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Synthesis of 2-(aminocarbonylmethylthio)-1*H*-imidazoles as novel Capravirine analogues

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Abstract—Different analogues of Capravirine (AG-1549) or S-1153 were prepared by synthesis of 2-(5-benzyl-4-isopropyl-1-methyl-2,3-dihydro-1*H*-imidazol-2-ylthio)acetamide (**3a–c**), ethyl [5-benzyl-1-(ethoxymethyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetate (**10**), 2-[5-alkyl-4-substituted 1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-ylthio]acetamides (**12a–f**), and 2-[5-benzyl-1-(benzyloxymethyl)-4-isopropyl-1*H*-imidazol-2-ylthio]acetamides (**14a–l**) from their corresponding amino acids through a sequence of reactions: Dakin–West reaction, hydrolysis, condensation with thiocyanate derivatives, alkylation with 2-iodoacetamide and ethyl chloroacetate, and coupling with 4-pyridylmethyl chloride, ethoxymethyl chloride and benzyloxymethyl chloride. All the synthesized compounds were screened for their activity against HIV-1 (wild type) and some of them (especially Capravirine like structures) were found active.

1. Introduction

A major challenge facing medicinal chemistry over the next few years will be the development of drugs with significantly improved resistance profiles for chronic use as anti-HIV combination therapy. An important component of such regimens will be non-nucleoside inhibitors of HIV-1 reverse transcriptase (NNRTIs). NNRTIs is a class of structurally diverse aromatic compounds, such as nevirapine, delavirdine, efavirenz, MKC-442 (emivirine), TIBO, and thiocarboxanilides.[1] Structural studies have revealed that NNRTIs inhibit HIV-1 RT by binding to an allosteric site, approximately 10 Å from the polymerase active site,[2–4] causing a distortion of the catalytic aspartate triad.[5] The high selectivity of NNRTIs for HIV-1 RT over HIV-2 RT and cellular polymerases contributes to lower cellular toxicity levels than observed with nucleoside analogues (NRTIs) such as AZT, ddI, or ddC. However, this selectivity together with the relatively unconserved amino acid sequence in the drug-binding site has also made most types of NNRTIs susceptible to the rapid selection of drug resistant vira, particularly when administered in monotherapy either in vitro or in vivo.[6,7] All reported NNRTI-resistant mutations occur in residues surrounding the inhibitor-binding site on the enzyme.[5] A commonly observed drug-resistant virus contains the single amino acid mutation Tyr181Cys.[8] Additionally, a Lys103Asn mutation appears relatively frequently in vivo giving resistance to many NNRTIs.[9] The crystal structures of a range of NNRTIs, including nevirapine, 1051U91, R-APA, HEPT, MKC-442, and TNK-651, complexed with RT5,12–15, show the importance of the interactions of the aromatic moiety of the inhibitors and the neighboring residues Tyr181, Tyr188, Phe227, and Trp229. The significant contribution of Tyr181 to the binding energy of many NNRTIs is demonstrated by the frequent selection of an escape mutation at this codon; normally with a change to cysteine.[8] The crystal structures have also revealed details of the orientation and geometry of the aromatic interactions between the inhibitors and the surrounding residues. Comparison of the bound conformations of these NNRTIs showed that the orientation

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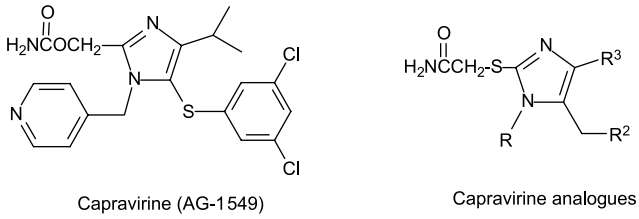


Figure 1.

of the aromatic groups of many of these inhibitors are conserved within the binding site.[10] An outlier in this analysis is the rather weak binding inhibitor HEPT, which has its phenyl ring rotated by 20°–25° due to the loss of interaction with Tyr181.[11] A comparative analysis of complexes of HEPT analogues has suggested structural features that give conformational changes in Tyr181 necessary for tight binding in this series.[11] Kinetic studies of reverse transcriptase that contain the Tyr181Cys mutation show the rate of dissociation of the inhibitor from the enzyme increases relative to wild type.[12]

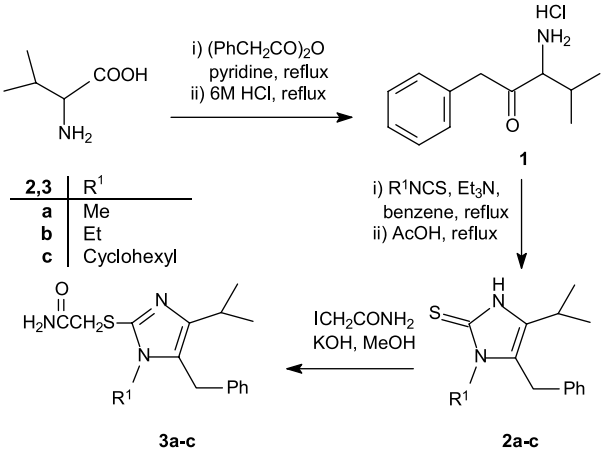
Capravirine (formerly known as S-1153 and AG-1549) is one of the most promising non-nucleoside inhibitors of HIV-1 reverse transcriptase currently under development as a potential anti-AIDS drug, because it has a favorable profile of resilience to many drug resistance mutations.[13] However, the use of Capravirine has recently been restricted due to vasculitis (an inflammation of the blood vessels) in animals that received high doses of Capravirine.[14]

In this article, the synthesis of novel Capravirine analogues was achieved by synthesis of 2-(aminocarbonylmethylthio)-1*H*-imidazoles and they were screened for their biological activity against HIV-1 (Fig. 1).

2. Chemistry

The Dakin–West reaction[15,16] was applied on DL-valine by refluxing it with a mixture of phenylacetic acid anhydride and pyridine to afford *N*-(1-isopropyl-2-oxo-3-phenylpropyl)-2-phenylacetamide, which was not isolated, but hydrolyzed with 6 M hydrochloric acid to furnish 3-amino-4-methyl-1-phenylpentan-2-one hydrochloride (**1**). 5-Benzyl-4-isopropyl-1-substituted 1,3-dihydroimidazole-2-thiones (**2a**–**c**) were obtained by refluxing compound **1** with isothiocyanate derivatives (methyl, ethyl, and cyclohexyl) in benzene in the presence of triethylamine followed by refluxing in acetic acid to convert the thiourea derivatives into the cyclized imidazoles (**2a**–**c**). The potassium salt of each of compounds **2a**–**c** was treated with 2-iodoacetamide to afford 2-(5-benzyl-4-isopropyl-1-methyl-2,3-dihydro-1*H*-imidazol-2-ylthio)acetamide (**3a**–**c**) (Scheme 1).

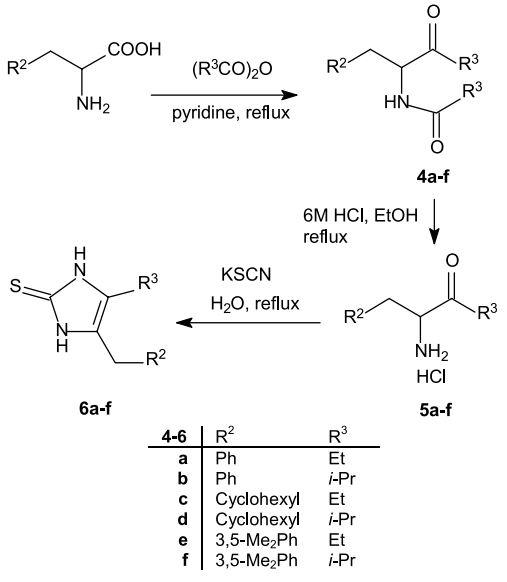
Compound **6a** has been previously prepared by Bullerwell and Lawson[21] and compounds **6b**–**d** have been prepared by Loksha et al.[19,22] The Dakin–West reaction[15,16] was applied on 3,5-dimethylphenylalanine[17] with aliphatic acid anhydride (propionic and isobutyric) and pyridine to afford the α-acylaminoketones (**4e**,**f**) in the same manner as described for **4a** by Cleland and Niemann[18] and for **4b** by Loksha et al.[19]



Scheme 1.

Hydrolysis of compounds **4e**,**f** with 6 M hydrochloric acid afforded the α-aminoketone hydrochlorides (**5e**,**f**) in the same procedure previously described by Sheppard et al.[20] for **4a** and by Loksha et al.[19] for **5b**. Treatment of **5e**,**f** with potassium thiocyanate furnished 5-alkyl-4-(3,5-dimethylbenzyl)-1,3-dihydroimidazole-2-thiones **6e**,**f** (Scheme 2).

The potassium salt of 4-benzyl-5-ethyl-1,3-dihydroimidazole-2-thione (**6a**) in anhydrous dimethylformamide was treated with ethyl chloroacetate to afford ethyl (5-benzyl-4-ethyl-1*H*-imidazol-2-ylthio)acetate (**7**). Refluxing compound **7** with aqueous ammonia in ethanol furnished 2-(5-benzyl-4-ethyl-1*H*-imidazol-2-ylthio)acetamide (**8a**) in low yield. Coupling compound **7** with



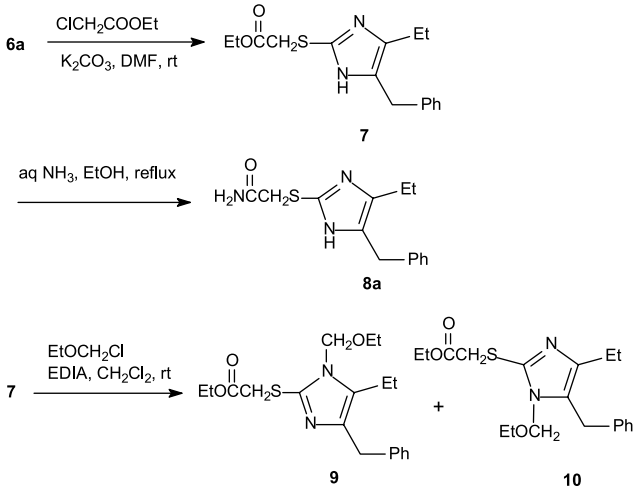
Scheme 2.

ethoxymethyl chloride in methylene chloride in the presence of *N*-ethyldiisopropylamine (EDIA) both afforded the two possible isomers due to coupling at N-1 and N-3 of the imidazole ring to furnish ethyl [4-benzyl-1-(ethoxymethyl)-5-ethyl-1*H*-imidazol-2-ylthio]acetate (**9**) and ethyl [5-benzyl-1-(ethoxymethyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetate (**10**) (Scheme 3).

