Synthesis and NMR Spectroscopic Characteristics of a Series of Hydrazide-Hydrazones Containing Furoxan Ring Derived from Isoeugenoxyacetic Acid

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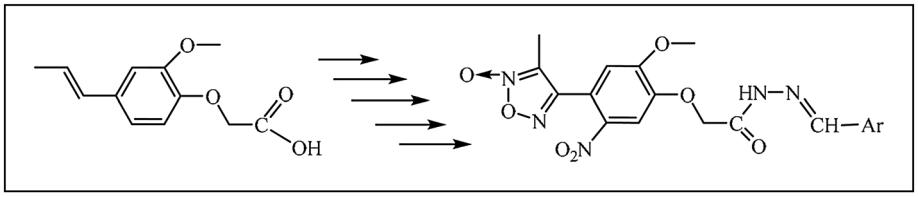

A novel hydrazide, 2-methoxy-4-(3-methyfuroxan-4-yl)-5-nitrophenoxyacetylhydrazine, was prepared from isoeugenoxyacetic acid. The hydrazide was condensed with aromatic aldehydes to give a series of 20 hydrazide-hydrazones incorporating the furoxan ring. The structure of obtained compounds was determined by analytical and spectral data. It was demonstrated that the two sets of resonance signals in the ^{1}H-NMR and ^{13}C-NMR spectra of the examined hydrazide-hydrazones are caused by $E_{N-C(O)}$ and $Z_{N-C(O)}$ conformers. The energy barriers for the conformation exchange were determined by ^{1}H-NMR-measurement at various temperatures. Among seven tested hydrazide-hydrazones, four compounds exhibit inhibition activities *in vitro* on human epidermis carcinoma (KB-cell) with IC_{50} = 47, 68, 79, and 103 μg/mL.

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INTRODUCTION

Hydrazide-hydrazones have long attracted attention owing to their remarkable biological and pharmacological properties such as antituberculosis [1–4], antibacterial, antifungal [5–11], anticonvulsant [12,13], anti-inflammatory [14], antimalarial [15], and anti-HIV [16] activities.

Many compounds containing furoxan ring, a nitric oxide (NO) releasing moiety, display a variety of biological activities. The anti-inflammatory activity, the vasodilator activity, and the inhibition of platelet aggregation are well known [17–20]. Also, antiparasitic properties, mutagenic and anticancer effects, and antimicrobial and fungicidal activities are reported [18,21]. In recent years, several classes of hybrid compounds, which obtained by combining appropriate pharmacophoric groups with NO-releasing functions, have been described [22], such as NO-aspirin [23], NO-steroids [24], and NO-guanidines [25]. Some compounds described in these works are now under clinical investigations. This has prompted us to synthesize a series of hydrazide-hydrazones containing furoxan ring derived from isoeugenoxyacetic acid (2-methoxy-4-(prop-1-enyl)phenoxyacetic acid) and to find out if the resulting compounds have any biological action.

RESULTS AND DISCUSSION

A key intermediate for the title compounds, 2-methoxy-4-(3-methyfuroxan-4-yl)-5-nitro-phenoxyacetylhydrazine (**N**), was prepared from isoeugenoxyacetic acid as described in Scheme 1. The numeration on these structures is used specifically for NMR analysis only.

Compound **K** was prepared by reaction of isoeugenoxyacetic acid with nitrous acid; the nitro compound **L** was obtained by nitration of **K** (see "Experimental" section). In the ^{1}H-NMR spectrum of **K**, there are three signals of three aromatic protons: 7.32 (d, ^{4}J = 2 Hz); 7.28 (dd, ^{3}J = 8, ^{4}J = 2 Hz); and 7.05 (d, ^{3}J = 8 Hz). In the spectrum of **L**, there are two singlets at 7.43 and 7.85 ppm, corresponding to two aromatic protons at *para*-positions relative to one another. This indicates that the nitro group is introduced into *para*-position relative to methoxy group. Acid **L** was esterified to form **M**, and then **M** reacted with hydrazine hydrate to give hydrazide **N**. The ^{1}H-NMR signals of **K**, **L**, **M**, and **N** are listed in Table 1.

Gasco et al. [26] showed that the chemical shift of a ring methyl group adjacent to the N-oxide oxygen of furoxans occurs at 2.30–2.33 ppm, while a ring methyl group remote from it or a ring methyl group of furazan appears at 2.50–2.53 ppm. The signal of the ring methyl group (10-H) of **K**–**N** appears as a singlet at 2.01–2.35 ppm (Table 1)

Scheme 1. Synthesis of hydrazides N from isoeugenoxyacetic acid.

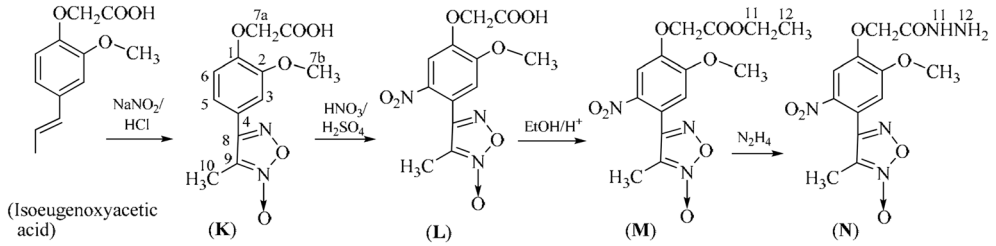


Table 1

^{1}H-NMR signals of **K**–**N**, δ (ppm), *J* (Hz).

Compd.	3-H	5-H	6-H	7a-H	7b-H	10-H	11-H	12-H
K	7.32, d, *J* 2	7.28, dd, *J* 8, 2	7.05, d, *J* 8	4.78, s	3.85, s	2.31, s	–	–
L	7.43, s	–	7.85, s	4.97, s	3.96, s	2.02, s	–	–
M	7.44, s	–	7.88, s	5.06, s	3.96, s	2.02, s	4.21, q, *J* 7	1.23, t, *J* 7
N	**7**.42, s	–	7.90, s	4.74, s	3.96, s	2.01, s	9.35, s	4.37, s

indicating that the methyl group is at position 3 of the furoxan ring and the furoxan ring was not reduced by hydrazine hydrate to furazan ring. The absence of signals at 4.21 ppm (2H) and 1.23 ppm (3H) and the presence of two singlets at 9.35 ppm (1H) and 4.37 ppm (2H) in the spectrum of **N** (Table 1) demonstrate that —OCH_2CH_3 group on **M** was replaced by —$NHNH_2$ group and the nitro group was not reduced during the refluxing **M** with hydrazine hydrate (see "Experimental" section).

