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Functionally substituted aromatic aldehydes as reagents in the synthesis of new substituted thioglycolurils

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Dedicated to Prof. Oleg A. Rakitin on the occasion of his 65th anniversary

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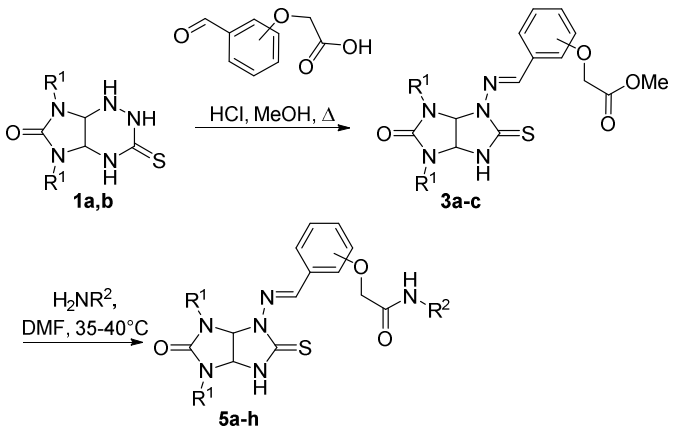
Abstract

Simple approach to the synthesis of 2-(4(2)-(((4,6-dialkyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)phenoxy)acetates or acetamides (new substituted thioglycolurils) based on the reaction of 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazine-6-ones with functionally substituted aromatic aldehydes has been developed. Synthesized thioglycolurils with acetate function can undergo further simple transformation to the corresponding acetamides.



R^1 = Me, Et; R^2 = Me, Et, Pr^n; HO_2CCH_2O-*para*, *ortho*

Keywords: Imidazotriazines, ring contraction, 4(2)-formylphenoxyacetic acids, thioglycolurils, primary amines

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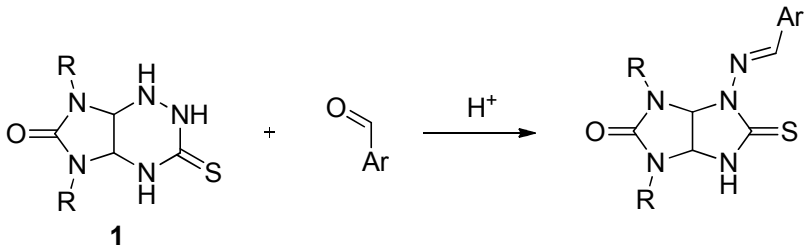
Introduction

The progress in the chemistry of 5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-ones (monothioanalogues of glycolurils) is of great interest due to various practically useful properties of both glycolurils[1-4] and their imino- and thioanalogues.[5-15] Thioanalogues of glycolurils have already been recognized as substrates for the template-directed crossed-Claisen condensation,[8-11] building blocks for the synthesis of semithiobambusurils,[12] organocatalysts for N-Boc protection of amines[13] or α-monobromination of 1,3-dicarbonyl compounds,[14] and as anxiolytic agents.[15]

There are different methods known for the synthesis of thioglycolurils, including recently reported approach based on the tandem hydrazone formation and triazine ring contraction of 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazine-6-ones **1** with aromatic aldehydes (Scheme 1).[16]



Scheme 1. Reaction of imidazotriazines **1** with aromatic aldehydes.

Some monothioanalogues of glycolurils prepared by this method demonstrated sedative[17] or cytotoxic[18] activities.

Substituted aromatic aldehydes bearing other functional groups could be used to introduce different additional moieties including pharmacophore ones in thioglycoluril framework.

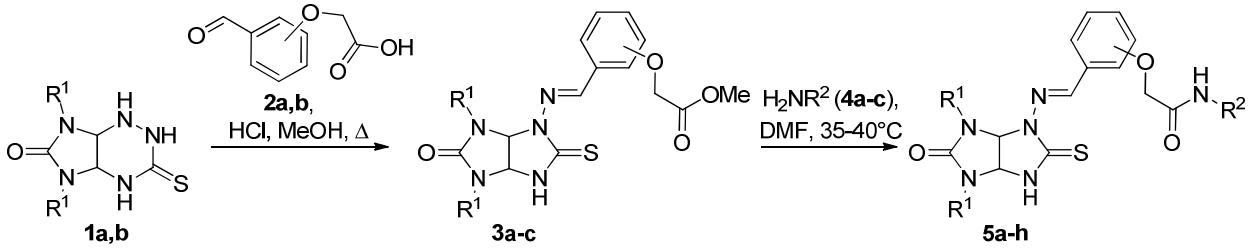
In the present paper we have synthesized monothioanalogues of glycoluril by the reaction of 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazine-6-ones **1** with aromatic aldehydes bearing substituent containing a carboxylic function and studied the reactivity of these thioglycolurils toward amines.

