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# A long range tautomeric effect on a new Schiff isoniazid analogue, NMR study and X-ray crystallography

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A long range tautomerism to a N,O-aminal by closing a tetrahydrofuran ring was put in evidence for an isoniazid analogue, whose accidental synthesis is presented in the paper. The isoniazid analogue was synthesized by the reaction of isoniazid with 2-hydroxy-tetrahydrofuran which was demonstrated to exist in old THF together with other peroxides, especially 2-HOO-THF. The same compound was efficiently obtained from a THF containing 2-HOO-THF, by reducing this peroxide in the presence of isoniazid. The 2,4-dinitrophenylhydrazone was also synthesized. The oxidation of 1,4-butanediol and the reaction of the resulted mono-aldehyde with isoniazid gave the same compound. The linear tautomer was put in evidence in the NMR spectra in DMSO-*d6* and confirmed to be the single tautomer in the crystal, by X-ray analysis. The cyclic N,O-aminal tautomer was found in the NMR spectra in $CDCl_3$, resulted by intramolecular HCl-catalyzed addition of the hydroxyl group to the double bond CH=N of the linear tautomer, by closing a tetrahydrofurane ring. This is a favoured cyclization according to Baldwin's rules (5-*exo*-trig). The same tautomerism was also present for two isoniazid analogues obtained from two lactols, used in prostaglandin synthesis. The compounds **1**, **4**, **6** and INH had no antibacterial or antifungal activity.

## 1. Introduction

N,O-aminals are compounds with a carbon atom geminally substituted by an amine and a hydroxy or alkoxy group [1, 2]. These compounds are important structural fragments encountered in many natural products [3-5], and in active substances studied in different clinical phases [5, 6]. Classified by Huang et al [2] into acyclic and cyclic-types, the N,O-aminals were observed to be more stable than imines in many chemical structures, a feature which makes the N,O- aminals more convenient to use in subsequent synthesis steps as a masked form of imines. In particular, the N,O-aminals are suitable to (un)catalytically generate *in situ* the reactive imines, which can then be used in the next specific reactions, for example in catalytic asymmetric reactions [2, 8].

N,O-aminals were found to be valuable reagents for the regio/stereoselective formation of C-C or C-N bonds, in asymmetric catalytic reactions [2], and for obtaining chiral complex chemical structures [2-7, 9]. The non-stereoselective synthesis of N,O-aminals or the catalytic asymmetric synthesis of chiral N,O-aminals are widely discussed in the literature [2, 10-15]. N,O-alkoxy-aminals are obtained from the corresponding imines by the nucleophilic addition of an alkoxy group [15,16] or by the substitution of a sulfonyl group of an α-amido sulfone by an alkoxy group [2, see ref. 2]. N,O-aminals with a hydroxy group are described as intermediates in the synthesis of imines, by the nucleophilic addition of an amine to aldehydes and ketones (followed by proton transfer) [17, 18, 2], but their synthesis is also described by the addition of an alcohol to the corresponding imines [18, 19]. The latter method is relevant for this paper.

The tautomerism of N,O-aminals is presented in some depth in the literature: Schiff base-oxazolidine (with two (un)substituted carbon atoms between the amine and the OH group) [17-18], Schiff base-oxazolidine/1,3-oxazine (with two/three carbon atoms between the amine and the OH group) [20, 21], bisimine of 4-chlorobenzaldehyde with 1,3-diamino-2-propanol in equilibrium with *cis*-and *trans*-mono-oxazolidines [22], in hydroxylated isoflavones [23], etc. The influence of the steric and/or electronic effects of the substituents (including positions and electron withdrawing/donating substituents) of the amine moiety or aromatic aldehyde/ketone moiety was also taken into account in explaining the sometimes complex tautomeric mixture of the Schiff base form, the oxazolidine or the 1,3-oxazine forms. Some theoretical calculations in this direction were described in [19, 20, 22, 24]. The ratio of the cyclized and open chain forms of the tautomeric equilibria was conveniently determined by NMR, by the integration of the O-C*H*-N and -C*H*=N protons which appeared as singlets. In many publications, the N,O-aminals are presented as intermediates, reagents, or starting compounds for asymmetric catalysis, or in the final structures [2, 20, 24], however, *to our*

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Electronic Supplementary Information (ESI) available: [$^1$H-NMR and $^{13}$C-NMR copy spectra for compounds: 1.1 to 1.11, crystallography data in Table S1, 2S and Figure 5S, and also Tables 1-8 for cifreport for compound **1**, TLC slides, 4.]. See DOI: 10.1039/x0xx00000x

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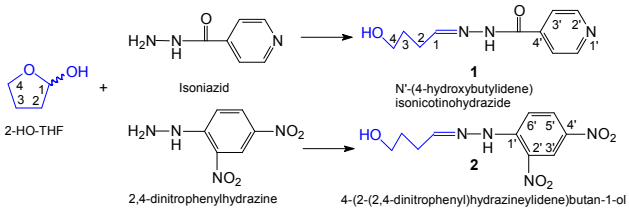
*knowledge, a similar cyclic N,O-aminal has not been encountered in the isoniazid analogues*.
In the present paper, we put in evidence a tautomerization of some isoniazid analogues from the Schiff form to a cyclic N,O-aminal, formed by the intramolecular acid catalysis addition of an alcohol group to the C=N double bond which closes a tetrahydrofuran ring.

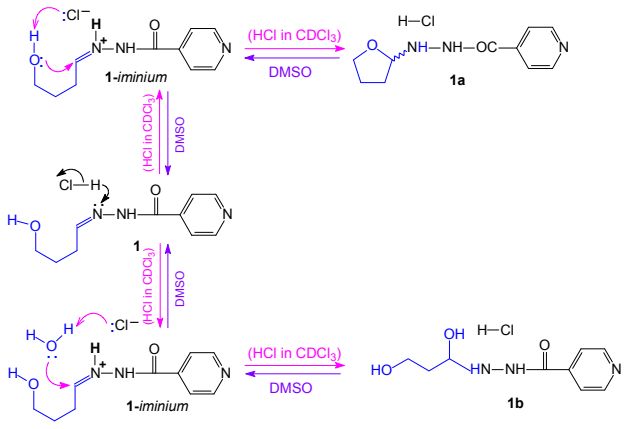
## 2. Results and discussion

A long range tautomerism to a N,O aminal by closing a tetrahydrofuran ring was put in evidence for a few isoniazid analogues. In a reaction of isoniazid (INH) with a sterically hindered ketone [25] in an old anh. tetrahydrofuran ($THF^X$) (See experimental), we discovered the formation of a secondary compound which did not look to originate from the skeleton of the ketone compound.
This compound was isolated by low pressure chromatography (LPC), crystallized in needles from acetonitrile, mp 146.3-147.5 ˚C, and analyzed by IR and NMR in $CDCl_3$. Its NMR spectrum in $CDCl_3$ showed, in addition to the INH fragment, the signals of four carbon atoms and 7 protons, indicating that we have probably a compound with formula **1** which could have resulted by the reaction of INH with the 2-hydroxy-tetrahydrofuran (2-HO-THF) (Scheme 1), present in $THF^X$:




**Scheme 1**. The reaction of 2-Hydroxy-tetrahydrofuran with INH and 2,4-dinitrophenylhydrazine

2-HO-THF is an intermediate in the synthesis of butyrolactone from THF [26-28], and in our case, it was formed by the air oxidation of THF through the corresponding peroxides, followed by their decomposition in time on sodium wire or during the THF distillation. The signals for all carbon atoms were in a ratio of ~1:1, and, for C-1 two signals were at $\delta$ 96.36, 91.59 ppm, which did not confirm the presence of a CH=N group for a hydrazone in **1** [ex. 1.1. and Electronic Supplementary Information (ESI), 1.1-NMR spectra]. These signals seemed to agree more with the structures of N,O-aminals, as described in the literature [ 20, 22]. The signal at $\delta$ 91.59 ppm could be attributed to a *cyclic* N,O-aminal **1a** resulting from the internal cyclization of compound **1** (**1** → **1a**), catalyzed by the traces of HCl in $CDCl_3$, both enantiomers giving the same NMR spectra (Scheme 2, **1a**).