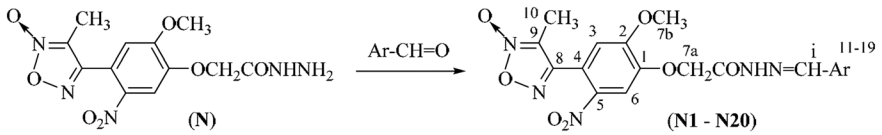
The investigated hydrazide-hydrazones were obtained by condensation of hydrazide **N** with aromatic aldehydes as shown in Scheme 2 with moderate yield expectedly. The numeration on the structures in Scheme 2 is used specifically for NMR analysis only.

It was observed that the ^{1}H-NMR and ^{13}C-NMR spectra of the hydrazide-hydrazones consist of two sets of resonance signals associated with two structures (major and minor compounds; see, e.g., Fig. 1). All resonance signals in the NMR spectra of examined compounds were accurately assigned based on analyzing the spin–spin splitting patterns, for some compounds, 2D NMR was also used. For example, in the case of **N20** (Ar = 3-indolyl, Table 4), the cross peaks *a*, *b*, *a′*, *b′*, and *c* in HMBC spectrum (Fig. 1) allow to assign signals of 13-C, 19-C, and 12-C; the cross peak *t* of 8-C indicates that the singlet at 7.43 ppm belongs to 3-H but not to 6-H; the cross peaks *v* of 14-C and *x* of 18-C show that the triplet at 7.21 ppm belongs to 16-H while the cross peaks *y* of 17-C and *z* of 19-C show that the triplet at 7.15 ppm belongs to 15-H. The NMR data of the hydrazide-hydrazones are listed in Tables 3, 4, 5, and 6 (see "Experimental" section).

It can be supposed that the two sets of resonance signals in the NMR spectra of the examined hydrazide-hydrazones are associated with two isomers (major and minor compounds). Thus, the question arises "What is the cause of these two structures?"

To answer the above question, firstly, it must be assessed whether the furoxan ring in the compounds

Scheme 2. Synthesized hydrazide-hydrazones.



Ar: C_6H_5 (**N1**), 2-$CH_3C_6H_4$ (**N2**), 4-$CH_3C_6H_4$ (**N3**), 2-ClC_6H_4 (**N4**), 4-ClC_6H_4 (**N5**), 3-$CH_3OC_6H_4$ (**N6**), 4-$CH_3OC_6H_4$ (**N7**), 3,4-$OCH_2OC_6H_3$ (**N8**), 3-CH_3O-4-OHC_6H_3 (**N9**), 4-$(CH_3)_2NC_6H_4$ (**N10**), 2-OHC_6H_4 (**N11**), 3-OHC_6H_4 (**N12**), 4-OHC_6H_4 (**N13**), 2,4 -$(OH)_2C_6H_3$ (**N14**), 2-$O_2NC_6H_4$ (**N15**), 3-$O_2NC_6H_4$ (**N16**), 4-$O_2NC_6H_4$ (**N17**), 3-pyridyl (**N18**), 2-furyl (**N19**), 3-Indolyl (**N20**).

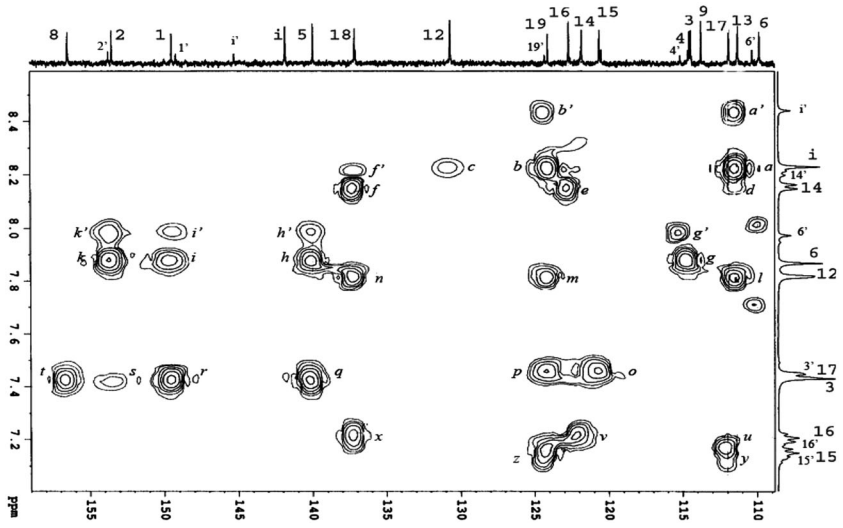


Figure 1. Partial HMBC spectrum of **N20**.

underwent isomerization in the condensation reaction (the position of N-oxide group is changed). The chemical shifts of H10 and C10 of the methyl group attached with the furoxan ring are in the range 2.02–2.35 ppm (Table 3) and 7.6–11.55 ppm (Table 5), respectively. These data indicate that the methyl group is adjacent to the N-oxide oxygen of the furoxan ring [26], as shown in Scheme 2, that is, the isomerization has not taken place.

Secondly, it is possible that the considered hydrazide-hydrazones may exist as geometrical isomers in respect to the N=C double bonds and as conformers about N—C(O) bond as shown in Figure 2.

