

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

Galina A. Gazieva,^{*a} Sergei A. Serkov,^a Natalya V. Sigay,^a Natalya N. Kostikova,^a
Leonid D. Popov,^b and Angelina N. Kravchenko^a

^a N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russia

^b Department of Chemistry, Southern Federal University, 7 Zorge Street, 344090 Rostov-on-Don, Russia
Email: gaz@ioc.ac.ru

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

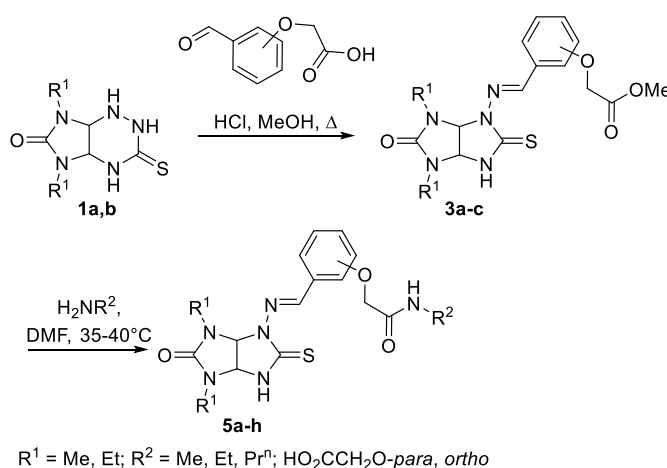
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Abstract

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.

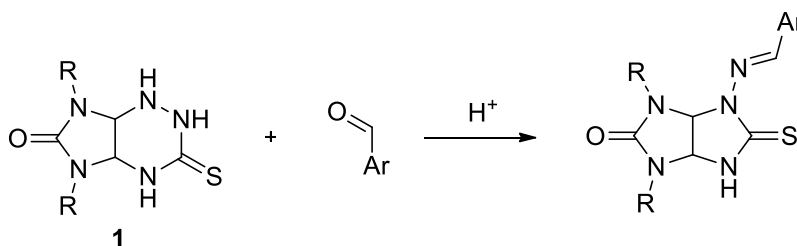


Keywords: Imidazotriazines, ring contraction, 4(2)-formylphenoxyacetic acids, thioglycolurils, primary amines

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 glycolurils¹⁻⁴ 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 amines¹³ 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 sedative¹⁷ or cytotoxic¹⁸ activities.

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

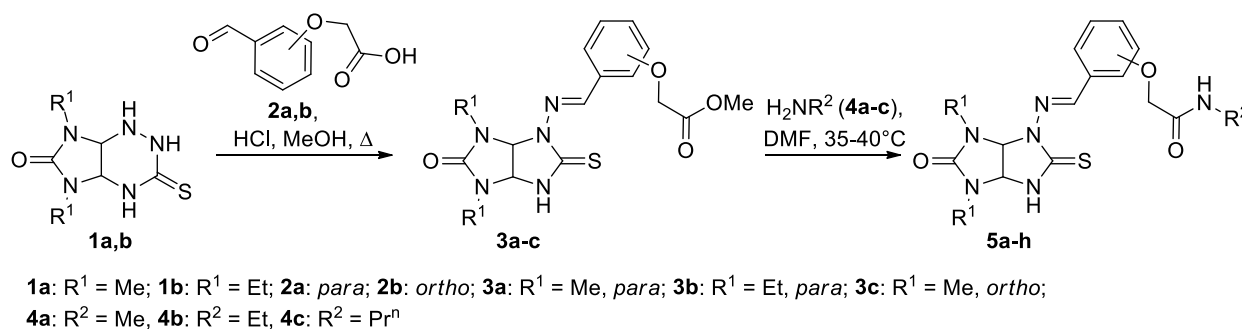
In the present paper we have synthesized monothioanalogues of glycoluril by the reaction of 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazine-6-ones **1** with aromatic aldehydes bearing substituent containing a carboxylic function and studied the reactivity of these thioglycolurils toward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



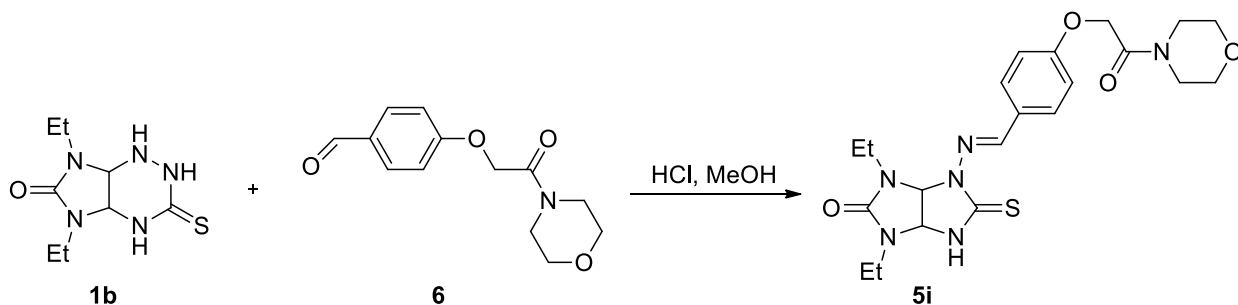
Scheme 2. Synthesis of thioglycolurils **3a-c** and their reaction with amines.

