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Microwave-Enhanced Efficient Regioselective Synthesis of 1,3,4-Trisubstituted 2-Mercaptoimidazoles on a Soluble Support

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Abstract: A novel efficient synthetic method for regioselective synthesis of optically active 2-mercaptoimidazoles with three points of structural diversity was investigated on a polyethylene glycol (PEG) support. The key synthetic steps involve (i) synthesis of thiourea derivatives of polymer-supported amino acids with isothiocyanates and (ii) one-pot regioselective condensation of PEG-linked thiourea with α-bromo ketones to furnish the 2-mercaptoimidazole skeleton under microwave conditions. An excellent regioselectivity was observed during this one-pot condensation reaction which was further supported by NOE studies. In addition to three sets of structural diversity, supplementary chirality at the α-position of the 2-mercaptoimidazole skeleton is the key feature of this synthesis. A representative set of 2-mercaptoimidazoles was efficiently assembled on soluble support utilizing various L-amino acids, isothiocyanates and α-bromoaryl ketones with good yields.

Keywords: mercaptoimidazoles; microwave chemistry; nitrogen heterocycles; polyethylene glycol; soluble supported synthesis

Introduction

Chemical genomics is a prevailing approach to explore biological profiles in the early discovery phase of new drugs. The principle of chemical genomics is based on the fact that small molecules may be used to agitate the functions of specific biological targets, thus aiding the understanding of molecular details of complex biological mechanisms.[1] Design and synthesis of small organic molecule libraries which span large areas of biologically relevant chemical space is the key chemical challenge in drug discovery. High-throughput synthesis and diversity-oriented synthesis have evolved as advanced tools to persue the increasing demand for small organic molecules in initial drug discovery. The diversity of chemical libraries may derive from the high substitutional, stereochemical and skeletal diversity of its members as used to explore the additional biological profile with known biological functions.[2]

In the annals of nitrogen-heterocyclic compounds, the 2-marcaptoimidazole system has its own identity as a key structural component of several bioactive molecules and has been widely employed in the design of potent pharmaceutical agents. Methimazole is an antithyroid drug[3] (Figure 1, **A**) and 4-substituted-2-mercaptoimidazoles exhibit promising anti-inflammatory activity.[4] The 1,4-diaryl-2-mercaptoimidazoles (KRM-III) are known for the inhibition of T-cell antigen receptors (Figure 1, **B**).[5] Highly substituted 2-mercaptoimidazoles are used as potent CCR2 antagonists (Figure 1, **C**) as well as antioxidants (Figure 1, **D**).[6] Pharmaceutical industries have great interest in heterocyclic compounds a encompassing natural amino acid units as they occupy a special posi-

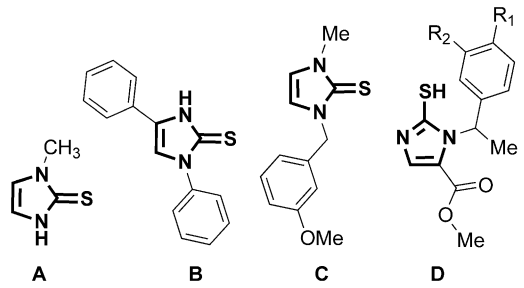
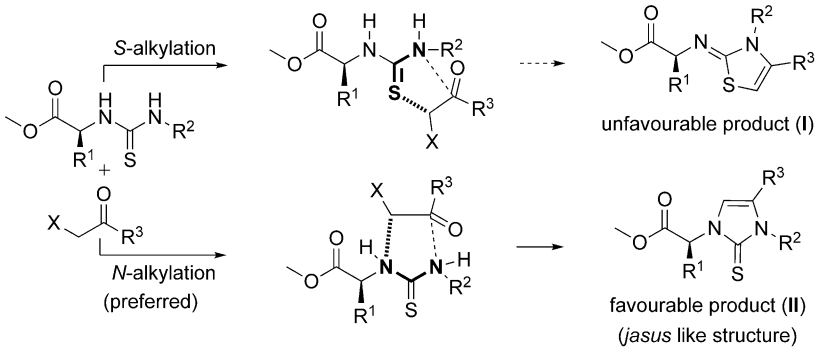


Figure 1. Pharmacologically important 2-mercaptoimidazoles



Scheme 1. Designed strategy towards trisubstituted 2-merchaptoimidazoles.

tion in biological activity profiles.[7] Hence further development of an advanced synthetic route for the synthesis of the mercaptoimidazole motif containing a chiral amino acid unit featuring substitutional and stereochemical diversity is warranted.

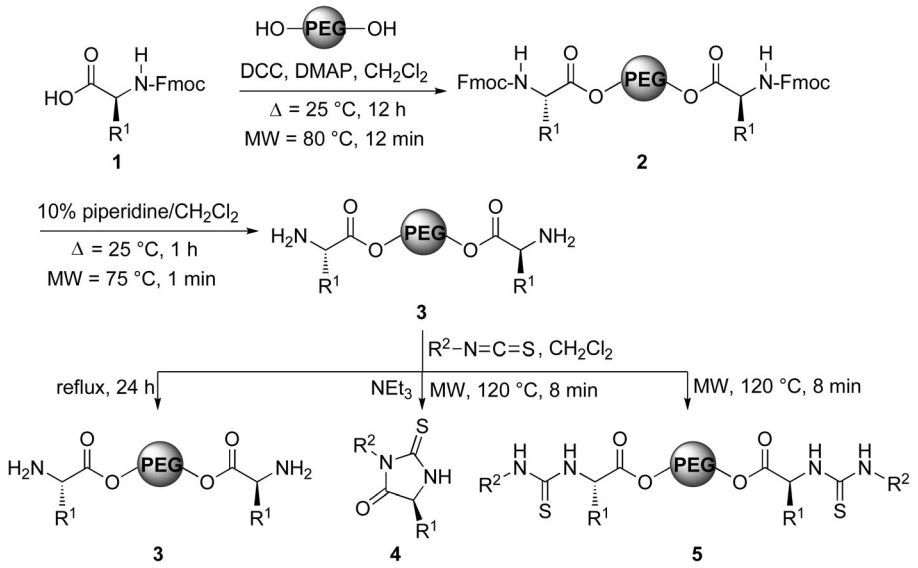
Apart from the regular [3+2] approach using the α-amino carbonyl compounds,[8] substituted imidazoline-2-thiones have been synthesized by the ring expansion of azirines,[9] direct metallation reactions[10] and by the reaction of trimethylsilyl cyanide with methyl isothiocyanate.[11] Previous studies to investigate the ambident nucleophilicity of 2-mercaptoimidazole revealed the preference for *S*-alkylation under alkaline conditions.[12] The *janus*-like orientation came to light during the conformational study of 4,5-isopropyl-1,3-benzylimidazoline-2-thione by NMR and molecular mechanics calculations and the results show that 1,3-disubstituted imidazoline-2-thiones prefer the crowded s*yn* conformation in which the two groups on the nitrogens are oriented away from the ring.[13] With this fact in mind, we have designed a new strategy towards the synthesis of thioureas-derived natural amino acids and their final cyclization with α-halo ketones between the two nitrogens of thiourea (Scheme 1). The *N*-alkylation is preferred over *S*-alkylation following the cyclization to generate product **II** regioselectively.

