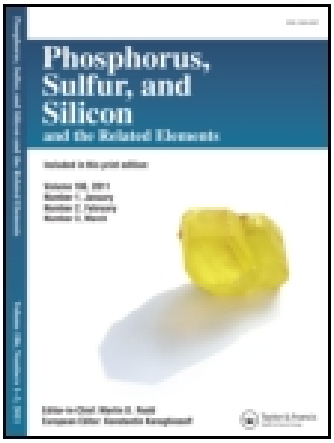

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Synthesis of Diversified Thioethers, 1-Aroylalkylisoquinolin-1-yl Thioethers, by Electrophilic S-Alkylation of 3-Phenyl Isoquinoline-1(2H)-thione

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SYNTHESIS OF DIVERSIFIED THIOETHERS, 1-AROYLALKYLISOQUINOLIN-1-YL THIOETHERS, BY ELECTROPHILIC S-ALKYLATION OF 3-PHENYL ISOQUINOLINE-1(2H)-THIONE

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A mild and efficient method for the synthesis of thioethers has been developed. The 3-phenylisoquinoline-1(2H)-thione underwent S-alkylation to afford structurally diverse sulfides in high yield.

Keywords Halides; single crystal study; thioethers; thiols

INTRODUCTION

Organosulfur compounds and sulfur containing drugs play a significant role in many biological processes and pharmaceutical applications and are useful synthetic intermediates and key reagents in synthesis with wide application in bio-organic, medicinal, and heterocyclic chemistry.[1–3] They are also useful as heteroatomic functional groups in organic synthesis; for example, by the oxidation of thioethers, chiral sulfoxides that can be used as auxiliaries in asymmetric syntheses can be generated.[4–7] Many syntheses have been reported for the preparation of thioethers.[8–18] Commonly employed methods are the alkylation of thiols.[19–22]

Thioethers have been prepared by many methods; however, the synthetic scope is often hampered by use of expensive materials, high temperature, hazardous and corrosive compounds such as alkylating agents and strong reducing agents, harsh reaction conditions, and tedious workup procedures, resulting in low product yield. Moreover, the method invariably results in the formation of several byproducts, which in turn results in lower yield. Thus, there is still a need to develop mild and efficient methodologies to synthesize

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aliphatic, aromatic, and hetero aromatic thioethers. To the best of our knowledge, there are only a few reports dealing with the formation of C—S bond in the compounds containing the isoquinoline heterocyclic moiety.[23–27] During the course of our synthetic studies toward organosulfur compounds containing the sulfide moiety, the need for a mild approach for the construction of the C—S bond is clearly warranted. This has prompted us to study the synthesis of sulfides by alkylation of isoquinoline-1-thiols with the corresponding halides (Scheme 1).

RESULTS AND DISCUSSION

In continuation of our studies on the synthesis of organosulphur compounds with medicinal potential,[28–34] in this article we wish to describe an efficient method of s-alkylation of isoquinoline-1-thiols using alkyl halides.

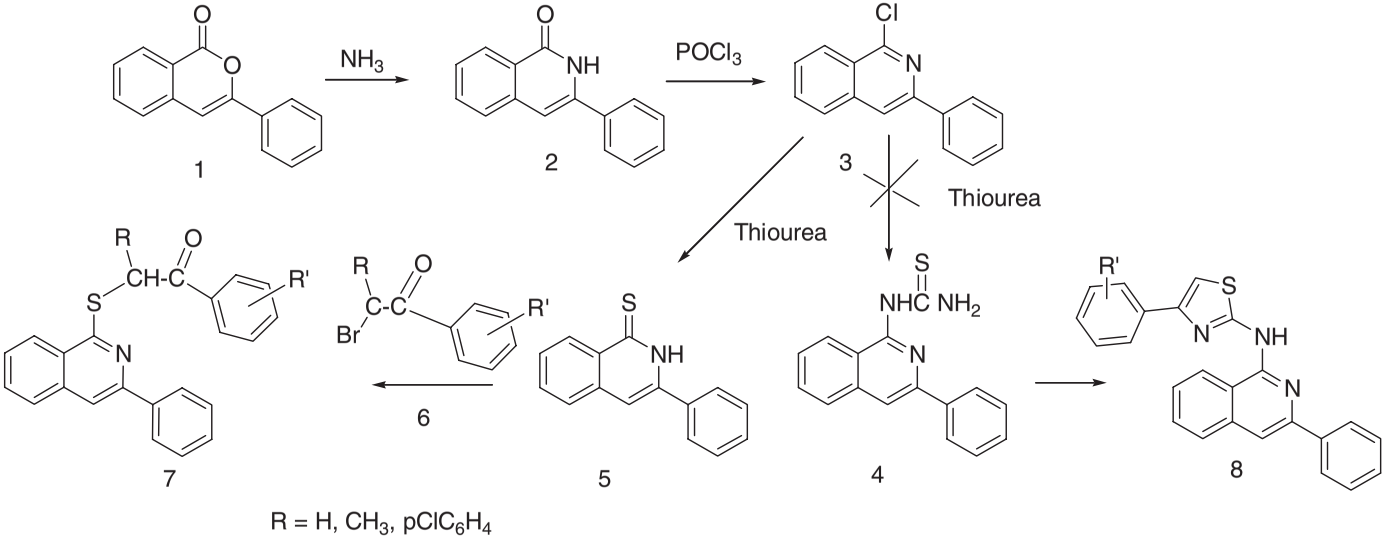
Initially, for the synthesis of thiazole, **8** was planned via a thiourea derivative of isoquinoline reaction that would employ a condensation reaction with keto halide as depicted in Scheme 1. However, in our experiment the 1-chloro, 3-phenylisoquinoline **3** required for the synthesis of the thiourea derivative **4** was prepared as reported earlier,[35–44] with slight modification by the reaction of 3-phenylisoquin-1(2H)-one **2** and phosphoryl chloride in a molar ratio of 1:1. Then reactions of 1-chloro, 3-phenylisoquinoline **3** with thiourea in a molar ratio of 1:1.2 in the presence of ethanol failed to furnish the expected thiourea derivative **4**, even in trace amounts. Instead, this reaction led to the formation of isoquniolinon-1-thione derivative **5**. The thiol derivative (S-nucleophile) is then further transformed into the corresponding S-alkylated product **7** thioether by the electrophilic alkylation using keto halides **6**.

