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OPTIMIZATION OF THE SYNTHESIS REACTIONS OF SOME NEW THIOSEMICARBAZIDES DERIVED FROM 5-NITROINDAZOLE

BY

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Abstract. New thiosemicarbazides derived from 5-nitroindazole with biological activity were synthesised. The 5-nitroindazol-1-yl formylhydrazide was treated with various aromatic isothiocyanates in order to obtain new thiosemicarbazides. The conditions in which the reactions take place with the highest yield were established. The optimization reactions were realized in a 3^2 factorial experiment. Some physico-chemical properties of the new synthesized compounds were theoretically established by using HyperChem 8.6.0. The chemical structure of the new synthesized compounds was confirmed by elemental and spectral analysis (FT-IR, ^{1}H-NMR). The new compounds were tested from the toxicity point of view.

Keywords: 5-nitroindazole derivatives; elemental and spectral analyses; factorial experiment for optimization; QSAR parameters.

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1. Introduction

The observation that compounds like thiosemicarbazides have an essential role in the structure and function of certain molecules of importance from a biological point of view, was only the begining for the search of such compounds with significant pharmacological application.

The various references seem to indicate that indazole molecule has a wide range of biological properties, like hepatoprotective (Berhe *et al*., 2010), anti-angiogenic (Huang *et al*., 2010), anti-inflamatory and analgesic (Ribeira *et al*., 2010), antibacterial (Rodriquez *et al*., 2009), citostatic (Yakaiah *et al*., 2007) as well as tuberculostatic (Cheptea *et al*., 2009) activity.

The research showed the importance of the thiosemicarbazides in the composition of drugs with antibacterial (Plech *et al*., 2011; Liesen *et al*., 2010; Shelke *et al*., 2010; Bhat *et al*., 2009), tuberculostatic (Moise *et al*., 2009; Bukovski *et al*., 1998; Ulusoy, 2002), antifungal (Fahmy, 2001) and cytostatic (Seleeman *et al*., 2005; El-Asmy *et al*., 2009) activities.

The aim of this study was to establish the most convenient conditions for synthesis reaction in factorial experiments with temperature and time of reactions considered as relevant variable and to perform a quantum mechanical characterization for the new compounds.

Some physico-chemical properties of the new thiosemicarbazides derived from 5-nitroindazole were theoretically estimated by using HyperChem 8.0.6 program (www.hyperchem.com). The toxicity potential of the obtained compounds was experimentally determined.

2. Experimental

2.1. Materials and Method

All reagents were used as purchased (Sigma-Aldrich, Merk, Fluka, S.C. Chemical Company SA). FT-IR spectra were recording using a FT-IR spectrophotometer (ATR) Brucker Tensor-27; ^{1}H-NMR analysis was performed on a Brucker ARX400 spectrometer (5 mm QNP probe; 1H/13C/31P/19F) and elemental analysis – on an Exeter Analytical CE 440 elemental analyser. The melting points of the obtained compounds were determined with a Mel-Temp melting point module, provided with a digital thermometer.

2.2. Synthesis of 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-arillhydrazincarbothioamide (III-VIII)

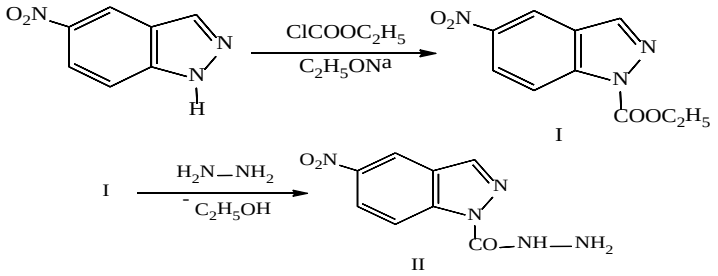
In a flask equipped with ascending refrigerator, in 100 mL absolute methyl alcohol 0.005 moles hydrazide are introduced. The resulting solution is mildly heating and stirring until becomes clear. In the next step, 0.005 moles different

isothiocyanates in 5 mL absolute methyl alcohol are added. The mixture was refluxed on water bath for 3 h separating an abundant precipitate. This was filtered in vacuum, was dried and finally purified by recrystalization from methyl alcohol.

