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Methyl 1-imidazolecarbodithioate as a thiocarbonyl transfer reagent: a facile one-pot, three-component synthesis of novel 2-substituted-5-aryl-1-oxo-3-thioxo-1,2,3,5,11,11a-hexahydro-6*H*-imidazo-[1,5-*b*]-β-carbolines

Balendu Singh, G. S. M. Sundaram, Nimesh C. Misra, Hiriyakkanavar Ila *

Department of Chemistry, Indian Institute of Technology, Kanpur-208 016, India

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ABSTRACT

An efficient one-pot, three-component synthesis of novel 2-substituted-5-aryl-1-oxo-3-thioxo-1,2,3,5,11,11a-hexahydro-6*H*-imidazo-[1,5-*b*]-β-carbolines employing 1-aryl-1,2,3,4-tetrahydro-β-carboline-3-carboxylates, primary amines (or amino acid esters) and methyl 1-imidazolecarbodithioate as the thiocarbonyl transfer reagent is reported.

Small molecule inhibition of a new class of proteins, that is, mitotic kinesin Eg5 (also known as kinesin spindle protein KSP) represents a novel antimitotic approach for the treatment of cancer.[1] Inhibition of Eg5 kinesin prevents normal bipolar spindle formation leading to cell-cycle arrest and ultimately to apoptosis.[2] Unlike existing antimitotic cancer drugs such as vinca alkaloids, Taxol and epothilone, which target the tubulin proteins which are essential for many other cellular processes besides formation of mitotic spindles,[3] inhibition of mitotic kinesin Eg5 leads only to mitotic arrest without interfering with other microtubule-dependant processes.

A number of Eg5 inhibitors including Monastrol **1**,[2a] (the first small molecule inhibitor of Eg5), have been reported.[2c,4] Subsequently, Kapoor and co-workers identified a tetracyclic β-carboline fused heterocyclic scaffold, HR22C16 **2** and its 2-aminoalkyl analog as very potent Eg5 inhibitors (IC_{50} = 800 ± 10 nM) inducing mitotic arrest and cell death in Taxol-resistant cancer cells (Fig. 1).[5] They have also developed an efficient diastereoselective traceless solid phase synthesis of HR22C16 analogs leading to a library of 16,000 small molecules.[5a] Based on the structure of HR22C16 as a known Eg5 inhibitor, Giannis and co-workers recently reported the synthesis and biological evaluation of a small library of hydantoin/thiohydantion fused tetrahydro-β-carboline derivatives.[6]

The reported method for the synthesis of these hydantion/thiohydantion fused tetrahydro-β-carboline derivatives involves cyclocondensation of 1-substituted-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (obtained by Pictet–Spengler cyclization) with pre-formed isocyanates or isothiocyanates.[5–7] Our own interest in the synthesis of these tetracyclic scaffolds derives from our recently reported efficient one-pot, three-component synthesis of 3,5- and 1,3,5-substituted thiohydantoins employing easily accessible amino acid esters, primary amines, and methyl 1-imidazolecarbodithioate **5** as a thiocarbonyl transfer reagent.[8,9]

Based on this strategy, we have now developed an efficient synthesis of 2-substituted-5-aryl-1-oxo-3-thioxo-1,2,3,5,11,11a-hexahydro-6*H*-imidazo-[1,5-*b*]-β-carboline derivatives **6** and **9** by the reaction of methyl 1-aryl-1,2,3,4-tetrahydro-β-carboline-3-carboxylates, primary amines (or amino acid esters), and methyl 1-imidazolecarbodithioate **5** in a one-pot, three-component procedure. The results of these studies are reported in this Letter.

Our initial attempts to obtain the tetracyclic β-carboline derivative **6a** from the reaction of *cis*-1-phenyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid **3a**[10] with **5**, and aniline under different reaction conditions were not successful affording either unreacted starting materials or 1,3-diphenylthiourea in varying yields. We therefore employed the corresponding methyl ester hydrochloride **4a**[11] in this cyclization reaction. Thus in a typical experiment,

Table 1
Synthesis of 2-substituted-5-aryl-1-oxo-3-thioxo-1,2,3,5,11,11a-hexahydro-6*H*-imidazo-[1,5-*b*]-β-carbolines **6a–k**