The synthesized compound **7a** gave the expected C=O group peaks in IR and ^{13}C NMR respectively at 1690 cm^{-1} and 194 ppm. Similarly the methylene protons and the methylene carbon appeared in both ^{1}H NMR and ^{13}C NMR spectra, respectively, at 5.06 (singlet) and 37.4ppm. Similarly all the compounds **7b–7l** gave the expected peaks in IR, ^{1}H, and ^{13}C NMR spectra.

The X-ray crystallographic structure of isoquinolin-1-one **2** intermediate and two thioethers **7b** and **7i** (both orthorhombic) were reported by us,[45–47] and the ORTEP diagram, packing diagram, crystal data of the unpublished derivative **7c** (monoclinic) are presented in Figure 1 and Table I.

The compound **7c** exhibits dihedral angles of 28.74 and 71.56°, respectively, between the mean plane of the isoquinoline system and the attached phenyl ring, and between the isoquinoline system and fluoro phenyl ring. The dihedral angle between the phenyl and fluoro phenyl rings is 42.84°. Moreover, the isoquinoline ring is planar, and the maximum deviation observed is −0.015° for atom C2. The S atom is also located in the plane. In the fluoro phenyl ring, the F—C bond distances is 1.355A°. The orientation of the isoquinoline ring system with respect to the phenyl ring given by the torsion angles for N1—C2—C10—C15 and C3—C2—C10—C11 is 151.2° and 152.4°, respectively. Similarly, angles for C16—S1—C1—N1 and C16—S1—C1—C8 are, respectively, 3.26(2)° and −176.5(3)°. The crystal packing is stabilized by C—H···O intermolecular hydrogen bonds. The carbonyl oxygen atom O1 is generating bifurcated C3—H3···O1 and C23—H23···O1 intermolecular hydrogen bonds.

Encouraged by these results, we have further examined this transformation using 3-phenylisoquinolin-1-thione **5** and different halides **6** and obtained the S-alkylated products



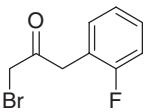
Scheme 1 Synthesis of thioether by S-alkylation of isoquinolinethiol.

Table I Crystallographic data for **7c**

Data	7c	Data	7c
Formula	C_{23} H_{16} F N O S	Density (gm/cm^3)	1.349
Formula weight	373.44	μ (mm^{-1})	0.198
Temperature/K	293(2)	F (000)	776
Radiation	Mo K_α	θ (min, max)	1.9, 25.5
Wavelength (A°)	0.71073	h, k, l (min, max)	(−14, 14) (−12, 12) (−15, 18)
Crystal system	Monoclinic	No. refl^n. Measured	13092
Crystal size (mm)	0.31 × 0.24 × 0.14	No. Unique refl^n	3309
Space group	P 21/c	No of parameters	308
a (Å)	12.0663(7)	Refinement method	Full matrix least squares on F^2
b (Å)	10.5372(6)	R_all	0.0823
c (Å)	15.1246(8)	R_obs	0.0789
α (°)	90.00	wR_2_all	0.1604
β (°)	107.062(1)	wR_2_obs	0.1589
γ (°)	90.00	$\Delta\rho_{max}$ (eÅ^{-3})	0.323
Volume (Å^3)	1838.38(18)	$\Delta\rho_{min}$ (eÅ^{-3})	−0.301
Z	4	GooF	1.280