Results and Discussion

Recently we described a new method for the synthesis of substituted thioglycolurils by reaction of imidazotriazines **1** with (hetero)aromatic aldehydes which includes a tandem hydrazone formation and triazine ring contraction.[19] Here we used this approach to the preparation of N-(benzylideneamino)thioglycolurils which are functionally substituted in aromatic ring. Reaction of compounds **1a,b** and 4(2)-formylphenoxyacetic acids **2a,b** in methanol in the presence of HCl led to methyl 2-(4(2)-(((4,6-dialkyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)phenoxy)acetates **3a-c** in 51-58% yield (Scheme 2). Apart from ring contraction reaction, esterification of carboxylic group with methanol occurred.

Reaction of methyl esters **3a-c** with primary amines **4a-c** proceeded in DMF at room temperature and at 35-40 °C (Scheme 2). The reaction progress was monitored by recording ^{1}H NMR spectra of samples taken from the reaction mixture after 24, 72, 96, and 120 h. The signals of starting compounds **3a-c** have

disappeared at temperature 35-40 °C after 120 h. The yields of corresponding amides **5a-h** were 52-93% (Table 1). At room temperature, conversion of starting compounds was not observed.



1a: R^1 = Me; **1b**: R^1 = Et; **2a**: *para*; **2b**: *ortho*; **3a**: R^1 = Me, *para*; **3b**: R^1 = Et, *para*; **3c**: R^1 = Me, *ortho*;
4a: R^2 = Me, **4b**: R^2 = Et, **4c**: R^2 = Pr^n

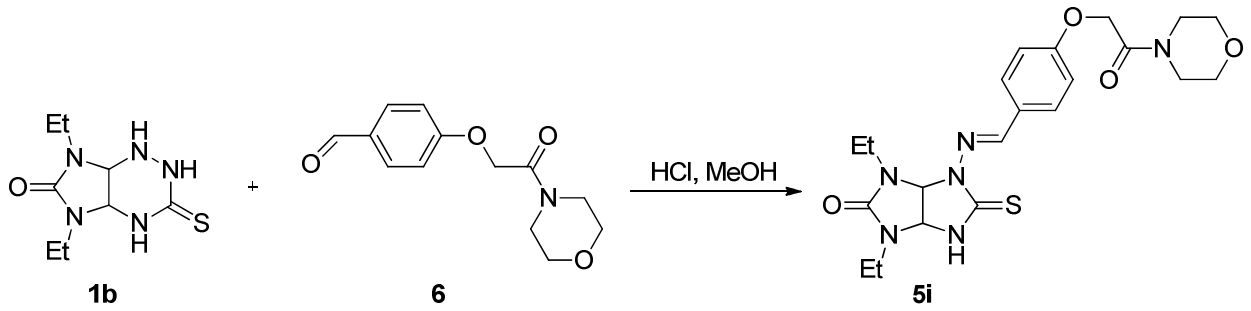
Scheme 2. Synthesis of thioglycolurils **3a-c** and their reaction with amines.

Table 1. Amides **5a-h** prepared via reaction of esters **3a-c** with primary amines **4a-c**

Amide **5**	R^1	R^2	Position of substituent	Yield (%)[a]
a	Me	Me	para	61
b	Me	Et	para	56
c	Me	Pr^n	para	65
d	Et	Me	para	74
e	Et	Et	para	82
f	Et	Pr^n	para	93
g	Me	Me	ortho	52
h	Me	Et	ortho	57

[a]Yield of isolated product.

We used another sequence of reactions to prepare amide **5i** containing morpholine fragment since its direct synthesis usually requires harsh conditions [20-22]. Imidazotriazine **1b** reacted with previously prepared[23] 4-(2-morpholino-2-oxoethoxy)benzaldehyde **6** (Scheme 3). Thioglycoluril **5i** was synthesized in 53% yield.



Scheme 3. Synthesis of amide **5i**.

