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Reactivity of β-Cetoesters Compounds, Synthesis of Nitrogenated Heterocycles (Derivatives of Tetrahydroacridin-9-ones and Pyrimidinone) and Biological Properties of Pyrimidinone Derivatives

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Ethyl 2-oxocyclohexanecarboxylate has undergone smooth condensation with arylamines under ethanol. The corresponding β-enaminoesters compounds were obtained in good yields. These compounds were then refluxed in biphenyl ether to attain the respective substituted tetrahydroacridin. The reaction of 2-amino-5,6-dimethylbenzimidazole with β-cetoesters gave access to an efficient synthesis of pyrimidinone derivatives in excellent yield. A series of novel heterocycles were prepared. Biological properties of compounds **11**-**14** have been distinctively evolved.

Keywords: β-Cetoesters, Tetrahydroacridin-9-ones, 2-Amino-5,6-dimethylbenzimidazole, Pyrimidinone.

INTRODUCTION

Nitrogen containing molecules are a group of compounds of high importance in organic chemistry because of their reactivity in addition to their presence in a large number of molecules of natural and synthetic origin[1]. In fact, they play a key role in various fields namely pharmacy, medicine, biology and agronomy.

Among the molecules containing a nitrogen atom, are the 1,2,3,4-tetrahydroacridine derivatives which encompass a very important role in the treatment of Alzheimer's system[2,3]. A variety of natural and synthetic acridine derivatives have also been tested for antimalarial[4], antiinflammatory[5,6] and analgesic[7]. Pyrimidinones derivatives possess various biological activities including the insulin-mimetic[8], antiinflammatory[9] and antiproliferative[10] properties.

This work enrolled in this context, aims to develop tetrahydroacridin-9-ones and pyrimidinones derivatives synthetic ways. For this, the reactivity of β-keto esters avers an ideal tool.

EXPERIMENTAL

The nuclear magnetic resonance (^{1}H, ^{13}C, DEPT) were recorded on a Bruker AC-300.

Synthesis of β-enamino ester: In a three-necked 100 mL flask equipped with a magnetic stirrer with heating and cooling, the β-keto ester (1 eq) was placed in 10 mL of ethanol and then one equivalent of aryl amines is added in the presence of acetic acid. The mixture is stirred and heated under reflux for 6 h. The solvent was evaporated under reduced pressure.

Ethyl 2-(phenylamino)cyclohex-1-enecarboxylate (4): Yield : 85 %; ^{1}H NMR (DMSO-d_6) δ ppm: 1.25 (t, J = 7 Hz, 3H, CH_3); 1.69 (d, J = 6.61, 4H); 2.27-2.44 (dt, J = 5.86 Hz, 22.66 Hz, 4H); 4. 14 (q, J = 7 Hz, 2H,-CH_2); 7.10-7.20 (m, 3H,H_{arom}); 7.30-7.40 (m, 2H,H_{arom}) 10.81 (s,1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm : 14,62 (CH_3); 21.93 (-CH_2-); 22.24 (-CH_2-); 23.75 (-CH_2-); 27.65(-CH_2-); 58.90(-CH_2-); 92.43(C); 124.20 (C_{arom}); 129.22 (C_{arom}) 139.37 (C); 156.51 (C_{arom}); 170.00 (C=O).

Ethyl 2-(3-methoxyphenylamino)cyclohex-1-enecarboxylate (5): Yield : 88 %; ^{1}H NMR ($CDCl_3$) δ ppm: 1.25 (t, J = 7 Hz, 3H, CH_3); 1.46-1.64 (m, 4H); 2.17-2.34 (m, 4H); 4.20 (q, J = 7 Hz, 2H, -CH_2); 6.75 (d, J = 2.2 Hz, 2H, H_{arom}); 8.10 (d, J = 2.2 Hz, 2H, H_{arom}); 9.10 (s,1H, NH); ^{13}C NMR ($CDCl_3$) δ ppm: 14.65 (CH_3); 22.25 (-CH_2-); 22.69 (-CH_2-); 23.82 (-CH_2-); 26.01 (-CH_2-); 58.64 (-CH_2-); 90.14 (C); 122.45 (C_{arom}); 127.37 (C_{arom}); 135.49 (C); 140.99 (C_{arom}); 152.50 (C_{arom}); 170.88 (C=O).