^{1}H-NMR spectra of **N3** were recorded at various temperatures. It is observed that when the temperature is increased in the range of 333–363 K, the ^{1}H signals broaden and subsequently coalesce, and the two sets of resonance signals become one set, that is, the two above-mentioned isomers associate with a chemical equilibrium. It is well known that the energy barrier for dynamic exchange processes ($\Delta G^{\ddagger}$) can be evaluated using the following equation [27]:

$$\Delta G^{\ddagger} = RT_c[22.96 + \ln(T_c/\delta\nu)] \text{ (J/mol)}$$

where T_c is the temperature at which two signals of a proton coalesce and $\delta\nu$ is the difference between the resonance frequencies of the proton in the two structures. For calculating $\Delta G^{\ddagger}$, the singlets of 7a-H and i-H in the ^{1}H-NMR spectra of **N3** are chosen and the data are listed as below:

Proton	T_c (K)	$\delta\nu$ (Hz)	$\Delta G^{\ddagger}$ (kJ/mol)
7a-H	363	243	70.5
i-H	353	150	69.9

It can be seen that the obtained $\Delta G^{\ddagger}$ values are comparable to the $\Delta G^{\ddagger}$ values of the conformation exchange at the single bond of N–C(O) (68–71 kJ/mol) of similar compounds [28,29], and therefore, the two observed structures are two conformers due to the hindered rotation around the hydrazide N—C(O) single bond, but they are not two geometrical isomers at the hydrazone N=CH double bond. It has been pointed out that hydrazones derived from aldehydes and substituted hydrazides are present in the solution in the *E*-configuration at N=CH bond [30]; in DMSO-d_6, the major compound is $E_{N—C(O)}E_{N=C}$ isomer and the minor compound is $Z_{N—C(O)}E_{N=C}$ isomer [28,29]. Thus, it is clearly demonstrated that the two sets of resonance signals in the NMR spectra of the examined hydrazide-hydrazones are caused by the $E_{N—C(O)}E_{N=C}$ and $Z_{N—C(O)}E_{N=C}$ isomers.

It was seen that, for some series of hydrazide-hydrazones such as the considering hydrazide-hydrazones, the hydrazide-hydrazones derived from eugenoxyacetic acid, 1,3-benzothiazol-2-ylthioacetic acid [31], 4-terbuthylphenoxyacetic acid [32], and 2-pyridinecarboxylic acid [33], two sets of NMR signals were observed. However, for many other series, such as hydrazide-hydrazones derived from substituted benzoic acid [1,34,35], nicotinic acid, isonicotinic acid [36,37], thiophene carboxylic acid [38], and others, only one set of NMR signals was observed. Considering the structure of these series of hydrazide-hydrazones, it was reasoned that the intramolecular hydrogen bond of hydrazide NH may be the cause of this difference as shown in Scheme 3.

For the hydrazide-hydrazones where the hydrazide NH cannot form intramolecular hydrogen bond (e.g., hydrazide-hydrazones derived from substituted benzoic acid) in solution, the hydrazide NH forms intermolecular hydrogen bond only; thus these hydrazide-hydrazones exist only in $E_{N—C(O)}E_{N=C}$ conformer.

Some reported compounds were tested for cell cytotoxicity on cancer cell KB; the results are listed as given below.

Table 2

Synthetical, analytical, and IR spectral data of the hydrazide-hydrazones **N1**–**N20**.

Compd.	Yield (%)	Mp (°C)/ cryst. from	IR, cm^{-1} ν_{NH}/ν_{OH}	IR, cm^{-1} ν_{CH}	IR, cm^{-1} $\nu_{C=O}$	IR, cm^{-1} $\nu_{C=N}$, $\nu_{C=C}$	Molecular formula/ M; +MS (*m/z*)	Analysis Calcd./found (%)		
N1	58	214–215 DMF–H_2O 2:1	3198	3091, 2970	1689	1611, 1577	$C_{19}H_{17}N_5O_7$ 427.36; 428	53.34 53.01	4.01 3.72	16.39 16.63
N2	69	197 DMF–H_2O 2:1	3211	3070, 2935	1693	1615, 1587	$C_{20}H_{19}N_5O_7$ 441.39; –	54.42 54.18	4.34 4.02	15.87 16.13
N3	70	206 Dioxan–EtOH 1:1	3199	3098, 2977	1691	1616, 1582, 1525	$C_{20}H_{19}N_5O_7$ 441.39; –	54.42 54.04	4.34 3.99	15.87 16.11
N4	72	209–210 DMF–EtOH 1:1	3344	3069, 2936	1707	1623, 1582, 1525	$C_{19}H_{16}N_5O_7Cl$ 461.86; 462	49.41 49.67	3.49 3.15	15.16 14.86
N5	75	207–208 EtOH–H_2O 2:1	3187	3095, 2968	1691	1611, 1529	$C_{19}H_{16}N_5O_7Cl$ 461.86; –	49.41 49.70	3.49 3.21	15.16 14.82
N6	57	199 Dioxan–H_2O 2:1	3199	3093, 2930	1684	1611, 1583, 1523	$C_{20}H_{19}N_5O_8$ 457.39; –	52.52 52.17	4.19 4.32	15.31 15.59
N7	54	215–216 Dioxan–H_2O 2:1	3336	3088, 2933	1691	1610, 1576, 1522	$C_{20}H_{19}N_5O_8$ 457.39; –	52.52 52.49	4.19 4.29	15.31 14.98
N8	70	226–227 DMSO–H_2O 3:1	3199	3086, 2923	1687	1615, 1578, 1529	$C_{20}H_{17}N_5O_9$ 471.39; –	50.96 51.24	3.63 3.45	14.86 14.59
N9	65	175–176 EtOH–H_2O 2:1	3562/3206	3060, 2926	1681	1616, 1521	$C_{20}H_{19}N_5O_9$ 473.39; –	50.74 51.05	4.05 3.87	14.79 15.12
N10	66	209 Dioxan–H_2O 2:1	3200	30812934	1690	1612 1529	$C_{21}H_{22}N_6O_7$ 470.42; –	53.62 53.91	4.71 4.47	17.86 17.98
N11	74	198–199 DMF–H_2O 2:1	3192/3100	2930, 2852	1686	1618, 1580, 1532	$C_{19}H_{17}N_5O_8$ 443.36; –	51.47 51.77	3.86 3.58	15.79 15.55
N12	69	227–228 Dioxan–H_2O 3:1	3290/3200	3070, 2935	1702	1612, 1531	$C_{19}H_{17}N_5O_8$ 443.36; 444	51.47 51.81	3.86 3.52	15.79 15.42
N13	53	230–231 DMF–H_2O 2:1	3573/3212	3096, 2939	1676	1606, 1537, 1509	$C_{19}H_{17}N_5O_8$ 443.36; –	51.47 51.69	3.86 3.59	15.79 15.63
N14	60	240–241 DMF–H_2O 1:1	3525/3454	3065, 2923	1670	1611, 1587, 1515	$C_{19}H_{17}N_5O_9$ 459.36; –	49.68 49.97	3.73 3.56	15.25 15.46
N15	78	213 Dioxan–H_2O 3:1	3210	3081, 2925	1712	1617, 1580, 1527	$C_{19}H_{16}N_6O_9$ 472.36; –	48.31 48.02	3.41 3.68	17.79 18.03
N16	71	202–203 DMF–H_2O 2:1	3191	3093, 2924	1691	1614, 1584, 1533	$C_{19}H_{16}N_6O_9$ 472.36; 473	48.31 48.62	3.41 3.66	17.79 17.47
N17	78	228 Dioxan–H_2O 3:1	3194	3095, 2975	1691	1611, 1582, 1530	$C_{19}H_{16}N_6O_9$ 472.36; –	48.31 48.59	3.41 3.65	17.79 17.56
N18	77	229–230 DMF–H_2O 1:1	3180	3095, 2982	1690	1617, 1576, 1519	$C_{18}H_{16}N_6O_7$ 428.35; –	50.47 50.14	3.76 3.90	19.62 19.88
N19	75	223–224 DMF–EtOH 1:1	3193	3065, 2936	1688	1614, 1577, 1523	$C_{17}H_{15}N_5O_8$ 417.32; –	48.93 50.24	3.62 3.24	16.78 16.46
N20	62	242–243 EtOH– H_2O 3:1	3341, 3250	3058, 2923	1694	1614, 1588, 1523	$C_{21}H_{18}N_6O_7$ 466.39; –	54.08 53.77	3.89 3.69	18.02 18.37

