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DIASTEREOSELECTIVE SYNTHESIS OF POLY-SUBSTITUTED *SYN*-IMIDAZOLIDINE-2-THIONES VIA MICROWAVE-ASSISTED THREE-COMPONENT [2+2+1] HETEROCYCLIZATIONS

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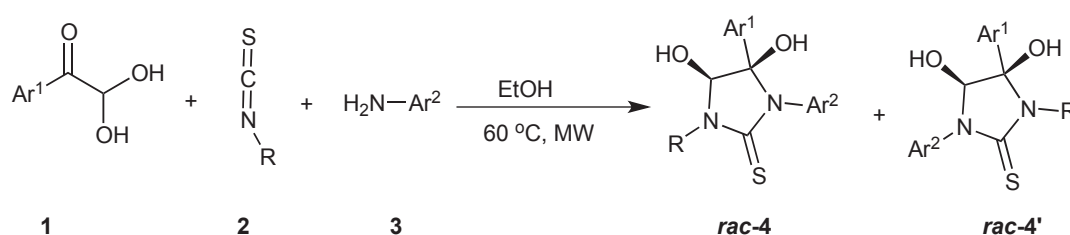
Abstract – An efficient and simple three-component reaction of arylglyoxals, isothiocyanates and arylamines has been developed, delivering poly-substituted *syn*-imidazolidine-2-thione derivatives with high diastereo- and regioselectivity (up to > 99:1). The microwave-assisted transformation is easy to perform simply by mixing readily available starting materials, thereby featuring mild reaction conditions, bond-forming efficiency and atom-economy.

INTRODUCTION

Imidazoles are one of the most important five-membered aza-heteroaromatic compounds that show a broad application in pharmaceutical chemistry and chemical industry. Imidazole derivatives have been found to exhibit various biological activities such as antitumor,¹ antibacterial,² anti-HIV,³ antiviral,⁴ anti-allergic,⁵ antioxidant,⁶ anti-inflammatory,⁷ antifungal,⁸ and antiparasitic,⁹ which have behaved them as new candidates in cancer therapy.¹⁰ Moreover, they can be found in many important drugs such as Omeprazole, Eprosartan, and Trifenagrel having functionalized imidazole motif.¹¹ Therefore, a broad utility range has made imidazoles prime synthetic targets, thereby accentuating the need to develop newer synthetic routes for imidazole derivatives.¹²

Multicomponent domino reactions (MDRs) are recognized as one of the key tools for assembling multiring-junction frameworks that can be predicted by controlling reaction processes.^{13,14} Our group¹⁵ and

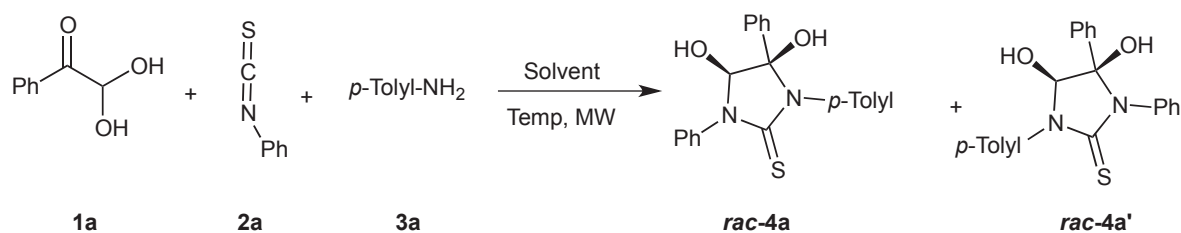
others¹⁶ have established a series of multicomponent domino reactions (MDRs) for the construction of multiple heterocyclic ring using arylglyoxals as a reaction partner. To continue our efforts in this project, we report a new three-component reaction of arylglyoxals **1**, isothiocyanates **2** and arylamines **3** for the rapid and diastereoselective synthesis of highly functionalized *syn*-imidazolidine-2-thione derivatives under microwave (MW) irradiation (Scheme 1). To the best of our knowledge, the current diastereoselective multicomponent [2+2+1] heterocyclization cascade toward poly-substituted *syn*-imidazolidine-2-thiones has not been documented yet. Notably the reaction features mild reaction conditions, broad functional group compatibility and good reaction yields.



