Convenient Synthesis and antimicrobial activity of some novel pyridazinone bearing triazole moieties

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Abstract:

2-(5-Mercapto-4-phenyl-4H-[1,2,4]triazol-3-ylmethyl)-6-p-tolyl-4,5-dihydro-2H-pyridazin-3-one **(3)** was prepared according to the established sequenced procedures [1-3]. Subsequently by using selected alkylating agents; compounds **4a-c** were prepared via regioselective *S* alkylation procedure4. Alternatively, compounds **5a-c** were prepared via regioselective addition procedure[4]. Under Mannich condition, some interesting compounds **7a,b** and **8a,b** were successfully prepared. On the other hand, the azides **10** and **15** coupled with amino acid esters **11a-d** and **15a-d** to give amino acids derivatives **12a-d** and **16a-d** in good to moderate yield respectively. The structural elucidation of products is reported and also some of the products were screened for their antimicrobial activity.

Keywords: pyridazinone, triazole, alkylation, addition, azide coupling, peptides, mannich.

Introduction

The pyridazinone derivatives represent a great important biologically active compounds[1] such as Milrinone **I** has vasorelaxant activity in vitro[5], 6-Phenyl pyridazinone **II** has antihypertensive activities[6], 6-piprazino pyridazinone derivative **III** has analgesic and anti-inflammatory activities [7,8] pyridazinone substituted benzenesulfonylurea derivatives **IV** has blood glucose lowering effect[9], pyridazinone-substituted phenylalanine amide **V** has effectiveness in a mouse leukocytosis[10] (figure 1).

On the other hand, the triazole nucleus was the back bone of many drugs production[3].