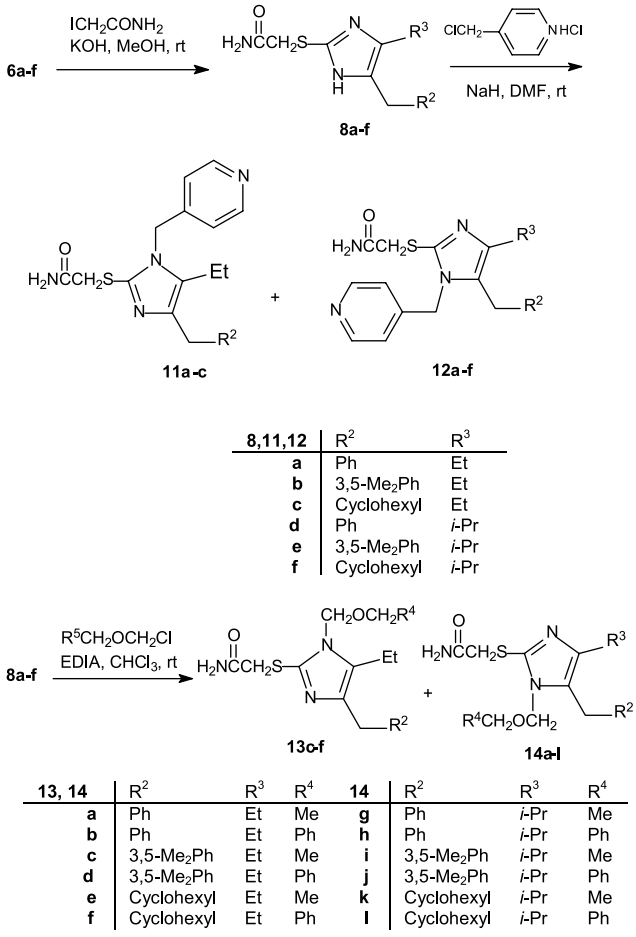
The assignment of structure of compounds **9** and **10** was confirmed by NOE. Irradiation of NCH_2O in compound **9** showed 1.8% NOE in CH_3CH_2 at C-5 and no NOE in CH_2Ph was detected, while irradiation of the same group in compound **10** showed no NOE in CH_3CH_2 at C-4, but showed 1.7% NOE in CH_2Ph.

The potassium salt of each of compounds **6a–f** was obtained by stirring the compound in methanolic potassium hydroxide solution. The salt was treated with 2-iodoacetamide to afford *S*-alkylated compounds (**8a–f**). The two possible tautomers of **8** were obtained as a mixture, which showed doubling of the carbon atoms or line broadening in the ^{13}C NMR spectra. In some cases, extensive line broadening caused disappearance of the lines. Reaction of compounds **8a–f** with 4-pyridylmethyl chloride hydrochloride using sodium hydride afforded coupling next to the ethyl group (compounds **11a–c**) and next to the benzyl or the cyclohexylmethyl group (compounds **12a–c**, Capravirine analogues) when R^3 was an ethyl group. Only one product (compounds **12d–f**) was obtained when R^3 was an isopropyl group due to a larger steric hindrance of the isopropyl group than for the ethyl group (Scheme 4). Each of the pairs of compounds **11a–c** and **12a–c** could not be separated by column chromatography and they were isolated as mixture in the ratio of 1:1.2 (**11a**, **12a**), 1:1.2 (**11b**, **12b**) and 1:1 (**11c**, **12c**). None of the mixtures showed significant biological activity against HIV-1 as described later on and therefore no further attempts were made to separate the mixtures.

Alkylation of compounds **8a–f** with ethoxymethyl chloride and benzyloxymethyl chloride was achieved in methylene chloride in the presence of *N*-ethyldiisopropylamine (EDIA). Coupling occurred next to the ethyl group (compounds **13c–f**) and next to the benzyl or the cyclohexylmethyl group (compounds **14a–l**). In all cases when R^3 was an isopropyl group, only one product (compounds **14g–l**) was obtained due to the steric hindrance of the isopropyl group (Scheme 4).



Scheme 3.



8,11,12	R^2	R^3
a	Ph	Et
b	3,5-Me_2Ph	Et
c	Cyclohexyl	Et
d	Ph	*i*-Pr
e	3,5-Me_2Ph	*i*-Pr
f	Cyclohexyl	*i*-Pr

13, 14	R^2	R^3	R^4	14	R^2	R^3	R^4
a	Ph	Et	Me	g	Ph	*i*-Pr	Me
b	Ph	Et	Ph	h	Ph	*i*-Pr	Ph
c	3,5-Me_2Ph	Et	Me	i	3,5-Me_2Ph	*i*-Pr	Me
d	3,5-Me_2Ph	Et	Ph	j	3,5-Me_2Ph	*i*-Pr	Ph
e	Cyclohexyl	Et	Me	k	Cyclohexyl	*i*-Pr	Me
f	Cyclohexyl	Et	Ph	l	Cyclohexyl	*i*-Pr	Ph

Scheme 4.

The assignment of the structure of compounds **12a–f**, **13c–f**, and **14a–l** was confirmed by NOE. Irradiation of CH_2N in each of compounds **13e**,**f** showed 1.9%, 1.8% NOE, respectively, in CH_3CH_2 at C-5 and no NOE was observed in CH_2 at C-4 for the same irradiation. Similarly, 2.1%, 2.7%, 1.3%, 1.3%, 2.2%, 1.4%, 1.4%, 1.8%, 1.9% NOE in CH_2 at C-5 in compounds **12e**,**f**, **14a**,**b**,**e**,**g**,**i**,**j**,**l**, respectively, were detected when CH_2N was irradiated and no NOE was observed for irradiation of the same group in R^3 at C-4.

3. Results of the anti-HIV-1 assay and discussion

The test for activity against HIV-1 was performed in MT-4 cell cultures infected with wild type HIV-1 (strain IIIB). Some of the synthesized compounds showed activity against HIV-1 as shown in Table 1 and the rest of the compounds are inactive at 100 μM.

Table 1. Anti-viral activity of compounds **2**–**14** against HIV-1 in MT-4 cells

Compound	IC_{50} (μM)[a]	CC_{50} (μM)[b]	SI[c]
2b	5.06	40.72	8
5f	32.77	>100	>3
6e	4.46	>100	>22.4
6f	0.62	38.61	62.3
11b + **12b**	4.84	>100	>20.7
11c + **12c**	42.17	>100	>2.4
12d	30.57	>100	>3.3
12e	0.31	64.04	206.5
12f	3.75	>100	>26.6
14c	1.33	>100	>75.2
14d	2.48	37.56	15.1
14e	22.85	>100	>4.4
14g	10.96	>100	>9.1
14i	0.31	>100	>322.5
14j	0.15	29.43	196.2
14k	2.11	>100	>47.4
14l	4.29	84.32	19.7
MKC-442	0.03	>100	>3333

[a] 50% Inhibitory concentration required to inhibit HIV-1 (wild type).
[b] 50% Cytotoxic concentration.
[c] Selectivity index: ratio CC_{50}/IC_{50}. IC_{50}.

The substituents in the 4- and 5-positions of the imidazole ring were selected from the work of Tanaka et al.[23] and Hopkins et al.[24] on uracil derivatives. Sulfur was introduced to the 2-position in order to have a resemblance to *S*-DABO derivatives.[25] The activity is increased when ethyl is replaced by an isopropyl at the 4-position of the imidazole ring as shown when the ethyl compounds **6e**, **12a**–**c**, **14a**,**c**–**f** are compared with the corresponding isopropyl compounds **6f**, **12d**–**f**, **14g**,**i**–**l**. Also, the activity of the compounds was affected by the group at the 5-position of the imidazole ring in the order 3,5-Me_2Ph > Cy > Ph in compounds **12e**, **14i**,**j** > **12f**, **14k**,**l** > **12d**, **14g**,**h**, respectively. The alkoxymethyl substituent at the 1-position of imidazole ring (compounds **14g**,**i**,**k** with an ethoxymethyl group and compounds **14j**,**l** with a benzyloxymethyl group) showed higher activity than compounds containing 4-pyridylmethyl group at the 1-position (compounds **12a**–**f**).

4. Conclusion

Although activities were found against HIV-1 for the novel Capravirine analogues, they were in all cases lower than the uracil reference compound MKC-442.

5. Experimental

NMR spectra were recorded on a Varian Gemini 2000 NMR spectrophotometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C with TMS as an internal standard. EI mass spectra were recorded on a Finnigan MAT SSQ 710. MALDI spectra were recorded on a 4.7 T Ultima Fourier transform Mass spectrometer (IonSpec, Irvine, CA). Melting points were determined in a Büchi melting point apparatus. The silica gel (0.040–0.063 mm) used for column chromatography was purchased from Merck. Microanalyses were carried out at Chemical Laboratory II at University of Copenhagen, Denmark.

5.1. 3-Amino-4-methyl-1-phenylpentan-2-one (1)

A mixture of DL-valine (3.4 g, 30 mmol), anhyd pyridine (12 mL, 0.15 mol), and phenylacetic acid anhydride (38 g, 0.15 mol) was heated in an oil bath at 150 °C for 6 h until carbon dioxide was no longer evolved. The excess of pyridine, acid anhydride, and the acid formed were removed under reduced pressure and the residue was treated with an aqueous satd solution of sodium bicarbonate (30 mL) to remove the acidic components and extracted with ether (3 × 50 mL). The combined ethereal extracts were dried over sodium sulfate (5 g), filtered and evaporated till dryness under vacuo. The residue was treated with 6 M hydrochloric acid (165 mL) and ethanol (90 mL). The mixture was refluxed for 7 h, cooled, and the solvents were removed under reduced pressure. Absolute ethanol (10 mL) was added to the residue and the hydrochloride **1** was precipitated by addition of ether (50 mL), which was filtered off and dried. Yield 1.2 g (17%) as a white solid; mp 208–210 °C. ^{1}H NMR (DMSO-d_6): δ 0.89 (d, 3H, J = 6.9 Hz, CH_3CH), 1.06 (d, 3H, J = 6.9 Hz, CH_3CH), 2.42–2.52 (m, 1H, $(CH_3)_2CH$), 4.02 (CH_2Ph), 4.17 (br s, 1H, CH), 7.21–7.36 (m, 5H, Ph), 8.50 (br s, 3H, NH_3^+). ^{13}C NMR (DMSO-d_6): δ 16.70 (CH_3CH), 18.95 (CH_3CH), 27.95 [$(CH_3)_2CH$], 46.10 (CH_2Ph), 62.63 (CH), 126.71, 128.19, 129.79, 133.52 (C_{arom}), 204.15 (CO).

5.2. General procedure for the synthesis of 5-benzyl-4-isopropyl-1-substituted 1,3-dihydroimidazole-2-thiones (2a–c)

A mixture of 3-amino-4-methyl-1-phenylpentan-2-one hydrochloride (**1**) (0.46 g, 2 mmol), isothiocyanate derivative (methyl, ethyl, and cyclohexyl) (2 mmol), and triethylamine (0.28 mL, 2 mmol) in anhyd benzene (20 mL) was refluxed for 3 h. The solvent was removed under reduced pressure, then acetic acid (15 mL) was added to the residual material and the mixture was refluxed for 2 h. The solvent was concentrated to 5 mL, then water (20 mL) was added and the solid product formed was filtered off, washed with ether (20 mL), and dried to afford compounds **2a**–**c**.

5.2.1. 5-Benzyl-4-isopropyl-1-methyl-1,3-dihydroimidazole-2-thione (2a). Yield 153 mg (30%) as a white solid; mp 133–135 °C. ^{1}H NMR (DMSO-d_6): δ 1.18 (d, 6H, J = 7.1 Hz, $(CH_3)_2CH$), 30.02 [hept, 1H, J = 7.1 Hz, $(CH_3)_2CH$], 3.19 (s, 3H, CH_3N), 3.92 (s, 2H, CH_2Ph), 7.11–7.34 (m, 6H, *H*NH and Ph), 12.07 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 21.86 [$(CH_3)_2CH$], 23.48 [$(CH_3)_2CH$], 30.53 (CH_3N), 121.72 (C-4), 126.36, 127.77, 128.58, 130.36 (C_{arom}), 138.06 (C-5), 160.14 (C=S). Anal. Calcd for $C_{14}H_{18}N_2S{\cdot}0.5H_2O$: C, 65.84; H, 7.50; N, 10.97. Found: C, 65.84; H, 7.52; N, 11.09.