**Scheme 2**. The cyclized tautomers **1a**, formed in $CDCl_3$ in the presence of catalytic HCl from **1**, and linear N,O-aminal **1b** formed by acid catalyzed addition of water to the C=N double bond through the iminium ion.

The signal at $\delta$ 96.36 ppm, could be attributed to a *linear* N,O-aminal **1b** (Scheme 2, **1b**) formed by hydrochloric acid catalyzed addition of water to the double bond of the Schiff base (**1** → **1b**); the water was later observed co-crystalized with **1**, from the X-ray crystallography. The addition of alcohols to imines, in the presence of an acid catalyst, is mentioned in the literature [29, 18, 19].

In the meantime, another compound was isolated from the reaction of an aldehyde [25] with INH in the same $THF^X$, and the NMR spectra in an *anhydrous* DMSO-*d6* confirmed its structure to be that of compound **1** (ex. 1.2, NMR copies in ESI, 1.2). The same Rf and mp were obtained for this compound as for the previous one.
We analyzed the crystals by X-ray crystallography and found that the structure of compound **1** is in agreement with the one presented in Scheme 1 (See also Fig. 3 to X-ray data).
Then we used an aliquot of 50 mL $THF^X$ to react with INH. We added INH in portions until 24 mmoles reacted (ex. 1.3). The main compound was **1** but it is worth mentioning that a less polar compound was also formed in the reaction, with Rf = 0.42, active in UV and DNFH, but inactive to $H_2SO_4$, which decomposed during the LPC purification (dichloromethane-methanol, 9:1, I) of the reaction mixture. Compound **1** was obtained in 43.4% yield based on INH, and crystallized from acetonitrile had mp 146.3-147.5 ˚C, similar to that of the previous compounds. The experiment was repeated three times and was reproducible. The NMR spectra of this compound in $CDCl_3$ (see ESI, 1.5.) presented the carbon atoms as double signals and the proton profile was similar to the one mentioned above for the *cyclic* N,O-aminal **1a** and the linear compound **1b**. These new crystals were analyzed by NMR in DMSO-*d6*, which confirmed the Schiff structure of the isoniazid analogue **1**, presented in Scheme 1. The same crystals were then analyzed by X-ray crystallography and the molecular structure **1** was undoubtedly confirmed (Fig. 3).
These experimental results indicate that compound **1** was formed, in all the reactions above, from the 2-HO-THF present in $THF^X$, through the intermediate 4-hydroxy-butanal, because these forms are known to be in equilibrium (Fig. 1) [26, 27, 30].

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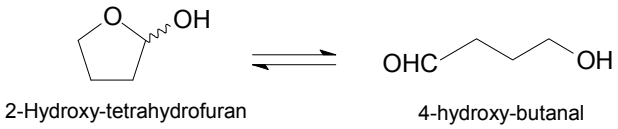


**Figure 1**. The equilibrium of 2-HO-THF and 4-hydroxy-butanal

To prove this fact (the existence of 2-HO-THF in $THF^X$), we purified an aliquot from $THF^X$ by LPC and analyzed the two isolated compounds, [which we believed to be responsible for the reaction with INH to the less polar (Rf = 0.44) and the more polar ($Rf_1$ = 0.21) isoniazid compounds]. The less polar compound (Rf = 0.76), was isolated as an oil and was identified as 2-hydroperoxide-tetrahydrofuran (2-HOO-THF) [31-33]. The more polar (Rf = 0.51) was isolated also as an oil and was proven to be 2-HO-THF [26-28, 30] (ex.1.4; ESI, NMR-spectra: 1.3-1.4). Surely, the presence of peroxides with higher boiling point was limited by distillation of THF until its boiling point, for $THF^X$ and then until 68 ˚C, for $THF^Y$. In the TLC studies, we than realized that the presence of 2-HO-THF and 2-HOO-THF could be simply checked on silica gel plates (eluent: $CH_2Cl_2$-Methanol, 9:1 or 95:5, or others) and visualized with 2,4-dinitrophenyl hydrazine reagent at r.t. (yellow spots for both compounds, more intense being that of 2-HO-THF), followed by heating at 110 ˚C, when both spots became very intensive gray-black). This finding is an easy method to verify the extent of 2-HO-THF and 2-HOO-THF in THF with greater content of peroxides.

In the literature, the 2-HOO-THF was found to be the major peroxide in the THF oxidation during prolonged exposure to air during storage, and was isolated by careful distillation [34, 35]. Moreover, 2-HOO-THF was obtained by the autoxidation of fresh THF for 24 h at 25˚C [35] or 65˚C [32] under UV light and isolated by vacuum distillation. Though 2-HOO-THF was stable in its purification by distillation, Criegee [35] assumed that it is the decomposition of 2-HOO-THF to a polymer hydroxy-acetal, $[HO-(CH_2)_3CH(O-)_2]_n$, that is responsible for the explosion of peroxides from old THF. Other peroxides or impurities from THF were discovered in the researches on 2-HOO-THF. For example, in the treatment of 2-HOO-THF with ferrous sulphate or sodium hydroxide, γ-butyrolactone was found to be formed [34]. Muroi [36] identified γ-butyrolactone, but also hexane-1,6-diol diformate and only small amounts of 4-hydroxy butanal. Certainly, peroxides with greater molecular weight, or products resulted from the decomposition of the peroxides, are present in the THF with high peroxide content, and their identification is waiting to be discovered. 2,2'-Peroxybis(tetrahydrofuran) was recently discovered in the crystal complex of perfluoro-*o*-phenylmercury, formed in time (a month on air) [37] or in a co-crystal with a polycyclitol [38]. Generally, the THF with more than 0.05% peroxides must be carefully checked before use, as it is well known in the art (see also ref. 1-7 in [42]).

After proving that 2-HOO-THF was present in $THF^X$, we decided to reduce it from a 50mL aliquot of $THF^X$. Aqueous reducing reagents like ferrous sulfate [36] or sodium sulfite/bisulfit [39] are not attractive because of the solubility of THF in water; the reflux of the THF over solid cuprous chloride [40], stannous chloride, or $LiAlH_4$ [41] and molecular sieve [42] are also mentioned in the literature. The absorption of peroxides on other absorbers is also mentioned: alumina, activated alumina, 13X molecular sieves, ion-exchange resins (see ref. 10-14 in [42]). We have chosen to reduce the peroxides (including 2-HOO-THF) with triphenylphosphine ($Ph_3P$) [43] to 2-HO-THF and after a rough separation of the excess $Ph_3P$ and of the resulting triphenylphosphinoxide, the crude 2-HO-THF was reacted with INH in methanol, at r.t. overnight. After removing the solvent under reduced pressure, the crude compound crystallized from acetonitrile and **1** was directly obtained in a quantity of 24.8 mmol; this means that in $THF^X$ at least 14.4 mmol 2-HOO-THF from the all peroxides were reduced to 2-HO-THF to react with INH.

An interesting fact is that the reduction of 2-HOO-THF (existing in the $THF^Y$) in the presence of INH with $Ph_3P$ was a very efficient way to obtain the isoniazid analogue **1** (Experimental, ex. 1.5.2.). During the reaction we did not observe the formation of 2-HO-THF, probably due to the rapid reaction of the 4-hydroxybutanal (in equilibrium with 2-HO-THF) with INH at ~ 50 ˚C, a temperature which was maintained during the $Ph_3P$ reduction.

