Synthesis of Dispiro[oxindole-pyrrolidine]-thiazolo [3,2-a][1,3,5]triazines by 1,3-Dipolar Cycloaddition

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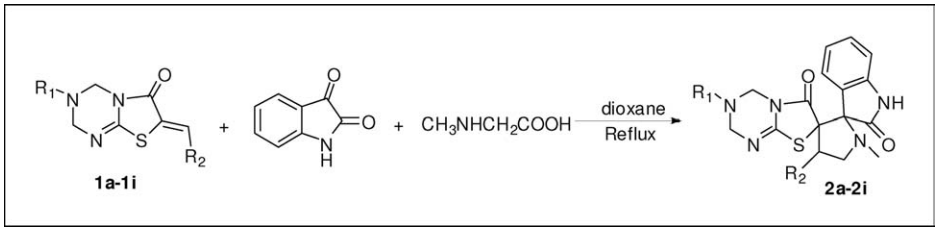

The 1,3-dipolar cycloaddition of an azomethine ylide generated by a decarboxylative route from sarcosine and isatin to 7-arylmethylidene-3-aryl-3,4-dihydro-2*H*-thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-ones afforded novel dispiro[oxindole-pyrrolidine]-thiazolo[3,2-*a*][1,3,5]triazines in moderate yields. The structures of the products were determined and characterized thoroughly by NMR, MS, IR, and elemental analysis. The results of experiment indicated that this 1,3-dipolar cycloaddition proceeded with high stereoselectivity and regioselectivity.

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INTRODUCTION

Spirooxindoles are motifs in many pharmacologically important alkaloids, as typified by rhyncophylline, corynoxeine, mitraphylline, horsifiline, and spirotryprostatins [1]. The derivatives of spirooxindole find very wide biological applications as antimicrobial, antitumoral, antibiotic agents, and inhibitors of human NK-1 receptor [2,3].

The 1,3-dipolar cycloaddition reaction of azomethine ylides generated by a decarboxylative route from amino acids and isatin with exocyclic olefins represents an efficient method for the construction of the spirooxindole structural unit [4,5].

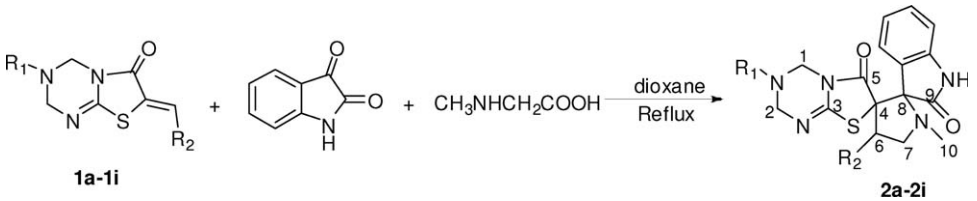
Triazine compounds are found to be associated with various biological activities [6]. The incorporation of triazine and spirooxindole into a dispiro heterocyclic system, which we believe could be a useful framework with potential biological activities, has not been investigated yet. In the present work, we report the synthesis of novel dispiro[oxindole-pyrrolidine]-thiazolo[3,2-*a*][1,3,5]triazines through the 1,3-dipolar cycloaddition of azomethine ylide and 7-arylmethylidene-3-aryl-3,4-dihydro-2*H*-thiazolo[3,2-*a*][1,3,5]triazin-6(7*H*)-ones (Scheme 1).