Scheme 1. Synthesis of *syn*-imidazolidine-2-thione derivatives

RESULTS AND DISCUSSION

Initially, 2,2-dihydroxy-1-phenylethanone (**1a**), isothiocyanatobenzene (**2a**) and *p*-toluidine (**3a**) were selected for the model reaction to examine the feasibility of the proposed reaction. The microwave-enabled reaction of **1a** with **2a** and **3a** was conducted in MeCN at 40 °C for 20 min, providing inseparable *cis*-imidazolidine-2-thione isomers **4a** and **4a'** in a 1.2:1 ratio, albeit with a low total 28% yield (Table 1, entry 1). The structure of **4a** and **4a'** was fully characterized by NMR spectroscopic analysis. Subsequently, the solvent effect was investigated to improve the reaction efficiency (entries 2-4). The use of chloroform (CHCl₃) and dichloromethane (DCM) as the solvent showed no improvement on the yield of isomers **4a** and **4a'**, whereas toluene remarkably suppressed the reaction process, providing a lower yield of **4a** and **4a'** (total 15% yield) as compared with MeCN. In another case of EtOH, it showed a good performance in the enhancement on the reaction efficiency, offering 51% total yield. Besides, we discovered that the conversion efficiency behaved a strong dependency on temperature (entries 6-8). A higher conversion of **1a** into **4a** and **4a'** (78%) was observed with the reaction temperature being at 60 °C (entry 6). Further raising the temperature to 80 °C or 100 °C did not improve the transformation (entries 7-8).

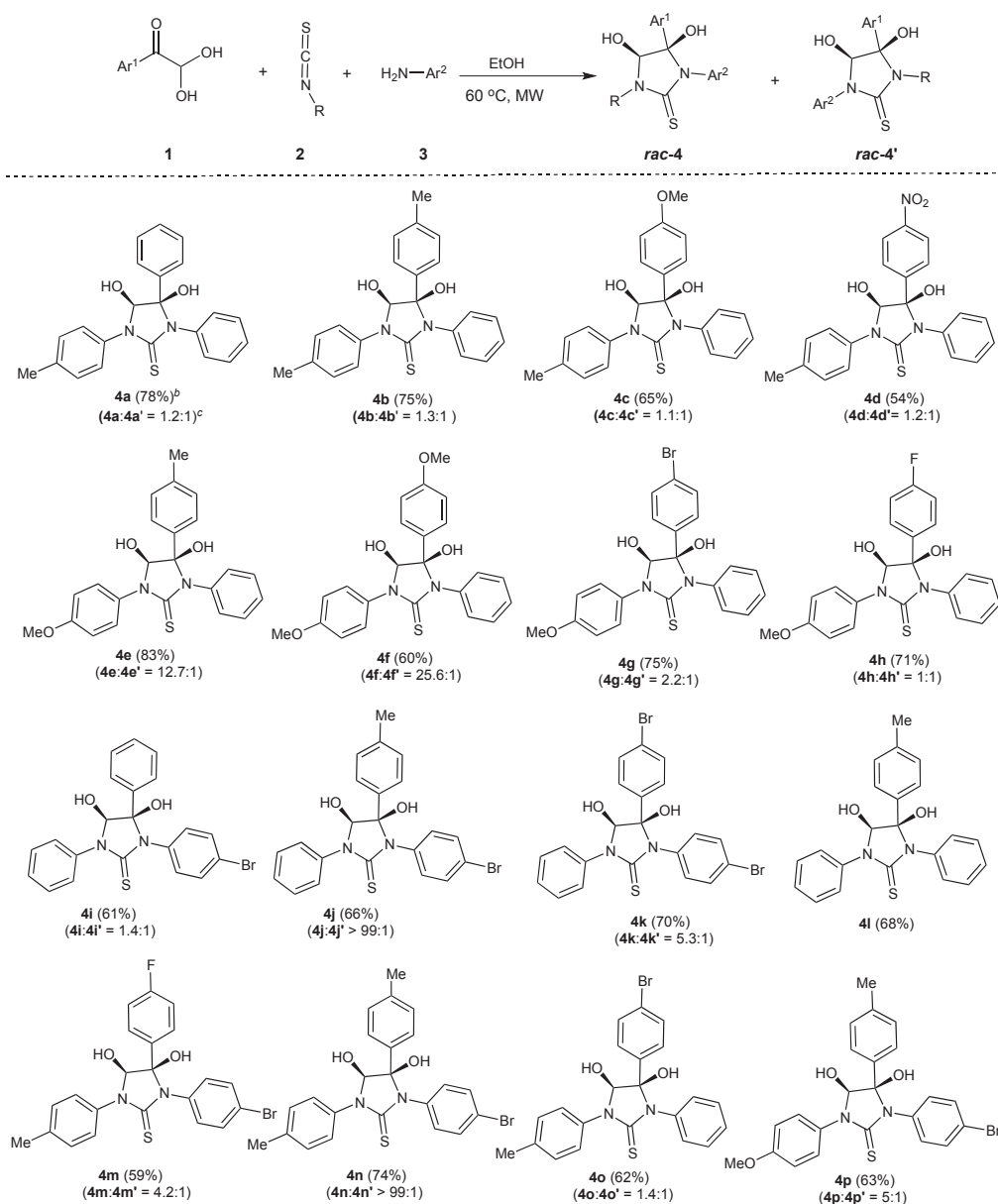
Table 1. Optimization of Reaction Conditions^a

Entry	Solvent	Temp (°C)	Yield ^b (%)
1	MeCN	40	28
2	DCM	40	22
3	CHCl ₃	40	26
4	toluene	40	15
5	EtOH	40	51
6	EtOH	60	78
7	EtOH	80	71
8	EtOH	100	66

^aReaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), solvent (2.0 mL) under microwave heating for 20 min. ^bIsolated total yield based on substrate **1a**.