Entry	4	R	R^1	R^2	R^3	6	Yield (%)
1	**4a**	Ph	H	H	H	**6a**	85
2	**4b**	*C*-C_6H_{11}	OMe	OMe	OMe	**6b**	81
3	**4b**	3,4-$(MeO)_2C_6H_3(CH_2)_2$	OMe	OMe	OMe	**6c**	78
4	**4b**	3-Indolyl$(CH_2)_2$	OMe	OMe	OMe	**6d**	83
5	**4b**	$PhCH_2$	OMe	OMe	OMe	**6e**	76
6	**4b**	3-$MeOC_6H_4$	OMe	OMe	OMe	**6f**	79
7	**4c**	Bu	H	OMe	H	**6g**	75
8	**4c**	2-Furylch$_2$	H	OMe	H	**6h**	79
9	**4d**	Bu	H	H	OH	**6i**	87
10	**4d**	*C*-C_6H_{11}	H	H	OH	**6j**	75
11	**4d**	3-$(CF_3)C_6H_4$	H	H	OH	**6k**	85

* Corresponding author. Tel.: +91 0512 2597436, fax: +91 0512 2590260.
E-mail address: hila@iitk.ac.in (H. Ila).

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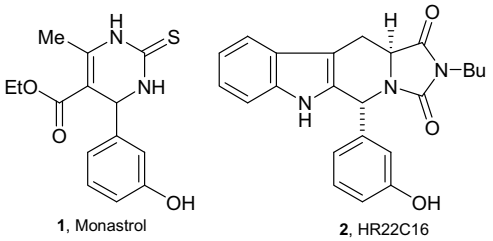
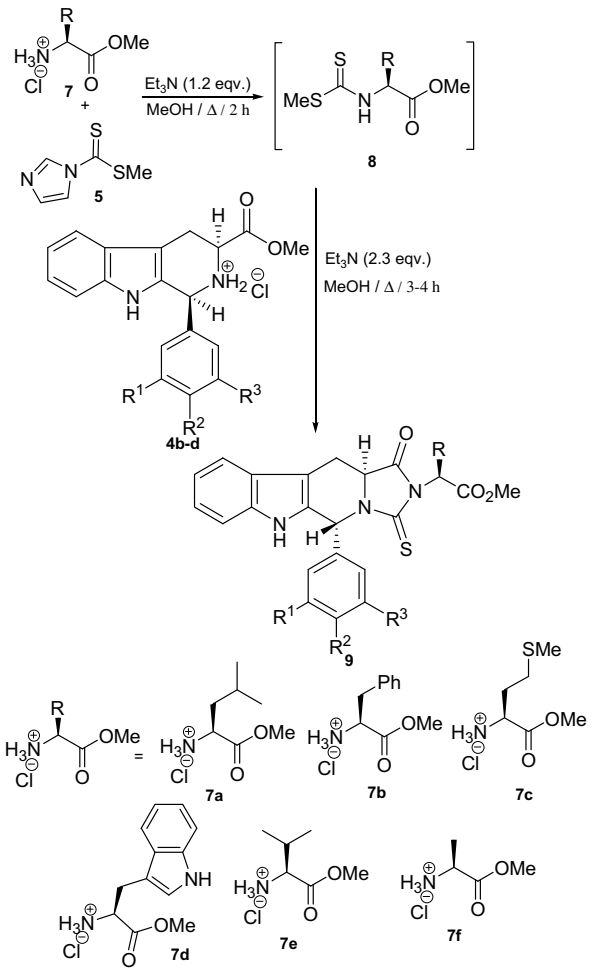


