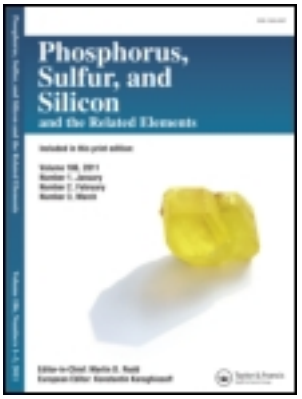

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Reaction of 2-Mercapto-3-Arylpropanoic Acids

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SYNTHESIS AND REACTION OF 2-MERCAPTO-3-ARYLPROPANOIC ACIDS

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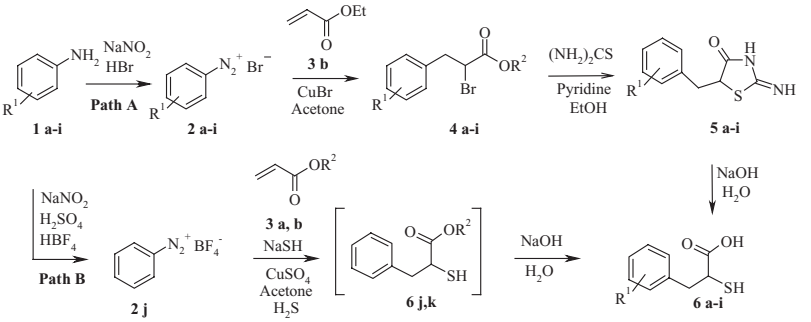
GRAPHICAL ABSTRACT



1, 2, 5, 6: R = H (a), 2-Me (b), 3-Me (c), 2-Cl (d), 3-Cl (e), 4-Br (f), 3-CF_3 (g), 3,4-Me_2 (h), 2,5-Cl_2 (i); R^2 = Me (3a,6j), Et (3b,6k).

Abstract *Two synthetic pathways for the preparation of 2-mercapto-3-arylpropanoic acids were developed. First, by the reaction of arenediazonium bromides with acrylic esters in the presence of CuBr, alkyl (2-bromo-3-aryl)propanoates were formed. Their cyclization with thiourea produced 5-(R-benzyl)-2-imino-4-thiazolidinones, which yielded 3-aryl-2-mercaptopropanoic acids by alkaline hydrolysis. Second, direct Meerwein arylation of acrylates in the presence of S-nucleophile (NaSH) allowed isolation of 3-phenyl-2-mercaptopropanoic acid in 8% yield. Such acids were used for cyclization with cyanoguanidine and phenyl isothiocyanate yielding 1-[5-(R-benzyl)-4-oxo-1,3-thiazolidin-2-ylidene]guanidines and new 5-(R-benzyl)-3-phenyl-2-thioxo-1,3-thiazolidin-4-one (rhodanine) derivatives correspondingly.*

Keywords Mercapto acids; thiazolidinone derivatives; arylation; Meerwein reaction; cyclization; cyanoguanidine

INTRODUCTION

2-Mercapto-3-arylpropanoic acids have been the subjects of great interest due to their application as close precursors of pharmaceutical substances. They are convenient reagents in [2+3]-cyclocondensation for preparation of 4-thiazolidinones, among which