With the optimal reaction conditions in hand, we set out to evaluate the substrate scope of the transformation by using a variety of different arylglyoxals, isothiocyanates and arylamines. The results are summarized in Scheme 2. Upon repeating the reaction with isothiocyanatobenzene (**2a**) and *p*-toluidine (**3a**), arylglyoxals **1** with different substituents such as methyl, methoxy, nitro groups all worked smoothly, efficiently furnishing the corresponding *syn*-imidazolidine-2-thiones **4b-4d** containing inseparable regioisomers in close 1:1 ratio with 54%-75% total yields. It is found that the regioselectivity was observed when different aryl groups were introduced into amines and isothiocyanates, respectively, due to the *in-situ* generated unsymmetrical *N,N*-bisarylthiourea. The different isomer ratio depends on the nucleophilicity of amino group attached by the unsymmetrical *N,N*-bisarylthiourea. The amino group with electron-donating aryl group show the higher nucleophilicity as compared with those with electron-neutral or poor aryl group, thus preferring to undergo the nucleophilic addition to highly reactive carbonyl groups of arylglyoxals and occupying a major proportion in regioisomers (see mechanism section). The other ascription proportion of products **4** was assigned by analogy. Next, the reaction of **2a** with *p*-methoxyaniline (**3b**) or 4-bromoaniline (**3c**) and various arylglyoxals **1** bearing methyl, methoxy, bromo and fluoro groups were performed under the optimal conditions, accessing the corresponding *syn*-imidazolidine-2-thiones isomers **4e-4k** and **4e'-4k'** with between >99:1 and 1:1 ratio and 60%-83%

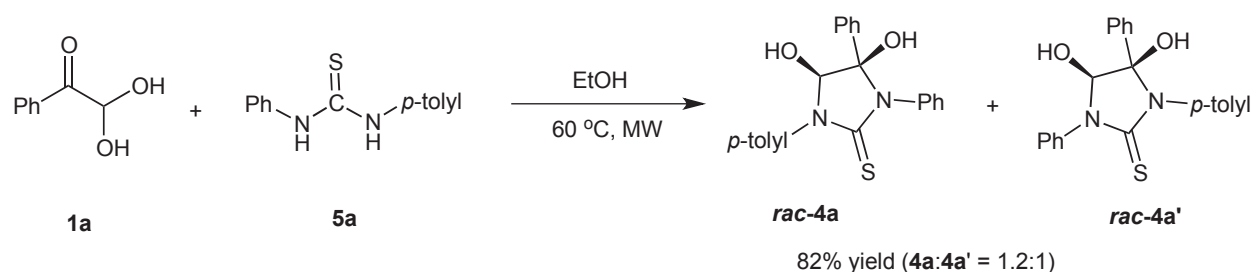
total yields. Product **4l** as a sole isomer was obtained in 68% yield through [2+2+1] cyclization cascade when the same aryl groups were tethered by isothiocyanate (**2a**) and amine (**3d**) units, respectively. Moreover, we changed the substituents (R) of isothiocyanates **2** to expand its synthetic utility. As we had expected, different substituents including 4-methylphenyl (**2b**) and 4-methoxyphenyl (**2c**) would be accommodated, giving access to isomers **4m–p** and **4m'–p'** with 59%–74% total yields. Among them, product **4n** was offered with an excellent regioselectivity (> 99:1 ratio). In general, the current protocol represents a new and practical pathway for the diastereoselective construction of richly decorated imidazolidine-2-thiones.



^aReaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), **3** (0.5 mmol), EtOH (2.0 mL), at 60 °C under microwave heating for 20 min. ^bIsolated total yield based on substrates **1**. ^cRegioisomer ratio based on the analysis of ¹H NMR.

Scheme 2. Substrate scope for synthesis of products **4a**^a

The structures of these imidazolidine-2-thiones were characterized by NMR spectroscopy and HRMS. Furthermore, the stereo-structure of **4l** was confirmed by carrying out single crystal X-ray diffraction (Figure 1), indicating that two hydroxyl groups are *cis* due to the intramolecular hydrogen bond interaction. The other analogues were assigned by analogy.



Scheme 3. Control experiment

To understand reaction mechanism for forming **4**, the reaction of the preformed unsymmetrical *N,N*-bisarylethylthiourea **5a** with 2,2-dihydroxy-1-phenylethanone (**1a**) was conducted under the optimized conditions (Table 1, entry 6) and the desired isomers *cis*-**4a** and *cis*-**4a'** was obtained in 82% yield (Scheme 3), indicating that *N,N*-bisarylethylthiourea may act as an intermediate for the synthesis of **4**.