Compounds	N4	N5	N10	N15	N17	N18	N20
IC_{50} (μg/mL)	103	>128	>128	47	>128	68	79

EXPERIMENTAL

IR spectra were recorded on a IMPACK-410 NICOLET spectrometer in KBr disks at 400–4000 cm^{-1}. The ESI mass spectra (+MS) of **N1**, **N4**, **N12**, **N16**, and **N18** were recorded using Agilent LC-MSD-Trap-SL series 1100. NMR spectra were recorded on Bruker AVANCE 500 MHz spectrometer, in DMSO-d_6 with TMS as the internal standard, all at 298–300 K, for **N3** also at 303–373 K. The cytotoxicity toward Human epidermis carcinoma (KB) was tested at the Experimental Biological Lab—Institute of Chemistry (Hanoi), according to the method described in ref. 39.

2-Methoxy-4-(3-methyfuroxan-4-yl)phenoxyacetic acid (K). Isoeugenoxyacetic acid (22.2 g, 0.1 mol) was dissolved in 50 mL of acetic acid. To this solution, $NaNO_2$ (15.1 g, 0.12 mol) was added in portions over 4 h and stirred at 25–30°C for an additional hour. The reaction mixture was poured into 100 mL of water. The resulting yellow precipitate was collected, washed by water, and recrystallized from ethanol–water 1:1 by volume to give light yellow leaf crystals. The yield 17.4 g (62%), mp 145–146°C. IR (KBr): 2500–3100, broad (OH); 3068; 3003; 2946 (C—H), 1727 (C=O); 1605, 1526 (ring). ^{1}H-NMR see Table 1. ^{13}C-NMR: 149.49 (1-C), 149.17 (2-C),

Table 3

^{1}H-NMR signals of hydrazide-moiety of examined compounds, δ (ppm).

Compd.	3-H	6-H	7a-H	7b-H	10-H	NH
N1	7.44; 7.50; s[a]	7.86; 7.95; s	5.47; 4.96; s	3.98; 3.99; s	2.03; 2.35; s	11.71; s
N2	7.42; 7.45; s	7.84; 7.95; s	5.44; 4.94; s	3.97; 3.98; s	2.02; 2.34; s	11.62; 11.69; s
N3	7.43; 7.45; s	7.84; 7.93; s	5.44; 4.93; s	3.97; 3.98; s	2.03; 2.13; s	11.64; 11.65; s
N4	7.42; 7.47; s	7.86; 7.94; s	5.47; 4.57; s	3.97; 3.98; s	2.02; s	11.86; 11.96 s
N5	7.42; 7.45; s	7.85; 7.93; s	5.46; 4.95; s	3.97; 3.98; s	2.02; 2.35; s	11.75; 11.76; s
N6	7.43; 7.45; s	7.85; 7.94; s	5.46; 4.95; s	3.98; 3.99; s	2.03; s	11.70; s
N7	7.42; 7.45; s	7.84; 7.94; s	5.42; 4.92; s	3.97; s 3.98; s	2.03; s	11.55; s
N8	7.40; 7.43; s	7.91; 7.93; s	5.14; 4.90; s	3.95; s	2.01; s	11.56; s
N9	7.43; 7.45; s	7.93; s	5.43; 4.92; s	3.93; 3.98; s	2.02; s	11.53; s
N10	7.43; 7.45; s	7.82; 7.84; s	5.40; 4.90; s	3.98; 3.99; s	2.03; s	11.41; 11.40; s
N11	7.42; 7.45; s	7.85; 7.95; s	5.43; 4.96; s	3.98; 3.97; s	2.02; s	10.95; 11.65; s
N12	7.43; 7.46; s	7.85; 7.93; s	5.44; 4.94; s	3.97; 3.98; s	2.02; 2.35; s	11.65; 11.66; s
N13	7.41; 7.43; s	7.92; 7.94; s	5.40; 4.91; s	3.97; 3.98; s	2.02; s	11.49; s
N14	7.41; 7.45; s	7.83; 7.94; s	5.38; 4.93; s	3.96; 3.98; s	2.02; s	11.11; 11.43; s
N15	7.43; 7.45; s	7.87; 7.94; s	5.45; 4.97; s	3.97; s	2.02; s	11.98; s
N16	7.43; 7.45; s	7.87; 7.94; s	5.52; 4.99; s	3.98; s	2.03; s	11.93; s
N17	7.43; s	7.87; 7.93; s	5.51; 4.99; s	3.97; s	2.02; s	11.99; s
N18	7.42; 7.45; s	7.86; 7.93; s	5.48; 4.96; s	3.97; 3.98; s	2.02; s	11.86; s
N19	7.42; 7.45; s	7.82; 7.92; s	5.36; 4.93; s	3.97; 3.98; s	2.03; s	11.63; s
N20	7.43; 7.45; s	7.87; 7.97; d	5.47; 4.92; s	3.98; s	2.02; s	11.38; 11.36; s

[a]Proton signals of the major compound were written before proton signals of the minor one, multiplicity is common for both.