Ethyl 2-(3-chlorophenylamino)cyclohex-1-enecarboxylate (6): Yield: 86 %; ^{1}H NMR ($CDCl_3$) δ ppm: 1.24 (t, *J* = 7 Hz, 3H, CH_3); 1.40-1.70 (m, 4H); 2.05-2.40 (m, 4H); 4.10 (q, *J* = 7 Hz, 2H,-CH_2); 6.25 (d, *J* = 2.2 Hz, 1H, H_{arom}); 6.80-7.15 (m, 3H, H_{arom}); 8.95 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ ppm: 14.30 (CH_3); 21.61 (-CH_2-); 21.92 (-CH_2-); 23.43 (-CH_2-); 27.33 (-CH_2-); 58.58 (-CH_2-); 92.11 (C); 118.88 (C_{arom}); 123.88 (C_{arom}); 128.90 (C_{arom}); 133.05 (C_{arom}); 136.95 (C); 139.05 (C_{arom}); 156.50 (C_{arom}); 169.68 (C=O).

Synthesis of tetrahydroacridin-9-ones derivatives: The prepared β-enamino-esters are then left in a diphenyl ether solution under stirring and heated under reflux (230 ° C) for 2 h. The residue is treated with a 50:50 mixture of ether and petrol ether and the solid is filtered and dried.

5,6,7,8-Tetrahydroacridin-9(10*H*)-one (7): Yield: 60 %; m.p. 240 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.60-1.80 (m,4H); 2.30 (t, *J* = 5.4, 2H); 2.75 (t, *J* = 5.8, 2H); 7.20 (t, *J* = 7.5, 1H); 7.40-7.60 (m, 2H); 8.3 (d, *J* = 8.0, 1H); 11.29 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 21.33 (-CH_2-); 21.56 (-CH_2-); 21.64 (-CH_2-); 29.39 (-CH_2-); 115.79 (C_q); 117.28 (C_{arom}); 121.26 (C_{arom}); 122.63 ($C_{q, arom}$); 124.89 (C_{arom}); 133.09 (C_{arom}); 139.26 ($C_{q, arom}$); 146.54 (C_q); 175.21 (C=O).

5,6,7,8-Tetrahydro-3-methoxyacridin-9(10*H*)-one (8): Yield: 65 %; m.p. 255 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.65-1.80 (m,4H); 2.41 (t, *J* = 5.4, 2H); 2.65 (d, *J* = 5.8, 2H); 7.10 (d, *J* = 10, 2H); 8 (d, *J* = 8.7, 1H); 11.38 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 22.13 (-CH_2-); 22.25 (-CH_2-); 22.55 (-CH_2-); 27.29 (-CH_2-); 55.97 (-CH_3); 98.68 (C_{arom}); 113.14 (C_{arom}); 115.67 (C_q); 118.14 ($C_{q, arom}$); 127.25 (C_{arom}); 141.57 ($C_{q, arom}$); 147.41 (C_q); 162.10 ($C_{q\ arom}$); 175.74 (C=O).

2-Chloro-5,6,7,8-tetrahydroacridin-9(10*H*)-one (9): Yield: 67 %; m.p. 248 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.73-1.85 (m,4H); 2.43 (t, *J* = 5.9, 2H); 2.71 (t, *J* = 5.8, 2H); 7.50 (d, *J* = 8.8, 1H); 7.40-7.60 (m, 2H); 7.60 (dd, *J* = 2, 1H); 7.97 (d, *J* = 2, 1H); 11.50 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 21.37 (-CH_2-); 21.63 (-CH_2-); 21.71 (-CH_2-); 27.10 (-CH_2-); 116.01 (C_q); 119.83 (C_{arom}); 123.68 ($C_{q\ arom}$); 124.07($C_{q, arom}$); 126.51 (C_{arom}); 131.04 (C_{arom}); 137.77 ($C_{q, arom}$); 147.32 (C_q); 174.70 (C=O).

Condensation of β-keto esters with 2-amino-5,6-dimethylbenzimidazole: In a three-necked 100 mL flask containing 30 mL of ethanol, β-keto ester (1 eq) was placed with 2-amino-5,6-dimethylbenzimidazole (1/1 eq), the mixture is heated under reflux. The reaction was followed by thin layer chroma-tography TLC. After evaporation of the solvent under reduced pressure, the resultant product is washed with ethyl ether.

8,9-Dimethyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo-[2,1-b]quinazolin-12(5*H*)-one (11): Yield: 77 %; m.p.: 255 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.60-1.85 (m,4H); 2.25 (s, 6H, 2-CH_3); 2.72-2.85 (m,4H); 7.51 (s,2H, H_{arom}); 11.25 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 18.01(2-CH_3); 22.30 (-CH_2-); 22.94 (-CH_2-); 23.30 (-CH_2-); 30.39(-CH_2-); 103.23(C); 114.85 (C_{arom}); 118.81 (C_{arom}); 122.86 (C_{arom}); 129.04 (C_{arom}); 147.43 (C); 152.04 (C) 159.29 (C=O).

