Roumanian Biotechnological Letters *Vol. 14, No. 3, 2009, pp. 4453-4459*

ORIGINAL PAPER

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

Received for publication, October 20, 2008
Accepted, May 15, 2009

ANGELA ANTOCHI[1], CORNELIU ONISCU[1], DENISA ILEANA NISTOR[2], DORU NECULAI MIRON[2]
[1]Technical University "Gh. Asachi" of Iasi, Faculty of Chemical Engineering, 71 D. Mangeron Blvd., 700050 Iasi, Romania
[2]University of Bacau, Faculty of Engineering, Department of Food Products Engineering, 157 Calea Marasesti, 600115, Bacau, Romania
Corresponding author: angelacostuleanu@yahoo.com

Abstract

We synthesized 1-[2'-(theophyllin-7-yl)sulfonyl-4-chlor-phenoxyacetyl]-3-methyl -5-pyrazolone starting from 4-chlor-2-(theophyllin-7'-yl)sulfonyl-phenoxyacetyl hydrazide. To establish the reaction conditions it was used a planned factorial experiment of 2nd order.

Keywords: theophyllin, pyrazolone, mathematical modelling

Introduction

Pyrazolones are an important class of compounds possessing a wide area of pharmacological properties as analgesic activities, antipyretics, disease-modifying antirheumatic drugs, antiarthritic activities, uricosuric activity and anti-inflammatory ones [1]. At the same time, they are useful intermediates for a series of industrial products as weed-killers, photographic colourings, liquid crystals and colourings [2-5].

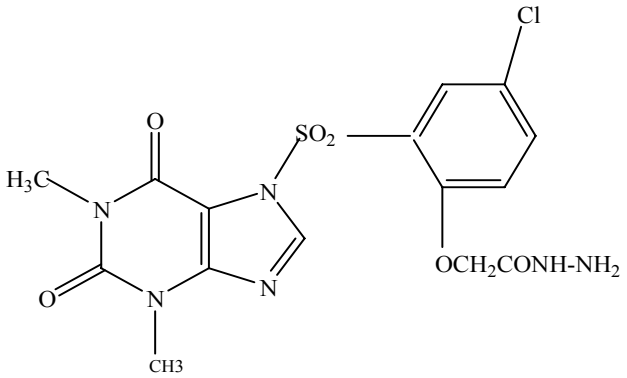
Materials and methods

All solvents and chemicals used were provided by Merck's Chemical Co., Darmstadt, Germany. 4-chlor-2-(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-[2'-(theophyllin-7-yl)sulfonyl-4-chlor-phenoxyacetyl]- 3-methyl -5-pyrazolone.

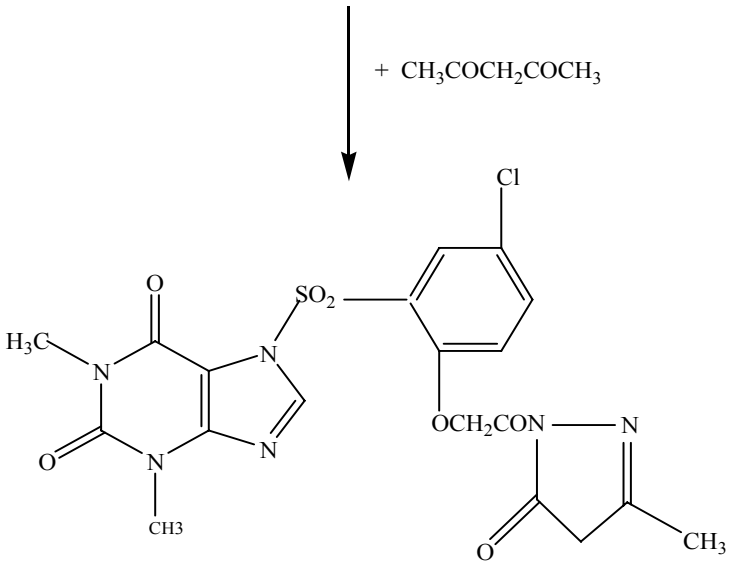
Melting points of synthesized compounds were determined in open capillaries and are uncorrected. IR (KBr) spectra were recorded on a DIGILAB SCIMITAR-SERIES spectrophotometer in the range 4000-400 cm^{-1}. ^{1}H-NMR spectra were recorded on a GEMINI 300A, 300MHz, using TMS as an internal standard (chemical 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-[2'-(theophyllin-7-yl)sulfonyl-4-chlor-phenoxyacetyl]- 3-methyl -5-pyrazolone: A mixture of 0.01 moles of 4-chlor-2-(theophyllin-7'-yl)sulfonyl-phenoxyacetyl hydrazide and 0.02 moles of ethyl acetoacetate is warmed at reflux for 18 hours in 30 ml of acetone. The formed precipitate, after cooling, is filtrated, is solved in DMF, is treated with active charcoal in warm conditions and, after the filtration of exhausted