5.2.2. 5-Benzyl-1-ethyl-4-isopropyl-1,3-dihydroimidazole-2-thione (2b). Yield 240 mg (46%) as a white solid; mp 162–164 °C. ^{1}H NMR ($CDCl_3$): δ 1.09 (t, 3H, J = 7.1 Hz, CH_3CH_2), 1.30 [d, 6H, J = 6.9 Hz,

(CH_3)$_2$CH], 2.93 [hept, 1H, J = 7.0 Hz, (CH_3)$_2$CH], 3.84–3.91 (m, 4H, CH_3CH_2 and CH_2Ph), 7.07–7.32 (m, 5H, Ph), 11.95 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.71 (CH_3CH_2), 22.55 [(CH_3)$_2$CH], 24.53 [(CH_3)$_2$CH], 29.23 (CH_2Ph), 39.53 (CH_3CH_2), 121.29 (C-4), 126.82, 127.69, 128.74, 131.91 (C_{arom}), 137.45 (C-5), 158.18 (C=S). EI-MS: m/z 260 (100%, M^+). Anal. Calcd for $C_{15}H_{20}N_2S{\cdot}0.25H_2O$: C, 68.01; H, 7.80; N, 10.57. Found: C, 67.87; H, 7.57; N, 10.40.

5.2.3. 5-Benzyl-1-cyclohexyl-4-isopropyl-1,3-dihydroimidazole-2-thione (2c). Yield 510 mg (79%) as a white solid; mp 130–132 °C. ^{1}H NMR (DMSO-d_6): δ 0.89–1.22 [m, 11H, (CH_3)$_2$CH and H_{cy}] 1.48–1.60 (m, 4H, H_{cy}), 2.92 (br s, 1H, CH–N), 3.07 [hept, 1H, J = 7.2 Hz, (CH_3)$_2$CH], 3.95 (s, 2H, CH_2Ph), 7.11–7.36 (m, 5H, Ph), 11.96 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 21.77 [(CH_3)$_2$CH], 23.51 [(CH_3)$_2$CH], 24.53, 25.57, 28.35, 56.03 (C_{cy}), 28.44 (CH_2Ph), 121.55 (C-4), 126.29, 128.39, 138.78 (C_{arom}),127.72 (C-4), 130.93 (C-5), 159.17 (C=S). EI-MS: 314 (62%, M^+), 232 (100%). Anal. Calcd for $C_{19}H_{26}N_2S{\cdot}0.5H_2O$: C, 70.54; H, 8.41; N, 8.66. Found: C, 70.10; H, 8.41; N, 8.92.

5.3. General procedure for the synthesis of 2-(5-benzyl-4-isopropyl-1-substituted 1*H*-imidazol-2-ylthio)acetamides (3a–c)

To a solution of potassium hydroxide (0.056 g, 1 mmol) in methanol (10 mL), compound **2** (1 mmol) was added and the mixture was stirred for 0.5 h. 2-Iodoacetamide (0.186 g, 1 mmol) was added to the reaction mixture and it was stirred at rt for an additional hour. The solvent was removed under reduced pressure and water (15 mL) was added to the residual material. The solid product formed was filtered off and recrystallized from ethanol/water to give **3a**–**c**.

5.3.1. 2-(5-Benzyl-4-isopropyl-1-methyl-1*H*-imidazol-2-ylthio)acetamide (3a). Yield 230 mg (76%) as a white solid; mp 148–150 °C. ^{1}H NMR (DMSO-d_6): δ 1.36 [d, 6H, J = 6.6 Hz, (CH_3)$_2$CH], 2.91 [hept, 1H, J = 6.6 Hz, (CH_3)$_2$CH], 3.32 (s, 3H, CH_3–N), 3.58 (s, 2H, CH_2S), 3.96 (s, 2H, CH_2Ph), 7.07–7.31 (m, 6H, HNH and Ph), 7.79 (br s, 1H, HNH). ^{13}C NMR (DMSO-d_6): δ 23.02 [(CH_3)$_2$CH], 25.61 [(CH_3)$_2$CH], 28.47 (CH_2Ph), 30.69 (CH_3–N), 37.29 (CH_2S), 125.99 (C-4), 126.10, 127.74, 128.48, 138.87 (C_{arom}), 137.60 (C-2), 144.23 (C-5), 169.82 (C=O); HRMS (MALDI) m/z calcd for $C_{16}H_{22}N_3OS^+$ (MH^+) 304.1471, found 304.1478.

5.3.2. 2-(5-Benzyl-1-ethyl-4-isopropyl-1*H*-imidazol-2-ylthio)acetamide (3b). Yield 260 mg (79%) as a white solid; mp 136–138 °C. ^{1}H NMR (DMSO-d_6): δ 0.88 (t, 3H, J = 7.0 Hz, CH_3CH$_2$), 1.15 [d, 6H, J = 6.8 Hz, (CH_3)$_2$CH], 2.90 [hept, 1H, J = 6.8 Hz, (CH_3)$_2$CH], 3.65 (s, 2H, CH_2S), 3.75 (q, 2H, J = 7.0 Hz, CH_3CH_2), 3.96 (s, 2H, CH_2Ph), 7.09–7.32 (m, 6H, HNH and Ph), 7.87 (br s, 1H, HNH). ^{13}C NMR (DMSO-d_6): δ 15.43 (CH_3CH_2), 23.06 [(CH_3)$_2$CH], 25.59 [(CH_3)$_2$CH], 28.36 (CH_2Ph), 37.17 (CH_2S), 38.59 (CH_2–N), 125.02 (C-4), 126.17, 127.82, 128.45, 137.39 (C_{arom}), 139.17 (C-5), 144.31 (C-2), 169.85 (C=O). EI-MS: m/z 317 (43%, M^+), 273 (100%). Anal. Calcd for $C_{17}H_{23}N_3OS{\cdot}0.5H_2O$: C, 62.55; H, 7.41; N, 2.87. Found: C, 62.59; H, 7.16; N, 2.61.

5.3.3. 2-(5-Benzyl-1-cyclohexyl-4-isopropyl-1*H*-imidazol-2-ylthio)acetamide (3c). Yield 310 mg (81%) as a white solid; mp 165–167 °C. ^{1}H NMR ($CDCl_3$): δ 1.01–1.27 [m, 11H, (CH_3)CH and H_{cy}], 1.43–2.00 (m, 5H, H_{cy}), 2.90 [hept, 1H, J = 6.8 Hz, (CH_3)$_2$CH], 6.64–3.72 (m, 3H, CH–N and CH_2S), 3.94 (s, 2H, CH_2Ph), 5.63 (br s, 1H, HNH), 7.05–7.30 (m, 5H, Ph), 9.37 (br s, HNH). ^{13}C NMR ($CDCl_3$): δ 23.13 [(CH_3)$_2$CH], 24.87 [(CH_3)$_2$CH], 26.14, 31.25, 56.46 (C_{cy}), 29.78 (CH_2Ph), 36.57 (CH_2S), 126.29 (C-4), 126.48, 127.81, 128.53, 138.84 (C_{arom}), 138.53 (C-2), 144.50 (C-5). EI-MS: m/z 371 (51%, M^+), 313 (100%). Anal. Calcd for $C_{21}H_{29}N_3OS{\cdot}0.6H_2O$: C, 65.97; H, 7.96; N, 10.99. Found: C, 65.78; H, 7.66; N, 10.73.

5.4. General procedure for the synthesis of α-acylaminoketones (4e,f)

A mixture of DL-3,5-dimethylphenylalanine (5.8 g, 30 mmol), anhydrous pyridine (25 mL) and aliphatic acid anhydride (propionic or isobutyric) (0.3 mol) was heated in an oil bath at 150 °C for 12 h until carbon dioxide was no longer evolved. The excess of pyridine, acid anhydride and the resulting acid were removed under reduced pressure, the residue was treated with an aqueous satd solution of sodium bicarbonate (20 mL) to remove the acidic components and then extracted with ether (3 × 50 mL). After removal of the solvent from the dried ether extract, the residue was treated with petroleum ether (60–80 °C) (50 mL) and left at 5 °C overnight. The solid product formed was filtered off, washed with petroleum ether (60–80 °C), dried, and recrystallized from xylene/petroleum ether (60–80 °C) to give compounds **4e**,**f**.

5.4.1. *N*-[1-(3,5-Dimethylbenzyl)-2-oxobutyl]propion-amide (4e). Yield 4.1 g (52%) as a white solid; mp 90–92 °C. ^{1}H NMR (DMSO-d_6): δ 0.88 (t, 3H, J = 7.2 Hz, CH_3CH$_2$), 0.93 (t, 3H, J = 7.8 Hz, CH_3CH$_2$), 2.07 (q, 2H, J = 7.2 Hz, CH_2CH$_3$), 2.22 (s, 6H, 2 × CH_3), 2.29–2.51 (m, 2H, CH_2CH$_3$), 2.66 (dd, 1H, J = 9.4, 13.6 Hz, HCH–CH), 2.91 (dd, 1H, J = 5.0, 13.9 Hz, HCH–CH), 4.34–4.41 (m, 1H, CH_2CHNH), 6.8 (s, 3H, H_{arom}), 8.15 (d, 1H, J = 7.2 Hz, NH). ^{13}C NMR (DMSO-d_6): δ 7.32 (CH_2CH_3), 9.72 (CH_2CH_3), 20.78 (2 × CH_3) 28.14 (CH_2CH_3), 32.20 (CH_2CH_3), 35.31 (CH_2CH), 59.09 (CH), 126.73, 127.62, 136.87, 137.66 (C_{arom}), 172.92 (CONH), 209.76 (COCH). EI-MS: m/z 261 (4%, M^+), 148 (100%). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.29; H, 8.75; N, 5.36.

5.4.2. *N*-[1-(3,5-Dimethylbenzyl)-3-methyl-2-oxobutyl]isobutyramide (4f). Yield 1.3 g (15%) as a white solid; mp 115–116 °C. ^{1}H NMR ($CDCl_3$): δ 1.02 (d, 3H, J = 6.6 Hz, CH_3), 1.03 (d, 3H, J = 6.7 Hz, CH_3), 1.11 (d, 3H, J = 6.7 Hz, CH_3), 1.13 (d, 3H, J = 6.3 Hz, CH_3), 2.27 (s, 6H, 2 × CH_3), 2.36 [hept, 1H, J = 7.0 Hz, CH(CH_3)$_3$], 2.65 [hept, 1H, J = 6.8 Hz, CH(CH_3)$_3$], 2.93 (dd, 1H, J = 5.8, 13.7 Hz, HCH–CH), 3.0 (dd, 1H, J = 7.1, 13.6 Hz, HCH–CH), 5.00 (q, 1H,

J = 7.2 Hz, CH_2CH–NH), 6.09 (d, 1H, J = 6.8 Hz, CH–NH), 6.72 (s, 2H, H_{arom}), 6.86 (s, 1H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ 16.87, 18.98, 19.26, 19.53 ($4\times CH_3$), 21.14 ($2\times CH_3$), 35.45 [$CH(CH_3)_2$], 3.66 (CH_2), 38.68 [$CH(CH_3)_2$], 56.66 (CH–NH), 127.05, 128.58, 135.74, 137.94 (C_{arom}), 176.22 (CONH), 212.89 (COCH). EI-MS: m/z 289 (5%, M^+), 148 (100%). Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.19; H, 9.71; N, 4.89.

