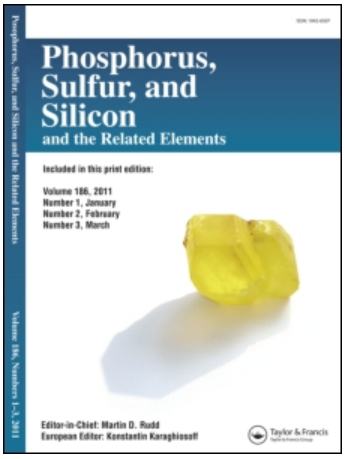

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Synthesis of Some New 2,4-Disubstituted Hydrazinothiazoles and 2,5-Disubstituted Thiazolidinones

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Synthesis of Some New 2,4-Disubstituted Hydrazinothiazoles and 2,5-Disubstituted Thiazolidinones

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A series of hydrazinothiazoles has been synthesized by the condensation of thiosemicarbazones and α-bromoketones. Similarly the hydrazinothiazolidiones were prepared by the condensation of thiosemicarbazone and α-bromoesters. The newly synthesized compounds were characterized by NMR and LCMS studies.

Keywords α-Haloketones; hydrazine; thiazole; thiazolidinones; thiosemicarbazone

INTRODUCTION

Thiazole and thiazolidinone derivatives find applications in many fields of chemistry including medicine and agriculture. Thiazoles and thiazolidinones find applications in drug development for the treatment of inflammation,[1] hypertension,[2] bacterial infections,[3–9] HIV infections,[10–16] allergies,[17] schizophrenia,[18] and as hypnotics.[19,20] They are also used as fungicides, as an ingredient of herbicides, and as schistosomicidal and anthelmintic drugs,[21–24] as anti-inflammatory agents, and they possess anti-tubercular properties.[25–27] In addition, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds. Thus the thiazole and thiazolidinone nucleus has been much studied in the fields of organic and medicinal chemistry.[28–31] The azo derivatives of thiazoles also have wide applications in the dyeing of synthetic fibers.[32,33]

Therefore, a general, simple, and efficient method for rapid synthesis of thiazoles and thiazolidinones would be greatly advantageous and

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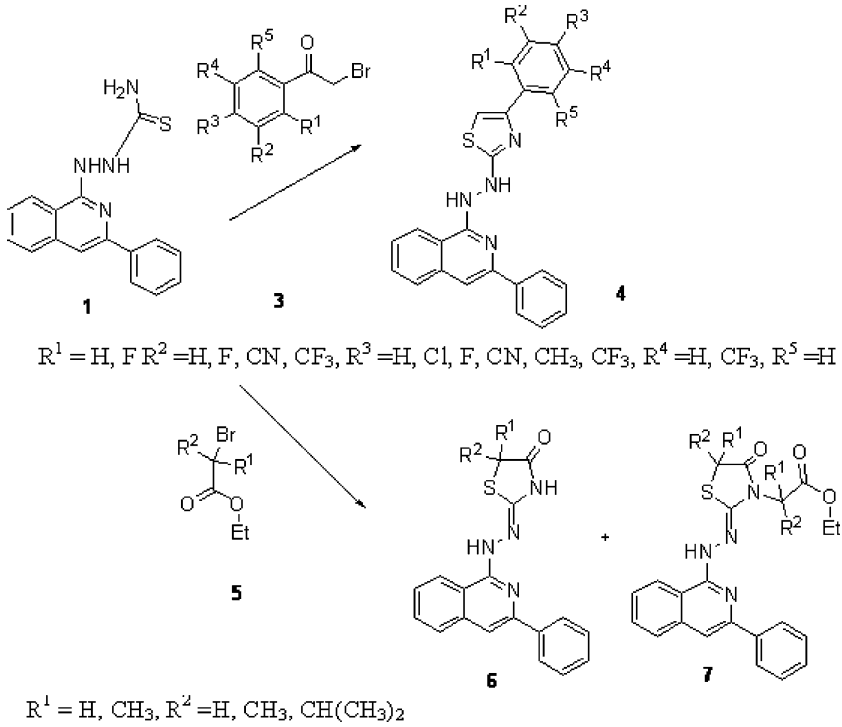
warrants further investigations in drug discovery. Hantzsch, Tchernic, Cook-Heilborn, Gabriel, and other groups have developed several methods for the synthesis of thiazole derivatives.[34–36] The most wildly used method is Hantzsch synthesis,[34–36] which originated in 1887, involving the reaction of α-halo carbonyl compounds with thioureas or thioamides. Among the various methodologies reported for the preparation of thiazoles, solid supported syntheses have been used to generate small organic libraries,[37] and solution-phase preparations of combinatorial libraries have been prepared in DMF,[38] as well as in 1,4-dioxane.[39] These methods require high temperatures, long reaction times, hazardous solvents, and often produce low yields. Recently, thiazole derivatives were synthesized by using catalysts such as ammonium molybdophosphate, cyclodextrin, iodine, and silica chloride in organic solvents at elevated temperature and solvents such as 1-methyl-2-pyrrolidinone, and with the use of microwave.[40–45] However, in spite of their potential utility, many of these reported methods suffer from drawbacks such as harsh reaction conditions and remain unsatisfactory.