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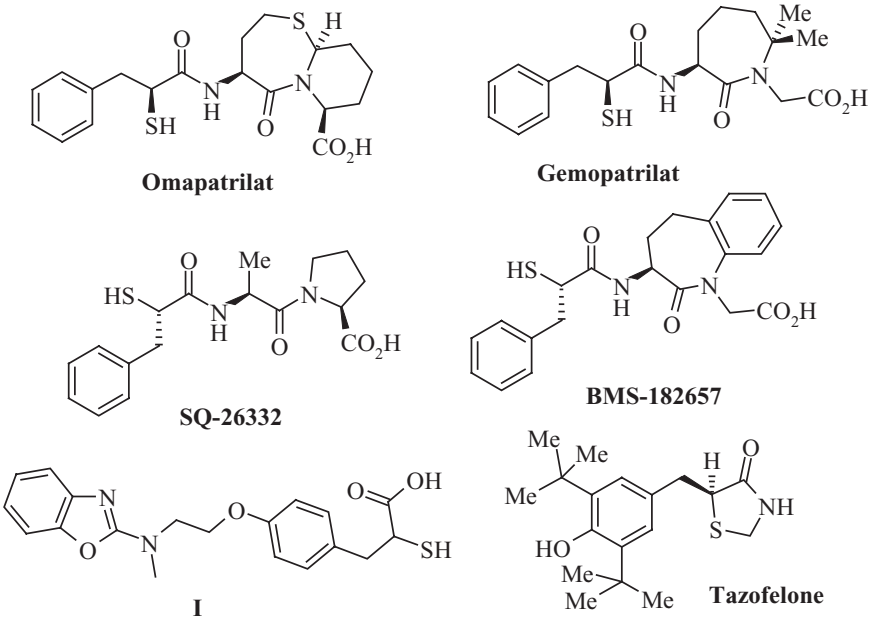
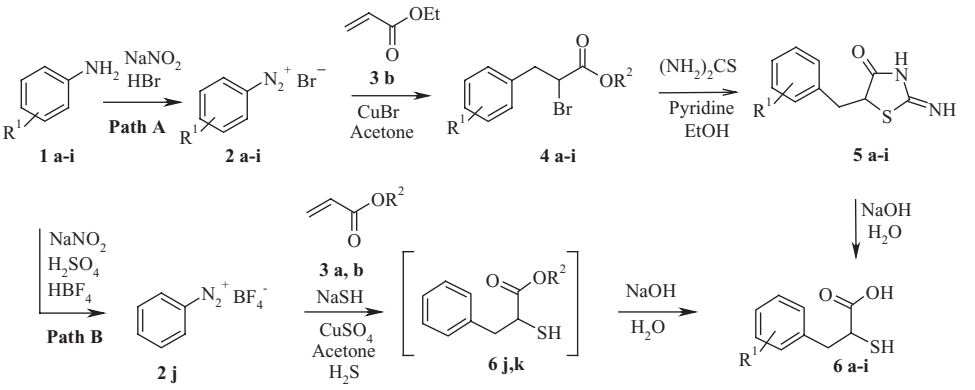


Figure 1 Biologically active compounds containing fragments of 2-mercapto-3-arylpropanoic acids derivatives.

there are many compounds with a broad and potent biological activity.[1] Compounds containing the mercapto moiety often exhibit strong inhibitory effects on metal-containing enzymes. For example, amides of 2-mercapto-3-phenylpropanoic acid *Omapatrilat* and *Gemopatrilat* (Figure 1) were developed as vasopeptidase inhibitors for the treatment of hypertension, congestive heart failure, and renal disease.[2] α-Mercaptoacyl dipeptides SQ-26332 and BMS-182657, shown in Figure 1, were demonstrated to be potent inhibitors of angiotensin converting enzyme (ACE) and neutral endopeptidase.[3] (S)-2-Mercapto-3-phenylpropanoic acid was found as an effective competitive inhibitor of carboxypeptidase A.[4] A number of thioester derivatives of 2-mercapto-3-arylpropanoic acids were shown as competitive inhibitors of IMP-1 metallo-L-lactamase.[5] Furthermore, compound **I** (substituted α-mercapto-β-phenylpropanoic acid) was discovered to be an antihyperglycaemic agent.[6] Consequently, the development of methods of 2-mercapto-3-arylpropanoic acid synthesis is an attractive target for researchers.

2-Mercapto-3-phenylpropanoic acid was first obtained by the sodium amalgam reduction of 3-phenyl-2-thioxo-propanoic acid.[7] Currently, the synthesis of enantioenriched α-mercapto carboxylic acids draws considerable attention.[8] Several synthetic routes for preparation of 2-mercapto-3-arylpropanoic acids have been recently proposed. For instance, optically pure (S)-2-acetylthio-3-phenylpropanoic acid can be prepared in good yield from inexpensive and commercially available L-phenylalanine via diazotization/bromination, chiral inversion, and thioacetate substitution reactions.[9] In addition, synthesis of enantioenriched 4-thiazolidinone (-)-LY213829 (Tazofelone; Figure 1), which is used for the treatment of inflammatory bowel disease, was performed from 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-sulfanylpropanoic acid[10a] or its amide,[10b] prepared by the rhodanine ring opening with 2M NaOH or ammonia correspondingly.



1, 2, 5, 6: R = H (a), 2-Me (b), 3-Me (c), 2-Cl (d), 3-Cl (e), 4-Br (f), 3-CF_3 (g), 3,4-Me_2 (h), 2,5-Cl_2 (i); R^2 = Me (3a,6j), Et (3b,6k).