5.5. General procedure for the synthesis of α-aminoketone hydrochlorides (5e,f)

A solution of compound **4** (10 mmol) in 6 M hydrochloric acid (55 mL) and ethanol (30 mL) was refluxed for 10 h, the solvent was removed under reduced pressure. The residue was dissolved in ethanol (5 mL) and the hydrochloride **5e**,**f** was precipitated by the addition of ether (30 mL), filtered off, and washed with ether (30 mL).

5.5.1. 2-Amino-1-(3,5-dimethylphenyl)pentan-3-one hydrochloride (5e). Yield 1.8 g (65%) as a white solid; mp 163–165 °C. ^{1}H NMR (DMSO-d_6): δ 0.86 (t, 3H, J = 7.1 Hz, CH_3CH$_2$), 2.24 (s, 6H, $2\times CH_3$), 2.28–2.52 (m, 2H, CH_2CH$_3$), 2.98 (dd, 1H, J = 7.5, 13.7 Hz, HCH–CH), 3.13 (dd, 1H, J = 6.0, 13.7 Hz, HCH–CH), 4.28 (br s, 1H, CH) 6.87 (s, 2H, H_{arom}), 6.90 (s, 1H, H_{arom}), 8.58 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6): δ 6.77 (CH$_3$CH$_2$), 20.79 ($2\times CH_3$), 33.60 (CH$_2$CH$_3$), 35.38 (CH$_2$–CH), 58.33 (CH), 126.96, 128.54, 134.75, 137.53 (C_{arom}), 20.80 (CO). Anal. Calcd for $C_{13}H_{20}ClNO\cdot 0.25H_2O$: C, 63.40; H, 8.39; N, 5.79. Found: C, 63.20; H, 8.16; N, 5.82.

5.5.2. 2-Amino-1-(3,5-dimethylphenyl)-4-methylpentan-3-one hydrochloride (5f). Yield 2.0 g (80%) as a white solid; mp 192–194 °C. ^{1}H NMR (DMSO-d_6): δ 0.85 (d, 3H, J = 6.4 Hz, CH_3CH), 1.03 (d, 3H, J = 6.9 Hz, CH_3CH), 2.25 (s, 6H, $2\times CH_3$), 2.57 (hept, 1H, J = 6.8 Hz, $(CH_3)_2$CH), 2.99 (dd, 1H, J = 7.3, 13.9 Hz, HCH–CH), 3.16 (dd, 1H, J = 6.0, 13.8 Hz, HCH–CH), 4,48 (br s, 1H, CH_2–CH), 6.89 (s, 2H, H_{arom}), 6.92 (s, 1H, H_{arom}), 8.61 (s, 3H, NH_3). ^{13}C NMR (DMSO-d_6): δ 16.32 (CH$_3$CH), 18.75 (CH$_3$CH), 20.78 ($2\times CH_3$), 35.57 (CH$_3$$C$H), 37.71 ($CH_2$–CH), 56.67 (CH$_2$$C$H), 127.05, 128.57, 134.49, 137.51 (C_{arom}), 209.91 (CO). Anal. Calcd for $C_{14}H_{22}ClNO\cdot 0.5H_2O$: C, 63.50; H, 8.76; N, 5.29. Found: C, 63.41; H, 8.42; N, 5.49.

5.6. General procedure for the synthesis of 5-alkyl-4-(3,5-dimethylbenzyl)-1,3-dihydroimidazole-2-thiones (6e,f)

To a hot solution of potassium thiocyanate (0.48 g, 5 mmol) in water (20 mL) was added compound **5** (5 mmol). The reaction mixture was refluxed for 3 h and cooled to rt. The solid product formed was filtered off, washed with ether (20 mL) and dried to give compounds **6e**,**f**.

5.6.1. 4-(3,5-Dimethylbenzyl)-5-ethyl-1,3-dihydroimidazole-2-thione (6e). Yield 0.91 g (81%) as a white solid; mp 250–252 °C. ^{1}H NMR (DMSO-d_6): δ 1.05 (t, 3H, J = 7.3 Hz, CH_3CH$_2$), 2.22 (s, 6H, $2\times CH_3$), 2.37 (q, 2H, J = 7.4 Hz, CH_2CH$_3$), 3.58 (s, 2H, CH_2–Ar), 6.81 (s, 3H, H_{arom}), 11.66 (s, 1H, NH), 11.71 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 13.88 (CH$_3$CH$_2$), 16.42 (CH$_2$-CH$_3$), 20.82 ($2\times CH_3$), 28.77 (CH$_2$–Ar), 122.28 (C-4), 125.98 (C-5), 125.85, 127.54, 137.20, 138.84 (C_{arom}). EI-MS: m/z 246 (100%, M^+). Anal. Calcd for $C_{14}H_{18}N_2S\cdot 0.25H_2O$: C, 67.03; H, 7.23; N, 11.17. Found: C, 66.62; H, 7.11; N, 11.07.

5.6.2. 4-(3,5-Dimethylbenzyl)-5-isopropyl-1,3-dihydroimidazole-2-thione (6f). Yield 1.0 g (84%) as a white solid; mp 230–232 °C. ^{1}H NMR (DMSO-d_6): δ 1.11 [d, 6H, J = 7.0 Hz, $(CH_3)_2$CH], 2.22 (s, 6H, $2\times CH_3$), 2.91 [hept, 1H, J = 6.9 Hz, CH(CH$_3$)$_2$], 3.58 (s, 2H, CH$_2$), 6.79 (s, 2H, H_{arom}), 6.81 (s, 1H, H_{arom}), 11.63 (s, 1H, NH), 11.74 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 20.83 ($2\times CH_3$), 21.73 [(CH_3)$_2$CH], 23.42 (CH), 28.80 (CH_2), 121.17 (C-4), 125.80, 127.52, 137.19, 138.94 (C_{arom}), 130.10 (C-5), 158.98 (C=S). EI-MS: m/z 260 (100%, M^+). Anal. Calcd for $C_{15}H_{20}N_2S\cdot 0.35H_2O$: C, 67.55; H, 7.82; N, 10.50. Found: C, 67.37; H, 7.56; N, 10.37.

5.7. Ethyl (5-benzyl-4-ethyl-1*H*-imidazol-2-ylthio)-acetate (7)

Compound **6a** (2.2 g, 10 mmol) was added to a stirred solution of potassium carbonate (1.38 g, 10 mmol) in dimethylformamide (15 mL) and the mixture was stirred at rt for 1 h. Ethyl chloroacetate (1.06 mL, 10 mmol) was added dropwise to the reaction mixture and stirred for additional 3 h at rt. The solvent was removed under reduced pressure and the residue was treated with water (20 mL). The product was filtered off and recrystallized from ethanol/water to afford compound **7**. Yield 1.6 g (53%) as a white solid; mp 53–55 °C. ^{1}H NMR (DMSO-d_6): δ 1.04 (t, 3H, J = 7.4 Hz, CH_3CH$_2$), 1.11 (t, 3H, CH_3CH$_2$), 2.45 (br s, 2H, CH$_3$CH_2), 3.72 (br s, 2H, CH_2Ph), 3.78 (s, 2H, CH_2S), 4.02 (q, 2H, J = 7.2 Hz, CH$_3$CH_2O), 7.15–7.23 (m, 5H, Ph), 11.10 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): 13.80 (CH$_3$CH$_2$), 14.39 (CH$_3$CH$_2$O), 17.15 (br s, CH$_3$$CH_2$), 32.44 (br s, CH$_2$Ph), 35.25 (CH$_2$S), 60.71 (CH$_3$$CH_2$O), 125.44, 128.09, 134.48 (C_{arom}), 168.89 (CO). EI-MS: m/z 304 (96%, M^+), 230 (100%). Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20. Found: C, 63.84; H, 6.61; N, 9.12.

5.8. 2-(5-Benzyl-4-ethyl-1*H*-imidazol-2-ylthio)acetamide (8a)

A mixture of compound **7** (0.6 g, 2 mmol) and 30% aqueous ammonia (10 mL) in ethanol (20 mL) was heated at 60 °C for 6 h. The solvent was evaporated under reduced pressure. The residue was treated with water, filtered off, dried, and chromatographed on a silica gel column with ethyl acetate to afford compound **8a**. Yield 0.1 g (18%) as a white solid; mp 128–130 °C. ^{1}H NMR (DMSO-d_6): δ 1.06 (t, 3H, J = 7.4 Hz, CH_3CH$_2$), 2.45 (q, 2H, J = 6.8 Hz, CH$_3$CH_2), 3.61 (s, 2H, CH_2Ph), 3.76 (s, 2H, CH_2S), 7.16–7.28 (m, 5H, H_{arom}), 7.72 (s, 2H, NH_2), 11.91 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.43 (CH$_3$CH$_2$), 36.87 (CH$_2$S), 125.64, 128.13,

135.83 (C_{arom}), 170.00 (C=O). EI-MS: *m/z* 275 (100%, M^+). Anal. Calcd for $C_{14}H_{17}N_3OS$: C, 61.07; H, 6.22; N, 15.26. Found: C, 60.53; H, 6.24; N, 14.96.

5.9. Synthesis of compounds 9 and 10

To a solution of compound **7** (0.61 g, 2 mmol) in methylene chloride (15 mL) under nitrogen was added *N*-ethyldiisopropylamine (EDIA) (0.36 mL, 2 mmol) followed by addition of ethoxymethyl chloride (2 mmol). The reaction mixture was stirred for 3 h at rt and quenched with water (20 mL). Methylene chloride (20 mL) was added and the two layers were separated. The organic layer was dried (sodium sulfate), filtered, and the solvent was removed under reduced pressure. The residual material was chromatographed on a silica gel column with CH_2Cl_2/EtOAc (5:1, v/v) to afford compounds **9** and **10**.

5.9.1. Ethyl [4-benzyl-1-(ethoxymethyl)-5-ethyl-1*H*-imidazol-2-ylthio]acetate (9). Yield 0.15 g (20%) obtained as an oil. ^{1}H NMR ($CDCl_3$): δ 1.04 (t, 3H, J = 7.5 Hz, CH_3CH$_2$), 1.18 (t, 3H, J = 7.1 Hz, CH_3CH$_2$O), 1.19 (t, 3H, J = 7.2 Hz, CH_3CH$_2$OCO), 2.58 (q, 2H, J = 7.5 Hz, CH$_3$CH_2), 3.49 (q, 2H, J = 7.1 Hz, CH_3CH$_2$O), 3.77 (s, 2H, CH$_2$S), 3.87 (s, 2H, CH_2Ph), 4.09 (q, 2H, J = 7.2 Hz, CH$_3$CH_2OCO), 5.33 (s, 2H, NCH$_2$O), 7.14–7.27 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 14.01 (*C*H$_3$CH$_2$), 14.39 (*C*H$_3$CH$_2$), 14.85 (*C*H$_3$CH$_2$), 17.01 (CH$_3$*C*H$_2$), 33.55 (*C*H$_2$Ph), 37.19 (CH$_2$S), 61.50 (CH$_3$*C*H$_2$OCO), 63.71 (CH$_3$*C*H$_2$O), 73.26 (NCH$_2$O), 125.74, 128.14, 128.43, 137.98 (C_{arom}), 132.13 (C-4), 137.88 (C-5), 140.58 (C-2), 169.17 (COO). FAB MS: ($CDCl_3$ + NBA) *m/z* 363 (100%, MH^+).