Prompted by these reports and in continuation of our search for bioactive molecules,[46–51] we report in this article the Hanzch synthesis of some new thiazole, thiazolidinone derivatives starting from 1-(3-phenylisoquinolin-1-yl) thiosemicarbazide **1**.

RESULTS AND DISCUSSION

The synthetic strategies adopted to obtain the target compounds are depicted in Scheme 1. The key intermediate was prepared in an excellent yield in three sequential steps. 1-(3-phenylisoquinolin-1-yl) thiosemicarbazide **1** was synthesized by the reaction of 1-chloro-3-phenylisoquinoline **2** and thiosemicarbazide. Compound **1** was then treated with substituted α-haloketones, **3**, to yield 2,4 disubstituted hydrazinothiazoles **4**.

The results of the synthesis of thiazoles **4a–i** are given in Table I. The formation of the thiazoles was confirmed by the ^{1}H NMR, ^{13}C NMR, and LCMS of the compounds. The IR spectrum of **4a** showed absorption bands at 3384, 3058, 2921, 1574, 1543, 823, and 695 cm^{-1} due to NH, C–H aromatic (str), aliphatic C–H, C = /N, C = C, C–H aromatic (ben), and C–S–C groups, respectively. The IR spectra of other thiazoles of the series showed similar absorption bands, and the data are presented in Table I. The ^{1}H NMR spectrum of **4a** showed a sharp singlet at δ 7.1 corresponding to C-5 proton of the thiazole ring. The ^{13}C NMR spectrum



SCHEME 1 Synthesis of hydrazinothiazoles and thiazolidinones.

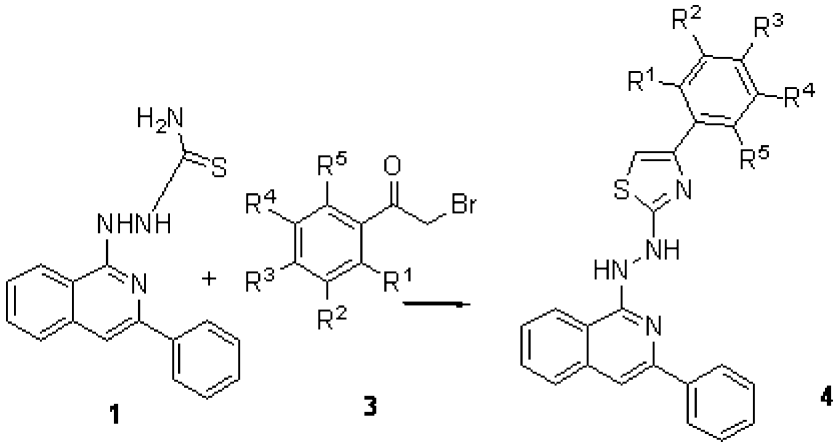
showed the presence of a thiazole ring, i.e., (d CHS), (s, N=CS), and (s, NC=CH) (see data in the Experimental section).

We have also cyclized the thiosemicarbazone, **1**, functionality into thiazolidinone, **6**, and **7**. Thus, treatment of thiosemicarbazone derivative **1** with one equivalent of ethyl bromoacetate or other α-bromoesters, **5**, in refluxing ethanol containing three equivalents of freshly fused sodium acetate afforded a single product, **6** (Table II, entries 1–4). However, if excess bromoesters were used, the N-alkylated product, **7**, formed as a major product with only trace of compounds **5**, (Table II, entries 5–8).

