Full Paper

Facile Synthesis and *In-Vitro* Antimalarial Activity of Novel α-Hydroxy Hydrazonates

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A series of previously unreported α-hydroxy hydrazonates were synthesized and tested for their antimalarial properties. Structure optimization of the antiplasmodially active α-hydroxy hydrazonate **III** furnished derivatives with strong *in-vitro* antimalarial activity against 3D7 strains of *Plasmodium falciparum* with IC_{50} values lower than 2.0 μM.

Keywords: Antimalarial activity / Hydrazonates / *Plasmodium falciparum* / α-Hydroxy imidates

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Introduction

Apart from their utility in synthetic heterocyclic chemistry [1–3], the esters of hydrazonoic acids, namely hydrazonates, are of interest for medicinal chemists because of their versatile biological properties. For instance, hydrazonates have been found to exhibit anthelmintic, antifungal and anti-inflammatory activities [4–6] and contribute as toxophores/pharmacophores to bactericides or herbicides [7, 8].

So far, the antimalarial activity of hydrazonates has not yet been reported, whereas aroylhydrazones (**I**) and thiosemicarbazones (**II**) (Fig. 1), structurally related to hydrazonates, have been shown to possess potent antimalarial activity (IC_{50} for **I**: 5 μM, for **II**: 4 μM, *Plasmodium falciparum* 3D7 strains) as reported by Walcourt and coworkers [9]. Over the past years, we have studied the synthesis and reactivity of α-hydroxy imidates (**2**) and α-hydroxy hydrazonates (**4**) as precursors for the preparation of various 5- and 6-membered functionalized heterocycles [10, 11]. Because of the finding that compound **III**, originally developed in our group as a building block for novel heterocycles, displayed strong *in vitro* activity against 3D7 strains of *P. falciparum* ($IC_{50} = 1.5$ μM), we became interested in the structure-activity relationship of **III**, and disclose here the synthesis and antiplasmodial evaluation of a variety of analogues of our lead compound **III** (Fig. 2).

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As shown in Fig. 2, the lead **III** was modified by altering the aryl group at C2 (A), by replacing the methyl group (B) or the hydroxyl group at the C2 atom (E) by hydrogen, by altering the ethyl residue of the hydrazonate functionality (C) and by replacement of the carbazone-ester group by a (thio)semicarbazone functionality (D). Toward this goal, efficient synthetic methods for the envisioned novel compounds had to be developed which are disclosed in the next section.

Results and discussion

Chemistry

We started the preparation of α-hydroxy hydrazonates **4** from cyanohydrins **1**, which were accessible according to literature [12]. Next, cyanohydrins **1** were converted by a Pinner reaction [13] into the corresponding α-hydroxy imidate hydrochlorides **2**. Since the reaction of **2** with carbazates was found to afford amidrazones as by-products and α-hydroxy hydrazonates **4** in only moderate yields, we developed a more efficient route as demonstrated in Scheme 1. Treatment of imidate hydrochlorides **2** with a saturated solution of hydrogen sulfide in dry dichloromethane-pyridine [14] furnished smoothly α-hydroxy thiocarboxylic *O*-esters **3** in 78–88% yield. Subsequent reaction of **3** with carbazates afforded the desired α-hydroxy hydrazonates **4** in 67–87% yields as mixtures of *E*- and *Z*-isomers (see Experimental section). The synthesis of α-hydroxy hydrazonates **5** and **6** was accomplished by reaction of **3** with semicarbazides or thiosemicarbazides [15] in ethyl acetate as a solvent, respectively.

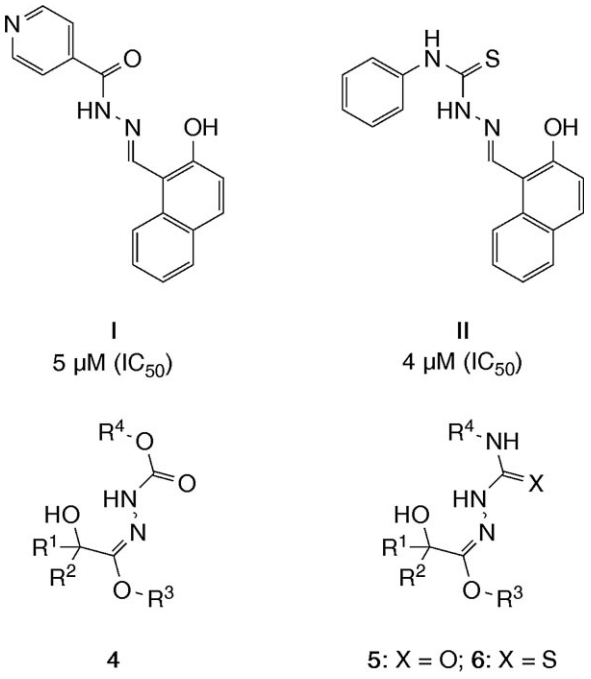
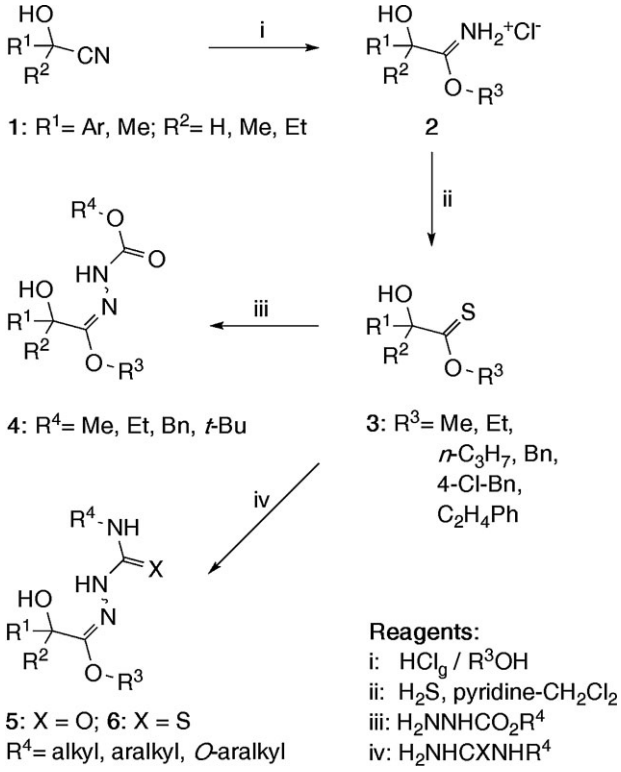


Figure 1. Known antiplasmodials **I** and **II**, and title compounds **4–6**.



Scheme 1. Synthesis of α-hydroxy hydrazonates **4–6**. For details see experimental part.

Biological activity

The *in-vitro* antiplasmodial activity of compounds **4–6** was evaluated by the 8-[^{3}H]-hypoxanthine incorporation assay according to the method of Desjardins using the chloroquine sensitive strain 3D7 of *Plasmodium falciparum* [16]. IC_{50} values as well as the inhibition of parasite growth at 5 μM have been determined. *Pyrimethamine* (Pyr) was used as reference compound (Tables 1, 2).

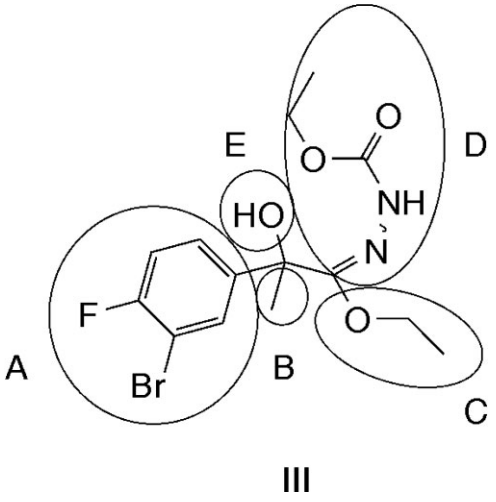


Figure 2. Structure modifications of the lead **III**.

The *in-vitro* studies revealed that derivatives of **4** with a dihalogenated phenyl ring or a naphthyl residue at C2 exhibit strongest antiplasmodial activity within the set of prepared compounds. Replacement of the C-2 methyl group by hydrogen caused a significant decrease of activity, whereas an ethyl residue at C-2 increased antiplasmodial activity as highlighted in Fig. 3. Compound **7** lacking a hydroxyl group at C-2 was almost devoid of antiplasmodial activity, hence indicating the importance of the α-hydroxyl group for antiplasmodial activity. Complete loss of antimalarial activity was observed for benzyl- and phenethyl imidates **4n** and **4o**, whereas the alkyl imidates **4a**, **4l** displayed remarkable activity. Modification of the carbazone-ester moiety generally caused a decrease of antiplasmodial activity, with the exception of the semicarbazone **5d**, exhibiting an IC_{50} value of 0.85 μM.

Experimental

Melting points were determined on an Electrothermal 9100 apparatus. Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on an ATI Genesis Series FT-IR. ^{1}H-NMR (400 MHz) and ^{13}C-NMR

Table 1. Inhibition of *P. falciparum* growth.

