Green chemistry. Mechanochemical synthesis of hydrazones, spectroscopic studies and biological activities

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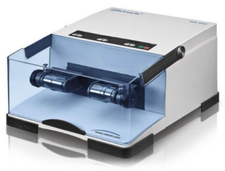
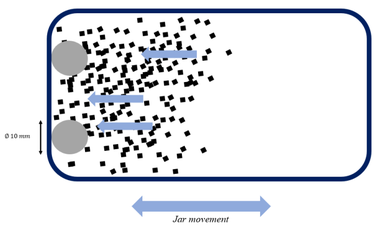
INTRODUCTION

In this work, we wish to report our findings in the construction by mechanochemical means of a series of hydrazones constructed by coupling a variety of 12 hydrazines (or hydrazinamides) with vanillin and furanyl aldehydes[1,2]. The choice concerning the furanyl aldehyde derivatives is dictated because many hydrazone derivatives of this type are active pharmaceutical ingredients[3,4].

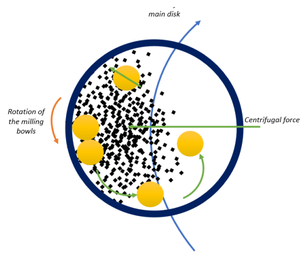
All compounds were obtained solvent free by using either a mixer mill MM400 or a planetary mill Pulverisette 7 (P7) and results compared. All compounds were obtained through total conversion of aldehydes reagents and in excellent yields (93%-99%) on the P7 apparatus after a maximum grinding time of 6 x 30min. An "aging approach"[5] on one compound was successfully conducted. A complete two-dimensional NMR spectra analysis showed that most compounds can be either in two forms (cis-E and trans-E) or two constrained rotamers. An X-Ray single crystal structure of one compound was obtained and analysed. Finally, all compounds were tested as antituberculosis, anti-infective, and antimicrobial agents; many different products present important specific activities and low cytotoxicities.

EQUIPMENT





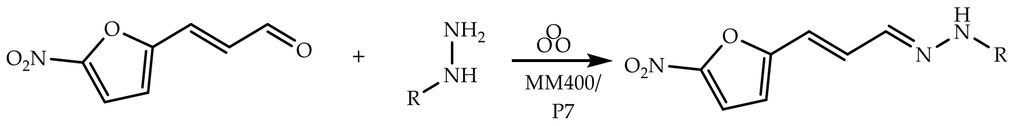
MM400 Retsch
30 Hz
2 (10ml) en ZrO_2
2 (Ø10mm) en ZrO_2
vibro-grinder (oscillating movements on the horizontal plane)



Pulverisette 7 (P7) *Fritsch*
13 Hz (800 rpm)
2 (20ml) en ZrO_2
5 (Ø10mm) en ZrO_2
planetary mill (bowls rotating around their axis are driven by a disc rotating in the opposite direction)

SYNTHESIS AND CHARACTERISATION OF HYDRAZONES

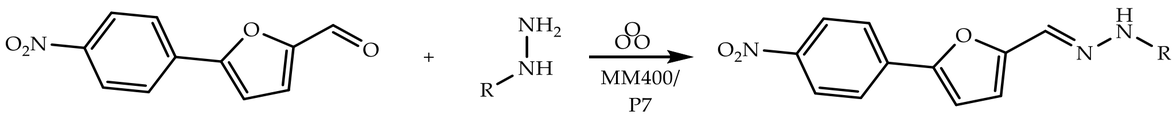
Hydrazones bearing the 5-nitrofuran-2-acrylaldehyde frame



Compounds **3 – 7**
Yields **63-99%**
Time **1,5 – 3 h**

Analysis - ^{13}C NMR, PXRD, ^{1}H NMR, MS, DSC
Primary identification - ^{1}H chemical shifts for HC=N between 7.83 and 8.59 ppm

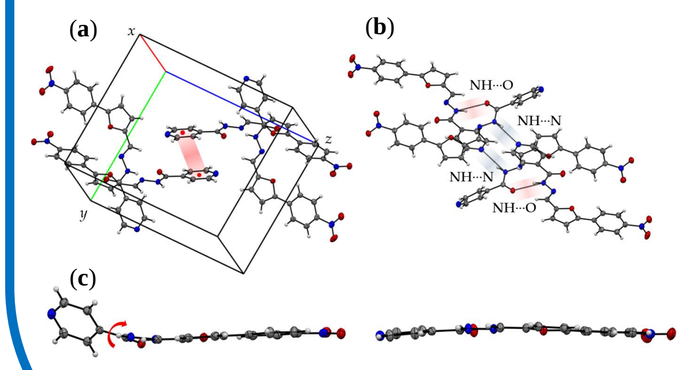
Hydrazones bearing the 5-(4-nitrophenyl)-2-furaldehyde frame



Compounds **8 – 17**
Yields **35-99%**
Time **1,5 – 3 h**

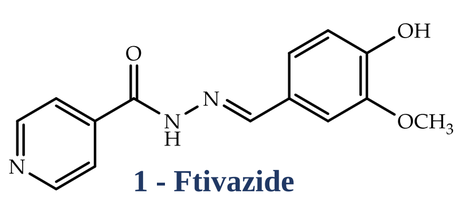
Analysis - ^{13}C NMR, PXRD, ^{1}H NMR, MS, DSC
Primary identification - ^{1}H chemical shifts for HC=N between 7.41 and 8.65 ppm