3. Results and Discussions

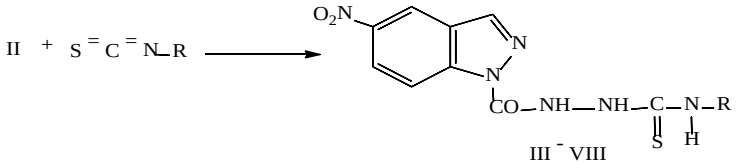
The synthesis of the new compounds was performed in several steps. In the first step, the ethyl ester of 5-nitroindazol-1'-il-formic acid was prepared through condensation of 5-nitroindazole with ethyl chloroformate, in the presence of sodium ethoxide, on refluxing in absolute ethyl alcohol.

In the next step, by treating the ester (I) with hydrazine hydrate 98% solution in anhydrous ethanol, the hydrazide of the 5-nitroindazol-formic acid (II) was obtained like a crystalline product after recrystallization from ethyl alcohol (Cigu *et al*., 2014) (Scheme 1).



Scheme 1 – Synthesis of the hydrazide of the 5-nitroindazolyl-1-yl-formic acid (II).

Further, the 5-nitro-1H-indazol-1-carboxhydrazide (II) was treated with phenyl-, p-tolyl, p-metoxyphenyl, p-bromophenyl, p-chlorophenyl- and p-iodophenyl-isothiocyanate in absolute ethyl alcohol on reflux for two hours, leading to new 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-arilhydrazincarbothioamide (thiosemicarbazides) (III – VIII) (Scheme 2).



III - VIII

III R = - C_6H_5
IV R = - C_6H_4 - CH_3
V R = - C_6H_4 - OCH_3
VI R = - C_6H_4 - Br(p)
VII R = - C_6H_4 - Cl(p)
VIII R = - C_6H_4 - I(p)

Scheme 2 – Synthesis of the new thiosemicarbazides (III-VIII).

3.1. Mathematical Modeling of Optimization Reactions

A 3^2 factorial experiment (Fisher, 1996; Azzouz, 1998) was organized for each reaction. The chemical reactions were made in a short variation domain of relevant variables in order to estimate the maximum of the reaction yield. Two relevant variables – temperature and reaction time – were considered being significant for the reaction yield (Table 1).

The real and the a-dimensional relevant coordinates are listed in Table 1 in which the measured yields in factorial experiments are also listed.

Table 1
Real (X_1, X_2) and a-Dimensional (x_1, x_2) Variables and Reaction Yield (η) in 3^2 Factorial Experiments

x_1 (X_1 °C)	x_2 (X_2 min)	η_{III} [%]	η_{IV} [%]	η_{V} [%]	η_{VI} [%]	η_{VII} [%]	η_{VIII} [%]
-1 (55)	-1(105)	79	82	75	74	76	78
-1 (55)	0 (120)	81	84	77	80	81	80
-1 (55)	1 (135)	80	83	74	78	77	79
0 (60)	-1 (105)	79	84	77	78	78	79
0 (60)	0 (120)	83	87	79	81	82	83
0 (60)	1 (135)	82	85	78	79	79	80
1 (65)	-1 (105)	80	83	76	75	78	78
1 (65)	0 (120)	82	86	78	80	81	82
1 (65)	1 (135)	81	84	77	79	79	80

The dependence of the reaction yield on the a-dimensional variables x_1 and x_2 was considered of the type:

$$\eta = a_0 + a_1 x_1 + a_2 x_2 + a_{12} x_1 x_2 + a_{11} x_1^2 + a_{22} x_2^2 \quad (1)$$

The coefficients a_0, a_1....a_{22} of Eq. (1) for each compound, obtained by statistical method (Moise *et al*., 2010; Hurjui *et al*., 2012), are listed in Table 2.