7 in good yields. The results of alkylation of isoquinolin-1-thione **5** are given in Table II (entries 1–12). From the data, it is obvious that the reaction proceeds very smoothly in a simple, clean, and easier protocol with very good yield. The method is very general, and a wide range of aliphatic and aromatic alkyl halides react readily with isoquinolin-1-thione

Table II S-Alkylation of 3-phenylisoquinolinthi-one using halides

Entry	Halide **6**	Product	**7**	Yield (%)
1	**6a**	R = R^1 = R^2 = R^3 = R^4 = R^5 = H	**7a**	**84**
2	**6b**	R = H; R^3 = Cl; R^1 = R^2 = R^4 = R^5 = H	**7b**	**81**
3	**6c**	R = H; R^3 = F; R^1 = R^2 = R^4 = R^5 = H	**7c**	**87**
4	**6d**	R = H; R^3 = CN; R^1 = R^2 = R^4 = R^5 = H	**7d**	**79**
5	**6e**	R = H; R^3 = CH_3; R^1 = R^2 = R^4 = R^5 = H	**7e**	**82**
6	**6f**	R = H; R^3 = CF_3; R^1 = R^2 = R^4 = R^5 = H	**7f**	**86**
7	**6g**	R = H; R^2 = R^4 = CF_3; R^1 = R^2 = R^5 = H	**7g**	**88**
8	**6h**	R = H; R^1 = OCH_3; R^3 = Cl; R^2 = R^4 = R^5 = H	**7h**	**83**
9	**6i**	R = H; R^2 = F; R^3 = Cl; R^1 = R^4 = R^5 = H	**7i**	**85**
10	**6j**	R = CH_3; R^3 = Cl; R^1 = R^2 = R^4 = R^5 = H	**7j**	**89**
11	**6k**	R = *p*-ClC_6H_4; R^1 = R^2 = R^3 = R^4 = R^5 = H	**7k**	**84**
12	**6l**		**7l**	**77**

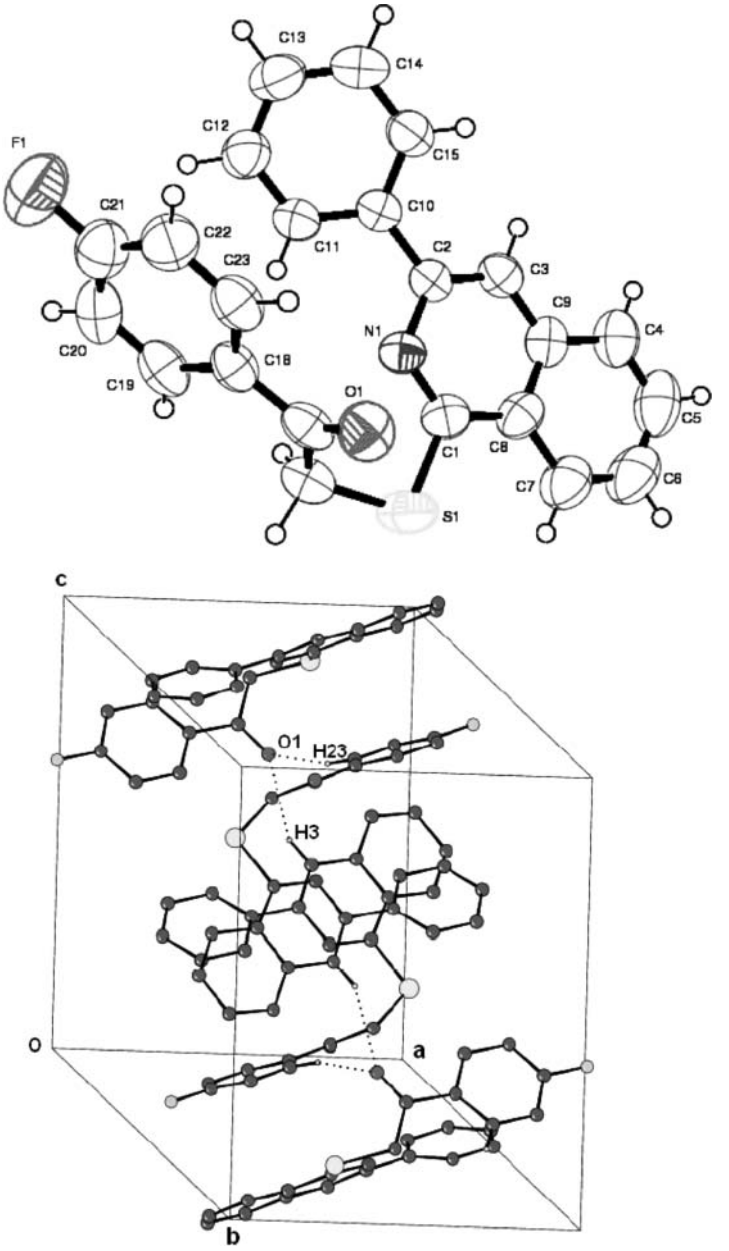


Figure 1 ORTEP and packing diagram of compound **7c** (CCDC No. 683298).