charcoal and the cooling of solution, it precipitates 1-[2'-(theophyllin-7-yl)sulfonyl-4-chlor-phenoxyacetyl]-3-methyl-5-pyrazolone. There are obtained 4.29 g (η=85%) with m. p. of 228-230°C. The obtained product with chemical formula $C_{19}H_{17}O_7N_6ClS$ is a substance which is white, crystalline, insoluble in water, acetone, ethyl acetate, chloroform, little soluble in warm conditions in alcohol, easy soluble in warm conditions in DMF and in cold conditions in DMSO; $N_{calculated}$ = 16.52%, $N_{founded}$ = 16.48%; IR, υ cm $^{-1}$: 3050 (Ar-H), 1714,1685, 1650 (C=O), 1600 (C=N), 1282, 1012 (C_{Ar}-O-C_{alif}), 1330, 1130 (-N-SO_2),1529, 1483, 1436 (C-C); ^{1}H-NMR (300 MHz, DMSO-d6, ppm): 10.2 (s, 1H, from tautomer form OH-pyrazolone), 8.53 (s, 1H, -N-**CH**-N-), 7.83 (s, 1H, SO_2-C-**CH**-C(Cl)-), 7.42 (d, 1H, -C(Cl)-**CH**-CH-), 7.33 (d, 1H, -C(Cl)-CH-**CH**-), 7.22 (s, 1H, -C-**CH_2**-C-), 4.98 (s, 2H, -O-**CH_2**-CO-), 3.29 (s, 3H, -N-**CH_3**), 2.89 (s, 3H, -N-**CH_3**), 2.55 (s, 3H, -CO-N-N-C(**CH_3**)-CH-) (figure no. 2 and figure no. 3).



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



1-[2'-(theophyllin-7-yl)sulfonyl-4-chlor-phenoxyacetyl]- 3-methyl -5-pyrazolone

Fig. 1. The obtaining of 1-[2'-(theophyllin-7-yl)sulfonyl-4-chlor-phenoxyacetyl]-3-methyl-5-pyrazolone.

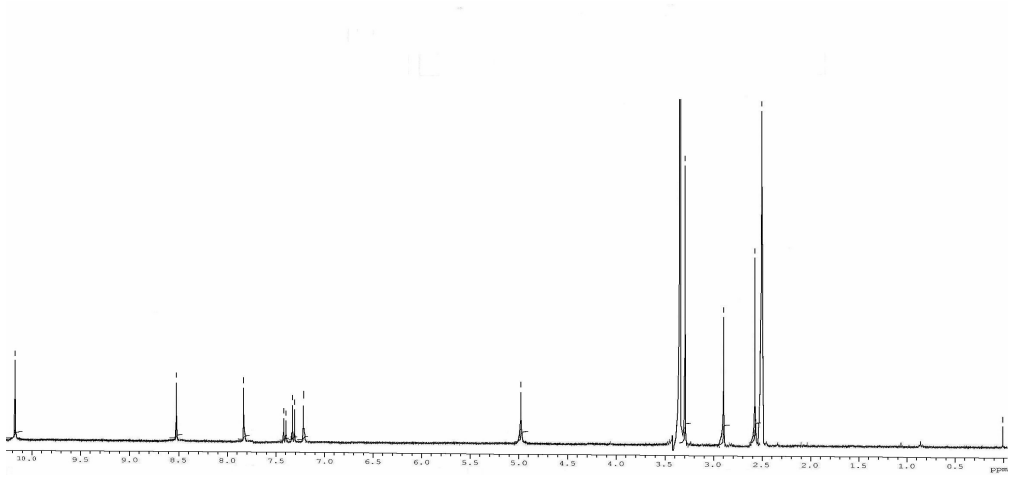


Fig. 2. [1]H-RMN spectrum of 1-[2'-(theophyllin-7-yl)sulfonyl-4-chlor-phenoxyacetyl]-3-methyl-5-pyrazolone.