Table 2
Regression Coefficients in Reaction (1) Obtained in Factorial Experiments

Compound	a_0	a_1	a_2	a_{12}	a_{11}	a_{22}
III	82.56	0.50	0.83	0	-0.83	-1.84
IV	86.78	0.67	0.50	0	-1.67	-2.17
V	79.11	0.83	0.17	0.50	-1.83	-1.83
VI	81.40	0.33	1.67	0	-1.67	-3.14
VII	81.66	0.55	0.48	0	-0.95	-2.95
VIII	82.27	0.32	0.58	0.18	-1.15	-2.25

The conditions for extremum values of the yield:

$$\frac{\partial \eta}{\partial x_1} = 0 \quad \text{and} \quad \frac{\partial \eta}{\partial x_2} = 0 \tag{2}$$

were used in order to determine the coordinates (x_{1e}, x_{2e}) corresponding to the extremum of the reaction yield. The sign minus of the coefficients a_{11} and a_{22} in Table 2 shows that the obtained extremum is a maximum (Cheptea *et al*., 2012).

The absolute values of the determined coefficients listed in Table 1 provide information on the intensity of individual effects (coefficients a_1 and a_2) or on the combined effects (a_{12}), of the temperature (x_1) and reaction time (x_2).

The signs (+) or (-) indicate if the variable which multiplies the corresponding coefficient favors or does not favor, respectively, the result of the chemical reaction. In order to determine the accuracy *P* of the experiments, new measurements were made in the center of the small range (Table 3) in which the maxima appeared.

Table 3
Reaction Yield η_c in Central Range of the 3^2 – Factorial Experiments and Accuracy (P, [%]) *of Determinations*

Compound	η_{c1} [%]	η_{c2} [%]	η_{c3} [%]	η_c [%]	P [%]
III	83.5	84.0	83.6	83.7	8.8
IV	87.7	88.0	87.8	87.8	7.5
V	78.7	79.0	78.9	78.9	5.2
VI	81.3	81.5	81.7	81.5	7.1
VII	81.5	81.7	81.8	81.7	5.2
VIII	82.5	82.3	82.20	82.3	5.2

t – Student parameters for the organized experiments were computed by using relation (3).

$$t_j = \frac{|a_j|}{P} \tag{3}$$

The values of the *t*-student parameters listed in the Table 4 attest the significance of the values of the yield in the organized experiments.

Table 4
t-Student Coefficients Obtained in Factorial Experiments for Obtaining the Studied Compounds

Compound	t_j – Student coefficients					
	a_0	a_1	a_2	a_{12}	a_{11}	a_{22}
III	938.20	5.68	9.43	0	9.43	20.91
IV	1157.07	8.93	6.67	0	22.27	28.93
V	1521.35	15.96	3.27	9,62	35.19	35.19
VI	1146.48	4.65	23.52	0	23.52	44.23
VII	1570.38	10.58	9.23	0	18.27	56.73
VIII	1582.11	6.15	11.15	3,46	22.12	43.27

The relations in which the reaction yield is expressed by relevant variables and by their products are the following:

$$\eta_{\mathrm{III}} = 82.56 + 0.50x_1 + 0.83x_2 + 0x_1x_2 - 0.83x_1^2 - 1.84x_2^2 \quad (4)$$

$$\eta_{\mathrm{IV}} = 86.78 + 0.67x_1 + 0.50x_2 + 0x_1x_2 - 1.67x_1^2 - 2.17x_2^2 \quad (5)$$