RESULTS AND DISCUSSION

The 1,3-dipolar cycloaddition of the 7-arylmethylidene-3-aryl-3,4-dihydro-2*H*-thiazolo[3,2-*a*][1,3,5]triazin-6(7H)-ones (**1a**–**1i**) to azomethine ylide generated *in situ* from isatin and sarcosine afforded novel dispiroheterocycles (**2a**–**2i**) in moderate yields (Table 1). This cycloaddition reaction proceeded with high stereo-and regio-selectivity to afford only one product, which was evidenced from TLC and ^{1}H-NMR of the crude reaction mixture. The structures of all compounds **2a–2i** were established by different spectroscopic techniques (IR, NMR, and MS) and elemental analysis. The IR spectrum of **2c** displayed $\nu_{C=O}$ at 1721.8 and 1700.7 cm^{-1}. The ^{1}H-NMR spectrum of **2c** revealed a singlet at δ 2.03 resulting from N—CH_3 (H-10), two doublets (J = 15.5 Hz) at δ 4.64 and 4.70 resulting from the protons of methylene (H-2), two doublets (J = 13.0 Hz) at δ 4.91 and 5.22 resulting from the protons of methylene (H-1). One doublet of doublets (J = 9.5, 8.5 Hz) at δ 4.35 assignable to the proton H-6, two triplets at δ 3.45 and 3.80 assignable to the protons of methylene (H-7) in pyrrolidine ring, several doublets and multiplets in the range of δ 6.69–7.34 for aromatic protons. The existence of a singlet at δ 10.74 corresponds to the —NH.

The ^{13}C-NMR spectrum of the product **2c** exhibits the presence of three methylenes carbons at δ 57.80 (C-7), 60.01 (C-1), and 65.51 (C-2), N-CH_3 carbon (C10) at δ 34.72, carbonyl carbons at δ 172.37 (C-5) and 176.57 (C-9). The signal at δ 51.45 is assignable for carbon of CH (C-6), which exists in pyrrolidine ring (based on

Scheme 1



HMQC). The signals at δ 67.80 and 79.21 are assignable for the spiro carbon of C-4 and C-8, respectively. In the ^{1}H-^{13}C HMBC map of **2c** (Fig. 1) ─NH correlate with C-9 (176.57 ppm), protons of -NH, H-7, and H-10 correlate with a spiro carbon C8 (79.21 ppm), protons of CH (H-6) and CH_2 (H-7) exist in pyrrolidine ring correlate with the spiro carbon C4 (67.80 ppm). The correlation of H-1 and H-6 with C-5 indicates the carbon atom of carbonyl carbon (C-5) at δ 172.37 ppm.

EXPERIMENTAL

1 [7] was prepared according to the reported procedures. All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer, operating at 500 MHz for ^{1}H, and 125 MHz for ^{13}C. TMS was used as an internal reference for ^{1}H and ^{13}C chemical shifts. $CDCl_3$ and DMSO-d_6 were as solvent. Elemental analysis was measured by an Elementar analyzer (varioELII). MS was measured by a Finnigan LCQ Advantage MAX mass spectrometer; IR spectra were recorded on Perkin-Elmer spectrometer. Melting points were measure by a Yanaco MP500 melting points apparatus and uncorrected.

General procedure for the synthesis of spirooxindoles (2a–g).. A solution of isatin (1 mmol), sarcosine (1 mmol) and 7-arylmethylidene-3-aryl-3,4-dihydro-2*H*-thiazolo[3,2-*a*]-[1,3,5]triazin-6(7*H*)-ones **1** (1mmol) in dioxane (30 mL) was refluxed overnight. Completion of the reaction was evidenced by TLC analysis. The solvent was removed *in vacuo*. The crude product was subjected to column chromatography using petroleum ether-ethyl acetate (*v*/*v* 5:1) as eluent to afford the corresponding **2**.