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	<i>para</i>	61
b	Me	Et	<i>para</i>	56
c	Me	Pr ⁿ	<i>para</i>	65
d	Et	Me	<i>para</i>	74
e	Et	Et	<i>para</i>	82
f	Et	Pr ⁿ	<i>para</i>	93
g	Me	Me	<i>ortho</i>	52
h	Me	Et	<i>ortho</i>	57

^aYield of isolated product.

We used another sequence of reactions to prepare amide **5i** containing morpholine fragment since its direct synthesis usually requires harsh conditions²⁰⁻²². Imidazotriazine **1b** reacted with previously prepared²³ 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 thioglycolurils **3** and **5** was ascertained by the IR, ¹H NMR, ¹³C NMR, and HRMS spectral data. Earlier: reported 1,3-dialkyl-4-(benzylideneamino)- and 4-((hetaryl)methylidene)amino)thioglycolurils

possessed only the *E*-configuration, which was confirmed both by NMR spectroscopy²⁴ 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 ¹H NMR and ¹³C 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-H₂O (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. ¹H 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, OCH₂), 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). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 28.2, 30.0 (NMe), 51.8 (OMe), 64.6 (OCH₂), 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 C₁₆H₁₉N₅O₄S+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. ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.01-1.10 (m, 6H, Me), 3.11-