COMPOUND 8: X-RAY STRUCTURE

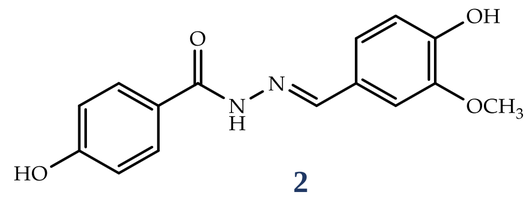


Crystal lattice and molecular arrangement of **8**: (**a**) π-π stacking interactions are highlighted in red, the centroids of the rings represented by red dots; (**b**) NH···O (red) and NH···N (blue) hydrogen-bonded of molecules **8** forming tetrameric arrangement; (**c**) two types of molecular geometries of molecule **8** present in a crystal lattice: pyridine ring rotation along C9-C10 bond is shown on the right, and a flat molecule on the left side of figure.

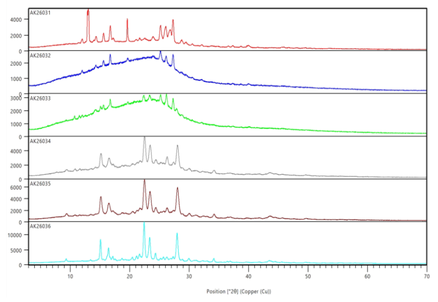
ISONIAZID DERIVATIVES & "AGING" ASSAYS



1 - Ftivazide

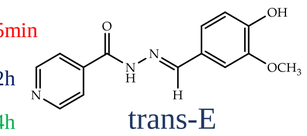


2



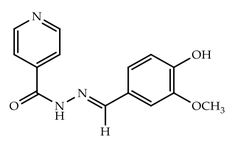
PXRD

5min
2h
4h

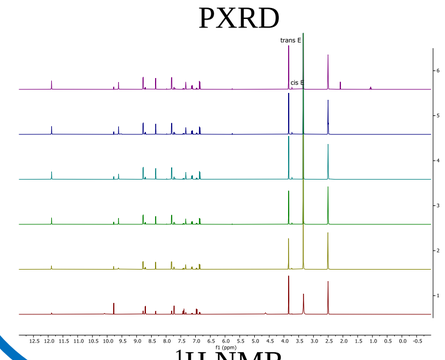


trans-E

6h
8h
24h

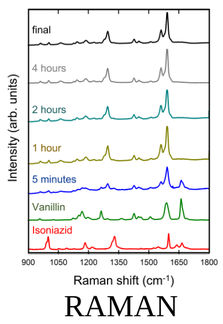


cis-E



^{1}H NMR

24h
8h
6h
4h
2h
5min



RAMAN

Without any initial energy input, when mixing the reactants and leaving them at 37° C, we observe after 7 h less than 5% conversion to the corresponding hydrazones-hydrazides.
When grinding together vanillin and isoniazid for 5 min in the Mixer Mill MM400 (30% - ^{1}H-NMR) or 5 min in the P7 (50% - ^{1}H-NMR) and then leave each amorphous yellowish solid obtained in sealed tubes at 37° C, the aging phenomenon occurs.

BIOLOGICAL ACTIVITIES

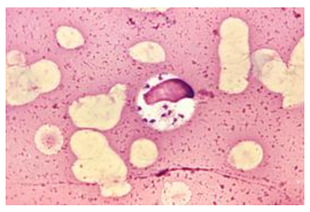
Compound	LV9 amastigote axenic form	SI* for *Leishmania* parasites	*M. tuberculosis* H37Rv	*S. aureus* ATCC25923 and (ATCC29213)	*E. coli* ATCC25922
	IC_{50}, µM		MIC, µM	MIC, µM	MIC, µM
1	**2**	**>31**	**0,6**	>944	>944
2			>100	>894	>894
3	2	ND	**1,0**	1,75 (7)	28
4	3	30	129	>828	>828
5	>100	ND	**1,0**	>814	>814
6	2,51	ND	4,1	13 (7)	>861
7	3,02	ND	7,4	**0,7 (3)**	47
8	**2**	**12**	**0,9**	>761	>761
9	5	4	>100	>711	>711
10	46	ND	>100	>703	>703
11	**4**	**9**	>100	>737	>737
12	>100	ND	52	>659	>659
13			>100	>661	>661
14			>100	>669	>669
15			>100	>678	>678
16			>100	>828	>828
17			>100	>701	>701
Ref.	3[a]	9[a]	0,4[b] ; 0,4[c]	3 (5)[d]	0,75[d]

* Selectivity index (SI) corresponds to CC_{50}: CI_{50}; IC_{50} is defined for the axenic form of L. d.; CC_{50} for macrophage RAW 264.7); [a]Miltefosine, [b]Isoniazid, [c]Streptomycin, [d]Ciprofloxacin, [e]Dihydroartemisinin (DHA).

Mycobacterium tuberculosis

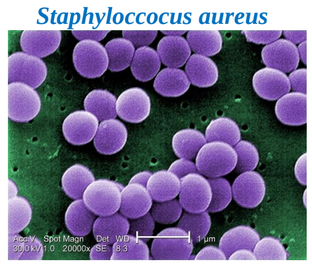
https://elifesciences.org/digests/41129/tuberculosis-bacteria-thrive-on-a-nitrogen-source-buffet

Leishmania donovani



https://uk.wikipedia.org/wiki/Leishmania_donovani

Staphyloccocus aureus



https://en.wikipedia.org/wiki/Staphylococcus_aureus

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