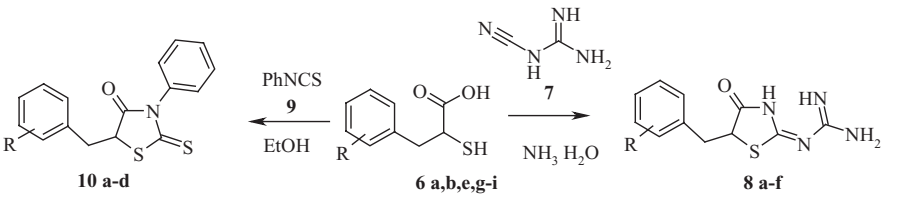
Scheme 1

RESULTS AND DISCUSSION

Herein, we suggest an approach to the synthesis of 2-mercapto-3-arylpropanoic acids *via* the products of Meerwein arylation of acrylates. We selected alkyl 3-aryl-2-bromopropanoates as precursors, which were previously used for preparation of target mercapto acids.[4,5b,8d] We have reported the synthesis of alkyl 3-aryl-2-bromopropanoates **4** by the reaction of arenediazonium bromides **2** with ethyl acrylate in acetone in the presence of CuBr earlier (Scheme 1, Path A).[11] It is noteworthy that Meerwein arylation afforded alkyl 3-aryl-2-bromopropanoates from available anilines **1** in moderate yields (40%–60%) and allowed slight variation of substituents in the aromatic fragment. Furthermore, it was shown that esters **4a–i** reacted with thiourea forming 5-(R^1-benzyl)-2-imino-4-thiazolidinones **5** in high yields,[11] while boiling in ethanol in the presence of pyridine. We also found that the obtained compounds **5a–i** could be readily transformed into the corresponding 2-mercapto-3-arylpropanoic acids **6a–i** *via* opening of the thiazolidine ring by alkaline hydrolyze. Acids were isolated in approximately theoretical yields after the HCl addition.

During the last years, we have focused our research on the development of an efficient methodology to Meerwein arylation of acrylates in the presence of S-nucleophile for the one-step preparation of 2-mercapto-3-arylpropanoic acids from anilines and acrylates (Scheme 1, Path B). Several experimental conditions were tested and finally 2-mercapto-3-phenylpropanoic acid was isolated in 8% yield only. The reason is that a few concurrent reactions occurred. When arenediazonium salts were decomposed in the presence of olefines and sulfur compounds (H_2S, NaSH), aryl radicals reacted more rapidly with S-nucleophile than with the olefine. Newly formed arenesulfanyl radicals led to the formation of arylsulfides and polysulfides. Moreover, the obtained 2-mercapto-3-phenylpropanoic acid, in the reaction of phenyl radical with the acrylic substrate and SH anion, was disposed to oxidation with arenediazonium salts and further radical reactions leading to formation of tarry by-products.

The structure of acids **6** was confirmed by the ^{1}H NMR spectroscopy. As a result of diastereotopic hydrogen atoms in a group CH_2, the fragment of CH_2CH appeared as a spin system of ABX and observed in spectra as three doublet of doublets.



10: R = 4-Br (a), 3-CF_3 (b), 3,4-Me_2 (c), 2,5-Cl_2 (d).

8: R = H (a), 2-Me (b), 3-Cl (c), 3-CF_3 (d), 3,4-Me_2 (e), 2,5-Cl_2 (f).

Scheme 2

The proposed synthetic route of preparation of 2-mercapto-3-arylpropanoic acids in good general yields by a multi-step procedure enables creation of the library of such compounds.

Additionally, two paths of subsequent cyclization of the obtained 2-mercapto-3-arylpropanoic acids were studied. By the reaction of mercapto acids **6a,b,e,g–i** with cyanoguanidine **7** under base catalysis, 1-(5-aryl-4-oxo-1,3-thiazolidin-2-ylidene)guanidines **8a–f** were prepared (Scheme 2). The isolated guanidines **8** were prospective reagents for further modification[12] and attractive from a biological viewpoint.[13] In the ^{1}H NMR spectra, the guanidine fragment was identified by the presence of br.s signals at $\delta = 7.07$ ppm for the hydrogen bonded NH_2 group and $\delta = 8.22$ ppm identified as the C=NH + C(O)NH. Simultaneously, the reactions of 2-mercapto-3-arylpropanoic acids with phenylisothiocyanate were studied. Heating the mixture of compounds **6** and **9** in ethanol under reflux led to formation of the rhodanine ring (**10a–d**, Scheme 2).