CONCLUSION

In conclusion, the condensation of α-bromoketones with thiosemicarbazide were effected by following a Hantzsch method to provide an excellent route to highly functionalized 2-hydrazinothiazoles. A new scheme for the formation of thiazolidinone and its N-alkylated product

TABLE I Synthesis of Hydrazinothiazoles from Isoquinoline Thiosemicarbazone[a]



		Substrate **3** and Product **4**					Yield[b]
Entry		R^1	R^2	R^3	R^4	R^5	%
1	a	H	H	CH_3	H	H	80
2	b	H	CN	H	H	H	82
3	c	H	F	Cl	H	H	85
4	d	H	H	CF_3	H	H	76
5	e	H	H	Cl	H	H	83
6	f	H	H	CN	H	H	87
7	g	H	H	F	H	H	85
8	h	F	H	Cl	H	H	83
9	i	H	CF_3	H	CF_3	H	81

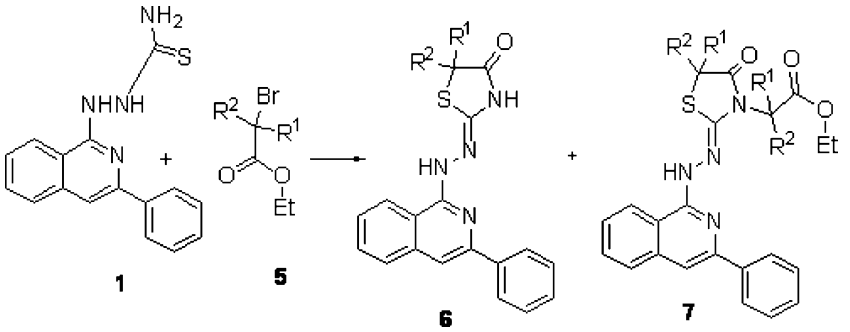
[a]All products were identified by ^1H, ^{13}C NMR, LCMS.
[b]Isolated Yields.

by treatment with α-bromoesters has also been reported. These reactions are simple and effective, and also possess interesting potential as a new method in hydrazinothiazoles synthesis.

EXPERIMENTAL

The materials were purchased from Sigma-Aldrich and Merck, and were used without any additional purification. All reactions were monitored by thin layer chromatography (TLC) on gel F254 plates. The silica gel (230–400 meshes) for column chromatography was purchased

TABLE II Synthesis of Hydrazinothiazolidinones from Isoquinoline Thiosemicarbazone[a]



		Substrates **5**, Product **6**	Yield[b]	
Entry		R^1	R^2	%
1	a	H	H	74
2	b	H	CH_3	71
3	c	CH_3	CH_3	69
4	d	H	$CH(CH_3)_2$	73
		Substrates **5**, Product **7**		
5	a	H	H	79
6	b	H	CH_3	82
7	c	CH_3	CH_3	81
8	d	H	$CH(CH_3)_2$	80

[a]Products 6b, 6c, 7a, 7b were identified by ^{1}H, ^{13}C NMR, LCMS.
[b]Isolated Yields.

from Spectrochem Pvt. Ltd., India. Melting points were taken in open capillary tubes and are corrected with reference to benzoic acid. IR spectra in KBr pellets were recorded on a Nucon Infrared spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$ or DMSO (with TMS for ^{1}H and DMSO for ^{13}C NMR as internal references).

Preparation of 3-Phenylisoquinolin-1(2H)-one

3-Phenylisocoumarin (20 g, 90 mmol) was dissolved in THF (100 mL), and to this, liq. ammonia in excess was added. The mixture was refluxed overnight in an oil bath until TLC showed completion of the reaction. Then ice-cold water (500 mL) was added to the reaction mixture, then it was extracted with ethyl acetate and the extract was dried over

anhydrous sodium sulfate. Removal of the solvent under vacuum gave the crude product, which was further purified by column chromatography on silica gel (100–200 mesh) with ethyl acetate-hexane (25%) as an eluent to afford pure product, 3-phenylisoquinolin-1(2H)-one in 70% yield, and is characterized by its ^{1}H and ^{13}C NMR spectra.

^{1}H NMR ($CDCl_3$): δ 6.79 (s, 1H, NH−C=C*H*), 7.45–7.55 (m, 4H), 7.60–7.62 (d, 1H), 7.67–7.73 (m, 3H), 8.41–8.44 (d, 1H), 9.68 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ 163.63 (*C*=O), 139.34 (NH−*C*=CH), 138.24, 134.37, 132.88, 129.60, 129.31, 127.52, 126.71, 126.56, 126.00, 125.05 (Aromatic Carbons), 104.28 (NH−C=*C*). LCMS-221.9. $C_{15}H_{11}NO$ requires Mol. Wt.: 221.25.

Preparation of 1-Chloro-3-phenylisoquinoline

To 3-phenylisoquinolin-1(2H)-one (15 g, 68 mmol), phosphoryl chloride (90 mL) was added. The mixture was refluxed overnight under a nitrogen atmosphere in an oil bath until TLC showed completion of the reaction. Then the reaction mixture was added to ice-cold water, and it was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate. Removal of the solvent under vacuum gave the crude product, which was further purified by column chromatography on silica gel (230–400 mesh) with ethyl acetate-hexane (2%) as an eluent to afford the pure product 1-chloro-3-phenylisoquinoline, **2**, in 92% yield and was characterized by its ^{1}H and ^{13}C NMR spectra.