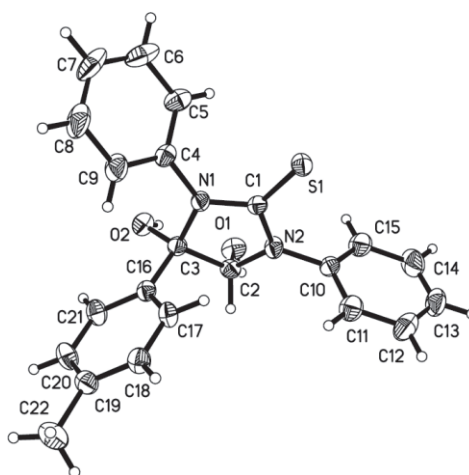
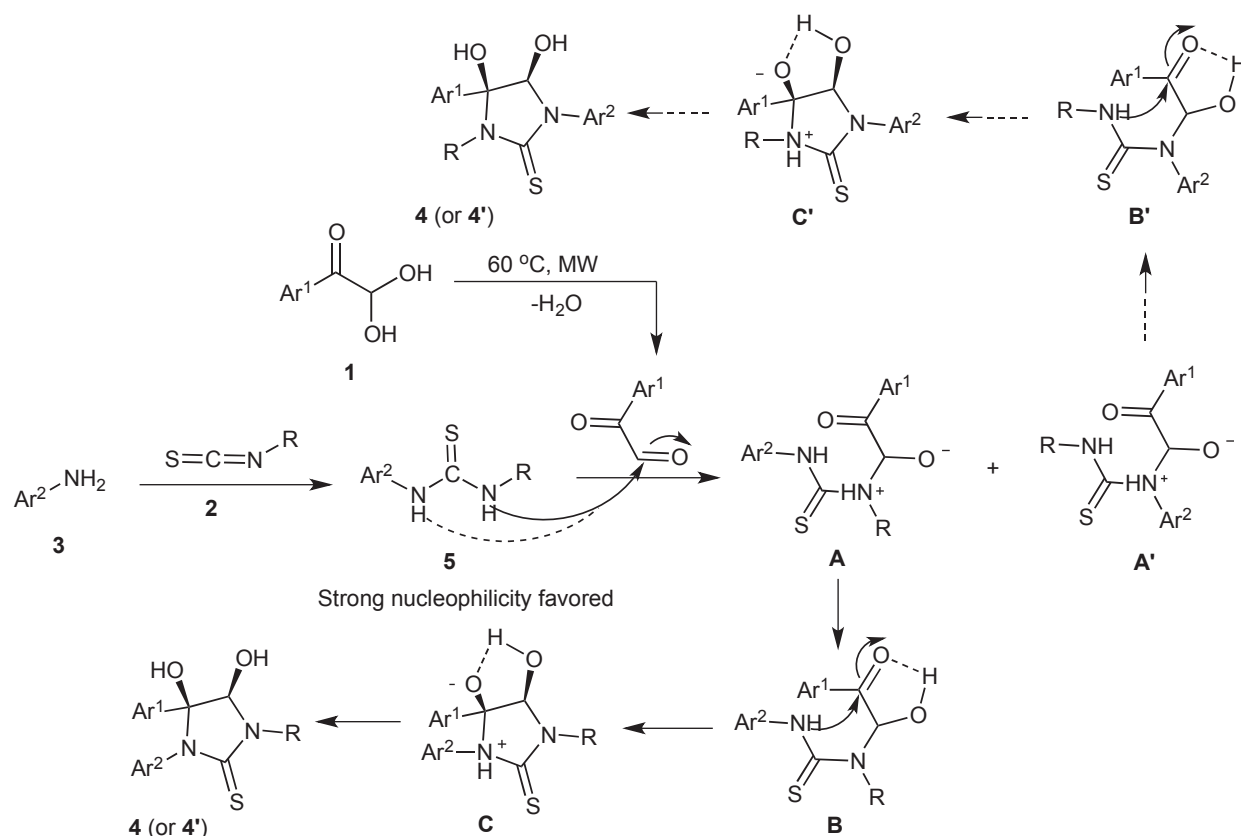


Figure 1. The crystal structure of compound **4l**

On the basis of the above results, a plausible reaction mechanism is proposed in Scheme 4. Nucleophilic addition of amines to isothiocyanates gives *N,N*-bisarylethylthioureas **5**. Next, amino group of *N,N*-bisarylethylthiourea with stronger nucleophilicity favors to attract the terminal carbonyl groups of arylglyoxals **1**, giving intermediates **A** and **A'**. Intermediates **A** undergo proton transfer and intramolecular nucleophilic addition to stereoselectively generate imidazolidine-2-thione intermediates **C**, due to the existence of intramolecular hydrogen bond, followed by second proton transfer to the final products *cis*-**4**. The formation of *cis*-**4'** proceeds through a similar process.