7,8-Dimethyl-2,3-dihydrobenzo[4,5]imidazo[1,2-a]cyclopenta[d]pyrimidin-11(4*H*)-one) (12): Yield : 80 %; m.p.: 250 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.98-2.09 (m,2H); 2.30 (s, 6H,2-CH_3); 2.70-2.85 (m,4H); 7.50 (s,2H, H_{arom}); 10.85 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 18.40 (2-CH_3); 21.69 (-CH_2-); 26.86 (-CH_2-); 34.26(-CH_2-); 101.34 (C); 114.69 (C_{arom}); 118.59 (C_{arom}); 122.48 (C_{arom}); 130.43 (C_{arom}); 145.82 (C); 151.86 (C); 159.87 (C=O).

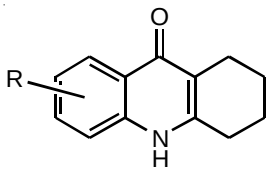
7,8-Dimethyl-2-methylbenzo[4,5]imidazo[1,2-a]pyrimidin-4(1*H*)-one (13): Yield: 74 %; m.p.: 225 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.75 (s,3H,CH_3); 2.80 (s, 6H,2-CH_3); 5.82 (s, 1H,=CH); 7.81 (s,2H, H_{arom}); 11.20 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 17.84 (2-CH_3); 22.82 (CH_3); 98.28 (=CH); 114.84 (C_{arom}); 119.46 (C_{arom}); 123.63 (C_{arom}); 131.28 (C_{arom}); 148.41 (C); 155.46(C); 159.95(C=O).

7,8-Dimethyl-2-methoxybenzo[4,5]imidazo[1,2-a]pyrimidin-4(1*H*)-one (14): Yield: 74 %; m.p.: 240 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 2.20 (s, 6H,2-CH_3); 3.75 (s,3H, O-CH_3); 5.75 (s, 1H,=CH); 7.25 (s,2H, H_{arom}); 11.00 11.20 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm : 17.76 (2-CH_3); 52.14 (CH_3); 100.14 (=CH); 114.76 (C_{arom}); 119.72 (C_{arom}); 123.77 (C_{arom}); 132.95 (C_{arom}); 146.21(C); 158.21 (C=O); 179.28 (C).

RESULTS AND DISCUSSION

Reactivity of β-keto esters with the arylamines

Synthesis of tetrahydroacridin-9-ones derivatives: Synthesis and reactivity of derivatives of tetrahydroacridin-9-ones **(I)** have been particularly enriched by the work of the teams of Elguero *et al.*[2] and Rodriguez *et al.*[11]. Their research permitted to clarify the notion of this chemistry compounds class.



I

For our part, having synthesized tetrahydroacridin-9-ones derivatives, we study their reactivity toward the alkylating agents.

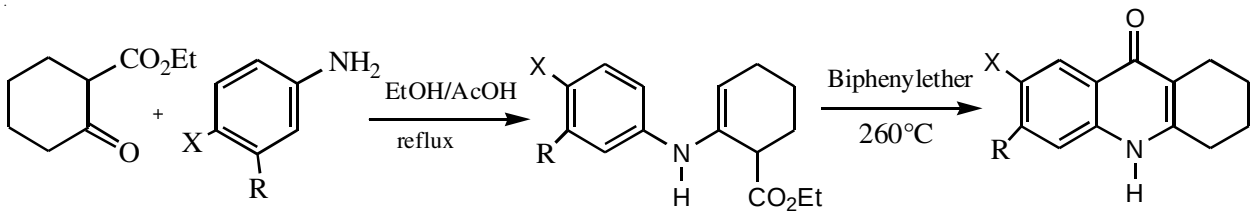
The synthesis method, we have adopted, carries out the condensation reaction of ethyl 2-oxocyclohexanecarboxylate with arylamines (**Scheme-I**).

In a first step, we have synthesized β-enamino ester derivatives by condensation of these β-keto esters with arylamines in ethanol under reflux in the presence of acetic acid. Then a cyclization was carried out in biphenyl ether solution, thus forming tetrahydroacridin-9-ones derivatives.

We have isolated, in all cases, a single product whose structure could match the tetrahydroacridin-9-ones derivative.

^{1}H NMR (DMSO-d_6) spectra of the obtained products, exhibit signals in the range of 7.25-8.43 ppm corresponding to the aromatic protons. We note the absence of the signals corresponding to the proton's groups ($CO_2C_2H_5$).