(Table II). Also, formation of disulfide, a common side reaction in thiol chemistry, is very much suppressed.

CONCLUSION

In conclusion, we have developed a simple and clean method for the synthesis of novel thioethers containing the isoquinoline moiety.

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 from Spectrochem Pvt. Ltd., India. ^{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.

X-Ray Crystallographic Data

The single crystal X-ray diffraction data were collected on an Oxford Xcalibur, Eos(Nova) CCD diffractometer. The X-ray generator was operated at 50 kV and 1 mA using Enhanced Mo Kα radiation. Data were collected with ω scan width of 1°. The data reduction, an empirical absorption correction, and space group determination were done using CrysAlisPro RED (Oxford Diffraction, 2009).[48] The crystal structure was solved by direct methods and refined by full matrix least-squares method using SHELXL97,[49] which is part of the program suite WinGx (Version 1.63.04a).[50] The molecular diagrams were generated using ORTEP-3,[51] and the packing diagrams were generated using Mercury.[52] Geometrical calculations were done using PARST95[53] and PLATON.[54] The positions of all hydrogen atoms were fixed geometrically and refined isotropically using the riding atom model.

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

3-Phenylisocoumarin **1** (22 g, 0.099 mol) was dissolved in THF (100 mL), and then liq. ammonia in excess was added. The mixture was refluxed overnight in an oil-bath until TLC showed the completion of the reaction. Then ice-cold water (500 mL) was added to the reaction mixture, then it was extracted with ethyl acetate (3 × 50 mL), 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 the eluent to afford the pure products, 3-phenylisoquinolin-1(2H)-one **2** in 70% yield, which are characterized by their ^{1}H, ^{13}C NMR spectra and compared with reports in the literature.

Preparation of 1-Chloro, 3-Phenylisoquinoline, 3

To **2** (15 g, 0.068 mol), phosphoryl chloride (90 mL) was added. The mixture was refluxed overnight under nitrogen atmosphere in an oil-bath until TLC showed completion of the reaction. Then 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 eluent to afford the pure products 1-chloro, 3-phenylisoquinoline **3** in 92% yield, which are characterized by their ^{1}H, ^{13}C NMR spectra and compared with reports in the literature.

Preparation of 3-Phenyl Isoquinoline-1(2H)-thione, 5

Compound **3** (10 g, 0.042 mole) was dissolved in ethanol (100 mL), and then thiourea (1.2 eq., 3.83 g, 0.0504 mol) was added. The mixture was refluxed in an oil-bath until TLC showed completion of the reaction. Then ice-cold water (250 mL) was added to the reaction mixture, then it was extracted with ethyl acetate (3 × 30 mL), 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 (230–400 mesh) with ethyl acetate–hexane (4%) as eluent to afford pure products 3-phenyl isoquinoline-1(2H)-thione **5** in 70% yield, which are characterized by their ^{1}H, ^{13}C NMR spectra.

General Procedure for S-Alkylation of 5 to the Ethanones or Propanones, 7a–l (Table II, entries 1–12)

In a typical experiment for the synthesis of sulfide, thiol **5**, and bromide **6** in the ratio 1:1.05, equivalents were mixed with ethanol in a round bottom flask. Then the mixture was heated under nitrogen atmosphere on an oil bath at 50°C. After 2 h, the products were filtered, dissolved in chloroform, washed with water, dried, and concentrated, and analyzed in on a liquid chromatography-mass spectrometer (LC-MS). Sulfides **7** are also actually isolated and are characterized by their ^{1}H, ^{13}C NMR spectra.

3-Phenylisoquinolin-1-one, 2. Mp 141–142°C, IR (ν cm^{-1}) 3163 (NH), 3060, 2912, 1666 (CONH), 1634, 1556, 1347, 1285, 1148, 937, 768, 690, 541. ^{1}H NMR ($CDCl_3$): δ 6.79 (s, 1H), 7.45 (m, 4H), 7.60 (d, J = 7.4 Hz,1H), 7.67 (m, 3H), 8.41 (m, 1H), 9.68 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 163.6 (CO), 139.3, 138.2, 134.4, 132.9, 129.6, 129.3 × 2, 127.5 × 2, 126.7, 126.5, 126.0, 125.1, 104.3. LCMS-221.9.