CONCLUSION

In conclusion, new synthetic paths for the synthesis of 2-mercapto-3-arylpropanoic acids from simple, cheap, and commercially available anilines and acrylates, which represent a category of versatile synthetic building blocks and potent biologically active substances, were introduced. The prepared mercapto acids were used to synthesize a variety of benzyl substituted 1-[4-oxo-1,3-thiazolidin-2-ylidene]guanidines and rhodanines.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury 400 (400 MHz) and Bruker 500 (500 MHz) instruments. The ^{1}H chemical shifts were reported in parts per million relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run using Agilent 1100 series LC/MSD with an APCI ionization mode. Low-resolution electron impact mass spectra (EIMS) were obtained on a 7683B LC/MS instrument (Agilent Technology), m/z (rel intensity in %); ionization energy 70 eV. The evolution of the reactions and purity of the synthesized compounds were monitored chromatographically on Silufol UV-254 plates.

General Procedure for the Synthesis of 3-aryl-2-sulfanylpropanoic Acids 6a–i

Path A. A solution of $NaNO_2$ (16.6 g, 0.24 mol) in H_2O (30 mL) was added dropwise to a stirred, ice-cooled mixture of the substituted aniline **1** (0.22 mol), aqueous HBr (47%,

95 g, 0.55 mol), and water (30 mL) below 0–5 °C. The cold diazonium salt solution was slowly added to a vigorously stirred solution of CuBr (3 g, 21 mmol) and ethyl acrylate **3b** (22.0 g, 0.22 mol) in acetone (150 mL) at 40 °C. The reaction was exothermic and the dropping rate was adjusted at such a rate that nitrogen was evolved at 2–3 bubbles/sec (0.5–1 h). The resulting homogeneous solution was stirred for 30 min at 40 °C and diluted with H_2O. The organic phase was dried with $MgSO_4$ and concentrated. The residue was purified by distillation under reduced pressure to give ethyl 3-aryl-2-bromopropanoates **4a–i** (40%–60% yield).

The mixture of compounds **4a–i** (4.1 mmol), pyridine (0.32 g, 4.1 mmol), thiourea (0.31 g, 4.1 mmol), and ethanol (15 mL) was refluxed for 20–30 min. After cooling, the crystals were collected by filtration and recrystallized from EtOH/DMF to yield 5-R-benzyl-2-iminothiazolidin-4-ones **5a–i**.

The solution of appropriate compound **5** (10 mmol) dissolved in 50% aqueous NaOH/EtOH (1:1, 20 mL) was heated under reflux until the starting compound **5** was completely consumed as indicated by reversed phase HPLC. The EtOH was removed in vacuo; then the residue was diluted in water (10 mL), cooled to 0 °C, and acidified using conc. HCl (pH ≈ 2). The solid was filtered, dried, and recrystallized from petroleum ether to give acids **6a–i**.

Path B. To the solution of aniline (1.84 g, 20 mmol) in H_2O (5 mL) and HBF_4 (50% solution in Et_2O, 5 mL) at 0 °C, the solution of sodium nitrite (1.4 g, 20 mmol) in H_2O (5 mL) was added dropwise. The resulting heterogeneous mixture was stirred for 30 min at 0 °C, filtered, and washed with cold EtOH (5 mL) and Et_2O (3 × 10 mL). The diazonium salt and freshly prepared NaSH (1.51 g, 27 mmol) were subsequently slowly added to a vigorously stirred solution of $CuSO_4$ (0.3 g, 2.1 mmol) and methyl/ethyl acrylate **3a,b** (22 mmol) in acetone (50 mL) at room temperature. The reaction was exothermic and the dropping rate was adjusted at such a rate that nitrogen was evolved at 2–3 bubbles/sec (0.5–1 h). The resulting homogeneous solution was stirred for 30 min at 40 °C and diluted with H_2O. The organic phase was separated and heated with 40% aqueous NaOH for 1 h. The water fraction was separated, acidified, and extracted with CH_2Cl_2. The crude product was concentrated under reduced pressure and purified by flash chromatography (15% EtOAc-petroleum ether) to give the target product **6a** in 8% yield.

3-Phenyl-2-sulfanylpropanoic acid (6a). This compound was isolated as a white powdered solid, mp 49–50 °C (light petroleum; Ref.[7] mp 49–50 °C) in 95% yield. ^{1}H NMR ppm: δ 2.17 (d, J = 8.8 Hz, 1H, SH), 3.01 (dd, J = 13.7, 6.8 Hz, 1H, CH_2), 3.25 (dd, J = 13.7, 8.8 Hz, 1H, CH_2), 3.62 (m, 1H, CH), 7.19–7.33 (m, 5H, H_{Ph}), 10.55 (br.s, 1H, COOH). MS m/z: 182 (M^+). Anal. requires for $C_9H_{10}O_2S$ (182.24) calcd./found: C, 59.32/59.70; H, 5.53/5.84; S, 17.59/17.11.