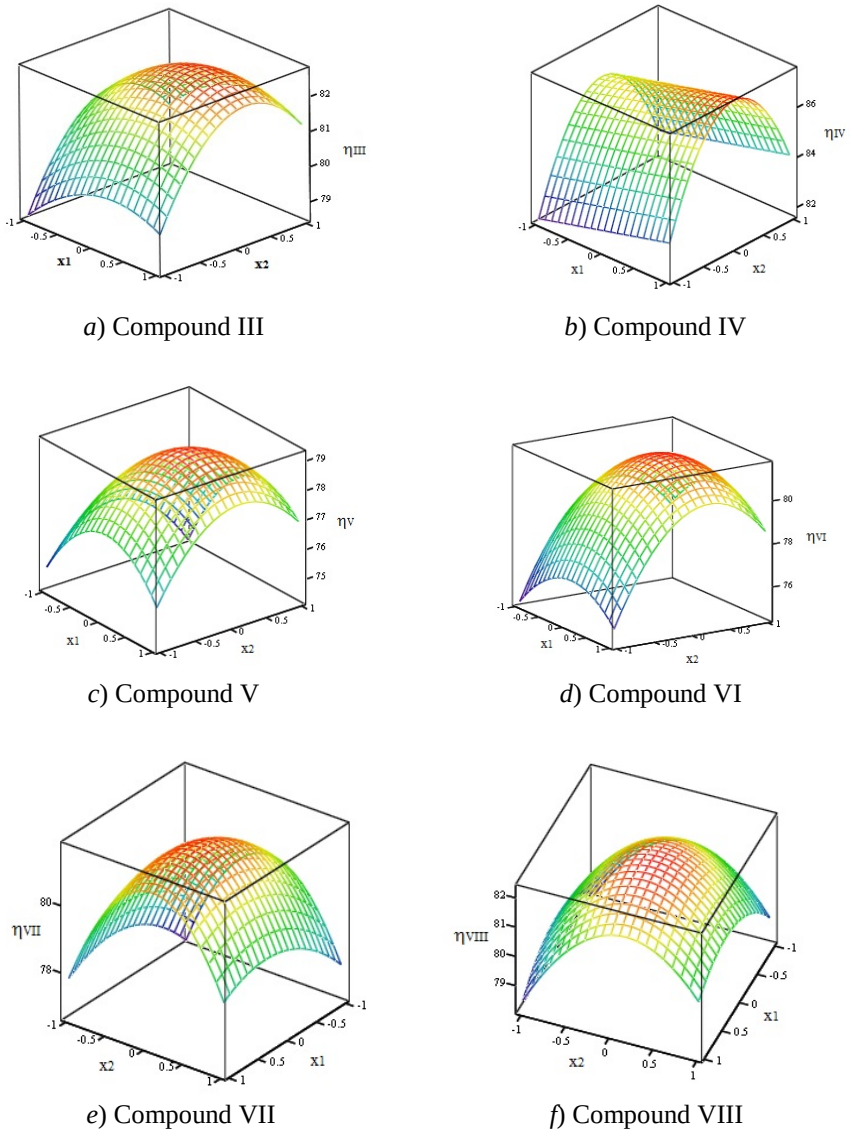
$$\eta_{\mathrm{V}} = 79.11 + 0.83x_1 + 0.17x_2 + 0.50x_1x_2 - 1.83x_1^2 - 1.83x_2^2 \quad (6)$$

$$\eta_{\mathrm{VI}} = 81.40 + 0.33x_1 + 1.67x_2 + 0x_1x_2 - 1.67x_1^2 - 3.14x_2^2 \quad (7)$$

$$\eta_{\mathrm{VII}} = 81.66 + 0.55x_1 + 0.48x_2 + 0x_1x_2 - 0.95x_1^2 - 2.95x_2^2 \quad (8)$$

$$\eta_{\mathrm{VIII}} = 82.27 + 0.32x_1 + 0.58x_2 + 0.18x_1x_2 - 1.15x_1^2 - 2.25x_2^2 \quad (9)$$

The dependences of the reaction yield of the compounds III-VIII on the relevant variables are illustrated in Figs. 1 *a-f*. In this figures the *a*-dimensional variables x_1 and x_2 vary between [-1, +1].



a) Compound III *b*) Compound IV

c) Compound V *d*) Compound VI

e) Compound VII *f*) Compound VIII

Fig. 1 – Three dimensional representation of the compounds III-VIII reaction yield *vs.* the adimensional temperature and time of the chemical reaction.

3.2. Elemental and Spectral Analysis

The structure of compounds III – VIII was confirmed by the results of elemental and spectral (FT-IR, ^{1}H-NMR) analyses.

Synthesis of 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-phenylhydrazincarbothioamide (III)

White yellowish solid, yield 81%, m.p.=158 – 160ºC, M=356

Anal. calc. for $C_{15}H_{12}N_6O_3S$; C% 50.56; H% 3.37; N% 23.59; S% 8.98. Found: C% 50.71; H% 3.59; N% 23.76; S% 9.12.