5.9.2. Ethyl [5-benzyl-1-(ethoxymethyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetate (10). Yield 0.25 g (35%) obtained as an oil. ^{1}H NMR ($CDCl_3$): δ 1.08 (t, 3H, J = 7.0 Hz, CH_3CH$_2$O), 1.20 (t, 3H, J = 7.2 Hz, CH_3CH$_2$OCO), 1.21 (t, 3H, J = 7.5 Hz, CH_3CH$_2$), 2.55 (q, 2H, J = 7.5 Hz, CH$_3$CH_2), 3.36 (q, 2H, J = 7.0 Hz, CH$_3$CH_2O), 3.79 (s, 2H, CH$_2$S), 4.00 (s, 2H, CH_2Ph), 4.11 (q, 2H, J = 7.2 Hz, CH$_3$CH_2OCO), 5.13 (s, 2H, NCH$_2$O), 7.07–7.29 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 14.03 (*C*H$_3$CH$_2$), 14.42 (*C*H$_3$CH$_2$), 14.69 (*C*H$_3$CH$_2$), 20.43 (CH$_3$*C*H$_2$), 29.22 (*C*H$_2$Ph), 37.13 (CH$_2$S), 61.49 (CH$_3$*C*H$_2$OCO), 63.58 (CH$_3$*C*H$_2$O), 73.38 (NCH$_2$O), 126.38, 127.91, 128.51, 138.55 (C_{arom}), 126.86 (C-4), 138.53 (C-5), 142.84 (C-2), 169.11 (COO). MALDI-MS: *m/z* 263 (100%, MH^+). Anal. Calcd for $C_{19}H_{26}N_2O_3S$: C, 62.95; H, 7.23; N, 7.73. Found: C, 62.99; H, 7.36; N, 7.63.

5.10. General procedure for the synthesis of 2-(4-alkyl-5-substituted 1*H*-imidazol-2-ylthio)acetamides (8a–f)

Compound **6** (7 mmol) was added to a solution of potassium hydroxide (0.4 g, 7 mmol) in methanol (15 mL) and the mixture was stirred for 0.5 h. 2-Iodoacetamide (1.3 g, 7 mmol) was added to the mixture and it was stirred at rt for 1 h. The solvent was removed under reduced pressure, and water (25 mL) was added to the residual material and the solid product formed was filtered off and recrystallized from ethanol/water to give compounds **8a**–**f**.

5.10.1. 2-[5-(3,5-Dimethylbenzyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetamide (8b). Yield 1.7 g (80%) as a white solid; mp 160–162 °C. ^{1}H NMR (DMSO-d_6): δ 1.07 (t, 3H, J = 7.5 Hz, CH_3CH$_2$), 2.20 (s, 6H, 2 × CH$_3$), 2.44 (q, 2H, J = 7.5 Hz, CH$_3$CH_2), 3.60 (s, 2H, CH_2–Ar), 3.71 (s, 2H, CH_2S), 6.77 (s, 3H, H_{arom}), 7.15 (s, 1H, *H*NH), 7.73 (s, 1H, HN*H*), 11.89 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.34, 14.50 (*C*H$_3$CH$_2$), 17.11, 19.54 (CH$_3$*C*H$_2$), 20.85 (2 × CH$_3$), 29.52, 32.45 (*C*H$_2$–Ar), 36.76, 36.89 (CH$_2$S), 125.85, 126.03, 126.93, 135.80, 136.83, 137.17, 140.89 (C_{arom}), 127.38, 129.74 (C-4), 135.62, 135.98 (C-5), 139.27, 139.56 (C-2), 170.06 (C=O). HRMS (MALDI) *m/z* calcd for $C_{16}H_{22}N_3OS^+$ (MH^+) 304.1510, found 304.1483.

5.10.2. 2-[5-(Cyclohexylmethyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetamide (8c). Yield 1.6 g (82%) as a white solid; mp 150–152 °C. ^{1}H NMR (DMSO-d_6): δ 0.82–0.93 (m, 2H, H_{cy}), 1.06–1.21 (m, 6H, CH_3CH$_2$ and H_{cy}), 1.45–1.61 (m, 6H, H_{cy}), 2.16–2.51 (m, 4H, CH$_3$CH_2 and CH_2Cy), 3.58 (s, 2H, CH_2S), 7.17 (s, 1H, *H*NH), 7.77 (s, 1H, HN*H*), 11.78 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.48, 14.57 (*C*H$_3$CH$_2$), 17.07, 19.55 (CH$_3$*C*H$_2$), 25.91, 26.01, 25.63, 32.39, 32.58 (C_{cy}), 31.30, 34.07 (*C*H$_2$–Cy), 36.88, 37.93 (CH$_2$S), 125.69, 129.67 (C-4), 135.30, 139.39 (C-5), 135.61, 139.36 (C-2), 170.14 (C=O). EI-MS: *m/z* 281 (43%, M^+), 141 (100%). Anal. Calcd for $C_{14}H_{23}N_3OS{\cdot}05H_2O$: C, 57.90; H, 8.33; N, 14.47. Found: C, 57.71; H, 8.05; N, 14.43.

5.10.3. 2-(5-Benzyl-4-isopropyl-1*H*-imidazol-2-ylthio)acetamide (8d). Yield 1.17 g (58%) as a white solid; mp 158–160 °C. ^{1}H NMR (DMSO-d_6): δ 1.11 [d, 6H, J = 6.7 Hz, (CH_3)$_2$CH], 2.93 [hept, 1H, J = 6.7 Hz, (CH$_3$)$_2$C*H*], 3.61 (s, 2H, CH_2Ph), 3.78 (s, 2H, CH$_2$S), 7.15–7.28 (m, 5H, H_{arom}), 7.77 (s, 2H, NH$_2$), 11.88 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 22.73 [(*C*H$_3$)$_2$CH], 24.59 [br s, (CH$_3$)$_2$*C*H], 31.80 (br s, *C*H$_2$Ph), 36.76 (CH$_2$S), 125.66, 128.10, 128.14, 136.06 (C_{arom}), 140.70 (br s, C-2), 170.12 (C=O). EI-MS: *m/z* 289 (100%, M^+). Anal. Calcd for $C_{15}H_{19}N_3OS{\cdot}0.5H_2O$: C, 60.38; H, 6.76; N, 14.08. Found: C, 60.50; H, 6.50; N, 14.10.

5.10.4. 2-[5-(3,5-Dimethylbenzyl)-4-isopropyl-1*H*-imidazol-2-ylthio]acetamide (8e). Yield 1.15 g (52%) as a white solid; mp 130–132 °C. ^{1}H NMR (DMSO-d_6): δ 1.12 [d, 6H, J = 6.9 Hz, (CH_3)$_2$CH], 2.21 (s, 6H, 2 × CH$_3$), 2.93 [hept, 1H, J = 6.9 Hz, (CH$_3$)$_2$C*H*], 3.61 (s, 2H, CH$_2$S), 3.69 (s, 2H, CH_2Ph), 6.76 (s, 3H, H_{arom}), 7.17 (s, 1H, *H*NH), 7.78 (s, 1H, HN*H*). ^{13}C NMR (DMSO-d_6): δ 20.85 (2CH$_3$), 22.71 [(*C*H$_3$)$_2$CH], 24.61 [(CH$_3$)$_2$*C*H], 31.22 (*C*H$_2$Ar), 36.74 (CH$_2$S), 125.91, 127.11, 135.93, 136.95 (C_{arom}), 140.34 (C-2), 170.13 (C=O). EI-MS: *m/z* 317 (100%, M^+). Anal. Calcd for $C_{17}H_{23}N_3OS{\cdot}0.5H_2O$: C, 62.55; H, 7.41; N, 12.87. Found: C, 62.71; H, 7.17; N, 12.89.

5.10.5. 2-[5-(Cyclohexylmethyl)-4-isopropyl-1*H*-imidazol-2-ylthio]acetamide (8f). Yield 1.7 g (82%) as a white solid; mp 156–158 °C. ^{1}H NMR (DMSO-d_6): δ 0.82–

0.93 (m, 2H, H_{cy}), 1.09–1.15 [m, 9H, $(CH_3)_2CH$ and H_{cy}], 1.46–1.61 (m, 6H, H_{cy}), 2.22, 2.32 (2 × d, 2H, J = 6.8, 7.0 Hz, CH_2–Cy), 2.76, 2.87 [2 × hept, 1H, J = 6.4, 6.4 Hz, $(CH_3)_2CH$], 3.57, 3.60 (s, 2H, CH_2S), 7.16 (s, 1H, *H*NH), 7.78, 7.86 (2 × s, 1H, HN*H*), 11.68 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 22.68, 23.16 [$(CH_3)_2CH$], 23.96, 25.31 [$(CH_3)_2CH$], 25.89, 26.06, 25.59, 25.72, 30.59, 32.39, 32.61, 36.55 (C_{cy}), 31.22, 34.13 (CH_2–Cy), 36.78, 37.89 (CH_2S), 124.72, 134.42 (C-4), 133.88, 143.41 (C-5), 135.28, 135.59 (C-2), 170.18, 170.29 (C=O). EI-MS: *m*/*z* 295 (10%, M^+), 55 (100%). Anal. Calcd for $C_{15}H_{25}N_3OS \cdot 0.25H_2O$: C, 60.06; H, 8.57; N, 14.01. Found: C, 60.00; H, 8.41; N, 13.82.

5.11. General procedure for the synthesis of compounds 11a–c and 12a–f

Compound **8** (1 mmol) was dissolved in dimethylformamide (10 mL) and sodium hydride (0.09 g, 55% suspension in paraffin oil, 2 mmol) was added to the solution portionwise under ice cooling. The reaction mixture was stirred for 0.5 h and 4-pyridylmethyl chloride hydrochloride (0.164 g, 1 mmol) was added portionwise to the reaction mixture under ice cooling and stirring at rt was continued for 4 h. The solvent was removed under reduced pressure and the residual material was treated with water (15 mL) and filtered off. The precipitate was dried, and chromatographed on a silica gel column with EtOAc/MeOH (20:1, v/v) to give compounds **11a**–**c** and **12a**–**f**. We were unable to separate compounds **11a**–**c** and **12a**–**c** from each other by column chromatography.

5.11.1. 2-[4-Benzyl-5-ethyl-1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-ylthio]acetamide (11a) and 2-[5-benzyl-4-ethyl-1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-ylthio]acetamide (12a). Yield 0.15 g (41%). ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 7.4 Hz, CH_3CH_2), 1.19 (t, 3H, J = 7.4 Hz, CH_3CH_2), 2.39 (q, 2H, J = 7.4 Hz, CH_3CH_2), 2.53 (q, 2H, J = 7.4 Hz, CH_3CH_2), 3.43 (s, 2H, CH_2S), 3.49 (s, 2H, CH_2S), 3.69 (s, 2H, CH_2Ph), 3.80 (s, 2H, CH_2Ph), 4.81 (s, 2H, CH_2N), 5.02 (s, 2H, CH_2N), 5.42 (s, 1H, *H*NH), 5.74 (s, 1H, *H*NH), 6.66 (d, 2H, J = 4.5 Hz, H_{py}), 6.81 (d, 2H, J = 4.6 Hz, H_{py}), 7.12–7.22 (m, 10H, H_{arom}), 8.32 (s, 1H, HN*H*), 8.39 (d, 2H, J = 4.7 Hz, H_{py}), 8.49 (d, 2H, J = 4.3 Hz, H_{py}), 8.69 (s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 14.37, 14.51 (2 × CH_3CH_2), 16.94, 20.33 (2 × CH_3CH_2), 29.46, 33.47 (2 × CH_2Ph), 36.27, 36.59 (2 × CH_2S), 46.52, 46.76 (2 × CH_2N), 120.77, 144.98, 145.28, 150.12, 150.34 (C_{py}), 126.05, 126.80 (C-4), 126.63, 127.73, 128.34, 128.44, 128.74, 131.25, 137.48, 137.65 (C_{arom}), 140.15 (C-2), 139.71, 140.27 (C-5), 171.93, 172.12 (CO). EI-MS: *m*/*z* 366 (100%, M^+).