^{1}H NMR ($CDCl_3$): δ 8.32–8.34 (d, 1H), 8.11–8.14 (m, 2H), 8.02 (s, 1H, NH−C=C*H*), 7.88–7.90 (m, 1H), 7.73–7.77 (m, 1H), 7.64–7.68 (m, 1H), 7.49–7.53 (m, 1H), 7.41–7.46 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 163.63 (*C*-Cl), 139.34 (NH−*C*=CH), 138.24, 134.37, 132.88, 129.60, 129.31, 127.52, 126.71, 126.56, 126.00, 125.05 (Aromatic carbons), 104.28 (NH-C=*C*H). LCMS-240.1. $C_{15}H_{10}ClN$ requires Mol. Wt.: 239.6.

Preparation of Thiosemicarbazide

The thiosemicarbazone derivative was prepared by refluxing an equimolar ratio of halo derivative of isoquinoline and thiosemicarbazide in the presence of ethanol. Removal of the solvent under vacuum gave the crude product, which was further purified by washing with petether to afford the pure product 1-(3-phenylisoquinolin-1-yl)thiosemicarbazide, **1**, in 95% yield and was characterized by its ^{1}H and ^{13}C NMR spectra.

^{1}H NMR (DMSO): δ 9.49 (s, 1H), 9.22 (s, 1H), 8.26–8.23 (m, 3H), 7.87–7.85 (d, J = 8.08 Hz, 1H), 7.80–7.77 (m, 1H), 7.71–7.61 (m, 2H), 7.53–7.49 (m, 1H), 7.46–7.42 (m, 2H), 7.37–7.34 (m, 1H). ^{13}C NMR

(DMSO): δ 183.75 (*C*=S), 154.35 (N=*C*–NH), 147.78 (NH–*C*=CH), 139.35, 138.17, 130.68, 128.83, 128.75, 127.55, 126.85, 126.30, 123.89, 116.88, 108.65 (NH–C=*C*H). LCMS-295.1. $C_{16}H_{14}N_4S$ requires Mol. Wt.: 294.3.

General Procedure for the Synthesis of Thiazole Derivatives (4a–4i)

To a solution of thiosemicarbazide, **1** (0.005 mol) in absolute ethanol (10 mL), equimolar amounts (0.005 mol) of the appropriate α-haloketone, **3**, were added. The reaction mixture was heated at 50°C for 2 h. The separated solid product was filtered, dissolved in chloroform, washed with water, dried over anhydrous sodium sulfate, and concentrated under vacuum to afford the thiazole compounds, **4**.

1-(3-Phenylisoquinolin-1-yl)-2-(4-p-tolylthiazol-2-yl)hydrazine, 4a

Brown solid, mp 272°C, (IR ν cm^{-1}) 3384, 3058, 2921, 1722, 1625, 1574, 1543, 1509, 1377, 1030, 764, 695. ^{1}H NMR (DMSO): δ 9.96 (s, 1H, N*H*), 9.42 (s, 1H, N*H*), 8.32–8.30 (t, J = 1.64 Hz, 1H), 8.08 (d, J = 1.68 Hz, 1H), 8.06 (s, 1H), 7.90–7.88 (d, J = 8.12 Hz, 1H), 7.77–7.69 (m, 4H), 7.59–7.55 (t, J = 7.88 Hz, 1H), 7.32–7.30 (m, 3H), 7.22–7.20 (d, J = 4.04 Hz, 2H), 7.09 (s, 1H, S–C*H*), 2.32 (s, 3H, *CH*$_3$). ^{13}C NMR (DMSO): δ 175.71 (S–*C*=N), 154.79 (HNNH–*C*=N isoquinoline ring), 151.17 (N–*C*=C–S), 147.86 (N–*C*=CH isoquinoline ring), 139.41, 138.23, 137.03, 132.85, 130.89, 129.58, 128.75, 127.86, 126.83, 126.73, 125.99, 123.20, (Aromatic carbons), 116.88, 108.80 (N–C=*C*H isoquinoline ring), 102.71 (S–*C*H), 21.28 (*C*H$_3$). LCMS-409.2. $C_{25}H_{20}N_4S$, Mol. Wt.: 408.52, Calculated C, 73.50; H, 4.93; N, 13.71; S, 7.85, found C, 73.42; H, 4.84; N, 13.66; S, 7.78.