This finding is important because it shows that 2-HOO-THF from old THF with peroxides (and also pure 2-HOO-THF or made from THF as mentioned in the literature [35]) could be also used as a source of 2-HO-THF for similar reactions with other functional groups in which, the reduction of the peroxide to 2-HO-THF with $Ph_3P$ does not disturb; the catalog price of 2-HO-THF is extremely high. However, the presence of 2-HO-THF and also of 2-HOO-THF, in the old THF with peroxides can be easily checked by TLC in the systems: dichloromethane-methanol, 9:1, 95:5 (or others) by visualization with DNFH at rt (yellow color) and then by heating at 110 ˚C (gray-black spots) (ESI, 4.1.).

The compound **1**, obtained above, had the same signals in $^1$H- and $^{13}$C-NMR in $CDCl_3$ and in DMSO-*d6* (Experimental, ex. 1.5.1; ESI 1.6-1.7). The following NMR studies were performed, all supporting the tautomerism:

1. the NMR tube with substance in $CDCl_3$ was heated for 5 min and we observed the tautomerization of the compound **1** to **1a**, and the reaction product of **1** with water, **1b** (ESI, 1.7. NMR spectra).

2. the $CDCl_3$ was then evaporated with a nitrogen stream, the residue was dissolved in DMSO-*d6* and the NMR spectroscopy showed very well the return of the cyclized tautomer **1a** to the tautomer with the linear structure **1** (**1a** → **1**), presented in Scheme 1, and also the elimination of water from **1b** giving **1**; this analysis confirmed that in DMSO this linear structure **1** is favored (ESI, 1.7. NMR spectra).

3. by adding $D_2O$ over DMSO-*d6*, the 4-O<u>H</u> was deuterated and the corresponding triplet at 4.55 ppm disappeared and H-4 simplified to a triplet (*J* = 6.3 Hz) (ESI, 1.8.).

4. by heating then for two hours at 100 ˚C, the CH=N proton was partially deuterated and more evidently, the $H_2$-protons were almost entirely deuterated (~ 85% deuterated) and the H-3 protons appeared as triplet (*J* = 6.3 Hz). Of course, the profile of the carbon atoms was not modified (ESI, 1.8).

It is clear that in DMSO, in DMSO + $D_2O$, like in the solid state (crystal) from X-ray analysis, the compound has the linear structure **1**, presented in the Scheme 2, while in the slightly acidic $CDCl_3$ a long range tautomerization takes place to the cyclic forms of N,O-aminals **1a**.

A tautomerism was observed in the literature between the amide-carbonyl and the vicinal NH (Fig. 2, line a) [44], in the chelates with metals [45], to over a few atoms, like in Schiff bases of 2-hydroxy-1-naphthylaldehyde (Fig. 2, line b, A ↔ B) [46], a Schiff base to a cyclized aminal with a primary alcohol (Fig. 2, line c, C↔ D) or a bis-Schiff base to a cyclized aminal with a secondary alcohol (Fig. 2, line d, F ↔ E ↔ G):

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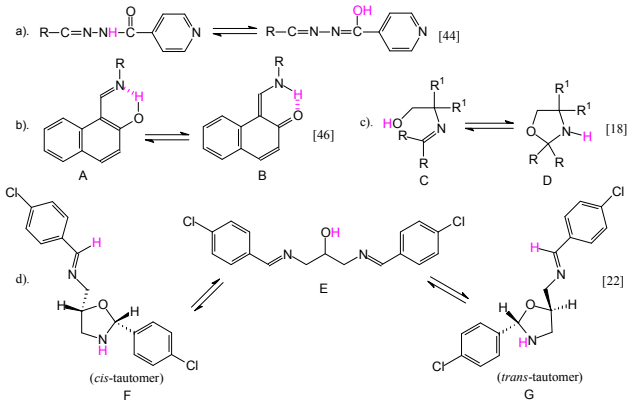



**Figure 2**. The tautomerism of different Schiff bases

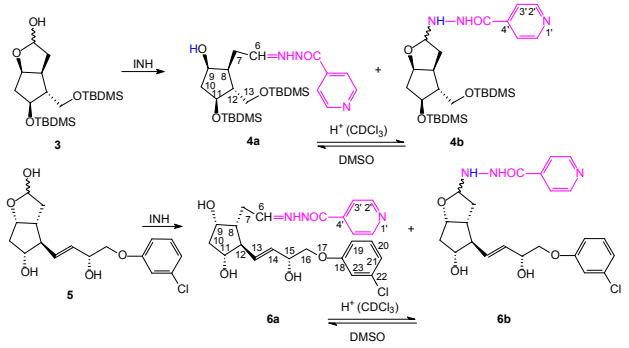
In our case there is a long range tautomerism (over 4 carbon atoms), from **1** to **1a**, due to the addition of the 4-hydroxyl proton to the Schiff double bond, with the concomitant formation of a tetrahydrofuran ring and the disappearance of the $sp^2$ character of the C-1 carbon atom, like in a N,O-aminal, as observed in $^{13}$C-NMR in $CDCl_3$; the addition of the water, present in the crystal, to **1** gave also a linear N,O-aminal **1b**.

N,O-Aminals with an exocyclic hydroxy or alkoxy group [2] and cyclic N,O-aminals like that presented in Fig. 2 (lines c and d) [18, 22] are mentioned in the literature, but our study presents an easier transform of the linear tautomer **1** to the cyclic tautomer **1a** favoured by the formation of a 5-atoms cycle, like in γ-butyrolactol (2-HO-THF), in agreement with the Baldwin's rule (5-*exo*-trig) [47, 48], and, to our knowledge, *such a tautomerization was never mentioned in the literature for an isoniazid analogue.*

Finally, we oxidized 1,4-butanediol [49-51] with PDC and the resulting crude carbonyl compound was reacted with INH (ex. 1.6.); the product obtained was identical to compound **1**.

We then reacted the same aliquot of $THF^X$ with the more reactive 2,4-dinitrophenylhydrazine and obtained 4-(2-(2,4-dinitrophenyl)hydrazineylidene)butan-1-ol, **2** (Scheme 1), in almost the same level as for **1** (ex. 1.7.); in $CDCl_3$ we did not observe an aminal formation for this compound. The NMR spectra in DMSO, and in $CDCl_3$ (at r.t and 60˚C) of the compound **2** show only a Schiff structure (ESI, 1.9), as for compound **1**, in agreement with the stronger linkage of the CH=N bond in 2,4-dinitrophenylhydrazone than in isonicotinoylhydrazone.

We then synthesized the isoniazid analogues **4** and **6**, with more complex structures than **1**, from two different single enantiomer γ-lactol-compounds, **3** and **5**, originated from the total stereocontrolled sequence for obtaining prostaglandins, to see if a similar tautomerism could be observed (Scheme 3). In both cases, $^{13}$C-NMR in DMSO shows the presence of the Schiff analogues **4a** and **6a** [$\delta$ 153.86, respectively 153.72 ppm for CH=N] as in the case of compound **1**, but also the presence of the cyclic N,O-aminals **4b** and **6b** [$\delta$ 91.72 (traces at 93.36), respectively 91.62 ppm for O-CH-NH], a little more favoured being the Schiff form. In $CDCl_3$, *$^{13}$C-NMR shows almost exclusively the presence of the N,O-aminals **4b** and **6b*** [$\delta$ 92.57 (traces 94.17), respectively 92.57 (traces 93.70) ppm] (Scheme 3) (ESI, 1.10-1.11), a favoured cyclization as predicted by Baldwin's rules (5-*exo*-trig) [47-48]. It is to be mentioned that in the case of the cyclic N,O-aminals, **4b** and **6b**, the two isomers are present, the major being probably the *exo*-form due to the less sterical hindrance and the traces isomer has the *endo*-form. These findings strengthen the above mentioned facts that the acidity presented in $CDCl_3$ favoured the cyclic N,O-aminal form of the isoniazid analogues, like in the case of compound **1**.




**Scheme 3**. The Schiff and N,O-aminal forms of the isoniazid analogues obtained from prostaglandin intermediates of lactol types, **3** and **5**; the carbon atoms are numbered as in the prostaglandins field.