In recent times, chemists are increasingly looking for the application of advanced reaction techniques such as microwave heating in conjunction with soluble polymer supports to develop multidisciplinary synergetic approaches that make compound synthesis easier, faster and more useful with an emphasis on quality and high-throughput purification techniques.[14] In continuation to our recent research aimed at the synthesis of biologically interesting heterocyclic molecules for new drug discovery,[15] here we report a novel and efficient synthetic protocol for the rapid synthesis of optically active 2-mercaptoimidazoles under microwave irradiation with three sets of diversity.

Result and Discussion

Polyethylene glycol (PEG 6000) was used as a soluble polymer support to the synthesis of 2-merchaptoimidazole. The solubility of PEG in most of polar organic solvents favour its use as soluble support as well as facilitating the reaction progress monitoring by conventional spectroscopic methods. The insolubility of PEG in less polar solvents facilitates the purification of all PEG-supported compounds by simple precipitation. The PEG support is not only stable under harsh microwave conditions but also provides a suitable polar medium for efficient microwave absorption. At the outset of our study, the commercially available, Fmoc-protected L-amino acids were loaded onto PEG through esterification. The *N*-Fmoc-L-amino acids were treated with dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dichloromethane at room temperature for 12 h to obtain the polymer-linked *N*-Fmoc-L-amino esters **2** (Scheme 2). The time required for the esterification reaction was brought down to 12 min under focused microwave irradiation at 80 °C. The resultant polymer-linked amino esters **2** were precipitated in ether solution. The precipitate was filtered and the residue washed successively to remove the side products and unreacted reagents. The separated polymer-linked amino esters **2** were used for next step without further purification. The removal of the Fmoc group from polymer conjugates **2** was carried out with 10% piperidine in dichloromethane at room temperature for 1 h to obtain polymer-bound amino esters **3**. However, under microwave irradiation the desired Fmoc deprotection was achieved in 1 min at 75 °C. It is worthy of mention that the polymer ester linkage remains intact under harsh microwave conditions. The same precipitation work-up protocol has been followed to purify the polymer-bound amino esters **3**. The removal of Fmoc group was cleanly observed by its ^{1}H NMR spectrum.

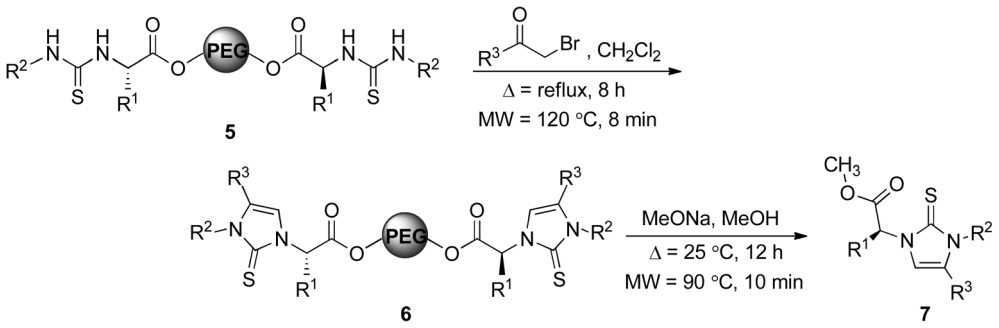
Towards the synthesis of 2-merchaptoimidazoles, we next focused our attention to synthesize thiourea



Scheme 2. Synthesis of soluble polymer-supported thiourea derivatives.

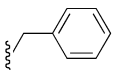
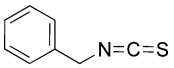
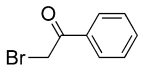
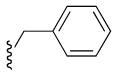
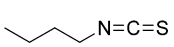
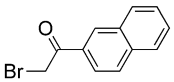
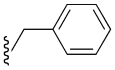
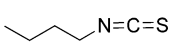
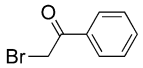
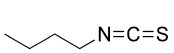
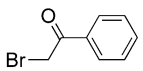
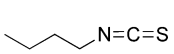
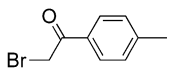
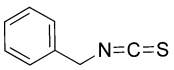
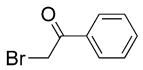
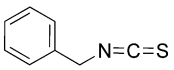
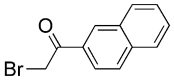
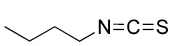
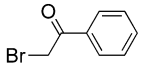
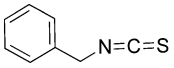
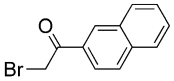
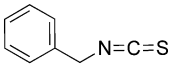
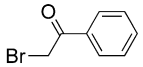
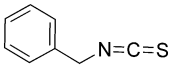
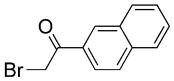
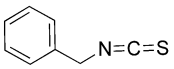
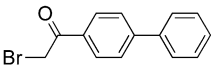
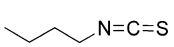
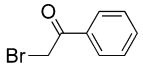
derivatives of polymer-bound amino esters **3**. Through the terminal amine functionality of compound **3**, it was envisaged that treatment of compounds **3** with isothiocyanate could deliver the expected thiourea in one step with the introduction of second diversity in the skeleton. The polymer-bound amino esters **3** was first treated with isothiocyanate for 24 h in dichloromethane which did not provide any expected result. The further refluxing of this reaction gave a trace amount of desired thiourea product, hence polymer-bound aminoester **3** was recovered from these reactions. Alternatively, the base-catalyzed nucleophilic attack of a primary amine to the isothiocyanate to generate the polymer-bound monothiourea derivatives was also attempted. However, when using triethylamine in dichloromethane under microwave heating an intramolecular cyclization took place to produce the thiohydantoin skeleton **4** in a traceless fashion.[16] The intramolecular cyclization was attributed to activation of the nitrogen in presence of a base. Hence it was decided to run the reaction without base. Gratifyingly, polymer-bound amino ester **3** reacts with isothiocyanate under focused microwave irradiation furnishing the desired polymer-immobilized thiourea **5** in 8 min at 120 °C (Scheme 2). The polymer thiourea conjugates **5** were purified by the precipitation-filtration protocol. The ^{1}H NMR analysis of compound **5** depicts the characteristic set of peak at 4.1 ppm corresponding to PEG in addition to introduction of isothiocyanate group peaks. The two NH peaks absorbing at 7.3 ppm and 11.8 ppm indicate the thiourea structure **5**. These results suggest that the microwave irradiation not only reduced the reaction time but significantly enhanced the reaction efficiency and outcome. On using various alkyl, aryl and heteroaryl isothiocyanates in this reaction proceeded smoothly to produce respective thiourea with introduction of additional set of diversity that highlights the versatility of this method.