Tetrahydroacridin-9-ones derivatives compounds: ^{13}C NMR spectra have, in particular, signals at 174.41-175.77 ppm, 121.26-121.92 ppm and 145.77-148.41 ppm, corresponding respectively to the carbonyl carbon (C=O) and two ethylenic carbons in α and β.



1 R:H, X H
2 R:OMe,X H
3 R:H,X:Cl

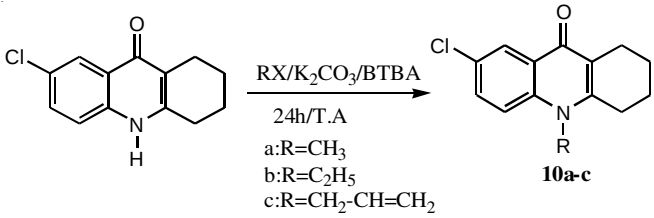
4 R:H, X H
5 R:OMe,X H
6 R:H,X:Cl

7 R:H, X H
8 R:OMe,X H
9 R:H,X:Cl

Scheme-I: Synthesis of tetrahydroacridin-9-ones derivatives

Reactivity of compound 9 with halogen derivatives: For our part, we examined the alkylation reaction under the catalysis conditions by transfer of solid-liquid phase of the tetrahydroacridin-9-ones derivatives with various halogenated derivatives using methyl iodomethane, bromoethane, propargyl bromide. Potassium carbonate is used as inorganic base in anhydrous tetrahydrofurane and bromide of tetra-*n*-butyl-ammonium (BTBA) as a catalyst.

It is found that, regardless of the used alkyl halide, alkylation of 2-chloro-5,6,7,8-tetrahydroacridin-9(10*H*)-one (**9**) led, after 24 h under stirring at ambient temperature, leads to N-alkyl compounds in good yield: 64-86 % (**Scheme-II**).

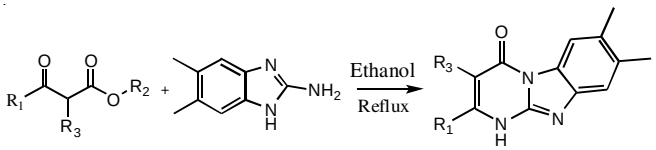


Scheme-II: Alkylation of 2-chloro-5,6,7,8-tetrahydroacridin-9(10*H*)-one (**9**), leading after 24 h, under stirring at ambient temperature, to N-alkyl compounds.

The structures of the isolated compounds were established on the basis of spectral data, ^{1}H NMR, ^{13}C NMR and IR. ^{1}H NMR spectra of compounds **10a-c**, recorded in DMSO-d_6,

The structures of the isolated compounds were established on the basis of spectral data, ^{1}H NMR spectra of compounds **10a-c**, recorded in DMSO-d_6, present, besides the signals corresponding to the protons of two methyl groups and aromatic protons, signals relating to the protons of the N-alkyl groups. The different chemical shifts are reported in Table-1. ^{13}C NMR spectra of compounds **10 a-c**, recorded in DMSO-d_6, are collected in Table-2.

Reactivity of β-keto esters with 2-amino-5,6-dimethyl-benzimidazole: We are interested in the preparation of new heterocyclic compounds bonding pyrimidinone nuclei by condensation, in ethanol under reflux of β-keto esters and 2-amino-5,6-dimethylbenzimidazole (**Scheme-III**).



Scheme-III: Synthesis of pyrimidinone derivatives

The condensation of 2-aminobenzimidazole with β-keto esters was carried out in ethanol under reflux. In all cases, we obtained pyrimidinone derivatives in good yields. The results of the condensation of these β-keto esters with amines are recorded on Table-3.

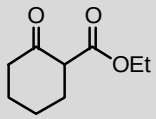
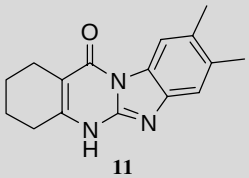
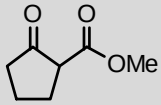
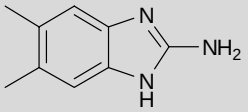
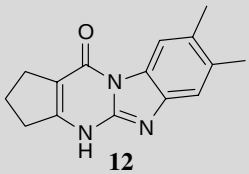
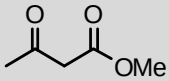
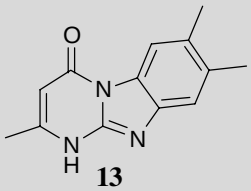
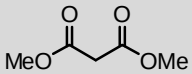
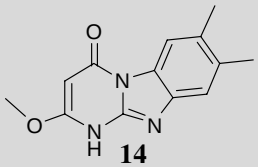
TABLE-1
^{1}H NMR SPECTRA OF **10a-c** COMPOUNDS

