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Research Article

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Synthesis of Some 5-Benzyl-6-Methylpyridazin-3(2h)-Ones Derivatives and their Antifungal Activity

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ABSTRACT

A series of pyridazin-3(2H)-ones derivatives were synthesized and characterized by their physical and spectral data. All the synthesized compounds were screened for their antifungal activity. Most of compounds show excellents activity.

Keywords: Pyridazin-3(2H)-ones ; Antifungal activity.

INTRODUCTION

Microscopic fungi cause many mucosal infections for humans and animals [1-4]. Furthermore, when the hosts have an immunodeficiency, infections become more dangerous and sometimes fatal [5]. Several mycosis developed resistance for treatments; traditional drugs are now inefficient against many pathogens fungi [6]. For this, the research of a new active product became urgent. A series of pyridazin-3(2H)-ones newly synthesized were investigated for their antifungal activity.

EXPERIMENTAL SECTION

Chemistry

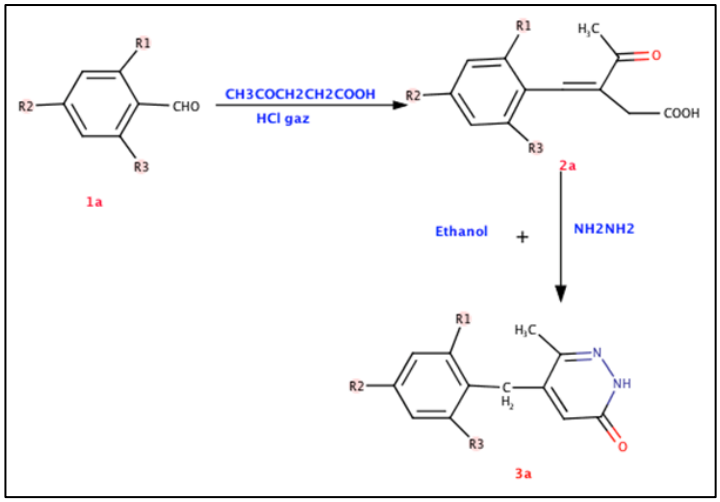
The synthesis of 5-(substituted benzyl)-6-methyl pyridazin-3(2H)-one is outlined in figure 1. Treatment of substituted aldehydes 1 with levulinic acid in the presence of HCl (chlorhydric acid) in acetic acid gave substituted 3-benzylidene levulinic acids 2, which were heated by hydrazine hydrate to afford the pyridazin-3(2H)-ones derivatives 3. Melting points were determined on a Büchi SMP 20 apparatus and are not corrected. IR spectra were recorded with an IR VERTEX 70 FT-IR (Bruker Optics) spectrometer. 1H NMR spectra were recorded on a Bruker Avance 300 (300 MHz) spectrometer, using tetramethylsilane (TMS) as internal standard and DMSO as solvent (Laboratory of application NMR, CNRST, Rabat, Morocco).

General procedures for the synthesis of substituted 3-benzylidene levulinic acids 2a-e. Method A

The mixture of levulinic acid and aromatic aldehyde 1 is placed in an ice bath until complete dissolution. This aldol condensation requires bubbling HCI for 30 min, after 48 hours of contact at room temperature, the product 2 is extracted with an organic solvent, the solution is dried over calcium chloride and the solvent was evaporated to dryness. The obtained residue was used crude for the continuation.

General procedures for the synthesis of substituted 5-benzyl-6-methylpyridazin-3(2H)-ones 3a-e. Method B

The mixture of substituted 3-benzylidene levulinic acids and hydrazine hydrate solution in ethanol was refluxed for 2h; the precipitate formed is filtered and recrystallized from ethanol.



Compound	R_1	R_2	R_3
3a	H	H	H
3b	Cl	H	H
3c	H	Cl	H
3d	H	Cl	Cl
3e	H	NO_2	H
3f	H	OCH_3	H

Figure 1: Synthesis of target compound

Biology

The synthesized compounds (3a-f), in measured quantities, were dissolved in dimethyl sulphoxide (DMSO) in a final concentration of 50 µg ml. The synthesized compounds were evaluated for antifungal activity by disc diffusion method [7]. Fungal species were provided from the parasitology laboratory of Military Hospital Mohammed V, Rabat Morocco (Rabat, Morocco). The fungal (48 h) cultures from the slants were diluted with sterile water and mixed thoroughly toprepare a clear homogeneous suspension. These suspensions were spread on solidified agar, potato dextrose agar for fungi. The filter paper disks prepared by only DMSO (as a negative control) and with a solution of 50 µg/ml concentrations of test compounds (3a-f) as well as standard compounds Econazole as positive control were carefully placed over the spread cultures and incubated the at 28-30 oC for 48 h for fungi. After the incubation period, the plates were examined for the zone of inhibition. The diameter for the zones of inhibition was measured, including the diameter of the disk also. All the concentrations were made in triplicate for each of the compounds and the average value was taken. The antifungal activity was evaluated against *Candida albicans, C. tropicalis, C. krusei et C. glabrata* using Econazole as the standard drug.