To accomplish the targeted 2-mercaptoimidazoles, we then turned our attention to the cyclization of the L-amino acid-derived thiourea derivatives **5** with α-bromo ketones. The various α-bromo aryl ketones were reacted with polymer-bound thiourea derivatives **5** in refluxing dichloromethane (Scheme 3). The reaction involves the regioselective nucleophilic substitu-



Scheme 3. Soluble supported synthesis of 2-mercaptoimidazoles.

Table 1. Soluble supported synthesis of 2-mercaptoimidazoles **7**.

Entry	R^1	R^2-N=C=S	R^3COCH_2Br	LR-MS	Yield [%][a]	HPLC [%][b]
7a				428	84	94
7b				444	70	66
7c				394	92	80
7d				346	85	88
7e				360	85	97
7f				380	89	87
7g				430	84	93
7h				360	87	94
7i				444	83	88
7j				352	84	93
7k				402	83	89
7l				428	86	92
7m				318	87	89
7n				368	72	70
7o				332	89	90
7p				415	63	92
7q				433	50	94
7r				445	52	83

[a] Yields were determined on the weight of purified samples (%).
[b] HPLC analysis (UV detection at 254 nm) of the crude samples (%).

tion of the α-bromo atom by thiourea and subsequent *in situ* intramolecular cyclization with the carbonyl moiety leading to the cyclized 2-mercaptoimidazole ring. The desired polymer-bound 2-mercaptoimidazoles **6** were obtained after 8 h in refluxing dichloromethane. However, upon exposure of the same reac-

tion to microwave irradiation it furnished polymer-bound 2-mercaptoimidazoles **6** in 8 min at 120 °C. The desired polymer-linked 2-mercaptoimidazoles **6** were purified by the same precipitation procedure and obtained in quantitative yields with three sets of structural diversity in the skeleton. The structure of compound **6** was characterized by ^{1}H NMR spectroscopy where a characteristic imidazole ring proton resonates at 5.78 ppm. Moreover, excellent regioselectivity was observed during this one-pot condensation reaction which was later confirmed by NOE analysis and an HMBC study after removal of the polymer support.

Finally, the removal of polymer support from **6** by cleaving the polymer ester linkage was achieved using sodium methoxide solution in methanol at ambient temperature for 12 h to furnish 2-mercaptoimidazoles **7**. However, with the utilization of microwave irradiation, the desired cleavage of the polymer support was achieved in 10 min at 90 °C. The released polymeric support was precipitated by cold ether and removed by filtration. The crude compound was then subjected to HPLC analysis which indicated moderate to good (66–97%) purity. Further chromatography purification afforded the 2-mercaptoimidazoles derivatives **7** in good overall yields (70–92%) as shown in Table 1. The removal of the PEG support was confirmed by the absence of the characteristic set of peaks of polyethylene glycol absorbing at 4.1 ppm. Through execution of the described reaction sequence, various 2-mercaptoimidazole derivatives **7** were synthesized with three diverse substitutions from amino acids, isothiocyanate and α-bromo aryl ketones as shown in Table 1. This developed strategy shows a significantly widened scope with various α-bromo ketones and isothiocyanates including aromatic isothiocyanates. With the utilization of chiral amino acids, we are able to introduce chirality at the α-position of the 2-mercaptoimidazole skeleton.

To confirm the results obtained along with the regioselectivity of the condensation reaction, we carried the 1D NOE analysis of compound **7j**. The characteristic NOE interaction pattern is shown in Figure 2. Irradiation of the Ha proton enhances the Hc proton signal by 0.34%. Irradiation of the Hc proton leads to the enhancement of the Ha proton signal by 1.01% which also enhanced the Hb and Hd proton signals by 0.56% and 1.81%, respectively. Similarly, irradiating the Hb proton enhances the Hc proton signals by 1.82%. There is no interaction observed between the Ha protons and the Hb protons showing their remoteness. Additionally, irradiating the Hd proton enhances the Hc proton signals by 1.002%. This suggests that the phenyl group bearing the Hc protons is in between the Ha proton and the benzyl group. Moreover the COSY and HMBC studies also support the structure **7j** (data in the Supporting Information). These combined observations clearly confirm the structure of compound **7j** and demonstrate the regioselectivity of the condensation reaction.

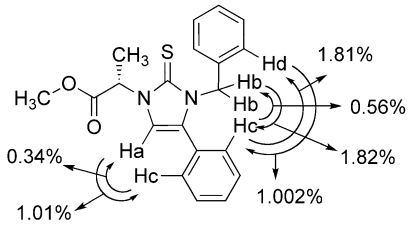
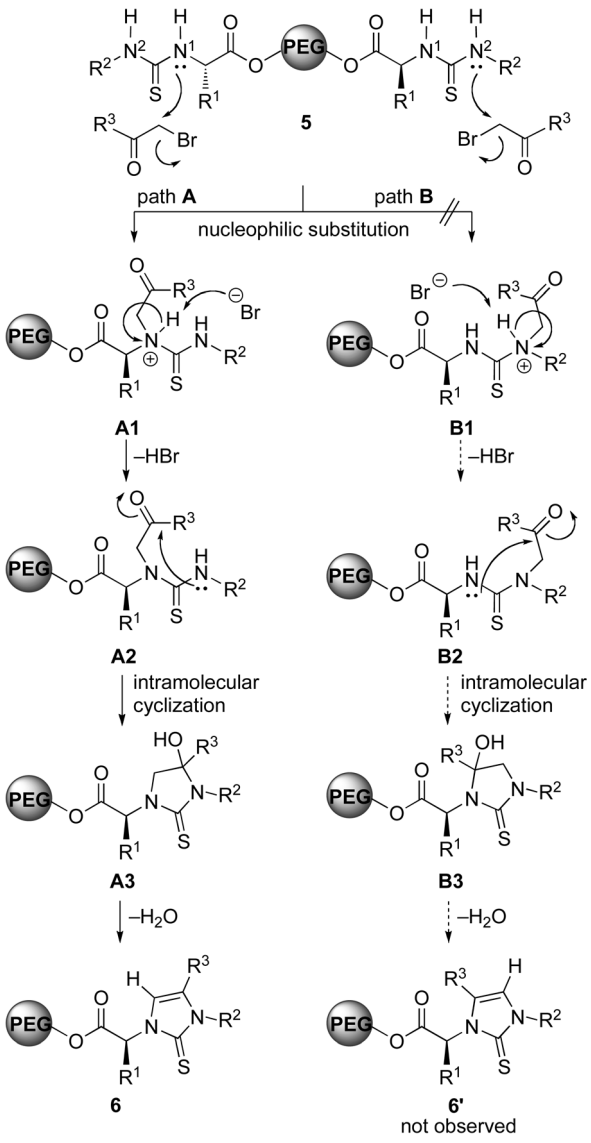