Entry	R^1	R^2	R^3	R^4	5 μM [%][a]
4a	3,4-Cl-Ph	Me	Et	*t*-Bu	75
4b	4-Cl-3-Me-Ph	Me	Et	Me	72
4c	2-Naphthyl	Me	Et	Et	83
4d	2-Naphthyl	Me	Et	*t*-Bu	56
4e	1-Naphthyl	H	Et	*t*-Bu	7
4f	3,4-Cl-Ph	H	Et	*t*-Bu	12
4g	3,4-Cl-Ph	Et	Et	Et	66
4h	4-CH_3-Ph	Me	Et	Bn	19
4i	3,4-CH_3-Ph	Me	Et	Me	19
4j	4-Cl-Ph	Me	Et	Et	75
4k	4-Cl-Ph	Me	4-Cl-Bn	Et	4
4l	3,4-Cl-Ph	Me	Me	*t*-Bu	66
4m	3,4-Cl-Ph	Me	*n*-Pr	*t*-Bu	43
4n	3,4-Cl-Ph	Me	Bn	*t*-Bu	0
4o	3,4-Cl-Ph	Me	C_2H_4Ph	*t*-Bu	0
4p	3-Br-4-F-Ph	Me	Et	Et	70
4q	2-Naphthyl	Me	Me	Et	76
4r	2-Naphthyl	Me	*n*-Pr	Et	85
4s	2-Naphthyl	Me	Bn	Et	0
4t	2-Naphthyl	Me	C_2H_4Ph	Et	0
5a	2-Naphthyl	Me	Et	Me	40
5b	2-Naphthyl	Me	Et	Bn	5
5c	2-Naphthyl	Me	Et	OBn	14
5d	3,4-Cl-Ph	Me	Et	Me	75
5e	3,4-Cl-Ph	Me	Et	Bn	19
5f	3,4-Cl-Ph	Me	Et	4-Me-Bn	15
5g	3,4-Cl-Ph	Me	Et	4-Cl-Bn	0
6a	2-Naphthyl	Me	Et	Et	7
7[b]	3,4-Cl-Ph	H	Et	*t*-Bu	5
Pyr[c]					80

[a] Mean values of four independent determinations. [b] Compound **7** represents **4f** without hydroxyl group at C2. [c] Pyr = pyrimethamine

Table 2. IC_{50} values of selected compounds **4** and **5** against *P. falciparum*

Compound	Activity against *P. falciparum*		
	IC_{50} [μM]	*n*[a]	SEM[b]
4a	4.9	4	0.7
4b	5.1	4	0.7
4c	2.0	4	0.1
4d	4.4	4	1.57
4g	2.9	4	1.14
4j	5.0	4	0.4
4l	2.5	4	0.79
4p	1.5	4	0.2
4q	1.1	4	0.45
4r	0.6	4	0.1
5a	6.2	4	2.54
5d	0.85	6	0.23
Pyr[c]	0.07	8	0.03

[a] *n* = number of determinations. [b] SEM = standard error of the mean. [c] Pyr = pyrimethamine.

(100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as internal standard and DMSO-d_6 or $CDCl_3$ as solvents. Mass spectra were recorded on a Micromass VG 70-250S mass spectrometer (HRFAB).

Chemistry

*General procedure for the synthesis of compounds **2a–t***

To a solution of the corresponding cyanohydrin **1** (30 mmol) in anhydrous Et_2O (50 mL), 1.2 equivalents of the appropriate anhydrous alcohol and HCl gas were added at 0°C according to the Pinner synthesis [13]. After 5 d at −10°C, the solid imidate hydrochlorides **2a–t** were isolated by filtration, suspended in anhydrous Et_2O and filtered. The structures of imidate hydrochlorides **2a–t** were confirmed by IR spectroscopy. All imidate hydrochlorides were used for the synthesis of compounds **3** without further purification.

*Ethyl 2-hydroxy-2-(4-methylphenyl)propanimidoate hydrochloride **2a***

Colorless solid, yield: 88%, mp: 89.7°C; IR ν_{max} (KBr) cm^{-1}: 1638.

*Ethyl 2-(4-chlorophenyl)-2-hydroxypropanimidoate hydrochloride **2b***

Colorless solid, yield: 79%; mp: 103.8°C; IR ν_{max} (KBr) cm^{-1}: 1638.

*4-Chlorobenzyl 2-(4-chlorophenyl)-2-hydroxypropan-imidoate hydrochloride **2c***

Colorless solid, yield: 84%; mp: 85.7°C; IR ν_{max} (KBr) cm^{-1}: 1643.

*Ethyl 2-(3,4-dimethylphenyl)-2-hydroxypropan-imidoate hydrochloride **2d***

Colorless solid, yield: 77%; mp: 82.5°C; IR ν_{max} (KBr) cm^{-1}: 1650.

*Ethyl 2-(3,4-dichlorophenyl)-2-hydroxypropanimidoate hydrochloride **2e***

Colorless solid, yield: 83%; mp: 106.7°C; IR ν_{max} (KBr) cm^{-1}: 1654.

*Methyl 2-(3,4-dichlorophenyl)-2-hydroxypropanimidoate hydrochloride **2f***

Colorless solid, yield: 91%; mp: 98.1°C; IR ν_{max} (KBr) cm^{-1}: 1651.

*Propyl 2-(3,4-dichlorophenyl)-2-hydroxypropanimidoate hydrochloride **2g***

Colorless solid, yield: 74%; mp: 93.8°C; IR ν_{max} (KBr) cm^{-1}: 1653.

*Benzyl 2-(3,4-dichlorophenyl)-2-hydroxypropanimidoate hydrochloride **2h***

Colorless solid, yield: 81%; mp: 82.7°C; IR ν_{max} (KBr) cm^{-1}: 1653.

*2-Phenylethyl 2-(3,4-dichlorophenyl)-2-hydroxy-propanimidoate hydrochloride **2i***

Colorless solid, yield: 79%; mp: 111.8°C; IR ν_{max} (KBr) cm^{-1}: 1653.

Ethyl 2-(3-bromo-4-fluorophenyl)-2-hydroxypropanimidoate hydrochloride ***2j***
Colorless solid, yield: 81%; mp: 99.4°C; IR ν_{max} (KBr) cm^{-1}: 1647.

Ethyl 2-(4-chloro-3-methylphenyl)-2-hydroxypropanimidoate hydrochloride ***2k***
Colorless solid, yield: 85%; mp: 101.3°C; IR ν_{max} (KBr) cm^{-1}: 1651.

Ethyl 2-hydroxy-2-(naphthalen-2-yl)propanimidoate hydrochloride ***2l***
Colorless solid, yield: 88%; mp: 119.2°C; IR ν_{max} (KBr) cm^{-1}: 1652.

Methyl 2-hydroxy-2-(naphthalen-2-yl)propanimidoate hydrochloride ***2m***
Colorless solid, yield: 85%; mp: 109.5°C; IR ν_{max} (KBr) cm^{-1}: 1651.

Propyl 2-hydroxy-2-(naphthalen-2-yl)propanimidoate hydrochloride ***2n***
Colorless solid, yield: 77%; mp: 93.5°C; IR ν_{max} (KBr) cm^{-1}: 1652.

Benzyl 2-hydroxy-2-(naphthalen-2-yl)propanimidoate hydrochloride ***2o***
Colorless solid, yield: 86%; mp: 85.7°C; IR ν_{max} (KBr) cm^{-1}: 1654.

2-Phenylethyl 2-hydroxy-2-(naphthalen-2-yl)propanimidoate hydrochloride ***2p***
Colorless solid, yield: 83%; mp: 119.3°C; IR ν_{max} (KBr) cm^{-1}: 1659.

Ethyl 2-hydroxy-2-(naphthalen-1-yl)ethanimidoate hydrochloride ***2q***
Colorless solid, yield: 86%; mp: 125.2°C; IR ν_{max} (KBr) cm^{-1}: 1647.

Ethyl 2-(3,4-dichlorophenyl)-2-hydroxyethanimidoate hydrochloride ***2r***
Colorless solid, yield: 63%; mp: 114.4°C; IR ν_{max} (KBr) cm^{-1}: 1652.

Ethyl 2-(3,4-dichlorophenyl)-2-hydroxybutanimidoate hydrochloride ***2s***
Colorless solid, yield: 67%; mp: 103.1°C; IR ν_{max} (KBr) cm^{-1}: 1654.

Benzyl 2-hydroxy-2-methylpropanimidoate hydrochloride ***2t***
Colorless solid, yield: 66%; mp: 66.7°C; IR ν_{max} (KBr) cm^{-1}: 1651.

General procedure for the synthesis of compounds ***3a–p***
20 mmol of the appropriate imidate hydrochlorides **2** were added to a saturated solution of hydrogen sulfide in anhydrous dichloromethane/pyridine (100 mL) at 5°C and the reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated, diethylether (40 mL) was added and the mixture was washed with 1 M hydrochloric acid (3 × 20 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent was evaporated. The remaining residues were purified by filtration through a short silica gel column (5 cm) with CH_2Cl_2/hexane (3:1) as an eluent to give compounds **3a–p** as pale yellow oils or solids.

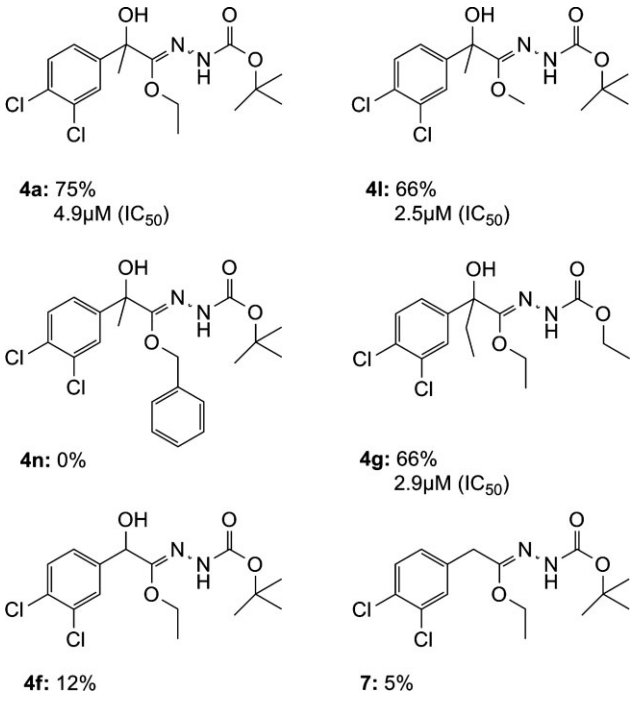


Figure 3. Structure-activity relationships on the example of **4a**. Inhibition of *P. falciparum* growth at 5 μM.