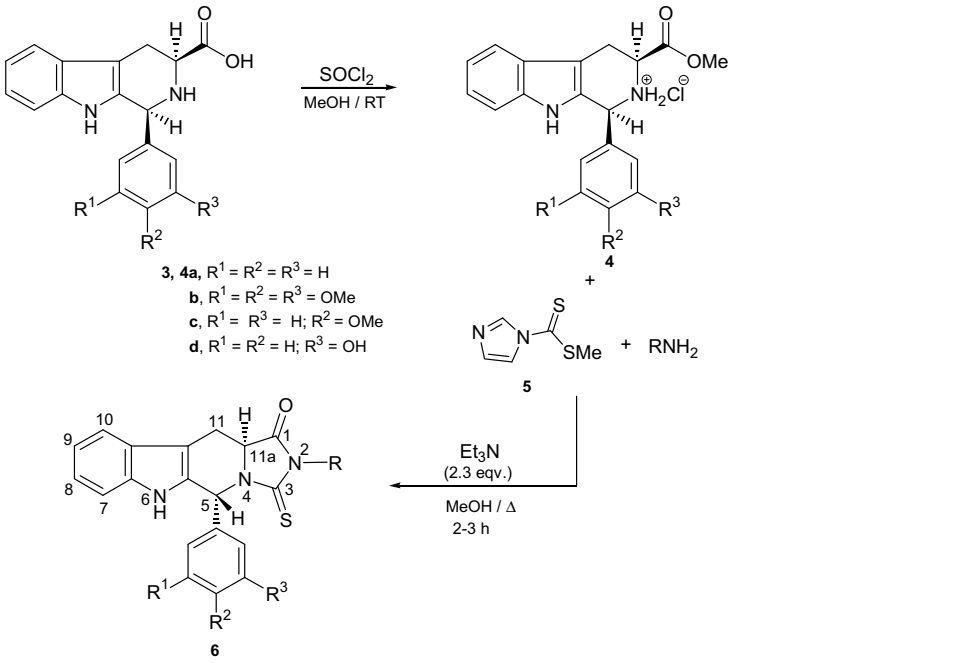
Figure 1.

when equimolar quantities of **4a**, **5** and aniline were heated in methanol at reflux in the presence of triethylamine (2.3 equiv), work-up of the reaction mixture yielded a solid (85%) which was characterized as *trans*-2,5-diphenyl-1-oxo-5,6,11,11a-tetrahydro-*1H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-3(*2H*)-thione (*trans*-2,5-diphenyl-1-oxo-3-thioxo-1,2,3,5,11,11a-hexahydro-6*H*-imidazo-[1,5-*b*]-β-carboline) **6a** by comparison of its physical and spectral (^{1}H and ^{13}C NMR) data with the previously reported compound.[7a] The other substituted 1-(3,4,5-trimethoxy)phenyl, 1-(4-methoxy)-phenyl, and 1-(3-hydroxy)phenyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylates hydrochlorides[11] **4b–d** were similarly reacted with **5** and various aliphatic and aromatic amines yielding only *trans*-2-substituted-5-aryl-1-oxo-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*] indole-3(2*H*)-thiones (*trans*-2-substituted-5-aryl-1-oxo-3-thioxo-1,2,3,5,11,11a-hexahydro-6*H*-imidazo-[1,5-*b*]-β-carbolines) **6b–k** in overall excellent yields and in highly diastereoselective fashion (Table 1).[12,13] Formation of only *trans* diastereomers in this reaction is in line with the earlier observations in the reaction of l-substituted-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acids and alkyl/aryl isothiocyanates[6,7a] (see Scheme 1).

We next extended our studies toward the synthesis of tetracyclic heterocycle peptidomimetics of type **9** by the reaction of amino acid esters as the amine component (Scheme 2). However, attempted reaction of β-carboline ester hydrochloride **4b** with **5** and L-leucine methyl ester hydrochloride **7a** in refluxing methanol in the presence of triethylamine under the earlier described condi-



Scheme 2.



Scheme 1.

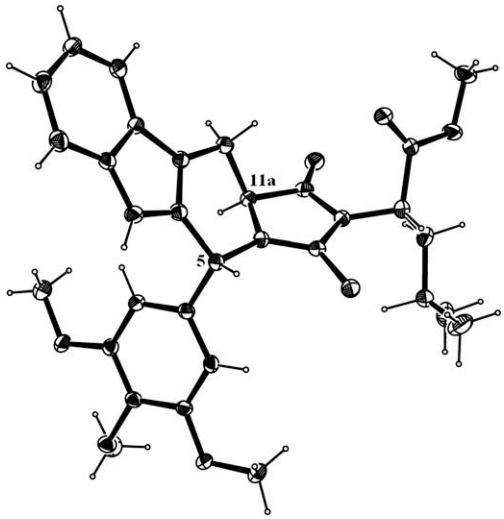


Figure 2. Ortep view of structure of **9a**.