1′-Methyl-3″,4′-diphenyl-3″,4″-dihydro-2″*H*-dispiro[indole-3,2′-pyrrolidine-3′,7″-[1,3]thiazolo[3,2-*a*][1,3,5]triazine]-2,6″(1*H*)-dione (2a). White solid, yield 65%; mp : 206–207°C; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 3.36 (s, 3H), 3.44 (t, J = 8.0 Hz, 1H), 3.85 (t, J = 9.5 Hz, 1H), 4.34 (dd, J = 10.0, 8.0 Hz, 1H), 4.64 (d, J = 15.5 Hz, 1H), 4.69 (d, J = 15.5 Hz, 1H), 4.89 (d, J = 13.0 Hz, 1H), 5.22 (d, J = 13.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 2H), 6.76 (d, J = 8.0 Hz, 1H), 6.91–6.96 (m, 2H), 7.14–7.18 (m, 2H), 7.23–7.25 (m, 7H), 10.70 (br, 1H); ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 35.25, 52.72, 58.01, 60.43, 66.01, 68.39, 79.76, 110.26, 118.71, 122.24, 122.65, 124.09, 126.97, 127.91, 128.87, 129.69, 130.49, 131.01, 138.54, 144.12, 147.59, 149.05, 172.98, 177.01; IR (KBr) *v*: 1718.5, 1701.1 cm^{-1}; ESI MS *m*/*z*: 496 [M+H]$^+$.Anal. calcd. for $C_{28}H_{25}N_5O_2S$: C 67.86, H 5.08, N 14.13; found C 67.74, H 5.15, N 14.10.

4′-(4-Chlorophenyl)-1′-methyl-3″-phenyl-3″,4″-dihydro-2″*H*-dispiro[indole-3,2′-pyrrolidine-3′,7″-[1,3]thiazolo[3,2-*a*][1,3,5]triazine]-2,6″(1*H*)-dione(2b). White solid, yield 75%; mp : 236–237°C; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 2.05 (s, 3H), 3.45 (t, J = 8.5 Hz, 1H), 3.81 (t, J = 9.5 Hz, 1H), 4.34 (t, J = 8.5 Hz, 1H), 4.65 (d, J = 15.5 Hz, 1H), 4.71 (d, J = 15.5 Hz, 1H), 4.91 (d, J = 13.0 Hz, 1H), 5.22 (d, J = 13.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 2H), 6.76 (d, J = 8.0 Hz, 1H), 6.93 (t, J = 7.5 Hz, 2H), 7.16 (t, J = 8.0 Hz, 2H), 7.23–7.29 (m, 2H), 7.31–7.35 (m, 4H), 10.70 (br, 1H); ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 34.72, 51.54, 57.53, 60.04, 65.51, 67.68, 79.22, 109.82, 118.22, 121.79, 122.20, 123.46, 126.47, 128.28, 129.20, 130.54, 131.88, 132.11, 137.11, 143.62, 147.06, 148.33, 172.26, 176.52; IR (KBr) *v*: 1738.5, 1718.2 cm^{-1}; MS(ESI) *m*/*z*: 530 [M+H]$^+$. Anal. calcd. for $C_{28}H_{24}ClN_5O_2S$: C 63.45, H 4.56, N 13.21; found C 63.37, H 4.70, N 13.16.

4′-(4-Fluorophenyl)-1′-methyl-3″-phenyl-3″,4″-dihydro-2″*H*-dispiro[indole-3,2′-pyrrolidine-3′,7″-[1,3]thiazolo[3,2-*a*][1,3,5]triazine]-2,6″(1*H*)-dione(2c).. White solid, yield 72%; mp: 229–230°C; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 2.05 (s, 3H), 3.45 (t, J = 8.5 Hz, 1H), 3.80 (t, J = 9.5 Hz, 1H), 4.35 (dd, J = 9.5 Hz, 8.5 Hz, 1H), 4.64 (d, J = 15.5 Hz, 1H), 4.70 (d, J = 15.5 Hz, 1H), 4.91 (d, J = 13.0 Hz, 1H), 5.22 (d, J = 13.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 2H), 6.76 (d, J = 7.5 Hz, 1H), 6.91–6.96 (m, 2H), 6.69 (d, J = 8.0 Hz, 1H), 6.77 (d, J

Table 1

The results of synthesis of 2a–2i.