O-Ethyl 2-hydroxy-2-(4-methylphenyl)propanethioate ***3a***
Pale yellow oil, yield: 87%; IR ν_{max} (KBr) cm^{-1}: 3387 (OH), 1279 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.37 (t, J = 7.0 Hz, 3H), 1.80 (s, 3H), 2.32 (s, 3H), 4.43–4.63 (m, 2H), 4.80 (s, 1H), 7.16–7.46 (m, 4H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 13.4, 21.0, 27.2, 70.6, 80.2, 125.5, 128.8, 137.2, 141.1, 222.2; HRFAB-MS $C_{12}H_{16}O_2S$ $[M+H]^+$: Calcd. 225.0949; found 225.0959.

O-Ethyl 2-(4-chlorophenyl)-2-hydroxypropanethioate ***3b***
Pale yellow oil, yield: 87%; IR ν_{max} (KBr) cm^{-1}: 3377 (OH), 1285 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.37 (t, J = 7.0 Hz, 3H), 1.80 (s, 3H), 4.44–4.64 (m, 2H), 4.81 (s, 1H), 7.26–7.52 (m, 4H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 13.4, 27.4, 70.9, 79.9, 127.2, 128.2, 133.6, 142.5, 225.5; HRFAB-MS $C_{11}H_{13}ClO_2S$ $[M+H]^+$: Calcd. 245.0403; found 245.0400.

O-(4-Chlorobenzyl) 2-(4-chlorophenyl)-2-hydroxypropanethioate ***3c***
Colorless solid, yield: 78%; mp: 48.7°C, IR ν_{max} (KBr) cm^{-1}: 3400 (OH), 1278 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.81, 5.39–5.50 (q, 2H), 7.12–7.48 (m, 8H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 27.6, 75.5, 80.5, 127.6, 128.7, 129.4, 129.9, 132.8, 134.1, 135.3, 142.5, 226.3; HRFAB-MS $C_{16}H_{14}Cl_2O_2S$ $[M+H]^+$: Calcd. 341.0170; found 341.0183.

O-Ethyl 2-(3,4-dimethylphenyl)-2-hydroxypropane-thioate ***3d***
Colorless solid, yield: 82%; mp: 43.1°C, IR ν_{max} (KBr) cm^{-1}: 3379 (OH), 1275 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.39

(t, J = 7.1 Hz, 3H), 1.79 (s, 3H), 2.26 (s, 6H), 4.44–4.65 (m, 2H), 4.73 (s, 1H), 7.07–7.33 (m, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 13.6, 29.0, 69.5, 81.1, 122.9, 126.6, 129.2, 135.3, 135.8, 142.5, 227.0; HRFAB-MS $C_{13}H_{18}O_2S$ $[M+H]^+$: Calcd. 239.1106; found 239.1099.

O-Ethyl 2-(3,4-dichlorophenyl)-2-hydroxypropane-thioate ***3e***

Colorless solid, yield: 86%; mp: 36.1°C, IR ν_{max} (KBr) cm^{-1}: 3364 (OH), 1281 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.39 (t, J = 7.0 Hz, 3H), 1.79 (s, 3H), 4.46–4.65 (m, 2H), 4.84 (s, 1H), 7.39–7.67 (m, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 13.4, 27.5, 71.1, 79.5, 125.3, 128.0, 130.0, 131.8, 132.3, 144.1, 226.7; HRFAB-MS $C_{11}H_{12}Cl_2O_2S$ $[M+H]^+$: Calcd. 279.0013; found 279.0008.

O-Methyl 2-(3,4-dichlorophenyl)-2-hydroxypropane-thioate ***3f***

Pale yellow oil, yield: 85%; IR ν_{max} (KBr) cm^{-1}: 3383 (OH), 1276 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.80 (s, 3H), 4.15 (s, 3H), 4.77 (s, 1H), 7.37–7.67 (m, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 27.4, 61.4, 79.6, 125.39, 128.0, 130.1, 131.8, 132.3, 143.9, 226.4; HRFAB-MS $C_{10}H_{10}Cl_2O_2S$ $[M+H]^+$: Calcd. 264.9857; found 264.9845.

O-Propyl 2-(3,4-dichlorophenyl)-2-hydroxypropane-thioate ***3g***

Pale yellow oil, yield: 84%; IR ν_{max} (KBr) cm^{-1}: 3373 (OH), 1284 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 0.95 (t, J = 7.0 Hz, 3H), 1.75–1.82 (m, 2H), 1.79 (s, 3H), 4.36–4.53 (m, 2H), 4.86 (s, 1H), 7.37–7.68 (m, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 10.8, 21.8, 27.3, 77.2, 79.9, 125.7, 128.5, 130.4, 132.2, 132.6, 144.5, 225.9; HRFAB-MS $C_{12}H_{14}Cl_2O_2S$ $[M+H]^+$: Calcd. 293.0170; found 293.0159.

O-Benzyl 2-(3,4-dichlorophenyl)-2-hydroxypropane-thioate ***3h***

Pale yellow oil, yield: 79%; IR ν_{max} (KBr) cm^{-1}: 3382 (OH), 1278 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.79 (s, 3H), 4.78 (s, 1H), 5.44–5.54 (q, 2H), 7.22–7.66 (m, 8H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 27.8, 76.9, 80.2, 125.7, 128.6, 128.7, 129.2, 129.4, 130.4, 132.3, 132.7, 134.2, 142.5, 225.4; HRFAB-MS $C_{16}H_{14}Cl_2O_2S$ $[M+H]^+$: Calcd. 341.0170; found 341.0178.

O-(2-Phenylethyl) 2-(3,4-dichlorophenyl)-2-hydroxy-propanethioate ***3i***

Pale yellow oil, yield: 81%; IR ν_{max} (KBr) cm^{-1}: 3378 (OH), 1285 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.69 (s, 3H), 3.06 (t, J = 6.5 Hz, 2H), 4.63–4.77 (m, 2H), 4.74 (s, 1H), 7.11–7.58 (m, 8H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 27.4, 34.3, 75.1, 79.5, 125.2, 126.9, 128.0, 128.7, 128.8, 130.0, 131.7, 132.2, 136.8, 143.8, 225.4; HRFAB-MS $C_{17}H_{16}Cl_2O_2S$ $[M+H]^+$: Calcd. 355.0326; found 355.0321.

O-Ethyl 2-(3-bromo-4-fluorophenyl)-2-hydroxy-propanethioate ***3j***

Pale yellow oil, yield: 84%; IR ν_{max} (KBr) cm^{-1}: 3375 (OH), 1285 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.38 (t, J = 7.1 Hz, 3H), 1.79 (s, 3H), 4.46–4.62 (m, 2H), 4.84 (s, 1H), 7.03–7.81 (m, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 13.9, 27.6, 71.0, 79.3, 108.6 (d, $^2J_{C,F}$ = 21.4 Hz), 115.7 (d, $^2J_{C,F}$ = 22.1 Hz), 126.6 (d, $^3J_{C,F}$ = 7.6 Hz), 131.1 (d, $^3J_{C,F}$ = 13.0 Hz), 141.3 (d, $^4J_{C,F}$ = 3.8 Hz), 158.4 (d, $^1J_{C,F}$ = 244.9 Hz), 225.3; HRFAB-MS $C_{11}H_{12}BrFO_2S$ $[M+H]^+$: Calcd. 306.9804; found 306.9816.

O-Ethyl 2-hydroxy-2-(naphthalen-2-yl)propanethioate ***3k***

Pale yellow oil, yield: 88%; IR ν_{max} (KBr) cm^{-1}: 3383 (OH), 1283 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.35 (t, J = 7.1 Hz, 3H), 1.93 (s, 3H), 4.42–4.64 (m, 2H), 4.93 (s, 1H), 7.43–8.06 (m, 7H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 13.4, 27.6, 70.8, 80.4, 123.8, 124.5, 126.1, 127.5, 127.7, 127.7, 128.4, 132.7, 133.0, 141.2, 226.8; HRFAB-MS $C_{15}H_{16}O_2S$ $[M+H]^+$: Calcd. 261.0949; found 261.0938.

O-Methyl 2-hydroxy-2-(naphthalen-2-yl)propane-thioate ***3l***

Colorless solid, yield: 82%; mp: 73.1°C, IR ν_{max} (KBr) cm^{-1}: 3372 (OH), 1273 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.94 (s, 3H), 4.13 (s, 3H), 4.86 (s, 1H), 7.37–8.04 (m, 7H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 27.2, 61.2, 80.5, 123.8, 124.6, 126.1, 126.2, 127.5, 127.9, 128.3, 132.7, 133.0, 141.1, 227.9; HRFAB-MS $C_{14}H_{14}O_2S$ $[M+H]^+$: Calcd. 247.0793; found 247.0782.

O-Propyl 2-hydroxy-2-(naphthalen-2-yl)propane-thioate ***3m***

Pale yellow oil, yield: 83%; IR ν_{max} (KBr) cm^{-1}: 3384 (OH), 1282 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 0.92 (t, J = 7.1 Hz, 3H), 1.73–1.83 (q, 2H), 1.94 (s, 3H), 4.33–4.54 (m, 2H), 4.95 (s, 1H), 7.37–8.06 (m, 7H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 10.4, 21.4, 27.3, 76.5, 80.4, 123.9, 124.6, 126.1, 126.1, 127.4, 127.8, 128.4, 132.7, 133.0, 141.2, 227.0; HRFAB-MS $C_{16}H_{18}O_2S$ $[M+H]^+$: Calcd. 275.1106; found 275.1094.

O-Benzyl 2-hydroxy-2-(naphthalen-2-yl)propane-thioate ***3n***

Pale yellow oil, yield: 80%, IR ν_{max} (KBr) cm^{-1}: 3388 (OH), 1275 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.75 (s, 3H), 4.87 (s, 1H), 5.42–5.54 (dd, 2H), 7.19–8.04 (m, 12H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 27.6, 76.5, 81.1, 124.2, 125.1, 126.5, 126.6, 127.9, 128.2, 128.5, 128.8, 129.1, 129.1, 133.2, 133.4, 134.5, 141.5, 227.4; HRFAB-MS $C_{20}H_{18}O_2S$ $[M+H]^+$: Calcd. 323.1106; found 323.1113.