Figure 2. Key NOE interaction in compound **7j**.

The plausible steps involved in the one-pot regioselective condensation of polymer-bound thiourea **5** with α-halo ketones to provide polymer-bound 2-mercaptoimidazoles **6** are described in Scheme 4. Based on the observed outcome of the reaction, we pro-



Scheme 4. Plausible mechanism for the regioselective condensation of **5** with α-bromo ketones.

posed that the reaction proceeded *via* a sequence of regioselective nucleophilic bromo substitution and intramolecular cyclization followed by dehydration. Initially, the bromo group was selectively substituted by the secondary nitrogen of thiourea **5**. The regioselectivity between the nucleophilic substitution and attack on carbonyl carbon is due to the character of secondary nitrogens as a soft nucleophile which preferentially reacts with a soft halide electrophile. A point of interest is the regiochemistry in the reaction of thiourea **5** with α-bromo ketones, in view of the similar nucleophilicities of the two thioamido nitrogens. Both possibilities were considered mechanistically to find out a workable route for comparison with the results obtained. Here it was contemplated that the attack through the N^1 nitrogen atom of thiourea follow mechanistic path A while N^2-nitrogen attack to bromo group could follow path B as shown in Scheme 4, both leading to the *N*-alkylated adduct **A1** and **B1**, respectively. Further liberation of protons from adducts **A1** could afford intermediate **A2**. Subsequently, intramolecular cyclization through condensation of the N^2-nitrogen with the carbonyl functionality of the ketone afforded adducts **A3**. Liberation of a water molecule from **A3** can furnish 2-mercaptoimidazoles **6** which exactly matched with the results obtained. Thus, the mechanistic pathway B was discarded as its final outcome **6′** was mismatched with the results obtained. This evidently proves the condensation of thiourea **5** with the α-halo ketone by the mechanistic path A to deliver 2-mercaptoimidazoles **6**.

With the designed sequence of reaction, we successfully synthesized the 2-merchaptoimidazole featuring chirality at the α-position. The preservation of chiral integrity of the conjugates **7** throughout the four-step reaction sequence on the polymer support under harsh microwave conditions was evaluated by chiral HPLC studies. For exact evaluation of chirality, we have synthesized the enantiomer of compound **7a** following the same reaction sequence and analyzed the chiral HPLC of both **7a** and its enantiomer **7s**. The comparative chiral HPLC (diacel chiralcel OD) analysis of **7a** and its enantiomer **7s** is depicted in Figure 3. This analysis showed practically a very insignificant loss of chirality (about 5% racemization, 90% *ee*). High enantiomeric excesses of 2-mercaptoimidazoles were observed in the majority of the cases, during the multistep reaction sequence on the soluble polymer support under microwave conditions.

Conclusions

In conclusion, we have developed an efficient and soluble polymer-supported regioselective synthesis of optically active 2-mercaptoimidazoles with three points of structural diversity under the focused microwave irradiation. The key step in this synthesis in-

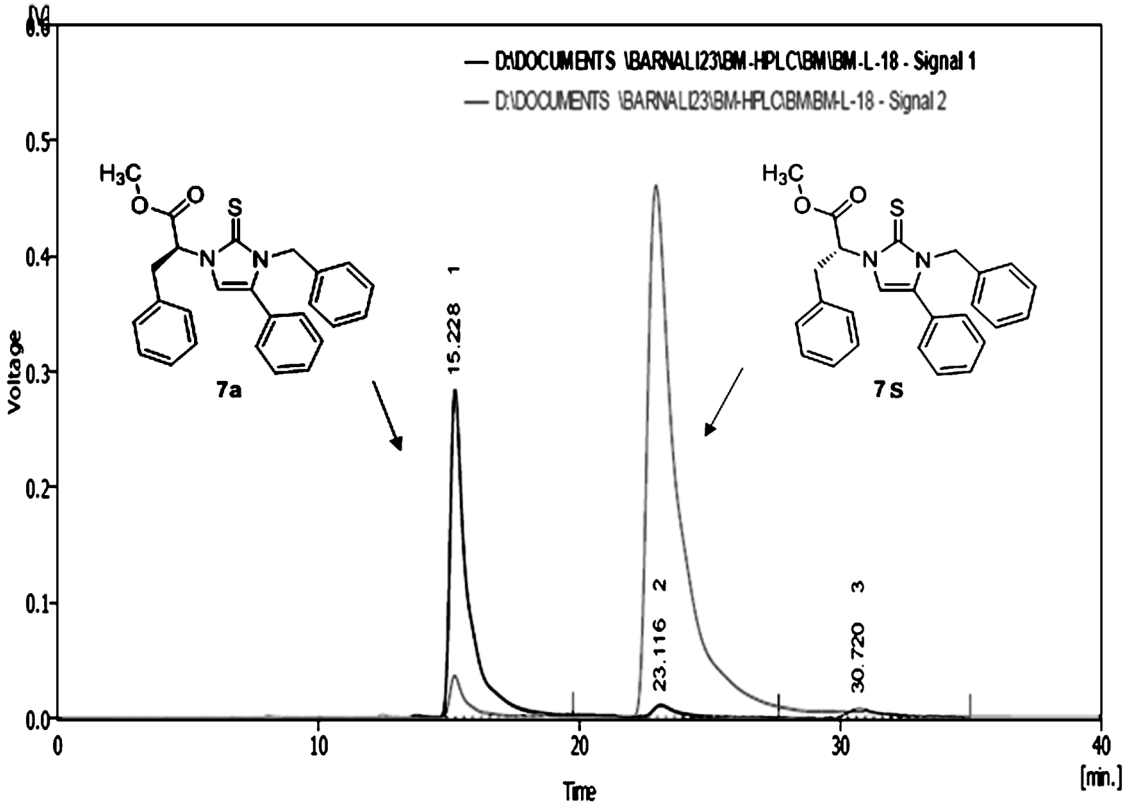


Figure 3. Comparative chiral HPLC analysis of **7a** and its enantiomer **7s**.