Scheme 4. Proposed mechanism for forming **4**

In conclusion, starting from easily available arylglyoxals, isothiocyanates and arylamines, we have established microwave-assisted three-component reactions for the synthesis of *cis*-imidazolidine-2-thione derivatives with generally good yields and high stereoselectivity. The [2+2+1] heterocyclization reaction allows to access blocks of *cis*-imidazolidine-2-thione with a wide diversity of substituents. The flexible structural modification, broad functional group compatibility and mild reaction conditions make this strategy highly viable for future applications.

EXPERIMENTAL

Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage Company, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1} . ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in $\text{DMSO-}d_6$ with chemical shift (δ) given in ppm relative to TMS as internal standard. HRMS (ESI) was determined by using microTOF-Q II HRMS/MS instrument (BRUKER). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General Procedure for the Synthesis of Compounds 4

Example for the synthesis of 4a

Microwave Heating: Typically, 2,2-dihydroxy-1-phenylethanone (**1a**, 0.5 mmol) was introduced in a 10 mL InitiatorTM reaction vial, isothiocyanatobenzene (**2a**, 0.5 mmol), *p*-toluidine (**3a**, 0.5 mmol) and EtOH (2.0 mL) were then successively added. Subsequently, the reaction vial was capped and then pre-stirring for 10 second. The mixture was irradiated (Time: 20 min, Temperature: 60 °C; Absorption Level: High; Fixed Hold Time) until TLC (petroleum ether: EtOAc 5:1) revealed that conversion of the starting material **1a** was completed. The reaction mixture was then cooled to room temperature and then diluted with cold water (20 mL). The solid product was collected by Büchner filtration and was purified by flash column chromatography (silica gel, mixtures of petroleum ether/ EtOAc, 10:1, v/v) to afford the desired imidazolidine-2-thiones **4a** as a white solid.

4,5-Dihydroxy-3,4-diphenyl-1-(*p*-tolyl)imidazolidine-2-thione (4a)

White solid, mp 149-150 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (δ, ppm): 7.58-7.52 (m, 3H), 7.48-7.38 (m, 4H), 7.35-7.16 (m, 6H), 7.12-7.03 (m, 3H), 5.40 (d, *J* = 6.4 Hz, 1H), 2.35 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm): 181.1, 141.5, 139.5, 136.8, 135.3, 130.2, 129.5, 129.0, 128.9, 128.7, 128.3, 127.4, 126.1, 91.8, 89.7, 21.1; IR (KBr, ν, cm⁻¹) 3675, 3133, 1772, 1717, 1700, 1653, 1558, 1398, 1087, 697; HRMS (APCI): *m/z* calcd for C₂₂H₂₀N₂NaO₂S, 399.1143 [M+Na]⁺, found: 399.1142.

4,5-Dihydroxy-3-phenyl-1,4-di-*p*-tolylimidazolidine-2-thione(4b)

White solid, mp 155-156 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (δ, ppm): 7.56 (d, *J* = 8.0 Hz, 1H), 7.47-7.39 (m, 4H), 7.33-7.20 (m, 7H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 5.35 (d, *J* = 6.4 Hz, 1H), 2.35 (s, 3H), 2.24 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm): 181.0, 139.5, 138.6, 138.0, 137.3, 136.7, 135.3, 133.9, 130.1, 129.4, 128.9, 128.7, 128.1, 127.3, 126.1, 94.6, 91.9, 89.8, 21.2; IR (KBr, ν, cm⁻¹) 3726, 3130, 2923, 1755, 1596, 1515, 1402, 1323, 1021, 816, 695; HRMS (APCI): *m/z* calcd for C₂₃H₂₂N₂NaO₂S, 413.1300 [M+Na]⁺, found: 413.1279.

4,5-Dihydroxy-4-(4-methoxyphenyl)-3-phenyl-1-(*p*-tolyl)imidazolidine-2-thione (4c)

White solid, mp 154-155 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (δ, ppm): 7.55-7.53 (m, 1H), 7.46-7.39 (m, 4H), 7.34-7.31 (m, 1H), 7.26-7.18 (m, 4H), 7.09-7.03 (m, 2H), 6.95-6.91 (m, 3H), 5.35 (d, *J* = 6.4 Hz, 1H), 3.74 (s, 3H), 2.34 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm): 180.9, 159.5, 139.5, 136.9, 136.6, 133.5, 130.3, 129.4, 128.9, 128.6, 128.2, 127.5, 114.1, 91.8, 89.9, 55.5, 21.2; IR (KBr, ν, cm⁻¹) 3427, 3136, 1539, 1429, 1407, 1342, 1263, 1058, 833 714; HRMS (APCI): *m/z* calcd for C₂₃H₂₂N₂NaO₃S, 429.1249 [M+Na]⁺, found: 429.1222.