Entry	R_1	R_2	Product	Time (h)	Yield (%)
1	C_6H_5	C_6H_5	**2a**	20	65
2	C_6H_5	4-ClC_6H_4	**2b**	18	75
3	C_6H_5	4-FC_6H_4	**2c**	18	72
4	C_6H_5	2,4-$Cl_2C_6H_3$	**2d**	20	75
5	C_6H_4	4-$CH_3C_6H_4$	**2e**	24	68
6	4-$CH_3OC_6H_4$	2,4-$Cl_2C_6H_3$	**2f**	24	76
7	4-$CH_3OC_6H_4$	C_6H_5	**2g**	24	65
8	4-$CH_3OC_6H_4$	4-ClC_6H_4	**2h**	24	70
9	4-$CH_3OC_6H_4$	4-FC_6H_4	**2i**	24	75

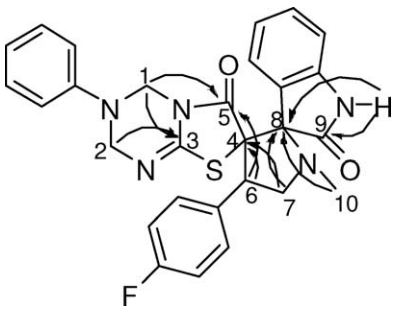


Figure 1. Part HMBC diagram of **2c**.

= 7.5 Hz, 2H), 6.91–6.95 (m, 2H), 7.11 (t, J = 8.5 Hz, 2H), 7.15–7.18 (m, 2H), 7.23–7.25 (m, 2H), 7.32 (dd, J = 8.5 Hz, 5.5 Hz, 2H), 10.74 (br, 1H); ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 34.72, 51.45, 57.80, 60.01, 65.51, 67.80, 79.21, 109.81, 115.01, 115.18, 118.22, 121.78, 122.21, 123.50, 126.46, 129.21, 130.54, 131.97, 132.04, 134.32, 134.35, 143.60, 147.07, 148.42, 172.37, 176.57; IR (KBr) v: 1721.8, 1700.7 cm^{-1}; MS(ESI) m/z: 514 $[M+H]^+$. Anal. calcd. for $C_{28}H_{24}FN_5O_2S$: C 65.48, H 4.71, N 13.64; found C 65.62, H 4.78, N 13.50.

4′-(2,4-Dichlorophenyl)-1′-methyl-3″-phenyl-3″,4″-dihydro-2″H-dispiro[indole-3,2′-pyrrolidine-3′,7″-[1,3]thiazolo[3,2-a][1,3,5]triazine]-2,6″(1H)-dione(2d). White solid, yield 75%; mp : 247–248°C; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 2.05 (s, 3H), 3.47 (t, J = 8.5 Hz, 1H), 3.95 (t, J = 9.5 Hz, 1H), 4.65 (d, J = 15.5 Hz, 1H), 4.70–4.74 (m, 2H), 4.89 (d, J = 13.0 Hz, 1H), 5.18 (d, J = 13.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 7.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 7.11–7.14 (m, 2H), 7.22 (d, J = 7.5 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.51 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 10.73 (br, 1H); ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 34.92, 46.06, 55.30, 60.10, 65.50, 66.32, 66.36, 79.21, 110.01, 118.23, 121.80, 122.30, 122.82, 126.04, 127.42, 128.47, 129.12, 130.67, 131.79, 132.72, 135.07, 136.39, 143.68, 147.07, 148.52, 171.95, 176.30; IR (KBr) v: 1718.2, 1709.5 cm^{-1}; MS(ESI) m/z: 564 $[M+H]^+$. Anal. calcd. for $C_{28}H_{23}Cl_2N_5O_2S$: C 59.58, H 4.11, N 12.41; found C 59.40, H 4.18, N 12.32.

