Novel isoniazid derivatives as antitubercular compounds

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Introduction

Tuberculosis (TB) is the leading cause of death from an infectious disease [1] and it is estimated that approximately one-quarter of the world's population is infected with TB [1]. Treatment of latent and active TB uses isoniazid (INH) in combination with other less effective active antibiotics. Resistance to INH arises mainly from mutations in the katG gene encoding the catalase-peroxidase KatG, in particular the S315T mutation.

A novel series of INH derivatives is here computationally investigated following a previously published, protocol [3]. The goal is to identify compounds that are simultaneously more reactive in forming the isonicotinoyl radical while keeping high membrane permeabilities as in INH-C_{10}. New compounds include deoxy alkyl (C2-C10), imine (C2-C10), methyl benzoate and diphenyl ether derivatives of INH.

Previous studies

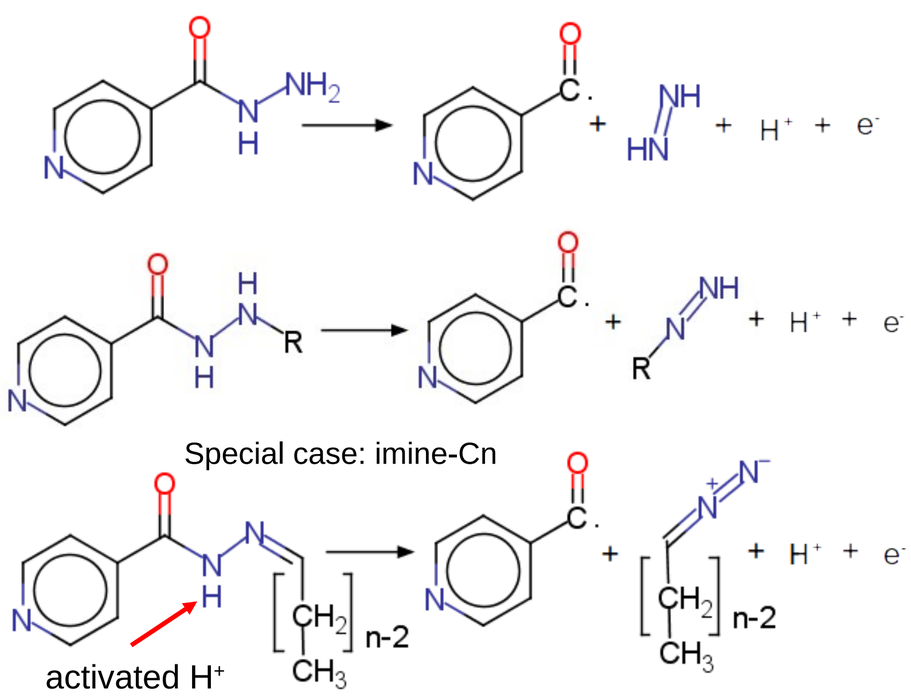
- Derivatives of INH, in particular the N′-acylated INH derivative with a 10-carbon alkyl chain (INH-C_{10}), have been reported to be more effective than INH against the S315T mutation of *Mycobacterium tuberculosis* [2].
- From a previous study of INH, INH-C_{10} and INH-C_2, it was proposed that the observed MIC values result from the interplay of membrane permeability and reactivity towards formation of the isonicotinoyl radicals (IN•) [3].

Goal

- To find INH derivatives that exhibit a combination of high membrane permeability and reactivity towards formation of the isonicotinoyl radical (IN•).