tions for **6** yielded only an intractable mixture of several products. On the other hand, prior generation of dithiocarbamate **8** by reaction of L-leucine ester **7a** with **5** followed by sequential addition of 1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-β-carboline ester **4b**, and triethylamine in refluxing methanol in one-pot yielded a single diastereomeric product (78%), which was characterized as methyl (α*S*,5*S*,11a*R*)-α-isobutyl-1-oxo-3-thioxo-5-(3,4,5-trimethoxyphenyl)-1,2,3,5,11,11a-hexahydro-2(6*H*)-imidazo-[1,5-*b*]-β-carbolineacetate (*trans* **9a**) on the basis of its ^{1}H, ^{13}C, and mass spectral data. Further confirmation of the *trans*-5,11a stereochemistry in **9a** was obtained from its X-ray diffraction data[14] (Fig. 2). The other 1-(4-methoxyphenyl)- and 1-(3-hydroxyphenyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylate hydrochlorides **4c–d** were also reacted with leucine methyl ester and **5** yielding only *trans* **9b–c** in 82% and 78% yields, respectively. Similarly, the reaction of other amino acid esters such as L-phenylalanine (**7b**), L-methionine (**7c**), L-tryptophan (**7d**), L-valine (**7e**), and L-alanine (**7f**) with either **4b** or **4c** and imidazole dithioate under identical conditions also proceeded smoothly yielding only *trans* tetrahydro-β-carboline peptidomimetics **9d-h** in high yields.[12,13]

All newly synthesized compounds **6a–k** and **9a–h** were found to be optically active as evidenced by their optical rotation. A study of the enantiomeric purity[15] of a few compounds (**6a, 6d, 6g, 6i–j**, and **9a–b**) however revealed that the reaction yields enantiomerically pure products in some cases (>91% ee) whereas racemization was observed in others (**9a–b**).

In summary, we have developed an efficient one-pot, three-component synthesis of novel 2-substituted-5-aryl-1-oxo-3-thioxo-1,2,3,5,11,11a-hexahydro-6*H*-imidazo-[1,5-*b*]-β-carbolines from easily accessible 1-aryl-1,2,3,4-tetrahydro-β-carboline esters, amines, and **5** as the thiocarbonyl transfer reagent. The present method does not require less readily available alkyl/aryl isothiocyanates which were previously employed in the synthesis of this class of compounds. The methodology has also been extended to the facile one-pot, three-component synthesis of a novel class of hexahydroimidazo-β-carboline peptidomimetic scaffolds such as **9**[16] by employing amino acid esters as amine partners in this reaction. In view of the broad spectrum of biological activity displayed by both thiohydantoin and β-carboline derivatives, our initial studies on the facile synthesis of this tetracyclic scaffold combining both thiohydantoin and β-carboline skeletons are highly encouraging. Further work to attempt this reaction on solid phase and to study the biological profile of these newly synthesized compounds are in progress (see Fig. 3).

Acknowledgments

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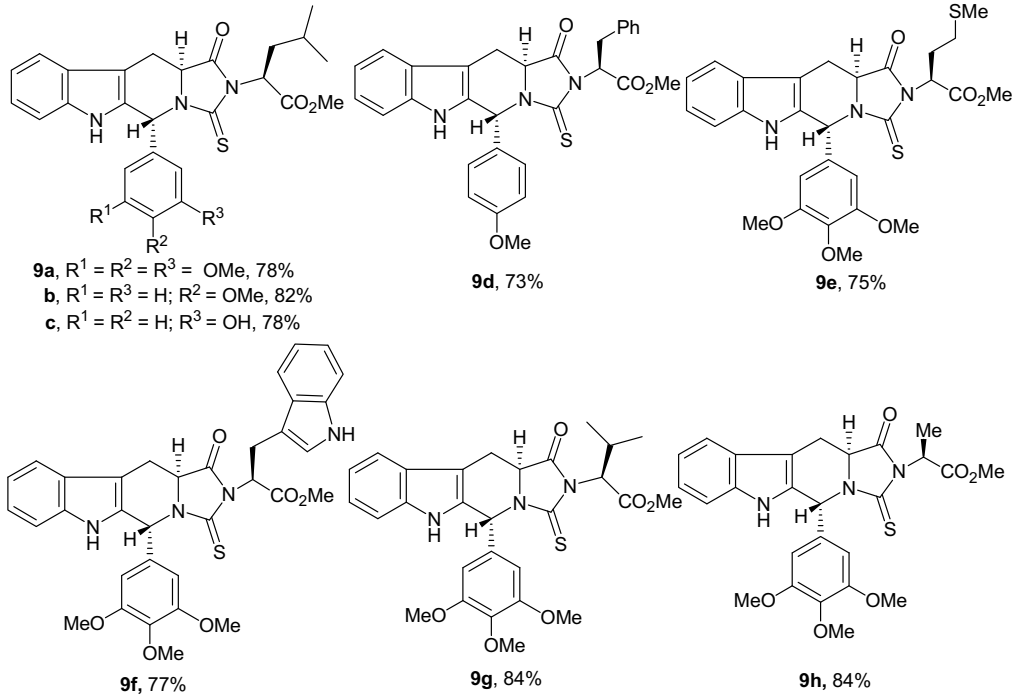