1′-Methyl-4′-(4-methylphenyl)-3″-phenyl-3″,4″-dihydro-2″H-dispiro[indole-3,2′-Pyrrolidine-3′,7″-[1,3]thiazolo[3,2-a][1,3,5]triazine]-2,6″(1H)-dione (2e). White solid, yield 68%; mp : 237–238°C; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 2.05 (s, 3H), 2.28 (s, 3H), 3.41 (t, J = 8.0 Hz, 1H), 3.84 (t, J = 9.5 Hz, 1H), 4.31 (dd, J = 9.5, 8.0 Hz, 1H), 4.63 (d, J = 15.5 Hz, 1H), 4.70 (d, J = 15.5 Hz, 1H), 4.88 (d, J = 13.0 Hz, 1H), 5.21 (d, J = 13.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 2H), 6.76 (d, J = 8.0 Hz, 1H), 6.91–6.96 (m, 2H), 7.08 (d, J = 7.5 Hz, 2H),7.15–7.18 (m, 4H), 7.23–7.28 (m, 2H), 10.70 (br, 1H); ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 21.18, 35.25, 52.43, 58.03, 60.36, 66.09, 68.57, 79.73, 110.25, 118.73, 122.26, 122.62, 124.15, 126.99, 129.46, 129.69, 130.35, 130.98, 135.51, 137.02, 144.14, 147.61, 149.13, 173.04, 177.02; IR (KBr) v: 1719.9, 1700.8 cm^{-1}; MS(ESI) m/z: 510 $[M+H]^+$. Anal. calcd. for $C_{29}H_{27}N_5O_2S$: C 68.35, H 5.34, N 13.74; found C 68.21, H 5.26, N 13.89.

4′-(2,4-Dichlorophenyl)-3″-(4-methoxyphenyl)-1′-methyl-3″,4″-dihydro-2″H-dispiro[indole-3,2′-pyrrolidine-3′,7″-[1,3]thiazolo[3,2-a][1,3,5]triazine]-2,6″(1H)-dione (2f). White solid, yield 76%; m.p.: 254–255°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.23 (s, 3H), 3.56 (t, J = 8.5 Hz, 1H), 3.83 (s, 3H), 4.13 (t, J = 9.5 Hz, 1H), 4.61 (d, J = 15.5 Hz, 1H), 4.67 (d, J = 15.5 Hz, 1H), 4.87 (d, J = 13.0 Hz, 1H), 4.96 (t, J = 9.0 Hz, 1H), 4.99 (d, J = 13.0 Hz, 1H), 6.64–6.67 (m, 3H), 6.72–6.73 (m, 2H), 6.77 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.35 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 8.52 (br, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 35.61, 46.31, 55.48, 56.14, 63.05, 66.28, 67.06, 79.94, 109.88, 114.60, 121.31, 122.91, 122.98, 126.48, 127.42, 129.08, 130.46, 131.44, 133.80, 134.71, 136.91, 140.92, 142.38, 150.99, 155.56, 172.81, 176.90; IR (KBr) v: 1721.1, 1707.6 cm^{-1}; MS(ESI) m/z: 594 $[M+H]^+$. Anal. calcd. for $C_{29}H_{25}Cl_2N_5O_3S$: C 58.59, H 4.24, N 11.78; found C 58.73, H 4.16, N 11.59.

3″-(4-Methoxyphenyl)-1′-methyl-4′-phenyl-3″,4″-dihydro-2″H-dispiro[indole-3,2′-pyrrolidine-3′,7″-[1,3]thiazolo[3,2-a][1,3,5]triazine]-2,6″(1H)-dione (2g). White solid, yield 65%; mp : 219–220°C; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 2.04 (s, 3H), 3.43 (t, J = 8.0 Hz, 1H), 3.72 (s, 3H), 3.85 (t, J = 9.5 Hz, 1H), 4.34 (dd, J = 9.5, 8.0 Hz, 1H), 4.52 (d, J = 15.5 Hz, 1H), 4.60 (d, J = 15.5 Hz, 1H), 4.82 (d, J = 13.0 Hz, 1H), 5.12 (d, J = 13.0 Hz, 1H), 6.58 (d, J = 9.0 Hz, 2H), 6.69 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 8.0 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 7.21–7.31 (m, 7H), 10.71 (br, 1H); ^{13}C NMR(DMSO-d_6, 125 MHz) δ: 35.23, 52.68, 55.65, 58.12, 61.52, 66.47, 68.22, 79.78, 110.28, 114.83, 120.35, 122.64, 124.10, 126.88, 127.93, 128.86, 130.58, 130.82, 138.63, 141.12, 144.11, 148.98, 154.93, 173.08, 177.03; IR (KBr) v: 1719.1, 1708.4 cm^{-1}; MS(ESI) m/z: 526 $[M+H]^+$. Anal. calcd. for $C_{29}H_{27}N_5O_3S$: C 66.27, H 5.18, N 13.32; found C 66.35, H 5.26, N 13.20.