5.11.2. 2-[4-(3,5-Dimethylbenzyl)-5-ethyl-1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-ylthio]acetamide (11b) and 2-[5-(3,5-dimethylbenzyl)-4-ethyl-1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-ylthio]acetamide (12b). Yield 0.23 g (59%). ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3H, J = 7.5 Hz, CH_3CH_2), 1.27 (t, 3H, J = 7.5 Hz, CH_3CH_2), 2.19 (s, 6H, 2CH_3), 2.27 (s, 6H, 2CH_3), 2.47 (q, 2H, J = 7.5 Hz, CH_3CH_2), 2.60 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.69 (s, 2H, CH_2S), 3.79 (s, 2H, CH_2S), 4.90 (s, 2H, CH_2N), 5.40 (s, 1H, *H*NH), 5.72 (s, 1H, *H*NH), 6.54 (s, 3H, H_{arom}), 6.71 (d, 2H, J = 5.1 Hz, H_{py}), 6.77 (s, 1H, H_{arom}), 6.82 (s, 2H, H_{arom}), 6.88 (d, 2H, J = 5.1 Hz, H_{py}), 8.01 (s, 1H, HN*H*), 8.46 (d, 2H, J = 5.1 Hz, H_{py}), 8.56 (d, 2H, J = 5.1 Hz, H_{py}), 8.83 (s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 14.38, 14.53 (CH_3CH_2), 16.96, 20.35 (CH_3CH_2), 21.13, 2.24 (4 × CH_3), 29.35, 33.29 (CH_2Ar), 36.22, 36.64 (CH_2S), 46.53, 46.79 (CH_2N), 120.74, 120.80, 145.06, 145.34, 149.97, 150.34 (C_{py}), 125.63, 126.29 (C-4), 126.98, 127.64, 128.33, 137.29, 137.79, 137.85, 138.28 (C_{arom}), 139.98, 141.99 (C-2), 139.63, 140.11 (C-5), 172.02, 172.17 (CO); EI-MS: *m*/*z* 394 (100%, M^+).

5.11.3. 2-[4-(Cyclohexylmethyl)-5-ethyl-1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-ylthio]acetamide (11c) and 2-[5-(cyclohexylmethyl)-4-ethyl-1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-ylthio]acetamide (12c). Yield 0.15 g (40%). ^{1}H NMR ($CDCl_3$): δ 0.81–1.29 (m, 16H, 2 × CH_3CH_2 and H_{cy}), 1.54–1.71 (m, 12H, H_{cy}), 2.27 (d, 2H, J = 7.3 Hz, CH_2Cy), 2.36–2.54 (m, 6H, CH_2Cy, 2 × CH_3CH_2), 3.51 (s, 2H, CH_2S), 3.52 (s, 2H, CH_2S), 5.09 (s, 2H, CH_2N), 5.12 (s, 2H, CH_2N), 5.86 (br s, 1H, *H*NH), 6.86 (d, 4H, J = 4.3 Hz, H_{py}), 8.56 (d, 4H, J = 4.5, H_{py}), 8.75 (br s, 1H, HN*H*), 8.84 (br s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 13.93, 14.64 (CH_3CH_2), 16.82, 20.36 (CH_3CH_2), 26.06, 26.44, 26.96, 26.18, 33.02, 33.18, 38.36 (C_{cy}), 34.75, 31.29 (CH_2Cy), 46.47, 46.61 (CH_2N), 120.68, 145.57, 145.60, 150.24, 150.28 (C_{py}), 127.35, 131.29 (C-4), 138.01, 141.59 (C-5), 138.93, 139.22 (C-2), 172.17, 172.24 (CO). EI-MS: *m*/*z* 372 (100%, M^+).

5.11.4. 2-[5-Benzyl-4-isopropyl-1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-ylthio]acetamide (12d). Yield 0.8 (30%) as a white solid; mp 158–160 °C. ^{1}H NMR (DMSO-d_6): δ 1.22 [d, 6H, J = 6.9 Hz, $(CH_3)_2CH$], 3.03 [hept, 1H, J = 6.9 Hz, $(CH_3)_2CH$], 3.79 (s, 2H, CH_2S), 3.94 (s, 2H, CH_2Ph), 5.25 (s, 2H, CH_2N), 6.86 (d, 2H, J = 5.1 Hz, H_{py}), 7.06–7.22 (m, 5H, Ph), 7.22 (s, 1H, *H*NH), 7.78 (s, 1H, HN*H*), 8.40 (d, 2H, J = 4.5 Hz, H_{py}). ^{13}C NMR ($CDCl_3$): δ 22.48 [$(CH_3)_2CH$], 25.17 [$(CH_3)_2CH$], 28.19 (CH_2Ph), 37.86 (CH_2S), 46.54 (CH_2N), 121.13, 145.83, 148.87 (C_{py}), 126.71 (C-4), 126.24, 127.81, 128.32, 137.67 (C_{arom}), 139.05 (C-5), 142.83 (C-2), 169.06 (CO). HRMS (MALDI) *m*/*z* calcd for $C_{21}H_{25}N_4OS^+$ (MH^+) 381.1747, found 381.1744.

5.11.5. 2-[5-(3,5-Dimethylbenzyl)-4-isopropyl-1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-ylthio]acetamide (12e). Yield 1 g (34%) as a white solid; mp 120–122 °C. ^{1}H NMR (DMSO-d_6): δ 1.19 [d, 6H, J = 6.8 Hz, $(CH_3)_2CH$], 2.09 (s, 6H, 2 × CH_3), 2.95 [hept, 1H, J = 6.8 Hz, $(CH_3)_2CH$], 3.64 (s, 2H, CH_2S), 3.78 (s, 2H, CH_2Ar), 5.09 (s, 2H, CH_2N), 6.53 (s, 2H, H_{arom}), 6.66 (s, 1H, H_{arom}), 6.74 (d, 2H, J = 5.5 Hz, H_{py}), 7.15 (br s, 1H, *H*NH), 7.78 (br s, 1H, HN*H*), 8.37 (d, 2H, J = 5.5 Hz, H_{py}). ^{13}C NMR (DMSO-d_6): δ 20.71 (2 × CH_3), 22.98 [$(CH_3)_2CH$], 25.68 [$(CH_3)_2CH$], 28.34 (CH_2Ar), 37.55 (CH_2S), 45.98 (CH_2N), 120.78, 145.78, 149.33 (C_{py}), 126.62 (C-4), 125.66, 127.39, 137.13, 138.14 (C_{arom}),

138.62 (C-2), 144.81 (C-5), 169.56 (CO). EI-MS: *m/z* 408 (100%, M^+). Anal. Calcd for $C_{23}H_{28}N_4OS{\cdot}0.25H_2O$: C, 66.88; H, 6.95; N, 13.56. Found: C, 66.70; H, 6.86; N, 13.48.

5.11.6. 2-[5-(Cyclohexylmethyl)-4-isopropyl-1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-ylthio]acetamide (12f). Yield 0.84 g (31%) as a white solid; mp 162–164 °C. ^{1}H NMR (DMSO-d_6): δ 0.82–1.23 [m, 11H, $(CH_3)_2CH$ and H_{cy}], 1.47–1.65 (m, 6H, H_{cy}), 2.30 (d, 2H, J = 6.9 Hz, CH_2Cy), 2.83 [hept, 1H, J = 6.9 Hz, $[(CH_3)_2CH]$], 3.60 (s, 2H, CH_2S), 5.21 (s, 2H, CH_2N), 6.92 (d, 2H, J = 5.1 Hz, H_{py}), 7.15 (br s, 1H, *H*NH), 7.79 (br s, 1H, HN*H*), 8.51 (d, 2H, J = 5.5 Hz, H_{py}). ^{13}C NMR (DMSO-d_6): δ 22.98 [$(CH_3)_2CH$], 25.57 [$(CH_3)_2CH$ and C_{cy}], 25.68, 32.18, 37.53 (C_{cy}), 30.23 (CH_2Cy), 37.37 (CH_2S), 45.86 (CH_2N), 120.80, 146.66, 149.75 (C_{py}), 125.77 (C-4), 138.16 (C-2), 169.61 (CO). HRMS (MALDI) *m/z* calcd for $C_{21}H_{31}N_4OS^+$ (MH^+) 387.2224, found 387.2213.

5.12. General procedure for the synthesis of compounds 13c–f and 14a–l

To a solution of compound **8** (1.5 mmol) in methylene chloride (10 mL) under nitrogen was added *N*-ethyldiisopropylamine (EDIA) (0.27 mL, 1.5 mmol) followed by addition of ethoxy or (benzyloxy)methyl chloride (1 mmol). The mixture was stirred for 2 h at rt and quenched with water (20 mL). Methylene chloride (30 mL) was added and the two layers were separated. The organic layer was dried using (sodium sulfate) and the solvent was removed under reduced pressure. The residual material was chromatographed on a silica gel column with ethyl acetate to afford compounds **13c–f** and **14a–l**.

5.12.1. 2-[5-(3,5-Dimethylbenzyl)-1-(ethoxymethyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetamide (13c). Yield 0.15 g (28%) as a white solid; mp 93–95 °C. ^{1}H NMR ($CDCl_3$): δ 1.05 (t, 3H, J = 7.5 Hz, CH_3CH_2), 1.12 (t, 3H, J = 6.9 Hz, CH_3CH_2O), 2.18 (s, 6H, $2\times CH_3$), 2.56 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.43 (q, 2H, J = 6.9 Hz, CH_3CH_2), 3.63 (s, 2H, CH_2S), 3.72 (s, 2H, CH_2Ph), 5.17 (s, 2H, NCH_2O), 5.27 (s, 1H, *H*NH), 6.76 (s, 3H, H_{arom}), 8.42 (s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 14.42 (CH_3CH_2), 14.77 (CH_3CH_2O), 16.76 (CH_3CH_2), 21.21 ($2\times CH_3$), 32.56 (CH_2Ar), 36.21 (CH_2S), 64.29 (CH_3CH_2O), 73.48 (NCH_2O), 126.35, 127.76, 136.42, 137.84 (C_{arom}), 131.82 (C-4), 139.40 (C-5), 140.02 (C-2), 171.62 (C=O). HRMS (MALDI) *m/z* calcd for $C_{19}H_{28}N_3O_2S^+$ (MH^+) 362.1892, found 362.1897.

5.12.2. 2-[1-(Benzyloxymethyl)-5-(3,5-dimethylbenzyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetamide (13d). Yield 0.15 g (24%) obtained as an oil. ^{1}H NMR ($CDCl_3$): δ 1.12 (t, 3H, J = 7.5 Hz, CH_3CH_2), 2.26 (s, 6H, $2\times CH_3$), 2.63 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.56 (s, 2H, CH_2S), 3.75 (s, 2H, CH_2Ar), 4.51 (s, 2H, OCH_2Ph), 5.21 (s, 1H, *H*NH), 5.27 (s, 2H, OCH_2N), 6.82 (s, 3H, H_{arom}), 7.24–7.35 (m, 5H, Ph), 8.49 (s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 14.68 (CH_3CH_2), 16.81 (CH_3CH_2), 21.25 ($2\times CH_3$), 33.14 (CH_2Ar), 36.12 (CH_2S), 70.51 (OCH_2Ph), 72.83 (NCH_2O), 125.65 (C-4), 126.39, 127.63, 127.75, 128.12, 128.53, 136.51, 137.49, 137.78 (C_{arom}), 140.02 (C-5), 140.34 (C-2). HRMS (MALDI) *m/z* calcd for $C_{24}H_{30}N_3O_2S^+$ (MH^+) 424.2051, found 424.2051.