*X-Ray crystallography of the compound **1***: According to the single crystal X-ray diffraction study, compound **1** crystallizes in *P*1 space group of triclinic system. Its asymmetric part comprises *four crystallographic independent but chemically equivalent molecular entities* (denoted **A B**, **C** and **D**) and *four co-crystalizes water molecules*. Due to their similarity, the perspective view of the molecule **A** is only shown in Figure 3.

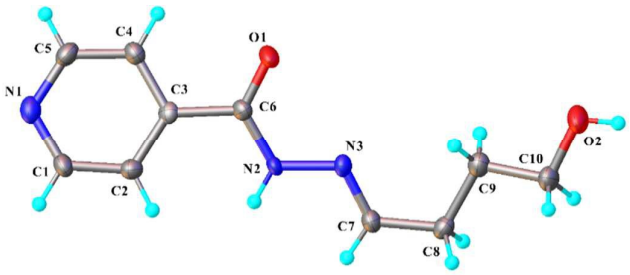



**Figure 3**. X-ray molecular structure of isoniazid analogue **1** (molecule **A**) with atom labeling scheme and thermal ellipsoids at 50% probability level. Selected bond and torsion angles (deg.): O1-C6-N2 = 123.9(2); O1-C6-C3 = 119.3(2); N2-C6-C3 = 116.8(2); N3-C7-C8 = 120.4(2); C6-N2-N3 = 118.2(2); C7-N3-N2 = 115.4(2); N3-C7-H7 = 119.8; C6-N2-N3-C7 = -178.3(2); N2-N3-C7-C8 = - 178.6(2); N3-N2-C6-C3 = - 176.8(2).

Bond distances and angles are summarized in Table 1S and Tables 4-6 (cifreport) (ESI). The structure of the molecule shows the *E*-configuration of the substituents linked to the double bond N3-C7, proved by the C6-N2-N3-C7 torsion angle of -178.3(2). This fact was observed in the literature in another case [52]. The O1 atom and the hydrazone N3 atom are *cis*-linked to the C6-N2 bond and N2 and C8 are *trans*-linked to the double bond N3-C7. The whole crystallographic data are presented in Tables 1-8 (ESI) and selected angles are presented in Figure 4.

All the components of the structure are interacting through numerous O-H···N, N-H···O, and N-H···N hydrogen bonds (Table 2S), which are completely realized in the crystal. These bonds determine

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the formation of two dimensional supramolecular layers running parallel to the 110 plane, as shown in Figure 5. There are two crystallographic distinct layers formed by molecules **A** + **B** and **C** + **D**, respectively. In turn, these layers are further linked via $\pi$-$\pi$-stacking interactions (Figure 6S) with a centroid-to-centroid distance of 3.622(6) Å. As the result, the main crystal structure packing motif can be characterized as a tree-dimensional supramolecular arrangement.

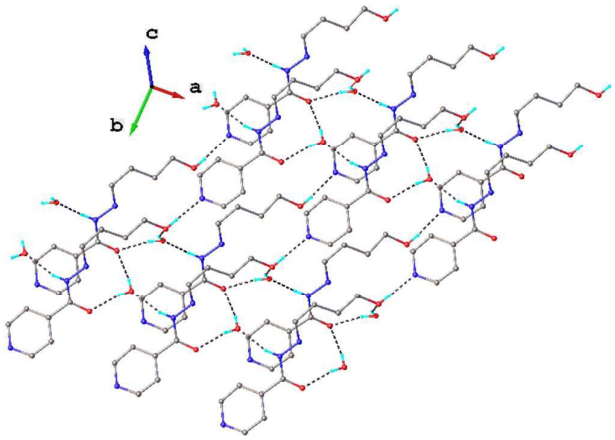


**Figure 4**. One of the two independent two-dimensional supramolecular layers (formed by **A** and **B** molecules). H-bonds are shown in dashed lines. Non-relevant H-atoms are omitted for clarity.

The compounds **1**, **4**, **6**, and INH as standard were sent to CO-ADD Community for Open Antimicrobial Drug Discovery (Institute for Molecular Biosciences, The University of Queensland, 4072 St Lucia QLD Australia**)** for primary antimicrobial screening study by whole cell growth inhibition assays, at a single concentration, in duplicate (n=2). The inhibition of growth was measured against 5 bacteria: *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, and 2 fungi: *Candida albicans* and *Cryptococcus neoformans* (ESI, Table 3S). The compounds **1**, **4**, **6** and INH were found to be inactive.

## 4. Experimental

Melting points (uncorrected) were determined in open capillary on an OptiMelt melting point apparatus. The progress of the reaction was monitored by TLC on silica gel $60F_{254}$ plates (Merck) eluted with the solvent system: I (Dichloromethane-methanol, 9:1), II (dichloromethane-methanol, 95:5). Spots were developed in UV, 2,4-dinitrophenylhydrazine reagent or with 15% $H_2SO_4$ in MeOH (heating at 110˚C, 10 min). IR spectra were recorded on FT-IR-100 Perkin Elmer spectrometer, in solid phase by ATR and frequencies expressed in $cm^{-1}$, with the following abbreviations: w = weak, m = medium, s = strong, v = very, br = broad. MS were recorded on 1200 L/MS/MS triple-quadrupole Varian with ESI interface, fragments, obtained by collision with Ar and relative abundances (%) are given in parenthesis. $^1$H-NMR and $^{13}$C-NMR spectra are recorded on Varian Gemini 300 BB spectrometer (300 MHz for $^1$H and 75 MHz for $^{13}$C), or Bruker Avance III 500 MHz spectrometer (500 MHz for $^1$H and 125 MHz for $^{13}$C), spectrometer chemical shifts are given in ppm relative to TMS as internal standard. Complementary spectra: 2D-NMR and decoupling were done for the correct assignment of NMR signals. The numbering of the atoms in the compounds is presented in Schemes 1 and 3.

*X-Ray crystallographic measurements* were carried out with an Oxford-Diffraction XCALIBUR E CCD diffractometer equipped with graphite-monochromated Mo-Kα radiation. Single crystals were positioned at 40 mm from the detector and 716 frames were measured each for 5 s over 1° scan width. The unit cell determination and data integration were carried out using the CrysAlis package of Oxford Diffraction [53]. The structure was solved by direct methods using Olex2 [54] and refined by full-matrix least-squares on $F^2$ with SHELXL-97 [55]. Atomic displacements for non-hydrogen atoms were refined using an anisotropic model. All H atoms attached to carbon were introduced in idealized positions ($d_{CH}$ = 0.96 Å) using the riding model with their isotropic displacement parameters fixed at 120% of the riding atom. Hydrogen atoms for OH and NH groups have been placed by Fourier Difference and refined accounting for hydrogen bonds parameters. In the absence of significant anomalous scattering, the absolute configuration of structure could not be reliably determined. As a result, Friedel pairs were merged and any references to the Flack parameter were removed. The molecular plots were obtained using the Olex2 program. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC- 1561067. Copies of the data can be obtained free of charge from CCDC (12 Union Road, Cambridge CB2 1EZ, UK; Tel.: + 44 1223 336 408; fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk; www:http://ccdc.cam.ac.uk).