4′-(4-Chlorophenyl)-3″-(4-methoxyphenyl)-1′-methyl-3″,4″-dihydro-2″H-dispiro[indole-3,2′-pyrrolidine-3′,7″-[1,3]thiazolo[3,2-a][1,3,5]triazine]-2,6″(1H)-dione (2h). White solid, yield 70%; m.p.: 236–237°C; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 2.03 (s, 3H), 3.45 (t, J = 8.0 Hz, 1H), 3.73 (s, 3H), 3.80 (t, J = 9.5 Hz, 1H), 4.35 (dd, J = 9.5, 8.0 Hz, 1H), 4.54 (d, J = 15.5 Hz, 1H), 4.62 (d, J = 15.5 Hz, 1H), 4.85 (d, J = 13.0 Hz, 1H), 5.13 (d, J = 13.0 Hz, 1H), 6.61 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 8.0 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 7.22–7.24 (m, 2H), 7.34–7.38 (m, 4H), 10.75 (br, 1H); ^{13}C-NMR(DMSO-d_6, 125 MHz) δ: 35.19, 52.01, 55.62, 58.14, 61.63, 66.45, 67.96, 79.72, 110.34, 114.82, 120.34, 122.69, 123.95, 126.88, 128.78, 130.85, 132.46, 132.62, 137.69, 141.07, 144.10, 148.76, 154.94, 172.87, 177.04; IR (KBr) v: 1718.2, 1706.6 cm^{-1}; MS(ESI) m/z: 560 $[M+H]^+$. Anal. calcd. for $C_{29}H_{26}ClN_5O_3S$: C 62.19, H 4.68, N 12.50; found C 62.30, H 4.57, N 12.40.

4′-(4-Fluorophenyl)-3″-(4-methoxyphenyl)-1′-methyl-3″,4″-dihydro-2″H-dispiro[indole-3,2′-pyrrolidine-3′,7″-[1,3]thiazolo[3,2-a][1,3,5]triazine]-2,6″(1H)-dione (2i). White solid, yield 75%; m.p.: 243–244°C; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 2.05 (s, 3H), 3.45 (t, J = 8.0 Hz, 1H), 3.72 (s, 3H), 3.78 (t, J = 9.5 Hz, 1H), 4.35 (dd, J = 9.5, 8.0 Hz, 1H), 4.54 (d, J = 15.5 Hz, 1H), 4.60 (d, J = 15.5 Hz, 1H), 4.84 (d, J = 13.0 Hz, 1H), 5.11 (d, J = 13.0 Hz, 1H), 6.58–6.60 (m, 2H), 6.67–6.70 (m, 2H), 6.77 (d, J = 7.5 Hz, 1H), 6.88 (t, J = 7.0 Hz, 1H), 7.13 (t, J = 8.5 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.36 (dd, J = 8.5 Hz, 5.5 Hz, 2H), 10.73 (br, 1H); ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 35.20, 51.88, 55.64, 58.40, 61.61, 66.44, 68.11, 79.73, 110.31, 114.83, 115.50, 115.67, 120.35,

122.69, 124.00, 126.85, 130.83, 132.55, 132.61, 134.92, 134.94, 141.10, 144.08, 148.83, 154.94, 172.94, 177.07; IR (KBr) *v*: 1721.4, 1709.9 cm^{-1}; MS(ESI) *m/z*: 544 $[M+H]^+$. Anal. calcd. for $C_{29}H_{26}FN_5O_3S$: C 64.07, H 4.82, N 12.88; found C 64.14, H 4.90, N 12.76.

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