4,5-Dihydroxy-4-(4-nitrophenyl)-3-phenyl-1-(*p*-tolyl)imidazolidine-2-thione (4d)

White solid, mp 191-192 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (δ, ppm): 8.24 (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.47-7.40 (m, 4H), 7.35-7.32 (m, 1H), 7.27-7.17 (m, 3H), 7.10

(d, $J = 8.4$ Hz, 1H), 7.04 (d, $J = 8.4$ Hz, 1H), 5.46 (d, $J = 6.4$ Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 181.3, 147.8, 139.0, 137.3, 136.4, 134.8, 130.2, 129.6, 129.1, 128.8, 128.6, 127.9, 124.1, 91.5, 89.3, 21.0; IR (KBr, ν , cm^{-1}) 3750, 3629, 3225, 1772, 1653, 1559, 1540, 1387, 1050, 711; HRMS (APCI): m/z calcd for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{NaO}_4\text{S}$, 444.0994 $[\text{M}+\text{Na}]^+$, found: 444.0995.

4,5-Dihydroxy-1-(4-methoxyphenyl)-3-phenyl-4-(*p*-tolyl)imidazolidine-2-thione (4e)

White solid, mp 160-161 °C; ^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 7.40-7.38 (m, 4H), 7.27-7.14 (m, 8H), 6.99 (d, $J = 8.8$ Hz, 2H), 6.94 (s, 1H), 5.22 (d, $J = 6.8$ Hz, 1H), 3.78 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 181.3, 158.6, 138.7, 138.0, 132.1, 130.2, 129.4, 128.9, 128.2, 127.3, 126.0, 114.2, 91.9, 90.0, 55.8, 21.1; IR (KBr, ν , cm^{-1}) 3699, 3130, 1726, 1605, 1516, 1431, 1255, 1053, 816, 710; HRMS (APCI): m/z calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{NaO}_3\text{S}$, 429.1249 $[\text{M}+\text{Na}]^+$, found: 429.1267.

4,5-Dihydroxy-1,4-bis(4-methoxyphenyl)-3-phenylimidazolidine-2-thione (4f)

White solid, mp 143-144 °C; ^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 7.40 (dd, $J = 8.4$, 6.0 Hz, 4H), 7.25-7.15 (m, 6H), 6.99 (d, $J = 8.8$ Hz, 2H), 6.92 (d, $J = 9.2$ Hz, 3H), 5.24 (d, $J = 6.4$ Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 182.3, 172.2, 160.1, 159.9, 137.6, 130.6, 130.0, 129.3, 127.4, 125.2, 114.6, 114.4, 89.7, 68.3, 55.9, 55.6, 18.8; IR (KBr, ν , cm^{-1}) 3441, 3131, 2839, 1737, 1607, 1517, 1394, 1253, 1053, 703; HRMS (APCI): m/z calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{NaO}_4\text{S}$, 445.1198 $[\text{M}+\text{Na}]^+$, found: 445.1187.

4-(4-Bromophenyl)-4,5-dihydroxy-1-(4-methoxyphenyl)-3-phenylimidazolidine-2-thione (4g)

White solid, mp 1560-161 °C; ^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 7.60-7.54 (m, 3H), 7.48-7.41 (m, 4H), 7.35-7.31 (m, 2H), 7.28-6.99 (m, 5H), 6.81 (d, $J = 9.2$ Hz, 1H), 5.40 (d, $J = 6.4$ Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 181.4, 158.5, 140.9, 139.4, 131.8, 130.3, 128.9, 128.8, 128.6, 128.3, 127.3, 122.1, 113.7, 91.5, 89.4, 55.6; IR (KBr, ν , cm^{-1}) 3696, 3122, 1589, 1515, 1401, 1251, 1051, 696; HRMS (APCI): m/z calcd for $\text{C}_{22}\text{H}_{19}\text{BrN}_2\text{NaO}_3\text{S}$, 493.0197 $[\text{M}+\text{Na}]^+$, found: 493.0229.

4-(4-Fluorophenyl)-4,5-dihydroxy-1-(4-methoxyphenyl)-3-phenylimidazolidine-2-thione (4h)

White solid, mp 138-140 °C; ^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 7.56-7.53 (m, 3H), 7.46-7.41 (m, 2H), 7.34-7.16 (m, 6H), 7.11-7.07 (m, 2H), 7.00 (d, $J = 8.4$ Hz, 1H), 6.79 (d, $J = 8.8$ Hz, 1H), 5.31 (d, $J = 6.4$ Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 181.4, 162.3 ($J_{\text{CF}} = 243.5$ Hz), 158.6, 137.7, 133.0 ($J_{\text{CF}} = 2.7$ Hz), 131.7, 131.1 ($J_{\text{CF}} = 7.1$ Hz), 130.3, 129.0, 128.6, 128.4, 115.6 ($J_{\text{CF}} = 21.4$ Hz), 114.3, 94.2, 91.4, 55.8; IR (KBr, ν , cm^{-1}) 3431, 3138, 1604, 1515, 1398, 1326, 1251, 1157, 1053, 834, 702; HRMS (APCI): m/z calcd for $\text{C}_{22}\text{H}_{19}\text{FN}_2\text{NaO}_3\text{S}$, 433.0998 $[\text{M}+\text{Na}]^+$, found: 433.1000.

