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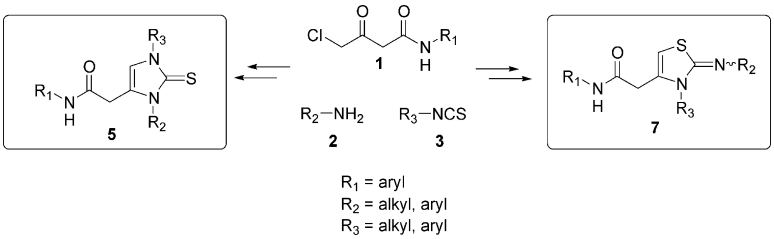

R_1 = aryl
R_2 = alkyl, aryl
R_3 = alkyl, aryl

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Syntheses of 1,3-Imidazoline-2-thione and 2-Phenylimino-1,3-thiazoline Combinatorial Libraries through Different Sequences of the Same Components

Suyeal Bae, Hoh-Gyu Hahn,* and Kee Dal Nam

Organic Chemistry Laboratory, Korea Institute of Science and Technology, Seoul 136-791, Korea

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We have developed combinatorial libraries of new 1,3-imidazoline-2-thiones **5** and 2-phenylimino-1,3-thiazolines **7** by way of different reaction sequences of the same three components, γ-chloroacetoacetanilides **1**, amines **2**, and isothiocyanates **3** in a parallel synthetic fashion. One of the building blocks, the γ-chloroacetoacetanilides **1**, was prepared by the sequential reaction of 4-methylene-oxetan-2-one (ketene dimer) with chlorine and various anilines. The condensation of **1** with amines gave dihydrofuran **4** intermediates that when reacted with **3** afforded the 1,3-imidazoline-2-thiones **5**. On the other hand, reaction of **3** with **2** provided substituted thioureas **6** that were reacted with **1** to yield 2-phenylimino-1,3-thiazolines **7**.

Introduction

Combinatorial chemistry serves as a powerful tool in lead discovery and lead optimization by allowing a rapid generation of potential candidates for screening. Introduction of high-throughput biological screening and the accelerated discovery of new biological targets have increased the demand for the preparation of large numbers of compounds. The development of new methods for the synthesis of heterocyclic compound libraries with molecular diversity is an ever-expanding area in combinatorial chemistry.[1] To respond to this demand, some new technologies, including multicomponent reactions[2] and click chemistry[3], have been developed.

γ-Chloroacetoacetanilides **1** are versatile reagents for preparing new heterocyclic compounds due to their three reactive centers. First, the methylene protons are activated by neighboring carbonyl moieties. Second, the amide is an ambident nucleophile by means of the nitrogen and oxygen atoms. Third, the chloride can serve as a good leaving group in nucleophilic displacement. Examples of heterocycles synthesized from γ-chloroacetoacetanilides **1** are pyridopyrimidines,[4] substituted pyridines,[5] quinolones,[6] dihydrothiazoles, pyridin-2-ones,[7] dihydrooxathiins,[8] and oxadiazolyl derivatives.[9] However, examples of combinatorial synthesis using γ-chloroacetoacetanilides **1** are limited. Recently, we reported a solid-phase synthesis of 2-phenylimino-1,3-thiazoline using a fully automated synthesizer for the development of new agrochemical fungicides.[10] In this paper, we report the syntheses of two combinatorial libraries, the 1,3-imidazoline-2-thiones **5** and the 2-phenylimino-1,3-thiazolines **7** by different combinations of the same three components, γ-chloroacetoacetanilides **1**, amines **2**, and isothiocyanates **3**, in a parallel synthetic fashion. A general approach to the two different chemical libraries, 1,3-imidazoline-2-thiones **5** and 2-phenylimino-1,3-thiazolines **7** is illustrated in Scheme 1.

* To whom correspondence should be addressed: Fax: +82-2-9585189. E-mail: hghahn@kist.re.kr.

Results and Discussion

Synthesis of the γ-Chloroacetoacetanilides Building Blocks. Syntheses of the γ-chloroacetoacetanilides **1** building blocks were achieved by the modification of the previously reported methods.[11] Hard and Abernethy reported a synthesis of only one compound, γ -chloroacetoacetanilide, by mixing pure γ-chloroacetoacetyl chloride with an equivalent amount of aniline but failed to mention the yield. We needed to investigate the optimal reaction conditions to produce γ-chloroacetoacetanilide derivatives **1** as building blocks. Dropwise addition of aniline derivatives to a −78 °C solution of γ-chloroacetacetyl chloride (1.1 mol equiv) and Et_3N (1.1 mol equiv) in CH_2Cl_2 yielded the γ-chloroacetoacetanilides (**1**).[12] These products could be isolated as solids by simple

filtration and were used for the subsequent reactions without further purification. Ninety-nine γ-chloroacetoacetanilides **1** were prepared in 5−91% yield (see Supporting Information for yields and melting points). Figure 1 lists the γ-chloroacetoacetanilides **1**{*1*−*34*} used as building blocks in this study. The other building blocks, aliphatic or aromatic amines **2** and isothiocyanates **3** were commercially available (see Figures 2 and 3).

Synthesis of a Combinatorial Library of 1,3-Imidazoline-2-thiones 5. 1,3-Imidazoline-2-thione derivatives have received attention because of their bioactivities and applications in pharmaceutical syntheses.[13,14] Marckwald's method

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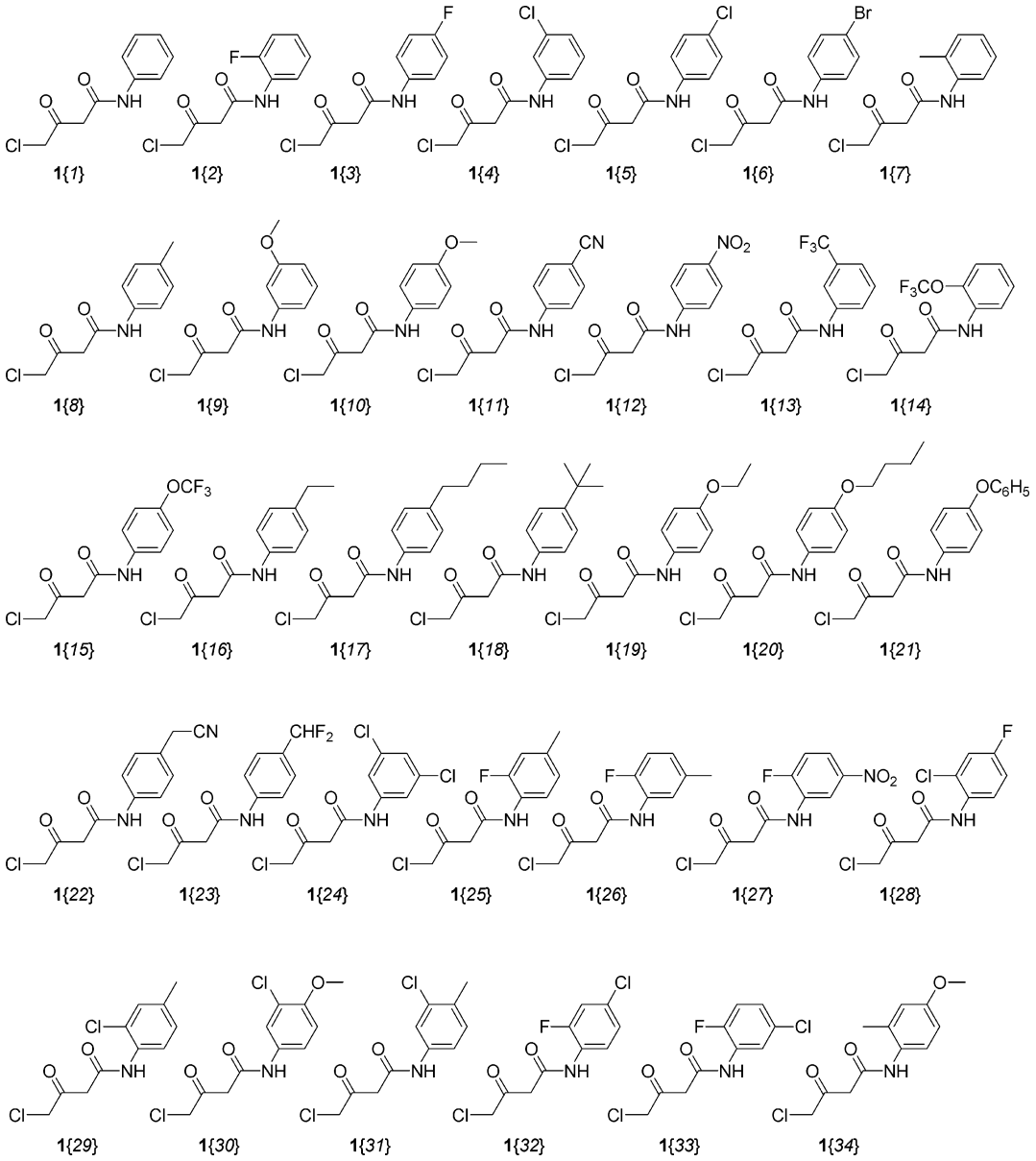
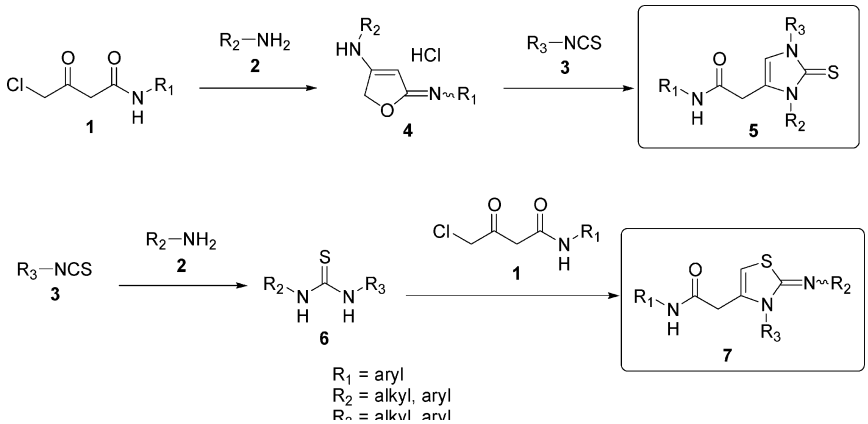


Figure 1. γ-Chloroacetoacetanilides **1**{*1*−*34*} used in the syntheses.

