The synthesis and modelling of the obtaining process of 1-[4'-(theophyllin-7-yl) sulfonyl – 2 – methyl – phenoxyacetyl] -3,5-dimethyl pyrazole

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Abstract

This paper presents the synthesis of 1-[4'-(theophyllin-7-yl) sulfonyl – 2 – methyl – phenoxyacetyl] - 3,5-dimethyl pyrazole starting from 2-methyl - 4- (theophyllin-7'-yl) sulfonyl - phenoxyacetyl hydrazide. To establish the reaction conditions it was used mathematical modelling.

Keywords: theophyllin, pyrazole, mathematical modelling

Introduction

Substituted pyrazoles are important synthetic targets because the pyrazole motif makes up the core structure of numerous biologically active compounds. They have applications as pharmaceuticals (analgesics, anti-inflamatory, anxiolitics, anti-bacterial, antidepressant, anticoagulants, canabinoid receptor ligands, antimicrobials), agrochemicals (insecticides, herbicides), dye stuff [1-8]. Various methods of synthesis of pyrazole are known and the most important involves the reaction between hydrazine derivatives with 1,3-difunctional compounds.

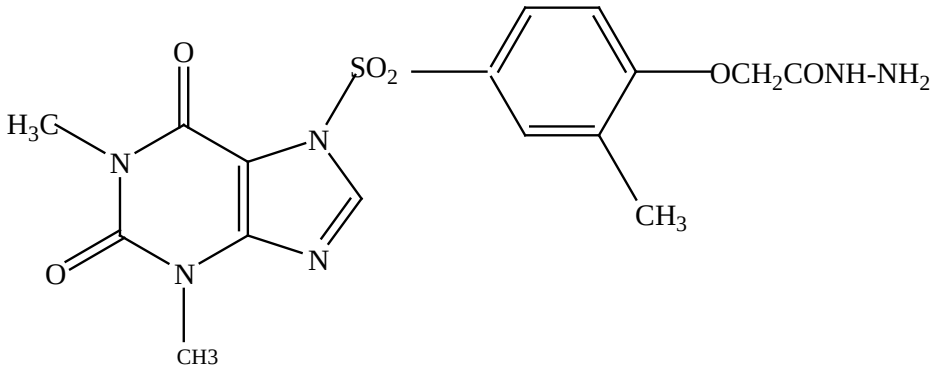
Materials and Methods

All solvents and chemicals used were provided by Merck's Chemical Co., Darmstadt, Germany. 2-methyl – 4 - (theophyllin-7'-yl) sulfonyl - phenoxyacetyl hydrazide was synthesized in accordance with the procedures from the literature. In the figure no. 1 it is stated the obtaining scheme for 1-[4'-(theophyllin-7-yl) sulfonyl – 2 – methyl – phenoxyacetyl] -3,5-dimethyl pyrazole.

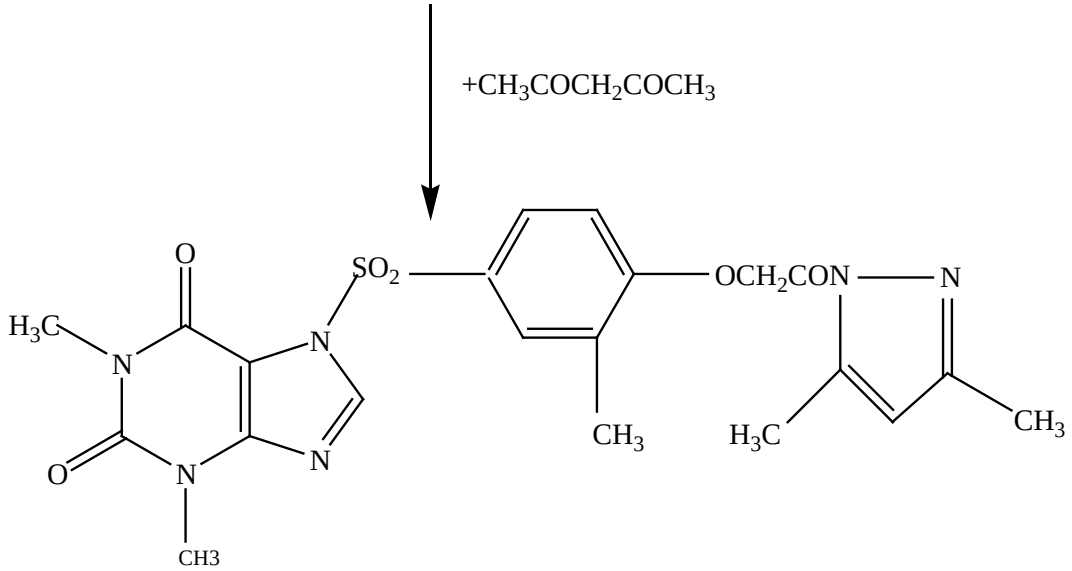
Melting points of synthesized compounds were determined in open capillaries and are uncorrected. IR (KBr) spectra were recorded on a DIGILAB SCIMITAR-SERIES spectrophotometer in the range 4000-400 cm^{-1}. ^{1}H-NMR spectra were recorded on a GEMINI 300A, 300MHz, using TMS as an internal standard (chemical shifts in δ ppm). The purities of the compounds were checked on silica gel coated Al plates (Merck) as adsorbent and UV light accomplished visualization.