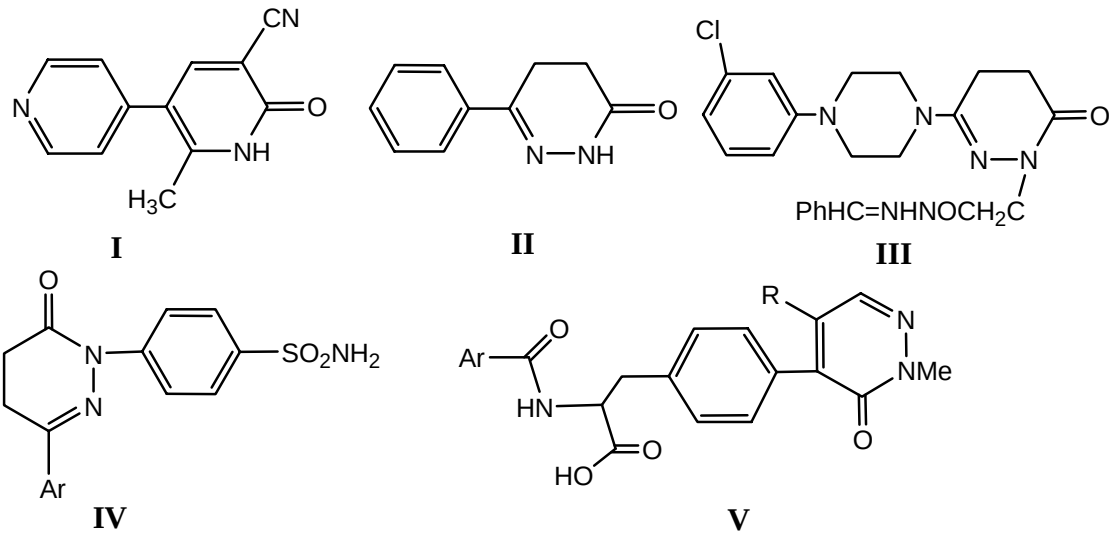


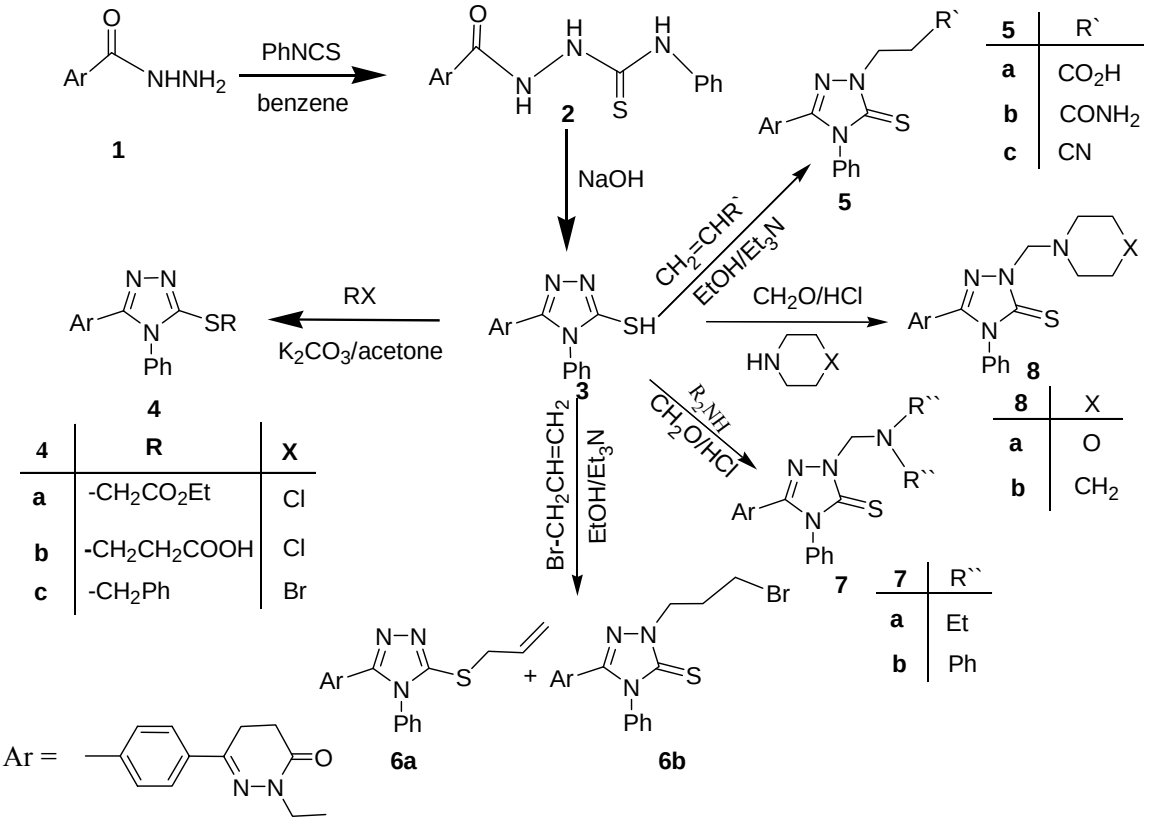
Figure 1. Biological active pyridazinones

In this paper, we describe the development of a new series of dihydro-2*H*-pyridazin-3-one which attached with triazole moiety coupled with amino acids.

Results and Discussion

As triazole applications in drug constructions were attracted scientist attention; we extended our studying for this nucleus *via* synthesis of novel triazole-pyridazinone derivatives. Reaction of hydrazide **1** with phenyl isothiocynate gave phenylthiosemicarbazide **2** which on treatment with NaOH cyclised to triazole **3**. One important study was based on regioselective *S*-alkylation of **3** with different alkylating agent such as ethylchlororacetate, 3-chloropropoinic acid and benzyl bromide to give **4a-c** respectively. On the other hand, we studied the regioselective *N*-addition with selected reagents such as acrylic, acrylomide, acrylonitrile to give **5a-c** respectively. Allyl Bromide underwent *S*-alkylation and *N*- addition at the same time to give **6a,b**. On treatment of