1-Chloro, 3-phenylisoquinoline, 3. Mp 151–153°C, IR (ν cm^{-1}) 3024, 2919, 1561, 1312, 1256, 977, 848 (C—Cl), 762, 686, 516. ^{1}H NMR ($CDCl_3$): δ 7.41 (m, 3H), 7.49 (m, 1H), 7.64 (m, 1H), 7.73 (m, 1H), 7.88 (m, 1H), 8.02 (s, 1H), 8.11 (m, 1H), 8.32 (d, J = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 163. 6 (C—Cl), 139.3, 138.3, 134.3, 132.9, 129.6, 129.3 × 2, 127.7 × 2, 126.7, 126.6, 126.0, 125.1, 104.3. LCMS-240.1.

3-Phenyl isoquinoline-1(2H)-thione, 5. Mp 137–139°C, ^{1}H NMR (DMSO): δ 7.35 (s, 1H), 7.49 (m, 5H), 7.57 (m, 1H), 7.77 (m, 3H), 8.77 (d, J = 7.6 Hz, 1H). ^{13}C NMR (DMSO) δ 184.1 (CS), 142, 134.6, 133.6, 133.5, 132.5, 131.9 × 2, 131. 4 × 2, 129.1, 128.4, 128.1, 128, 111.0. LCMS-238.0, $C_{15}H_{11}NS$, Mol. Wt.: 237.32, Calculated C, 75.91; H, 4.67; N, 5.90; S, 13.51, Found C, 75.84; H, 4.59; N, 5.80; S, 13.42.

2-(3-Phenylisoquinolin-1-ylthio)-1-phenylethanone, 7a. Colorless solid, mp 145–147°C, IR (ν cm^{-1}) 3056, 2904, 1690 (CO), 1554, 1308, 1200, 958, 768, 688, 517. ^{1}H NMR (DMSO): δ 5. 06 (s, 2H), 7.13 (t, J = 7.7 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.7 Hz, 2H), 7.67–7.72 (m, 2H), 7.79–7.82 (m, 2H), 7.85 (d, J = 7.3 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 8.14–8.17 (n, 2H), 8.19 (d, J = 8.3 Hz, 2H). ^{13}C NMR (DMSO) δ 194.00 (CO), 152.6, 148.8, 138.4, 136.7, 136.4, 133.9, 131.6, 129.3, 128.9 × 2, 128.9 × 2, 128.8, 128.4, 128.2 × 2, 126.7 × 2, 125.4, 124.3, 113.5, 37.4 (CH_2). LCMS-356.0. $C_{23}H_{17}NOS$, Mol. Wt.: 355.45 Calculated C, 77.72; H, 4.82; N, 3.94; O, 4.50; S, 9.02, Found C, 77.62; H, 4.78; N, 3.74; O, 4.45; S, 8.92.

2-(3-Phenylisoquinolin-1-ylthio)-1-(4-chlorophenyl)ethanone, 7b. Colorless solid, mp 154–156°C, IR (ν cm^{-1}) 3052, 2915, 1692, 1588, 1359, 1201, 987, 788, 691, 520. ^{1}H NMR (DMSO): δ 5. 03 (s, 2H), 7.15 (t, J = 7.6 Hz, 2H), 7.27 (t, J = 7.3 Hz, 1H), 7.64–7.70 (m, 3H), 7.78–7.83 (m, 3H), 7.98 (d, J = 8.2 Hz, 1H), 8.10–8.19 (m, 4H),

^{13}C NMR (DMSO) δ 193.2, 157.5, 148.9, 138.8, 138.5, 135.5, 131.6, 130.8, 129.4 × 2, 129.0 × 2, 128.7 × 2, 128.4 × 2, 128.2 × 2, 126.1, 125.4, 124.3, 113.6, 37.3. LCMS-390.1, $C_{23}H_{16}ClNOS$, Mol. Wt.: 389.9, Calculated C, 70.85; H, 4.14; Cl, 9.09; N, 3.59; O, 4.10; S, 8.22, Found C, 70.81; H, 4.04; Cl, 8.99; N, 3.52; O, 4.01; S, 8.17.