The structures of thioglycoluryls **3** and **5** was ascertained by the IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectral data. Earlier reported 1,3-dialkyl-4-(benzylideneamino)- and 4-((hetarylmethyliden)amino)thioglycolurils

possessed only the *E*-configuration, which was confirmed both by NMR spectroscopy[24] and by X-ray analysis data.[16,18,19]

Conclusions

A simple approach to the synthesis of new thioglycolurils with ester or amide function in the substituent based on reaction of 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazine-6-ones with functionally substituted aromatic aldehydes has been developed. This reaction comprises the tandem hydrazone formation and triazine ring contraction. An amide function can be previously introduced into molecule of benzaldehyde or obtained by the reaction of thioglycolurils bearing ester function in the substituent with primary amines. This approach allows to introduce different additional functionally groups including pharmacophore ones as morpholine for example.

Experimental Section

General. All reagents were purchased from Acros organics and used without further purification. Melting points were determined in open glass capillaries on a Gallenkamp (Sanyo) melting point apparatus. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM300 (300.13 MHz and 75.5 MHz, respectively) and Bruker DRX500 (500.13 MHz and 125.76 MHz, respectively) spectrometers using DMSO-d_6 as solvent. Chemical shifts (δ) are given in ppm from TMS as internal standard. Infrared (IR) spectra were recorded on a Bruker ALPHA instrument as KBr pellets. High resolution mass spectra (HRMS) were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI). 4(2)-Formylphenoxyacetic acids **2a,b** and 4-(2-morpholino-2-oxoethoxy)benzaldehyde (**6**) were prepared according to the known procedures.[23,25,26]

Methyl 2-(4(2)-(((4,6-dialkyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)-phenoxy)acetates (3a-c) and 1,3-diethyl-4-((4-(2-morpholino-2-oxoethoxy)benzylidene)amino)-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (5i). To a stirred suspension of 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-one **1a** or **1b** (2 mmol) in methanol (30 mL), two drops of concentrated HCl and an aldehyde **2a** or **2b** or **6** (2 mmol) were added. The resulting mixture was heated to reflux and stirred for 1.5 h (2 h for **5i**), then concentrated to dryness. The residue was recrystallized from EtOH (**3a-c**) or MeOH-H_2O (10 : 2) (**5i**) to give desired thioglycoluril **3** or **5i:**

Methyl 2-(4-(((4,6-dimethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)-phenoxy)acetate (3a). White solid (0.383 g, 51%), mp 169-171 °C. IR (KBr) ν, cm^{-1}: 3207, 1766, 1721, 1611, 1598, 1509, 1412, 1298, 1269, 1254, 1212, 1177, 1071, 1055, 1032. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.75 (s, 3H, NMe), 2.84 (s, 3H, NMe), 3.71 (s, 3H, OMe), 4.88 (s, 2H, OCH_2), 5.38 (d, ^{3}J 8.2 Hz, 1H, CH), 5.91 (d, ^{3}J 8.2 Hz, 1H, CH), 7.04 (d, ^{3}J 8.6 Hz, 2H, CH_{arom}), 7.71 (d, ^{3}J 8.6 Hz, 2H, CH_{arom}), 9.04 (s, 1H, N=CH), 9.91 (s, 1H, NH) . ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.2, 30.0 (NMe), 51.8 (OMe), 64.6 (OCH_2), 68.0, 75.3 (CH), 114.9 ($2CH_{arom}$), 127.0 (C_{arom}), 129.0 ($2CH_{arom}$), 152.7 (N=CH), 157.5 (C=O), 159.6 (C_{arom}), 168.9 (C=O), 178.9 (C=S). HRMS (ESI): *m/z* calcd for $C_{16}H_{19}N_5O_4S+Na^+$: 400.1050; found: 400.1039;

Methyl 2-(4-(((4,6-diethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)phenoxy)-acetate (3b). White solid (0.47 g, 58%), mp 207-209 °C. IR (KBr) ν, cm^{-1}: 3180, 1737, 1704, 1611, 1595, 1508, 1474, 1429, 1311, 1275, 1248, 1207, 1166, 1067. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.01-1.10 (m, 6H, Me), 3.11-

