

## AN EASY AND DIRECT METHOD FOR THE SYNTHESIS OF 1,2,4-TRIAZOLE DERIVATIVES THROUGH CARBOXYLIC ACIDS AND HYDRAZINOPHTHALAZINE

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We have developed an easy method for the synthesis of thirteen compounds derived from 1,2,4-triazoles through a carboxylic acid and hydrazinophthalazine reaction, with a 75-85% yield mediated by the use of agents such as 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride and 1-hydroxybenzotriazole. The operational simplicity of this method and the good yield of products make it valuable for the synthesis of new compounds with pharmacological activity.

Keywords: 1,2,4-triazoles; carboxylic acids; hydrazinophthalazine.

## INTRODUCTION

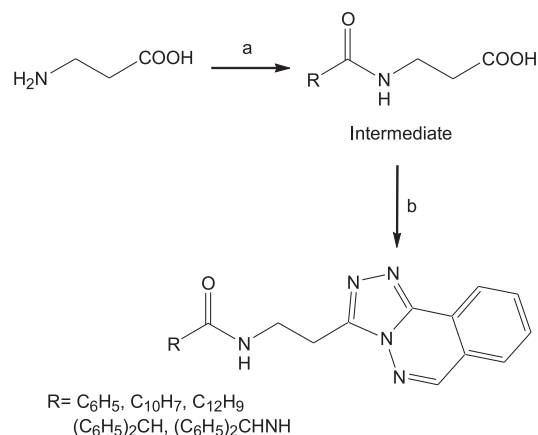
Triazoles constitute an important class of biologically active heterocyclic compounds that have received a great deal of attention since their discovery. Diverse compounds derived from 1,2,4-triazoles have a wide spectrum activities including antibacterial, antifungal, antiviral, antiinflammatory, antihypertensive, and hypoglycemic properties.<sup>1,2</sup>

Enders and co-workers developed the synthesis of triazole salts by amine reaction with oxadiazolium salt by condensation of *N,N'*-diformylhydrazine.<sup>3</sup> Triazole rings are typically synthesized by a process that represents a dehydrated condensation between hydrazides and nitrile derivatives. These procedures are carried out at high temperatures and depend on a stage derived from nitrile and a subsequent stage for the synthesis of acylamidrazone intermediate prior cyclization.<sup>4</sup> Additionally, the compounds derived from 1,2,4-triazoles have been prepared using several published methods of synthesis. Each of these procedures are unsatisfactory for several reasons, but mainly because they frequently involve reactions at high temperatures with long reaction times and result in low yields.<sup>4-8</sup> Additionally, most of the methods for obtaining of 1,2,4-triazole derivatives are based on heterocyclic hydrazide precursors. However, these methods have certain restrictions such as their applicability and the use of toxic reagents such as lead tetraacetate, bromine or phosphorus oxychloride.<sup>5,9-11</sup>

## EXPERIMENTAL

Initially, a solution of carbonyl chloride derivative (3 equiv.) in the minimum amount of  $\text{CHCl}_3$  was added, alternately and portionwise, to a solution of the corresponding carboxylic acid (1 equiv.) in 2M NaOH (200 mL), stirring for 30 min. After the addition of NaOH, the mixture was stirred at room temperature for 48 h. The aqueous layer was acidified with concentrated HCl to pH 1-2. The residue obtained was filtered and washed with  $\text{H}_2\text{O}$  and *n*-hexane in order to obtain carboxylic acid derivative (intermediate). The intermediate (1 equiv.), in dry  $\text{CH}_2\text{Cl}_2$  (150

mL) at 0 °C in an  $\text{N}_2$  atmosphere, was treated with 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) (1.1 equiv.) and 1-hydroxybenzotriazole (HOBt) (1.1 equiv.). After 1 h at 0 °C, the corresponding hydrazinophthalazine hydrochloride (1.1 equiv.) and triethylamine (1.1 equiv.) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) were added (Figure 1). The reaction was stirred at room temperature for 24 h. The solvent was evaporated and the residue was taken up with  $\text{H}_2\text{O}$  and diethyl ether in order to obtain several 1,2,4 triazole derivatives (Table 1). The compounds were purified by means of recrystallization with *i*:PrOH or by column chromatography ( $\text{CH}_2\text{Cl}_2$ - $\text{CH}_2\text{Cl}_2$ :MeOH).



**Figure 1.** Synthesis route of new compounds derivatives of 1,2,4 triazoles. Reagents and conditions: (a) carbonyl chloride derivative, 2M NaOH; (b) hydrazinophthalazine hydrochloride, EDC, HOBt,  $\text{N}_2$ ,  $\text{CH}_2\text{Cl}_2$

## RESULTS AND DISCUSSION

In our discovery program of melanin concentrating hormone R1 (MCH-R1) antagonists we found a simple and useful method for the preparation of new compounds derivatives of 1,2,4-triazoles. We found that hydrazinophthalazine can easily react with carboxylic acids derivatives, using reaction agents such as EDC and HOBt.