1-(4-Bromophenyl)-4,5-dihydroxy-3,4-diphenylimidazolidine-2-thione (4i)

White solid, mp 153-154 °C; ^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 7.65 (d, $J = 8.4$ Hz, 1H), 7.55-7.51 (m, 4H), 7.47-7.29 (m, 7H), 7.26-7.14 (m, 4H), 5.41 (d, $J = 6.4$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 180.8, 141.1, 139.2, 137.3, 132.2, 131.3, 130.2, 129.0, 128.8, 128.7, 127.5, 126.1,

120.5, 91.9, 89.8; IR (KBr, ν , cm^{-1}) 3436, 3135, 1597, 1490, 1401, 1322, 1213, 1046, 830, 696; HRMS (APCI): m/z calcd for $\text{C}_{21}\text{H}_{17}\text{BrN}_2\text{NaO}_2\text{S}$, 463.0092 $[\text{M}+\text{Na}]^+$, found: 463.0143.

1-(4-Bromophenyl)-4,5-dihydroxy-3-phenyl-4-(*p*-tolyl)imidazolidine-2-thione (4j)

White solid, mp 153-154 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) (δ , ppm): 7.52 (d, $J = 8.0$ Hz, 2H), 7.46-7.42 (m, 4H), 7.39 (d, $J = 8.0$ Hz, 2H), 7.34-7.32 (m, 2H), 7.22-7.18 (m, 4H), 7.11 (s, 1H), 5.34 (d, $J = 6.4$ Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) (δ , ppm): 180.7, 139.3, 138.2, 138.1, 137.4, 132.1, 131.3, 129.5, 129.0, 128.7, 127.5, 126.0, 120.4, 92.0, 89.9, 21.1; IR (KBr, ν , cm^{-1}) 3726, 2918, 1597, 1489, 1412, 1325, 1011, 823, 699; HRMS (APCI): m/z calcd for $\text{C}_{22}\text{H}_{19}\text{BrN}_2\text{NaO}_2\text{S}$, 477.0248 $[\text{M}+\text{Na}]^+$, found: 477.0247.

1,4-Bis(4-bromophenyl)-4,5-dihydroxy-3-phenylimidazolidine-2-thione (4k)

White solid, mp 176-178 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) (δ , ppm): 7.60 (d, $J = 8.8$ Hz, 2H), 7.56 (d, $J = 7.2$ Hz, 2H), 7.50-7.42 (m, 7H), 7.36-7.32 (m, 2H), 7.25-7.21 (m, 2H), 5.44 (d, $J = 6.8$ Hz, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) (δ , ppm): 180.9, 139.3, 138.0, 136.2, 131.9, 131.4, 131.3, 130.6, 128.8, 127.6, 122.0, 120.0, 94.2, 91.7, 89.6; IR (KBr, ν , cm^{-1}) 3472, 3159, 1603, 1578, 1492, 1423, 1200, 1044, 712; HRMS (APCI): m/z calcd for $\text{C}_{21}\text{H}_{16}\text{Br}_2\text{N}_2\text{NaO}_2\text{S}$, 540.9197 $[\text{M}+\text{Na}]^+$, found: 540.9213.

4,5-Dihydroxy-1,3-diphenyl-4-(*p*-tolyl)imidazolidine-2-thione (4l)

White solid, mp 161-163 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) (δ , ppm): 7.54-7.52 (m, 2H), 7.46-7.38 (m, 4H), 7.34-7.30 (m, 2H), 7.26-7.15 (m, 7H), 7.01 (s, 1H), 5.32 (d, $J = 6.4$ Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) (δ , ppm): 180.9, 139.5, 138.6, 138.0, 137.9(5), 130.2, 129.4, 128.9, 128.7, 128.3, 127.4, 127.3, 126.0, 92.0, 89.8, 21.1; IR (KBr, ν , cm^{-1}): 3442, 3220, 1594, 1497, 1431, 1275, 1151, 1081, 1049, 823, 701; HRMS (APCI-TOF): m/z Calcd For $\text{C}_{22}\text{H}_{20}\text{N}_2\text{NaO}_2\text{S}$, 399.1143 $[\text{M}+\text{Na}]^+$, found 399.1140.