2-(3-Phenylisoquinolin-1-ylthio)-1-(4-fluorophenyl)ethanone, 7c. Colorless solid, mp 147–149°C, IR (ν cm^{-1}) 3055, 2921, 1689, 1596, 1309, 1200, 988, 785, 689, 519. ^{1}H NMR (DMSO): δ 5. 034 (s, 2H), 7.15 (t, J = 7.64 Hz,2H), 7.28 (t, J = 7.30 Hz, 1H), 7.39 (t, J = 8.88 Hz, 2H), 7.67–7.71 (m, 1H), 7.79–7.85 (m, 3H), 7.99 (d, J = 8.12 Hz,1H), 8. 11 (s, 1H), 8.18–8.25 (m, 3H). ^{13}C NMR (DMSO) δ 192.7, 166.9, 164.4, 157.5, 148.9, 138.5, 136.4, 133.6, 133.5, 131.9, 131.8, 131.6, 129.0, 128.8, 128.4, 128.2, 126.7, 125.5, 124.3, 116.4, 116.2, 113.6, 37.4. LCMS-374.2, $C_{23}H_{16}FNOS$, Mol. Wt.: 373.44, Calculated C, 73.97; H, 4.32; F, 5.09; N, 3.75; O, 4.28; S, 8.59, Found C, 73.91; H, 4.22; F, 5.01; N, 3.65; O, 4.22; S, 8.51.

4-(2-(3-Phenylisoquinolin-1-ylthio) acetyl)benzonitrile, 7d. Colorless solid, mp 165–167°C, IR (ν cm^{-1}) 3058, 2921, 2231 (CN), 1693, 1554, 1311, 1203, 988, 828, 785, 699, 583, 519. ^{1}H NMR (DMSO): δ 5. 08 (s, 2H), 7.14 (t, J = 7.68 Hz, 2H), 7.27 (q, J = 4.88 Hz, 1H), 7.67 (t, J = 7.64 Hz, 1H), 7.79 (m, 3H), 7.98–8.09 (m, 3H), 8.17 (d, J = 8.32 Hz, 4H), 8.25 (d, J = 8.08 Hz, 1H). ^{13}C NMR (DMSO) δ 193.4, 156.8, 148.5, 139.6, 138.0, 136.0, 132.9, 131.3, 129.0 × 2, 128.6 × 2, 128.4 × 2, 128.0 × 2, 127.9, 126.3, 125.0, 123.8, 115.4, 113.3, 37.20. LCMS-381.0, $C_{24}H_{16}N_2OS$, Mol. Wt.: 380.46, Calculated C, 75.77; H, 4.24; N, 7.36; O, 4.21; S, 8.43, Found C, 75.67; H, 4.14; N, 7.39; O, 4.26; S, 8.47.

2-(3-Phenylisoquinolin-1-ylthio)-1-p-tolylethanone, 7e. Pale yellow solid, mp 156–158°C, IR (ν cm^{-1}) 3055, 2999, 2908, 1690, 1554, 1309, 1201, 983, 785, 694, 518. ^{1}H NMR (DMSO). δ 2.3 (s, 3H), 5.02 (s, 2H), 7.14 (t, J = 7.66 Hz, 2H), 7.26–7.30 (m, 1H), 7.38 (d, J = 8.08 Hz, 2H), 7.66–7.70 (m, 1H), 7.78 (q, J = 5.02 Hz, 1H), 7.86 (d, J = 8.08 Hz, 2H), 7. 98 (d, J = 8.08 Hz, 1H), 8.04 (d, J = 8.16 Hz, 2H), 8. 11 (s, 1H), 8.18 (d, J = 8.36 Hz, 1H). ^{13}C NMR (DMSO) δ 193.5, 157.6, 148.8, 144.4, 138.5, 136.4, 134.2, 131.6, 129.8, 128.9, 128.8, 128.4, 128.2, 126.6, 125.5, 124.3, 113.5, 37.3, 21.70. LCMS-370.1, $C_{24}H_{19}NOS$, Mol. Wt.: 369.48, Calculated C, 78.02; H, 5.18; N, 3.79; O, 4.33; S, 8.68, Found C, 77.92; H, 5.12; N, 3.74; O, 4.29; S, 8.62.

2-(3-Phenylisoquinolin-1-ylthio)-1-(4-(trifluoromethyl)phenyl) ethanone, 7f. Colorless solid, mp 179–181°C, IR (ν cm^{-1}) 3054, 2917, 1702, 1555, 1310, 1165, 1066, 990, 825, 768, 690, 518. ^{1}H NMR (DMSO): δ 5. 09 (s, 2H), 7.10 (t, J = 6.90 Hz, 2H), 7.24 (d, J = 8.28 Hz, 1H), 7.67 (t, J = 7.30 Hz, 1H), 7.78 (d, J = 6.76 Hz, 3H), 7.93–7.95 (d, J = 7.44 Hz, 3H), 7.99 (d, J = 7.64 Hz, 1H), 8.18 (d, J = 8.00 Hz, 1H), 8.30 (d, J = 7.32 Hz, 2H). ^{13}C NMR (DMSO) δ 193.8, 157.3, 148.9, 140.0, 138.4, 136.4, 133.3, 133.01, 131.6, 129.6, 128.9, 128.6, 128.4, 128.2, 126.6, 126.2, 126.2, 125.6, 125.4, 124.3, 122.9, 113.7, 37.5. LCMS-424, $C_{24}H_{16}F_3NOS$, Mol. Wt.: 423.45, Calculated C, 68.07; H, 3.81; F, 13.46; N, 3.31; O, 3.78; S, 7.57, Found C, 68.00; H, 3.76; F, 13.41; N, 3.21; O, 3.68; S, 7.49.