The obtaining of 1-[4'-(theophyllin-7-yl) sulfonyl – 2 – methyl – phenoxyacetyl] - 3,5-dimethyl pyrazole: A mixture of 0.01 moles of 2-methyl – 4 - (theophyllin-7'-yl) sulfonyl - phenoxyacetyl hydrazide, 0.02 moles of acetylacetone and 0.1 ml aqueous HCl 10

% is warmed at reflux for 8 hours in 30 ml of ethanol: methylene chloride mixture (volumetric ratio 3:2). The formed precipitate, after cooling, is filtrated, is solved in acetone is treated with active charcoal in warm conditions and, after the filtration of exhausted charcoal and the cooling of solution, it precipitates 1-[4'- (theophyllin-7-yl) sulfonyl – 2 – methyl – phenoxyacetyl] -3,5-dimethyl pyrazole. There are obtained 3.68 g (η=76 %) with m. p. of 160°C. The obtained product with chemical formula $C_{21}H_{22}O_6N_6S$ is a substance which is white, crystalline, insoluble in water, ethyl acetate, chloroform, little soluble in warm conditions in alcohol, easy soluble in warm conditions in acetone, DMF and in cold conditions in DMSO; $N_{calculated}$ = 17.28 %, $N_{founded}$ = 17.20%; IR, υ cm $^{-1}$: 3092 (Ar-H), 1770, 1714, 1675 (C=O), 1602 (C=N pyrazole), 1504, 1454 (C-C); 1274, 1030 (C_{Ar}-O-C_{alif}), 1330, 1130 (N-SO_2);^{1}H-NMR (300 MHz, DMSO-d6, ppm): 8.73 (s, 1H, -N-**CH**-N-), 7.58 (d, 1H, SO_2-C-**CH**-CH-), 7.54 (s, 1H, SO_2-C-**CH**-C(CH_3)-), 6.91 (d, 1H, SO_2-C-CH-**CH**-), 5.80 (s,1H, -C-**CH**-C-), 4.89 (s, 2H, -O-**CH_2**-CO-), 3.30 (s, 3H, -N-**CH_3**), 2.93 (s, 3H, -N-**CH_3**), 2.41 (s, 3H, -CO-N-C(**CH_3**)-CH-), 2.21 (s, 3H, -C-**CH_3**), 2.19 (s, 3H, -CO-N-N-C(**CH_3**)-CH-) (Figure no. 2).



2-methyl - 4 - (theophyllin-7'-yl) sulfonyl - phenoxyacetyl hydrazide



1-[4'-(theophyllin-7-yl) sulfonyl - 2 - methyl - phenoxyacetyl] -3,5-dimethyl pyrazole

Figure 1. The obtaining of 1-[4'-(theophyllin-7-yl) sulfonyl – 2 – methyl – phenoxyacetyl] -3,5-dimethyl pyrazole

Results and Discussions

The establishment of the optimum conditions for the obtaining of 1-[4'- (theophyllin-7-yl) sulfonyl – 2 – methyl – phenoxyacetyl] -3,5-dimethyl pyrazole in accordance with the presented recipe was realized through empirical modelling.