Scheme 1. Approaches to the Two Combinatorial Libraries, 1,3-Imidazoline-2-thiones **5** and 2-Phenylimino-1,3-thiazolines **7**, from the Same Three Components, **1**, **2**, and **3**



has long been known as a general synthetic pathway to 1,3-imidazoline-2-thione by the reaction of isothiocyanate with amino acetal.[15] Modification of this method into a one-pot reaction was reported by Matsuda et al.[13a] Recently, Zeng[16] established the synthesis of substituted imidazoline-2-thiones through cyclization of thiourea with a variety of carbonyl compounds bearing an α-hydrogen in the presence of bromine and triethylamine. Scheme 3 summarizes a synthetic

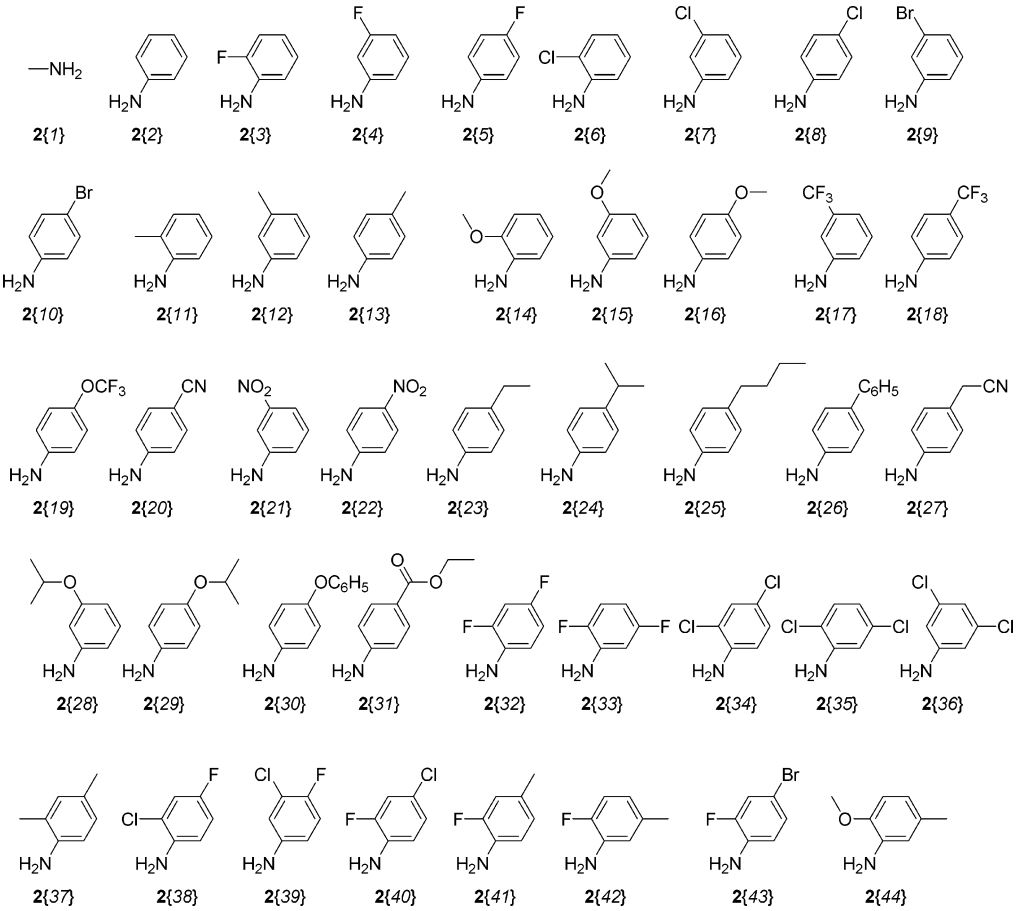


Figure 2. Amines **2**{*1*−*44*} used in the syntheses.

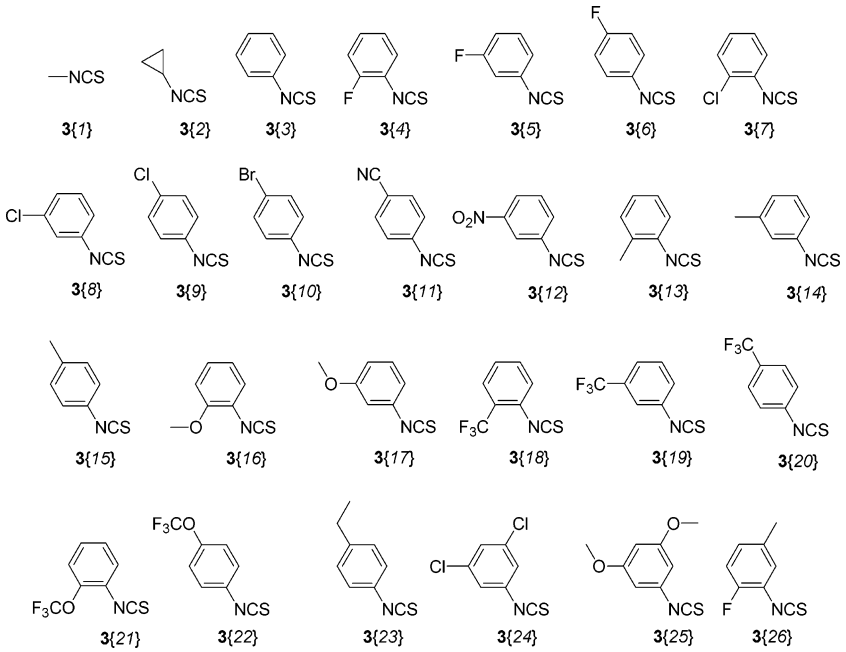
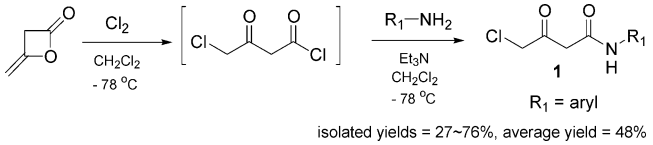


Figure 3. Isothiocyanates **3**{*1*−*26*} used in the syntheses.

route of 1,3-imidazoline-2-thione derivatives **5** by a parallel combinatorial method.

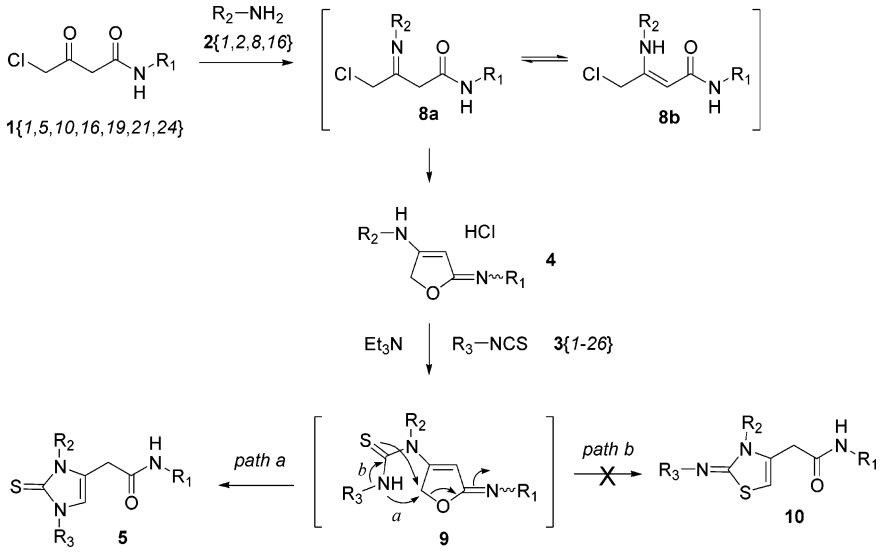
Reactions of γ-chloroacetoacetanilides **1** with primary alkyl or arylamines **2** in ethanol at ambient temperature gave dihydrofurans **4**.[17] In the case of alkylamine, the reaction proceeded smoothly at room temperature, whereas the

Scheme 2. Synthetic Route to the γ-Chloroacetoacetanilides **1** Building Blocks

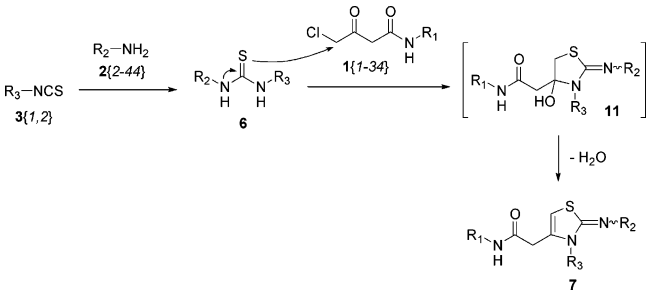


isolated yields = 27~76%, average yield = 48%

Scheme 3. Synthetic Route to a Combinatorial Library of 1,3-Imidazoline-2-thiones **5**