IR (ν, cm^{-1}): 3091 (NH); 1611 (CO); 747 (CHAr); 1129 (C=S); 1331 (NO_2 sym.); 1536 (NO_2 asym.).

^{1}H-NMR (DMSO-d6, 400 MHz), δ (ppm): 7.17-7.19 (d, 1H, CHAr); 7.33-7.40 (m, 4H, CHAr); 7.70-7.74 (d, 1H, CHAr); 8.03-8.05 (d, 1H, CHAr); 8.21 (S, 1H, CHAr); 8.39 (s, 1H, CHAr); 9.69-9.73 (d, 2H, NH); 10.50-10.57 (d, 1H, NH).

Synthesis of 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-(p-tolyl)-hydrazin carbothioamide (IV)

White solid, yield 86 %, m.p.=159 – 161ºC, M=370

Anal. calc. for $C_{16}H_{14}N_6O_3S$; C% 51.89; H% 3.78; N% 22.70; S% 8.64. Found: C% 52.08; H% 3.99; N% 22.92; S% 8.89.

IR (ν, cm^{-1}): 3093 (NH); 1698 (CO); 753, 789 (CHAr); 1231 (C=S); 1346 (NO_2 sym.); 1529 (NO_2 asym.).

^{1}H-NMR (DMSO-d_6, 400 MHz), δ (ppm): 2.32 (s, 3H, CH_3); 7.19-7.21 (d, 2H, CHAr); 7.27-7.29 (d, 2H, CHAr); 7.83-7.85 (d, 1H, CHAr); 8.34-8.36 (d, 1H, CHAr); 8.47 (s, 1H, CHAr); 8.90 (s, 1H, CHAr); 9.73-9.76 (d, 2H, NH); 10.52-10.58 (d, 1H, NH).

Synthesis of 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-(p-metoxiyphenyl)-hydrazincarbothioamide (V)

White solid, yield 78%, m.p.=206 – 208ºC, M=386

Anal. calc. for $C_{16}H_{14}N_6O_4S$; C% 49.74; H% 3.62; N% 21.76; S% 8.29. Found: C% 49.88; H% 3.93; N% 21.96; S% 8.58.

IR (ν, cm^{-1}): 3108 (NH); 1627 (CO); 756 (CHAr); 1253 (C=S); 1347 (NO_2 sym.); 1541 (NO_2 asym.).

^{1}H-NMR (DMSO-d6, 400 MHz), δ (ppm): 3.29 (s, 3H, OCH_3); 6.88-6.91 (d, 2H, CHAr); 7.21-7.23 (d, 2H, CHAr); 7.74-7.77 (d, 1H, CHAr); 8.24-8.27 (d, 1H, CHAr); 8.40 (s, 1H, CHAr); 8.89 (s, 1H, CHAr); 9.59-9.62 (d, 2H, NH); 10.39 (s, 1H, NH).

Synthesis of 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-(p-bromophenyl)-hydrazincarbothioamide (VI)

White solid, yield 80%, m.p.=146 – 148ºC. M=435

Anal. calc. for $C_{15}H_{11}BrN_6O_3S$; C% 41.37; H% 2.52; Br% 18.36; N% 19.31; S% 7.35. Found: C% 41.52; H% 2.85; Br% 18.55; N% 19.53; S% 7.66.

IR (ν, cm^{-1}): 3049 (NH); 1622 (CO); 751 (CHAr); 1255 (C=S); 1352 (NO_2 sym.); 1539 (NO_2 asym.); 628 (C-Br).

^{1}H-NMR (DMSO-d6, 400 MHz), δ (ppm): 7.46-7.49 (d, 2H, CHAr); 7.59-7.62 (d, 2H, CHAr); 7.84-7.86 (d, 1H, CHAr); 8.28-8.30 (d, 1H, CHAr); 8.47 (s, 1H, CHAr); 8.83 (s, 1H, CHAr); 9.89-9.95 (d, 2H, NH); 10.60 (s, 1H, NH).