We took into consideration for each considered parameter two levels of variability as presented in the table no. 1.

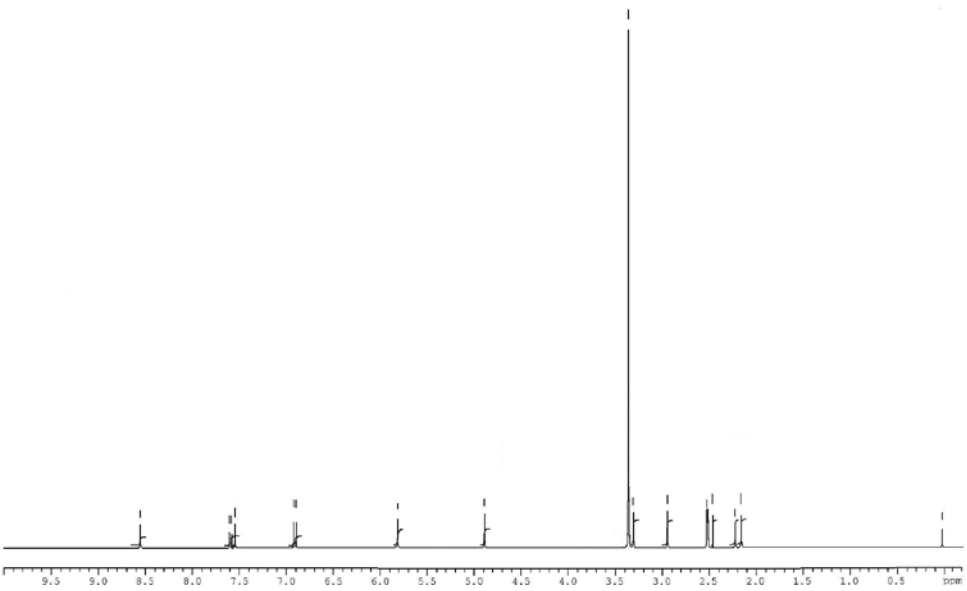


Figure 2. ^{1}H-RMN spectrum of 1-[4'-(theophyllin-7-yl) sulfonyl – 2 – methyl – phenoxyacetyl] -3,5-dimethyl pyrazole

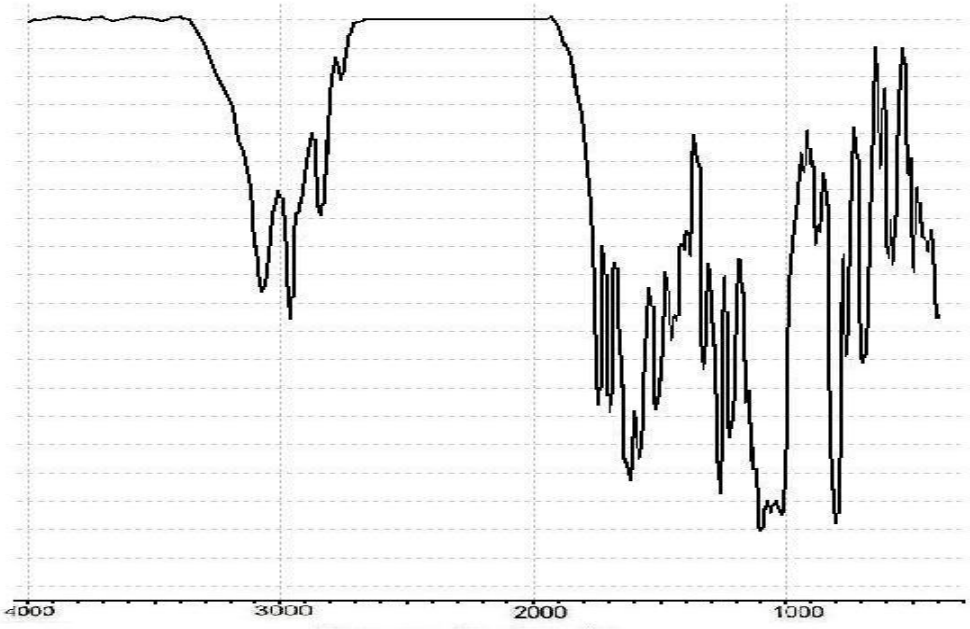


Figure 3. IR spectrum of 1-[4'-(theophyllin-7-yl) sulfonyl – 2 – methyl – phenoxyacetyl] -3,5-dimethyl pyrazole