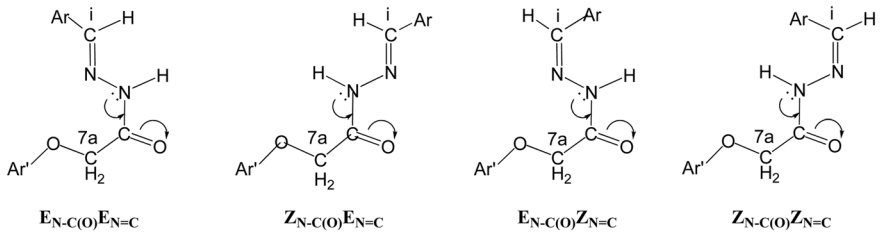


Figure 2. Four possible isomers of the considered hydrazide-hydrazones.

110.97 (3-C), 119.18 (4-C), 120.52 (5-C), 113.17 (6-C), 64.82 (7a-C), 55.78 (7b-C), 156.98 (8-C), 112.91 (9-C), 8.98 (10-C), 169.78 (C=O). Anal. Calcd. for $C_{12}H_{12}N_2O_6$, M 280.23 au: C, 51.43; H, 4.31; N, 10.00. Found: C, 51.68; H, 4.08; N, 10.25. ms: *m*/*z* 280 ($M^{+\cdot}$), 264 ($M^{+\cdot}-O$); 220 ($M^{+\cdot}-2NO$).

2-Methoxy-4-(3-methyfuroxan-4-yl)-5-nitrophenoxyacetic acid (L). To a stirred solution of HNO_3 (22 mL, *D* = 1.41 g/mL) and H_2SO_4 (32 mL, *D* = 1.84 g/mL), 14.01 g (0.05 mol) of **K** was slowly added over an hour at 0°C. The reaction mixture was stirred at 50–60°C for 4 h and then was allowed to cool to room temperature. The cooled mixture was poured into 50 mL of water. The solid was collected, washed by water, and recrystallized from ethanol–water 1:1 by volume to give white needle crystals. The yield 9.75 g (60%), mp 180°C. IR (KBr): 2700–3100, broad (OH); 3089, 2960, 2917 (C–H), 1738 (C=O); 1614, 1577, 1516 (ring). ^{1}H-NMR see Table 1. ^{13}C-NMR: 148.74 (1-C), 153.43 (2-C), 114.59 (3-C), 114.87 (4-C), 139.95 (5-C), 109.71 (6-C), 65.35 (7a-C), 56.85 (7b-C), 156.34 (8-C), 113.71 (9-C), 7.61 (10-C), 169.37 (C=O). Anal. Calcd. for $C_{12}H_{11}N_3O_8$, M 325.23 au: C, 44.32; H, 3.41; N, 12.92. Found: C, 44.65; H, 3.08; N, 12.65. ms: *m*/*z* 325($M^{+\cdot}$), 279 ($M^{+\cdot}-NO_2$), 265 ($M^{+\cdot}-2NO$).

Ethyl 2-methoxy-4-(3-methyfuroxan-4-yl)-5-nitrophenoxyacetate (M). A mixture of 3.25 g (0.01 mol) of **L**, 35 mL of ethanol, and 1.5 mL of H_2SO_4 was refluxed for 24 h. The reaction mixture was allowed to cool to room temperature and then was neutralized by

Scheme 3. Two conformers of the examined hydrazide-hydrazones.

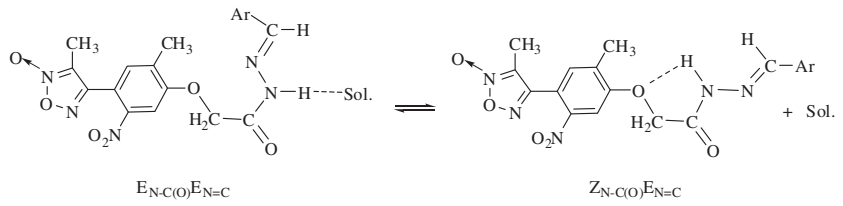
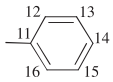
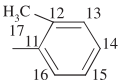
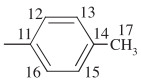
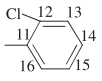
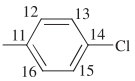
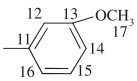
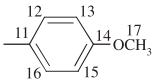
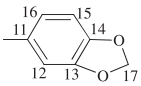
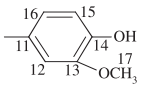
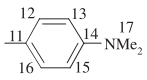
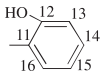
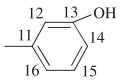
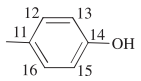
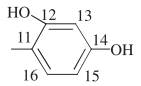
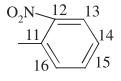
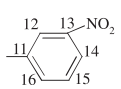


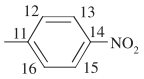
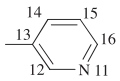
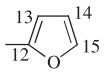
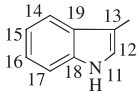
Table 4

^{1}H NMR signals of aldehyde-moiety of examined compounds, δ (ppm), J (Hz).