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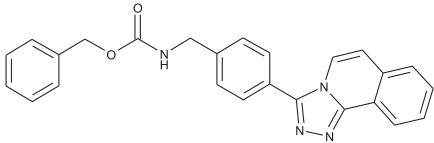
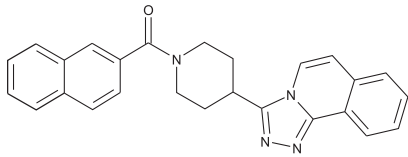
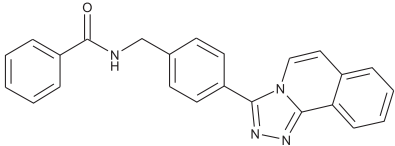
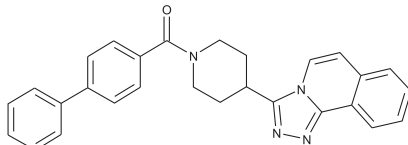
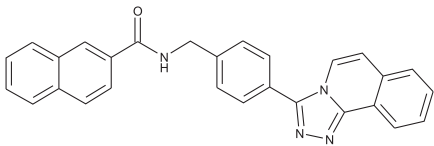
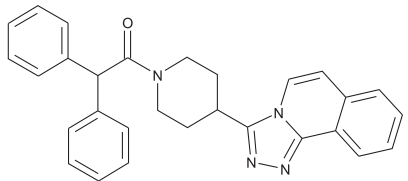
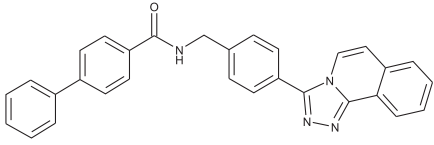
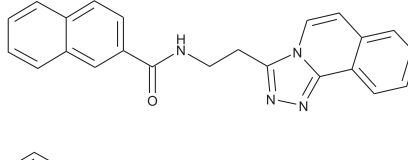
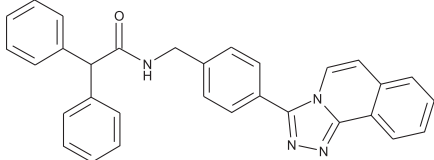
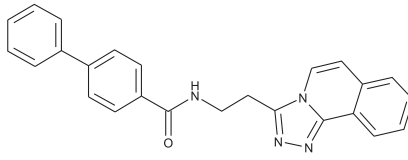
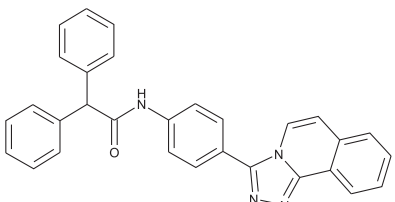
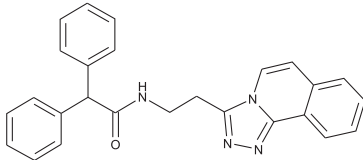
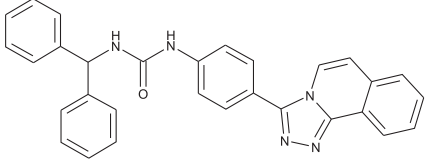
The yield of this procedure is strongly affected by reactions conditions, for example, changing solvents ( $\text{CH}_2\text{Cl}_2$ , MeOH, EtOH,  $\text{CH}_2\text{Cl}_2$ :MeOH and  $\text{CH}_2\text{Cl}_2$ :EtOH), anhydrous conditions and temperatures that exceeded  $10^\circ\text{C}$  had a dramatic effect on the rate of the reaction. Dichloromethane verified significantly better results in yield. A series of 13 compounds were obtained and confirmed by elemental analysis, IR and  $^1\text{H}$  NMR, with yield between 75 to 85% (Table 1).

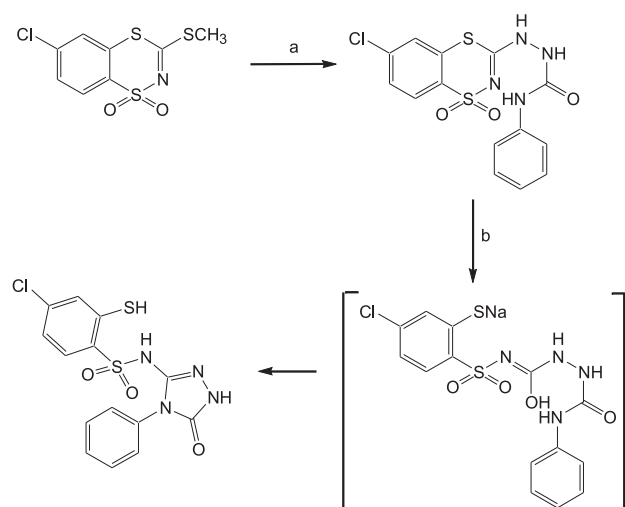
Initially, we based our procedure on the reaction for obtaining carbohydrazides.<sup>12</sup> We were pleasantly surprised to find that 1,2,4-triazole derivatives were produced using hydrazinophthalazine