O-(2-Phenylethyl) 2-hydroxy-2-(naphthalen-2-yl)-propanethioate ***3o***

Colorless solid, yield: 83%, mp: 65.5°C, IR ν_{max} (KBr) cm^{-1}: 3386 (OH), 1263 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.85 (s, 3H), 3.04–3.05 (m, 2H), 4.60–4.77 (m, 2H), 4.84 (s, 1H), 7.06–7.96 (m, 12H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 27.6, 34.8, 75.3, 80.9, 124.2, 125.0, 126.5, 126.5, 127.2, 127.8, 128.2, 128.8, 128.0, 129.2, 133.1, 133.4, 137.4, 141.4, 223.8; HRFAB-MS $C_{21}H_{20}O_2S$ $[M+H]^+$: Calcd. 337.1262; found 337.1248.

O-Benzyl 2-hydroxy-2-methylpropanethioate ***3p***

Pale yellow oil, yield: 88%, IR ν_{max} (KBr) cm^{-1}: 3405 (OH), 1270 (C=S); ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.47 (s, 6H), 3.96 (s, 1H), 5.55 (s, 2H), 7.32–7.43 (m, 5H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): 29.1, 46.1, 76.0, 128.6, 129.0, 129.1, 134.9, 229.8; HRFAB-MS $C_{11}H_{14}O_2S$ $[M+H]^+$: Calcd. 211.0714; found 211.0715.

*General procedure for the synthesis of compounds **4a–t, 7***

To a stirring solution of 5 mmol of α-hydroxy thiocarboxylic *O*-ester (**3**) in ethyl acetate (15 mL), 1.1 equivalents of the appropriate carbazate were added. The reaction mixture was stirred at room temperature and monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was washed with water (3 × 10 mL), the organic layer was separated, dried with $MgSO_4$ and evaporated under reduced pressure. The remaining residue was crystallized from Et_2O/*n*-hexane at 5°C, delivering **4a**, **c**, **h–t** as solid compounds. Recrystallization from EtOAc/*n*-hexane provided analytically pure products. Compounds **4b**, **e–g** and **7** were prepared as follows: The appropriate carbazate (5.5 mmol) was added dropwise to a solution of the imidate hydrochloride salt (5 mmol) in anhydrous ethanol (10 mL) and the reaction mixture was stirred at room temperature for 24 hours. Afterwards, the solvent was evaporated and the remaining residue was quenched with water (15 mL). The mixture was extracted with ethyl acetate (2 × 30 mL), and the combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The remaining residues were purified by column chromatography using EtOAc/*n*-hexane (1:1) as an eluent. Crystallisation from Et_2O/*n*-hexane at 5°C afforded **4b**, **e–g** as solid compounds. Recrystallization from EtOAc/*n*-hexane provided analytically pure products.

*tert-Butyl (2E/Z)-2-[2-(3,4-dichlorophenyl)-1-ethoxy-2-hydroxypropylidene]hydrazinecarboxylate **4a***

Colorless solid, yield: 76%; mp: 147.3°C; IR ν_{max} (KBr) cm^{-1}: 3392, 3366 (NH), 3279 (OH), (C=O), 1646 (C=N); ratio *E*/*Z* = 48:52; ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): *E*-isomer: 1.23 (t, *J* = 7.0 Hz, 3H), 1.35 (s, 9H), 1.62 (s, 3H), 4.00–4.06 (m, 2H), 7.33 (s, 1H), 7.15–7.26 (m, 3H), 9.75 (s, 1H). *Z*-isomer: 1.01 (t, *J* = 7.0 Hz, 3H), 1.44 (s, 9H), 1.57 (s, 3H), 3.59–3.67, 4.11–4.19 (m, 2H), 6.40 (s, 1H), 7.15–7.26 (m, 3H), 9.10 (s, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): *E*-isomer: 14.4, 28.5, 28.6, 62.5, 77.0, 79.4, 125.6, 126.8, 131.0, 129.9, 131.4, 145,3. *Z*-isomer: 15.5, 28.6, 31.8, 66.0, 75.0, 79.4, 125.4, 126.9, 131.1, 129.9, 131.4, 143.7; anal. calcd. for $C_{16}H_{22}Cl_2N_2O_4$: Calcd. C 50.94%, H 5.88%, N 7.43%; found C 50.76%, H 5.93%, N 7.33%.

*Methyl (2E/Z)-2-[2-(4-chloro-3-methylphenyl)-1-ethoxy-2-hydroxypropylidene]hydrazinecarboxylate **4b***

Colorless solid, yield: 37%; mp: 137.4°C; IR ν_{max} (KBr) cm^{-1}: 3372 (NH), 3319 (OH), 1720 (C=O), 1642 (C=N); ratio *E*/*Z* = 68:32; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.25 (t, *J* = 7.1 Hz, 3H), 1.59 (s, 3H), 2.33 (s, 3H), 3.54 (s, 3H), 4.01–4.06 (m, 2H), 7.22 (s, 1H), 7.32–7.42 (m, 3H), 9.95 (s, 1H). *Z*-isomer: 0.99 (t, *J* = 7.1 Hz, 3H), 1.55 (s, 3H), 2.34 (s, 3H), 3.65 (s, 3H), 3.59–3.63, 4.13–4.21 (m, 2H), 6.22 (s, 1H), 7.19–7.26 (m, 3H), 9.44 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.4, 20.2, 29.1, 52.1, 62.5, 77.1, 123.8, 127.6, 129.2, 132.7, 133.5, 135.7, 143.3, 144.9. *Z*-isomer: 15.4, 19.5, 32.3, 52.1, 65.9, 75.0, 124.1, 127.4, 129.0, 132.1, 135.0, 135.5, 143.3, 144.9; anal. calcd. for $C_{14}H_{19}ClN_2O_4$: Calcd. C 53.42%, H 6.08%, N 8.90%; found C 53.29%, H 6.25%, N 8.81%.

*Ethyl (2E/Z)-2-[1-ethoxy-2-hydroxy-2-(naphthalen-2-yl)-propylidene]hydrazinecarboxylate **4c***

Colorless solid, yield: 74%; mp: 122.7°C; IR ν_{max} (KBr) cm^{-1}: 3372 (NH, OH), 1717 (C=O), 1637 (C=N); ratio *E*/*Z* = 50:50; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.09 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.72 (s, 3H), 4.07–4.17 (m, 4H), 7.29 (s, 1H), 7.47–7.53, 7.86–7.97 (m, 7H), 10.05 (s, 1H). *Z*-isomer: 0.93 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.68 (s, 3H), 3.57–3.65, 4.19–4.27 (m, 4H), 6.33 (s, 1H), 7.47–7.53, 7.86–7.97 (m, 7H), 9.41 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.0, 14.6, 28.6, 60.1, 62.1, 75.1, 122.5, 123.0, 125.8, 126.1, 127.4, 127.9, 128.1, 132.2, 132.5, 141.3. *Z*-isomer: 14.4, 14.9, 32.0, 60.2, 65.4, 77.2, 122.5, 123.0, 126.1, 126.3, 127.3, 127.8, 128.0, 132.0, 132.7, 143.0; anal. calcd. for $C_{18}H_{22}N_2O_4$: Calcd. C 65.44%, H 6.71%, N 8.48%; found C 65.60%, H 6.72%, N 8.30%.

*tert-Butyl (2E/Z)-2-[1-ethoxy-2-hydroxy-2-(naphthalen-2-yl)-propylidene]hydrazinecarboxylate **4d***

Colorless solid, yield: 72%; mp: 160.2°C; IR ν_{max} (KBr) cm^{-1}: 3383 (NH), 3294 (OH), 1713 (C=O), 1643 (C=N); ratio *E*/*Z* = 37:63; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.27 (t, *J* = 7.1 Hz, 3H), 1.30 (s, 9H), 1.71 (s, 3H), 4.00–4.11 (m, 2H), 7.20 (s, 1H), 7.47–7.55, 7.88–7.97 (m, 7H), 9.90 (s, 1H). *Z*-isomer: 0.92 (t, *J* = 7.1 Hz, 3H), 1.47 (s, 9H), 1.71 (s, 3H), 3.56–3.63, 4.17–4.25 (m, 2H), 6.30 (s, 1H), 7.47–7.55, 7.88–7.97 (m, 7H), 9.00 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.5, 28.3, 29.0, 62.3, 77.5, 79.3, 123.0, 123.4, 126.5, 126.7, 127.8, 128.4, 128.5, 132.6, 132.9, 141.8. *Z*-isomer: 15.4, 28.5, 32.4, 65.8, 75.6, 79.4, 123.0, 123.4, 126.2, 126.8, 127.8, 128.2, 128.3, 132.4, 133.2, 143.4; anal. calcd. for $C_{20}H_{26}N_2O_4$: Calcd. C 67.02%, H 7.31%, N 7.82%; found C 67.12%, H 7.63%, N 7.79%.

*tert-Butyl (2E)-2-[1-ethoxy-2-hydroxy-2-(naphthalen-1-yl)-ethylidene]hydrazinecarboxylate **4e***

Colorless solid, yield: 34%; mp: 164.1°C, IR ν_{max} (KBr) cm^{-1}: 3359 (NH), 3292 (OH), 1707 (C=O), 1654 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): 1.07 (t, *J* = 7.1 Hz, 3H), 1.41 (s, 9H), 3.93–4.05 (m, 2H), 6.28 (d, 1H), 6.83 (d, 1H), 7.49–7.56, 7.89–7.91, 7.94–8.08 (m, 7H), 9.85 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): 14.3, 28.5, 62.1, 69.4, 79.3, 124.2, 124.7, 125.7, 126.2, 126.5, 128.9, 128.9, 130.9, 133.8, 135.0, 152.8, 156.6; anal. calcd. for $C_{19}H_{24}N_2O_4$: Calcd. C 66.26%, H 7.02%, N 8.13%; found C 66.59%, H 7.06%, N 8.04%.