Synthesis of 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-(p-chlorophenyl)-hydrazincarbothioamide (VII)

White solid, yield 81%, m.p.=200 – 202ºC, M=391

Anal. calc. for $C_{15}H_{11}ClN_6O_3S$; C% 46.03; H% 2.81; Cl% 9.07; N% 21.48; S% 8.18. Found: C% 46.17; H% 3.11; Cl% 9.26; N% 21.72; S% 8.43.

IR (ν, cm^{-1}): 3127 (NH); 1628 (CO); 754 (CHAr); 1252 (C=S); 1341 (NO_2 sym.); 1530 (NO_2 asym.); 667, 727 (C-Cl).

^{1}H-NMR (DMSO-d6, 400 MHz), δ (ppm): 7.41-7.46 (m, 4H, CHAr); 7.70-7.73 (d, 1H, CHAr); 8.41 (s, 2H, CHAr); 8.54 (s, 1H, CHAr); 9.76-9.79 (d, 2H, NH); 10.49 (s, 1H, NH).

Synthesis of 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-(p-iodophenyl)-hydrazincarbothioamide (VIII)

White solid, yield 82%, m.p.=172 – 174ºC, M=482

Anal. calc. for $C_{15}H_{11}IN_6O_3S$; C% 37.34; H% 2.28; I% 26.32; N% 17.42; S% 6.63. Found: C% 37.53; H% 2.52; I% 26.65; N% 17.66; S% 6.87.

IR (ν, cm^{-1}): 3117 (NH); 1616 (CO); 1229 (C=S); 1333 (NO_2 sym.); 1519 (NO_2 asym.); 788 cm^{-1} disubstituted aromatic ring, 623 (C-I).

^{1}H-NMR (DMSO-d6, 400 MHz), δ (ppm): 7.39-7.41 (m, 4H, CHAr); 7.67-7.71 (d, 1H, CHAr); 8.37 (s, 2H, CHAr); 8.53 (s, 1H, CHAr); 9.78-9.81 (d, 2H, NH); 10.56 (s, 1H, NH).

4. Quantum - Mechanical Characterization of the Studied Compounds

HyperChem 8.06 molecular modeling software was used (based on quantum mechanics method PM3, parameteric method 3) (Stewart, 1989), with Polak-Ribiere optimization algorithm, restricted Hartree-Fock wavefunction, the convergence limit of 0.0001 kcal/mol and RMS gradient of 0.0001 kcal/(Å mol).

The structural optimized formula of 2-[(5'-nitro-1H-indazol-1'-il)-carbonyl]-N-phenylhydrazincarbothioamide (III) is represented in Fig. 2.

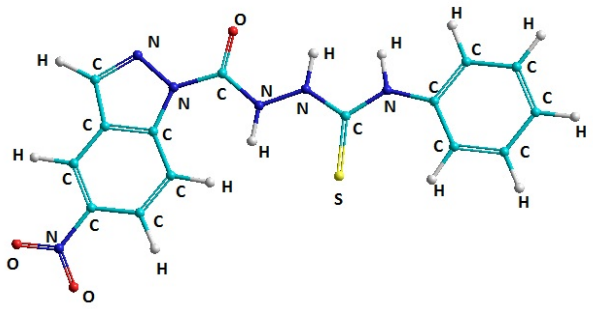


Fig. 2 – The structural optimized of compound III.

The structural optimized formula of 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-(p-tolyl)-hydrazincarbothioamide (IV) is represented in Fig. 3.

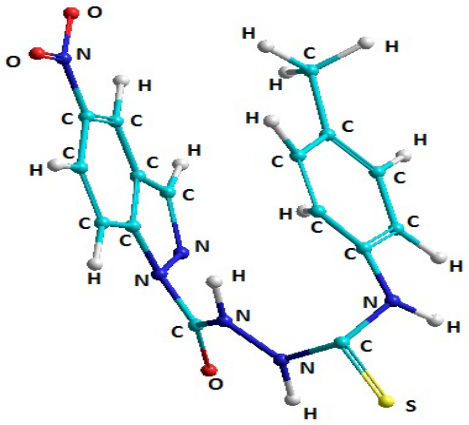


Fig. 3 – The structural optimized of compound IV.