Scheme 4. Synthetic Route to a Combinatorial Library of 2-Phenylimino-1,3-thiazolines **7**



arylamine derivatives required an elevated temperature (refluxing in ethanol) to drive the reaction to completion. Concerning the reaction mechanism, it is most likely that the condensation of **1** with amines **2** takes place initially to afford **8a**, a species in equilibrium with **8b**. Internal nucleophilic attack of the amide oxygen then provides the dihydrofurans **4** as a mixture of *E* and *Z* isomers with respect to the C═N in a ratio of ∼1:1, as determined by ^{1}H NMR spectroscopy. The mixture of two stereoisomers could be isolated by filtration. However, it was not necessary to separate these stereoisomers for the subsequent reaction because both yield the same product, **5**. Treatment of **4** with triethylamine followed by isothiocyanates **3** proceeded smoothly in a few hours in refluxing ethanol, yielding by a simple filtration 1,3-imidazoline-2-thiones **5** in high purity (>91% by LC detected at 220 nm). Opening of the furan ring by internal nucleophilic attack of the thiourea nitrogen yielded a single anilide **5**. The reaction mechanism could be rationalized as shown in Scheme 3. Nucleophilic addition of the secondary amine of the dihydrofurans **4** to isothiocyanates **3** could afford the thioureas **9**, which could undergo further transformation to provide either 2-imino-1,3-thiazolidines **10** (path b) or 1,3-imidazoline-2-thiones **5** (path a), depending on whether nitrogen[16,18] or sulfur[19] of the thiourea moiety acts as the nucleophile. Since the spectral data (e.g., NMR, IR, MS, and elemental analysis) were not conclusive, X-ray crystallographic analysis was conducted to verify product structure. As shown in Figure 4 (3-ethyl analogue

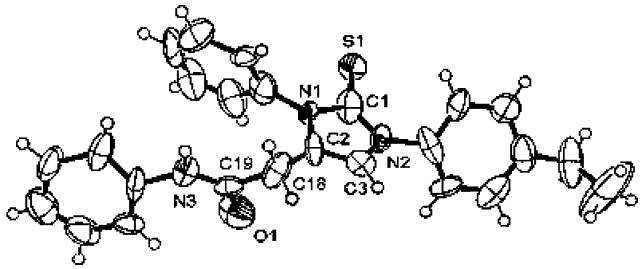


Figure 4. ORTEP plots of 1,3-imidazoline-2-thione **5**{*1,2,23*}.

of **5**), path a prevails to produce 1,3-imidazoline-2-thiones **5**.

One hundred and thirteen compounds **5** were synthesized according to Scheme 3 using a ChemSpeed 2000 automated synthesizer, starting from γ-chloroacetoacetanilides **1** without isolation of intermediates **4**. The overall yields were from 2 to 80%. Figure 5 provides representative structures of the prepared 1,3-imidazoline-2-thiones **5**, and Table 1 lists yields, purities (at 220 nm by HPLC), and MS data.

Synthesis of a Combinatorial Library of 2-Phenylimino-1,3-thiazolines 7. Another chemical library synthesized starting with the same three building blocks used for the synthesis of the 1,3-imidazoline-2-thione **5** library were 2-phenylimino-1,3-thiazoline derivatives **7** (see Scheme 1). Although the preparation of combinatorial libraries is rapidly growing in the pharmaceutical research fields, only a few papers have been reported on its use in the generation of leads for agrochemical purposes.[20] 2-Phenylimino-1,3-thiazolines are known to have selective fungitoxicity against rice blast,[21] and we recently reported a solid-phase synthesis of the analogues of these compounds.[4] For development of analogues with higher biological activities through an optimization of the lead that was selected from preliminary screening against rice blast, we decide to build a combinatorial library of this series for lead optimization of 2-phenylimino-1,3-thiazolines. Compound **7** has three possible sites (R_1, R_2, R_3) for derivatization (Scheme 4).

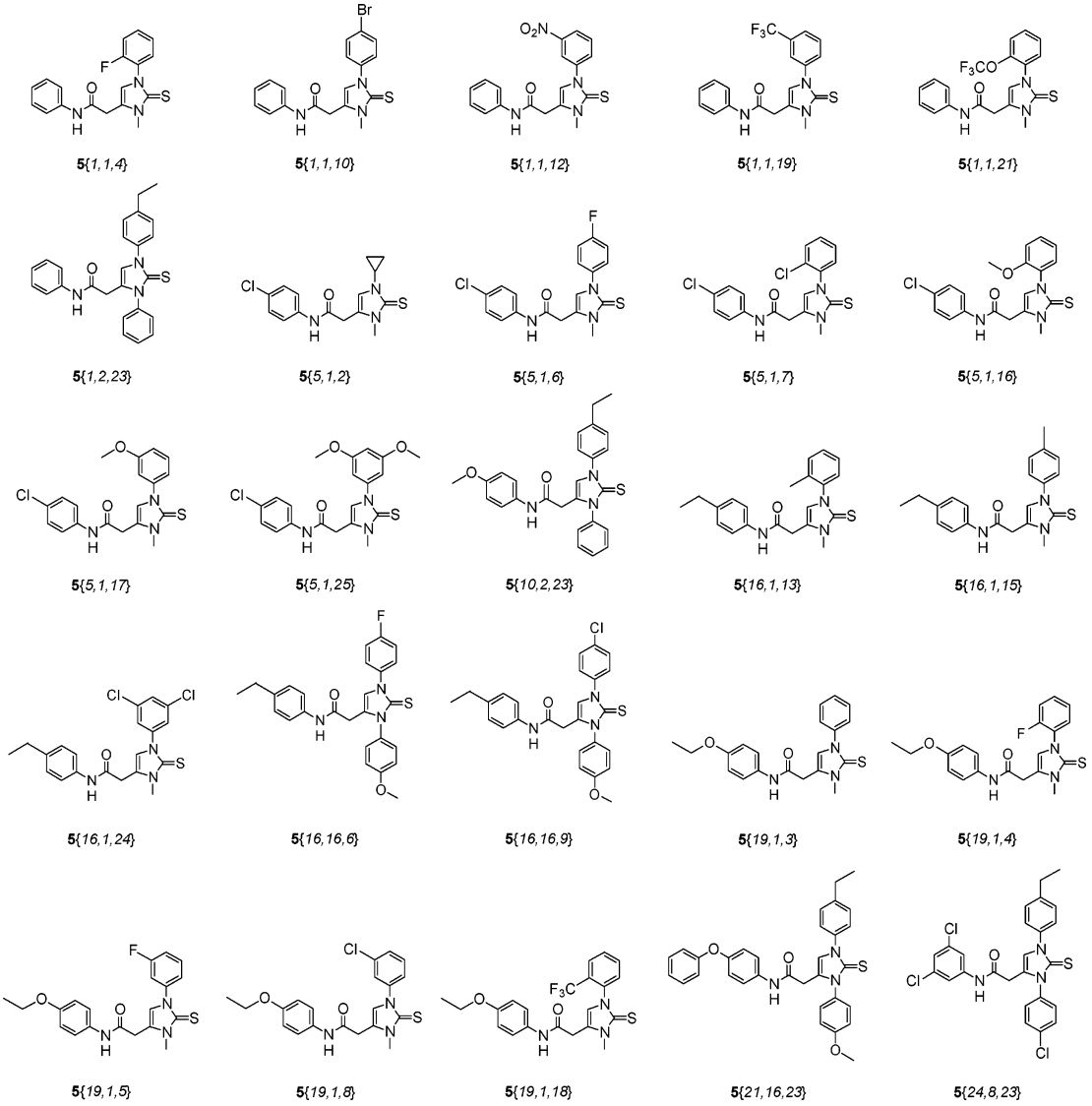


Figure 5. Representative structures of the1,3-imidazoline-2-thiones **5**{R_1,R_2,R_3}.

The construction of a chemical library of these compounds was achieved in a manner similar to that previously reported.[21] As shown in Scheme 4, the reaction of isothiocyanates **3** and anilines **2** in ethanol at room temperature provided thioureas **7**. Since the reaction proceeded quantitatively, the reaction mixture as such was treated with γ-chloroacetoacetanilides **1** under reflux to afford 2-phenylimino-1,3-thiazolines **7** in moderate to high yields. Nucleophilic attack of the sulfur of the thiourea **6**, presumably in the iminothiol form, conducted to intermediate **11**. Compounds **11** were unstable and slowly converted to **7** in deuterated chloroform. The reactions proceeded smoothly in 1−3 h after the addition of γ-chloroacetoacetanilides **1**. The desired products were obtained as solids, isolated by filtration from the reaction mixtures, and analyzed by ^{1}H NMR spectroscopy. These solids were the corresponding hydrogen chloride salts of 2-phenylimino-1,3-thiazolines **7**, which could be used directly for the antifungal activity screening. We constructed a library of 600 compounds **7** in this manner using carousel reaction stations in a parallel fashion without isolating intermediates **6** and **11**. The yields ranged from 15 to 99% for the final step. Figure 6 provides representative structures of 2-phenylimino-1,3-thiazolines **7**.

Conclusion

Two chemical libraries, 1,3-imidazoline-2-thiones **5** and 2-phenylimino-1,3-thiazolines **7** were synthesized from the same three building blocks, γ-chloroacetoacetanilides **1**, amines **2**, and isothiocyanates **3**, varying the reaction sequence. The chemical library of 1,3-imidazole-2-thiones **5** were synthesized by the sequential reaction of amines **2**, γ-chloroacetoacetanilides **1** and then isothiocyanates **3** through intermediate dihydrofurans **4**. Another chemical library of 2-phenylimino-1,3-thiazolines **7** was synthesized by the sequential reaction of amines **2**, isothiocyanates **3**, and then γ-chloroacetoacetanilides **1** through thioureas **6**.