*tert-Butyl (2E/Z)-2-[2-(3,4-dichlorophenyl)-1-ethoxy-2-hydroxyethylidene]hydrazinecarboxylate **4f***

Colorless solid, yield: 37%; mp: 108.9°C; IR ν_{max} (KBr) cm^{-1}: 3387 (NH), 3310 (OH), 1711 (C=O), 1655 (C=N); ratio *E*/*Z* = 60:40; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.15 (t, *J* = 7.1 Hz, 3H), 1.41 (s, 9H), 3.94–4.01 (m, 2H), 5.63 (d, 1H), 6.76 (d, 1H), 7.58–7.65 (m, 3H), 9,63 (s, 1H). *Z*-isomer: 1.15 (t, *J* = 7.1 Hz, 3H), 1.41 (s, 9H), 4.19–4.26 (m, 2H), 5.62 (d, 1H), 6.56 (d, 1H), 7.32–7.35 (m, 3H), 9.01 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 15.4, 28.4, 62.3, 68.5, 75.4, 126.9, 128.5, 130.6, 130.5, 131.2, 142.2. *Z*-isomer: 14.3, 28.4, 64.9, 70.24, 79.4, 127.3, 128.3, 130.7, 130.1, 131.1, 141.3; anal. calcd. for $C_{15}H_{20}Cl_2N_2O_4$: Calcd. C 49.60%, H 5.55%, N 7.71%; found C 49.28%, H 5.66%, N 7.64%.

*Ethyl (2E/Z)-2-[2-(3,4-dichlorophenyl)-1-ethoxy-2-hydroxybutylidene]hydrazinecarboxylate **4g***

Colorless solid, yield: 37%; mp: 107.8°C; IR ν_{max} (KBr) cm^{-1}: 3364 (NH), 3310 (OH), 1723 (C=O), 1648 (C=N); ratio *E*/*Z* = 93:7; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 0.82 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.79–1.88, 2.13–2.22 (m, 2H), 3.96–4.06 (m, 4H), 7.12 (s, 1H), 7.38–7.41, 7.61–7.66 (m, 3H), 10.16 (s, 1H). *Z*-isomer:

0.63 (t, $J = 7.1$ Hz, 3H), 1.01 (t, $J = 7.1$ Hz, 3H), 1.10 (t, $J = 7.1$ Hz, 3H), 1.90–1.95, 2.04–2.11 (m, 2H), 3.59–3.67, 4.08–4.19 (m, 4H), 6.08 (s, 1H), 7.29–7.31, 7.50–7.59 (m, 3H), 9.50 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 8.0, 14.3, 14.9, 32.7, 60.6, 62.5, 80.4, 125.8, 127.3, 130.9, 130.6, 131.3, 144.4, 152.2, 154.0. *Z*-isomer: 7.8, 15.0, 15.3, 34.6, 60.6, 65.8, 77.1, 126.1, 127.6, 130.7, 129.9, 131.2, 144.9, 152.2, 154.0; anal. calcd. for $C_{15}H_{20}Cl_2N_2O_4$: Calcd. C 49.60%, H 5.55%, N 7.71%; found C 49.51%, H 5.72%, N 7.63%.

Benzyl (2E/Z)-2-[1-ethoxy-2-hydroxy-2-(4-methylphenyl)propylidene]hydrazinecarboxylate ***4h***

Colorless solid, yield: 82%; mp: 101.7°C; IR ν_{max} (KBr) cm^{-1}: 3445 (NH), 3324 (OH), 1718, 1683 (C=O), 1653, 1637 (C=N); ratio *E*/*Z* = 70:30; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.27 (t, $J = 7.1$ Hz, 3H), 1.80 (s, 3H), 2.33 (s, 3H), 4.06–4.16 (m, 2H), 5.09 (s, 2H), 7.10 (s, 1H), 7.25–7.42 (m, 9H), 9.76 (s, 1H). *Z*-isomer: 1.01 (t, $J = 7.1$ Hz, 3H), 1.74 (s, 3H), 2.33 (s, 3H), 3.58–3.66, 4.13–4.20 (m, 2H), 5.22 (s, 2H), 6.06 (s, 1H), 7.25–7.42 (m, 9H), 8.23 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.2, 21.1, 29.2, 66.6, 66.7, 78.5, 124.5, 128.4, 128.6, 129.2, 137.7, 140.5. *Z*-isomer: 15.3, 21.1, 31.0, 62.8, 67.3, 76.7, 124.8, 128.0, 128.4, 128.4, 129.2, 137.2, 140.2; anal. calcd. for $C_{20}H_{24}N_2O_4$: Calcd. C 67.40%, H 6.79%, N 7.86%; found C 67.36%, H 6.80%, N 7.88%.

Methyl (2E/Z)-2-[2-(3,4-dimethylphenyl)-1-ethoxy-2-hydroxypropylidene]hydrazinecarboxylate ***4i***

Colorless solid, yield: 83%; mp: 142.3°C; IR ν_{max} (KBr) cm^{-1}: 3394 (NH), 3343 (OH), 1716, 1686 (C=O), 1637 (C=N); ratio *E*/*Z* = 37:63; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.26 (t, $J = 7.1$ Hz, 3H), 1.56 (s, 3H), 2.19 (s, 3H), 2.21 (s, 3H), 3.53 (s, 3H), 3.99–4.06 (m, 2H), 7.04 (s, 1H), 7.06–7.15 (m, 3H), 10.00 (s, 1H). *Z*-isomer: 0.97 (t, $J = 7.1$ Hz, 3H), 1.52 (s, 3H), 2.19 (s, 3H), 2.20 (s, 3H), 3.65 (s, 3H), 3.56–4.22 (m, 2H), 6.05 (s, 1H), 7.06–7.15 (m, 3H), 9.38 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.2, 19.4, 20.1, 29,4, 52.1, 62.4, 77.2, 122.0, 125.6, 129.7, 135.0, 136.2, 143.2, 171.6, 174.9. *Z*-isomer: 114.5, 19.4, 20.1, 32.6, 52.1, 65.7, 72.8, 121.9, 125.6, 129.7, 135.7, 136.4, 141.7, 171.6, 174.9; anal. calcd. for $C_{15}H_{22}N_2O_4$: Calcd. C 61.21%, H 7.53%, N 9.52%; found C 60.91%, H 7.50%, N 9.32%.

Ethyl (2E/Z)-2-[2-(4-chlorophenyl)-1-ethoxy-2-hydroxypropylidene]hydrazinecarboxylate ***4j***

Colorless solid, yield: 76%; mp: 108.9°C; IR ν_{max} (KBr) cm^{-1}: 3323 (NH), 3336 (OH), 1734, 1718 (C=O), 1654, 1638 (C=N); ratio *E*/*Z* = 50:50; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.13 (t, $J = 7.1$ Hz, 3H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.60 (s, 3H), 3.93–4.07 (m, 4H), 7.23 (s, 1H), 7.18–7.45 (m, 4H), 9.87 (s, 1H). *Z*-isomer: 0.98 (t, $J = 7.1$ Hz, 3H), 1.22 (t, $J = 7.1$ Hz, 3H), 1.56 (s, 3H), 3.57–4.17 (m, 4H), 6.24 (s, 1H), 7.18–7.45 (m, 4H), 8.36 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 13.9, 14.5, 28.6, 60.1, 62.1, 76.9, 126.2, 128.3, 132.2, 142.9. *Z*-isomer: 14.6, 16.0, 31.8, 60.2, 65.4, 74.8, 126.3, 128.2, 131.4, 144.5; anal. calcd. for $C_{14}H_{19}ClN_2O_4$: Calcd. C 53.42%, H 6.08%, N 8.90%; found C 53.31%, H 6.20%, N 8.83%.

Ethyl (2E)-2-{1-[(4-chlorobenzyl)oxy]-2-(4-chlorophenyl)-2-hydroxypropylidene}hydrazinecarboxylate ***4k***

Colorless solid, yield: 75%; mp: 151.7°C; IR ν_{max} (KBr) cm^{-1}: 3348 (NH), 3326 (OH), 1709 (C=O), 1638 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): 1.15 (t, $J = 7.1$ Hz, 3H), 1.64 (s, 3H), 3.98–4.10 (m, 2H), 5.00–5.08 (m, 2H), 7.32 (s, 1H), 7.42–7.46 (m, 8H), 9.99 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): 14.4, 28.3, 60.3, 67.0, 77.0, 126.3, 126.4, 127.5, 127.9, 128.2, 128.3, 129.2, 129.8, 132.1, 132.4, 135.5, 142.6, 144.1; anal. calcd. for $C_{19}H_{20}Cl_2N_2O_4$: Calcd. C 55.49%, H 4.90%, N 6.81%; found C 55.32%, H 5.06%, N 6.60%.

tert-Butyl (2E/Z)-2-[2-(3,4-dichlorophenyl)-2-hydroxy-1-methoxypropylidene]hydrazinecarboxylate ***4l***

Colorless solid, yield: 76%; mp: 155.3°C; IR ν_{max} (KBr) cm^{-1}: 3360 (NH), 3317 (OH), 1710 (C=O), 1643 (C=N); ratio *E*/*Z* = 94:6; ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): *E*-isomer: 1.36 (s, 9H), 1.63 (s, 3H), 3.63 (s, 3H), 7.35 (s, 1H), 7.33–7.64 (m, 3H), 9.77 (s, 1H). *Z*-isomer: 1.44 (s, 9H), 1.57 (s, 3H), 3.54 (s, 3H), 6.40 (s, 1H), 7.33–7.64 (m, 3H), 9.24 (s, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$), δ (ppm): *E*-isomer: 28.3, 28.5, 54.4, 77.1, 79.5, 125.5, 127.0, 131.0, 130.6, 131.4, 145.4; *Z*-isomer: 28.4, 31.7, 58.0, 74.9, 79.4, 125.5, 126.9, 131.0, 130.0, 131.4, 147.0; anal. calcd. for $C_{15}H_{20}Cl_2N_2O_4$: Calcd. C 49.60%, H 5.55%, N 7.71%; found C 49.38%, H 5.69%, N 7.60%.