Products	CH_2 (Caciques)	CH_3	CH_3	CH_2N	$CH_{Vinylique}$	$CH_{2Vinylique}$	CH_{arom}
10a	1.65-1.85 (m, 4H) 2.60-3.00 (m, 4H)	3.26 (s, 3H)	–	–	–	–	7.6(d, *J* = 8.9 Hz, 1H); 7.8 (dd, *J* = 8.9, 2.0 Hz, 1H); 8.3 (d, *J* = 2.0 Hz, 1H);
10b	1.70-2.00 (m, 4H) 2.70-3.10 (m, 4H)	–	1.51(s, 3H) *J* = 7.0 Hz	3.25 (q, 2H) *J* = 7.0 Hz	–	–	7.5(d, *J* = 8.9 Hz, 1H); 7.7 (dd, *J* = 8.9, 2.0 Hz, 1H); 8.2 (d, *J* = 2.0 Hz, 1H);
10c	1.70-2.00 (m, 4H) 2.65-2.90 (m, 4H)	–	–	3.76 (m, 2H)	5.80-6.00 (m, 1H)	5.00-5.30 (m, 2H)	7.50-8.20 (m, 3H)

TABLE-2
^{13}C NMR SPECTRA OF **10a-c** COMPOUNDS

Products	CH_2 (Caciques)	CH_3	CH_3	CH_2N	$CH_{Vinylique}$	$CH_{2Vinylique}$	CH_{arom}	C_q
10a	21.72; 21.81; 21.99; 29.48	44.05	–	–	–	–	117.16; 131.89; 126.48	121. 69; 123.96 125.69; 138.96; 145.77; 175.77
10b	21.01; 21.43; 21.86; 29. 37	–	18.21	48. 84	–	–	118.29; 132.91; 126.94	121. 84; 123.29 125.91; 138.29; 146. 08; 174.41
10c	21.14; 21.42; 21.69; 29.30	–	–	49.93	136.46	119.93	117.20; 131.66; 126.95	121. 92; 123.46 125.66; 138.46; 146.14; 175.31

TABLE-3
RESULTS OF THE CONDENSATION OF β-KETO ESTERS WITH AMINES

Entry	β-Keto esters	2-Amino-5,6-dimethylbenzimidazole	Conditions operators	Product obtained	Yield (%)
1			Ethanol, 8 h, reflux	 **11**	77
2			Sans solvent, 24 h, T.A.	 **12**	80
3			Ethanol, 8 h, reflux	 **13**	74
4			Ethanol, 9 h, reflux	 **14**	75

Pyrimidinones derivatives compounds structures were established from ^{1}H NMR and ^{13}C NMR spectral data.

^{1}H NMR spectra at 300 MHz in DMSO, we observe the characteristics of the signal pyrimidinones derivatives structure. These spectra differ slightly in the chemical shift, depending on the nature of the substituents, *i.e.* in their electronic effects.

All spectra show signals in the region 7.25-8.43 ppm corresponding to the aromatic protons. We note that the proton of the double bond of the compounds **13** and **14** appears in the form of a singlet signal between 5.75-5.82 ppm.

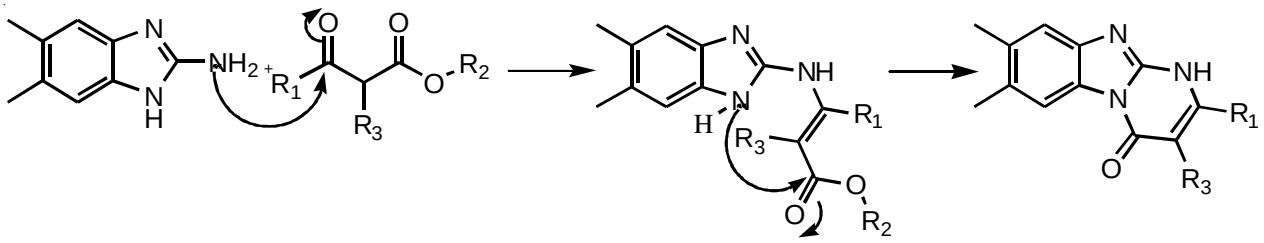
^{13}C NMR spectra of the pyrimidinone derivatives compounds exhibit, in particular, signals at 158.21-159.87 ppm; 98.29-103.23 ppm and 145.82-169 ppm, corresponding respectively to the carbonyl carbon (C=O) and two ethylenic carbons in α and β.