*THF$^X$ was obtained from old THF kept on sodium wire, (left for some years in small quantities in bottles) by distilling the solvent with a distillation column with Raschig rings not exceeding the boiling point of THF and then added sodium wire. We continued the distillation until 68 ˚C and obtained a THF$^Y$, containing 2-HOO-THF. We observed that it is easy to check and qualitatively evaluate the THFs with peroxides for 2-HO-THF or 2-HOO-THF simply by TLC in the solvent system dichloromethane-methanol 9:1 (or 95:5 for example) and to view the spots by spraying with 2,4-dinitrophenyl hydrazine reagent at r.t. (yellow spots), then heating to 110 ˚C (gray-black spots) (ESI, 4.). By iodide/thiosulfate titration, THF$^X$ had ~0.3 mequiv/mL and THF$^Y$ had ~2.9 mequiv/mL, with TLC mentioned in ESI, 4.1. No unusual sign was observed, even after its use in a Corey type γ-lactone to a γ-lactol reduction with DIBAL.*

***Example 1.1. NMR spectra of compound 1 isolated from a reaction of INH with a hindered ketone, in THF$^X$.***

Compound **1** was obtained as a by-product (active in UV light, and visualized with dinitrophenylhydrazine and $H_2SO_4$/MeOH reagent (15 min. heating at 110˚C) and isolated by LPC (eluent, I) in the purification of a crude product (reaction of INH with a ketone) as oil, which crystallized from acetonitrile, mp 146.0-147.6 ˚C, FT-IR spectrum: 3185 s, 2963m, 1653s, 1627m, 1552s, 1410m, 1345m, 1296m, 1051m, 1025m, 666w, $^1$H-NMR-500 MHz ($CDCl_3$, $\delta$ ppm, *J* Hz): 9.35 (br s, CONH), 8.74 (d, 2H, H-2', 6.0), 7.62 (d, 2H, H-3', 6.0), 5.12 (t, ~0.3H, H-1, 6.3), 4.97 (dd, ~0.6H, H-1, 4.9, 6.3), 4.00-3.68 (4m, 2H, H-4), 3.73 (br s, OH), 2.57-1.70 (m, 4H, 2H-2, 2H-3), $^{13}$C-NMR-125 MHz ($CDCl_3$, $\delta$ ppm): 165.74, 164.87 (CON), 150.79, 150.63 (C-2'), 140.20, 140.02 (C-4'), 121.01, 120.88, 120.73 (C-3'), 96.36, 91.57 (C-1), 68.96, 67.26 (C-4), 29.74, 29.32 (C-2), 25.05, 24.84 (C-3) (See ESI for all NMR spectra, 2.1.).

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***Example 1.2. NMR spectra of compound 1 isolated from a reaction of INH with a cyclopentane aldehyde, in the same THF$^X$.***

Compound **1** (coded: Cp-Clo-bis-INI for NMR spectra) was isolated as above by purification of a crude product obtained by the reaction of INH with a cyclopentane aldehyde in THF$^X$, $^1$H-NMR-500 MHz (DMSO-$d_6$, $\delta$ ppm, $J$ Hz): 11.65 (s, 1H, CONH), 8.745 (d, 2H, H-2', 5.6), 7.78 (t, 1H, CH=N, 5.3), 7.75 (d, 2H, H-3', 5.6), 4.54 (t, 1H, OH, 5.1), 3.45 (q, 2H, H-4, 6.1), 2.32 (dt, 2H, H-2, 5.7, 7.3), 1.65 (dt, 2H, H-3, 6.6, 14.2), $^{13}$C-NMR-125 MHz (DMSO-*d6*, $\delta$ ppm): 161.22 (CO), 153.83 (C-1), 150.24 (C-2'), 140.67 (C-4'), 121.47 (C-3'), 60.13 (C-4), 29.30, 28.94 (C-2, C-3) (ESI, 2.2.).

***Example 1.3. Synthesis of N'-(4-hydroxybutylidene)isonicotinohydrazide***

INH (5 mmol, 685 mg) was added to 50 mL tetrahydrofuran THF$^X$, and the mixture was heated to slight reflux under stirring for 90 min., monitoring the reaction by TLC (I, Rf $_1$ = 0.21). The INH was consumed and another INH (2.1 g) was added in portions and the mixture was stirred for 1h at slight reflux. TLC showed that all INH was reacted and that another compound was formed, active in UV and dinitrophenylhydrazine reagent, but inactive to 15% $H_2SO_4$ in MeOH reagent, Rf $_{by\text{-}product}$ = 0.44, See SM, 4.2). Another 500 mg INH (total 24 mmol) were added, reacted at slight reflux for 1 h and then at r.t. overnight. The products were adsorbed on 5 g silica gel and purified by LPC (eluent, II), resulting 2.16 g (10.42 mmol, 43.4% based on INH) of pure compound **1**, which was crystallized from acetonitrile, mp 146.3-147.5 ˚C, IR as in ex. 1, $^1$H-NMR-500 MHz ($CDCl_3$, $\delta$ ppm, $J$ Hz): 9.41, 9.06 (2s in a ratio of 2:1, CONH), 8.74 (d, 2H, H-2', 6.0), 7.63 (d, 2H, H-3', 6.0), 5.12 (t, ~0.3H, H-1, 6.3), 4.97 (dd, ~0.6H, H-1, 4.9, 6.3), 4.00-3.68 (4m, 2H, H-4), 3.37 (br s, OH), 2.57-1.70 (m, 4H, 2H-2, 2H-3), $^{13}$C-NMR-125 MHz ($CDCl_3$, $\delta$ ppm): 165.75, 164.87 (CON), 150.77, 150.71 (C-2'), 140.02 (C-4'), 121.02, 120.89, 120.74 (C-3'), 96.36, 91.59 (C-1), 68.95, 67.27 (C-4), 29.73, 29.31 (C-2), 25.05, 24.84 (C-3),
$^1$H-NMR-300 MHz (DMSO-$d_6$, $\delta$ ppm, $J$ Hz): 11.65 (s, 1H, NH), 8.75 (d, 2H, H-2', 6.1), 7.78 (t, 1H, CH=N, 5.2), 7.75 (d, 2H, H-3', 6.1), 4.54 (t, 1H, OH, 6.0), 3.45 (br dt, 2H, H-4, 6.0, 4.7), 2.33 (dd, 1H, H-2, 5.2, 7.7), 2.30 (dd, 1H, H-2, 5.5, 7.7), 1.65 (dt, 2H, H-3, 6.6, 14.8), $^{13}$C-NMR-75 MHz (DMSO-*d6*, $\delta$ ppm): 161.21 (CO), 153.81 (C-1), 150.25 (C-2'), 140.67 (C-4'), 121.48 (C-3'), 60.13 (C-4), 29.31, 28.95 (C-2, C-3), (See ESI, 2.3.), MS 207.23 calcd. for $C_{10}H_{13}N_3O_2$ [M+1]: th. 208.10805, found 208.10796 [121 ($C_6H_5N_2O$), 138 ($C_6H_8N_3O$), 105 ($C_6H_3NO$), 79 ($C_5H_5N$)].
No compound with Rf = 0.44 was isolated, as it probably decomposed during purification. The experiment was repeated three times and the weights of the compound **1**, were close to that presented above: 2.12 g, 2.21 g and 2.19 g.

***Example 1.4.1. Purification of an aliquot of THF$^X$.***

An aliquot of 15 mL THF$^X$ was purified by LPC (II), resulting a pure fraction of 234 mg as oil, of the compound with Rf = 0.76, identified to be 2-HOO-THF, IR: 3431 brs, 2953s, 1443w, 1412w, 1324w, 1174s, 1034s, 918s [33], $^1$H-NMR-300 MHz ($CDCl_3$, $\delta$ ppm, $J$ Hz): 8.90 (br s, 1H, OOH), 5.54 (t, 1H, H-1, 6.1), 4.29 (t, 1H, H-4, 7.1), 3.89 (t, 1H, H-4, 6.1), 2.43 (t, 1H, H-2, 8.0), 2.20 (q, 1H, H-2, 7.7), 2.00-1.75 (m, 2H, H-3), $^{13}$C-NMR-75 MHz ($CDCl_3$, $\delta$ ppm): 110.13m, 108.10 (C-1), 68.71m, 67.85 (C-4), 29.26, 27.95m (C-2), 24.05, 22.31m (C-3), (ESI, 2.3) $C_4H_8O_{23}$, Mwt: 104.11, MS 104.04, HRMS calc. for $C_4H_8O_{23}$, [M+H]: 105.05462, measured (APCI +) 105.0701 [M+H],
and 283 mg of the compound with Rf = 0.51 (which gave compound **1**), identified to be 2-HO-THF, as oil, IR: 3400 brs, 2954s, 2885s, 1720s, 1181m, 1031vs, 985vs, 918s, 3400 br s, 2954s, 2885s, 1443m, 1342m, 1260m, 1181m, 1031s, 985s, $^1$H-NMR-300 MHz ($CDCl_3$, $\delta$ ppm, $J$ Hz): 5.49 (d, 1H, H-1, 3.7), 3.80 (t, 2H, H-4, 6.6), 4.01 (t, 1H, H-4, 6.2), 2.18 (t, 1H, H-2, 7.8), 2.05-1.70 (m, 3H, H-2, 2H-3), $^{13}$C-NMR-75 MHz ($CDCl_3$, $\delta$ ppm): 103.92m, 98.53 (C-1), 67.52, 67.08m (C-4), 32.25, 32.41m (C-2), 23.55 (C-3), (ESI, 2.4.). MS: $C_4H_8O_2$, Mwt: 88.11, MS 88.05, HRMS calc. for $C_4H_9O_2$, [M+H]: 89.05971, measured APCI 91.0542.