Experimental Section

General Information. Melting points (°C) were measured with an Electrothermal IA 9000 series digital melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 300 (300 MHz), Bruker Avance 300 (300 MHz) or Varian 600 (600 MHz)

Table 1. Yield, Purity, and Molecular Mass of Representative 1,3-Imidazoline-2-thiones **5**

entry	compound	yield[a]	purity[b]	MW (found)[c]
1	**5**{*1*,*1*,*4*}	59	100	342 (MH^+)
2	**5**{*1*,*1*,*10*}	20	100	402 (MH^+)
3	**5**{*1*,*1*,*12*}	60	100	369 (MH^+)
4	**5**{*1*,*1*,*19*}	68	100	392 (MH^+)
5	**5**{*1*,*1*,*21*}	50	91	408 (MH^+)
6	**5**{*1*,*2*,*23*}	50	100	414 (MH^+)
7	**5**{*5*,*1*,*2*}	37	100	322 (MH^+)
8	**5**{*5*,*1*,*6*}	39	100	376 (MH^+)
9	**5**{*5*,*1*,*7*}	56	97	392 (MH^+)
10	**5**{*5*,*1*,*16*}	50	94	388 (MH^+)
11	**5**{*5*,*1*,*17*}	43	100	388 (MH^+)
12	**5**{*5*,*1*,*25*}	45	100	418 (MH^+)
13	**5**{*10*,*2*,*23*}	40	100	444 (MH^+)
14	**5**{*16*,*1*,*13*}	64	97	366 (MH^+)
15	**5**{*16*,*1*,*15*}	58	100	366 (MH^+)
16	**5**{*16*,*1*,*24*}	35	100	420 (MH^+)
17	**5**{*16*,*16*,*6*}	71	100	462 (MH^+)
18	**5**{*16*,*16*,*9*}	65	100	478 (MH^+)
19	**5**{*19*,*1*,*3*}	51	100	368 (MH^+)
20	**5**{*19*,*1*,*4*}	59	100	386 (MH^+)
21	**5**{*19*,*1*,*5*}	38	100	386 (MH^+)
22	**5**{*19*,*1*,*8*}	44	100	402 (MH^+)
23	**5**{*19*,*1*,*18*}	22	94	436 (MH^+)
24	**5**{*21*,*16*,*23*}	38	100	536 (MH^+)
25	**5**{*24*,*8*,*23*}	15	94	516 (MH^+)

[a] Yields were calculated on the basis of the weight of the solid obtained by filtration of the reaction mixture. [b] The purity (%) was determined by HPLC chromatography detected at 220 nm. [c] Molecular ion (MH^+) determined by mass spectrometry (ES).

spectrometer using TMS as an internal standard (chemical shifts are in parts per million, and coupling constants (*J*) are in hertz). Fourier transform infrared (FT-IR) analyses were obtained on a Perkin-Elmer 16FC-PC FT-IR and are reported in centimeters^{-1}. HRMS data were obtained on a JMS-700 mass spectrometer. Electrospray mass spectral analysis was obtained on a Micromass Quattro micro spectrometer for the ES-MS analysis by direct injection of the sample solubilized in methanol. Elemental analyses were performed using a Fison EA1108 analyzer. The X-ray data was collected on an Enraf-Nonius CAD4 automated diffractometer equipped with a Mo X-ray tube and a graphite monochromator and solved by SHELXS-86 using full-matrix least-squares techniques.

HPLC analysis was performed on a Zorbax Eclipse XDB-C_8 column (5 μm, 150 mm $\times$ 4.6 mm); linear gradient over 20 min using (A) 0.1% TFA in water and (B) 0.1% TFA in CH_3CN (from 9:1 to 5:5) with a flow rate of 2.0 mL/min and UV absorbance at 220 nm for 1,3-imidazoline-2-thione **5**. In the case of 2-phenylimino-1,3-thiazoline **7**, the linear gradient was changed to A and B (from 8:2 to 3:7).

Preparation of γ-Chloroacetoacetanilides 1 (General Procedure). To a solution of 4-methylene-oxetan-2-one (ketene dimer) (15.4 mL, 0.20 mol) in methylene chloride (100 mL) cooled with ice−salt was added a solution of chlorine (14.2 g, 0.20 mol) dissolved in methylene chloride (4%, v/v). This reaction mixture was then added dropwise to a solution of triethylamine (30.7 mL, 0.22 mol) and aniline **2**{*2*} (18.6 g, 0.20 mol) dissolved in methylene chloride (100 mL) cooled to −78 °C with acetone−dry ice. The reaction mixture was stirred for 2 h at this temperature, and then the cooling bath was removed. To the reaction mixture was added 0.2 N aq HCl (200 mL), and the mixture was stirred for 0.5 h at room temperature. The white precipitate was collected by filtration, washed with water and a small amount of cold ethyl ether, and then dried in air to yield **1**{*1*} (37.0 g, 88%).[12]

Table 2. Yield, Purity, and Molecular Mass of Representative 2-Phenylimino-1,3-thiazolines **7**

entry	compound	yield[a]	purity[b]	MW (found)[c]
1	**7**{*1*,*23*,*1*}	65	100	352 (MH^+)
2	**7**{*3*,*32*,*1*}	81	100	378 (MH^+)
3	**7**{*6*,*2*,*2*}	86	100	428 (MH^+)
4	**7**{*6*,*32*,*2*}	50	100	464 (MH^+)
5	**7**{*22*,*18*,*1*}	69	94	431 (MH^+)
6	**7**{*25*,*24*,*1*}	49	98	398 (MH^+)
7	**7**{*25*,*33*,*1*}	94	100	392 (MH^+)
8	**7**{*25*,*42*,*1*}	88	91	388 (MH^+)
9	**7**{*26*,*4*,*1*}	39	100	374 (MH^+)
10	**7**{*26*,*23*,*1*}	89	96	384 (MH^+)
11	**7**{*26*,*25*,*1*}	93	96	412 (MH^+)
12	**7**{*27*,*20*,*1*}	92	100	412 (MH^+)
13	**7**{*27*,*32*,*1*}	56	96	423 (MH^+)
14	**7**{*28*,*19*,*1*}	65	100	460 (MH^+)
15	**7**{*28*,*41*,*1*}	53	100	408 (MH^+)
16	**7**{*28*,*43*,*1*}	65	97	472 (MH^+)
17	**7**{*29*,*13*,*1*}	73	98	386 (MH^+)
18	**7**{*29*,*39*,*1*}	76	100	424 (MH^+)
19	**7**{*29*,*40*,*1*}	80	97	424 (MH^+)
20	**7**{*30*,*8*,*1*}	76	100	422 (MH^+)
21	**7**{*30*,*27*,*1*}	85	100	427 (MH^+)
22	**7**{*31*,*7*,*1*}	68	100	406 (MH^+)
23	**7**{*31*,*9*,*1*}	63	100	450 (MH^+)
24	**7**{*31*,*11*,*1*}	78	100	386 (MH^+)
25	**7**{*31*,*15*,*1*}	47	99	402 (MH^+)
26	**7**{*31*,*34*,*1*}	65	97	440 (MH^+)
27	**7**{*31*,*35*,*1*}	64	89	440 (MH^+)
28	**7**{*31*,*43*,*1*}	68	100	470 (MH^+)
29	**7**{*32*,*10*,*1*}	84	100	456 (MH^+)
30	**7**{*32*,*31*,*1*}	71	100	448 (MH^+)
31	**7**{*33*,*4*,*1*}	77	95	394 (MH^+)
32	**7**{*33*,*30*,*1*}	69	99	468 (MH^+)
33	**7**{*33*,*39*,*1*}	68	100	428 (MH^+)

[a] Yields were calculated based on the weight of the solid obtained by filtration of the reaction mixture. [b] The purity (%) was determined by HPLC chromatography detected at 220 nm. [c] Molecular ion (MH^+) determined by mass spectrometry (ES).

γ-Chloroacetoacetanilide 1{*1*}. Yield 88%; mp 136−137 °C; ^{1}H NMR (300 MHz, DMSO-d_6): keto/enol = 5.2/1. Keto form: δ 10.13 (s, 1H), 7.59−7.04 (m, 5H), 4.65 (s, 2H), 3.67 (s, 2H). Enol form: δ 13.78 (br, 1H), 10.25 (s, 1H), 7.59−7.04 (m, 5H), 5.55 (s, 1H), 4.30 (s, 2H). FT-IR (KBr) 3290 (NH), 1738 (C=O), 1654 (amide C=O).

2′-Fluoro-γ-chloroacetoacetanilide 1{*2*}. Yield 87%; mp 101−102 °C; ^{1}H NMR (300 MHz, DMSO-d_6): keto/enol = 5.2/1. Keto form: δ 9.95 (s, 1H), 7.98−7.13 (m, 4H), 4.63 (s, 2H), 3.77 (s, 2H). Enol form: δ 13.61 (br, 1H), 10.10 (s, 1H), 7.98−7.13 (m, 4H), 5.71 (s, 1H), 4.28 (s, 2H). FT-IR (KBr) 3318 (NH), 1730 (C=O), 1684 (amide C=O).

4′-Methoxy-γ-chloroacetoacetanilide 1{*10*}. Yield 51%; mp 144−145 °C; ^{1}H NMR (300 MHz, DMSO-d_6): keto/enol = 3.8/1. Keto form: δ 10.01 (s, 1H), 7.51−6.87 (m, 4H), 4.65 (s, 2H), 3.73 (s, 3H), 3.65 (s, 2H). Enol form: δ 13.87 (br, 1H), 10.13 (s, 1H), 7.51−6.87 (m, 4H), 5.50 (s, 1H), 4.28 (s, 2H), 3.73 (s, 3H). FT-IR (KBr) 3298 (NH), 1736 (C=O), 1650 (amide C=O).