Comp.	Ar	i-H	12-H	13-H	14-H	15-H	16-H	Others
N1		8.06; s 8.30; s	7.73; m 7.74; m	7.46; m	7.45; m	7.46; m	7.73; m 7.74; m	–
N2		8.31; s 8.55; s	–	7.25; m	7.32; t *J*: 7.5	7.27; m	7.77; m *J*: 7.5	17-H: 2.45; 2,50; s
N3		8.01; s 8.24; s	7.59; 7.62; d; *J*: 8 [a]	7.23; 7.26; d; *J*: 8	–	7,23; 7,26; d; *J*: 8	7.9; 7.62; d; *J*: 8	17-H: 2.33; 2,34; s
N4		8.42; s 8.68; s	–	7.53; d *J*: 7.5	7.45; t *J*: 7.5	7.42; d *J*: 7.5	7.97; 8.03; s; *J*: 7.5	–
N5		8.04; s 8.28; s	7.50; d *J*: 8.5	7.73; 7.75 d; *J*: 8.5	–	7.75; 7.73 d; *J*: 8.5	7.50; d *J*: 8.5	–
N6		8.02; s 8.26; s	7.30; s –	–	7.01; d *J*: 7	7.36; t *J*: 7.5	7.28; m	17-H: 3.80; s
N7		7.99; s 8.23; s	7.66; d *J*: 9	7.00; d *J*: 9	–	7.00; d *J*: 9	7.66; d *J*: 9	17-H: 3.81; s
N8		7.82; s 8.17; s	7.25; s 7.35; s	–	–	6.95; d *J*: 7.5	7.13; 7.15 d; *J*: 8	17-H: 6.06; s
N9		7.83; s 8.16; s	7.29; s 7.32; s	–	–	6.83; d *J*: 8	7.09; 7.11 d; *J*: 8	OH: 9.50; s 17-H: 3.83; s
N10		7.93; s 8.13; s	7.53; d *J*: 9	6.74; d *J*: 8.5	–	6.74; d *J*: 8.5	7.53; d *J*: 9	17-H: 2.97; s
N11		8.34; s 8.51; s	–	6.92; d *J*: 7.5	7.25; 7.30 t; *J*: 7.5	6.86; 6.91 t; *J*: 7.5	7.55; 7.72 d; *J*: 7.5	OH: 10.05; s 10.95; s
N12		7.96; s 8.18; s	7.13; s 7.17; s	–	6.83; dd *J*: 7; 1.5	7.24; t *J*: 8	7.09; 7.12; d; *J*: 8	OH: 9.61; s
N13		7.92; s 8.16; s	7.55; d *J*: 8.5	6.82; d *J*: 8.5	–	6.82; d *J*: 8.5	7.55; d *J*: 8.5	OH: 9.92; s 9.95; s
N14		8.21; s 8.36; s	–	6.30; s	–	6.35; m	7.32; 7.50 d; *J*: 8.5	OH: 9.94; s 11.75; s
N15		8.42; s 8.69; s	–	8.07; 8.13 d; *J*: 8	7.81; t *J*: 7.5	7.68; t *J*: 7.5	8.06; d *J*: 8.5	–
N16		8.17; s 8.41; s	8.53; s –	–	8.25; m 8.26; m	7.75; t *J*: 8	8,16; d 8,18;d	–

(*Continues*)

Table 4
(Continued)

Comp.	Ar	i-H	12-H	13-H	14-H	15-H	16-H	Others
N17		8,14; s 8,38; s	7,99; d *J*: 7	8,28; d *J*: 7	–	8,28; d *J*: 7	7,99; d *J*: 7	–
N18		8.11; s 8.34; s	8,90; s 8,85; s	–	8,14; d *J*: 8	7,47; dd *J*: 8; 5	8,61; m –	–
N19		7,93; s 8,18; s	–	6,93; d *J*: 3	6,63; m –	7.84; s –	–	–
N20		8,23; s 8,44; s	7,81; s 7,82; s	–	8.21; 8.15; d; *J*: 7,5	7.14; 7.15 t; *J*: 7.5	7.19; 7,21 t; *J*: 7,5	17-H: 7,45; d 11-H: 11,56; s

[a]Proton signals of the major compound were written before proton signals of the minor one, multiplicity and coupling constant are common for both.

Na_2CO_3. The resulting precipitate was collected, washed by water, and recrystallized from ethanol–water 3:1 by volume to give light yellow needle crystals. The yield 2.2 g (62%), mp 131–132°C. IR (KBr): 3110, 2981, 2924 (C—H), 1747 (C=O); 1616, 1573, 1480 (ring). ^{1}H-NMR see Table 1. ^{13}C-NMR: 148.50 (1-C), 153.44 (2-C), 114.66 (3-C), 115.06 (4-C), 139.93 (5-C), 110.12 (6-C), 65.56 (7a-C), 56.85 (7b-C), 156.22 (8-C), 113.62 (9-C), 7.56 (10-C), 167.91 (C=O), 60.89 (11-C), 13.97 (12-C). Anal. Calcd. for $C_{14}H_{15}N_3O_8$, M 353.29 au: C, 47.59; H, 4.28; N, 11.89. Found: C, 47.23; H, 4.52; N, 12.05.

Table 5

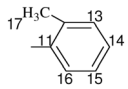
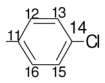
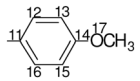
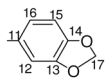
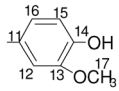
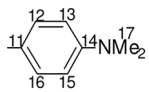
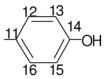
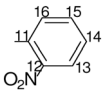
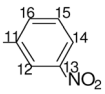
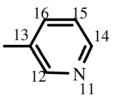
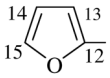
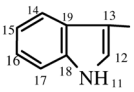
^{13}C NMR signals of hydrazide-moiety of examined compounds, δ (ppm).