3-(2-Methylphenyl)-2-sulfanylpropanoic acid (6b). This compound was isolated as a white powdered solid, mp 79–80 °C (light petroleum) in 93% yield. ^{1}H NMR ppm: δ 2.32 (s, 3H, CH_3), 2.77 (d, J = 8.6 Hz, 1H, SH), 2.89 (dd, J = 13.6, 6.8 Hz, 1H, CH_2), 3.16 (dd, J = 13.6, 7.8 Hz, 1H, CH_2), 3.51 (m, 1H, CH), 7.07–7.15 (m, 4H, H_{Ar}), 12.54 (br.s, 1H, COOH). MS m/z: 196 (M^+). Anal. requires for $C_{10}H_{12}O_2S$ (196.27) calcd./found: C, 61.20/61.13; H, 6.16/5.81; S, 16.34/16.06.

3-(3-Methylphenyl)-2-sulfanylpropanoic acid (6c). This compound was isolated as a white powdered solid, mp 75–76 °C (light petroleum) in 95% yield. ^{1}H NMR ppm: δ 2.30 (s, 3H, CH_3), 2.67 (d, J = 8.8 Hz, 1H, SH), 2.84 (dd, J = 13.7, 6.8 Hz, 1H, CH_2), 3.10 (dd, J = 13.7, 7.8 Hz, 1H, CH_2), 3.50 (m, CH), 6.96–7.03 (m, 3H, H_{Ar}), 7.14 (t, J = 7.5 Hz, 1H, H_{Ar}-5), 12.52 (br.s, 1H, COOH). MS m/z: 196 (M^+). Anal.

requires for $C_{10}H_{12}O_2S$ (196.27) calcd./found: C, 61.20/60.82; H, 6.16/6.46; S, 16.34/16.68.

3-(2-Chlorophenyl)-2-sulfanylpropanoic acid (6d). This compound was isolated as a white powdered solid, mp 103–104 °C (light petroleum) in 95% yield. ^{1}H NMR ppm: δ 2.85 (d, $J = 8.8$ Hz, 1H, SH), 3.02 (dd, $J = 13.7$, 6.8 Hz, 1H, CH_2), 3.25 (dd, $J = 14.0$, 8.2 Hz, 1H, CH_2), 3.58 (m, 1H, CH), 7.21–7.26 (m, 2H, H_{Ar}-4,5), 7.29–7.33 (m, 1H, H_{Ar}-6), 7.35–7.39 (m, 1H, H_{Ar}-3), 12.50 (br.s, 1H, COOH). MS m/z: 216 (M^+). Anal. requires for $C_9H_9ClO_2S$ (216.68) calcd./found: C, 49.89/49.62; H, 4.19/4.47; S, 14.80/14.61.

3-(3-Chlorophenyl)-2-sulfanylpropanoic acid (6e). This compound was isolated as a white powdered solid, mp 73–74 °C (light petroleum) in 93% yield. ^{1}H NMR ppm: δ 2.78 (d, $J = 8.9$ Hz, 1H, SH), 2.90 (dd, $J = 13.8$, 6.9 Hz, 1H, CH_2), 3.13 (dd, $J = 13.8$, 8.4 Hz, 1H, CH_2), 3.56 (m, 1H, CH), 7.18 (t, $J = 7.2$ Hz, 1H, H_{Ar}-5), 7.21 (d, $J = 6.81$ Hz, 1H, H_{Ar}-6), 7.25–7.30 (m, 2H, H_{Ar}-2,4), 12.62 (br.s, 1H, COOH). MS m/z: 216 (M^+). Anal. requires for $C_9H_9ClO_2S$ (216.68) calcd./found: C, 49.89/50.17; H, 4.19/3.90; S, 14.80/14.70.