1-(3, 5-Bis(trifluoromethyl)phenyl)-2-(3-phenylisoquinolin-1-ylthio)ethanone, 7g. Colorless solid, mp 157–159°C, IR (ν cm^{-1}) 3060, 2908, 1698, 1552, 1282, 1127, 913, 748, 681, 515. ^{1}H NMR (DMSO): δ 5.18 (s, 2H), 7.08 (t, J = 7.70 Hz, 2H), 7.24 (t, J = 7.34 Hz, 1H), 7.68 (t, J = 7.62 Hz, 1H), 7.75 (d, J = 7.56 Hz, 2H), 7.80 (t, J = 7.52 Hz, 2H), 7.99 (d, J = 8.16 Hz, 2H), 8.08 (s, 1H), 8.17 (d, J = 8.28 Hz, 1H), 8.46 (s, 1H), 8.64 (s, 2H). ^{13}C NMR (DMSO) δ 192.9, 157.1, 149.1, 139.0, 138.5, 136.4, 131.7, 131.5, 131.2 129.2, 128.9, 128.5, 128.4, 128.3, 126.9, 126.7, 125.4, 124.7, 124.3, 122.1,

114.0, 37.4. LCMS-492.1, $C_{25}H_{15}F_6NOS$, Mol. Wt.: 491.45, Calculated C, 61.10; H, 3.08; F, 23.19; N, 2.85; O, 3.26; S, 6.52, Found C, 61.02; H, 3.00; F, 23.11; N, 2.76; O, 3.14; S, 6.42.

2-(3-Phenylisoquinolin-1-ylthio)-1-(4-chloro-2-methoxyphenyl)ethanone, 7h. Colorless solid, mp 140–142°C, IR (ν cm^{-1}) 3025, 2924, 1666, 1588, 1310, 1251, 1098, 987, 830, 748, 686, 517. ^{1}H NMR (DMSO): δ 3.98 (s, 3H), 4.88 (s, 2H), 7.02 (q, J = 3.40 Hz, 1H), 7.30–7.37 (m, 4H), 7.52 (d, J = 8.32 Hz, 1H), 7.64–7.68 (m, 1H), 7.77–7.81 (m, 1H), 7.97–8.00 (m, 3H), 8.14 (d, J = 7.76 Hz, 2H). ^{13}C NMR (DMSO) δ 194.2, 159.2, 157.4 148.3, 138.7, 138.1, 135.9, 131.5, 131.1, 128.6, 128.5, 127.9, 127.7, 126.2, 125.4, 125.0, 123.8, 120.7, 113.0, 56.5, 41.2. LCMS-420.1, $C_{24}H_{18}ClNO_2S$, Mol. Wt.: 419.92, Calculated C, 68.65; H, 4.32; Cl, 8.44; N, 3.34; O, 7.62; S, 7.64, Found C, 68.52; H, 4.26; Cl, 8.37; N, 3.25; O, 7.49; S, 7.55.

2-(3-Phenylisoquinolin-1-ylthio)-1-(4-chloro-3-fluorophenyl)ethanone, 7i. Pale yellow solid, mp 159–161°C, IR (ν cm^{-1}) 3069, 2917, 1692, 1553, 1417, 1306, 1237, 989, 889, 741, 693, 517. ^{1}H NMR (DMSO): δ 5.04 (s, 2H), 7.15 (t, J = 7.68 Hz, 2H), 7.28 (t, J = 7.32 Hz, 1H), 7.67–7.71 (m, 2H), 7.80–7.84 (m, 2H), 7.98–8.00 (m, 2H), 8.12–8.15 (m, 2H), 8.19 (d, J = 8.28 Hz, 2H). ^{13}C NMR (DMSO) δ 192.7, 157.3, 156.5, 149.0, 138.5, 137.6, 137.6, 136.4, 131.7, 129.3, 129.0, 128.7, 128.4, 128.3, 126.7, 126.1, 125.4, 125.3, 124.3, 117.1, 116.9, 113.8, 97.5, 37.3. LCMS-408.0, $C_{23}H_{15}ClFNOS$, Mol. Wt.: 407.89, Calculated C, 67.73; H, 3.71; Cl, 8.69; F, 4.66; N, 3.43; O, 3.92; S, 7.86, Found C, 67.66; H, 3.64; Cl, 8.61; F, 4.49; N, 3.32; O, 3.86; S, 7.73.