3.38 (m, 4H, NCH₂), 3.71 (s, 3H, OMe), 4.88 (s, 2H, OCH₂), 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). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 12.9, 13.4 (Me), 35.9, 37.0 (NCH₂), 51.8 (OMe), 64.6 (OCH₂), 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 C₁₈H₂₃N₅O₄S+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) *v*, cm⁻¹: 3180, 1764, 1720, 1602, 1523, 1492, 1449, 1420, 1272, 1213, 1161, 1115, 1075, 1058, 1043, 748. ¹H 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, OCH₂), 4.94 (d, ²J 16.7 Hz, 1H, OCH₂), 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). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 28.2, 30.6 (NMe), 51.9 (OMe), 65.2 (OCH₂), 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 C₁₆H₁₉N₅O₄S+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) *v*, cm⁻¹: 3261, 1701, 1678, 1605, 1512, 1503, 1474, 1453, 1436, 1311, 1276, 1255, 1233, 1200, 1172, 1107, 1074, 1055, 1033, 795. ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.03-1.12 (m, 6H, Me), 3.12-3.37 (m, 4H, NCH₂), 3.46-3.37 (m, 8H, CH_{2morph}), 4.95 (s, 2H, OCH₂), 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). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 12.9, 13.4 (Me), 35.9, 37.0 (NCH₂), 41.6, 44.6 (NCH_{2morph}), 65.7 (OCH₂), 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 C₂₁H₂₈N₆O₄S+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) *v*, cm⁻¹: 3390, 3289, 1696, 1661, 1608, 1546, 1511, 1418, 1404, 1252, 1208, 1174, 1057, 1047. ¹H 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, OCH₂), 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). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 25.3 (NMe), 28.1, 29.9 (NMe), 67.0 (CH), 68.0 (OCH₂), 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 C₁₆H₂₀N₆O₃S+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) *v*, cm⁻¹: 3457, 3280, 1692, 1655, 1609, 1552, 1510, 1445, 1416, 1252, 1212, 1174, 1050, 793. ¹H 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, NCH₂), 4.52 (s, 2H, OCH₂), 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). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 14.7 (Me), 28.1, 29.9 (NMe), 33.2 (NCH₂), 67.0 (CH), 68.0 (OCH₂), 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 C₁₇H₂₂N₆O₃S+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. ¹H NMR (500 MHz, DMSO-*d*₆): δ 0.84 (t, ³*J* 7.3 Hz, 3H, Me), 1.43-1.47 (m, 2H, CH₂), 2.75 (s, 3H, NMe), 2.84 (s, 3H, NMe), 3.08-3.11 (m, 2H, NCH₂), 4.54 (s, 2H, OCH₂), 5.39 (d, ³*J* 8.1 Hz, 1H, CH), 5.91 (d, ³*J* 8.1 Hz, 1H, CH), 7.06 (d, ³*J* 8.2 Hz, 2H, CH_{arom}), 7.72 (d, ³*J* 8.2 Hz, 2H, CH_{arom}), 8.09 (br.s, 1H, NH), 9.05 (s, 1H, N=CH), 9.90 (s, 1H, NH). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 11.3 (Me), 22.3 (CH₂), 28.1, 30.0 (NMe), 40.1 (NCH₂), 67.0 (CH), 68.0 (OCH₂), 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 C₁₈H₂₄N₆O₃S+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. ¹H 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, NCH₂), 4.54 (s, 2H, OCH₂), 5.49 (d, ³*J* 8.0 Hz, 1H, CH), 5.94 (d, ³*J* 7.9 Hz, 1H, CH), 7.06 (d, ³*J* 7.9 Hz, 2H, CH_{arom}), 7.72 (d, ³*J* 7.9 Hz, 2H, CH_{arom}), 8.07 (br.s, 1H, NH), 9.14 (s, 1H, N=CH), 9.88 (s, 1H, NH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 12.8, 13.4 (Me), 25.3 (NMe), 35.9, 37.0 (NCH₂), 66.1 (CH), 67.0 (OCH₂), 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 C₁₈H₂₄N₆O₃S+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. ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.03-1.12 (m, 9H, Me), 3.14-3.24 (m, 4H, NCH₂), 3.25-3.33 (m, 2H, NCH₂), 4.53 (s, 2H, OCH₂), 5.49 (d, ³*J* 8.2 Hz, 1H, CH), 5.94 (d, ³*J* 8.1 Hz, 1H, CH), 7.06 (d, ³*J* 8.4 Hz, 2H, CH_{arom}), 7.72 (d, ³*J* 8.4 Hz, 2H, CH_{arom}), 8.14 (br.s, 1H, NH), 9.14 (s, 1H, N=CH), 9.89 (s, 1H, NH). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 12.8, 13.4, 14.7 (Me), 33.2, 35.9, 37.0 (NCH₂), 66.1 (CH), 67.0 (OCH₂), 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 C₁₉H₂₆N₆O₃S+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. ¹H NMR (300 MHz, DMSO-*d*₆): δ 0.83 (t, ³*J* 7.1 Hz, 3H, Me), 1.01-1.10 (m, 6H, Me), 1.41-1.48 (m, 2H, CH₂), 3.08-3.31 (m, 6H, NCH₂), 4.54 (s, 2H, OCH₂), 5.49 (d, ³*J* 8.2 Hz, 1H, CH), 5.94 (d, ³*J* 8.2 Hz, 1H, CH), 7.06 (d, ³*J* 8.0 Hz, 2H, CH_{arom}), 7.71 (d, ³*J* 8.0 Hz, 2H, CH_{arom}), 8.11 (br.s, 1H, NH), 9.14 (s, 1H, N=CH), 9.88 (s, 1H, NH). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 11.2, 12.8, 13.3 (Me), 22.3 (CH₂), 35.9, 37.0, 40.0 (NCH₂), 66.1, 67.0 (CH, OCH₂), 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 C₂₀H₂₈N₆O₃S+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. ¹H 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, ²*J* 14.7 Hz, 1H, OCH₂), 4.61 (d, ²*J* 14.7 Hz, 1H, OCH₂), 5.41 (d, ³*J* 8.0 Hz, 1H, CH), 6.01 (d, ³*J* 8.0 Hz, 1H, CH), 7.04-7.10 (m, 2H, CH_{arom}), 7.43 (t, ³*J* 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). ¹³C NMR (75 MHz,

DMSO-*d*₆): δ 25.3, 28.1, 30.3 (NMe), 67.6 (CH), 68.1 (OCH₂), 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 C₁₆H₂₀N₆O₃S+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. ¹H NMR (500 MHz, DMSO-*d*₆): δ 1.06 (t, ³*J* 7.2 Hz, 3H, Me), 2.76 (s, 3H, NMe), 2.89 (s, 3H, NMe), 3.15-3.22 (m, 2H, NCH₂), 4.55 (d, ²*J* 14.4 Hz, 1H, OCH₂), 4.60 (d, ²*J* 14.4 Hz, 1H, OCH₂), 5.41 (d, ³*J* 8.2 Hz, 1H, CH), 5.99 (d, ³*J* 8.3 Hz, 1H, CH), 7.05-7.10 (m, 2H, CH_{arom}), 7.45 (t, ³*J* 7.8 Hz, 1H, CH_{arom}), 7.87 (d, ³*J* 7.7 Hz, 1H, CH_{arom}), 7.98 (t, ³*J* 5.2 Hz, 1H, NH), 9.47 (s, 1H, N=CH), 10.03 (s, 1H, NH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 14.8 (Me), 28.2, 30.5 (NMe), 33.3 (NCH₂), 67.6 (CH), 68.2 (OCH₂), 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 C₁₇H₂₂N₆O₃S+H⁺: 391.1547; found: 391.1531.

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