3.38 (m, 4H, NCH_2), 3.71 (s, 3H, OMe), 4.88 (s, 2H, OCH_2), 5.49 (d, ^3J 8.4 Hz, 1H, CH), 5.94 (d, ^3J 8.4 Hz, 1H, CH), 7.04 (d, ^3J 8.6 Hz, 2H, CH_{arom}), 7.70 (d, ^3J 8.6 Hz, 2H, CH_{arom}), 9.15 (s, 1H, N=CH), 9.88 (s, 1H, NH) . ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.9, 13.4 (Me), 35.9, 37.0 (NCH_2), 51.8 (OMe), 64.6 (OCH_2), 66.1, 74.9 (CH), 115.0 ($2CH_{arom}$), 126.8 (C_{arom}), 129.1 ($2CH_{arom}$), 154.9 (N=CH), 156.8 (C=O), 159.7 (C_{arom}), 168.9 (C=O), 178.6 (C=S). HRMS (ESI): *m/z* calcd for $C_{18}H_{23}N_5O_4S+Na^+$: 428.1363; found: 428.1352.

Methyl 2-(2-(((4,6-dimethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)-phenoxy)acetate (3c). Pinkish solid (0.415 g, 55%), mp 178-179 °C. IR (KBr) ν, cm^{-1}: 3180, 1764, 1720, 1602, 1523, 1492, 1449, 1420, 1272, 1213, 1161, 1115, 1075, 1058, 1043, 748. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.76 (s, 3H, NMe), 2.90 (s, 3H, NMe), 3.71 (s, 3H, OMe), 4.90 (d, ^2J 16.7 Hz, 1H, OCH_2), 4.94 (d, ^2J 16.7 Hz, 1H, OCH_2), 5.40 (d, ^3J 8.3 Hz, 1H, CH), 5.97 (d, ^3J 8.3 Hz, 1H, CH), 7.06-7.10 (m, 2H, CH_{arom}), 7.43 (t, ^3J 7.7 Hz, 1H, CH_{arom}), 7.87 (d, ^3J 7.7 Hz, 1H, CH_{arom}), 9.35 (s, 1H, N=CH), 10.02 (s, 1H, NH) . ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.2, 30.6 (NMe), 51.9 (OMe), 65.2 (OCH_2), 68.1, 75.1 (CH), 113.1, 121.6 (CH_{arom}), 122.5 (C_{arom}), 125.8, 131.9 (CH_{arom}), 145.7 (N=CH), 156.5, 157.7 (C_{arom}, C=O), 168.9 (C=O), 179.0 (C=S). HRMS (ESI): *m/z* calcd for $C_{16}H_{19}N_5O_4S+Na^+$: 400.1050; found: 400.1041.

1,3-Diethyl-4-((4-(2-morpholino-2-oxoethoxy)benzylidene)amino)-5-thioxohexahydroimidazo[4,5-*d*]-imidazol-2(1*H*)-one (5i). White solid (0.488 g, 53%), mp 203-205 °C. IR (KBr) ν, cm^{-1}: 3261, 1701, 1678, 1605, 1512, 1503, 1474, 1453, 1436, 1311, 1276, 1255, 1233, 1200, 1172, 1107, 1074, 1055, 1033, 795. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03-1.12 (m, 6H, Me), 3.12-3.37 (m, 4H, NCH_2), 3.46-3.37 (m, 8H, CH_{2morph}), 4.95 (s, 2H, OCH_2), 5.51 (d, ^3J 8.4 Hz, 1H, CH), 5.96 (d, ^3J 8.4 Hz, 1H, CH), 7.04 (d, ^3J 8.5 Hz, 2H, CH_{arom}), 7.71 (d, ^3J 8.5 Hz, 2H, CH_{arom}), 9.16 (s, 1H, N=CH), 9.90 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.9, 13.4 (Me), 35.9, 37.0 (NCH_2), 41.6, 44.6 (NCH_{2morph}), 65.7 (OCH_2), 65.99 (CH), 66.05, 66.1 (OCH_{2morph}), 75.0 (CH), 115.1 (CH_{arom}), 126.4 (C_{arom}), 129.0 (CH_{arom}), 155.3 (N=CH), 156.8 (C=O), 160.3 (C_{arom}), 165.7 (C=O), 178.6 (C=S). HRMS (ESI): *m/z* calcd for $C_{21}H_{28}N_6O_4S+H^+$: 461.1966; found: 461.1964.