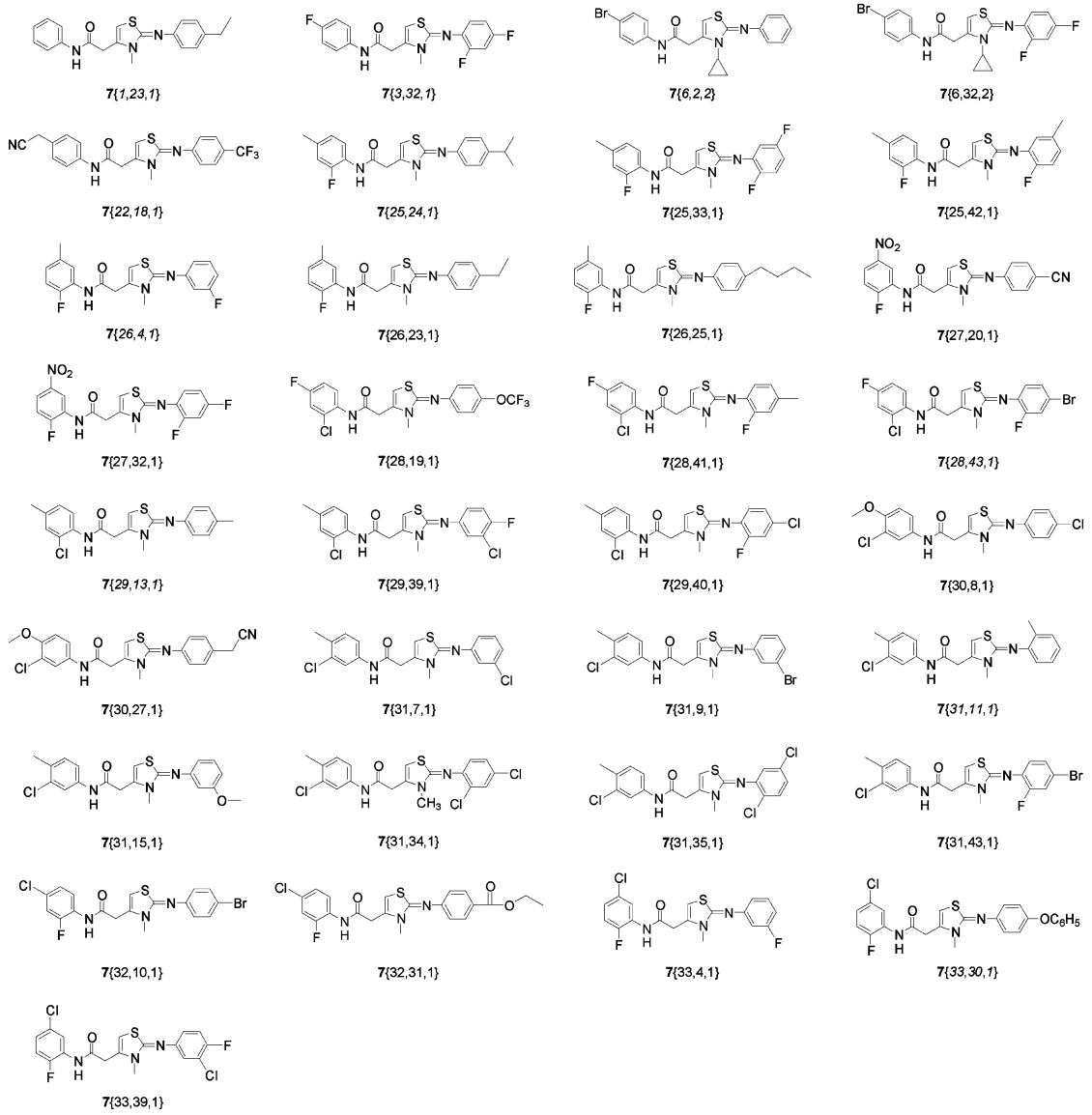


Figure 6. Representative structures of 2-phenylimino-1,3-thiazolines **7**{R_1,R_2,R_3}.

4′-Phenoxy-γ-chloroacetoacetanilide 1{***21***}**.** Yield 91%; mp 122−123 °C; ^{1}H NMR (300 MHz, DMSO-d_6): keto/enol = 4.3/1. Keto form: δ 10.17 (s, 1H), 7.59−6.95 (m, 9H), 4.65 (s, 2H), 3.68 (s, 2H). Enol form: δ 10.28 (s, 1H), 7.59−6.95 (m, 9H), 5.53 (s, 1H), 4.29 (s, 2H). FT-IR (KBr) 3248 (NH), 1736 (C═O), 1656 (amide C═O).

3′-Chloro-4′-methoxy-γ-chloroacetoacetanilide 1{***30***}**.** Yield 77%; mp 112 °C; ^{1}H NMR(300 MHz, DMSO-d_6): keto/enol = 2.7/1. Keto form: δ 10.15 (s, 1H), 7.76−7.10 (m, 3H), 4.65 (s, 2H), 3.82 (s, 3H), 3.66 (s, 2H). Enol form: δ 13.65 (br, 1H), 10.26 (s, 1H), 7.76−7.10 (m, 3H), 5.49 (s, 1H), 4.29 (s, 2H), 3.82 (s, 3H). FT-IR (KBr) 3268 (NH), 1734 (C═O), 1648 (amide C═O).

General Procedure for the Synthesis of 1,3-Imidazoline-2-thione 5. A Chemspeed ASW2000 automated synthesizer was used for the parallel solution-phase synthesis of 1,3-imidazoline-2-thione **5**. γ-Chloroacetoacetanilides **1** (0.5 mmol) and ethanol (4 mL) were placed into a glass reaction vessel (13 mL) and warmed to 40 °C. A solution of amine (0.5 mmol) diluted in ethanol (20%, v/v) was added to the reactor, and the reactor was shaken for 3 h under reflux. After cooling to 40 °C, a solution of isothiocyanate **3** (0.5 mmol) in ethanol (20%, v/v) was added slowly to the reactor. The reactor was shaken for 1 h under reflux and then cooled to room temperature. The reaction mixture was transferred to a Genevac model HT-4 evaporator and concentrated until the volume reached 2 mL. The precipitates were filtered, washed with cold ethyl ether, and then dried in air to afford 1,3-imidazoline-2-thione **5**.

To confirm the structure of **4**, typically the intermediate dihydrofuran **4**{*16,16*} was isolated as follows. A solution of γ-chloroacetoacetanilide **1**{*16*} (2.0 g, 8.34 mmol) and 4-methoxyaniline **2**{*16*} (1.03 g, 8.34 mmol) in ethanol (80 mL) was refluxed for 6 h. After cooling to room temperature, the precipitates were collected by filtration and washed with ethyl ether to give dihydrofuran hydrochloride **4**{*16,16*} (1.29 g, 45%). This was dissolved in methylene chloride and washed with 0.1 N aq NaOH and water and then dried (Na_2SO_4). Evaporation of the solvent afforded a yellow oily residue, which was crystallized from ethyl acetate to yield 5-[4-(ethylphenyl)imino]-3-[(4-methoxyphenyl)amino]-2,5-dihydrofuran (0.69 g, 27%). mp 190−192 °C (dec); ^{1}H NMR

(600 MHz, DMSO-d_6): δ 9.20 (s, 0.5H), 9.13 (s, 0.5H), 7.12 (d, 1H, J = 8.4), 7.05 (d, 1H, J = 7.8), 7.02 (d, 1H, J = 7.8), 6.99 (d, 1H, J = 8.4), 6.93 (app t, $J \sim$ 9.3), 6.88 (d, 1H, J = 8.4), 6.70 (d, 1H, J = 7.8), 5.35 (s, 0.5H), 5.06 (s, 0.5H), 4.95 (s, 1H), 4.91 (s, 1H), 3.73 (s, 1.5H), 3.68 (s, 1.5H), 2.52−2.49 (m, 2H), 1.14 (t, 3H, J = 7.3). ^{13}C NMR (151 MHz, DMSO-d_6) 168.83, 164.26, 158.06, 155.27, 154.71, 154.24, 147.32, 145.02, 136.55, 136.31, 133.57, 132.99, 127.56, 126.93, 122.46, 121.10, 120.10, 119.22, 114.11, 86.48, 79.19, 71.26, 69.07, 54.66, 27.06, 26.93, 15.25, 15.03. FT-IR (KBr) 3418 (NH), 1629 (C═C). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.0; H, 6.5; N, 9.1. Found: C, 73.8; H, 6.5; N, 9.1. HRMS (FAB) calcd for $C_{19}H_{21}N_2O_2$ (MH^+) 309.1603, found 309.4125.

1-(2-Fluorophenyl)-3-methyl-4-[*N*-(phenylcarbamoyl)-methyl]-1,3-imidazoline-2-thione 5{*1,1,4*}. Yield 59%; mp 239 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.26 (s, 1H), 7.60−7.06 (m, 9H), 7.19 (s, 1H), 3.83 (s, 2H), 3.54 (s, 3H). MS(ES): *m*/*z* 342 (MH^+).

1-(4-Bromophenyl)-3-methyl-4-[*N*-(phenylcarbamoyl)-methyl]-1,3-imidazoline-2-thione 5{*1,1,10*}. Yield 20%; mp 236−237 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.23 (s, 1H), 7.72−7.04 (m, 10H), 3.83 (s, 2H), 3.53 (s, 3H). MS-(ES): *m*/*z* 402 (MH^+).

