Synthesis of news furo[2,3-*d*] pyrimidine derivatives as potential inhibitors of DHFR

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INTRODUCTION

Heterocyclic compounds are promising agents in the development of synthetic molecules with bioactivity. Fused heterocyclic structures containing pyrimidine or furan rings exhibited diverse biological activities such as antimicrobial, anti-inflammatory, antiviral and anticancer.[1] The furo[2,3-*d*]pyrimidines, which are an important class of heterocyclic compounds, have been considered for many years as a model for the discovery of drugs for inhibition of the enzyme dihydrofolate reductase (DHFR).[2] In view of this biological activity, the objective of this work consists on the synthesis of new furo[2,3-*d*]pyrimidines as potential agents to act as antifolates inhibiting DHFR, which is present in various fungi, bacteria and protozoa. These compounds may be new agents for neglected diseases.

RESULTS AND DISCUSSION

The methodology for the synthesis furo[2,3-*d*] pyrimidine derivatives (**5**) consists of 2 steps as shown in **Figure 1**. The first step consists on the synthesis of benzylidene barbiturate (**3**) through of the Knoevenagel condensation reaction between of aromatic aldehyde (**1**) and the barbituric acid (**2**) at room temperature for 40 min. In the second step, the furo[2,3-*d*] pyrimidine was formed by reaction of the benzylidene barbiturate with cyclohexyl isonitrile (**4**) in dry dioxane under reflux for 3h.

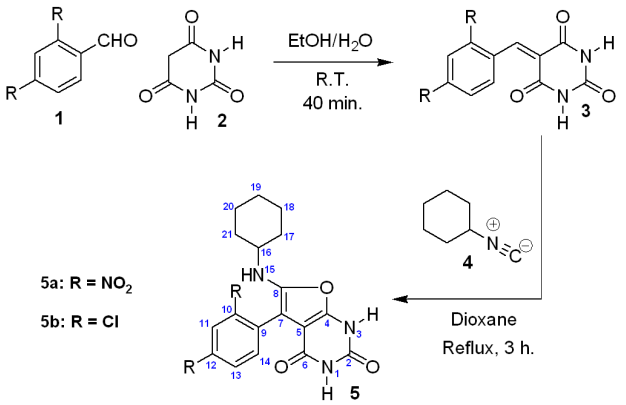

Figure1. Synthesis of news furo[2,3-*d*] pyrimidine derivatives (**5**)

The method to prepare furo[2,3-*d*]pyrimidines was invented by our research group in 1992,[3] using N,N-dimethyl-benzylidene barbiturates. That reaction was never executed with non N-alquilated barbiturates, process that we invented. The reaction of isonitriles with non N-methylated benzylidene barbiturates need low polarization of the exocyclic C=C bond to avoid Michael addition and induce 1+4 cycloaddition[4] (**Figure 2**).

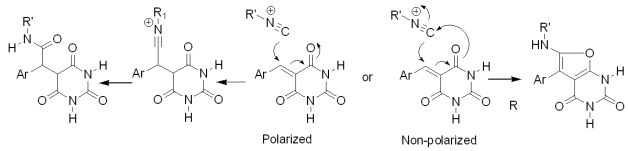

Figure 2. Mechanism of reaction of the isonitrile with the benzylidene barbiturate

All compounds were characterized by IR and NMR. The ^{1}H RMN spectrum of furo[2,3-*d*]pyrimidine (**5**) showed a doublet signal in 8.67 ppm, relative to the N-H connected to the cyclohexane ring and overlapping multiplets on the region of 1.25-1.84 ppm, relative to methylene groups of the cyclohexyl ring. The ^{13}C RMN spectrum showed the 24.30, 25.57 and 32.45 ppm signals relative to methylene groups of the cyclohexyl ring and 107.61, 134.92, 162.17 ppm signals of carbons of the furan ring.

CONCLUSION

This new developed method for preparation of furo[2,3-*d*]pyrimidines is only effective on less polarized benzylidene barbiturates, a process that requires the presence of electronic attractive groups on the aromatic ring. These furo[2,3-*d*] pyrimidine derivatives (**5a** and **5b**) and others that are synthesized will be evaluated biologically for inhibition the enzyme DHFR.

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