The results obtained from this study have enabled us to propose the mechanism of formation of pyrimidinone derivatives (**Scheme-IV**). The formation of these latter compounds can be explained by a nucleophilic attack of the free electron pair of the nitrogen atom of the amino group on the carbonyl of the ketonic function. The resultant intermediate formed by elimination of a molecule of water, followed by esterification reaction leads to the skeleton of the pyrimidinone derivatives. Cyclization involves the attack of intracyclic nitrogen yielding the pyrimidinone derivative.

This method enabled us to prepare poly and heterocyclic compounds in one step under simple conditions. We analyzed the biological activity of chemically synthesized molecules by investigating their antimicrobial and antifungal effect.

Evaluation of antimicrobial and antifungal activity of the resultant compounds: If antimicrobial activity of 2-amino-5,6-dimethylbenzimidazole (ABDI) is nil for all of the tested strains, it is otherwise for compounds (**11, 12, 13** and **14**) resulting from the condensation of the β-keto esters with the latter.

Antifungal activity of compounds (11, 12, 13 and 14): The antifungal activity of the products obtained from the condensation of β-keto esters with 2-amino-5,6-dimethylbenzimidazole is illustrated in Fig. 1.



Scheme-IV: Formation mechanism of pyrimidinone derivatives

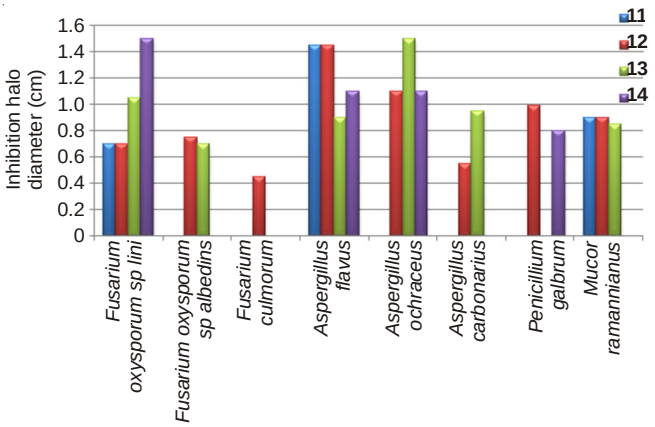


Fig. 1. Antifungal activity of compounds (**11, 12, 13** and **14**)

It is observed that the activity varies from one compound to another on the one hand and this activity depends on the tested strain, on the other hand. Indeed, it seems that *Aspergillus flavus* is the most sensitive to the tested compounds (the diameter of the inhibition halo varies from 0.6 to 1.45 cm) followed *by Fusarium oxysporum sp lini* species (diameter varies from 0.4 to 1.5 cm). For the other strains, there are always one or more compounds that are without effects. For example: *Fusarium oxysporum sp albedins* and *Aspergillus carbonarius* are resistant to compounds **11** and **14** (diameter of the halo zero), *Fusarium culmorum* is resistant to **11**, **13** and **14**, *Penicillium galbrum* is resistant to compounds **11** and **13**, *Mucor ramannianus* is resistant to the compound **14** and finally *Aspergillus ochraceus* is resistant to the compound **11**.

Antibacterial activity of compounds (11, 12, 13 and 14): Fig. 2 shows the antibacterial activity of the compounds (**11**, **12**, **13** and **14**) on the six tested strains.

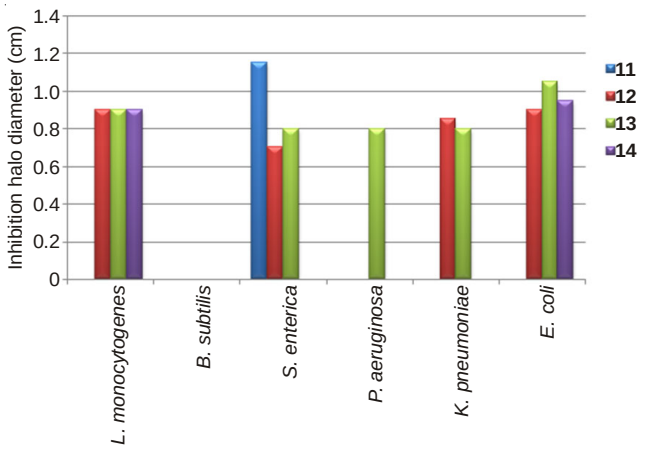


Fig. 2. Antibacterial activity of compounds (**11, 12, 13** and **14**)