5.12.3. 2-[4-(Cyclohexylmethyl)-1-(ethoxymethyl)-5-ethyl-1*H*-imidazol-2-ylthio]acetamide (13e). Yield 0.11 g (22%) as a white solid; mp 90–92 °C. ^{1}H NMR ($CDCl_3$): δ 0.87–0.98 (m, 2H, H_{cy}), 1.11–1.22 (m, 9H, CH_3CH_2, CH_3CH_2O and H_{cy}), 1.56–1.69 (m, 6H, H_{cy}), 2.33 (d, 2H, J = 6.8 Hz, CH_2Cy), 2.58 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.48 (q, 2H, J = 7.0 Hz, CH_3CH_2O), 3.56 (s, 2H, CH_2S), 5.23 (s, 2H, NCH_2O), 5.56 (br s, 1H, *H*NH), 8.83 (br s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 14.72 (CH_3CH_2), 14.83 (CH_3CH_2O), 16.72 (CH_3CH_2), 26.50, 26.25, 33.23, 38.13 (C_{cy}), 34.61 (CH_2Cy), 36.68 (CH_2S), 63.94 (CH_3CH_2O), 73.18 (NCH_2O), 131.79 (C-4), 137.56 (C-5), 139.45 (C-2), 172.45 (C=O). EI-MS: *m/z* 339 (16%, M^+), 59 (100%). Anal. Calcd for $C_{17}H_{29}N_3O_2S{\cdot}0.25H_2O$: C, 59.36; H, 8.64; N, 12.21. Found: C, 59.41; H, 8.63; N, 12.04.

5.12.4. 2-[1-(Benzyloxymethyl)-4-(cyclohexylmethyl)-5-ethyl-1*H*-imidazol-2-ylthio]acetamide (13f). Yield 0.13 g (22%) obtained as an oil. ^{1}H NMR ($CDCl_3$): δ 0.88 (m, 2H, H_{cy}), 1.09–1.28 (m, 6H, CH_3CH_2 and H_{cy}), 1.54–1.69 (m, 6H, H_{cy}), 2.33 (d, 2H, J = 6.9 Hz, CH_2Cy), 2.58 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.56 (s, 2H, CH_2S), 4.51 (s, 2H, CH_2Ph), 5.29 (s, 2H, NCH_2O), 5.56 (br s, 1H, *H*NH), 7.26–7.35 (m, 5H, Ph), 8.78 (br s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 14.72 (CH_3CH_2), 16.69 (CH_3CH_2), 26.48, 28.24, 33.21, 38.12 (C_{cy}), 34.60 (CH_2Cy), 36.69 (CH_2S), 70.44 (OCH_2Ph), 72.84 (NCH_2O), 127.71, 128.06, 128.49, 136.58 (C_{arom}), 131.78 (C-4), 137.68 (C-5), 139.61 (C-2), 172.38 (CO). HRMS (MALDI) *m/z* calcd for $C_{22}H_{32}N_3O_2S^+$ (MH^+) 402.2206, found 402.2210.

5.12.5. 2-[5-Benzyl-1-(ethoxymethyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetamide (14a). Yield 0.15 g (30%) as a white solid; mp 63–65 °C. ^{1}H NMR ($CDCl_3$): δ 1.09 (t, 3H, J = 7.0 Hz, CH_3CH_2O), 1.23 (t, 3H, J = 7.5 Hz, CH_3CH_2), 2.56 (t, 2H, J = 7.5 Hz, CH_3CH_2), 3.36 (t, 2H, J = 7.0 Hz, CH_3CH_2O), 3.62 (s, 2H, CH_2S), 4.00 (s, 2H, CH_2Ph), 5.04 (s, 1H, NCH_2O), 5.73 (br s, 1H, *H*NH), 7.08–7.31 (m, 5H, H_{arom}), 8.78 (br s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 14.20 (CH_3), 14.64 (CH_3), 20.15 (CH_3CH_2), 29.13 (CH_2Ph), 36.50 (CH_2S), 63.91 (CH_3CH_2O), 73.32 (NCH_2O), 126.82 (C-4), 126.54, 127.87, 128.61, 138.21 (C_{arom}), 140.57 (C-2), 141.83 (C-5), 172.40 (C=O). HRMS (MALDI) *m/z* calcd for $C_{17}H_{24}N_3O_2S^+$ (MH^+) 334.1579, found 334.1584.

5.12.6. 2-[5-Benzyl-1-(benzyloxymethyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetamide (14b). Yield 0.23 g (38%) as a white solid; mp 84–86 °C. ^{1}H NMR ($CDCl_3$): δ 1.13 (t, 3H, J = 7.5 Hz, CH_3CH_2), 2.48 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.56 (s, 2H, CH_2S), 3.89 (s, 2H, CH_2Ph), 4.31 (s, 2H, OCH_2Ph), 5.01 (s, 2H, NCH_2O), 5.47 (s, 1H, *H*NH), 6.94–7.27 (m, 10H, $2\times Ph$), 8.73 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.24 (CH_3CH_2), 20.08 (CH_3CH_2), 29.13 (CH_2Ph), 36.45 (CH_2S), 70.37 (OCH_2Ph), 72.98 (NCH_2O), 126.91 (C-4), 126.66, 127.65,

127.92, 128.06, 128.49, 128.71, 136.53, 138.02 (C_{arom}), 172.16 (C=O). HRMS (MALDI) *m/z* calcd for $C_{22}H_{26}N_3O_2S^+$ (MH^+) 396.1744, found 396.1740.

5.12.7. 2-[5-(3,5-Dimethylbenzyl)-1-(ethoxymethyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetamide (14c). Yield 0.15 g (28%) as a white solid; mp 93–95 °C. ^{1}H NMR ($CDCl_3$): δ 1.04 (t, 3H, J = 6.9 Hz, CH_3CH_2O), 1.15 (t, 3H, J = 7.5 Hz, CH_3CH_2), 2.18 (s, 6H, $2\times CH_3$), 2.47 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.29 (q, 2H, J = 6.9 Hz, CH_3CH_2O), 3.54 (s, 2H, CH_2S), 3.83 (s, 2H, CH_2Ph), 4.97 (s, 2H, NCH_2O), 5.53 (s, 1H, *H*NH), 6.61 (s, 2H, H_{arom}), 6.76 (s, 1H, H_{arom}), 8.79 (s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 14.20 (CH_3CH_2), 14.71 (CH_3CH_2O), 20.15 (CH_3CH_2), 21.23 ($2\times CH_3$), 28.95 (CH_2Ar), 36.54 (CH_2S), 63.94 (CH_3CH_2O), 73.36 (NCH_2O), 127.07 (C-4), 125.71, 128.19, 138.04, 138.18 (C_{arom}), 140.52 (C-2), 141.58 (C-5), 172.39 (C=O). EI-MS: *m/z* 361 (100%, M^+). Anal. Calcd for $C_{19}H_{27}N_3O_2S\cdot 0.2H_2O$: C, 62.50; H, 7.56; N, 11.51. Found: C, 62.66; H, 7.65; N, 11.33.

5.12.8. 2-[1-(Benzyloxymethyl)-5-(3,5-dimethylbenzyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetamide (14d). Yield 0.85 g (40%) as a white solid; mp 108–110 °C. ^{1}H NMR ($CDCl_3$): δ 1.23 (t, 3H, J = 7.5 Hz, CH_3CH_2), 2.23 (s, 6H, $2\times CH_3$), 2.55 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.60 (s, 2H, CH_2S), 3.88 (s, 2H, CH_2Ar), 4.39 (s, 2H, O–CH_2Ph), 5.09 (s, 2H, NCH_2O), 5.49 (s, 1H, *H*NH), 6.61 (s, 2H, H_{arom}), 6.82 (s, 1H, H_{arom}), 7.21–7.35 (m, 5H, Ph), 8.86 (s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 14.23 (CH_3CH_2), 20.19 (CH_3CH_2), 21.23 ($2\times CH_3$), 28.98 (CH_2Ar), 36.52 (CH_2S), 70.29 (O–CH_2Ph), 72.92 (NCH_2O), 127.09 (C-4), 125.72, 127.59, 128.02, 128.24, 128.48, 136.68, 137.99, 138.22 (C_{arom}), 140.79 (C-2), 141.71 (C-5), 172.36 (C=O). EI-MS: *m/z* 423 (100%, M^+). Anal. Calcd for $C_{24}H_{29}N_3O_2S\cdot 0.25H_2O$: C, 67.34; H, 6.95; N, 9.82. Found: C, 67.78; H, 6.99; N, 9.76.

5.12.9. 2-[5-(Cyclohexylmethyl)-1-(ethoxymethyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetamide (14e). Yield 0.11 g (21%) as a white solid; mp 100–102 °C. ^{1}H NMR ($CDCl_3$): δ 0.86–0.97 (m, 2H, H_{cy}), 1.14–1.25 (m, 9H, CH_3CH_2, CH_3CH_2O and H_{cy}), 1.39–1.53 (m, 1H, H_{cy}), 1.64–1.75 (m, 5H, H_{cy}), 2.42–2.49 (m, 4H, CH_3CH_2 and CH_2Cy), 3.47 (q, 2H, J = 7.0 Hz, CH_3CH_2O), 3.58 (s, 1H, CH_2S), 5.21 (s, 2H, NCH_2O), 5.61 (br s, 1H, *H*NH), 8.91 (br s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 13.90 (CH_3CH_2), 14.82 (CH_3CH_2O), 20.27 (CH_3CH_2), 26.30, 26.21, 33.20, 38.44 (C_{cy}), 31.09 (CH_2Cy), 36.64 (CH_2S), 63.91 (CH_3CH_2O), 73.18 (NCH_2O), 127.79 (C-4), 139.80 (C-2), 141.10 (C-5), 172.54 (C=O). HRMS (MALDI) *m/z* calcd for $C_{17}H_{30}N_3O_2S^+$ (MH^+) 340.2050, found 340.2053.

5.12.10. 2-[1-(Benzyloxymethyl)-5-(cyclohexylmethyl)-4-ethyl-1*H*-imidazol-2-ylthio]acetamide (14f). Yield 0.1 g (17%) as a white solid; mp 102–104 °C. ^{1}H NMR ($CDCl_3$): δ 0.84–0.94 (m, 2H, H_{cy}), 1.10–1.21 (m, 6H, CH_3CH_2 and H_{cy}), 1.38–1.47 (m, 1H, H_{cy}), 1.59–1.75 (m, 5H, H_{cy}), 2.40–2.49 (m, 4H, CH_3CH_2 and CH_2Cy), 3.57 (s, 2H, CH_2S), 4.50 (s, 2H, CH_2Ph), 5.26 (s, 2H, NCH_2O), 5.54 (br s, 1H, *H*NH), 7.26–7.37 (m, 5H, Ph), 8.88 (br s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 13.89 (CH_3CH_2), 20.26 (CH_3CH_2), 26.27, 26.12, 33.17, 38.43 (C_{cy}), 31.07 (CH_2Cy), 36.64 (CH_2S), 70.42 (CH_2Ph), 72.78 (NCH_2O), 127.80 (C-4), 127.73, 128.07, 128.49, 136.58 (C_{arom}), 139.99 (C-2), 141.19 (C-5), 172.45 (CO). EI-MS: *m/z* 401 (6%, M^+), 91 (100%). Anal. Calcd for $C_{22}H_{31}N_3O_2S\cdot 0.3H_2O$: C, 64.93; H, 7.86; N, 10.32. Found: C, 64.93; H, 7.81; N, 10.36.