cludes the one-pot regioselective nucleophilic substitution reaction of PEG-bound L-amino acid-derived thiourea with α-bromo ketones followed by intramolecular cyclization to furnish the 2-mercaptoimidazole skeleton. Different combinations of L-amino acids, isothiocyanates and α-bromo aryl ketones were used to create the substitutional diversity as well as chirality in the 2-mercpatoimidazole skeleton. A representative small library was rapidly synthesized through acceleration of the rates of all the reactions with microwave irradiation as well as separation and purification of each polymer-bound intermediate by simple precipitation. Thus, this synthetic strategy represents a well-defined tool for the rapid generation of a library of biologically important 2-mercaptoimidazoles from readily available building blocks.

Experimental Section

General Procedure for the Synthesis of PEG-bound Fmoc-L-amino Acid (2)

Fmoc-L-amino acid **1** (0.29 g, 0.96 mmol), PEG-6000 (1.00 g, 0.16 mmol) and *N,N'*-dimethylaminopyridine (DMAP) (0.005 g) were placed in a dry, nitrogen-purged 20-mL microwave vial in dry CH_2Cl_2 (7 mL). A solution of *N,N'*-dicyclohexylcarbodiimide (DCC) (0.19 g, 0.96 mmol) in CH_2Cl_2 (5 mL) was added drop wise to the reaction mixture for a period of 5 min at room temperature which was then irradiated by microwave at 80 °C (1 bar) for 12 min. The reaction mixture was cooled and filtered to remove insoluble DCU. The solvent was evaporated and the residue was precipitated with cold ether. The product was filtered through a fritted funnel and washed (50 mL × 2) to remove any unreacted reagents and then dried under vacuum to give PEG-bound Fmoc-L-amino acid **2** as a white solid; yield: 1.18 g (95%).

General Procedure for the Synthesis of PEG-Bound L-Amino Acid (3)

The PEG-bound Fmoc-L-amino acid **2** (1.2 g, 0.18 mmol) was placed in a dry, nitrogen-purged 20-mL microwave vial. Piperidine (10%) in dry CH_2Cl_2 (10 mL) was added to this vial. The vial was irradiated at 75 °C for 1 min. After completion, the reaction mixture was precipitated with cold ether. The precipitate was filtered through a fritted funnel and washed (50 mL × 2) and dried to afford PEG-bound L-amino acid **3**; yield: 0.92 g (98%).

General Procedure for the Preparation PEG-Bound Thiourea (5)

The PEG-bound L-amino acid **3** (0.92 g, 0.15 mmol) was dissolved in CH_2Cl_2 (10 mL) in a dry, nitrogen-purged 20-mL microwave vial. Isothiocyanate (0.051 g, 0.45 mmol) was added to the reaction mixture at room temperature. The reaction mixture was irradiated by microwave at 120 °C (2 bar) for 8 min. After completion, reaction mixture was precipitated with cold ether. The precipitate was filtered through a fritted funnel, washed with cold ether (50 mL × 2) and dried well to afford PEG-bound thio-urea **5**; yield: 1.0 g (87%).

General Procedure for the Preparation of PEG-Bound 2-Mercaptoimidazole (6)

Aryl α-bromo ketone (0.48 mmol) was added to a stirred solution of PEG bound-thiourea derivative **5** (1.0 g, 0.16 mmol**)** in dry CH_2Cl_2 (10 mL) in a dry, nitrogen-purged microwave vial at room temperature. Then reaction mixture was irradiated by microwave at 120 °C for 8 min. After completion, the reaction mixture was precipitated with cold ether (50 mL). The precipitate was filtered through a fritted funnel, washed with cold ether (50 mL × 2) and dried well to afford the PEG-bound 2-mercaptoimidazoles **6** in good yields.

General Procedure for the Synthesis of 2-Mercaptoimidazole (7)

NaOMe (0.10 g, 0.04 mmol) was added to a solution of PEG-bound 2-mercaptoimidazole **6** (1.2 g, 0.20 mmol) in methanol (20 mL) in a 20 mL microwave vial. The reaction mixture was stirred under microwave irradiation at 90 °C for 10 min. After completion of the reaction, methanol was removed under reduced pressure. A small quantity of dichloromethane was added and mixture was filtered to remove undissolved material. Then filtrate was again precipitated with cold ether (100 mL). The precipitated PEG was removed by filtration. The filtrate was concentrated under reduced pressure, dried well and subjected to HPLC analysis with UV detection at $\lambda = 254$ nm [column: Sphereclone 5μ Si (250 × 4.6 mm); gradient: 35% ethyl acetate in hexane; flow rate: 1 mL min^{-1}]. The residue was further purified by column chromatography (ethyl acetate/hexane, 2:3) to afford the 2-mercaptoimidazoles **7** in good yields.

Methyl (2*S*)-2-(3-benzyl-4-phenyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)-3-phenylpropanoate (7a): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.39$–7.28 (m, 3H), 7.24 (s, 5H), 7.21–7.14 (m, 5H), 6.92–6.90 (m, 2H), 5.74 (s, 1H), 5.17 (d, $J = 15.6$ Hz, 1H), 4.84 (d, $J = 15.6$ Hz, 1H), 4.00 (dd, $J = 7.9$, 5.7 Hz, 1H), 3.72 (s, 3H), 3.30 (dd, $J = 13.2$, 5.4 Hz, 1H), 3.13 (dd, $J = 13.5$, 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.2$, 161.9, 140.8, 138.5, 137.7, 131.7, 129.6, 129.1, 128.9, 128.5, 128.2, 127.9, 127.4, 126.9, 126.3, 95.6, 68.9, 51.9, 48.4, 40.3; MS (EI): $m/z = 428$; HR-MS (EI): $m/z = 428.1560$, calcd. for $C_{26}H_{24}N_2O_2S$: 428.1558; $[\alpha]_D^{25}$: −19.2 (*c* 1.0, CH_2Cl_2); IR (KBr): $\nu = 3028$, 1714, 1614, 1494, 1453 cm^{-1}.