It is noticed that *Bacillus subtilis* has developed a resistance towards all compounds, *Pseudomonas aeruginosa* is sensitive only towards the compound **13** (equal to 0.5 cm diameter of the zone of inhibition) and *Klebsiella pneumoniae* is sensitive towards compounds **12** and **13** (the diameter of the aureole is 0.85 and 0.8 cm respectively). For other species, strains are resistant against a single compound and that their sensitivity varies from one compound to another. *E. coli* is the most sensitive with the diameter of inhibition ranging from 0.9 to 1.05 cm; followed by *Listeria monocytogenes* and *Salmonella enterica*, which are more or less sensitive (the diameter of the inhibition halo is 0.9 cm for the first and varies from 0.7 to 1.15 cm for the second).

Antimicrobial activity of compound 11: The antimicrobial activity of compound **11** towards the fungal flora and bacterial flora is illustrated in Fig. 3.

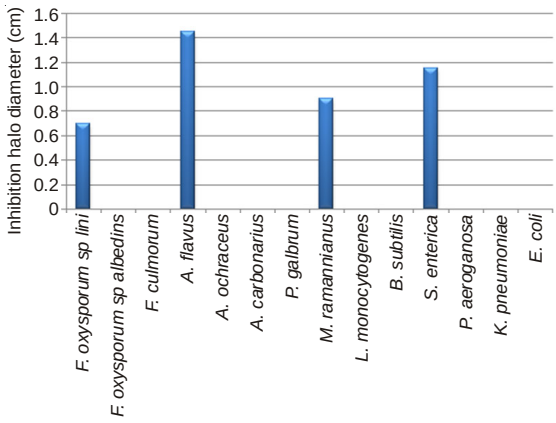


Fig. 3. Antimicrobial activity of compound **11**

Two facts should be noted, first compound **11** is ineffective against bacterial flora, except for *Salmonella enterica* where there is a halo of inhibition estimated at 1.15 cm, on the other hand only the three fungal strains, *Fusarium oxysporum sp lini*, *Aspergillus flavus* and *Mucor ramannianus*, are sensitive to the action of compound **11**. This sensitivity varies from one strain to another. It is highest for *Aspergillus flavus* (1.45 cm diameter) and lowest for *Fusarium oxysporum sp lini* and *Mucor ramannianus* the diameter of the aureole is respectively 0.7 and 0.9 cm.

Antimicrobial activity of compound 12: Fig. 4 reports the antimicrobial effect of compound **12** on the tested microbial strains.

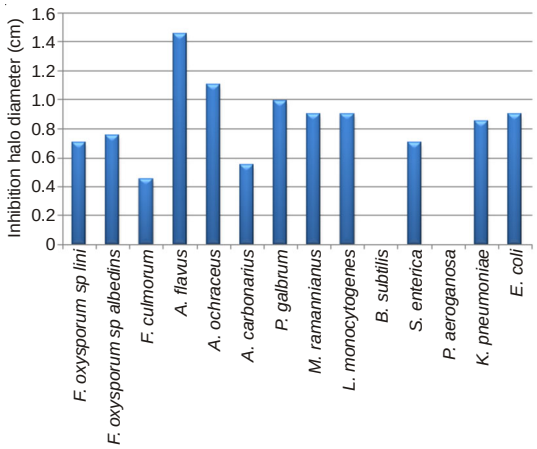


Fig. 4. Antimicrobial activity of compound **12**

There are only two bacterial strains *Bacillus subtilis* and *Pseudomonas aeruginosa* are resistant to the action of compound **12**. For other strains, the resistance (or sensitivity) is variable within the bacterial group either within the fungal group. Nevertheless, lowest resistance was observed for fungi: *Aspergillus flavus*, *Aspergillus ochraceus* and *Penicillium galbrum*, whose diameter is 1.45, 1.1 and 0.99 cm, respectively

and the highest resistance was observed for both fungi: *Fusarium culmorum* and *Aspergillus carbonarius*.

Antimicrobial activity of compound 13: The antimicrobial activity of compound **13** on the microbial flora is reported in Fig. 5. It is observed that only two fungi: *Fusarium culmorum* and *Penicillium galbrum* and bacteria: *Bacillus subtilis* have developed a resistance to the compound **13** that resulted in a nil diameter. Other strains have developed resistance more or less variable, thus *Fusarium oxysporum sp lini*, *Aspergillus ochraceus* and *E.coli* have shown to be the most sensitive (diameters of the aureole is estimated respectively at 1.05, 1.5 and 1.05 cm); the remains strains present considerable sensitivity.