Table 1. The considered parameters and their variability domain

Parameter	Reduced variable	Basic values (0)	Mimimum values (-1)	Maximum values (+1)	Step
Reaction time (h)	x_1	8	7	9	1
Acetylacetone: hydrazide reactants ratio	x_2	2:1	1.5:1	2.5:1	0.5
Ethanol: methylene chloride solvents ratio	x_3	1.5:1	1:1	2:1	0.5

The followed response function was represented by the pyrazole output. Into the parenthesis there are noticed the reduced values of the variable (table no.2).

Table 2. The values for reaction time, reactants ratio, solvents ratio and pyrazole output

Curr. No.	Reaction time (h)	Acetylacetone: hydrazide reactants ratio	Ethanol: methylene chloride solvents ratio	Pyrazole output %
	x_1	x_2	x_3	Y_1
1	-1 (7)	-1 (1.5:1)	-1 (1:1)	78.5
2			0 (1.5:1)	80.4
3			+1 (2:1)	81.2
4		0 (2:1)	-1 (1:1)	77.4
5			0 (1.5:1)	79.5
6			+1 (2:1)	82.3
7		+1 (2.5:1)	-1 (1:1)	78.7
8			0 (1.5:1)	80.9
9			+1 (2:1)	81.7
10	0 (8)	-1 (1.5:1)	-1 (1:1)	79.2
11			0 (1.5:1)	80.8
12			+1 (2:1)	81.5
13		0 (2:1)	-1 (1:1)	83.9
14			0 (1.5:1)	84.9
15			+1 (2:1)	84
16		+1 (2.5:1)	-1 (1:1)	83.7
17			0 (1.5:1)	84.1
18			+1 (2:1)	84.2
19	+1 (9)	-1 (1.5:1)	-1 (1:1)	83.8
20			0 (1.5:1)	82.7
21			+1 (2:1)	83.6
22		0 (2:1)	-1 (1:1)	84.3
23			0 (1.5:1)	84.5
24			+1 (2:1)	84.6
25		+1 (2.5:1)	-1 (1:1)	83.2
26			0 (1.5:1)	83.4
27			+1 (2:1)	83.5

For the calculation of the significance of the program performing we also realized three witness tests in the central point of the domain (0,0,0), thus obtaining the values presented in the table no. 3.

Table 3. The values in the central point of the domain

y_k^0	y_1^0	y_2^0	y_3^0
The value for the pyrazole output	84.7	84.9	84.8

To be able to elaborate the model of the regression function we determined the coefficients for the polynominal of the following type:

$$Y = a_0 + a_1 \cdot x_1 + a_2 \cdot x_2 + a_3 \cdot x_3 + a_{11} \cdot x_1^2 + a_{22} \cdot x_2^2 + a_{33} \cdot x_3^2 +$$

$$+a_{12} \cdot x_1 x_2 + a_{13} \cdot x_1 x_3 + a_{23} \cdot x_2 x_3 + a_{123} \cdot x_1 x_2 x_3$$

The values of the coefficients for the regression function are listed in the table no. 4.

Table 4. The values of the coefficients for the regression function.