3-(4-Bromophenyl)-2-sulfanylpropanoic acid (6f). This compound was isolated as a white powdered solid, mp 98–99 °C (light petroleum) in 96% yield. ^{1}H NMR ppm: δ 2.77 (d, $J = 9.0$ Hz, 1H, SH), 2.88 (dd, $J = 14.0$, 7.0 Hz, 1H, CH_2), 3.10 (dd, $J = 14.0$, 8.9 Hz, 1H, CH_2), 3.58 (dd, $J = 14.6$, 8.5 Hz, 1H, CH), 7.02 (d, 2H, $J = 8.4$ Hz, H_{Ar}-2,6), 7.24 (d, 2H, $J = 8.4$ Hz, H_{Ar}-3,5). MS m/z: 260, 262 (M^+). Anal. requires for $C_9H_9BrO_2S$ (261.14) calcd./found: C, 41.40/41.18; H, 3.47/3.26; S, 12.28/12.36.

2-Sulfanyl-3-[3-(trifluoromethyl)phenyl]propanoic acid (6g). This compound was isolated as an oil, bp 172 °C/5 mm Hg in 92% yield. ^{1}H NMR ppm: δ 2.72 (d, $J = 8.9$ Hz, 1H, SH), 2.84 (dd, $J = 13.9$, 7.0 Hz, 1H, CH_2), 3.17 (dd, $J = 14.0$, 8.5 Hz, 1H, CH_2), 3.74 (dd, $J = 15.6$, 8.5 Hz, 1H, CH), 7.38–7.49 (m, 4H, H_{Ar}). MS m/z: 250 (M^+). Anal. requires for $C_{10}H_9F_3O_2S$ (250.24) calcd./found: C, 48.00/48.29; H, 3.63/3.37; S, 12.81/13.10.

3-(3,4-Dimethylphenyl)-2-sulfanylpropanoic acid (6h). This compound was isolated as a white powdered solid, mp 83–84 °C (light petroleum) in 94% yield. ^{1}H NMR ppm: δ 2.21 (s, 6H, CH_3), 2.67 (d, $J = 8.7$ Hz, 1H, SH), 2.87 (dd, $J = 13.7$, 6.7 Hz, 1H, CH_2), 3.12 (dd, $J = 13.7$, 8.5 Hz, 1H, CH_2), 3.50 (dd, $J = 15.4$, 8.5 Hz, CH), 6.90 (d, $J = 7.8$ Hz, 1H, H_{Ar}-5), 6.95 (s, 1H, H_{Ar}-2), 6.97 (d, $J = 7.8$ Hz, 1H, H_{Ar}-6). MS m/z: 210 (M^+). Anal. requires for $C_{11}H_{14}O_2S$ (210.29) calcd./found: C, 62.83/62.57; H, 6.71/7.05; S, 15.25/15.03.

3-(2,5-Dichlorophenyl)-2-sulfanylpropanoic acid (6i). This compound was isolated as a white powdered solid, mp 116–117 °C (light petroleum) in 95% yield. ^{1}H NMR ppm: δ 2.82 (d, $J = 9.2$ Hz, 1H, SH), 2.95 (dd, $J = 14.2$, 7.0 Hz, 1H, CH_2), 3.19 (dd, $J = 14.2$, 8.4 Hz, 1H, CH_2), 3.59 (dd, $J = 15.6$, 8.4 Hz, 1H, CH), 7.18–7.36 (m, 3H, H_{Ar}). MS m/z: 250, 252 (M^+). Anal. requires for $C_9H_8Cl_2O_2S$ (251.13) calcd./found: C, 43.05/43.30; H, 3.21/3.43; S, 12.77/12.60.

General Procedure for the Synthesis of 1-[5-(R-benzyl)-4-oxo-1, 3-thiazolidin-2-ylidene]guanidines 8a–f

The mixture of appropriate 3-aryl-2-sulfanylpropanoic acid **6** (10 mmol), cyanoguanidine (0.84 g, 10 mmol), and a few drops of conc. NH_3 aqueous solution was dissolved in ethanol, heated under reflux for 2 h, and cooled to room temperature. The precipitate was filtered and successively washed with H_2O (30 mL) and petroleum ether. The crude product was purified by recrystallization (EtOH) to give pure compounds **8.**

1-[5-Benzyl-4-oxo-1,3-thiazolidin-2-ylidene]guanidine (8a). This compound was isolated as a white powdered solid, mp 203–204 °C (ethanol) in 70% yield. ^{1}H NMR ppm: δ 2.80 (dd, J = 14.0, 10.4 Hz, 1H, CH_2), 3.44 (dd, J = 14.0, 3.7 Hz, 1H, CH_2), 4.23 (dd, J = 10.4, 3.7 Hz, 1H, CH), 7.09 (br.s, 2H, NH_2), 7.18–7.30 (m, 5H, Ph), 8.21 (br.s, 2H, C=NH + C(O)NH). MS m/z: 248 (M^+). Anal. requires for $C_{11}H_{12}N_4OS$ (248.30) calcd./found: C, 53.21/53.56; H, 4.87/4.68; N, 22.56/22.44.