***Example 1.4.2. Synthesis of 2-HOO-THF.***

2-HOO-THF was synthesized by introducing a low stream of oxygen in THF at 65 ˚C overnight (without an UV lamp), as described by Criegee R. [35]. The THF was distilled at rotavapor, the residue was co-evaporated with benzene and 2-HOO-THF was used as so obtained.

***Example 1.5.1. Treatment of THF$^X$ with triphenylphosphine to reduce peroxides and reaction of 2-hydroxytetrahydrofurane with INH***

$Ph_3P$ (3.935 g, 15 mmol) was added to 50 mL tetrahydrofuran (THF$^X$) under stirring. The solution warmed from 18˚C to 35˚C and then the stirring was continued overnight (80h), monitoring the reaction by TLC (I, Rf $_{Triphenylphosphine}$ = 0.91, Rf $_{Triphenylphosphinoxid}$ = 0.69, Rf $_{2\text{-}OH\text{-}THF}$ = 0.50). Triphenylphosphinoxide did not crystallize from ether and the crude product was absorbed on 12 g silica gel and roughly purified by LPC (eluent, dichloromethane-methanol, 10:0.2), resulting 3.167 g of crude product containing ~ 70% 2-HO-THF by TLC (roughly densitometric).
The crude product was dissolved in methanol (70 mL), INH (3.46 g, 25.2 mmol) was added and stirred overnight at r.t. TLC showed the disappearance of the 2-hydroxy-tetrahydrofurane and the presence of some excess of INH. The solvent was removed under reduced pressure, taken in hot acetonitrile (70 mL), filtered and the filtrate was left at r.t. (18˚C) over weekend. The crystallized compound was filtered, washed with a little acetonitrile, dried at r.t., resulting 3.40 g (24.8 mmol) of pure compound **1**, crystallized in needles, mp 142.9-143.2 ˚C. By recrystallization from acetonitrile, the compound has mp 146.3-147.4˚C, Rf, IR and NMR in DMSO-*d6* identical with those of the compound obtained in example 1.
Complementary spectra were performed to gain more insight into the structure of and check the stability of compound **1** under different conditions:

-NMR spectra were done in $CDCl_3$ and then the solvent was evaporated and NMR spectra were performed in DMSO (ESI 2.5 and 2.6): NMR spectra in $CDCl_3$ are in agreement with those presented at ex. 1 and 3 and NMR spectra in DMSO to those presented in ex. 2 and 3.

- NMR spectra in DMSO-$d_6$ +$D_2O$, at r.t: $^1$H-NMR-300 MHz (DMSO-$d_6$ +$D_2O$), room temperature, $\delta$ ppm, $J$ Hz): 8.72 (d, 2H, H-2', 6.3), 7.75 (t, 1H, CH=N, 5.2), 7.73 (d, 2H, H-3', 6.3), 3.44 (t, 2H, 2H-4, 6.6), 2.31 (dt, 2H, H-2, 5.2, 7.3), 1.64 (cv, 2H, H-3, 6.6), $^{13}$C-NMR-75 MHz (DMSO-*d6*, $\delta$ ppm): 161.76 (CO), 154.54 (C-1), 150.57 (C-2'), 140.93 (C-4'), 121.89 (C-3'), 60.38 (C-4), 29.40, 29.23 (C-2, C-3), (ESI, 2.8).

- NMR spectra in DMSO-$d_6$ +$D_2O$, and warming two hours at 100 ˚C: $^1$H-NMR-300 MHz (DMSO-$d_6$ +$D_2O$), heating 2 h at 100 ˚C, δ): 8.72 (d, 2H, H-2', 6.3), 7.74 (t, 1H, CH=N, 5.2), 7.73 (d, 2H, H-3', 6.3), 3.43 (t, 2H, 2H-4, 6.3), 2.28 (m, ~0.15H non-deuterated, H-2),

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1.62 (t, 2H, H-3, 6.3), $^{13}$C-NMR-75 MHz (DMSO-d6, δ ppm): 161.23 (CO), 153.81 (C-1), 150.27 (C-2'), 140.68 (C-4'), 121.50 (C-3'), 60.15 (C-4), 29.32, 28.98 (C-2, C-3), (ESI, NMR: 2.8).

***Example 1.5.2. Synthesis of isoniazid analogue 1 by reducing the peroxides (mainly containing 2-HOO-THF) of an old THF$^{Y}$ with triphenylphosphine in the presence of isoniazid.***

Prior determination of the peroxide content, the reaction conditions were first tested and the established procedure is presented below. INH (7.543 g, 55 mmol) was added in a 100 mL round bottom flask and 25 mL THF$^{Y}$ with 2-HOO-THF as the major peroxide and 10 mL good anh. THF were added, and then, under stirring, triphenylphosphine (14.43 g, 55 mmol) was added in portions (the reaction of $Ph_3P$ with peroxides is exothermic), keeping the temperature of the reaction under 55 ˚C (in 2 h). The reaction mixture was stirred overnight at ~55˚C, though it looks that there is no presence of the peroxides by TLC (See ESI, 4.3). [Observation: In this procedure, the formation of the reduced intermediate 2-HO-THF was not observed, probably at the reaction temperature, this compound reacted rapidly with isoniazid, presented in the reaction mixture]. The reaction mixture was concentrated under reduced pressure, co-evaporated with toluene and the crystallized residue was extracted with hot dichloromethane-hexane (3 ×100 mL). The unified extraction solutions were cooled in refrigerator for 1 h, decanted and the residue unified with the previous insoluble, and crystallized and re-crystalized from acetonitrile. 8.528 g Crystalized compound 1 were obtained. All mother liquors were concentrated, the concentrate was purified by LPC (silica gel, eluent: solvent system, I), resulting 2.42 g crystalized compound **1** (Total: 10.948 g, 52.83 mmol). This result shows that, in 25 mL THF$^{Y}$ used in the reaction, 52.83 mmol of 2-HOO-THF was reduced to 2-HO-THF, which reacted with INH.

***Example 1.6. Oxidation of 1,4-butanediol and reaction of the resulted aldehyde with INH***

1,4-Butanediol (20 mmol, 1.80 g) in $CH_2Cl_2$ (150 mL) were oxidized with PDC (20 mmol, 7.52 g) and molecular sieves under stirring overnight at r.t., monitoring the reaction by TLC (I, Rf $_{\text{2-OH-THF}}$ = 0.51, identical with the compound from THF$^{X}$). The reaction mixture was diluted with 150 mL ethyl acetate, filtered through a sodium sulfate bed, the bed was washed with ethyl acetate, the filtrate was concentrated under reduced pressure, put in benzene, filtered, concentrated under reduced pressure, resulting 1.24 g crude product (the ethyl acetate was re-distilled and 120 mg 2-HO-THF were recovered after solvent concentration). The concentrate (1.36 g) was dissolved in 30 mL methanol, 1.92 g (14 mmol) INH were added and stirred overnight, TLC showing the end of the reaction. Methanol was distilled on rotavapor, the concentrate was taken in warm dichloromethane-methanol (9:1), filtered and concentrated to opalescent solution, left to crystallize in needles on r.t. and filtered, resulting 596 mg pure compound **1**. The filtrate was concentrated (2.19 g) and purified by LPC, as in example 1, resulting a pure fraction of 1.25 g compound **1** (total 1.846 g, 8.91 mmol, un-optimized reaction).