2-(4-(3-Cyanophenyl)thiazol-2-yl)-1-(3-phenylisoquinolin-1-yl) hydrazine, 4b

Brown solid, mp 292°C, (IR ν cm^{-1}) 3345, 3061, 2956, 2232, 1625, 1575, 1512, 1381, 1054, 767, 688. ^{1}H NMR (DMSO): δ 9.98 (s, 1H, N*H*), 9.55 (s, 1H, N*H*), 8.30–8.27 (m, 2H), 8.20–8.18 (d, J = 6.92 Hz, 1H), 8.03 (s, 2H), 7.89–7.87 (d, J = 7.36 Hz, 1H), 7.77–7.72 (m, 3H), 7.63–7.61 (d, J = 6.36 Hz, 2H), 7.58–7.56 (d, J = 9.44 Hz, 1H), 7.42–7.27 (m, 3H). ^{13}C NMR (DMSO): δ 176.19 (S–*C*=N), 154.68 (HNNH–*C*=N isoquinoline ring), 148.82 (N–*C*=C–S), 147.81 (N–*C*=CH isoquinoline ring), 139.37, 138.22, 136.44, 131.18, 130.92, 130.50, 130.43, 129.29, 128.73, 127.87, 126.77, 123.16, (Aromatic carbons), 119.28, 116.86, 112.20 (*C*N,

−*C*−CN), 108.94 (N−C=*C*H isoquinoline ring), 105.92 (S−*C*H). LCMS-420.0, $C_{25}H_{17}N_5S$, Mol. Wt.: 419.5, Calculated C 71.58; H, 4.08; N, 16.69; S, 7.64, Found C 71.51; H, 4.00; N, 16.62; S, 7.56.

2-(4-(4-Chloro-3-fluorophenyl)thiazol-2-yl)-1-(3-phenylisoquinolin-1-yl)hydrazine, 4c

Brown solid, mp 146°C, (IR ν cm^{-1}) 3234, 3062, 2953, 1897, 1623, 1574,1377, 1327, 1073, 817, 766, 693. ^{1}H NMR (DMSO): δ 9.98 (s, 1H, N*H*), 9.53 (s, 1H, N*H*), 8.30–8.28 (d, J = 8.28 Hz, 1H), 8.05–8.03 (m, 2H), 7.89–7.82 (m, 2H), 7.77–7.68 (m, 3H), 7.62–7.54 (m, 2H), 7.37 (s, 1H), 7.31–7.26 (m, 3H). ^{13}C NMR (DMSO): δ 176.04, (S−*C*=N), 156.64 (HNNH−*C*=N isoquinoline ring), 148.74 (N−*C*=C−S), 147.81 (N−*C*=CH isoquinoline ring), 139.36, 138.22, 136.61, 131.28, 130.91, 128.74, 127.86, 126.78, 123.16 (Aromatic carbons), 118.24, 116.85, 113.98 (*C*=*C*−F), 113.76, 108.93, (N−C=*C*H isoquinoline ring), 105.83 (S−*C*H). LCMS-447.0, $C_{24}H_{16}ClFN_4S$, Mol. Wt.: 446.93, Calculated C, 64.50; H, 3.61; Cl, 7.93; F, 4.25; N, 12.54; S, 7.17, Found C, 64.42; H, 3.53; Cl, 7.83; F, 4.16; N, 12.46; S, 7.08.

2-(4-(4-(Trifluoromethyl)phenyl)thiazol-2-yl)-1-(3-phenylisoquinolin-1-yl)hydrazine, 4d

Brown solid, mp 148°C, (IR ν cm^{-1}) 3224, 3114, 3053, 1626, 1574, 1380, 1322, 1202, 1167, 1070, 769, 694. ^{1}H NMR (DMSO): δ 9.98 (s, 1H, N*H*), 9.55 (s, 1H, N*H*), 8.31–8.29 (d, J = 8.40 Hz, 1H), 8.08–8.03 (m, 4H), 7.90–7.88 (d, J = 8.12 Hz, 1H), 7.77–7.68 (m, 4H), 7.58–7.54 (t, J = 8.1 Hz,1H), 7.41 (s, 1H), 7.30–7.25 (m, 3H). ^{13}C NMR (DMSO): δ 176.12 (S−*C*=N), 154.67 (HNNH−*C*=N isoquinoline ring), 149.51 (N−*C*=C−S), 147.82 (N−*C*=CH isoquinoline ring), 139.37, 139.10, 138.23, 130.91, 128.74, 127.87, 126.77, 126.52, 126.03, 123.16 (Aromatic carbons), 116.86, 108.91 (N−C=*C*H isoquinoline ring), 106.39 (S−*C*H). LCMS-463.1, $C_{25}H_{17}F_3N_4S$, Mol. Wt.: 462.49, Calculated C, 64.92; H, 3.70; F, 12.32; N, 12.11; S, 6.93, Found C, 64.85; H, 3.64; F, 12.22; N, 12.05; S, 6.84.