1-[5-(2-Methylbenzyl)-4-oxo-1,3-thiazolidin-2-ylidene]guanidine (8b). This compound was isolated as a white powdered solid, mp 251–252 °C (ethanol) in 63% yield. ^{1}H NMR ppm: δ 2.33 (s, 3H, CH_3), 2.73 (dd, J = 14.3, 11.3 Hz, 1H, CH_2), 3.50 (dd, J = 14.3, 3.4 Hz, 1H, CH_2), 4.20 (dd, J = 11.3, 3.4 Hz, 1H, CH), 7.08–7.16 (m, 6H, H_{Ar}+NH_2), 8.23 (br.s, 2H, C=NH + C(O)NH). MS m/z: 262 (M^+). Anal. requires for $C_{12}H_{14}N_4OS$ (262.33) calcd./found: C, 54.94/54.72; H, 5.38/5.21; N, 21.36/21.53.

1-[5-(3-Chlorobenzyl)-4-oxo-1,3-thiazolidin-2-ylidene]guanidine (8c). This compound was isolated as a white powdered solid, mp 237–238 °C (ethanol) in 62% yield. ^{1}H NMR ppm: δ 2.85 (dd, J = 14.0, 10.0 Hz, 1H, CH_2), 3.40 (dd, J = 14.0, 4.0 Hz, 1H, CH_2), 4.31 (dd, J = 9.7, 3.7 Hz, 1H, CH), 7.16–7.30 (m, 6H, H_{Ar}+NH_2), 8.20 (br.s, 2H, C=NH + C(O)NH). MS m/z: 282 (M^+). Anal. requires for $C_{11}H_{11}ClN_4OS$ (282.75) calcd./found: C, 46.73/46.54; H, 3.92/4.09; N, 19.82/19.67.

1-{4-Oxo-5-[3-(trifluoromethyl)benzyl]-1,3-thiazolidin-2-ylidene}guanidine (8d). This compound was isolated as a white powdered solid, mp 196–197 °C (ethanol) in 67% yield. ^{1}H NMR ppm: δ 2.95 (dd, J = 14.0, 9.8 Hz, 1H, CH_2), 3.49 (dd, J = 14.0, 3.9 Hz, 1H, CH_2), 4.22 (dd, J = 9.8, 4.0 Hz, 1H, CH), 7.07 (br.s, 2H, NH_2), 7.44–7.51 (m, 4H, H_{Ar}), 8.16 (br.s, 2H, C=NH + C(O)NH). MS m/z: 316 (M^+). Anal. requires for $C_{12}H_{11}F_3N_4OS$ (316.30) calcd./found: C, 45.57/45.77; H, 3.51/3.34; N, 17.71/17.90.

1-[5-(3,4-Dimethylbenzyl)-4-oxo-1,3-thiazolidin-2-ylidene]guanidine (8e). This compound was isolated as a white powdered solid, mp 240–241 °C (ethanol) in 72% yield. ^{1}H NMR ppm: δ 2.20 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.67 (dd, J = 13.9, 10.9 Hz, 1H, CH_2), 3.39 (dd, J = 14.0, 3.5 Hz, 1H, CH_2), 4.09 (dd, J = 10.8, 3.6 Hz, 1H, CH), 6.90 (d, J = 7.7 Hz, 1H, H_{Ar}-5), 6.95 (s, 1H, H_{Ar}-2), 6.97 (d, J = 7.9 Hz, 1H, H_{Ar}-6), 7.04 (br.s, 2H, NH_2), 8.19 (br.s, 2H, C=NH + C(O)NH). MS m/z: 276 (M^+). Anal. requires for $C_{13}H_{16}N_4OS$ (276.36) calcd./found: C, 56.50/56.33; H, 5.84/5.67; N, 20.27/20.45.