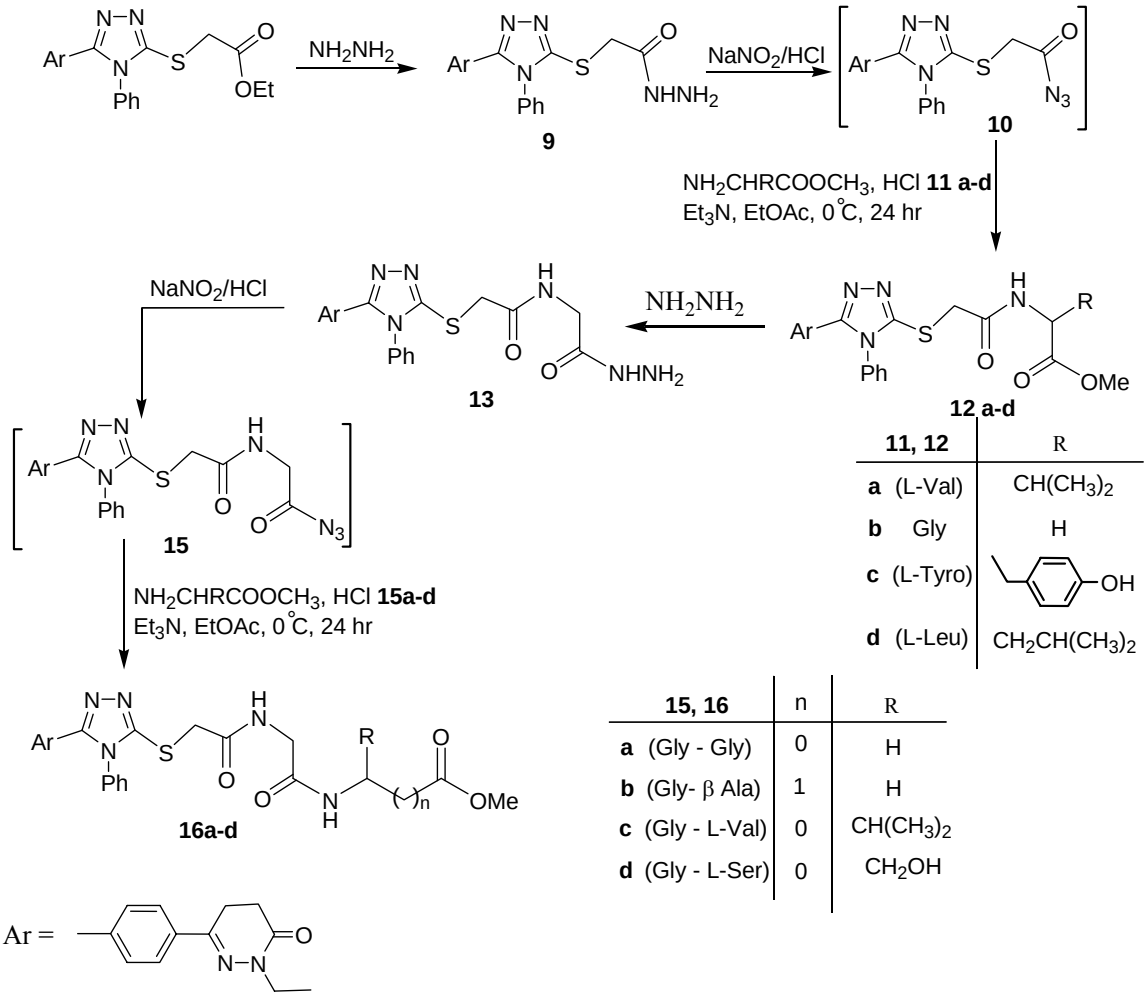
triazole thiole **3** with morpholine and/or pipridine under mannich condition gave **8a,b** scheme (1).



Scheme 1

Our study was extended to synthesis of new amino acid derivatives coupled with biologically active heterocyclic moieties such as triazolo-quinazoline[11], quinoline[12], pyradizinone[1] and triazole[3] attracted our attention. In this work we studied 2-(5-Mercapto-4-phenyl-4H-[1,2,4]triazol-3-ylmethyl)-6-p-tolyl-4,5-dihydro-2H-pyridazin-3-one (**3**) as biologically active heterocyclic precursor . The hydrazide **9** could be prepared by regioselective *S*-alkylation[11] from **3** with ethyl chloroactetate to give the corresponding ester **4a**, which was subsequently hydrazinolyzed by hydrazine hydrate.