2-(4(2)-(((4,6-Dialkyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)phenoxy)-*N*-alkylacetamides (5a-h). To a stirred solution of ester **3a** or **3b** or **3c** (1 mmol) in DMF (7 mL), corresponding primary amine **4a** or **4b** or **4c** (5 mmol) was added. The resulting mixture was stirred at temperature 35-40 °C for 5 days, then concentrated to dryness and diluted with water. A precipitate was recrystallized from EtOH or MeOH to give desired amide **5.**

2-(4-(((4,6-Dimethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)phenoxy)-*N*-methylacetamide (5a). White solid (0.229 g, 61%), mp 233-235 °C. IR (KBr) ν, cm^{-1}: 3390, 3289, 1696, 1661, 1608, 1546, 1511, 1418, 1404, 1252, 1208, 1174, 1057, 1047. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.66 (br.s, 3H, NMe), 2.75 (s, 3H, NMe), 2.84 (s, 3H, NMe), 4.53 (s, 2H, OCH_2), 5.38 (d, ^3J 8.0 Hz, 1H, CH), 5.92 (d, ^3J 7.9 Hz, 1H, CH), 7.06 (d, ^3J 7.6 Hz, 2H, CH_{arom}), 7.72 (d, ^3J 7.6 Hz, 2H, CH_{arom}), 8.07 (br.s, 1H, NH), 9.03 (s, 1H, N=CH), 9.92 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.3 (NMe), 28.1, 29.9 (NMe), 67.0 (CH), 68.0 (OCH_2), 75.3 (CH), 115.1 ($2CH_{arom}$), 126.9 (C_{arom}), 129.0 ($2CH_{arom}$), 152.8 (N=CH), 157.5 (C=O), 159.7 (C_{arom}), 167.6 (C=O), 178.8 (C=S). HRMS (ESI): *m/z* calcd for $C_{16}H_{20}N_6O_3S+Na^+$: 399.1210; found: 399.1204.

2-(4-(((4,6-Dimethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)phenoxy)-*N*-ethylacetamide (5b). White solid (0.219 g, 56%), mp 121-123 °C. IR (KBr) ν, cm^{-1}: 3457, 3280, 1692, 1655, 1609, 1552, 1510, 1445, 1416, 1252, 1212, 1174, 1050, 793. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.04 (t, ^3J 6.9 Hz, 3H, Me), 2.75 (s, 3H, NMe), 2.84 (s, 3H, NMe), 3.12-3.19 (m, 2H, NCH_2), 4.52 (s, 2H, OCH_2), 5.38 (d, ^3J 8.0 Hz, 1H, CH), 5.91 (d, ^3J 8.0 Hz, 1H, CH), 7.06 (d, ^3J 8.0 Hz, 2H, CH_{arom}), 7.72 (d, ^3J 8.0 Hz, 2H, CH_{arom}), 8.13 (br.s, 1H, NH), 9.03 (s, 1H, N=CH), 9.91 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.7 (Me), 28.1, 29.9 (NMe), 33.2 (NCH_2), 67.0 (CH), 68.0 (OCH_2), 75.3 (CH), 115.1 ($2CH_{arom}$), 126.9 (C_{arom}), 129.0 ($2CH_{arom}$), 152.9 (N=CH), 157.5

(C=O), 159.8 (C_{arom}), 166.9 (C=O), 178.8 (C=S). HRMS (ESI): *m/z* calcd for $C_{17}H_{22}N_6O_3S+Na^+$: 413.1366; found: 413.1370.

2-(4-(((4,6-Dimethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)phenoxy)-*N*-propylacetamide (5c). White solid (0.263 g, 65%), mp 211-214 °C. IR (KBr) ν, cm^{-1}: 3399, 3269, 1690, 1660, 1604, 1542, 1512, 1486, 1458, 1419, 1250, 1230, 1204, 1170, 1040. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.84 (t, ^3J 7.3 Hz, 3H, Me), 1.43-1.47 (m, 2H, CH_2), 2.75 (s, 3H, NMe), 2.84 (s, 3H, NMe), 3.08-3.11 (m, 2H, NCH_2), 4.54 (s, 2H, OCH_2), 5.39 (d, ^3J 8.1 Hz, 1H, CH), 5.91 (d, ^3J 8.1 Hz, 1H, CH), 7.06 (d, ^3J 8.2 Hz, 2H, CH_{arom}), 7.72 (d, ^3J 8.2 Hz, 2H, CH_{arom}), 8.09 (br.s, 1H, NH), 9.05 (s, 1H, N=CH), 9.90 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.3 (Me), 22.3 (CH_2), 28.1, 30.0 (NMe), 40.1 (NCH_2), 67.0 (CH), 68.0 (OCH_2), 75.2 (CH), 115.1 ($2CH_{arom}$), 126.9 (C_{arom}), 129.0 ($2CH_{arom}$), 152.7 (N=CH), 157.5 (C=O), 159.8 (C_{arom}), 167.0 (C=O), 178.9 (C=S). HRMS (ESI): *m/z* calcd for $C_{18}H_{24}N_6O_3S+H^+$: 405.1703; found: 405.1702.