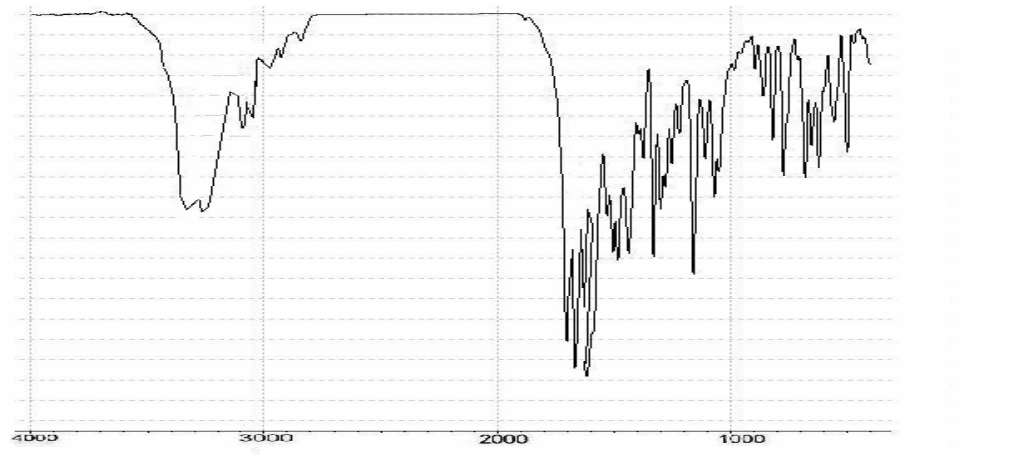


Fig. 3. IR spectrum of 1-[2'-(theophyllin-7-yl)sulfonyl-4-chlor-phenoxyacetyl]-3-methyl-5-pyrazolone.

Results and discussions

The establishment of the optimum conditions for the obtaining of 1-[2'-(theophyllin-7-yl)sulfonyl-4-chlor-phenoxyacetyl]-3-methyl-5-pyrazolone 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 1.

Parameter	Reduced variable	Basic values (0)	Mimimum values (-1)	Maximum values (+1)	Step
Reaction time (h)	x_1	18	17	19	1
Hydrazide: ethyl acetoacetate reactants ratio	x_2	1:2	1:1.5	1:2.5	0.5

Table 1. The considered parameters and their variability domain.

The followed response function was represented by the pyrazolone output. Into the parenthesis there are noticed the reduced values of the variable (table 2).

Curr. No.	Reaction time (h)	Hydrazide: ethyl acetoacetate reactant ratio	Pyrazolone output %
	x_1	x_2	Y
1	-1 (17)	-1 (1:1.5)	75.3
2		0 (1:2)	77.4
3		+1 (1:2,5)	77.1
4	0 (18)	-1 (1:1.5)	75.6
5		0 (1:2)	85.9
6		+1 (1:2.5)	84.3
7	+1 (19)	-1 (1:1.5)	83.1
8		0 (1:2)	84.1
9		+1 (1:2.5)	83.9

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

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), thus obtaining the values presented in the table 3.

y_k^0	y_1^0	y_2^0	y_3^0
The value for the pyrazolone output	85.6	85.9	85.8

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

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

$$Y = a_o + a_1 \cdot x_1 + a_2 \cdot x_2 + a_{12} \cdot x_1 \cdot x_2 + a_{11} \cdot x_1^2 + a_{22} \cdot x_2^2$$

The values of the coefficients for the regression function are listed in the table 4.

Coefficients	Response function
	Y (output)
a_0	83.656
a_1	1.833
a_2	3.55
a_{12}	- 0.25
a_{11}	- 2.583
a_{22}	- 1.783

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

The form for the elaborated model will be:

$$Y = 83.656 + 1.833 \cdot x_1 + 3.55 \cdot x_2 - 0.25 \cdot \cdot x_1 \cdot x_2 - 2.583 \cdot x_1^2 - 1.783 \cdot x_2^2$$

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):

$$y_{med}^0 = \frac{\sum_{i=1}^{3} y_i^0}{3} = \frac{85.6 + 85.9 + 85.8}{3} = 85.767$$

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

$$\varepsilon^2 = \sum_{i=1}^{n} \frac{\left(y_i^0 - y_{med}^0\right)^2}{n-1} = 0.023$$

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

$$\varepsilon = \sqrt{\varepsilon^2} = \sqrt{0.023} = 0.153$$

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 9:

$$S = \frac{\varepsilon}{\sqrt{N}} = \frac{0.153}{3} = 0.051$$

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. From the results of t-Student test it is observed that the term x_{12} 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,

t_i	t_0	t_1	t_2	t_{12}	t_{11}	t_{22}
Calculated value	1643	36.988	69.721	4.91	50.736	35.024

Table 5. The values of the t-Student test

is as follows: $$Y = 83.656 + 1.833 \cdot x_1 + 3.55 \cdot x_2 - 2.583 \cdot x_1^2 - 1.783 \cdot x_2^2$$

As follows we'll discuss the effects of the parameters. The a_0 value (83.656) shows that we have an optimum output for an appropriate level for this value.