1-[5-(2,5-Dichlorobenzyl)-4-oxo-1,3-thiazolidin-2-ylidene]guanidine (8f). This compound was isolated as a white powdered solid, mp 261–262 °C (ethanol) in 71% yield. ^{1}H NMR ppm: δ 2.85 (dd, J = 14.0, 11.0 Hz, 1H, CH_2), 3.67 (dd, J = 14.0, 3.5 Hz, 1H, CH_2), 4.26 (dd, J = 11.0, 3.6 Hz, 1H, CH), 6.96–7.38 (m, 5H, H_{Ar}+NH_2), 8.24 (br.s, 2H, C=NH + C(O)NH). MS m/z: 316, 318 (M^+). Anal. requires for $C_{11}H_{10}Cl_2N_4OS$ (317.19) calcd./found: C, 41.65/41.78; H, 3.18/3.03; N, 17.66/17.43.

General Procedure for the Synthesis of 5-(R-benzyl)-3-phenyl-2-thioxo-1,3-thiazolidin-4-ones (9a–d)

The mixture of appropriate 3-aryl-2-sulfanylpropanoic acid **6** (10 mmol) and phenylisothiocyanate (1.35 g, 10 mmol) was heated under reflux for 12 h. Then the mixture was cooled and H_2O was added dropwise until the solid started to precipitate. The product was filtered and purified by recrystallization from diluted EtOH.

5-(4-Bromobenzyl)-3-phenyl-2-thioxo-1,3-thiazolidin-4-one (9a). This compound was isolated as light yellow crystals, mp 148–149 °C (ethanol) in 84% yield. ^{1}H NMR ppm: δ 3.27 (dd, J = 14.2, 9.2 Hz, 1H, CH_2), 3.45 (dd, J = 14.2, 5.2 Hz, 1H, CH_2),

4.96 (dd, J = 9.2, 5.2 Hz, 1H, CH), 7.04 (d, 2H, J = 8.4 Hz, H_{Ar}-2,6), 7.27 (d, 2H, J = 8.4 Hz, H_{Ar}-3,5), 7.40–7.54 (m, 5H, Ph). MS m/z: 377, 379 (M^+). Anal. requires for $C_{16}H_{12}BrNOS_2$ (378.31) calcd./found: C, 50.80/50.59; H, 3.20/3.28; N, 3.70/3.87.

3-Phenyl-2-thioxo-5-[3-(trifluoromethyl)benzyl]-1,3-thiazolidin-4-one (9b). This compound was isolated as light yellow crystals, mp 78–79 °C (ethanol) in 86% yield. ^{1}H NMR ppm: δ 3.44 (dd, J = 14.0, 8.1 Hz, 1H, CH_2), 3.58 (dd, J = 14.0, 4.5 Hz, 1H, CH_2), 5.01 (dd, J = 8.0, 4.6 Hz, 1H, CH), 7.42–7.49 (m, 4H, Ar), 7.51–7.59 (m, 5H, Ph). MS m/z: 367 (M^+). Anal. requires for = $C_{17}H_{12}F_3NOS_2$ (367.41) calcd./found: C, 55.57/55.35; H, 3.29/3.18; N, 3.81/3.65.

5-(3,4-Dimethylbenzyl)-3-phenyl-2-thioxo-1,3-thiazolidin-4-one (9c). This compound was isolated as light yellow crystals, mp 77–78 °C (ethanol) in 75% yield. ^{1}H NMR ppm: δ 2.26 (s, 6H, CH_3), 3.20 (dd, J = 14.0, 9.0 Hz, 1H, CH_2), 3.43 (dd, J = 14.0, 4.0 Hz, 1H, CH_2), 4.87 (dd, J = 9.0, 4.0 Hz, 1H, CH), 6.95–7.07 (m, 5H, H_{Ph}), 7.43–7.51 (m, 3H, H_{Ar}). MS m/z: 327 (M^+). Anal. requires for $C_{18}H_{17}NOS_2$ (327.46) calcd./found: C, 66.02/66.14; H, 5.23/5.08; N, 4.28/4.16.

5-(2,5-Dichlorobenzyl)-3-phenyl-2-thioxo-1,3-thiazolidin-4-one (9d). This compound was isolated as light yellow crystals, mp 121–122 °C (ethanol) in 83% yield. ^{1}H NMR ppm: δ 3.39 (dd, J = 14.2, 9.2 Hz, 1H, CH_2), 3.72 (dd, J = 14.2, 5.2 Hz, 1H, CH_2), 5.01 (dd, J = 9.2, 5.2 Hz, 1H, CH), 7.18–7.36 (m, 3H, H_{Ar}), 7.40–7.54 (m, 5H, Ph). MS m/z: 368 (M^+). Anal. requires for $C_{16}H_{11}Cl_2NOS_2$ (368.30) calcd./found: C, 52.18/52.00; H, 3.01/2.89; N, 3.80/3.99.

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