2-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(3-phenylisoquinolin-1-yl) hydrazine, 4e

Brown solid, mp 170°C, (IR ν cm^{-1}) 3383, 3174, 3059, 2892, 1625, 1574, 1377, 1322, 1012, 825, 770, 695. ^{1}H NMR (DMSO): δ 9.98 (s, 1H, N*H*), 9.50 (s, 1H, N*H*), 8.32–8.30 (d, J = 8.28 Hz,1H), 8.07 (d, J = 1.92 Hz, 1H), 8.05 (d, J = 1.36 Hz, 1H), 7.90–7.88 (d, J = 8.52 Hz, 3H), 7.78 (s, 1H), 7.73–7.69 (t, J = 7.4 Hz, 1H), 7.59–7.55 (t, J = 7.24 Hz, 1H), 7.47–7.45 (d, J = 8.56 Hz, 3H), 7.32–7.24 (m, 4H).

^{13}C NMR (DMSO): δ 175.28 (S−*C*=N), 154.73 (HNNH−*C*=N isoquinoline ring), 149.81 (N−*C*=C−S), 147.84 (N−*C*=CH isoquinoline ring), 139.38, 138.23, 134.31, 132.18, 130.90, 129.04, 128.75, 127.87, 127.73, 126.80, 126.75, 123.18 (Aromatic carbons), 116.87, 108.87 (N−C=*C*H isoquinoline ring), 104.42 (S−*C*H). LCMS-429.0, $C_{24}H_{17}ClN_4S$, Mol. Wt.: 428.94, Calculated C, 67.20; H, 3.99; Cl, 8.27; N, 13.06; S, 7.48, Found C, 67.20; H, 3.99; Cl, 8.27; N, 13.06; S, 7.48.

2-(4-(4-Cyanophenyl)thiazol-2-yl)-1-(3-phenylisoquinolin-1-yl)hydrazine, 4f

Brown solid, mp 180°C, (IR ν cm^{-1}) 3340, 3178, 3060, 2926, 2224, 1624, 1573, 1409, 1381, 1327, 841, 767, 689. ^{1}H NMR (DMSO): δ 10.01 (s, 1H, N*H*), 9.59 (s, 1H, N*H*), 8.32–8.30 (m, 1H), 8.06–8.04 (m, 4H), 7.99–7.86 (m, 3H), 7.79 (s, H), 7.74–7.70 (m, 1H), 7.59–7.56 (m, 1H), 7.50 (s, 1H), 7.30–7.27(m, 3H). ^{13}C NMR (DMSO): δ 176.18 (S−*C*=N), 154.67 (HNNH−*C*=N isoquinoline ring), 149.32 (N−*C*=C−S), 147.66 (N−*C*=CH isoquinoline ring), 139.52, 139.37, 138.25, 133.15, 130.94, 128.77, 127.90, 126.78, 126.61, 123.18 (Aromatic carbons), 109.85 (N−C=*C*H isoquinoline ring), 107.53 (S−*C*H). LCMS-420.0, $C_{25}H_{17}N_5S$, Mol. Wt.: 419.5, Calculated C, 71.58; H, 4.08; N, 16.69; S, 7.64, Found C, 71.47; H, 4.00; N, 16.57; S, 7.57.

2-(4-(4-Fluorophenyl)thiazol-2-yl)-1-(3-phenylisoquinolin-1-yl) hydrazine, 4g

Brown solid, mp 194°C, (IR ν cm^{-1}) 3385, 3174, 3060, 2894, 1625, 1573, 1377, 1324, 1216, 770, 695. ^{1}H NMR (DMSO): δ 9.97 (s, 1H, N*H*), 9.46 (s, 1H, N*H*), 8.32–8.28 (m, 1H), 8.05–8.03 (d, J = 6.32 Hz, 1H), 7.90–7.87 (m, 3H), 7.75 (s, 1H), 7.71–7.68 (m, 1H), 7.57–7.53 (m, 1H), 7.27 (s, 1H), 7.23–7.19 (m, 5H), 7.14 (s, 1H). ^{13}C NMR (DMSO): δ 175.84 (S−*C*=N), 163.19, 160.76, 154.73 (HNNH−*C*=N isoquinoline ring), 149.97 (N−*C*=C−S), 138.22 (N−*C*=CH isoquinoline ring), 132.06, 130.97, 128.76, 128.01, 127.94, 127.88, 126.84, 123.22 (Aromatic carbons), 116.86, 115.95, 115.74 (*C*=*C*−F), 108.89 (N−C=*C*H isoquinoline ring), 103.36 (S−*C*H). LCMS-413, $C_{24}H_{17}FN_4S$, Mol. Wt.: 412.48, Calculated C, 69.88; H, 4.15; F, 4.61; N, 13.58; S, 7.77, Found C, 69.81; H, 4.07; F, 4.55; N, 13.51; S, 7.69.