Comp.	1-C	2-C	3-C	4-C	5-C	6-C	7a-C	7b-C	8-C	9-C	10-C	C=O
N1	149.81[a]	153.87	114.99	115.09	140.39	110.36	66.30	57.30	156.85	114.17	8.11	168.64
	149.48	154.10	114.97	115.19	140.49	110.74	67.66	57.39	155.72		11.55	163.84
N2	149.32	153.39	114.46	114.52	139.98	109.87	65.91	56.80	156.34	113.66	7.59	168.04
	148.95	153.50		115.24	139.90		66.33	56.89	155.20		11.03	163.26
N4	149.27	153.35	114.46	114.50	140.01	109.88	65.83	56.80	156.34	113.68	7.61	168.35
	148.90	153.60		114.80	139.90	110.40	67.05	56.89	155.40		10.08	163.70
N5	149.28	153.36	114.44	114.51	139.98	109.84	65.78	56.78	156.34	113.67	7.59	168.23
	148.94	153.59		114.67		110.30	67.12	56.87	155.30			163.46
N7	149.33	153.36	114.43	114.66	139.88	109.81	65.78	56.78	156.36	113.67	7.59	167.85
	149.00	153.59	114.46	115.16	139.96	110.26	67.18	56.86				163.04
N8	149.20	153.37	114.47	114.60	139.99	109.84	65.84	56.79	156.35	113.66	7.60	167.98
	148.99	153.60		115.10		110.20	67.20	56.84				163.00
N9	149.36	153.37	114.47	114.67	139.95	109.80	65.88	56.80	156.35	113.66	7.59	167.79
	149.16	153.50		115.15		110.33	67.23	56.88				163.00
N10	151.47	153.36	114.44	114.70	139.96	109.82	65.80	56.78	156.35	113.66	7.59	167.45
	151.49	153.40		115.20		110.20	67.27	56.87				162.80
N11	149.30	153.36	114.43	114.69	139.90	109.87	65.78	56.78	156.36	113.69	7.59	167.80
	148.92	153.62	114.48	115.24	139.98	110.41	67.08	56.88	156.43			163.27
N13	149.37	153.40	114.46	114.67	139.91	109.84	65.81	56.81	156.40	113.72	7.62	167.77
	149.04	153.63	114.50	115.18	139.99	110.30	67.23	56.90				162.96
N15	149.24	153.36	114.48	114.55	139.77	109.86	65.79	56.81	156.34	113.69	7.61	168.48
	148.90	153.70		114.70			68.00					164.80
N16	149.29	153.40	114.49	114.70	139.99	109.91	65.87	56.81	156.33	113.67	7.59	168.48
	149.00	153.60	114.56	115.30		110.37	67.10	56.90				163.77
N18	149.28	153.37	114.46	114.69	140.00	109.87	65.82	56.80	156.32	113.66	7.59	168.36
	149.00	153.60	114.51	115.30		110.34	67.13	56.88	156.60			163.50
N19	149.24	153.38	114.47	114.70	139.89	109.92	65.67	56.78	156.34	113.65	7.59	167.86
	149.07	152.90	114.54	115.22	139.98	110.38	67.22	56.87	153.62			163.28
N20	149.48	153.48	114.48	114.67	139.99	109.89	66.14	56.86	156.49	113.79	7.65	167.23
	149.19	153.71	114.58	115.19		110.36	67.41	56.93				162.50

[a]^{13}C signals of the major compound were written before ^{13}C signals of the minor compound.

Table 6

^{13}C-NMR signals of aldehyde-moiety of examined compounds, δ (ppm).

Compd.	Ar	i-C	11-C	12-C	13-C	14-C	15-C	16-C	17-C
N1		144.79[a] 148.42	134.36 134.46	127.48 127.66	129.26 129.29	130.53 130.73	129.26 129.29	127.48 127.66	–
N2		143.62 146.67	136.73 136.97	131.81 132.00	126.79	129.65 129.95	126.10	130.85 130.94	19.48 19.98
N4		140.29 143.84	131.47 131.80	133.00 133.20	129.87	131.15	127.11 127.00	127.53	–
N5		143.03 146.64	132.80 132.89	128.83 128.89	128.62	134.50 134.72	128.62	128.83 128.89	–
N7		144.18 147.80	126.45 126.48	128.57 128.78	114.24 114.30	160.78 160.97	114.24 114.30	128.57 128.78	55.26
N8		143.96 147.80	128.35	105.20	147.94 148.10	149.34	108.33 108.40	123.24 123.44	101.50
N9		144.64 148.47	125.34	109.24 109.71	147.94 148.15	148.89 149.02	115.49	121.45 122.19	55.57
N10		145.18 148.50	121.16	128.26 128.52	111.71	149.37 149.39	111.71	128.26 128.52	39.83
N11		141.89 148.09	131.30 131.59	157.30 157.70	116.13 116.35	129.14	118.57	119.91 119.35	–
N13		144.67 148.29	124.91	128.75 129.00	115.68	159.39 159.59	115.68	128.75 129.00	–
N15		140.01 143.50	128.06 128.10	149.24	124.50 124.70	130.66 130.80	133.51 133.70	128.56	–
N16		142.05 145.57	135.74 135.90	121.16	148.23	124.21 124.50	130.32 130.50	133.04 133.25	–
N18		141.49 145.28	–	148.50 148.78	129.81	133.62 133.50	123.81	150.56 150.80	–
N19		134.44 137.74	–	148.87 148.94	113.89 113.99	112.12	145.09 145.32	–	–
N20[b]		141.83 145.26	–	130.70	111.32	121.84	120.52 120.67	122.72	111.94

[a] ^{13}C signals of the major compound were written before ^{13}C signals of the minor compound.
[b] 18-C: 137.16; 19-C: 124.12; 124.33.

2-Methoxy-4-(3-methyfuroxan-4-yl)-5-nitrophenoxyacetylhydrazine (N). A solution of 3.53 g (0.01 mol) of **M**, 1.0 mL of $N_2H_4 \cdot H_2O$ 80% in 30 mL of ethanol was refluxed for 24 h. The reaction mixture was allowed to cool to room temperature. The resulting precipitate was collected and recrystallized from DMF–water 1:1 by volume to give yellow needle crystals. The yield 2.31 g (67%), mp 212–213°C. IR (KBr): 3333, 3290 (NH); 3090, 3053, 2917 (C—H), 1683 (C=O); 1578, 1520 (ring). ^{1}H-NMR see Table 1. ^{13}C-NMR: 149.01 (1-C), 153.64 (2-C), 114.58 (3-C), 115.06 (4-C), 139.91 (5-C), 110.27 (6-C), 67.13 (7a-C), 56.85 (7b-C), 156.32 (8-C), 113.65 (9-C), 7.57 (10-C), 165.77 (C=O). Anal. Calcd. for $C_{12}H_{13}N_5O_7$, M 339.26 au: C, 42.48; H, 3.86; N, 20.64. Found: C, 42.15; H, 3.58; N, 20.28.

General procedure for the preparation of hydrazide-hydrazones N1–N20. A solution of 1 mmol of **N** and 1 mmol of an aromatic aldehyde dissolved in 15–25 mL of ethanol was refluxed over 5–10 h. Upon cooling the mixture to room temperature, the resulting precipitate was collected and recrystallized. The synthetical, analytical, and spectral data of N^1- [2-methoxy-4-(3-methyfuroxan-4-yl)-5-nitrophenoxyacetyl]-N^2-(aryliden)hydrazines (**N1**–**N20**) are listed in Tables 2–6.

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REFERENCES AND NOTES

[1] Küçükgüzel, Ş. G.; Mazi, A.; Sahin, F.; Öztürk, S.; Stables, J. Eur J Med Chem 2003, 38, 1005.

[2] Kaymakçıoğlu, B. K.; Rollas, S. Farmaco 2002, 57, 595.