1-(3-Nitrophenyl)-3-methyl-4-[*N*-(phenylcarbamoyl)-methyl]-1,3-imidazoline-2-thione 5{*1,1,12*}. Yield 60%; mp 272 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.77−7.05 (m, 9H), 7.14 (s, 1H), 3.87 (s, 2H), 3.56 (s, 3H). MS(ES): *m*/*z* 369 (MH^+).

3-Methyl-4-[*N*-(phenylcarbamoyl)methyl]-1-(3-trifluoromethylphenyl)-1,3-imidazoline-2-thione 5{*1,1,19*}. Yield 68%; mp 223−225 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.26 (s, 1H), 8.12 (s, 1H), 8.00−7.77 (m, 3H), 7.61 (d, 2H, J = 7.5), 7.42 (s, 1H), 7.36−7.06 (m, 3H), 3.87 (s, 2H), 3.57 (s, 3H). MS(ES): *m*/*z* 392 (MH^+).

3-Methyl-4-[*N*-(phenylcarbamoyl)methyl]-1-(2-trifluoromethoxyphenyl)-1,3-imidazoline-2-thione 5{*1,1,21*}. Yield 50%; mp 176−177 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.25 (s, 1H), 7.67−7.05 (m, 9H), 7.16 (s, 1H), 3.85 (s, 2H), 3.55 (s, 3H). MS(ES): *m*/*z* 408 (MH^+).

1-(4-Ethylphenyl)-4-[*N*-(phenylcarbamoyl)methyl]-3-phenyl-1,3-imidazoline-2-thione 5{*1,2,23*}. Yield 50%; mp 221 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.84 (s, 1H), 7.62−7.23 (m, 15H), 3.53 (s, 2H), 2.68 (q, 2H, J = 7.8), 1.23 (t, 3H, J = 7.8). MS(ES): *m*/*z* 414 (MH^+). HRMS (EI) calcd for $C_{25}H_{23}N_3OS$ (M^+) 413.1562, found 413.1555.

4-[*N*-[(4-Chlorophenyl)carbamoyl]methyl]-1-cyclopropyl-3-methyl-1,3-imidazoline-2-thione 5{*5,1,2*}. Yield 37%; mp 243 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.34 (s, 1H), 7.63−7.38 (m, 4H), 6.88 (s, 1H), 3.74 (s, 2H), 3.47−3.45 (m, 4H), 1.00−0.88 (m, 4H). MS(ES): *m*/*z* 322 (MH^+).

1-(4-Chlorophenyl)-4-[*N*-[(4-chlorophenyl)carbamoyl]-methyl]-3-methyl-1,3-imidazoline-2-thione 5{*5,1,6*}. Yield 39%; mp 294 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.37 (s, 1H), 7.68−7.35 (m, 8H), 7.27 (s, 1H), 3.82 (s, 2H), 3.51 (s, 3H). MS(ES): *m*/*z* 376 (MH^+).

1-(2-Chlorophenyl)-4-[*N*-[(4-chlorophenyl)carbamoyl]-methyl]-3-methyl-1,3-imidazoline-2-thione 5{*5,1,7*}. Yield 56%; mp 250−252 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.39 (s, 1H), 7.65−7.36 (m, 8H), 7.13 (s, 1H), 3.83 (s, 2H), 3.52 (s, 3H). MS(ES): *m*/*z* 392 (MH^+).

4-[*N*-[(4-Chlorophenyl)carbamoyl]methyl]-1-(2-methoxyphenyl)-3-methyl-1,3-imidazoline-2-thione 5{*5,1,16*}. Yield 50%; mp 230−235 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.38 (s, 1H), 7.63−7.04 (m, 8H), 7.00 (s, 1H), 3.81 (s, 2H), 3.76 (s, 3H), 3.51 (s, 3H). MS(ES): *m*/*z* 388 (MH^+).

4-[*N*-[(4-Chlorophenyl)carbamoyl]methyl]-1-(3-methoxyphenyl)-3-methyl-1,3-imidazoline-2-thione 5{*5,1,17*}. Yield 43%; mp 220−221 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.38 (s, 1H), 7.63−6.96 (m, 8H), 7.25 (s, 1H), 3.83 (s, 2H), 3.79 (s, 3H), 3.51 (s, 3H). MS(ES): *m*/*z* 388 (MH^+).

4-[*N*-[(4-Chlorophenyl)carbamoyl]methyl]-1-(3,5-dimethoxyphenyl)-3-methyl-1,3-imidazoline-2-thione 5{*5,1,-25*}. Yield 45%; mp 222−223 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.41 (s, 1H), 7.67−7.38 (m, 4H), 7.28 (s, 1H), 6.85 (d, 2H, J = 2.4), 6.58 (t, 1H, J = 2.4), 3.86 (s, 2H), 3.80 (s, 6H), 3.54 (s, 3H). MS(ES): *m*/*z* 418 (MH^+).

1-(4-Ethylphenyl)-4-[*N*-[(4-methoxyphenyl)carbamoyl]-methyl]-3-phenyl-1,3-imidazoline-2-thione 5{*10,2,23*}. Yield 40%; mp 202−203 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.67 (s, 1H), 7.62−7.28 (m, 12H), 6.85−6.82 (m, 2H), 3.70 (s, 3H), 3.48 (s, 2H), 2.68 (q, 2H, J = 7.8), 1.23 (t, 3H, J = 7.8). MS(ES): *m*/*z* 444 (MH^+).

4-[*N*-[(4-Ethylphenyl)carbamoyl]methyl]-3-methyl-1-(2-methylphenyl)-1,3-imidazoline-2-thione 5{*16,1,13*}. Yield 64%; mp 146−148 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.18 (s, 1H), 7.51−7.13 (m, 8H), 3.79 (s, 2H), 3.53 (s, 3H), 2.56 (q, 2H, J = 7.6), 2.07 (s, 3H), 1.15 (t, 3H, J = 7.6). MS(ES): *m*/*z* 366 (MH^+).

4-[*N*-[(4-Ethylphenyl)carbamoyl]methyl]-3-methyl-1-(4-methylphenyl)-1,3-imidazoline-2-thione 5{*16,1,15*}. Yield 58%; mp 208−209 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.15 (s, 1H), 7.49−7.13 (m, 8H), 7.18 (s, 1H), 3.79 (s, 2H), 3.51 (s, 3H), 2.54 (q, 2H, J = 7.6), 2.35 (s, 3H), 1.15 (t, 3H, J = 7.6). MS(ES): *m*/*z* 366 (MH^+).

1-(3,5-Dichlorophenyl)-4-[*N*-[(4-ethylphenyl)carbamoyl]-methyl]-3-methyl-1,3-imidazoline-2-thione 5{*16,1,24*}. Yield 35%; mp 204−205 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61−7.17 (m, 8H, Ar−H and NH), 6.91 (s, 1H), 3.68 (s, 5H), 2.63 (q, 2H, J = 7.6), 1.25 (t, 3H, J = 7.6). MS(ES): *m*/*z* 421 (MH^+).

4-[*N*-[(4-Ethylphenyl)carbamoyl]methyl]-1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1,3-imidazoline-2-thione 5{*16,16,6*}. Yield 71%; mp 194−196 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.67−6.99 (m, 13H, Ar−H and NH), 6.91 (s, 1H), 3.80 (s, 6H, N−CH_3 and OCH_3), 3.82 (s, 2H), 3.42 (s, 3H), 2.61 (q, 2H, J = 7.6), 1.21 (t, 3H, J = 7.6). MS(ES): *m*/*z* 462 (MH^+).

1-(4-Chlorophenyl)-4-[*N*-[(4-ethylphenyl)carbamoyl]-methyl]-3-(4-methoxyphenyl)-1,3-imidazoline-2-thione 5{*16,16,9*}. Yield 65%; mp 209−210 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.76 (s, 1H), 7.77 (d, 2H, J = 9.0), 7.60 (d, 2H, J = 8.7), 7.43 (s, 1H), 7.32 (d, 1H, J = 8.4), 7.27 (d, 2H, J = 8.7), 7.10 (d, 2H, J = 8.4), 7.01 (d, 2H, J = 9.3), 3.08 (s, 3H), 2.49 (s, 2H), 2.53 (q, 2H, J = 7.8), 1.14 (t, 3H, J = 7.8). MS(ES): *m*/*z* 478 (MH^+).

4-[*N*-[(4-Ethoxyphenyl)carbamoyl]methyl]-3-methyl-1-phenyl-1,3-imidazoline-2-thione 5{*19,1,3*}. Yield 51%; mp

200 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.06 (s, 1H), 7.63−6.86 (m, 9H), 7.24 (s, 1H), 3.97 (q, 2H, J = 6.9), 3.78 (s, 2H), 3.53 (s, 3H), 1.30 (t, 3H, J = 6.9). MS(ES): m/z 368 (MH^+).

4-[*N*-[(4-Ethoxyphenyl)carbamoyl]methyl]-1-(4-fluorophenyl)-3-methyl-1,3-imidazoline-2-thione 5{*19,1,4*}. Yield 59%; mp 211−213 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.10 (s, 1H), 7.53−7.33 (m, 6H), 7.17 (s, 1H), 6.87 (d, 2H, J = 9.0), 3.97 (q, 2H, J = 6.9), 3.78 (s, 2H), 3.53 (s, 3H), 1.30 (t, 3H, J = 6.9). MS(ES): m/z 386 (MH^+).

4-[*N*-[(4-Ethoxyphenyl)carbamoyl]methyl]-1-(3-fluorophenyl)-3-methyl-1,3-imidazoline-2-thione 5{*19,1,5*}. Yield 38%; mp 209−211 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.08 (s, 1H), 7.65−6.85 (m, 8H), 7.29 (s, 1H), 3.99 (q, 2H, J = 6.9), 3.55 (s, 2H), 3.52 (s, 3H), 1.29 (t, 3H, J = 6.9). MS(ES): m/z 386 (MH^+).