Quantum mechanical calculations: reactivity

Spontaneous activation of INH and derivatives



Special case: imine-Cn

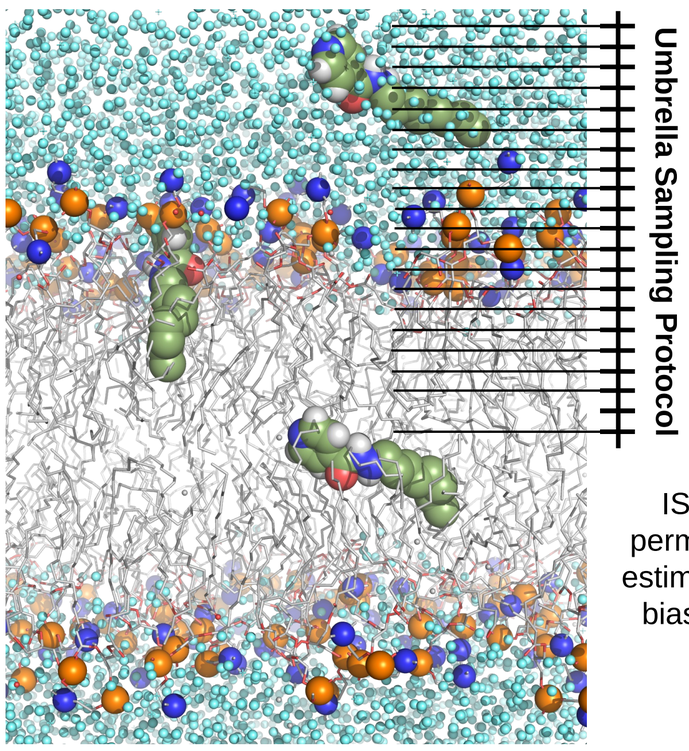
IN• radical Gibbs free energies of formation relative to INH

$\Delta G(INR) \rightarrow \Delta G(IN\cdot) + \Delta G(NHNR) + \Delta G(H^+) + \Delta G(e^-)$

$\Delta G(INH) \rightarrow \Delta G(IN\cdot) + \Delta G(NHNH) + \Delta G(H^+) + \Delta G(e^-)$

$\Delta\Delta G(INR\text{-}INH) = \Delta G(NHNR) - \Delta G(NHNH) + \Delta G(INH) - \Delta G(INR)$

Cpd	ΔΔG (kcal/mol)	Cpd	ΔΔG (kcal/mol)	Cpd	ΔΔG (kcal/mol)
INH	0.0	N33	-8.0	N34	-6.5
INH-C_n		**Deoxy-C_n**		**Imine-C_n**	
C2	9.1	C2	-6.8	C2	-1.3
C4	9.7	C4	-9.1	C4	-1.3
C6	8.9	C6	-9.8	C6	-1.7
C8	10.3	C8	-10.4	C8	-2.8
C10	10.8	C10	-10.5	C10	-2.4



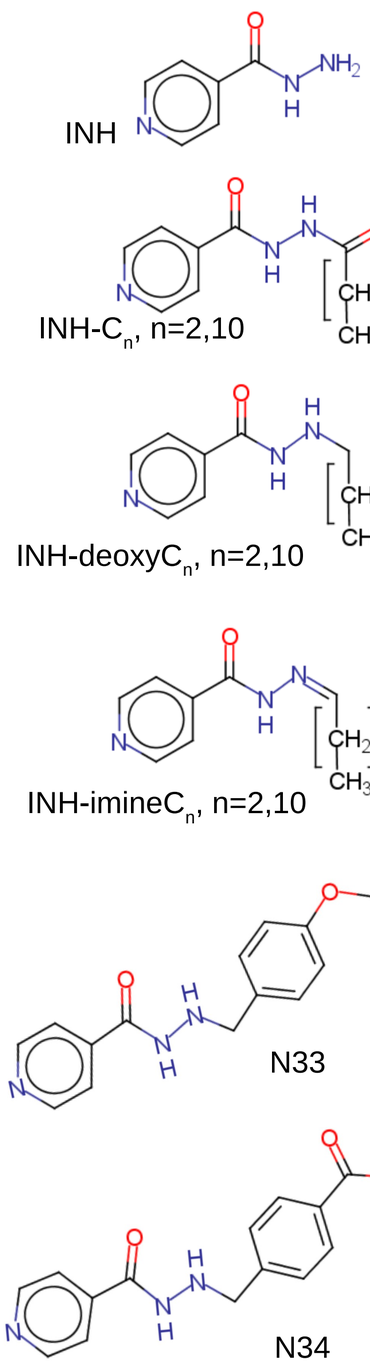
ISDM model[3] permeability rates estimated from MD bias simulations

Membrane permeability calculations

Cpd	Perm. (cm s-1)	Cpd	Perm. (cm s-1)	Cpd	Perm. (cm s-1)
INH	1.3	N33	4.7		
INH-Cn		Deoxy-Cn		Imine-Cn	
C2	3.8	C2	0.6	C4	2.0
C10	27.9	C4	3.8	C6	3.8
		C6	5.8	C8	4.2
		C8	22.0	C10	8.1
		C10	14.0		

Selected compounds with the best reactivities and membrane permeabilities will be tested experimentally

Compound list



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