5.12.11. 2-[5-Benzyl-1-(ethoxymethyl)-4-isopropyl-1*H*-imidazol-2-ylthio]acetamide (14g). Yield 0.22 g (43%) as a white solid; mp 96–98 °C. ^{1}H NMR ($CDCl_3$): δ 1.08 (t, 3H, J = 7.0 Hz, CH_3CH_2), 1.23 [d, 6H, J = 6.8 Hz, $(CH_3)_2CH$], 2.92 [hept, 1H, J = 6.8 Hz, $(CH_3)_2CH$], 3.35 (q, 2H, J = 7.0 Hz, CH_3CH_2), 3.61 (s, 2H, CH_2S), 4.00 (s, 2H, CH_2Ph), 5.00 (s, 2H, NCH_2O), 5.70 (br s, 1H, *H*NH), 7.07–7.30 (m, 5H, Ph), 9.04 (br s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 14.62 (CH_3CH_2), 22.91 [$(CH_3)_2CH$], 26.04 [$(CH_3)_2CH$], 28.98 (CH_2Ph), 36.37 (CH_2S), 63.92 (CH_3CH_2O), 73.28 (NCH_2O), 125.66 (C-4), 126.51, 127.83, 128.59, 138.29 (C_{arom}), 140.80 (C-2), 145.77 (C-5), 172.59 (CO). EI-MS: *m/z* 347 (24%, M^+), 59 (100%). Anal. Calcd for $C_{18}H_{25}N_3O_2S$: C, 62.22; H, 7.25; N, 12.09. Found: C, 62.18; H, 7.25; N, 12.09.

5.12.12. 2-[5-Benzyl-1-(benzyloxymethyl)-4-isopropyl-1*H*-imidazol-2-ylthio]acetamide (14h). Yield 0.27 g (44%) as a white solid; mp 102–104 °C. ^{1}H NMR ($CDCl_3$): δ 1.23 [d, 6H, J = 6.7 Hz, $(CH_3)_2CH$], 2.92 [hept, 1H, J = 6.7 Hz, $(CH_3)_2CH$], 3.59 (s, 2H, CH_2S), 3.98 (s, 2H, CH_2Ph), 4.38 (s, 2H, OCH_2Ph), 5.05 (s, 2H, NCH_2O), 5.59 (br s, 1H, *H*NH), 7.01–7.35 (m, 10H, 2Ph), 9.02 (br s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 22.93 [$(CH_3)_2CH$], 26.06 [$(CH_3)_2CH$], 28.98 (CH_2Ph), 36.36 (CH_2S), 70.38 (OCH_2Ph), 72.91 (NCH_2O), 125.69 (C-4), 126.57, 127.59, 127.87, 128.45, 128.66, 136.60, 138.19 (C_{arom}), 141.06 (C-2), 145.83 (C-5), 172.51 (CO). EI-MS: *m/z* 409 (27%, M^+), 91 (100%). Anal. Calcd for $C_{23}H_{27}N_3O_2S\cdot 1H_2O$: C, 64.61; H, 6.84; N, 9.83. Found: C, 64.68; H, 6.37; N, 9.76.

5.12.13. 2-[5-(3,5-Dimethylbenzyl)-1-(ethoxymethyl)-4-isopropyl-1*H*-imidazol-2-ylthio]acetamide (14i). Yield 0.34 g (61%) as a white solid; mp 100–102 °C. ^{1}H NMR ($CDCl_3$): δ 1.11 (t, 3H, J = 6.9 Hz, CH_3CH_2O), 1.24 [d, 6H, J = 6.8 Hz, $(CH_3)_2CH$], 2.92 [hept, 1H, J = 6.8 Hz, $(CH_3)_2CH$], 3.37 (q, 2H, J = 6.9 Hz, CH_3CH_2O), 3.61 (s, 2H, CH_2S), 3.92 (s, 2H, CH_2Ar), 5.03 (s, 2H, NCH_2O), 5.70 (s, 1H, *H*NH), 6.68 (s, 2H, H_{arom}), 6.84 (s, 1H, H_{arom}), 9.05 (s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 14.66 (CH_3CH_2O), 21.20 ($2CH_3$), 22.89 [$(CH_3)_2CH$], 25.99 [$(CH_3)_2CH$], 28.78 (CH_2Ar), 36.43 (CH_2S), 63.94 (CH_3CH_2O), 73.32 (NCH_2O), 125.96 (C-4), 125.65, 128.14, 138.04, 138.13 (C_{arom}), 140.64 (C-2), 145.42 (C-5), 172.58 (CO). EI-MS: *m/z* 375 (63%, M^+), 59 (100%). Anal. Calcd for $C_{20}H_{29}N_3O_2S\cdot 0.5H_2O$: C, 62.47; H, 7.86; N, 10.93. Found: C, 62.38; H, 7.61; N, 10.76.

5.12.14. 2-[1-(Benzyloxymethyl)-5-(3,5-dimethylbenzyl)-4-isopropyl-1*H*-imidazol-2-ylthio]acetamide (14j). Yield 0.31 g (48%) as a white solid; mp 92–94 °C. ^{1}H NMR ($CDCl_3$): δ 1.24 [d, 6H, J = 6.8 Hz, $(CH_3)_2CH$], 2.23

(s, 6H, $2CH_3$), 2.91 [hept, 1H, $J = 6.8$ Hz, $(CH_3)_2CH$], 3.59 (s, 2H, CH_2S), 3.89 (s, 2H, CH_2Ar), 4.39 (s, 2H, OCH_2Ph), 5.07 (s, 2H, NCH_2O), 5.59 (s, 1H, *H*NH), 6.62 (s, 2H, H_{arom}), 6.82 (s, 1H, H_{arom}), 7.19–7.32 (m, 5H, Ph), 9.06 (s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 21.21 ($2 \times CH_3$), 22.95 [$(CH_3)_2CH$], 26.05 [$(CH_3)_2CH$], 28.79 (CH_2Ar), 36.40 (CH_2S), 70.34 (OCH_2Ph), 77.00 (NCH_2O), 125.93 (C-4), 125.68, 127.53, 127.96, 128.18, 128.44, 136.71, 138.03, 138.17 (C_{arom}), 140.91 (C-2), 145.64 (C-5). EI-MS: *m*/*z* 437 (6%, M^+), 91 (100%). Anal. Calcd for $C_{25}H_{31}N_3O_2S$: C, 68.62; H, 7.14; N, 9.60. Found: C, 68.24; H, 7.15; N, 9.53.

5.12.15. 2-[5-(Cyclohexylmethyl)-1-(ethoxymethyl)-4-isopropyl-1*H*-imidazol-2-ylthio]acetamide (14k). Yield 0.24 g (45%) as a white solid; mp 90–92 °C. ^1H NMR ($CDCl_3$): δ 0.87–0.98 (m, 2H, H_{cy}), 1,18–1.28 [m, 12H, $(CH_3)_2CH$, CH_3CH_2 and H_{cy}], 1.31–1.69 (m, 6H, H_{cy}), 2.45 (d, 2H, $J = 7.4$ Hz, CH_2Cy), 2.84 [hept, 1H, $J = 6.8$ Hz, $(CH_3)_2CH$], 3.48 (q, 2H, $J = 6.8$ Hz, CH_3CH_2O), 3.59 (s, 2H, CH_2S), 5.20 (s, 2H, NCH_2O), 5.49 (br s, 1H, *H*NH), 9.15 (br s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 14.83 (CH_3CH_2), 22.89 [$(CH_3)_2CH$], 25.98 [$(CH_3)_2CH$], 26.32, 26.26, 33.23, 38.34 (C_{cy}), 30.97 (CH_2Cy), 36.53 (CH_2S), 63.98 (CH_3CH_2O), 73.20 (NCH_2O), 126.72 (C-4), 140.07 (C-2), 145.04 (C-5), 172.65 (CO). EI-MS: *m*/*z* 353 (18%, M^+), 55 (100%). Anal. Calcd for $C_{18}H_{31}N_3O_2S \cdot 0.7H_2O$: C, 59.05; H, 8.92; N, 11.48. Found: C, 59.02; H, 8.83; N, 11.42.

5.12.16. 2-[1-(Benzyloxymethyl)-5-(cyclohexylmethyl)-4-isopropyl-1*H*-imidazol-2-ylthio]acetamide (14l). Yield 0.27 g (43%) as a white solid; mp 98–100 °C. ^1H NMR ($CDCl_3$): δ 0.84–0.97 (m, 2H, H_{cy}), 1.11–1.28 [m, 9H, $(CH_3)_2CH$ and H_{cy}], 1.40–1.49 (m. 1H, H_{cy}), 1.61–169 (m, 5H, H_{cy}), 2.42 (d, 2H, $J = 7.3$ Hz, CH_2Cy), 2.82 [hept, 1H, $J = 6.8$ Hz, $(CH_3)CH$], 3.57 (s, 2H, CH_2S), 4.51 (s, 2H, CH_2Ph), 5.24 (s, 2H, NCH_2O), 5.48 (br s, 1H, *H*NH), 7.26–7.37 (m, 5H, Ph), 9.10 (br s, 1H, HN*H*). ^{13}C NMR ($CDCl_3$): δ 22.89 [$(CH_3)_2CH$], 25.99 [$(CH_3)_2CH$], 26.28, 26.16, 33.19, 38.34 (C_{cy}), 30.95 (CH_2Cy), 36.52 (CH_2S), 70.50 (CH_2Ph), 72.81 (NCH_2O), 126.68 (C-4), 127.73, 128.08, 128.49, 136.63 (C_{arom}), 140.23 (C-2), 145.22 (C-5), 172.65 (CO). HRMS (MALDI) *m*/*z* calcd for $C_{23}H_{34}N_3O_2S^+$ (MH^+) 416.2367, found 416.2366.

5.13. Viruses and cells

The HIV-1 strain HTLV-IIIB[26] were propagated in H9 cells[27] at 37 °C, 5% CO_2 using RPMI 1640 with 10% heat-inactivated fetal calf serum (FCS) and antibiotics (growth medium). Culture supernatant was filtered (0.45 nm), aliquotted, and stored at −80 °C until use. The HIV-1 strain was obtained from NIH AIDS Research and Reference Program.

5.14. Inhibition of HIV-1 replication

Compounds were examined for possible anti-viral activity against HIV-1 using MT4 cells as target cells. MT4 cells were incubated with virus (0.005 MOI) and growth medium containing the test dilutions of compound for six days in parallel with virus-infected and uninfected control cultures without compound added. Expression of HIV in the cultures was indirectly quantified using the MTT assay.[28] Compounds mediating less than 30% reduction of HIV expression were considered without biological activity. Compounds were tested in parallel for cytotoxic effect in uninfected MT4 cultures containing the test dilutions of compound as described above. A 30% inhibition of cell growth relative to control cultures was considered significant.

The 50% inhibitory concentration (IC_{50}) and the 50% cytotoxic concentration (CC_{50}) were determined by interpolation from the plots of percent inhibition versus concentration of compound.

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