tert-Butyl (2E/Z)-2-[2-(3,4-dichlorophenyl)-2-hydroxy-1-propoxypropylidene]hydrazinecarboxylate ***4m***

Colorless solid, yield: 67%; mp: 55.9°C; IR ν_{max} (KBr) cm^{-1}: 3354 (NH), 3314 (OH), 1708 (C=O), 1647 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 0.90 (t, $J = 7.1$ Hz, 3H), 1.36 (s, 9H), 1.63 (s, 3H), 1.61–1.66 (m, 2H), 3.86–3.96 (m, 2H), 7.34 (s, 1H), 7.30–7.70 (m, 3H), 9.77 (s, 1H). *Z*-isomer: 0.66 (t, $J = 7.1$ Hz, 3H), 1.44 (s, 9H), 1.57 (s, 3H), 1.34–1.39 (m, 2H), 3.53–4.07 (m, 2H), 6.39 (s, 1H), 7.30–7.70 (m, 3H), 9.02 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 10.8, 21.8, 28.3, 28.5, 68.2, 77.1, 79.4, 125.4, 127.0, 131.0, 130.5, 131.4, 145.5; *Z*-isomer: 10.3, 22.7, 28.4, 31.8, 71.5, 75.0, 79.5, 125.5, 126.9, 130.9, 130.5, 131.4, 147.1; anal. calcd. for $C_{17}H_{24}Cl_2N_2O_4$: Calcd. C 52.18%, H 6.18%, N 7.16%; found C 52.25%, H 6.49%, N 7.03%.

tert-Butyl (2E/Z)-2-[1-(benzyloxy)-2-(3,4-dichloro-phenyl)-2-hydroxypropylidene]hydrazinecarboxylate ***4n***

Colorless solid, yield: 81%; mp: 131.8°C; IR ν_{max} (KBr) cm^{-1}: 3380 cm^{-1} (NH), 1701 cm^{-1} (C=O), 1637 cm^{-1} (C=N); ratio *E*/*Z* = 75:25; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.38 (s, 9H), 1.66 (s, 3H), 5.05 (s, 2H), 7.40 (s, 1H), 7.12–7.64 (m, 8H), 9.81 (s, 1H). *Z*-isomer: 1.43 (s, 9H), 1.61 (s, 3H), 4.80–5.15 (dd, 2H), 6.56 (s, 1H), 7.12–7.64 (m, 8H), 9.11 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 27.9, 28.0, 67.7, 76.7, 79.1, 125.0, 126.6, 127.3, 127.8, 127.9, 128.2, 130.6, 130.2, 130.9, 136.50, 144.82. *Z*-isomer: 28.0, 31.4, 70.8, 74.7, 79.2, 124.6, 126.5, 127.3, 127.7, 127.9, 128.2, 130.5, 129.5, 130.1, 136.7, 143.4; anal. calcd. for $C_{21}H_{24}Cl_2N_2O_4$: Calcd. C 57.41%, H 5.51%, N 6.38%; found C 57.21%, H 5.63%, N 6.26%.

tert-Butyl (2E/Z)-2-[2-(3,4-dichlorophenyl)-2-hydroxy-1-(2-phenylethoxy)propylidene]hydrazinecarboxylate ***4o***

Colorless solid, yield: 75%; mp: 147.9°C; IR ν_{max} (KBr) cm^{-1}: 3393 (NH), 3336 (OH), 1704 (C=O), 1654 (C=N); ratio *E*/*Z* = 57:43; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.35 (s, 9H), 1.55 (s, 3H), 2.90–2.97 (m, 2H), 4.09–4.19 (m, 2H), 7.32 (s, 1H), 7.02–7.60 (m, 8H), 9.76 (s, 1H). *Z*-isomer: 1.44 (s, 9H), 1.55 (s, 3H), 2.65–2.80 (m, 2H), 3.84–4.29 (m, 2H), 6.45 (s, 1H), 7.02–7.60 (m, 8H), 8.76 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm):

E-isomer: 27.9, 28.0, 34.2, 70.1, 76.5, 79.1, 124.9, 126.1, 126.4, 128.2, 128.8, 130.4, 130.1, 130.9, 138.6, 144.8. *Z*-isomer: 27.9, 31.2, 35.1, 67.2, 74.5, 79.0, 125.0, 126.1, 126.4, 128.2, 128.5, 130.5, 123.0, 131.0, 137.8, 146.4; anal. calcd. for $C_{22}H_{26}Cl_2N_2O_4$: Calcd. C 58.28%, H 5.78%, N 6.18%; found C 58.16%, H 5.91%, N 6.09%.

Ethyl (2E/Z)-2-[2-(3-bromo-4-fluorophenyl)-1-ethoxy-2-hydroxypropylidene]hydrazinecarboxylate ***4p***

Colorless solid, yield: 82%; mp: 102.3°C; IR ν_{max} (KBr) cm^{-1}: 3358 (NH), 3334 (OH), 1720 (C=O), 1637 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.13 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.62 (s, 3H), 3.95–4.06 (m, 4H), 7.37 (s, 1H), 7.39–7.69 (m, 3H), 9.94 (s, 1H). *Z*-isomer: 1.01 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.57 (s, 3H), 3.61–4.16 (m, 4H), 6.36 (s, 1H), 7.42–7.44 (m, 3H), 9.47 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.4, 14.9, 28.9, 60.6, 62.6, 77.1, 107.8 (d, $^2J_{C,F}$ = 21.4 Hz), 117.0 (d, $^2J_{C,F}$ = 22.1 Hz), 126.3 (d, $^3J_{C,F}$ = 7.6 Hz), 128.6 (d, $^3J_{C,F}$ = 7.6 Hz), 142.2 (d, $^4J_{C,F}$ = 3.1 Hz), 157.8 (d, $^1J_{C,F}$ = 244.9 Hz). *Z*-isomer: 14.9, 15.4, 32.2, 60.6, 66.0, 75.0, 107.8 (d, $^2J_{C,F}$ = 21.4 Hz), 117.0 (d, $^2J_{C,F}$ = 22.1 Hz), 126.3 (d, $^3J_{C,F}$ = 7.6 Hz), 128.6 (d, $^3J_{C,F}$ = 7.6 Hz), 142.2 (d, $^4J_{C,F}$ = 3.1 Hz), 157.8 (d, $^1J_{C,F}$ = 244.9 Hz); anal. calcd. for $C_{14}H_{18}BrFN_2O_4$: Calcd. C 44.58%, H 4.81%, N 7.43%; found C 44.40%, H 4.95%, N 7.45%.

Ethyl (2E)-2-[2-hydroxy-1-methoxy-2-(naphthalen-2-yl)-propylidene]hydrazinecarboxylate ***4q***

Colorless solid, yield: 80%; mp: 138.3°C; IR ν_{max} (KBr) cm^{-1}: 3349 (NH), 1718 (C=O), 1641 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): 1.10 (t, J = 7.1 Hz, 3H), 1.72 (s, 3H), 3.69 (s, 3H), 3.93–4.04 (m, 2H), 7.31 (s, 1H), 7.50–7.98 (m, 7H), 10.07 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): 14.8, 29.0, 54.9, 60.6, 77.8, 123.0, 123.4, 126.6, 126.8, 127.8, 128.5, 128.5, 132.6, 132.9, 141.7; anal. calcd. for $C_{17}H_{20}N_2O_4$: Calcd. C 64.54%, H 6.37%, N 8.86%; found C 64.42%, H 6.45%, N 8.70%.

Ethyl (2E/Z)-2-[2-hydroxy-2-(naphthalen-2-yl)-1-propoxypropylidene]hydrazinecarboxylate ***4r***

Colorless solid, yield: 81%; mp: 122.8°C; IR ν_{max} (KBr) cm^{-1}: 3369 (NH), 3326 (OH), 1718, 1686 (C=O), 1637, 1622 (C=N); ratio *E*/*Z* = 57:43; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 0.94 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H), 1.64–1.71 (m, 2H), 1.74 (s, 3H), 3.92–4.03 (m, 4H), 7.31 (s, 1H), 7.47–7.96 (m, 7H), 10.07 (s, 1H). *Z*-isomer: 0.56 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.29–1.41 (m, 2H), 1.67 (s, 3H), 3.51–4.18 (m, 4H), 6.33 (s, 1H), 7.47–7.96 (m, 7H), 9.32 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 10.5, 14.4, 21.4, 28.5, 60.2, 67.8, 77.4, 122.5, 122.9, 126.1, 126.3, 127.3, 127.9, 128.0, 132.2, 132.7, 141.3, 153.5. *Z*-isomer: 9.8, 14.6, 22.2, 32.0, 60.1, 71.0, 75.1, 122.6, 123.0, 125.8, 126.1, 127.4, 127.8, 128.0, 132.0, 132.5, 142.9, 152.4; anal. calcd. for $C_{19}H_{24}N_2O_4$: Calcd. C 66.26%, H 7.02%, N 8.13%; found C 66.14%, H 6.98%, N 8.20%.

Ethyl (2E/Z)-2-[1-(benzyloxy)-2-hydroxy-2-(naphthalen-2-yl)propylidene]hydrazinecarboxylate ***4s***

Colorless solid, yield: 87%; mp: 133.9°C; IR ν_{max} (KBr) cm^{-1}: 3356 (NH), 3326 (OH), 1715, 1709 (C=O), 1655, 1637 (C=N); ratio *E*/*Z* = 70:30; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.12 (t, J = 7.1 Hz, 3H), 1.76 (s, 3H), 3.95–4.05 (m, 2H), 5.13 (s, 2H), 7.36 (s, 1H), 7.06–8.02 (m, 7H), 10.11 (s, 1H). *Z*-isomer: 1.23 (t, J = 7.1 Hz, 3H), 1.72 (s, 3H), 4.10–4.15 (m, 2H), 4.70–5.24 (dd, 2H), 6.50 (s, 1H), 7.06–8.02 (m, 7H), 9.39 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.8, 29.0, 60.7, 68.2, 77.8, 123.1, 123.4, 126.6, 126.7, 127.8, 128.2, 128.3, 128.5, 128.7, 132.6, 132.9, 137.1, 141.6. *Z*-isomer: 15.0, 32.4, 60.7, 71.2, 75.7, 123.2, 123.4, 126.3, 126.7, 127.8, 128.0, 128.1, 128.4, 128.5, 132.5, 133.2, 137.1, 143.3; anal. calcd. for $C_{23}H_{24}N_2O_4$: Calcd. C 70.39%, H 6.16%, N 7.14%; found C 70.19%, H 6.24%, N 6.94%.