The structural optimized formula of 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-(p-metoxiyphenyl)-hydrazincarbothioamide (V) is represented in Fig. 4.

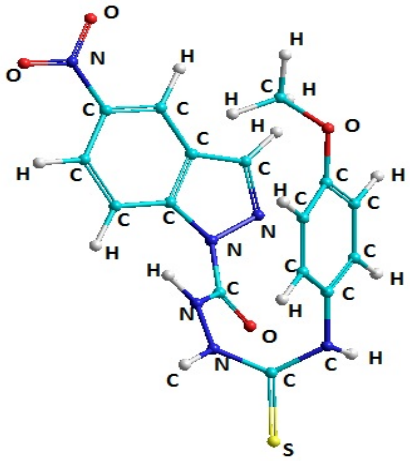


Fig. 4 – The structural optimized of compound V.

The structural optimized formula of 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-(p-bromophenyl)-hydrazincarbothioamide (VI) is represented in Fig. 5.

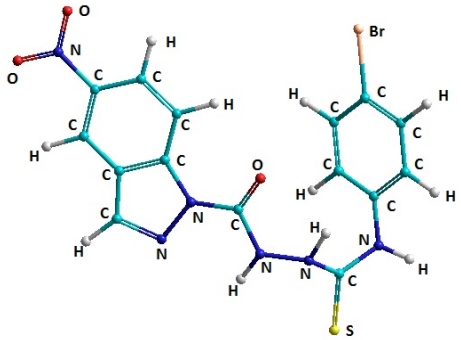


Fig. 5 – The structural optimized of compound VI.

The structural optimized formula of 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-(p-chlorophenyl)-hydrazincarbothioamide (VII) is represented in Fig. 6.

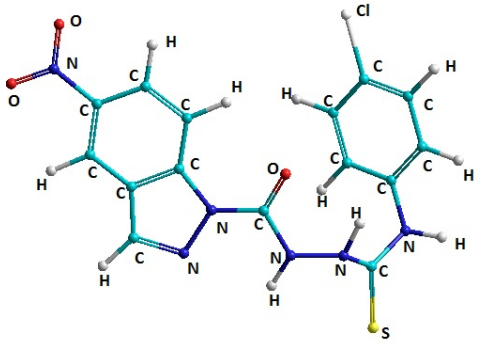


Fig. 6 – The structural optimized of compound VII.

The structural optimized formula of 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-(p-iodophenyl)-hydrazincarbothioamide (VIII) is represented in Fig. 7.

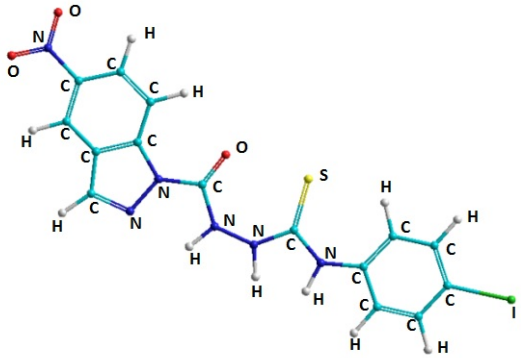


Fig. 7 – The structural optimized of compound VIII.

In Table 5 some of the most representative structural and energetic parameters are presented.