***Example 1.7. Treatment of THF$^{X}$ with 2,4-dinitrophenylhydrazine***

In 50 mL THF$^{X}$, 2,4-dinitrophenylhydrazine (DNFH, 4.76 g, 24 mmol)) was added in portions in 30 min. and good THF (50 mL) was added until a clear solution was obtained. TLC (II, Rf $_2$ = 0.33, Rf $_{\text{sec. product}}$ = 0.81, Rf $_{\text{DNFH}}$ = 0.58) showed that after 3 h, no DNFH was present. The solvent was removed under reduced pressure, and purified by LPC (eluent, I), resulting 2.81 g (10.6 mmol) 4-(2-(2,4-dinitrophenyl)hydrazineylidene)butan-1-ol **2**, mp 112.3-113.9 ˚C, $^{1}$H-NMR-300 MHz (DMSO-$d_6$, $\delta$ ppm, $J$ Hz): 11.30 (s, 1H, NH), 8.82 (d, 1H, H-3', 2.6), 8.31 (dd, 1H, H-5', 2.6, 9.7), 8.02 (t, 1H, CH=N, 5.1), 7.83 (d, 1H, H-6', 9.7), 3.47 (t, 2H, H-4, 6.3), 3.38 (brs, 1H, OH), 2.38 (dt, 2H, H-2, 5.1, 7.3), 1.70 (cv, 2H, H-3, 6.3), $^{13}$C-NMR-75 MHz (DMSO-d6, $\delta$ ppm): 155.00 (C-1), 144.65 (C-1'), 136.34 (C-4'), 129.68 (C-5'), 128.50 (C-2'), 122.96 (C-3'), 116.12 (C-6'), 59.92 (C-4), 29.10, 29.02 (2C, C-2, C-3). (ESI, 2.9).

$^{1}$H-NMR-500 MHz ($CDCl_3$, $\delta$ ppm, $J$ Hz): 11.23, 11.03 (2s in a ratio of 0.17: 0.83, 1H, NH), 9.10 (s, 1H, H-3'), 8.29 (d, 1H, H-5', 9.5), 7.95, 7.91 (2d, in a ratio of 0.17: 0.83, 1H, H-6', 9.5), 7.61 (br t, (t, 1H, CH=N, 5.0), 3.78 (t, 2H, H-4, 5.5), 2.56 (dt, 2H, H-2, 6.4, 6.6), 1.92 (m, 2H, H-3, 6.4), $^{13}$C-NMR-125 MHz ($CDCl_3$, $\delta$ ppm): 151.98 (C-1), 144.07 (C-1'), 137.81 (C-4'), 129.97 (C-2', C-5'), 123.49 (C-3'), 116.44 (C-6'), 61.97 (C-4), 29.22, 28.98 (2C, C-2, C-3).

***1.8 Synthesis of N'-((E)-((1R,2R,3S,5R)-3-((tert-butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-hydroxycyclopentyl)methylene)isonicotinohydrazide, 4***

Starting from 2 mmol *ent*-Corey lactone 3,2-1'-bis-OTBDMS ether, by reduction with DIBAL (0.9 mL), the corresponding lactol (3aS,4R,5S,6aR)-5-((tert-butyldimethylsilyl)oxy)-4-(((tert-butyl-dimethylsilyl)oxy)methyl)hexahydro-2H-cyclopenta[b]furan-2-ol, **3**, was obtained in quantitative yield as oil, $[\alpha]_D$ = + 31.79 ° (1% in THF); TLC (toluene-ethyl acetate 1:1, R$_{\text{f Corey}}$ lactone = 0.73, R$_{\text{f 3}}$ = 0.63).

The lactol **3** was dissolved in MeOH (15 mL), INA (2.2 mmol, 280 mg) was added and stirred 72 hrs; TLC (toluene-ethyl acetate 1:1, R$_{\text{f 3}}$ = 0.63, R$_{\text{f 4}}$ = 0.12). The crude compound was purified by LPC (toluene-ethyl acetate 1:1), resulting a pure fraction of 578 mg (44.3%) **4** as oil, $[\alpha]_D$ = +32.03° (1% in THF), IR: 3269brm, 2953vs, 2930vs, 2889s, 2857s, 1661s, 1551m, 1467m, 1253s, 1102s, 1004m, 880m, 832vs, 773vs, 667m, $^{1}$H-NMR-500 MHz (DMSO-$d_6$, $\delta$ ppm, $J$ Hz): 11.61 (s, 1H, NH*OC*), 10.27m (d, 0.18H, NH, 4.9), 10.22 (d, 0.79H, NH, 5.5), 8.80 (d, 1H, H-2', 4.9), 8.70 (d, 1H, H-2', 5.7), 7.85 (t, ~0.5H, CH=N, 5.2), 7.74 (d, 1H, H-3', 5.7), 7.73 (d, 1H, H-3', 4.9), 5.63 (t, minor, 5.2), 5.56 (t, major, both OH), 4.97 [(q, M, 4.84 (q, m), ~0.5H, O-CH-N), 4.8], 4.53 (d, ~0.5H, H-11, 5.0), 4.49-4.41 (m, 0.5H, H-11), 4.03-3.93 (m, 1H, H-9), 3.63-3.52 (m, 2H, H-13), 2.35 (m, 1H, H-7), 2.20 (m, 1H, H-10), 1.95 (t, 1H, H-7, 5.5), 1.86 (m, H, H-8), 1.76, 1.61 (2m, 1H, H-12), 1.49 (m, 1H, H-10), 0.87-0.79 (m, 18H, $CH_3$C), 0.03, 0.02 (2s, 12H, $CH_3$Si), $^{13}$C-NMR-125 MHz (DMSO-$d_6$, $\delta$ ppm) (the minor aminal isomer was omitted): 163.51 (CONHNH), 161.02 (CONH), 153.86 (CH=N), 150.16 (2C-2'), 140.61, 140.16 (C-4'), 121.56, 121.16 (2C-3'), *93.36m*, 91.72 (O-CH-N), 79.68 (C-9), 73.64, 71.94, 69.81 (C-11), 61.43, 60.48 (C-13), 54.96, 52.57 (C-12), 43.54, 40.91 (C-10), 41.88, 41.21 (C-8), 35.17, 31.02 (C-7), 25.72 (*C*$H_3$-C), 18.93, 17.64 (C-$CH_3$), - 4.60, -4.97, -5.55 (ESI 1.10). The slightly impure fractions of (-)-**6** were not purified.

$^{1}$H-NMR-500 MHz ($CDCl_3$, $\delta$ ppm, $J$ Hz): 11.48 (s, 1H, NH), 8.73 (d, 1.56H, H-2', 4.7), 8.71 (d, 0.44H, H-2', 4.8), the isomers are in a ratio of 0.78:0.22; 8.06 (s, CH-NH), 7.69m (d, 0.44H, H-3', 4.8), 7.62 (d, 1.56H, H-3', 4.8), 5.10, 4.95m (2m, 3:1, 1H, O-CH-N), 4.55 (m, 1H, H-9), 3.97 (m, 1H, H-11), 3.57-3.48 (m, 2H H-13), 2.52-1.65 (m, 6H, 2H-7, H-8, H-12, 2H-10), 0.88, 0.86 (2s, 18H, C$H_3$C), 0.03, 0.02 (2s, 12H, C$H_3$Si), $^{13}$C-NMR-125 MHz ($CDCl_3$, $\delta$ ppm) (the minor isomer omitted): 164.79 (CO), 150.62, (2C-2'), 140.28 (C-4'), 121.49 minor (C-3'), 121.01 (C-3'), 92.57, 94.17 minor (O-CH-N), 81.30 (C-9), 74.13 (C-11), 62.00 (C-13), 55.66 (C-12), 42.48 (C-8), 41.63 (C-10), 35.88 (C-7), 25.83 (*C*$H_3$-C), 18.26, 17.93 (C-$CH_3$),- 4.79, -4.90, -5.57 (ESI

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1.10), MS 521.84 calctd. for $C_{22}H_{47}N_3O_4Si_2$ $[M+1]^+$: th. 522.31785, found 522.31757 [121 ($C_6H_5N_2O$), 138 ($C_6H_8N_3O$), 385 ($C_{20}H_{41}O_3Si_2$), 253 ($C_{14}H_{25}O_2Si$), 209 ($C_{12}H_{21}OSi$)].