Ethyl (2E/Z)-2-[2-hydroxy-2-(naphthalen-2-yl)-1-(2-phenylethoxy)propylidene]hydrazinecarboxylate ***4t***

Colorless solid, yield: 77%; mp: 150.1°C; IR ν_{max} (KBr) cm^{-1}: 3373 (NH), 3326 (OH), 1710 (C=O), 1654 (C=N); ratio *E*/*Z* = 90:10; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.09 (t, J = 7.1 Hz, 3H), 1.65 (s, 3H), 2.98 (t, J = 5.9 Hz, 2H), 3.90–4.04 (m, 2H), 4.18–4.24 (m, 2H), 7.29 (s, 1H), 7.23–7.89 (m, 12H), 10.04 (s, 1H). *Z*-isomer: 1.24 (t, J = 7.1 Hz, 3H), 1.67 (s, 3H), 2.53–2.76 (m, 2H), 4.10–4.16 (m, 2H), 4.27–4.37 (m, 2H), 6.39 (s, 1H), 6.84–7.89 (m, 12H), 9.17 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.4, 28.5, 34.3, 60.1, 67.3, 77.2, 122.4, 122.8, 126.1, 126.2, 126.2, 127.3, 127.9, 128.0, 128.2, 128.9, 132.1, 132.4, 138.8, 141.1. *Z*-isomer: 14.5, 31.8, 35.1, 60.2, 69.8, 75.1, 122.7, 123.0, 125.8, 126.0, 126.2, 127.4, 127.9, 128.1, 128.4, 128.9, 132.0, 132.7, 137.7, 142.7; anal. calcd. for $C_{24}H_{26}N_2O_4$: Calcd. C 70.92%, H 6.45%, N 6.89%; found C 70.67%, H 6.60%, N 6.63%.

tert-Butyl (2E/Z)-2-[2-(3,4-dichlorophenyl)-1-ethoxy-ethylidene]hydrazinecarboxylate ***7***

Colorless solid, yield: 84%; mp: 128.1°C; IR ν_{max} (KBr) cm^{-1}: 3221, 3192 (NH), 1717, 1694 (C=O), 1655 (C=N); ratio *E*/*Z* = 56:44; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.16 (t, J = 7.1 Hz, 3H), 1.42 (s, 9H), 3.73 (s, 2H), 3.96–4.05 (m, 2H), 7.18–7.61 (m, 3H), 9.39 (s, 1H). *Z*-isomer: 1.18 (t, J = 7.1 Hz, 3H), 1.41 (s, 9H), 3.76 (s, 2H), 3.96–4.05 (m, 2H), 7.18–7.61 (m, 3H), 8.95 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 15.6, 28.7, 36.1, 64.9, 81.3, 128.0, 130.5, 131.2, 131.7, 133.3, 136.0. *Z*-isomer: 14.5, 28.7, 34.5, 63.3, 81.1, 128.6, 130.5, 131.0, 131.5, 133.1, 135.0; anal. calcd. for $C_{15}H_{20}Cl_2N_2O$: Calcd. C 51.88%, H 5.81%, N 8.07%; found C 51.49%, H 5.88%, N 8.31%.

General procedure for the synthesis of compounds ***5a–g***, ***6a***

To a stirring solution of the appropriate α-hydroxy thiocarboxylic *O*-ester **3** (5 mmol) in ethyl acetate (15 mL), the appropriate (thio)semicarbazide [15] (6 mmol) was added. The reaction mixture was stirred at room temperature and monitored by thin-layer chromatography (TLC). After completion of the reaction the organic layer was washed with water (3 × 10 mL), dried with $MgSO_4$ and evaporated. After removal of the solvent the remaining residue was crystallized from Et_2O/*n*-hexane at 5°C to afford **5a–g**, **6a** as solid compounds. Recrystallization from EtOAc/*n*-hexane provided analytically pure products.

Ethyl (1E/Z)-2-hydroxy-N-(methylcarbamoyl)-2-(naphthalen-2-yl)propanehydrazonoate ***5a***

Colorless solid, yield: 84%; mp: 173.6°C; IR ν_{max} (KBr) cm^{-1}: 3432, 3302, 3177 (NH, OH), 1654 (C=O), 1644 (C=N); ratio *E*/*Z* = 62:38; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.28 (t, J = 7.0 Hz, 3H), 1.69 (s, 3H), 2.58 (d, 3H), 4.09–4.14 (m, 2H), 6.70 (d, 1H), 7.08 (s, 1H), 7.48–7.97 (m, 7H), 9.13 (s, 1H). *Z*-isomer:

0.93 (t, $J = 7.0$ Hz, 3H), 1.71 (s, 3H), 2.71 (d, 3H), 3.55–4.22 (m, 2H), 6.22 (s, 1H), 6,35 (d, 1H), 7.48–7.97 (m, 7H), 8.54 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.5, 26.4, 29.2, 62.4, 77.2, 122.9, 123.4, 126.5, 126.7, 127.8, 128.4, 128.5, 132.6, 132.9, 141.9, 152.4, 156.1. *Z*-isomer: 15.4, 26.6, 31.9, 65.7, 75.4, 123.1, 123.7, 126.2 126.6, 127.8, 128.1, 128.3, 132.4, 133.1, 143.5, 156.1, 156.6; anal. calcd. for $C_{17}H_{21}N_3O_3$: Calcd. C 64.74%, H 6.71%, N 13.32%; found C 64.89%, H 6.86%, N 13.11%.

Ethyl (1E/Z)-N-(benzylcarbamoyl)-2-hydroxy-2-(naphthalen-2-yl)propanehydrazonoate ***5b***

Colorless solid, yield: 82%; mp: 158.8°C; IR ν_{max} (KBr) cm^{-1}: 3424, 3318, 3254 (NH, OH), 1649 (C=O), 1632 (C=N); ratio *E*/*Z* = 60:40; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.28 (t, $J = 7.0$ Hz, 3H),1.71 (s, 3H), 4.11–4.16 (m, 2H), 4.20–4.26 (m, 2H), 7.17 (s, 1H), 7.13–8.00 (m, 12H), 7.03 (t, $J = 6.6$ Hz, 1H), 9.27 (s, 1H). *Z*-isomer: 0.94 (t, $J = 7.0$ Hz, 3H), 1.73 (s, 3H), 3.57–4.45 (m, 4H), 6.25 (s, 1H), 7.13–8.00 (m, 13H), 8.72 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.0, 28.7, 42.3, 62.0, 76,8, 122.7, 123.2, 125.9, 126.1, 126.5, 126.7, 126.9, 127.4, 127.7, 127.9, 128.0, 128.1, 132.0, 132.7, 140.7, 143.0, 150.0, 155.7. *Z*-isomer: 15.0, 31.5, 42.5, 65.4, 75.0, 122.5, 122.9, 126.0, 126.2, 126.3, 126.8, 126.9, 127.3, 127.8, 127.9, 128.0, 128.1, 132.1, 132.5, 141.4, 143.0, 152.2, 155.3; anal. calcd. for $C_{23}H_{25}N_3O_3$: Calcd. C 70.57%, H 6.44%, N 10.73%; found C 70.51%, H 6.44%, N 10.39%.

Ethyl (1E/Z)-N-[(benzyloxy)carbamoyl]-2-hydroxy-2-(naphthalen-2-yl)propanehydrazonoate ***5c***

Colorless solid, yield: 78%; mp: 129.6°C; IR ν_{max} (KBr) cm^{-1}: 3365, 3223 (NH, OH), 1678 (C=O), 1647 (C=N); ratio *E*/*Z* = 5:95; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.31 (t, $J = 7.1$ Hz, 3H), 1.72 (s, 3H), 4.07–4.13 (m, 2H), 4.81 (s, 2H), 7.26 (s, 1H), 7.33–7.95 (m, 12H), 9.39 (s, 1H), 10.40 (s, 1H). *Z*-isomer: 0.91 (t, $J = 7.1$ Hz, 3H), 1,67 (s, 3H), 3.55–4.29 (m, 2H), 4.84 (s, 2H), 6.33 (s, 1H), 7.33–7.95 (m, 12H), 9.02 (s, 1H), 9.79 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.5, 29.2, 62.5, 75.2, 77.8, 122.9, 123.3, 126.5, 126.7, 127.8, 128.4, 128.5, 128.7, 128.9, 129.2, 132.5, 133.1, 136.4, 143.3, 152.3, 156.2. *Z*-isomer: 15.5, 32.2, 66.0, 75.2, 77.9, 123.0, 123.5, 126.3, 126.6, 127.9, 128.3, 128.4, 128.6, 128.7, 129.2, 132.5, 133.1, 136.4, 143.3, 152.3, 156.2; anal. calcd. for $C_{23}H_{25}N_3O_4$: Calcd. C 67.80%, H 6.18%, N 10.31%; found C 67.67%, H 6.08%, N 10.38%.

