9.36 and 9.21 ppm were found indicating –CONH– proton. ^{13}C spectra clearly supported the results obtained from ^1H NMR spectra and also justified the number of carbon atoms in corresponding compounds.

Table 2
Molecular docking results of the target compounds (**1–16**)

Mol. No.	Binding energy (kcal/mol)	Inhibition constant (μM)	*C*log*P*
1	−7.44	3.53	0.80
2	−6.33	22.87	−0.56
3	−6.69	12.48	−0.10
4	−6.78	10.79	−0.10
5	−7.09	6.38	−0.63
6	−6.98	7.68	1.37
7	−6.87	9.21	1.25
8	−7.03	7.01	−0.89
9	−7.20	5.25	−0.89
10	−6.66	13.13	0.82
11	−6.24	26.51	1.55
12	−6.88	9.04	1.02
13	−6.98	7.59	−3.18
14	−7.01	7.32	0.26
15	−7.48	3.86	−0.36
16	−6.46	18.46	−1.20

Table 1
Characterization & anti-tubercular activity of substituted 3-hydrazinyl-3-oxo-propanamides (**1–16**)

S. No.		Molecular formula	Mp (°C)	% Yield	MIC[a] (μg/mL) H37Rv
1	3-Cl-4-F	$C_9H_9N_3O_2FCl$	162–164	79.20	50
2	2-NO_2	$C_9H_{10}N_4O_4$	156–159	58.51	>100
3	3-NO_2	$C_9H_{10}N_4O_4$	152–154	85.96	>100
4	4-NO_2	$C_9H_{10}N_4O_4$	185–186	71.49	>100
5	2,4-$(NO_2)_2$	$C_9H_9N_5O_6$	154–156	75.17	>100
6	3,5-$(Cl)_2$	$C_9H_9N_3O_2Cl_2$	169–171	78.61	>100
7	3,4-$(Cl)_2$	$C_9H_9N_3O_2Cl_2$	183–185	74.29	>100
8	2,5-$(OCH_3)_2$	$C_{11}H_{15}N_3O_4$	111–114	69.38	>100
9	2,4-$(OCH_3)_2$	$C_{11}H_{15}N_3O_4$	105–106	73.42	>100
10	4-$N(C_2H_5)_2$	$C_{13}H_{20}N_4O_2$	150–152	79.70	100
11	4-C_4H_9	$C_{13}H_{19}N_3O_2$	160–163	81.33	12.5
12	4-C_3H_7	$C_{12}H_{17}N_3O_2$	156–157	78.37	12.5
13	4-SO_3H	$C_9H_{11}N_3O_5S$	152–153	85.51	50
14	2-COOH	$C_{10}H_{11}N_3O_4$	143–146	85.53	50
15	4-COOH	$C_{10}H_{11}N_3O_4$	158–159	88.51	12.5
16		$C_8H_{11}N_3O_3$	151–153	60.58	>100

[a] MIC INH: 0.02 μg/mL, RIF: 0.01 μg/mL.