Figure 3.

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9. Mohanta, P. K.; Dhar, S.; Samal, S. K.; Ila, H.; Junjappa, H. *Tetrahedron* **2000**, *56*, 629.
10. The 1-aryl-β-carboline-3-carboxylic acids **3a–d** were synthesized by Pictet–Spengler cyclization of L-tryptophan with various aryl aldehydes according to the reported procedure.[6]
11. All the methyl ester hydrochlorides **4a–d** were prepared by treatment of the corresponding acids **3a–d** with thionyl chloride in methanol at rt. The ester hydrochlorides **4a–d** thus obtained were used as such in further reactions.
12. The structures and stereochemistry of the newly prepared products **6b–k** and **9a–h** were confirmed from their spectral and analytical data and by comparison of the chemical shifts and coupling constants with those of reported values for the known compounds (**6a** and **6i**).[6,7a]
13. *General procedure for the synthesis of hexahydroimidazo-β-carbolines* **6a–k**: A mixture of appropriate amine (2.0 mmol), 1-(methyldithiocarbonyl)imidazole (0.32 g, 2.0 mmol), appropriate β-carboline-3-carboxylic acid methyl ester hydrochlorides **4a-d** (2.0 mmol) and Et_3N (0.64 mL, 4.6 mmol) in 10 mL absolute MeOH was heated at reflux for 3–4 h (monitored using TLC). The reaction was then cooled to room temperature and the solvent was removed in vacuum. The residue was dissolved in $CHCl_3$ (25 mL) and washed with water (2×20 mL) followed by brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude products **6a–k**, which were purified by column chromatography over silica gel using hexane/EtOAc (1:4) as eluent.
General procedure for synthesis of hexahydroimidazo-β-carboline peptidomimetics **9a**–**h**: A mixture of appropriate L-amino acid methyl ester hydrochloride salt (2.0 mmol) neutralized with Et_3N (0.28 mL, 2.2 mmol) and 1-(methyldithiocarbonyl)imidazole (0.32 g, 2.0 mmol) in 10 mL of absolute MeOH was heated at reflux for 1 h with constant stirring. After the complete consumption of 1-(methyldithiocarbonyl)imidazole (as shown using TLC), a mixture of appropriate β-carboline-3-carboxylic acid methyl ester hydrochloride **4b–d** (2.0 mmol) and Et_3N (0.64 mL, 4.6 mmol) in absolute MeOH (5 mL) was added and the reaction mixture was further heated at reflux for 3–4 h (monitored using TLC). The reaction was then cooled to room temperature and the solvent was removed under vacuum. The residue was dissolved in $CHCl_3$ (25 mL) and washed with water (2×20 mL) followed by brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude products **9a–h**, which were purified by column chromatography over silica gel using hexane/EtOAc (1:4) as eluent.
Data for selected compounds:
Compound **6d**: Yield 83% (0.42 g); yellow solid; mp 216–217 °C ($CHCl_3$/hexane); R_f 0.8 (1:1 hexane/EtOAc); $[\alpha]_D^{25}$ −18.8 (*c* 0.5, DMSO); IR (KBr): 3420, 3334, 2928, 1738, 1466, 1149, 1007, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.62 (t, *J* = 13.2 Hz, 2H), 3.18 (t, *J* = 7.6 Hz, 2H), 3.39 (dd, *J* = 15.5, 5.7 Hz, 1H), 3.74 (s, 6H), 3.85 (s, 3H), 4.14 (dd, *J* = 12.7, 6.5 Hz, 2H), 4.29 (dd, *J* = 10.9, 5.8 Hz, 1H), 6.73 (s, 2H,) 6.91 (t, *J* = 7.31 Hz, 1H), 6.99 (s, 1H), 7.08 (s, 1H,), 7.17 (t, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.33 (ddd, *J* = 5.9, 5.9, 3.92 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 8.01 (br s, 1H), 8.24 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 23.5, 42.3, 55.3, 55.6, 56.2, 60.7, 105.9, 107.6, 111.0, 111.2, 112.3, 118.4, 118.8, 119.4, 120.0, 121.9, 122.2, 122.8, 125.8, 127.6, 130.4, 133.7, 136.0, 136.7, 153.3, 172.9, 180.3 MS-FAB (*m/z*, %): 566 (M^+, 33); Anal. Calcd for $C_{32}H_{30}N_4O_4S$ (566.20): C, 67.82; H, 5.34; N, 9.89. Found: C, 67.94; H, 5.38; N, 9.81.
Compound **6g**: Yield 75% (0.37 g); yellow solid; mp 143–144 °C ($CHCl_3$/hexane); R_f 0.5 (1:1 hexane/EtOAc); $[\alpha]_D^{25}$ −10 (*c* 0.5, DMSO); IR (KBr): 3450, 2998, 1727, 1607, 1510, 1460, 1302, 1203, 1064, 782, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.32 Hz, 3H), 1.27(q, *J* = 7.50 Hz, 2H), 1.57 (q, *J* = 3.66 Hz, 2H), 2.88 (dd, *J* = 11.0, 1.58 Hz, 1H), 3.45 (dd, *J* = 15.36, 5.84 Hz, 1H), 3.69 (s, 3H), 3.75 (t, *J* = 7.36 Hz, 2H), 4.33 (dd, *J* = 11.0, 5.5 Hz, 1H), 6.77 (dd, *J* = 8.8, 1.96 Hz, 2H), 6.95 (s, 1H), 7.06 (dt, *J* = 7.56, 0.96 Hz, 1H), 7.12 (dt, *J* = 7.96, 1.48 Hz, 1H), 7.24 (d, *J* = 8.56 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 9.05 (br s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.56, 19.87, 23.17, 29.59, 41.17, 54.27, 55.18, 55.26, 106.65, 111.32, 113.97, 118.22, 119.66, 122.38, 125.72, 129.95, 130.72, 136.42, 159.78, 173.21, 186.14; MS-FAB (*m/z*, %): 420 (M+1, 100); Anal. Calcd for $C_{24}H_{25}N_3O_2S$ (419.17): C, 68.71; H, 6.01; N, 10.02. Found: C, 68.79; H, 5.96; N, 10.06.
Compound **6j**: Yield 81% (0.54 g); yellow solid; mp 207–208 °C ($CHCl_3$/hexane); R_f 0.33 (1:1 hexane/EtOAc); $[\alpha]_D^{25}$ −21.2 (*c* 0.5, DMSO); IR (KBr): 3350, 2930, 1722, 1595, 1454, 1262, 992, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20–1.40 (m, 3H), 1.6 (br s, 5H), 2.20 (t, *J* = 11.48 Hz, 2H), 2.89 (dd, *J* = 14.64, 12.48 Hz, 1H), 3.46 (dd, *J* = 15.2, 5.8 Hz, 1H), 4.33 (dd, *J* = 10.76, 5.88 Hz, 1H), 4.55–4.61 (m, 1H), 5.61 (br s, 1H), 6.80 (s, 1H), 6.94 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 1H), 7.14–7.22 (m, 2H), 7.28 (d, *J* = 8.04 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.75, 25.03, 25.85, 28.57, 55.49, 55.56, 107.25, 111.25, 115.55, 116.14, 118.39, 120.17, 122.88, 125.89, 130.26, 130.67, 136.64, 139.75, 156.17, 173.47, 181.13, MS-FAB (*m/z*, %): 432 (M+1, 100). Anal. Calcd for $C_{25}H_{25}N_3O_2S$ (431.17): C, 69.58; H, 5.84; N, 9.74. Found: C, 69.67; H, 5.77; N, 9.82.