1-(4-Bromophenyl)-4-(4-fluorophenyl)-4,5-dihydroxy-3-(*p*-tolyl)imidazolidine-2-thione (4m)

White solid, mp 168-169 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) (δ , ppm): 7.66-7.54 (m, 5H), 7.48-7.41 (m, 1H), 7.34 (d, $J = 6.8$ Hz, 1H), 7.27-7.17 (m, 4H), 7.09-7.03 (m, 3H), 5.49 (d, $J = 6.4$ Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) (δ , ppm): 180.9, 162.3 ($J_{\text{CF}} = 243.2$ Hz), 138.7, 137.3 ($J_{\text{CF}} = 2.7$ Hz), 136.9, 135.1, 131.8, 130.8, 130.1, 129.0, 128.7 ($J_{\text{CF}} = 8.6$ Hz), 120.1, 115.5 ($J_{\text{CF}} = 21.2$ Hz), 91.6, 89.7, 21.1; IR (KBr, ν , cm^{-1}) 3018, 2866, 2145, 1772, 1717, 1653, 1558, 1450, 1041, 827, 720; HRMS (APCI): m/z calcd for $\text{C}_{22}\text{H}_{18}\text{BrFN}_2\text{NaO}_2\text{S}$, 495.0154 $[\text{M}+\text{Na}]^+$, found: 495.0166.

1-(4-Bromophenyl)-4,5-dihydroxy-3,4-di-*p*-tolylimidazolidine-2-thione (4n)

White solid, mp 152-153 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) (δ , ppm): 7.60-7.57 (m, 2H), 7.49-7.46 (m, 2H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 6.4$ Hz, 1H), 7.25 (d, $J = 8.0$ Hz, 2H), 7.17 (s, 1H), 7.11 (d, $J = 8.4$ Hz, 2H), 7.05 (d, $J = 8.4$ Hz, 2H), 5.35 (d, $J = 6.8$ Hz, 1H), 2.35 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) (δ , ppm): 181.3, 141.0, 136.8, 136.7, 135.2, 131.8, 130.2, 129.5, 128.9, 128.7, 128.6,

122.1, 91.5, 89.5, 21.2, 21.1; IR (KBr, ν , cm^{-1}) 3726, 3411, 3153, 1514, 1436, 1323, 1214, 1091, 1049, 821, 750, 669; HRMS (APCI): m/z calcd for $\text{C}_{23}\text{H}_{21}\text{BrN}_2\text{NaO}_2\text{S}$, 491.0405 $[\text{M}+\text{Na}]^+$, found: 491.0417.

4-(4-Bromophenyl)-4,5-dihydroxy-1-phenyl-3-(*p*-tolyl)imidazolidine-2-thione (4o)

White solid, mp 174-175 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) (δ , ppm): 7.61-7.56 (m, 3H), 7.50-7.40 (m, 5H), 7.36-7.29 (m, 1H), 7.27-7.18 (m, 4H), 7.13 (d, $J = 8.4$ Hz, 1H), 7.06 (d, $J = 8.0$ Hz, 1H), 5.43 (d, $J = 6.8$ Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) (δ , ppm): 181.2, 140.9, 139.4, 136.9, 135.1, 131.8, 130.2, 129.5, 128.9, 128.8, 128.6, 128.4, 122.1, 91.6, 89.5, 21.1; IR (KBr, ν , cm^{-1}) 3406, 3161, 1590, 1499, 1444, 1398, 1323, 1089, 1052, 831, 706; HRMS (APCI): m/z calcd for $\text{C}_{22}\text{H}_{19}\text{BrN}_2\text{NaO}_2\text{S}$, 477.0248 $[\text{M}+\text{Na}]^+$, found: 477.0241.

1-(4-Bromophenyl)-4,5-dihydroxy-3-(4-methoxyphenyl)-4-(*p*-tolyl)imidazolidine-2-thione (4p)

A white solid, mp 162-163 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) (δ , ppm): 7.50-7.39 (m, 6H), 7.29 (d, $J = 6.4$ Hz, 1H), 7.22-7.20 (m, 4H), 7.12-7.07 (m, 1H), 7.05-6.99 (m, 2H), 5.26 (d, $J = 6.4$ Hz, 1H), 3.79 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) (δ , ppm): 181.1, 158.7, 138.3, 137.5, 132.1, 131.8, 131.3, 130.2, 129.5, 128.9, 126.0, 120.3, 114.3, 91.9, 90.0, 55.8, 21.1; IR (KBr, ν , cm^{-1}) 3649, 3124, 1588, 1399, 1322, 1213, 1047, 968, 702; HRMS (APCI): m/z calcd for $\text{C}_{23}\text{H}_{21}\text{BrN}_2\text{NaO}_3\text{S}$, 485.0535 $[\text{M}+\text{Na}]^+$, found: 485.0547.

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17. Crystal data for **4I** (CCDC 1845594): C₂₂H₂₀N₂O₂S, Monoclinic, space group P2(1), $a = 7.3487(7)$ Å, $b = 13.0372(11)$ Å, $c = 10.3704(9)$ Å, $\alpha = \gamma = 90^\circ$, $\beta = 106.874(3)^\circ$, $V = 950.77(15)$ Å³, $M_r = 376.46$, $Z = 2$, $D_c = 1.315$ Mg/m³, $\lambda = 0.71073$ Å, $\mu(\text{Mo K}\alpha) = 0.190$ mm⁻¹, $F(000) = 396$, $R = 0.0416$, $wR_2 = 0.0974$, largest diff. Peak and hole: 0.205 and -0.132 e/Å³.