2-(4-(((4,6-Diethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)phenoxy)-*N*-methylacetamide (5d). White solid (0.299 g, 74%), mp 211-213 °C. IR (KBr) ν, cm^{-1}: 3453, 3177, 1708, 1686, 16089, 1594, 1506, 1474, 1457, 1428, 1416, 1246, 1206, 1165, 1073, 1045. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02-1.08 (m, 6H, Me), 2.66 (br.s, 3H, NMe), 3.08-3.34 (m, 4H, NCH_2), 4.54 (s, 2H, OCH_2), 5.49 (d, ^3J 8.0 Hz, 1H, CH), 5.94 (d, ^3J 7.9 Hz, 1H, CH), 7.06 (d, ^3J 7.9 Hz, 2H, CH_{arom}), 7.72 (d, ^3J 7.9 Hz, 2H, CH_{arom}), 8.07 (br.s, 1H, NH), 9.14 (s, 1H, N=CH), 9.88 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.8, 13.4 (Me), 25.3 (NMe), 35.9, 37.0 (NCH_2), 66.1 (CH), 67.0 (OCH_2), 74.9 (CH), 115.2 ($2CH_{arom}$), 126.7 (C_{arom}), 129.1 ($2CH_{arom}$), 155.0 (N=CH), 156.8 (C=O), 159.9 (C_{arom}), 167.6 (C=O), 178.6 (C=S). HRMS (ESI): *m/z* calcd for $C_{18}H_{24}N_6O_3S+Na^+$: 427.1523; found: 427.1519.

2-(4-(((4,6-Diethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)phenoxy)-*N*-ethylacetamide (5e). White solid (0.343 g, 82%), mp 222-224 °C (decomp). IR (KBr) ν, cm^{-1}: 3446, 3165, 1709, 1683, 1609, 1594, 1534, 1507, 1472, 1451, 1428, 1279, 1243, 1206, 1165, 1073, 1046. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03-1.12 (m, 9H, Me), 3.14-3.24 (m, 4H, NCH_2), 3.25-3.33 (m, 2H, NCH_2), 4.53 (s, 2H, OCH_2), 5.49 (d, ^3J 8.2 Hz, 1H, CH), 5.94 (d, ^3J 8.1 Hz, 1H, CH), 7.06 (d, ^3J 8.4 Hz, 2H, CH_{arom}), 7.72 (d, ^3J 8.4 Hz, 2H, CH_{arom}), 8.14 (br.s, 1H, NH), 9.14 (s, 1H, N=CH), 9.89 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.8, 13.4, 14.7 (Me), 33.2, 35.9, 37.0 (NCH_2), 66.1 (CH), 67.0 (OCH_2), 74.9 (CH), 115.2 ($2CH_{arom}$), 126.7 (C_{arom}), 129.0 ($2CH_{arom}$), 154.9 (N=CH), 156.8 (C=O), 159.9 (C_{arom}), 166.9 (C=O), 178.6 (C=S). HRMS (ESI): *m/z* calcd for $C_{19}H_{26}N_6O_3S+H^+$: 419.1860; found: 418.1849.

2-(4-(((4,6-Diethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)phenoxy)-*N*-propylacetamide (5f). White solid (0.402 g, 93%), mp 190-192 °C. IR (KBr) ν, cm^{-1}: 3434, 3179, 1709, 1687, 1595, 1539, 1507, 1471, 1444, 1428, 1277, 1245, 1206, 1166, 1072, 1048. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.83 (t, ^3J 7.1 Hz, 3H, Me), 1.01-1.10 (m, 6H, Me), 1.41-1.48 (m, 2H, CH_2), 3.08-3.31 (m, 6H, NCH_2), 4.54 (s, 2H, OCH_2), 5.49 (d, ^3J 8.2 Hz, 1H, CH), 5.94 (d, ^3J 8.2 Hz, 1H, CH), 7.06 (d, ^3J 8.0 Hz, 2H, CH_{arom}), 7.71 (d, ^3J 8.0 Hz, 2H, CH_{arom}), 8.11 (br.s, 1H, NH), 9.14 (s, 1H, N=CH), 9.88 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.2, 12.8, 13.3 (Me), 22.3 (CH_2), 35.9, 37.0, 40.0 (NCH_2), 66.1, 67.0 (CH, OCH_2), 74.9 (CH), 115.2 ($2CH_{arom}$), 126.7 (C_{arom}), 129.0 ($2CH_{arom}$), 154.9 (N=CH), 156.8 (C=O), 159.9 (C_{arom}), 167.0 (C=O), 178.6 (C=S). HRMS (ESI): *m/z* calcd for $C_{20}H_{28}N_6O_3S+Na^+$: 455.1836; found: 455.1831.