Ethyl (1E/Z)-2-(3,4-dichlorophenyl)-2-hydroxy-N-(methylcarbamoyl)propanehydrazonoate ***5d***

Colorless solid, yield: 81%; mp: 173.8°C; IR ν_{max} (KBr) cm^{-1}: 3430, 3369, 3318, 3298, 3219 (NH, OH), 1654 (C=O), 1648 (C=N); ratio *E*/*Z* = 60:40; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.25 (t, $J = 7.0$ Hz, 3H), 1.60 (s, 3H), 2.58 (d, 3H), 4.05–4.10 (m, 2H), 6.40–6.43 (q, 1H), 7.22 (s, 1H), 7.60–7.65 (m, 3H), 9.02 (s, 1H). *Z*-isomer: 1.02 (t, $J = 7.0$ Hz, 3H), 1.63 (s, 3H), 2.68 (d, 3H), 3.59–4.16 (m, 2H), 6.30 (s, 1H), 6.67–6.71 (q, 1H), 7.34–7.37 (m, 3H), 8.61 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.4, 26.4, 28.6, 62.5, 76.5, 125.3, 126.8, 131.0, 130.4, 131.3, 145.6, 151.4, 156.1. *Z*-isomer: 15.4, 26.5, 31.4, 66.0, 74.8, 125.6, 127.0, 130.9, 129.9, 131.3, 147.2, 149.3, 156.5; anal. calcd. for $C_{13}H_{17}Cl_2N_3O_3$: Calcd. C 46.72%, H 5.13%, N 12.57%; found C 46.43%, H 5.18%, N 12.59%.

Ethyl (1E/Z)-N-(benzylcarbamoyl)-2-(3,4-dichlorophenyl)-2-hydroxypropanehydrazonoate ***5e***

Colorless solid, yield: 83%; mp: 158.4°C; IR ν_{max} (KBr) cm^{-1}: 3424, 3408, 3301 (NH, OH), 1656 (C=O), 1647 (C=N); ratio *E*/*Z* = 58:42; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.24 (t, $J = 7.0$ Hz, 3H), 1.64 (s, 3H), 4.07–4.12 (m, 2H), 4.23–4.30 (m, 2H), 7.26 (s, 1H), 7.06–7.66 (m, 9H), 9.16 (s, 1H). *Z*-isomer: 1.03 (t, $J = 7.0$ Hz, 3H), 1.62 (s, 3H), 3.62–4.21 (m, 2H), 4.30–4.41 (m, 2H), 6.33 (s, 1H), 7.06–7.66 (m, 9H), 8.79 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.4, 28.8, 42.8, 62.6, 76.6, 125.4, 126.8, 131.0, 127.1, 127.2, 128.5, 130.5, 131.4, 141.1, 145.5, 149.7, 155.8. *Z*-isomer: 15.4, 31.3, 42.9, 66.0, 74.8, 125.6, 126.9, 130.9, 127.1, 127.3, 128.6, 129.9, 131.3, 141.1, 147.2, 149.6, 156.0; anal. calcd. for $C_{19}H_{21}Cl_2N_3O_3$: Calcd. C 55.62%, H 5.16%, N 10.24%; found C 55.88%, H 5.48%, N 10.51%.

Ethyl (1E/Z)-2-(3,4-dichlorophenyl)-2-hydroxy-N-[(4-methylbenzyl)carbamoyl]propanehydrazonoate ***5f***

Colorless solid, yield: 79%; mp: 157.4°C; IR ν_{max} (KBr) cm^{-1}: 3487, 3354, 3246 (NH, OH), 1655 (C=O), 1646 (C=N); ratio *E*/*Z* = 8:92; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.24 (t, $J = 7.0$ Hz, 3H),1.60 (s, 3H), 2.25 (s, 3H), 4.08–4.18 (m, 2H), 4.23–4.36 (m, 2H), **7**.09 (s, 1H), 7.12–7.63 (m, 8H), 9.14 (s, 1H). *Z*-isomer: 1.03 (t, $J = 7.0$ Hz, 3H), 1.63 (s, 3H), 2.28 (s, 3H), 3.61–4.18 (m, 2H), 4.23–4.36 (m, 2H), 6.32 (s, 1H), 7.01 (s, 1H), 7.12–7.63 (m, 7H), 8.77 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.4, 21.0, 28.8, 42.7, 62.6, 76.6, 125.3, 126.8, 131.0, 127.2, 129.0, 130.5, 131.4, 135.8, 138.1, 145.5, 151.6, 155.7. *Z*-isomer: 15.5, 21.0, 31.3, 42.5, 66.0, 74.8, 125.6, 127.1, 130.9, 127.4, 129.1, 129.9, 131.3, 135.9, 138.0, 147.2, 149.6, 156.0; anal. calcd. for $C_{20}H_{23}Cl_2N_3O_3$: Calcd. C 56.61%, H 5.46%, N 9.90%; found C 56.25%, H 5.60%, N 9.82%.

Ethyl (1E/Z)-N-[(4-chlorobenzyl)carbamoyl]-2-(3,4-dichlorophenyl)-2-hydroxypropanehydrazonoate ***5g***

Colorless solid, yield: 80%; mp: 180.6°C; IR ν_{max} (KBr) cm^{-1}: 3423, 3400, 3300 (NH, OH), 1647 (C=O, C=N); ratio *E*/*Z* = 92:8; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.25 (t, $J = 7.0$ Hz, 3H), 1.62 (s, 3H), 4.07–4.13 (m, 2H), 4.14–4.40 (m, 2H), 6.33 (s, 1H), 7.23–7.66 (m, 8H), 9.18 (s, 1H). *Z*-isomer: 1.03 (t, $J = 7.0$ Hz, 3H), 1.64 (s, 3H), 3.61–4.06 (m, 2H), 4.14–4.40 (m, 2H), 6.33 (s, 1H), 7.23–7.66 (m, 8H), 8.81 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 14.4, 28.8, 42.2, 62.7, 76.6, 125.3, 126.6, 131.0, 128.4, 129.1, 130.5, 131.4, 131.3, 140.3, 145.5, 151.8, 155.7. *Z*-isomer: 15.4, 31.4, 42.3, 66.0, 74.8, 125.6, 127.0, 130.9, 128.5, 129.2, 129.9, 131.4, 131.3, 140.2, 147.2, 149.7, 156.1; anal. calcd. for $C_{19}H_{20}Cl_3N_3O_3$: Calcd. C 51.31%, H 4.53%, N 9.45%; found C 51.13%, H 4.70%, N 9.30%.

Ethyl (1E/Z)-N-(ethylcarbamothioyl)-2-hydroxy-2-(naphthalen-2-yl)propanehydrazonoate ***6a***

Colorless solid, yield: 84%; Mp: 118.3°C; IR ν_{max} (KBr) cm^{-1}: 3358, 3325, 3140, 3123 (NH, OH), 1637 (C=N), 1128 (C=S); ratio *E*/*Z* = 85:15; ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): *E*-isomer: 1.04 (t, $J = 7.1$ Hz, 3H), 1.28 (t, $J = 7.0$ Hz, 3H), 1.74 (s, 3H), 3.39–3.51 (m, 2H), 4.15–4.21 (q, 2H), 7.33 (s, 1H), 7.50–7.98 (m, 7H), 7.79 (t, $J = 6.0$ Hz, 1H), 10.54 (s, 1H). *Z*-isomer: 0.94 (t, $J = 7.1$ Hz, 3H), 1.17 (t, $J = 7.0$ Hz, 3H), 1.75 (s, 3H), 3.55–3.71 (m, 2H), 4.27–4.35 (q, 2H), 6.43 (s, 1H), 7.50–7.98 (m, 7H), 8.24 (t, $J = 6.0$ Hz, 1H), 9.18 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6),

δ (ppm): *E*-isomer: 14.4, 15.1, 28.9, 38.1, 63.1, 77.6, 123.0, 123.3, 126.6, 126.8, 127.8, 128.5, 128.6, 132.6, 132.9, 141.5, 154.6, 175.4. *Z*-isomer: 15.0, 15.4, 32.1, 38.9, 66.5, 75.6, 123.2, 123.4, 126.3, 126.6, 127.9, 128.4, 128.5, 132.5, 133.1, 142.9, 151.9, 176.9; anal. calcd. for $C_{18}H_{23}N_3O_2S$: Calcd. C 62.58%, H 6.71%, N 12.16%; found C 62.41%, H 6.73%, N 12.15%.

Determination of *in-vitro* antimalarial activity

Culture of P. falciparum

The *P. falciparum* 3D7 strain was maintained in continuous culture, according to Trager and Jensen [17]. The parasites were grown in human red blood cells (RBCs blood group A positive), RPMI 1640 medium supplemented with 25 mM HEPES, 20 mM sodium bicarbonate, and 0.5% AlbuMAX (Invitrogen, Karlsruhe, Germany) at 5% hematocrit. The flasks were gassed with 90% N_2, 5% O_2, and 5% CO_2 and incubated at 37°C. The development of the cultures and the percentage of infected RBCs were determined by light microscopy of Giemsa-stained thin smears.

Preparation of drug solutions

45 μmol of the respective compounds were solved in 4.5 mL DMSO/ethanol (50:50) and further diluted with water/ethanol (50:50) to obtain concentrations of 5 μM. In order to ensure that the solvent *per se* had no effect on parasite growth, negative control tests were performed using Me_2SO at the same concentration.

Determination of parasite growth inhibition

The tests were carried out in 96-well microtiter plates under strict aseptic conditions, according to literature [16]. Dilutions of each compound were added to 250 μL of a suspension of *P. falciparum* infected erythrocytes (1.5% hematocrit, 1.5–2% parasitemia). The plates were flushed with a gas mixture consisting of 90% N_2, 5% O_2 and 5% CO_2, closed tightly and incubated at 37°C for 24 h. Afterwards, 0.1 μCi of 8-[^{3}H]-hypoxanthine was added to each well. The plates were flushed with the above mentioned gas mixture, incubated for additional 24 h at 37°C and subsequently harvested with a cell harvester system (Inotech, Dottikon, Switzerland). Infected erythrocytes were washed four times with distilled water before they were analyzed for incorporated radioactivity in a multidetector liquid scintillation counter (Wallac, Turku, Finland).

Conclusions

In conclusion, novel α-hydroxy hydrazonates have been prepared in good yields and evaluated as antiplasmodials. Remarkable antiplasmodial activity was ascertained for compounds **4r**, **5d** and **4q** with IC_{50} values of 0.6, 0.85 and 1.1 μM, making these α-hydroxy hydrazonates promising candidates for further drug-design.

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