[3] Patole, J.; Sandbhor, U.; Badhye, S.; Deobagkar, D. N.; Anson, C. E.; Powell, A. Bioorg Med Chem Lett 2003, 13, 51.

[4] Maccari, R.; Ottanà, R.; Vigorita, M. G. Bioorg Med Chem Lett 2005, 15, 2509.

[5] Metwally, K. A.; Lobna, L. M.; Abdel-Aziz, M.; Lashine, M.; El-Sayed Husseiny, M. I.; Badawy, R. H. Bioorg Med Chem 2006, 14, 8675.

[6] Loncle, C.; Brunel, J. M.; Vidal, N.; Dherbomez, M.; Letournex, Y. Eur J Med Chem 2004, 39, 1067.

[7] Garoufalias, S. P.; Pouli, N.; Marakos, P.; Chytyroglou-Ladas, A. Farmaco 2002, 57, 973.

[8] Cadellini, M.; Claudi, F.; Gripantini, M.; Gulini, U.; Martelli, S.; J Pharm Sci 1977, 66, 259.

[9] Gurkok, G., Altanlar, N., Süzen, S. Chemotherapy, 2009, 55, 15.

[10] Küçükgüzel, Ş. G.; Oruç E. E.; Rollas, S.; Şahin, F.; Özbek, A. Eur J Med Chem 2002, 37, 197.

[11] Rollas, S.; Küçükgüzel, Ş. G. Molecules 2007, 12, 1910.

[12] Sridhar, S. K.; Pandeya, S. N.; Stables, J. P.; Atmakuru, R. Eur J Pharm Sci 2002, 16, 129.

[13] Kulandasamy, R.; Adhikari, A. V., Stables, J. P. Eur J Med Chem 2009, 44, 3672.

[14] Todeschini, A. R.; Miranda, A. L. P.; Silva, K. C. M.; Parrini, S. C.; Barreiro, E. J. Eur J Med Chem 1998, 33, 189.

[15] Melnyk, P.; Leroux, V.; Sergheraert, C.; Grellier, P. Bioorg Med Chem Lett 2006, 16, 31.

[16] Vicini, P.; Inserti, M.; La Colla, P.; Loddo, R. Eur J Med Chem 2009, 44, 1801.

[17] Köse, E.; Küçükgüzel, Ş. G. Mini Rev Med Chem 2009, 9, 611.

[18] Hugo, C.; Porcal, W.; Mini Rev Med Chem 2005, 5, 57.

[19] Ferioli Polco, G. C.; Ferretti, C.; Gasco, A. M.; Medana, C.; Fruttero, R.; Civelli, M.; Gasco, A. Br J Pharmacol 1995, 114, 816.

[20] Pirogov, S. V.; Mel'nikova, S. F.; Zelinskii, I. V.; Romanova, T. V.; Spiridonova, N. P.; Medvedeva, N. A.; Bularina, T. V. Rus. Pat. RU 2240321 C2, November 20, 2004.

[21] Hwang, K.-J.; Park Young, C.; Kim, H. J.; Lee, J. H. Biosci Biotechnol Biochem 1998, 62, 1693.

[22] Wang, P. G.; Xian, M.; Tang, X.; Wu, X.; Wan, Z.; Cai, T.; Janczuk, A. J Chem Rev 2002, 102, 1109.

[23] Freduzzi, S.; Mariucci, G.; Tantucci, M.; del Soldato, P.; Ambrosini, M. V. Neurosci. Lett. 2001, 302, 121.

[24] Tallet, D.; del Soldato, P.; Oudart, N.; Burgaud, J. L. Biochem Biophys Res. Commun 2002, 290, 125.

[25] Bertinaria, M.; Di Stilo, A.; Tosco, P.; Sorba, G.; Poli, E.; Pozzoli, C.; Coruzzi, G.; Fruttero, R.; Gasco, A. Bioorg Med Chem 2003, 11, 1197.

[26] Gasco, A.; Mortarini, G. R.; Menziani, E. J. Heterocycl Chem 1972, 9, 837.

[27] Günther, H., NMR Spectroscopy, 2nd ed.; Wiley: New York, 1995, p 344.

[28] Himmerlreich, U.; Tschwatschal, F.; Borsdorf, R. Monatsh Chem 1993, 124, 1041.

[29] Syakaev, V. V.; Podyachev, S. N.; Buzukin, B. I.; Latipov, S. K.; Habicher, W. D.; Konovalov, A. I. J Mol Struct 2006, 788, 55.

[30] Palla, G.; Pelizzi, G.; Predieri, G.; Vignali, C. Gazz Chim Ital 1982, 112, 339.

[31] Dinh, N. H.; Hoan, D. Q.; Tuu, T. T. Proceedings of the 8th Eurasia Conference on Chemical Sciences, Session of Organic Chemistry, Hanoi, October 2003, p 57–62.

[32] Podyachev, S. N.; Litvinov, I. A.; Shagidullin, R. R.; Buzykin, B. I.; Bauer, I.; Osyanina, D. V.; Avvakumova, L. V.; Sudakova, S. N.; Habicher, W. D.; Konovalov, A. I. Spectrochim Acta A, 2007, 66, 250.

[33] Garric, J.; Léger, J.-M.; Grelard, A.; Ohkita, M.; Huc, I. Tetrahedron Lett 2007, 44, 1421.

[34] Joshi, S. D.; Vagdevi, H. M.; Vaidya, V. P.; Gadaginamath, G. S. Eur J Med Chem 2008, 43, 1989.

[35] Kaymakçıoğlu, B. K.; Elçin, O.; Seda, U.; Fatma, K.; Nathaly, S.; Sevim, R.; Dimoglo, A. Eur J Med Chem 2006, 41, 1253.

[36] Galič, N.; Perič, B.; Kojič, B.; Cimerman, Z. J Mol Struct 2001, 559, 187.

[37] El-Asmy Ahmed Al-Abdeen, A. Z.; Abo El-Maaty, W. M.; Mostafa, M. M. Spectrochim Acta A, 2010, 75, 1516.

[38] Kulandasamy, R.; Adhikari, A. V.; Stables, J. P. Eur J Med Chem 2009, 44, 3672.

[39] Scudiego, D. A.; Shoemaker, R. H.; Kenneth, D. P.; Monks, A.; Tierney, S.; Nofziger, T. H.; Curens, M. J.; Seniff, D.; Boyd, M. R. Cancer Res 1988, 48, 4827.