The a_1 and a_2 coefficients being positives it results that x_1 and x_2 variables have an individual favourable action.Since the individual effect of the x_{12} 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:

$$\frac{\partial y}{\partial x_1} = 1.833 - 2 \cdot 2.583 \cdot x_1$$

$$\frac{\partial y}{\partial x_2} = 3.55 - 2 \cdot 1.783 \cdot x_2$$

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

$$\begin{cases} 1.833 - 2 \cdot 2.583 \cdot x_1 = 0 \\ 3.55 - 2 \cdot 1.783 \cdot x_2 = 0 \end{cases} \Rightarrow \begin{cases} x_1 = 0.35 \\ x_2 = 0.99 \end{cases}$$

The optimum point to seek for (0.35; 0.99) is represented in non-dimensional coordinates. As one can see the optimum values for x_1 and x_2 are framed in the admissible limits (-1, 1) initially established. Knowing the variation domains of the reaction time and of the hydrazide:ethyl acetoacetate reactants ratio we'll obtain the real values of the optimum point using the following relations:

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

in which: X_1, X_2 – the real values of the optimum;
x_1, x_2 – the non-dimensional values of the optimum;
ΔX_1, ΔX_2 – the step of each variation domain;
X_1^{med}, X_2^{med} – the real medium value of each parameter.

$$X_1 = 1 \cdot 0.35 + 18 = 18.35 \ \ h$$
$$X_2 = 0.5 \cdot 0.99 + 2 = 2.49$$

As following this study we established the dependence of the pyrazolone output as a function of the two factors, respectively the reaction time and the hydrazide:ethyl acetoacetate ratio, this dependence being illustrated by the response curve presented in the figure no. 4.

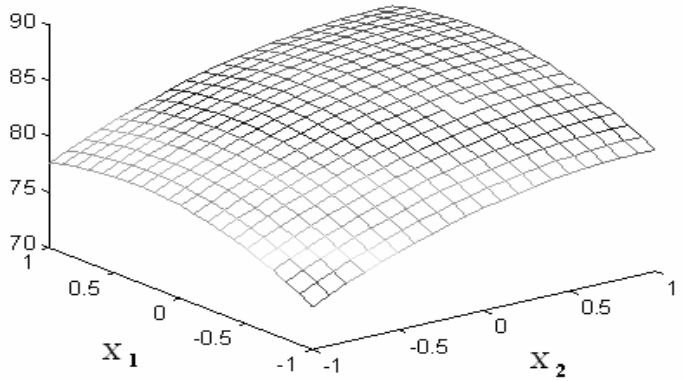


Fig.4. The influence of the reaction time and of the hydrazide:ethyl acetoacetate ratio on the pyrazolone output,
$Y = 83.656 + 1.833 \cdot x_1 + 3.55 \cdot x_2 - 2.583 \cdot x_1^2 - 1.783 \cdot x_2^2$

From the illustrated graphic we can observe the roundness of the surfaces, the maximum owned to the effects of quadratic coefficients as well as the inflexion point.

Conclusions

From the real values of the optimum we can obtain the following observations:

- The optimum reaction time is 18.35 hours;
- The optimum ratio of the reactants hydrazide and ethyl acetoacetate is of 1/2.49.

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

References

1. HUKKI J., LAITINEN P., ALBERTY J.E., Pharm. Acta Helv., 43, 704-712, 1968.
2. PLATH P., ROHR W., WUERZER N. (BASF A-G).Ger Offen, 42,pp; Appl. DE 79-2920933, 19790523,1980.
3. KENDALL J.D., DUFFIN G.F, US Patent, 2688, 548, 1954.
4. CATIVIELA C., SERRANO J.L., ZURBANO M.M., J.Org.Chem., 60, 3074-3083, 1995.
5. SUGIURA S., OHNO S., OHTANI O., IZUMI K., KITAMIKADO T., ASAI H., KATO K., HORI M., FUJIMURA H., J. Med. Chem., 20, 80 – 85, 1977.
6. JUNG J.C., WATKINS E.B., AVERY M.A., Synth. Commun., 32, 24, 2002.
7. DINOIU V., LU JM., J. Serb.Chem.Soc., 71(4), 323-330, 2006.
8. KOREBAK., WIETRZYYK J., OPOLSKI A., Acta Poloniae Pharm.- Drug Res., 63(3), 189-194, 2006.
9. HAVALDAR F.H., PATIL A.R., Eur.J. of Chem., 5(2), 347 – 354, 2008.
10.NISTOR I.D., AZZOUZ A., MIRON N.D., The Engineering of Chemical and Biochemical Processes, Technical Publ. H. – Info, Chisinau, 2006.
11. DUMITRASCU A., ONISCU C., Roum Biotechnol Lett, 11(3), 2767, 2006.