2-(4-(4-Chloro-2-fluorophenyl)thiazol-2-yl)-1-(3-phenylisoquinolin-1-yl)hydrazine, 4h

Brown solid, mp 170°C, (IR ν cm^{-1}) 3381, 3182, 3060, 2894, 1625, 1574, 1415, 1377, 877, 769, 698. ^{1}H NMR (DMSO): δ 10.05 (s, 1H, N*H*), 9.55 (s, 1H, N*H*), 8.32–8.30 (m, 1H), 8.12–8.04 (m, 3H), 7.91–7.89 (d,

J = 8.08 Hz, 1H), 7.79 (s, 1H), 7.74–7.70 (m, 1H), 7.59–7.50 (m, 2H), 7.42–7.39 (m, 1H), 7.33–7.28(m, 2H), 7.15–7.14 (d, J = 2.52 Hz, 1H). ^{13}C NMR (DMSO): δ 174.94 (S−*C*=N), 160.55, 158.04, 154.28 (HNNH-*C*=N isoquinoline ring), 147.41 (N−*C*=C−S), 143.23 (N−*C*=CH isoquinoline ring), 138.96, 137.84, 132.14, 132.04, 130.52, 128.35, 127.48, 126.38, 125.04, 122.77(Aromatic carbons), 121.70, 121.58, 116.77, 116.51, 161.47, 108.52 (N−C=*C*H isoquinoline ring), 108.42 (S−*C*H). LCMS-447.1, $C_{24}H_{16}ClFN_4S$, Mol. Wt.: 446.93, Calculated C, 64.50; H, 3.61; Cl, 7.93; F, 4.25; N, 12.54; S, 7.17, Found C, 64.42; H, 3.56; Cl, 7.86; F, 4.17; N, 12.43; S, 7.11.

2-(4-(3,5-Bis(trifluoromethyl)phenyl)thiazol-2-yl)-1-(3-phenylisoquinolin-1-yl) hydrazine, 4i

Brown solid, mp 182°C, (IR ν cm^{-1}) 3310, 3116, 2914, 1627, 1578, 1377, 1278, 1125, 769, 697. ^{1}H NMR (DMSO): δ 10.04 (s, 1H, N*H*), 9.69 (s, 1H, N*H*), 8.52 (s, 2H), 8.32–8.29 (d, J = 10.8 Hz, 1H), 8.06–8.01 (m, 3H), 7.91–7.89 (d, J = 10.6 Hz, 1H), 7.79–7.69 (m, 3H), 7.60–7.55 (m, 1H), 7.27–7.25 (m, 2H). ^{13}C NMR (DMSO): δ 176.60 (S−*C*=N), 154.66 (HNNH−*C*=N isoquinoline ring), 147.79 (N−*C*=C−S), 147.70 (N−*C*=CH isoquinoline ring), 139.37, 138.25, 137.65, 131.39, 131.06, 130.95, 130.74, 128.74, 128.68, 127.89, 126.78, 126.18, 125.23, 123.16 (Aromatic carbons), 122.52, 120.86, 116.88, 109.04 (N−C=*C*H isoquinoline ring), 107.85 (S−*C*H).. LCMS-531.1, $C_{26}H_{16}F_6N_4S$, Mol. Wt.: 530.49, Calculated C, 58.87; H, 3.04; F, 21.49; N, 10.56; S, 6.04, Found C, 58.77; H, 2.95; F, 21.41; N, 10.46; S, 5.92.

General Procedure for the Synthesis of Thiazolidinone Derivatives (6a–6d, 7a–7d)

A mixture of compound **1** (0.01 mol), α-bromoesters **5** (0.01 mol), and anhydrous sodium acetate (0.03 mol) in ethanol (15 mL) was heated under reflux for 8 h. The reaction mixture was left to cool, poured into ice-cold water, extracted with ethyl acetate, dried, and concentrated. The crude product was purified by column chromatography to give compound **6a–d**. However if an excess quantity of α-bromoesters (2.5 eq.) was used, it resulted in the formation of **7a–d**.