Methyl (2*S*)-2-[3-butyl-4-(naphthalen-2-yl)-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl]-3-phenylpropanoate (7b): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.89$–7.82 (m, 4H), 7.57–7.52 (m, 2H), 7.42–7.38 (m, 1H), 7.33–7.18 (m, 5H), 5.78 (s, 1H), 3.96–3.87 (m, 2H), 3.73 (s, 3H), 3.70–3.65 (m, 1H), 3.31 (dd, $J = 13.2$, 5.7 Hz, 1H), 3.15 (dd, $J = 13.5$, 8.1 Hz, 1H), 1.45–1.33 (m, 2H), 1.09–1.01 (m, 2H), 0.69 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.2$, 140.9, 138.5, 133.2, 133.0, 129.6, 128.4, 128.2, 128.2, 127.8, 126.9, 126.8, 126.3, 125.9, 95.9, 68.7, 52.0, 45.3, 29.8, 29.8, 19.7, 13.7; MS (EI): $m/z = 444$; HR-MS (EI): $m/z = 444.1871$, calcd. for $C_{27}H_{28}N_2O_2S$ 444.1871; $[\alpha]_D^{25}$: −43.8 (*c* 1.0, CH_2Cl_2); IR (KBr): $\nu = 2954$, 1742, 1614, 1434 cm^{-1}.

Methyl (2*S*)-2-(3-butyl-4-phenyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)-3-phenylpropanoate (7c): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 3H), 7.34–7.29 (m, 5H), 7.24–7.17 (m, 2H), 5.69 (s, 1H), 3.92–3.81 (m, 2H), 3.71 (s, 3H), 3.65–3.58 (m, 1H), 3.29 (dd, J = 13.4, 5.4 Hz, 1H), 3.15–3.12 (m, 1H), 1.42–1.29 (m, 2H), 1.11–1.02 (m, 2H), 0.71 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 161.7, 140.9, 138.5, 131.9, 129.6, 129.0, 128.8, 128.6, 128.1, 126.3, 95.2, 68.8, 52.0, 44.9, 40.2, 29.8, 19.6, 13.7; MS (EI): m/z = 394; HR-MS (EI): m/z = 394.1714, calcd. for $C_{23}H_{26}N_2O_2S$: 394.1715; $[\alpha]_D^{25}$: −21.9 (c 1.0, CH_2Cl_2); IR (KBr): ν = 3027, 2954, 2859, 2359, 1742, 1612 cm^{-1}.

Methyl (2*S*)-2-(3-butyl-4-phenyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)-3-methylbutanoate (7d): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.36 (m, 3H), 7.35–7.31 (m, 2H), 5.68 (s, 1H), 3.95–3.84 (m, 1H), 3.71 (s, 3H), 3.66–3.57 (m, 1H), 3.39 (d, J = 6.3 Hz, 1H), 2.33–2.22 (m, 1H), 1.59–1.37 (m, 2H), 1.16–1.04 (m, 2H), 0.98 (t, J = 5.7 Hz, 6H), 0.73 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 161.1, 140.8, 132.2, 128.9, 128.8, 128.6, 94.9, 73.6, 51.6, 44.8, 32.8, 29.9, 19.7, 18.5, 13.7; MS (EI): m/z = 346; HR-MS (EI): m/z = 346.1710, calcd. for $C_{19}H_{26}N_2O_2S$: 346.1715; $[\alpha]_D^{25}$: −41.8 (c 1.0, CH_2Cl_2); IR (KBr): ν = 2957, 1742, 1615, 1444 cm^{-1}.

Methyl (2*S*)-2-[3-butyl-4-(4-methylphenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl]-3-methylbutanoate (7e): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18 (s, 4H), 5.16 (s, 1H), 3.90–3.81 (m, 1H), 3.67 (s, 3H), 3.65–3.55 (m, 1H), 3.37 (d, J = 6.3 Hz, 1H), 2.35 (s, 3H), 2.29–2.20 (m, 1H), 1.59–1.37 (m, 2H), 1.17–1.03 (m, 2H), 0.97 (t, J = 6.6 Hz, 6H), 0.72 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 161.1, 140.8, 138.8, 129.3, 129.3, 128.6, 94.5, 73.5, 51.5, 44.8, 32.8, 29.9, 21.3, 19.7, 18.3, 13.7; MS (EI): m/z = 360; HR-MS (EI): m/z = 360.1875, calcd. for $C_{20}H_{28}N_2O_2S$: 360.1871; $[\alpha]_D^{25}$: −40.2 (c 1.0, CH_2Cl_2); IR (KBr): ν = 2957, 1743, 1610, 1509, 1433 cm^{-1}.

Methyl (2*S*)-2-[3-benzyl-4-(4-methylphenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl]-3-methylbutanoate (7f): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 3H), 7.23–7.16 (m, 5H), 7.04–7.02 (m, 2H), 5.77 (s, 1H), 5.11 (d, J = 15.6 Hz, 1H), 4.90 (d, J = 15.6 Hz, 1H), 3.72 (s, 3H), 3.45 (d, J = 6.3 Hz, 1H), 2.30–2.20 (m, 1H), 0.90 (dd, J = 6.7, 3.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 161.1, 140.7, 137.8, 131.7, 128.9, 128.8, 128.4, 128.0, 127.1, 126.7, 95.2, 73.4, 51.5, 48.3, 32.6, 19.5, 18.2; MS (EI): m/z = 380; HR-MS (EI): m/z = 380.1558, calcd. for $C_{22}H_{24}N_2O_2S$: 380.1558; $[\alpha]_D^{25}$: −24.3 (c 1.0, CH_2Cl_2); IR (KBr): ν = 2957, 1740, 1617, 1444 cm^{-1}.

Methyl (2*S*)-2-[3-benzyl-4-(naphthalen-2-yl)-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl]-3-methylbutanoate (7g): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.71 (m, 3H), 7.69 (s, 1H), 7.54–7.48 (m, 2H), 7.31–7.28 (m, 1H), 7.25–7.20 (m, 3H), 7.10–7.08 (m, 2H), 5.87 (s, 1H), 5.17 (d, J = 15.6 Hz, 1H), 4.98 (d, J = 15.6 Hz, 1H), 3.92 (dd, J = 13.4, 6.9 Hz, 1H), 3.76 (s, 3H), 2.38–2.27 (m, 1H), 0.98–0.95 (m 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 161.4, 140.9, 138.1, 133.2, 132.9, 129.2, 128.5, 128.2, 127.8, 127.4, 126.9, 126.9, 126.7, 126.1, 95.8, 73.6, 51.7, 48.8, 32.8, 19.7, 18.5; MS (EI): m/z = 430; HR-MS (EI): m/z = 430.1714, calcd. for $C_{26}H_{26}N_2O_2S$: 430.1715; $[\alpha]_D^{25}$: −20.3 (c 1.0, CH_2Cl_2); IR (KBr): ν = 2957, 1739, 1617, 1453 cm^{-1}.