Coefficients	Response function
	Y (output)
a_0	83.619
a_1	1.833
a_2	0.65
a_3	0.772
a_{11}	-1.022
a_{22}	-0.872
a_{33}	-0.172
a_{12}	-0.1
a_{13}	-0.85
a_{23}	-0.083
a_{123}	0.025

The form for the elaborated model will be:

$$Y = 83.619 + 1.833 \cdot x_1 + 0.65 \cdot x_2 + 0.772 \cdot x_3 - 1.022 \cdot x_1^2 - 0.872 \cdot x_2^2 - 0.172 \cdot x_3^2 -$$

$$- 0.1 \cdot x_1 \cdot x_2 - 0.85 \cdot x_1 \cdot x_3 - 0.083 \cdot x_2 \cdot x_3 + 0.025 \cdot x_1 \cdot x_2 \cdot x_3$$

Will be calculated the medium value of the three realized witness tests for the regression function (output) in the central point of the domain (0,0,0):

$$y_{med}^0 = \frac{\sum_{i=1}^{3} y_i^0}{3} = \frac{84.7 + 84.9 + 84.8}{3} = 84.8$$

We'll calculate the square of the medium error, knowing that the number of the test probes, *n*, is of 3, through the relation:

$$\varepsilon^2 = \sum_{i=1}^{n} \frac{\left(y_i^0 - y_{med}^0\right)^2}{n-1} = 0.01$$

It will be calculated the error for accomplishing the witness test:

$$\varepsilon = \sqrt{\varepsilon^2} = \sqrt{0.01} = 0.1$$

The determination of the coefficients significance will be realized with the help of the following equation, knowing that the number of experiments, *N*, is of 27:

$$S = \frac{\varepsilon}{\sqrt{N}} = \frac{0{,}1}{5.196} = 0.019$$

The significance of the coefficients will be tested with the help of the t-Student test using the relation:

$$t_j = \left|a_j\right| / S$$

The values of the t-Student test for each coefficient are presented in the table no. 5.

Table 5. The values of the t-Student test

t_j	t_0	t_1	t_2	t_3	t_{12}	t_{13}	t_{23}	t_{11}	t_{22}	t_{33}	t_{123}
Calculated value	4345	95.263	33.775	40.126	5.196	44.167	4.33	1.299	53.116	45.322	8.949

From the results of the t-Student test it is observed that the terms x_{12}, x_{23}, x_{33} and x_{123} could be eliminated.

The mathematic model which describes the response functions of the optimization criterion, after the elimination of the non-significant terms with the help of t-Student test, is as follows:

$$Y = 83.619 + 1.833 \cdot x_1 + 0.65 \cdot x_2 + 0.772 \cdot x_3 - 1.022 \cdot x_1^2 - 0.872 \cdot x_2^2 - 0.85 \cdot x_1 \cdot x_3$$

As follows we'll discuss the effects of the parameters. The a_0 value (83.619) shows that we have an optimum output for an appropriate level for this value.

The a_1, a_2 and a_3 coefficients being positives it results that x_1, x_2 and x_3 variables have an individual favourable action.

The coefficient of interaction a_{13} being negative we can conclude that x_1 and x_3, through their interaction, have an unfavourable effect to the process, with the same intensity as its interaction.

Since the individual effect of the x_{12}, x_{23}, x_{33} and x_{123} was determined through the t-Student test as being non-significant we won't discuss it.

Analyzing the quadratic coefficients a_{11} and a_{22} it results that response function is characterized through a maximum as reported to the variable x_1 and x_2.

For the response function obtained after the elimination of the non-significant terms with the help of t-Student test it will be calculated the partial derivative of 1st order as reported to each variable:

$$\frac{\partial y}{\partial x_1} = 1.833 - 0.85 \cdot x_3 - 2.044 \cdot x_1$$

$$\frac{\partial y}{\partial x_2} = 0.65 - 2 \cdot 0.872 \cdot x_2$$

$$\frac{\partial y}{\partial x_3} = 0.772 - 0.85 \cdot x_1$$

The obtained partial derivatives of 1st order are equalized with 0 and will be solved the linear system:

$$\begin{cases} 1.833 - 0.85 \cdot x_3 - 2.044 \cdot x_1 = 0 \\ 0.65 - 2 \cdot 0.872 \cdot x_2 = 0 \\ 0.772 - 0.85 \cdot x_1 = 0 \end{cases} \Rightarrow \begin{cases} x_1 = 0.91 \\ x_2 = 0.37 \\ x_3 = 0.98 \end{cases}$$