1-(3-Chlorophenyl)-4-[*N*-[(4-ethoxyphenyl)carbamoyl]-methyl]-3-methyl-1,3-imidazoline-2-thione 5{*19,1,8*}. Yield 44%; mp 207−208 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.08 (s, 1H), 7.81−6.85 (m, 8H), 7.31 (s, 1H), 3.99 (q, 2H, J = 6.9), 3.78 (s, 2H), 3.52 (s, 3H), 1.29 (t, 3H, J = 6.9). MS(ES): m/z 402 (MH^+).

4-[*N*-[(4-Ethoxyphenyl)carbamoyl]methyl]-3-methyl-1-(2-trifluoromethylphenyl)-1,3-imidazoline-2-thione 5{*19,1,18*}. Yield 22%; mp 148−151 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.08 (s, 1H), 7.92−7.70 (m, 3H), 7.50−7.45 (m, 3H), 7.11 (s, 1H), 6.87 (d, 2H, J = 9.0), 3.97 (q, 2H, J = 6.9), 3.78 (s, 2H), 3.53 (s, 3H), 1.30 (t, 3H, J = 6.9). MS(ES): m/z 436 (MH^+).

1-(4-Ethylphenyl)-3-(4-methoxyphenyl)-4-[*N*-[(4-phenoxyphenyl)carbamoyl]methyl]-1,3-imidazoline-2-thione 5{*21,16,23*}. Yield 38%; mp 148 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.85 (s, 1H), 7.62−6.94 (m, 18H), 3.76 (s, 3H), 3.50 (s, 2H), 2.68 (q, 2H, J = 7.5), 1.23 (t, 3H, J = 7.5). MS(ES): m/z 536 (MH^+).

3-(4-Chlorophenyl)-4-[*N*-[(3,5-dichlorophenyl)carbamoyl]methyl]-1-(4-ethylphenyl)-1,3-imidazoline-2-thione 5{*24,8,23*}. Yield 15%; mp 231−233 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.61−7.36 (m, 12H), 7.27 (s, 1H), 3.58 (s, 2H), 3.96 (q, 2H, J = 7.8), 1.23 (t, 3H, J = 7.8). MS(ES): m/z 516 (MH^+).

General Procedure for the Synthesis of 2-Phenylimino-1,3-thiazoline 7. The parallel solution-phase synthesis of 2-phenylimino-1,3-thiazoline **7** was accomplished using a parallel synthesizer carousel 12-place reaction station (Radleys Discovery Technologies, U.K.). To a solution of isothiocyanate **3** (1.5 mmol) in ethanol (5 mL) was added amine **2** (1.5 mmol), and the mixture was stirred at room temperature for 12 h. To the resulting reaction mixture was added γ-chloroacetoacetanilide **1** (1.5 mmol), and then the misture was heated under reflux for 3 h. The reaction mixture was cooled to room temperature, and the precipitates were filtered, washed with cold ethyl ether, and then dried in air to afford **7**.

2-[(4-Ethylphenyl)imino]-3-methyl-4-[*N*-(phenylcarbamoyl)methyl]-1,3-thiazoline Monohydrochloride 7{*1,23,1*}. Yield 65%; mp 235−236 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.51 (s, 1H), 7.61 (d, 2H, J = 7.5), 7.38−7.31 (m, 6H), 7.11−7.06 (m, 1H), 7.08 (s, 1H), 4.01 (s, 2H), 3.70 (s, 3H), 2.66 (q, 2H, J = 7.8), 1.21 (t, 3H, J = 7.8). MS(ES): m/z 352 (MH^+).

2-[(2,4-Difluorophenyl)imino]-4-[*N*-[(4-fluorophenyl)-carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*3,32,1*}. Yield 81%; mp 220−221 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.46 (s, 1H), 7.65−7.51 (m, 4H), 7.29−7.12 (m, 3H), 3.96 (s, 2H), 3.63 (s, 3H). MS(ES): m/z 378 (MH^+).

4-[*N*-[(4-Bromophenyl)carbamoyl]methyl]-3-cyclopropyl-2-phenylimino-1,3-thiazoline Monohydrochloride 7{*6,2,2*}. Yield 86%; mp 231−236 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.83 (s, 1H), 7.64−7.40 (m, 9H), 6.94 (s, 1H), 4.07 (s, 2H), 3.45 (s, 3H), 3.15 (m, 1H), 1.31−1.24 (m, 4H). MS(ES): m/z 428 (MH^+).

4-[*N*-[(4-Bromophenyl)carbamoyl]methyl]-3-cyclopropyl-2-[(2,4-difluorophenyl)imino]-1,3-thiazoline Monohydrochloride 7{*6,32,2*}. Yield 50%; mp 194−196 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.75−7.26 (m, 7H), 6.96 (s, 1H), 4.10 (s, 2H), 3.18 (m, 1H), 1.31−1.15 (m, 4H). MS(ES): m/z 464 (MH^+).

4-[*N*-[(4-Cyanomethylphenyl)carbamoyl]methyl]-3-methyl-2-[(4-trifluoromethylphenyl)imino]-1,3-thiazoline Monohydrochloride 7{*22,18,1*}. Yield 69%; mp 230−231 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.65 (s, 1H), 7.84 (d, 2H, J = 8.4), 7.67−7.58 (m, 4H), 7.31 (d, 2H, J = 8.4), 3.99 (s, 4H), 3.69 (s, 3H). MS(ES): m/z 431 (MH^+).

4-[*N*-[(2-Fluoro-4-methylphenyl)carbamoyl]methyl]-2-[(4-isopropylphenyl)imino]-3-methyl-1,3-thiazoline Monohydrochloride 7{*25,24,1*}. Yield 49%; mp 200−202 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.67 (t, 1H), 7.42 (m, 4H), 7.13−6.98 (m, 3H), 4.05 (s, 2H), 3.76 (s, 3H), 2.95 (septet, 1H, J = 6.9), 2.29 (s, 3H), 1.23 (d, 6H, J = 6.9). MS(ES): m/z 398 (MH^+).

2-[(2,4-Difluorophenyl)imino]-4-[*N*-[(2-fluoro-4-methylphenyl)carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*25,33,1*}. Yield 94%; mp 121−122 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.13 (s, 1H), 7.69−6.99 (m, 6H), 6.69 (s, 1H), 3.96 (s, 2H), 3.61 (s, 3H), 2.29 (s, 3H). MS(ES): m/z 392 (MH^+).

4-[*N*-[(2-Fluoro-4-methylphenyl)carbamoyl]methyl]-2-[(2-fluoro-5-methylphenyl)imino]-3-methyl-1,3-thiazoline Monohydrochloride 7{*25,42,1*}. Yield 88%; mp 223−225 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.67−6.96 (m, 6H), 6.93 (s, 1H), 4.03 (s, 2H), 3.75 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H). MS(ES): m/z 388 (MH^+).

4-[*N*-[(2-Fluoro-5-methylphenyl)carbamoyl]methyl]-2-[(3-fluorophenyl)imino]-3-methyl-1,3-thiazoline Monohydrochloride 7{*26,4,1*}. Yield 39%; mp 219−221 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.23 (s, 1H), 7.68−6.99 (m, 8H), 4.07 (s, 2H), 3.75 (s, 3H), 2.27 (s, 3H). MS(ES): m/z 374 (MH^+).

2-[(4-Ethylphenyl)imino]-4-[*N*-[(2-fluoro-5-methylphenyl)carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*26,23,1*}. Yield 89%; mp 224−226 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.66−7.00 (m, 7H), 6.97 (s, 1H), 4.06 (s, 2H), 3.77 (s, 3H), 2.65 (q, 2H, J = 7.5), 2.27 (s, 3H), 1.21 (t, 3H, J = 7.6). MS(ES): m/z 384 (MH^+).

2-[(4-Butylphenyl)imino]-4-[*N*-[(2-fluoro-5-methylphenyl)carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*26,25,1*}. Yield 93%; mp 224−225 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.24 (s, 1H), 7.65−6.98 (m, 7H), 6.96 (s, 1H), 4.07 (s, 2H), 3.72 (s, 3H), 2.49 (t, 2H, J = 7.5), 2.26 (s, 3H), 1.56 (m, 2H), 1.30 (m, 2H), 0.90 (t, 3H, J = 7.3). MS(ES): *m*/*z* 412 (MH^+).

2-[(4-Cyanophenyl)imino]-4-[*N*-[(2-fluoro-5-nitrophenyl)carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*27,20,1*}. Yield 92%; mp 239−240 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.02 (s, 1H), 7.89−7.08 (m, 7H), 6.98 (s, 1H), 3.82 (s, 2H), 3.74 (s, 3H). MS(ES): *m*/*z* 412 (MH^+).

2-[(2,4-Difluorophenyl)imino]-4-[*N*-[(2-fluoro-5-nitrophenyl)carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*27,32,1*}. Yield 56%; mp 229−230 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.73 (s, 1H), 8.99−7.24 (m, 6H), 6.84 (s, 1H), 4.10 (s, 2H), 3.67 (s, 3H). MS(ES): *m*/*z* 423 (MH^+).

4-[*N*-[(2-Chloro-4-fluorophenyl)carbamoyl]methyl]-3-methyl-2-[(4-trifluoromethoxyphenyl)imino]-1,3-thiazoline Monohydrochloride 7{*28,19,1*}. Yield 65%; mp 226−227 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.23 (s, 1H), 7.69−7.24 (m, 7H), 7.03 (s, 1H), 4.09 (s, 2H), 3.80 (s, 3H). MS(ES): *m*/*z* 460 (MH^+).