Compound **9a**: Yield 78% (0.46 g); yellow solid; mp 220–221 °C ($CHCl_3$/hexane); R_f 0.3 (1:1 hexane/EtOAc); $[\alpha]_D^{25}$ −32 (*c* 0.5, DMSO); IR (KBr): 3411, 3345, 1747, 1594, 1461, 1321, 1237, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 1.53 (br m, 1H), 2.00 (ddd, *J* = 16.1, 8.33, 4.88 Hz, 1H), 2.27 (ddd, *J* = 16.1, 8.8, 4.7 Hz, 1H), 2.98 (dd, *J* = 15.2, 11.0 Hz, 1H), 3.51 (dd, *J* = 15.2, 5.40 Hz, 1H), 3.68 (s, 6H), 3.70 (s, 3H), 3.83 (s, 3H), 4.4 (dd, *J* = 11.0, 5.5 Hz, 1H), 5.45 (dd, *J* = 8.8, 4.5 Hz, 1H), 6.63 (s, 2H), 6.99 (s, 1H), 7.15 (t, *J* = 7.08 Hz, 1H); 7.22 (t, *J* = 8.0 Hz,1H), 7.35 (d, *J* = 8.04 Hz, 1H); 7.52 (d, *J* = 7.8 Hz, 1H), 8.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 23.0, 24.1, 25.1, 37.2, 52.7, 54.5, 55.4, 55.7, 56.0, 60.6, 105.5, 107.1, 111.3, 118.3, 120.0, 122.8, 125.8, 130.2, 134.1, 136.7, 137.6, 153.0, 170.0, 173.0, 180.6; MS-FAB (*m/z*, %): 551 (M^+, 100); Anal. Calcd for $C_{29}H_{33}N_3O_6S$ (551.21): C, 63.14; H, 6.03; N, 7.62. Found: C, 63.54; H, 5.97; N, 7.69.
Compound **9d**: Yield 81% (0.53 g); white solid; mp 171–172 °C ($CHCl_3$/hexane); R_f 0.6 (1:1 hexane/EtOAc); $[\alpha]_D^{25}$ −28 (*c* 0.5, DMSO); IR (KBr): 3378, 3292, 1751, 1609, 1509, 1462, 1374, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.60 (dd, *J* = 15.4, 11.0 Hz, 1H), 3.32 (dd, *J* = 15.4, 5.5 Hz, 1H), 3.48 (dd, *J* = 13.5, 5.8 Hz, 1H), 3.56–3.70 (m, 1H,), 3.74 (s, 3H), 3.75 (s, 3H), 4.21 (dd, *J* = 11.5, 5.5 Hz, 1H), 5.57 (br s, 1H), 6.80–6.90 (m, 3H), 7.0–7.36 (m, 10H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 34.2, 52.8, 54.6, 55.3, 55.4, 55.6, 107.4, 111.2, 114.1, 118.3, 120.2, 123.0, 126.0, 126.7, 128.3, 129.2, 129.7, 130.1, 130.6, 136.3, 136.5, 160.0, 169.0, 172.5, 179.2; MS-FAB (*m/z*, %): 525 (M^+, 90); Anal. Calcd for $C_{30}H_{27}N_3O_4S$ (525.17): C, 68.55; H, 5.18; N, 7.99. Found: C, 68.76; H, 5.27; N, 7.87.
14. X-ray crystallographic data of structure **9a** have been deposited at the Cambridge Crystallographic Data Centre and has been allocated the deposition number CCDC 695508.
15. The optical purity was determined by chiral HPLC [Chiralcel OD-H column, 25% IPA/*n*-hexane]; ee (%): **6a**, 91; **6d**, 91; **6g,** >93 (IA column); **6i**, >99.9; **6j**, > 99.9; **9a**, 25, **9b**, 26.
16. For a few hydantoin/thiohydantoins containing N-terminal amino acids and peptidomimetics, see: (a) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1201; (b) Xiao, X.-Y.; Ngu, K.; Chao, C.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 6968; (c) Nefzi, A.; Dooley, C.; Ostresh, J. M.; Houghten, R. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2273; (d) Nefzi, A.; Ostresh, J. M.; Giulianotti, M.; Houghten, R. A. *Tetrahedron Lett.* **1998**, *39*, 8199; (e) Chong, P. Y.; Petillo, R. A. *Tetrahedron Lett.* **1999**, *40*, 2493; (f) Zhang, D.; Xing, X.; Cuny, G. D. *J. Org. Chem.* **2006**, *71*, 1750.