The optimum point to seek for (0.91; 0.37; 0.98) is represented in non-dimensional coordinates. As one can see the optimum values for x_1, x_2 and x_3 are framed in the admissible limits (-1, 1) initially established. Knowing the variation domains of the reaction time, of the acetylacetone:hydrazide reactants ratio and of ethanol:methylene chloride solvents ratio we'll obtain the real values of the optimum point using the following relations:

$$X_1 = \Delta X_1 \cdot x_1 + X_1^{med}$$
$$X_2 = \Delta X_2 \cdot x_2 + X_2^{med}$$
$$X_3 = \Delta X_3 \cdot x_3 + X_3^{med}$$

in which: X_1, X_2, X_3 – the real values of the optimum;

x_1, x_2, x_3 – the non-dimensional values of the optimum;

ΔX_1, ΔX_2, ΔX_3 – the step of each variation domain;

X_1^{med}, X_2^{med}, X_3^{med} – the real medium value of each parameter.

$$X_1 = 1 \cdot 0.91 + 8 = 8.91 \ h$$
$$X_2 = 0.5 \cdot 0.37 + 2 = 2.185$$
$$X_3 = 0.5 \cdot 0.98 + 1.5 = 1.99$$

The obtained models will be graphically represented as a function of two parameters, the other remaining constant at the value 0 which represents the centre of the variation domain. For Y will be three response surfaces characterized by the following mathematical models:

$x_1 = 0$	$Y = 83.619 + 0.65 \cdot x_2 + 0.772 \cdot x_3 - 0.872 \cdot x_2^2$
$x_2 = 0$	$Y = 83.619 + 1.833 \cdot x_1 + 0.772 \cdot x_3 - 1.022 \cdot x_1^2 - 0.85 \cdot x_1 \cdot x_3$
$x_3 = 0$	$Y = 83.619 + 1.833 \cdot x_1 + 0.65 \cdot x_2 - 1.022 \cdot x_1^2 - 0.872 \cdot x_2^2$

The graphics of these mathematical models are represented in the figures no. 4-6.
From the graphic representations are distinguishable the roundness of the surfaces, the minimum owned to the effects of quadratic coefficients as well as the inflexion point.

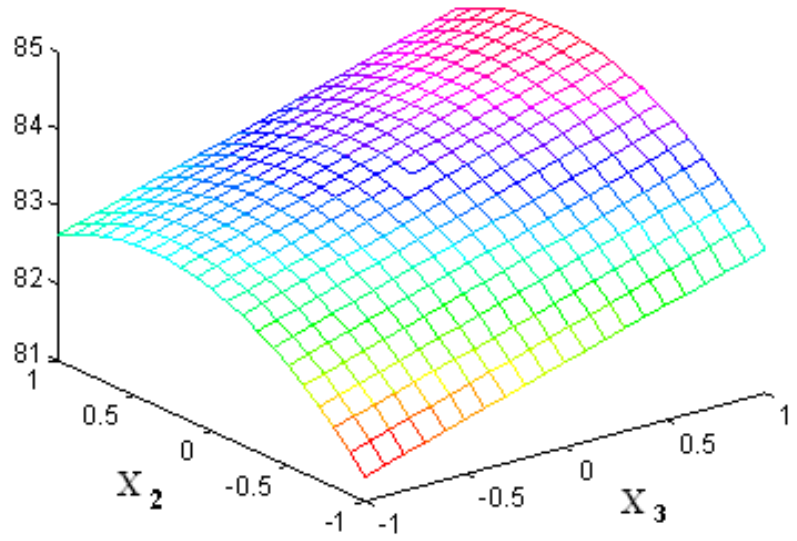


Figure 4. The influence of the reactants ratio acetylacetone: hydrazide and of the solvents ratio ethanol:methylene chloride on the pyrazole output when the reaction time is maintained in the centred domain