4-[*N*-[(2-Chloro-4-fluorophenyl)carbamoyl]methyl]-2-[(2-fluoro-4-methylphenyl)imino]-3-methyl-1,3-thiazoline Monohydrochloride 7{*28,41,1*}. Yield 53%; mp 184−185 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.20 (s, 1H), 7.70−7.24 (m, 6H), 6.94 (s, 1H), 4.06 (s, 2H), 3.75 (s, 3H), 2.34 (s, 3H), MS(ES): *m*/*z* 408 (MH^+).

2-[(4-Bromo-2-fluorophenyl)imino]-4-[*N*-[(2-chloro-4-fluorophenyl)carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*28,43,1*}. Yield 65%; mp 194−195 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.08 (s, 1H), 7.72−7.22 (m, 6H), 6.64 (s, 1H), 3.95 (s, 2H), 3.57 (s, 3H). MS(ES): *m*/*z* 472 (MH^+).

4-[*N*-[(2-Chloro-4-methylphenyl)carbamoyl]methyl]-3-methyl-2-[(4-methylphenyl)imino]-1,3-thiazoline Monohydrochloride 7{*29,13,1*}. Yield 73%; mp 220−221 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.01 (s, 1H), 7.52 (d, 1H, J = 8.6), 7.40−7.33 (m, 5H), 7.16 (d, 1H, J = 7.5), 6.99 (s, 1H), 4.05 (s, 2H), 3.74 (s, 3H), 2.34 (s, 3H). MS(ES): *m*/*z* 386 (MH^+).

2-[(3-Chloro-4-fluorophenyl)imino]-4-[*N*-[(2-chloro-4-methylphenyl)carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*29,39,1*}. Yield 76%; mp 184−185 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.98 (s, 1H), 7.66−7.15 (m, 6H), 6.73 (s, 1H), 3.98 (s, 2H), 3.64 (s, 3H), 2.31 (s, 3H). MS(ES): *m*/*z* 424 (MH^+).

2-[(4-Chloro-2-fluorophenyl)imino]-4-[*N*-[(2-chloro-4-methylphenyl)carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*29,40,1*}. Yield 80%; mp 202−203 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.98 (s, 1H), 7.75−7.15 (m, 6H), 6.71 (s, 1H), 3.97 (s, 2H), 3.62 (s, 3H), 2.31 (s, 3H). MS(ES): *m*/*z* 424 (MH^+).

4-[*N*-[(3-Chloro-4-methoxyphenyl)carbamoyl]methyl]-2-[(4-chlorophenyl)imino]-3-methyl-1,3-thiazoline Monohydrochloride 7{*30,8,1*}. Yield 76%; mp 212−213 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.45 (s, 1H), 7.88−7.02 (m, 7H), 6.88 (s, 1H), 3.84 (s, 2H), 3.82 (s, 3H), 3.72 (s, 3H). MS(ES): *m*/*z* 422 (MH^+).

4-[*N*-[(3-Chloro-4-methoxyphenyl)carbamoyl]methyl]-2-[[(4-cyanomethyl)phenyl]imino]-3-methyl-1,3-thiazoline Monohydrochloride 7{*30,27,1*}. Yield 85%; mp 249−250 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.65 (s, 1H), 7.83−7.13 (m, 7H), 6.98 (s, 1H), 4.12 (s, 2H), 4.00 (s, 2H), 3.84 (s, 3H), 3.72 (s, 3H). MS(ES): *m*/*z* 427 (MH^+).

4-[*N*-[(3-Chloro-4-methylphenyl)carbamoyl]methyl]-2-[(3-chlorophenyl)imino]-3-methyl-1,3-thiazoline Monohydrochloride 7{*31,7,1*}. Yield 68%; mp 219−220 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.85 (s, 1H), 7.89−7.24 (m, 6H), 6.97 (s, 1H), 4.02 (s, 2H), 3.64 (s, 3H), 2.27 (s, 3H). MS(ES): *m*/*z* 406 (MH^+).

2-[(3-Bromophenyl)imino]-4-[*N*-[(3-chloro-4-methylphenyl)carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*31,9,1*}. Yield 63%; mp 228−230 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.75 (s, 1H), 7.89−7.27 (m, 6H), 6.91 (s, 1H), 3.99 (s, 2H), 3.63 (s, 3H), 2.22 (s, 3H). MS(ES): *m*/*z* 450 (MH^+).

4-[*N*-[(3-Chloro-4-methylphenyl)carbamoyl]methyl]-3-methyl-2-[(2-methylphenyl)imino]-1,3-thiazoline Monohydrochloride 7{*31,11,1*}. Yield 78%; mp 243−245 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.92 (s, 1H), 7.86 (d, 1H, J = 2.1), 7.48−7.38 (m, 5H), 7.30 (d, 1H, J = 8.4), 6.97 (s, 1H), 4.40 (s, 2H), 3.77 (s, 3H), 2.28 (s, 6H). MS(ES): *m*/*z* 386 (MH^+).

4-[*N*-[(3-Chloro-4-methylphenyl)carbamoyl]methyl]-2-[(3-methoxyphenyl)imino]-3-methyl-1,3-thiazoline Monohydrochloride 7{*31,15,1*}. Yield 47%; mp 240−241 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.90 (s, 1H), 7.84−7.08 (m, 6H), 6.99 (s, 1H), 4.08 (s, 2H), 3.84 (s, 3H), 3.74 (s, 3H), 2.27 (s, 3H). MS(ES): *m*/*z* 402 (MH^+).

4-[*N*-[(3-Chloro-4-methylphenyl)carbamoyl]methyl]-2-[(2,4-dichlorophenyl)imino]-3-methyl-1,3-thiazoline Monohydrochloride 7{*31,34,1*}. Yield 65%; mp 226−227 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.70 (s, 1H), 7.89−7.24 (m, 7H), 3.90 (s, 2H), 3.55 (s, 3H), 2.26 (s, 3H). MS(ES): *m*/*z* 440 (MH^+).

4-[*N*-[(3-Chloro-4-methylphenyl)carbamoyl]methyl]-2-[(2,5-dichlorophenyl)imino]-3-methyl-1,3-thiazoline Monohydrochloride 7{*31,35,1*}. Yield 64%; mp 203−206 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.76 (s, 1H), 7.89−7.26 (m, 6H), 6.65 (s, 1H), 3.92 (s, 2H), 3.58 (s, 3H), 2.25 (s, 3H). MS(ES): *m*/*z* 440 (MH^+).

4-[*N*-[(3-Chloro-4-methylphenyl)carbamoyl]methyl]-2-[(2-fluoro-4-bromophenyl)imino]-3-methyl-1,3-thiazoline Monohydrochloride 7{*31,43,1*}. Yield 68%; mp 228−230 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.76 (s, 1H), 7.89−7.27 (m, 6H), 6.73 (s, 1H), 3.93 (s, 2H), 3.60 (s, 3H), 2.21 (s, 3H). MS(ES): *m*/*z* 470 (MH^+).

2-[(4-Butylphenyl)imino]-4-[*N*-[(2-fluoro-4-chlorophenyl)carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*32,10,1*}. Yield 84%; mp 239−240 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.47 (s, 1H), 7.94−7.29 (m, 7H), 7.04 (s, 1H), 4.12 (s, 2H), 3.79 (s, 3H). MS(ES): *m*/*z* 456 (MH^+).

2-[[(4-Ethoxycarbonyl)phenyl]imino]-4-[*N*-[(2-fluoro-4-chlorophenyl)carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*32,31,1*}. Yield 71%; mp 214−215 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.43 (s, 1H), 8.09−7.29 (m, 7H), 7.02 (s, 1H), 4.38−4.31 (q, 2H, J = 7.5), 4.11 (s, 2H), 3.76 (s, 3H), 1.37−1.32 (t, 3H, J = 7.6). MS(ES): *m*/*z* 448 (MH^+).

4-[*N*-[(2-Fluoro-5-chlorophenyl)carbamoyl]methyl]-2-[(3-fluorophenyl)imino]-3-methyl-1,3-thiazoline Monohydrochloride 7{*33,4,1*}. Yield 77%; mp 217−219 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.54 (s, 1H), 8.08−7.23 (m, 7H), 7.04 (s, 1H), 4.13 (s, 2H), 3.78 (s, 3H). MS(ES): *m*/*z* 394 (MH^+).

4-[*N*-[(5-Chloro-2-fluorophenyl)carbamoyl]methyl]-3-methyl-2-[(4-phenoxyphenyl)imino]-1,3-thiazoline Monohydrochloride 7{*33,30,1*}. Yield 69%; mp 212−214 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.51 (s, 1H), 8.06 (dd, 1H, J = 6.9, 2.4), 7.53−6.97 (m, 12H), 4.11 (s, 2H), 3.75 (s, 3H). MS(ES): *m*/*z* 468 (MH^+).

2-[(3-Chloro-4-fluorophenyl)imino]-4-[*N*-[(2-fluoro-5-chlorophenyl)carbamoyl]methyl]-3-methyl-1,3-thiazoline Monohydrochloride 7{*33,39,1*}. Yield 68%; mp 205−207 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.52 (s, 1H), 8.08−7.25 (m, 6H), 6.98 (s, 1H), 4.12 (s, 2H), 3.74 (s, 3H). MS(ES): *m*/*z* 428 (MH^+).

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Supporting Information Available. Characterization data, ^{1}H NMR, and MS spectra for representative compounds. General crystallographic data and tables of bond lengths and angles, positional and thermal parameters for 1,3-imidazoline-2-thione **5**{*1,2,23*} (Tables S2−S6). This material is available free of charge via the Internet at http://pubs.acs.org.

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