RESULTS AND DISCUSSION

In the present study in vitro antifungal activity of synthesizing pyridazin-3(2H)-ones and 3-benzylidene levulinic acids derivatives was studied using disc diffusion method.

Synthesis

5-benzyl-6-methylpyridazin-3(2H)-one 3a: Yield 80%; M.p. 174 °C (ethanol); IR (KBr, ν (cm-1)) : 3100 (NH), 1640 (C=O); 1H NMR (300 MHz, CDCl3, δ (ppm)) : δ = 2.3 (s, 3H), 3.9 (s, 2H), 6.4 (s, 1H), 7.0 (m, 5H), 12.6 (ls, 1H).

5-(2-chlorobenzyl)-6-méthylpyridazin-3(2H)-one 3b: Yield 70%; M.p. 209 °C (ethanol); IR (KBr, ν (cm-1)) : 3100 (NH), 1660 (C=O); 1H NMR (300 MHz, CDCl3, δ (ppm)) : δ = 2.2 (s, 3H), 2.5 (s, 3H), 3.8 (s, 2H), 6.4 (s, 1H), 7.2 (m, 4H), 12.5 (ls, 1H).

5-(4-chlorobenzyl)-6-méthylpyridazin-3(2H)-one 3c: Yield 70%; M.p. 220 °C (ethanol); IR (KBr, ν (cm-1)) : 3100 (NH), 1650 (C=O); 1H NMR (300 MHz, CDCl3, δ (ppm)) : δ = 2.1 (s, 3H), 3.7 (s, 2H), 6.2 (s, 1H), 7.2 (m, 4H), 12,1 (ls, 1H).

5-(2,6-dichlorobenzyl)-6-méthylpyridazin-3(2H)-one 3d: Yield 80%; M.p.222 °C (ethanol); IR (KBr, ν (cm-1)) : 3100 (NH), 1654 (C=O); 1H NMR (300 MHz, CDCl3, δ (ppm)) : δ = 2.1 (s, 3H), 3.9 (s, 2H), 6.3 (s, 1H), 8.1 (m, 4H), 12.1 (ls, 1H).

5-(4-nitrobenzyl)-6-méthylpyridazin-3(2H)-one 3e: Yield 74%; M.p.239 °C (ethanol); IR (KBr, ν (cm-1)) : 3100 (NH), 1660 (C=O); 1H NMR (300 MHz, CDCl3, δ (ppm)) : δ = 2.3 (s, 3H), 3.8 (s, 2H), 6.7 (s, 1H), 7.6 (m, 4H), 12.5 (ls, 1H).

5-(4-méthoxybenzyl)-6-méthylpyridazin-3(2H)-one 3f : Yield 76%; M.p.190 °C (ethanol); IR (KBr, ν (cm-1)): 3100 (NH), 1659 (C=O); 1H NMR (300 MHz, CDCl3, δ (ppm)) : δ = 2.2 (s, 3H), 4.2 (s, 2H), 6.2 (s, 1H), 7.8 (m, 4H), 12.1 (ls, 1H).

Biology

The antifungal activity of the synthesized 5-benzyl-6-methylpyridazin-3(2H)-ones derivatives (3a-f) (50µg/mL concentration) was compared with the standard drug Econazole. The results of the investigation have been presented in Table 1. It is observed that all the (5-benzyl-6-methylpyridazin-3(2H)-ones derivatives (3a-f) exhibited excellent antifungal activity against standard drug antifungal (Econazole, 50 µg/ml concentration). The preliminary antifungal screening of (5-benzyl-6-methylpyridazin-3(2H)-ones derivatives (6a-f) revealed that most of the compounds in the series showed potent activity. Therefore, the present study is useful in the light of development of new leads for antifungal research.

Table 1: Antifungal activity of 5-benzyl-6-methylpyridazin-3(2H)-ones derivatives (6a-f)

Sr .No	Compound Code	Fungi		
		C. albicans	*C. tropicalis*	*Aspergillus flavus*
1	3a	20	18	22
2	3b	21	22	22
3	3c	20	20	20
4	3d	20	21	18
5	3e	19	20	19
6	3f	22	19	19
7	Econazole	20	20	20

CONCLUSION

Pyridazin-3(2H)-ones derivatives possess many biological activities. Nevertheless, few papers have described their antifungal activity. The present study revealed that pyridazin-3(2H)-ones derivatives exhibit promising antifungal properties, achieved by disc diffusion method. we could affirm that Pyridazin-3(2H)-ones derivatives had a significant antifungal activity. So, they could be used as new treatment of mycosis. However, each derivatives was more active against a specific kind of fungi. The Compound 3f had the best antifungal activity against C. albicans and the Compound 3b were more active against C. tropicalis and Aspergillus flavus.

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