2-(3-Phenylisoquinolin-1-ylthio)-1-(4-chlorophenyl)propan-1-one, 7j. Colorless solid, mp 136–138 °C, IR (ν cm^{-1}) 3057, 2929, 1692, 1552, 1307, 1201, 1092, 989, 842, 766, 689, 518. ^{1}H NMR (DMSO): δ 1. 67 (d, J = 7.16 Hz, 3H), 5.99 (q, J = 7.16 Hz, 1H), 7.26 (t, J = 7.44 Hz, 1H), 7.31–7.33 (m, 2H), 7.54–7.56 (m, 2H), 7.65–7.67 (m, 1H), 7.79–7.81 (m, 2H), 7.87–7.89 (m, 2H), 7. 98 (d, J = 8.16 Hz, 2H), 8.11 (t, J = 8.00 Hz, 2H). ^{13}C NMR (DMSO) δ 196.9, 157.2, 149.2, 138.8, 138.5, 136.5, 134.3, 131.7, 130.8, 129.4, 129.0, 128.8, 128.4, 128.3, 126.8, 125.2, 124.3, 114.1, 43.6 (CH), 17.2 (CH_3). LCMS-404.1, $C_{24}H_{18}ClNOS$, Mol. Wt.: 403.92, Calculated C, 71.36; H, 4.49; Cal, 8.78; N, 3.47; O, 3.96; S, 7.94, Found C, 71.28; H, 4.37; Cal, 8.65; N, 3.39; O, 3.88; S, 7.81.

2-(3-Phenylisoquinolin-1-ylthio)-2-(4-chlorophenyl)-1-phenylethanone, 7k. Pale yellow solid, mp 145–147°C, IR (ν cm^{-1}) 3055, 2924, 1681, 1552, 1305, 1209, 1091, 988, 742, 697, 517. ^{1}H NMR (DMSO): δ 7.04 (t, J = 7.7 Hz, 2H), 7.21 (t, J = 6.9 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.63–7.71 (m, 5H), 7.78 (t, J = 7.6 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H), 8.09 (s, 2H), 8.19 (d, J = 8.6 Hz, 2H). ^{13}C NMR (DMSO) δ 192.9 (CO), 158.4, 149.4, 139.1, 138.4, 136.4, 134.6, 133.9, 131.4, 131.7, 131.4, 129.9 × 2, 129.8 × 2, 129.7, 129.5, 129.1, 128.8, 128.5 × 2, 128.4 × 2, 128.3, 126.8, 124.7, 124.3, 114.2, 54.1 (CH_2). LCMS-465.94, $C_{29}H_{20}ClNOS$, Mol. Wt.: 465.99, Calculated C, 74.75; H, 4.33; Cl, 7.61; N, 3.01; O, 3.43; S, 6.88, Found C, 74.68; H, 4.26; Cl, 7.52; N, 2.91; O, 3.31; S, 6.76.

1-(3-Phenylisoquinolin-1-ylthio)-3-(2-fluorophenyl)propan-2-one, 7l. Colorless solid, mp 146–148°C, IR (ν cm^{-1}) 3056, 2909, 1728, 1554, 1494, 1309, 1232, 1045, 989, 757, 690, 519. ^{1}H NMR (DMSO): δ 4.11 (s, 2H, CH_2), 4.54 (s, 2H, CH_2), 7.02–7.04 (m, 3H), 7.08 (d, J = 7.7 Hz, 1H), 7.43–7.51 (m, 3H), 7.68 (t, J = 7.4 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 8.13–8.18 (m, 4H), ^{13}C NMR (DMSO) δ 217.1 (CO), 162.8, 159.0, 157.5, 149.3, 138.9, 136.5, 132.5, 132.4, 131.7, 129.2, 128.4, 128.2, 127.0, 125.5, 124.6, 124.6, 124.3, 122.3, 122.1, 115.6, 115.3, 113.9, 41.60 (CH_2).

LCMS-388, $C_{24}H_{18}FNOS$, Mol. Wt.: 387.47, Calculated C, 74.39; H, 4.68; F, 4.90; N, 3.61; O, 4.13; S, 8.28, Found C, 74.29; H, 4.59; F, 4.79; N, 354; O, 4.06; S, 8.19.

Supplementary Material

CCDC 683298 contains the supplementary crystallographic data for this article. Copies may be obtained free of charge from the Director, CDC, 12 Union Road, Cambridge, CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk.

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