2-(2-(((4,6-Dimethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)phenoxy)-*N*-methylacetamide (5g). White solid (0.196 g, 52%), mp 242-245 °C (decomp). IR (KBr) ν, cm^{-1}: 3387, 3184, 1714, 1666, 1548, 1500, 1492, 1458, 1414, 1402, 1296, 1267, 1237, 1213, 1162, 1042, 749. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.68 (br.s, 3H, NMe), 2.76 (s, 3H, NMe), 2.88 (s, 3H, NMe), 4.55 (d, ^2J 14.7 Hz, 1H, OCH_2), 4.61 (d, ^2J 14.7 Hz, 1H, OCH_2), 5.41 (d, ^3J 8.0 Hz, 1H, CH), 6.01 (d, ^3J 8.0 Hz, 1H, CH), 7.04-7.10 (m, 2H, CH_{arom}), 7.43 (t, ^3J 7.2 Hz, 1H, CH_{arom}), 7.85-7.93 (m, 2H, CH_{arom}, NH), 9.38 (s, 1H, N=CH), 10.03 (s, 1H, NH). ^{13}C NMR (75 MHz,

DMSO-d_6): δ 25.3, 28.1, 30.3 (NMe), 67.6 (CH), 68.1 (OCH_2), 75.1 (CH), 113.1 (CH_{arom}), 121.5 (CH_{arom}), 122.4 (C_{arom}), 126.2 (CH_{arom}), 132.0 (CH_{arom}), 147.0 (N=CH), 156.4, 157.6 (C_{arom}, C=O), 167.6 (C=O), 178.9 (C=S). HRMS (ESI): *m/z* calcd for $C_{16}H_{20}N_6O_3S+Na^+$: 399.1210; found: 399.1202.

2-(2-(((4,6-Dimethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)imino)methyl)phenoxy)-*N*-ethylacetamide (5h). White solid (0.222 g, 57%), mp 216-218 °C. IR (KBr) ν, cm^{-1}: 3377, 3175, 1741, 1722, 1657, 1608, 1548, 1507, 1490, 1459, 1450, 1433, 1401, 1316, 1290, 1253, 1235, 1213, 1158, 1108, 1073, 1056, 849, 747. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.06 (t, ^3J 7.2 Hz, 3H, Me), 2.76 (s, 3H, NMe), 2.89 (s, 3H, NMe), 3.15-3.22 (m, 2H, NCH_2), 4.55 (d, ^2J 14.4 Hz, 1H, OCH_2), 4.60 (d, ^2J 14.4 Hz, 1H, OCH_2), 5.41 (d, ^3J 8.2 Hz, 1H, CH), 5.99 (d, ^3J 8.3 Hz, 1H, CH), 7.05-7.10 (m, 2H, CH_{arom}), 7.45 (t, ^3J 7.8 Hz, 1H, CH_{arom}), 7.87 (d, ^3J 7.7 Hz, 1H, CH_{arom}), 7.98 (t, ^3J 5.2 Hz, 1H, NH), 9.47 (s, 1H, N=CH), 10.03 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.8 (Me), 28.2, 30.5 (NMe), 33.3 (NCH_2), 67.6 (CH), 68.2 (OCH_2), 75.3 (CH), 113.2 (CH_{arom}), 121.6 (CH_{arom}), 122.5 (C_{arom}), 126.1 (CH_{arom}), 132.1 (CH_{arom}), 147.0 (N=CH), 156.5, 157.7 (C=O, C_{arom}), 166.9 (C=O), 178.9 (C=S). HRMS (ESI): *m/z* calcd for $C_{17}H_{22}N_6O_3S+H^+$: 391.1547; found: 391.1531.

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