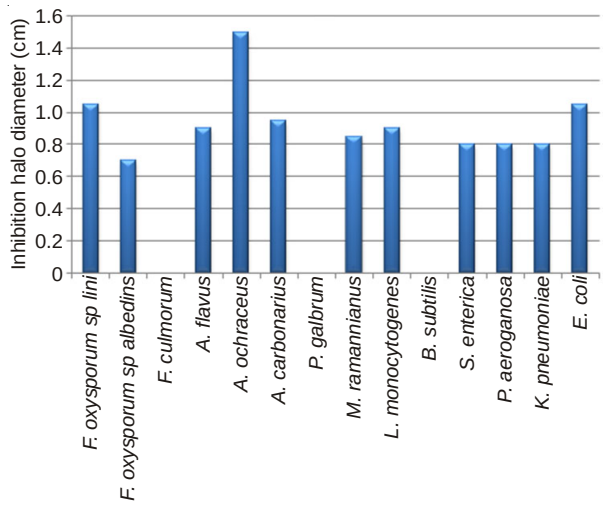


Fig. 5. Antimicrobial activity of compound **13**

Antimicrobial activity of compound 14: Fig. 6 shows the antimicrobial activity of compound **14** against bacterial and fungal strains.

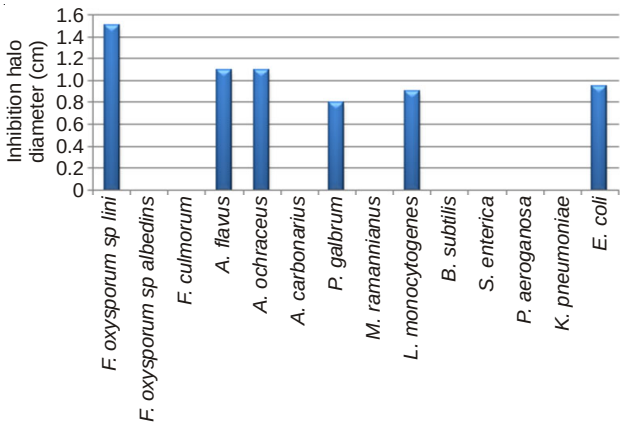


Fig. 6. Antimicrobial activity of compound **14**

It seems clear that the compound **14** may effective against bacterial strains where the diameter of the aureole is nil, except for *E. coli* and *Listeria monocytogenes* where the diameter is 0.95 and 0.9, respectively. For fungi, we observed that four strains: *Fusarium oxysporum sp lini*, *Aspergillus flavus*, *Aspergillus ochraceus* and *Penicillium galbrum* are sensitive to the action of the compound **14** where the diameter of the aureole is respectively 1.5, 1.1, 1.1 and 0.5 cm. The remaining three fungal strains have developed no resistance to the **14** compounds.

Sensitivity of strains according Duraffourd: The sensitivity of strains towards different compounds is reported in Fig. 7.

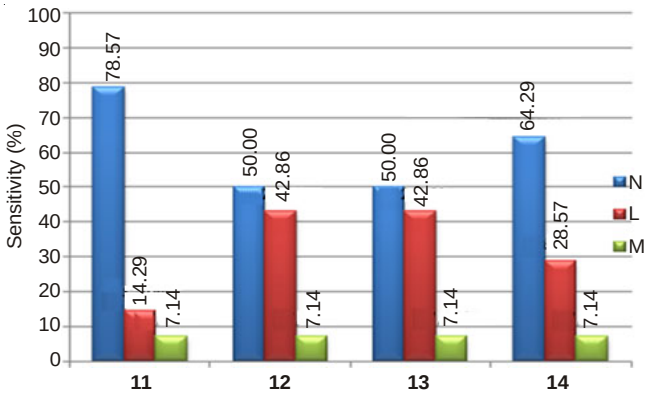


Fig. 7. Susceptibility frequency of strains to different compounds

The sensitivity is nil for 78.57 % of the tested strains (35.71 % for bacteria and 42.86 % for fungi) by compound **11** and 14.29 % having limited sensitivity (7.14 % for bacteria and 7.14 % for fungi). Strains tested by compounds **12** and **13** whose sensitivity is nil are estimated at 50 % (21.43 % for bacteria 28.57 % and for fungi), 7.14 % of the strains have limited sensitivity (3.57 % for bacteria and 3.57 % for fungi). And for the compound **14**, 64.29 % of strains have a nil sensitivity (28.57 % for bacteria 35.72 % and for fungi); 28.57 % have limited sensitivity (14.28 % for bacteria and 14.28 % for fungi). We also note that the average sensitivity is 7.14 % (for all fungi) by the four compounds.

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