The acyl azide pathway is one of the first method developed for peptide coupling by Curtius.[13] Synthesis of the target amino acid derivatives **12a-h** were successfully obtained *via* the azide coupling method [1,11,12] which was reported to minimize the degree of racemization in amino acid coupling. The in situ generated azide **10** solution in ethyl acetate reacted with an amino acid methyl esters hydrochloride **11a-d** in the presence of triethyl amine to afford [2-(5-benzyl-4-phenyl-4H-[1,2,4]triazol-3-thio)-acetyl]-amino acid methyl esters **12a-d** in good to moderate yield. Also further development of the azide coupling was obtained by the synthesis of *N*-substituted dipeptide derivatives **16a-d**. Thus, boiling the amino acid ester derivatives **12b** (Gly) with hydrazine hydrate gave the acyl hydrazide **13**. Nitrosation of acyl hydrazide **13** finally gave the acyl azide **15** by treatment with $NaNO_2$ and HCl mixture. The *in situ* generated azide **15** in ethyl acetate reacted with amino acid methyl esters hydrochloride **15a-d** in the presence of triethyl amine produced dipeptide derivatives **16a-d** in reasonable yield (Scheme 2).



11, 12	R
a (L-Val)	$CH(CH_3)_2$
b Gly	H
c (L-Tyro)	
d (L-Leu)	$CH_2CH(CH_3)_2$

15, 16	n	R
a (Gly - Gly)	0	H
b (Gly- β Ala)	1	H
c (Gly - L-Val)	0	$CH(CH_3)_2$
d (Gly - L-Ser)	0	CH_2OH

Scheme 2

Antimicrobial studies

Antimicrobial activity of eighteen triazoles derivatives was assayed by the agar well diffusion method [(14)] against two bacterial colonies (*Escherechia coli* and *Bacillus subtilis*) and two fungal cultures (*Phytophthora infestans* and *Colletotricum gloeosporioides*). Five-millimeter diameter wells were cut out in agar plates using sterile cork-borer. 50 µl of (4 mg/ml) solution were transferred aseptically to the wells. Plates were incubated at 25 ºC for 24 hours and 4 days for bacteria and fungi respectively. Antimicrobial activity was evaluated by measuring the inhibition

zone formed around the wells. Wells containing sterile distilled water or the solvent (ethanol) were served as control.

The results showed that not all derivatives were active against the tested microorganisms (*E. coli*, *B. subtilis*, *P. infestans* and *C. gloeosporioides*). All studied compounds were not effective against *C. gloeosporioides*, and *P. infestans* (Table 1).

On the other hand, for bacteria, derivatives No. **5a** and **5c** inhibited the growth of the bacterium *B. subtilis*, while derivative No. **12c** was inhibitors to the growth of the bacterium *E. coli* .

Interaction of a compound or a group of compounds with biological system includes a wide spectrum of activity. One of these activities is the inhibition of the growth of microorganisms through different mechanisms. They could be physiological and/or biochemical mechanisms. Exploration of these mechanisms needs further investigations.

Table1. Antimicrobial activity of triazoles drivatives

Com. NO	antifungal		antibacterial	
	Phytophthora infestans	*Colletotricum gloeosporioides*	*Bacillus subtilis*	*Escherechia coli*
2	-	-	-	-
3	-	-	-	-
4a	-	-	-	-
4b	-	-	-	-
4c	-	-	-	-
5a	-	-	++	-
5b	-	-	-	-
5c	-	-	++	-
6a	-	-	-	-
6b	-	-	-	-
7a	-	-	-	-
8a	-	-	-	-
8b	-	-	-	-
9	-	-	-	-
12a	-	-	-	-
12b	-	-	-	-
12c	-	-	-	+
12d	-	-	-	-

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