$$Y = 83.619 + 0.65 \cdot x_2 + 0.772 \cdot x_3 - 0.872 \cdot x_2^2$$

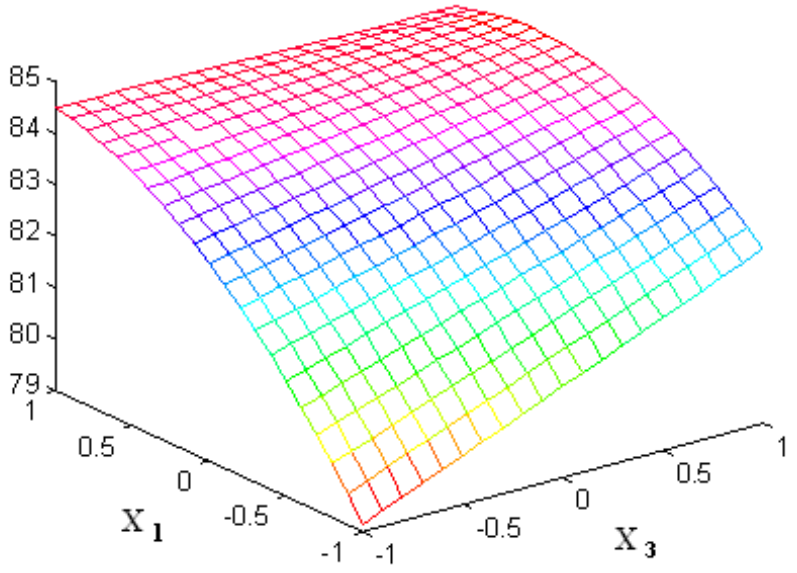


Figure 5. The influence of reaction time and of solvents ratio ethanol:methylene chloride on the pyrazole output when the reactants ratio acetylacetone: hydrazide is maintained in the centred domain

$$Y = 83.619 + 1.833 \cdot x_1 + 0.772 \cdot x_3 - 1.022 \cdot x_1^2 - 0.85 \cdot x_1 \cdot x_3$$

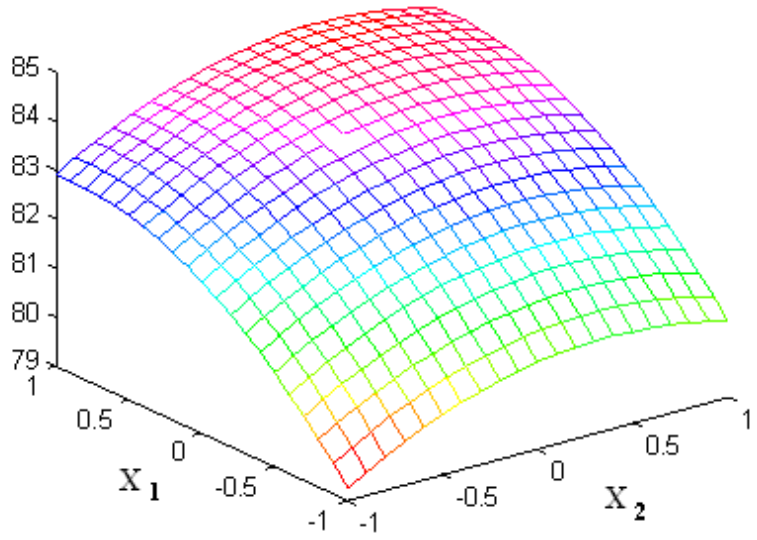


Figure 6. The influence of the reaction time and of the reactants ratio acetylacetone: hydrazide on the pyrazole output when the solvents ratio ethanol:methylene chloride is maintained in the centred domain

$$Y = 83.619 + 1.833 \cdot x_1 + 0.65 \cdot x_2 - 1.022 \cdot x_1^2 - 0.872 \cdot x_2^2$$

Conclusions

From the real values of the optimum we can observe the following:

- the optimum reaction time is of 8.91 hours;
- the optimum reactants ratio acetylacetone: hydrazide is of 2.185:1;
- the optimum solvents ratio ethanol:methylene chloride is of 1.99:1.

We can conclude that the obtaining output for the 1-[4'-(theophyllin-7-yl) sulfonyl – 2 – methyl – phenoxyacetyl] -3,5-dimethyl pyrazole tends toward optimum when all the considered variables remain in the limits of the variation domain initially established.

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