2-(2-(3-Phenylisoquinolin-1-yl)hydrazono)-5-methylthiazolidin-4-one, 6b

^{1}H NMR (DMSO): δ 11.59 (s, 1H), 9.14 (s, 1H), 8.12–8.10 (d, J = 7.64 Hz, 1H), 7.68–7.67 (d, J = 6.4 Hz, 2H), 7.52–7.47 (m, 6H), 7.37–7.34 (m, 1H), 6.60 (s, 1H), 1.48–1.46 (d, J = 7.16 Hz, 3H). ^{13}C

NMR (DMSO): δ 176.72, 148.94, 138.29, 135.63, 134.50, 131.72, 130.02, 129.73, 127.15, 126.95, 125.63, 124.20, 123.91, 101.80, 19.56. LCMS-349.0, $C_{19}H_{16}N_4OS$, Mol. Wt.: 348.42, Calculated C, 65.50; H, 4.63; N, 16.08; O, 4.59; S, 9.20, Found C, 65.42; H, 4.56; N, 16.01; S, 9.13.

2-(2-(3-Phenylisoquinolin-1-yl)hydrazono)-5,5-dimethylthiazolidin-4-one, 6c

^{1}H NMR (DMSO): δ 11.59 (s, 1H), 9.16 (s, 1H), 8.11–8.09 (d, J = 8.04 Hz, 1H), 7.69–7.67 (m, 2H), 7.55–7.47 (m, 5H), 7.37–7.34 (m, 1H), 6.60 (s, 1H), 1.54 (s, 6H). ^{13}C NMR (DMSO): δ 179.05, 153.01, 148.90, 138.30, 135.63, 134.50, 131.71, 130.02, 129.72, 127.13, 126.25, 125.64, 124.18, 123.91, 101.81, 51.99, 31.14, 28.42. LCMS-363.0, $C_{20}H_{18}N_4OS$, Mol. Wt.: 362.45, Calculated C, 66.28; H, 5.01; N, 15.46; O, 4.41; S, 8.85, Found C, 66.21; H, 4.93; N, 15.37; S, 8.77.

Ethyl 2-(2-(2-(3-Phenylisoquinolin-1-yl)hydrazono)-4-oxothiazolidin-3-yl)acetate, 7a

^{1}H NMR (DMSO): δ 9.43 (s, 1H), 8.19–8.17 (d, J = 8.28 Hz, 1H), 7.73–7.71 (m, 2H), 7.57–7.51 (m, 5H), 7.42–7.40 (m, 1H), 6.67 (s, 1H), 4.68 (s, 2H), 4.14–4.08 (m, 4H), 1.13–1.10 (t, J = 7.12 Hz, 3H). ^{13}C NMR (DMSO): δ 171.44, 167.52, 153.84, 149.53, 138.15, 135.29, 134.10, 131.43, 129.52, 129.13, 126.77, 126.53, 125.54, 124.02, 123.40, 101.94, 61.15, 43.80, 40.22, 32.13, 14.01. LCMS-421.3, $C_{22}H_{20}N_4O_3S$, Mol. Wt.: 420.48, Calculated C, 62.84; H, 4.79; N, 13.32; O, 11.41; S, 7.63, Found C, 62.75; H, 4.70; N, 13.24; S, 7.56.

Ethyl 2-(2-(2-(3-Phenylisoquinolin-1-yl)hydrazono)-5-methyl-4-oxothiazolidin-3-yl)propanoate, 7b

^{1}H NMR (DMSO): δ 9.11 (s, 1H), 8.15–8.13 (d, J = 7.88 Hz, 1H), 7.77–7.74 (m, 2H), 7.55–7.47 (m, 5H), 7.39–7.35 (m, 1H), 6.67–6.64 (d, J = 10.8 Hz, 1H), 5.34–5.24 (m, 1H), 4.33–4.29 (m, 1H), 4.06–4.04 (m, 1H), 3.98–3.96 (m, 1H), 1.53–1.49 (m, 6H), 1.03–0.97 (m, 3H). ^{13}C NMR (DMSO): δ 174.50, 174.42, 170.20, 170.12, 152.35, 152.32, 149.84, 138.44, 138.25, 135.67, 134.20, 134.08, 131.90, 131.88, 130.00, 129.96, 129.55, 127.22, 126.99, 125.90, 125.76, 124.39, 123.74, 123.70, 102.37, 102.27, 61.40, 61.3, 51.35, 51.29, 41.71, 19.91, 19.82, 14.29, 14.23. LCMS-449.2, C24H24N4O3S, Mol. Wt.: 448.54, Calculated C, 64.27; H, 5.39; N, 12.49; O, 10.70; S, 7.15, Found C, 64.19; H, 5.32; N, 12.39; S, 7.05.

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