### *1.9. Synthesis of N'-((Z)-2-((1R,2R,3R,5S)-2-((R,E)-4-(3-chlorophenoxy)-3-hydroxybut-1-en-1-yl)-3,5-dihydroxycyclopentyl)ethylidene)isonicotinohydrazide, (-)-6*

Prostaglandin lactol **5** (241 mg, 0.71 mmol) and INH (150 mg, 1.09 mmol) in MeOH (12 mL) were refluxed for 5h; TLC (ethyl acetate-hexane-acetic acid, 5:1:0.1, $R_{f\,5}$ = 0.32, $R_{f\,6}$ = 0.07); 253 mg (63.0%) of pure **(-)-6** were obtained as foam, $[\alpha]_D$ = -23.85° (1% in methanol), IR: 3248vs br, 2929m, 1660vs, 1594vs, 1579s, 1551s, 1479s, 1453m, 1431m, 1412m, 1285s, 1248m, 1230s, 1068m, 1033s, 972m, 680m, $^1$H-NMR 500 MHz (DMSO-$d_6$, $\delta$ ppm, $J$ Hz): 11.63 (s, 0.5H, NHOC), 10.27 (d, 0.5H, NHNHOC, 6.1), 8.71 (2d, 2H, H-2', 4.9), 7.83 (t, 0.5H, H-6, 5.2), 7.75 (d, 2H, H-3', 4.9), 7.28 (2t, 1H, H-22, 8.1), 7.02-6.92 (m, 3H, H-19, H-21, H-23), 5.70 (dd, 0.5H, H-14, 7.4, 15.4), 5.62-5.52 (m, 0.5H-14, H-13), 5.16 (2d, 1H, OH-15, 5.1), 4.98 (q, ~0.5H, CH-NH, 5.6), 4.78 and 4.65 (2d, 1H, OH-11, 6.0, 5.7), 4.61 (d, 1H, OH-9, 4.8), 4.41 (2m, 1H, H-11), 4.32, 4.03 (2brs, 1H, H-15), 3.93-3.85 (m, 2H, H-16), 3.71 (m, 1H, H-9, 7.1), (In water 0.5H, CH-NH), 2.47-1.98 (3m, 3H, H-7, H-10, H-12), 1.84-1.66 (2m, 1H, H-8), 1.47 (m, 1H, H-10), $^{13}$C-NMR-125MHz (DMSO-$d_6$, $\delta$ ppm): 163.53 (CONHNH), 161.13 (CONH), 159.64, 159.60 (C-18), 153.72 (CHN, C-6), 150.20 (2C-2'), 140.64, 140.18m (C-4'), 133.66 (Cq, C-20), 133.23, 132.25 (C-13), 131.51, 130.55 (C-14), 130.83 (C-22), 121.44, 121.19 (2C-3'), 120.43 (C-21), 114.64, 114.57 (C-19), 113.77 (C-23), 91.62 (OCH-NH), 78.88, 76.53 (C-11), 75.21 (C-9), 72.44m, 72.33 (C-16), 69.32, 69.19m (C-15), 55.59m, 54.18 (C-12), 45.97, 45.30m (C-8), 43.96, 40.68m (C-10), 34.32m, 30.39 (C-7) (ESI 1.11), MS 459.92 calctd. for $C_{23}H_{26}ClN_3O_5$ [M+1]: th. 460.16490, found 460.16392 [121 ($C_6H_5N_2O$), 138 ($C_6H_8N_3O$), 442 ($C_{23}H_{25}ClN_3O_4$), 424 ($C_{23}H_{26}ClN_3O_5$)]. The slightly impure fractions of (-)-**6** were not purified.

$^1$H-NMR 500 MHz ($CDCl_3$, $\delta$ ppm, $J$ Hz): 8.75 (2d, 2H, H-2', 5.3), 7.63 (d, 1H, H-3', 5.3), 7.66, 7.59 (2d, 1H, H-3', 5.3), 7.21 (t, 1H, H-22, 8.2), 6.96 (d, 1H, H-21, 8.2), 6.91 (s, 1H, H-19), 6.80 (d, 1H, H-23, 8.2), 5.74 (dd, 1H, H-14, 7.9, 15.5), 5.64 (m, 1H, H-13), 5.12 (t, ~0.5H, CH-NH, 4.4), 5.01 (m, ~0.5H, CH-NH), 4.61-4.50 (2m, 1H, H-11, H-15), 3.93-3.85 (m, 3H, H-9, 2H-16), 2.64 (m, minor H-12), 2.46 (m, 1H, H-8), 2.42 (m, 1H, H-10), 2.26 (m, 1H, H-12), 2.08 (m, 1H, H-7), 1.93 (m, 1H, H-7), 1.81 (m, 1H, H-10), $^{13}$C-NMR-125MHz ($CDCl_3$, $\delta$ ppm): 164.94 (CONH), 159.10 (C-18), 150.63 (2C-2'), 139.87 (C-4'), 134.98 (Cq, C-20), 133.76 (C-13), 130.36 (C-22), 130.00 (C-14), 121.54, 121.05 (2C-3'), 120.91 (C-21), 115.07 (C-19), 113.11 (C-23), 93.70m, 92.57 (OCH-NH), 80.91m, 80.78 (C-11), 78.77m, 77.87 (C-9), 71.96 (C-16), 70.60, 70.42m (C-15), 58.24m, 57.06 (C-12), 47.18m, 46.55 (C-8), 41.28m, 40.05 (C-10), 36.10m, 35.30 (C-7) (ESI 1.11).

## Conclusions

In conclusion, an isoniazid analogue **1** was synthesized by the reaction of INH with the 2-HO-THF present in an old THF$^X$; The reduction of 2-HOO-THF prior to the reaction with INH or better in the presence of INH were also efficiently performed. We also obtained it by a two-step reaction from 1,4-butanediol; the corresponding 2,4-dinitrophenyl hydrazone was also synthesized and shows no tautomerism. A study of the tautomer forms by NMR spectroscopy shows that only the Schiff form **1** is present in DMSO while the N,O-aminal tautomers **1a** are present in $CDCl_3$; the reverse of **1a** to **1** was also put in evidence, by changing $CDCl_3$ to DMSO-*d6* in the NMR spectra. The X-ray crystallography confirmed that the linear structure of compound **1** in the crystal is the same as that found in the NMR spectra in DMSO and DMSO + $D_2O$. Two isoniazid analogues from two single enantiomer γ-lactols intermediates in prostaglandin synthesis, were also obtained and their NMR spectra shows the presence of the Schiff **4a** and **6a** and N,O-aminal **4b** and **6b** tautomers in DMSO and only of N,O-aminals, **4b** and **6b**, in $CDCl_3$, like in the case of the isoniazid analogue **1**, by closing a tetrahydrofurane ring, as predicted by Baldwin's rules for cyclization (5-exo-trig). Compounds **1**, **4** and **6** had no antimicrobial and antifungal activity, like also INH.

## Conflicts of interest

There are no conflicts to declare.

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# A long range tautomeric effect on a new Schiff isoniazid analogue, NMR study and X-ray crystallography

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Text

Isoniazid analogues which are cyclized in acid catalysis by closing a THF ring, favoured by Baldwin's rules (5-*exo*-trig)