Methyl (2*S*)-2-(3-butyl-4-phenyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)-4-methylpentanoate (7h): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.38 (m, 3H), 7.33–7.31 (m, 2H), 5.70 (s, 1H), 3.94–3.76 (m, 1H), 3.70 (s, 3H), 3.69–3.59 (m, 2H), 1.85–1.69 (m, 3H), 1.54–1.36 (m, 2H), 1.13–1.01 (m, 2H); 0.96–0.86 (m, 6H); 0.70 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 161.2, 140.8, 132.2, 128.9, 128.8, 128.6, 95.0, 65.7, 51.8, 44.7, 43.1, 29.9, 24.9, 23.3, 21.9, 19.6, 13.7; MS (EI): m/z = 360; HR-MS (EI): m/z = 360.1871, calcd. for $C_{20}H_{28}N_2O_2S$: 360.1871; $[\alpha]_D^{25}$: −31.4 (c 1.0, CH_2Cl_2); IR (KBr): ν = 2954, 1745, 1613, 1444 cm^{-1}.

Methyl (2*S*)-2-[3-benzyl-4-(naphthalen-2-yl)-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl]-4-methylpentanoate (7i): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.71 (m, 3H), 7.69 (s, 1H), 7.54–7.47 (m, 2H), 7.30–7.27 (m, 1H), 7.24–7.19 (m, 3H), 7.07–7.05 (m, 2H), 5.88 (s, 1H), 5.16–4.97 (m, 2H), 3.84–3.80 (m, 1H), 3.76 (s, 3H), 1.93–1.84 (m, 1H), 1.79–1.71 (m, 1H), 1.69–1.56 (m, 1H), 0.92 (dd, J = 8.2, 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 161.4, 140.9, 138.0, 133.2, 132.9, 129.1, 128.5, 128.3, 128.2, 127.8, 127.3, 126.9, 126.9, 126.7, 126.1, 95.9, 65.6, 51.9, 48.7, 43.1, 24.7, 23.4, 21.8; MS (EI): m/z = 444; HR-MS (EI): m/z = 444.1871, calcd. for $C_{27}H_{28}N_2O_2S$: 444.1871; $[\alpha]_D^{25}$: −32.7 (c 1.0, CH_2Cl_2); IR (KBr): ν = 2952, 1741, 1615, 1433 cm^{-1}.

Methyl (2*S*)-2-(3-benzyl-4-phenyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl) propanoate (7j): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 3H), 7.16–7.14 (m, 5H), 7.02–6.99 (m, 2H), 5.76 (s, 1H), 4.99 (s, 2H), 3.85 (dd, J = 13.6, 6.6 Hz, 1H), 3.71 (s, 3H), 1.49 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 161.3, 140.8, 137.7, 131.8, 129.1, 128.9, 128.5, 128.2, 127.5, 127.0, 95.5, 62.3, 51.9, 48.3, 19.1; MS (EI): m/z = 352; HR-MS (EI): m/z = 352.1246, calcd. for $C_{20}H_{20}N_2O_2S$: 352.1245; $[\alpha]_D^{25}$: −47.5 (c 1.0, CH_2Cl_2); IR (KBr): ν = 2948, 1741, 1615, 1444 cm^{-1}.

Methyl (2*S*)-2-[3-benzyl-4-(naphthalen-2-yl)-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl]propanoate (7k): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86–7.71 (m, 3H), 7.66 (s, 1H), 7.55–7.48 (m, 2H), 7.28–7.26 (m, 1H), 7.21–7.19 (m, 3H), 7.08–7.06 (m, 2H), 5.88 (s, 1H), 5.07 (s, 2H), 3.92 (dd, J = 13.4, 6.9 Hz, 1H), 3.76 (s, 3H), 1.55 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 161.4, 140.9, 137.8, 133.3, 132.9, 129.1, 128.5, 128.3, 128.2, 127.8, 127.6, 127.1, 126.9, 126.8, 126.2, 95.9, 62.4, 52.0, 48.7, 19.1; MS (EI): m/z = 402; HR-MS (EI): m/z = 402.1398, calcd. for $C_{24}H_{22}N_2O_2S$: 402.1402; $[\alpha]_D^{25}$: −29.4 (c 1.0, CH_2Cl_2); IR (KBr): ν = 2957, 1741, 1615, 1453 cm^{-1}.

Methyl (2*S*)-2-[3-benzyl-4-(biphenyl-4-yl)-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl]propanoate (7l): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63–7.56 (m, 4H), 7.48 (t, J = 7.2 Hz, 2H), 7.42–7.37 (m, 1H), 7.28–7.23 (m, 5H), 7.13–7.11 (m, 2H), 5.84 (s, 1H), 5.09 (s, 2H), 3.93 (dd, J = 13.5, 6.6 Hz, 1H), 3.76 (s, 3H), 1.56 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 161.3, 141.8, 140.6, 140.1, 137.8, 130.7, 129.3, 129.0, 128.3, 127.9, 127.5, 127.2, 127.1, 95.7, 62.4, 52.0, 48.5, 19.2; MS (EI): m/z = 428; HR-MS (EI): m/z = 428.1557, calcd. for $C_{26}H_{24}N_2O_2S$: 428.1558; $[\alpha]_D^{25}$: −29.4 (c 1.0, CH_2Cl_2); IR (KBr): ν = 2948, 1740, 1608, 1453 cm^{-1}.

Methyl (2*S*)-2-(3-butyl-4-phenyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)propanoate (7m): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.37 (m, 3H), 7.35–7.30 (m, 2H), 5.71 (s, 1H), 3.80–3.67 (m, 3H), 3.72 (s, 3H), 1.49–1.40 (m, 5H), 1.14–1.02 (m, 2H), 0.71 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 161.0, 140.9, 132.2, 128.9, 128.7,

128.6, 95.0, 62.4, 51.9, 44.7, 29.9, 19.6, 19.0, 13.7; MS (EI): $m/z=318$; HR-MS (EI): $m/z=318.1404$, calcd. for $C_{17}H_{22}N_2O_2S$: 318.1402; $[\alpha]_D^{25}$: −27.8 (*c* 1.0, CH_2Cl_2); IR (KBr): $\nu=2955$, 1743, 1614, 1445 cm^{-1}.