Table 5
Some Electro-Optical and Structural Propertiers for Molecules Studied

Properties	Molecule III	Molecule IV	Molecule V	Molecule VI	Molecule VII	Molecule VIII
Dipole moment [D]	6.73	5.82	3.82	3.07	2.94	9.72
Total energy [kcal/mol]	-92082.51	-95295.49	-102250.41	-99847.01	-98999.80	-98341.02
Binding energy [kcal/mol]	-3932.07	-3977.02	-4259.42	-3868.12	-3882.12	-3843.20
Heat of formation [kcal/mol]	179.59	409.72	186.88	218.17	206.42	241.87
Log P	-3.91	-3.76	-4.90	-3.86	-4.13	-3.39
Hydration energy [kcal/mol]	-18.79	-14.83	-17.08	-17.54	-17.50	-18.50
Refractivity [$Å^2$]	102.68	106.97	109.06	110.22	107.40	115.00
Polarizability [$Å^2$]	36.34	38.17	38.81	38.96	38.26	41.36
Mass [u. a.m]	356.36	370.39	386.38	435.25	390.80	482.26
Volume [$Å^3$]	912.84	881.85	911.11	949.06	925.51	983.69
Surface Area [$Å^2$]	549.90	496.63	516.35	553.64	540.59	588.29
E_{HOMO} [eV]	-9.06	-9.27	-8.85	-9.18	-9.19	-8.35
E_{LUMO} [eV]	-1.56	-2.43	-1.89	-2.02	-2.06	-1.49
$\Delta E=\lvert E_{HOMO}-E_{LUMO}\rvert$ [eV]	10.62	11.69	10.74	11.19	11.25	9.83

The difference $E_{HOMO} - E_{LUMO}$ represents the lowest energy electronic excitation that is possible in a molecule.

$$\Delta E = |E_{HOMO} - E_{LUMO}| \quad (9)$$

The QSAR (Quantitative Structure – Activity Relationships) parameters (Gallegos, 2004) correlate the molecular structure or the properties derived from molecular structure with a particular kind of chemical or biochemical activity.

LogP (Parthasarathi *et al*., 2012) is related to the hydrophobic character of the molecule, which plays an important role in biochemical interactions. A negative value of log P indicates the hydrophilicity, for the studied compounds, that plays an important role in biochemical interactions.

5. Toxicity of New Compounds

The synthesized compounds were tested for their toxicity degree and their lethal dose (LD_{50}) was determined. The toxicological data obtained (Table 6) confirm that 2-[(5'-nitro-1H-indazol-1'-yl)-carbonyl]-N-arilhydrazin-carbothioamide (thiosemicarbazides) (III - VIII) have low toxicity, which recommends them for further biological tests.

Table 6
The LD_{50} Values of the Tested Compounds

Compound	Administration route	Test animals	LD_{50} [mg/kilobody]
III	i.p.	mice	8443
IV	i.p.	mice	9223
V	i.p.	mice	9621
VI	i.p.	mice	9201
VII	i.p.	mice	8922
VIII	i.p.	mice	9274

Toxicity was estimated through intraperitoneal administration of the substances under analysis, as suspensions, in Tween 80, on groups formed of 14 mice each 20±5 g, according to the Kärber method (Hamilton *et al*., 1978). The animals tested were followed, their mortality being recorded at intervals of 7 days.

6. Conclusions

The ethyl ester of the ethyl ester of 5-nitroindazol-1-yl-formic acid and the 5-nitroindazol-formic hydrazide were prepared.

The optimal conditions in which, six new thiosemicarbazides (III – VIII) were synthesized by the reaction of hydrazide with different isothiocyanates.

The structure of the compounds III – VIII was confirmed through elemental and spectral (FT-IR and 1H-NMR) analyses.

The structural features of new thiosemicarbazides III-VIII and their QSAR parameters were established using HyperChem 8.06.

The toxicity of the new thiosemicarbazides was established and the lethal dose (LD_{50}) was determined.

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OPTIMIZAREA REACȚIILOR DE SINTEZĂ ALE UNOR NOI TIOSEMICARBAZIDE PROVENITE DIN 5-NITROINDAZOL

(Rezumat)

Noi tiosemicarbazide cu activitate biologică, derivate din 5-nitroindazol, au fost sintetizate. Pentru a obține tiosemicarbazidele, formil hidrazida 5-nitroindazol-1-yl

se tratează cu diferiți izotiocianați aromatici. Au fost stabilite condițiile în care reacțiile au loc cu cel mai mare randament. Reacțiile de optimizare au fost realizate într-un experiment factorial de tip 3^2. Unele proprietăți fizico-chimice ale noilor compuși sintetizați au fost stabilite teoretic prin utilizarea HyperChem 8.6.0. Structura chimică a noilor compuși sintetizați a fost confirmată prin analiză elementară și spectrală (FT-IR, 1H-RMN). Noii compuși au fost testați din punct de vedere al toxicității.