hydrochloride. However, the use of different hydralazine derivatives such as 2-hydrazinopyridine, 2-hydrazino-4(trifluoromethyl) pyrimidine and 3-chloro-6-hydrazinopyridazine in the acylation of the carboxylic group did not produce 1,2,4-triazole derivatives. According to the literature, Pomarnacka and Kozlarska-Kedra used a benzodithiazine with semicarbazide hydrochloride in methanol at reflux for 30 h and aqueous sodium hydroxide at  $95^\circ\text{C}$  for the synthesis of 1,2,4-triazoles (Figure 2). They assumed that the presence of an electron-withdrawing aromatic substituent at the N-4 nitrogen atom of the semicarbazide moiety is necessary for the synthesis of the triazole ring.<sup>13</sup>

Using our experimental settings, the 4-phenylsemicarbazide

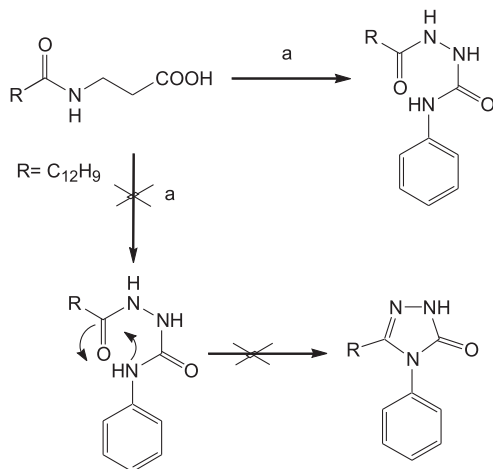
**Table 1.** New compounds derivatives of 1,2,4-triazoles

Compound	Yield %	Compound	Yield %
	85		79
	79		81
	83		83
	82		76
	82		79
	75		76
	78		



**Figure 2.** Procedure that described Pomarnacka and Kozlarska-Kedra for the synthesis of 1,2,4-triazole derivatives. Reagents and conditions: (a) semicarbazide hydrochloride, MeOH, reflux 30 h; (b) NaOH/H<sub>2</sub>O 95 °C, 1 h

reaction, along with a 3-[(biphenyl-4-ylcarbonyl)amino]propionic acid reaction was carried out without resulting in a triazole derivative as Pomarnacka and Kozlarska-Kedra indicated (Figure 3). However, because we used different reaction conditions, the formation of 1,2,4-triazole derivatives may depend on other factors besides the ones proposed by Pomarnacka and Kozlarska-Kedra.

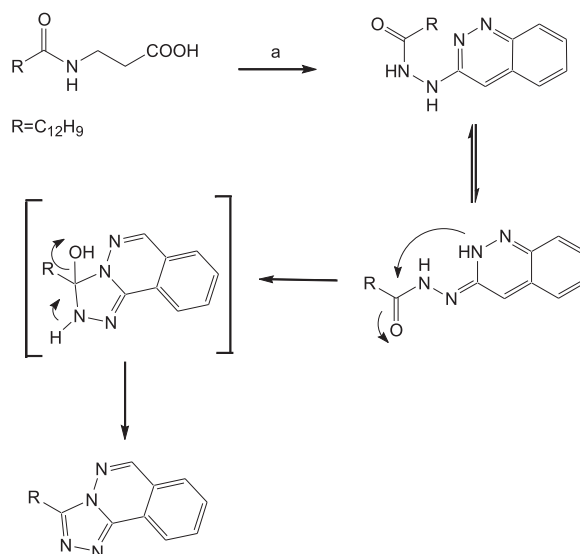


**Figure 3.** Carboxylic acid derivative with 4-phenylsemicarbazide reaction was carried out without resulting in 1,2,4-triazole derivatives. Reagents and conditions: (a) 4-phenylsemicarbazide, EDC, HBOT, N<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>

Considering the above we propose a possible mechanism in figure 4 for the formation of 1,2,4-triazole derivatives that implies the participation of the corresponding tautomerism in the molecules involved with the expected intramolecular cyclization, producing the 1,2,4-triazole derivatives.

## CONCLUSION

In conclusion, we found an easy method for the synthesis of compounds derived from 1,2,4-triazoles with good performance through the use of agents such as EDC and HOBT. The operational



**Figure 4.** Proposed mechanisms for the formation of 1,2,4-triazole derivatives. Reagents and conditions: (a) hydrazinophthalazine hydrochloride, EDC, HBOT, N<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>

simplicity of this method and the good yield of the products make it valuable. Additionally, this reaction eliminates the use of toxic reagents such as lead tetraacetate or phosphorus oxychloride with each reaction. We propose a procedure that can be used in the synthesis of new compounds with pharmacological activity.

## ACKNOWLEDGMENTS

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