Methyl (2*S*)-2-[3-butyl-4-(naphthalen-2-yl)-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl]propanoate (7n): ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.89$–7.84 (m, 4H), 7.56–7.52 (m, 2H), 7.41 (dd, $J=8.4$, 1.5 Hz, 1H), 5.82 (s, 1H), 3.86–3.77 (m, 3H), 3.75 (s, 3H), 1.59–1.47 (m, 5H), 1.15–1.03 (m, 2H), 0.70 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 174.4, 161.1, 140.9, 133.2, 133.1, 129.5, 128.3, 128.2, 128.1, 127.8, 126.9, 126.8, 125.9, 95.6, 62.5, 52.0, 45.0, 29.9, 19.6, 19.1, 13.7; MS (EI): $m/z=368$; HR-MS (EI): $m/z=368.1560$, calcd. for $C_{21}H_{24}N_2O_2S$: 368.1558; $[\alpha]_D^{25}$: −29.4 (*c* 1.0, CH_2Cl_2); IR (KBr): $\nu=2954$, 1742, 1614, 1434 cm^{-1}.

Methyl (2*S*)-2-[3-butyl-4-(4-methylphenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl]propanoate (7o): ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.19$ (m, 4H), 5.66 (s, 1H), 3.81–3.65 (m, 3H), 3.70 (s, 3H), 2.36 (s, 3H), 1.50–1.40 (m, 5H), 1.14–1.02 (m, 2H), 0.71 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=174.4$, 161.0, 140.9, 138.9, 129.3, 129.2, 128.6, 94.6, 62.4, 51.9, 44.7, 29.9, 21.3, 19.6, 19.0, 13.7; MS (EI): $m/z=332$; HR-MS (EI): $m/z=332.1559$, calcd for $C_{18}H_{24}N_2O_2S$ 332.1558; $[\alpha]_D^{25}$: −48.1 (*c* 1.0, CH_2Cl_2); IR (KBr): $\nu=2955$, 2871, 1743, 1608, 1434 cm^{-1}.

Methyl 2-(3,4-diphenyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)-3-phenylpropanoate (7p): ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.34$ (d, $J=7.2$ Hz, 2H), 7.30 (t, $J=7.2$ Hz, 1H), 7.22–7.12 (m, 6H), 7.10 (d, $J=7.2$ Hz, 2H), 7.04 (t, $J=7.2$ Hz, 1H), 6.90 (d, $J=7.2$ Hz, 2H), 6.69 (m, 1H), 5.49 (s, 1H), 4.52 (dd, $J=10.8$, 3.6 Hz, 1H), 3.94 (dd, $J=13.8$, 10.8 Hz, 1H), 3.82 (s, 3H), 3.22 (dd, $J=13.8$, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=170.3$, 156.4, 150.4, 140.1, 137.5, 130.8, 129.8, 129.3, 129.2, 128.9, 128.3, 128.2, 126.5, 122.9, 121.2, 95.0, 60.0, 52.5, 32.8; MS (ESI): $m/z=415$ [M+1]; $[\alpha]_D^{25}$: +122.5 (*c* 0.025, CH_2Cl_2); IR (KBr): $\nu=3025$, 1745, 1616, 1488 cm^{-1}.

Methyl 2-[3-(4-fluorophenyl)-4-phenyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl]-3-phenylpropanoate (7q): ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.35$ (t, $J=8.1$ Hz, 1H), 7.26–7.14 (m, 8H), 7.12–7.08 (m, 2H), 6.92–6.86 (m, 2H), 6.69 (m, 1H), 5.52 (s, 1H), 4.48 (dd, $J=10.8$, 3.6 Hz, 1H), 3.94 (dd, $J=13.8$, 10.8 Hz, 1H), 3.83 (s, 3H), 3.20 (dd, $J=13.8$, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=170.4$, 160.0, 158.1, 157.0, 146.8, 140.3, 137.5, 130.8, 129.4, 129.1, 128.5, 126.6, 122.5, 115.9, 115.8, 95.0, 60.1, 52.6, 32.9; MS (ESI): $m/z=433$ [M+1]; $[\alpha]_D^{25}$: −230.5 (*c* 0.025, CH_2Cl_2); IR (KBr): $\nu=2948$, 1745, 1616, 1500 cm^{-1}.

Methyl 2-[3-(4-methoxyphenyl)-4-phenyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl]-3-phenylpropanoate (7r): ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.32$ (t, $J=7.8$ Hz, 1H), 7.24–7.08 (m, 5H), 7.06 (d, $J=7.8$ Hz, 2H), 6.98–6.87 (m, 5H), 6.69 (m, 1H), 5.49 (s, 1H), 4.51 (dd, $J=10.8$, 3.6 Hz, 1H), 3.95 (dd, $J=13.8$, 10.8 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.22 (dd, $J=13.8$, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 170.5, 156.1, 155.5, 144.0, 140.2, 137.7, 131.0, 129.4, 129.0, 128.9, 128.4, 128.3, 126.5, 122.1, 114.6, 94.9, 60.0, 55.5, 52.6, 32.9; MS (ESI): $m/z=445$ [M+1]; $[\alpha]_D^{25}$: −67.4 (*c* 0.025, CH_2Cl_2); IR (KBr): $\nu=2948$, 1745, 1616, 1504 cm^{-1}.

Methyl (2*S*)-2-(3-benzyl-4-phenyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)-3-phenylpropanoate (7s): ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.34$–7.25 (m, 3H), 7.20 (s, 5H), 7.15–7.10 (m, 5H), 6.87–6.85 (m, 2H), 5.72 (s, 1H), 5.12 (d, $J=15.6$ Hz, 1H), 4.80 (d, $J=15.6$ Hz, 1H), 3.94 (dd, $J=7.9$, 5.7 Hz, 1H), 3.69 (s, 3H), 3.25 (dd, $J=13.2$, 5.4 Hz, 1H), 3.07 (dd, $J=13.5$, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=173.1$, 161.9, 140.7, 138.4, 137.7, 131.7, 129.6, 129.3, 129.0, 128.9, 128.3, 128.1, 127.3, 126.8, 126.1, 95.5, 68.8, 51.9, 48.3, 40.2; $[\alpha]_D^{25}$: −0.37 (*c* 1.0, CH_2Cl_2).

Supporting Information

The ^1H NMR, ^{13}C NMR, IR and HR-MS for compounds **7**. These data are available as Supporting Information.

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